

Synthesis and Characterization of a Brønsted Pair Functionalized Shape-Persistent Macrocycle

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Supporting Information

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1. General informations

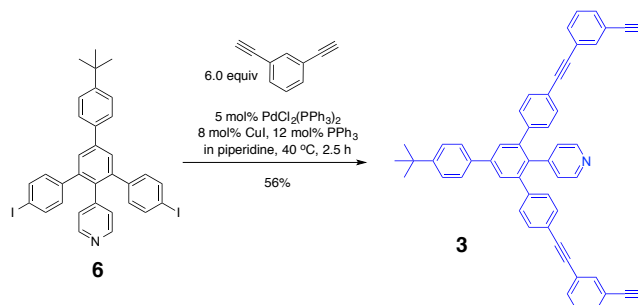
All reactions involving air- or moisture sensitive compounds were carried out under Nitrogen using standard Schlenk and vacuum line techniques. All reagents were purchased from commercial sources and used as received unless stated otherwise. Dichloromethane (DCM) and methanol (MeOH) were distilled over calcium hydride. Tetrahydrofurane (THF) was distilled over sodium/benzophenone or taken from a MBRAUN MB SPS-80 solvent purification system. Triethylamine (Et₃N), piperidine and THF were degassed by bubbling N₂ through the liquid for at least 10 minutes. Deuterated DCM (CD₂Cl₂) was degassed using the freeze-thaw-pump cycle according to the procedure found in literature^[S1] and subsequently stored over molecular sieves. Tetrahydrofuran (THF) was distilled over sodium/benzophenone before use, degassed by bubbling N₂ through it and stored over molecular sieves.

¹H and ¹³C NMR spectra (respectively 400 and 100 MHz) were recorded on an Agilent MRF400 or Varian VNMR-S400 spectrometer at 25°C. ¹H and ¹³C NMR chemical shifts are reported in ppm relative to TMS using the residual solvent resonance as internal standard. Infrared spectra were recorded using a Perkin Elmer Spectrum One FT-IR spectrometer. MS measurements were performed on a Waters LCT Premier XE KE317. Samples were prepared by solving the products in dichloromethane, acetonitrile and/or water. Where necessary, reagents such as formic acid, silver nitrate or pyridine were added in order to obtain ionization.

2. Experiments

Compounds **5**,^[S2] **6**^[S2] and **S1**^[S3] were synthesized as described in literature.

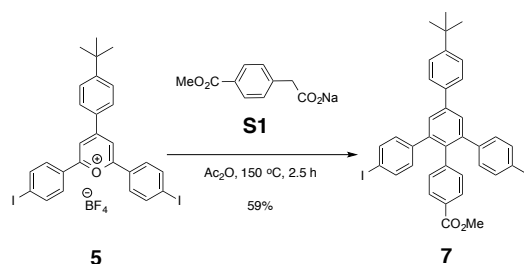
2.1. Synthesis of **3**.



6 (2.40 g, 3.48 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (112 mg, 0.16 mmol), CuI (56 mg, 0.29 mmol) and PPh_3 (112 mg, 0.43 mmol) were added to a dry Schlenk-flask under nitrogen. Degassed piperidine (40 mL) and 1,3-diethynylbenzene (2.62 g, 20.84 mmol) were added to the mixture. The mixture was stirred for 2.5 h at 40 °C and cooled to room temperature afterwards. Diethylether (ca. 50 mL) and water (ca. 50 mL) were added to the reaction mixture and the phases were separated. The organic phase was washed with aqueous acetic acid (20%, ca. 40 mL) and water. The washing procedure was repeated one time. The organic phase was dried over MgSO_4 and filtered. Removal of solvents under reduced pressure gave the crude product that was further purified by flash column chromatography using CHCl_3 ($R_F = 0.10$) as eluent. The product is obtained as a slightly yellowish solid (1.34 g, 1.95 mmol, 56%). $^1\text{H-NMR}$ (400 MHz, CD_2Cl_2): 8.27 (d, $J = 6.0$ Hz, 2H), 7.73 (s, 2H), 7.68 (d, $J = 8.4$ Hz, 2H), 7.65 (m, 2H), 7.54 (d, $J = 7.2$ Hz, 2H), 7.52 (d, $J = 7.2$ Hz, 2H), 7.47 (d, $J = 7.9$ Hz, 2H), 7.40 (d, $J = 8.2$ Hz, 4H), 7.35 (t, $J = 7.8$ Hz, 2H), 7.16 (d, $J = 8.2$ Hz, 4H), 6.85 (d, $J = 6.0$ Hz, 2H), 3.18 (s, 2H), 1.38 (s, 9H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 151.20, 148.54, 148.05, 141.52, 141.41, 141.06, 136.81, 135.05, 134.56, 131.84, 131.31, 129.81, 128.49, 128.43, 126.86, 126.71, 125.95, 123.49, 122.47, 121.58, 89.68, 89.01, 82.73, 77.80, 34.63, 31.33. IR (neat): 3275, 3060, 2960, 1595, 1510, 1450, 1265, 1015, 830, 730, 625, 555, 525 cm^{-1} . Exact mass ESI-MS: $\text{C}_{53}\text{H}_{37}\text{NH}$ calculated: 688.3004 found: 688.3056. Elemental analysis: measured: C = 92.67%, H = 5.57%, N = 1.97%; calculated: C = 92.54%, H = 5.42%, N = 2.04%.

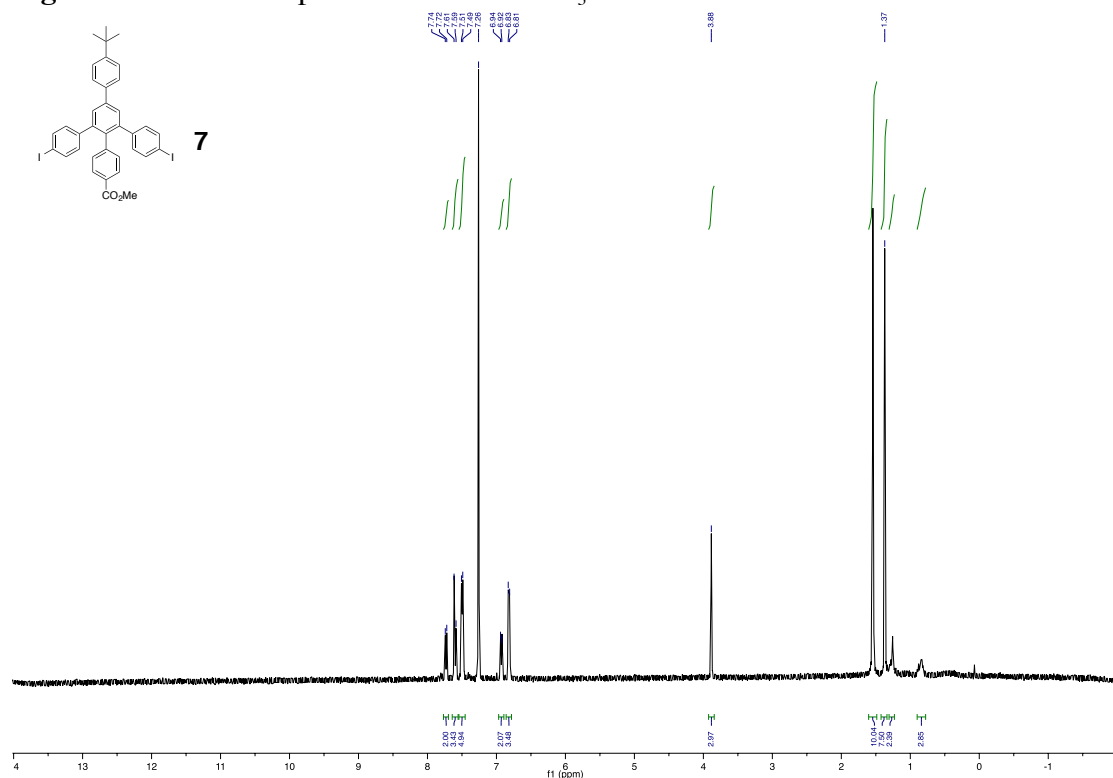
[illegible]

2.2. Synthesis of **7**.



S1 (1.98 g, 10.2 mmol) was solved in methanol (30 mL). NaOH (409 mg, 10.2 mmol) have been added to the mixture. The mixture is stirred for 15 minutes at room temperature. The solvent is removed under reduced pressure. **5** (5.28 g, 7.5 mmol) and acetic anhydride (Ac_2O ; 40 mL) were added to the obtained solids. The reaction mixture was stirred for 2.5 h at 150 °C. The mixture was allowed to cool to room temperature and filtered afterwards. The residue was washed with water and methanol. The crude product was purified via flash column chromatography using CHCl_3 ($R_F = 0.93$) to yield **7** (3.32 g, 4.44 mmol, 59%) as a white solid. ^1H -NMR (400 MHz, CDCl_3): 7.73 (d, $J = 8.0$ Hz, 2H), 7.61 (s, 2H), 7.59 (d, $J = 8.4$ Hz, 2H), 7.53 - 7.43 (m, 6H), 6.93 (d, $J = 8.0$ Hz, 2H), 6.82 (d, $J = 8.3$ Hz, 4H), 3.88 (s, 3H), 1.37 (s, 9H). ^{13}C -NMR (100 MHz, CDCl_3): 169.83, 166.89, 163.71, 151.03, 143.92, 141.22, 140.92, 140.80, 136.94, 131.63, 131.57, 128.90, 128.31, 128.03, 126.78, 125.91, 92.60, 52.05, 34.61, 31.32. IR (neat): 2960, 1915, 1725, 1610, 1480, 1400, 1265, 1185, 1115, 1005, 815, 720, 555, 470 cm^{-1} . Exact mass ESI-MS: $\text{C}_{36}\text{H}_{30}\text{I}_2\text{O}_2\text{Ag}$ calculated: 854.9387 found: 854.9469. Elemental analysis: measured: C = 57.89%, H = 3.79%; calculated: C = 57.77%, H = 3.79%.

Figure S3: ^1H -NMR spectrum of **7** in CDCl_3 .



7

CCOC(=O)c1ccc(cc1C2=CC=C(C=C2)C3=CC=C(C=C3)I)C4=CC=C(C=C4)C5=CC=C(C=C5)C(C)(C)C

¹³C NMR spectrum (CDCl₃) of compound **7**. The spectrum shows peaks at the following chemical shifts (ppm): 166.89, 166.89, 163.37, 151.05, 143.92, 143.92, 140.92, 140.92, 140.80, 137.65, 131.87, 131.87, 128.41, 128.41, 125.78, 125.78, 52.05, 34.81, 31.32.

Reaction scheme for the synthesis of **8** from **7**:

1) 2.4 equiv $\equiv\text{—TMS}$
7 mol% $\text{PdCl}_2(\text{PPh}_3)_2$
14 mol% CuI , 22 mol% PPh_3
in NET_3 , 45 °C, 24 h

2) K_2CO_3 , MeOH, THF
rt, 2 h

74%

Structure **7** is a triphenylmethane derivative with a central carbon atom bonded to three phenyl rings. One phenyl ring is substituted with a tert-butyl group and a methyl ester group (CO_2Me). The other two phenyl rings are substituted with a tert-butyl group and an iodine atom (I).

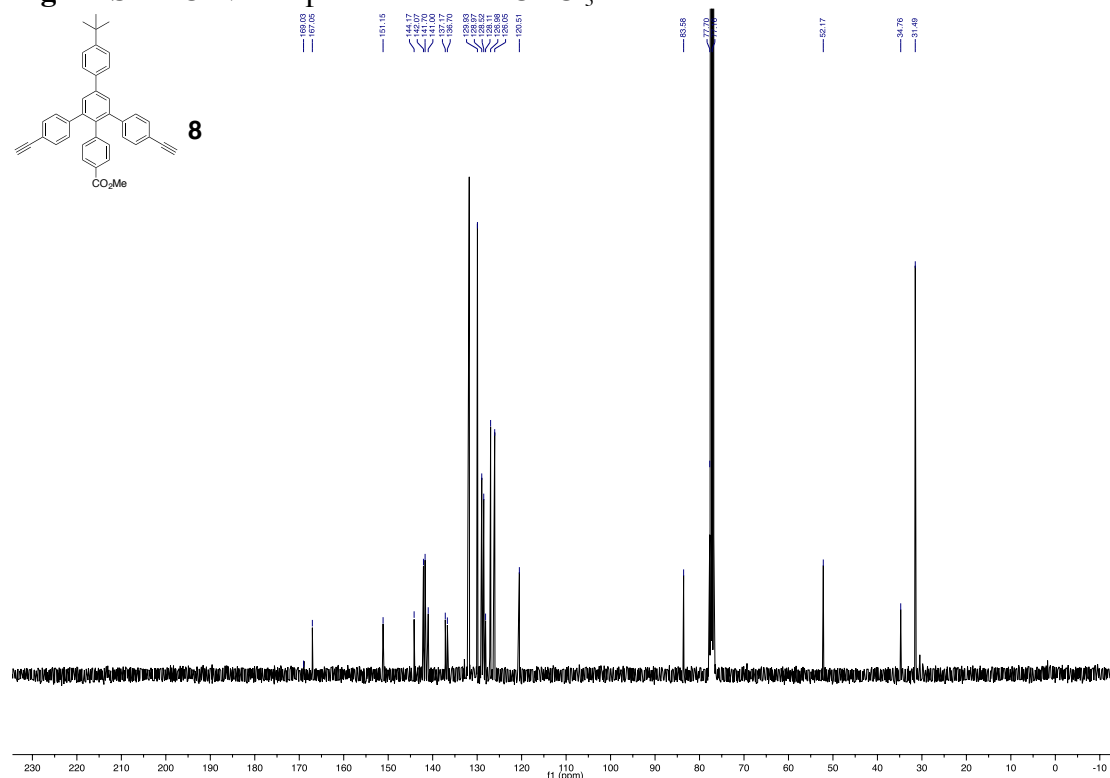
Structure **8** is a triphenylmethane derivative with a central carbon atom bonded to three phenyl rings. One phenyl ring is substituted with a tert-butyl group and a methyl ester group (CO_2Me). The other two phenyl rings are substituted with a tert-butyl group and an ethynyl group (\equiv).

5

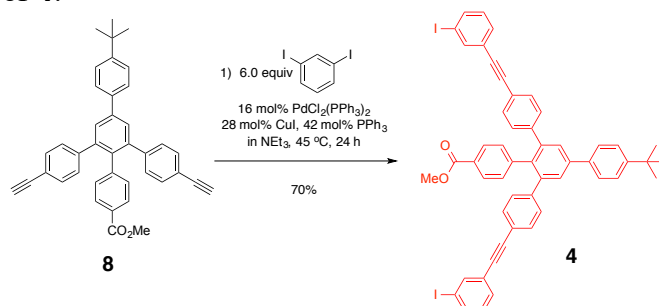
Figure S5: ^1H -NMR spectrum of **8** in CDCl_3 .



Figure S6: ^{13}C -NMR spectrum of **8** in CDCl_3 .

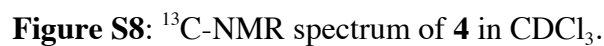


2.4. Synthesis of **4**.

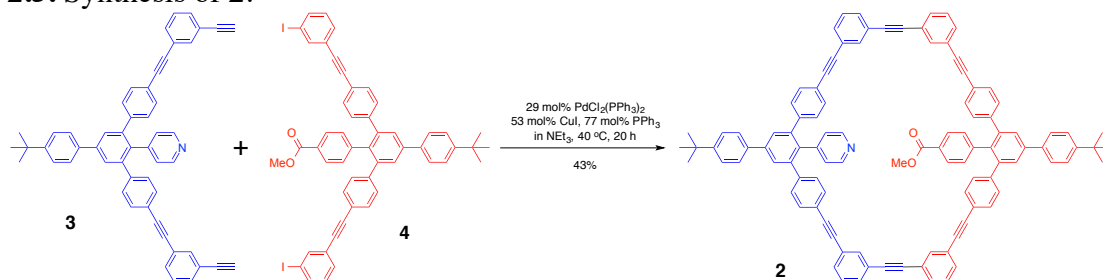


8 (1.00 g, 1.80 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (200 mg, 0.28 mmol), CuI (100 mg, 0.52 mmol), PPh_3 (200 mg, 0.76 mmol) and 1,3-diiodobenzene (3.60 g, 10.9 mmol) were added to a dry Schlenk-flask under nitrogen. Degassed triethylamine (80 mL) was added to the mixture. The mixture was stirred for 24 h at 45 °C and cooled to room temperature afterwards. Diethylether (ca. 50 mL) and water (ca. 50 mL) were added to the reaction mixture and the phases were separated. The organic phase was washed with aqueous saturated NH_4Cl (2x ca. 40 mL) and brine (ca. 40 mL). The organic phase was dried over MgSO_4 and filtered. Removal of solvents under reduced pressure gave the crude product that was further purified via flash column chromatography using CHCl_3 ($R_F = 0.83$) to give **4** and 1,3-diiodobenzene. The solid was washed with petroleum ether and cyclohexane until pure **4** (1.20 g, 1.26 mmol, 70%) was obtained as a slightly greyish solid. ^1H -NMR (400 MHz, CD_2Cl_2): 7.89 (t, $J = 1.7$ Hz, 2H), 7.72 (s, 2H), 7.72 - 7.66 (m, 4H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.49 (d, $J = 7.7$ Hz, 2H), 7.36 (d, $J = 8.3$ Hz, 4H), 7.15 (d, $J = 8.3$ Hz, 4H), 7.10 (t, $J = 7.9$ Hz, 1H), 7.01 (d, $J = 8.2$ Hz, 2H), 3.84 (s, 3H), 1.38 (s, 9H). ^{13}C -NMR (100 MHz, CDCl_3): 166.90, 151.00, 144.09, 141.71, 141.60, 140.88, 140.10, 137.21, 137.04, 136.57, 135.03, 131.65, 131.13, 130.63, 129.89, 129.77, 128.84, 128.37, 127.95, 126.84, 125.90, 125.28, 121.02, 109.99, 93.65, 90.53, 88.08, 52.01, 34.61, 31.34. IR (neat): 2950, 2930, 2350, 1720,

Figure S7: ^1H -NMR spectrum of **4** in CD_2Cl_2 .



2.5. Synthesis of **2**.



$\text{PdCl}_2(\text{PPh}_3)_2$ (30 mg, 0.043 mmol), CuI (15 mg, 0.079 mmol) and PPh_3 (30 mg, 0.114 mmol) were added to a dry Schlenk-flask under nitrogen. Degassed triethylamine (10 mL) and freshly distilled and degassed THF (20 mL) were added to the mixture. The mixture was stirred at 40 °C. In a separate Schlenk-flask **3** (103 mg, 0.150 mmol) and **4** (142 mg, 0.150 mmol) were solved in freshly distilled and degassed THF (18 mL). The mixture containing **3** and **4** was added drop wise over 3.5 h to the catalyst mixture. After complete addition the mixture was stirred additional 20 h at 40 °C. The warm reaction mixture was filtered. Water (ca. 20 mL) and diethyl ether (ca. 20 mL) were added to the filtrate and the phases were separated. The organic phase was washed with aqueous saturated NH_4Cl (2x ca. 40 mL) and water (ca. 40 mL) which gave a precipitate. The solid was filtered and dried under reduce pressure. The crude product was further purified via flash column chromatography using CHCl_3 (R_F = 0.06) to yield **2** (90 mg, 0.065 mmol, 43%) as a yellowish foil (see picture S1). ^1H -NMR (400 MHz, CD_2Cl_2): 8.27 (br, 2H), 7.75-7.62 (m, 14H), 7.57-7.45 (m, 12H), 7.42-7.30 (m, 12H) 7.16-7.10 (m, 8H), 7.01 (d, J = 7.6 Hz, 2H), 6.86 (br, 2H), 3.83 (s, 3H), 1.37 (s, 18H). ^{13}C -NMR (100 MHz, CD_2Cl_2): 166.56, 151.19, 151.06, 148.96, 147.33, 144.16, 141.78, 141.66, 141.50, 141.33, 140.94, 140.57, 136.91, 136.73, 134.36, 131.92, 131.83, 131.73, 131.68, 131.44, 131.36, 131.27, 131.12, 131.00, 130.00, 129.94, 128.61, 128.56, 128.49, 128.37, 128.21, 128.19, 128.12, 126.67, 126.57, 125.92, 123.73, 123.54, 123.29, 121.88, 121.37, 121.23, 121.08, 89.76, 89.66, 88.95, 88.93, 88.82, 88.71, 51.83, 34.47, 31.02. IR (neat): 2960, 2925, 1720, 1595, 1505, 1480, 1435, 1405, 1260, 1090, 1015, 890, 860, 790, 755, 685 cm^{-1} . Exact mass ESI-MS: $\text{C}_{105}\text{H}_{73}\text{NO}_2\text{H}$ calculated: 1380.5719 found: 1380.5781. Elemental analysis: measured: C = 91.20%, H = 5.27%, N = 0.99%; calculated: C = 91.34%, H = 5.33%, N = 1.01%.

Picture S1: Isolated **2**.



[illegible]

Figure S10. ¹H NMR spectrum of compound 2 in CDCl₃. The chemical structure of compound 2 is shown in the inset. The spectrum displays peaks in the aromatic region (6.7-8.4 ppm) and aliphatic region (0.8-1.0 ppm), with integration values provided below the baseline.

Figure S11: DOSY-NMR spectrum of **2** in CD₂Cl₂.

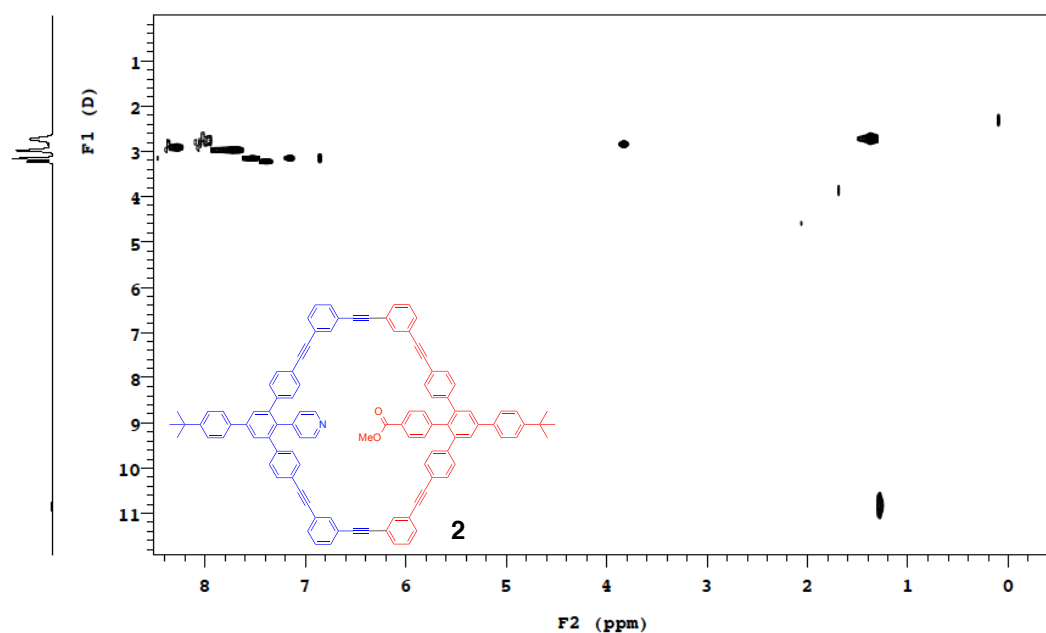
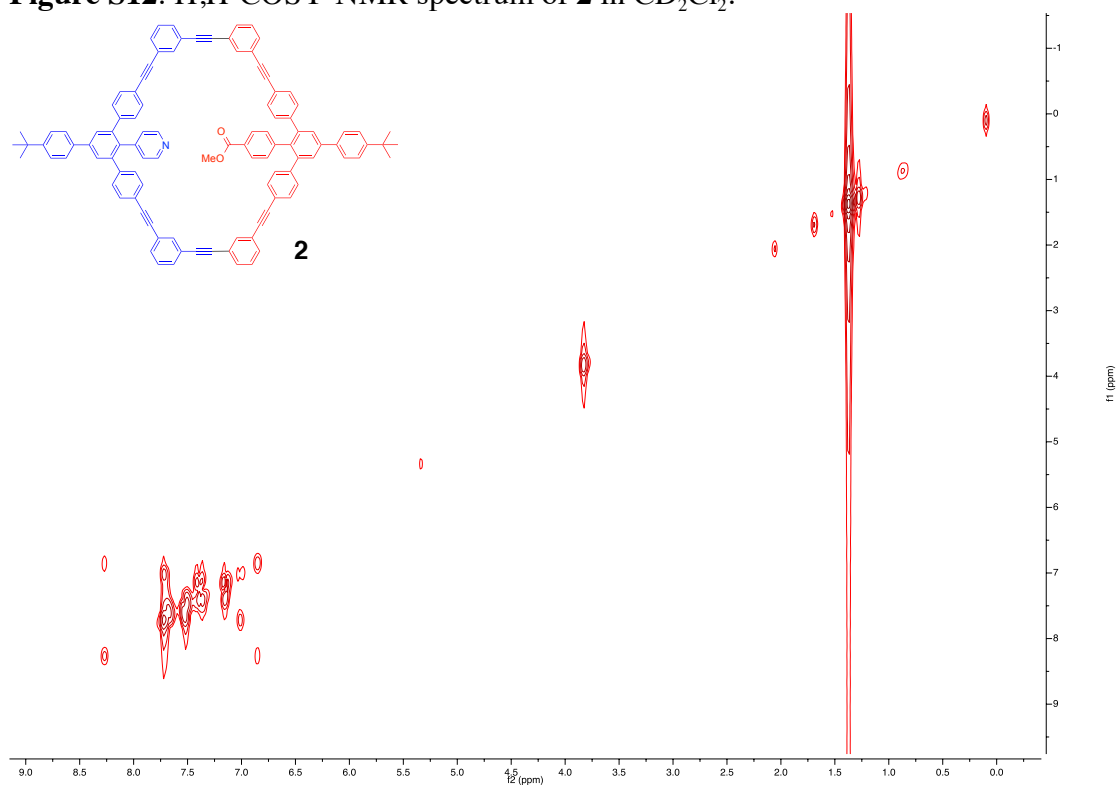


Figure S12: H,H-COSY-NMR spectrum of **2** in CD₂Cl₂.



The DOSY- and H,H-COSY-NMR spectra of **2** are shown in the Figures S11 and S12. The DOSY spectrum indicates that all signals assigned to the product belong indeed to species of the same size. As the H,H-COSY shows coupling between those signals it can be concluded that the signals in the DOSY spectrum belong to one compound.

[illegible]

Chemical reaction scheme showing the synthesis of compound **1** from compound **2**.

Compound **2** (a macrocyclic precursor with a methoxy ester group) reacts with:

- 1) NBU_4OH , H_2O , THF
- 2) aq HCl

The reaction proceeds in 74% yield to form compound **1** (the macrocyclic product with a carboxylic acid group).

12

[illegible]

1 (20 mg, 0.014 mmol) was added to a dry Schlenk-flask under nitrogen. CD_2Cl_2 (2 mL) was added to the Schlenk-flask. The resulting suspension was stirred for 10 minutes at room temperature. After 10 minutes a sample was taken and a ^1H -NMR was measured (Figure S15 top). The sample was backfilled into the Schlenk-flask. In a vial 22 mg DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene, 0.145 mmol) were solved in 1 mL CD_2Cl_2 . 0.1 mL DBU solution were added to the suspension containing **1**. The mixture was allowed to stir 10 minutes at room temperature. Within this time a color change of the liquid from colorless to yellow/orange has been observed. After 10 minutes a sample was taken and ^1H -NMR was measured (Figure S15 bottom).

Figure S15: ^1H -NMR spectra of **1** (top) and **1** plus DBU (bottom) in CD_2Cl_2 .

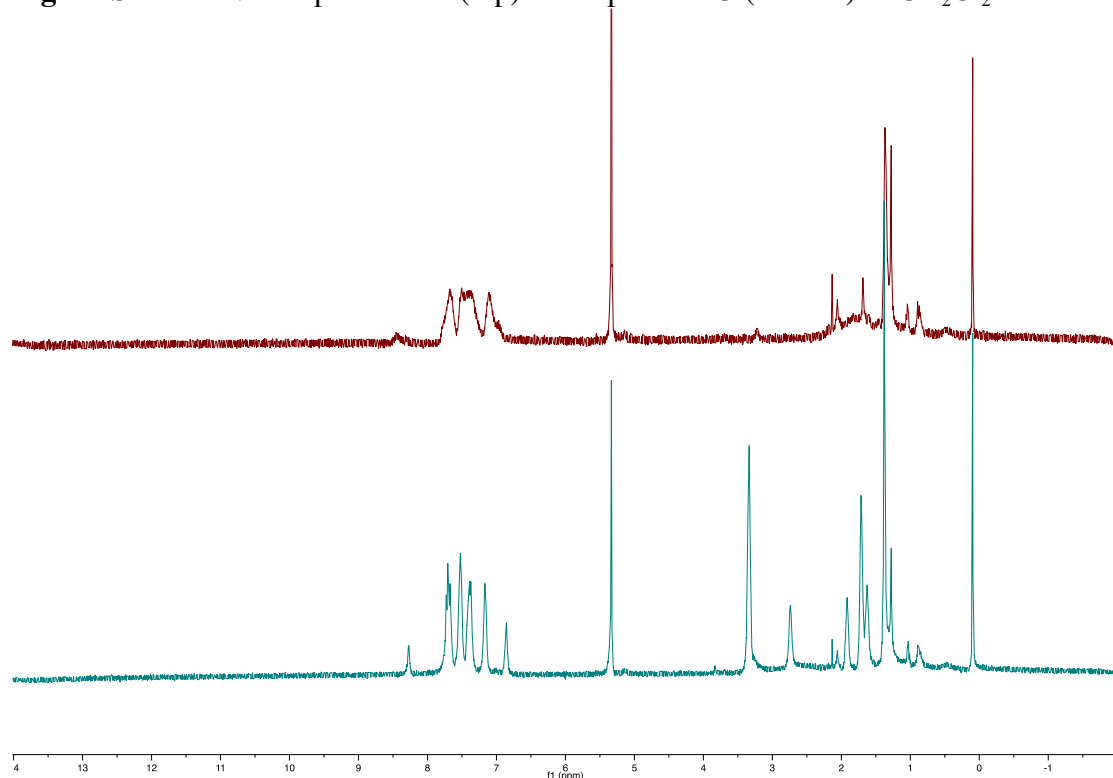
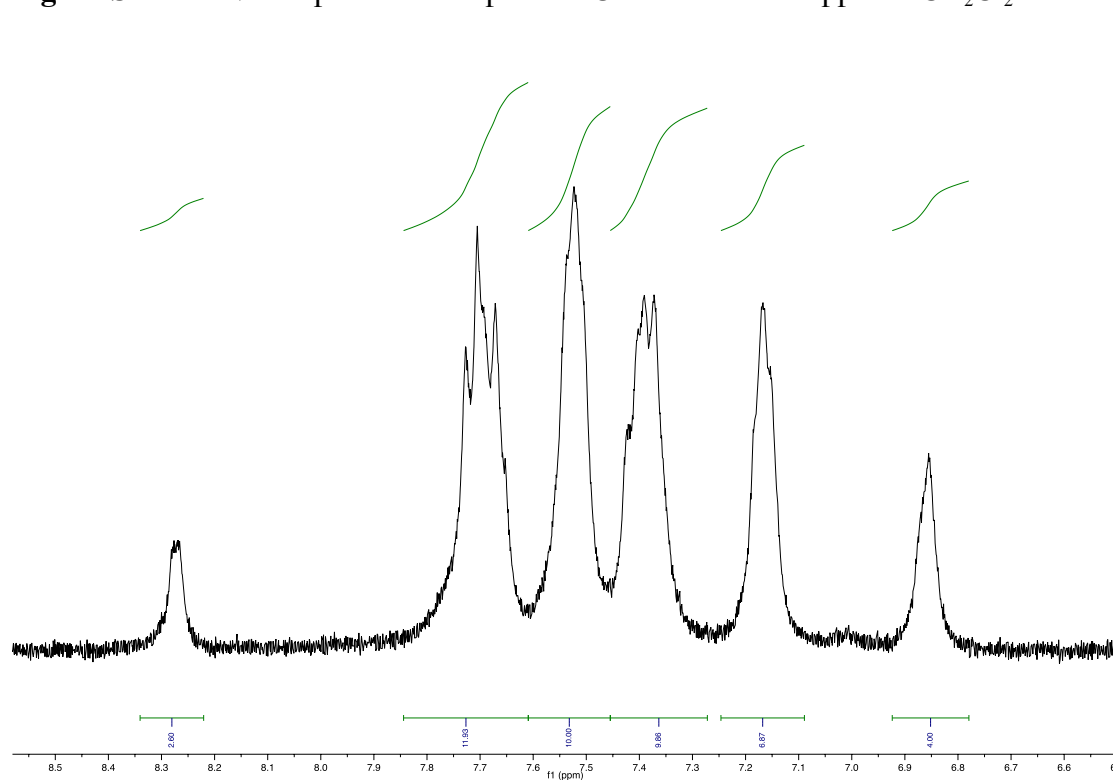


Figure S16: ^1H -NMR spectrum of **1** plus DBU from 8.6 to 6.5 ppm in CD_2Cl_2 .

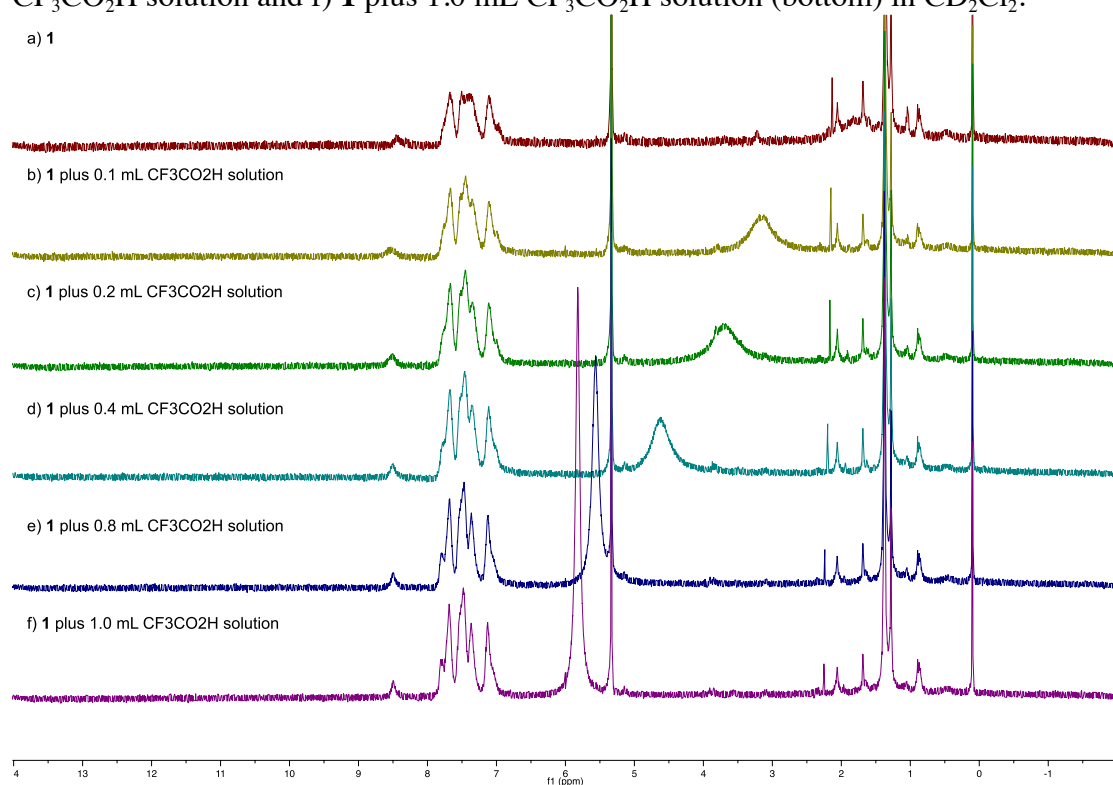


2.8 Addition of $\text{CF}_3\text{CO}_2\text{H}$ to **1**

1 (20 mg, 0.014 mmol) was added to a dry Schlenk-flask under nitrogen. CD_2Cl_2 (2 mL) was added to the Schlenk-flask. The resulting suspension was stirred for 10 minutes at room temperature. After 10 minutes a sample was taken and a ^1H -NMR was measured (Figure S17 top). The sample was backfilled into the Schlenk-flask. In

a vial 47 mg $\text{CF}_3\text{CO}_2\text{H}$ (0.412 mmol; Note: $\text{CF}_3\text{CO}_2\text{H}$ is fuming the amount of solved acid might be less then 47 mg) were solved in 3 mL CD_2Cl_2 . 0.1 mL $\text{CF}_3\text{CO}_2\text{H}$ solution were added to the suspension containing **1**. The mixture was allowed to stir 10 minutes at room temperature. Afterwards a sample was taken and ^1H -NMR was measured (Figure S15 bottom).

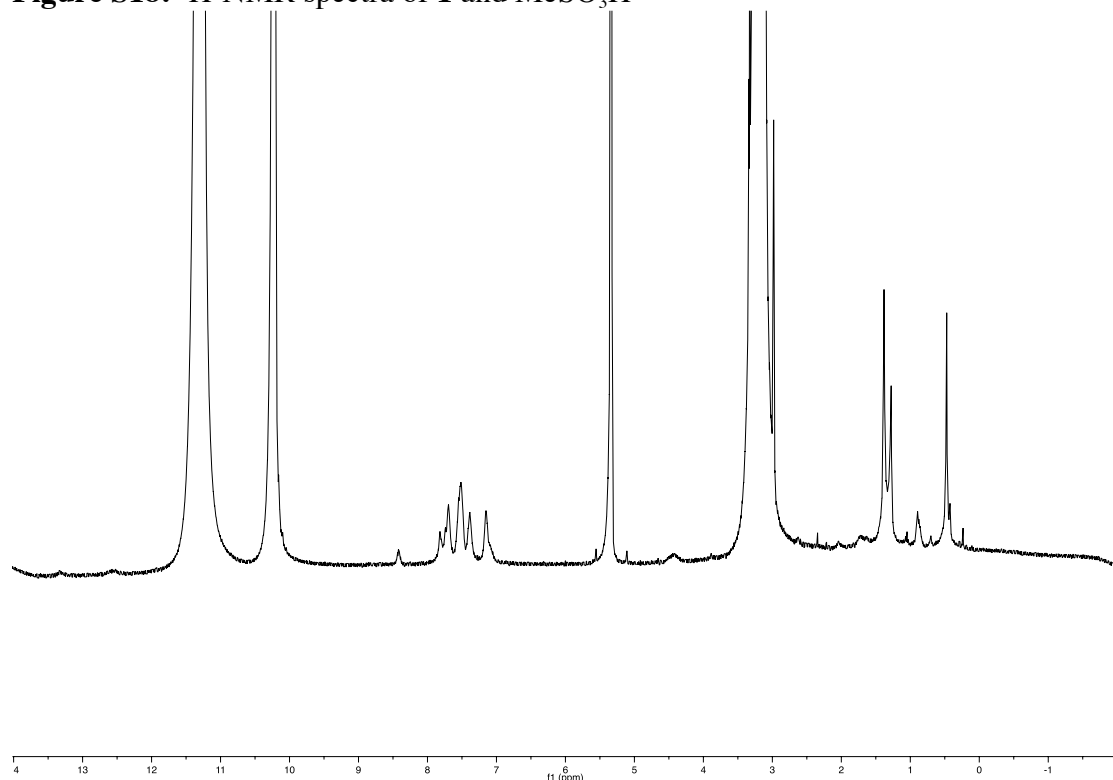
Figure S17: ^1H -NMR spectra of a) **1** b) **1** plus 0.1 mL $\text{CF}_3\text{CO}_2\text{H}$ solution, c) **1** plus 0.2 mL $\text{CF}_3\text{CO}_2\text{H}$ solution, d) **1** plus 0.4 mL $\text{CF}_3\text{CO}_2\text{H}$ solution, e) **1** plus 0.8 mL $\text{CF}_3\text{CO}_2\text{H}$ solution and f) **1** plus 1.0 mL $\text{CF}_3\text{CO}_2\text{H}$ solution (bottom) in CD_2Cl_2 .



2.9 Addition of MeSO_3H to **1**

1 (5 mg, 0.004 mmol) was added to a NMR tube under air. 0.6 mL CD_2Cl_2 was added to the NMR tube. One drop MeSO_3H was added to the resulting mixture. After 10 minutes of shaking the NMR tube manually a spectrum has been recorded.

Figure S18: ^1H -NMR spectra of **1** and MeSO_3H



3. Computational Aspects

All calculations were carried out with the ORCA program package.^{S4} The geometries of **1**, **2** as well as $\mathbf{1}+\text{H}^+$ and $\mathbf{1}-\text{H}^+$ were optimized using the TPSS functional in conjunction with the def2-TZVP(-f) basis set and the corresponding Coulomb fitting basis set by Weigend.^{S5-7} During the optimizations dispersion interactions were accounted for by Grimme's empirical D3 correction.^{S8} For the numerical integration of the exchange-correlation potential a dense grid (ORCA Grid4) was employed. The used computational setup yielded accurate results for geometries and thermochemical data in a large set of benchmark calculations on organic molecules.^{S9}

Figure S19. A metastable structure of **1** featuring no N-H-O hydrogen bond

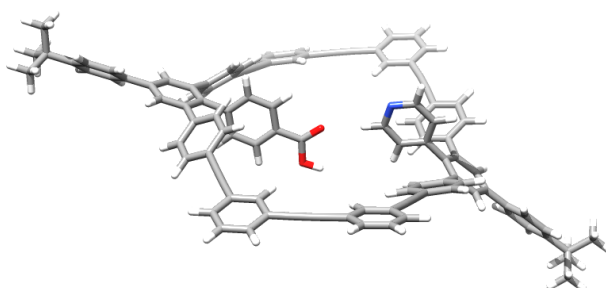


Figure S20. The optimized structures of **1-H⁺** (a) and **1+H⁺** (b)

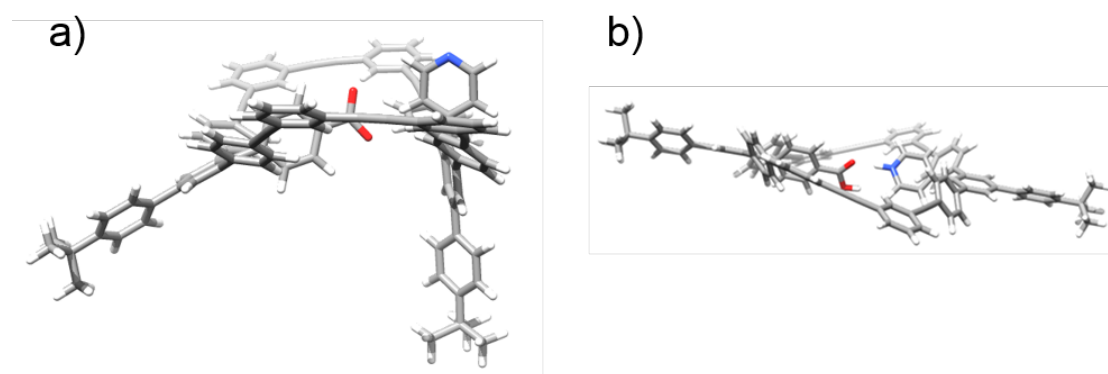
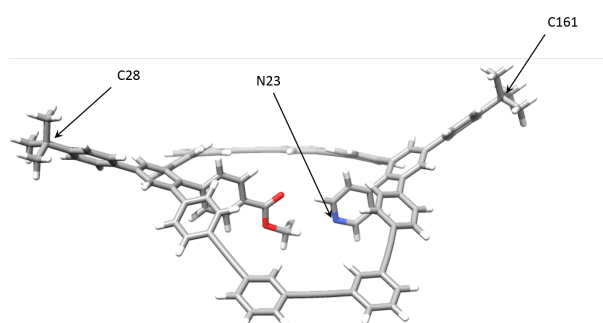
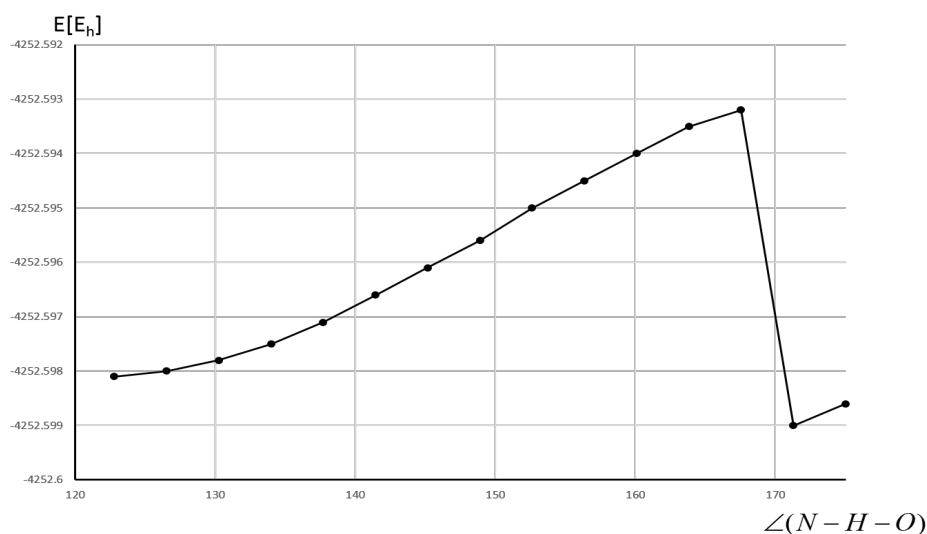


Figure S21. The boat-like structure of **2**. A relaxed surface scan along the angle between atoms C28, N23 and C161 was performed.



A relaxed surface scan along the angle generated by the atoms C28, N23 and C161 (Figure S16) was performed (Figure S17). At each point of the scan the geometry is optimized by the semiempirical AM1 method.^{S10} However, the total energies were calculated with the DFT setup described above. The scan covers a range of angles from 123° corresponding to a boat-like structure, through 175° which corresponds to a chair-like structure. Approaching a value of 168° the energy increases monotonously from its starting value by ~4.8 mEh. At higher values the energy drops again immediately by ~4.8 mEh. Note, that the sudden drop in energy is associated with a major reorganization of the molecule after the conversion from its boat-like to its chair-like structure.

Figure S22. Relaxed surface scan of **2** along the angle generated by C28, N23 and C161.



4. References

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