Copper (II) Serves as an Efficient Additive for Metal-Directed Self-Assembly of Over 20 Thiacyclophanes

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Supporting Information

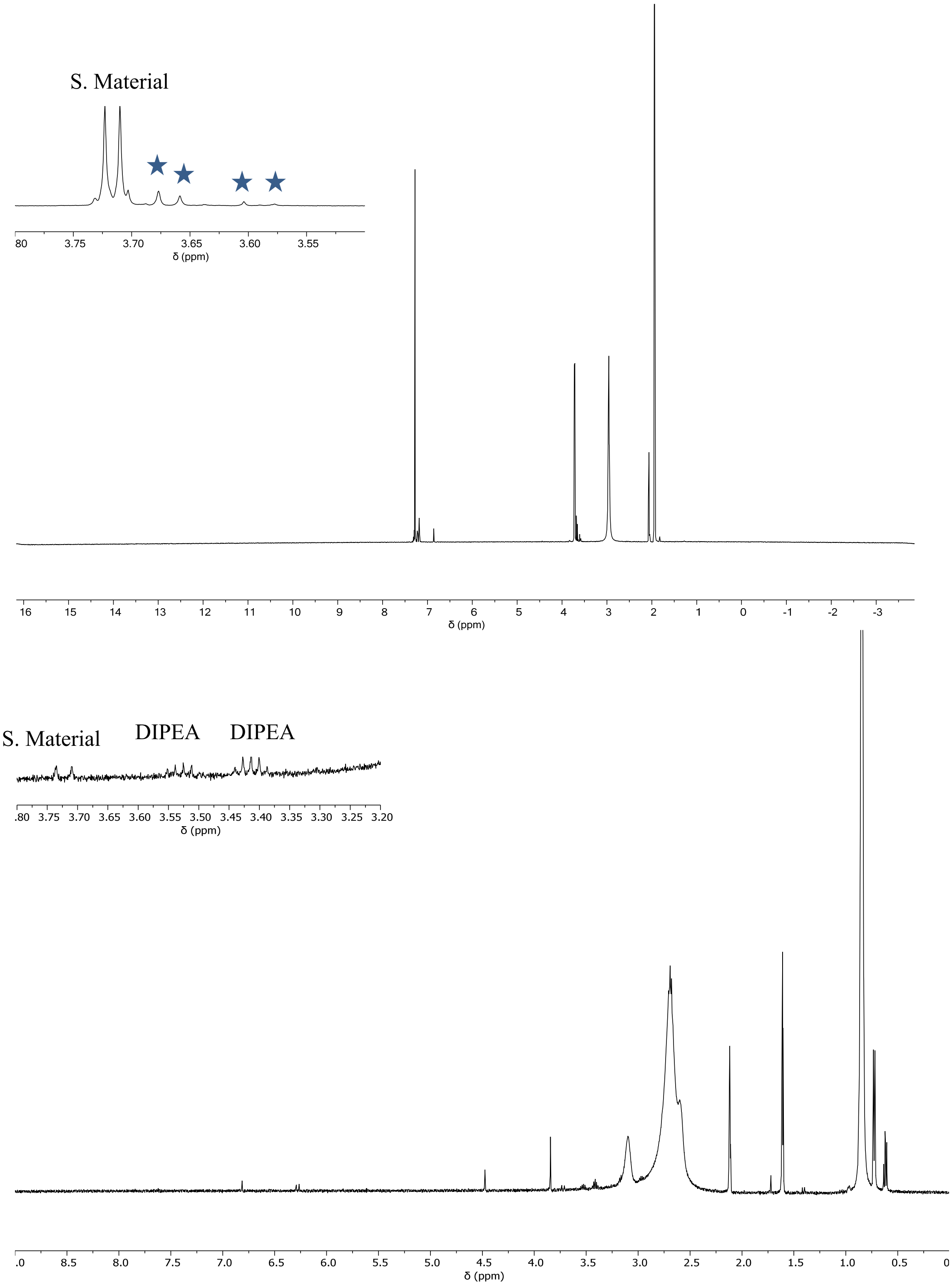

Figure S1: Control reaction of $H_2\mathbf{L}^1$ and I_2 in acetonitrile-*d*$_3$ (singlet at 1.94 ppm) in the absence of a pnictogen or Cu(II) source taken after 5 minutes: trace amounts of $\mathbf{L}^1{}_n$ (blue stars), mostly unreacted $H_2\mathbf{L}^1$. Top: just I_2. Bottom: I_2 and DIPEA.

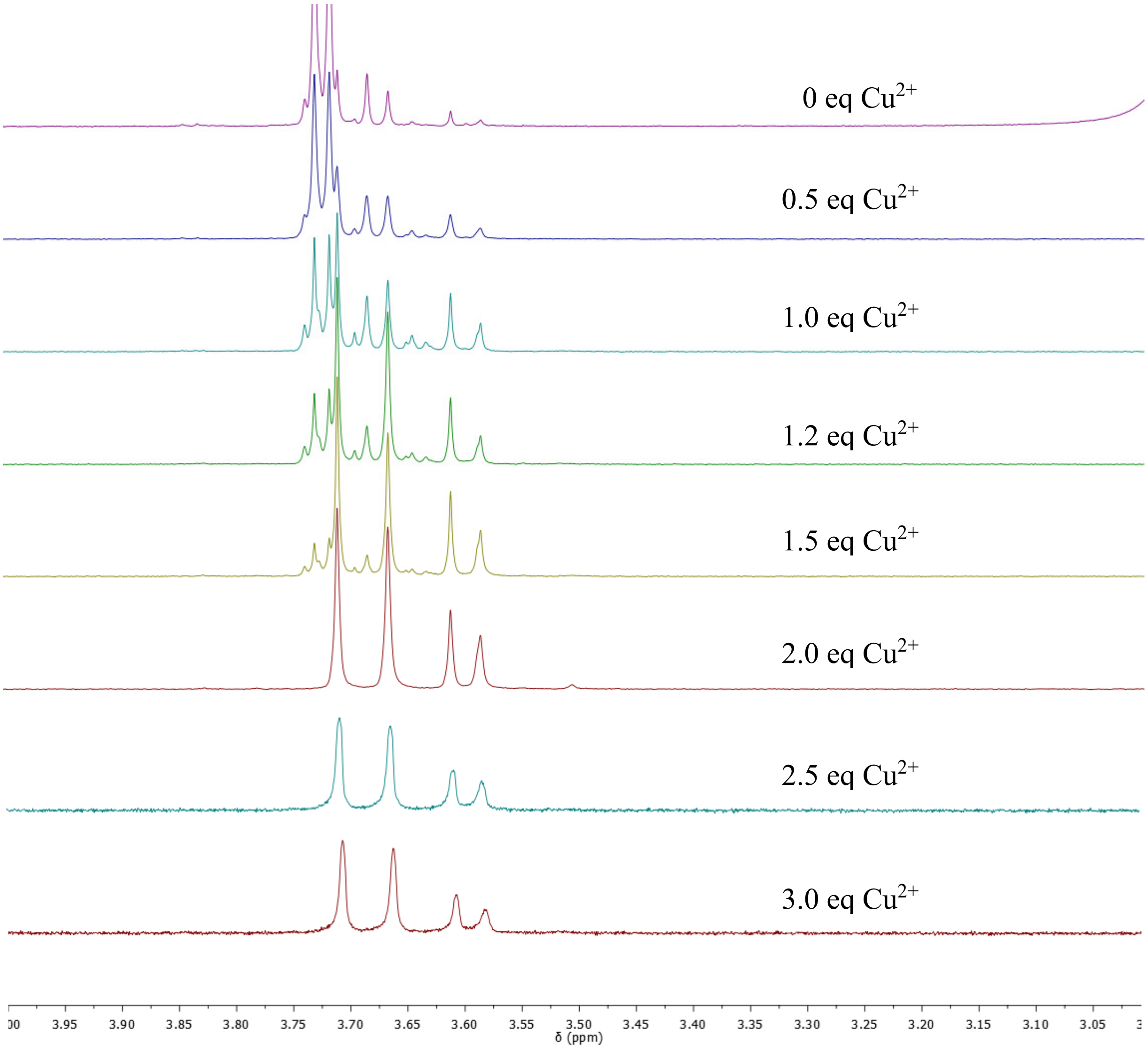

Figure S2: Reaction of $H_2\mathbf{L}^1$ (1 equiv) and I_2 (2 equiv) with varying amount of $CuCl_2$ in acetonitrile-*d3* (singlet at 1.94 ppm) taken after 10 minutes: reaction was done instantaneously with stoichiometric amount or excess $CuCl_2$ while reaction did not go to completion with sub-stoichiometric amount of $CuCl_2$.

Table S1. Total yield of the mixture of disulfide products with varying equivalents of Cu^{2+}

Equivalents of Cu^{2+}	**Yield after 10 min (%)**	**Yield after 2 hours (%)**	**Yield after 4 hours (%)**
0	19	22	37
0.2	22	22	26
0.5	26	26	29
1.0	43	44	44
1.2	57	59	61
1.5	68	76	75
2.0	>99	>99	>99
2.5	>99	>99	>99
3.0	>99	>99	>99

Sub-stoichiometric amount of $CuCl_2$ produces less product than the reaction with no Cu^{2+}. However, in these conditions, a smaller amount of oligomers/polymers is also observed. Thus, Cu^{2+} is still required for minimizing the presence of oligomers/polymers.

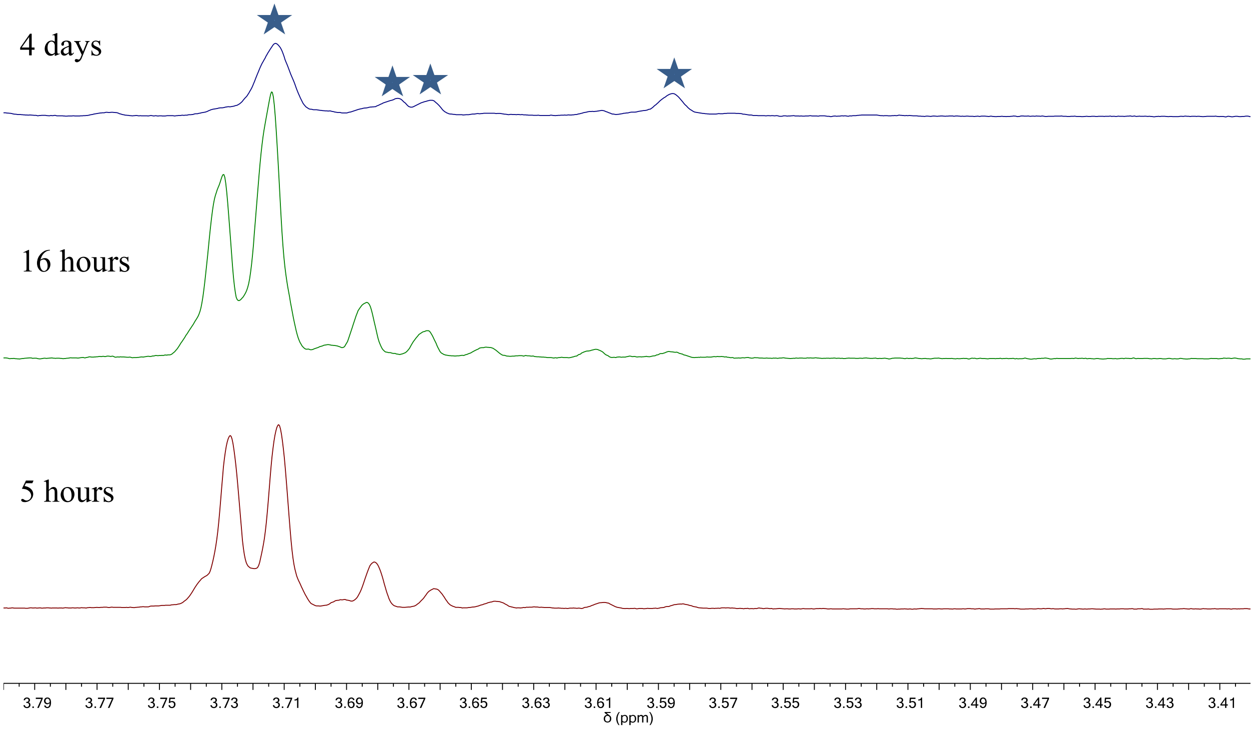

Figure S3: Reaction of $H_2\mathbf{L}^1$ (1 equiv) and $CuCl_2$ (2 equiv) (no I_2): metal-thiolate intermediate disappeared over time, leaving only disulfides ($\mathbf{L}^1{}_n$, blue stars).

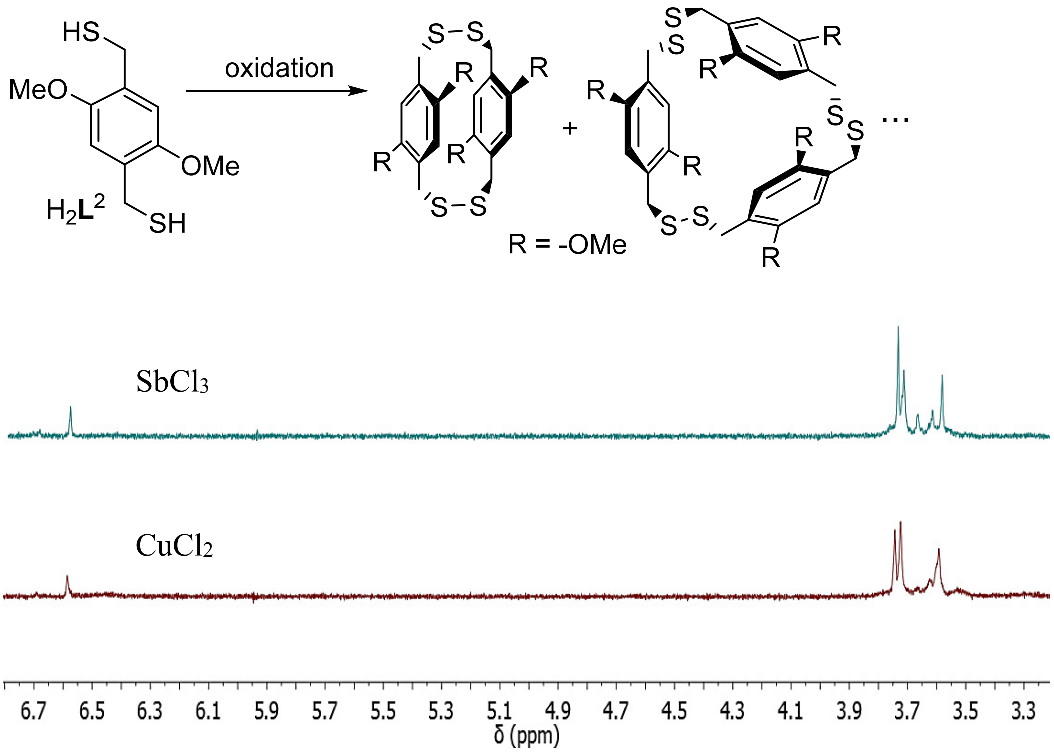

Figure S4. Functional group tolerance testing: oxidation of $H_2\mathbf{L}^2$ to form disulfide macrocycles. Top: Sb^{3+} additive. Bottom: Cu^{2+} additive. Two spectra look alike indicating Cu-assisted oxidation is also functional group tolerant.

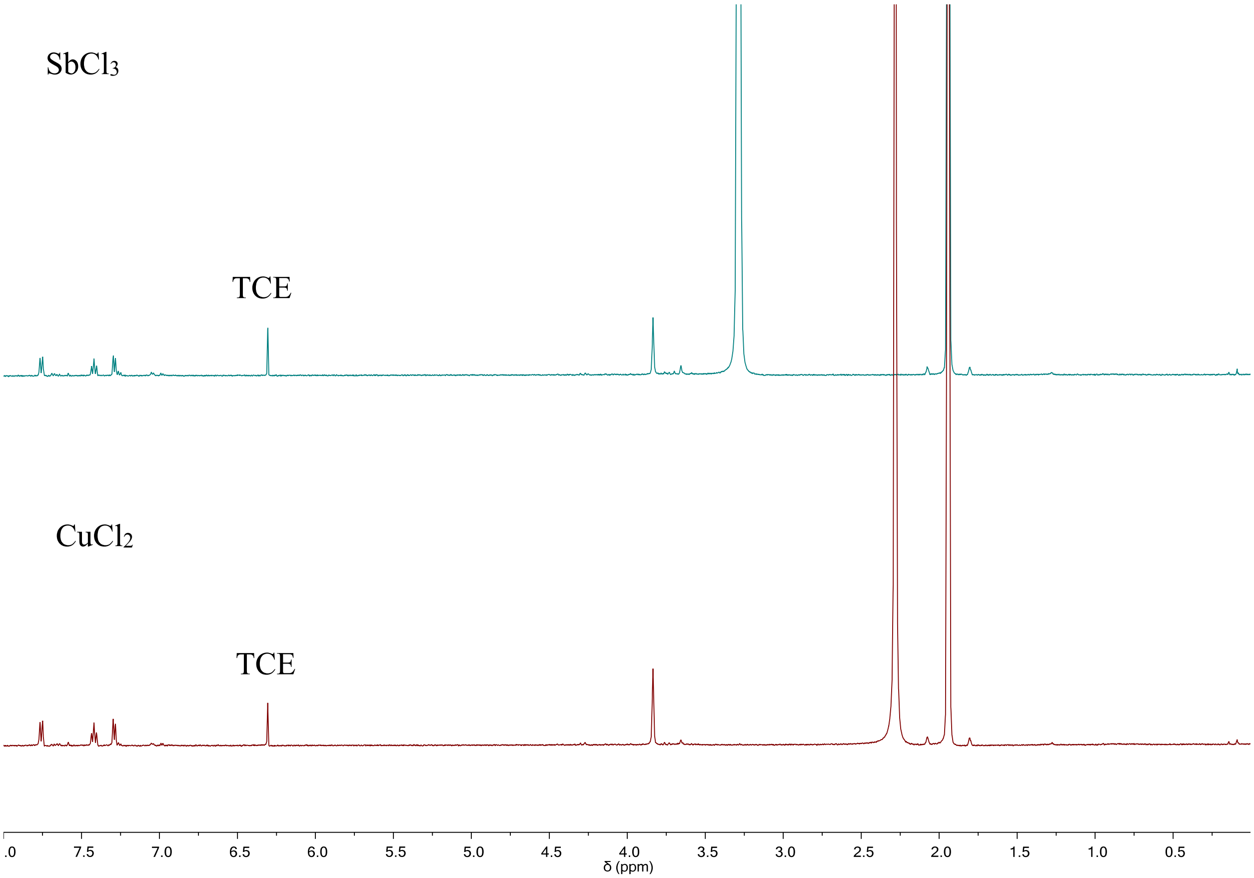

Figure S5: Reaction of $H_3\mathbf{L}^3$ (1 equiv) with I_2 (2 equiv) and $CuCl_2$ (1.2 equiv) in acetonitrile-d_3 (singlet at 1.94 ppm) taken after 5 minutes. Integration of the methylene peaks and referencing to TCE reveals the faster reaction with Cu^{2+} (ratio of $\mathbf{L}^2{}_3$ for Cu^{2+}system: Sb^{3+}system = 1.0 : 0.8).

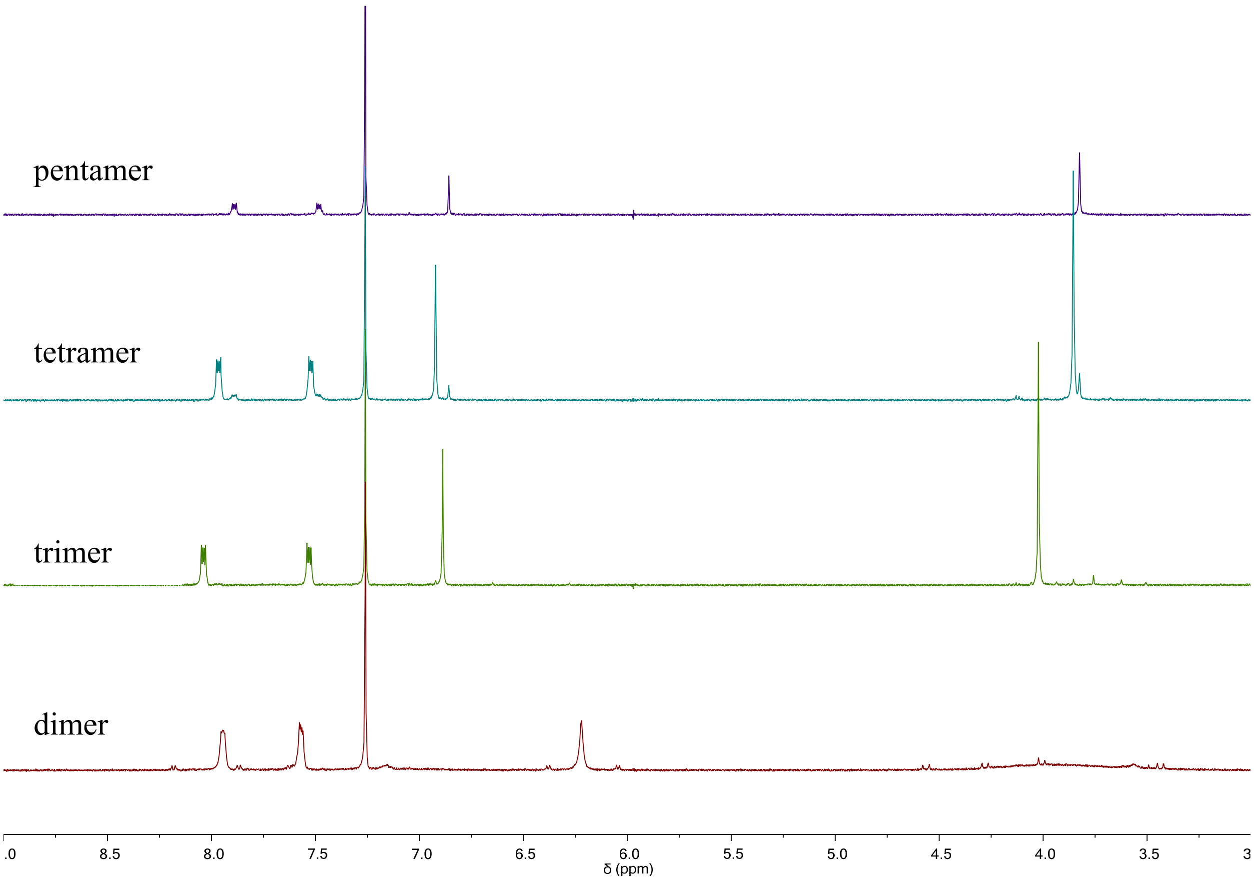

Figure S6: ^{1}H NMR (CDCl$_3$, 500 MHz) of 1,4-napthalene disulfide pentamer (top), tetramer, trimer and dimer (bottom) (CDCl$_3$ – 7.26 ppm).

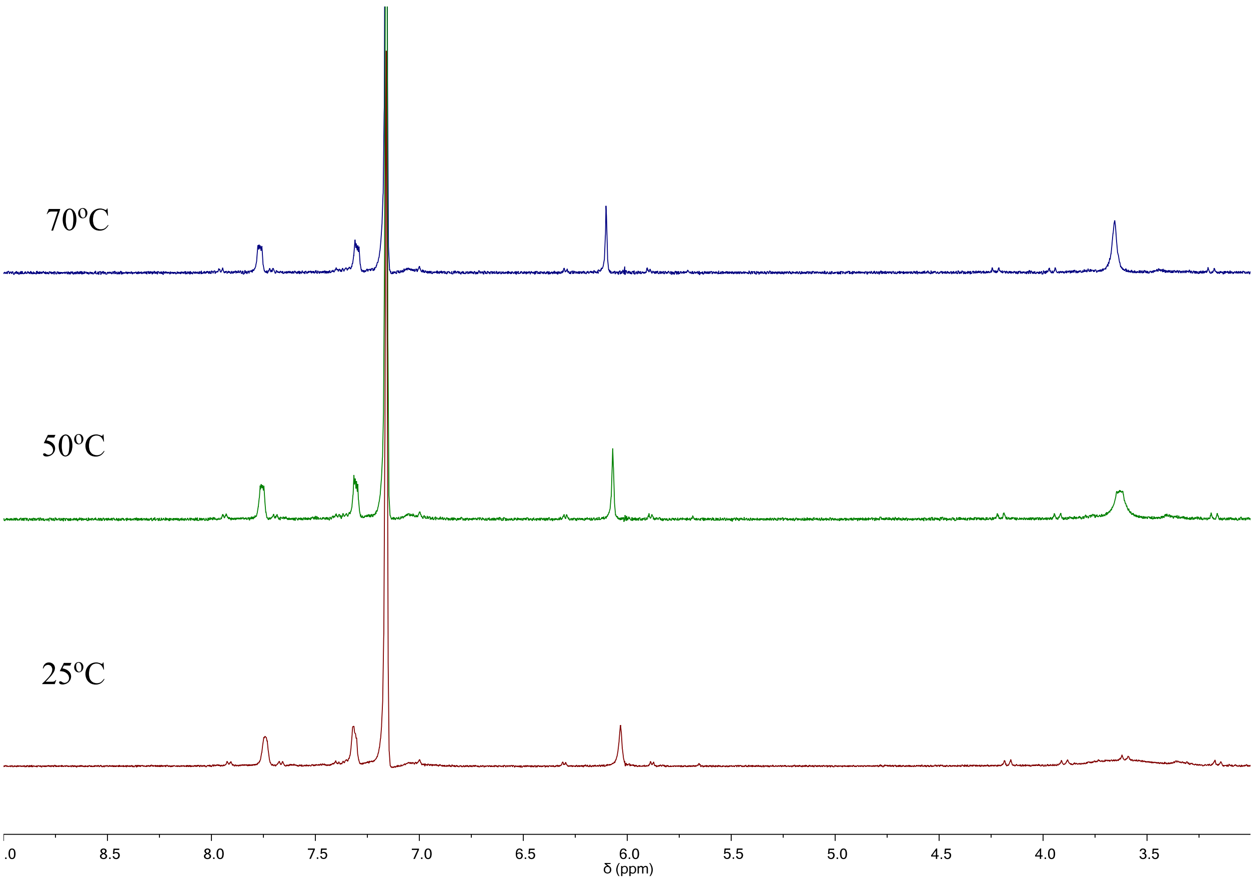

Figure S7: VT-^{1}H NMR of 1,4-napthalene disulfide dimer in C_6D_6 (C_6D_6 - 7.16 ppm). The small peaks in the methylene region are not impurities, but rather the two different conformational isomers.

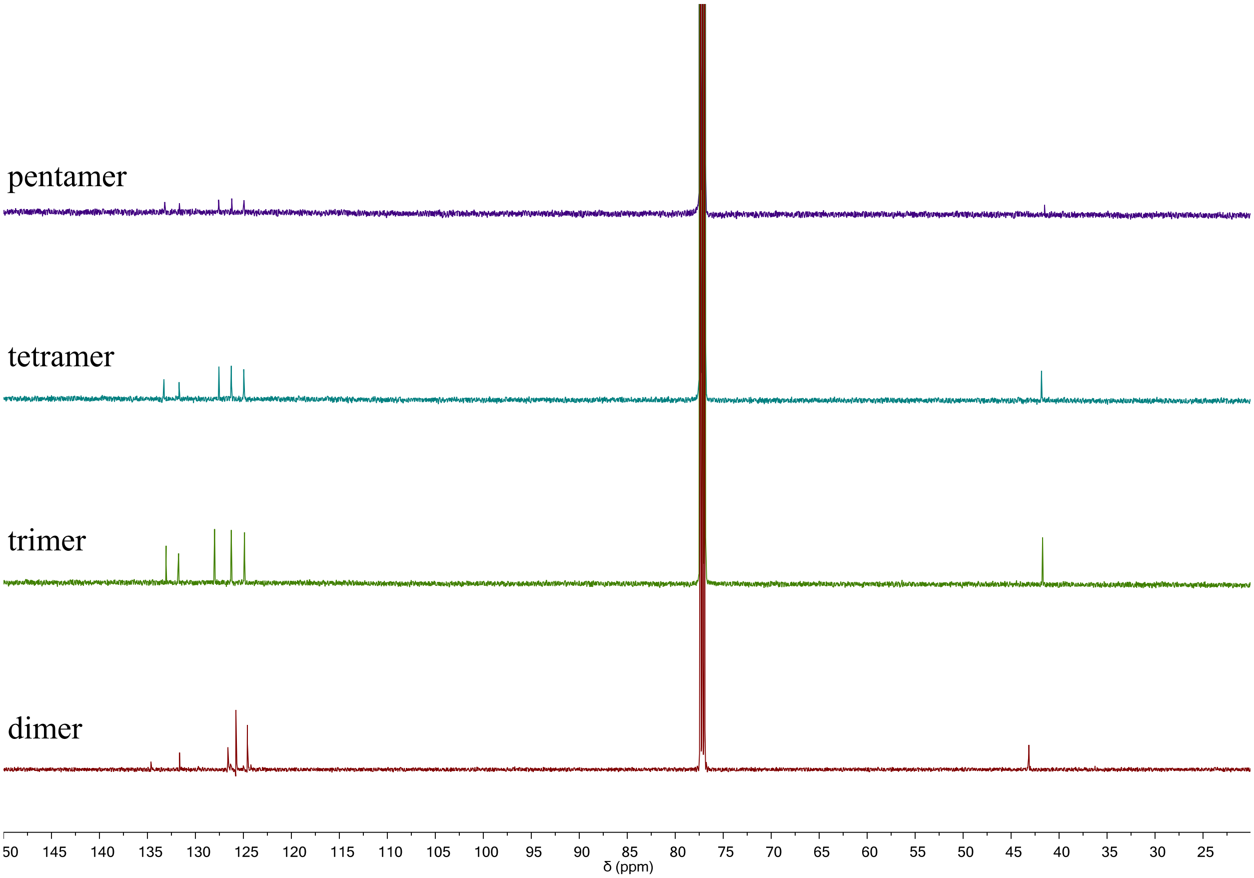

Figure S8: ^{13}C NMR (CDCl$_3$, 500 MHz) of 1,4-napthalene disulfide pentamer (top), tetramer, trimer and dimer (bottom) (CDCl$_3$ – 77.16 ppm).

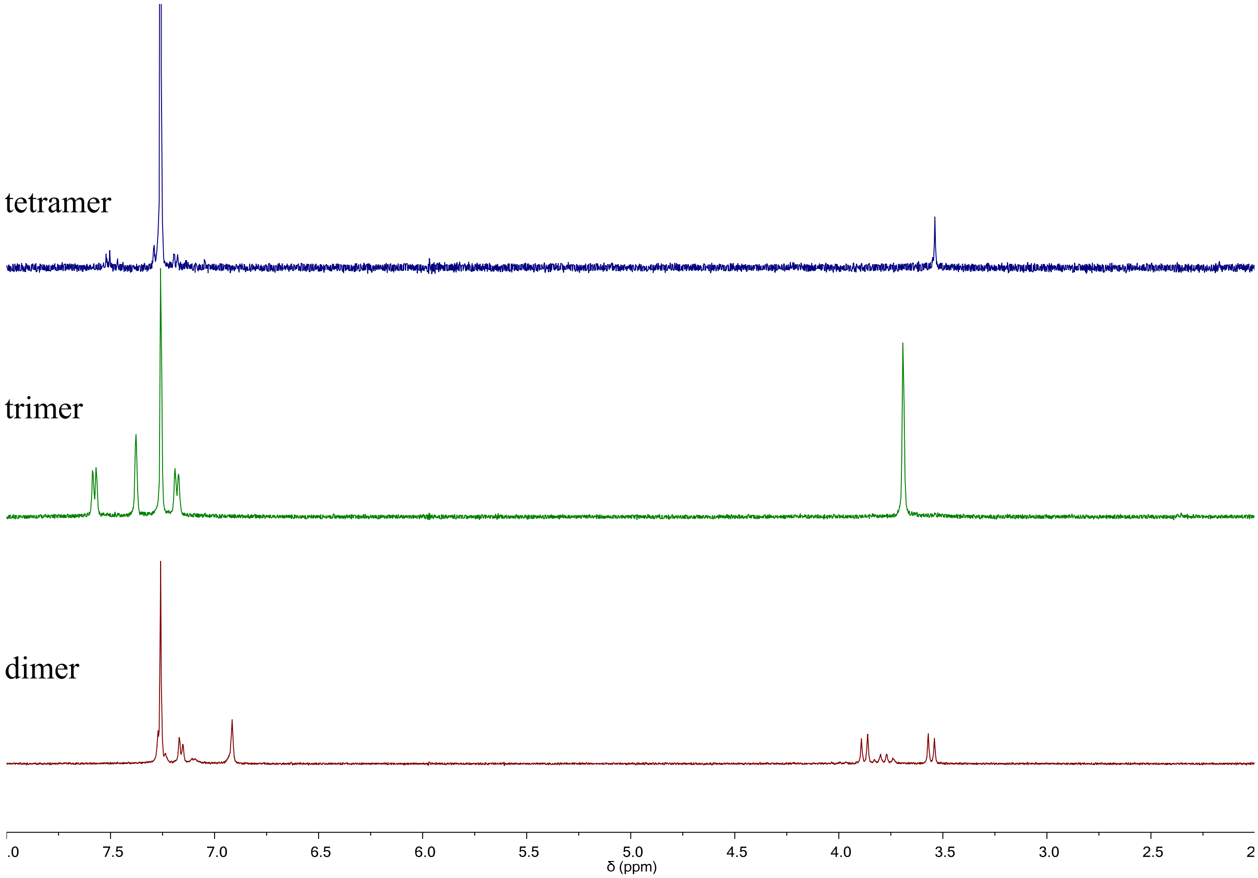

Figure S9: ^{1}H NMR ($CDCl_3$, 500 MHz) of 2,6-napthalene disulfide tetramer (top), trimer and dimer (bottom) ($CDCl_3$ – 7.26 ppm). The smaller peaks in the dimer spectrum correspond to conformational isomers that in this system coalesce upon heating (Figure S10).

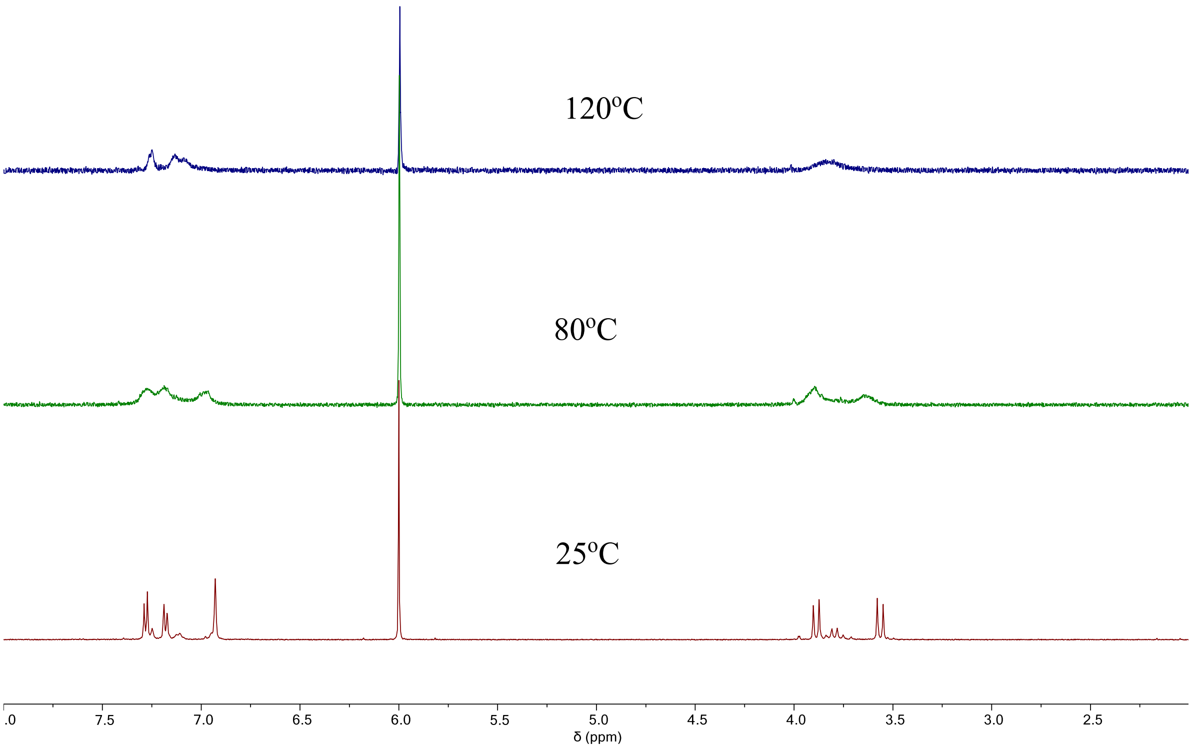

Figure S10: VT-^{1}H NMR of 2,6-napthalene disulfide dimer in TCE-*d₂* (TCE-*d₂* – 6.00 ppm).

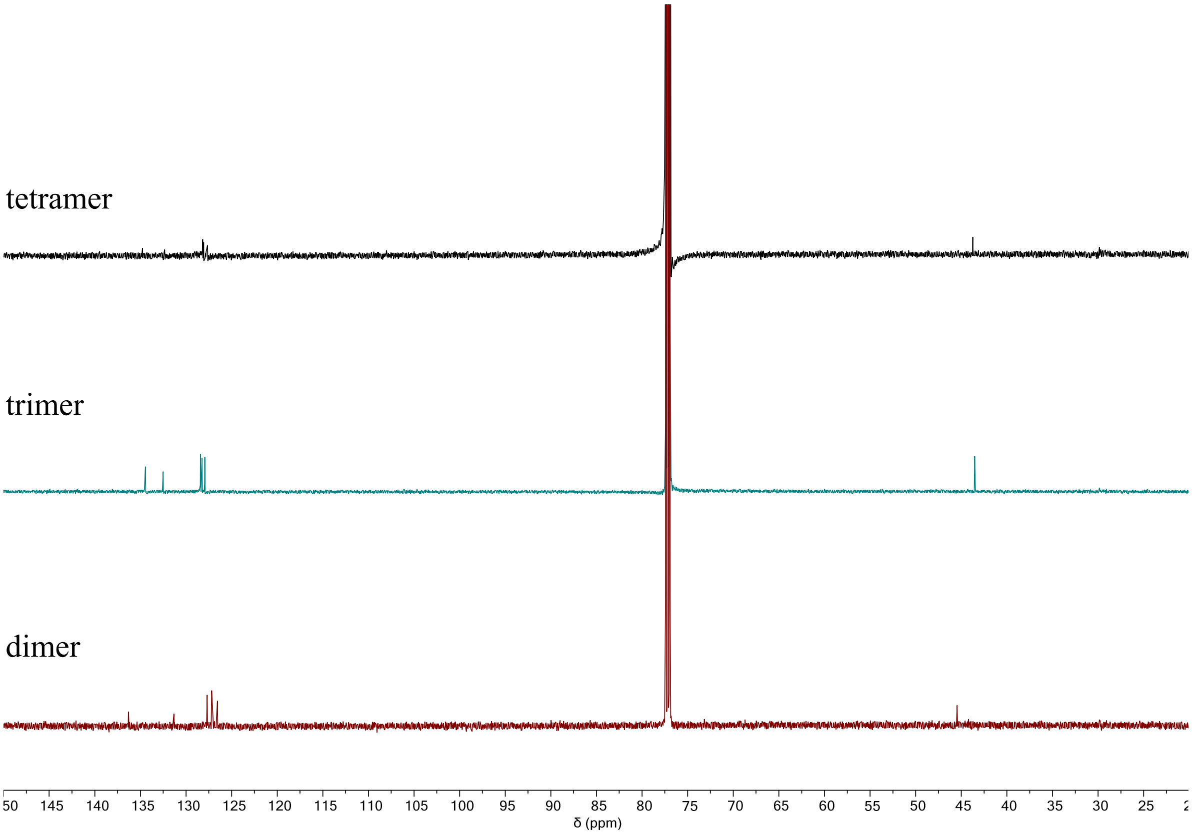

Figure S11: ^{13}C NMR ($CDCl_3$, 500 MHz) of 2,6-napthalene disulfide tetramer (top) and dimer (bottom) ($CDCl_3$ – 77.16 ppm).

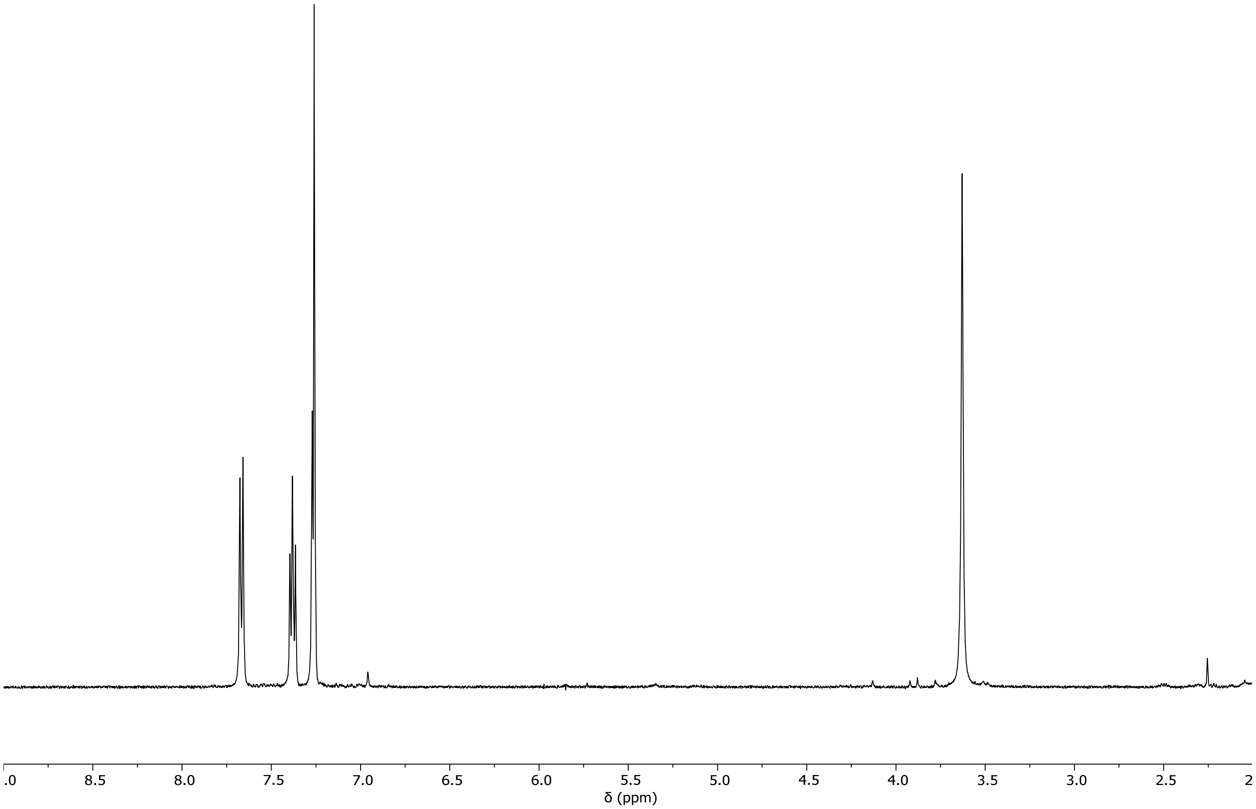

Figure S12: ^{1}H NMR (CDCl$_3$, 500 MHz) of $\mathbf{L}^{1,5\text{nap}}{}_3$ (CDCl$_3$ – 7.26 ppm).

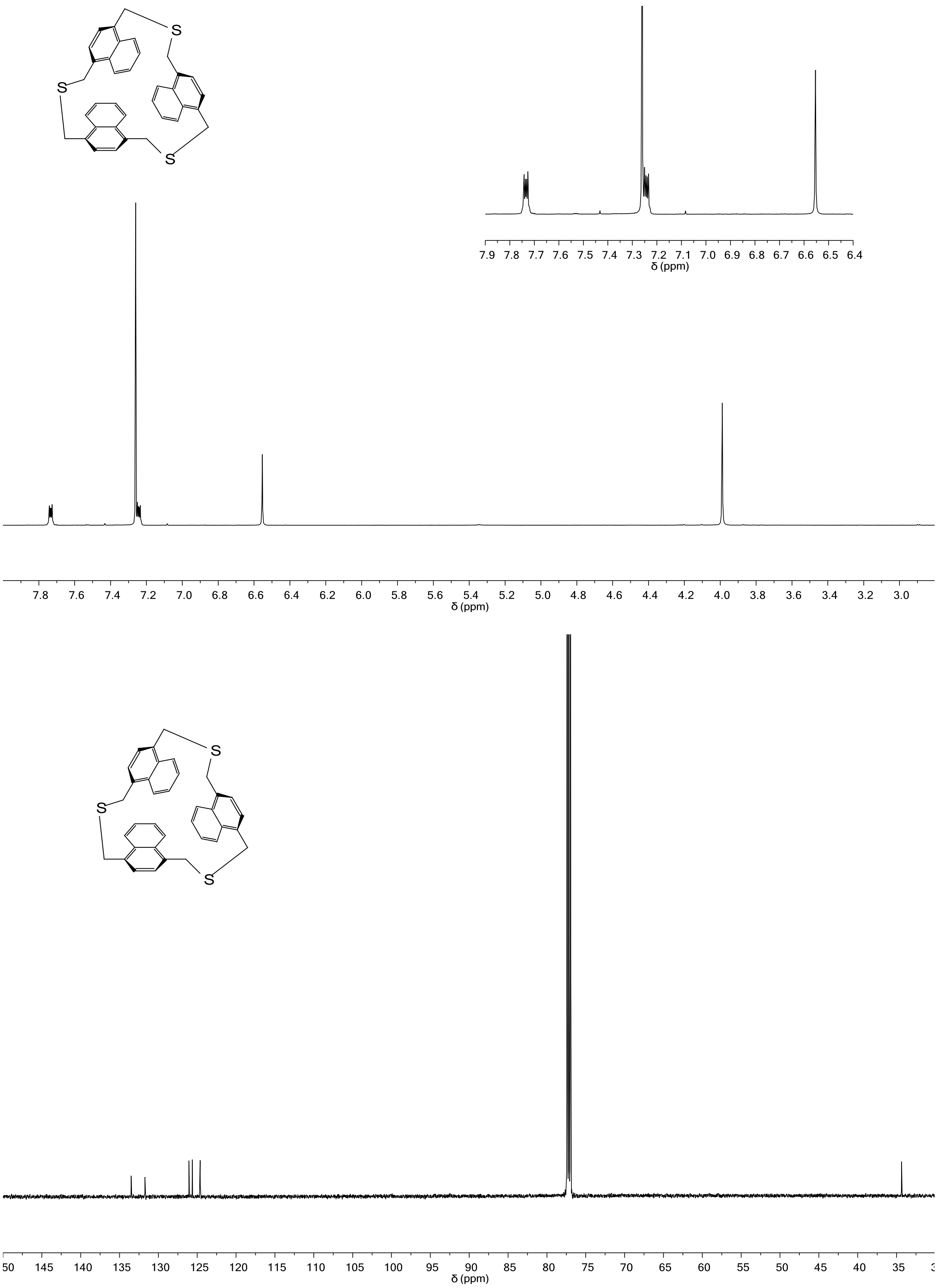

Figure S13: ^{1}H NMR and ^{13}C NMR of compound **1** in $CDCl_3$. Top: ^{1}H NMR ($CDCl_3$—7.26 ppm). Bottom: ^{13}C NMR ($CDCl_3$—77.16 pppm).

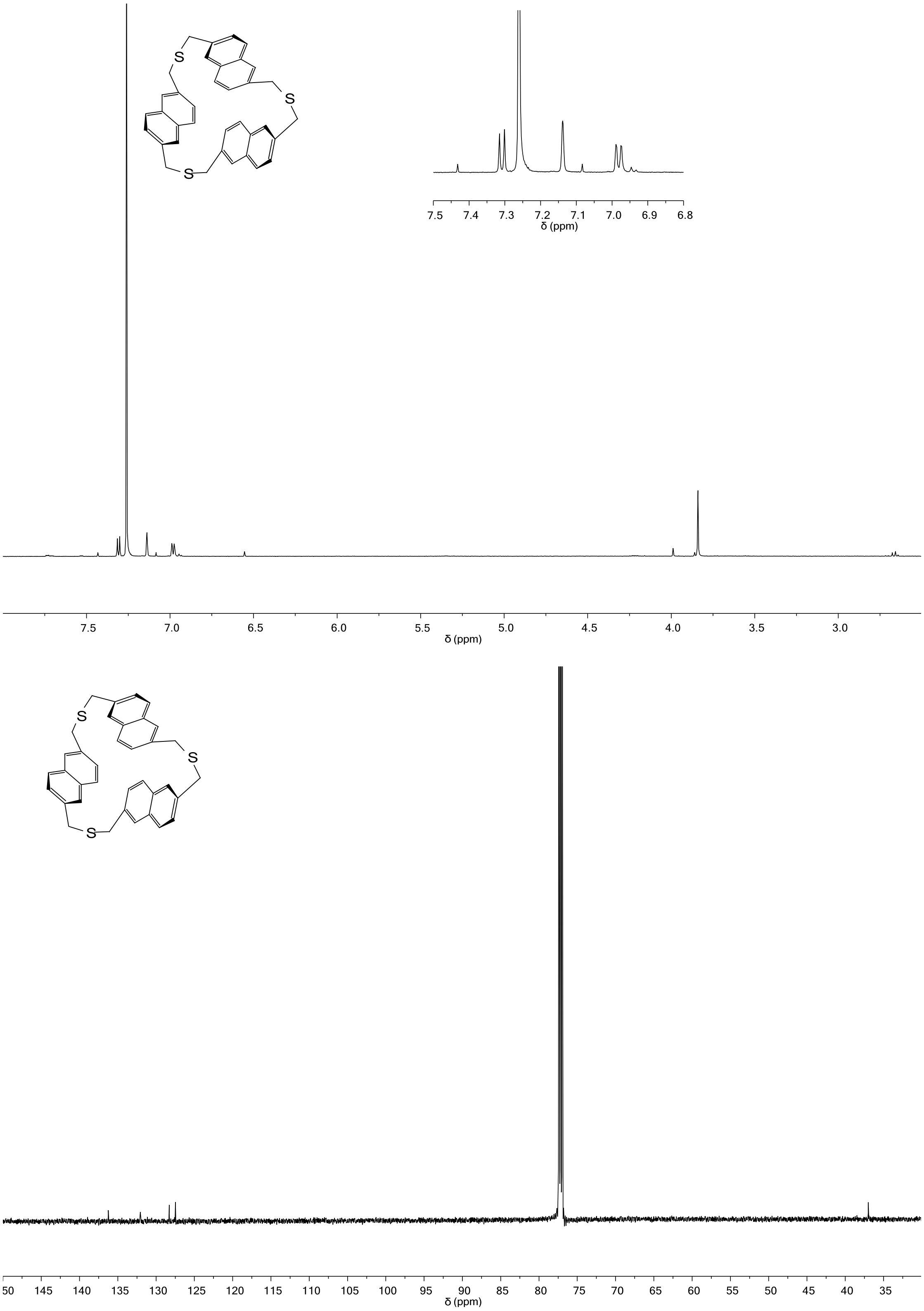

Figure S14-: ^{1}H NMR and ^{13}C NMR of compound **2** in $CDCl_3$. Top: ^{1}H NMR ($CDCl_3$—7.26 ppm). Bottom: ^{13}C NMR ($CDCl_3$—77.2 pppm).

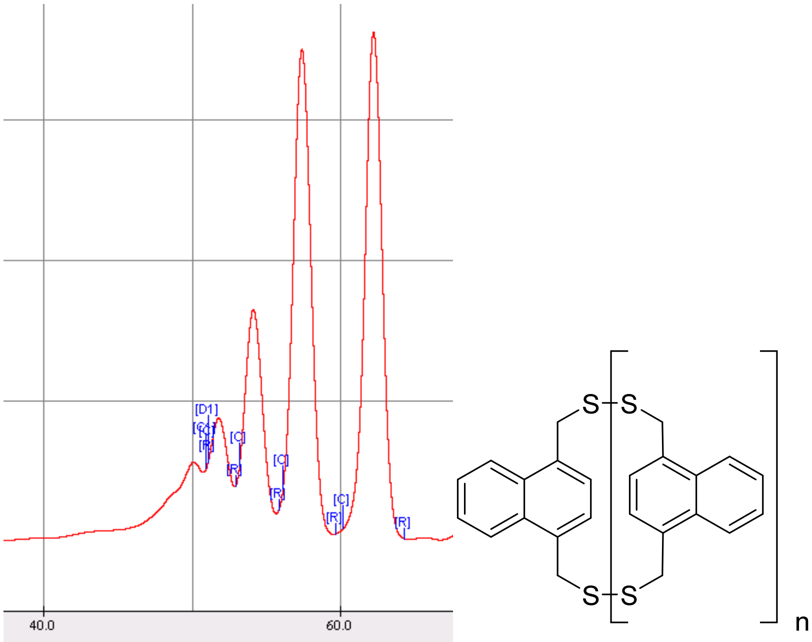

Figure S15: Gel permeation chromatogram of 1,4-napthalene disulfide species from dimer to hexamer (peaks going from right to left). The mixture was purified in chloroform using a recycling HPLC.

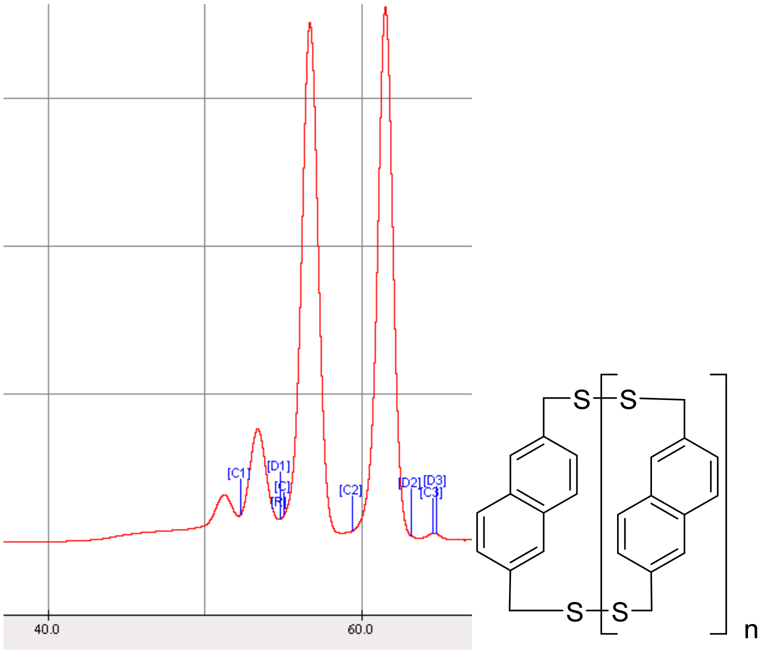

Figure S16: Gel permeation chromatogram of 2,6-napthalene disulfide species from dimer to pentamer (peaks going from right to left). The mixture was purified in chloroform using a recycling HPLC.

The following reactions were conducted in acetonitrile due to $CuCl_2$'s great solubility in this solvent. These reactions can also be conducted in any other solvents and even mixed solvent system.

General Conditions for pnictogen and Cu^{2+} additive in the oxidation of dithiol ligand to produce disulfides (corresponds to Scheme 2)

In two separate 100 mL round bottom flasks, $H_2\mathbf{L}^1$ (25.5 mg, 0.30 mmol) and I_2 (51.2 mg, 0.30 mmol) were added in 50 mL acetonitrile. $CuCl_2{\cdot}2H_2O$ (51.2 mg, 0.30 mmol) was added to the first flask and $SbCl_3$ (68.1 mg, 0.30 mmol) was added to the second flask. The solution with $CuCl_2{\cdot}2H_2O$ was stirred for two hours. Reaction was quenched with saturated sodium sulfite and diluted with ethyl acetate. The organic layer was washed with deionized water (2X). The solution was dried with $MgSO_4$, filtered and concentrated. The powder was then redissolved in 3 mL of chloroform and purified by GPC (96% combined yield: 32% dimer; 30% trimer, 21% tetramer; 6% pentamer; 7% hexamer). The solution with $SbCl_3$ was allowed to stir for 16 hours (2 hours was not enough for the reaction to complete by GPC). After 16 hours, reaction was quenched with saturated sodium sulfite and diluted with ethyl acetate. The organic layer was washed with deionized water (2X). The solution was dried with $MgSO_4$, filtered and concentrated. The powder was then redissolved in 3 mL of chloroform and purified by GPC (84% combined yield: 18% dimer; 42% trimer; 16% tetramer; 4% pentamer; 4% hexamer).

Quantitative study of the role of $CuCl_2$ (corresponds to Table S1)

Nine NMR tubes were dried in the oven. Each was charged with $H_2\mathbf{L}^1$ (0.425 mg, 0.0025 mmol) in 800 µL acetonitrile-*d₃*. The amount of $CuCl_2{\cdot}2H_2O$ added to each tube was 0 equiv.; 0.2 equiv.; 0.5 equiv.; 1.0 equiv.; 1.2 equiv.; 1.5 equiv.; 2.0 equiv.; 2.5 equiv. and 3.0 equiv. respectively. I_2 (1.27 mg, 0.0050 mmol) was added to each NMR tube. For each NMR tube, NMR spectra were taken as a function of time: 1 min after all reagents were added, 2 hours and 4 hours. Integration of the disulfide peaks gave the yields of disulfide products

Functional group tolerance with $H_2\mathbf{L}^2$ (corresponds to Figure 1)

In two separate NMR tubes, $H_2\mathbf{L}^2$ (0.575 mg, 0.0025 mmol) and I_2 (1.27 mg, 0.0050 mmol) were added in 1.6 mL acetonitrile-*d₃*. $CuCl_2{\cdot}2H_2O$ (0.852 mg, 0.0050 mmol) was added to the first tube and $SbCl_3$ (1.135 mg, 0.0050 mmol) was added to the second tube. NMR spectra were taken immediately after all the reagents were added in. Similarity in the two spectra indicated the functional group tolerance of Cu-assisted iodine oxidation.

Synthesis of dodecathiatetrahedrophane $\mathbf{L}^3{}_4$ and thiadimer $\mathbf{L}^3{}_2$ (corresponds to Figure 2)

In two separate NMR tubes, $H_3\mathbf{L}^3$ (0.54 mg, 0.0025 mmol) and I_2 (1.90 mg, 0.0075 mmol) were added in 1.6 mL acetonitrile-*d₃*. $CuCl_2{\cdot}2H_2O$ (0.638 mg, 0.0038 mmol) was added to the first tube and $SbCl_3$ (0.85 mg, 0.0038 mmol) was added to the second tube. NMR spectra were taken immediately after all the reagents were added in.

Synthesis of naphthyl thiacyclophane $L^{1,5nap}{}_3$ (corresponds to Scheme 3)

In two separate NMR tubes, H_2**L**^{3} (0.55 mg, 0.0025 mmol) and I_2 (1.27 mg, 0.0050 mmol) were added in 1.6 mL acetonitrile-*d₃*. $CuCl_2{\cdot}2H_2O$ (0.341 mg, 0.0020 mmol) was added to the first tube and $SbCl_3$ (0.454 mg, 0.0020 mmol) was added to the second tube. NMR spectra were taken immediately after all the reagents were added in.

Synthesis of 1,4-naphthalene disulfide structures ($L^{1,4nap}{}_2$ - $L^{1,4nap}{}_6$)

In a 50 mL round bottom flask, 1,4-naphthalene dithiol (11 mg, 0.050 mmol) and I_2 (38 mg, 0.15 mmol) were added in 15 mL acetonitrile. $CuCl_2{\cdot}2H_2O$ (6.8 mg, 0.040 mmol) was added to the flask. The solution was stirred for 30 minutes. Reaction was quenched with saturated sodium sulfite and diluted with toluene. The organic layer was washed with deionized water (2X). The solution was dried with $MgSO_4$, filtered and concentrated. The powder was then redissolved in 3 mL of chloroform and purified by GPC (96% combined yield: 26% dimer; 43% trimer, 16% tetramer; 8% pentamer; 3% hexamer). ^{1}H NMR (500 MHz, C_6D_6, 70°C) Dimer: δ = 7.76-7.78 (m, 4H, $C_{10}H_2$), 7.29-7.31 (m, 4H, $C_{10}H_2$), 6.10 (s, 4H, $C_{10}H_2$), 3.65 (s, 8H, CH_2); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 134.63, 131.65, 126.62, 125.79, 124.59, 43.16 ppm; ^{1}H NMR (500 MHz, $CDCl_3$) trimer: δ = 8.03-8.05 (m, 6H, $C_{10}H_2$), 7.52-7.54 (m, 6H, $C_{10}H_2$), 6.89 (s, 6H, $C_{10}H_2$), 4.02 (s, 12H, CH_2); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 133.06, 131.75, 128.00, 126.27, 124.89, 41.72 ppm; tetramer: δ = 7.96-7.98 (m, 8H, $C_{10}H_2$), 7.51-7.53 (m, 8H, $C_{10}H_2$), 6.92 (s, 8H, $C_{10}H_2$), 3.85 (s, 16H, CH_2); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 133.28, 131.70, 127.56, 126.27, 124.97, 41.85 ppm; pentamer: δ = 7.88-7.90 (m, 10H, $C_{10}H_2$), 7.47-7.49 (m, 10H, $C_{10}H_2$), 6.86 (s, 10H, $C_{10}H_2$), 3.83 (s, 20H, CH_2); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 133.20, 131.68, 127.59, 126.23, 124.93, 41.51 ppm.

Synthesis of structure 1

An oven-dried NMR tube was charged with 1,4-naphthalene trimer disulfide (5.0 mg, 0.008 mmol) in dried chloroform-*d* (1 mL). Under a cone of nitrogen, HMPT (9 µL, 0.049 mmol) was added to the NMR tube and the tube was inverted gently several times to mix. The reaction was allowed to sit at ambient temperature for 2 hours. The solution was then concentrated down and the crude solid was sonicated with 30 mL of deionized water giving a cloudy white solution. The solid was separated from its aqueous counterpart by centrifugation and washed a second time with fresh deionized water. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73-7.74 (m, 6H, $C_{10}H_2$), 7.23-7.25 (m, 6H, $C_{10}H_2$), 6.55 (s, 6H, $C_{10}H_2$), 3.99 (s, 12H, CH_2); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 133.50, 131.73, 126.06, 125.63, 124.62, 34.36 ppm.

Synthesis of 2,6-naphthalene disulfide structures ($L^{2,6nap}{}_2$ – $L^{2,6nap}{}_5$)

In a 50 mL round bottom flask, 2,6-naphthalene dithiol (10 mg, 0.045 mmol) and I_2 (34.6 mg, 0.136 mmol) were added in 15 mL acetonitrile. $CuCl_2{\cdot}2H_2O$ (6.2 mg, 0.036 mmol) was added to the flask. The solution was stirred for 30 minutes. The reaction was quenched with saturated sodium sulfite and diluted with toluene. The organic layer was washed with deionized water (2X). The solution was dried with $MgSO_4$, filtered, and concentrated. The powder was then redissolved in 3 mL of chloroform and purified by GPC (90% combined yield: 30% dimer; 45% trimer, 10% tetramer, 5% pentamer). ^{1}H NMR: Dimer: δ = 7.27 (d, 4H, $C_{10}H_2$), 7.16 (d, 4H, $C_{10}H_2$, J = 8.5 Hz), 6.92 (s, 4H, $C_{10}H_2$), 3.86 (d, 4H, CH_2, J = 15.0 Hz), 3.57 (d, 4H, CH_2, J =

15.0 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 136.29, 131.33, 127.68, 127.18, 126.55, 45.45 ppm; trimer: δ = 7.58 (d, 6H, $C_{10}H_2$, J = 8.0 Hz), 7.38 (s, 6H, $C_{10}H_2$), 7.18 (d, 6H, $C_{10}H_2$, J = 8.5 Hz), 3.69 (s, 12H, CH_2); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 134.45, 132.51, 128.41, 128.24, 127.94, 43.52 ppm; tetramer: δ = 7.51 (d, 8H, $C_{10}H_2$, J = 8.5 Hz), 7.47 (s, 8H, $C_{10}H_2$), 7.18 (d, 8H, $C_{10}H_2$, J = 8.0 Hz), 3.54 (s, 16H, CH_2).

Synthesis of structure 2

An oven-dried NMR tube was charged with 2,6-naphthalene trimer disulfide (4.5 mg, 0.007 mmol) in dried chloroform-*d* (1 mL). Under a cone of nitrogen, HMPT (8 µL, 0.044 mmol) was added to the NMR tube and the tube was inverted gently several times to mix. The reaction was allowed to sit at ambient temperature for 2 hours. The solution was then concentrated down and the crude solid was sonicated with 30 mL of deionized water giving a cloudy white solution. The solid was separated from its aqueous counterpart by centrifugation and washed a second time with fresh deionized water. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31 (d, 6H, $C_{10}H_2$, J = 7.0 Hz), 7.14 (s, 6H, $C_{10}H_2$), 6.98 (d, 6H, $C_{10}H_2$, J = 7.0 Hz), 3.84 (s, 12H, CH_2); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 136.23, 132.05, 128.29, 127.47, 127.44, 36.99 ppm.

X-ray Crystallography. Diffraction intensities for $\mathbf{L}^{1,4nap}{}_2$ and $\mathbf{L}^{2,6nap}{}_2$ were collected at 173 K on a Bruker Apex2 DUO CCD diffractometer using CuKα radiation, λ= 1.54178 Å. Absorption corrections were applied by SADABS.[1] Space groups were determined based on systematic absences. Symmetry of the molecule in $\mathbf{L}^{2,6nap}{}_2$ is close to *C*2 and it provides a pseudo-symmetry in the crystal structure. The structure of $\mathbf{L}^{2,6nap}{}_2$ was determined in orthorombic (*Cmca* and *Aba*2) and monoclinic (*P*2₁/*c* and *Pc*) space groups. In centro-symmetrical space groups the ligand is disordered over two positions related to two possible orientations of the molecule in the crystal structure. In non-centrosymmetrical space groups there is no such the disorder. The Flack parameter is 0.43(2) in *Aba*2 and 0.46(2) in *Pc*. The structure of $\mathbf{L}^{2,6nap}{}_2$ refined in space group *Aba*2 is given as the final in the paper as having the highest symmetry but without the mentioned disorder. The C-C bond distances in $\mathbf{L}^{2,6nap}{}_2$ have been determined with limited precision due to the disorder. All calculations were performed by the Bruker SHELXL-2014/7 package.[2]

Crystallographic Data for $\mathbf{L}^{1,4nap}{}_2$ (CCDC 1859804): $C_{24}H_{20}S_4$, M = 436.64, 0.13 x 0.10 x 0.03 mm, T = 173(2) K, Monoclinic, space group $P2_1/n$, a = 7.1311(2) Å, b = 8.3942(3) Å, c = 17.2693(6) Å, β = 95.931(2)°, V = 1028.20(6) Å^3, Z = 2, D_c = 1.410 Mg/m^3, μ(Cu) = 4.289 mm^{-1}, F(000) = 456, $2\theta_{max}$ = 133.14°, 6792 reflections, 1808 independent reflections [R_{int} = 0.0438], R1 = 0.0323, wR2 = 0.0859 and GOF = 1.040 for 1808 reflections (127 parameters) with I>2σ(I), R1 = 0.0345, wR2 = 0.0881 and GOF = 1.040 for all reflections, max/min residual electron density +0.311/-0.217 eÅ^{-3}.

Crystallographic Data for $\mathbf{L}^{2,6nap}{}_2$ (CCDC 1859805): $C_{24}H_{20}S_4$, M = 436.64, 0.09 x 0.08 x 0.02 mm, T = 173(2) K, Orthorhombic, space group *Aba*2, a = 10.8663(5) Å, b = 8.5571(3) Å, c = 22.5617(10) Å, V = 2097.88(15) Å^3, Z = 4, D_c = 1.382 Mg/m^3, μ(Cu) = 4.204 mm^{-1}, F(000) = 912, $2\theta_{max}$ = 133.09°, 7433 reflections, 1802 independent reflections [R_{int} = 0.0521], R1 = 0.0705, wR2 = 0.1777 and GOF = 1.020 for 1802 reflections (127 parameters) with I>2σ(I), R1 = 0.0799, wR2 = 0.1885 and GOF = 1.021 for all reflections, max/min residual electron density +0.582/-0.257 eÅ^{-3}.

References:

[1] G. M. Sheldrick, *Bruker/Siemens Area Detector Absorption Correction Program*, Bruker AXS, Madison, WI, 1998.

[2] Sheldrick, G. M. (2015). *Acta Cryst.* **C**71, 3-8.