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Synthesis of highly water-soluble cyclodextrin sulfonates by addition of hydrogen sulfite to cyclodextrin allyl ethers

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Abstract

Highly water-soluble cyclodextrin sulfonates were synthesised by the addition of hydrogen sulfite to allyl ethers of α- and β-cyclodextrin (α- and β-CD). The allyl derivatives were obtained by etherification of β-CD with allyl bromide or 1-allyloxy-2,3-epoxypropane. In this way, it was possible to isolate 2^{I}-*O*-allyl-β-CD, 2^{I}-*O*-(3-allyloxy-2-hydroxypropyl)-β-CD and 6^{I}-*O*-(3-allyloxy-2-hydroxypropyl)-β-CD after column chromatography. Statistically polysubstituted (3-allyloxy-2-hydroxypropyl)-ethers of α- and β-CD were also synthesised. The subsequent addition of HSO_3^- to the terminal C–C double bonds was complete after 3 h at 120–140 °C. The allyl groups were converted to propylsulfonic acid groups. Sulfinic acids were formed as side products. The resulting cyclodextrin sulfonates are highly water soluble and able to solubilize hydrophobic guest molecules, such as naphthalene.

Keywords: Cyclodextrin allyl ethers; Cyclodextrin sulfonates; Solubilisation in water

1. Introduction

Cyclomaltooligosaccharides, especially cyclomaltohexaose (α-cyclodextrin), cyclomaltoheptaose (β-cyclodextrin), and cyclomaltooctaose (γ-cyclodextrin), α-, β-, γ-CD, respectively, are well known to include hydrophobic guest molecules in aqueous solution [1–3]. This inclusion can lead to an increase in the aqueous solubility of guests such as drugs [4–6]. For instance, the solubilization of the anti-inflammatory drug Piroxicam leads to faster uptake into the human body [7]. The solubilizing effect of β-cyclodextrin is, however, limited by its own solubility of only 1.85% in water [8]. The inclusion compounds of totally hydrophobic guests like toluene in β-CD are even less soluble than β-CD itself.

The solubility of β-CD can be improved by the attachment of substituents [9]. These can be either neutral (e.g., methyl [10], hydroxypropyl [11,12], thioureido [13,14]) or charged [15,16]. Even a single charged substituent leads to a very efficient increase in the solubilities of cyclodextrins and their inclusion compounds, as association of the hosts is prevented by the mutual repulsion of the charges. Both cationic cyclodextrin derivatives, such as protonated 6-amino-6-deoxy-β-cyclodextrin [17], and anionic derivatives, like β-cyclodextrin carboxymethyl ethers [18],

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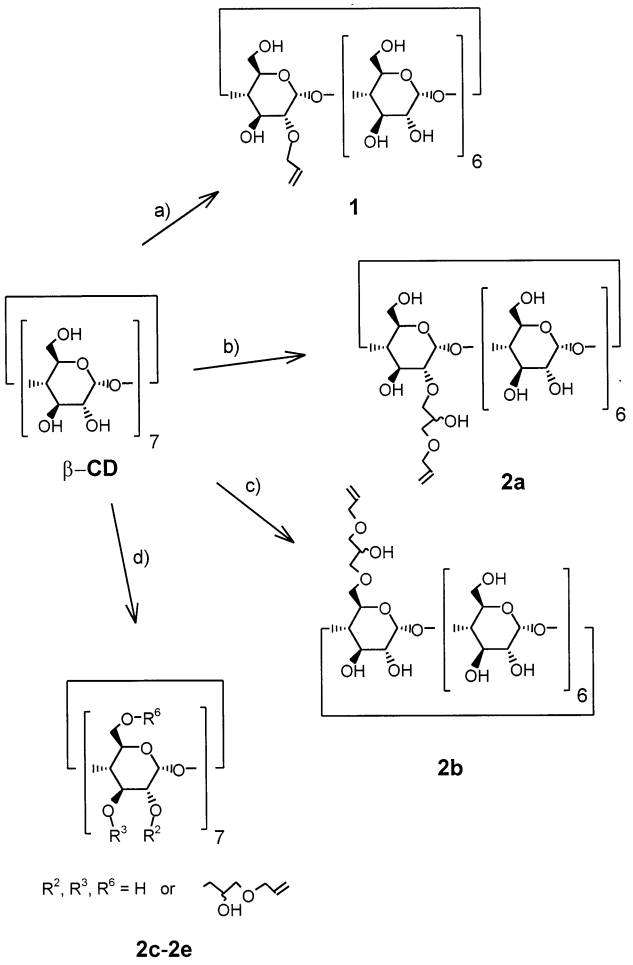
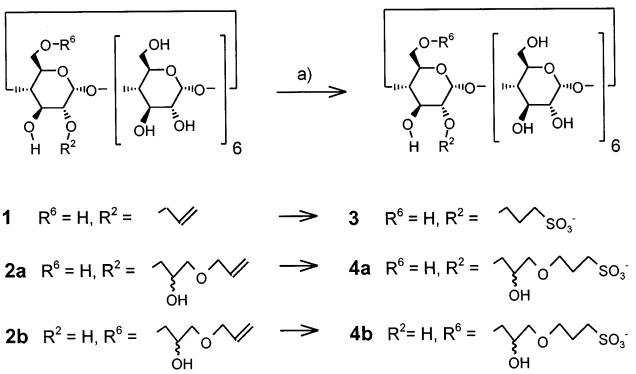
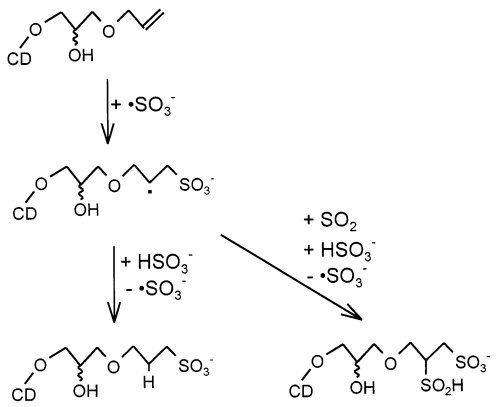
phosphates [19], sulfates [20], and sulfonates, are known. Cyclodextrin sulfonates have been synthesised by the statistical etherification of cyclodextrin with sultones [21]. Recently, sulfonatopropyl- and sulfonatobutyl-cyclodextrins have gained increasing interest for the solubilisation of drugs [22] and as enantioselective carriers for capillary electrophoresis [23,24]. Cyclodextrin carbonic acids have been synthesised by the radical addition of thio acids to cyclodextrin allyl ethers and tested as antiviral drugs [16].



Scheme 1. Synthesis of cyclodextrin allylethers: (a) NaH, allyl bromide in DMF; (b) NaH, allyl glycidyl ether (AGE) in DMF; (c) 20% NaOH, AGE; (d) 2.5–20% NaOH, excess AGE.



Scheme 2. Synthesis of monofunctional cyclodextrin sulfonates: (a) $Na_2S_2O_5$, 120–140 °C, 1–3 h, in water.



Scheme 3. Mechanism of the radical additions of sulfite and SO_2 to C–C double bonds under formation of sulfonates (left) and sulfinates (right).

In this paper, we describe a new two-step synthesis for cyclodextrin sulfonates that circumvents the use of hazardous sultones and, in addition, allows the regioselective synthesis of monosubstituted cyclodextrin derivatives. We synthesised various cyclodextrin allyl ethers [16,25] (Scheme 1) and applied the well-known radical addition of hydrogen sulfite (HSO_3^-) to double bonds [26] to introduce sulfonate groups (Scheme 2). Pyrosulfite anions ($S_2O_5^{2-}$) can be used instead of HSO_3^- as they are in thermodynamic equilibrium with HSO_3^- in aqueous solution. This addition, called olefin sulfonation, is widely used in industry for the synthesis of alkyl sulfonates [27]. The mechanism is a radical chain reaction involving sulfite radicals as the active species [28,29]. Sulfinates are formed as side products by addition of SO_2 after the initial addition of sulfite to a double bond (Scheme 3) [28,30].

2. Results and discussion

Synthesis of cyclodextrin allyl ethers.—As the first step, derivatives of α- and β-cyclodextrin with one or several pending allyl groups were synthesised by etherification reactions (Scheme 1).

Pure 2^{I}-*O*-allyl-β-cyclodextrin (**1**) was synthesised in 4% yield according to the method of Hanessian et al. [25] by etherification of the monosodium salt of β-CD in *N*,*N*-dimethylformamide at room temperature with allyl bromide [31]. The other products were higher β-cyclodextrin allyl ethers and unmodified β-CD. In a similar way 2^{I}-*O*-(-(3-allyloxy-2-hydroxypropyl)-β-cyclodextrin (**2a**) was obtained in a 10% isolated yield by alkylation of the monosodium salt of β-CD with racemic 1-allyloxy-2,3-epoxypropane (allyl glycidyl ether, AGE).

The predominant etherification at the primary positions OH-6 with propylene oxide in 30% aqueous sodium hydroxide had already been described by Pitha et al. [11]. Consequently, we too performed the etherification of β-CD with AGE in 30% sodium hydroxide. We succeeded in isolating the 6^{I}-*O*-(3-allyloxy-2-hydroxypropyl)-β-cyclodextrin (**2b**) by repetitive recrystallisation or column chromatography in an 8–12% yield. The isolation of the allyl ether **2b** is straightforward, as it has a rather low solubility of 0.19% in water. The ^{13}C NMR spectrum of **2b** demonstrates the high regioselectivity of the etherification (Fig. 1). The two regioisomers **2a** and **2b** were also readily distinguishable by reversed phase high performance liquid chromatography (HPLC) (Fig. 2). The sample of **2a** clearly contained a small amount of **2b**. Exclusive substitution at the O-2 position would require protection of all the primary hydroxyl functions, e.g., by *tert*-butyl-dimethylsilyl groups [32].

In addition, we synthesised a series of statistically substituted allyl ethers **2c**–**i** by reaction of β-CD with AGE in aqueous sodium hydroxide of various concentrations. The degrees of substitution (DS) of compounds **2c**–**h**, defined as the number of 3-allyloxy-2-hydroxypropyl groups per cyclodextrin molecule regardless of the position, were obtained by FABMS. The MS signal of the molecular ion with the highest intensity was selected for the calculation of the DS. The distribution of substituents between the primary and secondary positions was determined by ^{1}H NMR spectroscopy of the resulting sulfonated products **4c**–**h**. The signal of H-1′ at 5.25 ppm was assigned to those glucopyranose units substituted at one of the secondary positions, while the signal of H-1 at 5.05 ppm was assigned to unsubstituted glucopyranose units or those substituted in the primary position. The DS in the secondary position, $DS_{2,3}$, was calculated from the integrals *I* according to $DS_{2,3} = nI(\text{H-1}')/(I(\text{H-1}) + I(\text{H-1}'))$ where *n* is the number of glucopyranose units per cyclodextrin molecule (Table 1).

If the alkylation was performed in a 2.5% sodium hydroxide solution, a statistically substituted *O*-(3-allyloxy-2-hydroxypropyl)-β-cyclodextrin (**2c**) with DS 8 was obtained in 52% yield. On average, four substituents were found on both the primary and secondary sides. If the same reaction was carried out in 5% sodium hydroxide, the derivative **2d** with DS 9 was isolated in only 34% yield. On average, six substituents were then at the primary and three at the secondary positions. An even lower yield of 24% for derivative **2e** was found for the reaction in 20% sodium hydroxide. Most of the substituents (4.6 on average) were at the primary positions and only a few (0.4 on average) at the secondary positions. Thus, at low sodium hydroxide concentration the more acidic secondary hydroxyl groups are favoured, while at high sodium hydroxide concentration etherification dominates at the less sterically hindered primary hydroxyl groups [11].

Similar results were found for the synthesis of statistically substituted *O*-(3-allyloxy-2-hydroxypropyl)-α-cyclodextrins. Compared with the corresponding ethers of β-cyclodextrin, yields and DS were both lower. This result might be a consequence of the lower reactivity in general for α-CD compared with that of β-CD [33]. In particular, the secondary hydroxyl groups appeared to be less reactive than those of β-CD. Even for a 2.5% sodium hydroxide concentration, the alkylation took place predominantly at the primary hydroxyl groups. The low reactivity of the secondary hydroxyl groups might be a result of relatively strong intramolecular hydrogen bonds formed between these groups in neighbouring glucopyranosyl residues of α-CD [34,35].

Sulfonation of the allyl cyclodextrins.—As a second step, the allyl ethers **1** and **2** were reacted in an autoclave with sodium pyro-

sulfite in an aqueous solution of pH 4.4, at 120–140 °C. Small amounts of potassium nitrate were added as catalyst. The resulting products, cyclodextrin sulfonates **3** and **4**, were highly water soluble at room temperature. Therefore they could not be isolated by recrystallisation, but required ultrafiltration. Yields of the products were between 27 and 59% for the mono-substituted allyl derivatives **1** and **2a**,**b** and 58–93% for the statistical derivatives **2c**–**h** (Table 2). The lower yields for the monofunctional derivatives might be

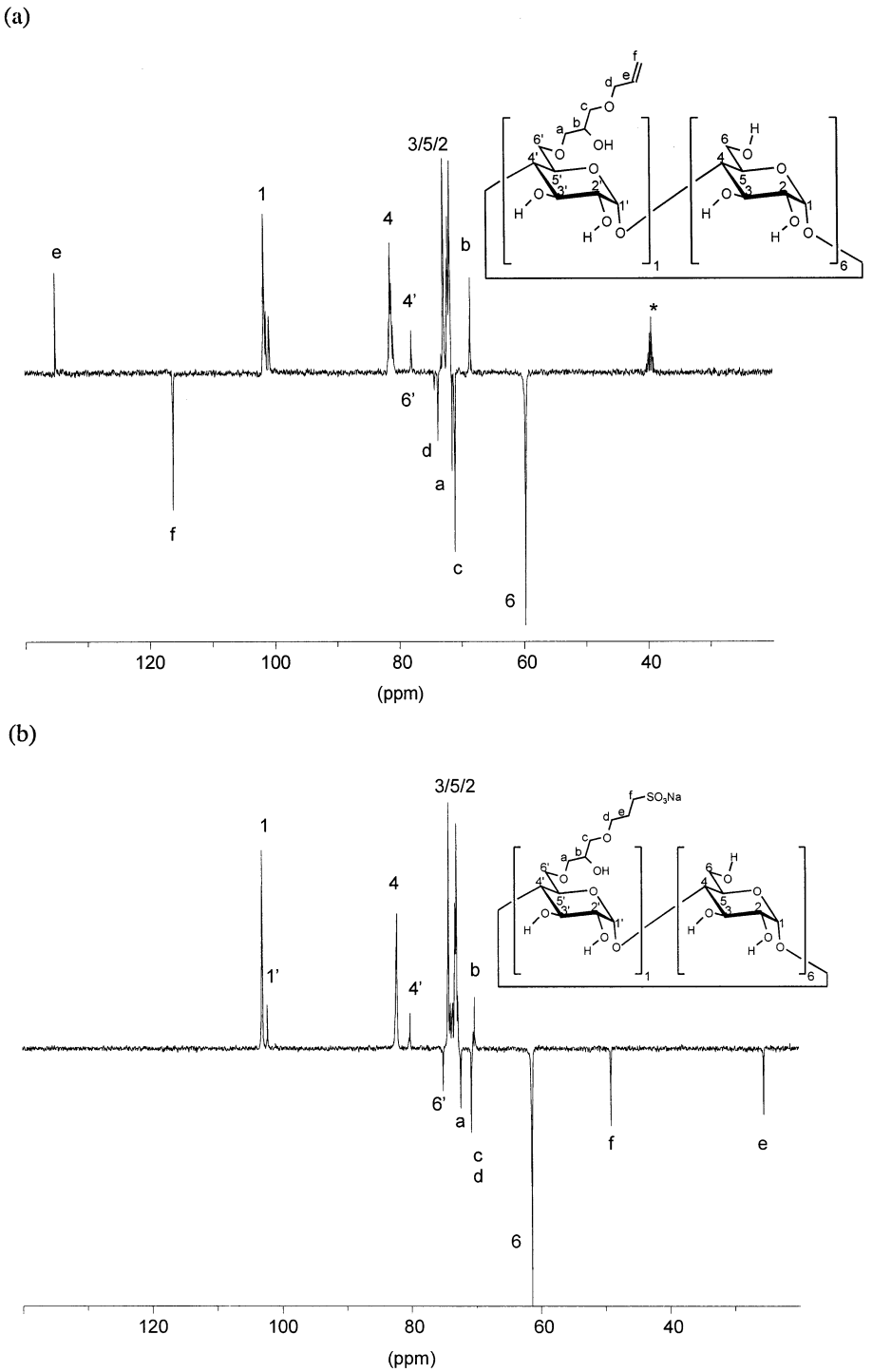


Fig. 1. DEPT NMR spectra of (a) **2b** in Me_2SO-d_6 and (b) **4b** in D_2O.

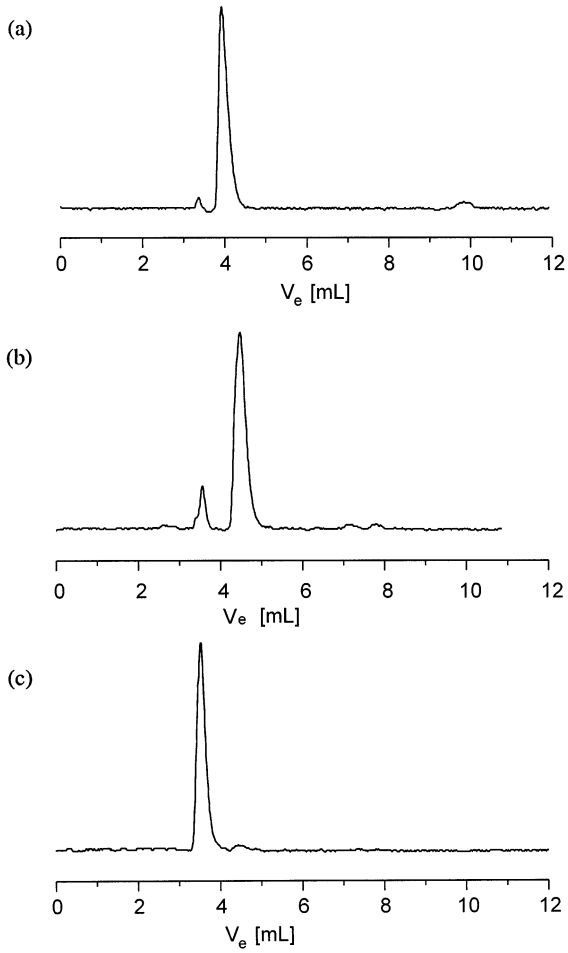


Fig. 2. HPLC chromatograms (RP-18, 90:10:0.5 water–MeCN–AcOH) of (a) **1** (V_e 3.9 mL); (b) **2a** (V_e 4.5 mL) and (c) **2b** (V_e 3.6 mL).

due to the lower water solubility of the corresponding starting materials and some loss during the ultrafiltration process of the products.

Table 2
Addition of HSO_3^- to cyclodextrin allyl ethers [a]

Educt	DS	Total yield (%)	Content of sulfinate (mol%)	Product
β-Cyclodextrin derivatives				
1	1	42	0	**3**
2a	1	59	0	**4a**
2b	1	27	0	**4b**
2c	8	64	25	**4c**
2d	9	58	21	**4d**
2e	5	79	14	**4e**
α-Cyclodextrin derivatives				
2f	3	27	14	**4f**
2g	5	93	30	**4g**
2h	3	82	16	**4h**

[a] DS, degree of substitution, number of substituents per cyclodextrin moiety.

Completion of the radical addition of hydrogen sulfite to the double bonds was demonstrated by both ^1H and ^{13}C NMR spectroscopy (Fig. 1). The characteristic ^1H NMR signals of the allyl groups at 5.93 and 5.26 ppm disappeared. In their place new signals emerged at 2.97 and 2.04 ppm for the sulfonatopropyl groups. After a reaction time of 3 h, no allyl substituents remained. For the statistically polysubstituted cyclodextrin derivatives in particular, we found some indication of the formation of sulfinates as well as sulfonates. Sulfinates are known to be formed as side products by the addition of SO_2 to the radical initially produced by addition of a sulfite radical to the C–C double bond (Scheme 3)

Table 1
Etherification of β-cyclodextrin by allyl glycidyl ether in aqueous NaOH [a]

Educt	[NaOH] (wt.%)	[AGE]/[CD]	Yield (%)	DS	DS_6	$DS_{2,3}$	Product
β-CD	30.0 [b]	3	8 [c]	1	0.0	1.0	**2b**
β-CD	2.5	14	52	8	4.0	4.0	**2c**
β-CD	5.0	14	34	9	5.8	3.2	**2d**
β-CD	20.0	30	24	5	4.6	0.4	**2e**
α-CD	2.5	3	74	3	2.4	0.6	**2f**
α-CD	2.5	7	36	5	3.6	1.4	**2g**
α-CD	20.0 [c]	14	34	3	2.7	0.3	**2h**

[a] [NaOH], concentration of NaOH; [AGE], molar concentration of allyl glycidyl ether; [CD], molar concentration of cyclodextrin; DS, total degree of substitution; DS_6 and $DS_{2,3}$, partial degree of substitution in positions O-6 and O-2 or O-3, respectively.

[b] Reaction at 0 °C.

[c] After column chromatography.

[28,30]. The ^{1}H NMR signal of H-f′ at 2.68 ppm was assigned to the terminal methylene group of the substituent with sulfonate and sulfinate groups; and the H-f signal at 2.97 ppm was assigned to those substituents bearing only a sulfonate group. The content of sulfinate in the product was determined from the ratio of the integrals I(H-f′)/(I(H-f) + I(H-f′)). It ranged from 14 to 30% for the polysubstituted cyclodextrin derivatives, while for the monosubstituted β-CD derivatives no sulfinate was found at all.

The absence of sulfinate in the monosubstituted derivatives **3**, **4a**, and **4b** might be due to the pH of the reaction mixture being scarcely higher than that for the statistically polysubstituted cyclodextrins **4c**–**4h**. It was already known that an increase in pH leads to a drop in the amount of sulfinate [28,36]. Therefore, we carried out the sulfonations of the polysubstituted allyl cyclodextrins again at pH 7. The sulfinate content could be significantly lowered but the sulfonation became rather sluggish. Only 40–60% conversion of the double bonds could be achieved.

Solubilisation of guests by the cyclodextrin sulfonates.—The resulting cyclodextrin sulfonates were white powders, totally soluble in water. Even the monosubstituted β-cyclodextrin sulfonates showed some very high water solubilities at room temperature ranging from 40 g/100 mL for **4b**, and 53 g/100 mL for **4a** to 93 g/100 mL for **3**. They are able to solubilise even very hydrophobic guest molecules like benzene or naphthalene in water. The rise in naphthalene solubility with increasing concentration of **4e** is shown in Fig. 3. Aqueous concentrations of naphthalene of 1 g/L could be achieved by its inclusion in **4e**. From the slope of this solubility isotherm, $m = 0.12$, and the solubility of the guest, $[G]_0 = 0.16$ mM, a binding constant of $K_s = 852\ M^{-1}$ was derived in accordance with Eq. (1) [37]. This value is quite common for the inclusion of aromatic guest molecules in β-cyclodextrin [38].

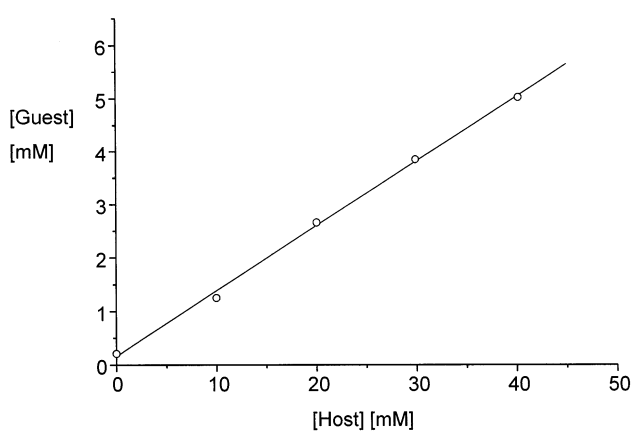


Fig. 3. Solubility of the guest naphthalene in water as a function of the concentration of the host **4e** at 20 °C.

$$K_s = \frac{m}{(1-m)[G]_0} \quad (1)$$

3. Conclusions

The addition of hydrogen sulfite to cyclodextrin allyl ethers appears to be a feasible approach for the synthesis of negatively charged cyclodextrins. It circumvents the use of hazardous sultones and allows the generation of well-defined and highly water-soluble cyclodextrin derivatives. They should be well suited to the aqueous solubilisation of hydrophobic compounds such as drugs. The highly charged polysubstituted derivatives might also be applicable to the inhibition of virus replication [16]. The binding properties of the new cyclodextrin sulfonates and the construction of zwitterionic polyrotaxanes will be the subject of further work.

4. Experimental

General methods.—α- and β-Cyclodextrin were obtained from Wacker–Chemie GmbH, Munich, Germany in 99% purity. They were dried before use under vacuum at 90 °C. Racemic ± 1-allyloxy-2,3-epoxypropane (allyl glycidyl ether, AGE) was purchased from Aldrich. Sodium pyrosulfite ($Na_2S_2O_5$) was obtained from Fluka. All the other chemicals were purchased from Aldrich in p.a. grade and used without further purification. *N*,*N*-Dimethylformamide (DMF) was dried by distillation over CaH_2.

NMR spectroscopy was carried out with a Bruker AM400 spectrometer (^{1}H: 400.14 MHz, ^{13}C: 100.62 MHz) at 25 °C. The δ-val-

ues are given in parts per million (ppm) relative to Me_4Si. For ^1H NMR spectra with D_2O as solvent the HOD signal at δ 4.80 ppm, and for Me_2SO-d_6 the signal at δ 2.50 ppm, were used as internal reference. For ^{13}C NMR spectra with D_2O as solvent, the Na 3-(trimethylsilyl)propionate-2,2,3,3-d_4 was used as internal standard at δ 0.0 ppm. In the case of Me_2SO-d_6, the solvent signal at δ 39.5 ppm was used as the reference signal for ^{13}C NMR spectroscopy. Carbon atoms of the substituents were labelled a,b,c,…, commencing with the C atom connected to the glucopyranosyl unit. Those positions influenced by a substituent are denoted 1′,2′,3′,... or a′,b′,c′,… respectively. FAB mass spectra were recorded with a Fisons ZAB2-SE-FPD spectrometer at the MPI für Polymerforschung in Mainz. UV spectra were recorded by a Perkin–Elmer Lambda 19 spectrometer. Optical rotation was determined at 20 °C and λ 589 nm with a IBZ-Meßtechnik Polarmonitor (Hanover, Germany) with an optical length of 10 cm. The samples were dispersed in a glycerol matrix and bombarded with Cs^+ ions (voltage 8 kV). The elemental analyses (Anal.) were carried out in the Institut für Organische Chemie der Universität Mainz. The accuracy was $\pm$ 0.2%.

Thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} plates (5 × 7 cm, E. Merck). Eluent 1: 6:3:1:1: *n*-PrOH–water–toluene–aq NH_3, eluent 2: 1:1:1 *n*-PrOH–water–EtOAc. We developed the spots by spraying the plates with 5% H_2SO_4 in EtOH and heating them briefly with a heat gun. Preparative column chromatography was performed using Silica Gel 60 (E. Merck, 230–400 mesh ASTM) under a pressure of 0.3 bar. For 1 g crude product, 100 g silica was used. Eluents were the same as for TLC. For HPLC we used a reversed-phase column (E. Merck LiCroCART 250-4, 100 RP18) with 90:10:0.5 water–MeCN–AcOH of flux 0.5 mL/min. Peaks were monitored by an optical rotation detector (CHIRALYSER, IBZ, Hanover, Germany). The data were recorded by a PC, and the peak areas were integrated using the programme Origin 2.9. pH values were determined with a Mettler Delta 320 pH meter with a Mettler–Toledo U402-M6-S7/100 glass electrode, calibrated with standard buffer solutions at pH 4.0 and 7.0 (E. Merck).

An autoclave (100 mL) made of high grade steel was used for olefin sulfonation. It was equipped with a pressure gauge (0–10 bar). For 100 mg experiments, a test tube was inserted in the autoclave. The total inner volume was reduced by insertion of a suitable high grade steel tube, and the test tube was covered with a loose-fitting lid made from PTFE to prevent evaporation of SO_2. The autoclave was heated by a temperature-controlled electrical heater. The reaction mixture was stirred magnetically. Ultrafiltration was carried out with an ultrafiltration autoclave (Berghof GH-100, membranes: Berghof BM-5, 500 Dalton or Hoechst UF-CA-1, 1000 Dalton) with continuous water influx under a pressure of 9.5 bar. The autoclave was filled with 140 mL of the crude product solution.

Solubility isotherms were determined for five concentrations (0, 10, 20, 30 and 40 mM) of **4e** in water. Naphthalene (20 mg) was added to all samples. The mixtures were stirred overnight at 20 ± 1 °C, and then the residual naphthalene was filtered off. The filtrates (0.5 mL) were diluted with 10–50 volumes of water. Extinction E was measured at λ 276 nm. From E the concentration of the guest $[G]$ was calculated using an extinction coefficient of ε 6898 M^{-1} cm^{-1}. This value was determined from the extinction E at λ 276 nm of a solution of naphthalene of a known concentration (5.3 mg/500 mL (0.0827 mM)) in the presence of excess (4 mM) host **4e**.

2′-O-Allyl-cyclomaltoheptaose (**1**).—Under N_2 dried β-CD (8.0 g, 7.04 mmol) was dissolved in dry DMF (140 mL) and NaH (60 wt.% suspension in paraffin oil (0.28 g, 7.0 mmol)) was added. The mixture was stirred overnight at rt, then 0.61 mL (0.85 g, 7.0 mmol) allyl bromide was added, and the solution was again stirred at rt. After 3 h, small amounts of more highly substituted cyclodextrin were detectable by TLC (eluent 1). The mixture was poured into acetone (150 mL), and the resulting precipitate filtered off and washed with acetone (150 mL) and water (100 mL). The combined rinsings were poured into acetone (200 mL). The new precipitate was filtered, combined with the first, and washed

with water (100 mL). After drying, the crude product was washed with water (25 mL), and dried again in vacuo. The crude product (0.84 g) was dissolved in a boiling 1:4 mixture of MeOH and water to which silica (6 g) was added, then the solvent was evaporated. The adsorbed crude product was placed on a chromatography column filled with silica (100 g). After elution with eluent 1 (260 mL), the product was eluted within the same eluent (200 mL). Yield 0.334 g (4%), white powder; $[\alpha]_D^{20}$ + 134.1° (*c* 0.41, water); R_f 0.42 eluent 1, RP18-HPLC: V_e 3.9 mL; ^{1}H NMR (D_2O): δ 5.96 (m, 1 H, H-b), 5.38 (dd, $J_{c^{trans},c^{cis}}$ 1.5 Hz, $J_{c^{trans},b}$ 18.4 Hz, 1 H, H-c^{trans}), 5.30 (dd, $J_{c^{cis},b}$ 10.3 Hz, 1 H, H-c^{cis}), 5.17 (d, $J_{1}I_{,2}$ 3.5 Hz, 1 H, H-1^I), 5.05 (d, $J_{1,2}$ 3.5 Hz, 6 H, H-1), 4.25 (d, $J_{a,b}$ 6.4 Hz, 2 H, H-a), 4.04 (dd, $J_3I_{,2} = J_3I_{,4}$ 9.3 Hz, 1 H, H-3^I), 3.95 (dd, $J_{3,2} = J_{3,4}$ 9.3 Hz, 6 H, H-3), 3.87 (m, 14 H, H-6A,B), 3.84 (m, 7 H, H-5), 3.67–3.51(m, 14 H, H-2^I,2,4,4^I) ppm; ^{13}C NMR (Me_2SO-d_6): δ 134.5 (C-b), 117.7 (C-c), 101.7 (C-1), 101.5, 100.1 (C-1^I), 82.0 (C-4^I), 81.3 (C-4), 79.5 (C-4^I), 72.8 (C-3), 72.44 (C-5), 72.38 (C-a), 72.2 (C-3^I), 71.8 (C-2), 71.6 (C-2^I), 59.7 (C-6) ppm; FABMS: *m*/*z* 1175.4 $[MH]^+$, 1197.3 $[M + Na]^+$, M ($C_{45}H_{74}O_{35}$) 1175.07; Anal. Calcd for $C_{45}H_{74}O_{35}\cdot 10H_2O$: C, 39.98; H, 6.99. Found: C, 39.91; H, 6.70.

2^I-O-(3-Allyloxy-2-hydroxypropyl)-cyclomaltoheptaose (**2a**).—Dried β-CD (12.0 g, 10.57 mmol) was dissolved under N_2 in dry DMF (200 mL) and NaH (60 wt.% suspension in paraffin oil (0.42 g, 10.50 mmol)) was added. The mixture was stirred overnight at rt, then AGE (1.25 mL, 1.21 g, 10.57 mmol) was added and the solution heated to 80 °C. After 24 h, small amounts of the disubstituted cyclodextrin could be detected by TLC at R_f 0.47 (eluent 2). Therefore the reaction was stopped. Silica (78 g) was added and the solvent evaporated. The adsorbed crude product was purified by chromatography in three portions on a silica column (280 g each, eluent 2, waste: 900 mL, product within 700 mL). Yield 1.44 g (10%), white powder; $[\alpha]_D^{20}$ + 132.0° (*c* 0.40, water); R_f 0.37 (eluent 2); RP18-HPLC: V_e 4.5 mL; ^{1}H NMR (D_2O): δ 5.93 (m, 1 H, H-e), 5.32 (d, $J_{f^{trans},e}$ 16 Hz, 1 H, H-f^{trans}), 5.26 (d, $J_f cis_{,e}$ 12 Hz, 1 H, H-f^{cis}), 5.20 (m, 1 H, H-1^I), 5.05 (d, $J_{1,2}$ 4 Hz, 6 H, H-1), 4.08–3.97 (m, 3 H, H-3^I, H-d), 3.95 (dd, $J_{3,2} = J_{3,4}$ 9.3 Hz, 6 H, H-3), 3.86 (m, 14 H, H-6A,B), 3.84 (m, 7 H, H-5), 3.66–3.48 (m, 19 H, H-2^I,2,4^I,4, H-a,b,c) ppm; ^{13}C NMR (Me_2SO-d_6): δ 135.1 (C-e), 116.3 (C-f), 101.8 (C-1), 101.5, 99.92 (C-1^I), 81.8 (C-4^I), 81.4 (C-4), 81.1 (C-4^I), 73.7 (C-d), 72.9 (C-3), 72.2 (C-5), 71.9 (C-2), 71.4 (C-a), 71.2 (C-c), 68.7 68.5 (C-b), 59.7 (C-6) ppm; FABMS: *m*/*z* 1250.1 $[MH]^+$, 1272.1 $[M + Na]^+$, M ($C_{48}H_{80}O_{37}$) 1249.14; Anal. Calcd $C_{48}H_{80}O_{37}\cdot 10H_2O$: C, 40.34; H, 7.05. Found: C, 40.30; H, 5.91.

6^I-O-(3-Allyloxy-2-hydroxypropyl)-cyclomaltoheptaose (**2b**).—NaOH (17.18 g, 0.429 mol) was divided in two. One part was dissolved in water (40 mL) using a 250 mL three-necked flask cooled by an ice bath equipped with an overhead stirrer. After getting a clear solution, β-CD (10 g, 7.58 mmol, containing 10% crystal water) was added and the mixture stirred further at 0 °C. After the complete dissolution of β-CD, the remaining NaOH was added, and after it too had gone fully into solution, the mixture was stirred for 1 h at 0 °C. Then AGE (2.55 mL, 2.45 g, 21.49 mmol) was added and the mixture stirred for 3 days at 0 °C. The reaction was stopped by adding phosphoric acid (14 mL, 85 wt.%). The precipitate consisted of crude product and sodium phosphate. The crude product was recrystallized six times in water (30–50 mL). Yield 1.18 g (12%), white powder, containing 5 wt.% residual **1b**). The alternative purification of the crude product by column chromatography over silica with eluent 2 afforded **2b** in 8% yield. White powder; R_f 0.37 (eluent 2); RP18-HPLC: V_e 3.6 mL; $[\alpha]_D^{20}$ + 144.9° (*c* 0.14, water); ^{1}H NMR (D_2O): δ 5.94 (m, 1 H, H-e), 5.33 (d, $J_{f^{trans},e}$ 18.2 Hz, 1 H, H-f^{trans}), 5.27 (d, $J_{f^{cis},e}$ 10.3 Hz, 1 H, H-f^{cis}), 5.04 (m, 7 H, H-1), 4.07 (d, $J_{d,e}$ 5.9 Hz, 2 H, H-d), 3.95 (dd, $J_{3,2} = J_{3,4}$ 8.4 Hz, 7 H, H-3), 3.91–3.79 (m, 21 H, H-6,5), 3.67–3.55 (m, 19 H, H-2,4, H-a,b,c) ppm; ^{13}C NMR (Me_2SO-d_6): δ 135.1 (C-e), 116.3 (C-f), 101.7 (C-1), 101.4, 100.9 (C-1^I), 81.6 (C-4^I), 81.4 (C-4), 81.2, 81.0, 78.0 (C-4^I), 74.3 (C-6^I), 73.8 (C-a), 72.9 (C-3), 72.2 (C-5), 71.9 (C-2), 71.5 (C-c), 71.1 (C-d), 68.6 (C-b), 59.7 (C-6) ppm; FABMS *m*/*z* 1250.0 $[MH]^+$, 1271.9 $[M + Na]^+$, M ($C_{48}H_{80}O_{37}$)

1249.14; Anal. Calcd for $C_{48}H_{80}O_{37}\cdot 10H_2O$: C, 40.34; H, 7.05. Found: C, 39.55; H, 6.35.

O - *(3 - Allyloxy - 2 - hydroxypropyl) - cyclo - maltoheptaose DS 8* (**2c**).—Dried β-CD (10.0 g, 8.81 mmol) was dissolved in NaOH (40 mL, 2.5 wt.%). To this solution AGE (14.6 mL, 14.08 g, 123 mmol) was added and the mixture was stirred for 14 h at rt. The reaction was stopped by neutralisation with 85 wt.% phosphoric acid in an ice bath. The reaction mixture was then extracted three times with CH_2Cl_2 (30 mL). The combined extracts were washed with water (30 mL). After freeze-drying of the combined aq phases, the crude product was dissolved in water (100 mL) and filtered through nylon filter, 0.45 mm and ultrafiltered through a UF-CA-1 membrane. The retentate was freeze-dried. Yield 12.6 g (52%), white powder; $[\alpha]_D^{20}$ +60.5° (*c* 0.41, water); ^{1}H NMR (D_2O): δ 5.92 (m, H-e), 5.34–5.23 (m, H-f), 5.20 (m, H-1′, superimposed by H-f), 5.05 (m, H-1), 4.14–3.97 (m, H-d, H-3′,3), 3.96–3.42 (m, H-6A,B, H-5,2′,2,4, H-a,b,c) ppm; ^{13}C NMR (Me_2SO-d_6): δ 135.1 (C-e), 116.2 (C-f), 101.5, 100.7, 100.4 (C-1), 81.6 (C-4), 79.8, 78.1 (C-4′), 74.3 (C-6′), 73.7 (C-a), 72.9 (C-3), 72.2 (C-5), 71.9 (C-2), 71.5 (C-c), 71.1 (C-d), 70.3 (CH), 68.6, 68.4 (C-b), 59.7 (C-6) ppm; FABMS: *m/z* 1727.6, 1841.6, 1955.7, 2070.3, 2185.1, 2296.8, 2410.7 $[M+Na]^+$ for DS 5,6,7,8,9,10,11; Anal. Calcd $C_{90}H_{150}O_{51}\cdot 8H_2O$: C, 49.31; H 7.63. Found: C, 49.88; H, 7.15.

O - *(3 - Allyloxy - 2 - hydroxypropyl) - cyclo - maltoheptaose DS 9* (**2d**).—Dried β-CD (20.0 g, 17.62 mmol) was dissolved in NaOH (80 mL, 5 wt.%). To this solution AGE (29.2 mL, 28.09 g, 246 mmol) was added and the mixture was stirred for 14 h at rt. The subsequent workup followed the procedure for **2c**. Yield 16.46 g (34%), white powder; ^{1}H NMR (D_2O): δ 5.92 (m, H-e), 5.34–5.23 (m, H-f), 5.20 (m, H-1′, overlapped by H-f), 5.05 (m, H-1), 4.14–3.97 (m, H-d, H-3′,3), 3.96–3.42 (m, H-6A,B, H-5,2′,2,4, H-a,b,c) ppm; ^{13}C NMR (Me_2SO-d_6): δ 135.1 (C-e), 116.1 (C-f), 101.7 (C-1), 100.7, 99.8, 98.7 (C-1′), 81.5 (C-4), 79.8, 78.0, 77.7 (C-4′), 74.3 (C-6′), 73.7 (C-a), 72.9 (C-3), 72.5 (CH_2), 72.1 (C-5), 71.8 (C-2), 71.5 (C-c), 71.1 (C-d), 70.3 (CH), 69.1 (CH_2), 68.6, 68.3 (C-b), 59.7 (C-6) ppm; FABMS: *m/z* 1614.6, 1728.5, 1842.9, 1956.8, 2070.5, 2184.3, 2298.5, 2413.1, 2526.2, 2640.7 $[M+Na]^+$ for DS 4,5,6,7,8,9,10,11,12,13; Anal. Calcd for $C_{96}H_{160}O_{53}\cdot 10H_2O$: C, 49.22; H, 7.75. Found: C, 49.02; H, 7.02.

O - *(3 - Allyloxy - 2 - hydroxypropyl) - cyclo - maltoheptaose DS 5* (**2e**).—Dried β-CD (10.0 g, 8.81 mmol) was dissolved in NaOH (40 mL, 20 wt.%). To this solution AGE (31.4 mL, 30.17 g, 264 mmol) was added and the mixture was stirred for 7 h at rt. The subsequent workup followed the procedure for **2c**. Yield 9.66 g (24%), white powder; $[\alpha]_D^{20}$ +115.8° (*c* 0.41, water); ^{1}H NMR (D_2O): δ 5.93 (m, H-e), 5.33–5.19 (m, H-f), 5.19 (m, H-1′, overlapped by H-f), 5.05 (m, H-1), 4.05–3.98 (m, H-d, H-3′,3), 3.93–3.42 (m, H-6A,B, H-5,2′,2,4, H-a,b,c) ppm; ^{13}C NMR (Me_2SO-d_6): δ 135.1 (C-e), 116.2 (C-f), 101.8 (C-1), 100.9 (C-1′), 81.5 (C-4), 78.0 (C-4′), 74.3 (C-6′), 73.7 (C-a), 72.9 (C-3), 72.5 (CH_2), 72.2 (C-5), 71.8 (C-2), 71.5 (C-c), 71.1 (C-d), 70.4 (CH), 69.1, 68.4 (C-b), 59.7 (C-6) ppm; FABMS: *m/z* 1271.3, 1385.3, 1499.4, 1613.5, 1727.5, 1841.6, 1955.6, 2069.7, 2183.7 $[M+Na]^+$ for DS 1,2,3,4,5,6,7,8,9; Anal. Calcd for $C_{72}H_{120}O_{45}$: C, 50.70; H, 7.09. Found: C, 48.38; H, 7.04.

O - *(3 - Allyloxy - 2 - hydroxypropyl) - cyclo - maltohexaose DS 3* (**2f**).—Dried α-CD (5.0 g, 5.14 mmol) was dissolved in NaOH (20 mL, 2.5 wt.%). To this solution AGE (1.8 mL, 1.76 g, 15.42 mmol) was added and the mixture was stirred for 16 h at rt. The subsequent workup followed the procedure for **2c**. Yield 5.42 g (74%), white powder; $[\alpha]_D^{20}$ +109.2° (*c* 0.41, water); ^{1}H NMR (D_2O): δ 6.10–5.88 (m, 2.1 H, H-e), 5.40–5.24 (m, 4.2 H, H-f), 5.18 (m, 0.6 H, H-1′), 5.03–4.96 (m, 5.4 H, H-1), 4.37–3.43 (m, H-3,3′, H-d, H-6A,B, H-5,2,2′,4, H-a,b,c) ppm; ^{13}C NMR (Me_2SO-d_6): δ 135.1 (C-e), 116.3 (C-f), 101.8 (C-1), 82.2 (C-4′), 81.8 (C-4), 80.9, 79.6 (C-4′), 73.8–73.5 (C-6′,C-d), 73.1, 72.8, 71.9 (C-3,5,2), 72.2, 71.9 (C-a,c), 68.7, 68.3 (C-b), 59.8 (C-6) ppm; FABMS: *m/z* 1222.7, 1336.8, 1450.9, 1564.9 $[M+Na]^+$ for DS 2,3,4,5; Anal. Calcd for $C_{54}H_{90}O_{36}\cdot 6H_2O$: C, 45.57; H, 7.22. Found: C, 46.04; H, 6.99.

O - *(3 - Allyloxy - 2 - hydroxypropyl) - cyclo - maltohexaose DS 5* (**2g**).—Dried α-CD (5.0 g, 5.14 mmol) was dissolved in NaOH (20 mL, 2.5 wt.%). To this solution AGE (4.25 mL, 4.1

g, 35.9 mmol) was added and the mixture was stirred for 16 h at rt. The subsequent workup followed the procedure for **2c**. Yield 3.25 g (36%), white powder; $[\alpha]_D^{20}$ +90.0° (*c* 0.40, water); ^{1}H NMR (D_2O): δ 6.08–5.88 (m, 3.4 H, H-e), 5.40–5.23 (m, 7.5 H, H-f), 5.18 (m, 1.4 H, H-1′), 5.04–4.98 (m, 4.6 H, H-1,1′), 4.30–3.40 (m, H-3,3′, H-d, H-6A,B, H-5,2,2′,4, H-a,b,c) ppm; ^{13}C NMR (Me_2SO-d_6): δ 135.1 (C-e), 116.2 (C-f), 101.8 (C-1), 99.5 (C-1′), 81.8 (C-4), 80.9, 79.5 (C-4′), 73.9–73.3 (C-6′,C-d), 73.0, 72.6, 71.8 (C-3,5,2), 71.4, 71.1 (C-a,c), 68.7, 68.5 (C-b), 59.8 (C-6) ppm; MS: *m*/*z* 1337.6, 1451.6, 1565.7, 1679.8, 1793.8, 1908.2 $[M + Na]^+$ for DS 3,4,5,6,7,8; Anal. Calcd for $C_{66}H_{110}O_{40}\cdot 6H_2O$: C, 48.00; H, 7.45. Found: C, 48.05; H, 7.08.

O-(3-Allyloxy-2-hydroxypropyl)-cyclomaltohexaose DS 3 (**2h**).—Dried α-CD (5.0 g, 5.14 mmol) was dissolved in NaOH (20 mL, 20 wt.%). In an ice bath AGE (8.54 mL, 8.21 g, 71.9 mmol) was added, and the mixture was stirred for 3 h at 0 °C and for 12 h at rt. The subsequent workup followed the procedure for **2c**. The solution was made up to 140 mL and purified by continuous ultrafiltration against a BM-5 membrane (Berghof) with water (1900 mL). The retentate was freeze-dried. Yield 4.49 g (34%), white powder; $[\alpha]_D^{20}$ +104.0° (*c* 0.40, water); ^{1}H NMR (D_2O): δ 6.12–5.88 (m, 3 H, H-e), 5.40–5.24 (m, 6 H, H-f), 5.19 (m, 0.3 H, H-1′), 5.04–4.98 (m, 5.7 H, H-1), 4.31–3.45 (m, H-d, H-3, H-6A,B, H-5,2,4, H-a,b,c) ppm; ^{13}C NMR (Me_2SO-d_6): δ 135.1 (C-e), 116.2 (C-f), 101.8 (C-1), 82.3 (C-4′), 81.8 (C-4), 81.0, 79.6 (C-4′), 73.9, 73.7 (C-6′,CH_2), 73.1, 72.4, 71.9 (C-3,5,2), 71.2 (C-a), 71.0 (C-c), 70.5 (CH), 69.2 (CH_2), 68.7, 68.4, 68.3 (C-b), 59.8 (C-6) ppm; FABMS: *m*/*z* 1199.7, 1313.5, 1427.5, 1541.6 $[M]^+$ for DS 2,3,4 or 5): M ($C_{54}H_{90}O_{36}$) 1315.29; Anal. Calcd for $C_{54}H_{90}O_{36}\cdot 10H_2O$: C, 43.37; H, 7.41. Found: C, 43.66, 7.54.

2′-O-(3-Sulfonatopropyl)-cyclomaltoheptaose (**3**).—In a test tube (20 × 150 mm) equipped with magnetic stirrer **1** (200 mg, 0.170 mmol) was dispersed in an aq solution (5.6 mL) containing $Na_2S_2O_5$ (57 mg, 0.30 mmol) and KNO_3 (3 mg, 0.030 mmol). Before **1** was added the pH was adjusted to 7.1 with NaOH. The suspension in the test tube was stirred for 5 min and placed in an autoclave, which was filled with water (5 mL). The autoclave was stirred and heated to 120 °C for 3 h. Then it was cooled to rt. Some turbidity resulted when it was cooled to 0 °C. This was removed by passing the solution through a nylon filter 0.45 mm (Millipore syringe filter). The filtrate was freeze-dried. If some turbidity reappeared after dissolution of the sample in water (1 mL), the filtration was repeated. The solution was diluted to 80 mL and ultrafiltered against a UF-CA-1 membrane with water (800 mL). The retentate was freeze-dried. Yield 90 mg (42%), white powder; $[\alpha]_D^{20}$ +128.0° (*c* 0.21, water); ^{1}H NMR (D_2O): δ 5.21 (d, $J_{1',2}$ 3.4 Hz, 1 H, H-1′), 5.07 (d, $J_{1,2}$ 3.4 Hz, 6 H, H-1), 4.04 (dd, $J_{3',2} = J_{3',4}$ 9.4 Hz, 1 H, H-3′), 3.96 (dd, $J_{3,2} = J_{3,4}$ 9.4 Hz, 6 H, H-3), 3.92–3.78 (m, 14 H, H-6A,B), 3.70–3.46 (m, 16 H, H-2,2′,4, H-a), 3.01 (m, 2 H, H-c), 2.03 (dd, $J_{b,a} = J_{b,c}$ 7.4 Hz, 2 H, H-b) ppm; ^{13}C NMR (D_2O): δ 103.3 (C-1), 101.5 (C-1′), 83.0 (C-4′), 82.5 (C-4), 81.7 (C-4′), 74.4 (C-3), 73.4 (C-5), 73.1 (C-2), 71.9 (C-a), 61.5 (C-6), 49.0 (C-c), 26.0 (C-b) ppm; FABMS: *m*/*z* 1279.1 $[M]^+$, 1301.1 $[M + Na]^+$, M ($C_{45}H_{75}O_{38}NaS$) 1279.12.

2′-O-(3-Sulfonatopropyl-oxy-2-hydroxypropyl)-cyclomaltoheptaose (**4a**).—In a test tube (20 × 150 mm) equipped with a magnetic stirrer **2a** (200 mg, 0.160 mmol) was dispersed in an aq solution (6 mL) containing $Na_2S_2O_5$ (60 mg, 0.32 mmol) and KNO_3 (3.2 mg, 0.032 mmol). Before the addition of **2a**, the pH was adjusted to 7.1 with NaOH. The subsequent workup was the same as for **3**. After freeze-drying of the filtrate, the crude product was dissolved in water (1 mL), filtered through a Millipore syringe filter, 0.45 mm. The solution was made up to 50 mL and the crude product purified by continuous ultrafiltration through a BM-5 membrane with water (1000 mL). The retentate was freeze-dried. Yield 127 mg (59%), white powder; $[\alpha]_D^{20}$ +101.0° (*c* 0.30, water); ^{1}H NMR (D_2O): δ 5.21 (m, 1 H, H-1′), 5.06 (m, 6 H, H-1), 4.09–4.03 (m, 1 H, H-3′), 3.95 (dd, $J_{3,2} = J_{3,4}$ 9.4 Hz, 6 H, H-3), 3.89–3.83 (m, 21 H, H-6A,B,5), 3.76–3.48 (m, 21 H, H-2′,2,4, H-a,b,c,d), 2.96 (m, 2 H, H-f), 2.01 (tt, $J_{e,d} = J_{e,f}$ 6.4 Hz, 2 H, H-e) ppm; ^{13}C NMR (D_2O): δ 103.5 (C-1), 101.6 (C-1′), 83.2,

83.1 (C-4′), 82.5 (C-4), 74.6 (C-3), 73.7–73.2 (C-5,2), 73.4 (C-a), 71.0 (C-c,d), 70.5 (C-b), 61.6 (C-6), 49.4 (C-f), 25.7 (C-e) ppm; FABMS: *m/z* 1353.8 $[M]^+$, 1375.7 $[M + Na]^+$, M ($C_{48}H_{81}O_{40}NaS$) 1353.2.

6-O-(3-Sulfonatopropyloxy-2-hydroxypropyl)-cyclomaltoheptaose (**4b**).—In a test tube (20 × 150 mm) equipped with magnetic stirrer **2b** (1.0 g, 0.80 mmol) was dispersed in an aq solution (30 mL) containing $Na_2S_2O_5$ (0.304 g, 1.60 mmol) and KNO_3 (16 mg, 0.16 mmol). Before the addition of **2b**, the pH was adjusted to 7.1 by the addition of NaOH. The subsequent workup was the same as for **3**. Yield 0.295 g (27%), white powder; $[\alpha]_D^{20}$ + 128.7° (*c* 0.29, water); ^{1}H NMR (D_2O): δ 5.08 (m, 6 H, H-1), 3.93 (dd, $J_{3,2} = J_{3,4}$ 9.8 Hz, 7 H, H-3), 3.85 (m, 21 H, H-6,6′,5,5′), 3.77–3.55 (m, 21 H, H-2,4, H-a,b,c,d), 2.95 (m, 2 H, H-f), 2.03 (dd, $J_{e,d}$ $J_{e,f}$ 6.4 Hz, 2 H, H-e) ppm; ^{13}C NMR (D_2O): δ 103.1 (C-1), 102.2 (C-1′), 82.4 (C-4), 80.2 (C-4′), 75.0 (C-6′), 73.9 (C-3), 73.7, 73.6 (C-3′,C-5′), 73.3 (C-5), 73.2 (C-2), 73.1 (C-a,c), 70.6 (C-d), 70.2 (C-b), 61.3 (C-6), 49.1 (C-f), 25.5 (C-e) ppm; MS: *m/z* 1353.2 $[M]^+$, 1375.6 $[M + Na]^+$, M ($C_{48}H_{81}O_{40}NaS$) 1353.2; Anal. Calcd for $C_{48}H_{81}O_{40}NaS{\cdot}8H_2O$: C, 38.50; H, 6.53; S, 2.14. Found: C, 38.35; H, 6.25; S, 3.13.

General procedure for the synthesis of statistically substituted cyclodextrin sulfonates.—In a test tube equipped with a magnetic stirrer $Na_2S_2O_5$ (1 equiv), KNO_3 (0.005 equiv), and the cyclodextrin derivative **2** (1 equiv C=C) were mixed in water (4 mL) per gram of cyclodextrin derivative. The test tube was immersed in the autoclave, which was filled with water (5 mL). The autoclave was stirred and heated to 120 °C for 1.5 h and to 140 °C for an additional 1.5 h. After cooling to rt, the reaction mixture was filtered through a 0.45 μm nylon filter, diluted to 100 mL and ultrafiltered with 1600–1900 mL of water. For the derivatives **4c** and **4d**, a Hoechst UF-CA-1 membrane was used, and for **4e**–**4h** a Berghof BM-5 membrane. The retentate was freeze-dried.

O-(3-Sulfonatopropyloxy-2-hydroxypropyl)-cyclomaltoheptaose DS 8 (**4c**).—White powder, yield 4.68 g (64%) from **2c** (6.0 g, 2.93 mmol); $[\alpha]_D^{20}$ + 70.8° (*c* 0.42, water); ^{1}H NMR (D_2O): δ 5.28 (m, 4.0 H, H-1′), 5.12 (m, 3.0 H, H-1), 4.20–3.39 (m, H-2-H-6, H-a,b,c,d,e′), 3.33 (d, $J_{d',e'}$ 14.3 Hz, H-d′), 3.03 (m, 10.72 H, H-f), 2.73 (m, 3.45 H, H-f′), 2.07 (m, 7.18 H, H-e) ppm; ^{13}C NMR (D_2O): δ 103.9–101.0 (C-1,1′), 82.6 (C-4), 80.0 (C-4′), 74.8 (C-6′), 74.7-70.6 (C-3,5,2), 74.1, 73.2, 71.3, 70.2 (CH_2), 71.0, 70.7 (C-b), 64.5 (C-e′), 62.1 (C-6), 58.6, 57.7 (CH), 49.7 (C-f′), 45.9 (C-f), 25.1 (C-e) ppm; Anal. Calcd for $(C_6H_{10}O_5)_7$-$(C_6H_{11}SNaO_5)_6(C_6H_{10}S_2Na_2O_7)_2{\cdot}13H_2O$: C, 32.80; H, 5.58; S, 9.75. Found: C, 32.83; H, 5.26; S, 9.89.

O-(3-Sulfonatopropyloxy-2-hydroxypropyl)-cyclomaltoheptaose DS 9 (**4d**).—White powder, yield 1.07 g (58%) from **2d** (1.2 g, 0.555 mmol); $[\alpha]_D^{20}$ + 68.6° (*c* 0.40, water); ^{1}H NMR (D_2O): δ 5.23 (m, 3.2 H, H-1′), 5.08 (m, 3.8 H, H-1), 4.14–3.98 (m, 7 H, H-3′,H-3), 4.14–3.98 (m, 7 H, H-3′,3), 3.97–3.75 (m, 21 H, H-6A,B, 5), 3.74–3.45 (m, H-2,2′,4, H-a,b,c,d,e′), 3.27 (d, $J_{d',e'}$ 14.3 Hz, H-d′), 2.98 (m, 9.54 H, H-f), 2.67 (m, 2.48 H, H-f′), 2.02 (m, 7.07 H, H-e) ppm; ^{13}C NMR (D_2O): δ 103.3 (C-1), 102.7, 101.0 (C-1′), 82.5 (C-4), 80.0 (C-4′), 75.1 (C-6′), 74.1–70.2 (C-3,5,2), 73.7, 72.8 (CH_2), 70.9 (C-d), 70.6, 70.2 (C-b), 69.8 (CH_2), 64.2 (C-e′), 61.8 (C-6), 49.4 (C-f′), 45.6 (C-f), 25.6 (C-e) ppm. Anal. Calcd for $(C_6H_{10}O_5)_7(C_6H_{11}$-$SNaO_5)_7(C_6H_{10}S_2Na_2O_7)_2{\cdot}11H_2O$: C, 33.24; H, 5.49; S, 10.17. Found: C, 33.17; H, 5.58; S, 10.27.

O-(3-Sulfonatopropyloxy-2-hydroxypropyl)-cyclomaltoheptaose DS 5 (**4e**).—White powder, yield 6.40 g (79%) from **2e** (6.0 g, 3.51 mmol); $[\alpha]_D^{20}$ + 88.2° (*c* 0.40, water); ^{1}H NMR (D_2O): δ 5.24 (m, 0.4 H, H-1′), 5.08 (m, 6.6 H, H-1), 4.07–3.78 (m, H-3′,3,6A,6B,5), 3.76–3.38 (m, H-2′,2,4, H-a,b,c,d,e′), 3.28 (d, $J_{d',e'}$ 14.3 Hz, H-d′), 2.97 (m, 6.58 H, H-f), 2.68 (m, 1.32 H, H-f′), 2.04 (m, 5.28 H, H-e) ppm; ^{13}C NMR (D_2O): δ 103.3 (C-1), 102.5 (C-1′), 82.3 (C-4), 80.3 (C-4′), 75.3 (C-6′), 74.4–73.2 (C-3,5,2), 73.5 (CH_2), 72.6 (C-a,c), 72.0 (CH), 70.7 (C-d), 70.3, 70.0 (C-b), 69.6 (CH_2), 64.1 (C-e′), 61.4 (C-6), 49.2 (C-f′), 45.4 (C-f), 25.6 (C-e) ppm; Anal. Calcd for $(C_6H_{10}O_5)_7(C_6H_{11}$-$SNaO_5)_{4.3}(C_6H_{10}S_2Na_2O_7)_{0.7}{\cdot}8H_2O$: C, 35.58; H, 5.82; S, 7.52. Found: C, 35.33; H, 6.09; S, 7.70.

O-*(3-Sulfonatopropyloxy-2-hydroxypropyl)-cyclomaltohexaose DS 3* (**4f**).—White powder, yield 8.31 g (27%) from **2f** (22 g, 18.31 mmol); $[\alpha]_D^{20}$ +85.3° (*c* 0.41, water); ^{1}H NMR (D_2O): δ 5.20 (m, 0.6 H, H-1′), 5.04 (m, 5.4 H, H-1), 4.13–3.33 (m, H-3, H-6A,6B, H-5,2,4, H-a,b,c,d,e′), 3.26 (d, $J_{d',e'}$ 14.4 Hz, H-d′), 2.96 (m, 4 H, H-f), 2.66 (m, 0.65 H, H-f′), 2.00 (m, 3.4 H, H-e) ppm; ^{13}C NMR (D_2O): δ 103.7 (C-1), 103.1 (C-1′), 83.3 (C-4), 82.4, 81.5 (C-4′), 75.2–73.4 (C-3,5,2), 74.8 (C-6′), 71.7 (C-a,c), 71.3, 70.9 (C-b), 70.5 (C-d), 65.0 (C-e′), 62.5 (C-6), 50.1 (C-f′), 50.1 (C-f), 26.4 (C-e) ppm; Anal. Calcd for $(C_6H_{10}O_5)_6(C_6H_{11}SNaO_5)_{2.6}(C_6H_{10}S_2Na_2O_7)_{0.4}\cdot 10H_2O$ C, 35.21; H, 6.16; S, 5.92. Found: C, 35.12; H, 5.94; S, 6.64.

O-*(3-Sulfonatopropyloxy-2-hydroxypropyl)-cyclomaltohexaose DS 5* (**4g**).—White powder (1.29 g, 93%) from **2g** (1.0 g, 0.603 mmol) was obtained; $[\alpha]_D^{20}$ +72.0° (*c* 0.40, water); ^{1}H NMR (D_2O): δ 5.21 (m, 1.4 H, H-1′), 5.05 (m, 4.6 H, H-1), 4.14–3.30 (m, H-3,6A,6B, H-5,2,4, H-a,b,c,d,e′), 3.26 (d, $J_{d',e'}$ 14.2 Hz, H-d′), 2.97 (m, 6.74 H, H-f), 2.66 (m, 2.94 H, H-f′), 2.01 (m, 3.80 H, H-e) ppm; ^{13}C NMR (D_2O): δ 103.5 (C-1), 103.1, 102.7 (C-1′), 83.2 (C-4), 82.4, 81.2 (C-4′), 74.9–70.8 (C-3,5,2), 74.3 (C-6′), 71.5 (C-a,c), 71.3, 70.8 (C-b), 70.4 (C-d), 64.8 (C-e′), 62.7, 62.3 (C-6,6′), 49.9 (C-f′), 46.2 (C-f), 26.3 (C-e) ppm; Anal. Calcd for $(C_6H_{10}O_5)_6(C_6H_{11}SNaO_5)_{3.5}(C_6H_{10}S_2Na_2O_7)_{1.5}\cdot 14H_2O$: C, 32.42; H, 5.83; S, 8.52. Found: C; 32.29; H, 5.43; S, 10.39.

O-*(3-Sulfonatopropyloxy-2-hydroxypropyl)-cyclomaltohexaose DS 3* (**4h**).—White powder (1.57 g, 82%) from **2h** (1.5 g, 1.14 mmol); $[\alpha]_D^{20}$ +91.3° (*c* 0.40, water); ^{1}H NMR (D_2O): δ 5.39–5.21 (m, 0.3 H, H-1′), 5.04 (m, 5.7 H, H-1), 4.13–3.33 (m, H-3,H-6A,B,H-5,2,4, H-a,b,c,d,e′), 3.26 (d, $J_{d',e'}$ 14.4 Hz, H-d′), 2.96 (m, 3.36 H, H-f), 2.67 (m, 0.62 H, H-f′), 2.02 (m, 2.71 H, H-e) ppm; ^{13}C NMR (D_2O): δ 103.2 (C-1), 102.7 (C-1′), 82.7 (C-4), 81.1 (C-4′), 75.0, 74.2, 73.5 (C-3,5,2), 73.9 (C-6′), 71.2 (CH_2), 70.9, 70.5 (C-b), 70.0 (C-d), 64.6 (C-e′), 62.0 (C-6), 49.7 (C-f′), 45.9 (C-f), 26.0 (C-e) ppm; Anal. Calcd for $(C_6H_{10}O_5)_6(C_6H_{11}SNaO_5)_{2.5}(C_6H_{10}S_2Na_2O_7)_{0.5}\cdot 10H_2O$: C, 35.05; H, 6.13; S, 6.06. Found: C, 35.12; H, 5.94; S, 6.64.

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