

## Reversing the Stereoselectivity of Intramolecular [2+2] Photocycloaddition Utilizing Cucurbit[8]uril as a Molecular Flask

Xujun Qiu,<sup>a</sup> Jasmin Seibert,<sup>a</sup> Olaf Fuhr,<sup>b,c</sup> Frank Biedermann,<sup>\*b</sup> and Stefan Bräse<sup>\*a,d</sup>

<sup>a</sup> Institute of Organic Chemistry (IOC), Karlsruhe Institute of Technology (KIT), Kaiserstraße 12, 76131 Karlsruhe, Germany. E-mail: [braese@kit.edu](mailto:braese@kit.edu).

<sup>b</sup> Institute of Nanotechnology (INT), Karlsruhe Institute of Technology (KIT), Kaiserstraße 12, 76131 Karlsruhe, Germany. E-mail: [frank.biedermann@kit.edu](mailto:frank.biedermann@kit.edu).

<sup>c</sup> Karlsruhe Nano Micro Facility (KNMFi), Karlsruhe Institute of Technology (KIT), Kaiserstraße 12, 76131 Karlsruhe, Germany.

<sup>d</sup> Institute of Biological and Chemical Systems – Functional Molecular Systems (IBCS-FMS), Karlsruhe Institute of Technology (KIT), Kaiserstraße 12, 76131 Karlsruhe, Germany.

\* Corresponding author

## Table of Contents

1.	General Remarks .....	1
2.	Synthetic Procedures .....	3
3.	Additional Spectra .....	6
4.	Competitive binding assay for binding constant determination.....	24
5.	References.....	27

# 1. General Remarks

## Materials and Methods

The starting materials, solvents, and reagents were purchased from ABCR, ACROS, ALFA AESAR, APOLLO SCIENTIFIC, CARBOLUTION, CHEMPUR, FLUKA, FLUOROCHEM, MERCK, RIEDEL-DE HAËN, SIGMA ALDRICH, STREM, TCI, or THERMO FISHER SCIENTIFIC and used without further purification unless stated otherwise.

Solvents of technical quality were purified by distillation or with the solvent purification system MB SPS5 (acetonitrile, dichloromethane, diethyl ether) from MBRAUN. Solvents of *p.a.* quality were purchased from ACROS, FISHER SCIENTIFIC, SIGMA ALDRICH, Roth, or RIEDEL-DE HAËN and were used without further purification.

Flat-bottom crimp neck vials from ChromaGlobe with aluminum crimp caps were used for certain reactions.

Solvents were evaporated under reduced pressure at 45 °C using a rotary evaporator. For solvent mixtures, each solvent was measured volumetrically.

Flash column chromatography was performed using MERCK silica 60 (0.040 × 0.063 mm, 230–400 mesh ASTM) and quartz sand (glowed and purified with hydrochloric acid).

## Reaction Monitoring

All reactions were monitored by thin-layer chromatography (TLC) using silica-coated aluminum plates (MERCK, silica 60, F254). UV active compounds were detected with a UV lamp at 254 nm and 366 nm excitation.

GC-MS (gas chromatography-mass spectrometry) measurements were performed on an AGILENT TECHNOLOGIES model 6890N (electron impact ionization), equipped with an AGILENT 19091S-433 column (5% phenyl methyl siloxane, 30 m, 0.25 μm) and a 5975B VL MSD detector with a turbopump. Helium was used as a carrier gas.

## Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectra were recorded on a BRUKER Avance 500 NMR instrument at 500 MHz for <sup>1</sup>H NMR and 126 MHz for <sup>13</sup>C NMR. The NMR spectra were recorded at room temperature in deuterated solvents acquired from EURISOTOP, SIGMA ALDRICH, or DEUTERO.

## Infrared Spectroscopy (IR)

The infrared spectra were recorded with a BRUKER, Alpha P instrument. All samples were measured by attenuated total reflection (ATR). The positions of the absorption bands are given in wavenumbers  $\tilde{\nu}$  in cm<sup>-1</sup> and were measured in the range from 3600 cm<sup>-1</sup> to 500 cm<sup>-1</sup>.

Characterization of the absorption bands was done in dependence of the absorption strength with the following abbreviations: vs (very strong, 0–9%), s (strong, 10–39%), m (medium, 40–69%), w (weak, 70–89%), vw (very weak, 90–100%).

## Mass Spectrometry (MS)

APCI (atmospheric pressure chemical ionization) and ESI (electrospray ionization) experiments were recorded on a Q-Exactive (Orbitrap) mass spectrometer (THERMO FISHER SCIENTIFIC, San Jose, CA, USA) equipped with a HESI II probe to record high resolution. The tolerated error is  $\pm 5$  ppm of the molecular mass. The spectra were interpreted by molecular peaks  $[M]^+$ , or peaks of protonated molecules  $[M+H]^+$  and characteristic fragment peaks and indicated with their mass-to-charge ratio ( $m/z$ ) and intensity in percent, relative to the base peak (100%).

### Photoreactions

Photoreactions were performed in a standard photoreactor LZC-4X equipped with 14 UVA (365 nm) lamps, six top lamps, and eight side lamps. The reaction mixture was loaded in a four-face quartz cuvette with stirring on, which was placed in the middle of the photoreactor.

### Preparative Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC)

Preparative Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC) was performed on the Puriflash™ 4125 system from Interchim. A VDSpher® C18-M-SE precolumn (10  $\mu$ m, 40 x 16 mm) followed by a VDSpher® C18-M-SE separation column (10  $\mu$ m, 250 x 20 mm, VDS Optilab) was used as the stationary phase. A linear gradient of acetonitrile and double distilled water supplemented with 0.1% trifluoroacetic acid (TFA) at a flow rate of 15 mL/min served as the mobile phase.

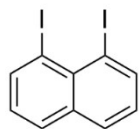
### Crystallographic Information

Single crystals of  $C_{32}H_{34}Cl_2N_2O_4$  (**4**) were obtained by slowly evaporating aqueous solution of **4**. A suitable crystal was selected and studied on a Stoe StadiVari diffractometer with Dectris Eiger 4M detector at 180 K using  $GaK\alpha$  radiation ( $\lambda = 1.34143$  Å) generated by a Excilium Metal-Jet D2 X-ray source. Using Olex2<sup>1</sup> the structure was solved with the ShelXT<sup>2</sup> structure solution program using Intrinsic Phasing and refined with the ShelXL<sup>3</sup> refinement package using Least Squares minimization. Refinement was performed with anisotropic temperature factors for all non-hydrogen atoms; hydrogen atoms were calculated on idealized positions. Crystallographic data and structure refinement details are summarized in table S1.

Crystallographic data for compound **4** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary information no. CCDC-2309696. Copies of the data can be obtained free of charge from <https://www.ccdc.cam.ac.uk/structures/>.

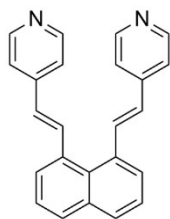
## 2. Synthetic Procedures

### Diiodonaphthalene<sup>4</sup>



1,8-Diaminonaphthalene (2.00 g, 12.6 mmol, 1.00 equiv.) was suspended in 6.9 M sulfuric acid (24.0 mL) and cooled to  $-20\text{ }^{\circ}\text{C}$ . A solution of sodium nitrite (2.62 g, 37.9 mmol, 2.00 equiv.) in water (10.0 mL) was added dropwise. During this process, the temperature was kept below  $-15\text{ }^{\circ}\text{C}$ . Subsequently, a solution of potassium iodide (12.6 g, 75.6 mmol, 3.00 equiv.) in water (12.0 mL) was added at the same temperature. If required, small amounts of sulfuric acid were added to avoid freezing of the solution. The mixture was heated to  $80\text{ }^{\circ}\text{C}$  and stirred for 30 min. Then, the solution was cooled to  $0\text{ }^{\circ}\text{C}$  and adjusted to  $\text{pH}=10$  by adding a concentrated sodium hydroxide solution. The black precipitate was filtered off, ground, and extracted five times with 10.0 mL of DCM. The combined organic layers were washed with 10% hydrochloric acid, a saturated aqueous sodium thiosulfate solution, dilute aqueous sodium hydroxide, dried over magnesium sulfate, and concentrated in a vacuum. The resulting brown residue was recrystallized from hexane to afford the product diiodonaphthalene (2.20 g, 5.79 mmol, 46%). The results of the analysis are consistent with the literature.<sup>4</sup>

### 1,8-bis[(E)-2-(4-pyridyl)ethenyl]naphthalene



1,8-bis[(E)-2-(4-pyridyl)ethenyl]naphthalene was synthesized with the method reported from literature<sup>5</sup>. To an oven-dried flask, diiodonaphthalene (1.00 g, 2.63 mmol, 1.00 equiv.), 4-vinylpyridine (1.12 mL, 1.11 g, 10.5 mmol, 4.00 equiv.), palladium(II)acetate (11.8 mg, 0.05 mmol, 0.02 equiv.), tri-*o*-tolylphosphine (32.0 mg, 0.11 mmol, 0.04 equiv.), triethylamine (2.0 mL), and acetonitrile (25 mL) were added. The flask was charged with argon, sealed, heated to  $90\text{ }^{\circ}\text{C}$ , and stirred for 48 h. Subsequently, the flask was removed from heat and cooled at room temperature. The mixture was poured into cold water, and the precipitate was collected via vacuum filtration. The resulting solid was purified through column chromatography on a silica column using DCM: MeOH=10:1 as mobile phase to obtain product 1,8-bis[(E)-2-(4-pyridyl)ethenyl]naphthalene as a yellow solid (0.59 g, 1.76 mmol, 67%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , ppm)  $\delta$  = 8.47–8.42 (m, 4H,  $H_{\text{Ar}}$ ), 8.14 (d,  $J$  = 15.9 Hz, 2H,  $H_{\text{vinyl}}$ ), 7.88 (dd,  $J$  = 8.1, 1.3 Hz, 2H,  $H_{\text{Ar}}$ ), 7.66 (dt,  $J$  = 7.1, 1.1 Hz, 2H,  $H_{\text{Ar}}$ ), 7.52 (dd,  $J$  = 8.2, 7.1 Hz, 2H,  $H_{\text{Ar}}$ ), 7.25–7.23 (m, 4H,  $H_{\text{Ar}}$ ), 6.88 (d,  $J$  = 15.9 Hz, 2H,  $H_{\text{vinyl}}$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ , ppm)  $\delta$  = 150.4 (4C,  $C_{\text{Ar}}$ ), 144.4 (2C,  $C_{\text{Ar}}$ ), 136.6 (2C,  $C_{\text{vinyl}}$ ), 135.7 (2C,  $C_{\text{Ar}}$ ), 134.8 (2C,  $C_{\text{Ar}}$ ), 129.9 (2C,  $C_{\text{Ar}}$ ), 127.6 (2C,  $C_{\text{Ar}}$ ), 127.1 (2C,  $C_{\text{vinyl}}$ ), 126.1 (2C,  $C_{\text{Ar}}$ ), 120.9 (4C,  $C_{\text{Ar}}$ ).

ESI-MS for  $[\text{C}_{24}\text{H}_{19}\text{N}_2]^+$ : Calc.  $m/z$  = 335.1543, found  $m/z$  = 335.1542.

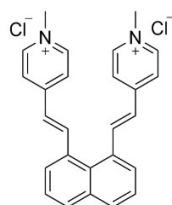
IR (ATR,  $\text{cm}^{-1}$ )  $\tilde{\nu}$  = 3397 (s), 3325 (m), 2997 (m), 2996 (m), 2993 (m), 2968 (vs), 2965 (vs), 2956 (vs), 2935 (vs), 2892 (s), 2885 (s), 2884 (s), 2883 (s), 2877 (s), 2874 (s), 2872 (s), 2870 (s), 2868 (s), 2792 (vs), 2780 (s), 2759 (vs), 2679 (vs), 1616 (m), 1421 (s), 1419 (m), 1165 (s), 1161 (s), 1153 (s), 1152 (s), 1131 (s), 1128 (s), 1121 (s), 1087 (s), 1034 (s)  $\text{cm}^{-1}$ .

Additional information on the chemical synthesis is available *via* the Chemotion repository:

<https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-DVJQLQKAHJ-UHFFFADPSC-NUHFF-NJMCZ-NUHFF-ZZZ>

Additional information on the analysis of the target compound is available *via* the Chemotion repository:

<https://dx.doi.org/10.14272/DVJQLQKAHJQNJU-FIFLTTUSA-N.1>



**4,4'-((1E,1'E)-naphthalene-1,8-diylbis(ethene-2,1-diyl))bis(1-methylpyridin-1-ium) chloride (1)**

1,8-bis[(E)-2-(4-pyridyl)ethenyl]naphthalene (0.10 g, 0.30 mmol, 1.00 equiv.) and iodomethane (0.17 g, 1.20 mmol, 4.00 equiv.) were suspended in DMF (10 mL), the mixture was heated at 50 °C for 16 hours. After cooling down, the precipitation was collected and washed with acetone several times. The solid was dissolved in water (500 mL), and AgCl (0.17 g, 1.20 mmol, 4.00 equiv.) was added. The mixture was stirred at 25 °C for 5 days. After filtration, the water was evaporated and the desired product 4,4'-((1E,1'E)-naphthalene-1,8-diylbis(ethene-2,1-diyl))bis(1-methylpyridin-1-ium) chloride was obtained as a light yellow powder (0.12 g, 0.28 mmol, 92%).

<sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O, ppm)  $\delta$  = 8.46 (d,  $J$  = 6.4 Hz, 4H,  $H_{Ar}$ ), 8.21 (d,  $J$  = 16.0 Hz, 2H,  $H_{vinyl}$ ), 8.02 (d,  $J$  = 8.2 Hz, 2H,  $H_{Ar}$ ), 7.84 (d,  $J$  = 6.5 Hz, 4H,  $H_{Ar}$ ), 7.80 (d,  $J$  = 7.2 Hz, 2H,  $H_{Ar}$ ), 7.63 (t,  $J$  = 7.7 Hz, 2H,  $H_{Ar}$ ), 7.15 (d,  $J$  = 16.0 Hz, 2H,  $H_{vinyl}$ ), 4.25 (s, 6H,  $CH_3$ ).

<sup>13</sup>C NMR (126 MHz, D<sub>2</sub>O, ppm)  $\delta$  = 152.9 (2C,  $C_{Ar}$ ), 144.4 (4C,  $C_{Ar}$ ), 142.9 (2C,  $C_{vinyl}$ ), 134.2 (1C,  $C_{Ar}$ ), 133.8 (2C,  $C_{Ar}$ ), 131.1 (2C,  $C_{Ar}$ ), 129.6 (1C,  $C_{Ar}$ ), 128.8 (2C,  $C_{Ar}$ ), 126.4 (2C,  $C_{Ar}$ ), 124.1 (2C,  $C_{vinyl}$ ), 123.6 (4C,  $C_{Ar}$ ), 47.0 (2C,  $CH_3$ ).

ESI-MS for  $[C_{26}H_{24}N_2]^{2+}$ : Calc.  $m/z$  = 182.0964, found  $m/z$  = 182.0965.

IR (ATR,  $\tilde{\nu}$ ) = 3424 (vs), 3420 (vs), 3417 (vs), 3414 (vs), 3413 (vs), 3412 (vs), 3410 (vs), 3406 (vs), 3404 (vs), 3402 (vs), 3401 (vs), 3396 (vs), 3391 (vs), 3389 (vs), 3387 (vs), 3384 (vs), 3382 (vs), 3380 (vs), 3378 (vs), 3376 (vs), 3373 (vs), 3370 (vs), 3368 (vs), 3364 (vs), 3363 (vs), 3361 (vs), 3359 (vs), 3356 (vs), 3354 (vs), 3353 (vs), 3351 (vs), 3350 (vs), 3348 (vs), 3347 (vs), 3345 (vs), 3343 (vs), 3341 (vs), 3340 (vs), 3338 (vs), 3336 (vs), 3333 (vs), 3329 (vs), 3326 (vs), 3325 (vs), 3321 (vs), 3319 (vs), 3315 (vs), 3313 (vs), 3311 (vs), 3307 (vs), 3305 (vs), 3303 (vs), 3302 (vs), 3300 (vs), 3298 (vs), 3296 (vs), 3293 (vs), 3291 (vs), 3288 (vs), 3287 (vs), 3286 (vs), 3284 (vs), 3283 (vs), 3280 (vs), 3279 (vs), 3277 (vs), 3274 (vs), 3272 (vs), 3268 (vs), 3264 (vs), 3263 (vs), 3261 (vs), 3258 (vs), 3254 (vs), 3252 (vs), 3249 (vs), 3247 (vs), 3245 (vs), 3244 (vs), 3241 (vs), 3238 (vs), 3233 (vs), 3231 (vs), 3230 (vs), 3227 (vs), 3226 (vs), 3222 (vs), 3221 (vs), 3218 (vs), 3215 (vs), 3213 (vs), 3212 (vs), 3209 (vs), 3205 (vs), 3202 (vs), 3199 (vs), 3195 (vs), 1621 (vs), 1616 (vs), 1614 (vs)  $cm^{-1}$ .

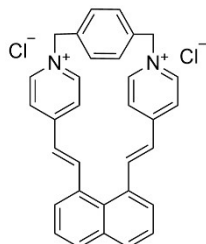
Additional information on the chemical synthesis is available *via* the Chemotion repository:

<https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-VIRCVYOPUF-UHFFFADPSC-NUHFF-LGEIA-NUHFF-ZZZ>

Additional information on the analysis of the target compound is available *via* the Chemotion repository:

<https://dx.doi.org/10.14272/VIRCVYOPUFMLML-JDDKLYJPSA-L.1>

**(6E,9E)-1,5(1,4)-dipyridin-1-iuma-8(1,8)-naphthalena-3(1,4)-benzenacyclodecaphane-6,9-diene-11,51-dium chloride (4)**



1,8-bis[(E)-2-(4-pyridyl)ethenyl]naphthalene (100 mg, 0.30 mmol, 1.00 equiv.), 1,4-bis(bromomethyl)benzene (78.9 mg, 0.30 mmol, 1.00 equiv.), and Tetra-n-butylammonium iodide (11.1 mg, 0.30 mmol, 0.10 equiv.) were suspended in DMF (10 mL), the mixture was heated at 50 °C for 16 hours. After cooling down, the precipitation was collected and washed with acetone several times. The solid was dissolved in water (500 mL) and AgCl (0.17 g, 1.20 mmol, 4.00 equiv.) was added. The mixture was stirred at 25 °C for 5 days. After filtration, the water was evaporated, and the desired product (6E,9E)-1,5(1,4)-dipyridin-1-iuma-8(1,8)-naphthalena-3(1,4)-benzenacyclodecaphane-6,9-diene-11,51-dium chloride was obtained as a yellow powder (96.0 mg, 0.18 mmol, 63%).

$^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ , ppm)  $\delta$  = 8.54 (d,  $J$  = 6.6 Hz, 4H,  $H_{\text{Ar}}$ ), 8.05 (d,  $J$  = 8.2 Hz, 2H,  $H_{\text{Ar}}$ ), 8.02 (d,  $J$  = 15.7 Hz, 2H,  $H_{\text{vinyl}}$ ), 7.82 (d,  $J$  = 7.2 Hz, 2H,  $H_{\text{Ar}}$ ), 7.71 (d,  $J$  = 6.6 Hz, 4H,  $H_{\text{Ar}}$ ), 7.64 (d,  $J$  = 7.8 Hz, 2H,  $H_{\text{Ar}}$ ), 7.62 (s, 4H,  $H_{\text{Ar}}$ ), 7.20 (d,  $J$  = 15.7 Hz, 2H,  $H_{\text{vinyl}}$ ), 5.67 (s, 4H,  $\text{CH}_2$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{D}_2\text{O}$ , ppm)  $\delta$  = 153.9 (2C,  $C_{\text{Ar}}$ ), 143.2 (2C,  $C_{\text{vinyl}}$ ), 143.0 (4C,  $C_{\text{Ar}}$ ), 138.3 (2C,  $C_{\text{Ar}}$ ), 134.2 (1C,  $C_{\text{Ar}}$ ), 133.8 (2C,  $C_{\text{Ar}}$ ), 131.3 (2C,  $C_{\text{Ar}}$ ), 130.0 (1C,  $C_{\text{Ar}}$ ), 129.9 (4C,  $C_{\text{Ar}}$ ), 129.1 (2C,  $C_{\text{Ar}}$ ), 126.4 (2C,  $C_{\text{Ar}}$ ), 124.1 (4C,  $C_{\text{Ar}}$ ), 123.3 (2C,  $C_{\text{vinyl}}$ ), 64.4 (2C,  $\text{CH}_2$ ).

ESI-MS for  $[\text{C}_{32}\text{H}_{26}\text{N}_2]^{2+}$ : Calc.  $m/z$  = 219.1043, found  $m/z$  = 219.1040.

IR (ATR,  $\tilde{\nu}$ ) = 3994 (s), 3987 (s), 3979 (s), 3972 (s), 3966 (s), 3959 (s), 3951 (s), 3945 (s), 3935 (s), 3929 (s), 3921 (s), 3914 (s), 3908 (s), 3896 (s), 3889 (s), 3882 (s), 3877 (s), 3871 (s), 3867 (s), 3859 (s), 3850 (s), 3842 (s), 3832 (s), 3825 (s), 3818 (s), 3813 (s), 3804 (s), 3798 (s), 3793 (s), 3787 (s), 3776 (s), 3768 (s), 3762 (s), 3756 (s), 3747 (s), 3741 (s), 3729 (s), 3720 (s), 3716 (s), 3707 (s), 3699 (s), 3686 (s), 3672 (s), 3666 (s), 3653 (s), 3645 (s), 3625 (s), 3616 (s), 3605 (s), 3598 (s), 3584 (s), 3571 (s), 3563 (s), 3557 (s), 3538 (s), 3451 (vs), 3440 (vs), 3360 (vs), 3344 (vs), 3333 (vs), 3326 (vs), 3319 (vs), 3263 (vs), 3164 (vs), 3123 (vs), 3091 (vs), 3086 (vs), 3027 (vs), 3000 (vs), 2965 (vs), 2953 (vs), 2942 (vs), 2878 (s), 2772 (s), 2765 (s), 2714 (m), 2685 (m), 2645 (m), 2610 (m), 1679 (m), 1638 (vs), 1616 (vs), 1565 (m), 1517 (s), 1474 (m), 1197 (s), 1148 (s), 1127 (m), 779 (m)  $\text{cm}^{-1}$ .

Additional information on the chemical synthesis is available *via* the Chemotion repository:

<https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-ZJSPYAOLG-UHFFFADPSC-NUHFF-LGTAG-NUHFF-ZZZ>

Additional information on the analysis of the target compound is available *via* the Chemotion repository:

<https://dx.doi.org/10.14272/ZJSPYAOLGYBTI-VCHVFRDLSA-L.1>

### 3. Additional Spectra

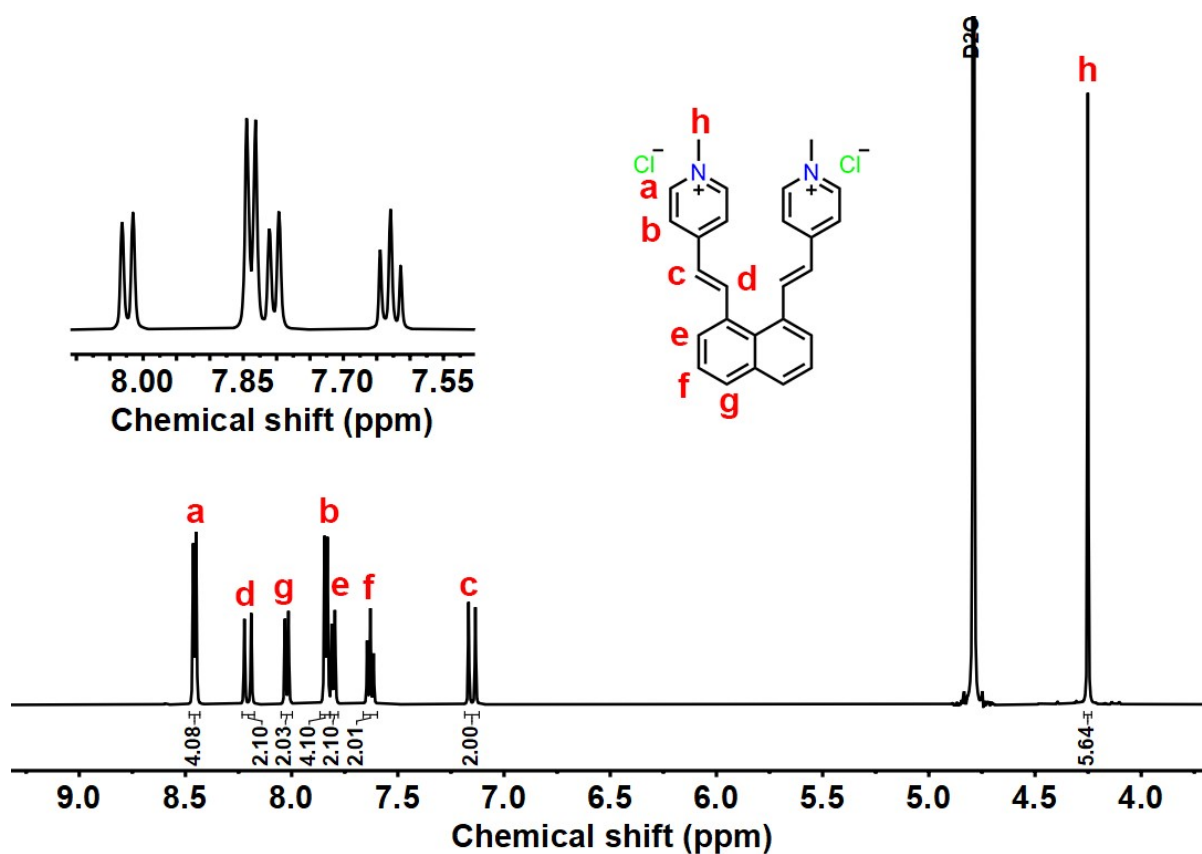
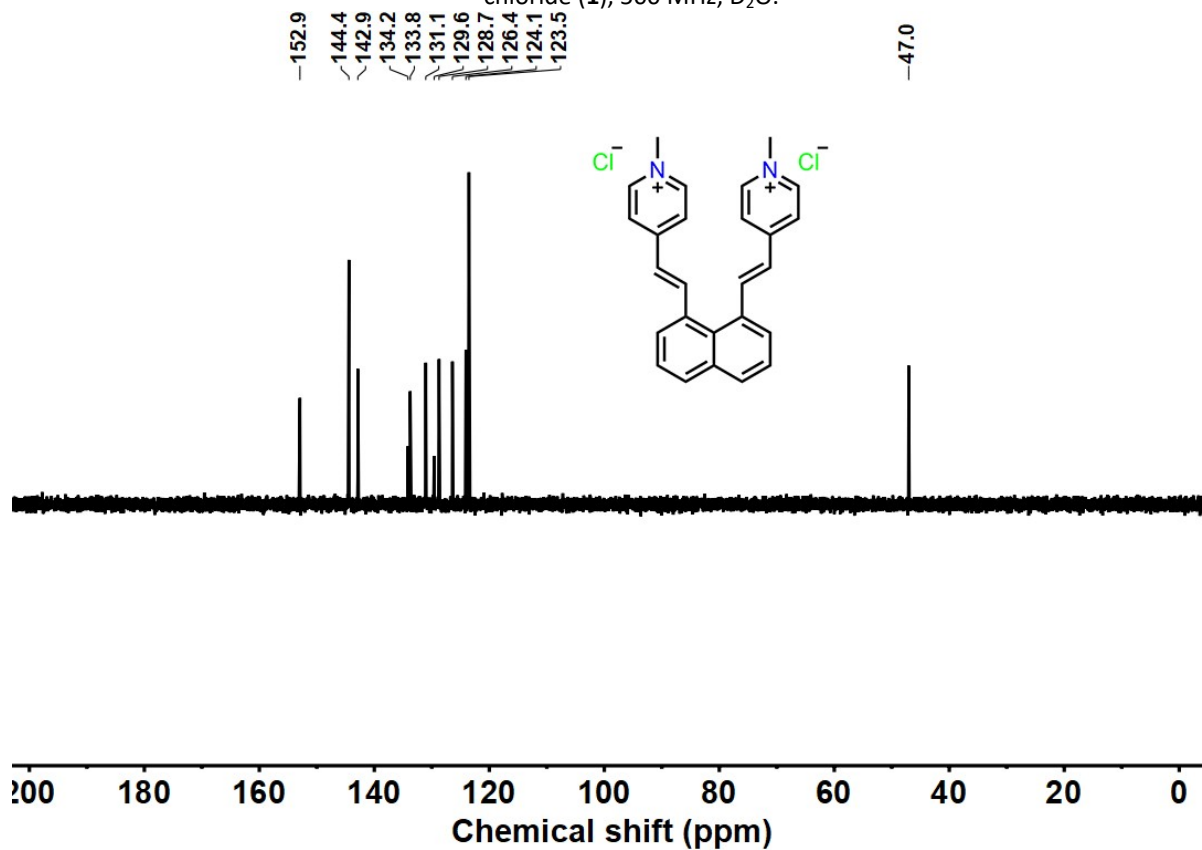
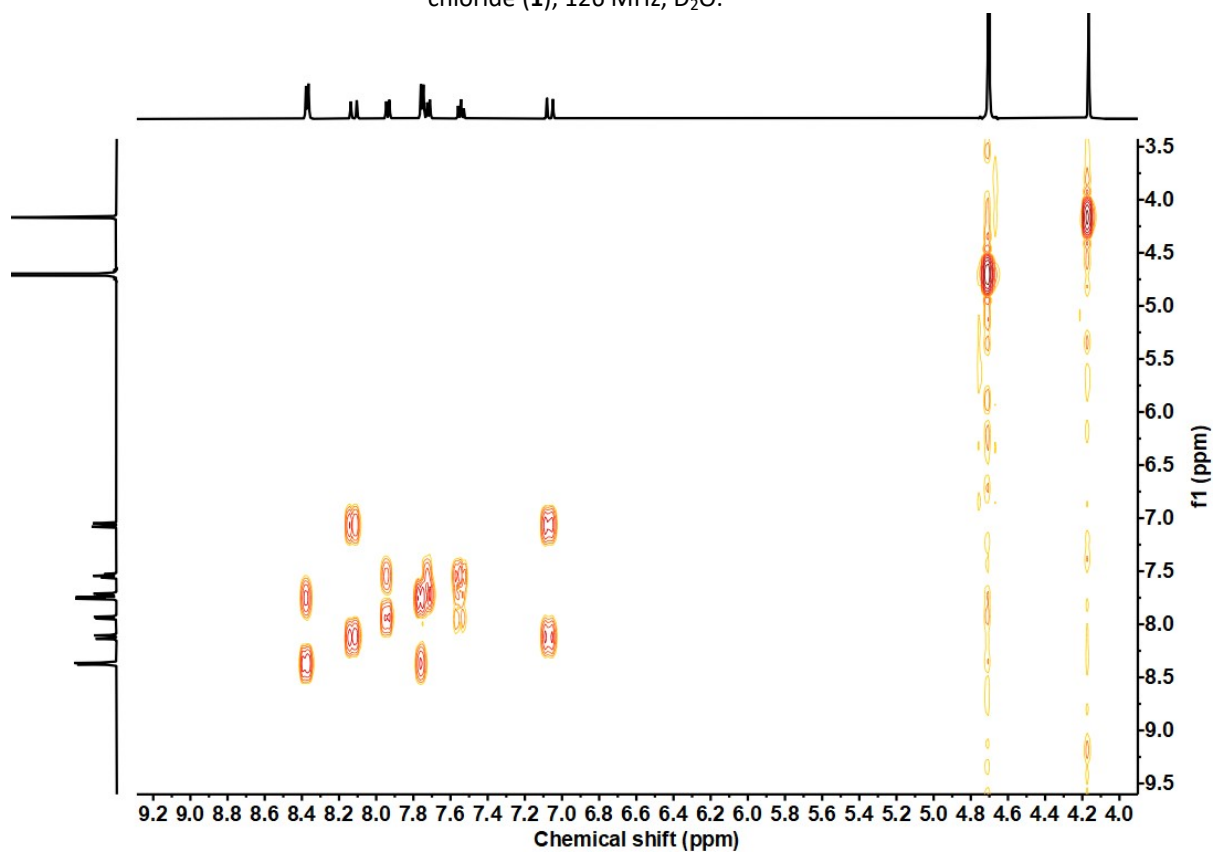


Figure S1.  $^1\text{H}$  NMR  $-4,4'-((1\text{E},1'\text{E})\text{-naphthalene-1,8-diybis(ethene-2,1-diy))bis(1-methylpyridin-1-ium)}$  chloride (**1**), 500 MHz,  $\text{D}_2\text{O}$ .

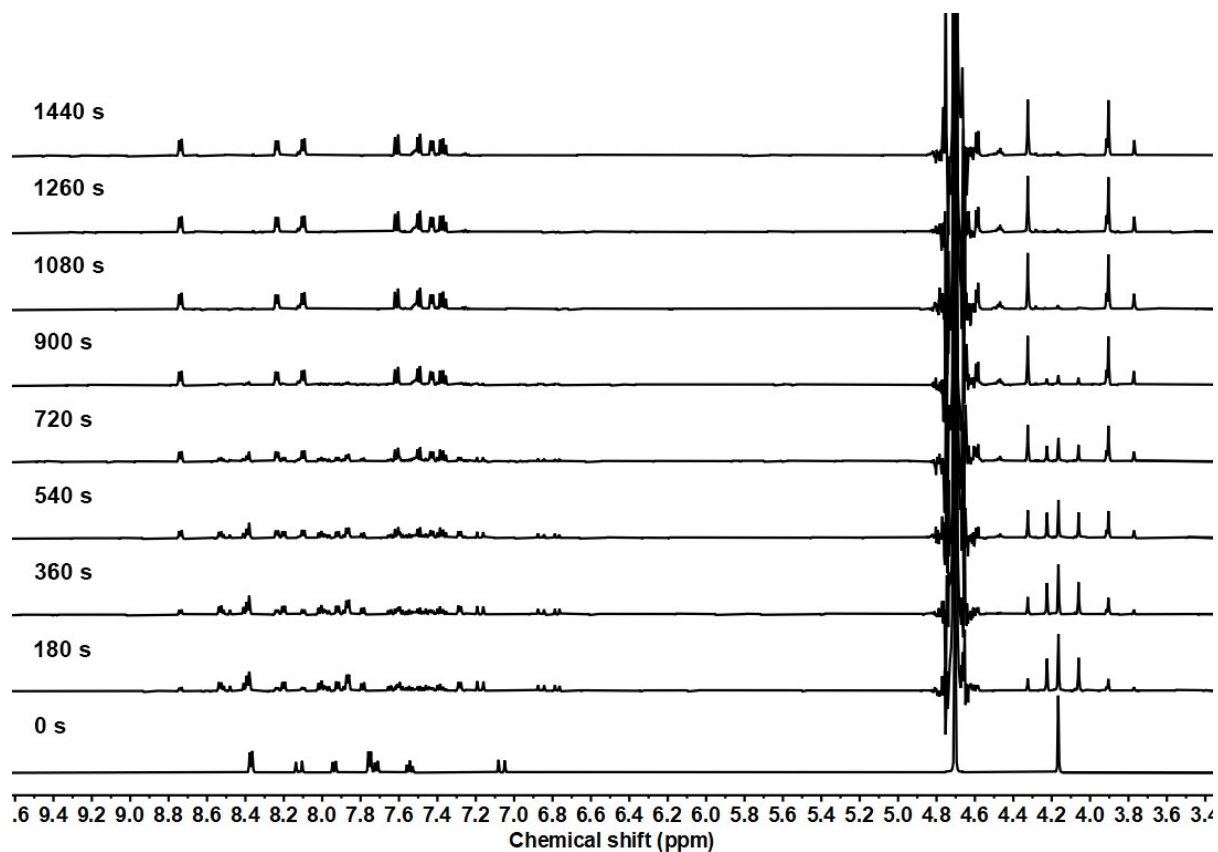




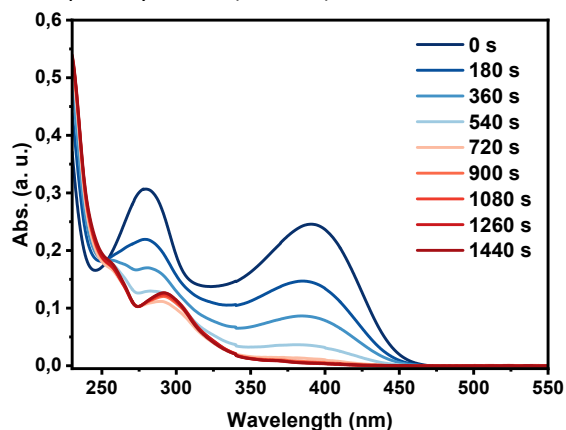
**Figure S2.**  $^{13}\text{C}$  NMR –4,4'-((1E,1'E)-naphthalene-1,8-diylbis(ethene-2,1-diyl))bis(1-methylpyridin-1-ium) chloride (**1**), 126 MHz,  $\text{D}_2\text{O}$ .



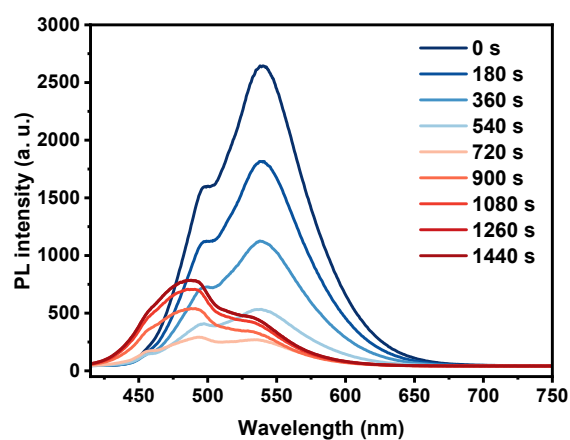
**Figure S3.**  $^1\text{H}$ - $^1\text{H}$  COSY –4,4'-((1E,1'E)-naphthalene-1,8-diylbis(ethene-2,1-diyl))bis(1-methylpyridin-1-ium) chloride (**1**),  $\text{D}_2\text{O}$ .



**Figure S4.**  $^1\text{H}$  NMR spectra of photolysis of **1** (0.5 mM) after different reaction times, 500 MHz,  $\text{D}_2\text{O}$ .



**Figure S5.** UV spectra of photolysis of **1** (0.5 mM) after different reaction times in Milli Q water at 25 °C. The reaction mixture was diluted with Milli Q water to  $2 \times 10^{-4}$  M for UV measurement.



**Figure S6.** Emission spectra ( $\lambda_{\text{exc}} = 394$  nm) of photolysis of **1** (0.5 mM) after different reaction times in Milli Q water at 25 °C. The reaction mixture was diluted with Milli Q water to  $2 \times 10^{-4}$  M for emission measurement.

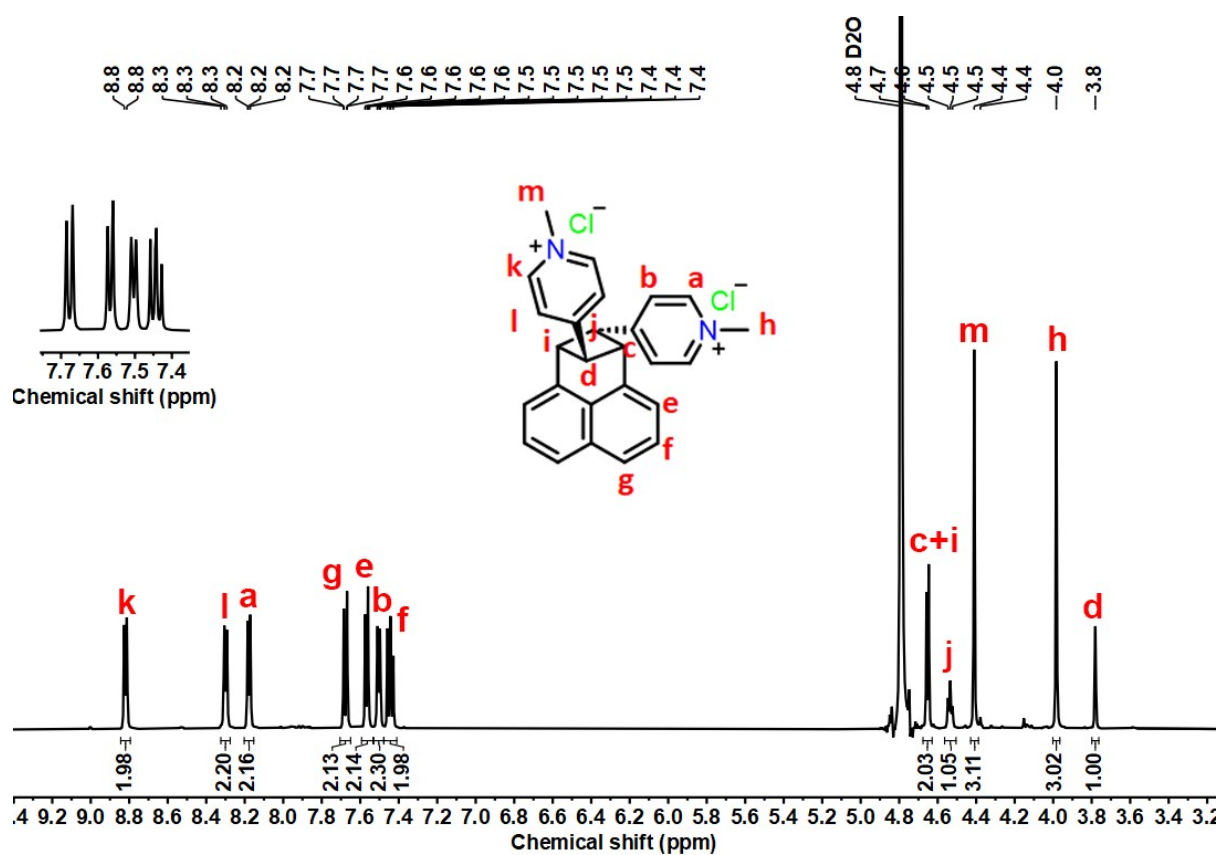
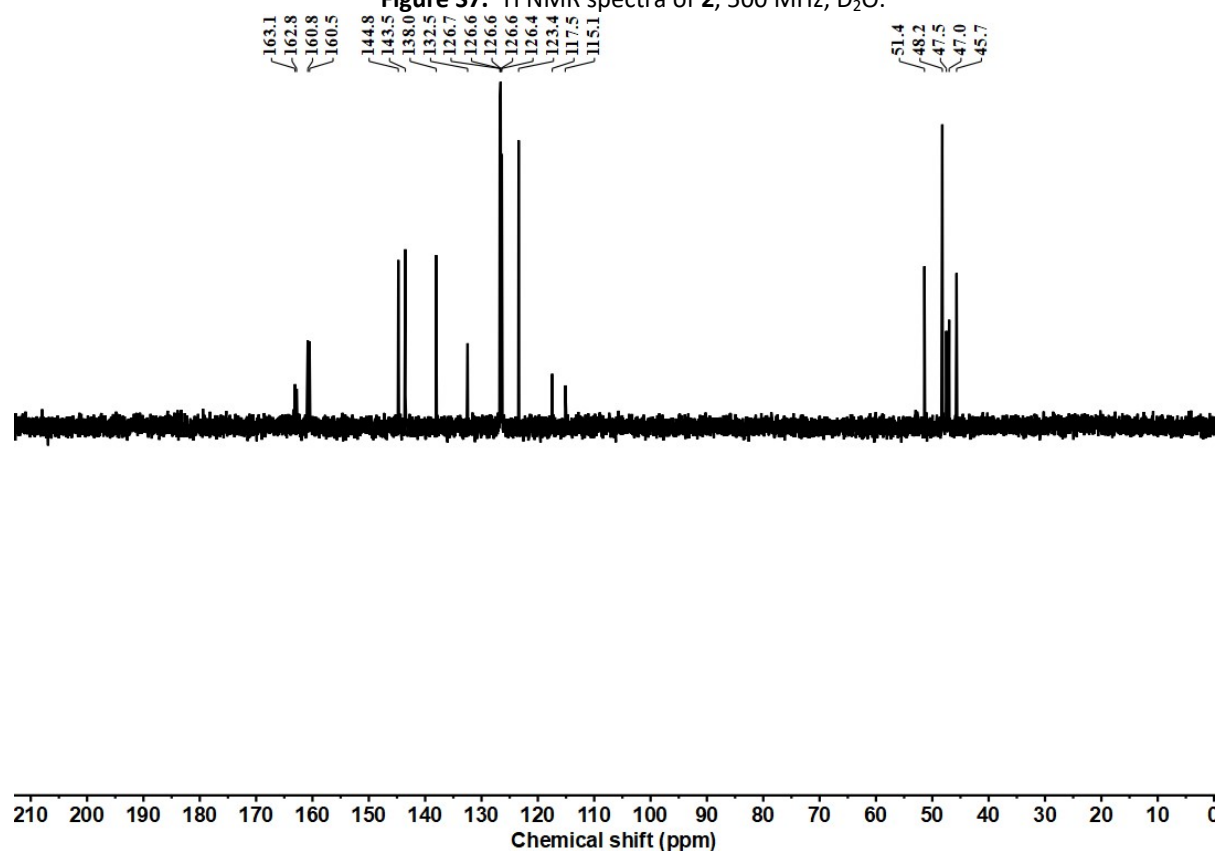


Figure S7.  ${}^1\text{H}$  NMR spectra of **2**, 500 MHz,  $\text{D}_2\text{O}$ .



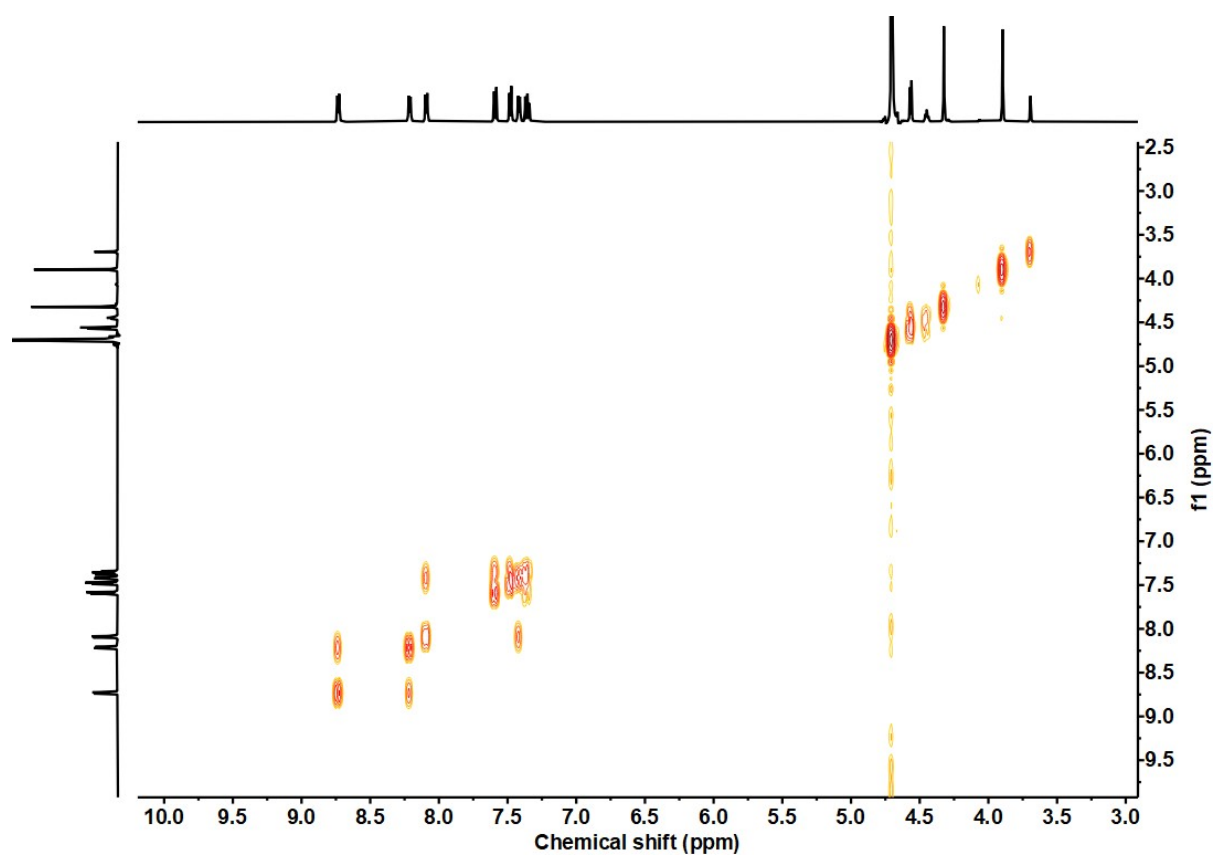


Figure S9.  $^1\text{H}$ - $^1\text{H}$  COSY spectra of **2**,  $\text{D}_2\text{O}$ .

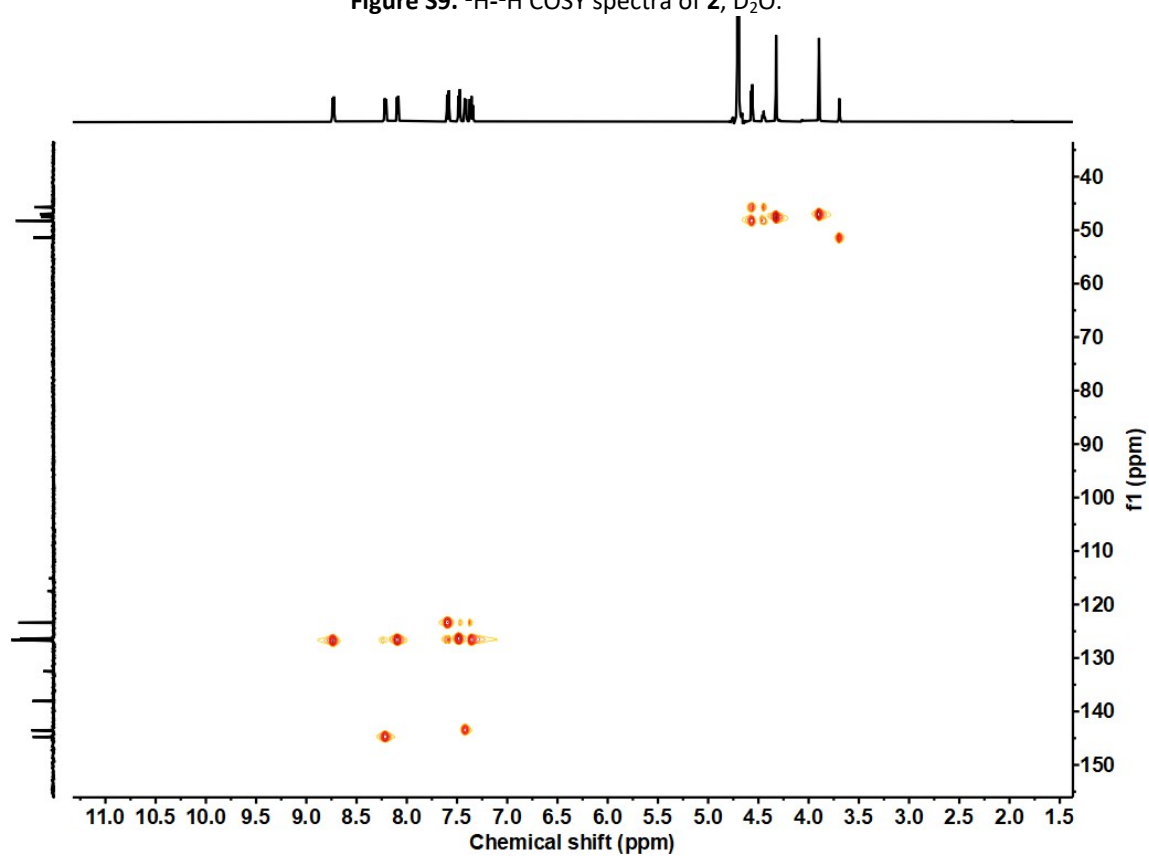


Figure S10. HSQC spectra of **2**,  $\text{D}_2\text{O}$ .

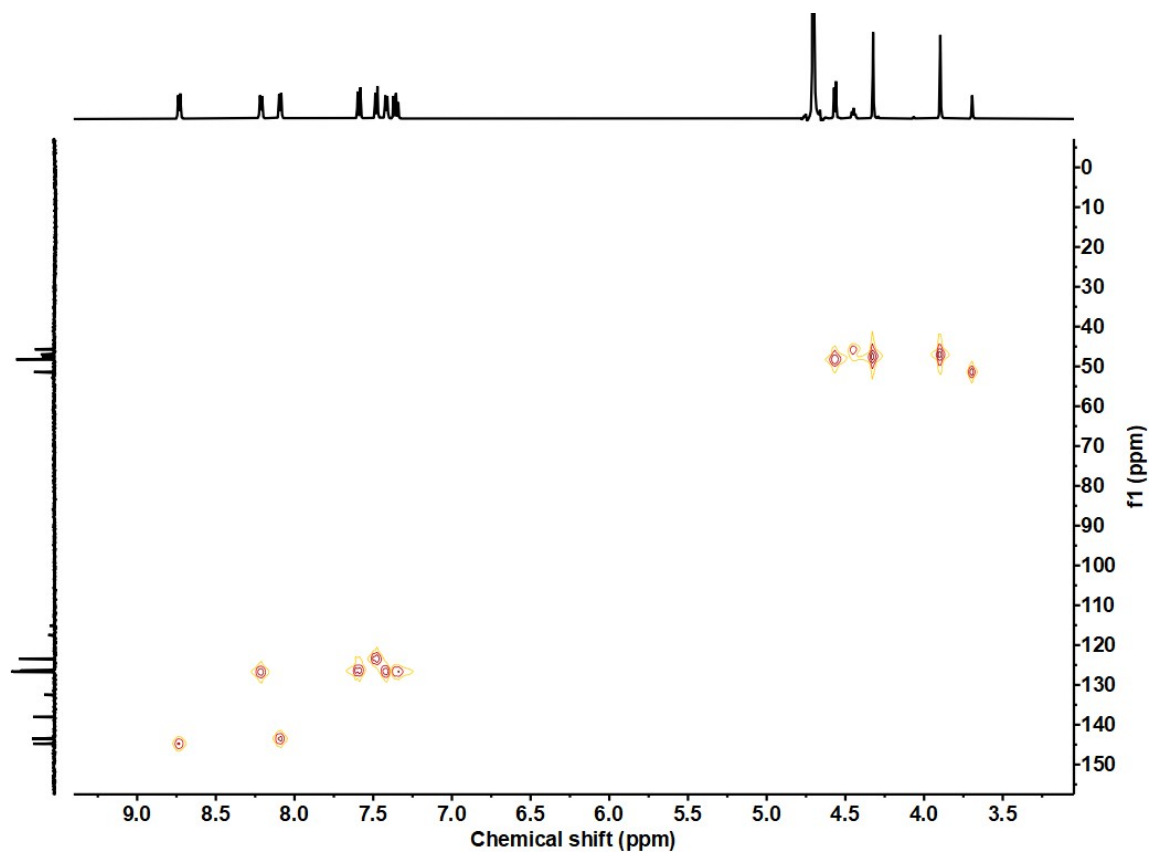


Figure S11. HMQC spectra of **2**, D<sub>2</sub>O.

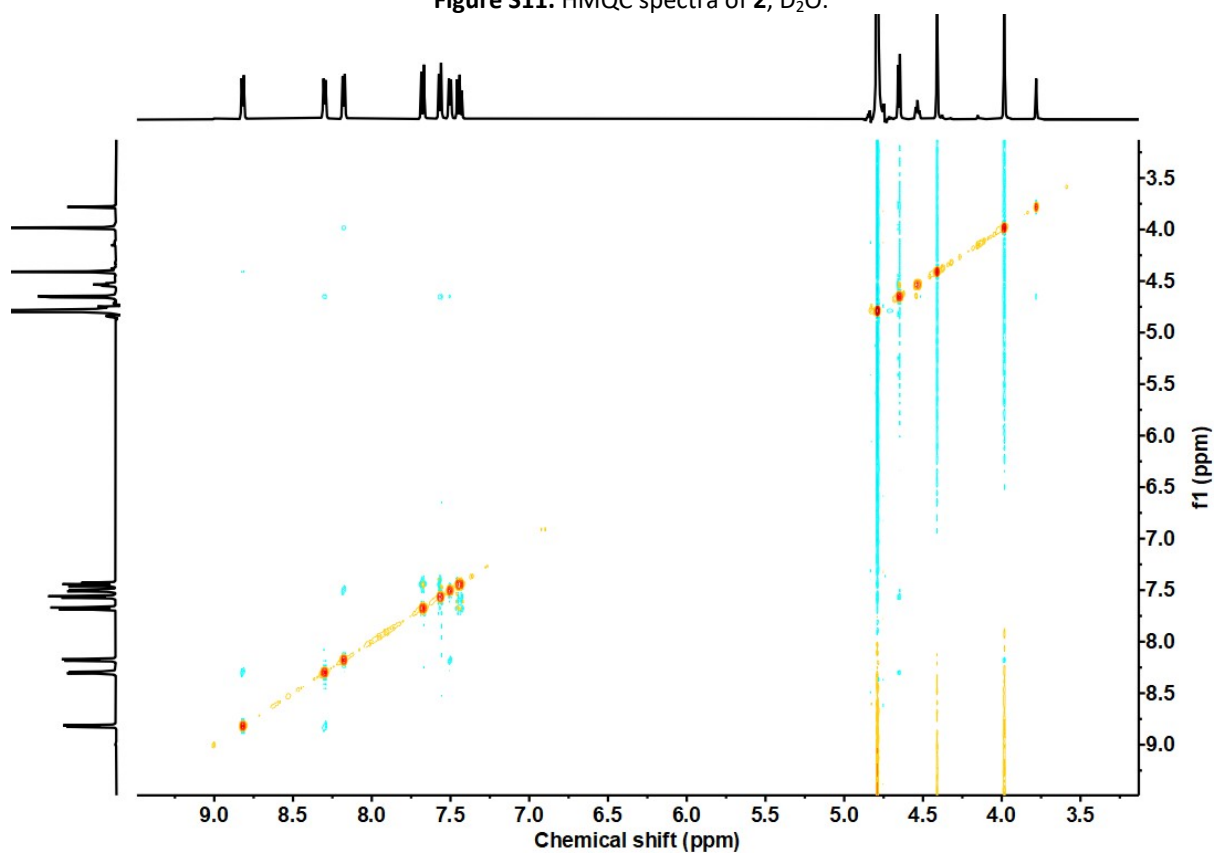


Figure S12. NOESY spectra of **2**, D<sub>2</sub>O.

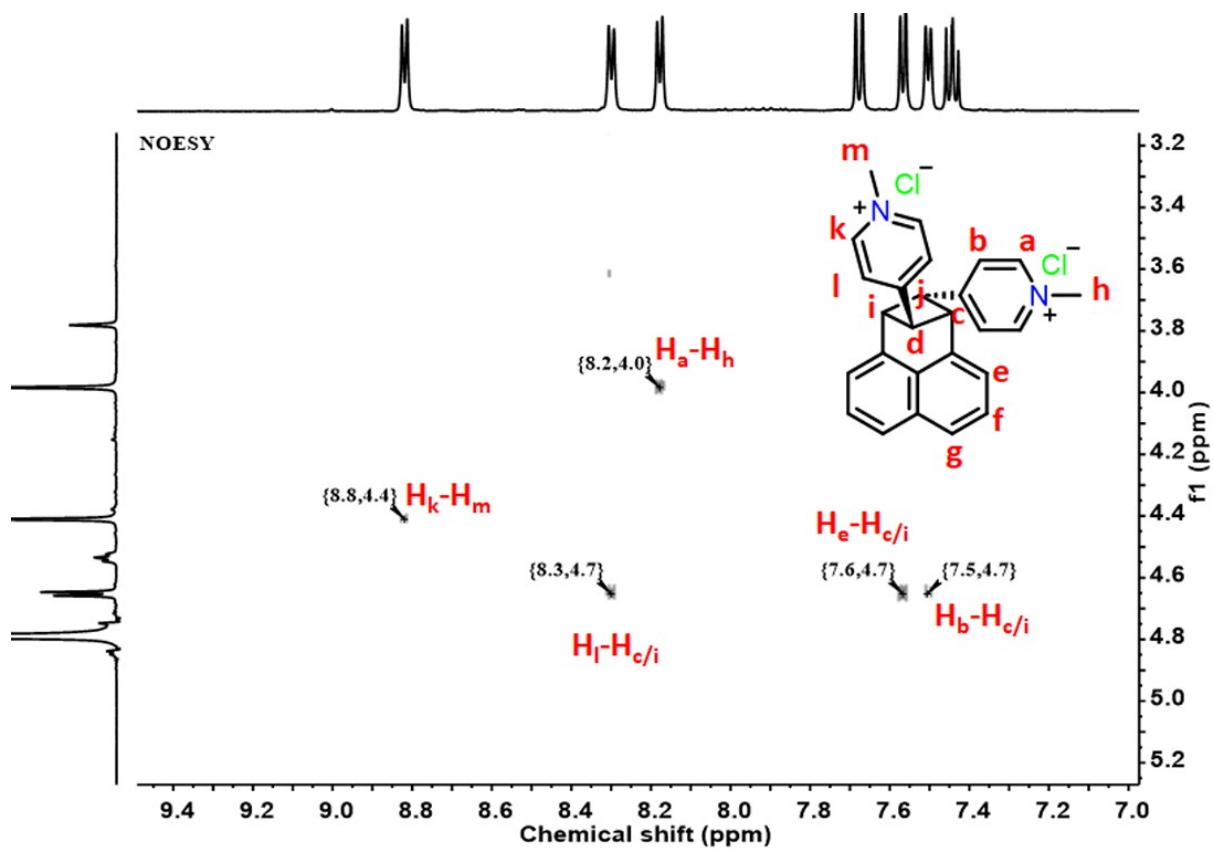


Figure S13. Zoomed NOESY spectra of 2, D<sub>2</sub>O.

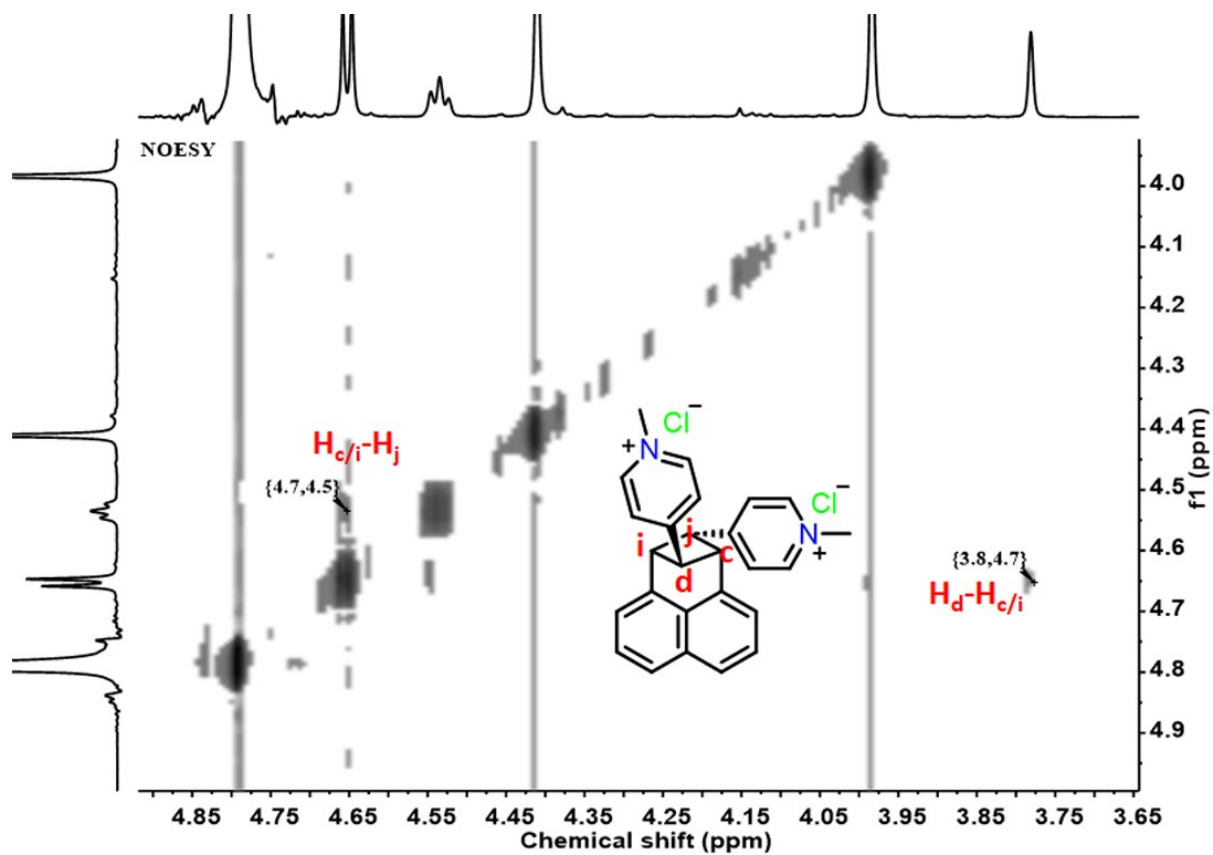
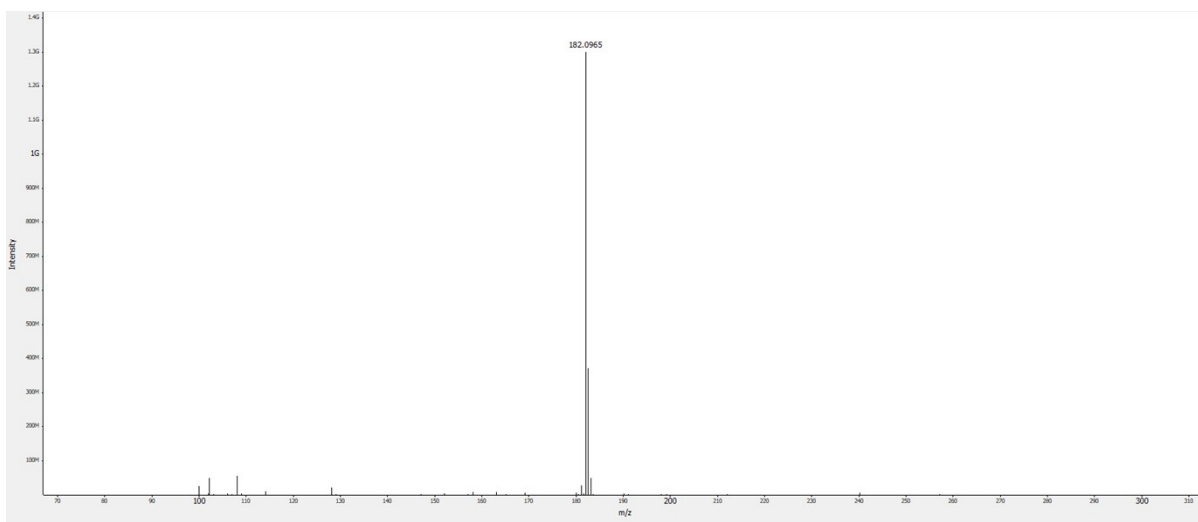
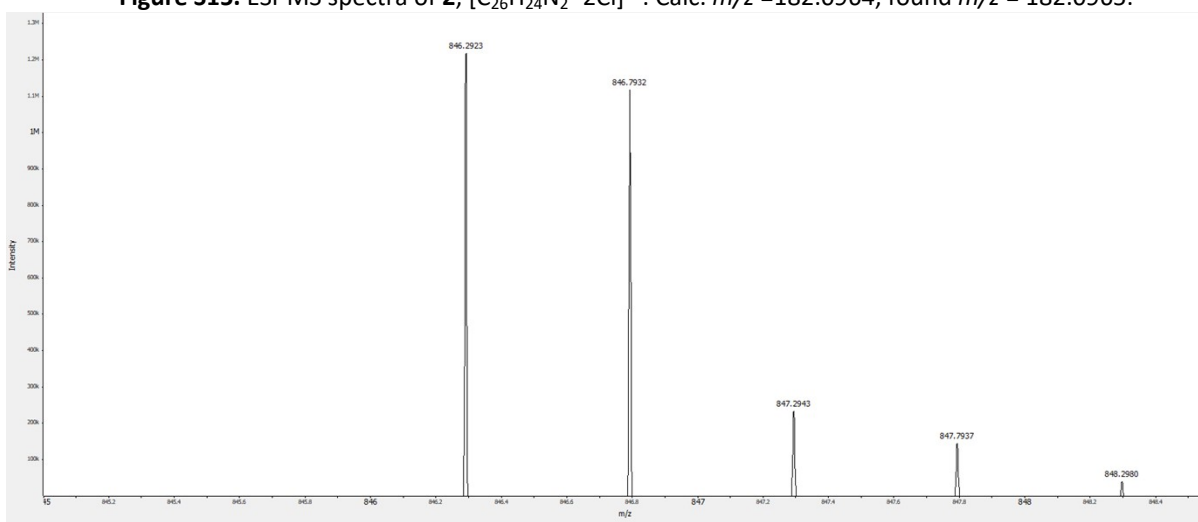


Figure S14. Zoomed NOESY spectra of 2, D<sub>2</sub>O.



**Figure S15.** ESI-MS spectra of **2**,  $[\text{C}_{26}\text{H}_{24}\text{N}_2 - 2\text{Cl}]^{2+}$ : Calc.  $m/z = 182.0964$ , found  $m/z = 182.0965$ .



**Figure S16.** HRESI-MS spectra of **1•CB8** (1:1), HRESI-MS( $m/z$ ):  $[\text{M} - 2\text{Cl}]^{2+}$ , calc. for  $\text{C}_{74}\text{H}_{72}\text{N}_{34}\text{O}_{16}^{2+}$ , 846.2928, 846.7944, 847.2961, 847.7946, 848.2982; found 846.2923, 846.7932, 847.2943, 847.7937, 848.2980.

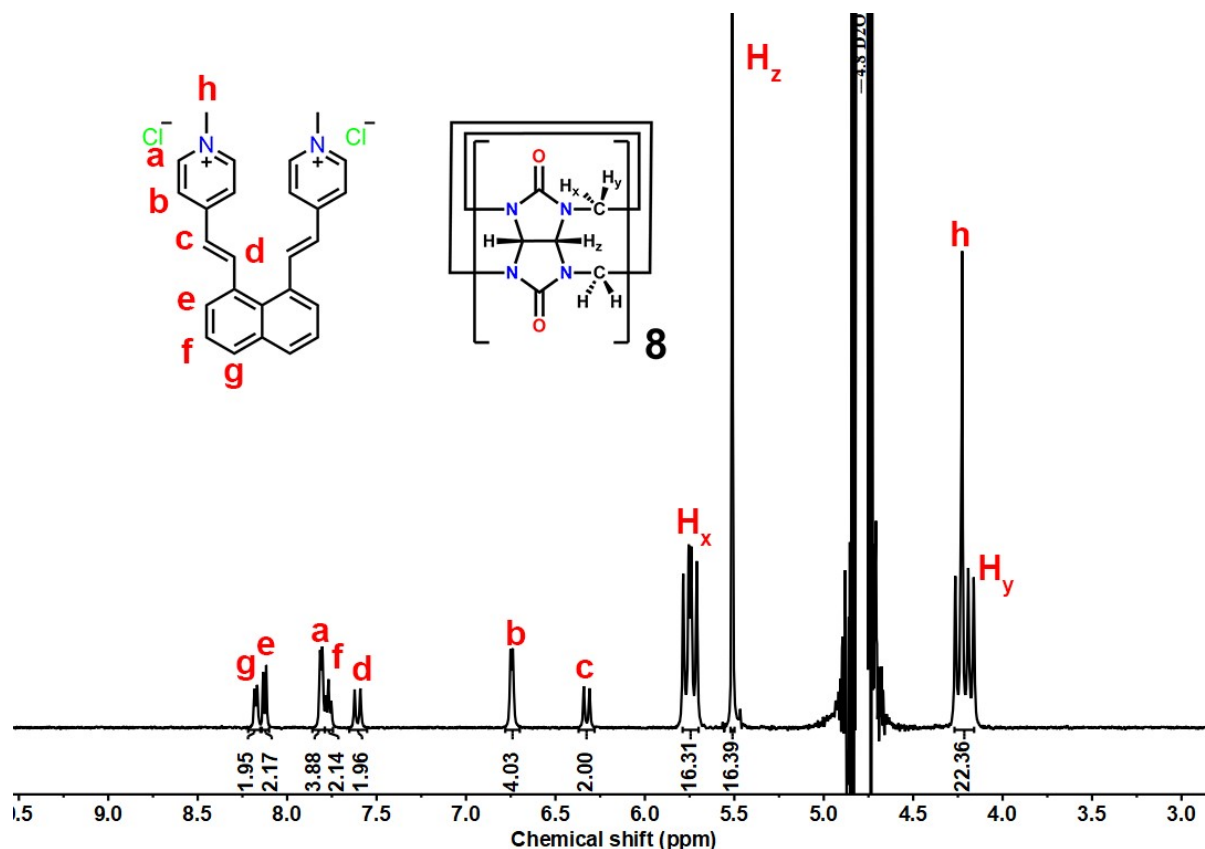
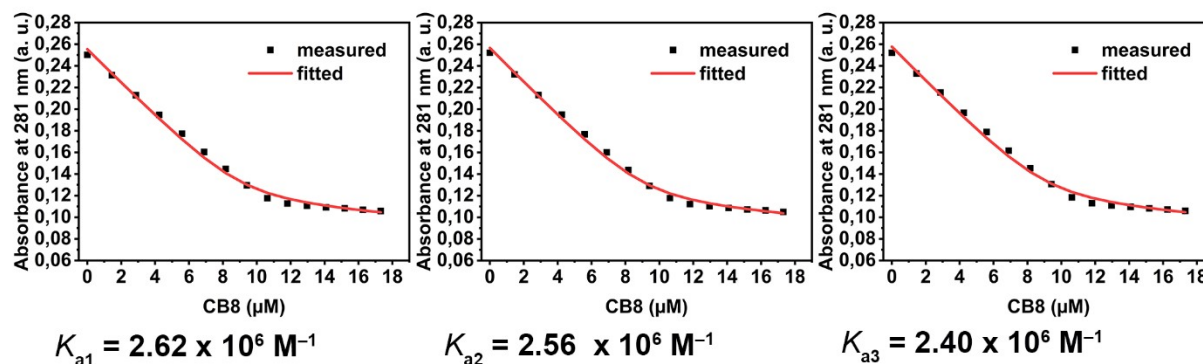


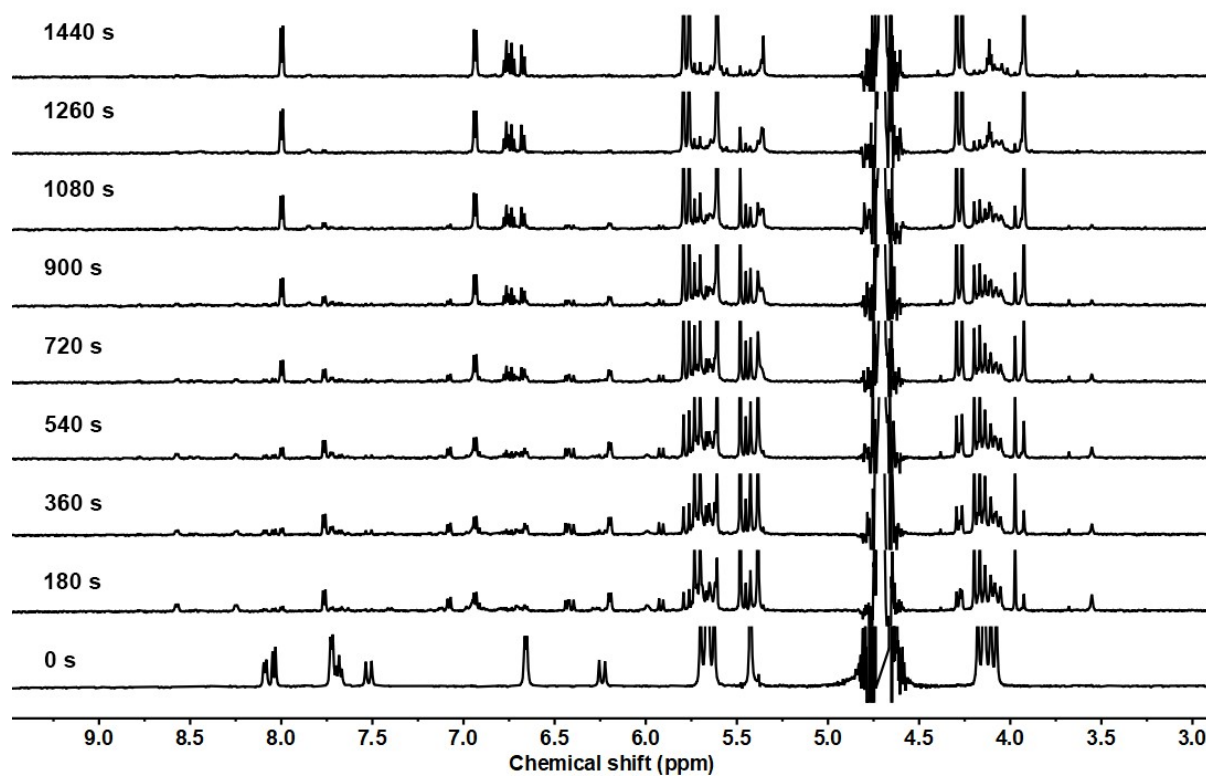
Figure S17.  $^1\text{H}$  NMR spectra of  $1\bullet\text{CB8}$  (1:1) in 0.5mM, 500 MHz,  $\text{D}_2\text{O}$ .



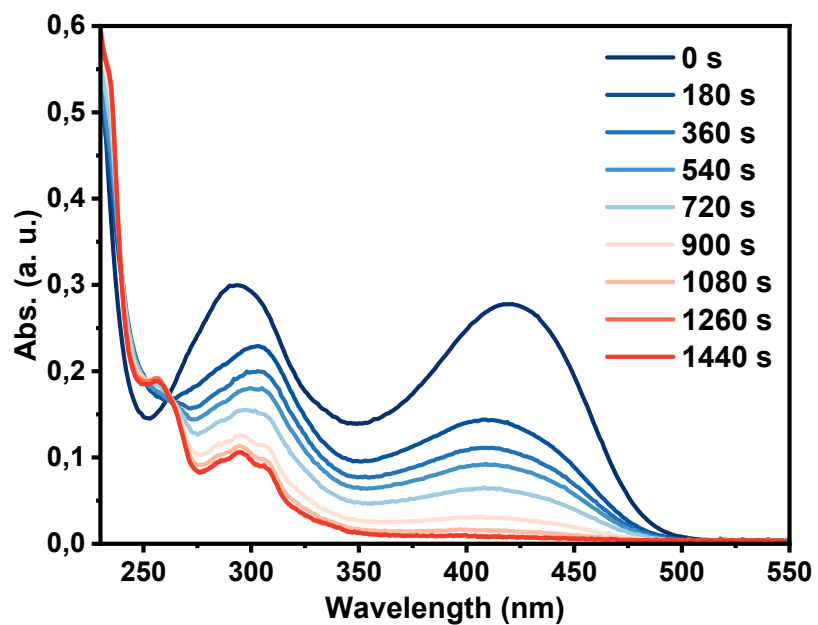
$$\text{Average } K_a = (2.53 \pm 0.11) \times 10^6 \text{ M}^{-1}$$

Figure S18. UV absorbance changes of  $1$  at 281 nm upon increasing the concentration of CB8 in Milli Q water. The binding constant value was determined by a non-linear curve fitting. The black squares represent acquired data. The fitting according to the 1:1 model is shown as a red line. The error was calculated from 3 replica experiments as the standard deviation. The binding properties can be found at <https://suprabank.org/interactions/9355>.

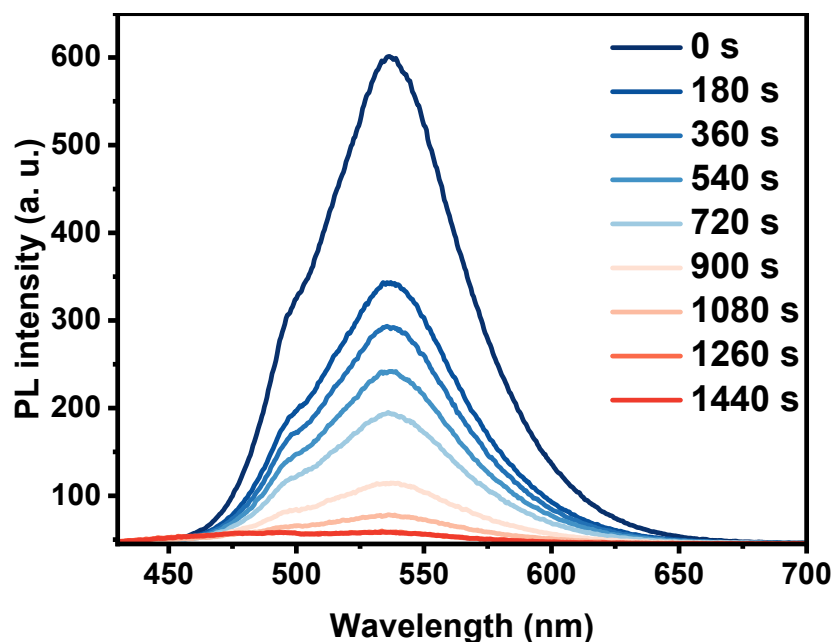




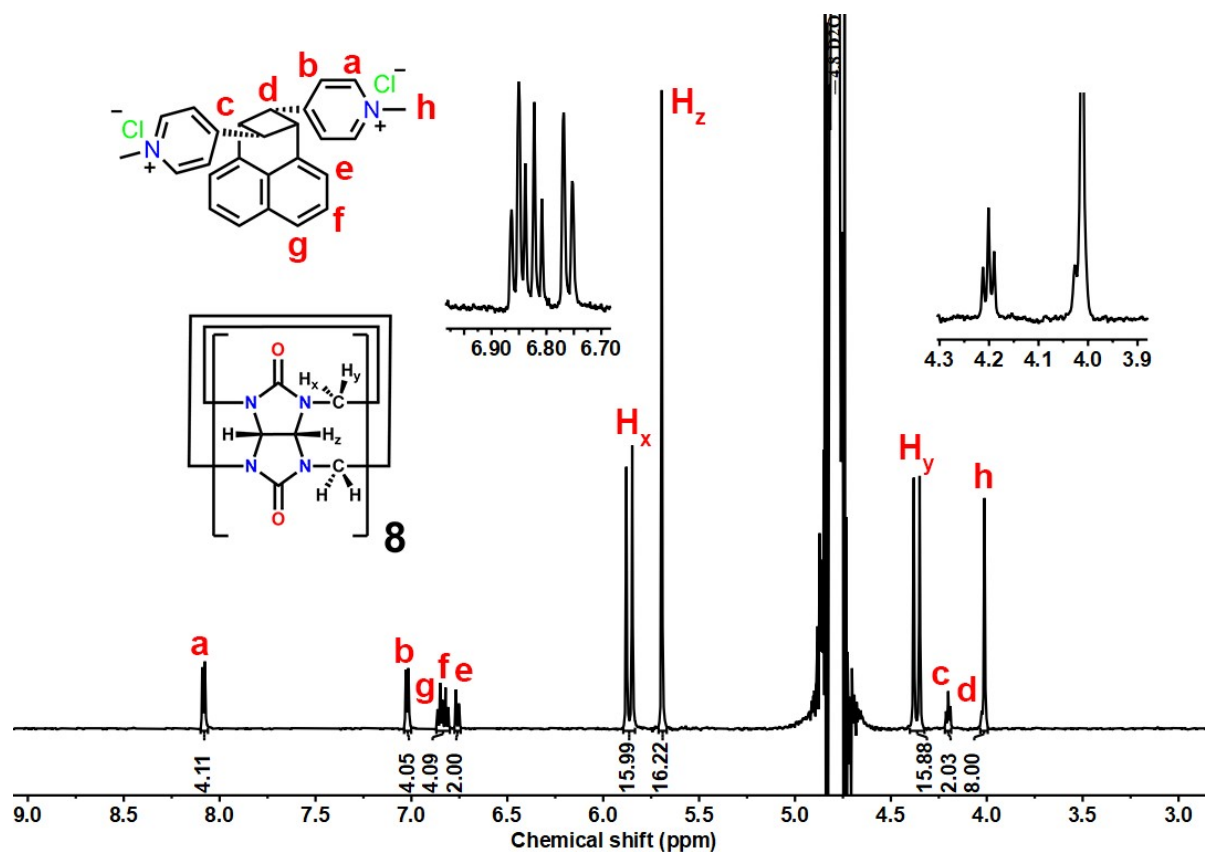
**Figure S19.**  $^1\text{H}$  NMR spectra of photolysis of  $1\bullet\text{CB8}$  (1:1, 0.5 mM) after different reaction, 500 MHz,  $\text{D}_2\text{O}$ .



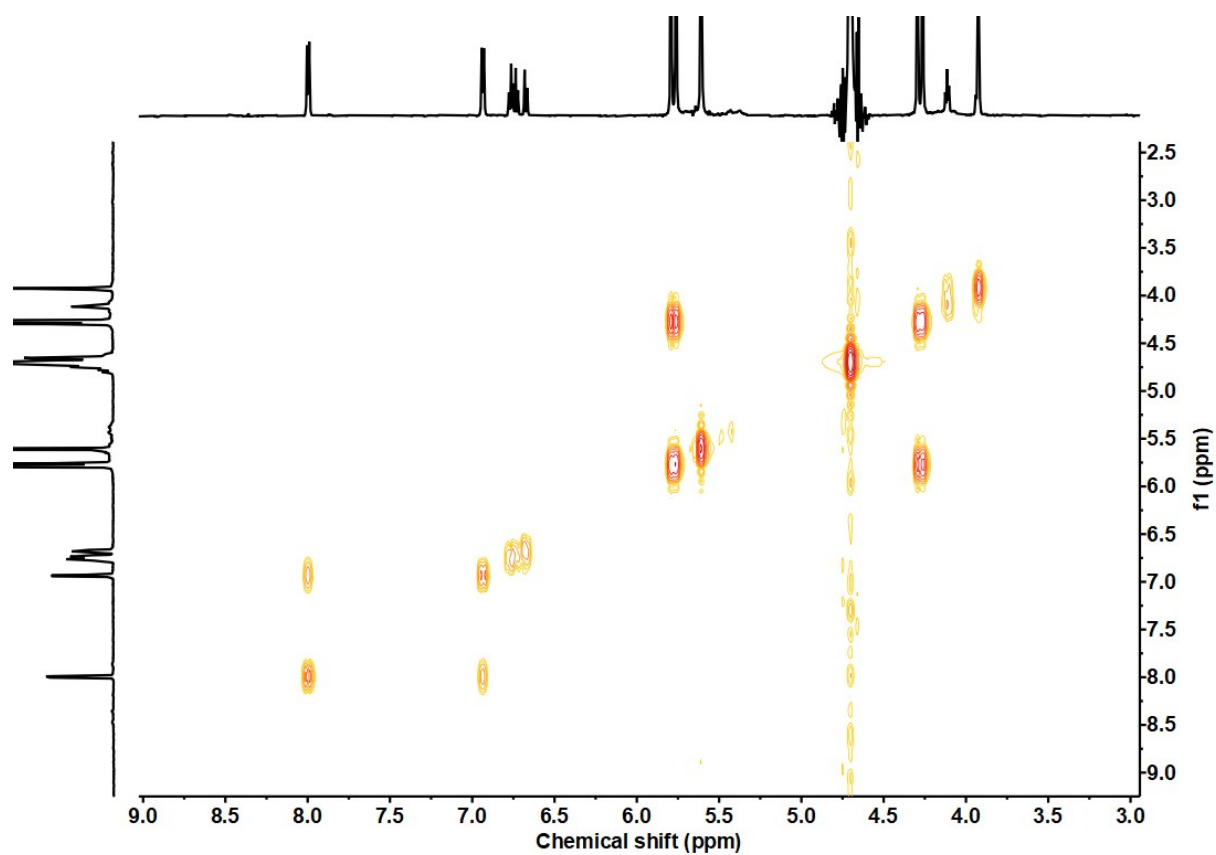
**Figure S20.** UV spectra of photolysis of  $1\bullet\text{CB8}$  (1:1, 0.5 mM) after different reaction times in Milli Q water at 25 °C. The reaction mixture was diluted with Milli Q water to  $2 \times 10^{-4}$  M for UV measurement.



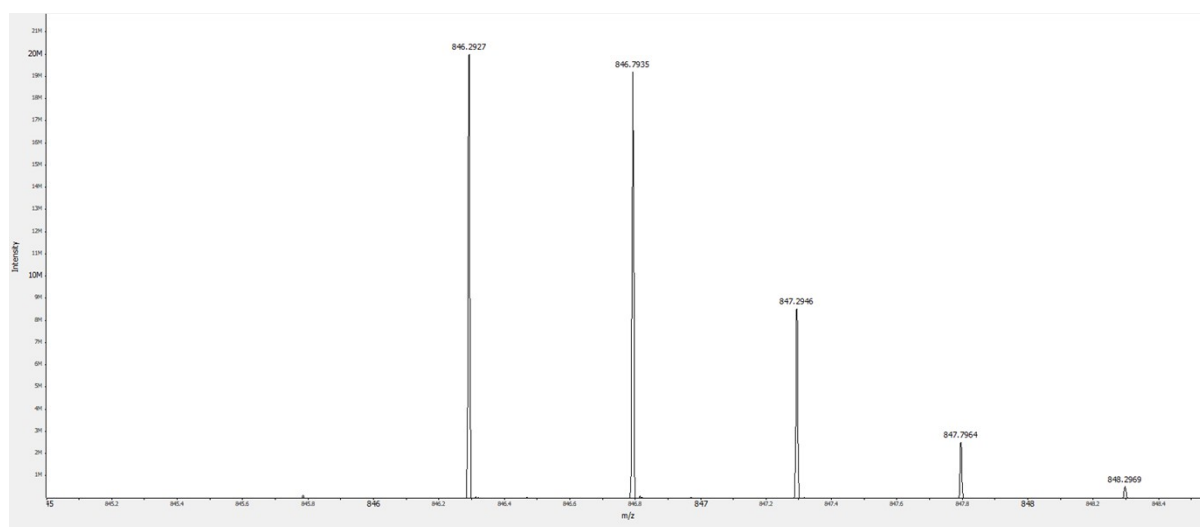
**Figure S21.** Emission spectra ( $\lambda_{exc}=410$  nm) of photolysis of **1**•CB8 (1:1, 0.5 mM) after different reaction times in Milli Q water at 25 °C. The reaction mixture was diluted with Milli Q water to  $2 \times 10^{-4}$  M for UV measurement.



**Figure S22.**  $^1\text{H}$  NMR spectra of **3**•CB8 (1:1, 0.5mM), 500 MHz,  $\text{D}_2\text{O}$ .



**Figure S23.**  $^1\text{H}$ - $^1\text{H}$  COSY spectra of **3**•CB8 (1:1, 0.5mM),  $\text{D}_2\text{O}$ .



**Figure S24.** ESI-MS spectra of **3**•CB8 (1:1), HRESI-MS( $m/z$ ):  $[\text{M}-2\text{Cl}]^{2+}$ , calc. for  $\text{C}_{74}\text{H}_{72}\text{N}_{34}\text{O}_{16}^{2+}$ , 846.2928, 846.7944, 847.2961, 847.7946, 848.2963; found 846.2927, 846.7935, 847.2946, 847.7964, 848.2969.

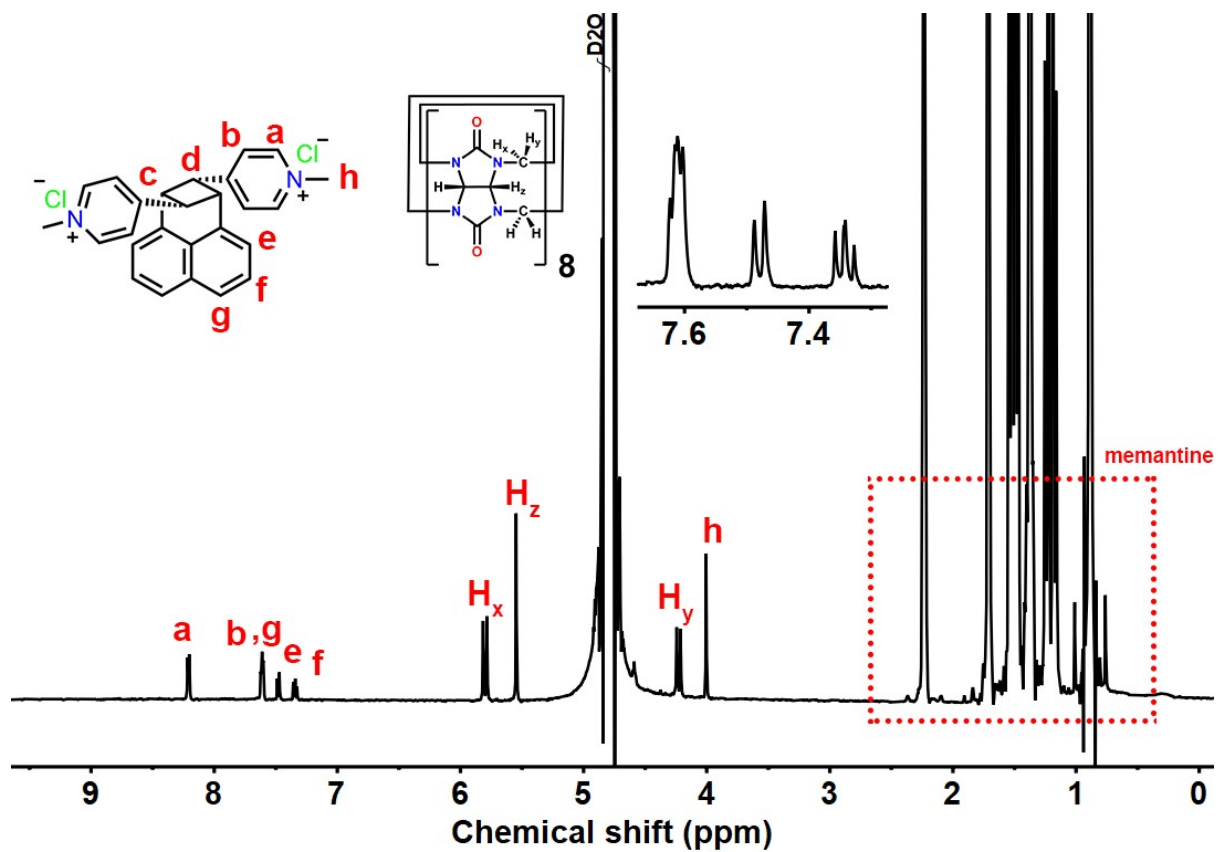


Figure S25.  $^1\text{H}$  NMR spectra of  $3 \cdot \text{CB8}$  (1:1, 0.5 mM) with over amount of memantine, 500 MHz,  $\text{D}_2\text{O}$ .

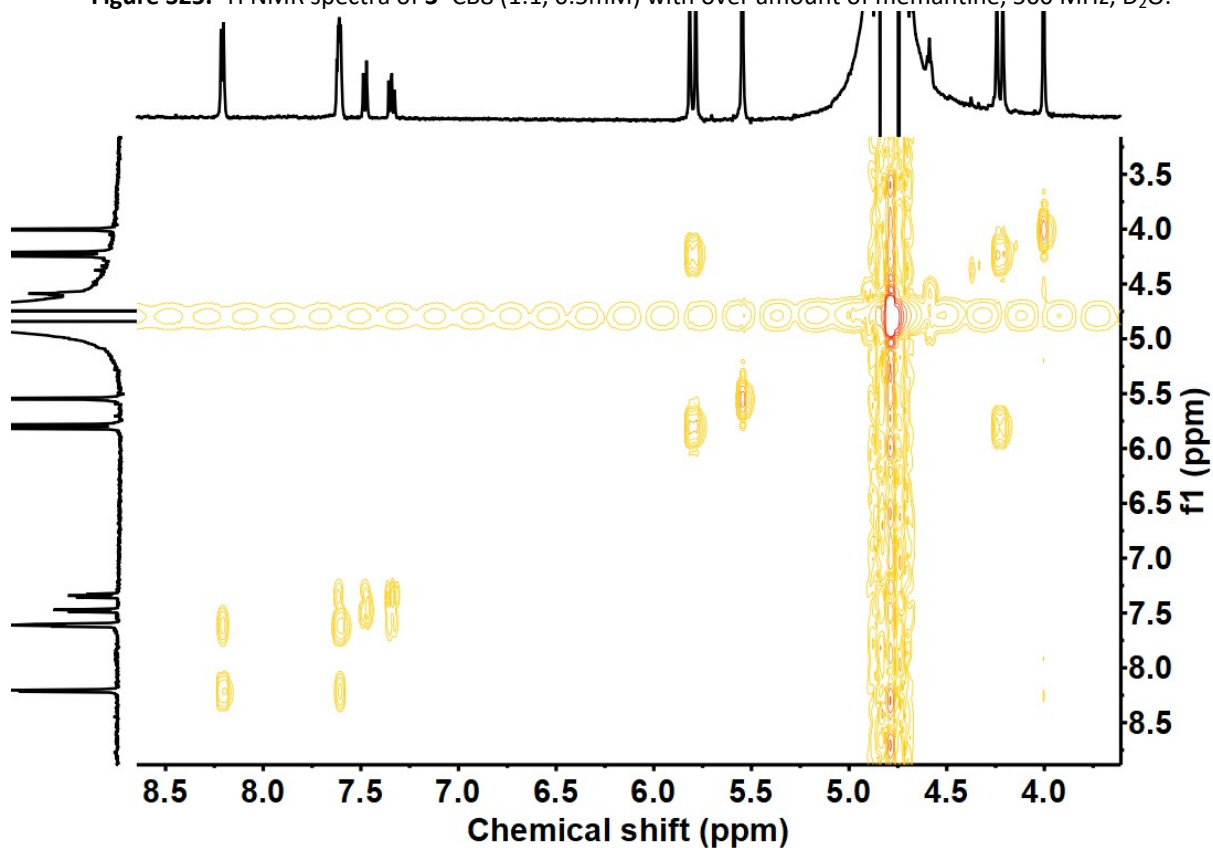
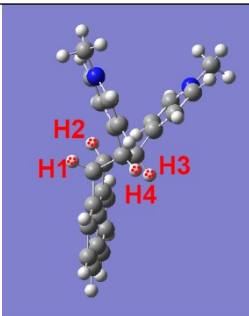
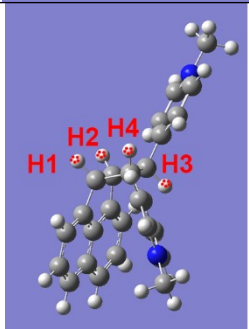
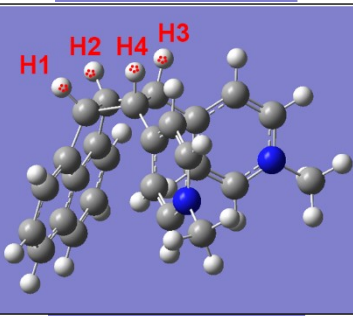
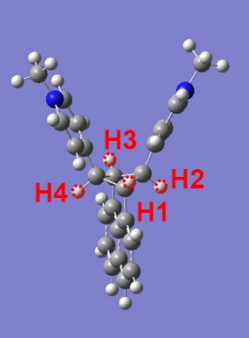
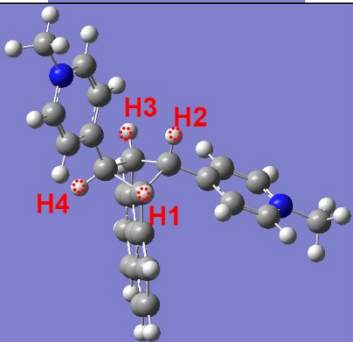



Figure S26.  $^1\text{H}$ - $^1\text{H}$  COSY spectra of  $3 \cdot \text{CB8}$  (1:1, 0.5 mM) with over amount of memantine,  $\text{D}_2\text{O}$ .

**Table S1** summary of the computed NMR predication

3D structure <sup>a</sup>	Predicted NMR	Observed NMR	Comment
	H1 s 4.56 ppm H3 s 4.49 ppm H2 s 4.56 ppm H4 s 4.49 ppm		Not fit to the NMR observed
	H1 dd 5.04 ppm H3 dd 4.53 ppm H2 s 4.74 ppm H4 dd 3.93 ppm		Not fit to the NMR observed
	H1 d 5.28 ppm H3 d 5.00 ppm H2 d 5.28 ppm H4 d 5.00 ppm		Not fit to the NMR observed
	H1 t 4.42 ppm H3 t 4.42 ppm H2 t 4.22 ppm H4 t 4.22 ppm		Similar size compared with <b>1</b> , pyridinium and naphthyl protons are not likely to be completely included within the CB8 cavity. The binding constant should be similar to <b>1</b> .
 <p data-bbox="443 1928 568 1957">Molecule 2</p>	H1 s 4.17 ppm H3 dd 4.65 ppm H2 d 4.16 ppm H4 d 4.22 ppm	4.66 ppm, 4.65 ppm doublet peak with two protons, 4.53 ppm triplet peak with one proton, 3.78 ppm with one proton.	One singlet peak refers to H4, one triplet peak refers to H2, and one doublet peak refers to H1 and H3. Expected to show a largely different binding constant than <b>1</b> .

 <p>Molecule 3</p>	<p>H1 t 4.85 ppm  H3 t 4.85 ppm  H2 t 4.38 ppm  H4 t 4.38 ppm</p>	<p>4.20 ppm triplet  peak with two  protons, 4.02  ppm hidden  triplet peak with  two protons.</p>	<p>Different NMR spectra  than molecule 2 with two  triplet peaks were  observed. Pyridinium and  naphthyl protons will  likely be completely  included within the CB8  cavity with a smaller  molecular size. Expected  to show a largely different  binding constant than 1.</p>
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a: The computation was performed using  $\omega$ B97X-D 6-31G\* method.

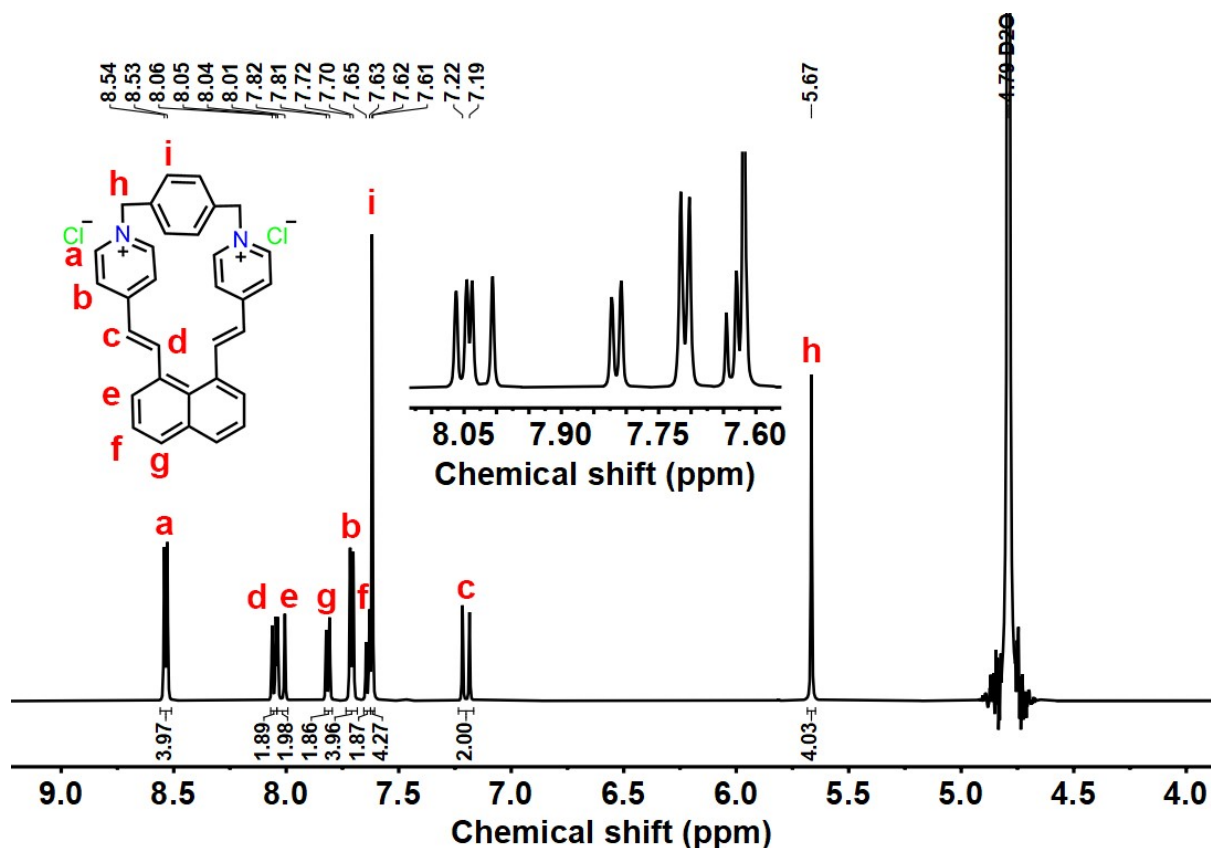


Figure S27.  $^1\text{H}$  NMR – (6E,9E)-1,5(1,4)-dipyridin-1-iuma-8(1,8)-naphthalena-3(1,4)-benzenacyclodecaphane-6,9-diene-11,51-dium chloride (**4**), 500 MHz,  $\text{D}_2\text{O}$ .

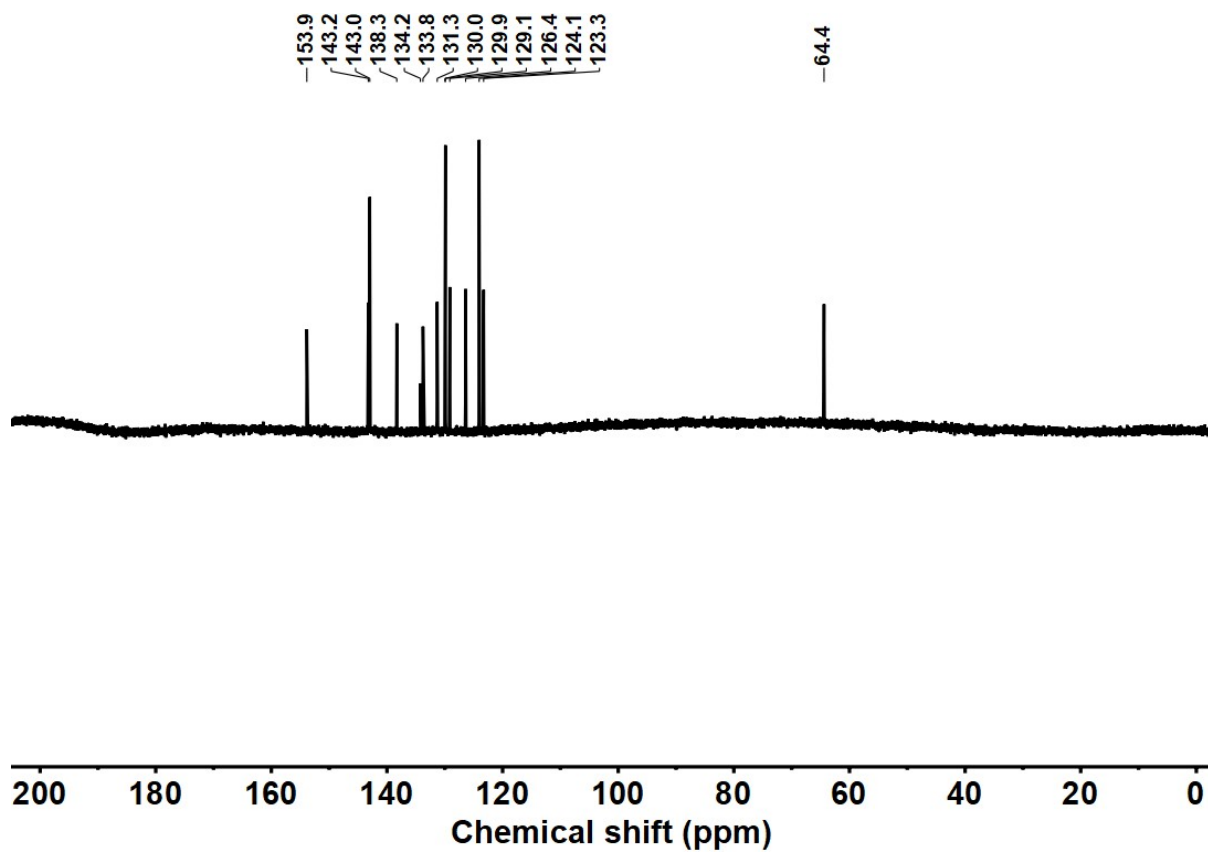


Figure S28.  $^{13}\text{C}$  NMR – (6E,9E)-1,5(1,4)-dipyridin-1-iuma-8(1,8)-naphthalena-3(1,4)-benzenacyclodecaphane-6,9-diene-11,51-dium chloride (**4**), 126 MHz,  $\text{D}_2\text{O}$ .

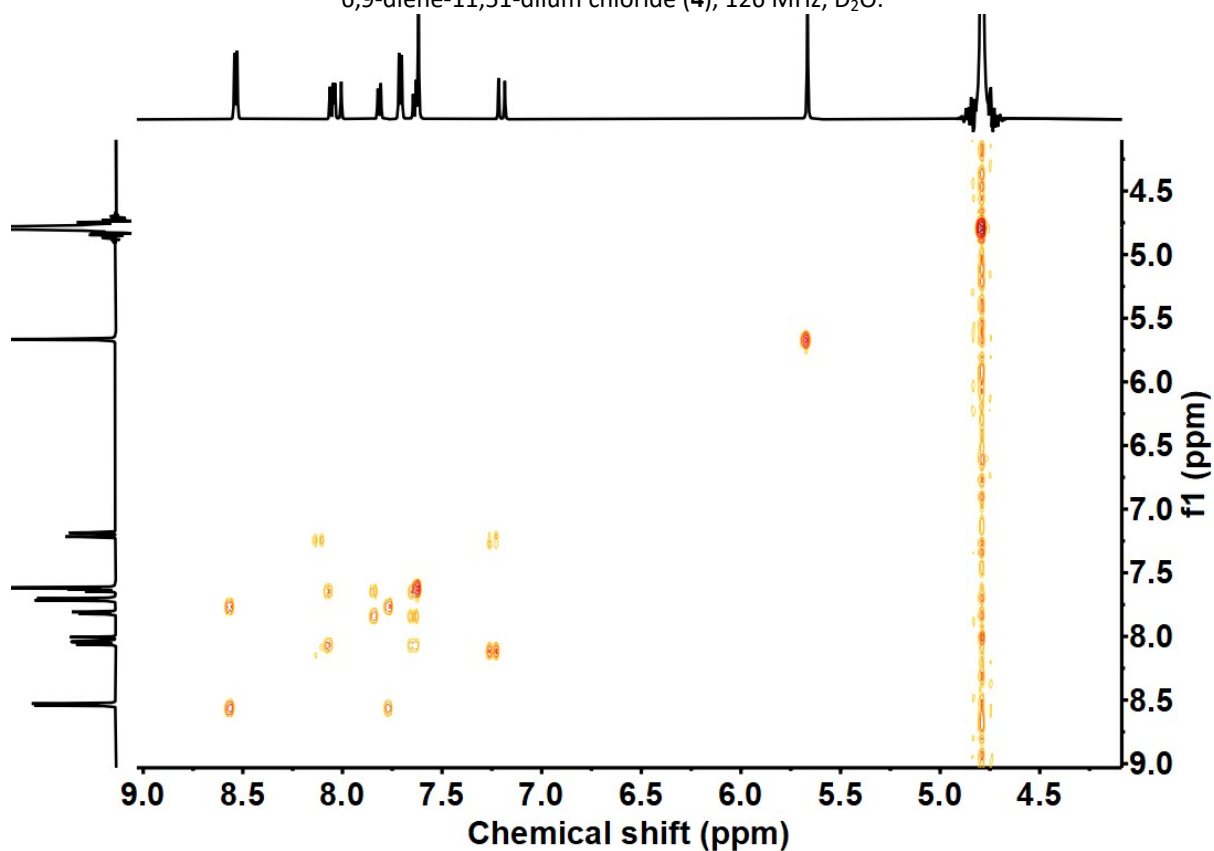
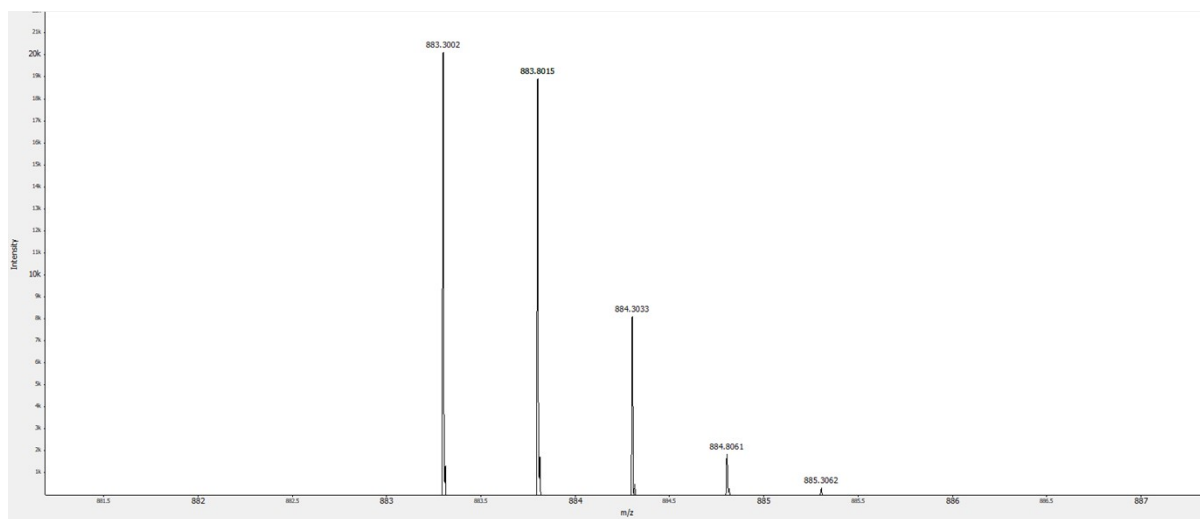
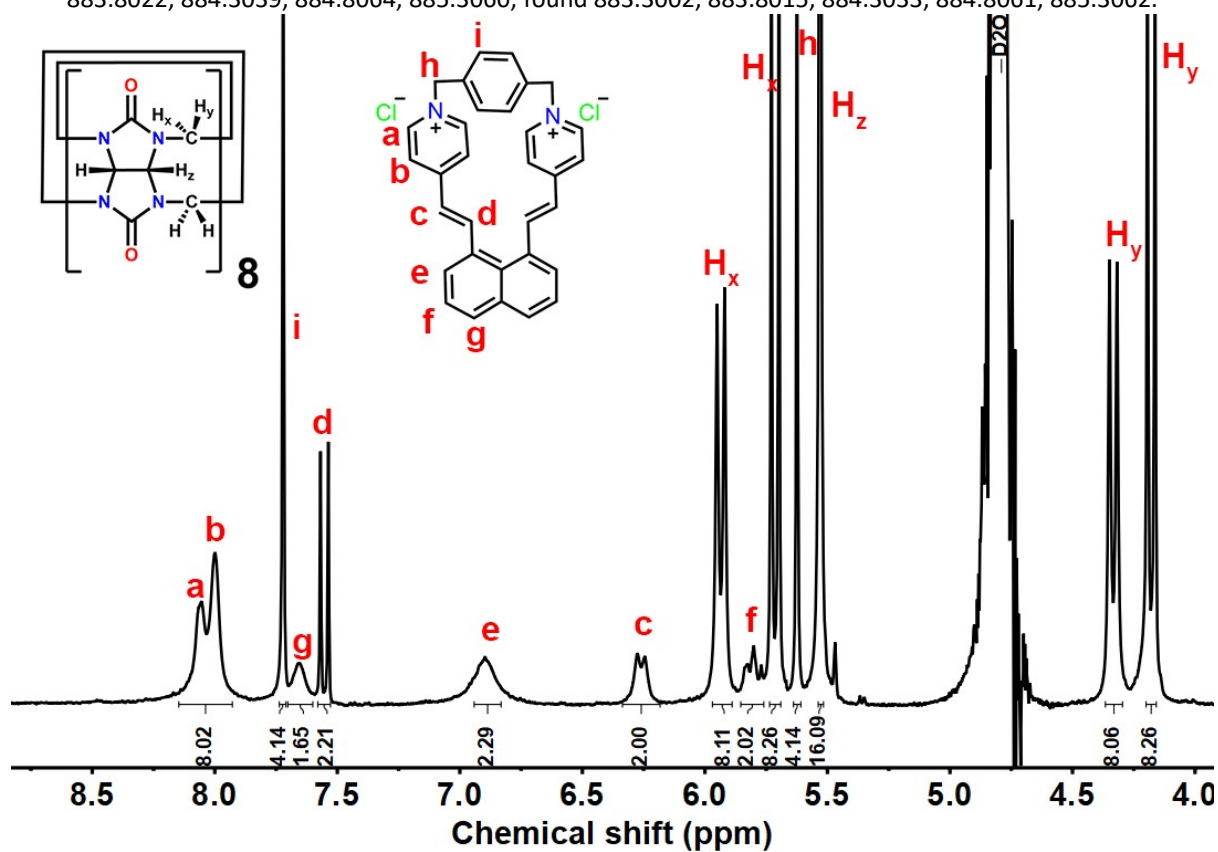


Figure S29.  $^1\text{H}$ - $^1\text{H}$  COSY – (6E,9E)-1,5(1,4)-dipyridin-1-iuma-8(1,8)-naphthalena-3(1,4)-benzenacyclodecaphane-6,9-diene-11,51-dium chloride (**4**),  $\text{D}_2\text{O}$ .



**Figure S30.** HRESI-MS spectra of **4•CB8** (1:1), HRESI-MS(*m/z*): [M-2Cl]<sup>2+</sup>, calc. for C<sub>80</sub>H<sub>74</sub>N<sub>34</sub>O<sub>16</sub><sup>2+</sup>, 883.3006, 883.8022, 884.3039, 884.8064, 885.3060; found 883.3002, 883.8015, 884.3033, 884.8061, 885.3062.



**Figure S31.** <sup>1</sup>H NMR spectra of **4•CB8** (1:1) in 0.5mM, 500 MHz, D<sub>2</sub>O.



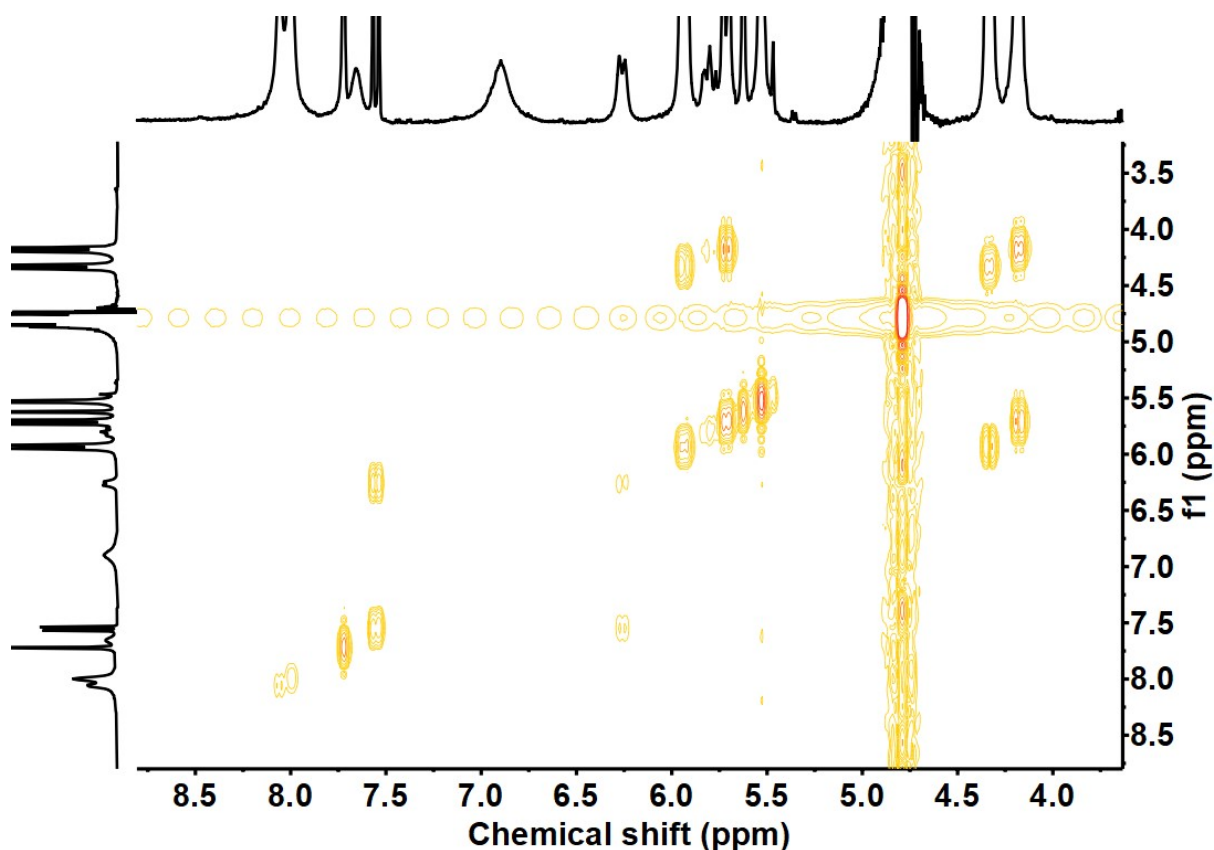
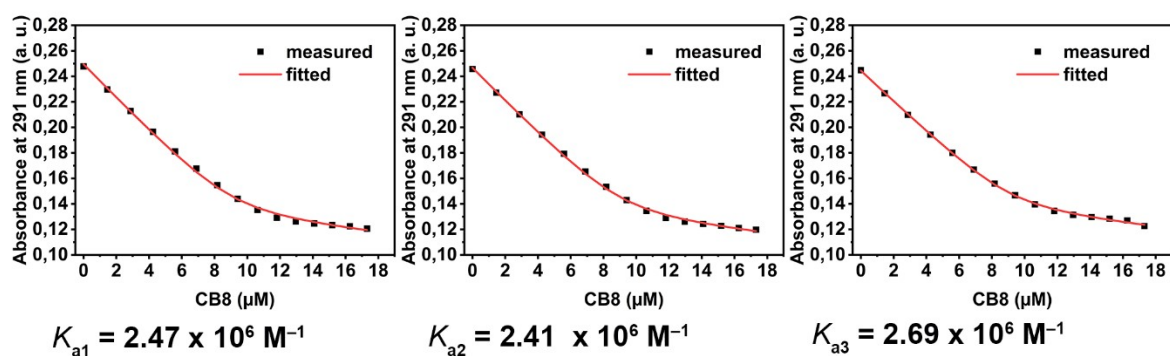


Figure S32.  $^1\text{H}$ - $^1\text{H}$  COSY spectra of  $4\bullet\text{CB8}$  (1:1) in 0.5mM,  $\text{D}_2\text{O}$ .



$$\text{Average } K_a = (2.52 \pm 0.15) \times 10^6 \text{ M}^{-1}$$

Figure S33. UV absorbance changes of **4** at 291 nm upon increasing the concentration of CB8 in Milli Q water. The binding constant value was determined by a non-linear curve fitting. The black squares represent acquired data. The fitting according to a 1:1 model is shown as a red line. The error was calculated from 3 replica experiments as the standard deviation. The binding properties can be found at

<https://suprabank.org/interactions/9354>.

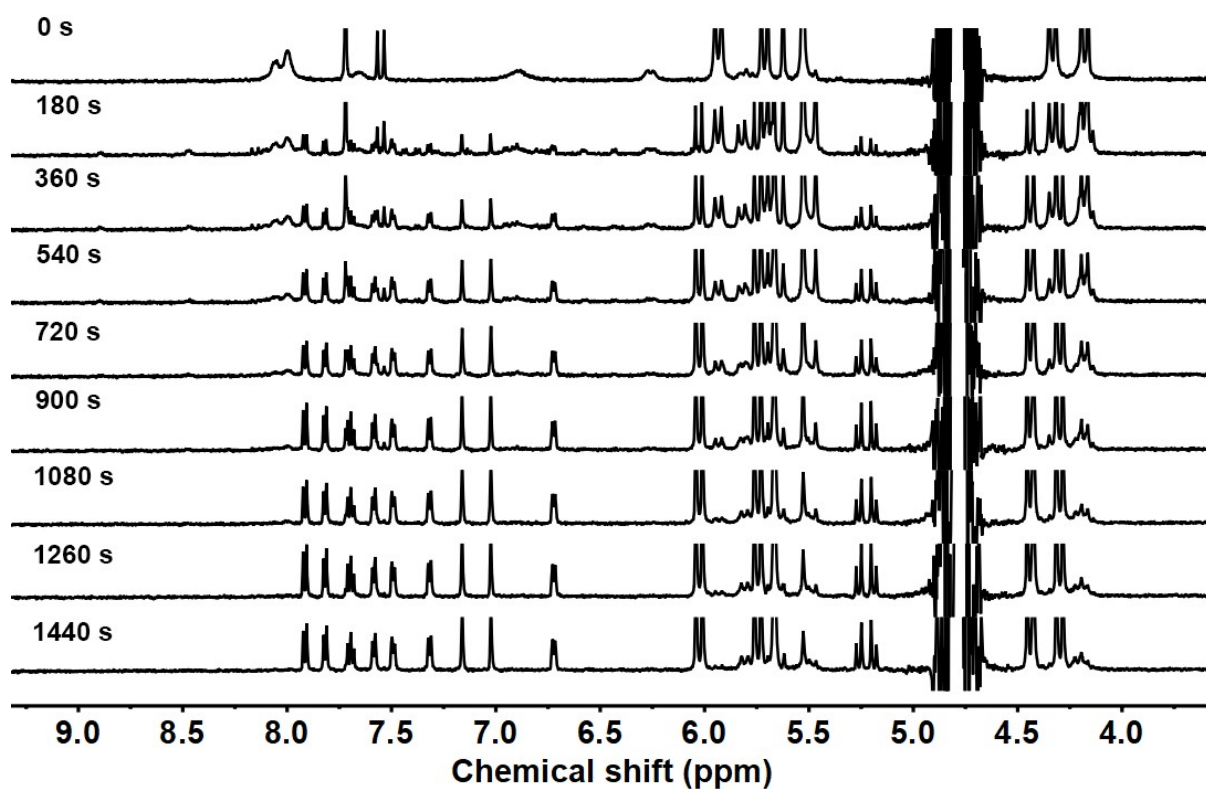


Figure S34.  $^1\text{H}$  NMR spectra of photolysis of  $4\bullet\text{CB8}$  (1:1, 0.5 mM) after different reaction, 500 MHz,  $\text{D}_2\text{O}$ .

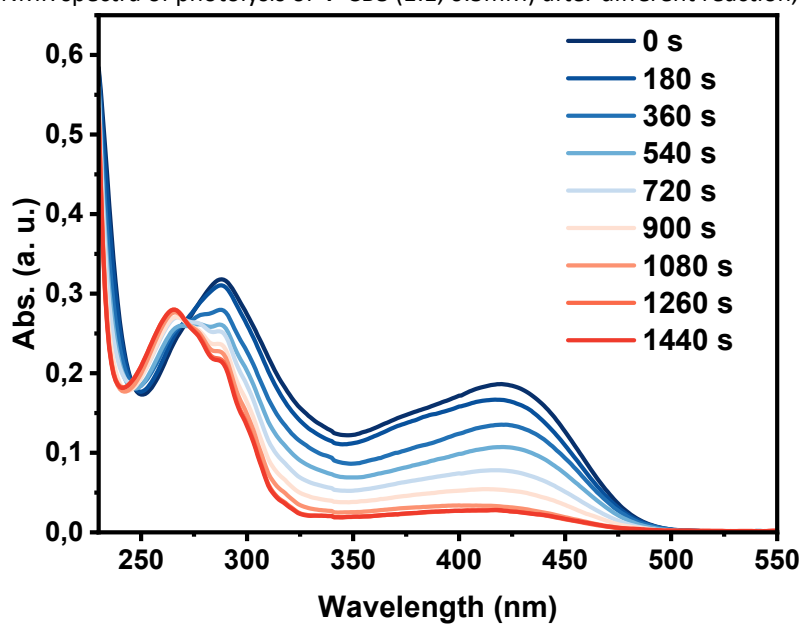
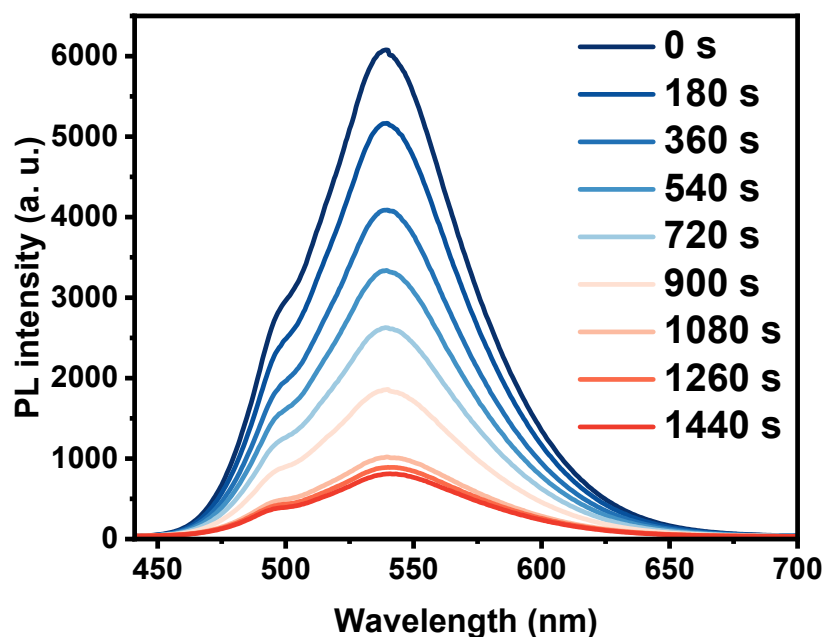
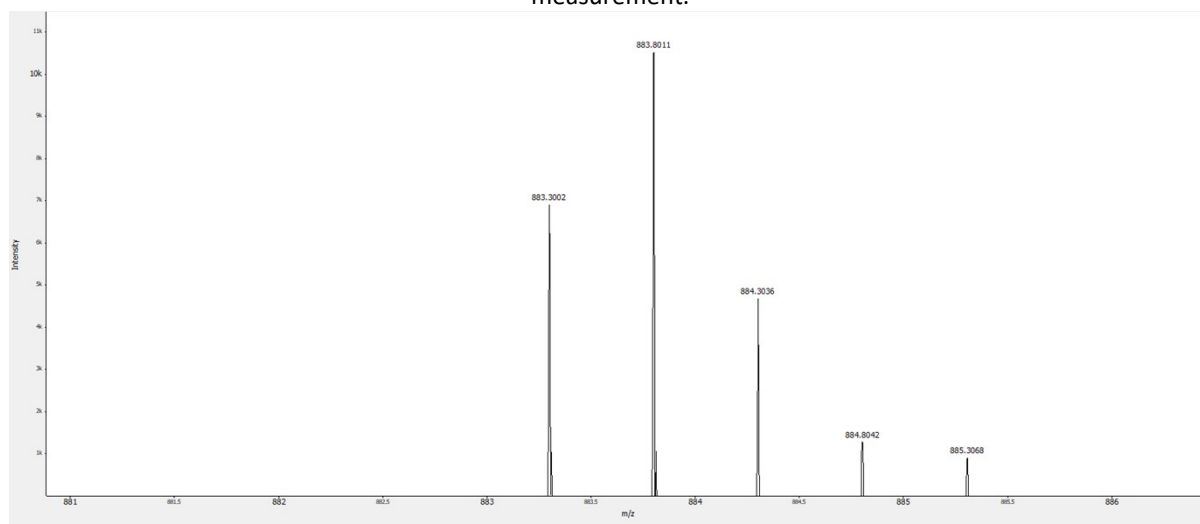


Figure S35. UV spectra of photolysis of  $4\bullet\text{CB8}$  (1:1, 0.5 mM) after different reaction times in Milli Q water at 25 °C. The reaction mixture was diluted with Milli Q water to  $2 \times 10^{-4}$  M for UV measurement.



**Figure S36.** Emission spectra ( $\lambda_{exc}=421\text{ nm}$ ) of photolysis of  $4\bullet\text{CB8}$  (1:1, 0.5 mM) after different reaction times in Milli Q water at 25 °C. The reaction mixture was diluted with Milli Q water to  $2\times 10^{-4}\text{ M}$  for UV measurement.



**Figure S37.** HRESI-MS spectra of  $5\bullet\text{CB8}$  (1:1), HRESI-MS(m/z):  $[\text{M}-2\text{Cl}]^{2+}$ , calc. for  $\text{C}_{80}\text{H}_{74}\text{N}_{34}\text{O}_{16}^{2+}$ , 883.3006, 883.8022, 884.3039, 884.8064, 885.3060; found 883.3002, 883.8011, 884.3036, 884.8042, 885.3068.

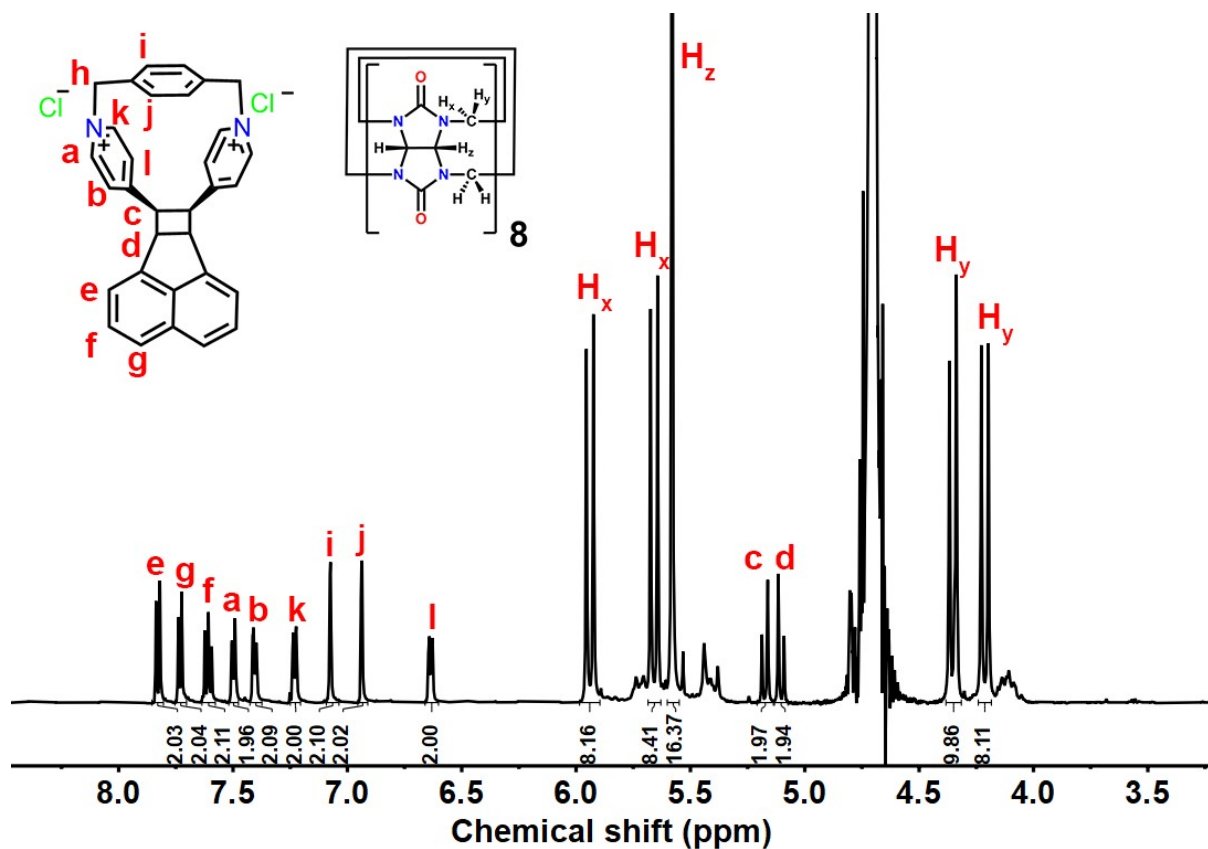


Figure S38.  $^1\text{H}$  NMR spectra of  $5 \cdot \text{CB8}$  (1:1, 0.5mM), 500 MHz,  $\text{D}_2\text{O}$ .

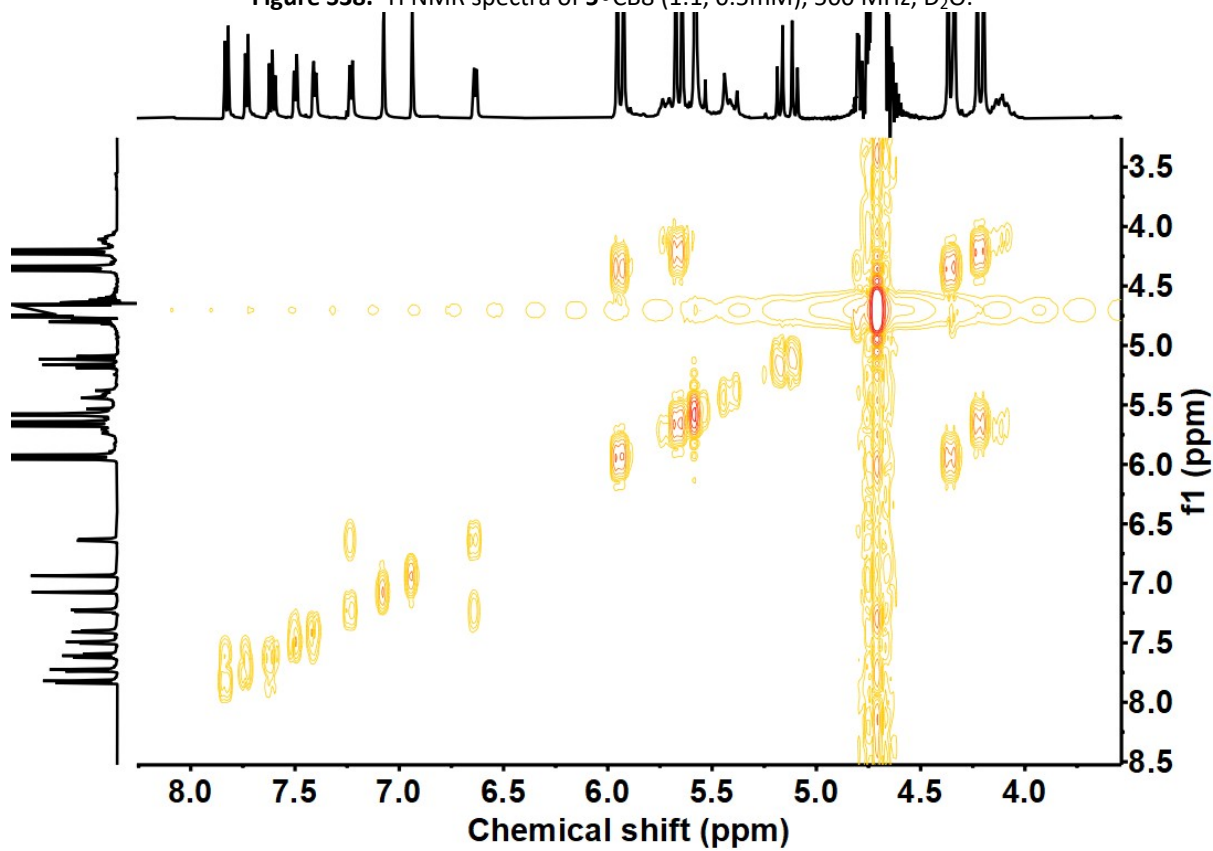


Figure S39.  $^1\text{H}$ - $^1\text{H}$  COSY spectra of  $5 \cdot \text{CB8}$  (1:1, 0.5mM),  $\text{D}_2\text{O}$ .

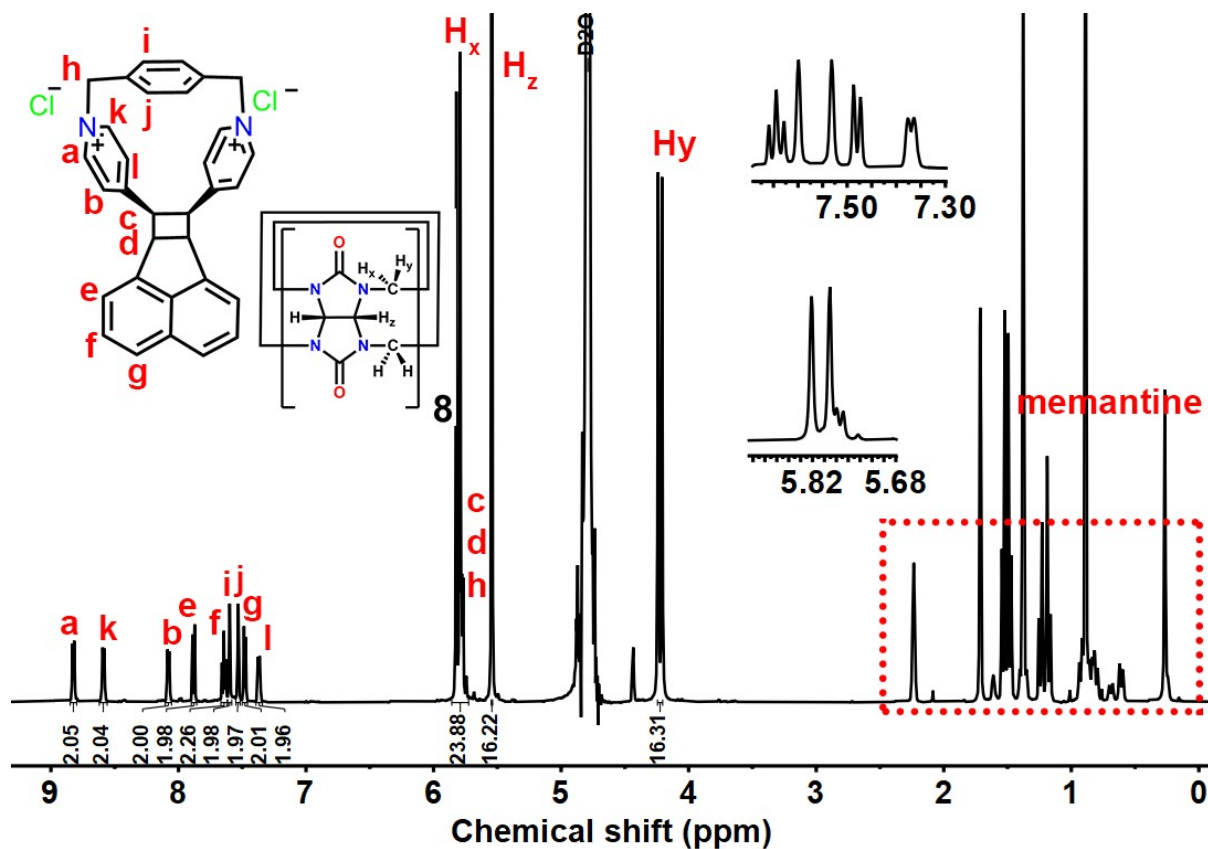


Figure S40.  $^1\text{H}$  NMR spectra of  $5\cdot\text{CB8}$  (1:1, 0.5mM) with over amount of memantine, 500 MHz,  $\text{D}_2\text{O}$ .

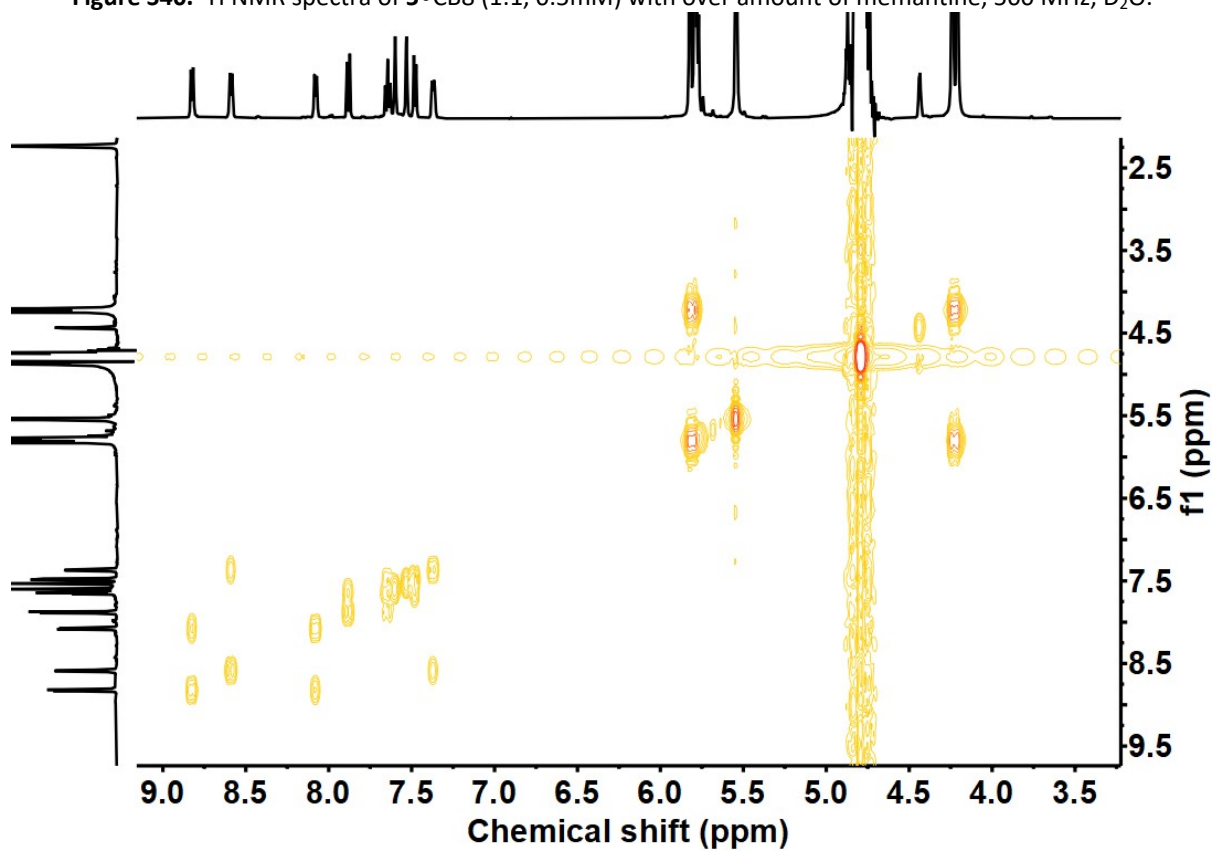


Figure S41.  $^1\text{H}$ - $^1\text{H}$  COSY spectra of  $5\cdot\text{CB8}$  (1:1, 0.5mM) with over amount of memantine,  $\text{D}_2\text{O}$ .

## 4. Competitive binding assay for binding constant determination

The binding constant determination using the method which was reported in the literature<sup>6</sup>. The method was based on the competitive binding assay (CBA), in which memantine hydrochloride was utilized as a competitive guest whose binding constant with cucurbit[8]uril  $K_{CB8\cdot Mem} = (4.3 \pm 1.1) \times 10^{11} M^{-1}$  was reported.<sup>6</sup>

$$K_{rel} = \frac{[CB8\cdot 3][Mem]_{free}}{[CB8\cdot Mem][3]_{free}} \quad \text{Eq.1}$$

$$[CB8]_{Total} = 0.5023 \text{ mM} = [CB8\cdot 3] + [CB8\cdot Mem] \quad \text{Eq.2}$$

$$[Mem]_{Total} = 4.6348 \text{ mM} = [Mem]_{free} + [CB8\cdot Mem] \quad \text{Eq.3}$$

$$[3]_{Total} = 0.5011 \text{ mM} = [3]_{free} + [CB8\cdot 3] \quad \text{Eq.4}$$

The interaction of **3** and memantine with cucurbit[8]uril  $K_{rel}$  was determined by equation 1. The equilibrium of CB[8] (0.5023 mM), Mem (4.6348 mM), and **3** were attained in the D<sub>2</sub>O, where two similar proportions peaks with 5.54ppm [CB8•Mem] and 5.70ppm [CB8•3] chemical shift in NMR spectra were observed. The relative concentration of [CB8•3] was calculated as 0.1430 mM by integrating the relative resonances in the NMR spectra. Then, equation 2 allows us to calculate the [CB8•Mem] as 0.3593 mM, which was substituted in equation 3 to calculate [Mem]<sub>free</sub> as 4.2755 mM. With the same method, [3]<sub>free</sub> was calculated as 0.3581 mM using equation 4.

The  $K_{rel}$  value was calculated by substitution of [CB8•3], [3]<sub>free</sub>, [CB8•Mem], and [Mem]<sub>free</sub> into equation 1, which was obtained as 4.7518. Substitution of  $K_{CB8\cdot Mem} = (4.3 \pm 1.1) \times 10^{11} M^{-1}$  and  $K_{rel}$  in equation 5 to obtain  $K_{CB8\cdot 3} = 2.04 \times 10^{12} M^{-1}$  (equation 6). The uncertainty of  $\sigma K_{CB8\cdot 3}$  can be calculated by equation 7, where  $\sigma(K_{CB8\cdot Mem})/\sigma K_{CB8\cdot Mem} = 0.1006$  and  $\sigma(K_{rel})/\sigma K_{rel} = 0.10$  [Note that we are using the even more conservative 10% error in this analysis] to give the percent error in  $K_{CB8\cdot 3}$  equation 8. Substituting equation 6 into equation 9 gives  $\sigma K_{CB8\cdot 3}$  as  $0.29 \times 10^{12} M^{-1}$ , which was finally combined into equation 10 to give the final binding constant  $K_{CB8\cdot 3} = (2.04 \pm 0.29) \times 10^{12} M^{-1}$ .

$$K_{CB8\cdot 3} = (K_{CB8\cdot Mem})(K_{rel}) \quad \text{Eq.5}$$

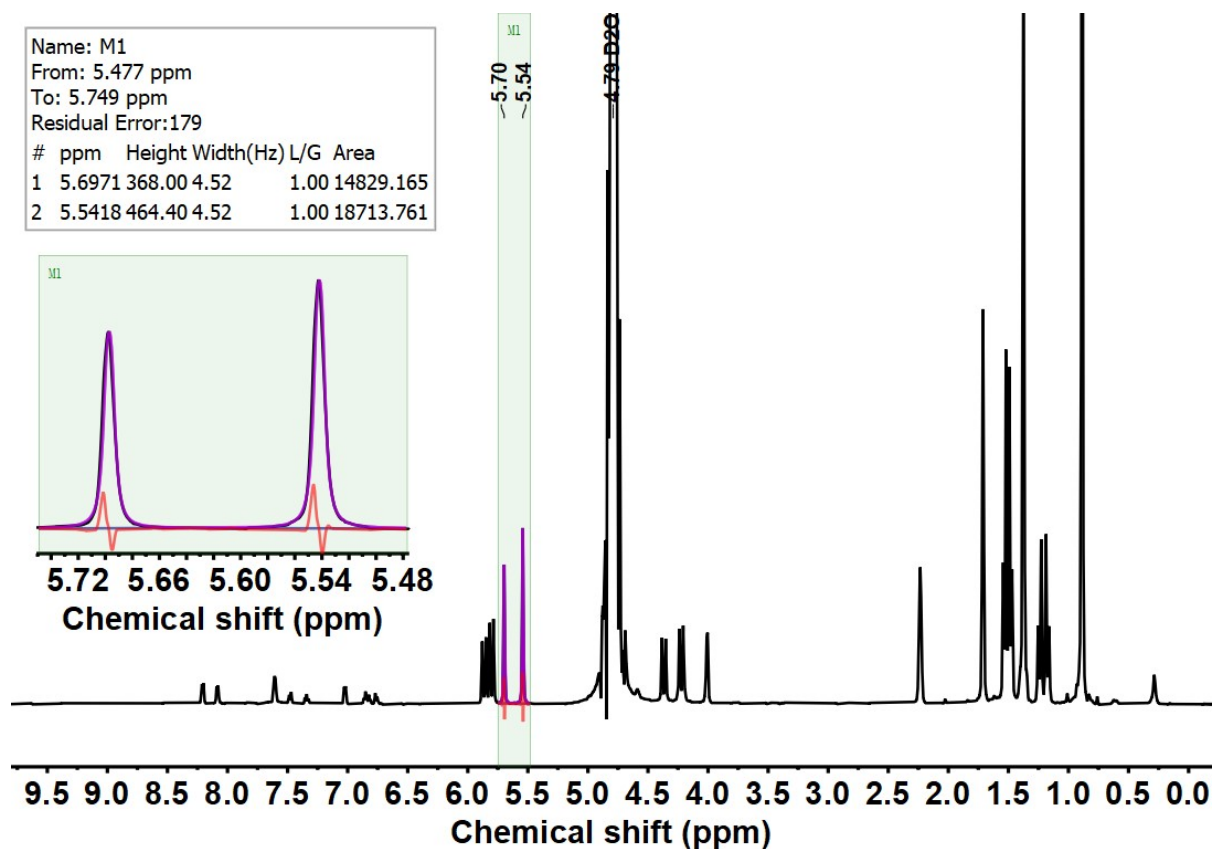
$$K_{CB8\cdot 3} = 2.04 \times 10^{12} M^{-1} \quad \text{Eq.6}$$

$$\left( \frac{\sigma K_{CB8\cdot 3}}{K_{CB8\cdot 3}} \right)^2 = \left( \frac{\sigma K_{CB8\cdot Mem}}{K_{CB8\cdot Mem}} \right)^2 + \left( \frac{\sigma K_{rel}}{K_{rel}} \right)^2 \quad \text{Eq.7}$$

$$\frac{\sigma K_{CB8\cdot 3}}{K_{CB8\cdot 3}} = 0.1418 \text{ (14.18\%)} \quad \text{Eq.8}$$

$$\sigma K_{CB8\cdot 3} = 0.1418 \times (2.04 \times 10^{12} M^{-1}) = 0.29 \times 10^{12} M^{-1} \quad \text{Eq.9}$$

$$K_{CB8\cdot 3} = (2.04 \pm 0.29) \times 10^{12} M^{-1}. \quad \text{Eq.10}$$

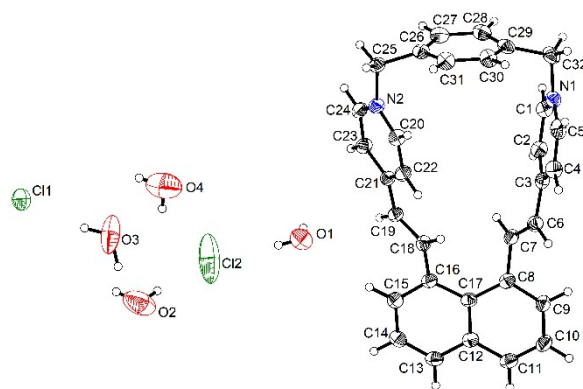


**Figure S42.**  $^1\text{H}$  NMR spectra were used in the competitive binding assay determination of  $K_{\text{rel}}$  value for  $[\text{CB8}\cdot\mathbf{3}]$  and  $[\text{CB8}\cdot\text{Mem}]$ .  $[\text{CB8}]_{\text{Total}} = 0.5023$  mM,  $[\text{Mem}]_{\text{Total}} = 4.6348$  mM,  $[\mathbf{3}]_{\text{Total}} = 0.5011$  mM, 500 MHz,  $\text{D}_2\text{O}$ .

## 5. X-Ray Diffraction

Single crystals of  $\text{C}_{32}\text{H}_{34}\text{Cl}_2\text{N}_2\text{O}_4$  (**4**) were obtained by slowly evaporating aqueous solution of **4**. A suitable crystal was selected and studied on a Stoe StadiVari diffractometer. The crystal was kept at 180 K during data collection. Using Olex2<sup>4</sup>, the structure was solved with the ShelXT<sup>5</sup> structure solution program using Intrinsic Phasing and refined with the ShelXL<sup>6</sup> refinement package using Least Squares minimisation.

**Crystal Data** for  $\text{C}_{32}\text{H}_{34}\text{Cl}_2\text{N}_2\text{O}_4$  ( $M = 581.51$  g/mol): orthorhombic, space group  $P2_12_12_1$  (no. 19),  $a = 10.2222(3)$  Å,  $b = 10.4342(4)$  Å,  $c = 27.3088(11)$  Å,  $V = 2912.77(18)$  Å<sup>3</sup>,  $Z = 4$ ,  $T = 180$  K,  $\mu(\text{GaK}\alpha) = 1.516$  mm<sup>-1</sup>,  $D_{\text{calc}} = 1.326$  g/cm<sup>3</sup>, 18886 reflections measured ( $7.892^\circ \leq 2\theta \leq 124.976^\circ$ ), 6909 unique ( $R_{\text{int}} = 0.0147$ ,  $R_{\text{sigma}} = 0.0131$ ) which were used in all calculations. The final  $R_1$  was 0.0692 ( $I > 2\sigma(I)$ ) and  $wR_2$  was 0.1850 (all data).



**Figure S43.** Molecular structure of **4·4H<sub>2</sub>O** (displacement parameters are drawn at a 50 % probability level).

**Table S2** Crystallographic data and structure refinement details of **4·4H<sub>2</sub>O**.

Compound	<b>4·4H<sub>2</sub>O</b>
Empirical formula	C <sub>32</sub> H <sub>34</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub>
Formula weight	581.51
Temperature/K	180
Crystal system	orthorhombic
Space group	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
<i>a</i> /Å	10.2222(3)
<i>b</i> /Å	10.4342(4)
<i>c</i> /Å	27.3088(11)
$\alpha$ /°	90
$\beta$ /°	90
$\gamma$ /°	90
Volume/Å <sup>3</sup>	2912.77(18)
<i>Z</i>	4
$\rho_{\text{calc}}$ /cm <sup>3</sup>	1.326
$\mu$ /mm <sup>-1</sup>	1.516
<i>F</i> (000)	1224.0
Crystal size/mm <sup>3</sup>	0.15 × 0.13 × 0.11
Radiation	GaK $\alpha$ ( $\lambda$ = 1.34143)
2 $\theta$ range for data collection/°	7.892 to 124.976
Index ranges	-13 ≤ <i>h</i> ≤ 5, -13 ≤ <i>k</i> ≤ 11, -33 ≤ <i>l</i> ≤ 36
Reflections collected	18886
Independent reflections	6909 [ <i>R</i> <sub>int</sub> = 0.0147, <i>R</i> <sub>sigma</sub> = 0.0131]
Indep. refl. with <i>I</i> ≥ 2 $\sigma$ ( <i>I</i> )	6647
Data/restraints/parameters	6909/0/388
Goodness-of-fit on <i>F</i> <sup>2</sup>	1.041
Final <i>R</i> indexes [ <i>I</i> ≥ 2 $\sigma$ ( <i>I</i> )]	<i>R</i> <sub>1</sub> = 0.0692, <i>wR</i> <sub>2</sub> = 0.1833
Final <i>R</i> indexes [all data]	<i>R</i> <sub>1</sub> = 0.0710, <i>wR</i> <sub>2</sub> = 0.1850
Largest diff. peak/hole / e Å <sup>-3</sup>	1.77/-1.36
Flack parameter	0.022(6)
CCDC number	2309696



## 6. References

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