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An attempt to synthesize the two monomers of CDTOH: Unexpected NMR and X-ray diffraction crystal analysis

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Abstract

Two monomer compounds of CDTOH, 6^A-deoxy-6^A-(4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl)-per-O-methylated *β*-cyclodextrin **4** and 6^A-deoxy-6^A-(4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl) *β*-cyclodextrin **7**, have been synthesized via click chemistry. The structures were confirmed by ^{1}H NMR, ^{13}C NMR and ESI-HRMS. In comparison to the ^{1}H NMR spectra of compound **4** and intermediate **6**, two sets of peaks in the high field of **7** are somewhat unusual. The X-ray single-crystal analysis of **7** showed the existence of an intramolecular hydrogen bond between the CH_2OH donor of glucose B and the terminal hydroxy acceptor of the side chain, leading to the 4-(2-hydroxyethyl)-1*H*-1,2,3-triazole group protruding outside the cavity and embedding in the hydrophobic cavity of the adjacent molecule (interinclusion) to form an interlocked helical columnar superstructure.

Keywords:

CDTOH; *β*-cyclodextrin; Crystal structure; Click chemistry; Interinclusion

1. Introduction

Cyclodextrins (CDs) are naturally occurring cyclic oligomers of (*α*-1,4)-linked D-glucopyranoside and are commonly known as hexamers to octamers.[1] Due to their toroid cone structures, CDs have many interesting biological properties resulting in hydrophobic cores and hydrophilic exteriors. They can form inclusion complexes with a broad variety of guest molecules with sizes compatible with the cavity size,[2] which have a vast range of applications from drug delivery systems and enzyme mimics to chemical and biological sensors.[2-4] Over the past several decades, randomly methylated *β*-CD (RAME-*β*-CD) has attracted increasing attention given its unique properties such as high solubility both in water and in nonaqueous solvents.[5,6] The solubility of RAME-*β*-CD in water at 25 °C (50 g/100 mL) is 27-fold greater than that of *β*-CD (1.85 g/100 mL). Therefore, RAME-*β*-CD has a superior effect on the aqueous solubility of various active molecules. In addition, the addition of RAME-*β*-CD and RAME-*β*-CD-NEt_2 has an effect on the efficiency and selectivity of palladium-catalyzed Heck arylation.[7] Interestingly, RAME-*β*-CDs with hydrophilic moieties in the 4-position of the 1,2,3-triazole group on the primary face, such as $CDTSO_3Na$, CDTpolyOH and CDTOH (Figure 1), can constitute a new class of multiwall carbon nanotube (MWNT) dispersion agents.[8] The

1,4-disubstituted-1,2,3-triazole-linked RAME-β-CD dimers are also well known to be very effective mass transfer promoters to convert long alkyl-chain substrates in the palladium-catalyzed Tsuji-Trost reaction.[9] Despite extensive research on RAME-β-CDs, many of them are a mixture of partially methylated β-CDs with an average degree of substitution of 1.8 methyl groups per glucopyranose unit. In addition, their biological effect has been shown to be concentration-dependent and variable based on the type of modified CD and degree of substitution.[10]

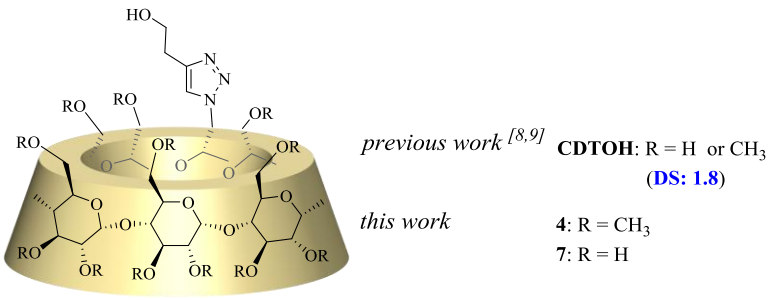


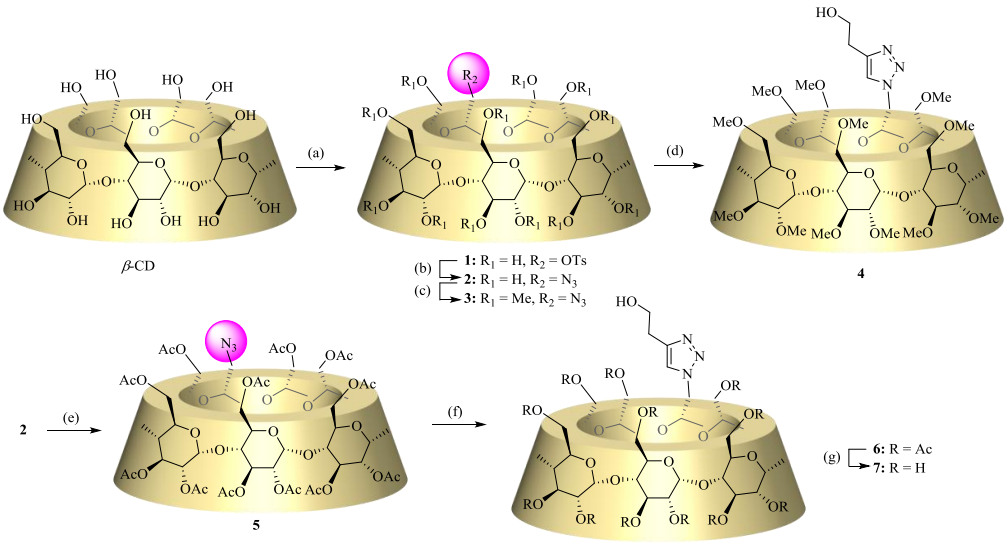
Fig. 1. Structures of CDTOH and its two monomer compounds **4** and **7**. DS: average number of methyl groups per glucopyranose unit

In order to further study the effect of the substituents of CDTOH on their chemistry and biology activity, we attempt to synthesize the two monomer compounds of CDTOH, 6^A-deoxy-6^A-[4-(2-hydroxyethyl)-1,2,3-triazol-1-yl] per-*O*-methylated β-CD (HETPM-β-CD, **4**) and 6^A-deoxy-6^A-[4-(2-hydroxyethyl)-1,2,3-triazol-1-yl] β-CD (HET-β-CD, **7**). To our surprise, two sets of unusual signals were observed clearly at δ 2.83 ppm and 3.19 ppm in the high-field ^{1}H NMR spectrum of **7**. To better understand this, a single crystal of compound **7** was obtained for X-ray diffraction and the intermolecular threading was observed in solid state. As compared with the crystal analysis, the concentration-dependent NMR spectroscopy indicated that the 1,2,3-triazole group included in the β-CD cavity. Herein, we report the synthesis and unambiguous structural characterization of triazole-functionalized β-CDs by NMR, together with an investigation of the structural characterization of **7** by X-ray diffraction analysis.

2 Results and discussion

The synthesis route of the two mono-4-(2-hydroxyethyl)-1,2,3-triazole functionalized β-CD derivatives **4** and **7** is summarized in Scheme 1. Briefly, β-CD was converted into 6^A-deoxy-6^A-azide per-*O*-methylated β-CD (**3**) or 6^A-deoxy-6^A-azide per-*O*-acetylated β-CD (**5**)

through a previously described easy and efficient three-step reaction procedure.[11] Compounds **4** and **6** were prepared by direct click reaction between **3** or **5** and 3-butyn-1-ol in the presence of $CuSO_4$ and *L*-ascorbic acid at room temperature in 74% and 45% yields after column purification (CH_3OH in CH_2Cl_2 gradient). The NMR and ESI-HRMS spectra of **4** and **6** showed satisfactory agreement with the expected structures (see the supporting information). The ^1H NMR spectrum of compound **4** shows not only the characteristic resonance peaks at δ 5.24-5.09 ppm (H_1 of β-CD), 4.99 ppm (H_6^B of β-CD), 4.62 ppm (H_6^A of β-CD) and 4.08 ppm (H_5^A of β-CD) for the β-CD unit, but also the proton signals at 7.53 ppm (triazole) and 2.94 ppm (triazole-CH_2) for the 4-(2-hydroxyethyl)-1*H*-1,2,3-triazole side chain. An example of the assignment of the 4-(2-hydroxyethyl)-1,2,3-triazole intermediate **6** is shown in Figures S1 and S2. The introduction of a 4-(2-hydroxyethyl)-1*H*-1,2,3-triazole group was further confirmed by positive mode electrospray ionization-high resolution mass spectrometry (ESI-HRMS), which showed the presence of monocharged ions at m/z ratios of 2070.6348 ($[M + H]^+$), 2092.6116 ($[M + Na]^+$) and 2108.5845 ($[M + K]^+$), corresponding to the desired compound **6**.



Scheme 1. Reagents and conditions: (a) NaOH, H_2O, TsCl, 13%; (b) NaN_3, DMF, 80 °C, 86%; (c) NaH, CH_3I, DMF, 65%; (d) 3-butyr-1-ol, $CuSO_4$, Na-*L*-ascorbate, THF-H_2O (1:1, V/V), 74%; (e) Ac_2O, pyridine, DMAP; (f) 3-butyr-1-ol, $CuSO_4$, Na-*L*-ascorbate, THF-H_2O (1:1, V/V), 45%; (g) CH_3ONa/CH_3OH, rt, 100%

The acetyl groups of **6** were further removed by a Zemblén reaction in the presence of CH_3ONa to quantitatively afford **7**. Although the synthesis of compound **7** has been previously

described via a click reaction between 6^A-deoxy-6^A-azide β-CD and 3-butyn-1-ol under different conditions ($CuSO_4$, Na-*L*-ascorbate, DMSO),[12] to our knowledge, the NMR signals have not been fully assigned thus far because the peaks extensively overlapped and broadened. The ^{1}H NMR spectrum of **7** shows that the anomeric protons appear as three doublets at 5.19 (J = 3.7 Hz), 5.02 (J = 3.5 Hz) and 5.00 (J = 3.3 Hz) ppm and a multiple signal at 5.07-5.09 ppm. Moreover, the low-field multiple at 5.01 ppm (overlap with H_1) and doublets of doublets at 4.71 ppm (J = 14.6, 9.5 Hz), each referring to 1H, were assigned to H_{6a}^A and H_{6b}^A, respectively, and a triplet appearing at 4.20 (J = 11.9 Hz) ppm could be assigned to H_5^A as a consequence of the presence of the 4-(2-hydroxyethyl)-1,2,3-triazole group. Compared the ^{1}H NMR spectra of the two monomer compounds of CDTOH, **4** and **7**, each observed a triplet centered around 2.94 – 2.97 ppm, referring to 2H, could be assigned to the methylene next to the triazole group.

To our surprise, two sets of relatively broad double peaks at 2.83 ppm (J = 11.9 Hz) and 3.19 ppm (J = 12.3 Hz), each referring to 1H, were clearly observed, which was unlike its analogs of **4** and **6** (Figure 2). Analysis of the COSY and HSQC spectra of **7** (Figures S3 and S4) reveals that they should be CH_2 of one glucose unit of β-CD. To gain more information about the structure of **7**, we performed a ROESY experiment. After careful analysis, the ROESY spectrum indicated that the CH_2 group should be close to glucose A, possibly glucose B or F, due to it shows strong cross peaks between $H_{6a}^{B(F)}$ and $H_{6b}^{B(F)}$ and $H_4^{B(F)}$ (peaks A and B) and weak cross peaks between $H_{6a}^{B(F)}$ and H_5^A and H_{6b}^A (peaks C and D) (Figure 3). However, we are curious why it is unlike the CH_2 group of the other five glucoses.

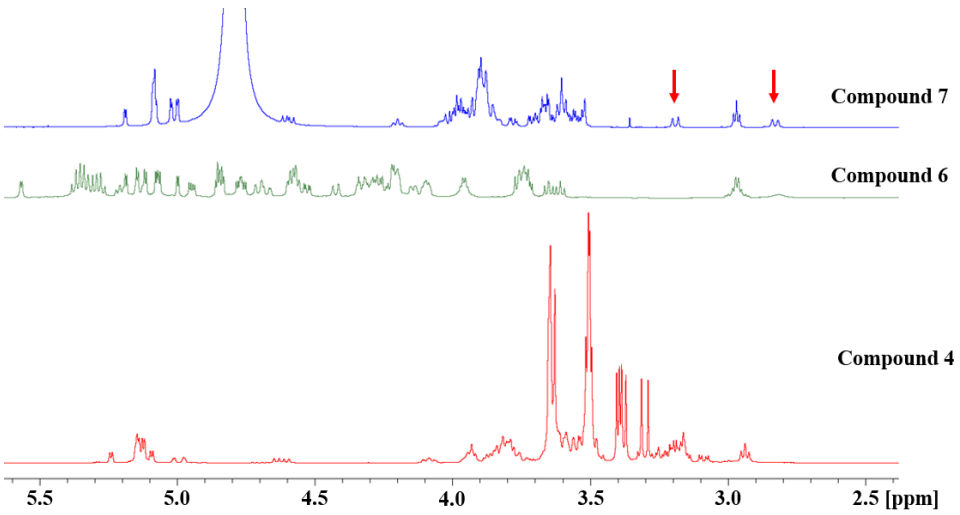


Figure 2. Partial 1D ^{1}H NMR spectra of (a) compound **4** ($CDCl_3$, 298K, 400 MHz), (b) compound

6 ($CDCl_3$, 298K, 600 MHz), (c) compound **7** (D_2O, 298K, 600 MHz).

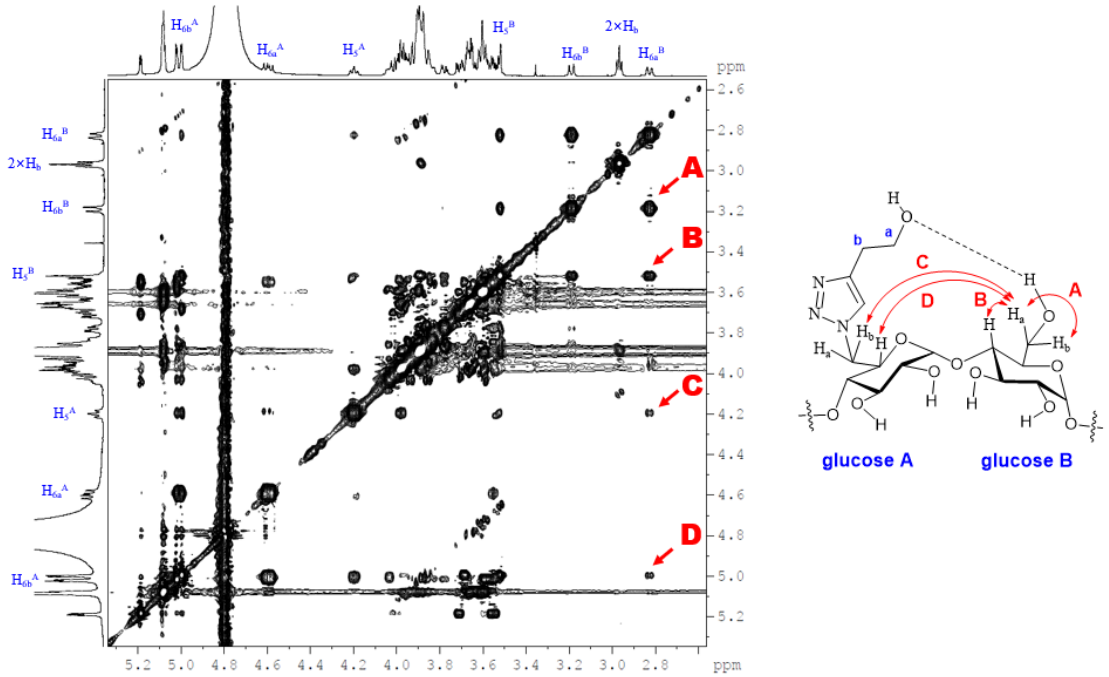


Figure 3. ^{1}H ROESY spectrum (600 MHz) of **7** in D_2O at 298 K. Key NOE correlations (red arrows) observed for the CH_2OH group of glucoses A and B

To provide a definitive answer to the structure of **7**, a single crystal was obtained for X-ray diffraction analysis. Crystallographic data are given in Table 1 and have been deposited at the Cambridge Crystallographic Data Centre (deposition no.). A tetragonal crystal with the space Group $P4_12_12$ was obtained from a water solution. An ORTEP drawing of **7** is shown in Figure 4, while the fractional atomic coordinates and equivalent isotropic displacement parameters, anisotropic displacement parameters, bond lengths, bond angles, hydrogen bonds and torsion angles are given in the Supporting Information (Tables S1-S6). In the crystalline form, the *β*-CD ring presents a bottomless bowl-shaped molecule stiffened by hydrogen bonding between the 3-OH and 2-OH groups around the outer rim (Figure 4A),[13] with the 4-(2-hydroxyethyl)-1*H*-1,2,3-triazol side chain protruding outside from the primary face of the cavity. In addition, it was determined that a short intramolecular hydrogen bond (O6B–H6BB···O10A, with O···O 2.745(8) Å and angle O–H···O 169.6°) between the CH_2CH_2OH proton acceptor side chain and the 6-OH proton donor group of glucose B causes the protons of CH_2^A and CH_2^B to be close enough in distance, resulting in the observation of anomalous NOEs in

the ROESY spectrum. Additionally, due to the formation of the hydrogen bond, the CH_2 group of glucose B is located in the shielding region (ring currents affect) less than 3.3 Å from the centroid of the triazole, which explains why the chemical shifts of CH_2^A are unlike those of the CH_2 group of glucoses C-G.

Table 1. Crystallographic data for **7**

Empirical Formula	$C_{46}H_{75}N_3O_{35}$
Formula weight	1230.09
Temperature/K	100.00 (10)
Crystal system	tetragonal
Space group	$P4_12_12$
a/Å	21.65007 (13)
b/Å	21.65007 (13)
c/Å	28.6778 (3)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	13442.0 (2)
Z	8
ρ_{calc}g/cm^3	1.216
μ/mm^{-1}	0.913
F (000)	5216.0
Crystal size/mm^3	0.21 × 0.18 × 0.12
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.544 to 140.132
Index ranges	$-26 \leq h \leq 26$, $-25 \leq k \leq 26$, $-34 \leq l \leq 33$
Reflections collected	112688
Independent reflections	12711 [R_{int} = 0.0628, R_{sigma} = 0.0264]
Data/restraints/parameters	12711/30/842
Goodness-of-fit on F^2	1.054

Final R indices [I ≥ 2σ (I)]	R_1 = 0.0647, wR_2 = 0.1898
Final R indices [all data]	R_1 = 0.0679, wR_2 = 0.1947
Largest diff. peak/hole/e $Å^{-3}$	0.25/-0.30
Flack parameter	0.17 (6)
CCDC deposition no.	CCDC 2123295

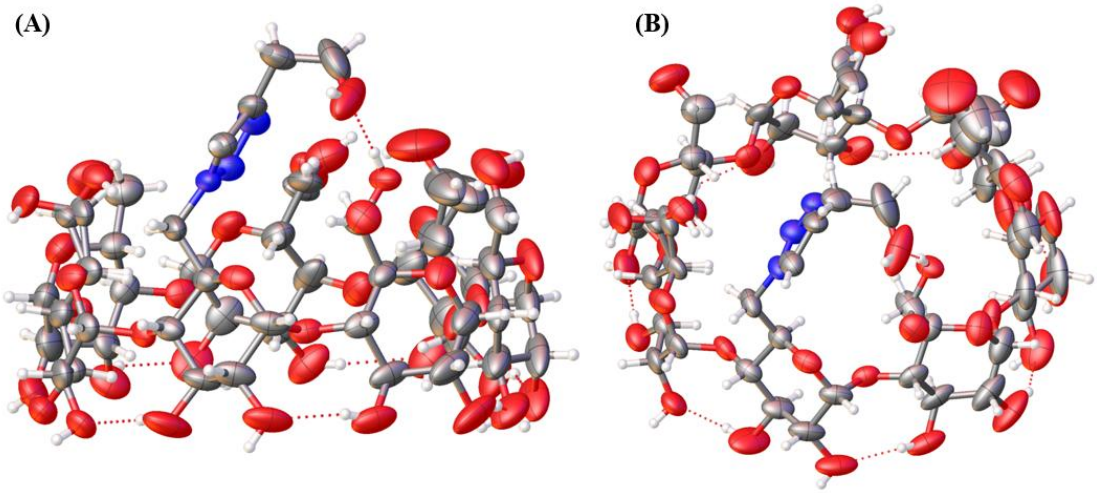


Figure 4. ORTEP view of **7**. (A) Side view showing the 4-(2-hydroxyethyl)-1*H*-1,2,3-triazol side group at position C-6 on glucose A protruding outside the cavity. (B) Top-down view from the 4-(2-hydroxyethyl)-1*H*-1,2,3-triazol side chain. Intermolecular hydrogen bond assigned by red dashed line (Carbon: gray; hydrogen: white; oxygen: red and nitrogen: blue)

The unique layering that results in the extended crystal structure is shown in Figure 5. The crystal structure clearly reveals that the 4-(2-hydroxyethyl)-1*H*-1,2,3-triazole side group is consecutively inserted into the adjacent *β*-CD cavity from the secondary face, as expected, thus giving rise to an interlocked helical supramolecular formed by self-assembly in which the 4-(2-hydroxyethyl)-1*H*-1,2,3-triazole side group acts as bridge between the cyclodextrin units. Each molecule behaves as both a host and a guest.

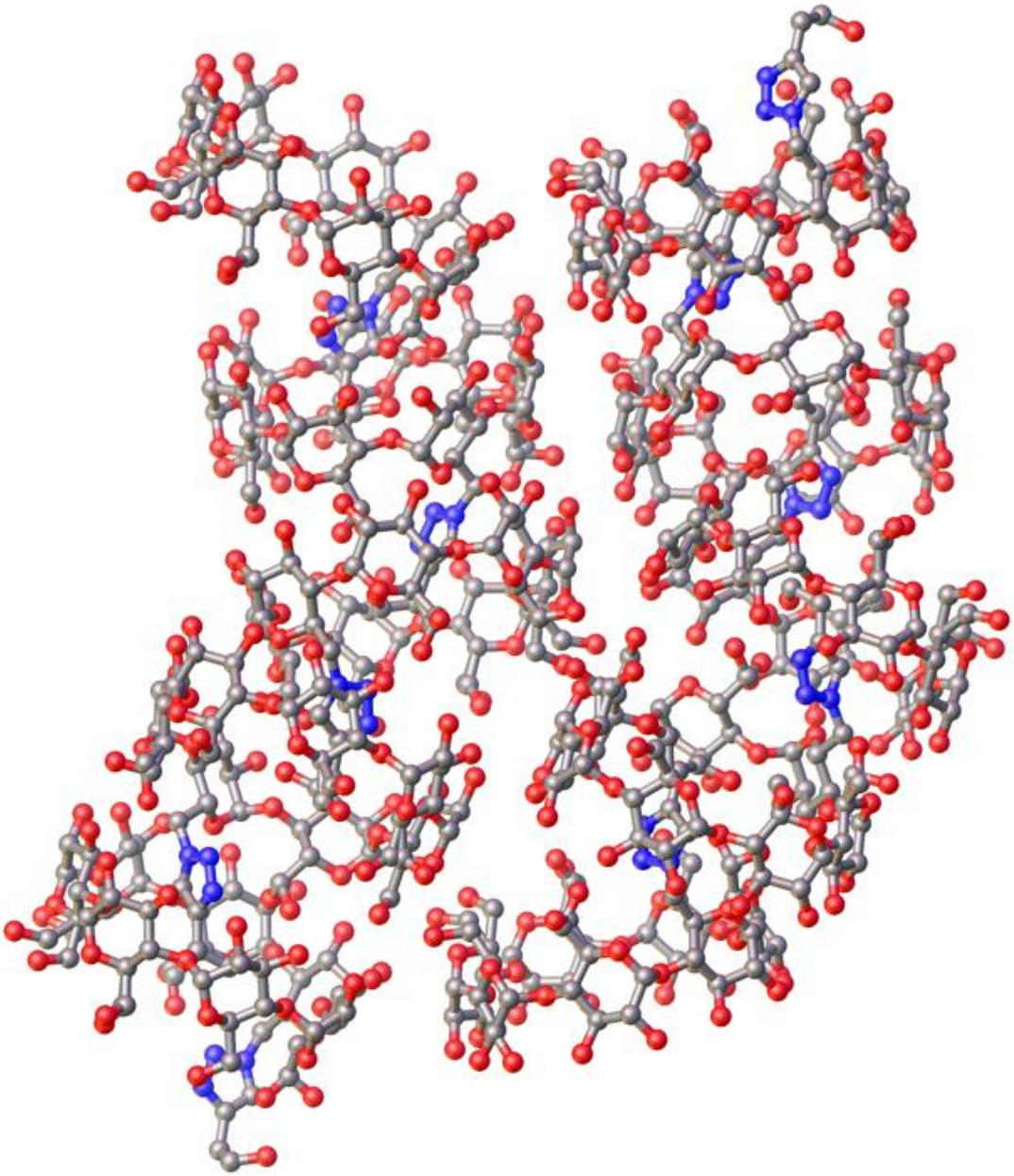


Figure 5. Interlocked helical superstructure of compound **7**. The column is located on a 4-fold screw axis. (Carbon: gray; oxygen: red and nitrogen: blue)

It was reported that a cross shift of two broad signals of the triazole proton was observed in the ^{1}H NMR spectrum of CDTOH in D_2O,[9] highlighting a capping process of the *β*-CD cavity by the triazole substituent. However, the ^{1}H NMR spectra of compounds **4** and **6** in $CDCl_3$ and **7** in D_2O all show one signal of the triazole proton, indicating that the threading and de-threading process may faster than the NMR time scale. Therefore, the concentration-dependent NMR spectroscopy was carried out (Figures S5). Both triazole-H and *β*-CD-H_5^A are slightly shifted upfield giving chemical shifts of the range from 0.0002 to 0.0025 ppm and from 0.0013 to 0.0069

ppm, respectively, with the increasing concentration of the compound **7** in the range from 0.625 mM to 5.0 mM, suggesting that the 4-(2-hydroxyethyl)-1*H*-1,2,3-triazole side chain is included in the *β*-CD cavity in solution to form noncovalent inclusion complexes (species B or C, Figure 6). According to the X-ray crystal analysis (Figure 5), it is clearly that the triazole side chain can be embedded in the cavity of the adjacent molecule to form interinclusions (species C, Figure 6).

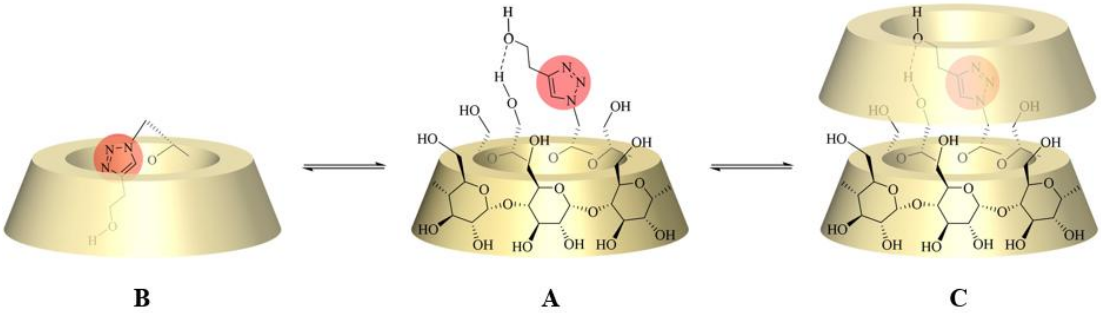


Figure 6. Schematic representations of **7** (A) and its inclusion complexes (B and C).

3 Conclusion

In summary, we successfully synthesized and characterized two monomer compounds of CDTOH, **4** and **7**. Due to the formation of an intramolecular hydrogen bond between the terminal hydroxy group of the side chain and glucose B of **7**, as indicated by the 2D ROESY spectrum and single crystal X-ray diffraction analysis; the chemical shifts of CH_2 of glucose B shift upfield. The 1,2,3-triazole group of **7** inserted into the hydrophobic cavity of the adjacent *β*-CD (interinclusion) from the second rim to form an interlocked helical columnar superstructure.

4 Experimental

4.1 General

Reagents and solvents were obtained from several commercial sources and used as received. Electrospray ionization high-resolution mass spectra (ESI-HRMS) were acquired using an APEX IV FT_MS (7.0 T) spectrometer (Bruker) operating in positive mode. NMR spectra were recorded on a Bruker DRX 400 or 600 spectrometer at ambient temperature. Reaction progress was monitored by thin-layer chromatography (TLC) on commercial silica gel plates (E. Merck 60 F_{254} on aluminum sheets, Germany) and visualized by spraying with a solution of 6% H_2SO_4 in ethanol, followed by heating.

β-CD derivatives **1-3** and **5** were synthesized by literature methods,[11] and the data were consistent with those previously published.

4.2 6^A-Deoxy-6^A-[4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl] per-*O*-methylated *β*-CD (4)

A solution of compound **3** (154 mg, 0.11 mmol) and 3-butyn-1-ol (11.2 mg, 0.16 mmol) in 1:1 CH_3OH-H_2O (4 mL), $CuSO_4$ (10 mg, 0.06 mmol) and sodium ascorbate (20 mg, 0.10 mmol) was added. After stirring at room temperature for 10 h, the crude product was extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and then filtered. The filtrate was evaporated and then purified by silica gel column chromatography (CH_2Cl_2/CH_3OH= 9:1) to obtain compound **4** (120 mg, 74%). R_f = 0.36 (eluent:CH_2Cl_2/CH_3OH = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 5.24 (d, *J* = 3.7 Hz, 1H), 5.17–5.11 (m, 5H), 5.09 (d, *J* = 3.6 Hz, 1H), 4.99 (dd, *J* = 14.3, 2.1 Hz, 1H), 4.62 (dd, *J* = 14.4, 7.3 Hz, 1H), 4.13–4.04 (m, 1H), 3.98–3.90 (m, 3H), 3.90–3.74 (m, 9H), 3.70–3.46 (m, 62H), 3.40 (s, 3H), 3.39 (s, 3H), 3.39 (s, 3H), 3.37 (s, 3H), 3.31 (s, 3H), 3.29 (s, 3H), 3.27–3.12 (m, 9H), 3.09 (dd, *J* = 9.8, 3.4 Hz, 1H), 2.94 (t, *J* = 5.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.15, 123.46, 99.40, 99.20, 98.95, 98.90, 98.87, 98.81, 98.26, 83.02, 82.10, 82.03, 81.97, 81.89, 81.86, 81.76, 81.74, 81.67, 81.13, 80.34, 80.25, 80.23, 80.13, 80.01, 79.20, 71.42, 71.41, 71.36, 71.30, 71.24, 71.01, 70.96, 70.85, 70.73, 70.67, 70.56, 61.65, 61.54, 61.39, 61.37, 61.31, 59.10, 59.09, 59.04, 59.02, 58.92, 58.78, 58.65, 58.54, 58.52, 58.49, 58.46, 51.36, 28.75; ESI-HRMS (m/z) $[M + H]^+$ calcd for $C_{66}H_{116}N_3O_{35}$, 1510.7384, found, 1510.7385.

4.3 6^A-Deoxy-6^A-[4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl] per-*O*-acetylated *β*-CD (6)

A solution of compound **5** (150.0 mg, 0.075 mmol) and 3-butyn-1-ol (6.7 mg, 0.097 mmol) in 1:1 CH_3OH-H_2O (4 mL), $CuSO_4$ (20 mg, 0.12 mmol) and sodium ascorbate (40 mg, 0.20 mmol) was added. After stirring at room temperature for 10 h, the crude product was extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and then filtered. The filtrate was evaporated and then purified by silica gel column chromatography (CH_2Cl_2/CH_3OH= 20:1) to obtain compound **6** (70 mg, 45%). R_f = 0.30 (eluent: ethyl acetate/CH_3OH = 20:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 (s, 1H), 5.53 (d, *J* = 3.9 Hz, 1H), 5.37–5.21 (m, 6H), 5.17 (t, *J* = 7.8 Hz, 1H), 5.15 (d, *J* = 3.9 Hz, 1H), 5.12–5.07 (m, 3H), 5.04 (d, *J* = 3.7 Hz, 1H), 5.03 (d, *J* = 3.8 Hz, 1H), 4.96 (d, *J* = 3.6 Hz, 1H), 4.91 (dd, *J* = 8.6, 4.0 Hz, 1H), 4.84–4.78 (m, 3H), 4.74 (dd, *J* = 7.4, 3.8 Hz, 1H), 4.72 (dd, *J* = 7.6, 3.6 Hz, 1H), 4.67 (br d, *J* = 12.5 Hz, 1H), 4.63 (dd, *J* = 14.8, 3.0 Hz, 1H), 4.59–4.51 (m, 4H), 4.49 (dd, *J* = 10.2, 3.6 Hz, 1H), 4.39 (br d, *J* = 11.6 Hz, 1H), 4.34–4.13 (m, 10H), 4.11 (br d, *J* = 9.5 Hz, 1H), 4.06 (m, 2H), 3.95–3.90 (m, 2H), 3.76–3.66 (m, 5H), 3.62 (t, *J* =

9.5 Hz, 1H), 3.57 (t, J = 9.0 Hz, 1H), 2.96–2.89 (m, 2H), 2.14–1.97 (m, 60H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 170.88, 170.76, 170.74, 170.71, 170.69, 170.61, 170.54, 170.50, 170.40, 170.30, 169.58, 169.42, 169.41, 169.38, 169.34, 169.31, 169.19, 145.32, 124.45, 97.07, 96.88, 96.76, 96.72, 96.50, 96.44, 77.49, 77.11, 76.85, 76.51, 76.36, 75.86, 71.60, 71.35, 71.30, 71.01, 70.85, 70.61, 70.35, 70.28, 70.22, 70.07, 70.01, 69.86, 69.67, 69.62, 69.57, 69.41, 69.27, 62.75, 62.66, 62.62, 62.59, 62.50, 62.21, 61.53, 49.32, 28.66, 20.88, 20.85, 20.83, 20.82, 20.81, 20.79, 20.75, 20.72, 20.70, 20.67, 20.65; ESI-HRMS (m/z) $[M + H]^+$ calcd for $C_{86}H_{116}N_3O_{55}$, 2070.6367, found, 2070.6348.

4.4 6^A-Deoxy-6^A-[4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl] *β*-CD (7)

To a solution of compound **6** (62 mg, 0.030 mmol) in dry MeOH (3 mL) was added 30% NaOMe (100 μL), and the solution was stirred for 2 h at room temperature. After neutralization with an Amberlite® IR 120-H ion exchange resin, the solvent was evaporated by an oil pump to afford compound **7** (37 mg, 100%). ^{1}H NMR (600 MHz, D_2O): δ 7.88 (s, 1H), 5.19 (d, J = 3.7 Hz, 1H), 5.13–5.06 (m, 4H), 5.04–4.98 (m, 3H), 4.60 (dd, J = 14.6, 9.5 Hz, 1H), 4.20 (t, J = 9.6 Hz, 1H), 4.08–3.81 (m, 24H), 3.78 (dd, J = 12.0, 4.1 Hz, 1H), 3.71 (dd, J = 10.1, 3.8 Hz, 1H), 3.70–3.50 (m, 13H), 3.19 (br d, J = 12.3 Hz, 1H), 2.97 (t, J = 6.5 Hz, 2H), 2.83 (br d, J = 11.9 Hz, 1H); ^{13}C NMR (151 MHz, D_2O): δ 125.29, 102.07, 101.93, 101.86, 101.83, 101.44, 83.16, 81.27, 81.09, 81.04, 80.65, 73.06, 73.02, 73.00, 72.79, 72.04, 72.02, 71.95, 71.89, 71.82, 71.80, 71.77, 71.69, 71.41, 70.70, 60.50, 60.31, 60.19, 60.12, 58.98, 51.12, 27.78; ESI-HRMS (m/z) $[M + H]^+$ calcd for $C_{46}H_{76}N_3O_{35}$, 1230.4254, found, 1230.4271.

4.5 X-ray diffraction of 7

A concentrated solution of **7** in water at room temperature was allowed to cool to 4 °C, and rod-shaped crystals were obtained after 3 days. Single-crystal data were collected on a XtaLAB Synergy R HyPix diffractometer. The crystal was kept at 100.00 (10) K during data collection. Using Olex2,[14] the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package using least squares minimization.[15] Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no 2123295.

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Appendix A. Supplementary data

Full crystallographic details have been deposited with the Cambridge Crystallographic Data Center. These data may be obtained on request from The Director, CCDC, 12 Road, Cambridge CB2 1EZ, UK (Tel.: +44-1223-336408; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk.1 or www: http://www.ccdc.cam.ac.uk). The other supplementary data related to this article can be found online at

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