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Efficient synthesis of pure monotosylated beta-cyclodextrin and its dimers

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Abstract

6-*O*-Monotosyl-β-cyclodextrin (mono-Ts-βCD) is one of the most important intermediate in the production of substituted βCD. So far, performing the monotosylation reaction and, in particular, the purification steps is challenging, relies on toxic solvents, and results in long and expensive procedures at, importantly, low yields. Here, the reaction of cyclodextrin with *p*-toluenesulfonyl chloride in aqueous environment is described to obtain a highly pure mono-Ts-βCD, for which a single-step purification with a cation exchange resin was applied. With this synthetic route and purification, yields could be increased from typically < 10-15% to 35%, and organic solvents could be avoided. As characterized by FTIR, mass spectrometry, elemental analysis, and NMR, mono-Ts-βCD was obtained with a molar purity of >98 mol %. From mono-Ts-βCD, β-cyclodextrin dimers linked by ethylenediamine (bis-Et-βCD) were successfully prepared (yield 93%, purity 96 mol %) in a one-step approach using an anion exchange resin to trap leaving groups that typically interfere in the reaction. This synthesis procedure with a direct collection of side-products may be a general strategy applicable for nucleophilic substitution of tosylated cyclodextrins.

Keywords: β-Cyclodextrin, Monotosyl β-Cyclodextrin, β-Cyclodextrin dimer, Ion exchange resin

Establishing synthetic approaches for mono-tosylation of β-cyclodextrin (βCD) was a milestone in cyclodextrin derivatization, since it allowed subsequent derivatization or coupling of βCD at its primary hydroxyl group.[1-7] While different methods to selectively functionalize one single primary hydroxyl group of cyclodextrins were reported, several by-products may be formed requiring extensive subsequent purification procedures. The most common synthetic strategies exploit either organic or aqueous solvent/base systems. In some cases, pyridine served as both solvent and organic base,[8-10] but generally should be avoided because of difficulties to remove residual toxic pyridine and of the massively formed by-products. One approach for selective monotosylation at position 2 of βCD employs a dimethylformamide/carbonate buffer medium, but also requires extensive purification based on large quantities of organic solvents.[10, 11]

One of the first strategies to avoid organic solvents in monotosylation reaction of αCD and βCD has been reported by Iwakura et al., who used an aqueous solution of pH 11[12] and enabled a preferential monotosylation at the primary hydroxyl groups as desired.[11] Subsequently, reactions in water/NaOH have been widely employed to obtain mono-Ts-βCD, e.g., using copper complexes to direct the reaction toward a more regioselective monofunctionalization of the primary hydroxyl groups while the secondary hydroxyl groups of cyclodextrin are complexed with copper.[13] Alternatively, a selective monotosylation of *O*-2 secondary hydroxyl groups is possible by 1-(p-tolylsulfonyl)-(1H)-1,2,4-triazole.[14] Still, the required subsequent purification step remains critical due to the presence of a large amount of impurities including (i) inorganic salts, (ii) p-toluenesulfonic acid or its chloride salt either free or complexed by βCD, and (iii) multi-tosylated βCD.[15-17]

Additionally, it should be noted that molar ratios of tosyl-chloride to βCD up to 23.8 were employed,[18] which represents an inefficient reaction and could lead to extensive purification procedures. By performing the synthesis with a molar excess of tosyl-chloride in the range 1.8-6.0,[6, 15, 17] yields of 10-

48% were reported. Still, the purification by crystallization is critical and often results only in lower yields of < 10-15% of the isolated pure product.

However, the availability of pure mono-Ts-βCD at suitable quantities is required as a key substance for subsequent nucleophilic substitution, for example with ethylenediamine to obtain monoamine-βCD or bis-Et-βCD, which are of interest for instance as enzyme-like models or to create host-guest inclusion complexes.[19, 20] Bis-Et-βCD is typically prepared in a two-step synthesis, in which first monoamine-βCD is formed, purified, and isolated, and subsequently reacted with mono-Ts-βCD to give the bis-Et-βCD.[19-21] An alternative one-step synthesis relies on DMF as an undesired solvent.[22] All these methods showed low, variable yields of this reaction.

Here, methods should be provided to obtain pure mono-Ts-βCD by facile and reproducible chemistry that does not employ organic solvents. Furthermore, a one-step synthesis procedure for bis-Et-βCD with direct collection of side products should be developed, which results in higher yields and avoids DMF as a solvent. For both synthetic steps, ion exchange resins as easily removable substances were proposed to overcome the existing limitations by (i) enabling an efficient isolation of mono-Ts-βCD with high yields and purity, and (ii) supporting the one-step preparation of bis-Et-βCD by capturing leaving groups that compete with the progress of the reaction.

The monotosylation reaction of βCD was performed in aqueous NaOH at pH 11 for 1 h as generally established in the literature. However, the reported subsequent purification by crystallization or precipitation in organic solvents did not result in pure product at reasonable yields (often ≈ 10%).[17] Therefore, it was proposed that suspending a cation exchange resin in the H^+ form in the crude product may efficiently induce the precipitation of the product. This purification should occur due to the fast lowering of the pH from pH 11 to acidic conditions by exchange of H^+ from the resin with sodium cations from NaOH solution causing a reduction of mono-Ts-βCD solubility. The precipitation of mono-Ts-βCD was observed as hypothesized. Since the aqueous solubility of mono-Ts-βCD is much

lower (< 0.04 g/100 mL)[11] than that of βCD (≈1.85 g/100 mL), the non-reacted βCD as well as the water-soluble *p*-toluenesulfonic acid were efficiently removed by thrice washing the precipitate with water.

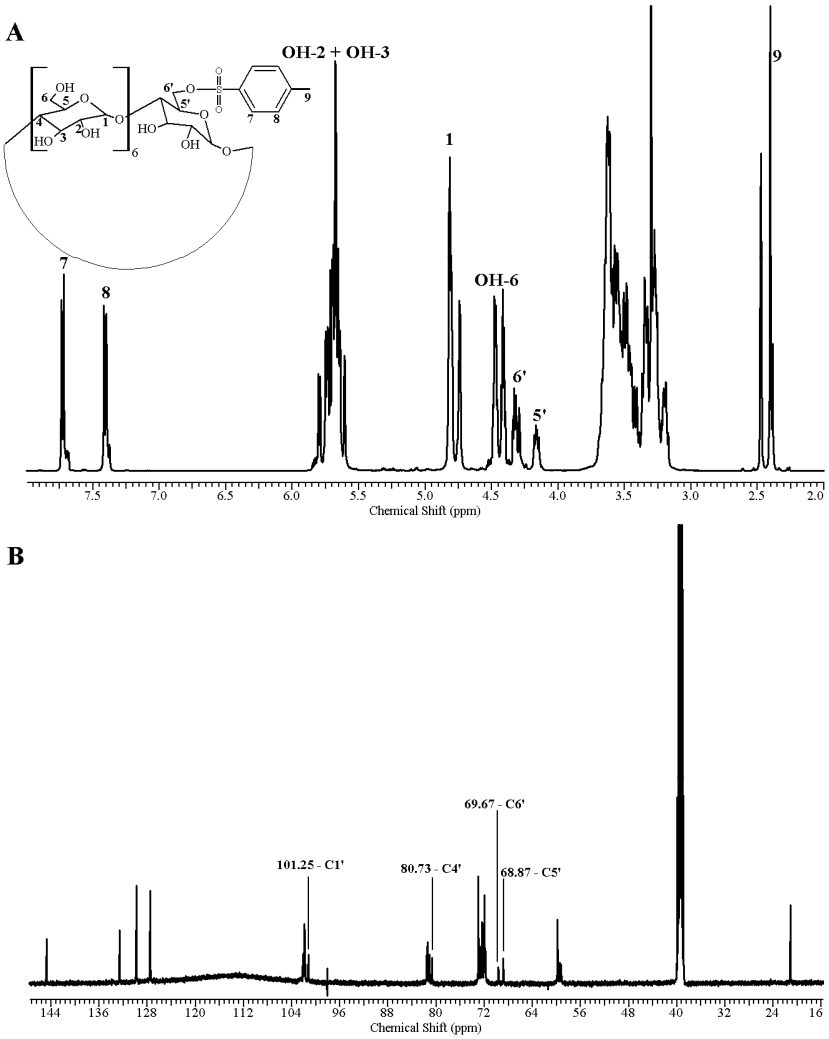

Figure 1: NMR spectra of mono-Ts-βCD as obtained from the purification procedure with the cation exchange resin. (A) ^{1}H-NMR. (B) ^{13}C-NMR.

Importantly, several grams of sodium cations, which may reduce an effective crystallization of the product, could also be eliminated by using the cation exchange resin, which subsequently was easily removed by filtration.

The functionalization of βCD with *p*-toluenesulfonyl groups was confirmed by FTIR based on the peaks at 1230 cm^{-1} (Ph-SO_2-R) and 815 cm^{-1} (Ph-SO_2-O-R), which both were not present in βCD or *p*-toluenesulfonyl chloride and could be attributed to alkyl substituted tosyl groups. Additionally, the ^{1}H-NMR spectrum (Fig. 1A) showed the characteristic peaks of aromatic protons at 7.77 and 7.43 ppm. A molar amount of >98% of tosyl groups in the mono-Ts-βCD was detected by comparing the integral of the anomeric protons (H1) at 4.85-4.77 ppm with that of Ph-CH_3 at 2.44 ppm, which stresses the high purity of the obtained product. Furthermore, based on the integral ratios of the anomeric proton and the multiplet at 4.51-4.45 ppm (OH-6), which were calculated to be 7:6, it was confirmed that only one of the seven primary hydroxyl groups of βCD was tosylated. Unshielding effects of the tosyl substituent resulted in a downfield peak shift at 4.35 for the two protons of the derivatized C6' and at 4.20 ppm for the adjacent C5' proton, respectively, which proved binding of the tosyl group to the C6' carbon.

In the ^{13}C-NMR spectrum (Fig. 1B), peak shifts could be detected due to the functionalization of one (C6') out of a total of seven C6 carbons of βCD, namely, (i) a downfield shift of C6' to 69.67 ppm, (ii) an upfield shift of adjacent C5' to 68.87 ppm, and (iii) upfield shifts of C4' (80.73 ppm) and C1' (101.25 ppm). These values are in accordance with the theory of Breslow, according to which the tosylation of a hydroxyl group leads to a downfield shift of the carbon carrying the hydroxyl (the α carbon), a small upfield shift of the β carbon as well as an even smaller upfield shift of the γ carbon.[11] All ^{13}C-NMR peaks of non-functionalized carbon atoms showed the same chemical shift as the starting βCD supporting that a mono-functionalized product was obtained.

Mass spectrometry (MS) revealed a molecular weight of the molecular ion $[M+H]^+$ of 1289.377 $g \cdot mol^{-1}$, which perfectly agreed with the calculated value for mono-functionalized βCD. Importantly, compared to previous approaches to obtain mono-Ts-βCD, the entire process, that was scaled up to 60 g batches being purified by treatment with 546 mL of pre-swollen cation exchange

resin (see Section 1), required not more than 5 h. Furthermore, this procedure allowed to use lower amounts of *p*-toluenesulfonyl chloride (molar ratio *p*-toluenesulfonyl chloride/cyclodextrin = 1.5) compared to some of the previously reported approaches in NaOH/water environment.[10, 13, 16] The average yield for several prepared mono-Ts-βCD batches was reproducible at 35 ± 3% with a remarkable purity.

In the next step of this work, an efficient synthesis of bis-Et-βCD is introduced, which enabled high yields and avoided DMF as a solvent. While being frequently suggested as an effective complexing agent,[19-21] the synthesis of bis-Et-βCD from mono-Ts-βCD by reaction with ethylenediamine as reported in the literature was associated with the following challenges: (i) the presence of free *p*-toluenesulfonic acid produced from the nucleophilic attack of ethylenediamine on mono-Ts-βCD apparently reduced the reactivity of the ethylenediamine by forming ion pairs, (ii) cross-reactions between mono-Ts-βCD and the reaction medium occur when DMF is used as solvent, (iii) toxicological concerns impede the use of DMF in biomedical applications, (iv) monoamine-βCD is often formed as impurity due to the employed high molar excess of ethylenediamine, and (v) a low yield due to the two step reaction with intermediate purification.

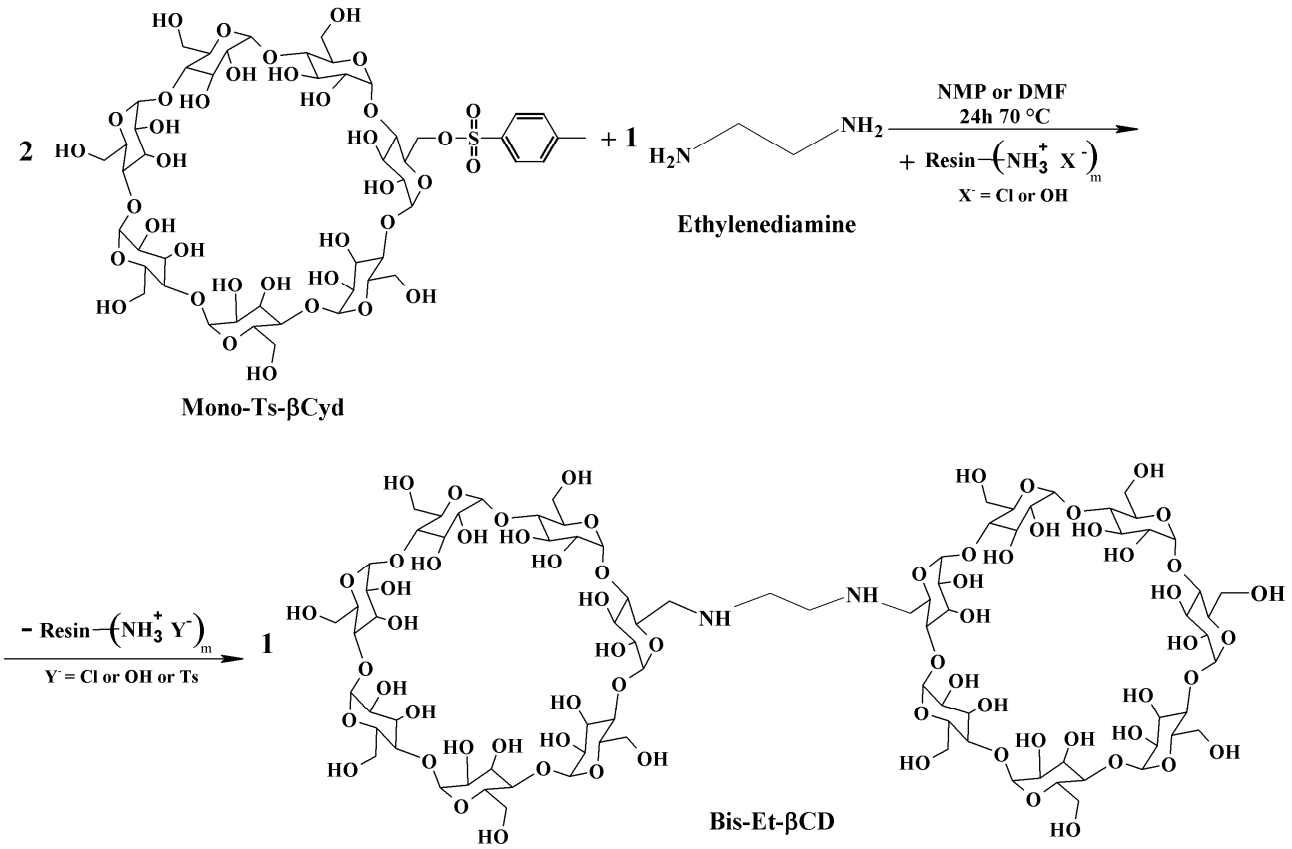

Figure 2: Formation of bis-Et-βCD in the presence of the anion exchange resin.

It was proposed that at least some of these issues could be overcome, if the release of *p*-toluenesulfonic acid from the reactant as a leaving group during the nucleophilic attack of ethylenediamine (pKb_1=4.11 ± 0.10) to the mono-Ts-βCD may be compensated. Since *p*-toluenesulfonic acid will be in its anionic form in the presence of a base such as ethylenediamine, an anion exchange resin (Dowex® 1 x 8 200-400 mesh [2 meq, exchange capacity 1.0 meq/mL] either with Cl^- or OH^- counter-ions) was directly added to the reaction mixture. In this way, *p*-toluenesulfonic acid as a leaving group that can cause side reactions could be collected *in situ*, while the easy filtration of the resin facilitated its removal from the reaction mixture (Fig. 2).

In contrast to the cyclodextrin monotosylation performed in water, the formation of bis-Et-βCD requires the use of an organic polar-aprotic solvent to reduce the possible hydrolysis of mono-Ts-βCD during the reaction at relatively high temperatures. In control experiments studying solvent effects, mono-Ts-βCD in DMF was subjected to the reaction conditions without any resin or ethylenediamine. This resulted in a 40 mol % reduction of the peaks of the tosyl group and the appearance of a multiplet at 7.99 ppm corresponding to the formamide proton of DMF as observed in ^{1}H-NMR (data not shown). It can be expected that DMF may have attacked mono-Ts-βCD as a nucleophile, thereby reducing the available amount of mono-Ts-βCD for subsequent reactions and forming undesired side products.[23, 24] When the same experiment was performed with 1-methyl-2-pyrrolidone (NMP) as solvent, no alterations of the starting mono-Ts-βCD were detected. Despite the failure in the mentioned control experiments, DMF was included as solvent candidate in order to evaluate, whether the presence of the resin can improve the reaction in this solvent. In particular, the anion exchange resin was used with two different counter-ions, namely, hydroxyl (OH^- form) or chloride (Cl^- form). The OH^- form resin led to products with a similar derivatization degree of ≈ 90 mol % for both solvents, which were lower than for the Cl^- form (96 mol %) of the resin. This may be explained by the hydrolysis of the tosyl group of mono-Ts-βCD in the presence of OH^- anions at reaction conditions of 80 °C for 24 h. Another explanation for the higher degree of derivatization with the Cl^- form resin might be a higher binding affinity of *p*-toluenesulfonic acid due to the acid-base reaction occurring between the anion exchange resin and *p*-toluenesulfonic acid. This may lead to the release of the stronger acid HCl that ultimately shifts the chemical equilibrium toward the desired products (Fig. 2). Considering (i) the higher degree of functionalization obtained by using the resin in the Cl^- form, (ii) the reasonable yield of 93%, and (iii) that NMP, differently from DMF, did not take part in the reactions, these reaction conditions have been considered the first choice and were further applied. Furthermore, differently from DMF that is generally considered toxic even at low concentrations, NMP can be used also for injection in humans.[25]

^{1}H-NMR (DMSO-d_6) showed an almost complete disappearance of the peaks of the tosyl groups (7.77, 7.43, and 2.44 ppm), the presence of a new multiplet at 2.51-3.02 ppm corresponding to -CH_2CH_2- of ethylenediamine, and an upfield shift of derivatized C6' protons (Fig. 3A). A small amount of *p*-toluenesulfonic acid (<2 mol %) as impurity and mono-Ts-βCD (<2 mol %) were found in the product without additional purification, as could also be visualized by TLC.

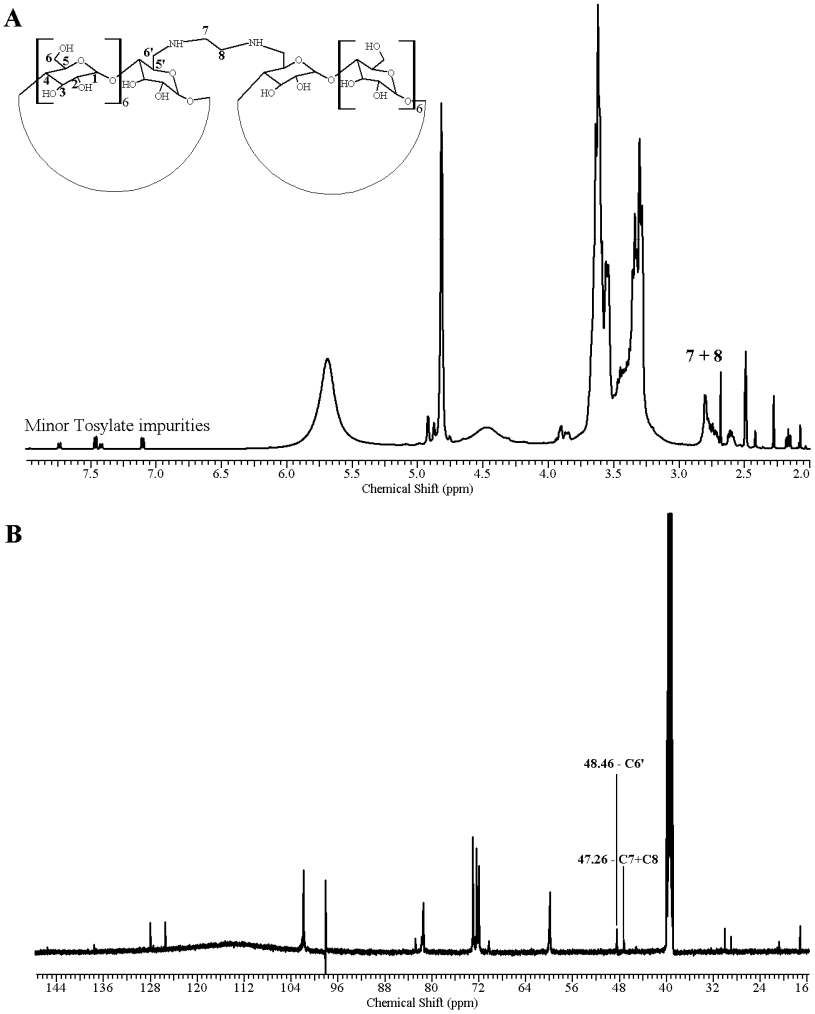

Figure 3: NMR spectra of bis-Et-βCD as obtained from the reaction procedure in presence of the anion exchange resin. (A) ^{1}H-NMR. (B) ^{13}C-NMR.

^{13}C-NMR (DMSO-d_6) spectra (Fig. 3B) also showed bis-Et-βCD formation by the peaks at 48.46 and 47.26 ppm, which correspond to the upfield shifted C6' bonded to ethylenediamine as well as the CD-bonded ethylene carbons of ethylenediamine. Peaks of carbons of non-reacted ethylenediamine at around 40.2 ppm were not observed in the product. MS studies also confirmed the formation of the bis-Et-βCD by the molecular ion at *m/z* 2315.991 $[M+Na]^+$.

Overall, the established synthetic procedure with integrated purification based on a reusable cation exchange resin finally removed by filtration allowed the preparation of pure mono-Ts-βCD in a new, fast, ecologic, and selective method, which may be of interest also for an industrial process. Furthermore, a single-step procedure to improve the nucleophilic substitution to tosyl-cyclodextrin by amines such as ethylenediamine has been introduced using an anion exchange resin. In this way, bis-Et-βCD could be obtained in high molar yield using only a slight excess of ethylendiamine.

1. Experimental

1.1 Materials

β-CD, *p*-toluenesulfonyl chloride, ethylenediamine (99.5%), cation exchange resin 50W x 4 20-50 mesh in hydrogen form (Dowex®), anion exchange resin 1 x 8 200-400 mesh in Cl^- form (Dowex®), 1-methyl-2-pyrrolidinone (NMP; anhydrous, 99.5%), N,N-dimethylformamide (DMF; anhydrous, 99.8%), and acetone (99.5%) were from Sigma-Aldrich (Taufkirchen, Germany).

1.2 Equipment

Melting points were determined on a melting point apparatus B-540 (Büchi, Essen, Germany). ESI-MS spectrometry was performed on APCI-Q-TOFmicro (Waters GmbH, Eschborn, Germany). FT-IR spectra were acquired on an 8400S spectrometer (Shimadzu, Duisburg, Germany). NMR spectroscopy was carried out on a Bruker Avance 500 MHz (Bruker Biospin GmbH, Rheinstetten, Germany). Elemental analysis was performed with a Flash EA 1112 CHNS/O automatic elemental analyzer (Thermo scientific, Braunschweig, Germany).

1.3 Synthesis of 6-O-Monotosyl-β-cyclodextrin (mono-Ts-βCD)

A solution of βCD was prepared by slowly adding 35.2 mL (88 mmol) of aqueous 2.5 N NaOH to 10 g (8.8 mmol) of βCD being suspended in 90 mL water. After 5 min, 2.52 g (13.22 mmol) of *p*-toluenesulfonyl chloride was added in five portions and the formed suspension was continuously stirred for 1 h at 25 °C (400 rpm, magnetic stirrer). After filtration and washing of the residue (2 x 10 mL water), a total of 91 mL of pre-swollen cation exchange resin 50W x 4 20-50 mesh in the H^+ form (100 meq, exchange capacity 1.1 meq/mL) was added to the filtered solution. After 20 min, the mixture was first filtered through a Büchner funnel provided with glass wool to collect the exchange resin. Second, the precipitated white product was collected on filter paper. After washing with 3 x 30 mL water, the product was lyophilized.

Yield: 35 % (based on starting β-cyclodextrin).
Melting point: 160-162 °C.
FTIR: 1600 cm^{-1} (Ph-SO_2-), 1230 cm^{-1} (Ph-SO_2-R), 815 cm^{-1} (Ph-SO_2-O-R), 665 cm^{-1} (Ph-SO_2-).
^{1}H-NMR (DMSO-d_6): δ = 7.77 (mc, 2H Ph), 7.43 (mc, 2H Ph), 5.83-5.63 (m, 14H, OH1 and OH3 Cyd), 4.85-4.77 (m, 7H, H1 Cyd), 4.51-4.45 (m, 6H, OH6 CyD), 4.35 (mc, 2H, H6' CyD), 4.20 (mc, 1H, H5' CyD), 3.75-3.40 (m, 25H, H3, H5 and H6 CyD), 3.40-3.15 (m, H2, H4 overlap with water), 2.44 (s, 3H, Ph-CH_3) ppm.
Derivatization Degree (DD): >98 mol %.
^{13}C-NMR (DMSO-d_6): δ = 144.77 (C Ts); 132.846 (C Ts); 129.98 (C Ts); 127.55 (C Ts); 101.89 (C1); 98.14 (C1'); 81.47(C4); 81.15 (C4'); 73.02, 72.40, 72.00 (C2, C3, C5); 69.67 (C5'); 68.87 (C6'); 59.88 (C6); 21.17 (CH_3 Ts) ppm.
m/z (ESI): calculated 1289.1970, found 1289.3770 $[M+H]^+$.
Elemental analysis: calculated – C: 45.65%, H: 5.94%, S: 2.49%; detected – C: 45.71%, H: 6.29%, S: 2.84%.

1.4 Synthesis of N,N'-Bis-6-(6-deoxy-β-cyclodextrin)ethylenediamine (bis-Et-βCD)

After complete solubilization of 1 g (0.77 mmol) of mono-Ts-βCD in 15 mL NMP (standard procedure) or DMF, a total volume of 2 mL of pre-swollen anion exchange resin 1 x 8 200-400 mesh (2 meq, exchange capacity 1.0 meq/mL) either with Cl^- or OH^- counter-ions were added followed by 77.8 µL (1.16 mmol) of ethylenediamine. The OH^- form was obtained from the Cl^- form by flushing with 1.5 N NaOH, washing with water, and finally swelling in NMP or DMF. The reaction mixture was incubated at 80 °C under argon atmosphere for 24 h. Then, the reaction solution was filtered on paper

to remove the resin. The product was precipitated in acetone (20-fold excess v/v), collected by centrifugation, and washed 5 times in acetone. The pellet was dried under reduced pressure, subsequently solubilized in 70 mL water, filtered (0.45 μm syringe filter), and freeze dried.

Thin layer chromatography (TLC) was performed on precoated-silica gel 60 plates (Merck, Darmstadt, Germany) with *n*-butanol:methanol:water:30 wt.% ammonia in water (4:3:2:3) as eluent with subsequent staining (*p*-anisaldehyde/methanol/acetic acid/sulfuric acid solution 1:200:20:10) and heating.[19]

Yield 93% respect to starting mono-Ts-βCD for the system of NMP/Cl^- form resin.

TLC: R_f= 0.29 and two small spots at R_f= 0.12 (monoamine) and R_f= 0.40 (monotosyl).

^{1}H-NMR (DMSO-d_6): δ = 6.18-5.31 (m, 28H), 5.04-4.73 (m, 14H), 4.72-4.21 (m, 12H), 3.95-3.82 (m, 4H), 3.80-3.20 (m, 80H), 3.02-2.51 (m, 8H -C$\underline{H_2}$NHC$\underline{H_2}$C$\underline{H_2}$NHC$\underline{H_2}$-) ppm.

Derivatization Degree (DD) for this sample: 96 mol % (for the system NMP/Cl^- form resin).

^{13}C-NMR (DMSO-d_6): δ = 101.90 (C1); 81.49 (C4); 73.01, 72.38, 72.01 (C3, C5, C2); 70.32 (C5'); 59.88 (C6); 48.47 (C6'); 47.26 (-NH-CH_2-CH_2-NH-) ppm.

m/z (ESI): calculated 2292; found 2315 $[M+Na]^+$.

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Graphical abstract