

Enzyme-like Hydrogen Atom Transfer (HAT) based Endo-Functionalized Molecular Receptors

Wenkai Pan, Anastasia Grigoryeva, Corrado Bacchiocchi, Pablo
Ballester, Luca Valgimigli,* and Manuel Petroselli*

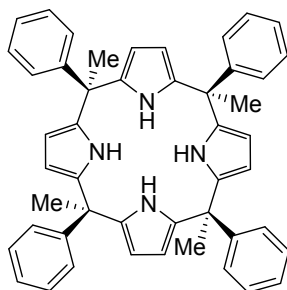
Table of Contents

1.	General Information, Material & Methods	2
2.	Synthesis Procedures & Spectral Data	3
3.	Products Characterization	10
4.	Synthetic Schemes & Equilibria	18
5.	Antioxidant Response & Radical Kinetics	24
6.	Stability & Binding Studies	28
7.	EPR Study	38
8.	DFT Study	42

1. General Information, Material & Methods

All reagents and solvents for the synthetic part were purchased from commercial sources (mainly Merck and Alfa Aesar) and used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded at 298 K on a Bruker Avance 400 (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR) or Bruker Avance 500 (500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR). Chemical shifts are reported in ppm relative to the residual ^1H signal of the deuterated solvent used (CDCl_3 at 7.26 ppm and DMSO-d_6 at 2.50 ppm). ^1H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Full characterization is reported for all the host involved in this study (**1-4**), while ^1H NMR spectrum is reported for already published products or other synthetic intermediates to prove their synthesis. HRMS spectra were recorded on a Waters Synapt MALDI-Q-TOF apparatus using alpha-cyano-4-hydroxycinnamic acid as the assisting matrix. Reference inhibitors for autoxidation kinetic studies, 2,2,5,7,8-pentamethyl-6-chromanol (PMHC) and 2,6-di-*tert*-butyl-4-methylphenol, were commercially available (Merck, Milan, Italy) and used as received. Solvents were of the highest grade commercially available (Merck, VWR; HPLC grade) and used as received. Cumene was percolated on alumina and on silica before use in order to remove traces of peroxides. 2,2'-Azobis (2-methylpropionitrile) (AIBN, Merck) was recrystallized from methanol before use. Stock solutions of AIBN in the desired solvents were prepared daily and maintained at 4°C between subsequent uses, to avoid significant decomposition.

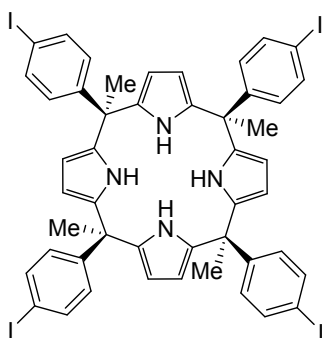
2. Synthesis Procedures & Spectral Data



Tetra-phenyl-tetramethylcalix[4]pyrrole (**1**)

In a 500 ml round bottom flask acetophenone (6 gr, 49.9 mmol, 1 equiv.) was dissolved in 200 ml of dichloromethane. 1.46 ml of 37% HCl (aq.) (49.9 mmol, 1 equiv.) was added dropwise followed by the addition over the course of 30 minutes of 3.43 ml of freshly distilled pyrrole (49.9 mmol, 1 equiv.). The flask was protected from light and the reaction was left stirring 48 hours at room temperature. The precipitated formed was filtered on a filter paper, to discard oligomeric pyrrolic by-products, and 300 ml of methanol were added to the solution. The solution was concentrated under reduced pressure to remove the dichloromethane and a pale pink/white solid precipitate is observed. The solid was filtered and washed with acetonitrile (200 ml). The resulting solution (solid suspended in acetonitrile) was sonicated at room temperature for 20 minutes and then filtered, affording a pale pink/white solid. The crude was recrystallized (DCM/MeOH) to afford a white solid, containing mainly the cone-isomer. If necessary, a second recrystallization in DCM/MeOH can be performed to further improve the purity of the product. The resulting solid was added in a round bottom flask with 30 ml of MeOH. The resulting mixture was sonicated for 30 minutes, filtered on buchner, and dried under high vacuum for 24 hours, to afford the desired product as a white solid (2.38 gr, Yield: 7.1%).

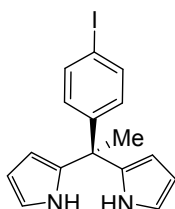
¹H-NMR (500 MHz, CDCl₃, 298 K): δ 7.87 (br s, 4H), 7.23 (m, 8H), 7.18 (m, 4H), 7.12 (m, 8H), 5.77 (d, 8H), 1.98 (s, 12H); ¹³C-NMR (126 MHz, CDCl₃, 298 K) δ 148.3, 137.0, 127.8, 127.6, 126.5, 106.3, 50.6, 44.8, and 28.6; HRMS (MALDI/ESI): Exact mass calculated for C₄₈H₄₅N₄⁺ [M+H]⁺ 677.3639, found 677.3613; TLC: R_f = 0.34 (1:1 DCM/hexane; reacts to vanilline stain).



Tetra-*p*-iodophenyl-tetramethylcalix[4]pyrrole (**2**)

Compound **2** was synthesized following a modified procedure reported in the literature. ^[38] In a 500 ml round bottom flask 4-iodoacetophenone (10 gr, 40.6 mmol, 1 equiv.) was dissolved in 200 ml of dichloromethane. 1.2 ml of 37% HCl (aq.) (40.6 mmol, 1 equiv.) was added dropwise followed by the addition over the course of 30 minutes of 2.8 ml of freshly distilled pyrrole (40.6 mmol, 1 equiv.). The flask was protected from light and the reaction was left stirring 48 hours at room temperature. The precipitated formed was filtered to discard oligomeric pyrrolic by-products, and 300 ml of methanol were added to the solution. The solution was concentrated under reduced pressure to remove the dichloromethane and a brown solid precipitate is observed. The solid was filtered and washed with 200 ml of acetonitrile. The resulting solution was sonicated at room temperature for 20 minutes and then filtered, affording a brown/dark beige solid. The crude was recrystallized (DCM/MeOH) to afford a crude, containing mainly the cone-isomer. The resulting solid was purified on silica gel (100% DCM). The fractions containing the product are collected and the solvent removed under reduced pressure. A white/beige solid is obtained and crystallized in DCM/MeOH, affording a beige solid. The obtained solid was further washed with MeOH to remove potential traces of side product(s), affording the desired product as a white/beige solid (1.97 gr, 16% yield).

¹H-NMR (500 MHz, CDCl₃, 298 K): δ 8.23 (very broad s, 4H), 7.53 (d, 8H), 6.80 (d, 8H), 5.88 (s, 8H), and 1.89 (s, 12H); TLC: *R_f* = 0.95-0.98 (100% DCM; reacts to vanilline stain).

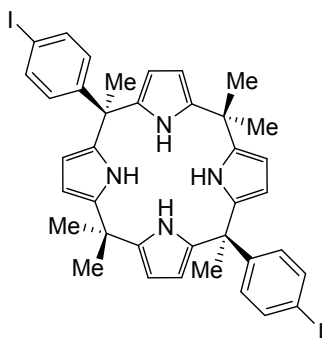


5-methyl-5'-(4-iodophenyl)dipyrromethane (**A**)

Into a 250 ml round bottom flask, 4-iodoacetophenone (10 gr, 40.6 mmol, 1 equiv.) was added and vacuum/argon cycles were performed to guarantee an inter atmosphere. Under argon atmosphere,

freshly distilled pyrrole was added (71 ml, 25 equiv.). To the resulting dark orange/brown solution, trifluoroacetic acid (9.39 ml, 122 mmol, 3 equiv.) was added dropwise in 30 minutes via syringe pump at 0 °C. The color of the solution turned to dark brown/black during the trifluoroacetic acid addition. The solution was stirred at room temperature overnight. After this time, 50 ml of distilled water are added to the flask and the pH was adjusted to pH 7 with a NaOH solution 1M. The water solution was washed twice with 100 ml DCM. The combined organic layers dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude oil was left under reduced pressure (15-30 mbar at 60 °C) for 90 minutes to get rid of as much pyrrole as possible. Then, the oily crude (around 36 gr) was dissolved in 300 ml of DCM, assisted by a sonication process, and partitioned in two different round bottom flask. Silica gel (20 gr) was added in each solution and the organic solvent removed under reduced pressure. The resulting mixture adsorbed on silica gel was purified on silica gel (dry loading) using DCM as a eluent, leading to obtain a colorless/pale yellow oil. The oil was washed with a solution 9:1 hexane:DCM, assisted by a sonication process. The resulting solution was filtered and dried under reduced pressure, leading to obtain the desired product as a white solid (6.29 gr, 43% yield).

¹H-NMR (500 MHz, DMSO-d₆, 298 K): δ 10.36 (s, 2H), 7.60 (d, 2H), 6.76 (d, 2H), 6.64 (q, 2H), 5.88 (q, 2H), 5.55 (q, 2H), and 1.92 (t, 3H); TLC: *R_f* = 0.4 (1:1 DCM/hexane; reacts to vanilline stain).

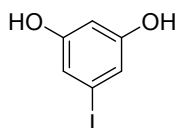


10α,20α-bis(4-iodophenyl)calix[4]pyrrole (3)

Compound **3** was synthesized following a modified procedure reported in the literature. ^[62] To a solution of **A** (6.29 gr, 17.4 mmol, 1 equiv.) in HPLC grade acetone (400 ml, 350 equiv.) was added boron trifluoride diethyl etherate 82.2 ml, 17.4 mmol, 1 equiv.) dropwise at 0 °C in a time of 30 minutes. The initial yellow solution turned orange and then red after the addition of boron trifluoride diethyl etherate. The resulting reaction mixture was stirred for 18 hours at room temperature. Acetone was reduced to 100 ml and 100 ml of water was added. A dark red/brown solid is immediately formed. The pH was adjusted to 7 by adding a 1M NaOH solution. The resulting mixture was extracted with DCM.

The combined organic phase was dried over anhydrous sodium sulfate, filtered and the organic solvent removed under reduced pressure. The resulting dark red crude was purified on silica gel (dry loading), using initially hexane as an eluent and then, a solution hexane/ethyl acetate (95:5), leading to obtain 561 mg of the desired product (4% yield) as a white/pale yellow solid.

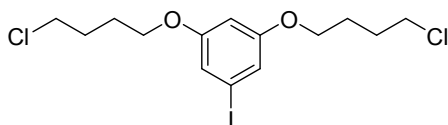
$^1\text{H-NMR}$ (500 MHz, CDCl_3 , 298 K): δ 7.54 (d, 4H), 7.17 (s, 4H), 6.71 (d, 4H), 5.91 (t, 4H), 5.61 (t, 4H), 1.85 (s, 6H), 1.61 (s, 6H), and 1.52 (s, 6H); **TLC**: R_f (α,α -conformer) = 0.50 (95:5 hexane/ethyl acetate; reacts to vanilline stain).



5-iodobenzene-1,3-diol (B)

Intermedaite **B** was synthesized following a modified procedure reported in the literature. ^[63] 1-iodo-3,5-dimethoxybenzene (2.0 gr, 7.57 mmol) in 40 ml of dry dichloromethane, protected with argon atmosphere, was cooled down to 4 °C. Then, 1 M solution of boron tribromide in dichloromethane (25 ml, 25 mmol) was added. The reaction mixture was slowly warmed to room temperature and stirred 24 hours. After cooling the mixture to 4 °C, a saturated NaHCO_3 solution was slowly added until no more gas evolution was observed. A 6 M NaOH solution was then carefully added until the mixture reached a pH of *ca.* 11. The DCM phase was separated from the aqueous phase and discarded. The latter was acidified to a pH of *ca.* 2, and extracted twice with ethyl acetate. The collected organic layers were dried over MgSO_4 and filtered. Concentration in vacuo affords the reaction crude as an orange oil, which became a solid after a night. Flash column chromatography (SiO_2 ; hexane-ethyl acetate 80 : 20) yielded the desired compound in 94% yield (1.64 gr) as a colorless oil (initially), and then as a white solid.

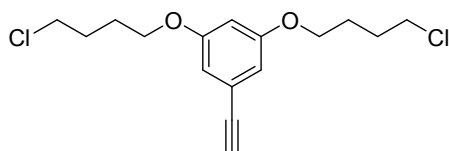
$^1\text{H-NMR}$ (500 MHz, DMSO-d_6 , 298 K): δ 9.55 (s, 2H), 6.56 (d, 2H), and 6.18 (t, 1H); **TLC**: R_f = 0.38 (70:30 hexane/ethyl acetate; reacts to vanilline and KMnO_4 stain).



1-iodo-3,5-bis(4-chlorobutoxy)benzene (C)

Intermediate **B** (400 mg, 1.69 mmol, 1 equiv.) was dissolved in dry DMF (50 ml) and stirred at room temperature under argon atmosphere. K_2CO_3 (703 mg, 5.08 mmol, 3 equiv.) was added and the reaction mixture was stirred for 2 hours. 1-bromo-4-chlorobutane (469 μ L, 4.07 mmol, 2.4 equiv.) was added and the solution stirred for 22 hours. After that, the reaction was stopped and the pH adjusted at pH 5 with a 1 N HCl solution. The reaction crude was extracted by adding dichloromethane and water. The organic layer was washed with water, dried over Na_2SO_4 , filtered and concentrated. The resulting crude was purified by silica gel column chromatography (eluent 3:7 DCM/hexane), affording 465 mg of the desired product (66% yield) as a colorless oil (initially), and then as a white solid after one night at 4 °C.

1H -NMR (500 MHz, $DMSO-d_6$, 298 K): δ 6.84 (d, 2H), 6.38 (t, 1H), 3.94 (t, 4H), 3.61 (t, 4H), and 1.94 (m, 8H).

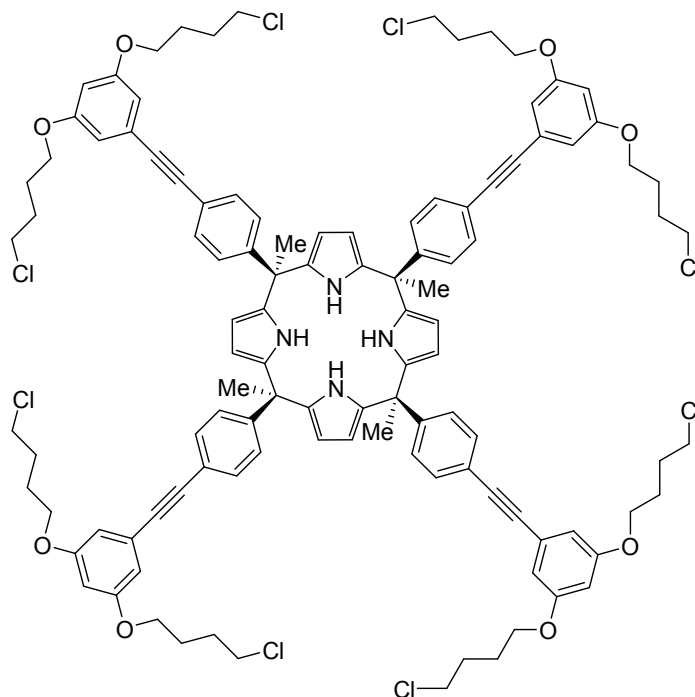


1,3-bis(4-chlorobutoxy)-5-ethynylbenzene (D)

In a Schlenk flask, Intermediate **C** (465 mg, 1.11 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (156 mg, 0.223 mmol, 0.2 equiv.), and CuI (64 mg, 0.334 mmol, 0.3 equiv.) were kept for 30 minutes under high vacuum and then, under argon atmosphere. Dry and degassed THF (25 ml) and DIPEA (1.2 ml, 6.69 mmol, 6 equiv.) were added to the previous Schlenk flask and the solution stirred for few minutes. Ethynyltrimethylsilane (0.48 ml, 3.34 mmol, 3 equiv.) was added in a single portion, and the resulting mixture stirred at 45 °C in an oil bath for 4 hours. After this time, the reaction was stopped and the crude concentrated. The resulting crude was dissolved in dichloromethane (50 ml), and washed with a 1 N HCl solution (50 ml), brine (50 ml), and water (50 ml). The organic layer was dried over Na_2SO_4 , filtered, and concentrated. The resulting dark brown/black oil was quickly filtered on a pad of silica gel to remove the remaining catalyst. The dark orange oil crude was directly used for the next step without further purification. The reaction crude, containing (theoretically) 432 mg (1.12 mmol, 1 equiv.) of the desired intermediate was dissolved in THF (25 ml). A solution 1 M of TBAF in THF (1.23 ml, 1.23 mmol, 1.1 equiv.) was added dropwise to the previous solution. The reaction mixture was stirred at room temperature under argon atmosphere for 90 minutes. The reaction was quenched with NH_4Cl (12 ml), and the THF removed under reduced pressure to favor the liquid-liquid extraction. The water solution was washed with AcOEt (12 ml x 3) and the organic layer washed with brine (15 ml). The organic layer was dried over Na_2SO_4 , filtered and concentrated. The resulting pale yellow/orange oil

was suspended in 2:8 DCM:hexane, filtered and purified by silica gel column chromatography (2:8 DCM:hexane), giving the desired product in 59% overall yield (206 mg) as a colorless oil.

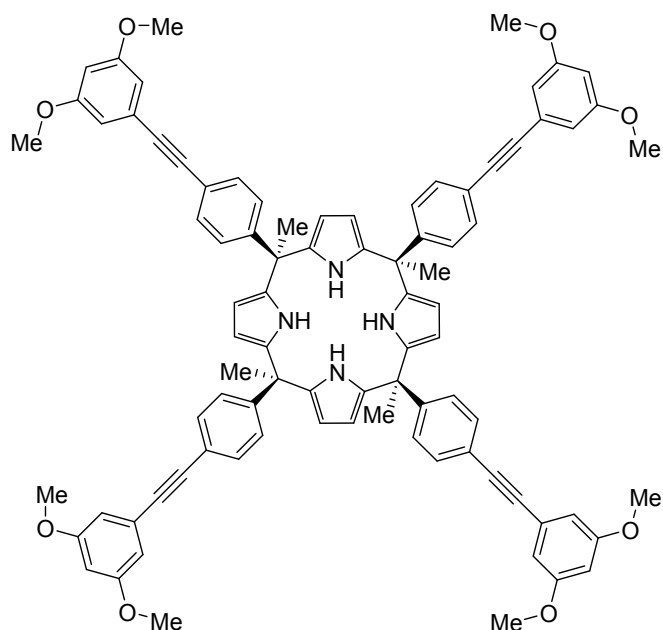
$^1\text{H-NMR}$ (500 MHz, DMSO- d_6 , 298 K): δ 6.63 (d, 2H), 6.44 (t, 1H), 3.96 (t, 4H), 3.61 (t, 4H), 3.03 (s, 1H), and 1.94 (m, 8H). TLC: R_f = 0.29 (30:70 DCM/hexane).



Tetra-[1,3-bis(4-chlorobutoxy)-5-ethynylphenyl]-tetramethylcalix[4]pyrrole (E)

In a Schlenk flask, compound **2** (36 mg, 0.030 mmol, 1 equiv.), compound **D** (57 mg, 0.18 mmol, 6 equiv.), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (2.1 mg, 0.003 mmol, 0.1 equiv.), and CuI (1.1 mg, 0.006 mmol, 0.2 equiv.) were kept for 30 minutes under high vacuum, then under argon atmosphere. Dry and degassed THF (5 ml) and DIPEA (5 ml) were added to the Schlenk flask. The resulting solution was stirred at 45 °C in an oil bath for 12 hours. After that, the reaction was stopped and the crude concentrated. The crude was dissolved in DCM (10 ml), and washed with a 0.5 M HCl solution (10 ml), brine (10 ml), and water (10 ml). The organic layer was dried over Na_2SO_4 , filtered, concentrated, and purified by chromatographic column (gradient from 1:1 then 8:2 DCM/hexane, dry loading), affording the desired product in 91% yield as a pale orange solid.

$^1\text{H-NMR}$ (500 MHz, CDCl_3 , 298 K): δ 7.65 (br s, 4H), 7.42 (d, 8H), 7.12 (d, 8H), 6.66 (dd, 8H), 6.43 (d, 4H), 3.98 (t, 16H), 3.60 (t, 16H), 1.99 (s, 12H), and 1.93 (m, 32H). $^{13}\text{C-NMR}$ (126 MHz, CDCl_3 , 298 K) δ 159.8, 148.3, 136.1, 131.1, 127.5, 124.6, 121.3, 110.0, 106.7, 102.7, 89.3, 88.8, 67.2, 53.4, 44.7, 29.3, 27.8, and 26.6; TLC: R_f = 0.37 (70:30 DCM/hexane).



Tetra-[1-ethynyl-3,5-dimethoxyphenyl]-tetramethylcalix[4]pyrrole (**4**)

Intermediate **E** (30 mg, 0.016 mmol, 1 equiv.) and NaCN (15 mg, 0.31 mmol, 20 equiv.) were dissolved in anhydrous DMF (5 ml), and stirred at 100 °C in an oil bath for 16 hours under argon atmosphere. The reaction was cooled down at room temperature, water (40 ml) was added, and the resulting solution was washed with DCM (2 x 15 ml). The organic was dried over Na₂SO₄, filtered, and the organic solvent removed under reduced pressure, affording an orange/pale yellow solid as a crude. The crude was purified on silica gel (9:1 DCM/hexane), affording 18.5 mg of the desired product 95% yield as a pale yellow solid.

¹H-NMR (500 MHz, CDCl₃, 298 K): δ 7.90 (br s, 4H), 7.42 (d, 8H), 7.09 (d, 8H), 6.67 (dd, 8H), 6.44 (d, 4H), 5.81 (s, 8H), and 3.77 (s, 24H). ¹³C-NMR (126 MHz, DMSO-d₆, 298 K) δ 160.2, 150.6, 136.7, 131.3, 127.2, 123.5, 120.2, 108.8, 105.3, 101.9, 89.4, 88.6, 55.2, 44.2, and 13.9; HRMS (MALDI/ESI): Exact mass calculated for C₈₈H₇₆N₄O₈Na⁺ [M+Na]⁺ 1339.5561, found 1339.5560 TLC: R_f = 0.47 (100% DCM).

3. Products Characterization

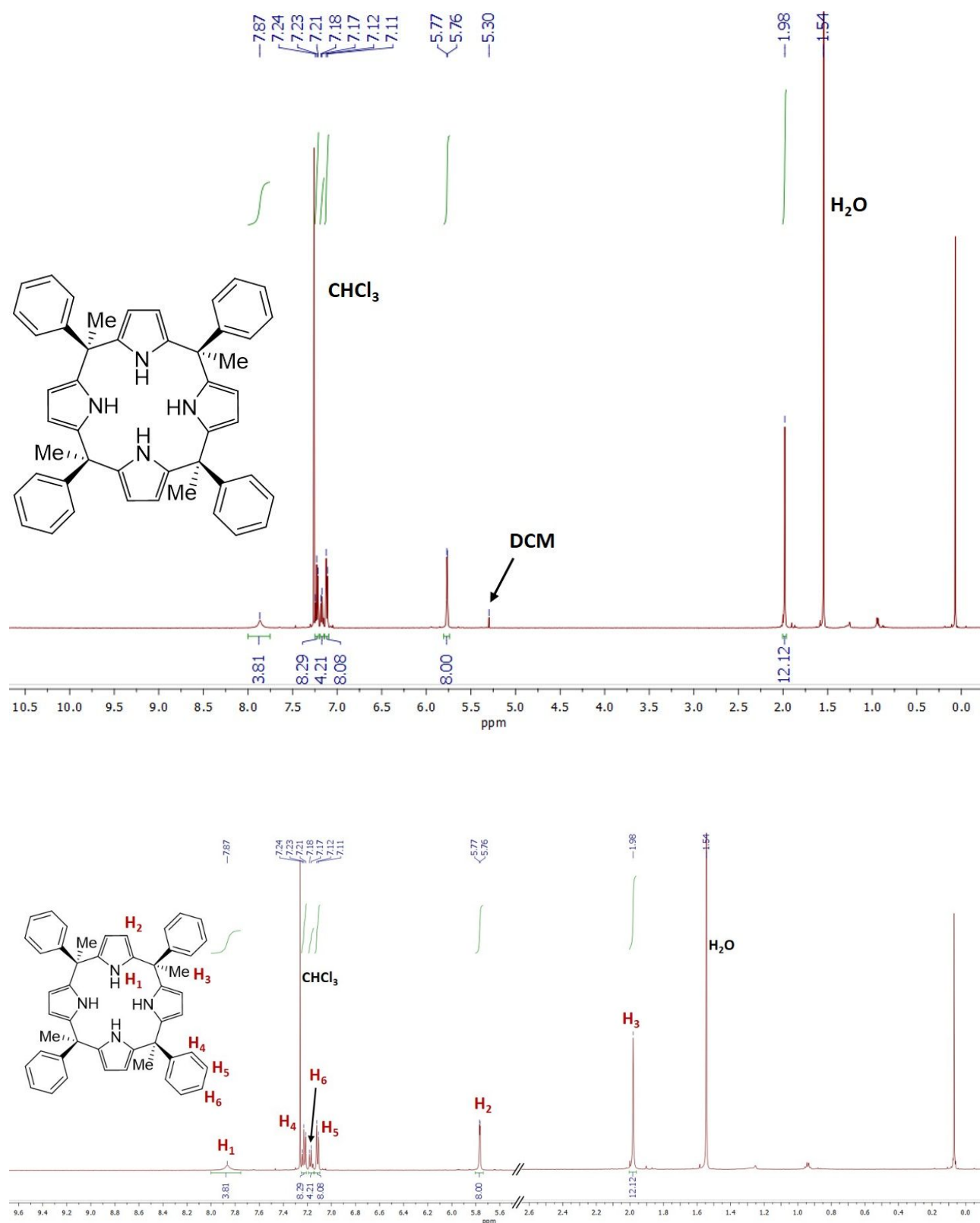


Figure S1. Full (top) and cropped (bottom) ^1H NMR spectrum (500 MHz, CDCl_3 , 298 K) of Host **1**.

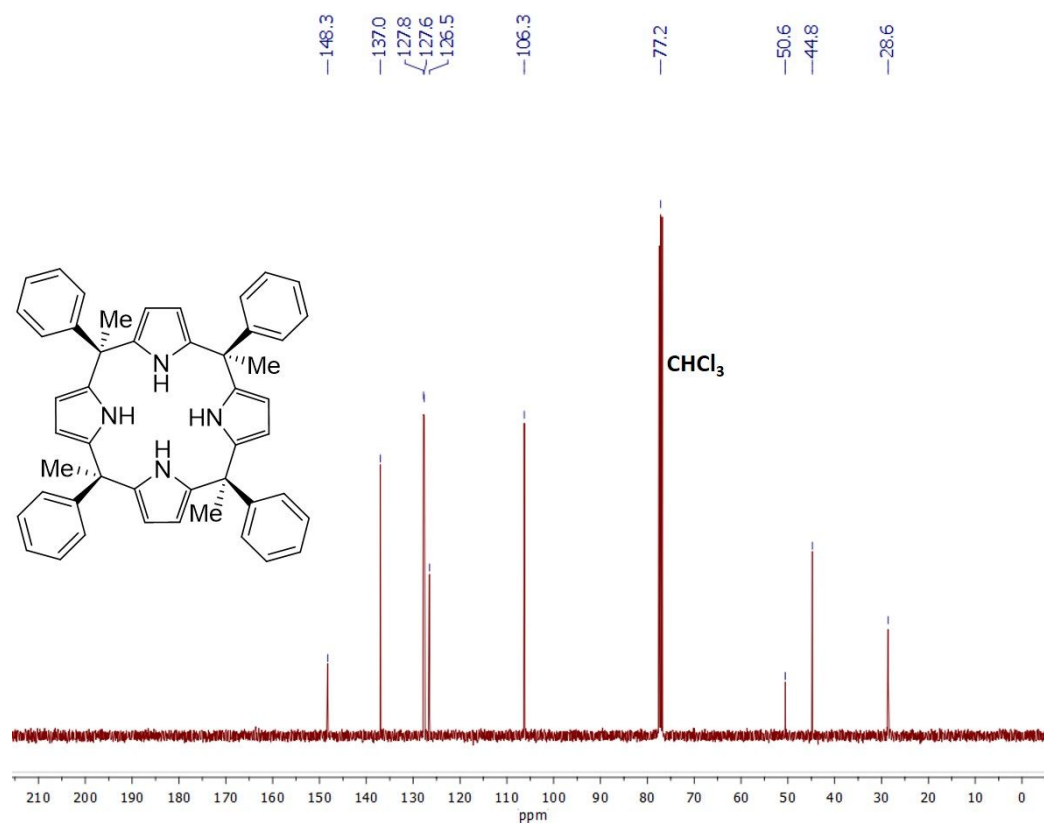


Figure S2. ^{13}C NMR spectrum (126 MHz, CDCl_3 , 298 K) of Host **1**.

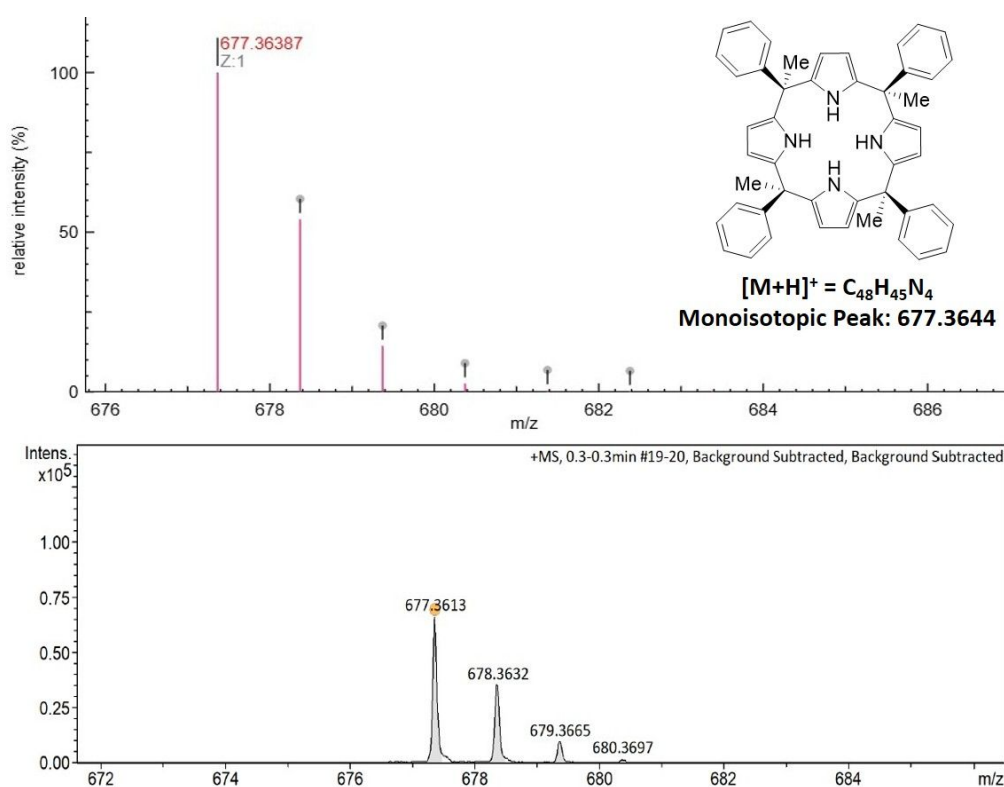


Figure S3. Theoretical (top) and experimental (bottom) HRMS of Host **1**. Information of the charged species observed and relative monoisotopic peak are reported for better clarity.

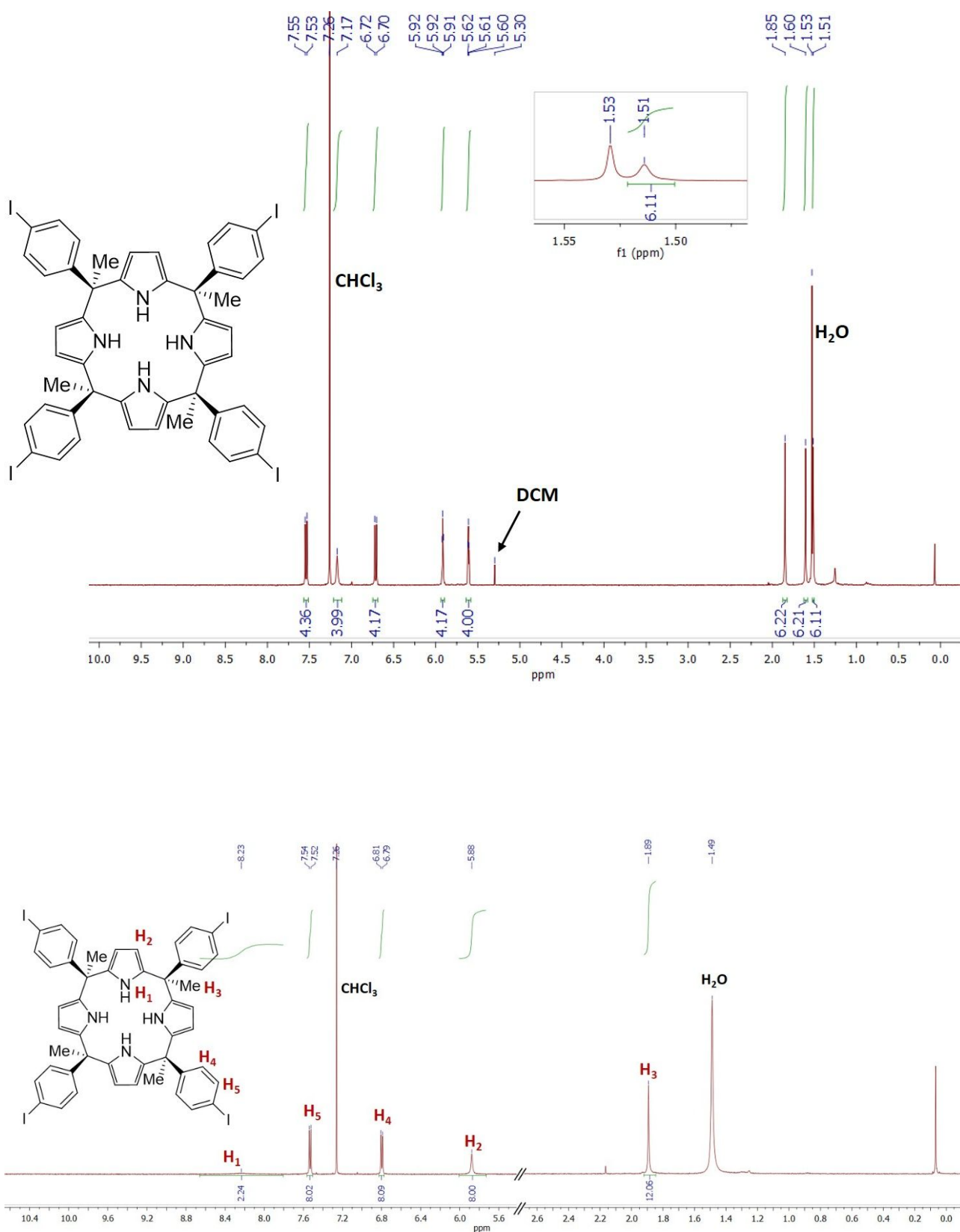


Figure S4. Full (top) and cropped (bottom) ¹H NMR spectrum (500 MHz, CDCl₃, 298 K) of Host **2**.

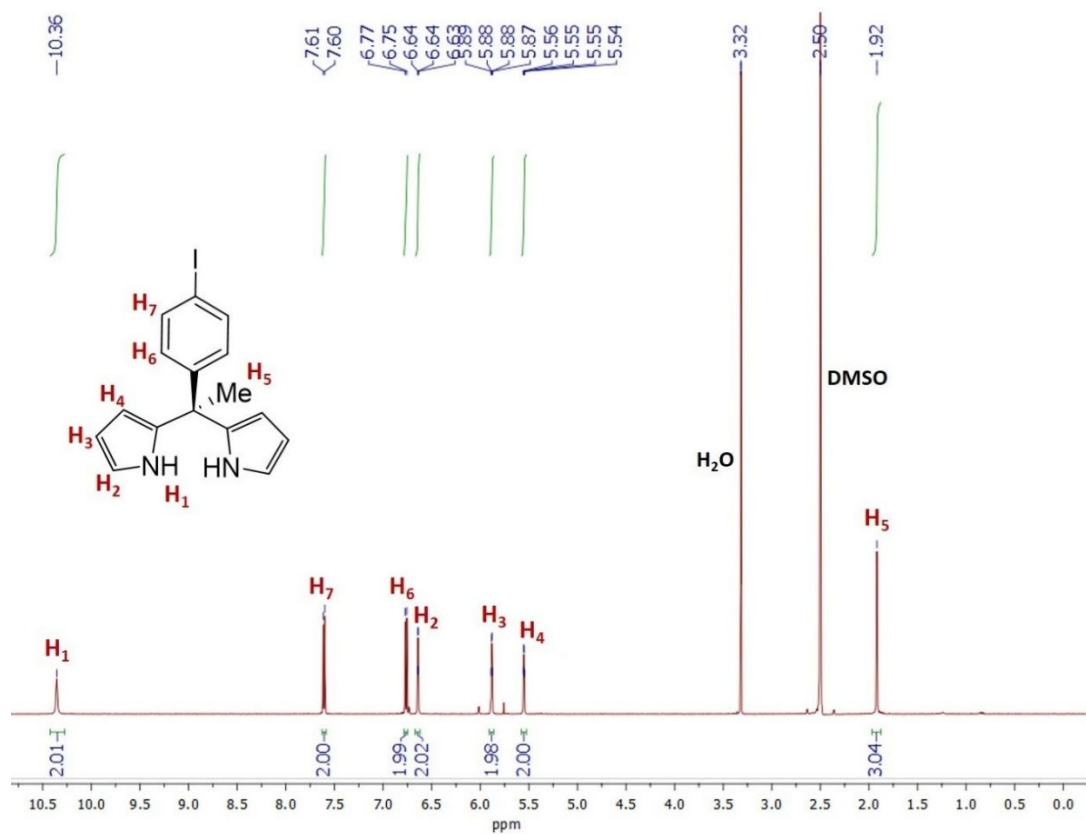


Figure S5. ¹H NMR spectrum (500 MHz, DMSO-d₆, 298 K) of Intermediate A.

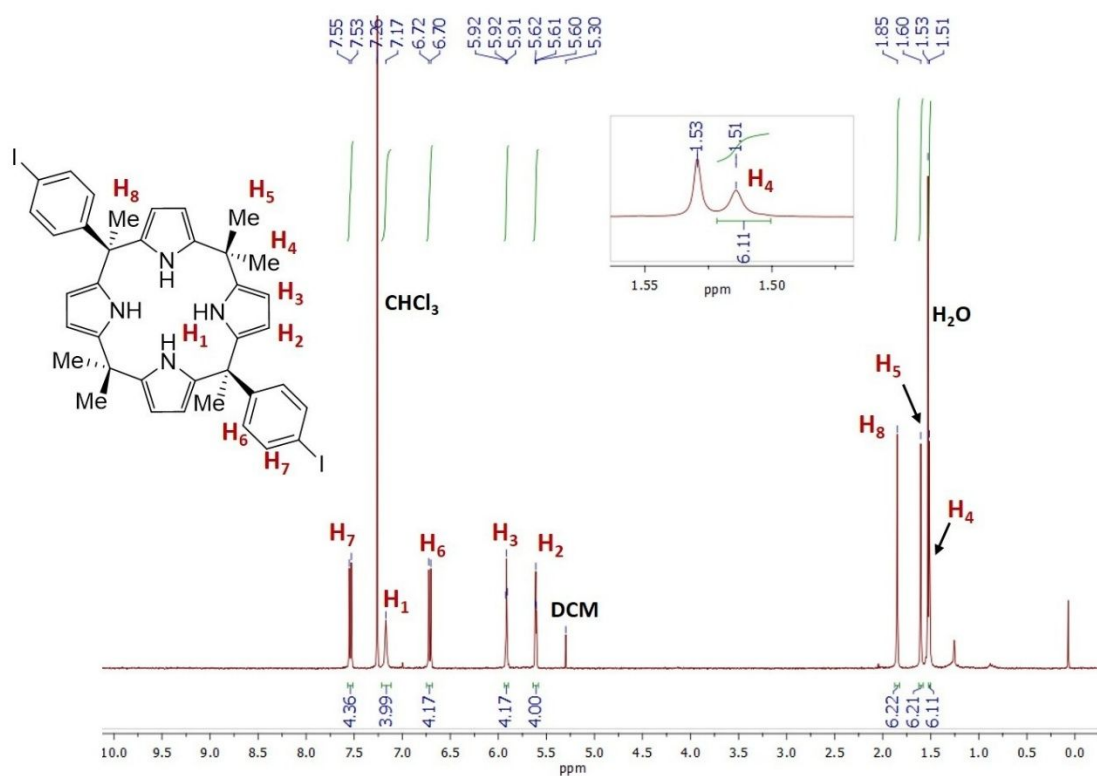


Figure S6. ¹H NMR spectrum (500 MHz, CDCl₃, 298 K) of Host 3.

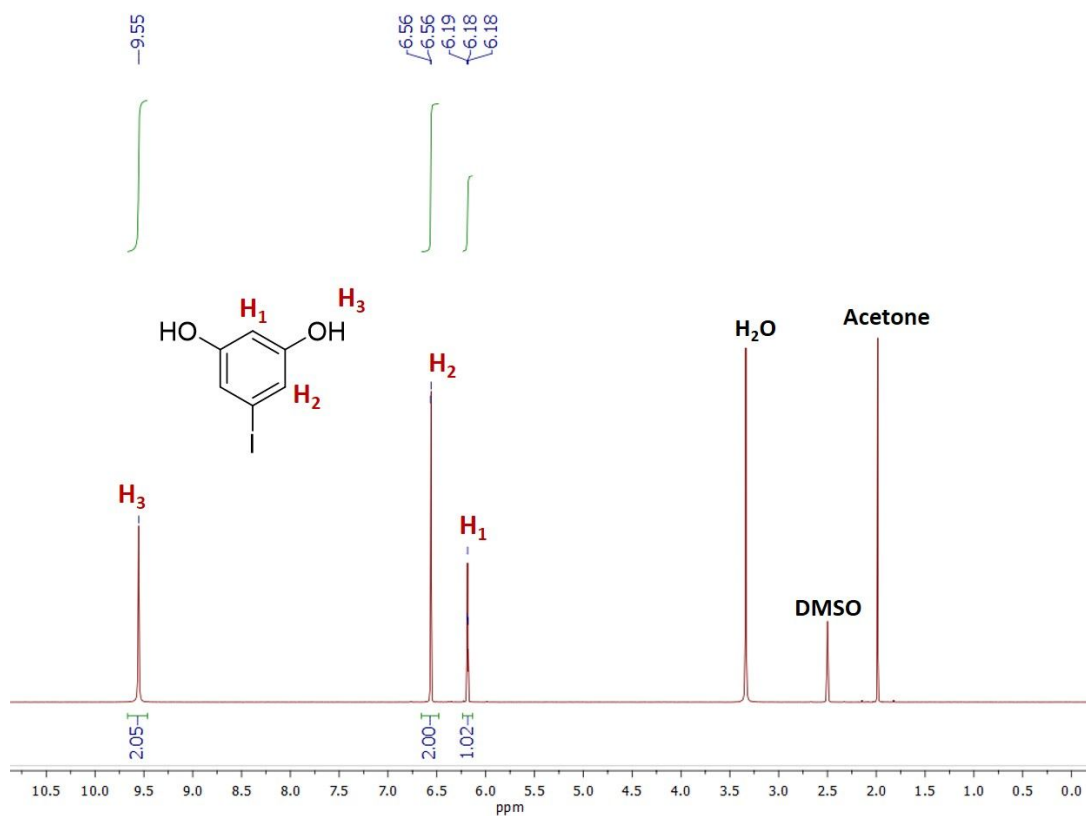


Figure S7. ¹H NMR spectrum (500 MHz, DMSO-d₆, 298 K) of Intermediate B.

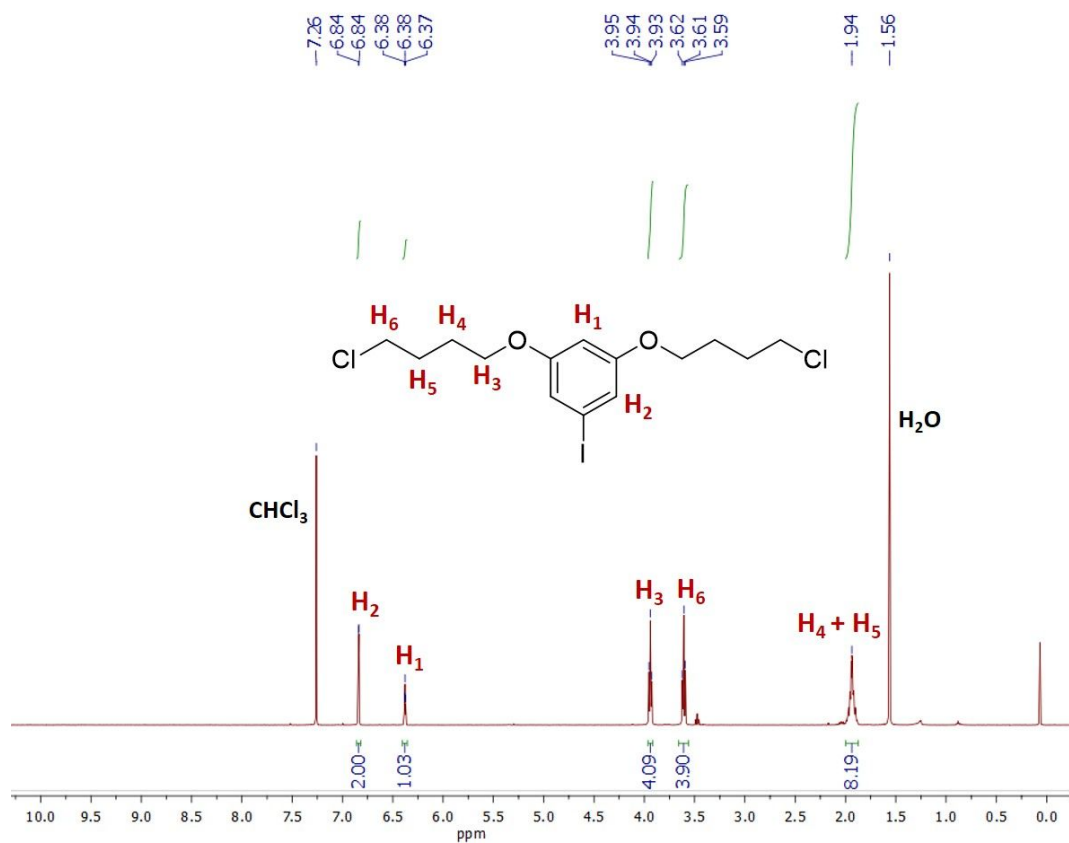


Figure S8. ¹H NMR spectrum (500 MHz, CDCl₃, 298 K) of Intermediate C.

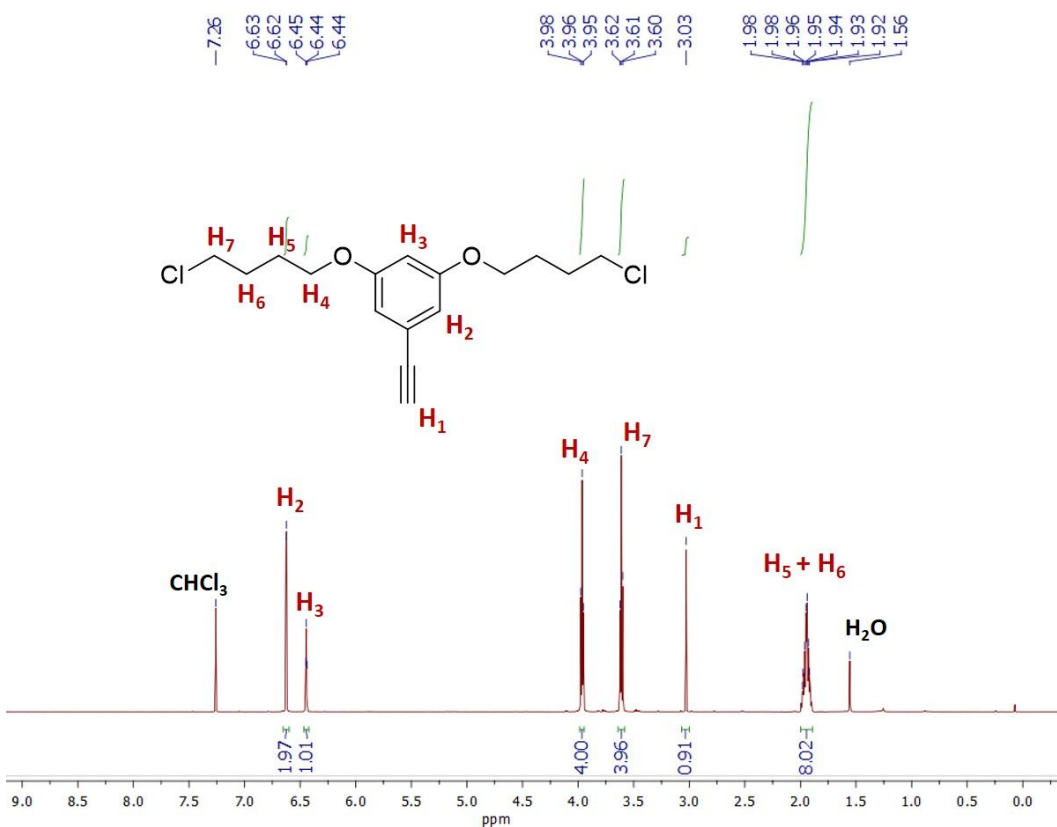


Figure S9. ^1H NMR spectrum (500 MHz, CDCl_3 , 298 K) of Intermediate D.

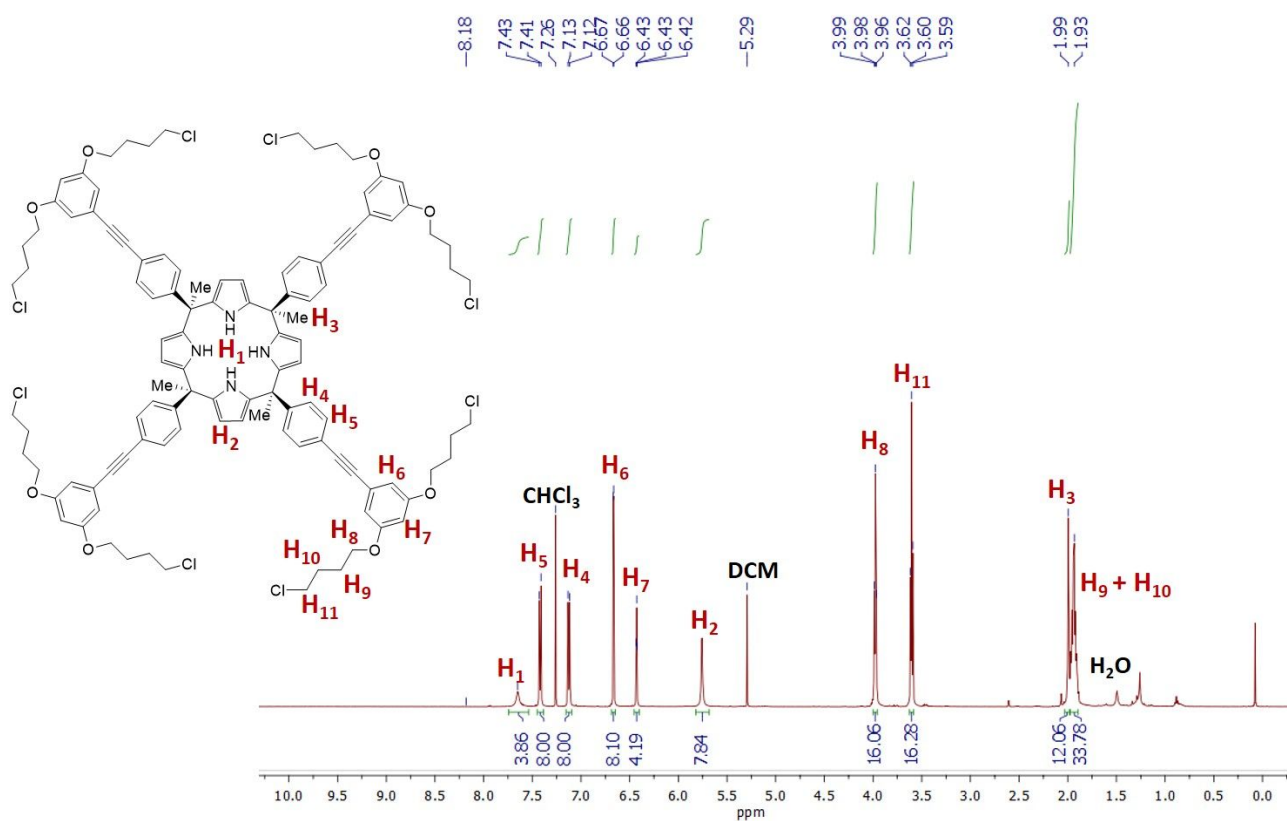


Figure S10. ^1H NMR spectrum (500 MHz, CDCl_3 , 298 K) of Intermediate E.

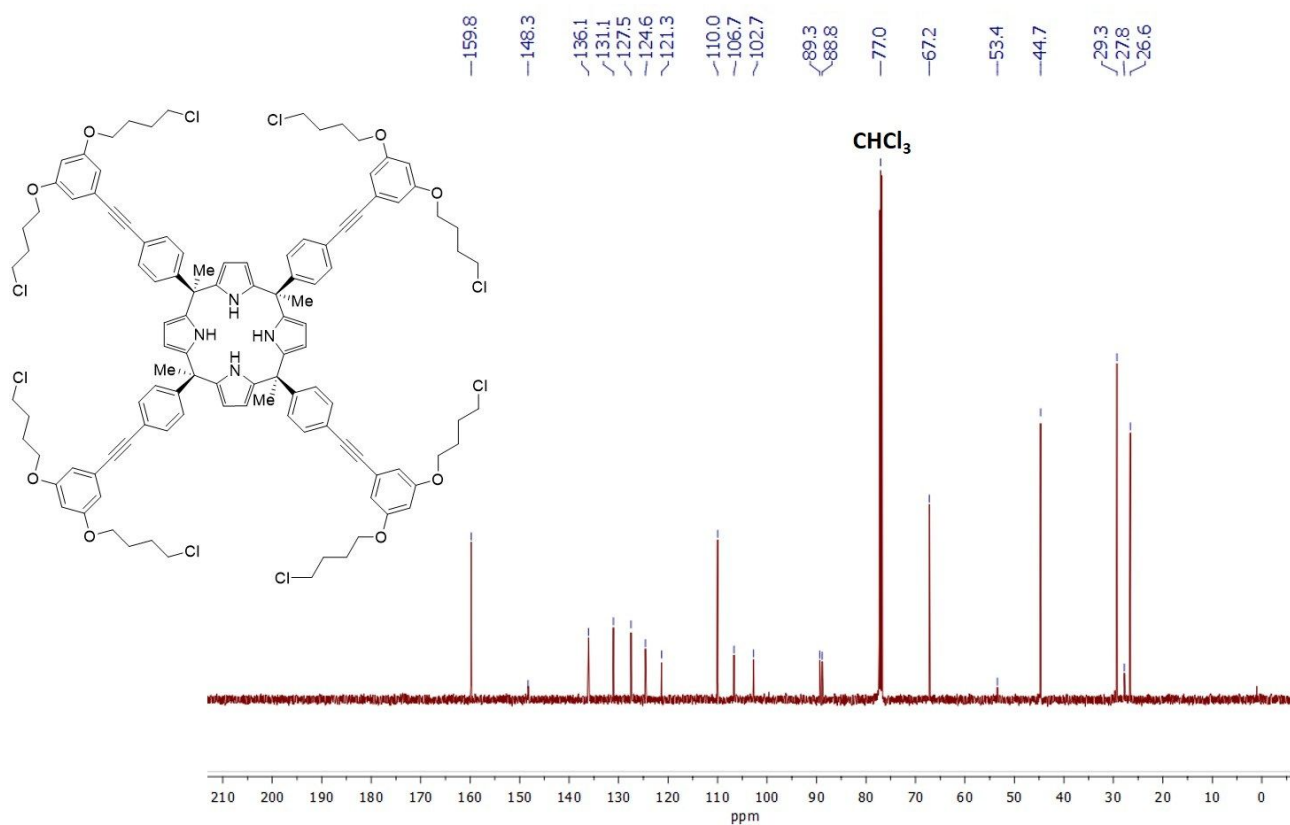


Figure S11. ¹³C NMR spectrum (126 MHz, CDCl₃, 298 K) of Intermediate E.

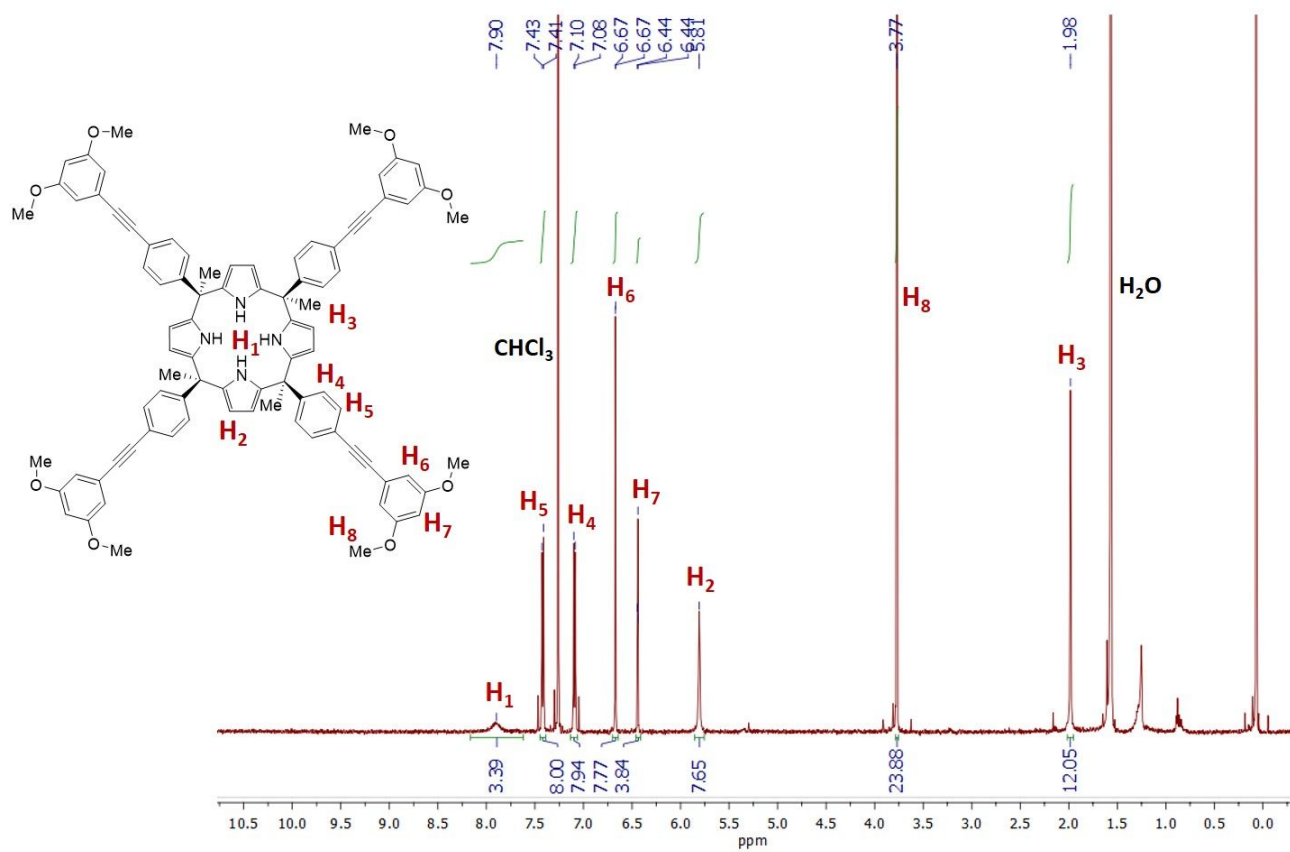


Figure S12. ¹H NMR spectrum (500 MHz, CDCl₃, 298 K) of Host 4.

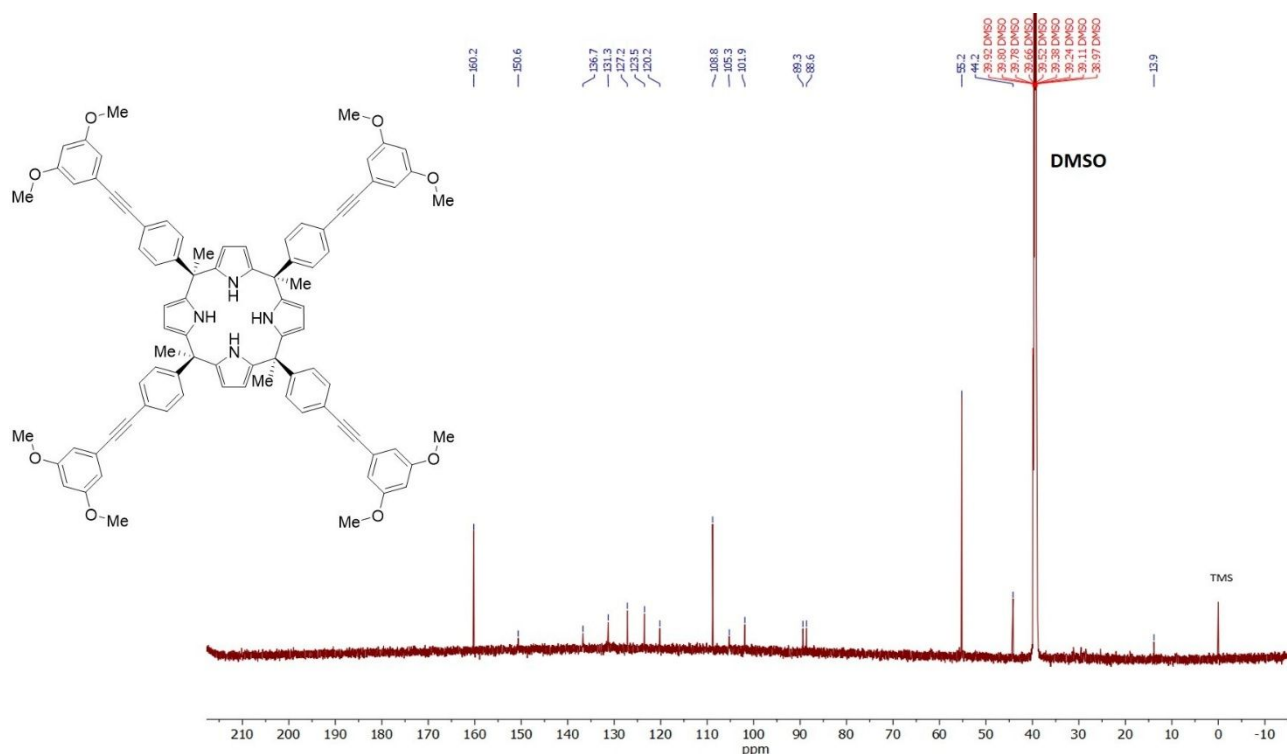


Figure S13. ^{13}C NMR spectrum (126 MHz, DMSO-d_6 , 298 K) of Host **4**. DMSO-d_6 was used as a solvent due to the relatively low solubility of **4** in CDCl_3 .

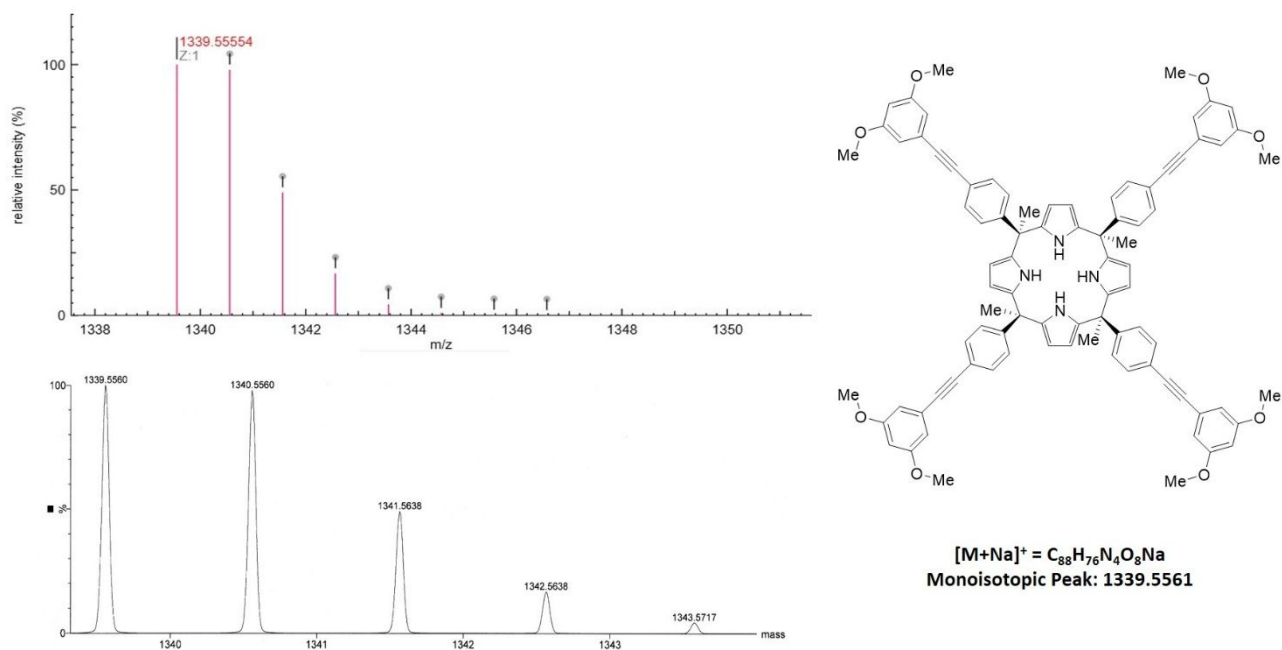
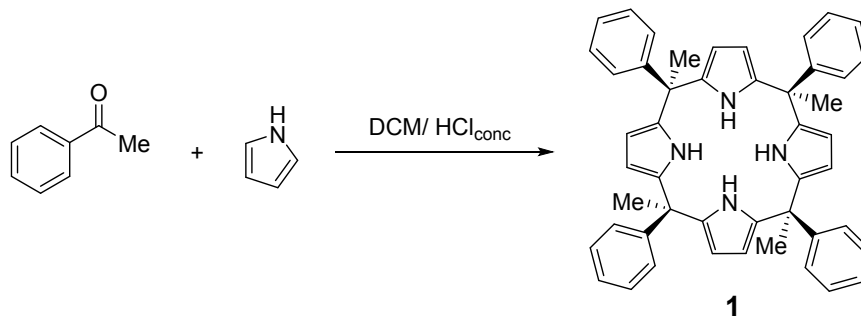
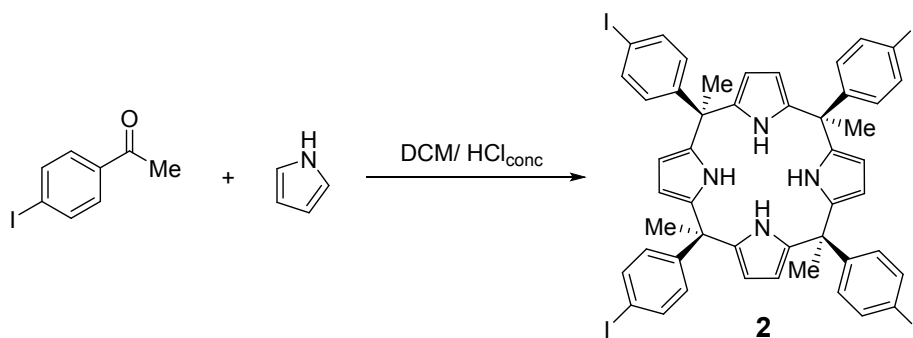


Figure S14. Theoretical (top) and experimental (bottom) HRMS of Host **4**. Information of the charged species observed and relative monoisotopic peak are reported for better clarity.

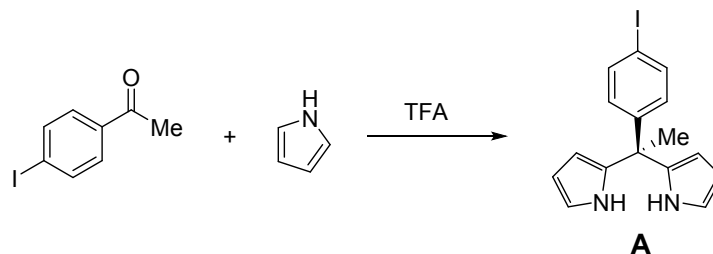
4. Synthetic Schemes & Equilibria



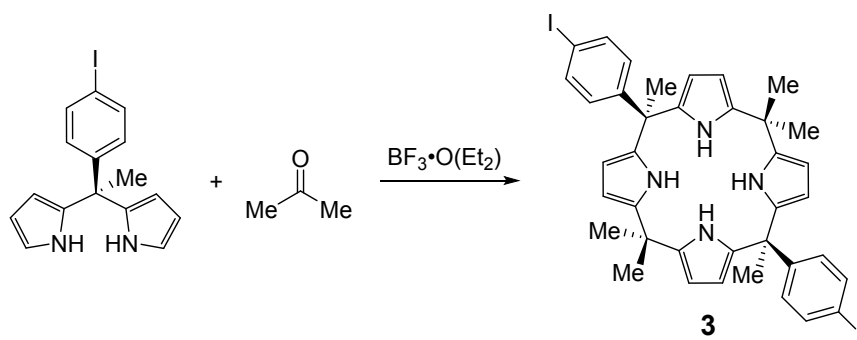
Scheme S1. Synthetic protocol for the synthesis of Host **1**.



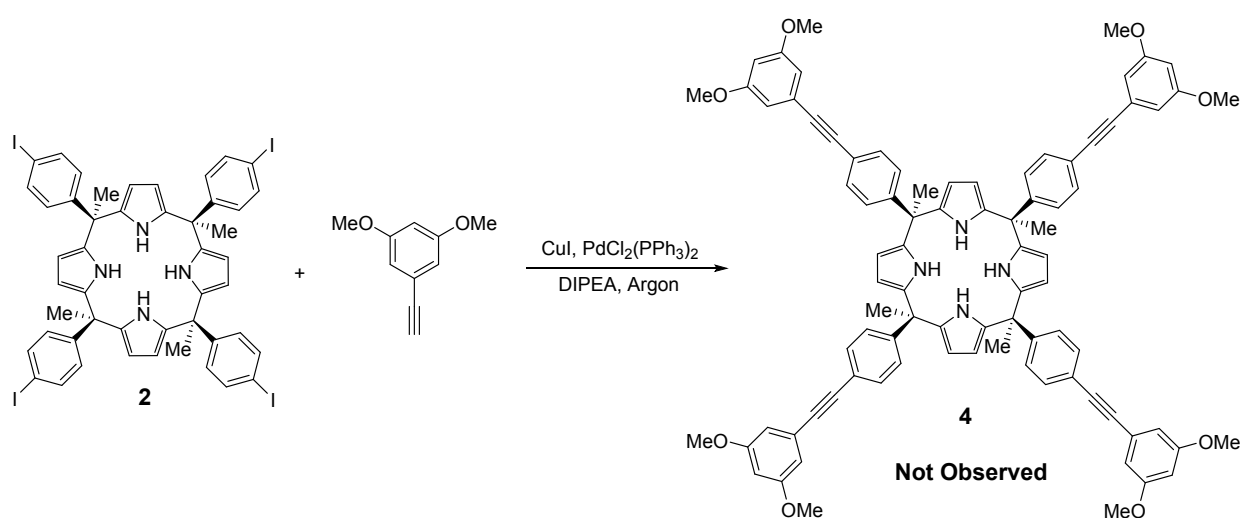
Scheme S2. Synthetic protocol for the synthesis of Host **2**.



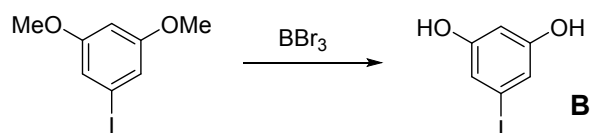
Scheme S3. Synthetic protocol for the synthesis of dipyrromethane intermediate **A**.



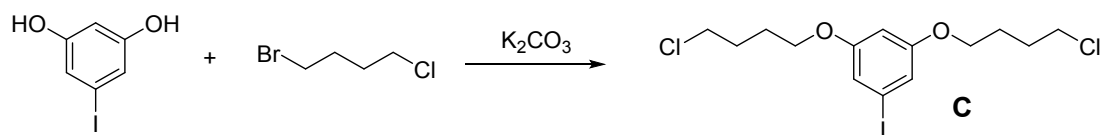
Scheme S4. Synthetic protocol for the synthesis of Host **3**.



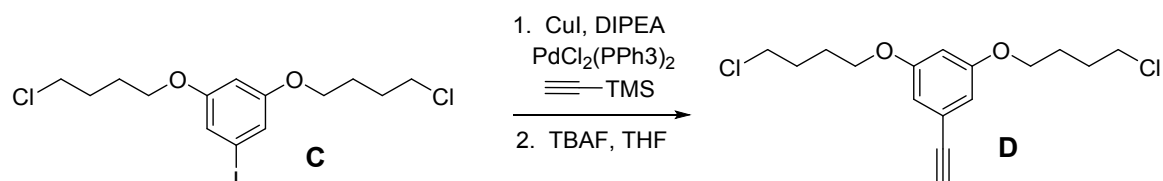
Scheme S5. Direct synthetic protocol for the synthesis of Host **4** through Sonogashira coupling between Host **2** and 1-ethynyl-3,5-dimethoxybenzene. No desired product (**4**) was detected following this procedure, due to the low solubility of the acetylene derivative and relative intermediates, which did not allow the tetra-functionalization of **2**.



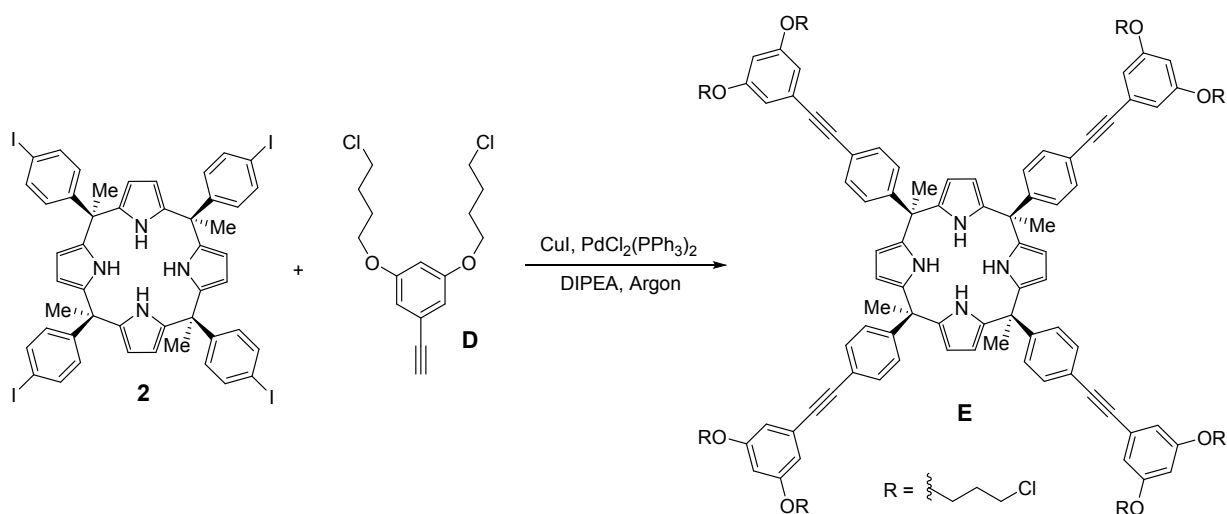
Scheme S6. Synthetic protocol for the synthesis of Intermediate **B**.



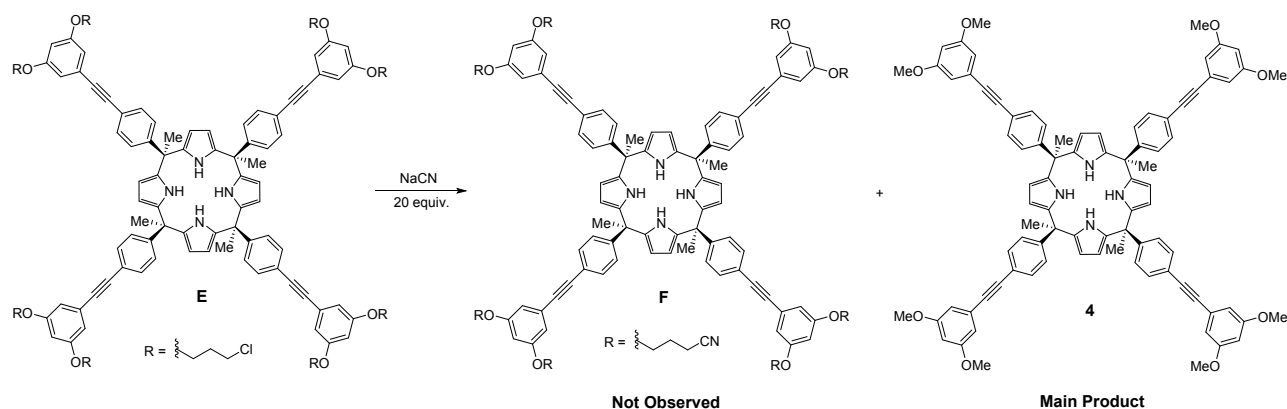
Scheme S7. Synthetic protocol for the synthesis of Intermediate **C**.



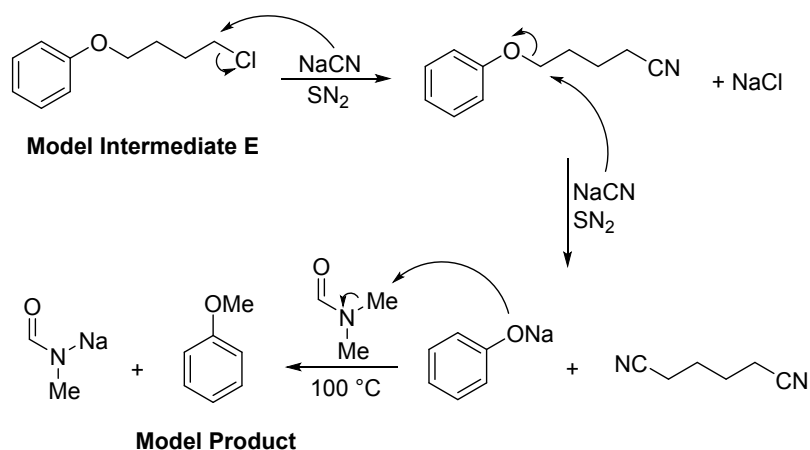
Scheme S8. Synthetic protocol for the synthesis of Intermediate **D**.



Scheme S9. Synthetic protocol for the synthesis of Intermediate **E**.



Scheme S10. Synthetic protocol for the synthesis of Host **4** from Intermediate **E** using a large excess of NaCN (20 equiv.).



Scheme S11. Proposed mechanism for the formation of model Host **4** from a model intermediate **E** at 100 °C under large excess of NaCN (20 equiv.).

The use of Intermediate **E** to synthesize Host **4** via subsequent nucleophilic substitutions in the presence of NaCN was hypothesized based on the use of ethyl nitrile groups ($-\text{CH}_2-\text{CH}_2-\text{CN}$) in the literature as protecting groups for oxygen-based nucleophile, such as phosphate derivatives.^[64] Another reason to select Intermediate **E** as initial building block is because it is a known product in our lab, with a well-optimized protocol already established for its synthesis.

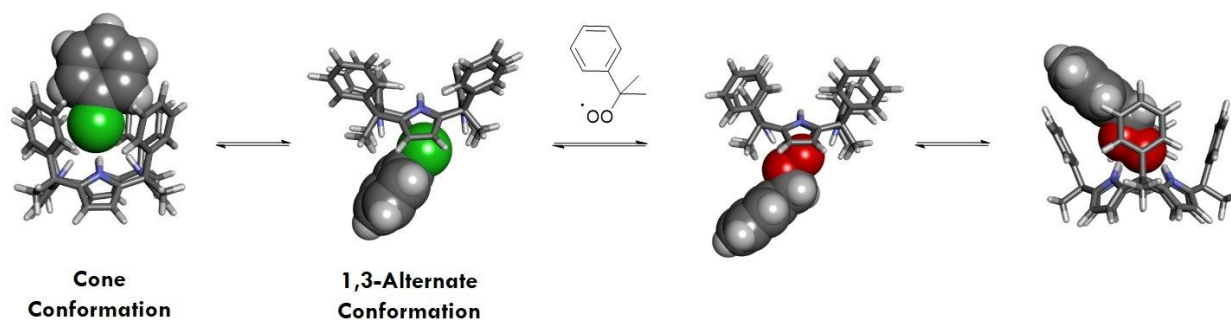


Figure S15. General equilibria for host **1** in chlorobenzene (PhCl) in the presence of cumylperoxyl radical (CumOO•).

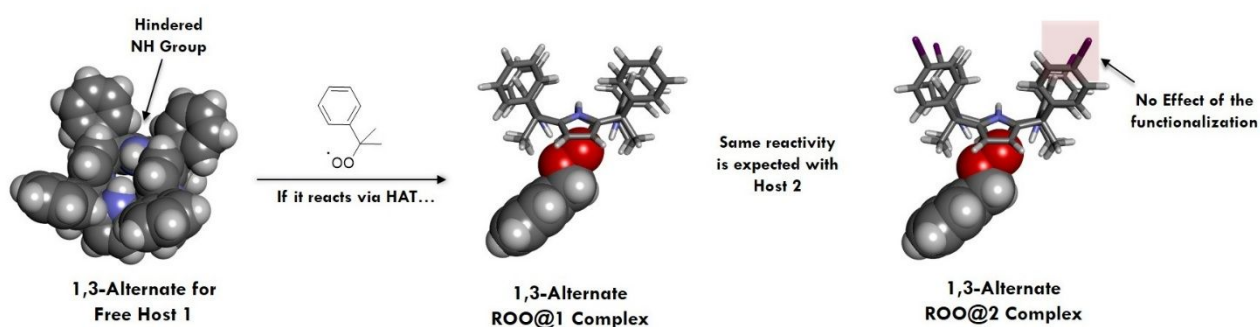


Figure S16. Optimized structures at DFT level of theory, representing the host-guest (HG) complex between cumylperoxyl radical and host **1** (left) and host **2** (right) in the 1,3-alternate conformation. Structural differences between **1** and **2** (iodine atom in *para*-position) are squared in red to highlight the distance of the added group from the binding site, suggesting no effect on the binding event.

5. Antioxidant Response & Radical Kinetics

Measurement of the reactivity with peroxy radicals

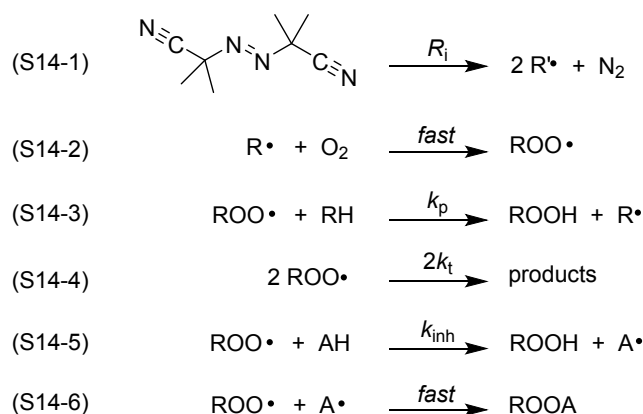
The reactivity of calix[4]pyrroles and reference compounds with transient peroxy radicals ($\text{ROO}\cdot$) was investigated by studying the controlled inhibited autoxidation of cumene as reference substrate (RH).^[65-68] The testing equipment is a differential oxygen uptake apparatus built in our lab,^[64] comprising two identical reaction vessels (6 mL) held in a thermostatic bath set at 30°C. Both the sample and reference flasks are attached to the opposite sides of a differential pressure sensor (based on a variable reluctance membrane) through PEEK (or stainless steel) high performance liquid chromatography (HPLC) tubes. The equilibration and isolation of the two channels is achieved through a three-way valve, which is connected to the outer environment and the two channels. The two reaction vessels are continuously stirred by submersible magnetic stirrers to ensure oxygen equilibration between the air in the head space and solutions, within each vial. Monitoring of oxygen consumption is achieved by continuous recording of the pressure difference between the reaction vessel and the reference.

In a typical experiment, 2 mL of AIBN (25 mM to 200 mM) in the desired solvent 2 mL of cumene, are transferred in both vessels, while an excess of an excellent antioxidant (0.5 mM PMHC) is added only into the reference vessel to block any autoxidation. After thermal equilibration the two channels are isolated from the environment and the pressure difference between the channels reveals oxygen consumption only in the reaction vessel. If needed a stock solution of the inhibitor to be tested is injected in the sample vessel via a sealed glass tap prior (to achieve low micromolar concentration in the reaction vessel) prior to monitoring the pressure difference. The rate constant of quenching peroxy radicals by the tested inhibitor (Eq. S14-5 in Scheme S14) is obtained via eq. 1 where R_{inh} and R_0 are respectively the rate of oxygen consumption recorded in the presence of the tested inhibitor and the rate of oxygen consumption in a reference autoxidation in the absence of the inhibitor.

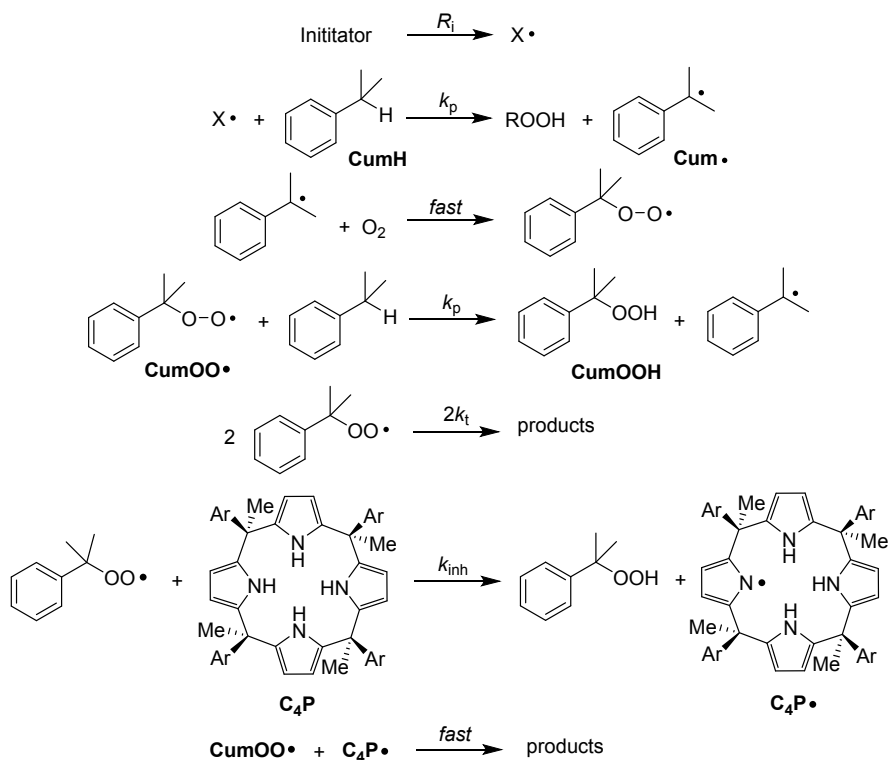
The rate of initiation (R_i) due to the thermal decomposition of AIBN is calculated from a preliminary set of experiments using 2,2,5,7,8-pentamethyl-6-chromanol as a reference antioxidant also in the reaction vessel albeit at low micromolar concentration. Since PMHC produces a neat inhibition period of length τ and its stoichiometric factor n (the number of trapped peroxy radical per molecule of inhibitor) is known as $n = 2$, from the length of the inhibition period, R_i can be obtained by equation 2. The same equation is then used to determine the stoichiometric coefficient n of the investigated inhibitors.^[65,66-69] The rate constants describing cumene autoxidation at 30°C ($k_p = 0.34 \text{ M}^{-1}\text{S}^{-1}$; $2k_t = 4.5 \times 10^4 \text{ M}^{-1}\text{S}^{-1}$) are available from the literature.^[68-69]

$$\frac{R_0}{R_{inh}} - \frac{R_{inh}}{R_0} = \frac{nk_{inh}[AH]k_p}{\sqrt{nk_{inh}R_i}} \quad (1)$$

$$n = \frac{R_i \tau}{[AH]} \quad (2)$$



Scheme S14. Simplified reaction scheme describing the autoxidation of a substrate RH initiated by the thermal decomposition of AIBN as the source of radicals, and inhibited by a chain-breaking antioxidant AH. ^[65-69]



Scheme S15. Reaction scheme describing the initiated autoxidation of cumene, ^[65-69] and its inhibition by C₄P.

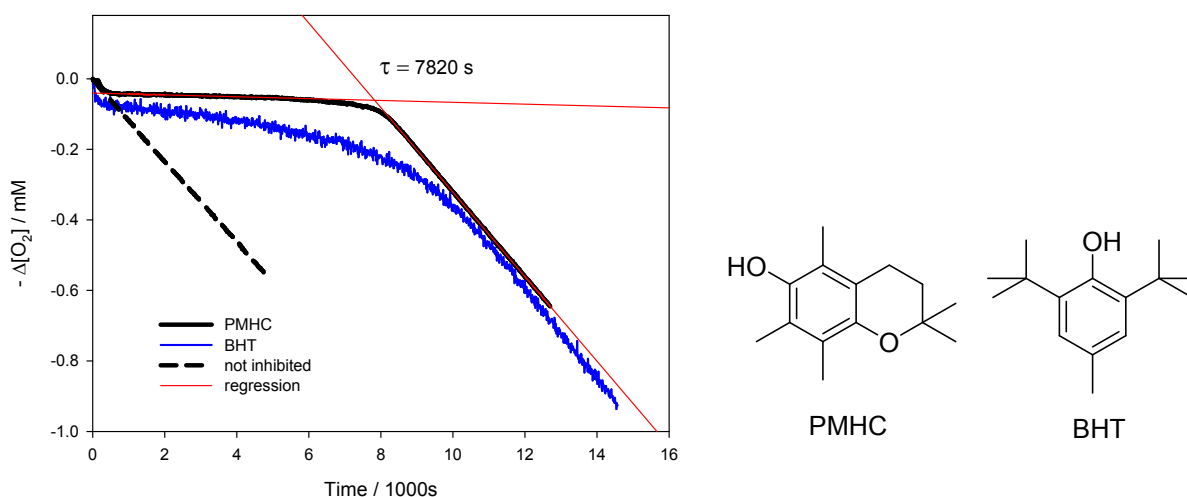


Figure S17. Oxygen uptake plot during the autoxidation of 3.6 M cumene in chlorobenzene initiated by 12.5 mM AIBN at 30°C, in the absence of inhibitors (dashed line) or in the presence of 5 μM PMHC or 5 μM BHT, as indicated in the legend. The duration of inhibited period τ is indicated as the crosspoint between inhibited and uninhibited regression lines.

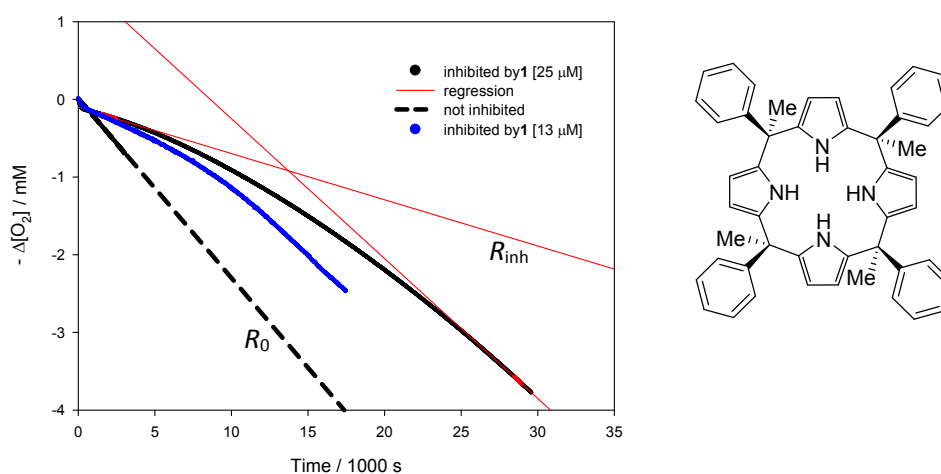


Figure S18. Oxygen uptake plot during the autoxidation of 3.6 M cumene in PhCl initiated by 12.5 mM AIBN at 30°C, in the absence of inhibitors (dashed line) and in the presence of 13 or 25 μM **1**.

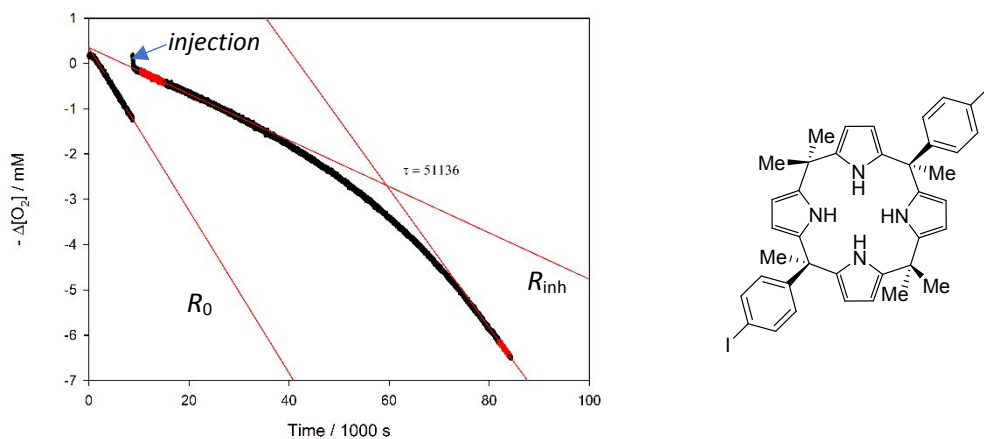


Figure S19. Oxygen uptake plot during the autoxidation of 3.6 M cumene in chlorobenzene initiated by 12.5 mM AIBN at 30°C, in the absence of inhibitors (R_0) and upon injection of 25 μM **3**.

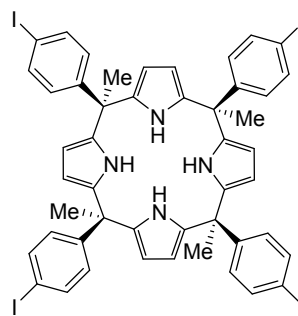
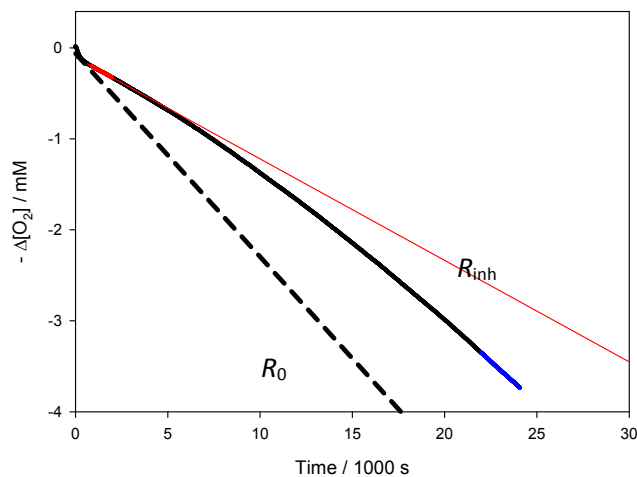


Figure S20. Oxygen uptake plot during the autoxidation of 3.6 M cumene in chlorobenzene initiated by 12.5 mM AIBN at 30°C, in the absence of inhibitors (R_0 , dashed line) and upon injection of 25 μM **2**.

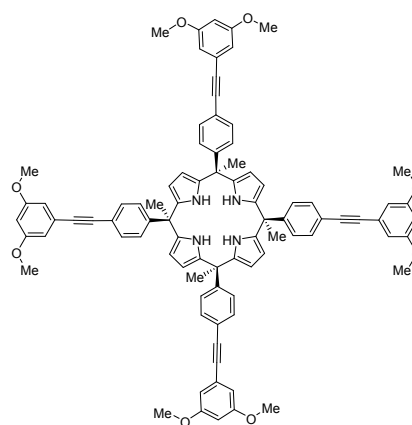
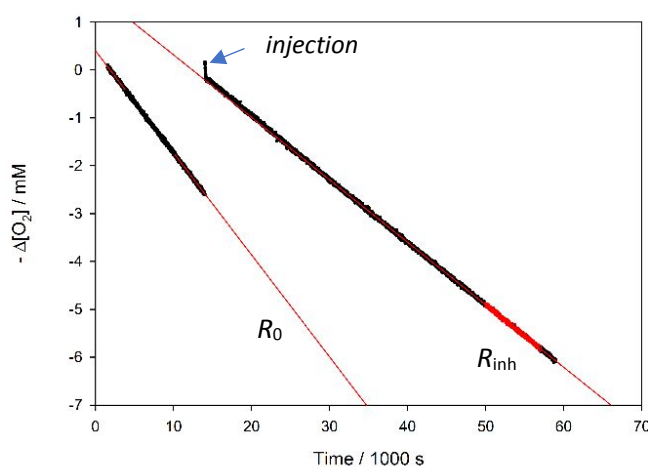


Figure S21. Oxygen uptake plot during the autoxidation of 3.6 M cumene in chlorobenzene initiated by 12.5 mM AIBN at 30°C, in the absence of inhibitors (R_0) and upon injection of 25 μM **4**.

6. Stability & Binding Studies

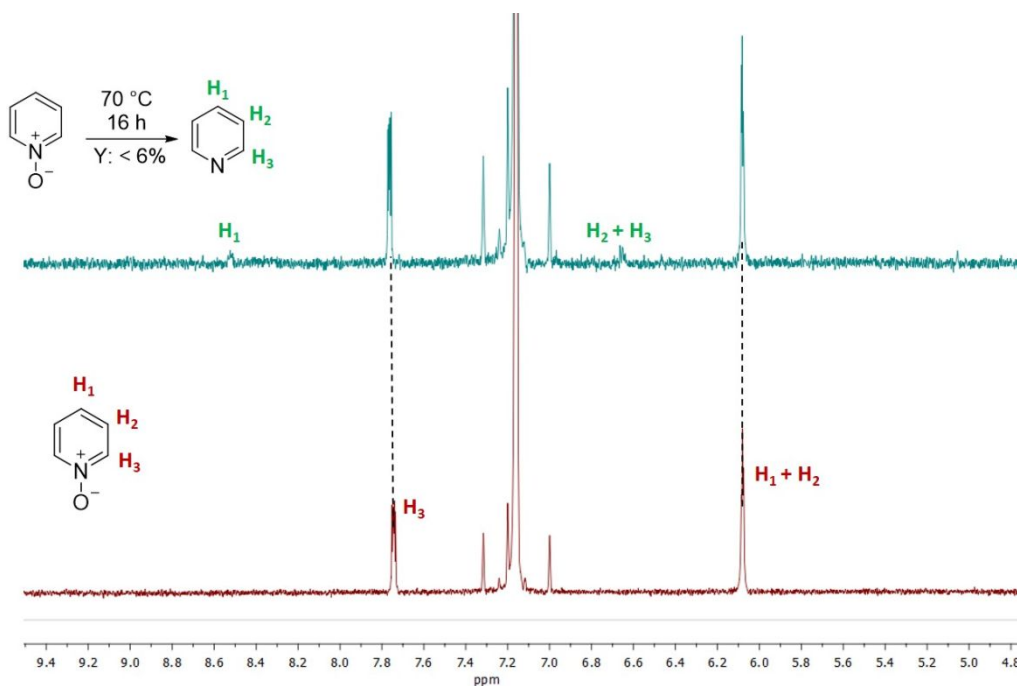


Figure S22. Partial ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of 1 mM PNO solution (bottom) and after 16 hours at 70 °C (top). Pyridine (< 6%) is observed due to the thermal decomposition of PNO.

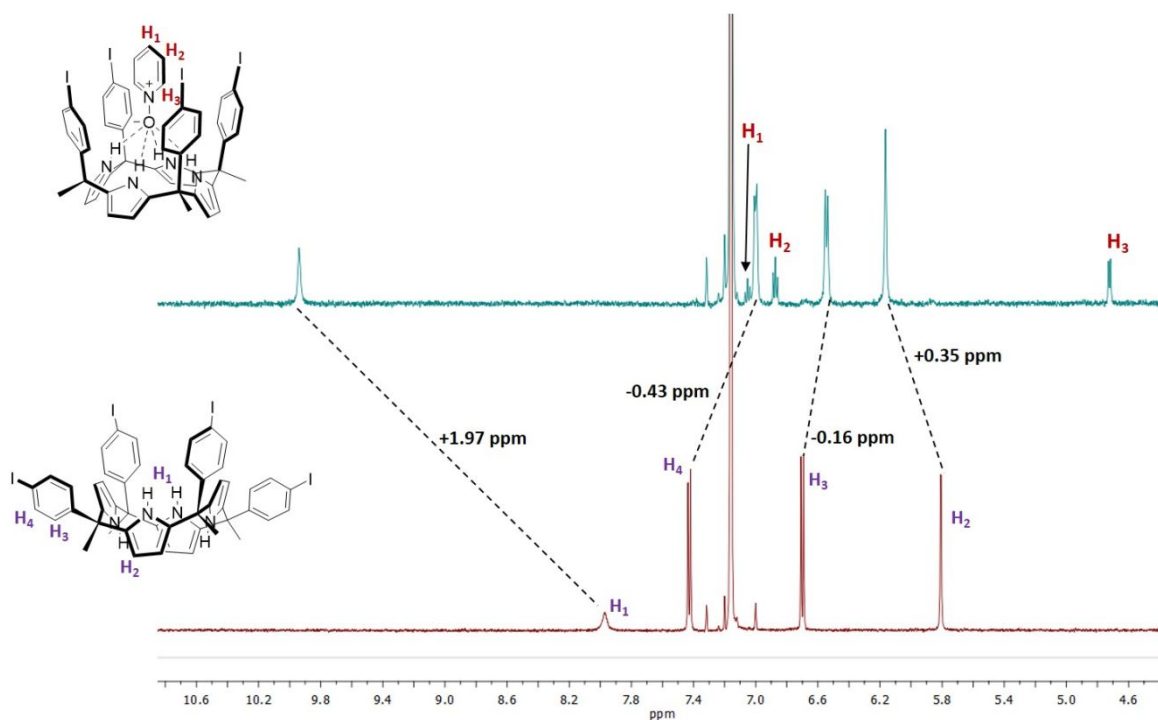


Figure S23. Partial ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of 1 mM solution of host **2** (bottom), and after the addition of 1 equivalent of PNO (top). Free Host **2**'s and bound PNO's signals are marked in purple and dark red, respectively. Chemical shifts changes are reported in ppm and highlighted by a black dashed line.

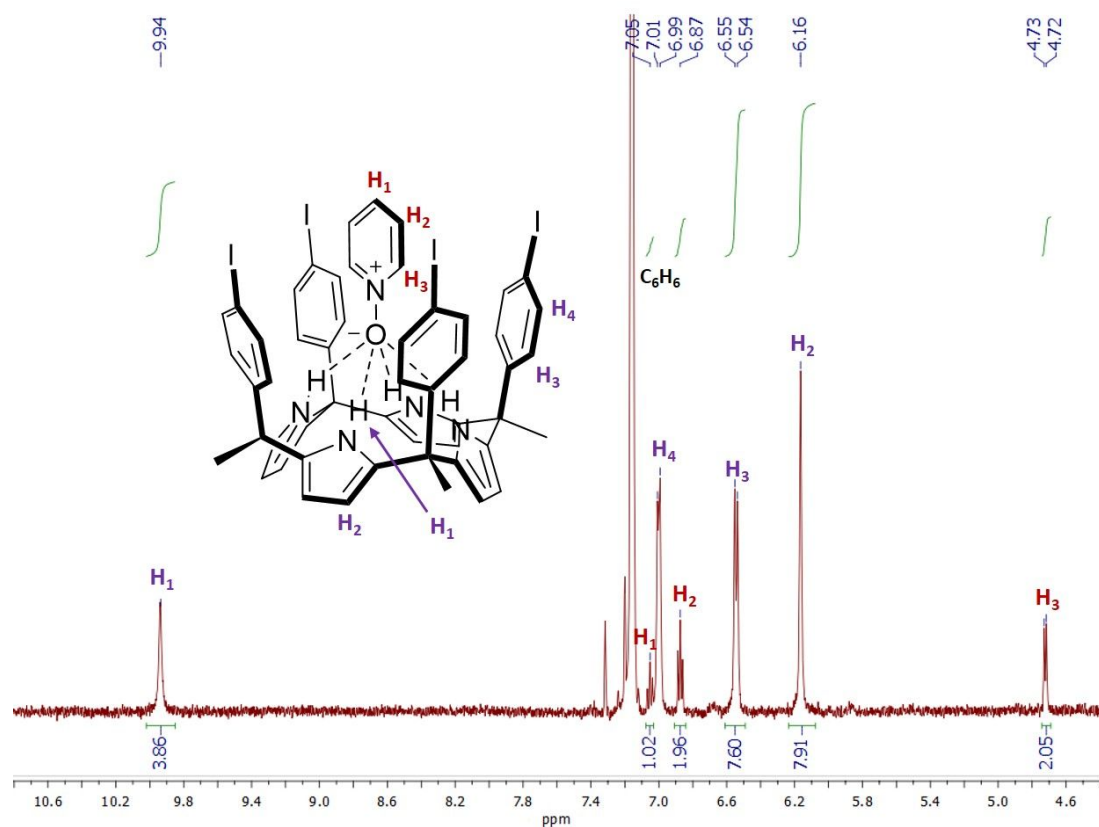


Figure S24. Partial ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of the HG complex (1:1) between **2** and PNO. NMR integrations of the PNO and host **2**'s signals confirmed 1:1 complex.

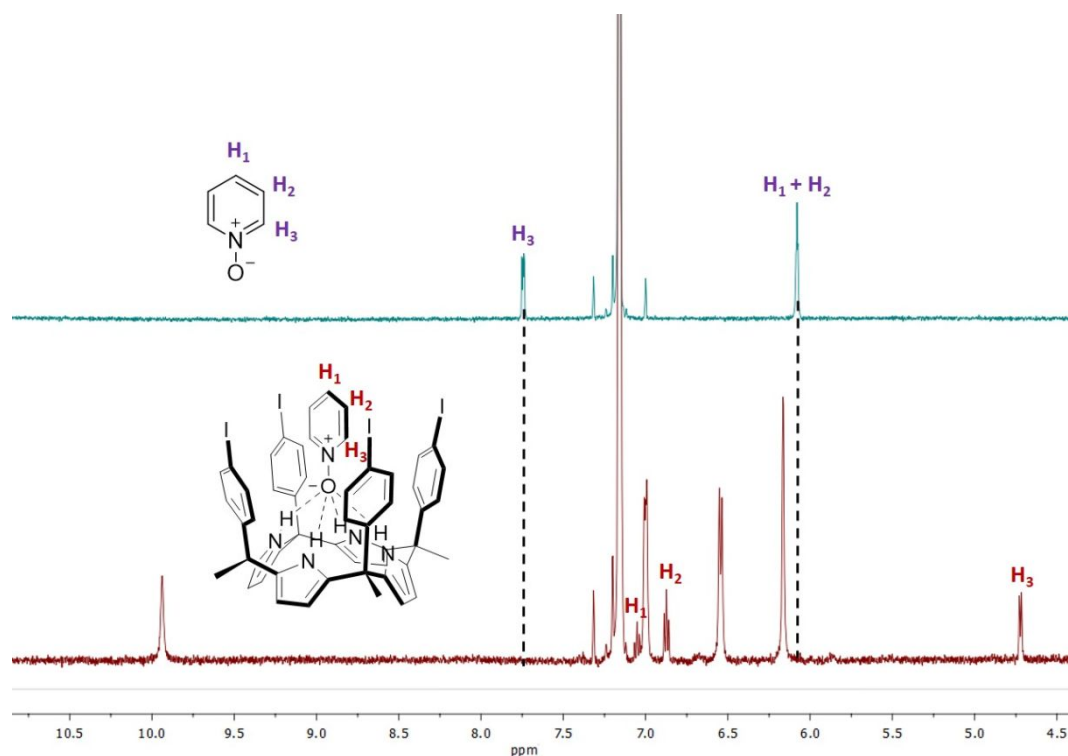


Figure S25. Partial ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of the host-guest complex (1:1) between **2** (1 mM) and 1 equiv. of PNO (bottom), and free PNO in bulk solution (top). No free guest was detected, confirming a K_a value higher than $1 \times 10^4 \text{ M}^{-1}$.

Table S1. $-\Delta\delta$ (ppm) calculation for PNO@**2** complex reported in Figure S23.

Hydrogen	δ in C_6D_6 (ppm)	δ in Host 2 / C_6D_6 (ppm)	$-\Delta\delta$ (ppm)
H ₁	7.74	4.72	3.02
H ₂	6.08	6.54	-0.46
H ₃	6.08	7.05	-0.97

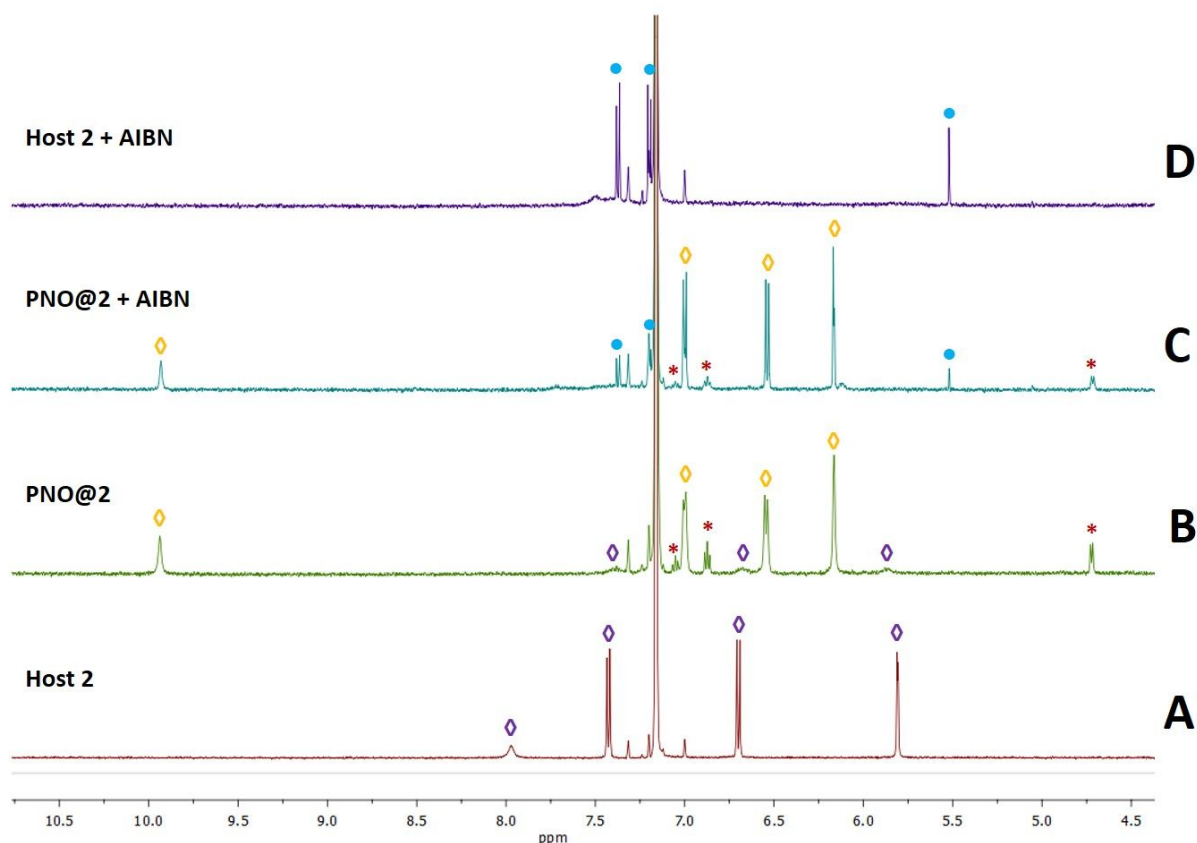


Figure S26. Partial 1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of a 1mM solution of: (A) free host **2**, (B) host-guest complex (1:1:1) between **2** and PNO, (C) HG complex (PNO@**2**) in the presence of **2** equiv. of AIBN after 12 hours at 70 °C, and (D) free host **2** in the presence of **2** equiv. of AIBN after 12 hours at 70 °C. Free host **2** is marked with purple diamonds while bound **2** with yellow diamonds. Bound PNO in PNO@**2** is marked with red stars, while the “product”, derived by the reaction of free **2** with AIBN, is marked with sky-blue circles.

A slightly excess of **2** (1.1:1 host:guest ratio) was intentionally used during the stability test to emphasize the different reactivity of **2** when involved in the formation of HG complexes. Free **2** can readily react with radical species from AIBN via HAT reactions involving the pyrrole N-H bond(s). In contrast, HG complex (PNO@**2**) exhibits significantly higher stability toward free-radicals due to the inclusion of PNO within the cavity. This inclusion leads to strong hydrogen bonding between PNO's N-O group and the pyrrole N-H bonds, effectively preventing the HAT reaction with transient radical species from AIBN.

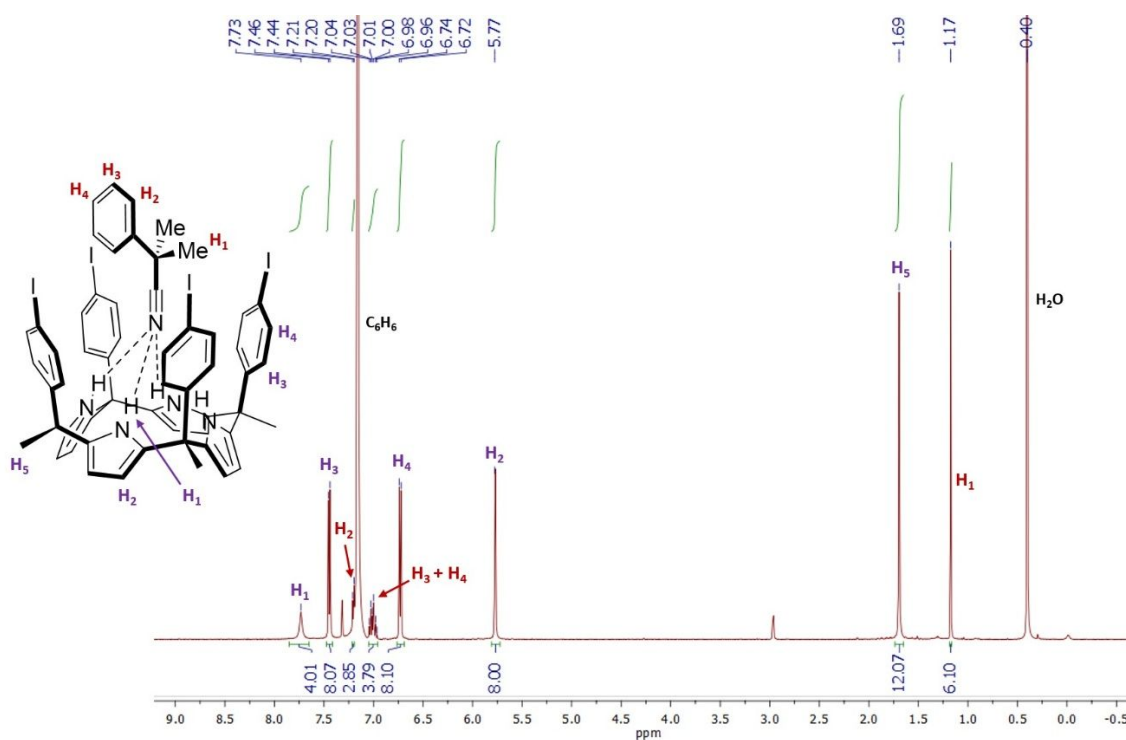


Figure S27. Full ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of the HG complex (1:1) between **2** and PPN. NMR integrations of the PPN and host **2**'s signals confirmed 1:1 complex.

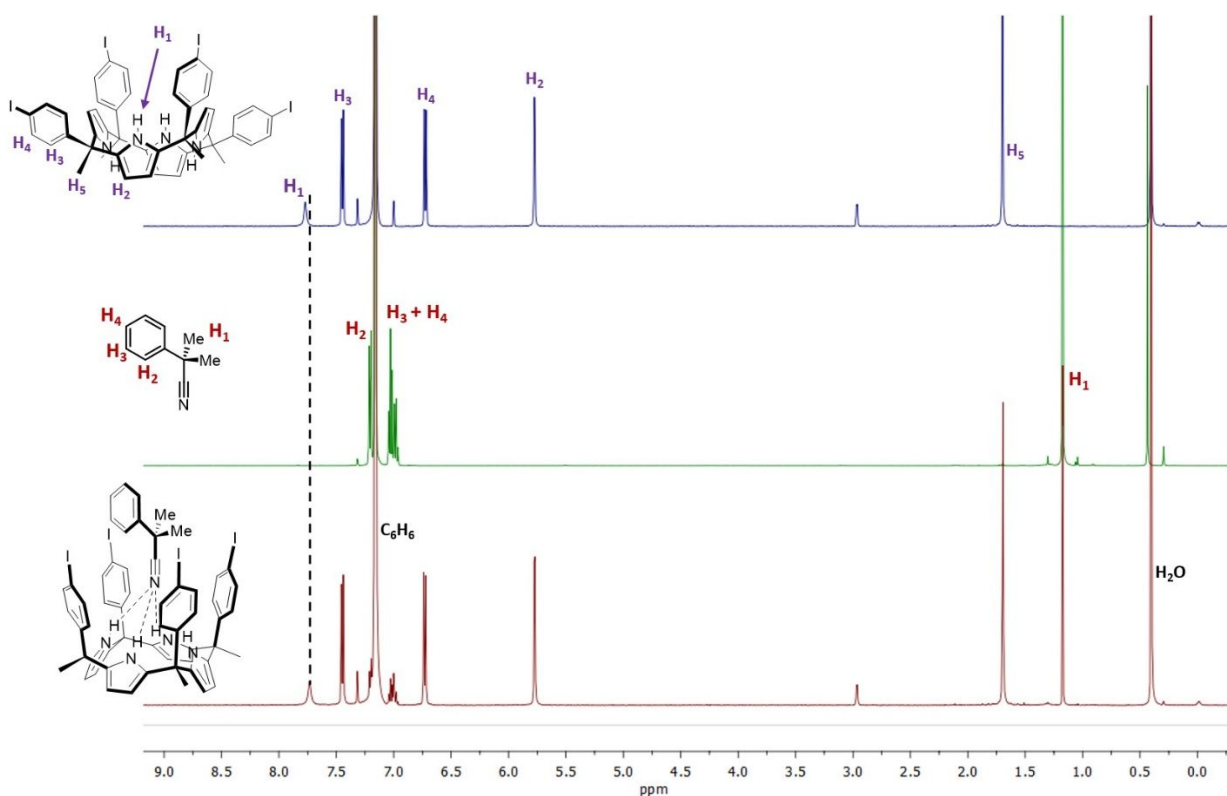


Figure S28. Full ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of the HG complex (1:1) between **2** and PPN (bottom), free PPN (middle), and free **2** (top). Averaged signals for PPN guest are observed, confirming a binding event in fast-exchange regime compared to the NMR time scale.

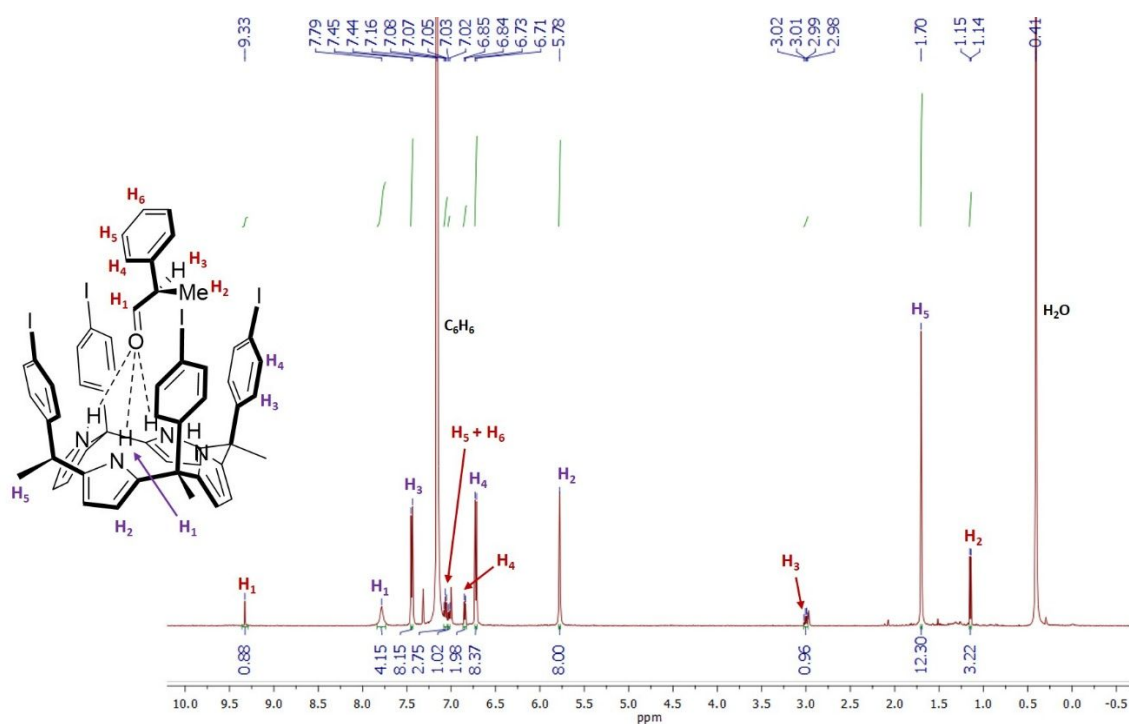


Figure S29. Full ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of the HG complex (1:1) between **2** and PPA. NMR integrations of the PPA and host **2**'s signals confirmed 1:1 complex.

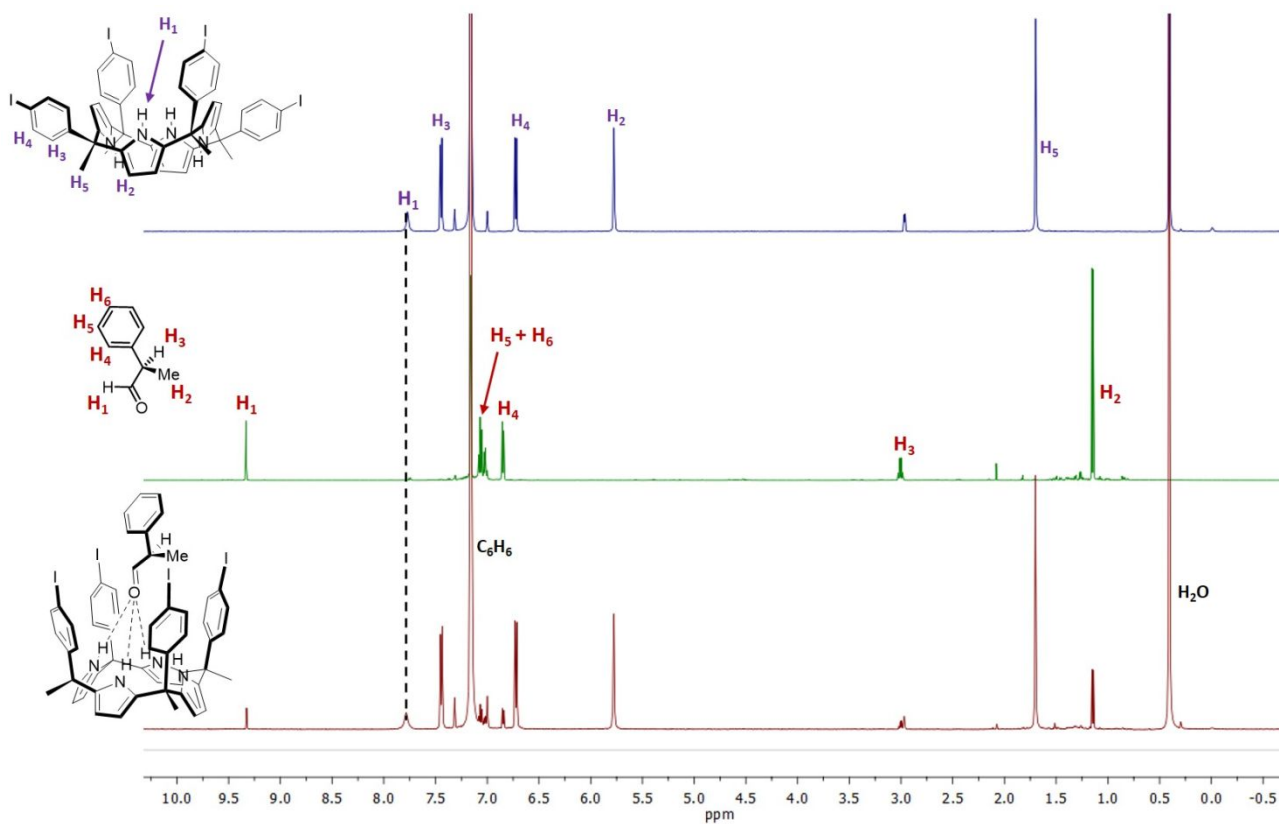


Figure S30. Full ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of the HG complex (1:1) between **2** and PPA (bottom), free PPA (middle), and free **2** (top). Averaged signals for PPA guest are observed, confirming a binding event in fast-exchange regime compared to the NMR time scale.

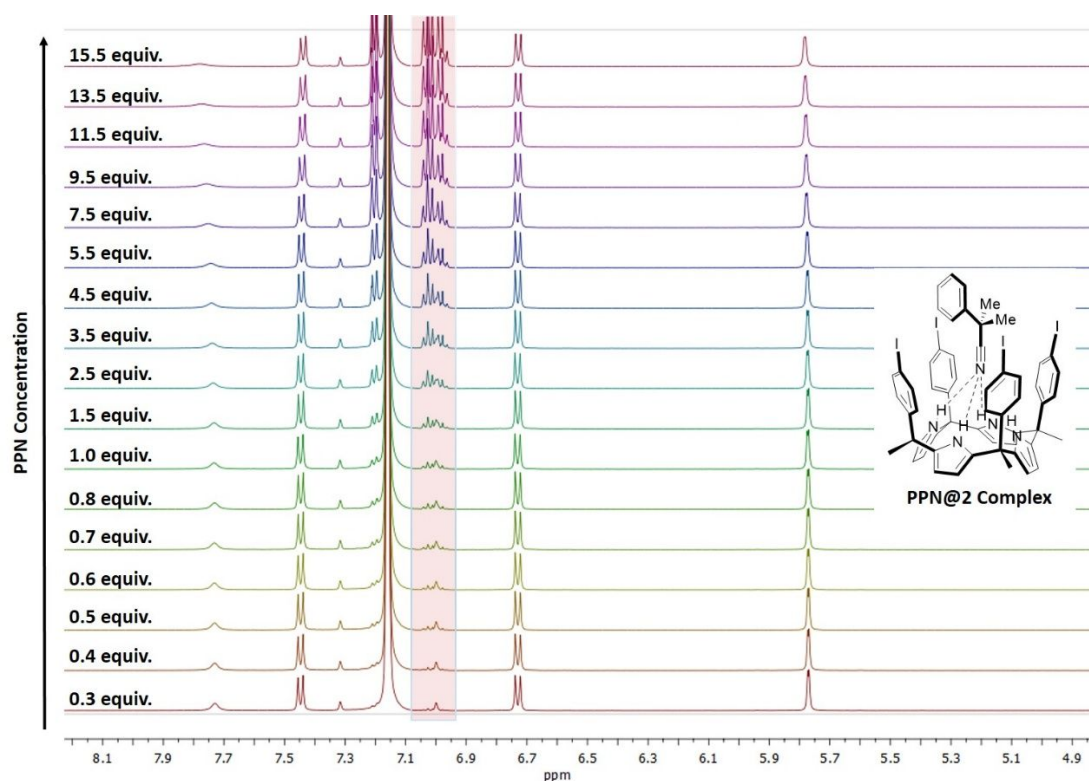


Figure S31. Partial ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of a 1 mM solution of host **2** with increased amount of PPN guest (0.3 to 15.5 equiv.). A 50 and 200 mM stock solution of PPN in C_6D_6 was used to add the proper amount of PPN (final volume 550 μL). The PPN's peaks are marked in red.

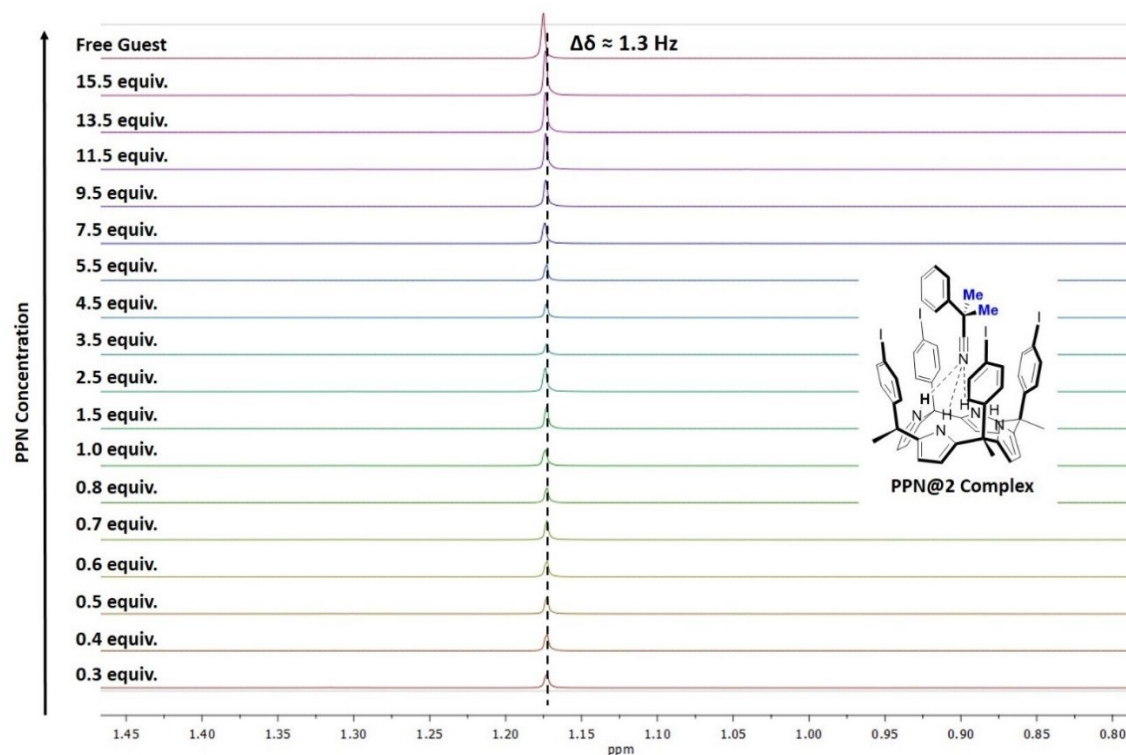


Figure S32. Partial ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of a 1 mM solution of host **2** with increased amount of PPN guest (0.3 to 15.5 equiv.). NMR signal of the PPN's methyl groups (marked in blue) was used to measure the binding constant.

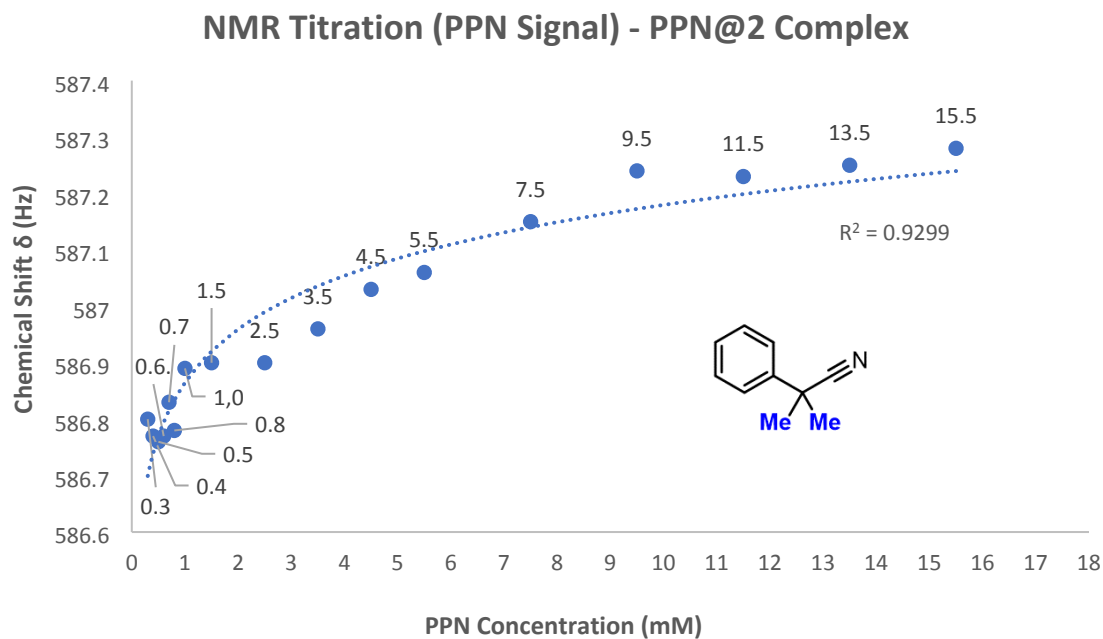


Figure S33. Chemical shift-PPN concentration curve related to the NMR titration shown in Figure S32. The fitting of the resulting curve for a 1:1 complex gives a K_a value lower than 10 M^{-1} .

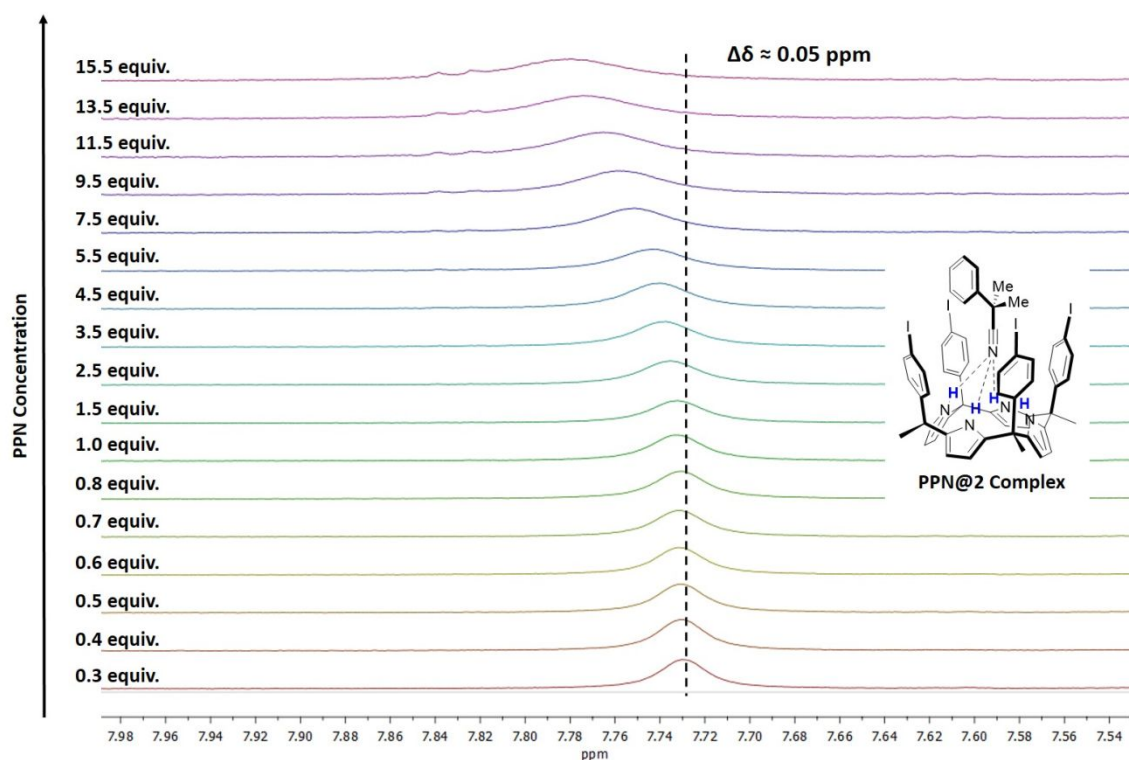


Figure S34. Partial ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of a 1 mM solution of host **2** with increased amount of PPN guest (0.3 to 15.5 equiv.). NMR signal of the host's NH groups (marked in blue) were used to double check the binding constant value.

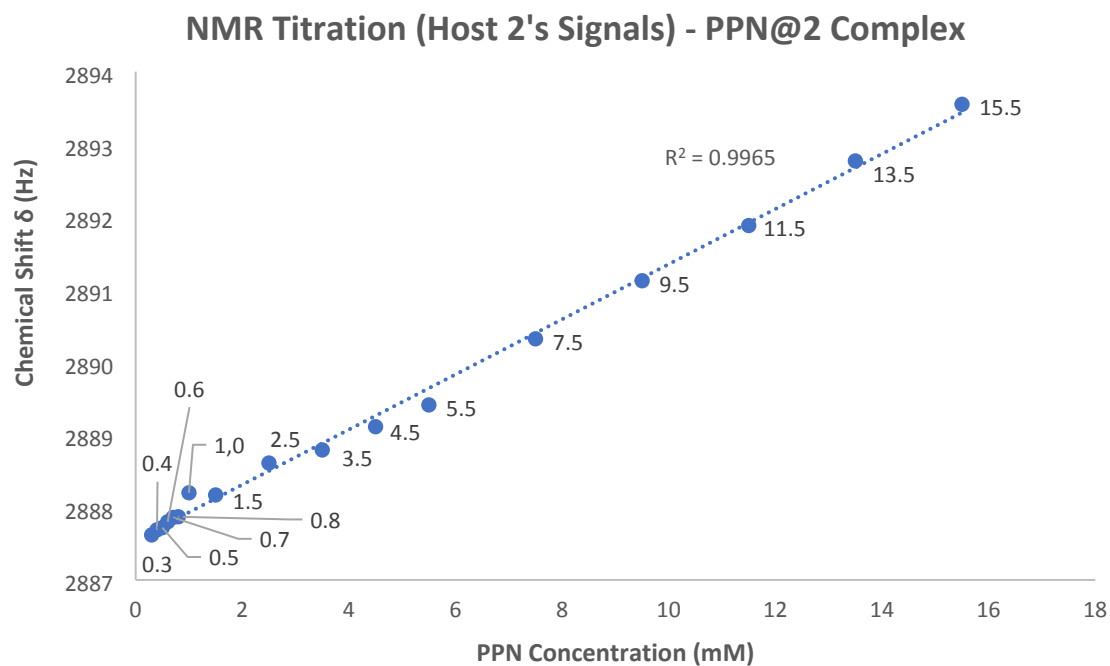


Figure S35. Chemical shift-PPN concentration curve related to the NMR titration shown in Figure S34. The nearly linear fitting ($R^2 = 0.9965$) confirms the very low affinity of PPN guest for host **2**'s cavity, in agreement with the binding constant reported in Fig. S33.

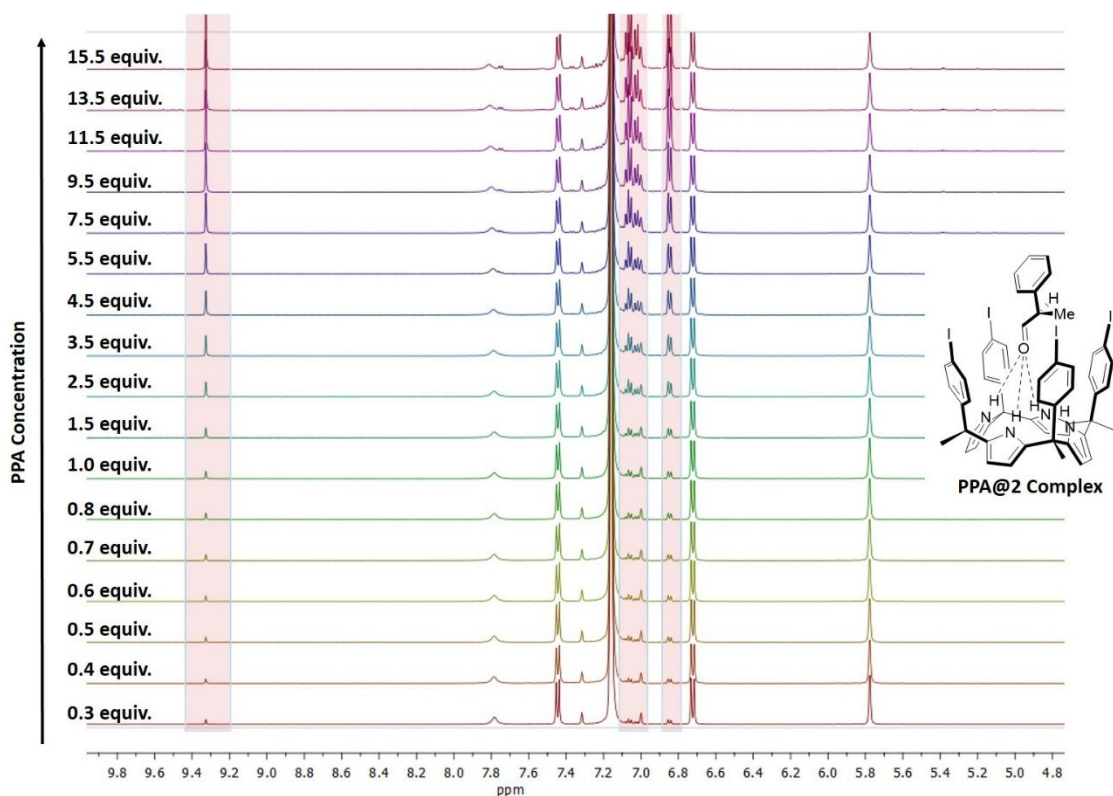


Figure S36. Partial ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of a 1 mM solution of host **2** with increased amount of PPA guest (0.3 to 15.5 equiv.). A 50 and 200 mM stock solution of PPA in C_6D_6 was used to add the proper amount of PPA (final volume 550 μL). The PPA's peaks are marked in red.

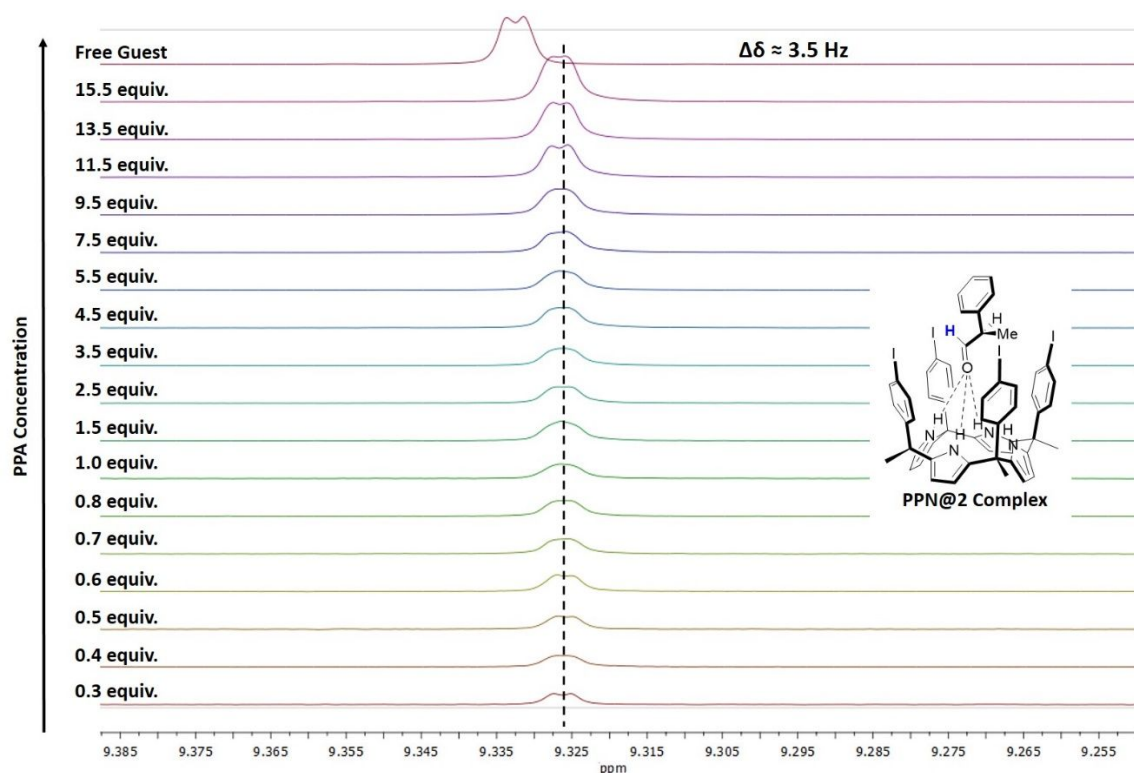


Figure S37. Partial ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of a 1 mM solution of host **2** with increased amount of PPA guest (0.3 to 15.5 equiv.). NMR signal of the PPA's aldehyde group (marked in blue) was used to measure the binding constant.

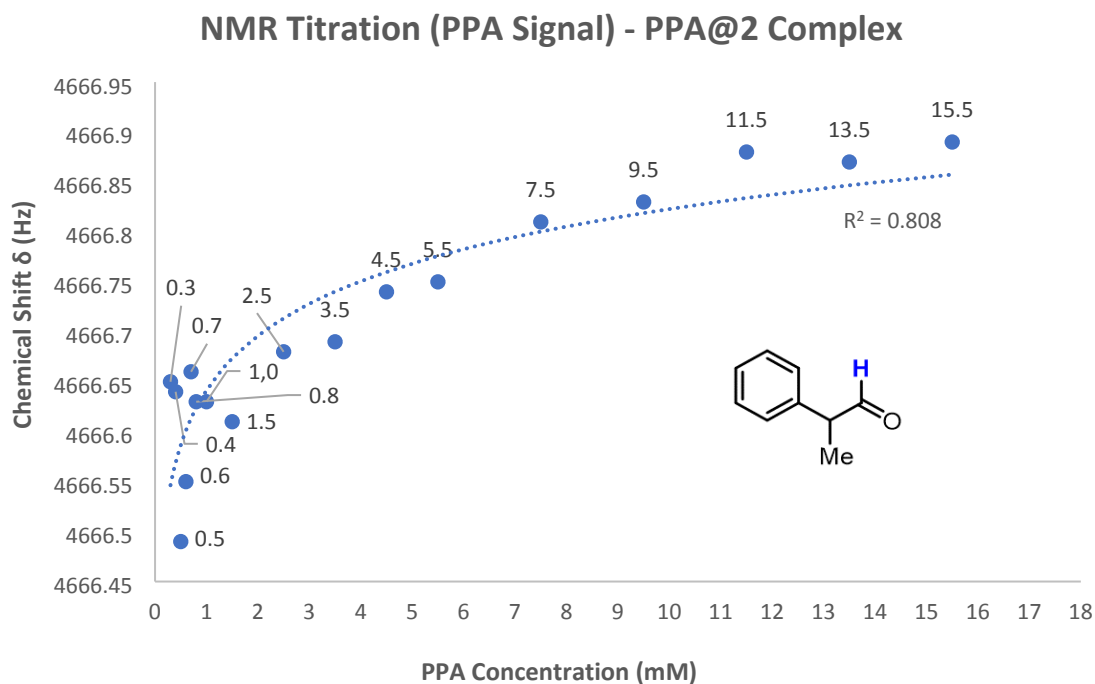


Figure S38. Chemical shift-PPA concentration curve related to the NMR titration shown in Figure S37. The fitting of the resulting curve for a 1:1 complex gives a K_a value around $25\text{--}30\text{ M}^{-1}$.

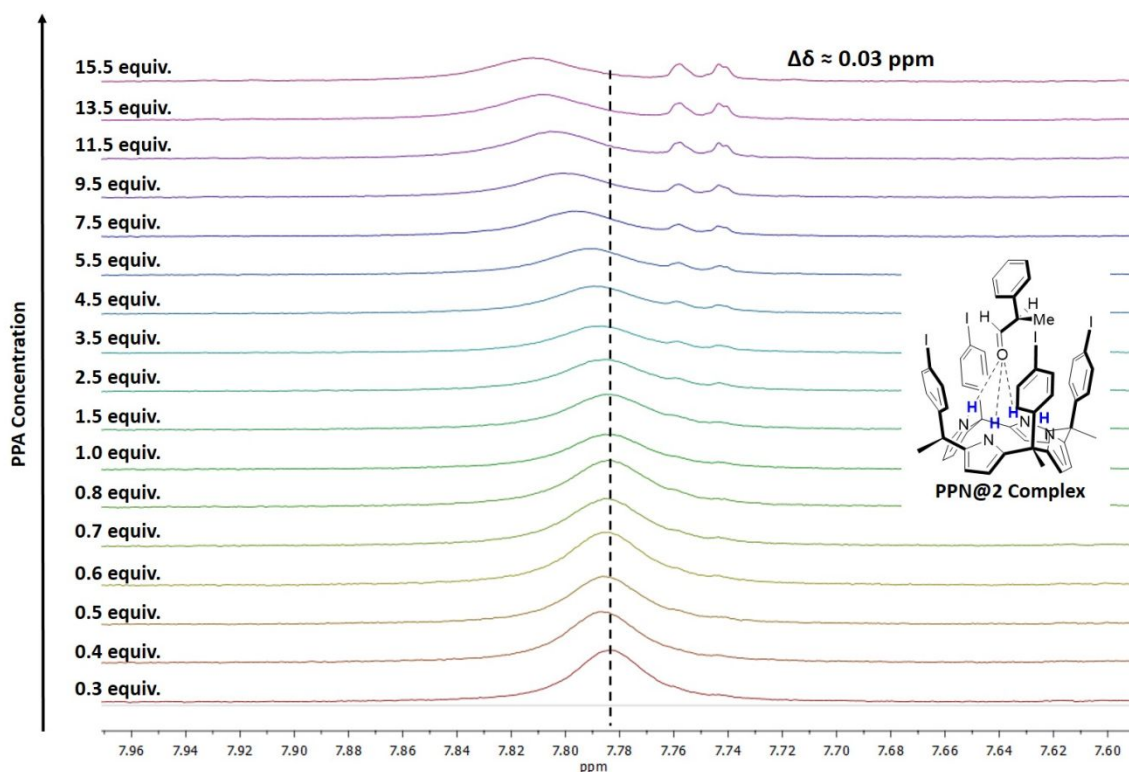


Figure S39. Partial ^1H NMR spectrum (500 MHz, C_6D_6 , 298 K) of a 1 mM solution of host **2** with increased amount of PPA guest (0.3 to 15.5 equiv.). NMR signal of the host's NH groups (marked in blue) were used to double check the binding constant value. Small impurities from the PPA guest at 7.74 ppm are observed at high concentration of PPA guest.

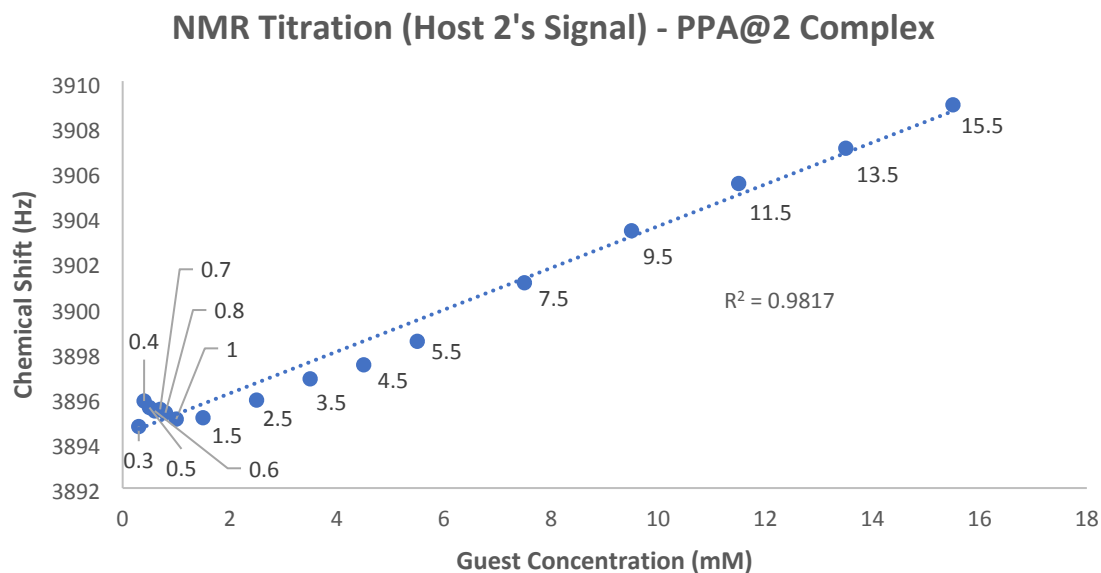


Figure S40. Chemical shift-PPA concentration curve related to the NMR titration shown in Figure S39. The linear fitting ($R^2 = 0.9817$) confirms a slightly higher affinity of PPA guest to host **2**'s cavity compared to PPN guest, but still quite low. This trend is consistent with the slightly higher binding constant proposed in Fig. S38.

7. EPR Study

EPR spectroscopy was used to identify the radical species involved in the antioxidant behavior of the calix[4]pyrroles (C₄Ps) in this study. X-Band spectra were recorded in a Magnettech Miniscope MS-5000 equipped with Bio-temperature Controller and connected with a Hamamatsu L9588-02A irradiation unit, working with a mercury-xenon lamp (240–400 nm, max 4500 mW/cm²), via an optical fiber for in-cavity photolysis. The following settings were typically used: field sweep 8–12 mT, field $B_0 \sim 336$ mT, sweep time 60 s, modulation frequency 100 KHz, modulation amplitude 0.03–0.1 mT, MW Power 5 mW, 1–4-scans signal accumulation. Measured g -factors were corrected with respect of that of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) radical in *t*-butylbenzene ($g = 2.0064$).^[42] Spectral interpretation was aided by simulation and interactive fitting based on Monte Carlo method, using the software WinESR Commander (developed by Prof. Marco Lucarini, University of Bologna).^[43] The monitoring of autoxidation mixtures by EPR spectroscopy during typical inhibited autoxidation experiments did not afford any detectable signal, owing to the very low steady-state concentration of transient radical species under such settings. Therefore, to boost radical initiation and identify the species involved in the process, a solution of host **1** (5 mM) in air-saturated cumene containing 20% (v/v) di-*tert*-butylperoxide was subjected to continuous photolysis (50% power) in the spectrometer cavity, at 30°C.

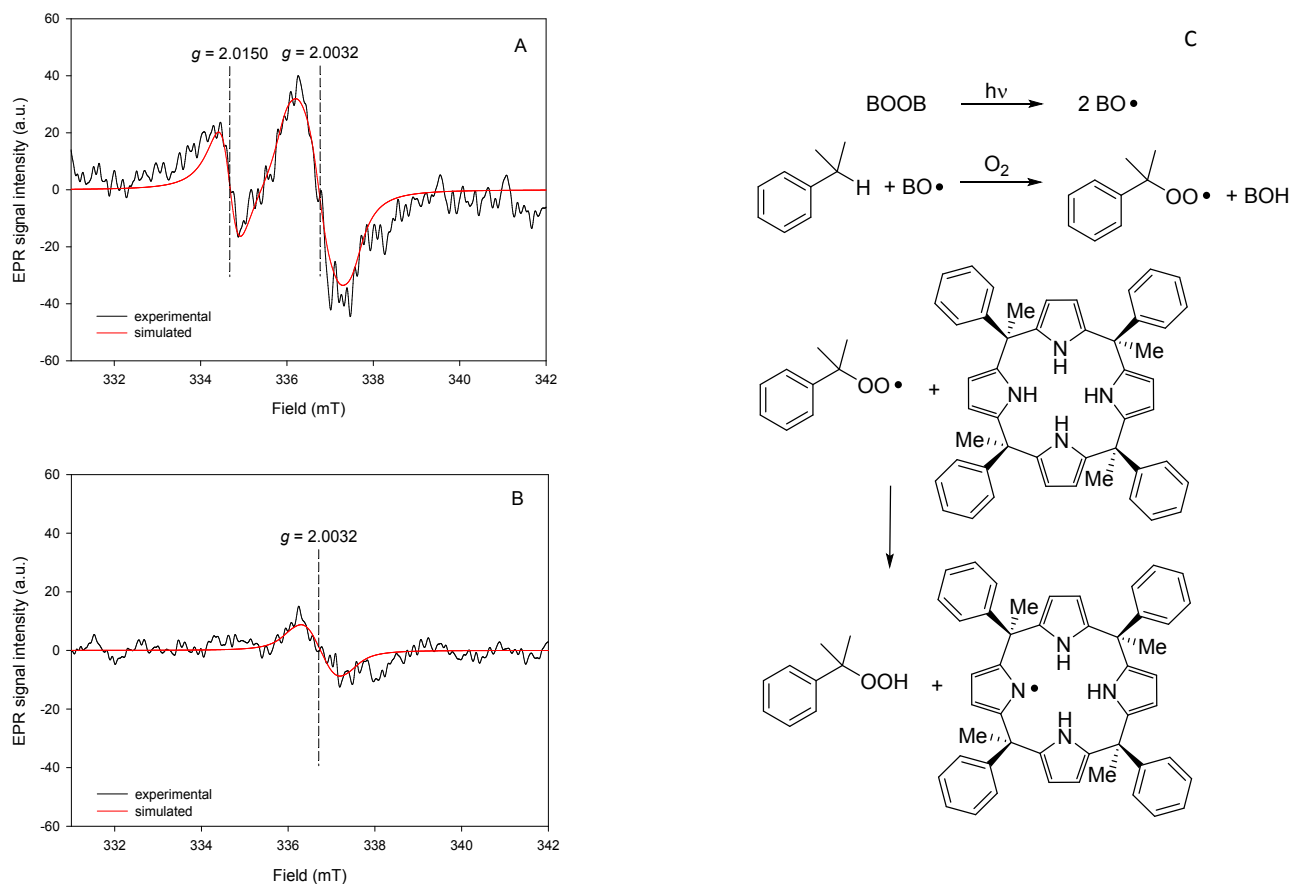


Figure S41. EPR spectra recorded at 30°C on a solution of host **1** (5 mM) in air saturated cumene containing 20% (v/v) di-*tert*-butylperoxide (A) under continuous in-cavity photolysis by a mercury-

xenon lamp (240–400 nm), and (B) 60 s after shutting off irradiation. Reactions leading to the formation of the assigned species (C).

The resulting EPR spectrum displayed two broad (~ 1 mT) signals with unresolved fine structure (Figure S41A) respectively centered at $g = 2.0032$ and $g = 2.0150$, which on the basis of the respective g -factor, were attributed to the pyrrolyl (N -centered) radical,^[45,70] of calix[4]pyrrole, and the cumylperoxyl radical.^[46,71]

On shutting off irradiation (Figure S41B) the signal at $g = 2.0150$ “immediately” disappeared, while that at higher field showed some persistence with an apparent $t_{1/2} \sim 30$ s, indicative of a resonance stabilized and/or sterically hindered radical. To confirm the nature of the signal centered at $g = 2.0032$ the system was changed by removing cumene. Solution of compound **1** in chlorobenzene containing 20% di-*tert*-butylperoxide was deoxygenated by bubbling nitrogen and irradiated in the EPR cavity, so to afford the putative pyrrolyl radical without intermediation of peroxy radicals. The resulting signal had identical $g = 2.0032$ (Figure S42) indicating that the same species was produced. Owing to O_2 removal higher resolution was achieved, which allowed some analysis of the hyperfine structure, despite the rather noisy spectrum. Our findings were in line with previous literature on the pyrrolyl radical,^[45] reporting a π radical with relatively low coupling at nitrogen and relatively larger coupling with hydrogens in 3,4-positions. Interesting, however, our species also showed a relatively large coupling with an additional hydrogen and much lower coupling with an additional nitrogen and two equivalent protons, possibly owing to the occurrence of H-bonding to another pyrrole moiety in the C4P structure (Figure S42, right), as also predicted by DFT calculations.

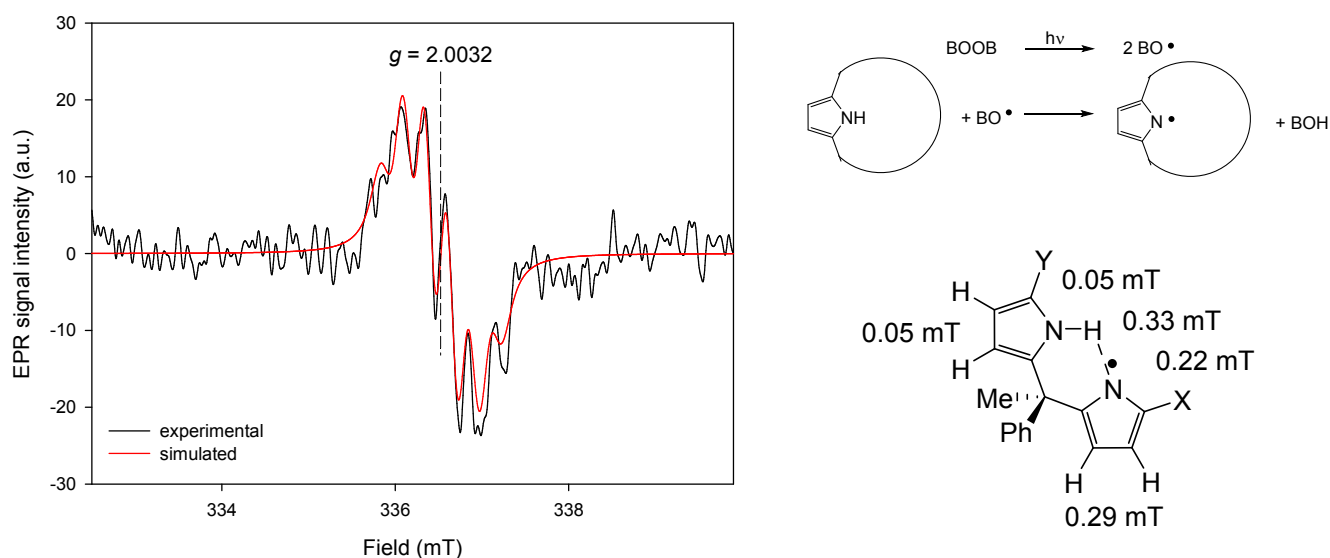


Figure S42. EPR spectra recorded at 30°C on a solution of host **1** (5 mM) in degassed chlorobenzene containing 20% (v/v) di-*tert*-butylperoxide under continuous in-cavity photolysis by a mercury-xenon lamp (240–400 nm). Recorded with modulation amplitude 0.3 mT. Red trace represents the simulation using the spectral parameters indicated in the figure. Shutting off irradiation confirmed the decay of the species with an apparent $t_{1/2} \sim 30$ s as shown in Figure S43.

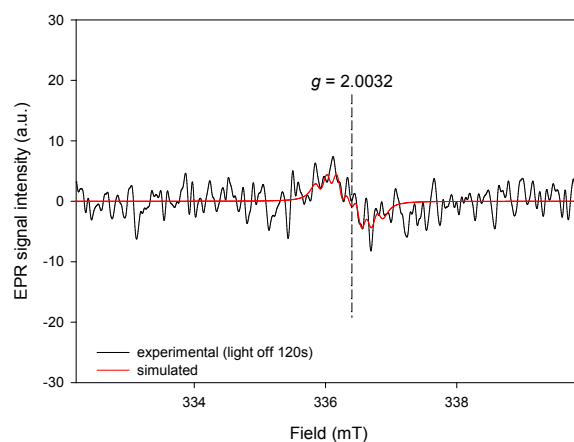


Figure S43. EPR spectra recorded at 30°C on a solution of host **1** (5 mM) in degassed chlorobenzene containing 20% (v/v) di-*tert*-butylperoxide, produced by continuous in cavity photolysis (as in Figure S42), recorded 120 s after shutting off irradiation.

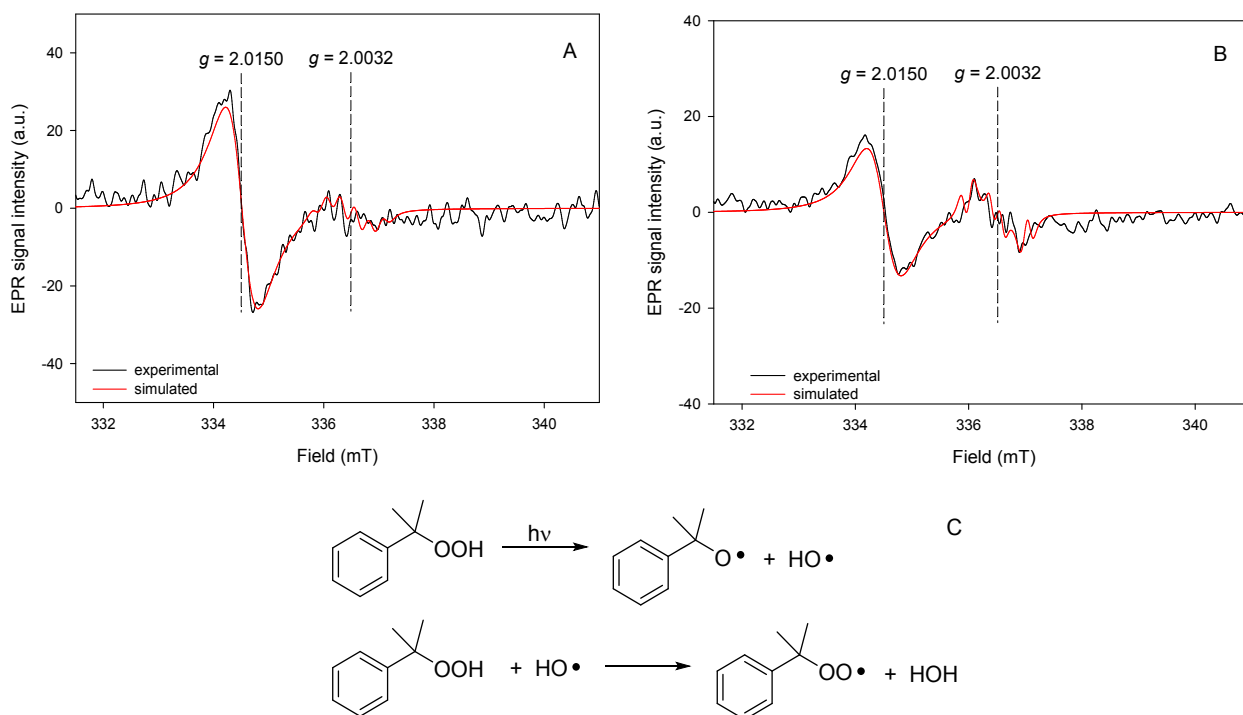


Figure S44. EPR spectra recorded at 30°C on a solution of host **1** (5 mM) in chlorobenzene containing 20% (v/v) cumylhydroperoxide under continuous in-cavity photolysis by a mercury-xenon lamp (240–400 nm), immediately after starting irradiation (A) and after about 90 s continuous irradiation (B). The reactions leading to formation of CumOO• are illustrated (C).

To gain independent confirmation that the generation of the pyrrolyl radical could arise from reaction with cumylperoxyl radicals, as shown in Figure S41, an oxygen-free source of CumOO• was obtained by photolyzing a degassed solution of **1** in chlorobenzene in the

presence of an excess of cumyl hydroperoxide in the cavity of the EPR spectrometer. As shown in Figure S44, the resulting spectrum was similar to that previously obtained from cumene in the presence of air. A broad signal centered at $g = 2.0150$ typical of the cumyl peroxy radical was observed along with a much weaker signal at $g = 2.0032$ that built up on prolonging irradiation time (Figure S44B), which could be reproduced by fitting to the same hyperfine structure observed in Figure S42. It can therefore be attributed to the same radical species. While finer analysis was not favored by the modest intensity of the EPR signal, the observed species are in agreement with DFT calculations and support the proposed mechanism of peroxy radical trapping by C4Ps. To further confirm the identity of the radical species observed at $g = 2.0032$ as a pyrrolyl radical, we studied the EPR spectrum of the aminyl radical generated from 2,5-dimethylpyrrole (DMP) as a reference compound. Indeed, while the hyperfine splitting constants determined for our observed species are in excellent agreement with those reported by Samuni and Neta for pyrrole and some of its derivatives in water,^[45] the reported g -factors were slightly lower (range 2.0023 to 2.0029) compared to our finding in chlorobenzene. While such differences are likely due to the different solvent polarity, we set to gain independent confirmation of our assignment. In cavity continuous photolysis of a degassed PhCl solution of DMP in the presence of di-*tert*-butylperoxide afforded a broad poorly resolved signal centered at $g = 2.0031$. The high BDE_{N-H} of DMP and the resulting poor stability and persistency of the aminyl radical did not allow to record spectra with clearer hyperfine structure. However, it was possible to reasonably simulate it with the set of hfsc shown in Figure S45. Interestingly, coupling at N and at the protons in 3,4-positions had magnitude close to that previously found for the radical species attributed to the C4P pyrrolyl radical, along with larger coupling at the positions 2 and 5, in line with expectations based on similar structures and on spin density distribution.^[45]

Therefore, both the hyperfine structure and the g -value found for reference DMP aminyl radical fully support our previous attribution of the signal at $g = 2.0032$ to the intramolecular H-bond stabilized pyrrolyl radical from C4P.

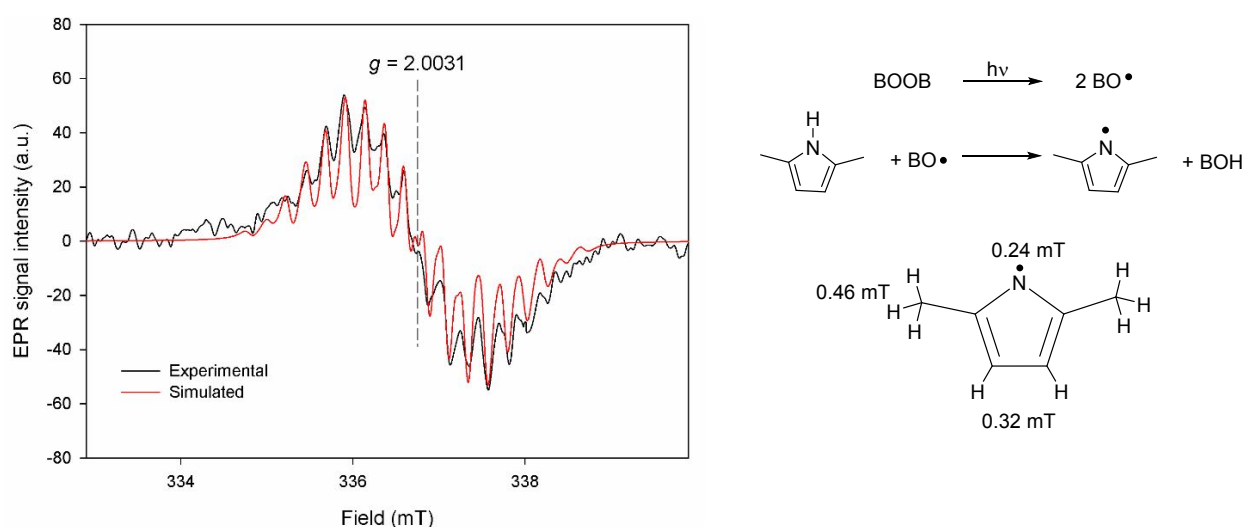


Figure S45. EPR spectra recorded at 30°C on a solution of compound 2,5-dimethylpyrrole (50 mM) in degassed chlorobenzene containing 30% (v/v) di-*tert*-butylperoxide under continuous in-cavity photolysis by a mercury-xenon lamp (240–400 nm). Simulation with the parameters reported on the right is given in red.

8. DFT Study

Ab initio and density functional calculations were performed using the Gaussian 16 (G16) program package^[72] and Gaussview,^[73] and BIOVIA Discovery Studio as graphical interfaces. Optimization of all the structures has been performed at B₃LYP/6-31G(d,p) level of theory in gas phase. All structures were subjected to a full conformational search and frequencies were calculated and checked out to make sure that all of them were positive and no imaginary frequencies were present. All stationary state structures presented were the result of an optimization followed by a frequency calculation terminated with “Stationary point found”, indicating that the four convergence criteria (standard G16 thresholds) were met. Transition states (TSs) were located via relaxed PES scans performed at the B₃LYP/6-31G(d,p) level of theory in gas phase. Initial geometries were prepared based on chemical intuition or previously optimized structures, modified as required for the scan. Optimized TS structures had only one imaginary frequency, confirming a saddle point. IRC calculations at the same level of theory, performed in two separate runs for the forward and reverse path, were executed for each TS structure, to unambiguously identify the corresponding reactants and products. Gibbs energy of activation (*E_a*) and energy barrier from TS study were calculated taking into account the Gibbs free energy and electronic energies, respectively.

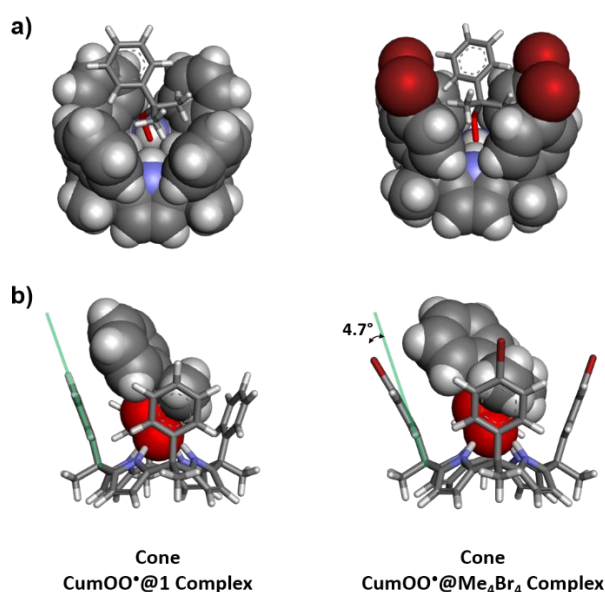


Figure S46. Optimized structures at DFT level of theory in the left side (a) and front side (b), representing the HG complex between cumylperoxyl radical (CumOO•) and host **1** (left) and host **2** (right). Bromo derivative of **2** (**Me₄Br₄**) was used to reduce the computational cost. Distortion of the panel in **Me₄Br₄** compared to **1** is highlighted with a green line. More hindered panels, such as those in **Me₄Br₄**, reduce accessibility to the pyrrole moieties within the cavity compared to hosts functionalized with less hindered panels (e.g., compound **1**).

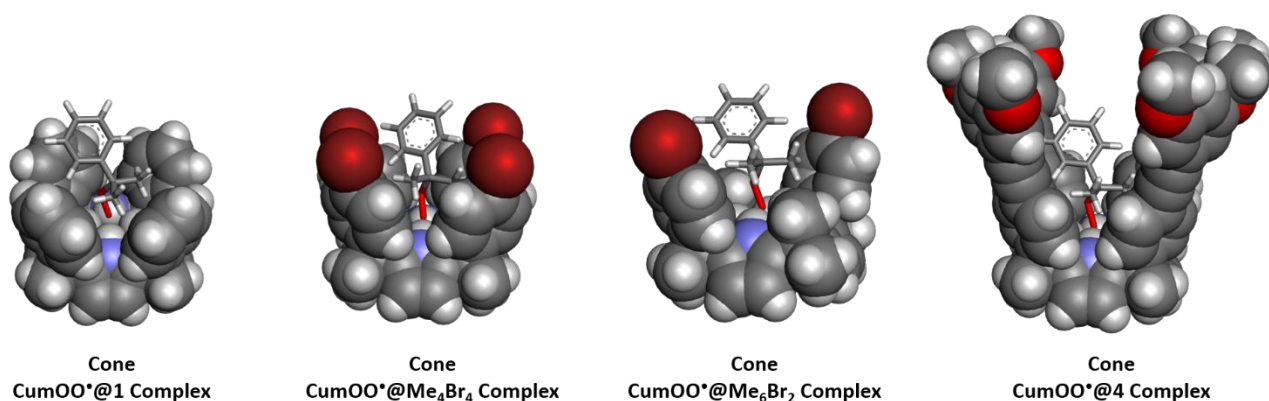


Figure S47. Optimized structures at DFT level of theory, representing the HG complex between cumylperoxyl radical (CumOO•) and host **1**, the bromo derivative of **2** (Me₄Br₄) and **3** (Me₆Br₂), and host **4**. Bromo derivatives of **2** and **3** were used to reduce the computational costs.

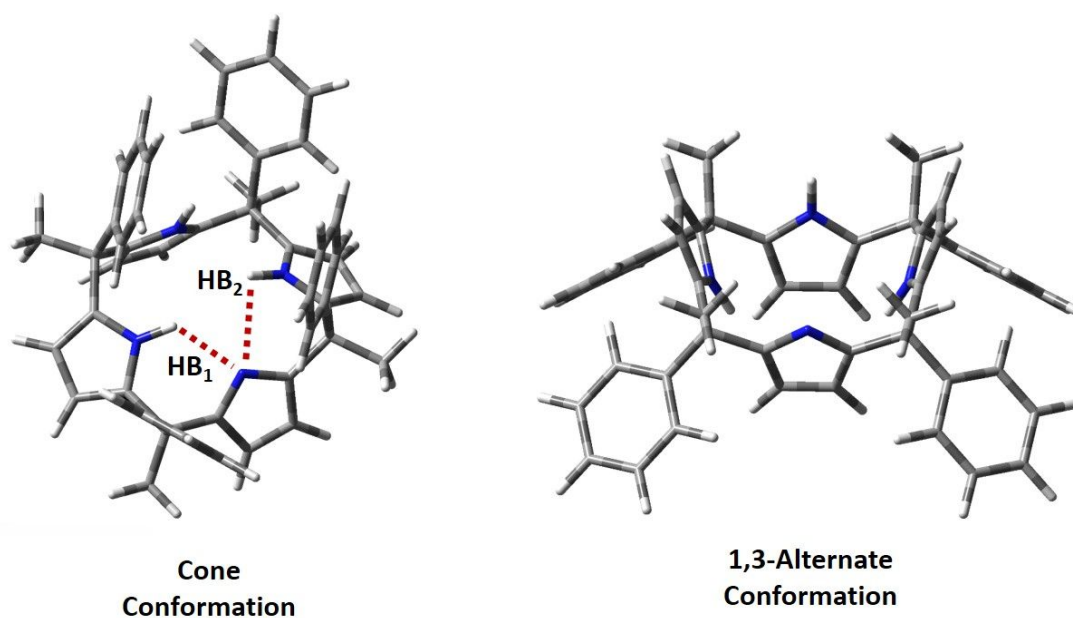


Figure S48. Optimized structure of the radical species from **1** in the cone (left) and 1,3-alternate (right) conformations. Red dashed lines point out the intramolecular hydrogen bonds in the radical species.

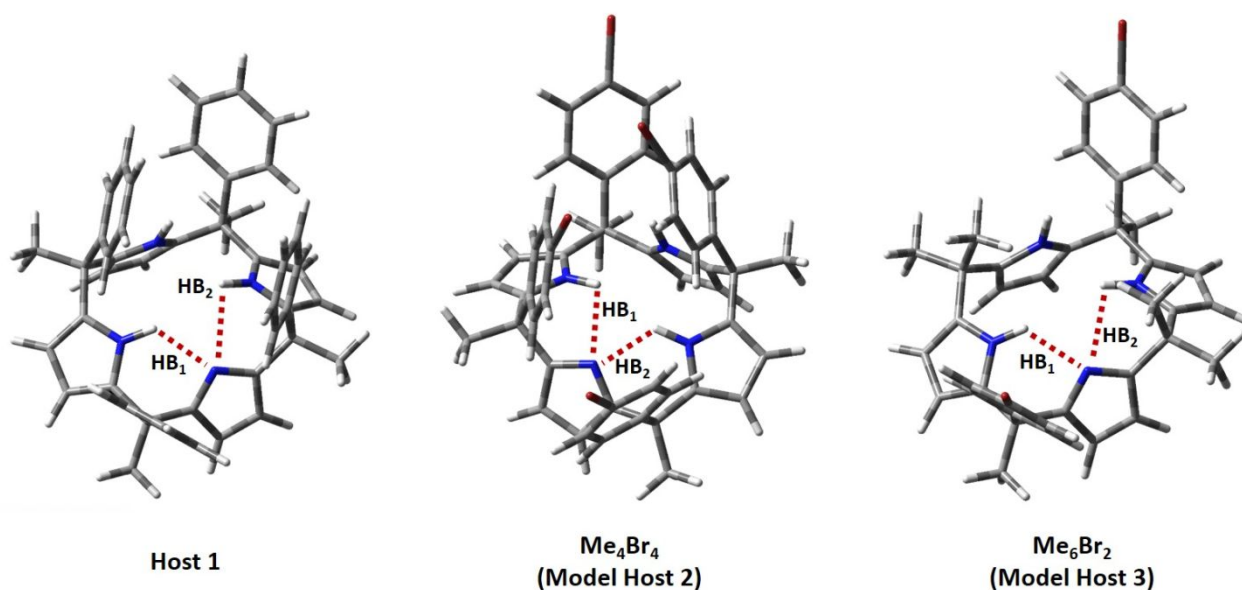


Figure S49. Optimized structures of the radical species from **1** (left), **Me₄Br₄** (middle), and **Me₆Br₂** (right). Red dashed lines point out the intramolecular hydrogen bonds in the radical species.

Table S2. Theoretical N-H BDE, calculated at B₃LYP/6-31G(d,p) level of theory for host **1**, **Me₄Br₄**, and **Me₆Br₂**. The N-H BDE was calculated for both conformations, cone and 1,3-alternate, only for host **1**, which was considered as the model host to highlight the different behavior of the two conformations.

* In accordance with the reference in the literature. ^[55]

System	Cone N-H BDE (kcal/mol)	1,3-Alternate N-H BDE (kcal/mol)
1	64.8	86.6
Me₄Br₄	62.0	-
Me₆Br₂	50.9	-
2,5-DMP		84.9*

The N-H BDE was theoretically calculated through the following mathematical formula:

$$H_{\text{System-NH}} - H_{\text{System-N}\cdot} - E_{\text{H}\cdot} \quad (3)$$

The initial system (System-NH) was obtained from the optimized geometry of the corresponding HG complex with the cumylperoxyl radical (ROO•). The ROO• was removed, and a frequency calculation was performed on the (empty) host in the cone conformation. This approach was chosen due to the low stability of the cone conformation in absence of a proper guest (empty cavity), which would otherwise relax into the 1,3-alternate conformation, significantly altering the initial geometry of the system. All other species underwent classical optimization and frequency calculations.

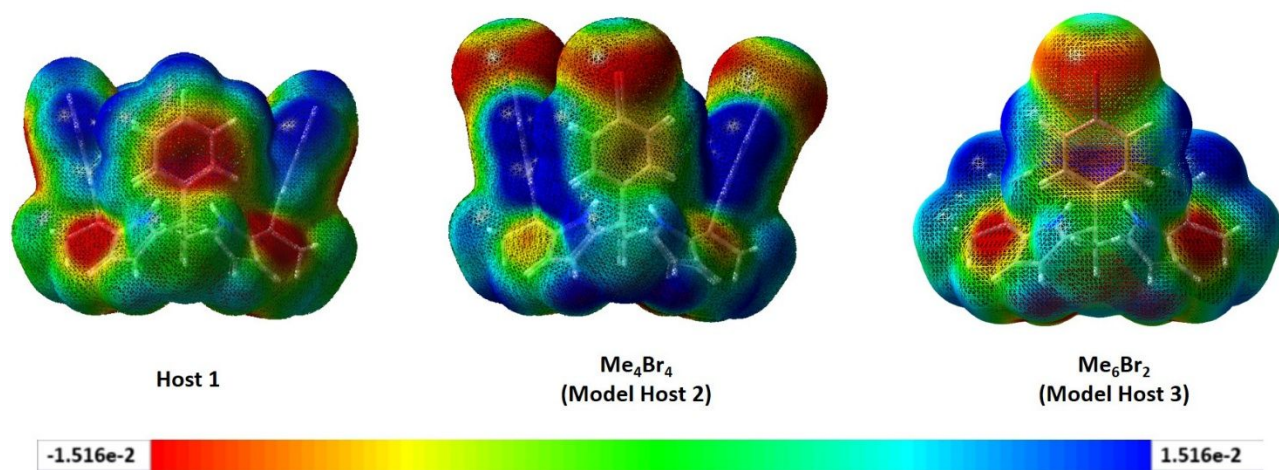


Figure S50. Molecular electrostatic potential (MEP) for host **1** (left), Me_4Br_4 (middle), and Me_6Br_2 (right) in the cone conformation.

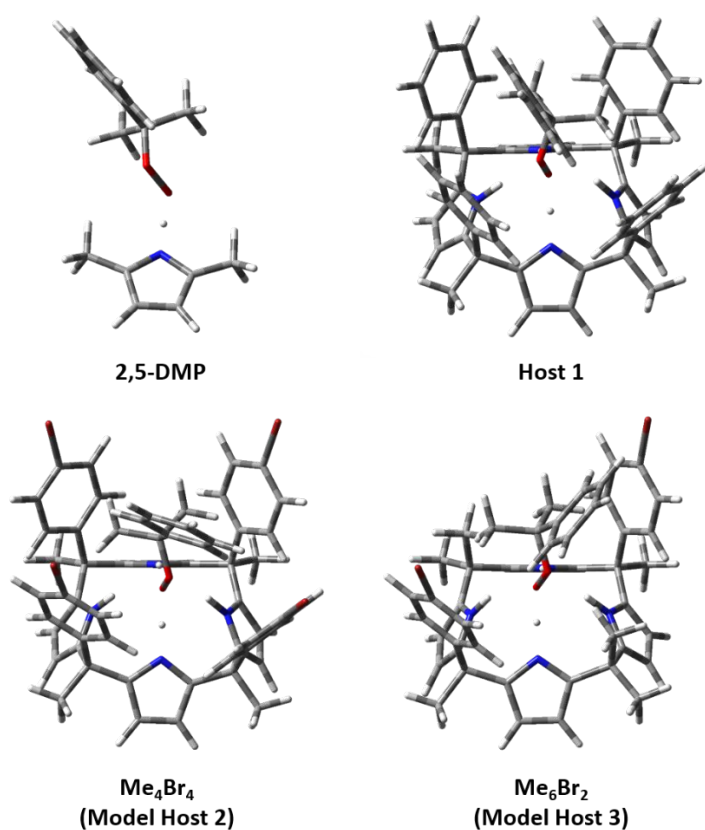


Figure S51. Transition state (TS) structures for the HAT reaction with cumylperoxyl radical ($\text{CumOO}\bullet$) for reference compound 2,5-DMP, host **1**, and Me_4Br_4 and Me_6Br_2 as models for hosts **2** and **3**, respectively.

Table S3. Theoretical energy barrier and activation energy (E_a), calculated at B3LYP/6-31G(d,p) level of theory for host **1**, **Me₄Br₄**, **Me₆Br₂**, and reference compound **2,5-DMP** for the HAT reaction with the cumylperoxyl radical (CumOO•). The thermodynamic profiles obtained for **1**, **Me₄Br₄**, and **Me₆Br₂** indicate that the HAT reaction is essentially barrierless. ^aThe negative E_a values are attributed to the structural similarity between the CumOO•@Host complexes and the corresponding TS structures, which minimizes the energetic barrier required to reach the TS geometry. This hypothesis is further supported by the positive E_a value calculated for the less hindered two-wall receptor (**Me₆Br₂**), where the bound CumOO• retains greater conformational freedom. Additionally, the HAT, described by the TS, makes the initial CumOO• a better hydrogen bond acceptor, enabling slightly stronger interactions with the pyrrole units through hydrogen bonding (enthalpic effect).

System	Energy Barrier (kcal/mol)	Activation Energy (E_a) (kcal/mol)
1	1.22	-0.63 ^a
Me₄Br₄	1.14	-0.89 ^a
Me₆Br₂	2.75	0.77
2,5-DMP	12.64	10.58

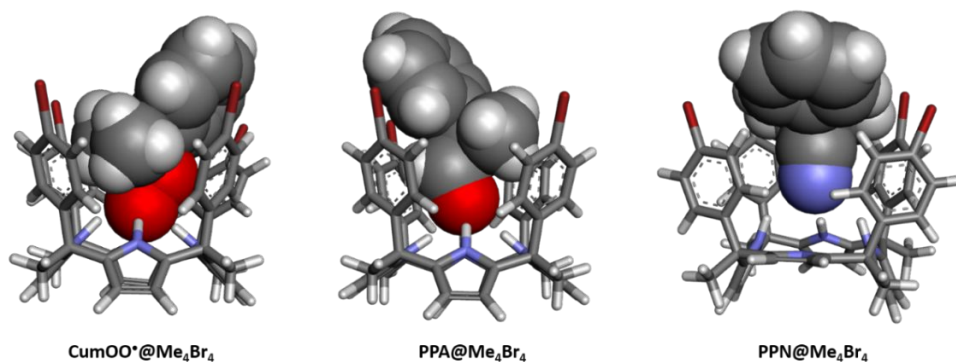


Figure S52. Optimized structures at DFT level of theory, representing the HG complexes between the bromo derivative of **2** (**Me₄Br₄**) and cumylperoxyl radical (left), 2-phenylpropanal (PPA) (middle), and 2-methyl-2-phenylpropanenitrile (PPN) (right). Bromo derivatives of **2** was used to reduce the computational costs.

To estimate the binding constant of CumOO• in the host cavity, we used 2-phenylpropanal (PPA) and 2-methyl-2-phenylpropanenitrile (PPN) as models, so we performed comparative calculations on their binding vs CumOO•. It is worth nothing that the conformation of the bound PPA (quasi-linear orientation) in the HG complex is not the most stable one (Figure S53). This PPA's conformation is still accessible during its inclusion in the host's cavity; however, the energetic cost of the conformational change results in a lower binding constant.

In contrast, this is not observed for CumOO $\cdot$, where the most stable conformation (quasi-linear orientation) perfectly fits within the host's cavity, leading to higher K_a values. The steric repulsions in PPN@**2** complex, due to the quasi-perpendicular orientation of the PPN guest, partially prevent inclusion, as confirmed by the distorted conformation of the C₄P core.

Table S4. Theoretical averaged distance (Å) of the NH $\cdots$ X (with X = hydrogen bond acceptor), calculated at B₃LYP/6-31G(d,p) level of theory, for the HG complex formed between **Me₄Br₄** and CumOO $\cdot$, PPA, and PPN model guests shown in Figure S52. ^a Relative orientation of the pyrrole groups with respect to the bound guest.

HG Complex	Averaged NH $\cdots$ X (Å)	Pyrrole Orientation ^a
CumOO $\cdot$	1.78	Symmetric
PPA	2.28	Partially Symmetric
PPN	2.75	Distorted

The structural and electronic differences between PPA and PPN, compared to CumOO $\cdot$, significantly influence their interactions with **Me₄Br₄**. The unique structure of CumOO $\cdot$ cannot be replicated by PPA and PPN, as evidenced by the averaged HB distance (NH $\cdots$ X) between the pyrrole moieties and the guest. In CumOO $\cdot$ @**Me₄Br₄**, the averaged NH $\cdots$ X distance is 1.78 Å - 0.50 Å and 0.97 Å shorter than those found in PPA@**Me₄Br₄** and PPN@**Me₄Br₄**, respectively. This indicates probably stronger HB interactions and reduced steric repulsion.

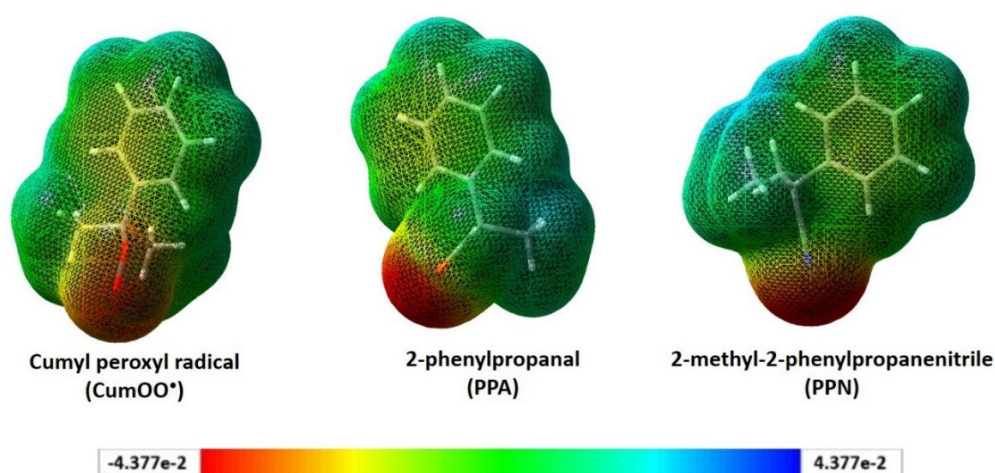


Figure S53. Molecular electrostatic potential (MEP) for the optimized structures of CumOO $\cdot$ (left), PPA (middle), and PPA (right) at DFT level theory. It is worth nothing that in the most stable conformation of PPA, the carbonyl group is placed perpendicularly with respect to the phenyl group, while a “parallel” orientation of the carbonyl moiety is observed in the HG complex with host **2**.