Electronic Supplementary Information

A Water-soluble Aza-adamantyl Nitroxide Radical and Its Complexes with β-Cyclodextrin Derivatives

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1. General Procedures and Materials

The reactions, unless otherwise indicated, were carried under N_2 atmosphere with anhydrous solvents. All solvents were used directly from solvent purification system (Inert, PS-MD-5). Triethylamine was freshly distilled from calcium hydride prior to use. Per-deuterated solvents for NMR spectroscopy were obtained from Innochem. All other commercially available chemicals were obtained from either Aldrich、Alfa Aesar、J&K、Aladdin or Innochem. Microwave-assisted reactions were performed in a Biotage Sweden AB Box 8 microwave reactor with the standard mode and an initial 400 W power. Column chromatography (0–20 psig pressure) was performed by using silica gel. Analytical TLC plates were carried out on 0.25 mm MilliporeSigma silica plates (60F-254), using UV light as the visualizing agent, or ninhydrin as the TLC stain. NMR spectra were obtained with JEOL Delta spectrometers (^{1}H, 400 and 600 MHz) using chloroform-*d* ($CDCl_3$), water-d_2, or DMSO-d_6 as the solvent. The chemical shift references were as follows: (^{1}H) chloroform-*d*, 7.26 ppm; (^{13}C) chloroform-*d*, 77.00 ppm; (^{1}H) water-d_2, 4.79 ppm; (^{1}H) DMSO-d_6, 2.50 ppm; (^{13}C) DMSO-d_6, 39.51 ppm. X-band EPR spectra were recorded on a Bruker E500 spectrometer equipped with an Oxford ESR900 liquid helium cryostat and ITC-503 temperature controller. UV-Vis spectra were recorded on Shimadzu UV-3600. DSC spectra were recorded on STA 449 F5 Jupiter. Mass spectra (ESI) were acquired on GCT spectrometer (Bruker Daltonics Inc).

2. Synthesis and Characterization of Z-3

2.a Synthesis of Nitroxide Z-3

Scheme S1. Synthetic Scheme for Nitroxide **Z-3**.

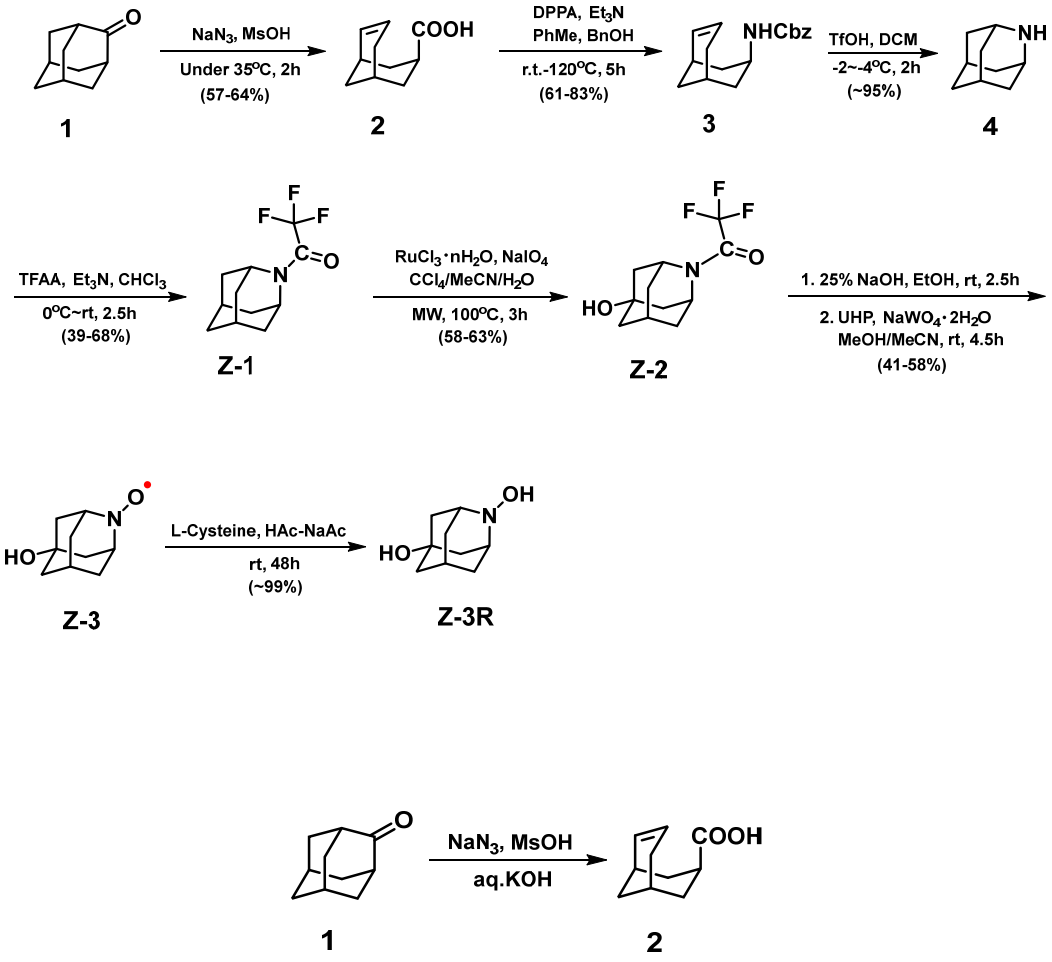


Table S1. Summary for preparation of **2**.[a]

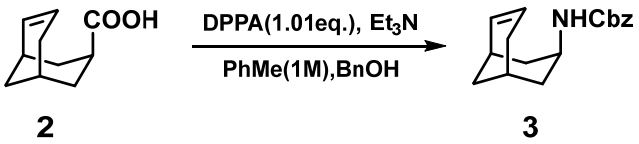
Run	SM		MsOH (mL/equiv)	NaN_3 (g/equiv)	50%KOH (mL)	Condition	Solvent	Product	
	1							**2**	
	Label	g/equiv						TM Label	Yield
1	ZYN-1-65	0.50/1.0	2.2/10	0.24/1.1	4.5	< 35°C/2 h	H_2O	1-P65-2	58%/0.32 g
2	ZYN-1-66	2.31/1.0	10.0/10	1.1/1.1	22.0	< 35°C/2 h	H_2O	1-P66-2	57%/1.46 g
3	ZYN-2-6	25.0 /1.0	102.0/10	12.0/1.1	235.0	< 35°C/2 h	H_2O	2-P6-2	64%/17.0 g

[a] The compound was prepared according to the procedure reported in the literature.[S1]

ZYN-1-66: In a three-necks flask with condenser and thermometer, 2-adamantanone (**1**, 0.50 g, 3.33 mmol, 1.0 equiv) and methanesulfonic acid (MsOH, 33.3 mmol, 2.2 mL, 10 equiv) were added to get a clear solution through stirring. Then NaN_3 (0.24 g, 3.67 mmol, 1.1 equiv) was added to the above-mentioned solution slowly, and the temperature of solution was kept under

35 °C. When it was added completely, the solution was stirred for 2 h at room temperature. Then 1 mL water and 4.5 mL 50% KOH (aq.) were added for quenching and the temperature was kept under 35 °C without external disturbance. The mixture was washed with 30 mL ethyl ether. And then 1.2 mL conc. HCl was added to aqueous phase. The precipitate was filtered off, which was washed with water and evacuated under high vacuum at ambient temperature to yield the product **2** (0.32 g, 1.93 mmol, yield: 58%; label: 1-P65-2) as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 – 5.63 (m, 1H), 5.59 (dt, J = 9.9, 3.2 Hz, 1H), 2.58 (t, J = 6.8 Hz, 1H), 2.40 (d, J = 14.1 Hz, 1H), 2.32 (d, J = 9.4 Hz, 2H), 2.22 (m, 2H), 1.73 (m, 3H), 1.54 (d, J = 12.1 Hz, 1H). (*Lit.*[S1] *^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65(m, 1H), 5.58 (dt, J = 9.5, 3.2 Hz, 1H), 2.57 (t, J = 6.3 Hz, 1H), 2.39 (d, J = 14.0 Hz, 1H), 2.36 – 2.20 (m, 4H), 2.06 (br s, 1H), 1.78 – 1.66 (m, 3H), 1.54 (br d, J = 12.3 Hz, 1H)*).



2 **3**

Table S2. Summary for preparation of Compound **3**. [a]

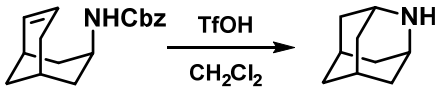
Run	SM		DPPA (mL/equiv)	Et_3N (mL/equiv)	BnOH (mL/equiv)	Condition	Solvent	Product	
	2							**3**	
	Label	g/equiv						Label	Yield
1	ZYN-1-67	0.32/1.0	0.42/1.01	0.64/2.4	1.6/8	r.t./1.5 h 120°C/1.5 h	PhMe	1-P67-3	64%/0.33 g
2	ZYN-1-127	2.0/1.0	2.6/1.01	4.0/2.4	10.0/8	r.t./1.5 h 120°C/1.5 h	PhMe	1-P127-3	61%/2.0 g
3	ZYN-2-13	9.4/1.0	13.0/1.05	20.0/2.5	30.0/5	r.t./3 h 126°C/ 2 h	PhMe	2-P13-3	83%/13.85 g

[a] The compound was prepared according to the procedure reported in the literatures.[S1,S2]

ZYN-2-13: To a stirred solution of **2** (9.4 g, 56.63 mmol, 1.0 equiv) in anhydrous toluene (57.0 mL), diphenylphosphoryl azide (DPPA, 13.0 mL, 59.46 mmol, 1.05 equiv) and triethylamine (20.0 mL, 141.57 mmol, 2.5 equiv) were added under N_2 atmosphere. The mixture was stirred for 3 h at room temperature. Then BnOH (1.6 mL, 283.13 mmol, 5.0 equiv) was added to above-mentioned solution, and the mixture was refluxed for 2 h at 126 °C. The reaction solution was cooled down to room temperature, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, then concentrated under reduced pressure. Purification on silica gel flash column chromatography (petroleum ether /ethyl acetate, 20/1 to 10/1) to give the product **3** (13.85 g, 47 mmol, Yield: 83%, label: 2-P13-3) as a slight yellow oil. R_f = 0.47

(PE/EA, 5/1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.27 (m, 5H), 6.14 – 6.00 (m, 1H), 5.92 (d, J = 8.4 Hz, 1H), 5.80 (dt, J = 9.8, 3.3 Hz, 1H), 5.16 – 4.98 (m, 2H), 4.17 – 3.92 (m, 1H), 2.51 – 2.38 (m, 1H), 2.34 (br s, 1H), 2.18 (br s, 1H), 2.11 – 2.02 (m, 1H), 2.03 – 1.93 (m, 1H), 1.90 – 1.65 (m, 4H), 1.56 (d, J = 12.1 Hz, 1H). (*Lit.*[S2] *^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5H), 6.05 (t, J = 7.8 Hz, 1H), 5.92 (d, J = 8.4 Hz, 1H), 5.79 (dt, J = 9.9, 3.2 Hz, 1H), 5.08 (d, J = 12.4 Hz, 1H), 5.03 (d, J = 12.4 Hz, 1H), 4.03 (m, 1H), 2.43 (dd, J = 18.8, 7.2 Hz, 1H), 2.34 (br s, 1H), 2.18 (br s, 1H), 2.06 (br d, J = 18.1 Hz, 1H), 2.00 (dt, J = 14.7, 5.5 Hz, 1H), 1.89 – 1.66 (m, 4H), 1.55 (br d, J = 12.1 Hz, 1H)*).



3 **4**

Table S3. Summary for preparation of Compound **4**. [a]

Run	SM		TfOH (mL/equiv)	Et_3N (mL/equiv)	10%NaOH mL	Condition	Solvent	Product	
	3							**4**	
	Label	g/equiv						Label	Yield
1	ZYN-1-74	0.1/1.0	0.13/4	0.25/4.8	0.5	0 °C/1.5 h	DCM	1-P74-4	15%/7.6 mg
2	ZYN-2-1	0.265/1.0	0.35/4	0.65/4.8	2.7	-2 ~ -4 °C/2 h	DCM	2-P1-4	40%/52 mg
3	ZYN-4-2	2.7/1.0	3.6/4	6.3/4.5	28.0	-2 ~ -4 °C/2 h	DCM	4-P2-4	95%/1.3 g

[a] The compound was prepared according to the procedure reported in the literature.[S3]

ZYN-4-2: In a two-necks flask, to a solution of compound **3** (2.7 g, 9.96 mmol, 1.0 equiv) in DCM (57 mL, 0.18 M), trifluoromethanesulfonic acid (TfOH, 3.6 mL, 39.84 mmol, 4.0 equiv) was added under N_2 atmosphere at -2 ~ -4 °C and the mixture was stirred for 1 h at this temperature. Then Et_3N (6.3 mL, 44.82 mmol, 4.5 equiv) and 10% NaOH solution (28.0 mL) were added to the above-mentioned solution under N_2 atmosphere and the mixture was stirred for 1 h at -2 ~ -4 °C. After the reaction done shown by TLC, the solution was extracted with DCM. The organic layer was washed with 10% HCl. The pH of the obtained aqueous phase was adjusted to 14 using aq. NaOH solution. It was extracted with DCM, and the organic layer was concentrated under reduced pressure to give the product **4** (1.3 g, 9.46 mmol, yield: 95%; label: 4-P2-4) as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.17 (s, 2H), 2.05 (s, 2H), 1.97 (d, J = 12.1 Hz, 4H), 1.87 (s,

2H), 1.78 (d, J = 11.6 Hz, 4H). (*Lit.*[S3] *^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.13 (s, 2H), 2.04 (s, 2H), 1.94 (d, J = 11.4 Hz, 4H), 1.87 (s, 2H), 1.77 (d, J = 11.4 Hz, 4H)*).

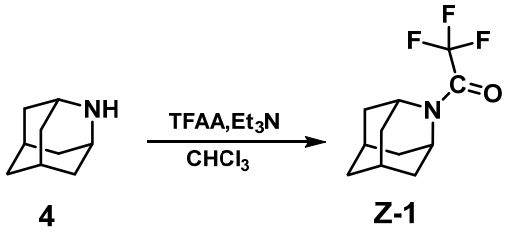


Table S4. Summary for preparation of **Z-1**.[a]

Run	SM		TFAA (mL/equiv)	Et_3N (mL/equiv)	Condition	Solvent	Product	
	4						**Z-1**	
	Label	g/equiv					Label	Yield
1	ZYN-1-92	0.24/1.0	0.37/1.5	0.37/1.5	r.t./2 h	$CHCl_3$	1-P93-Z-1	39%/0.16 g
2	ZYN-2-2	0.053/1.0	0.045/0.83	0.045/0.83	0 °C/30 min r.t./1 h	DCM/Et_2O	2-P2-Z-1	40%/0.036 g
3	ZYN-2-5	0.22/1.0	0.3/1.5	0.3/1.5	r.t./2.5 h	$CHCl_3$	2-P5-Z-1	68%/0.25 g

[a] The compound was prepared according to the procedure reported in the literatures.[S2–S4]

ZYN-2-5: In a two-necks flask, to a solution of compound **4** (0.22 g, 1.6 mmol, 1 equiv) in $CHCl_3$ (0.2 M, 8 mL), trifluoromethanesulfonic anhydride (TFAA, 0.3 mL, 2.4 mmol, 1.5 equiv) and Et_3N (0.3 mL, 2.4 mmol, 1.5 equiv) were added under N_2 atmosphere at 0 °C and the mixture was stirred for 2.5 h at room temperature. To the reaction mixture, sat. aqueous $NaHCO_3$ solution was added and the obtained mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, then concentrated under reduced pressure. Purification on silica gel flash column chromatography (petroleum ether /ethyl acetate, 50/1 to 10/1) to give the product **Z-1** (0.25 g, 1.09 mmol, Yield: 68%, label: 2-P5-Z-1) as a slight yellow oil. R_f = 0.55 (PE/EA, 10/1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.75 (s, 1H), 4.21 (s, 1H), 2.12 (s, 2H), 2.03 – 1.61 (m, 10H). (*Lit.*[S4] *^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.76 (br s, 1H), 4.23 (br s, 1H), 2.14 (br s, 2H), 1.83 – 1.91 (m, 10H)*).

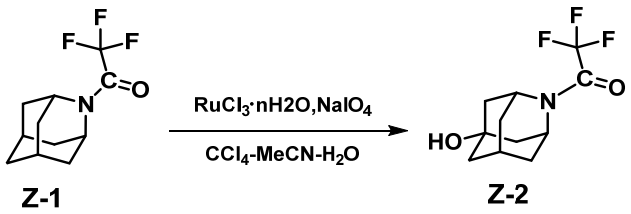


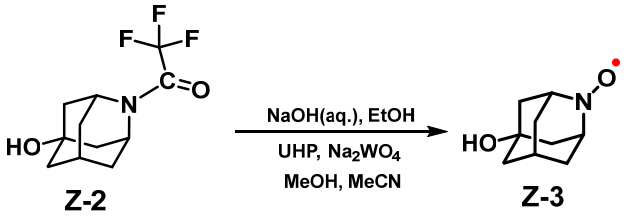
Table S5. Summary for preparation of Compound **Z-2**. [a]

Run	SM		$RuCl_3$•nH_2O (mg/equiv)	$NaIO_4$ (mg/equiv)	Solvent	Condition	Product	
	Z-1						**Z-2**	
	Label	mg/equiv					Label	Yield
1	ZYN-1-94	81.1/1.0	7.26/0.1	172.18/2.3	CCl_4/MeCN/H_2O	70°C/20 h	/	8.7 mg, 10% [b]
2	ZYN-1-99	82.9/1.0	7.38/0.1	174.86/2.3	CCl_4/MeCN/H_2O	80°C/4 d	/	57.6 mg, 65% [b]
3	ZYN-1-100	37.0 /1.0	3.29/0.1	78.04/2.3	CCl_4/MeCN/H_2O	MW/90°C/2 h 100°C/2 h	1-P100-Z-2	12.4 mg, 42%
4	ZYN-1-163	24.0 /1.0	2.13/0.1	88.04/3.6	CCl_4/H_2O	MW/110°C/2 h	/	12.8 mg, 50% [b]
5	ZYN-1-180	49.0 /1.0	10.26/0.24	166/3.6	CCl_4/MeCN/H_2O	MW/100°C/3 h	1-P182-Z-2	20 mg, 58%
6	ZYN-3-59	1.54 /1.0	330.01/0.24	5100/3.6	CCl_4/MeCN/H_2O	MW/100°C/3 h	3-P59-Z-2	555.0 mg, 63%

[a] The compound was prepared according to the procedure reported in the literature.[S4] [b]Determined based on the recovered starting material.

ZYN-3-59: In a microwave tube, the compound **Z-1** (1.54 g, 6.6 mmol, 1.0 equiv), $NaIO_4$ (5.1 g, 23.77 mmol, 3.6 equiv) and $RuCl_3 \cdot nH_2O$ (330.01 mg, 1.58 mmol, 0.24 equiv) were dissolved using the solvent mixture CCl_4/MeCN/H_2O (1.65 M, 4 mL/1.65 M, 4 mL/0.8 M, 8 mL). The tube was sealed firmly and microwaved at 100 °C for 3 h. The reaction was quenched with saturated $Na_2S_2O_3$ and $NaHCO_3$ solution. The mixture was extracted with ethyl acetate and the obtained organic layer was washed with brine, dried over Na_2SO_4, then concentrated under reduced pressure. Purification on silica gel flash column chromatography (petroleum ether /ethyl acetate, 10/1 to 2/1) gave the product **Z-2** (555.0 mg, 4.16 mmol, Yield: 63%, label: 3-P59-Z-2) as a pale-yellow oil. The unreacted **Z-1** (714.0 mg, 3.06 mmol, 46%) was recovered. R_f = 0.57 (PE/EA, 1/1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.96 (s, 1H), 4.42 (s, 1H), 2.39 (s, 1H), 2.00 – 1.49 (m, 12H). (*Lit.*[S4] *^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.97 (br s, 1H), 4.43 (br s, 1H), 2.40 (br s, 1H), 1.8 – 1.73 (m, 10H)*).



Z-2 Z-3

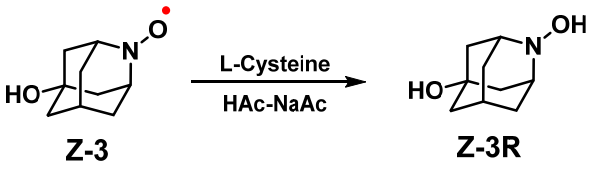
Table S6. Summary for preparation of Compound **Z-3**. [a]

Run		1	2	3	4
SM **Z-2**	Label	ZYN-1-186	ZYN-1-186	ZYN-2-14	ZYN-2-21
	g/equiv	0.01/1.0	0.01/1.0	0.05/1.0	1.55/1

Base	5 M KOH/33 μL		10% NaOH/85 μL	50% NaOH/0.5 mL	25% NaOH/16 mL
Solvent	MeOH/2 mL		EtOH/0.17 mL	EtOH/1.0 mL	EtOH/31 mL
Condition	r.t./12 h		r.t./2.5 h	r.t./2 h	r.t./2 h
UHP (m/equiv)	/		/	91.46 mg/4.8 22.65 mg/1.2	2.64 g/4.8 660 mg/1.2
$NaWO_4•2H_2O$ (m/equiv)	/		/	39.94 mg/0.6	1.16 g/0.6
Solvent	/		/	MeOH/MeCN	MeOH/MeCN
Condition	/		/	r.t./4.5 h	r.t./4.5 h
Product **Z-3**	Label	/	/	2-P17-Z-3	2-P131-Z-3
	Yield	/	/	41%/13.9mg	58%/0.61 g
	Spin Conc.	/	/	67%	97%

ZYN-2-21: To a solution of compound **Z-2** (1.55 g, 6.22 mmol, 1 equiv) in EtOH (31 mL), aq. NaOH (25%, 16 mL) was added at ambient temperature. After the reaction mixture was stirred for 2 h, it was diluted with H_2O and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated. The crude amine was used without further purification. After a solution of the crude amine and $Na_2WO_4·2H_2O$ (1.16 g, 3.5 mmol, 0.6 equiv) in MeOH (58 mL) and MeCN (58 mL) was stirred at ambient temperature for 30 min, urea-hydrogen peroxide complex (UHP) (2.64 g, 28.04 mmol, 4.8 equiv) was added under stirring. One hour later, additional UHP (660 mg, 7.0 mmol, 1.2 equiv) was added and the mixture was stirred for another 3.5 h. The solvent was evaporated and the residue was purified with column chromatography (petroleum ether /ethyl acetate, 1/1 to 1/10) to give the product **Z-3** (0.61 g, 3.62 mmol, Yield: 58%, label: 2-P131-Z-3) as an orange solid. R_f = 0.27 (PE/EA, 1/6). M.P.: Under Ar, the compound starts to become darken at around 190 °C and a melt of the solid was observed at 217.9–219.8 ℃ (A similar phenomenon was also observed in the case of **AZADO**, with the "apparent" melting point of 219.8–220.3 ℃.)

EPR (0.96 mM in $CHCl_3$): g-value = 2.0063; a_N = 19.3 G; IR (KBr): 3426.69, 2931.93, 2831.62, 2715.89, 1627.03, 1599.06, 1365.66, 1188.20, 1122.62, 1071.50, 872.83, 775.42, 610.50, 553.59 cm^{-1}. HRMS-ESI, $[M]^+$ (N-oxoammonium cation) calculated for $C_9H_{14}NO_2$, 168.1025, found 168.0659; $[M+2H]^+$ (protonated hydroxylamine) calculated for $C_9H_{16}NO_2$, 170.1181; found 170.1175.



Z-3 Z-3R

Table S7. Summary for preparation of Compound **Z-3R**.

SM		L-Cysteine (mg/equiv)	Solvent (mL)	Condition	Product	
Z-3					**Z-3R**	
Label	g/equiv				Label	Yield
ZYN-1-188	0.04/1.0	5.8 /0.2	HAc-NaAc (1.6)	r.t./48 h	1-P188-Z-3R	0.04 g/99%

ZYN-1-188: To a solution of **Z-3** (0.04 g, 0.24 mmol, 1.0 equiv) in 1 M HAc-NaAc (1.6 mL), *L*-cysteine (5.8 mg, 0.048 mmol, 0.2 equiv) was added and the mixture was stirred for 48 h at the room temperature. The mixture was purified on silica gel (reverse phase, C18, 40% surface coverage) flash column chromatography (butyl alcohol/ acetic acid /H_2O, 4/1/1) to give the product **Z-3R** (0.04 g, 0.237 mmol, Yield: 99%, label: 1-P188-Z-3R) as a white solid. ^{1}H NMR (400 MHz, D_2O, 298K): δ = 3.65 (d, J = 24.4 Hz, 1H), 2.32 (dd, J = 39.8, 15.5 Hz, 2H), 1.93 (s, 11H), 1.61 (dd, J = 34.8, 13.2 Hz, 1H). HRMS (ESI−TOF), $[M + H]^{1+}$: calcd. 170.1181, found 170.1180 (–0.59 ppm). ^{13}C NMR (150 MHz, D_2O, 298K): δ = 60.74, 42.04, 40.90, 35.58, 33.24, 26.90, 26.87, 23.25.

2.b X-ray Crystallography

The single crystals of nitroxide **Z-3** were obtained by slow solvent evaporation from a *n*-hexane/chloroform solvent mixture at the ambient temperature. Orange, flat, block-shaped crystals were obtained.

X–ray single crystal diffraction was performed on XtalLAB Synergy X–ray diffractometer equipped with Cu Kα radiation (λ = 1.54184 Å) source. The crystal was kept at 100.00(10) K during data collection. Using Olex2S, the structure was solved with the ShelXTS structure solution program using Direct Methods and refined with the ShelXLS refinement package using Least Squares Minimization. The disordered solvent molecules were removed with the SQUEEZE routine in PLATONS and the solvent-free model was employed for the final

refinement. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were positioned by geometric idealization. Details of some important structural parameters and a summary of the crystal and refinement information for **Z-3** are listed in Table S8–S9. The crystallographic data were deposited at the Cambridge Crystallographic Data Center (CCDC 2352292). The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures. For comparisons, the parameters of the X–ray structure of **AZADO**, which derived from the X–ray molecular structure reported in the literature[S5], as well as those of the DFT (ub3lyp/6-31g(d,p)) energy-minimized structures of **Z-3** and **AZADO** (For computational details, see Part 5 in this SI), are also listed in Table S8.

Table S8. Some important parameters for the X-ray and the DFT energy-minimized structures of **Z-3** and **AZADO**: average bond lengths (*d*, Å) and bond angles (*θ*, °).

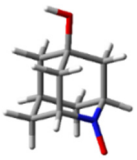
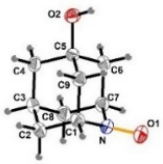
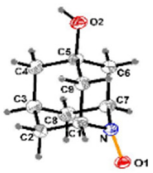
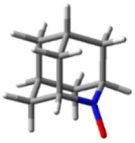
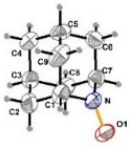
Species		**Z-3**			**AZADO**	
		Calcd. Structure	**X-ray structure**		**Calcd. Structure**	**X-ray structure** [S5]
		 *trans*-**Z-3**	 *cis*-**Z-3**	 *trans*-**Z-3**		
d	**N-O1**	1.287	1.294 (2)	1.292 (4)	1.288	1.284
	N-C1	1.484	1.473 (4)	1.476 (3)	1.484	1.467
	N-C7	1.484	1.474 (2)	1.475 (2)	1.484	1.467
	C5-C4	1.542	1.527 (6)	1.525 (4)	1.544	1.524
	C5-C6	1.537	1.534 (1)	1.528 (2)	1.542	1.534
	C5-C9	1.542	1.533 (3)	1.530 (4)	1.542	1.533
θ	**O1-N-C1**	118.29	117.79 (76)	118.11 (47)	118.18	118.05
	O1-N-C7	118.26	117.58 (95)	117.57 (77)	118.17	118.05
	C1-N-C7	114.16	114.34 (37)	114.49 (2)	114.28	113.24

Table S9. X-ray crystallography parameters of **Z-3**.

Identification code	Z-3
Empirical formula	$C_{63}H_{107.65}N_7O_{18.82}$
Formula weight	1264.40
Temperature/K	100.00(13)
Crystal system	triclinic
Space group	P-1
a/Å	6.63740(10)
b/Å	16.5830(3)
c/Å	28.8082(4)
α/°	101.7560(10)
β/°	90.9180(10)
γ/°	90.584(2)
Volume/Å^3	3103.66(9)
Z	2
ρ_{calc}g/cm^3	1.353
μ/mm^{-1}	0.816
F(000)	1370.0
Crystal size/mm^3	0.50 × 0.10 × 0.14
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.814 to 153.082
Index ranges	$-7 \le h \le 8$, $-20 \le k \le 20$, $-35 \le l \le 36$
Reflections collected	40168
Independent reflections	12532 [R_{int} = 0.0395, R_{sigma} = 0.0357]
Data/restraints/parameters	12532/163/951
Goodness-of-fit on F^2	1.032
Final R indexes [I>=2σ (I)]	R_1 = 0.0493, wR_2 = 0.1360
Final R indexes [all data]	R_1 = 0.0581, wR_2 = 0.1423
Largest diff. peak/hole / e Å^{-3}	0.36/-0.29

2.c Solubility of Z-3 in Water

The solubility of **Z-3** in water was determined based on the "excess solid"[S6] method. First, the compound **Z-3** was added gradually to a small amount of deionized water in a vial until a suspension was formed. The mixing solution was stirred by a magnetic stirring device at 25 °C for 3 h to ensure achieving dissolution equilibrium. The suspension was centrifuged, and the apparently homogenous solution was filtered with a syringe filter (aqueous phase, 0.22 μm). A 0.2 mL solution of the transparent filtrate was transferred to another vial. It was dried and the

solubility of **Z-3** was determined based on the weight of the residue and the volume of the transferred solution. The determined water solubility of **Z-3** is shown in Table 2, main text.

2.d EPR and UV-vis Spectroscopic Characterizations of Z-3

EPR measurements: DPPH powder (g = 2.0037) was used as a *g*-value reference. Spin concentrations of the radical samples were measured versus a 1.0 mM solution of a stable radical, 3-Carboxy-Proxyl.

Compound **Z-3** (4.18 mg) was dissolved with chloroform or PBS buffer solution (100 mM, pH = 7.40 ± 0.01) in a 25 mL volumetric flask to give a roughly 1 mM sample solution. Similarly, 3-Carboxy-Proxyl was dissolved with chloroform or PBS buffer solution in 25 mL volumetric bottle to give a 1.0 mM standard radical sample. Each of the solutions was drawn into an EPR-quality quartz capillary tube (0.6-mm I.D.). The capillary was stoppered with parafilm and placed in a 5-mm O.D. EPR sample tube, then positioned immediately in the EPR cavity. Series of spectra was obtained at 295 K.

The EPR spectra of **Z-3** are shown in Figure S1 and Figure 4a, the main text.

UV-vis measurements: The compounds, **AZADO**, **Z-3** and **Z-3R**, were first dissolved into dichloromethane or deionized water to obtain a stock solution, respectively. Subsequently, the stock solutions were diluted in a UV-vis quartz cuvette, and then a serial UV–vis measurements were carried out rapidly.

The UV-Vis spectra of **AZADO** and **Z-3** in DCM as well as **Z-3R** and **Z-3** in H_2O are shown in Figure 4a and b.

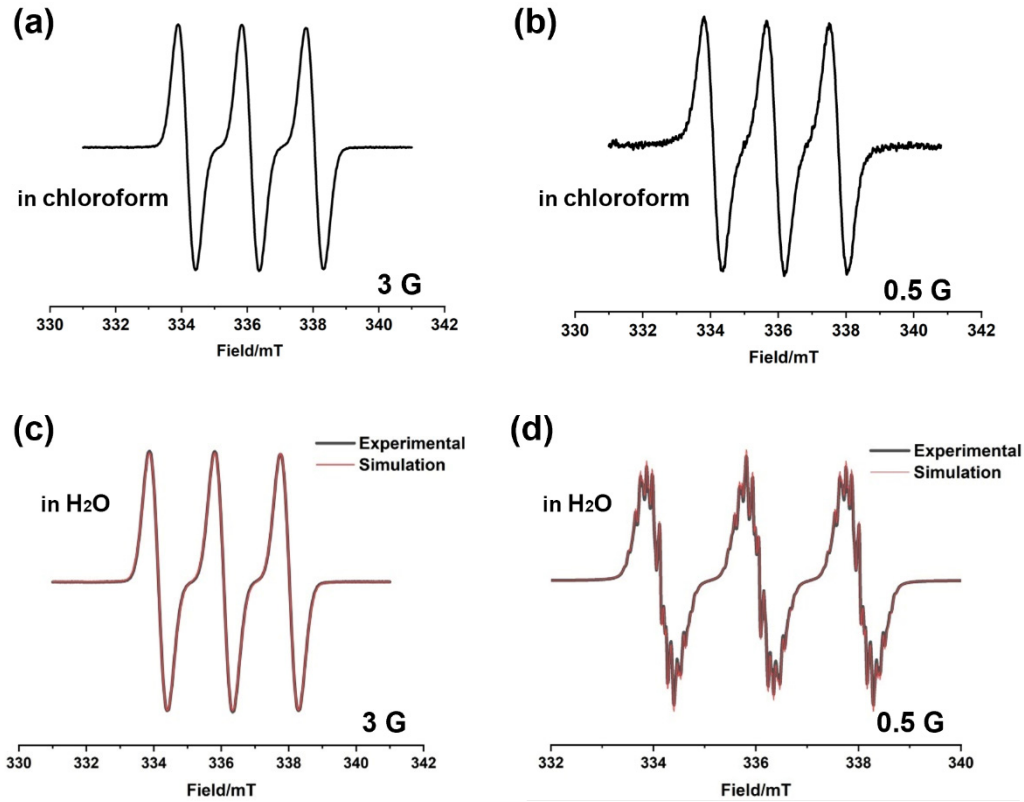


Figure S1. (a) EPR spectra of **Z-3** in chloroform (0.96 mM, modulation amplitude (Mod. Ampl.) = 3 G, 298 K); (b) EPR spectra of **Z-3** in chloroform (0.67 mM, Mod. Ampl. = 0.5 G, 298 K); (c) Experimental (black line) and simulated (red line) EPR spectra of **Z-3** (0.96 mM, Mod. Ampl. = 3 G) in PBS buffer (100 mM, pH = 7.40 ± 0.01); (d) Experimental (black line) and simulated (red line) EPR spectra **Z-3** (0.67 mM, Mod. Ampl. = 0.5 G) in PBS buffer (100 mM, pH = 7.40 ± 0.01).

2.e DSC Measurements

The DSC Measurements were performed on a STA 449 F5 Jupiter® (Netzsch, GER) instrument. Empty crucible was used as the reference. In the measurements, **Z-3** (3.2 mg) and **AZADO** (4.9 mg) was placed in a 40 µL flat-bottom aluminum crucible (6.0 mm × 1.7 mm), respectively. Samples were measured in the temperature range of 25 ~ 500 °C with the scanning speed fixed at 10 °C min^{-1} and a nitrogen flowing of 100 mL min^{-1}. The obtained DSC spectra are shown in Figure 5b, main text.

3. Synthesis and Characterization of β-cyclodextrin derivatives

3.a Synthesis of β-CD Derivatives

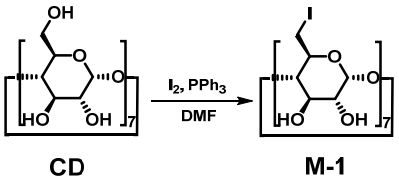


Table S10. Summary for preparation of Compound **M-1**.

Run	SM		Ph_3P (g/equiv)	I_2 (g/equiv)	Solvent	Condition	Product	
	CD						**M-1**	
	Label	g/equiv					Label	Yield
1	ZYN-2-94	0.1/1.0	0.49/21.0	0.47/21.0	DMF (dry)	r.t./30 min 70°C/24 h	2-P95-M-1	90%/0.15 g
2	ZYN-2-97	5.0/1.0	24.26/21.0	23.31/21.0	DMF (dry)	r.t./30 min 70°C/24 h	2-P97-M-1	86%/7.2 g
3	ZYN-2-123	25.0/1.0	121.0/21.0	117/21.0	DMF (dry)	r.t./30 min 70°C/24 h	2-P123-M-1	90%/38.0 g

The compound was prepared according to the procedure reported in the literature.[S7]

ZYN-2-97: The β-cyclodextrin was added to the eggplant shaped flask and stirred for over 4 h at 80 ℃ under high vacuum. Ph_3P (24.26 g, 92.51 mmol, 21.0 equiv) was dissolved with stirring in dry DMF (90 mL). To this solution was carefully added I_2 (23.31 g, 92.51 mmol, 21.0 equiv) over 10 min and it was vigorously stirred for 30 min at room temperature. The 25 mL DMF solution of dry β-cyclodextrin (**CD**, 5.0 g, 4.41 mmol, 1.0 equiv) was then added to this dark brown solution, and the temperature was raised to 70 °C. At this temperature, the solution was stirred under an atmosphere of N_2 for 24 h. When the mixture was cooled to room temperature, MeOH (90 mL) was added and stirred for 30 min. At 15 °C, 3 M MeOH/MeONa was added, and the pH was adjusted to 9 ~ 10. Then the mixture was stirred for 30 min. The above mixture was poured into MeOH to form a precipitate. The precipitate was filtered off, which was washed with MeOH and evacuated under high vacuum at ambient temperature to yield the product **M-1** (7.2 g, 3.79 mmol, yield: 86%; label: 2-P97-CD-2) as a white powder.

^{1}H NMR (400 M, DMSO-d_6): δ = 6.04 (s, 11H), 4.98 (s, 7 H), 3.80 (d, J = 10.1 Hz, 7 H), 3.72 – 3.55 (m, 14 H), 3.49 – 3.24 (m, 28 H). (*Lit.*[S7] *^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.28 (t, J = 9 Hz, 7H), 3.34-3.48 (m, 14H), 3.54-3.68 (m, 14H), 3.80 (bd, J = 9 Hz, 7H), 4.99 (d, J = 3 Hz, 7H), 5.94 (d, J = 2 Hz, 7H), 6.05 (d, J = 6.5 Hz, 7H)*). HRMS-ESI, $[M+Na]^+$ calculated for $C_{42}H_{63}O_{28}NaI_7$, 1926.6711, found 1926.6723.

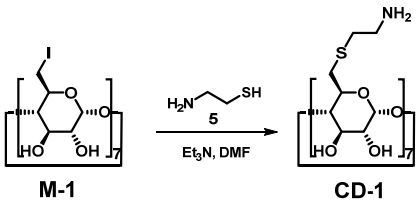


Table S11. Summary for preparation of Compound **CD-1**.

Run	SM		Et_3N (mL/equiv)	**5** (mg/equiv)	Solvent	Condition	Product	
	M-1						**CD-1**	
	Label	g/equiv					Label	Yield
1	ZYN-2-96	0.050 /1.0	0.1/27.0	37.07/17.5	DMF	60℃/3 days	2-P96-CD-1	40%/16.0 mg
2	ZYN-2-107	1.0/1.0	1.3/17.53	770/17.5	DMF	60℃/3 days	2-P107-CD-1	42%/0.34 g

The compound was prepared according to the procedure reported in the literature.[S8]

ZYN-2-96: A solution of heptakis-[6-deoxy-6-iodo]-β-cyclodextrin **M-1** (0.050 g, 0.026 mmol, 1.0 equiv) in dry DMF (0.5 mL) was mixed with triethylamine (0.1 mL, 0.702 mol, 27.0 equiv) and cysteamine (**5**, 37.07 mg, 0.46 mmol, 17.5 equiv). After stirring for 3 d at 60 ℃ under N_2, the product was concentrated in vacuo, precipitated by addition of ethanol or acetone, and filtered. The product was stirred in 1 M aq. NaOH (50 mL) for 18 h. The resultant solution was dialyzed (500 D membrane) for 48 h to yield the product **CD-1** (16.0 mg, 0.0104 mmol, yield: 40%; label: 2-P96-CD-1) as a white powder.

^{1}H NMR (600 MHz, D_2O): δ = 5.14 (s, 7H), 3.99 – 3.84 (m, 14H), 3.76 – 3.64 (m, 7H), 3.62 – 3.47 (m, 7H), 3.38 – 3.21 (m, 14H), 2.92 (s, 7H), 2.81 (s, 21H). (*Lit.[S8] ^{1}H NMR (D_2O): δ = 5.00 (d, J = 4 Hz, 7H; 1-H), 3.80 (m, 7H; 5-H), 3.74 (t, J = 9 Hz, 7H; 3-H), 3.51 (m, 14H; 2/4-H), 3.09 (m, 21H; 6a/7-H), 2.87 (m, 21H; 6b/8-H)*). HRMS-ESI, $[M+Na]^+$ calculated for $C_{56}H_{105}N_7O_{28}NaS_7$, 1570.5053, found 1570.4927.

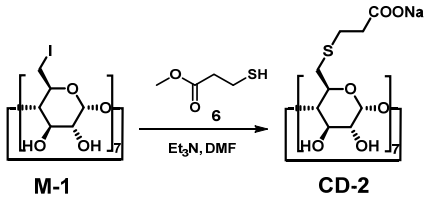


Table S12. Summary for preparation of Compound **CD-2**.

Run	SM		Et_3N (mL/equiv)	**6** (mL/equiv)	Solvent	Condition	Product	
	M-1						**CD-2**	
	Label	g/equiv					Label	Yield
1	ZYN-2-98	0.05 /1.0	0.1/28.0	0.05/17.5	DMF	60℃/3 days	2-P98-CD-2	65%/32.0 mg
2	ZYN-2-114	1.0 /1.0	1.3/18.0	1.1/18	DMF	60℃/3 days	2-P114-CD-2	62%/620.0 mg

The compound was prepared according to the procedure reported in the literature.[S8]

ZYN-2-98: A solution of heptakis-[6-deoxy-6-iodo]- β-cyclodextrin **M-1** (0.05 g, 0.026 mmol, 1.0 equiv) in dry DMF (0.5 mL) was mixed with triethylamine (0.1 mL, 0.728 mol, 28.0 equiv) and methyl 3-mercaptopropionate (**6**, 51 μL, 0.46 mmol, 17.5 equiv). After stirring for 3 d at 60 ℃ under N_2, the product was concentrated in vacuo, precipitated by addition of ethanol or acetone, and filtered. This product was stirred in 1 M aq. NaOH (50 mL) for 18 h. The resultant solution was dialyzed (500 D membrane) for 48 h to yield the product **CD-2** (32.0 mg, 0.0169 mmol, yield: 65%; label: 2-P98-CD-2) as a white powder.

^{1}H NMR (400 MHz, D_2O): δ = 5.15 (s, 7H), 4.10 – 3.80 (m, 14H), 3.75 – 3.47 (m, 14H), 3.24 (d, J = 12.0 Hz, 7H), 2.98 (dd, J = 13.6, 8.3 Hz, 7H), 2.90 (s, 14H), 2.63 (t, J = 7.0 Hz, 14H). (*Lit.*[S8] *^{1}H NMR (D_2O): δ = 5.03 (7H, s), 3.88-3.79 (14H, m), 3.50-3.46 (7H, m), 3.10 (7H, d), 2.89-2.78 (21H, m), 2.51(14H, s)*). HRMS-ESI, $[M-6Na+7H]^+$ calculated for $C_{63}H_{98}NaO_{42}S_7$, 1773.3475, found 1774.1157.

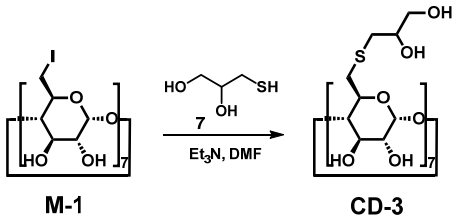


Table S13. Summary for preparation of Compound **CD-3**.

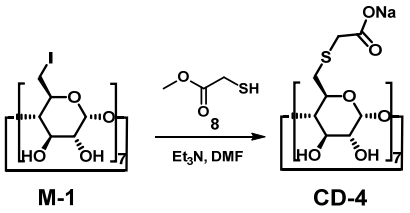
Run	SM		Et_3N (mL/equiv)	**7** (mL/equiv)	Solvent	Condition	Product	
	M-1						**CD-3**	
	Label	g/equiv					Label	Yield
1	ZYN-2-101	0.1/1.0	0.2/27.0	0.08/17.5	DMF (dry)	60℃/3 days	2-P101-CD-3	72%/0.067 g
2	ZYN-2-108	1.0/1.0	1.3/27.0	0.8/17.5	DMF (dry)	60℃/3 days	2-P108-CD-3	59%/0.59 g

The compound was prepared according to the procedure reported in the literature.[S8]

ZYN-2-101: A solution of heptakis-[6-deoxy-6-iodo]- β-cyclodextrin **M-1** (0.1 g, 0.053 mmol, 1.0 equiv) in dry DMF (2 mL) was mixed with triethylamine (0.2 mL, 1.431 mol, 27.0 equiv) and 1-thioglycerol (**7**, 0.08 mL, 0.92 mmol, 17.5 equiv). After stirring for 3 d at 60 ℃ under N_2, the product was concentrated in vacuo, precipitated by addition of ethanol or acetone. Purification of the resultant solid compound by dialysis (500 D membrane) gave the product **CD-3** (0.067 g, 0.0382 mmol, yield: 72%; label: 2-P101-CD-3) as a white powder.

^{1}H NMR (400 MHz, D_2O): δ = 5.13 (s, 7H), 4.01 – 3.89 (m, 21H), 3.71 – 3.56 (m, 42H), 3.28

(d, J = 13.1 Hz, 7H), 3.00 (d, J = 4.7 Hz, 7H), 2.92 – 2.85 (m, 7H), 2.80 – 2.73 (m, 7H). HRMS-ESI, $[M+H]^+$ calculated for $C_{63}H_{113}O_{42}S_7$, 1765.4673, found 1765.4745; $[M+Na]^+$ calculated for $C_{63}H_{112}O_{42}NaS_7$, 1787.4571, found 1788.1506.



M-1 **CD-4**

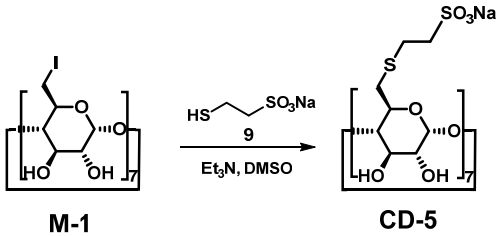
Table S14. Summary for preparation of Compound **CD-4**.

Run	SM		Et_3N (mL/equiv)	**8** (mL/equiv)	Solvent	Condition	Product	
	M-1						**CD-4**	
	Label	g/equiv					Label	Yield
1	ZYN-2-102	0.1/1.0	0.2/27	0.08/17.5	DMF	60℃/3 days	2-P102-CD-4	70%/0.067 g
2	ZYN-2-109	1/1.0	1.3/27	0.8/17.5	DMF	60℃/3 days	2-P109-CD-4	68%.645.0 mg

The compound was prepared according to the procedure reported in the literature.[S8]

ZYN-2-102: A solution of heptakis-[6-deoxy-6-iodo]- β-cyclodextrin**M-1** (0.1 g, 0.053 mmol) in dry DMF (2 mL) was mixed with triethylamine (0.2 mL, 1.431 mol) and methyl thioglycolate (**8**, 0.08 mL, 0.92 mmol). After stirring for 3 d at 60 ℃ under N_2, the product was concentrated in vacuo, precipitated by addition of ethanol or acetone, and filtered. This product was stirred in 1 M aq. NaOH (50 mL) for 18 h. The resultant mixture was dialyzed (500 D membrane) for 48 h to yield the product **CD-4** (0.067 g, 0.0371 mmol, yield: 70%; label: 2-P102-CD-4) as a white powder.

^{1}H NMR (400 MHz, D_2O): δ = 5.13 (d, J = 3.5 Hz, 7H), 4.06 (t, J = 7.7 Hz, 7H), 3.94 (t, J = 9.4 Hz, 7H), 3.75 – 3.58 (m, 14H), 3.44 (s, 14H), 3.23 (d, J = 11.6 Hz, 7H), 3.09 – 2.90 (m, 7H). (*Lit.*[S8] *^{1}H NMR (D_2O): δ = 4.95 (d, 7H; 1-H), 3.86 (m, 7H; 5-H), 3.75 (t, J = 9 Hz, 7H; 3-H), 3.49 (m, 14H; 2/4-H), 3.24 (m, 14H; 7-H), 3.02 (m, 7H; 6a-H), 2.81 (m, 7H; 6b-H)*). HRMS-ESI, $[M-6Na^+7H]^+$ calculated for $C_{56}H_{84}Na_1O_{42}S_7$, 1675.2380, found 1675.9632.



M-1 **CD-5**

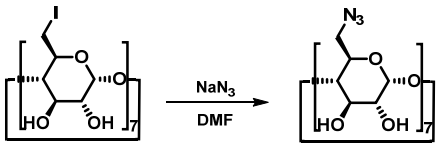
Table S15. Summary for preparation of Compound **CD-5**.

Run	SM		Et_3N (mL/equiv)	Reagent **9** (g/equiv)	Solvent	Condition	Product	
	M-1						**CD-5**	
	Label	g/equiv					Label	Yield
1	ZYN-2-103	0.1/1.0	/	$Na_2S_2O_3$/0.3/17.5	DMSO	60℃/3 days	/	/[a]
2	ZYN-2-97	1.33/1.0	1.7/17.5	5/2/17.5	DMSO	60℃/3 days	2-P97-CD-5	71%/1.07g

The compound was prepared according to the procedure reported in the literature.[S8]

[a] The reaction was failed.

ZYN-2-97: A solution of heptakis-[6-deoxy-6-iodo]- β-cyclodextrin **M-1** (1.33 g, 0.7 mmol, 1.0 equiv) in dry DMSO (10 mL) was mixed with triethylamine (1.7 mL, 12.2 mol, 17.5 equiv) and sodium 2-mercaptoethanesulfonate (**9**, 2 g, 12.2 mmol, 17.5 equiv). After stirring for 3 d at 60 ℃ under N_2, the product was concentrated in vacuo, precipitated by addition of ethanol or acetone. Purification of the resultant solid compound by dialysis (500 D membrane) for 48 h gave the product **CD-5** (1.07 g, 0.497 mmol, yield: 71%; label: 2-P97-CD-5) as a white powder. ^{1}H NMR (600 MHz, D_2O): δ = 5.18 (d, J = 3.4 Hz, 7H), 4.11 (t, J = 7.4 Hz, 7H), 3.99 (t, J = 9.4 Hz, 7H), 3.67 (d, J = 9.7 Hz, 14H), 3.37 – 3.16 (m, 21H), 3.13 – 2.90 (m, 21H). (*Lit.*[S8] *^{1}H NMR (D_2O): δ = 4.99 (d, J = 4 Hz, 7H; 1-H), 3.91 (m, 7H; 5-H), 3.80 (t, J = 10 Hz, 7H; 3-H), 3.48 (m, 14H; 2/4-H), 3.04 (m, 21H; 6a/8-H), 2.85 (m, 21H; 6b/7-H)*). HRMS-ESI, $[M-2Na]^{2-}$ calculated for $C_{56}H_{91}Na_5O_{49}S_{14}$, 1055.0104, found 1054.9414, 1055.4407, 1055.9447; $[M-4Na]^{4-}$ calculated for $C_{56}H_{91}Na_3O_{49}S_{14}$, 516.0103, found 515.9806, 516.2273, 516.2273; $[M-5Na]^{5-}$ calculated for $C_{56}H_{91}Na_2O_{49}S_{14}$, 408.2103, found 408.1786, 408.589, 408.3810.



M-1 **M-2**

Table S16. Summary for preparation of Compound **M-2**.

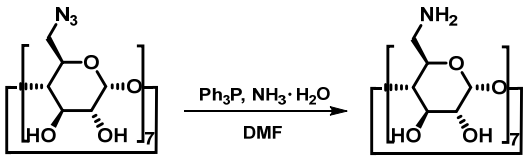
Run	SM		NaN_3 (g/equiv)	Solvent	Condition	Product	
	M-1					**M-2**	
	Label	g/equiv				Label	Yield
1	ZYN-2-116	1.0/1.0	0.37/10.0	DMF (dry)	60℃/20 h	2-P116-M-2	52%/0.36 g
2	ZYN-2-157	5.0/1.0	1.7/10.0	DMF (dry)	60℃/20 h	2-P157-M-2	61%/2.1 g

The compound was prepared according to the procedure reported in the literature.[S7]

ZYN-2-116: Per-6-iodo-β-cyclodextrin **M-1** (1.0 g, 0.53 mmol, 1.0 equiv) was dissolved in dry

DMF (17 mL), and NaN_3 (0.37 mg, 5.3 mmol, 10.0 equiv) was added. The resulting suspension was stirred at 60 °C under an atmosphere of N_2 for 20 h. The suspension was then concentrated under reduced pressure to a few milliliters before a large excess of H_2O was added. A fine white precipitate was formed and was filtered off carefully. The precipitate was washed with H_2O and dried under high vacuum to yield the product **M-2** (0.36 g, 0.276 mmol, yield: 52%; label: 2-P116-M-2) as a white powder.

^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ = 4.96 (s, 7H), 4.81 (s, 7H), 3.94 (d, *J* = 3.4 Hz, 7H), 2.81(d, *J* = 12.0 Hz, 7H), 2.76 (t, *J* = 9.3 Hz, 7H), 2.65 – 2.61 (m, 14H), 2.43 – 2.35 (m, 14H). *(Lit.*[S7] *^{1}H NMR (300 MHz, CD_3SOCD_3): δ = 3.30-3.42 (m, 14H), 3.53-3.65 (m, 14H), 3.68-3.82 (m, 14H), 4.91 (d, J = 3Hz, 7H), 5.77 (d, J = 2 Hz, 7H), 5.92 (d, J = 7 Hz, 7H)).* HRMS-ESI, $[M+Na]^+$ calculated for $C_{42}H_{63}N_{21}O_{28}Na$, 1332.4049, found 1332.9608.



M-2 **M-3**

Table S17. Summary for preparation of Compound **M-3**.

Run	SM		Ph_3P (g/equiv)	$NH_3•H_2O$ (mL)	Solvent	Condition	Product	
	M-2						**M-3**	
	Label	g/equiv					Label	Yield
1	ZYN-2-117	0.15/1.0	0.49/16.0	1.5	DMF (dry)	r.t. /18 h	2-P117-M-3	69%/ 0.093g
2	ZYN-2-142	0.6/1.0	1.94/16.0	6	DMF (dry)	r.t. /18 h	2-P142-M-3	74%/0.38 g

The compound was prepared according to the procedure reported in the literature.[S7]

ZYN-2-117: The compound **M-2**(0.15 g, 0.12 mmol, 1.0 equiv) was dissolved in DMF (3 mL), and Ph_3P (490 mg, 1.92 mmol, 16.0 equiv) was added. The evolution of N_2 can be observed from the formation of bubbles in the reaction vessel. After 1 h, during which time the evolution of N_2 ceased, $NH_3•H_2O$ (1.5 mL, 25%) was added dropwise to the solution. Shortly after the addition of the $NH_3•H_2O$ solution, the reaction mixture turned into an off-white suspension. It was stirred at r.t. for 18 h before the resulting suspension was concentrated under reduced pressure to approximately 10 mL. The product was then precipitated by the addition of EtOH (30 ~ 40 mL). The precipitate was washed with EtOH and dried under high vacuum to yield the product **M-3** (0.093 g, 0.0828 mmol, yield: 69%; label: 2-P117-M-3) as a white powder.

^{1}H NMR (400 MHz, D_2O): δ = 5.19 (s, 7H), 4.18 (s, 10H), 4.00 (s, 9H), 3.71 (s, 9H), 3.60 (s, 9H), 3.47 (s, 7H), 3.30 (s, 7H). (*Lit.*[S7] *^{1}H NMR (300 MHz, D_2O): δ = 3.26 (dd, J = 7, 13 Hz, 7H), 3.44 (dd, J = 3, 13 Hz, 7H), 3.57 (t, J = 9 Hz, 7H), 3.66 (dd, J = 3.5, 9.5 Hz, 7H), 3.98 (dd, J = 9, 9.5 Hz, 7H), 4.15-4.25 (ddd, J = 3, 7, 9 Hz, 7H), 5.15 (d, J = 3.5 Hz, 7H)*). HRMS-ESI, $[M+H]^+$ calculated for $C_{42}H_{78}N_7O_{28}$, 1129.1070, found 1129.0317.

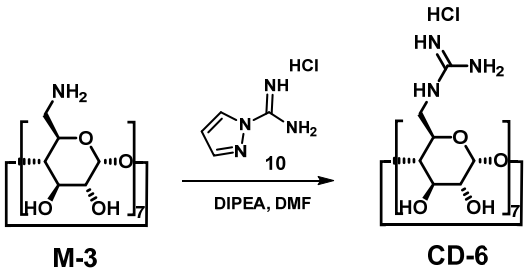


Table S18. Summary for preparation of Compound **CD-6**.

Run	SM		**10** (g/equiv)	DIPEA (mL/equiv)	Solvent	Condition	Product	
	M-3						**CD-6**	
	Label	g/equiv					Label	Yield
1	ZYN-2-128	0.043/1.0	0.084/15.0	0.2/30.0	DMF (dry)	70°C/22 h	/	/[a]
2	ZYN-2-109	0.05/1.0	0.13/20.0	0.2/30.0	DMF (dry)	r. t.	/	/[a]
3	ZYN-3-15	0.31/1.0	1.98/50.0	2.4/50.0	H_2O	r.t./48 h	3-P15-CD-6	72%/0.28 g

The compound was prepared according to the procedure reported in the literature.[S9]

[a] The reaction was failed.

ZYN-3-15: To the solution of hexakis(6-amino-6-deoxy) cyclodextrin **M-3** (0.31 g, 0.27 mmol, 1.0 equiv) and 1*H*-pyrazolecarboxamidine hydrochloride (**10**, 1.98 g, 13.5 mmol, 15.0 equiv) in water (3 mL), *N*, *N*-diisopropylethylamine (DIPEA, 2.4 mL, 13.5 mmol, 50.0 equiv) was added. The mixture was stirred at room temperature for 48 h under a nitrogen atmosphere. Then acetone was added dropwise and a suspension was formed. The solvent was decanted and the collected sticky solid was dissolved in a very small amount of water. Addition of acetone resulted in the precipitation of a white substance. The above experimental operation was repeated more than 3 times. This precipitate was filtered and dried under vacuum to yield the product **CD-6** (0.28 g, 0.194 mmol, yield: 72%; label: 3-P15-CD-6) as a white powder.

^{1}H NMR (600 MHz, D_2O): δ = 5.13 (d, *J* = 3.5 Hz, 7H), 4.09 (t, *J* = 7.6 Hz, 7H), 3.99 (t, *J* = 9.4 Hz, 7H), 3.73 – 3.62 (m, 14H), 3.57 – 3.53 (m, 14H). (*Lit.*[S9] *^{1}H NMR (500 MHz, D_2O, 300 K): δ = 5.20 (d, J = 3.3 Hz, 7H, H1), 4.00 (t, J = 9.7 Hz, 7H, H5), 3.92 (t, J = 9.5 Hz, 7H, H3),*

3.65 (dd, J = 3.5 Hz, J = 9.5 Hz, 7H, H2), 3.61 (d, J = 14.9 Hz, 7H, H6), 3.43–3.41 (m, 14H, H4, H6')).

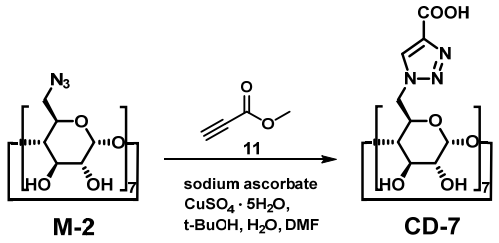


Table S19. Summary for preparation of Compound **CD-7**.

Run	SM		**11** (mL/equiv)	Reagent (g/equiv)	Solvent	Condition	Product	
	M-2						**CD-7**	
	Label	g/equiv					Label	Yield
1	ZYN-2-122	0.15/1.0	0.25/20	CuI/0.23/10	DMF	60°C/48 h	/	/[a]
2	ZYN-2-132	0.10/1.0	0.15/20	$CuSO_4$•5H_2O/0.02/1.0 sodium ascorbate/0.045/3.0	*t*-BuOH/ water/DMF	r.t./36 h 35 °C/24 h	2-P133-CD-7	34%/0.047 g
3	ZYN-3-8	1.0/1.0	1.6/20	$CuSO_4$•5H_2O/0.19/1.0 sodium ascorbate/0.45/3.0	*t*-BuOH/ water/DMF	r.t./72 h	3-P8-CD-7	17%/0.32 g

The compound was prepared according to the procedure reported in the literature.[S10]

[a] The reaction was failed.

ZYN-3-8: To the solution of per-6-azide-permethyl-β- cyclodextrin **M-2** (1.0 g, 0.76 mmol, 1.0 equiv), sodium ascorbate (0.45 mg, 2.3 mmol, 3.0 equiv) and $CuSO_4$•5H_2O (0.19 g, 0.76 mmol, 1.0 equiv) in mix-solvent (DMF/*t*-BuOH/H_2O, 15 mL/25 mL/15 mL), methyl propiolate (**11**, 1.6 mL, 15.3 mmol) was added. The mixture was stirred at room temperature for 72 h under a nitrogen atmosphere. After cooling to room temperature, the mixture was filtered to remove any insoluble copper salt, and a solution of KOH (1.7 g, 80 mM) in 30 mL H_2O/MeOH (1/1) was added into the filtrate, and heated under reflux for 3 h at 90 ~ 100 °C. The reaction mixture was acidified with 1 M HCl to pH 3 ~ 4, then dried under reduced pressure. The obtained product was dissolved in water and was dialyzed (500 D membrane) for 48 h, then dried under reduced pressure to yield the product **CD-7** (0.32 g, yield: 17%; label: 3-P8-CD-7) as a brown powder.

^{1}H NMR (400 MHz, D_2O): δ = 8.17 (s, 4H), 5.23 (d, J = 3.7 Hz, 9H), 4.62 (d, J = 12.3 Hz, 7H), 4.34 (t, J = 9.1 Hz, 14H), 4.05 (t, J = 9.5 Hz, 9H), 3.73 – 3.51 (m, 12H), 3.41 (t, J = 9.1 Hz, 8H). (*Lit.*[S10] *^{1}H NMR (400 MHz, D_2O): δ = 8.11 (s, 7H), 5.10 (d, J = 3.5 Hz, 7H), 4.45 (d, J = 12.2 Hz, 7H), 4.26–4.10 (m, 14H), 3.93 (t, J = 9.4 Hz, 7H), 3.53 (dd, J = 10.0, 3.4 Hz, 7H), 3.34 (t, J = 9.1 Hz, 7H)*).

Scheme S2. Synthetic scheme for β-cyclodextrin **CD-8**.

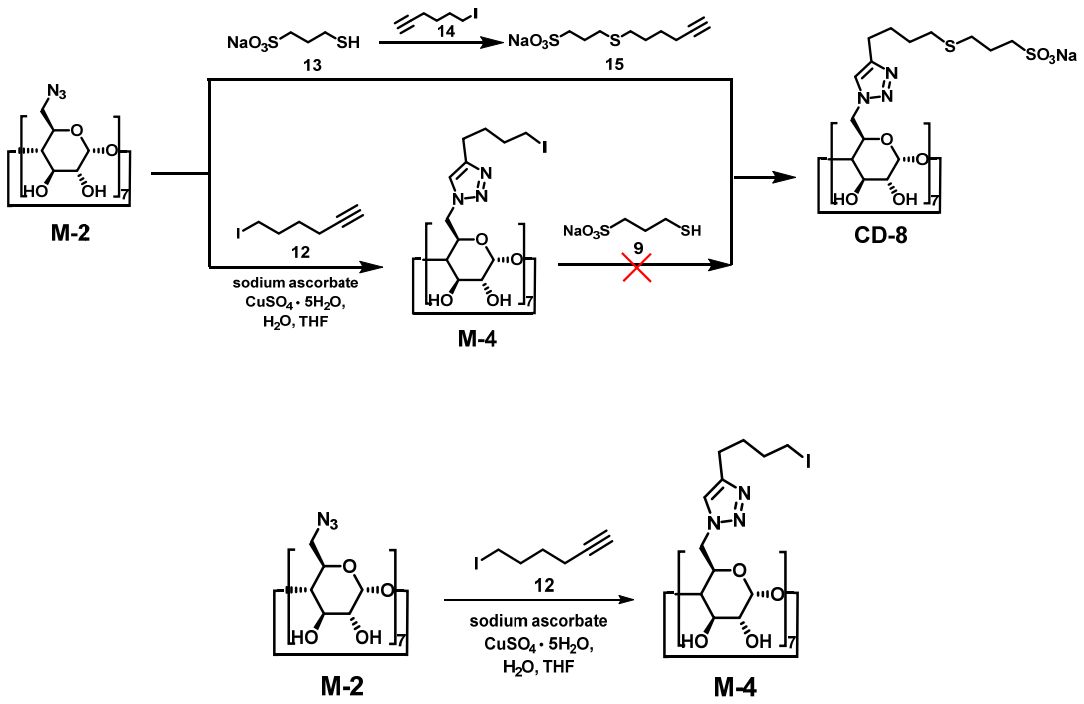


Table S20. Summary for preparation of Compound **M-4**.

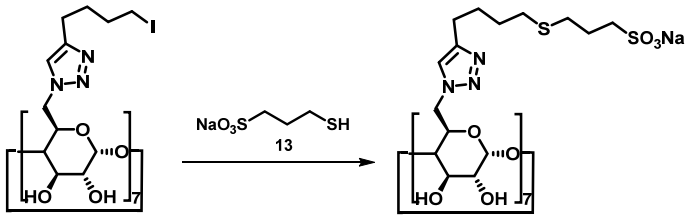
Run	SM		**12** (μL/equiv)	$CuSO_4$•$5H_2O$ (mg/equiv)	sodium ascorbate (mg/equiv)	Solvent	Condition	Product	
	M-2							**M-4**	
	Label	mg/equiv						Label	Yield
1	ZYN-4-105	100.1/1.0	80/8.0	8.1/0.8	12.2/1.6	dioxane/ water	r.t. 3 days	/	/[a]
2	ZYN-4-107	100.2/1.0	80/8.0	20.0/1.0	46.1/3.0	*t*-BuOH/ DMF/water	r.t. 3 days	/	/[a]
3	ZYN-4-111	50.2/1.0	40/8.0	10.1/1.0	25.3/3.0	THF/water	r.t. 3 days	4-P111-M-4	65%/77.2 mg
4	ZYN-4-113	300.1/1.0	422/14.0	81.1/1.4	190.4/4.2	THF/water	r.t. 3 days	4-P113-M-4	58%/370.2 mg

[a] The reaction was failed.

ZYN-4-113: To the solution of per-6-azide-permethyl-β-cyclodextrin **M-2** (300.1 mg, 0.228 mmol, 1.0 equiv) and 6-iodo-1-hexyne (**12**, 422 μL, 3.19 mmol, 14.0 equiv) in dry THF (6 mL), a solution of sodium ascorbate (190.4 mg, 0.96 mmol, 4.2 equiv) and $CuSO_4$•$5H_2O$ (81.1 mg, 0.32 mmol, 1.4 equiv) in water (1.5 mL) was added. The mixture was stirred at room temperature for 72 h under a nitrogen atmosphere. The solution was dried under reduced pressure and washed with DCM to remove 6-iodo-1-hexyne. The residue was dialyzed (500 D membrane) for 48 h and dried under reduced pressure to yield the product **M-4** (370.2 mg, 0.132 mmol yield: 58%; label: 4-P113-M-4) as a slightly brown powder.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.82 (s, 7H), 6.09 – 5.90 (m, 17H), 5.17 – 4.91 (m, 22H), 4.57 (s, 6H), 3.90 – 3.52 (m, 27H), 2.20 – 1.36 (m, 72H). ^{13}C NMR (150 MHz, DMSO-d_6): δ =

139.93, 128.99, 101.83, 81.47, 72.14, 71.40, 68.27, 53.77, 48.91, 20.88, 20.01, 17.55. IR (KBr): 3362.07, 2922.28, 1757.23, 1631.85, 1573.98, 1446.63, 1386.88, 1329.01, 1294.29, 1224.85, 1155.41, 1078.25, 1047.39, 831.36, 804.35, 754.20, 651.97, 590.24 cm^{-1}. HRMS-ESI, $[M+2H]^{2+}$ calculated for $C_{84}H_{128}N_{21}O_{28}I_7$, 1383.6467, found 1381.6982, 1382.2112, 1382.7101, 1383.2032, 1383.7112; $[M-2I]^{2+}$ calculated for $C_{84}H_{126}N_{21}O_{28}I_5$, 1256.6467, found 1255.7249, 1256.2297, 1256.7296, 1257.2246.



M-4 **CD-8**

Table S21. Summary for preparation of Compound **CD-8**.

Run	SM		**13** (g/equiv)	Base (equiv)	Solvent	Condition	Product	
	M-4						**CD-8**	
	Label	g/equiv					Label	Yield
1	ZYN-4-131	0.05/1.0	0.045/14.0	K_2CO_3/10.0 Cs_2CO_3/10.0	DMF (dry)	60 °C/3 days	/	/[a]
2	ZYN-4-135	0.05/1.0	0.045/14.0	TEA/20.0	DMSO (dry)	60 °C/3 days	/	/[a]
3	ZYN-4-138	0.035/1.0	0.039/17.0	TEA/20.0	DMSO (dry)	MW/120 °C/4 h	/	/[a]
4	ZYN-4-137	0.035/1.0	0.039/17.0	K_2CO_3/10.0 Cs_2CO_3/10.0	DMF (dry)	MW/100 °C/3 h	/	/[a]

[a] The reaction was failed.

Compound CD-8: To the solution of **M-4** (1.0 equiv) and sodium 3-mercapto-1-propanesulfonate (**13**, 14 ~ 17.0 equiv) in dry DMSO or DMF, base (20.0 equiv) was added. The mixture was stirred at different temperature under a nitrogen atmosphere. The solution was concentrated under reduced pressure. The residue was dialyzed (500 D membrane) for 48 h. However, we were failed to obtain the desired product.

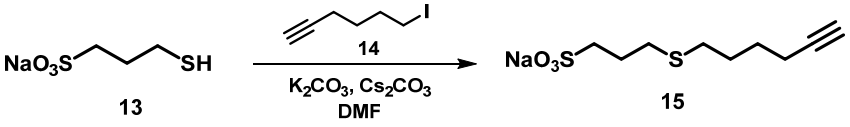
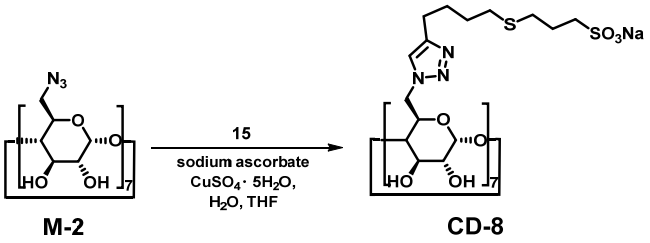


Table S22. Summary for preparation of Compound **10**.

Run	SM		**14** (mL/equiv)	Base (g/equiv)	Solvent	Condition	Product	
	13						**15**	
	Label	g/equiv					Label	Yield

1	ZYN-4-134	0.05/1.2	0.03/1	K_2CO_3/0.04/1.2 Cs_2CO_3/0.094/1.2	DMF (dry)	45℃/20 h	4-P134-10	0.18 g/crude
2	ZYN-4-140	1.1 /1.2	0.65/1	K_2CO_3/0.82/1.2 Cs_2CO_3/1.93/1.2	DMF (dry)	45℃/16 h	4-P140-10	3.6 g/Crude

ZYN-4-134: To the solution of 3-mercapto-1-propanesulfonate (**13**, 0.05 g，0.288 mmol, 1.2 equiv), Cs_2CO_3 (94 mg，0.288 mmol, 1.2 equiv) and K_2CO_3 (40 mg，0.288 mmol, 1.2 equiv) in dry DMF (2 mL), 6-iodo-1-hexyne (**14**, 32 μL，0.24 mmol, 1.0 equiv) was added dropwise to the solution. The mixture was stirred at 45 ℃ for 20 h under a nitrogen atmosphere. The crude product was used without further purification.



M-2 CD-8

Table S23. Summary for preparation of Compound **CD-8**.

Run	SM		**15** (g/equiv)	$CuSO_4$•$5H_2O$ (g/equiv)	sodium ascorbate (g/equiv)	Solvent	Condition	Product	
	M-2							**CD-8**	
	Label	g/equiv						Label	Yield
1	ZYN-4-136	0.018/1.0	0.18 g Crude	0.009/2.4	0.014/4.8	THF water	r.t./3 days	4-P136-CD-9	75%/0.02 g
2	ZYN-4-141	0.4/1.0	3.6 g Crude	0.26/2.4	0.35/4.8	THF water	r.t./3 days	4-P141-CD-9	67%/0.65 g

ZYN-4-141: To the solution of per-6-azide-permethyl-β- cyclodextrin **M-2** (0.4 g, 0.304 mmol, 1.0 equiv) and **crude 15** (3.6 g) in dry THF (13 mL), a solution of sodium ascorbate (0.35 g, 1.46 mmol, 4.8 equiv) and $CuSO_4$•$5H_2O$ (0.26 g, 0.73 mmol, 2.4 equiv) in water (10 mL) was added. The mixture was stirred at room temperature for 72 h under a nitrogen atmosphere. The solution was concentrated under reduced pressure and the residue was dialyzed (500 D membrane) for 48 h, then dried under reduced pressure to yield the product **CD-8** (0.65 mg, 0.204 mmol, yield: 67%; label: 4-P141-CD-9) as a brown powder.

^{1}H NMR (600 MHz, D_2O : DMSO-d_6 = 1 : 1, add NaOH): δ = 8.10 (s, 7H), 5.34 (s, 7H), 4.45 (s, 7H), 4.30 – 3.88 (m, 21H), 3.76 (s, 10H), 3.57(s, 7H), 3.00 (s, 28H), 2.12 (s, 21H), 1.73 (s, 42H). ^{13}C NMR (150 MHz, D_2O): δ = 148.17, 125.08, 102.44, 102.07, 72.20, 49.99, 49.54, 49.41, 31.45, 27.94, 24.38. IR (KBr): 3426.69, 2929.03, 2831.62, 2715.89, 2360.97, 1628.95, 1603.88, 1455.35, 1365.66, 1189.17, 1153.48, 1074.40, 1045.46, 776.38, 604.71, 533.34 cm^{-1}. HRMS-ESI, $[M-4Na]^{4-}$ calculated for $C_{105}H_{168}N_{21}Na_3O_{49}S_{14}$, 755.9271, found 754.9360,

755.4281, 755.6840, 755.9360, 756.4323; $[M-5Na]^{5-}$ calculated for $C_{105}H_{168}N_{21}Na_2O_{49}S_{14}$, 600.1437, found 603.7416, 603.9425, 604.1456, 604.3446, 604.5456, 604.7434, 604.9445.

3.b UV-vis Spectra of β-CD Derivatives

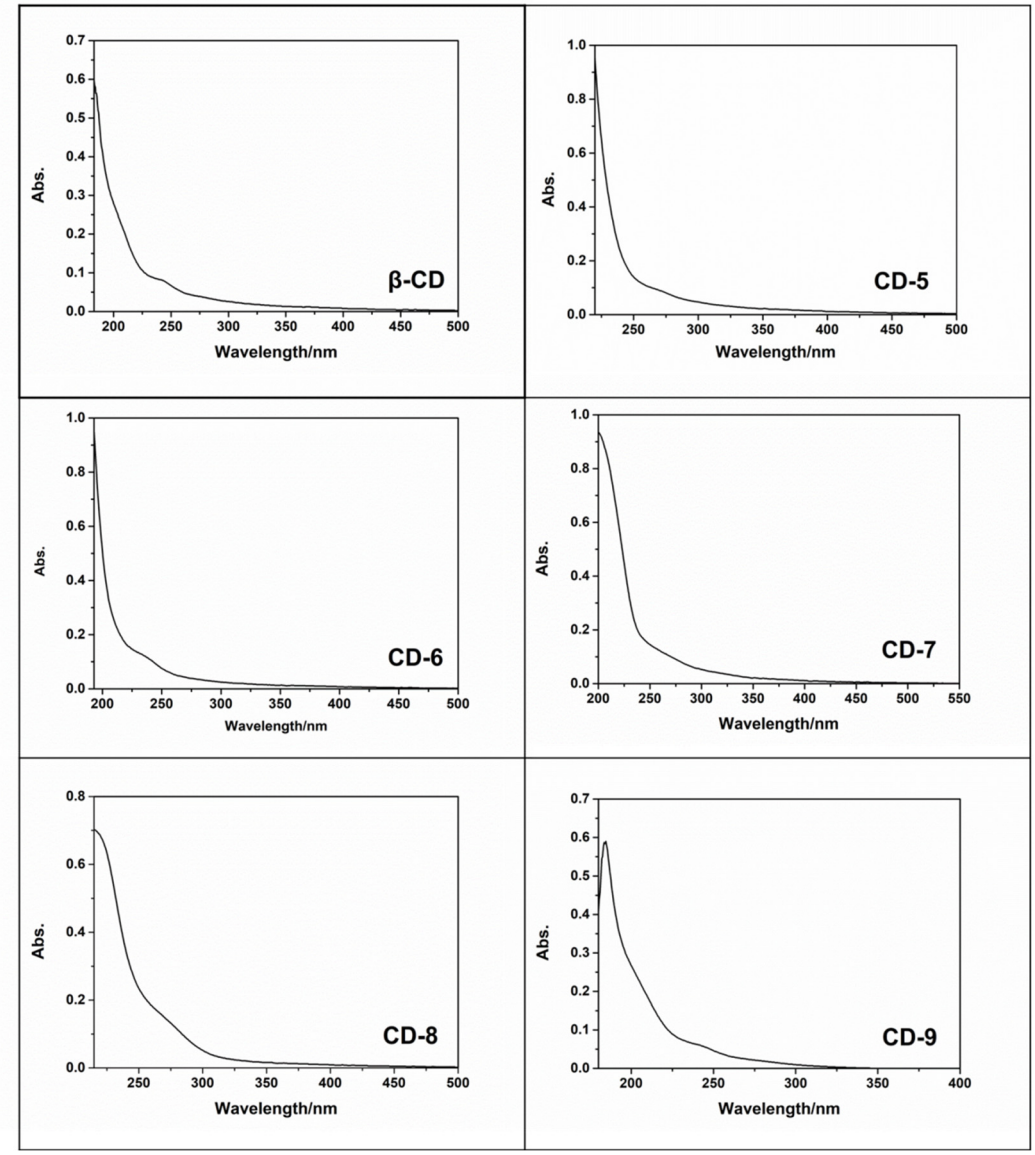


Figure S2. UV-vis Spectra of the β-CDs at 25 °C in water. The concentration: β-CD (0.40 mM), **CD-5** (0.40 mM), **CD-6** (0.20 mM), **CD-7** (0.08 mM), **CD-8** (0.10 mM), **CD-9** (0.40 mM).

3.c Water-solubility Measurements of β-CD and its derivatives

Excess of β-CD or its derivatives **CD-1 ~ CD-9** was added to a small amount of deionized water in a vial to form a suspension mixture. The mixture was stirred at 25 °C for 5 hours to ensure achieving dissolution equilibrium. The suspension was centrifuged, and the apparently homogenous solution was filtered with a syringe filter (aqueous phase, 0.22 μm). A 0.2 mL

solution of the transparent filtrate was transferred to another vial. It was dried and the solubility of the compound was determined based on the weight of the residue and the volume of the transferred solution. The determined water solubilities are shown in Table 1, main text.

4. Host-guest Chemistry and Properties of Z-3/β-CDs Complexes

4.a ITC Studies on the Complexation of Z-3 with β-CDs

The complexations of nitroxides **Z-3** with β-CD or its derivatives, **CD-5** ~ **CD-9**, were evaluated by ITC (VP-ITC Microcal Inc., Northampton, MA). The experiments were carried out at 298 K (25 °C) in water. A degassed aliquot (1.42 mL) of a solution was filled in the reaction cell, an identical volume of pure water was placed in the reference cell. On the other hand, another 300 µL degassed solution was loaded in the titration syringe. The binding experiments involved 28 sequential additions of a small aliquot (10 µL) of this latter solution in the reaction cell under continuous stirring at 349 rpm. The titrant was injected over 10 s with an interval of 310 s. After each addition, the heat was recorded. Control experiments were carried out under identical conditions to obtain the heats of dilution and mixing involved in injection of nitroxides **Z-3** or β-cyclodextrin derivatives into water. The integrated heat effects of each injection were corrected by subtracting from the corresponding control experimental data.

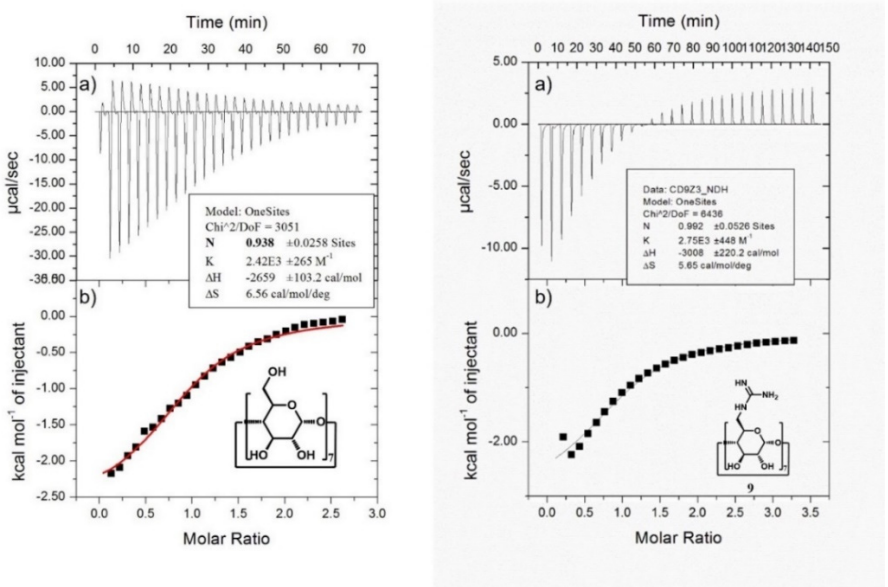


Figure S3. (a) Calorimetric titration enthalpogram, injection of 10 µL aliquots of 25 mM **CD** into the sample cell containing 2.2 mM of nitroxide **Z-3** in water; (b) Calorimetric titration enthalpogram, injection of 10 µL aliquots of 20 mM **CD-6** into the sample cell containing 1.3 mM of nitroxide **Z-3** in water.

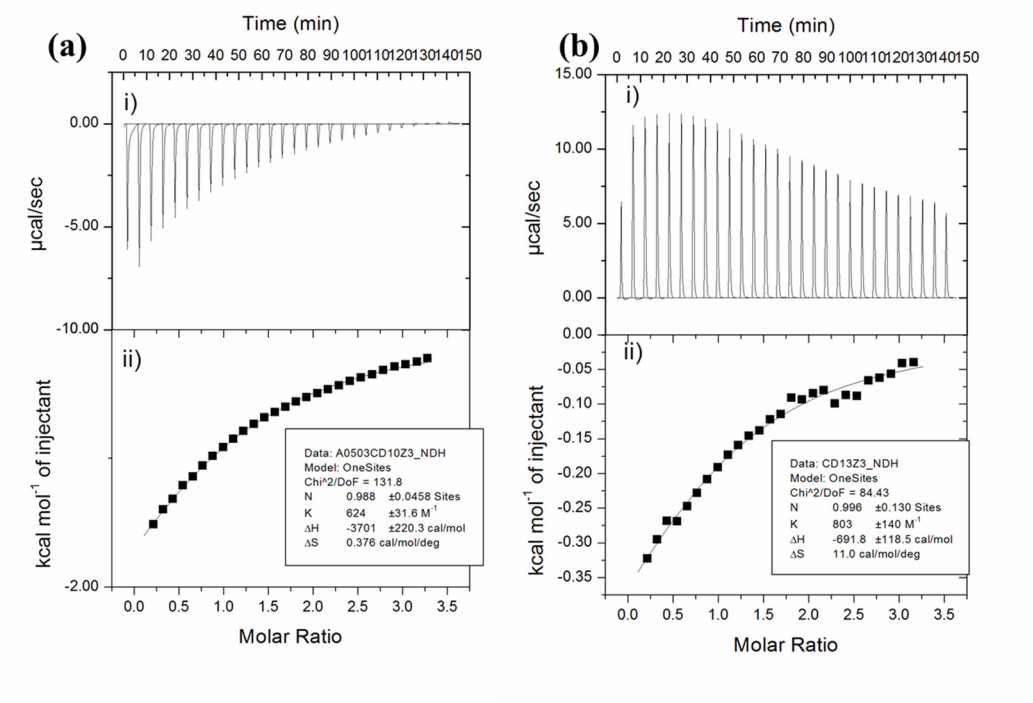


Figure S4. (a) Calorimetric titration enthalpogram, injection of 10 µL aliquots of 20 mM **CD-7** into the sample cell containing 1.3 mM of nitroxide **Z-3** in water; (b) Calorimetric titration enthalpogram, injection of 10 µL aliquots of 20 mM nitroxide **Z-3** into the sample cell containing 1.3 mM of **CD-8** in water.

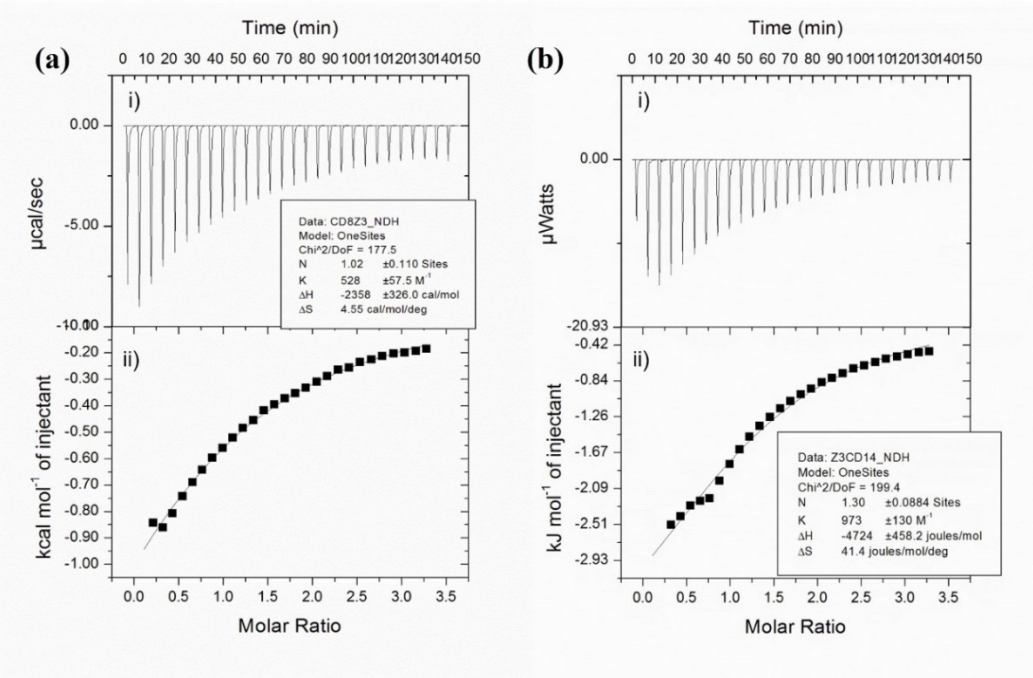


Figure S5. (a) Calorimetric titration enthalpogram, injection of 10 µL aliquots of 20 mM **CD-5** into the sample cell containing 1.3 mM of nitroxide **Z-3** in water; (B) Calorimetric titration enthalpogram, injection of 10 µL aliquots of 20 mM nitroxide **Z-3** into the sample cell containing 1.3 mM of **CD-9** in water.

Table S24. Thermodynamic parameters for the association of **Z-3** with β-CD and its derivatives obtained based on "one set of binding sites" model.

Compound	K/M^{-1}	ΔH kcal/mol	TΔS kcal/mol	ΔG kcal/mol
Z-3 ⊂ β-CD	$(2.42 \pm 0.27) \times 10^3$	$(-2.66 \pm 0.10) \times 10^3$	$(1.95 \pm 0.12) \times 10^3$	$(-4.61 \pm 0.07) \times 10^3$
Z-3 ⊂ CD-5	$(5.28 \pm 0.58) \times 10^2$	$(-2.36 \pm 0.33) \times 10^3$	$(4.55 \pm 0.34) \times 10^3$	$(-3.71 \pm 0.07) \times 10^3$
Z-3 ⊂ CD-6	$(2.75 \pm 0.45) \times 10^3$	$(-3.01 \pm 0.22) \times 10^3$	$(5.65 \pm 0.38) \times 10^3$	$-(4.69 \pm 0.10) \times 10^3$
Z-3 ⊂ CD-7	$(6.24 \pm 0.32) \times 10^2$	$(-3.70 \pm 0.22) \times 10^3$	$(1.47 \pm 0.22) \times 10^3$	$(-5.17 \pm 0.03) \times 10^3$
Z-3 ⊂ CD-8	$(8.03 \pm 0.14) \times 10^2$	$(-6.92 \pm 0.12) \times 10^2$	$(3.27 \pm 0.18) \times 10^3$	$(-3.96 \pm 0.01) \times 10^3$
Z-3 ⊂ CD-9	$(9.73 \pm 0.13) \times 10^2$	$(-4.72 \pm 0.46) \times 10^3$	$-(6.50 \pm 4.60) \times 10^2$	$(-4.07 \pm 0.06) \times 10^3$

4.b Water-solubilities of Z-3/β-CDs Complexes

The **Z-3**/β-CDs complexes were prepared by mixing **Z-3** and the corresponding β-CD or its derivative in deionized water, followed by concentrating under a reduced pressure and dried under high vacuum for overnight. Excess of the complexes was added to a small amount of deionized water in a vial to form a suspension mixture. The mixture was stirred at 25 °C for 5 hours to achieve dissolution equilibrium. The suspension was centrifuged, and the solution was filtered with a syringe filter (aqueous phase, 0.22 μm). A 0.2 mL filtrate was transferred to another vial and dried. The solubilities of the complexes were determined based on the weight of the residue and the volume of the solution transferred. The determined water solubilities are shown in Table 2, main text.

4.c EPR Spectra of Z-3/β-CDs Complexes in Water

X-band EPR spectra for complexes were acquired on a Bruker E500 instrument. DPPH powder (g = 2.0037) was used as a g-value reference. Spin concentrations of the radical samples were measured versus a 1.0 mM solution (in PBS, 100 mM, pH = 7.40 ± 0.01) of a stable radical, 3-Carboxy-Proxyl.

Equivalent amounts of **Z-3** and β-CD or its derivatives were weighed and dissolved in a 2 mL volumetric flask with 100 mM PBS buffer solution (pH = 7.40 ± 0.01) to give a solution of complexes with a nominal concentration of 1 mM. The solution was drawn into an EPR-quality quartz capillary tube (0.6-mm I.D.), and the capillary was stoppered with parafilm and placed in a 5-mm O.D. EPR sample tube for EPR test. A series of spectra were recorded at 295 K. The obtained EPR spectra and spectral simulations are shown in Figure 4b and Figure S6. The detailed parameters are summarized in Table S25.

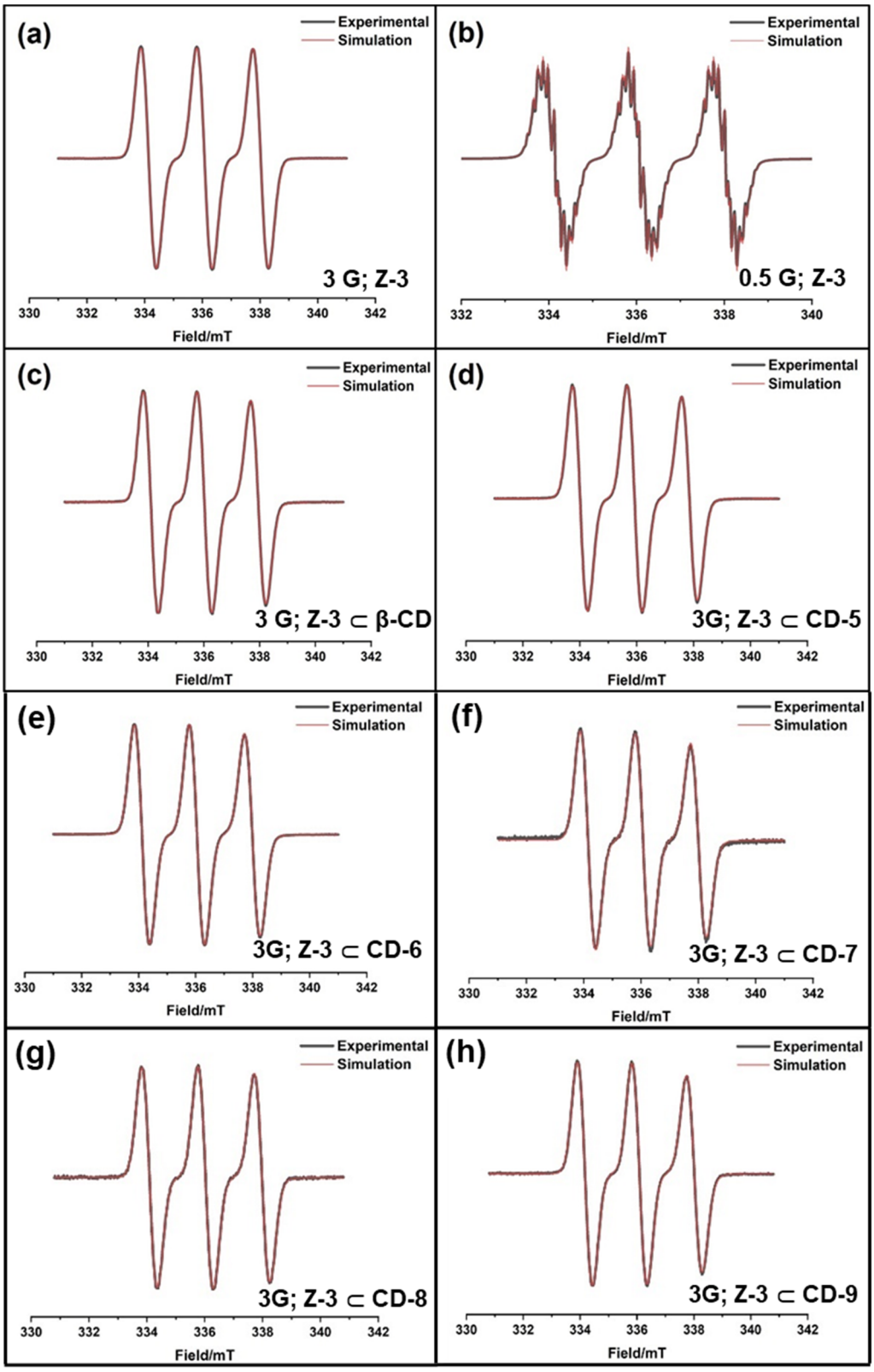


Figure S6. Experimental (black line) and simulated (red line) EPR spectra of **Z-3** and **Z-3**/β-CDs complexes in water: (a) **Z-3** (0.96 mM, modulation amplitude (Mod. Ampl.) = 3 G); (b) **Z-3** (0.67 mM, Mod. Ampl. = 0.5 G); (c) **Z-3 ⊂ β-CD** complexes (1.59 mM, M.A.= 3 G); (d) **Z-3 ⊂ CD-5** complexes (0.69 mM, Mod. Ampl. = 3 G); (e) EPR spectra and spectral simulations of complexes **Z-3 ⊂ CD-6** (2.03 mM, Mod. Ampl. = 3 G); (f) EPR spectra and spectral simulations of complexes **Z-3 ⊂ CD-7** (0.27 mM, Mod. Ampl. = 3 G); (g) EPR spectra and spectral simulations of complexes **Z-3 ⊂ CD-8** (0.31 mM, Mod. Ampl. = 3 G); (h) EPR spectra and spectral simulations of complexes **Z-3 ⊂ CD-9** (1.0 mM, Mod. Ampl. = 3 G).

Table S25. EPR parameters for Z-3 and its complexes with β-CDs in PBS buffer.

Compound	Experimental						Simulations						
	g	a_{N1}/G	a_{N2}/G	H2[a]	H3[a]	Compl. ratio[b]	a_{Nx}/G	a_{Ny}/G	a_{Nz}/G	lwpp/G		Corr Time (ns)[e]	RMSD[f]
Z-3	2.0063	19.255	19.454	6.891	6.840	/	19.83	18.84	19.65	5.271[c]	0.0449[d]	0.0485	0.00167
Z-3 ⊂ β-CD	2.0063	19.257	19.453	11.854	10.93	97%	14.02	31.53	12.28	5.256[c]	-0.1054[d]	0.2885	0.002123
Z-3 ⊂ CD-5	2.0072	19.159	19.356	22.449	20.302	93%	14.82	31.62	9.84	5.251[c]	-0.00894[d]	0.2493	0.001899
Z-3 ⊂ CD-6	2.0065	19.257	19.354	14.569	13.397	97%	13.95	28.40	12.37	5.274[c]	-0.05049[d]	0.3090	0.001282
Z-3 ⊂ CD-7	2.0063	18.963	19.355	1.921	1.716	92%	21.40	27.29	9.16	5.259[c]	0.0387[d]	0.2700	0.005300
Z-3 ⊂ CD-8	2.0060	19.257	19.452	3.077	2.859	94%	14.10	29.02	15.26	5.250[c]	-0.0647[d]	0.2286	0.004484
Z-3 ⊂ CD-9	2.0063	19.159	19.452	5.394	4.748	95%	33.21	10.49	13.97	5.265[c]	-0.3422[d]	0.2805	/

[a] The heights (a.u.) of the middle- (H2) and the high-field (H3) EPR peaks. [b]Complexation ratio. [c] The lineshape Gaussian broadening in EPR spectra. [d] The lineshape Lorentzian broadening in EPR spectra. [e] Rotational correlation time. [f] The root-mean-square deviation for the simulation.

4.d Decay Studies on Z-3 and Z-3/β-CDs Complexes in Water via UV-vis spectroscopy

Decay of Z-3. The radical **Z-3** (0.4 mM) in deionized water was transferred to a UV-vis quartz cuvette equipped with a stopcock. UV-vis spectrum of the solution in the absence of light was recorded at 25 °C periodically.

Decay of Z-3/β-CDs Complexes. β-CD or its derivatives was dissolved into deionized water in 5 mL volumetric flask to give a host solution of with a concentration in the range of 250~400 μM. Similarly, a stock solution of **Z-3** (89 mM) in deionized water was separately prepared. In the UV-vis measurements, a 2.0 mL solution of β-CD or its derivatives was first transferred to a UV-vis quartz cuvette equipped with a stopcock and its UV-vis spectrum was recorded as the background. Next, an equivalent amount of **Z-3** from the stock solution was added into the UV-vis cuvette. While the mixture was stored at a fixed temperature of 25 °C, the corresponding UV-vis spectrum was recorded from time to time. After subtracting the background of β-CD or its derivatives, a series of time-dependent UV-vis spectra (Figure S7) corresponding to the decay of **Z-3** in the complexes at 25 °C were obtained.

Decay Kinetics. The kinetics were studied by monitoring their absorption at a point in the range of $\lambda \approx 241-280$ nm in the UV-vis spectra (Figure S7). Given the additivity of absorbances (A), we have

$$A_{obsv} = \varepsilon_{\mathbf{Z\text{-}3}}[\mathbf{Z\text{-}3}] + \varepsilon_{\mathbf{Z\text{-}3R}}[\mathbf{Z\text{-}3R}] \quad \text{(S1)}$$

$$[\mathbf{Z\text{-}3}]_0 = [\mathbf{Z\text{-}3}] + [\mathbf{Z\text{-}3R}] \quad \text{(S2)}$$

where A_{obsv} is the absorbance we observed, $\varepsilon_{Z\text{-}3}$ and $\varepsilon_{Z\text{-}3R}$ is the molar absorptivity of **Z-3** and **Z-3R**, respectively, [**Z-3**] and [**Z-3R**] are the analytical concentrations correspondingly, and $[\mathbf{Z\text{-}3}]_0$ is the initial concentration of **Z-3**.

Combining the Equations (S1) and (S2) gives,

$$A_{obsv} = (\varepsilon_{\mathbf{Z\text{-}3}} + \varepsilon_{\mathbf{Z\text{-}3R}})[\mathbf{Z\text{-}3}] + \varepsilon_{\mathbf{Z\text{-}3R}}[\mathbf{Z\text{-}3}]_0 \quad \text{(S3)}$$

The kinetic equation for the decay of **Z-3** can be expressed as,

$$[\mathbf{Z\text{-}3}] = [\mathbf{Z\text{-}3}]_0 e^{-kt} \quad \text{(S4)}$$

in which k is the rate constant, and t is the cumulative annealing time. Based on Equations (S3) and (S4), we therefore have

$$-\ln\left(A_{obsv} - \varepsilon_{\mathbf{Z\text{-}3R}}[\mathbf{Z\text{-}3}]_0\right) = -kt + \ln(\varepsilon_{\mathbf{Z\text{-}3}} - \varepsilon_{\mathbf{Z\text{-}3R}})[\mathbf{Z\text{-}3}]_0 \quad \text{(S5)}$$

Software Orgin was used to fit $-\ln(A_{obsv} - \varepsilon_{\mathbf{Z\text{-}3R}}[\mathbf{Z\text{-}3}]_0)$ versus t. The first order rate constants (k) and corresponding statistical analyses of the fits are summarized in Tables 2 in the main text.

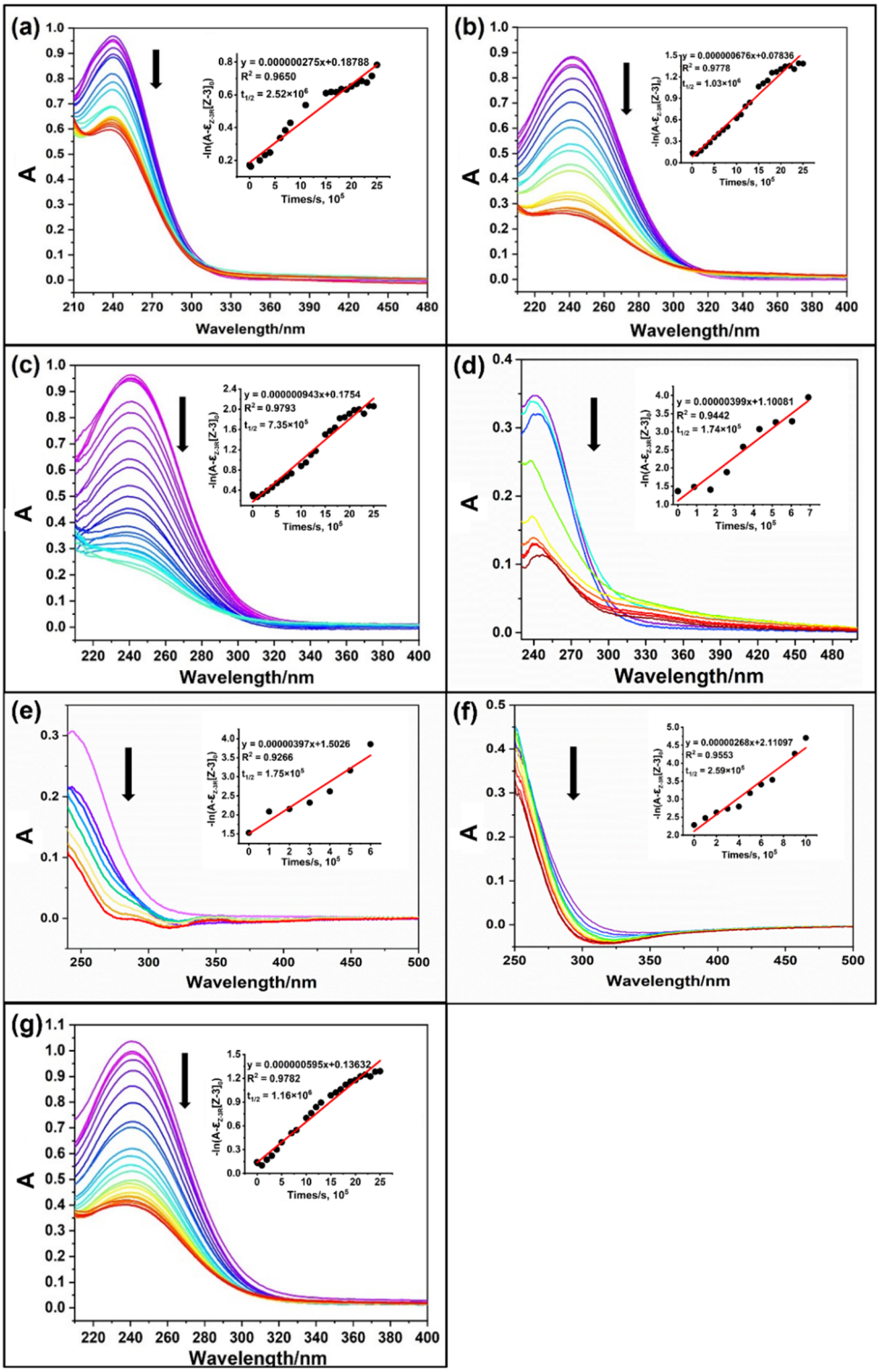


Figure S7. UV−vis spectrum monitoring of the decay of **Z-3** as well as **Z-3** inside β-CDs in pure water at 25 °C. The absorptions of β-CDs, if present, were subtracted as backgrounds. Inset plots: $-\ln(A-\varepsilon_{\mathbf{Z\text{-}3R}}[\mathbf{Z\text{-}3}]_0)$ vs t, in which $[\mathbf{Z\text{-}3}]_0$ corresponds to the initial concentration of **Z-3**, A and $\varepsilon_{\mathbf{Z\text{-}3R}}$ is the observed absorption and the molar absorption coefficient of **Z-3R**, respectively, at a point in the range of $\lambda \approx 241-280$ nm in the UV-vis spectra. (a) **Z-3** (0.4 mM, Inset plot: $\lambda = 241$ nm); (b) **Z-3 ⊂ CD** (0.4 mM, Inset plot: $\lambda = 241$ nm); (c) **Z-3 ⊂ CD-5** (0.4 mM, Inset plot: $\lambda = 241$ nm); (d) **Z-3 ⊂ CD-6** (0.3 mM, Inset plot: $\lambda = 241$ nm). (e) **Z-3 ⊂ CD-7** (0.3 mM, Inset plot: $\lambda = 255$ nm); (f) **Z-3 ⊂ CD-8** (0.25 mM, Inset plot: $\lambda = 280$ nm); (g) **Z-3 ⊂ CD-9** (0.4 mM, Inset plot: $\lambda = 245$ nm).

5. Computational Details

DFT calculations were performed using the Gaussian 09 program package[S11] in Linux operating system. The geometries for the triplet ground states were obtained by full system optimization at the UB3LYP/6-31G(d,p) levels of theory without symmetry constraints, using the default (Gaussian 09) polarizable continuum model for water.[S12,S13] Frequencies were also calculated at the same level of theory to ensure the stationary points represented the minima on the potential energy surfaces. Based on the optimized geometries, the single-point energy computations were done at the same level of theory. Orbital localization analyses were carried out using Multiwfn3.4[14]. Spin density surfaces were calculated at the UB3LYP/6-31G(d,p) level. The spin density maps were illustrated by GaussView 6.0, using "medium" setting and an isodensity of 0.004 electron Bohr^{-3} for plotting the surfaces.

The results are shown in Figure 6 (main text), Figure S8 and Table S26. The spin density distribution of **Z-3** is basically similar to **AZADO** (Table S26). The unpaired single electron is mainly distributed on the nitrogen oxygen bond N9-O21, and it can transfer through δ bonds to C4, C6, C7 and C8, which proves that the substitution of hydroxyl group has no obvious effect on the spin density distribution.

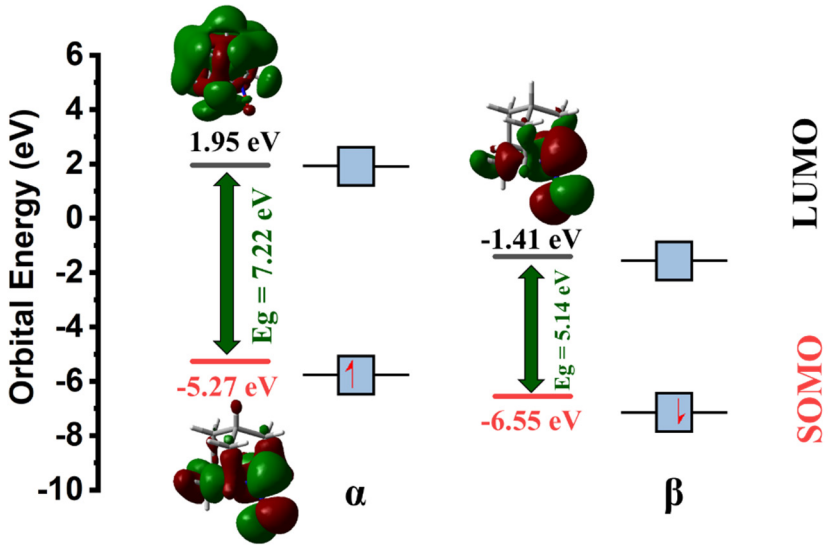
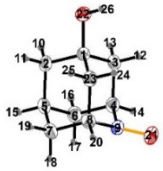
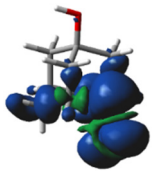
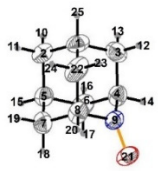
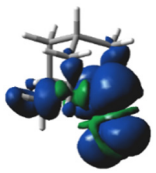


Figure S8. Frontier orbitals and energies of **AZADO**.

Table S26. Mulliken atomic charge distributions and spin densities for nitroxide radical **Z-3** and **AZADO** at the UB3LYP/6-31G(d,p)/PCM-UFF(water) level.

Z-3				**AZADO**			
							
Charges		**Spin densities**		**Charges**		**Spin densities**	
1 C	0.270649	1 C	-0.000711	1 C	-0.08366	1 C	-0.00117
2 C	-0.191413	2 C	0.001075	2 C	-0.17631	2 C	0.001309
3 C	-0.177804	3 C	0.005476	3 C	-0.17633	3 C	0.005648
4 C	0.031873	4 C	-0.019358	4 C	0.040736	4 C	-0.0195
5 C	-0.089057	5 C	-0.003056	5 C	-0.08039	5 C	-0.00297
6 C	-0.171700	6 C	0.030938	6 C	-0.17262	6 C	0.03145
7 C	-0.172305	7 C	0.030928	7 C	-0.17289	7 C	0.031441
8 C	0.033700	8 C	-0.019407	8 C	0.041349	8 C	-0.01949
9 N	-0.018172	9 N	0.452730	9 N	-0.02061	9 N	0.456777
10 H	0.102456	10 H	-0.000101	10 H	0.096081	10 H	-0.000095
11 H	0.097814	11 H	-0.000105	11 H	0.096116	11 H	-0.000095
12 H	0.110747	12 H	0.000460	12 H	0.105211	12 H	0.000533
13 H	0.112474	13 H	-0.000142	13 H	0.106892	13 H	-0.000095
14 H	0.116193	14 H	0.002654	14 H	0.109746	14 H	0.002375
15 H	0.098301	15 H	0.000940	15 H	0.091787	15 H	0.001117
16 H	0.111203	16 H	0.003177	16 H	0.10669	16 H	0.002994
17 H	0.108952	17 H	-0.002077	17 H	0.104791	17 H	-0.002167
18 H	0.109196	18 H	-0.002084	18 H	0.104758	18 H	-0.002167
19 H	0.111228	19 H	0.003167	19 H	0.106718	19 H	0.002988
20 H	0.115567	20 H	0.002660	20 H	0.109695	20 H	0.002375
21 O	-0.459688	21 O	0.506229	21 O	-0.46491	21 O	0.501711
22 O	-0.601004	22 O	0.000556	22 C	-0.17668	22 C	0.005639
23 C	-0.189497	23 C	0.005534	23 H	0.105202	23 H	0.000536
24 H	0.110773	24 H	0.000450	24 H	0.106931	24 H	-0.000091
25 H	0.108761	25 H	-0.000128	25 H	0.091689	25 H	0.000950
26 H	0.320754	26 H	0.000192				

To further investigate the spectral properties of compound **Z-3**, the absorption spectra of compound **Z-3** in aqueous solution were calculated at the TD-DFT/B3LYP/6-31+G(d,p) level with the IEF-PCM-UFF solvent model for water. As shown in Table S27, the absorption of **Z-3** is mainly attributed to β-HOMO-4 → β-LUMO (f = 0.0148, λ_{calc} = 262.57 nm), α-HOMO →

α-LUMO (f = 0.0076, λ_{calc} = 247.81 nm), β-HOMO-2 → β-LUMO (f = 0.0659, λ_{calc} = 244.7 nm) and β-HOMO → β-LUMO (f = 0.0210, λ_{calc} = 228.63 nm).

Table S27. Electronic transitions of **Z-3** calculated at the TD-DFT/B3LYP/6-31+G(d,p) level: main contribution, $<S^2>$, energies, wavelength, and oscillator strength.

Excited Sate	Main contribution	$<S^2>$	Energy [eV]	Wavelength [nm]	Oscillator strength
1	β-HOMO→ β-LUMO	0.756	2.6872	461.39	0.0002
2	β-HOMO-4→ β-LUMO	0.771	4.7219	262.57	0.0148
3	α-HOMO→ α-LUMO	0.783	5.0031	247.81	0.0076
4	β-HOMO-2→ β-LUMO	0.764	5.0668	244.70	0.0659
5	β-HOMO→ β-LUMO	0.769	5.4229	228.63	0.0210
6	α-HOMO→ α-LUMO+1	0.785	5.4869	225.96	0.0030
7	α-HOMO→ α-LUMO+2	0.786	5.6123	220.91	0.0044
8	α-HOMO→ α-LUMO+3	0.787	5.6624	218.96	0.0007
9	β -HOMO-4→ β-LUMO	0.772	5.7539	215.48	0.0119
10	α-HOMO→ α-LUMO+4	0.785	6.0179	206.03	0.0023
11	β-HOMO-5→ β-LUMO	0.775	6.0521	204.86	0.0044
12	α-HOMO→ α-LUMO+5 β-HOMO-5→ β-LUMO	0.783	6.1332	202.15	0.0038
13	α-HOMO→ α-LUMO+6	0.788	6.2040	199.85	0.0013
14	α-HOMO→ α-LUMO+7 α-HOMO→ α-LUMO+8	0.784	6.2925	197.03	0.0064
15	β-HOMO→ β-LUMO+1	1.801	6.3690	194.67	0.0018
16	α-HOMO→ α-LUMO+8 α-HOMO→ α-LUMO+7	0.897	6.3727	194.55	0.0010
17	β-HOMO-6→ β-LUMO	0.782	6.3813	194.29	0.0069
18	α-HOMO-2→ α-LUMO α-HOMO-2→ α-LUMO+1 β-HOMO-1→ β-LUMO+1 β-HOMO-1→ β-LUMO+2	2.539	6.5991	187.88	0.0010
19	β-HOMO-7→ β-LUMO+2	0.946	6.6418	186.67	0.0065
20	α-HOMO-1→ α-LUMO	1.599	6.6716	185.84	0.0029

6. Optimized Geometries/Coordinate Outputs of DFT Calculations

Z-3 :

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.426418	-0.299669	0.007006
2	6	0	-1.351828	1.240417	0.028105
3	6	0	-0.705727	-0.864013	1.241491
4	6	0	0.759022	-0.397952	1.236892
5	6	0	0.122078	1.705911	0.023444
6	6	0	0.839787	1.143414	1.269104
7	6	0	0.827182	1.178675	-1.244774
8	6	0	0.750072	-0.363120	-1.254292
9	7	0	1.402842	-0.860297	-0.017803
10	1	0	-1.871007	1.611044	0.919876
11	1	0	-1.878891	1.643235	-0.847211
12	1	0	-0.762217	-1.957755	1.233170
13	1	0	-1.199881	-0.510229	2.152735
14	1	0	1.326676	-0.848674	2.053669
15	1	0	0.162931	2.800573	0.038503
16	1	0	0.374363	1.515003	2.189114
17	1	0	1.891844	1.448738	1.280764
18	1	0	1.878275	1.487101	-1.259263
19	1	0	0.351339	1.574059	-2.149485
20	1	0	1.311746	-0.790558	-2.087698
21	8	0	2.679859	-1.020297	-0.024290
22	8	0	-2.776067	-0.760986	0.074872
23	6	0	-0.714934	-0.830811	-1.254255
24	1	0	-0.771284	-1.924328	-1.274492
25	1	0	-1.212855	-0.453568	-2.155732
26	1	0	-3.246675	-0.399411	-0.690316

Z-3R :

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.441063	-0.044264	0.975496
2	6	0	1.951729	0.021426	-0.480127
3	6	0	0.573531	-1.305122	1.164963
4	6	0	-0.612237	-1.256547	0.186497
5	6	0	0.755664	0.065720	-1.457079
6	6	0	-0.108764	-1.200629	-1.272496
7	6	0	-0.108006	1.310650	-1.159379
8	6	0	-0.611865	1.234813	0.298654
9	7	0	-1.391791	-0.019865	0.444313
10	1	0	2.579567	-0.852117	-0.696314
11	1	0	2.580358	0.910382	-0.616524
12	1	0	0.205557	-1.367708	2.195395
13	1	0	1.158656	-2.211061	0.969561
14	1	0	-1.304210	-2.087675	0.341765
15	1	0	1.120580	0.112330	-2.489601
16	1	0	0.471785	-2.104138	-1.492906
17	1	0	-0.969217	-1.185232	-1.951119
18	1	0	-0.968192	1.356871	-1.836965
19	1	0	0.473205	2.229994	-1.297354
20	1	0	-1.303401	2.048859	0.528153
21	8	0	-2.635628	-0.004879	0.111052
22	6	0	0.573566	1.194737	1.277706
23	1	0	0.205346	1.164038	2.309506
24	1	0	1.159024	2.114449	1.165118
25	1	0	2.290417	-0.075610	1.667268

7. Routine ^{1}H NMR, ^{13}C NMR Spectra and HR-MS Spectra

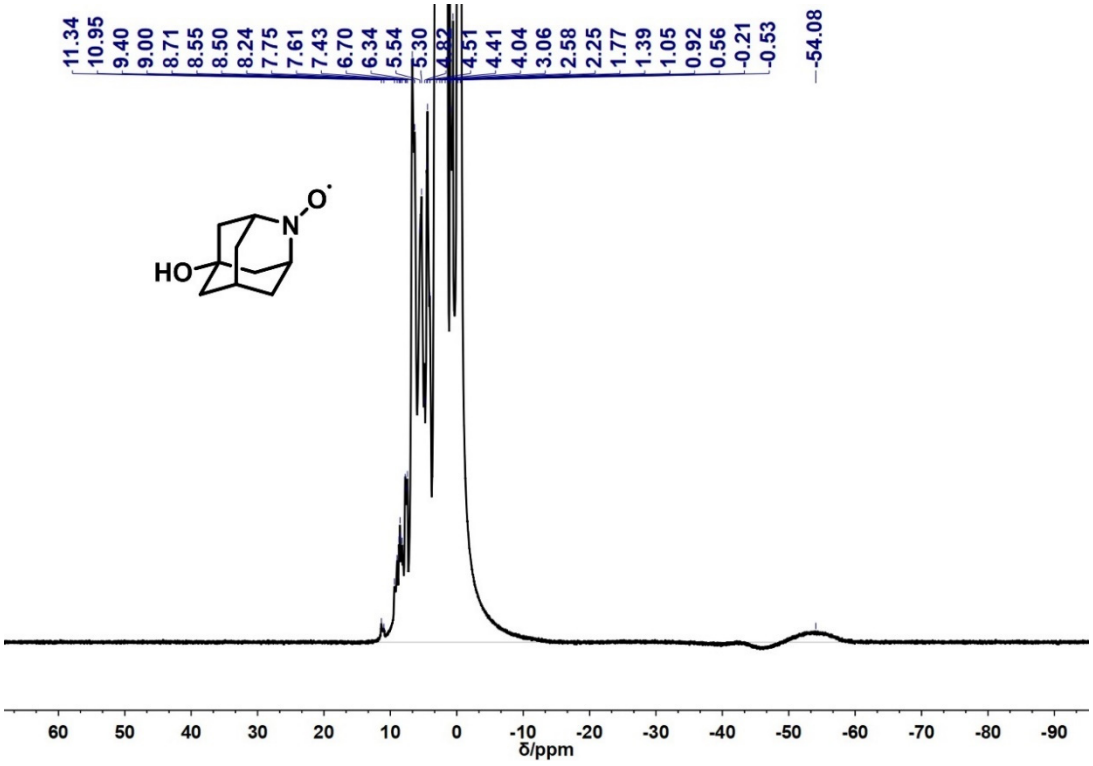


Figure S9. ^{1}H NMR spectrum (600 MHz, 298 K, 0.55 M, $CDCl_3$) of **Z-3**.

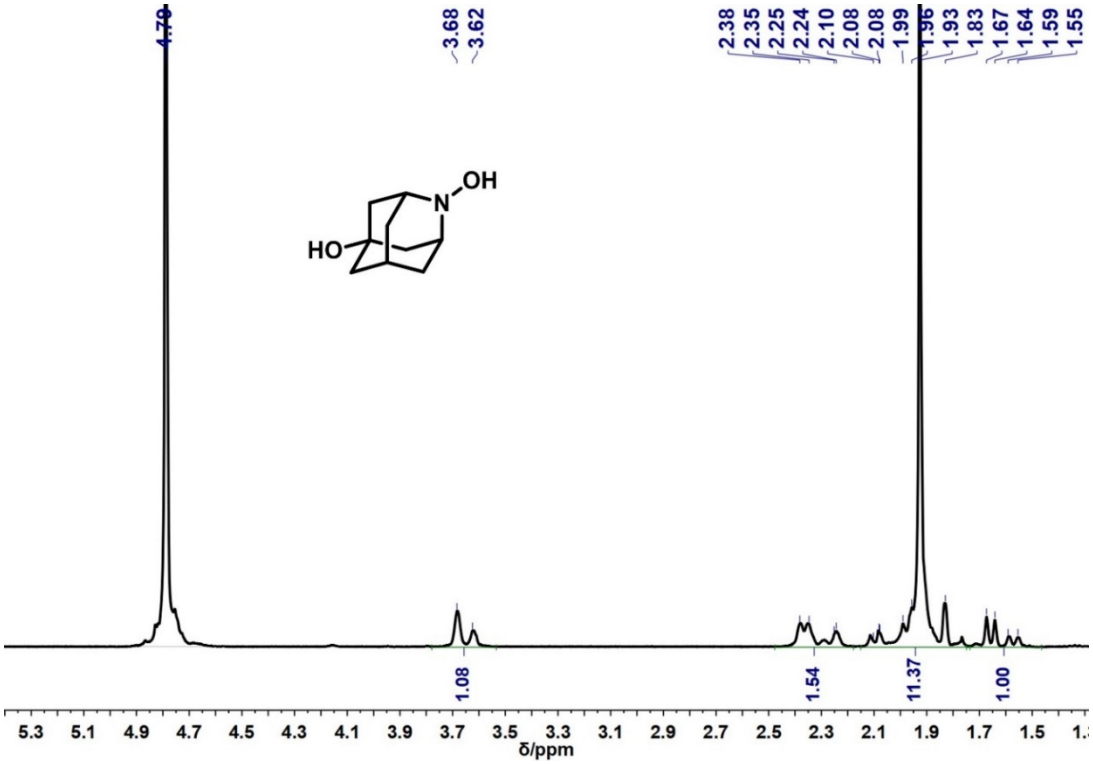


Figure S10. ^{1}H NMR spectrum (400 MHz, 298 K, D_2O) of **Z-3R**.

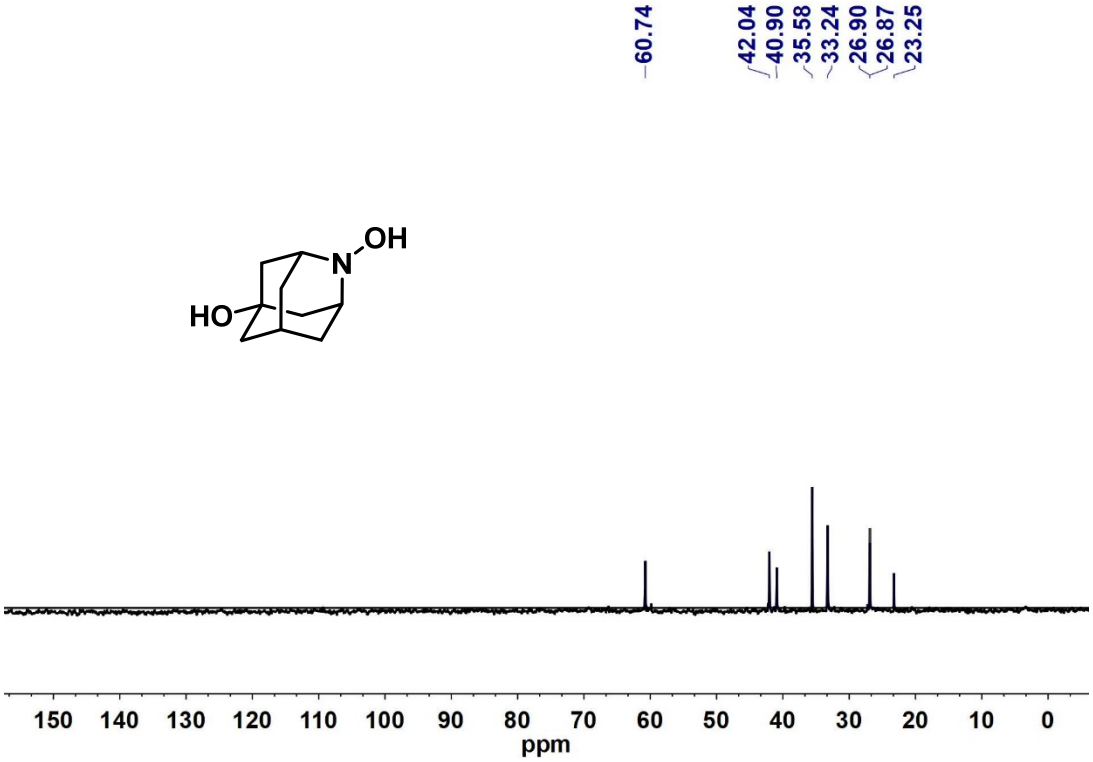


Figure S11. ^{13}C NMR spectrum (150 MHz, 298 K, D_2O) of **Z-3R**.

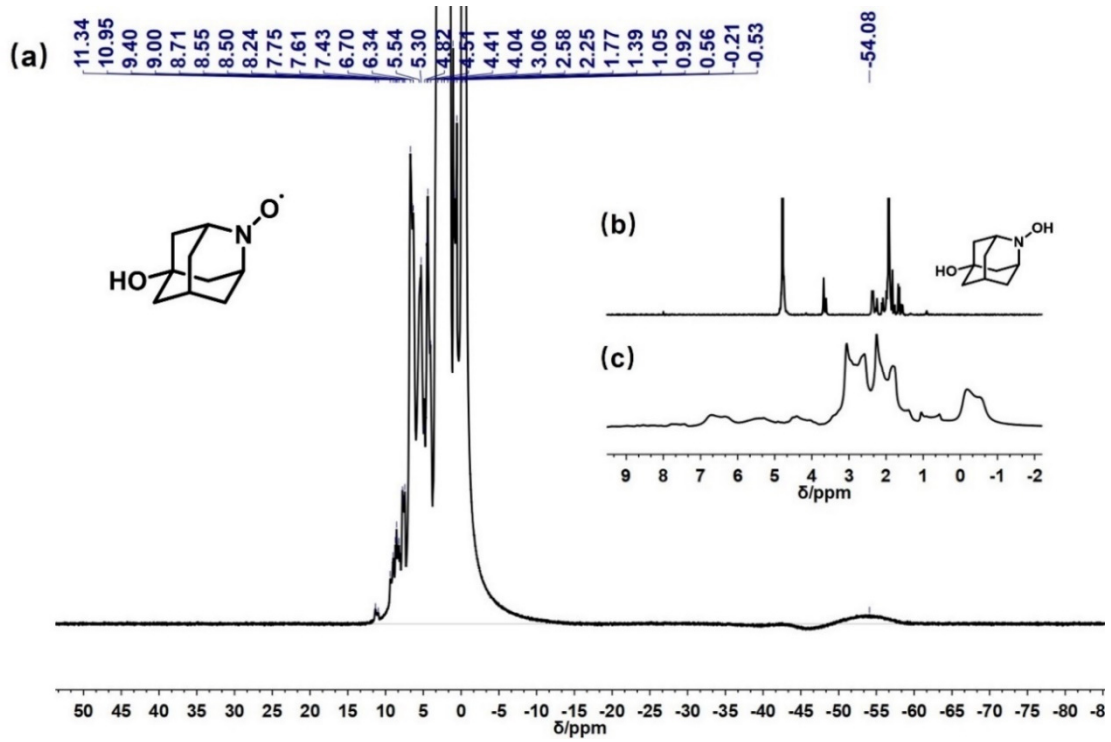


Figure S12. ^{1}H NMR spectrum (400 MHz, 298 K, D_2O). (a) ^{1}H NMR spectrum of **Z-3**; (b) partial enlarged drawing of ^{1}H NMR spectrum of **Z-3R**; (c) partial enlarged drawing of ^{1}H NMR spectrum of **Z-3.**

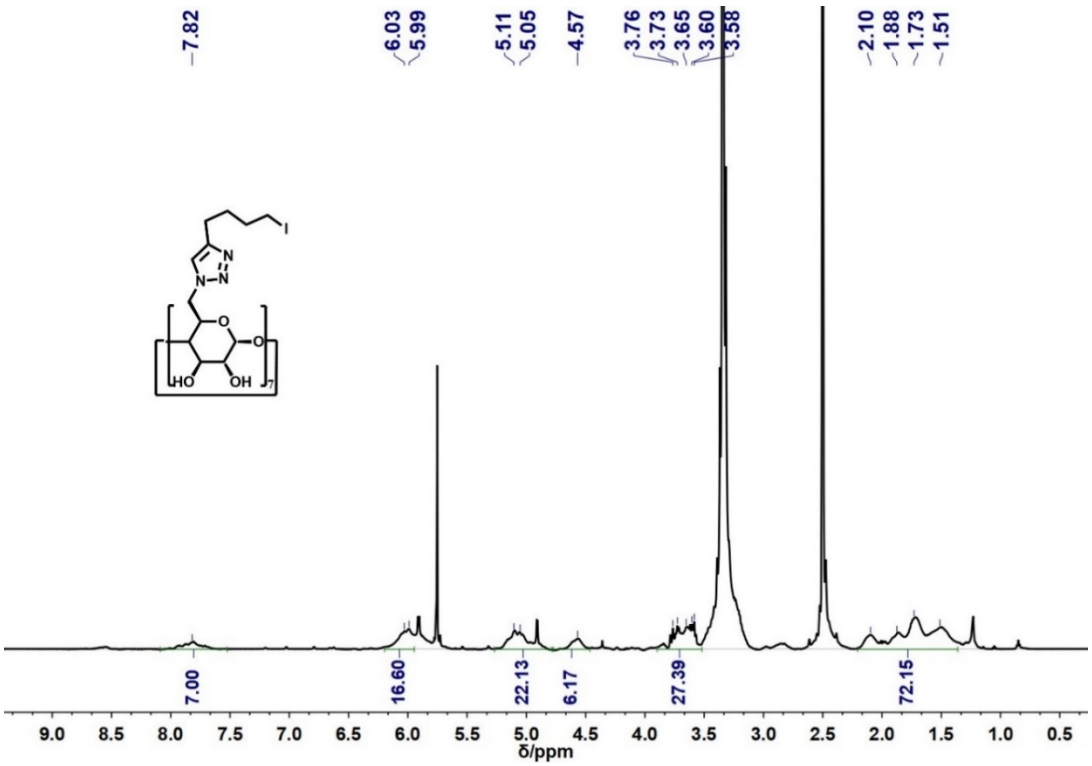


Figure S13. ^{1}H NMR spectrum (600 MHz, 298 K, DMSO-d_6) of **M-4**.

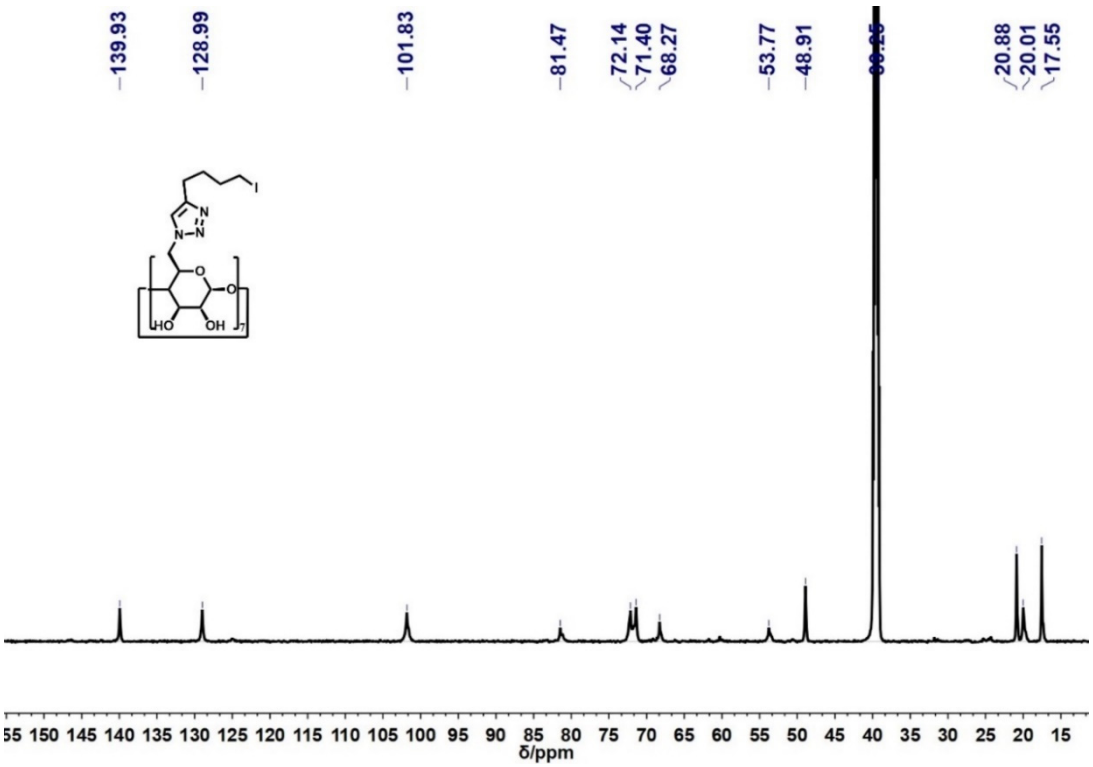


Figure S14. ^{13}C NMR spectrum (150 MHz, 298 K, DMSO-d_6) of **M-4**.

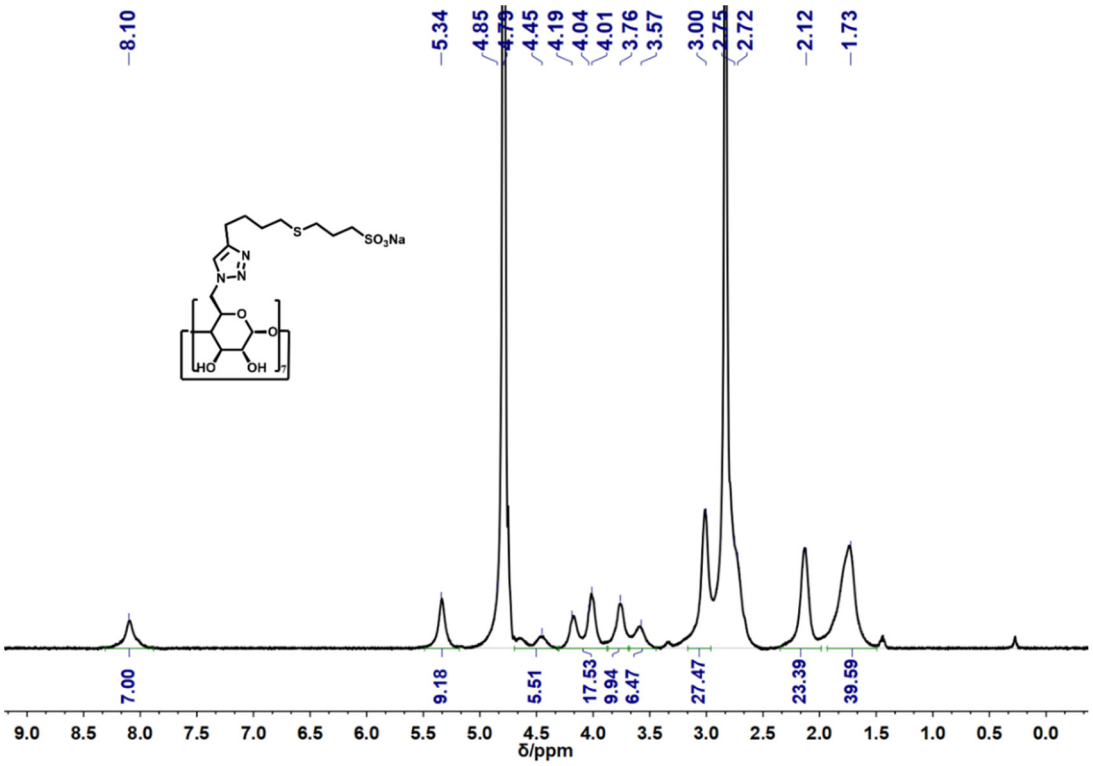


Figure S15. ^{1}H NMR spectrum (600 MHz, 298 K, D_2O/DMSO-d_6, 1/1, add NaOH) of **CD-8**.

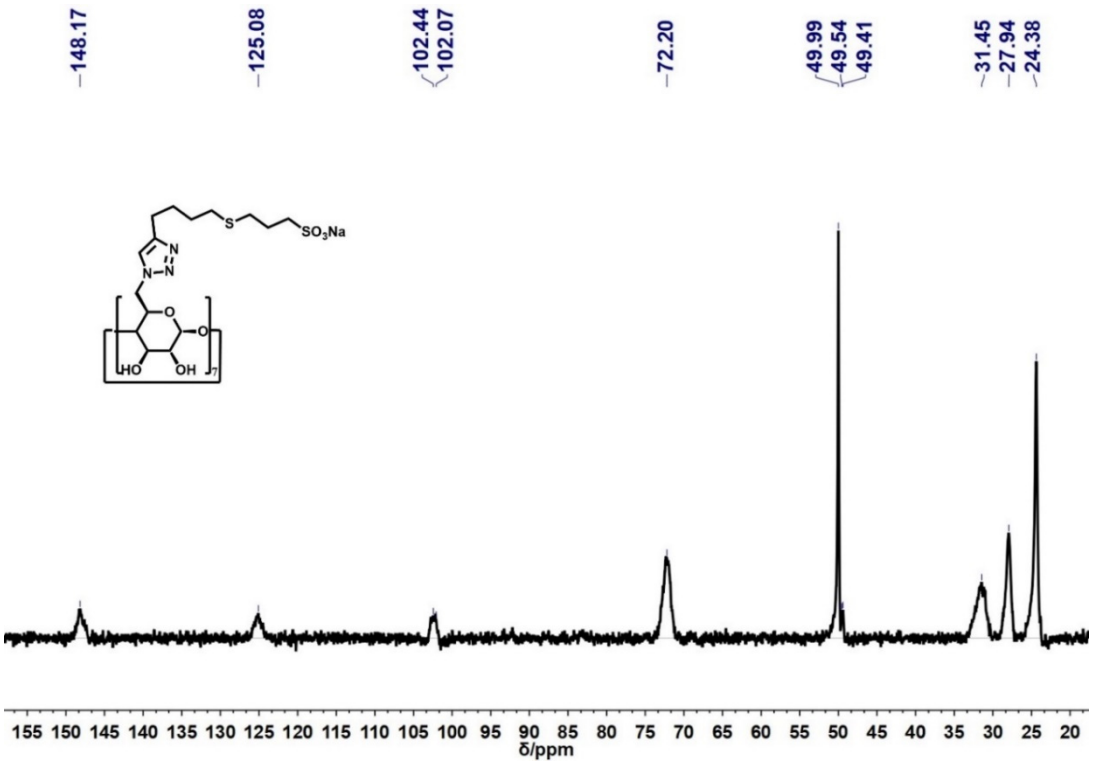


Figure S16. ^{13}C NMR spectrum (150 MHz, 298 K, D_2O) of **CD-8**.

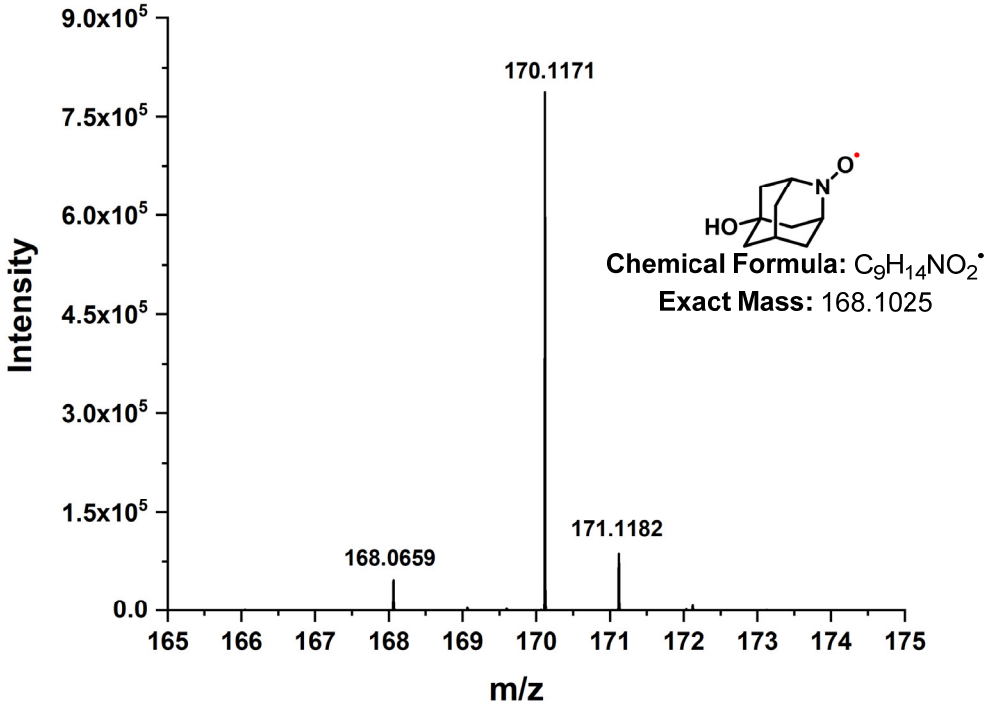


Figure S17. HRMS (ESI−TOF) spectrum of compound **Z-3** $[M+2H]^+$.

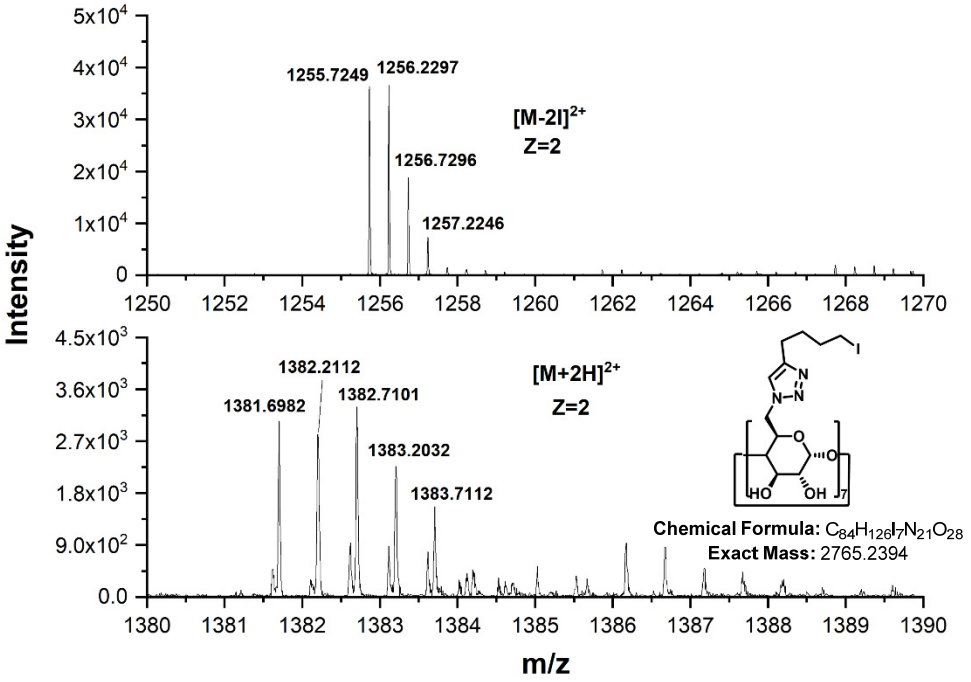


Figure S18. HRMS (ESI−TOF) spectrum of compound **M-4**.

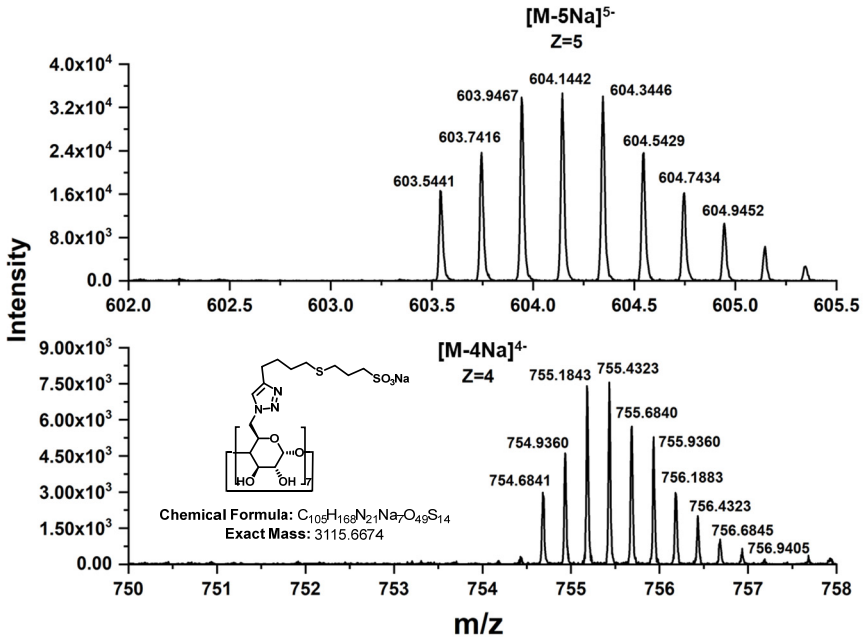


Figure S19. HRMS (ESI−TOF) spectrum of compound **CD-8**.

8. Supporting References

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