

Solvation Rules: Aromatic Interactions Outcompete Cation- π Interactions in Synthetic Host-Guest Complexes in Water

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Supporting Information

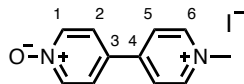
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1. General methods

All the reagents and materials used in the synthesis of the compounds described below were obtained from commercial sources and used without prior purification. Compounds **1** and **2** were prepared as reported in literature.^{1,2} Thin layer chromatography was carried out using Silica gel 60F on glass plates. Flash chromatography was carried out on an automated system (Combiflash Companion, Combiflash Rf+ or Combiflash Rf Lumen) using prepacked cartridges of silica (25 μm or 50 μm PuriFlash® Columns). ¹H and ¹³C NMR spectra were recorded on Bruker 400 MHz DPX400, 400 MHz AVIII400, 500 MHz DCH cryoprobe or 500 MHz TCI Cryoprobe spectrometer at 298.0 \pm 0.1 K unless specifically stated otherwise. Residual solvent was used as an internal standard for referencing. In chloroform-*d*, ¹H spectra were referenced to δ 7.26 ppm and ¹³C spectra to δ 77.06 ppm for the solvent signal. In dimethyl sulfoxide-*d*₆, ¹H spectra were referenced to δ 2.50 ppm and ¹³C spectra to δ 39.52 ppm. In deuterium oxide, ¹H spectra were referenced to δ 4.79 ppm. All chemical shifts are quoted in ppm on the δ scale and the coupling constants expressed in Hz. Signal splitting patterns are described as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). FT-IR spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer equipped with an ATR cell. The LCMS analysis of samples was performed using a Waters Acquity H-Class UPLC coupled with a single quadrupole Waters SQD2 or a Waters Xevo G2-S bench top QTOF machine. Melting points were measured on a Mettler Toledo MP90 melting point apparatus. ITC titrations were carried out on a Malvern MicroCal VP-ITC MicroCalorimeter.

2. Synthesis

1'-Methyl-[4,4'-bipyridin]-1'-ium 1-oxide iodide (5)



4-Phenylpyridine *N*-oxide (34 mg, 0.20 mmol, 1 equivalent) was dissolved in acetonitrile (2 mL) and iodomethane (0.1 mL, 1.5 mmol, 7.5 equivalents) was added. The flask was sealed, and the mixture stirred at 50 °C for 16 h. The volatiles were evaporated off under to yield 1'-methyl-[4,4'-bipyridin]-1'-ium 1-oxide iodide (51 mg, 0.16 mmol, 82 %) as a yellow solid.

Mpt: 225.0 – 226.2 °C

¹H NMR (400 MHz, DMSO-*d*₆): δ_H 9.05 (d, *J* = 7.0 Hz, 2H, H-6), 8.56 (d, *J* = 7.0 Hz, 2H, H-5), 8.48 (d, *J* = 7.4 Hz, 2H, H-1), 8.17 (d, *J* = 7.4 Hz, 2H, H-2), 4.32 (s, 3H, H-2, CH₃).

¹³C NMR (101 MHz, DMSO-*d*₆): δ_C 150.3 (C-4), 146.3 (C-6), 140.2 (C-1), 129.3 (C-3), 125.7 (C-2), 124.1 (C-5), 47.7 (CH₃).

HRMS (ES⁺): calculated for C₁₁H₁₁IN₂O 187.0866 [M⁺], found 187.0861 [M⁺].

FT-IR (ATR): ν_{max} 2970, 1738, 1366, 1217, 831, 687, 539, 496 cm⁻¹.

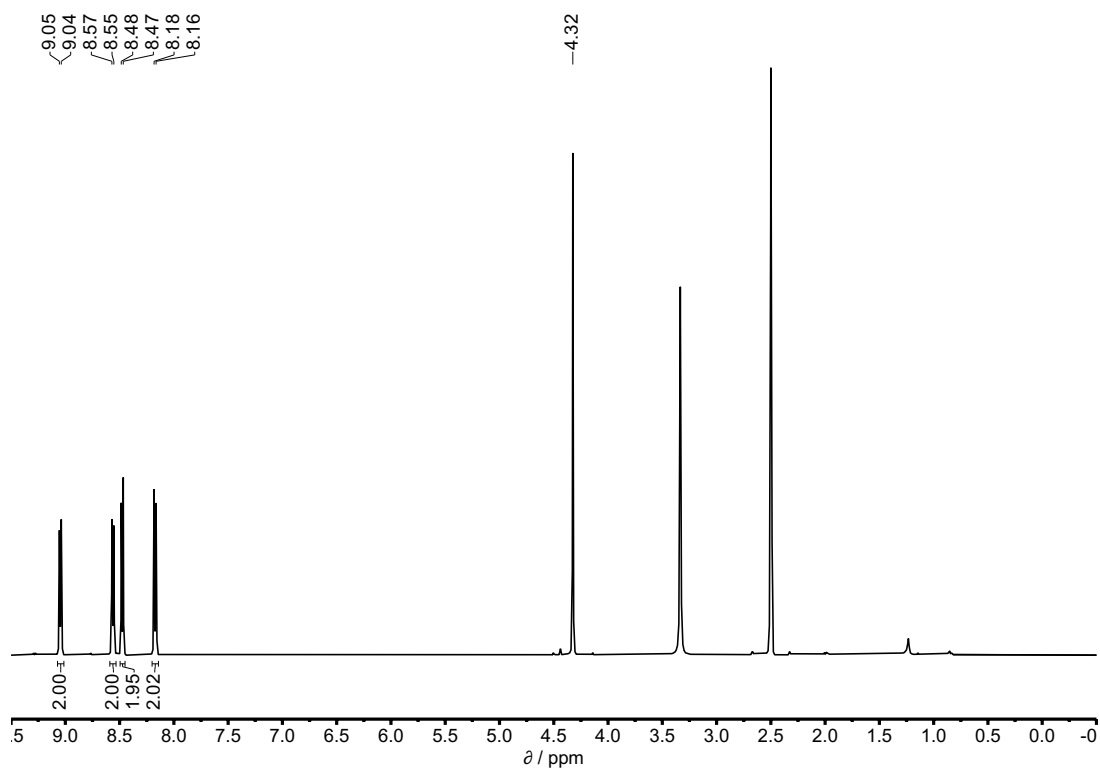


Figure S1. ^1H NMR spectrum (400 MHz, DMSO-d_6) of compound **5**.

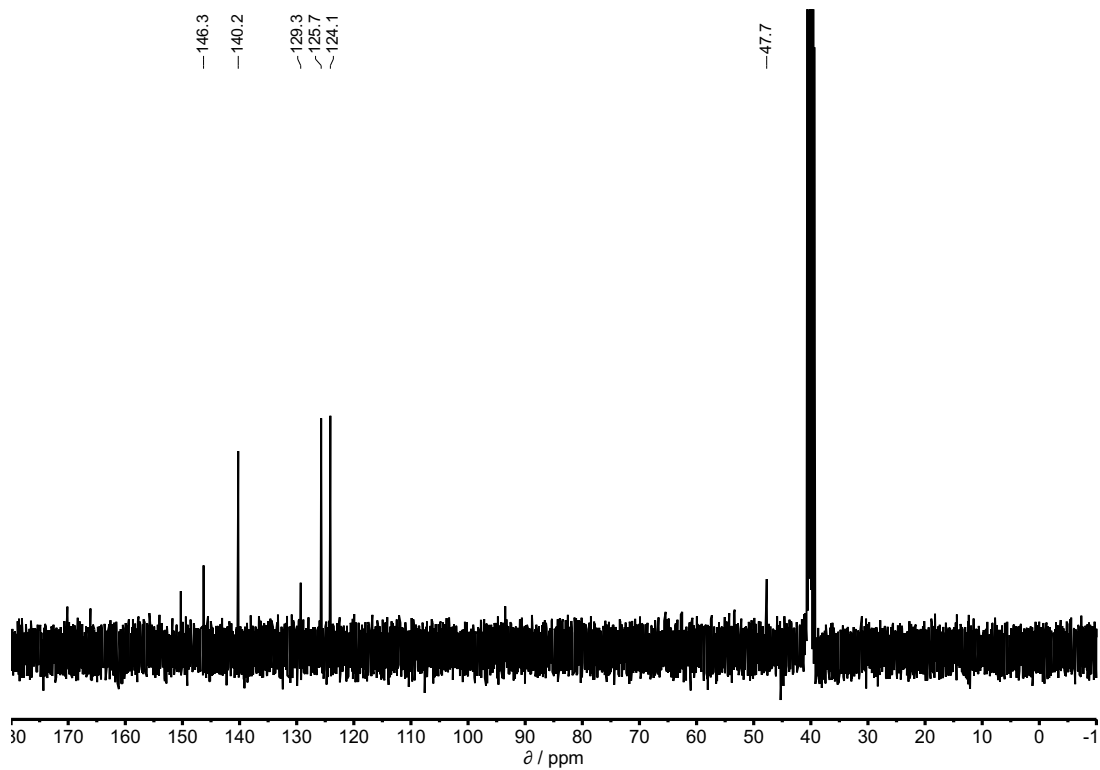


Figure S2. ^{13}C NMR spectrum (101 MHz, DMSO-d_6) of compound **5**.

3. Isothermal titration calorimetry (ITC) experiments

In a typical ITC experiment, the host (**2**) was dissolved in HPLC grade water with a concentration 30-40 times the expected dissociation constant, and the solution was loaded into the sample cell of the microcalorimeter. A 7-10 times more concentrated solution of guest (**3-6**) was loaded into the injection syringe. The number of injections was 35, and the volume of the injections was 8 μL . The thermogram peaks were integrated and thermodynamic parameters were calculated using the MicroCal PEAQ-ITC Analysis Software which uses the least-squares minimisation to obtain globally minimised parameters. In all cases the data fitted well to a simple 1:1 binding model. Blank experiments on the guests showed no self-association.

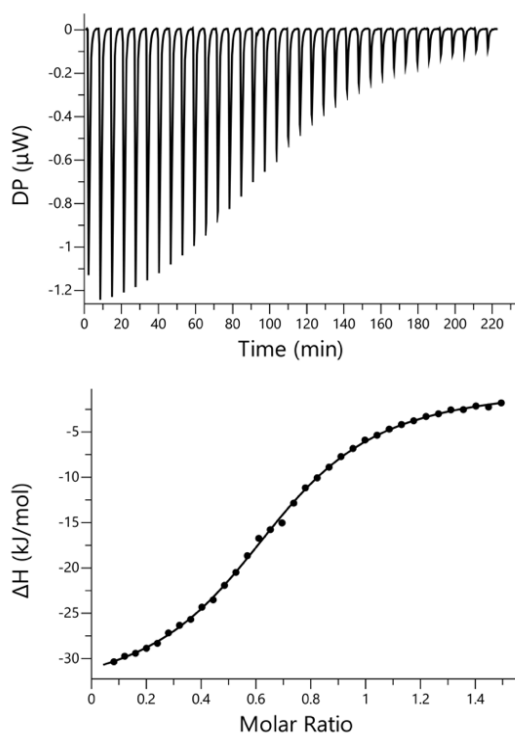


Figure S3. ITC data for titration of **3** (0.28 mM) into **2** (0.04 mM) in water at 298 K. The raw data for each injection is shown (differential power, DP), along with the least-squares-fit of the enthalpy change per mole of guest (ΔH) to a 1:1 binding isotherm.

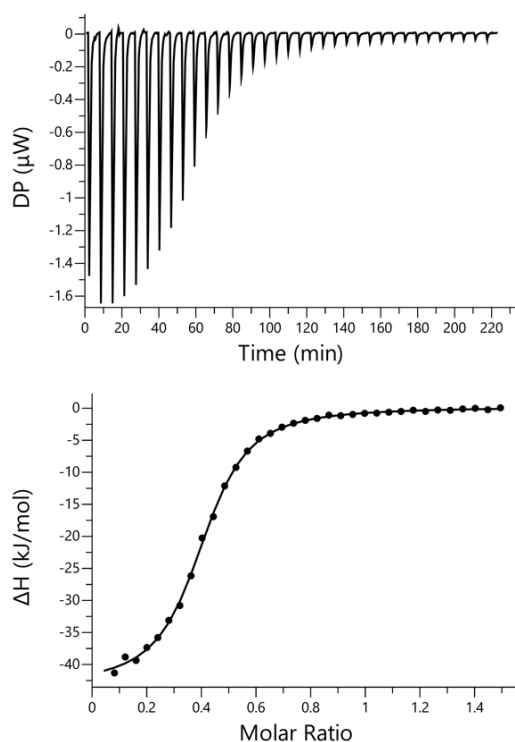


Figure S4. ITC data for titration of **4** (0.28 mM) into **2** (0.04 mM) in water at 298 K. The raw data for each injection is shown (differential power, DP), along with the least-squares-fit of the enthalpy change per mole of guest (ΔH) to a 1:1 binding isotherm.

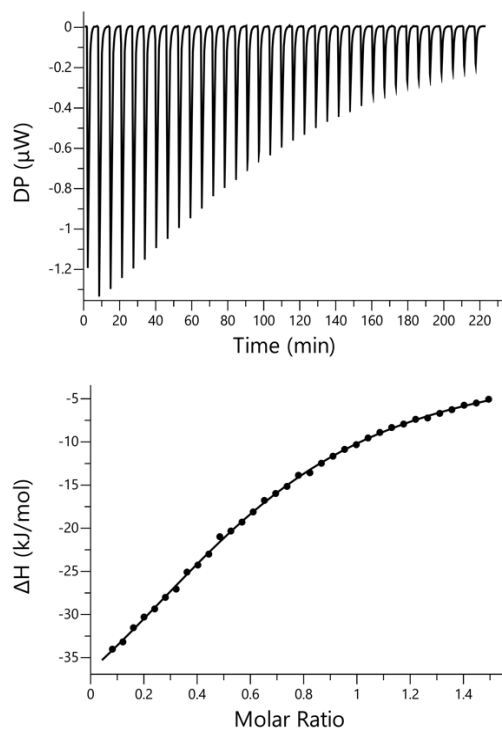


Figure S5. ITC data for titration of **5** (0.28 mM) into **2** (0.04 mM) in water at 298 K. The raw data for each injection is shown (differential power, DP), along with the least-squares-fit of the enthalpy change per mole of guest (ΔH) to a 1:1 binding isotherm.

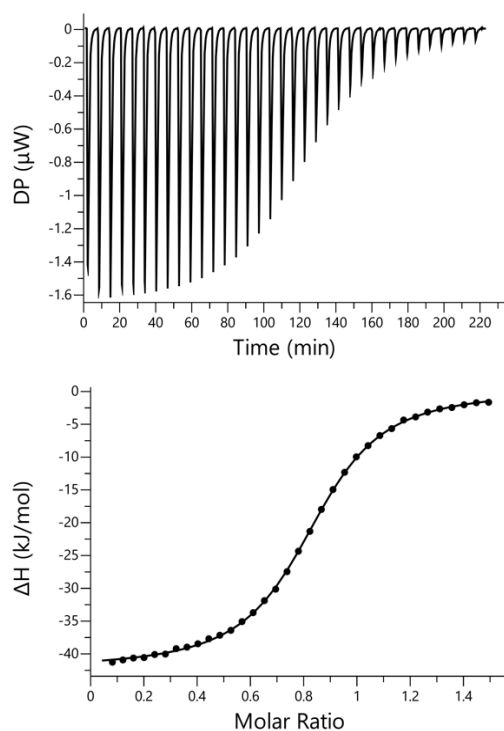


Figure S6. ITC data for titration of **6** (0.28 mM) into **2** (0.04 mM) in water at 298 K. The raw data for each injection is shown (differential power, DP), along with the least-squares-fit of the enthalpy change per mole of guest (ΔH) to a 1:1 binding isotherm.

Table S1. Thermodynamic parameters for formation of 1:1 complexes with host **2** in water at 298 K.^a

Guest	K / M^{-1}	$\Delta G^\circ / kJ mol^{-1}$	$\Delta H^\circ / kJ mol^{-1}$	$\Delta S^\circ / kJ mol^{-1}$	N
3 ^d	$3.3 \pm 0.6 \times 10^5$	-31.5 ± 0.4	-34.3 ± 0.3	2.8 ± 0.6	0.7 ± 0.0
4 ^d	$1.4 \pm 0.1 \times 10^6$	-35.0 ± 0.2	-43.6 ± 2.2	8.6 ± 2.3	0.8 ± 0.0
5	$7.6 \pm 0.2 \times 10^4$	-27.9 ± 0.1	-54.2 ± 0.0	26.3 ± 0.0	0.6 ± 0.0
6	$1.1 \pm 0.1 \times 10^6$	-34.5 ± 0.1	-42.2 ± 0.6	7.9 ± 0.7	0.8 ± 0.0

^a Errors are quoted as twice the standard deviation of at least three measurements.

4. Pairwise ^1H NMR competitive titrations

Competitive titration experiments were performed using calix[4]pyrrole **1**, and pyridine *N*-oxides **5** and **6** in non-buffered deuterium oxide. The association constant ratios between two competing complexes were determined by integrating selected proton signals in the acquired ^1H NMR spectra.

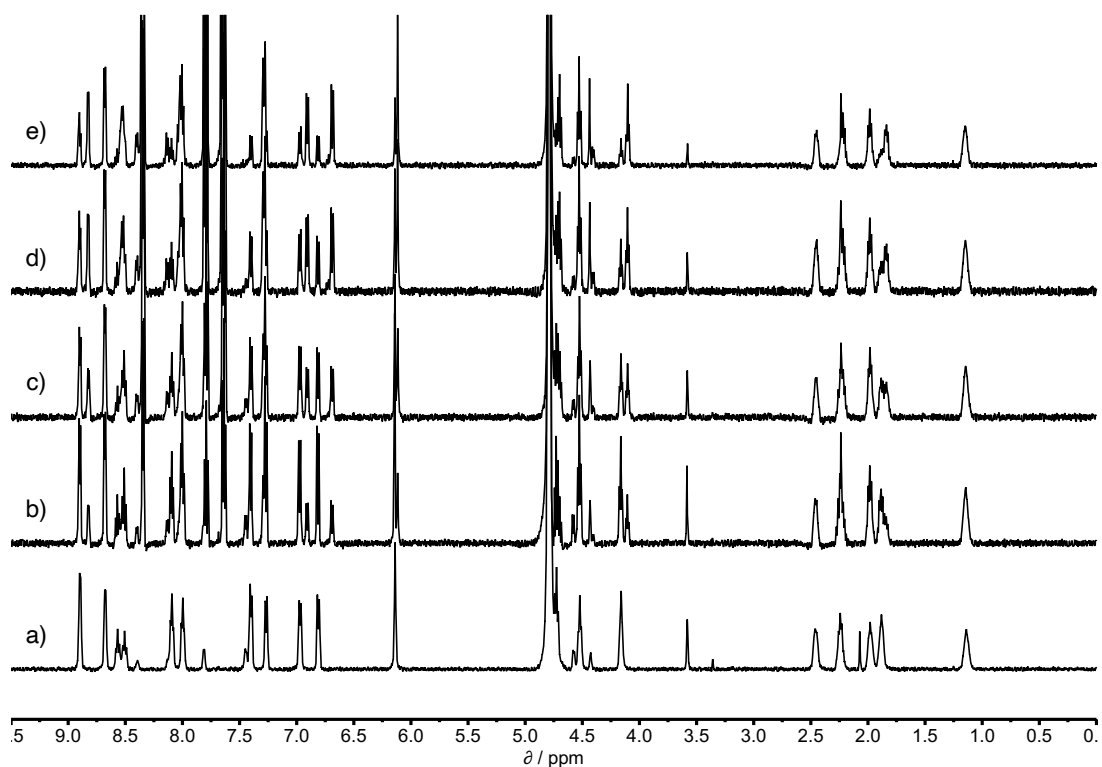


Figure S7. 500MHz ^1H NMR for titration of **3** into a mixture of **1** and **5** in D_2O at 298K. Concentrations are: a) **1**: 0.45 mM; **3**: 0 mM; **5**: 0.47 mM; b) **1**: 0.40 mM; **3**: 1.91 mM; **5**: 0.42 mM; c) **1**: 0.36 mM; **3**: 3.62 mM; **5**: 0.38 mM; d) **1**: 0.303 mM; **3**: 6.18 mM; **5**: 0.32 mM; e) **1**: 0.25 mM; **3**: 8.73 mM; **5**: 0.25 mM. Integration of selected proton signals indicated that $K(\mathbf{1}\cdot\mathbf{5}) = 21.1 \pm 10 \times K(\mathbf{1}\cdot\mathbf{3})$.

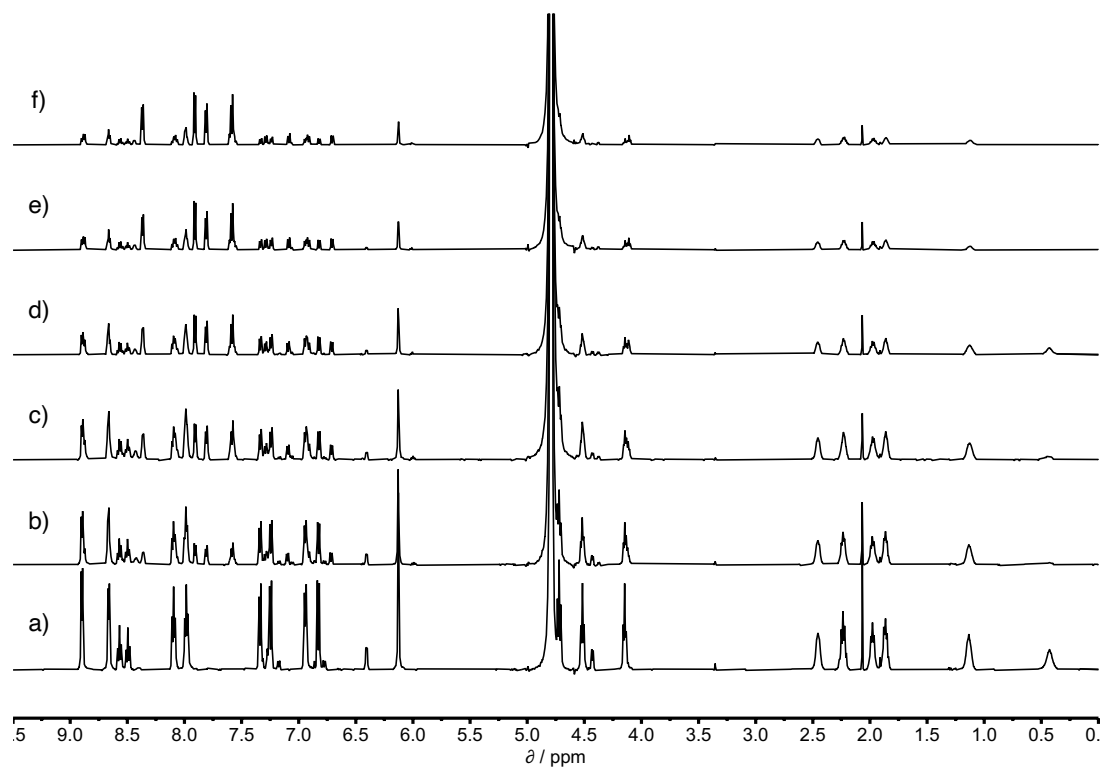


Figure S8. 500MHz ^1H NMR for titration of phenylpyridine *N*-oxide (**PPNO**) into a mixture of **1** and **6** in D_2O at 298K. Concentrations are: a) **1**: 0.50 mM; **PPNO**: 0 mM; **6**: 0.58 mM; b) **1**: 0.37 mM; **PPNO**: 0.42 mM; **6**: 0.43 mM; c) **1**: 0.29 mM; **PPNO**: 0.67 mM; **6**: 0.34 mM; d) **1**: 0.24 mM; **PPNO**: 0.83 mM; **6**: 0.28 mM; e) **1**: 0.18 mM; **PPNO**: 1.03 mM; **6**: 0.21 mM; f) **1**: 0.14 mM; **PPNO**: 1.15 mM; **6**: 0.17 mM. Integration of selected proton signals indicated that $K(\mathbf{1}\cdot\mathbf{6}) = 7.1 \pm 0.4 \times K(\mathbf{1}\cdot\mathbf{PPNO})^{\text{a}}$.

^a $K(\mathbf{1}\cdot\mathbf{PPNO})$ value reported previously in reference 2.

5. Error analysis

The propagation of errors (S) through ΔG° and the DMC $\Delta\Delta G^\circ$ has been calculated as follows:

$$S_{\Delta G^\circ} = RT \left(\frac{S_K}{K} \right) \quad \text{Eq. (1)}$$

where K is the experimentally measured association constant with an error of S_K .

$$S_{\Delta\Delta G^\circ} = \sqrt{S_{\Delta G^\circ A}^2 + S_{\Delta G^\circ B}^2 + S_{\Delta G^\circ C}^2 + S_{\Delta G^\circ D}^2} \quad \text{Eq. (2)}$$

Complexation-induced ^1H NMR chemical shifts

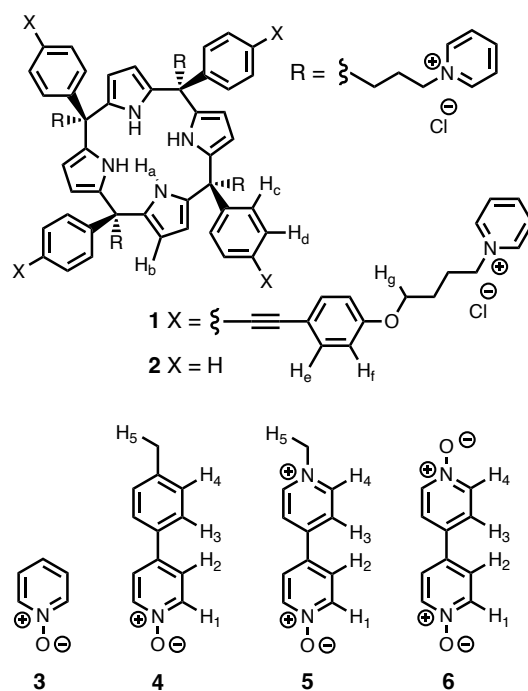


Figure S9. ^1H NMR proton labelling scheme.

Table S2. Differences between the ^1H NMR chemical shifts ($\Delta\delta$ in ppm) of the host signals in 1:1 complexes compared with the $1\cdot 3$ complex in deuterium oxide at 298 K.^a

Complex	H _a	H _b	H _c	H _d	H _e	H _f	H _g
$1\cdot 4$ ^b	n.d.	0.0	0.0	0.0	0.0	0.0	0.0
$1\cdot 5$	n.d.	0.0	+0.1	+0.1	+0.2	+0.1	0.0
$1\cdot 6$	n.d.	0.0	0.0	0.0	0.0	0.0	0.0

^a n.d. values could not be determined. ^b Values reported previously in reference 3.

Table S3. Limiting complexation-induced changes in ^1H NMR chemical shift ($\Delta\delta$ in ppm) for the guest signals in complex **A** of the DMC in deuterium oxide at 298 K.

Complex	H ₁	H ₂	H ₃	H ₄	H ₅
$1\cdot 4$ ^a	-4.0	-0.7	-0.9	-1.9	-0.8
$1\cdot 5$	-4.0	-0.7	n.d.	-1.1	-0.9
$1\cdot 6$	-4.0	-0.7	-1.0	-2.0	-

^a Values reported previously in reference 3.³

6. References

- 1 L. Escobar, A. Díaz-Moscoso and P. Ballester, *Chem. Sci.*, 2018, **9**, 7186–7192.
- 2 L. Escobar and P. Ballester, *Org. Chem. Front.*, 2019, **6**, 1738–1748.
- 3 G. Tobajas-Curiel, Q. Sun, J. K. M. Sanders, P. Ballester and C. A. Hunter, *Chem. Sci.*, 2023, **14**, 6226–6236.