Preparation and self-inclusion properties of *p*-xylylenediamine-modified β-cyclodextrins: dependence on the side of modification

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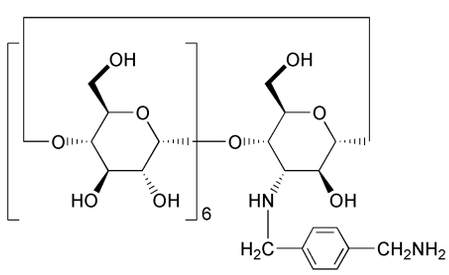
β-Cyclodextrin (β-CDx) derivatives modified with *p*-xylylenediamine at the 3-position, mono-3-deoxy-3-[4-(aminomethyl)benzylamino]-β-CDx (**1**; β-CDx-3-*p*-xylylenediamine) was prepared by the reaction of β-CDx-2,3-*manno*-epoxide with *p*-xylylenediamine. The circular dichroism properties of **1** are compared with those of the corresponding β-CDx derivative modified at the primary side (**2**; β-CDx-6-*p*-xylylenediamine), in the presence and in the absence of 1-adamantanamine·HCl. The results indicate that the xylylenediamine group of **2** is self-included in the β-CDx cavity, whereas that of **1** stays outside the cavity. The energy obtained by molecular modeling showed the same trend. The dependence of self-inclusion behavior of a pendant group in modified cyclodextrins on the position of modification could be a useful guide for designing cyclodextrin derivatives for various applications.

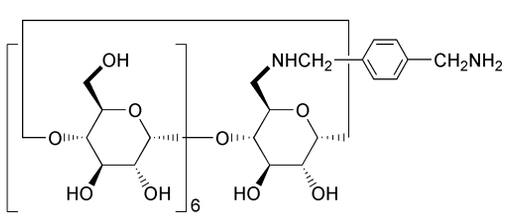
Introduction

Cyclodextrins (CDx) are cyclic oligosaccharides which have hydrophobic cavities capable of forming inclusion complexes with a variety of organic molecules in aqueous solution. They have attracted widespread interest as enzyme mimics and as hosts for molecular recognition, and much effort has been made to modifify the CDx to improve their catalytic and molecular recognition properties.[1] Modified CDx with suitable pendant groups often form self-inclusion complexes in which the pendant groups are inside the CDx cavity.[2–11] If the pendant group bears a chromophore, the modified CDx can be utilized as optical chemo-sensors for organic guests: upon binding of the guest, the chromophore is excluded from the CDx cavity with an associated change in color,[3] fluorescence,[4–7] or circular dichroism.[8] It has also been reported that the co-inclusion of the pendant group and guest molecule in a CDx cavity causes great differences in the stability and physical properties of the CDx–guest complexes.[11,12] Recently, we reported that β-CDx modified by xylylenediamine on the primary side forms a co-inclusion complex with α-methoxyphenylacetic acid, which can be used as a chiral NMR shift reagent for the determination of the enantiomeric composition of the guest.[11]

Either the primary or secondary side of a CDx can be utilized for attachment of a pendant group,[13] and CDx derivatives with the same pendant group but on different sides sometimes exhibit quite contrasting properties.[14] However, derivatization of CDx has been carried out mostly on the primary side, and not many CDx derivatives with a pendant group on the secondary side, especially at the 3-position of the secondary side, have been reported, presumably because they are more difficult to synthesize. Moreover, most of the CDx derivatives exhibiting self-inclusion properties are those having the pendant group on the primary side: McAlpine and Garcia-Garibay postulated that 3-*O*-(2-methylnaphthyl)-β-CDx forms a self-inclusion complex,[15] but the interpretation was changed to intermolecular association in a subsequent study by the same authors.[16] To examine the dependence of self-inclusion behavior on the side of attachment, it is necessary to prepare the CDx derivatives modified with the same group but on different sides and compare their properties. Here, we report the synthesis of *p*-xylylenediamine-modified β-CDx at the 3-position, mono-3-deoxy-3-[4-(aminomethyl)benzylamino]-β-CDx (**1**; β-CDx-3-*p*-xylylenediamine). Its circular dichroic (CD) spectral properties are compared with those of the corresponding β-CDx derivative modified on the primary side, **2**. It was found that the xylyl group of **1** stays outside the β-CDx cavity, while that of **2** is deeply embedded in the cavity. This is supported by the results of a molecular modeling study (see later).



1, β-CDx-3-xylylenediamine



2, β-CDx-6-xylylenediamine

Results and discussion

Synthesis of *p*-xylylenediamine-modified β-CDx

The most common method for monomodification of β-CDx on the primary side is the nucleophilic substitution reaction of β-CDx-6-OTs, which is prepared by reacting β-CDx with tosyl chloride in aqueous NaOH solution, with suitable nucleophiles.[13] Using *p*-xylylenediamine as a nucleophile, β-CDx-6-xylylenediamine **2** is prepared in yields of *ca.* 20%.[11] Direct selective modification at the 3-position of β-CDx is not usually

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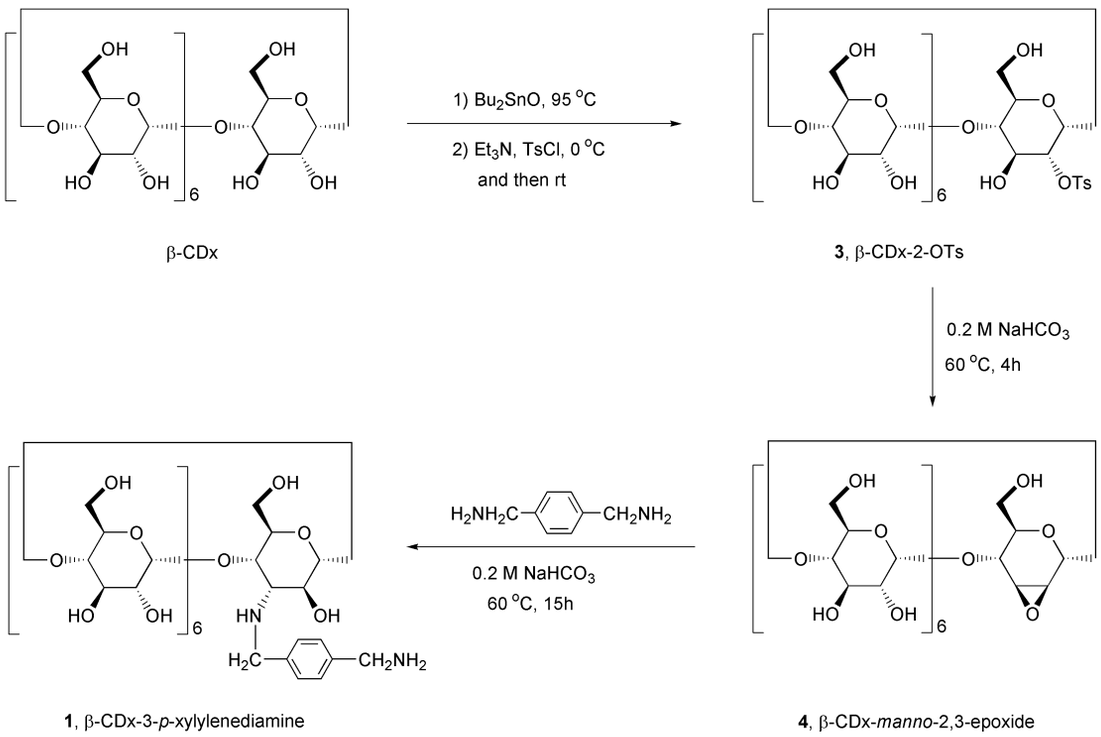


Scheme 1 Synthesis of mono-3-deoxy-3-[4′-(aminomethyl)benzylamino]-β-CDx (**1**; β-CDx-3-*p*-xylylenediamine).

feasible, because of the higher reactivity of the 2- or 6-hydroxy groups. Modifications at the 3-position are mostly carried out by reacting *manno*-2,3-epoxycyclodextrin with a nucleophile.[12,14a] The synthesis of β-CDx-3-*p*-xylylenediamine **1** is outlined in Scheme 1.

Mono-[2-*O*-(*p*-tolylsulfonyl)]-β-CDx (**3**; β-CDx-2-OTs) was prepared by Murakami's method using dibutyltin oxide and purified by reverse-phase column chromatography.[17] Scale-up of the reaction using 5 g (*ca.* 20 times the amount of the reported procedure) of β-CDx did not lower the yield significantly. The expected 4 : 7 integral ratio of aromatic protons at δ 7.99 (d, 2H, J = 8.0 Hz) and 7.52 (d, 2H, J = 8.0 Hz) to anomeric protons at δ 5.0–5.1 was obtained in the ^{1}H NMR spectrum in D_2O. β-CDx-*manno*-2,3-Epoxide **4** was prepared from β-CDx-2-OTs **3** using the reported procedure.[14a,18] Purification of **4** was better accomplished by reverse-phase column chromatography (Licroprep Rp-18, Merck) rather than the reported method utilizing Sephadex G-15 resin. The ^{1}H NMR spectrum (in D_2O) of compound **4** showed the expected signal at δ 3.51 with a 3.7 Hz coupling to H-3, for the C-2 proton of the glucose epoxide residue, and an unsplit one-proton signal at δ 5.30 for the C-1 proton of that residue.[14a] The reaction of the epoxide with a twofold amount of *p*-xylylenediamine in 0.2 M $NaHCO_3$ for 15 h followed by purification by reverse-phase column chromatography provided β-CDx-3-*p*-xylylenediamine **1** in 65% yield, which was characterized by ^{1}H and ^{13}C NMR and FAB MS data. The ^{1}H NMR spectrum of **1** showed the expected integral ratio of 4 : 7 corresponding to the phenyl protons at δ 7.38–7.46 and anomeric protons of the β-CDx moiety at δ 5.00–5.15. It also showed a one-proton signal at δ 2.88 as a doublet of doublets with J = 10.4 and 3.2 Hz for the C-3 proton carrying the nitrogen atom of *p*-xylylenediamine, which indicates that the C-2 and C-3 protons are axial and C-4 proton is equatorial, and thus a ring flip of the modified glucose unit (actually an altrose unit) accompanying conformational change has occurred. This result is consistent with previous reports by other groups[14a,18] for the nucleophilic ring opening of the epoxide **4**.

Circular dichroism and self-inclusion properties of β-CDx-3-*p*-xylylenediamine 1 and β-CDx-6-*p*-xylylenediamine 2

The UV–VIS and circular dichroism (CD) spectra of *p*-xylylenediamine-modified β-CDx **1** and **2** in 0.01 M HCl are shown in Fig. 1. Both compounds show positive circular dichroism spectra around 260 nm, which corresponds to the ^1L_b band.[8] To check the possibility of intermolecular association of the *p*-xylylenediamine-modified β-CDx **1** and **2**, we measured CD spectra at various concentrations from 1 mM to 13 mM and found no appreciable dependence of molar ellipticities on concentration. This indicates that intermolecular association of the *p*-xylylenediamine-modified β-CDx is insignificant in the concentration range.

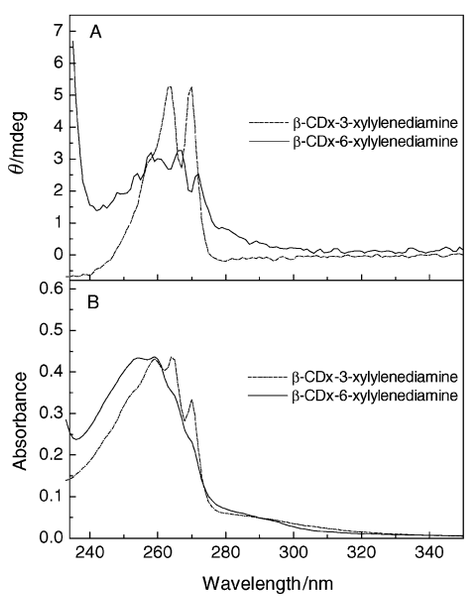


Fig. 1 Circular dichroism (A) and UV–VIS (B) spectra of *p*-xylylenediamine-modified β-CDx derivatives in 0.01 M HCl. The concentration was 1.0×10^{-3} M for UV–VIS and 3.0×10^{-3} M for circular dichroism measurements. The cell pathlength was 1.0 cm.

As the 1-adamantyl group has strong binding affinity to the β-CDx cavity, it displaces any group or molecule included inside the β-CDx cavity to the outside.[3,4,6–8,15,19] When the included group or molecule contains a chromophore, it results in a large CD spectral change as the sign and magnitude of a

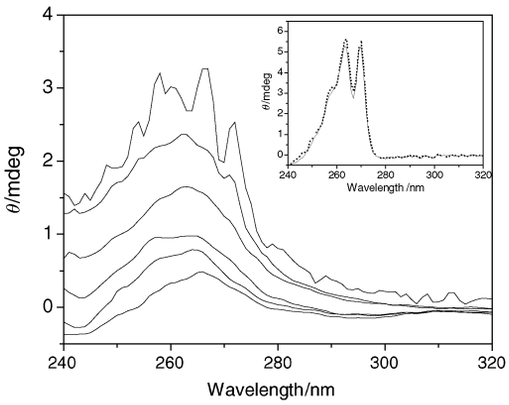
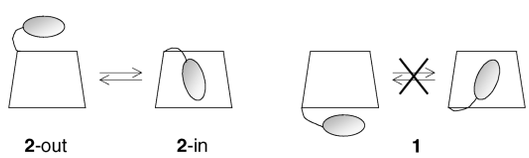


Fig. 2 Effect of 1-adamantanamine·HCl (ADA) on the circular dichroism spectrum of 3.0×10^{-3} M β-CDx-6-*p*-xylylenediamine in 0.01 M HCl. The concentrations of ADA are 0.00, 1.7, 2.9, 4.9, 7.0, and 11.7 mM (from top to bottom). The inset shows the circular dichroism spectra of β-CDx-3-*p*-xylylenediamine in the absence (solid line) and in the presence (broken line) of 10 mM ADA.

CD spectrum vary sensitively with the position and orientation of the chromophore in CDx complexes.[8,20–24] Fig. 2 shows the circular dichroism spectra of **2** in the presence of various concentrations of 1-adamantanamine·HCl (ADA). The CD peak of **2** decreased upon the addition of ADA. However, the CD spectrum of **1** was unaffected by the addition of ADA (see inset of Fig. 2). This result indicates clearly that the *p*-xylylenediamine moiety attached to the primary side of β-CDx in **2** is included inside the β-CDx cavity, whereas the same group at the 3-position in **1** stays outside the cavity. Since significant intermolecular association is ruled out from the independence of molar ellipticity of **2** on its concentration, it is certain that **2** forms an intramolecular self-inclusion complex as depicted below.



The CD spectral change upon the addition of ADA reflects the complexation between **2** and ADA [eqn. (1)]. Since the

$$\mathbf{2} + \text{ADA} \rightleftharpoons \mathbf{2}\text{–ADA}\ K_{app} = [\mathbf{2}\text{–ADA}]/([\mathbf{2}][\text{ADA}]) \quad (1)$$

adamantyl group is too large for co-inclusion with xylylenediamine group in the β-CDx cavity, ADA can form the complex only with the **2**-out conformer [eqn. (2)] and thus depletes the

$$\mathbf{2}\text{-out} + \text{ADA} \rightleftharpoons \mathbf{2}\text{–ADA}\ K_{2\text{-out/ADA}} = [\mathbf{2}\text{–ADA}]/([\mathbf{2}\text{-out}][\text{ADA}]) \quad (2)$$

2-in conformer by shifting the equilibrium between **2**-in and **2**-out [eqn. (3)].

$$\mathbf{2}\text{-out} \rightleftharpoons \mathbf{2}\text{-in}\ K_{in} = [\mathbf{2}\text{-in}]/[\mathbf{2}\text{-out}] \quad (3)$$

The variation of CD ellipticity ($\Delta\theta$) of a given solution of **2** with the concentration of ADA is related to the total concentrations of **2** and ADA, $[\mathbf{2}]_o$ and $[\text{ADA}]_o$, and the apparent association constant (K_{app}) by eqn. (4).[25] K_{app} is related to the microscopic equilibrium constants in eqns (2) and (3) by $K_{app} =$

$$\Delta\theta/\Delta\theta_\infty = 0.5[(1 + [\text{ADA}]_o/[\mathbf{2}]_o + 1/K_{app}[\mathbf{2}]_o) \pm \{(1 + [\text{ADA}]_o/[\mathbf{2}]_o + 1/K_{app}[\mathbf{2}]_o)^2 - 4[\text{ADA}]_o/[\mathbf{2}]_o\}^{1/2}] \quad (4)$$

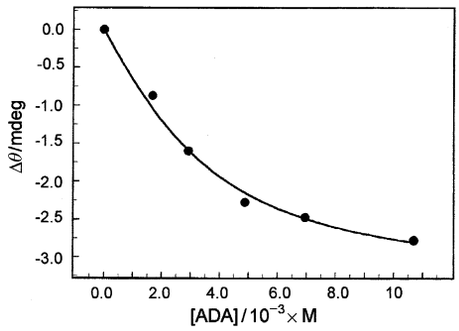


Fig. 3 Plot of ellipticity change at 262 nm caused by the addition of 1-adamantanamine·HCl (ADA) to a solution of 3.0×10^{-3} M β-CDx-6-*p*-xylylenediamine in 0.01 M HCl. The solid line is the result of fitting to eqn. (4) with $K_{app} = 590\ \text{M}^{-1}$ and $\Delta\theta_\infty = -3.4$ mdeg.

$K_{2\text{-out/ADA}}/(1 + K_{in})$, and $\Delta\theta_\infty$ is the ellipticity change expected when all of the **2** forms complex with ADA. Fig. 3 shows the variation of the ellipticity of a 3.03×10^{-3} M solution of **2** at 262 nm with the concentration of ADA. Non-linear least-squares fitting of the data to eqn. (4) gave K_{app} and $\Delta\theta_\infty$ values of $590 \pm 200\ \text{M}^{-1}$ and -3.4 ± 0.3 mdeg, respectively. The latter value corresponds to a molar ellipticity of $-110\ \text{M}^{-1}\ \text{cm}^{-1}$ for the **2**–ADA complex. If we assume that the binding constant of ADA with the '**2**-out' conformer is not significantly different from that of unmodified β-CDx, $18000\ \text{M}^{-1}$,[19] the equilibrium constant (K_{in}) for self-inclusion of xylylenediamine in **2** [eqn. (3)] is estimated to be 30.

The sign and magnitude of the CD spectra of CDx complexes with a chromophore depend on the position and orientation of the chromophore.[20–24] Kodaka predicted that the sign of CD spectrum of a chromophore tends to be reversed when the chromophore moves from the inside of the CDx cavity to the outside.[23,24] The effect of ADA on the CD spectrum of **2** is consistent with this prediction. A detailed interpretation of the sign and magnitude of the CD spectra of **1**, **2**, and **2**–ADA is beyond the scope of this work.

Molecular model calculations

Molecular modeling provides useful information on molecular structure, usually complementary to the experimental techniques. In an effort to obtain further information on the difference in the self-inclusion properties of **1** and **2**, we conducted a molecular modeling calculation using the CVFF force field. To simulate the aqueous environment of the compounds, a water sphere of diameter 15 Å and relative permittivity of 78 were used. Energy minimization from various initial conformations converged into two conformations: one with the xylylenediamine group included in the β-CDx cavity, and the other with the group capping the face where it is attached. For **1**, the energy of the capped conformation was 4.1 kcal mol^{-1} lower than that of self-included one, whereas the energy of the self-included conformation (**2**-in) was lower than that of the capped one (**2**-out) by 1.5 kcal mol^{-1}. Fig. 4 shows the energy minimum conformations. This agrees well with the results obtained from CD measurements.

Conclusions

β-CDx-3-*p*-Xylylenediamine **1** was prepared by the reaction of β-CDx-*manno*-2,3-epoxide **4** with *p*-xylylenediamine; **4** was synthesized from β-CDx-2-OTs **3**, which was prepared by Murakami's method using dibutyltin oxide. The circular dichroism properties of **1** were compared with those of β-CDx-6-*p*-xylylenediamine **2**, in the presence and in the absence of 1-adamantanamine·HCl. The results indicated that xylylenediamine group of **2** is deeply embedded in the β-CDx cavity, whereas that of **1** stays outside the cavity. This was supported

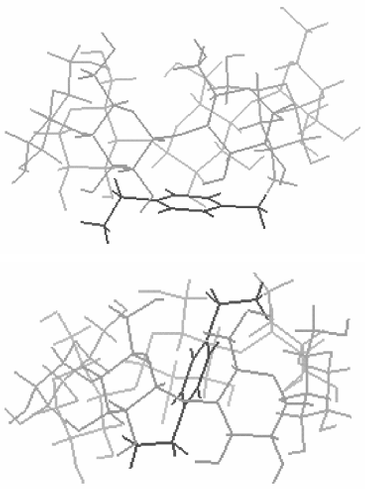


Fig. 4 Energy minimum conformations of β-CDx-3-*p*-xylylenediamine **1** (above) and β-CDx-6-*p*-xylylenediamine **2** (below) viewed from the side. The *p*-xylylenediamine moiety is represented in bold. Both of the amine groups are protonated. Note that the substituted carbohydrate moiety of **1** takes a different conformation from the unsubstituted glucose residues (see text).

by a molecular modeling calculation. As far as we know, this is the first demonstration that the self-inclusion properties of CDx modified with the same group depend on the position of the modification. Such dependence of self-inclusion behavior of modified-CDx on the position of modification might give useful guidance for designing modified-CDx for various applications.

Experimental

Spectral measurements

NMR spectra were recorded on a Varian Unity INOVA 400 spectrometer at the Central Research Facilities of Chungnam National University: chemical shifts are reported in δ relative to the residual solvent peak (D_2O or DMSO-d_6) and J values are given in Hz. Mass spectra were taken at the Korea Basic Science Institute. Solutions for circular dichroism measurements of **1** and **2** were prepared by dissolving HCl salts of the compounds in 0.01 M HCl. Circular dichroism spectra were taken with a JASCO J-810 spectropolarimeter equipped with thermostatted cell holder at 25 °C. The bandwidth was set at 2 nm and the response time was 2 s. Spectra of ten repetitive scans at scan speed of 50 nm min^{-1} were averaged and smoothed using JASCO software.

Molecular modeling

The molecular modeling calculation was performed using the CVFF force field in the Insight II/Discover program package (Molecular Simulation Inc., 1995). A water sphere of diameter 15 Å provided by Insight II and relative permittivity of 78 were used. The cut-off distances for van der Waals and electrostatic interactions were set to 100 Å to include all possible interactions. Both of the amine groups of the xylylenediamine moiety were assumed to be protonated as pK_a's of the conjugate acids of primary and secondary alkyl amines are much higher than 2. For β-CDx-3-*p*-xylylenediamine **1**, the structure with the conformational change accompanied by the ring flip of the substituted carbohydrate residue was used for the calculation.

Syntheses of *p*-xylylenediamine-modified β-CDx derivatives

The synthesis and characteristics of β-CDx-6-*p*-xylylenediamine **2** have been reported in a previous paper.[11]

Mono-[2-*O*-(*p*-tolylsulfonyl)]-β-CDx (3; β-CDx-2-OTs). The title compound was prepared by Murakami's method using dibutyltin oxide.[17] A yield of 1.42 g (25%) of **3** was obtained starting from 5.00 g of β-CDx.

β-CDx-*manno*-2,3-Epoxide, 4. Compound **4** was prepared from β-CDx-2-OTs, **3**, using the reported procedure,[14a,18] but an improved purification method was applied: a yield of 0.828 g (95%) of **2** was obtained from 1.00 g of β-CDx-2-OTs after purification utilizing reverse-phase column chromatography (Licroprep Rp-18, Merck).

Mono-3-deoxy-3-[4-(aminomethyl)benzylamino]-β-CDx. To a solution of 1.00 g (0.90 mmol) of β-CDx-*manno*-2,3-epoxide in 40 ml of 0.2 M $NaHCO_3$ was added *p*-xylylenediamine (0.24 g, 1.80 mmol) dissolved in 40 ml of DMF and the reaction mixture was stirred for 15 h at 60 °C under a nitrogen atmosphere. The reaction mixture was concentrated to *ca.* 4 ml under reduced pressure and subjected to reverse-phase column chromatography (Licroprep Rp-18, Merck), eluting with distilled water and then 10% CH_3CN and finally with methanol. When eluted with methanol, the product came out together with a small amount of unreacted *p*-xylylenediamine. It was further purified by being washed with acetone to yield 0.733 g (65% yield) of analytically pure β-CDx-*p*-xylylenediamine, **1**: mp 260 °C (decomp.); ^{1}H NMR spectra of **1** in D_2O at 25 °C, δ (relative to the residual solvent at δ 4.81) 7.44 (d, 2H, J = 8.0), 7.39 (d, 2H, J = 8.0), 5.15 (d, 1H, J = 4.0), 5.13 (d, 1H, J = 4.0), 5.09 (d, 1H, J = 3.2), 5.06 (d, 1H, J = 3.6), 5.05–5.02 (m, 3H), 4.35–4.29 (m, 1H, H5A), 4.08–3.53 (m, 44H, H2, H3, H4, H5, H6, 2-CH_2), 2.88 (dd, 1H, H3A, J = 10.4 and 3.2); ^{1}H NMR spectra of **1**·2HCl in D_2O at 25 °C, 7.64 (d, 2H, J = 8.0), 7.57 (d, 2H, J = 8.0), 5.22 (d, 1H, J = 4.0), 5.18 (d,1H, J = 3.6), 5.16 (d, 1H, J = 4.4), 5.09 (d, 2H, J = 3.6), 5.06 (d, 1H, J = 2.8), 5.00 (d, 1H, J = 6.8), 4.59 (d, 1H, J = 13.6), 4.44–4.34 (m, 3H), 4.25 (s, 2H), 4.08–3.57 (m, 40H); ^{13}C NMR spectra of **1** in DMSO-d_6 at 25 °C, δ 141.67, 138.51, 128.20, 127.07, 104.17, 102.28, 102.17, 102.01, 101.85, 101.59, 81.97, 81.84, 81.43, 81.36, 81.03, 80.38, 76.05, 73.4–71.7, 71.00, 60.28, 59.96, 59.45, 58.82, 50.45, 45.17; MS (positive ion FAB): 1253.48 (calcd. for $C_{50}H_{80}O_{34}N_2 + H^+$, 1253.47).

Acknowledgements

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