Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Cyclodextrin-adamantane conjugates, self-inclusion and aggregation versus supramolecular polymer formation

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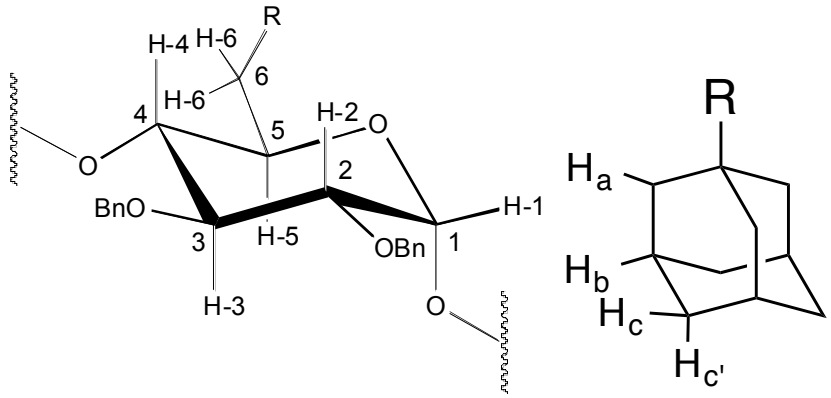
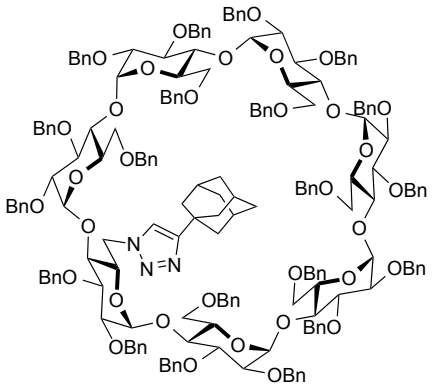
General Information

Dichloromethane was freshly distilled from P_2O_5, THF from sodium/benzophenone, pyridine from CaH_2. DMF was dried over molecular sieves. Reactants were purchased from commercial sources and used without further purification. HRMS were recorded on a Bruker micrOTOF spectrometer, using Agilent ESI-L Low Concentration Tuning-Mix as reference. Optical rotations were measured on a Perkin–Elmer 341 digital polarimeter or a Jasco P-2000 polarimeter with a path length of 1 dm. NMR spectra were recorded on a Bruker Avance II 600 MHz or Brüker AM-400 MHz using residual solvant signal as internal reference. Assignments were aided by COSY, HSQC, NOESY, ROESY, TOCSY, J-Res and HMBC experiments.



2,3,6-*O*-perbenzyl-6-monodeoxy-6-mono(4-adamantyl-*1H*-1,2,3-triazol-1-yl)-β-cyclodextrin 3



The azido- β-CD **2**[1] (200 mg, 67 mmol) and alkyne adamantane (11 mg, 67 mmol) were dissolved in anhydrous DMF (1.7 mL) under nitrogen in a microwave vial. Then DIPEA (35 mg, 268 mmol), TBTA (14 mg, 27 mmol) and $Cu(CH_3CN)_4PF_6$ (10 mg, 27 mmol) were added successively. The reaction mixture was purged with nitrogen and was heated at 150 °C under microwaves for 1 h. The solvent was evaporated and after purification by silica gel chromatography (cyclohexane/EtOAc 9:1) to give **3** (181 mg, 86%).

R_f 0.55 (cyclohexane/EtOAc 3:1)

$[\alpha]_D^{20}$ +35.5 (*c* 0.5, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.06 (m, 101H, 100xH arom., 1xH triaz.), 5.51 (d, 1H, $^3J_{1,2}$ 3.6 Hz, H-1), 5.24 (d, 1H, $^3J_{1,2}$ 3.6 Hz, H-1), 5.23 (d, 1H, $^3J_{1,2}$ 3.1 Hz, H-1), 5.21 (d, 1H, $^3J_{1,2}$ 3.3 Hz, H-1), 5.20 (d, 1H, $^3J_{1,2}$ 2.7 Hz, H-1), 5.19 (d, 1H, $^3J_{1,2}$ 2.7 Hz, H-1), 5.16 (d, 1H, $^3J_{1,2}$ 3.5 Hz, H-1), 5.10 (d, 1H, ^2J 11.1 Hz, CHPh), 5.09 (d, 1H, ^2J 12.2 Hz, CHPh), 5.06 (d, 1H, ^2J 12.5 Hz, CHPh), 5.03 (d, 1H, ^2J 11.9 Hz, CHPh), 4.98 (d, 1H, ^2J 11.2 Hz, CHPh), 4.95 (d, 1H, ^2J 10.8 Hz, CHPh), 4.83-4.73 (m, 7H, 6xCHPh, H-6), 4.66 (d, 1H, ^2J 10.7 Hz, CHPh), 4.60-4.37 (m, 28H, H-6, 27xCHPh), 4.21 (m, 1H, H-5), 4.15-3.90 (m, 25H, 6xH-5, 7xH-4, 5xH-6, 7xH-3), 3.84 (d, 1H, ^2J 10.7 Hz, H-6), 3.66-3.40 (m, 12H, 6xH-6, 6xH-2), 3.30 (dd, 1H, $^3J_{1,2}$ 3.5 Hz, $^3J_{2,3}$ 9.5 Hz, H-2), 2.03 (bs, 3H, CH^b-Ad), 1.93 (bs, 6H, CH_2^a-Ad), 1.77 (d, 3H, *J* 12.5 Hz, CH_2^c-Ad), 1.72 (d, 3H, *J* 12.5 Hz, $CH_2^{c'}$-Ad).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.26 (C triaz. quat.), 139.40, 139.35, 139.34, 139.22, 139.12, 138.94, 138.50, 138.47, 138.40, 138.30, 138.17 (20xC arom. quat.), 128.48-126.97 (m, 100xCH arom.), 120.86 (CH triaz.), 98.82, 98.65, 98.56, 98.42 (2C), 98.32, 97.95 (7xC-1), 81.18, 81.08, 81.04, 80.95, 80.90, 80.55, 80.32, 79.25, 79.03, 78.99, 78.94, 78.86, 78.72, 78.52, 78.36 (21C, 7xC-2, 14xC-3 or C-4), 75.68,

75.63, 75.51, 75.33, 75.29, 73.57, 73.50, 73.43, 73.41, 73.37, 73.33, 72.84, 72.80, 72.76, 72.67, 72.65 (20xCH_2Ph), 72.07, 71.66 (2C), 71.59 (2C), 71.45, 70.34 (7xC-5), 69.60, 69.52, 69.47, 69.39 (3C), 50.70 (7xC-6), 42.73 (3xCH_2^a-Ad), 36.81 (3xCH_2^c-Ad), 32.66 (C^{IV}-Ad), 28.56 (3xCH^b-Ad).

HRMS (ESI): Calcd. For $C_{194}H_{205}O_{34}N_3Na$ $[M+Na]^+$: 3143.4297; Found: 3143.4479

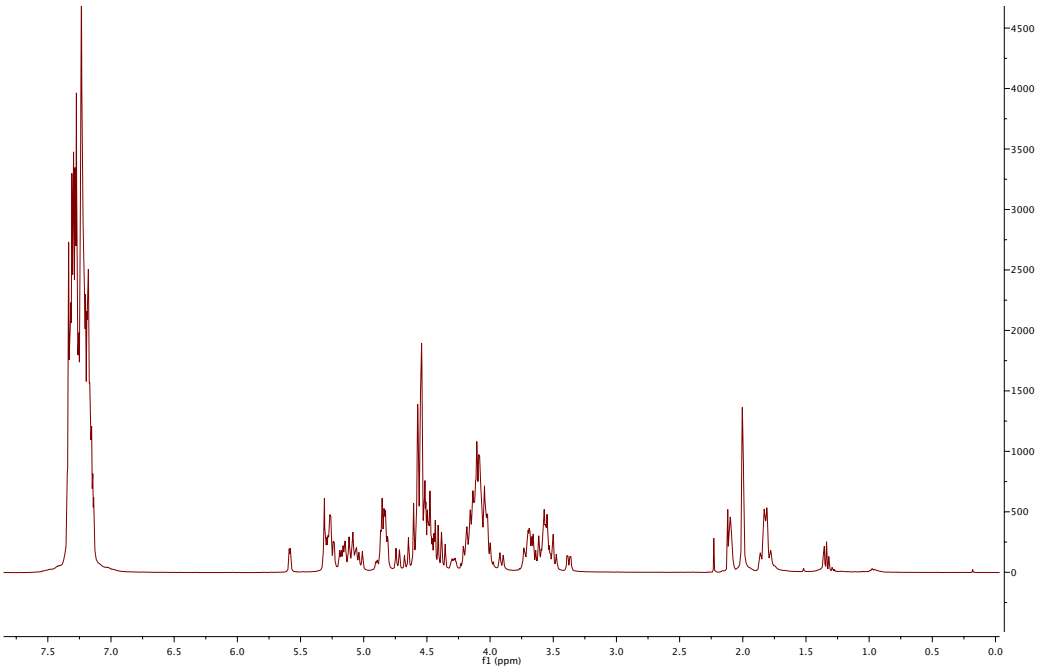


Figure SI1. ^{1}H-NMR of CD **3** (400 MHz, $CDCl_3$, 300K)

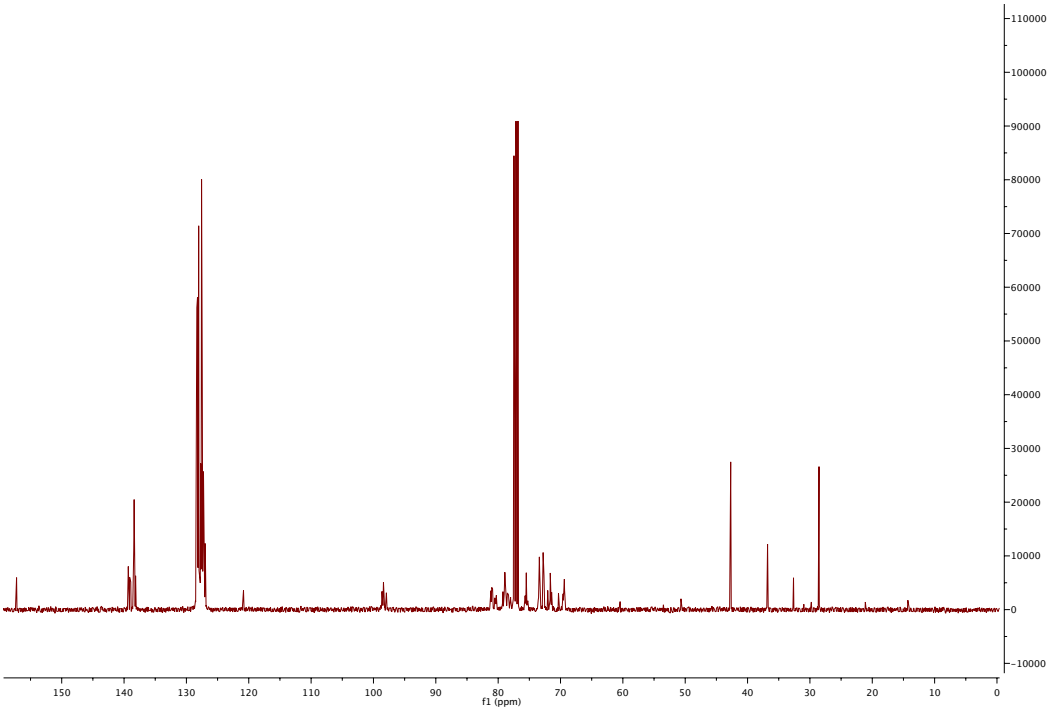
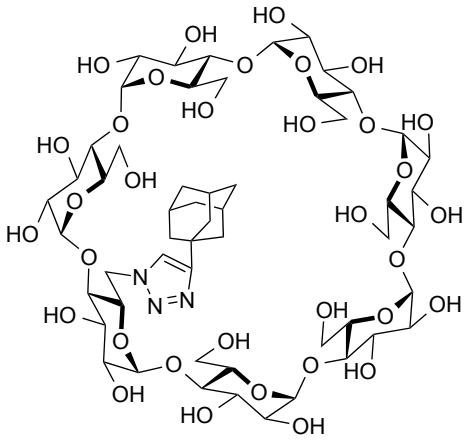


Figure SI2. ^{13}C-NMR of CD **3** (100 MHz, $CDCl_3$, 300K)

6-monodeoxy-6-mono(4-adamantyl-*1H*-1,2,3-triazol-1-yl)-β-cyclodextrin 4



Chemical Formula: $C_{54}H_{85}N_3O_{34}$
Exact Mass: 1319,50145

Perbenzylated CD **3** (181 mg, 57 mmol) were dissolved in THF/MeOH/H_2O (28 mL, 10:4:1) under nitrogen. $Pd(OH)_2/C$ (181 mg) was added and the reaction mixture was stirred under an H_2 atmosphere for 12 h. Then, the mixture was filtered through a Celite® pad and was washed with MeOH/H_2O. The solvents were evaporated and the residue was in suspension in water and was freeze dried. CD **4** (55 mg, 72%)was obtained as a white amorphous powder.

$[\alpha]_D^{20}$ -74.5 (*c* 0.2, DMSO)

^{1}H NMR (DMSO+D_2O, 600 MHz): δ 7.84 (bs, 1H, H triaz.), 4.95 (bs, 1H, H-1), 4.83-4.75 (m, 7H, 6xH-1, H-6), 3.70-3.24 (m, 41H, 7xH-2, 7xH-3, 7xH-4, 7xH-5, 13xH-6), 2.06 (bs, 3H, CH^b-Ad), 1.87-1.67 (m, 12H, 6xCH_2^a-Ad, 6xCH_2^c-Ad).

^{13}C NMR (DMSO+D_2O, 150 MHz): δ 157.45 (C triaz. quat.), 121.10 (CH triaz.), 102.67 (3C), 102.43 (3C), 100.07 (7xC-1), 81.76 (C-2), 73.42-72.16 (m, 27C, 7xC-5, 7xC-4, 7xC-3, 6xC-2), 60.14 (6xC-6), 51.05 (C-6), 42.50 (3xCH_2^c-Ad), 36.67 (3xCH_2^a-Ad), 32.58 (C^{IV}-Ad), 28.07 (3xCH^b-Ad).

HRMS (ESI): Calcd. for $C_{54}H_{85}N_3O_{34}Na$ $[M+Na]^+$: 1342.4907; Found: 1342.4948.

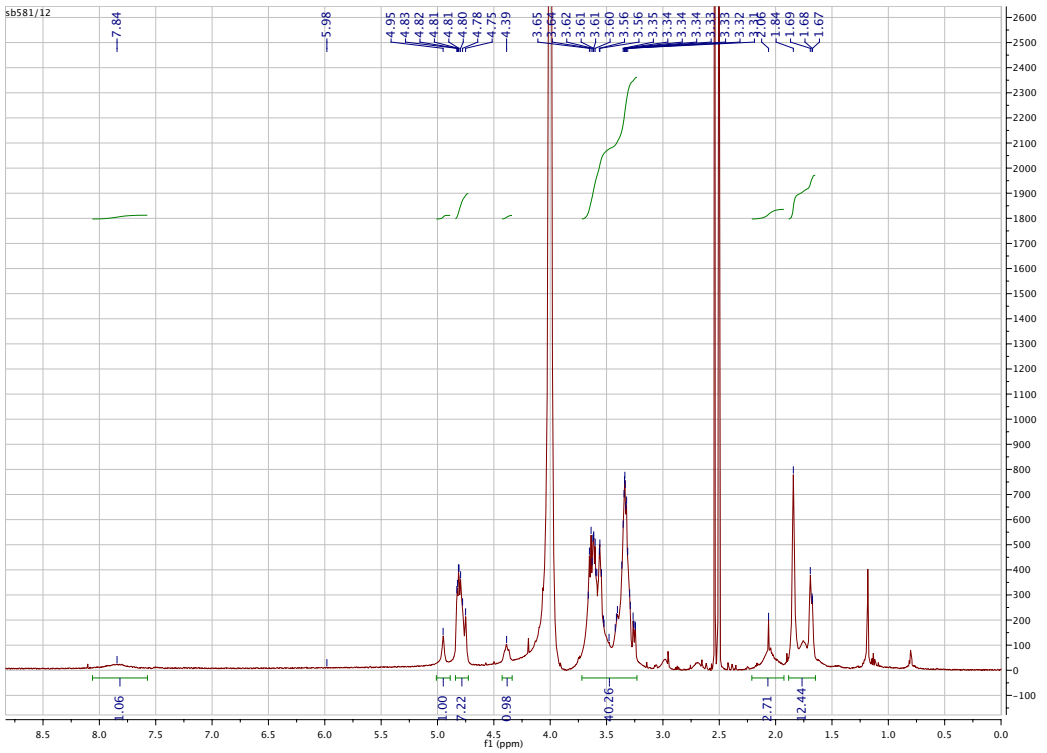


Figure SI3. ^{1}H-NMR of CD **4** (600 MHz, DMSO + D_2O, 300K)

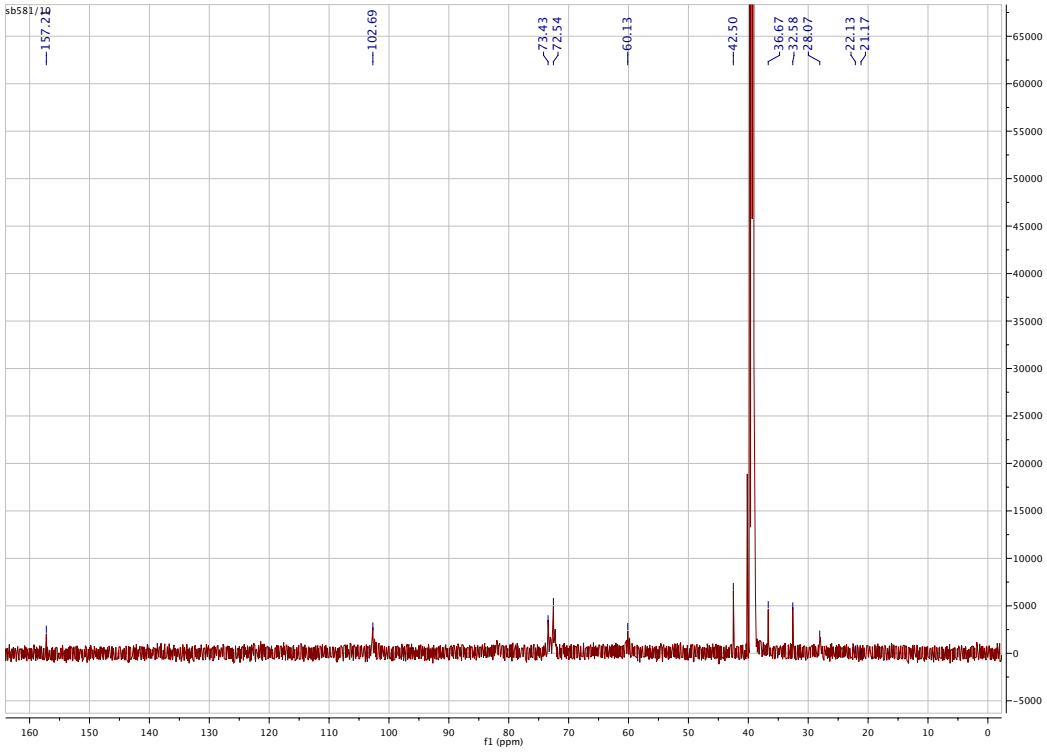
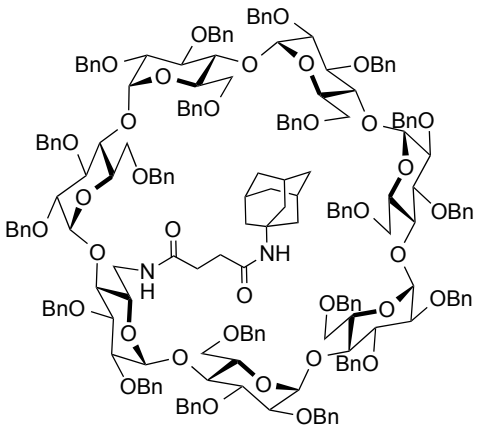


Figure SI4. ^{13}C-NMR of CD **4** (150 MHz, DMSO + D_2O, 300K)

2,3,6-*O*-perbenzyl-6-monodeoxy-6-*N*-(*N*-Adamantylamide)-Succinamide-β-cyclodextrin 7



Chemical Formula: $C_{196}H_{210}N_2O_{36}$
Exact Mass: 3167,47

Acid **6** (128 mg, 0.51 mmol), HOBt (76 mg, 0.56 mmol) and EDC.HCl (108 mg, 0.56 mmol) were dissolved in DMF (20 ml) and the suspension was stirred for 15 min. The solution of **amino-CD 5**[1] (1.5 g, 0.51 mmol) in DMF (20 ml) and DIPEA (120 µl, 0.69 mmol) were added. After stirring for 22 hours at room temperature, water (100 ml) was added into the reaction solution. The product was extracted with EtOAc (3x100 ml). The organic fraction was washed with water and brine solution, was dried on $MgSO_4$ and then concentrated. The residue was purified by flash chromatography using eluent Cyclohexane/EtOAc : 65/35 to give CD **7** (907 mg, 56 %).

R_f 0.30 (Cyclohexane/EtOAc : 65/35)

$[\alpha]_D^{20}$ +43 (*c* 1.0, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 600 MHz, 300K): δ 7.27-7.06 (m, 100H, 100xH arom.), 6.02 (bs, 1H, NH), 5.48 (s, 1H, NH), 5.31 (d, $^3J_{1,2}$ 3.7 Hz, 1H, H-1), 5.24 (s, 1H, H-1), 5.17 (m, 2H, 2xH-1), 5.14 (d, $^3J_{1,2}$ 3.4 Hz, 1H, H-1), 5.12 (d, $^3J_{1,2}$ 3.4 Hz, 1H, H-1), 5.07 (m, 4H, H-1, 3xCHPh), 5.00 (d, ^2J 11.0 Hz, 1H, CHPh), 4.98 (d, ^2J 11.4 Hz, 1H, CHPh), 4.93 (d, ^2J 9.6 Hz, 1H, CHPh), 4.82 (d, ^2J 10.9 Hz, 1H, CHPh), 4.77-4.32 (m, 33H, 33xCHPh), 4.05-3.91 (m, 26H, 7xH-3, 6xH-4, 7xH-5, 6xH-6), 3.72 (d, ^2J 10.3 Hz, 2H, 2xH-6), 3.57-3.42 (m, 13H, 6xH-2, H-4, 6xH-6), 3.36 (dd, $^3J_{2,3}$ 9.1 Hz, $^3J_{1,2}$ 3.5 Hz, 1H, H-2), 2.30 (m, 2H, CH_2), 2.23 (m, 2H, CH_2), 1.98 (s, 3H, 3xH-b Ad), 1.92 (s, 6H, 6xH-a Ad), 1.59 (s, 6H, 6xH-c Ad).

^{13}C-NMR ($CDCl_3$, 150 MHz, 300K): δ 172.18, 171.03 (2xN-C=O), 139.52-138.30 (20xC arom. quat.), 128.45-126.95 (100xCH arom.), 98.74 (2xC-1), 98.80, 98.49, 98.42, 98.25, 98.05 (5xC-1), 81.13-78.36 (21C, 7xC-2, 7xC-3, 7xC-4), 75.71-72.59 (20xCH_2Ph), 72.12, 71.68, 71.66 (3xC-5), 71.59 (3xC-5), 70.63 (C-5), 69.51, 69.40

(2xC-6), 69.34 (3xC-6), 68.91 (C-6), 51.87 (C Ad quat.), 41.71 (3xCH_2-a Ad), 40.16 (C-6), 36.44 (3xCH_2-c Ad), 32.90, 31.84 (2xCH_2), 29.50 (3xCH-b Ad).

HRMS (ESI): Calcd. for $C_{196}H_{210}N_2O_{36}Na$ $[M+Na]^+$: 3192.4556; Found: 3192.4852.

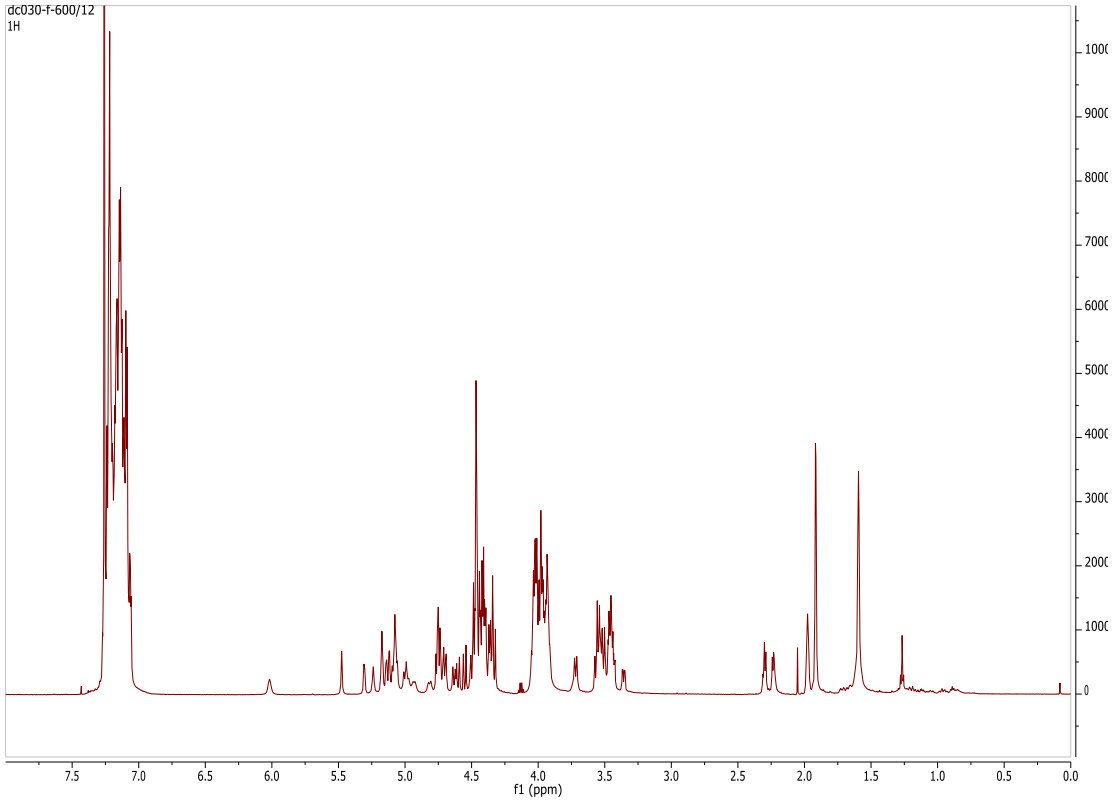


Figure SI5. ^{1}H-NMR of CD **7** (600 MHz, $CDCl_3$, 300K)

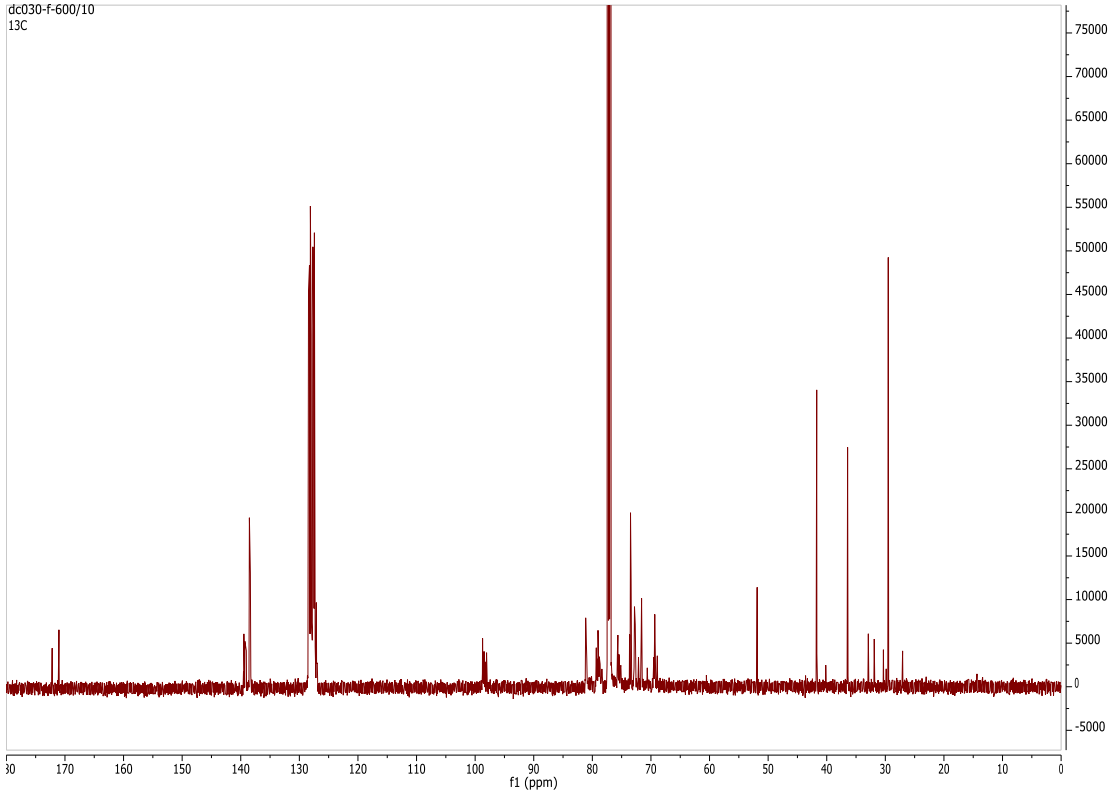
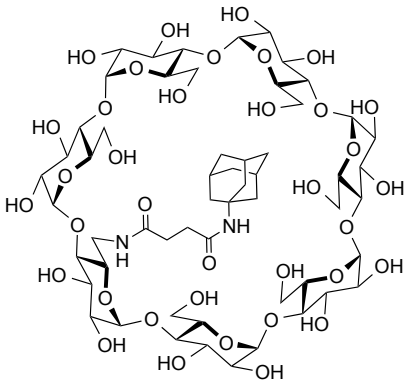


Figure SI6. ^{13}C-NMR of CD **7** (150 MHz, $CDCl_3$, 300K)

6^A-Deoxy-6^A-*N*-(*N*-Adamantylamide)-Succinamide-β-cyclodextrin 8



Chemical Formula: $C_{56}H_{90}N_2O_{36}$
Exact Mass: 1366,53

The compound **7** (400 mg, 0.29 mmol) was dissolved in THF/MeOH/H_2O (10/4/1, 120 ml). $Pd(OH)_2/C$ (400 mg) was added. The reaction mixture was stirred under hydrogen atmosphere overnight. The palladium was filtered on a Celite® pad and the residue was washed with MeOH/H_2O (1/1, 3x100 ml). The filtrate was filtered on μ-filter (250 μm), and then was evaporated. The residue was dissolved in water and was freeze dried to give CD **8** (140 mg, 81 %).

$[\alpha]_D^{20}$ +82.2 (*c* 0.1, H_2O)

^{1}H-NMR (D_2O, 600 MHz, 298K): δ 5.17 (d, $^3J_{1,2}$ 3.6 Hz, 1H, H-1X), 5.11 (d, $^3J_{1,2}$ 3.7 Hz, 1H, H-1), 5.10 (d, $^3J_{1,2}$ 3.8 Hz, 1H, H-1), 5.09 (d, $^3J_{1,2}$ 3.6 Hz, 1H, H-1), 5.08 (d, $^3J_{1,2}$ 4.2 Hz, 1H, H-1), 5.07 (d, $^3J_{1,2}$ 4.2 Hz, 1H, H-1), 5.06 (d, $^3J_{1,2}$ 3.6 Hz, 1H, H-1A), 4.33 (ddd, $^3J_{4,5}$ 10.1 Hz, $^3J_{5,6a}$ 4.0 Hz, $^3J_{5,6b}$ 2.2 Hz, 1H, H-5X), 4.26 (dd, $^2J_{6a,6b}$ 14.6 Hz, $^3J_{5,6a}$ 1.6 Hz, 1H, H-6aA), 4.06-3.82 (m, 21H, 12xH-6, 9x(H-3, H-5)), 3.77 (dd, $^3J_{2,3}$ 10.1 Hz, $^3J_{3,4}$ 8.7 Hz, 1H, H-3A), 3.72 (dd, $^3J_{2,3}$ 10.2 Hz, $^3J_{1,2}$ 3.6 Hz, 1H, H-2X), 3.71 (dd, $^3J_{4,5}$ 10.2 Hz, $^3J_{5,6b}$ 8.4 Hz, 1H, H-5A), 3.69-3.57 (m, 14H, 6H-4, 6H-2, 2x(H-3, H-5)), 3.46 (dd, $^3J_{4,5}$ 10.2 Hz, $^3J_{3,4}$ 8.7 Hz, 1H, H-4A), 2.90 (dd, $^2J_{6a,6b}$ 14.4 Hz, $^3J_{5,6b}$ 8.4 Hz, 1H, H-6bA), 2.61-2.55 (m, 2H, CH-a, CH-b), 2.48 (m, 1H, CH-a), 2.24 (s, 3H, 3xH-b Ad), 2.18 (m, 1H, CH-b), 1.97 (s, 6H, 6xH-a Ad), 1.91 (d, $^2J_{c,c'}$ 12.0 Hz, 3H, 3xH-c'Ad), 1.76 (d, $^2J_{c,c'}$ 12.0 Hz, 3H, 3xH-c Ad).

^{13}C-NMR (D_2O, 150 MHz, 298K): δ 173.93, 173.54 (2xN-C=O), 102.53, 102.45, 102.38, 102.33, 102.18 (2C), 101.55 (7xC-1), 83.39 (C-4A), 81.80, 81.56, 81.40, 81.38, 80.96, 80.50 (6xC-4), 74.53 (C-5A), 74.09 (C-3A), 73.39 (2C), 73.31, 73.27, 73.06 (2C), 72.43, 72.36, 72.31, 72.24, 72.18, 71.98, 71.96, 71.94 (3C), 71.79, 71.74 (6xC-3, 5xC-5, 7xC-2), 71.61 (C-5), 60.46, 60.35, 60.04, 60.00, 59.92, 59.82 (6xC-6), 52.15 (C Ad quat.), 42.07 (3xCH_2-a Ad), 40.15 (C-6A), 35.62 (3xCH_2-c Ad), 32.98 (CH_2b), 32.40 (CH_2a), 28.97 (3xCH-b Ad).

HRMS (ESI): Calcd. For $C_{56}H_{90}O_{36}N_2Na$ $[M+Na]^+$: 1389.5165; Found: 1389.5292

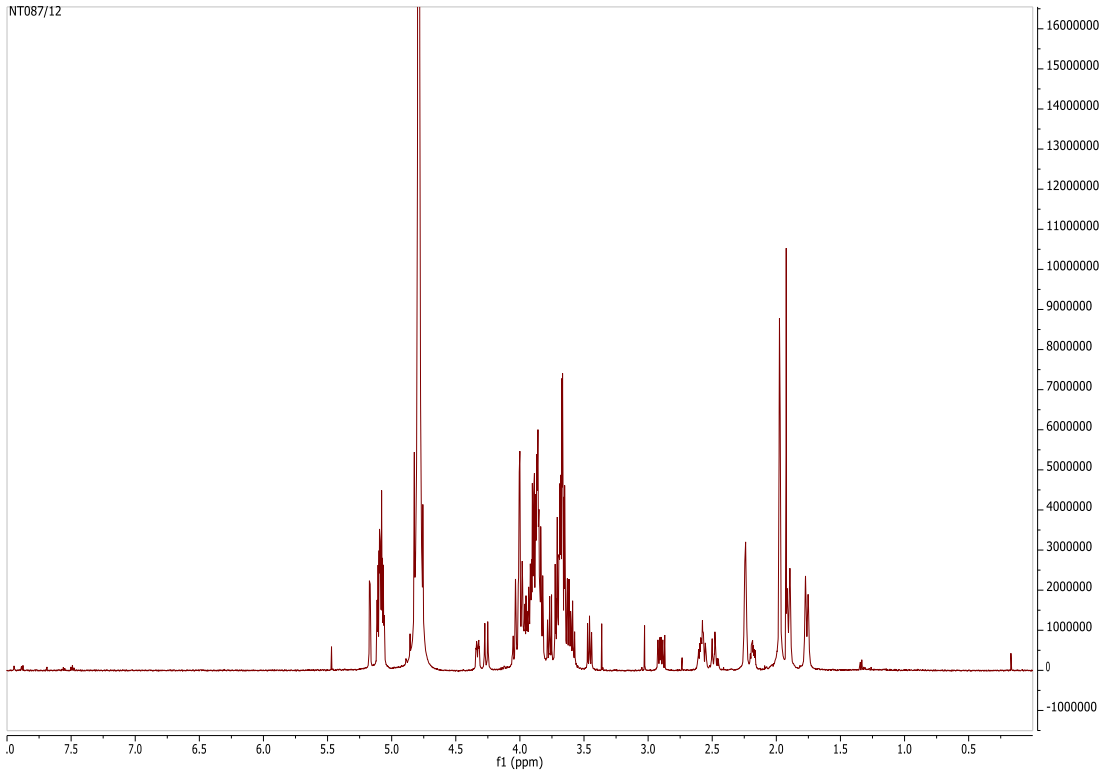


Figure SI7. ^{1}H-NMR of CD **8** (600 MHz, D_2O, 298K)

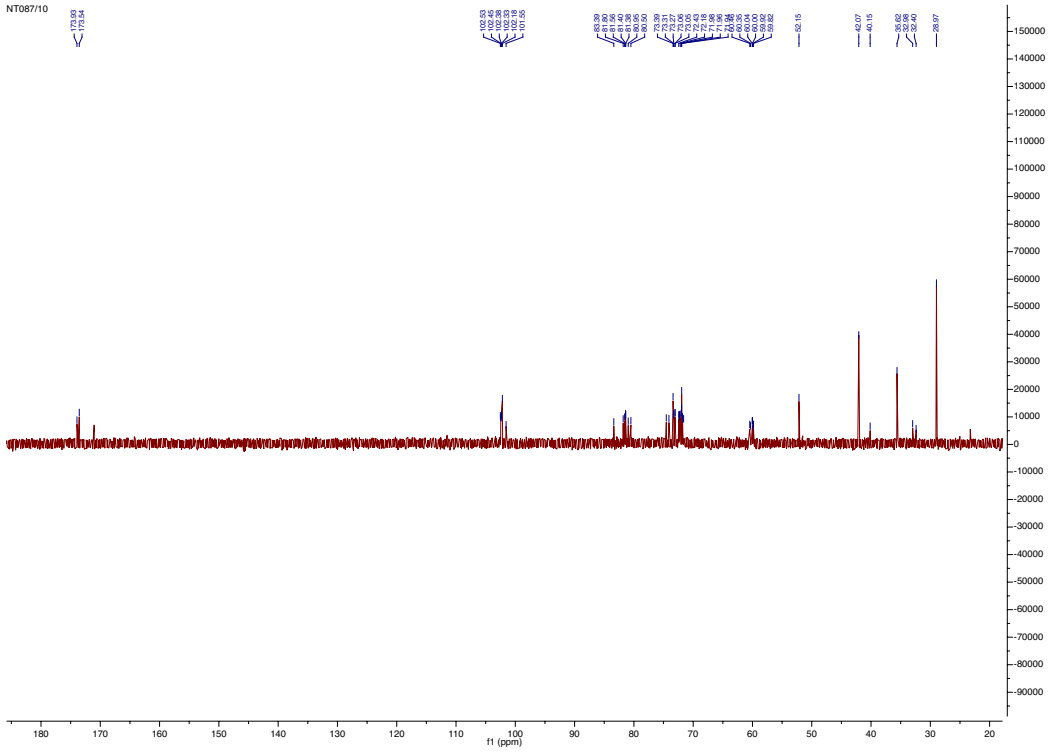


Figure SI8. ^{13}C-NMR of CD **8** (150 MHz, D_2O, 298K)

Identification of H-3s and H-5s in CD **8**

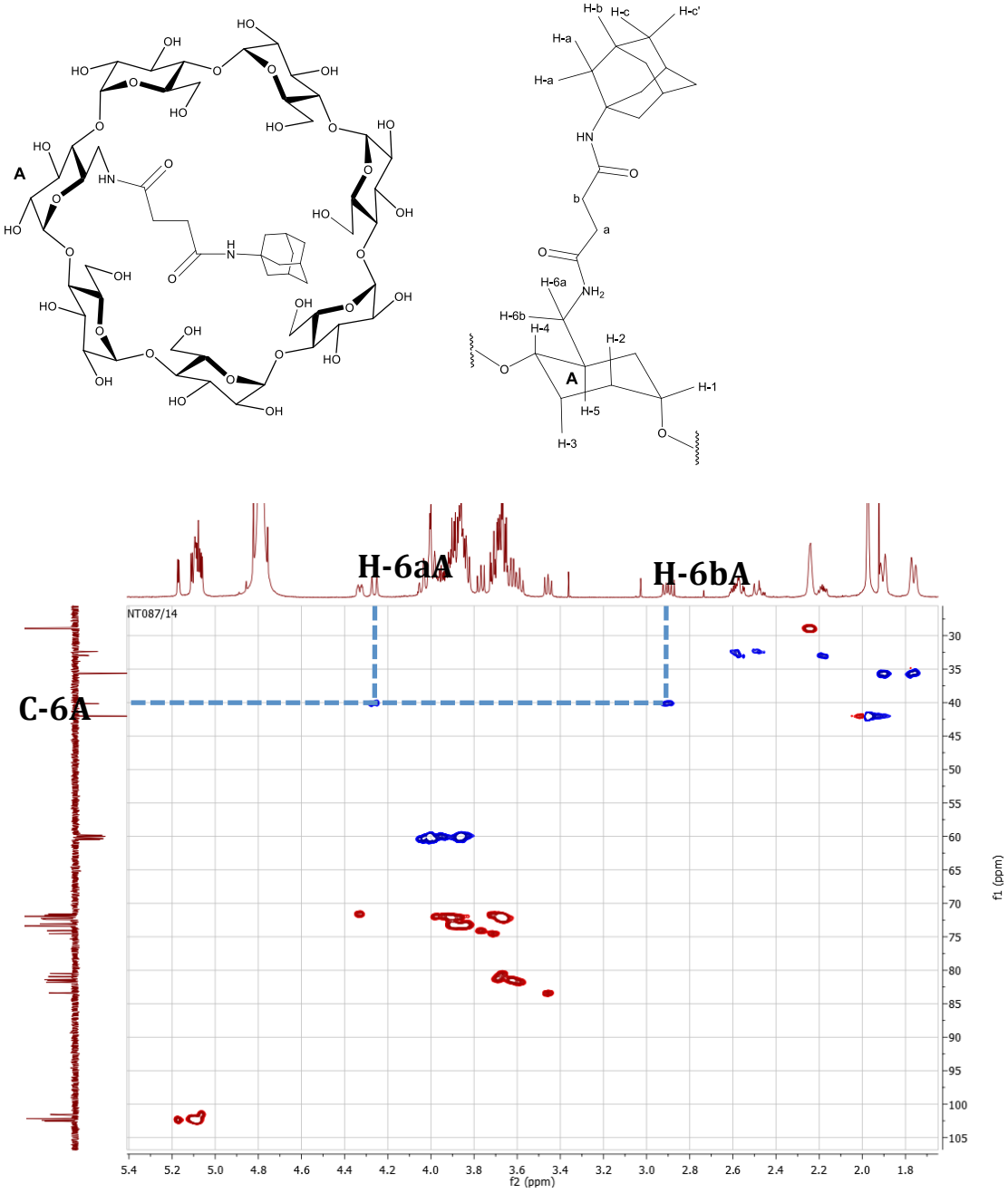


Figure SI9. HSQC : cross-correlations between C-6A and H-6aA, H-6bA

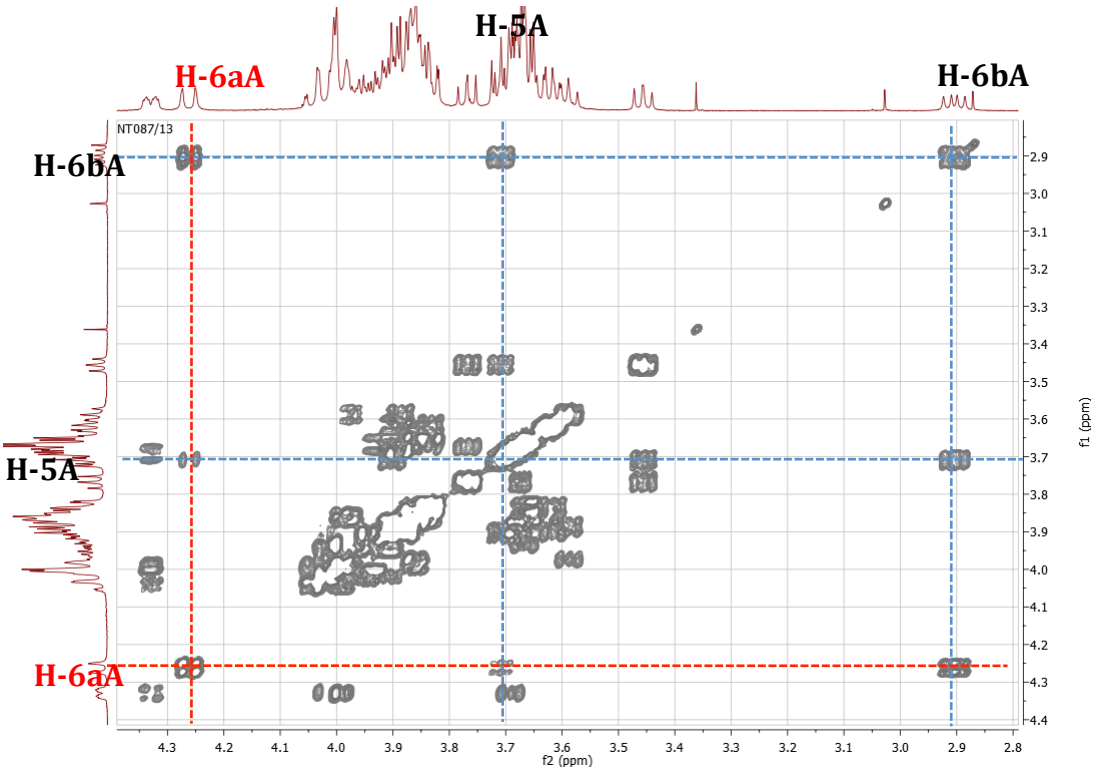


Figure SI10. COSY : cross-correlations between H-6aA and H-5A, H-6bA and H-5A

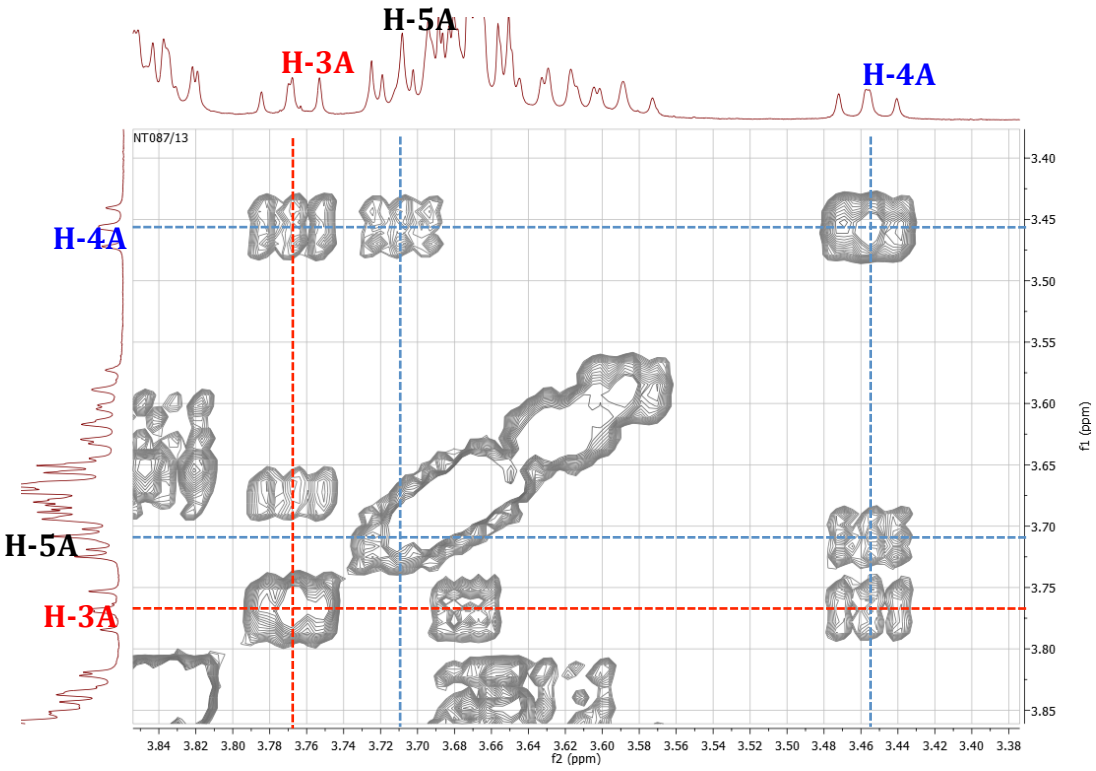


Figure SI11. COSY : cross-correlations between H-5A and H-4A, H-4A and H-3A

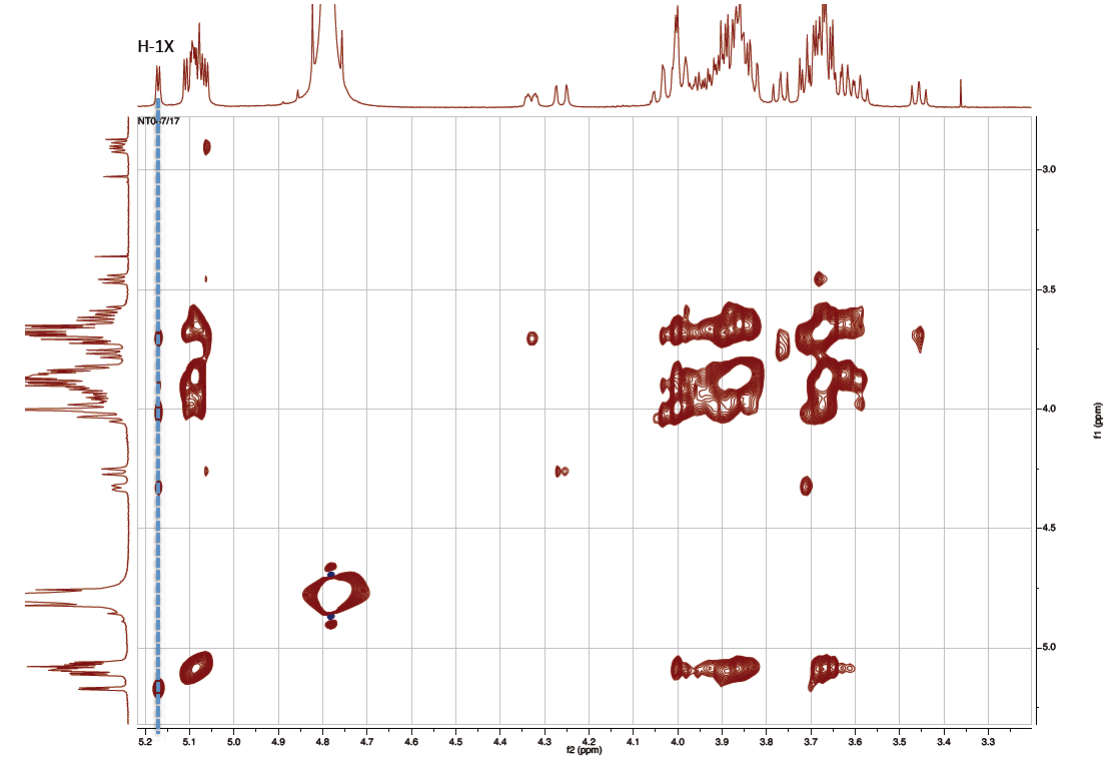


Figure SI12. TOCSY (240ms) protons on cycle X.

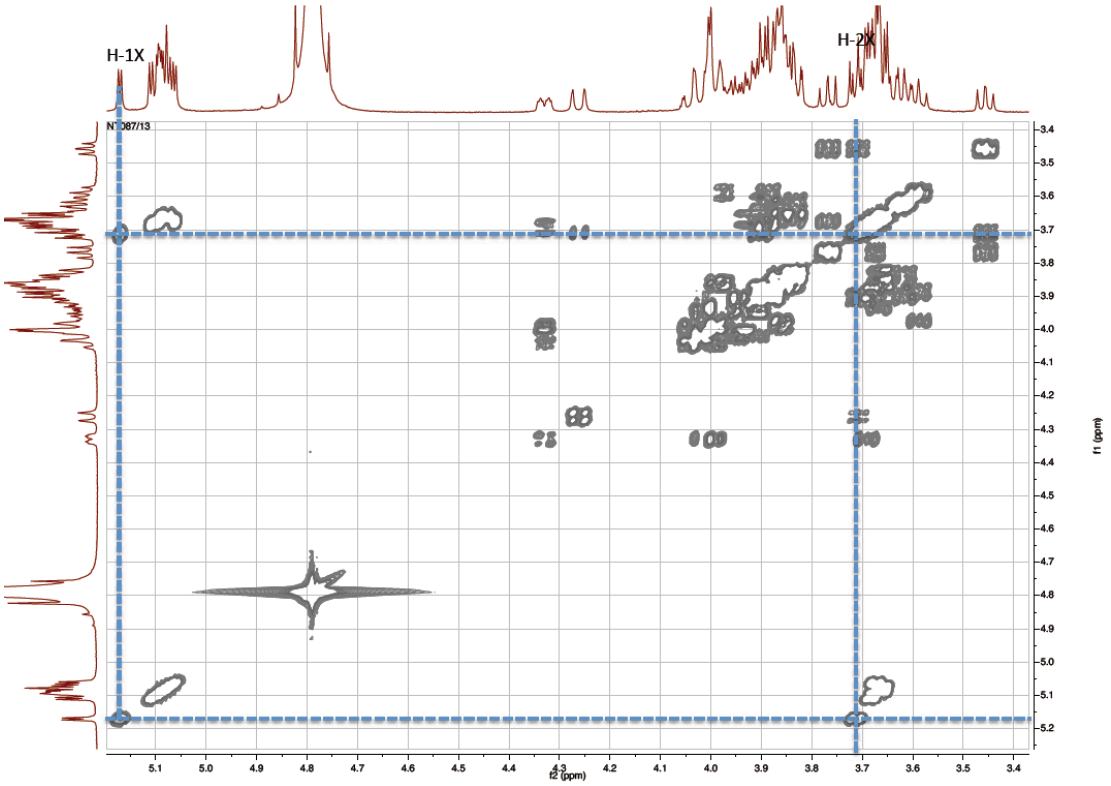


Figure SI13. COSY : cross-correlation between H-1X and H-2X

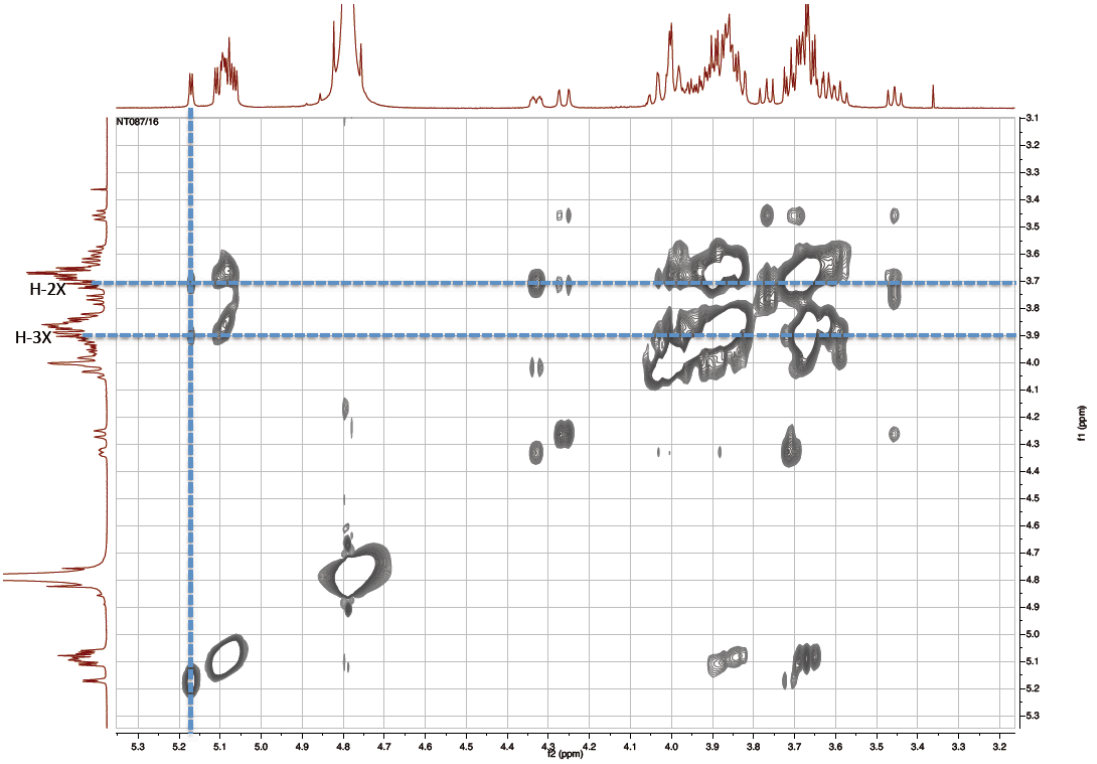


Figure SI14. TOCSY (60ms) cross correlations between H1X and H-2X and H-3X. H-3X is deduced by elimination as we have already assigned H-2X.

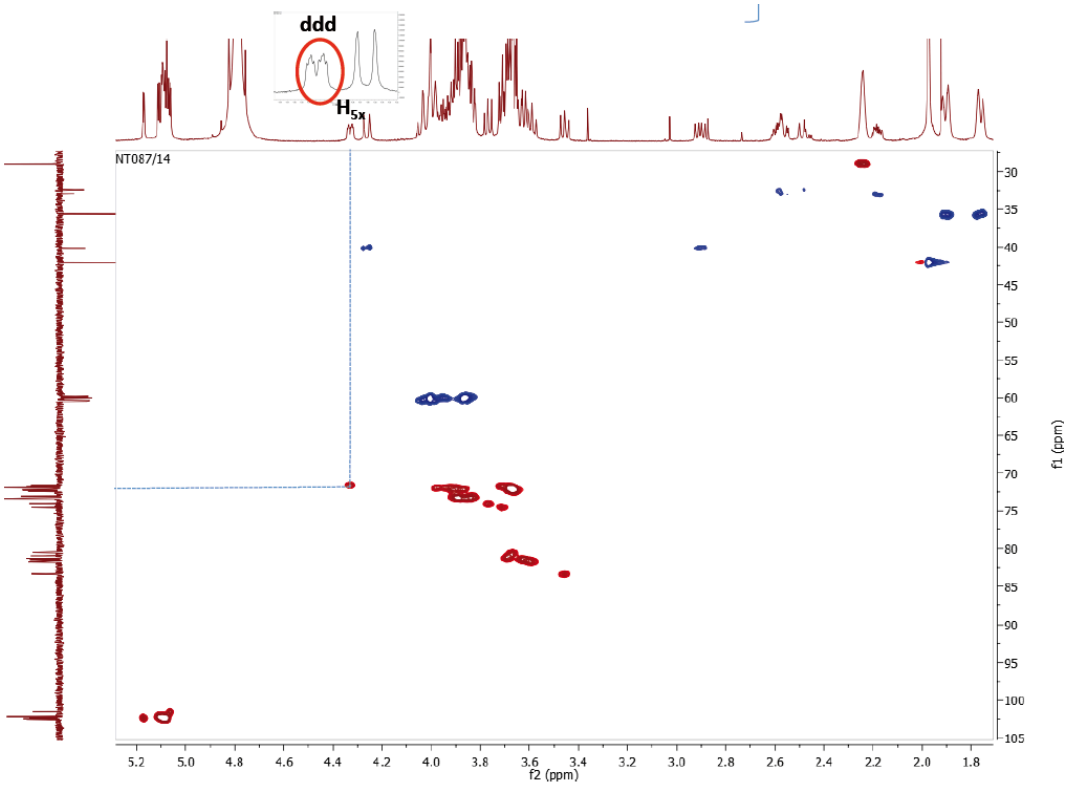


Figure SI15. HSQC : the proton at 4.33ppm is not an H-6.

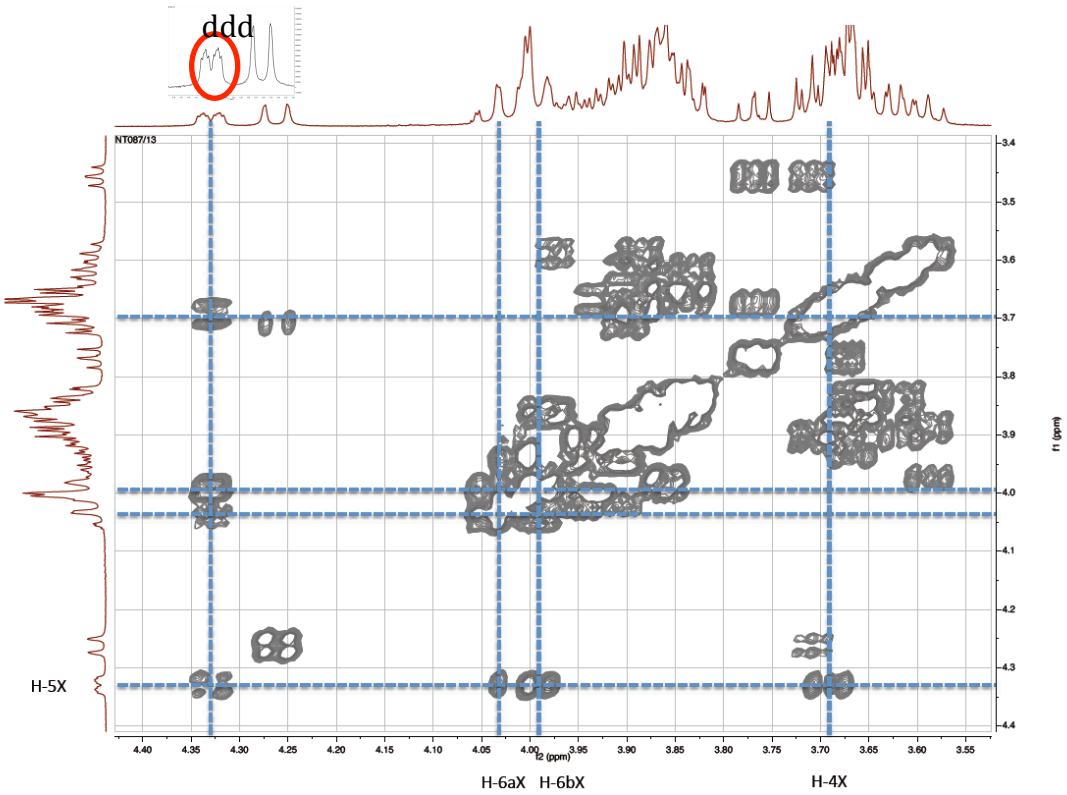


Figure SI16. COSY : cross-correlations between proton at 4.33ppm and 3 other protons. We deduce that this proton is H-5X, correlating with H-6aX (4.03ppm), H-6bX (3.99ppm) and H-4X (3.69ppm), hence the ddd shape.

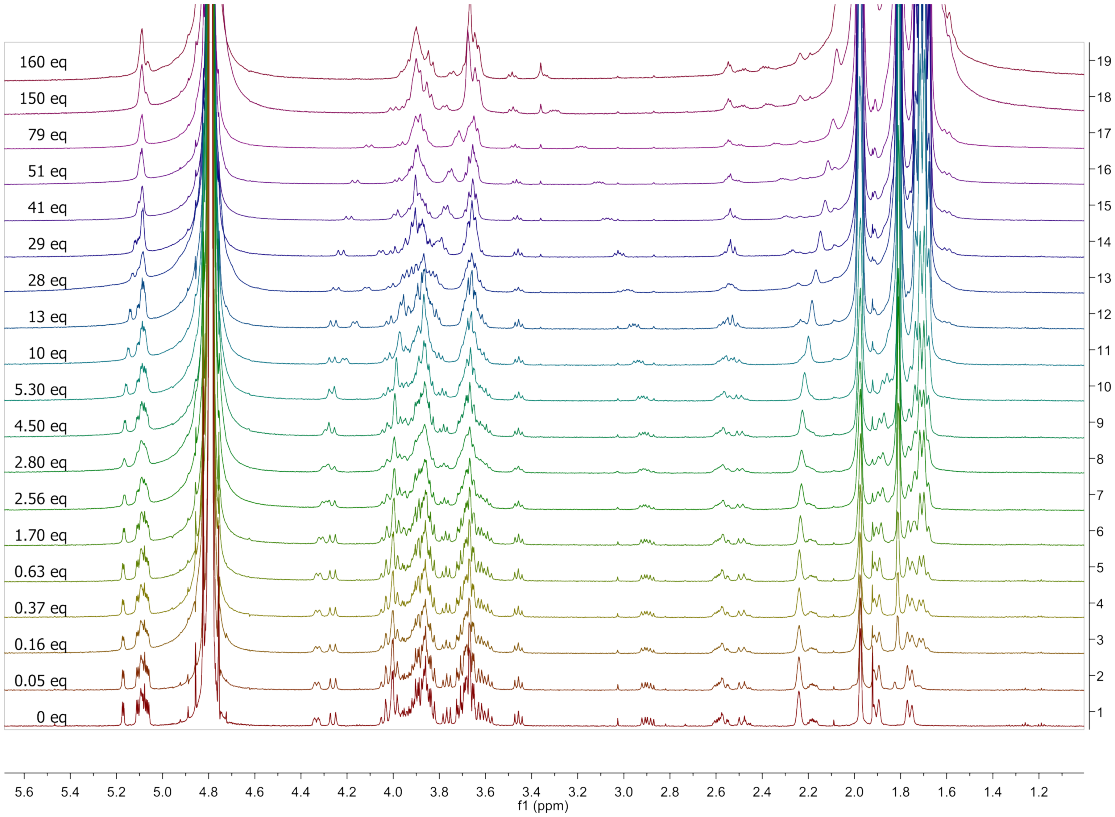


Figure SI17. ^{1}H NMR spectra of successive additions of AdaCOONa to a 5mM solution of CD **8** in D_2O.

Isothermal Titration Calorimetry (ITC) Measurements were carried at 20°C with a VP-ITC instrument from Microcal Inc.. The sample cell (V_c=1.4mL) was initially filled with NaN_3 (10g/L) aqueous solution, while a CD-adamantyl **8** solution (2.5mM) in NaN_3 (10g/L) aqueous solution was introduced into a 300µL syringe. The dilution was carried out by a step-by-step injection of the CD solution (10µL aliquots) into the sample cell and under continuous stirring (260 rpm). As a reference experiment, an equimolar mixture of β-CD and adamantyl derivative **6** solution (2.5mM each) in NaN_3 (10g/L) was diluted into the cell, in the same conditions. The results were analyzed using the "Origin for ITC" software supplied with VP-iTC Microcalorimeter and fitted according to reference 2.

Viscometry. Measurements were performed with Cannon-Manning semi-microcapillary viscometers. The capillary was set at 20°C and flow time was measured for a 20° tilt angle. Measurements were performed for CD-adamantyl **8** solution (5mM) in NaN_3 (10g/L) and compared to a blank solution of NaN_3 (10g/L).

Dynamic light scattering. Hydrodynamic radius of CD-adamantyl **8** solution (5mM) in NaN_3 (10g/L) was determined by dynamic light scattering (DLS). Measurement was performed at an angle of 90° at 25°C, with a Zetasizer Nano S90 from Malvern using a 4 mW He–Ne laser at 633 nm. Samples were filtered through 0.45 µm membrane before analysis. All calculations were performed using the Nano DTS software.

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[1] S. Guieu, M. Sollogoub *Angew. Chem. Int. Ed*. 2008, **47**, 7060-7063.
[2] A. Arnaud, L. Bouteiller *Langmuir* **2004**, *20*, 6858-6863