

Electronic Supplementary Information

Controlled Synthesis and Alkaline Earth Ion Binding of Switchable Formamidoxime-Based Crown Ether Analogs

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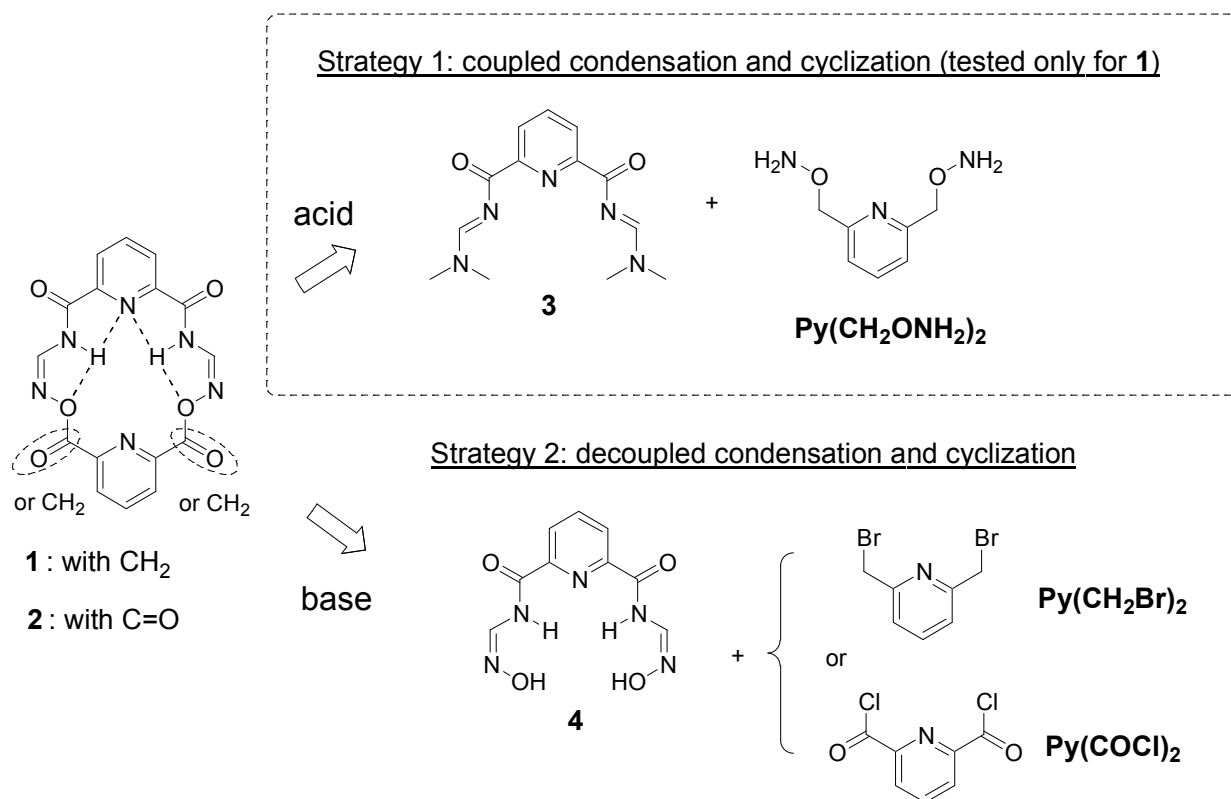
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A. Synthesis

A.1: Materials and Methods:

Commercially available compounds were used as received. Anhydrous diethyl ether, dichloromethane, tetrahydrofuran, acetonitrile, toluene were dried by passing through an activated alumina column. All reactions were performed under Argon (Ar) unless stated otherwise. Deuterated solvents were used as received, except for CDCl_3 which was sometimes neutralized by passing through a short column of basic alumina (such treated CDCl_3 will be signaled below by an asterisk, i. e. ' CDCl_3^* '). ^1H NMR and ^{13}C NMR were performed using 300 MHz, 400 MHz and 500 MHz Bruker instruments. Peak listings for all NMR spectra are given in ppm and referenced against the solvent residual signal. Thin layer chromatography (TLC) analysis was performed on silica gel with a pore diameter of 60 Å or activated basic Aluminum oxide with a pore diameter of 58 Å. Column chromatography was performed on silica gel with a particle size of 40-63 µm and a pore diameter of 60 Å.

A.2. Retrosynthetic analysis of **1** and **2**



*Scheme S1: Two strategies to access macrocycles **1** and **2** via acid-mediated addition/elimination (strategy 1, top) and base-mediated SN and addition/elimination reactions (strategy 2, bottom).*

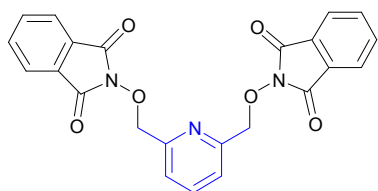
Other monofunctional formamidoximes were synthesized using a similar sequence: (i) formation of a reactive N,N-dimethylformamidine by reaction with DMF-DMA, (ii) reaction with nucleophilic alkoxyamines, promoted by acids.

A.3. Strategy 1 ^[1,2]

Bis(N',N'-dimethylformamidyl-N-acyl)-2,6-pyridine (3**):**^[1] Pyridyl-2,6-dicarboxamide (11 mmol, 1.0 equiv) was mixed with N,N-dimethylformamide dimethyl-acetal (DMF-DMA, 35 mmol, 3.2 equiv) in dimethyl sulfoxide (20 mL). The reaction was heated at 85 °C for 3.5 hours while the methanol by-product distilled off. After cooling to room temperature, the white precipitate was filtered and washed with diethyl ether. The resulting N,N-dimethylformamidine product (74 %) was then used without further purification. ¹H NMR (CDCl₃*, 500 MHz, 25 °C) 8.59 (s, 2 H), 8.31 (d, ³J = 7.5 Hz, 2 H), 7.82

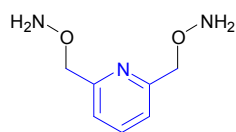
(t, $^3J = 7.5$ Hz, 1 H), 3.16 (br s, 6 H), 3.11 (br s, 6 H). ^{13}C NMR (CDCl_3^* , 125 MHz, 25 °C) 176.0, 161.3, 153.5, 137.0, 126.5, 41.3, 35.4. EI^+ -HRMS: calc. for $\text{C}_{13}\text{H}_{17}\text{N}_5\text{O}_2$: 275.1382; found: 275.1382 $[\text{M}]^+$, 232.0981 $[\text{M}-\text{Me}_2\text{N}-\text{H}]^+$, 220.0929 $[\text{M}-\text{Me}_2\text{N}-\text{H}-\text{C}]^+$, 205.0839 $[\text{M}-\text{Me}_2\text{N}-\text{H}-\text{C}-\text{NH}]^+$. EA calc. for $\text{C}_{13}\text{H}_{17}\text{N}_5\text{O}_2$: %C 56.71, %H 6.22, %N 25.44; found %C 56.38, %H 6.20, %N 25.22. Mp decomposed around 204 °C.

Py(CH₂ONPh₂)₂.^[2] Sodium hydride in mineral oil (60%, 1.24 g, 31 mmol, 2.8 eq) was washed with hexanes under argon, and suspended in dry DMF under argon. N-hydroxyphthalimide (4.24 g, 26 mmol, 2.4 eq) was then added portionwise as a solid, as the mixture was stirred in an ice / water bath. 2,6-Dibromomethylpyridine (3.0 g, 11 mmol, 1.0 eq) was then added at once and the mixture was stirred at 60 °C for 21 hours under argon. Water was then added at room temperature, the precipitate filtered and washed with copious amounts of water. The solid was then dis-



-solved in dichloromethane and washed with water. The organic layer was isolated, dried on sodium sulphate and concentrated in vacuo to give a white solid (3.83 g, 81 %). ^1H NMR (300 MHz; CDCl_3 ; 25 °C): 7.7-7.9 (m, 11 H), 5.26 (s, 4H).

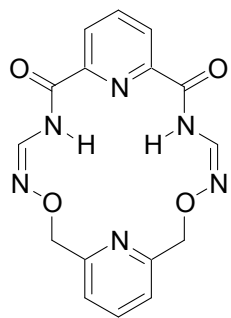
Py(CH₂ONH₂)₂.^[2] **Py(CH₂ONPh₂)₂** (3.83 g, 8.9 mmol, 1.0 eq) was suspended in 95% ethanol (150 mL). Most of the reagent was dissolved by heating gently, and hydrazine hydrate (1.1 mL, 22 mmol, 2.5 eq) was added. The mixture was then heated at 80 °C for 4 hours. Back to room temperature, the suspension was concentrated in vacuo to give a white solid which was taken up in diethyl ether (80 mL). The precipitate was filtered and washed with more diethyl ether (6 × 50 mL). The combined filtrates were concentrated in vacuo to give 1.53 g of a crude oil which was purified by column chromatography (silica gel, 100:1:5 Et₂O/Et₃N/CH₃OH) to give of a colourless oil (1.12 g, 6.63 mmol, 73 %). ^1H NMR (300 MHz; CDCl_3^* ; 25 °C): 7.72 (t, $^3J = 7.8$ Hz, 1 H), 7.32 (d, $^3J = 7.8$ Hz, 2 H), 5.61 (s, 4 H), 4.83 (s, 4 H). ^{13}C NMR (CDCl_3^* , 125 MHz, 25 °C)



157.6, 137.2, 120.7, 78.4. R_f (SiO_2 , 100:1:15 Et₂O/Et₃N/CH₃OH) = 0.25; $\text{C}_7\text{H}_{11}\text{N}_3\text{O}_2 \cdot 0.45 \text{ H}_2\text{O}$: calc. %C 47.42, %H 6.77, %N 23.70; found %C 47.66, %H 6.83, %N 23.31.

Macrocycle 1.^[2] Bis-reactive **Py(CH₂ONH₂)₂** nucleophile (18.4 mg, 0.108 mmol, 1.0 eq) and bis-reactive electrophile **3** (29.9 mg, 0.108 mmol, 1.0 eq) were mixed in 2 mL of anhydrous dichloromethane in the presence of acetic acid (24.7 μL , 0.43 mmol, 4.0 eq). The solution was

stirred at room temperature for 3 days, and washed with saturated aqueous potassium bicarbonate (2 mL). The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over sodium sulphate, concentrated in vacuo and purified by preparative TLC with 2:100 MeOH/ CH₂Cl₂ as an eluent to give pure **1** (10 mg, 26%). ¹H NMR (CDCl₃*, 500 MHz, 25



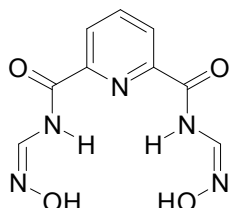
1

°C) 10.63 (d, ³J = 10 Hz, 2 H), 8.48 (d, ³J = 7.5 Hz, 2 H), 8.11 (t, ³J = 7.5 Hz, 1 H), 7.86 (d, ³J = 10 Hz, 2 H), 7.75 (t, ³J = 7.5 Hz, 1 H), 7.31 (d, ³J = 7.5 Hz, 2 H), 5.29 (s, 4 H). ¹H NMR (CD₃OD, 300 MHz, 25°C, low solubility) 8.65 (dd, ³J = 7.8 Hz, ³J = 8 Hz, 2 H), 8.27 (dd, ³J = 7.4 Hz, ³J = 8.2 Hz, 1 H), 7.93 (t, ³J = 7.7 Hz, 1 H), 7.89 (s, 1 H), 7.48 (d, ³J = 7.6 Hz, 2 H), 5.31 (s, 4 H). ¹³C NMR (CDCl₃*, 100 MHz, 25 °C) 162.0, 155.7, 148.1, 137.9, 134.3, 127.6, 122.6, 76.7. Mp: 200 °C (dec.). See details of crystal structures further in the electronic supplementary information.

Macrocycle 2: The synthesis of **2** was not attempted using this strategy because the preparation of the bis-alkoxyamino ester was difficult to complete.

A.4. Strategy 2

N2,N6-bis((Z)-(hydroxyimino)methyl)pyridine-2,6-dicarboxamide (4): Bis(N',N'-dimethyl-

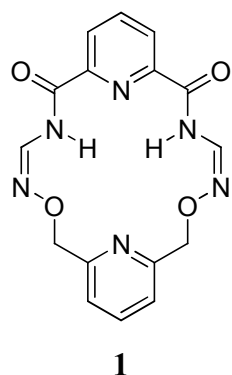


4

formamidyl-N-acyl)-2,6-pyridine (**3**) (3.09 g, 11.2 mmol) was mixed with a suspension of hydroxylamine hydrochloride (1.716 g, 24.7 mmol, 2.2 equiv.) in anhydrous dichloromethane (100 mL). Acetic acid (1.28 mL, 22 mmol, 2 equiv.) was then added at once and the suspension was stirred for 5 hours. The resulting white precipitate was collected,

washed with a small amount of dichloromethane then recrystallized in hot ethanol to give 2.10 g (76%) of the desired product as a white needle-like solid. ¹H NMR (DMSO-d₆, 400 MHz, 25 °C) 11.10 (s, 2 H), 10.71 (d, ³J = 10.0 Hz, 2 H), 8.36 (m, 2 H), 8.31 (m, 1 H), 7.74 (d, ³J = 10.0 Hz, 2 H). ¹³C NMR (DMSO-d₆, 100 MHz, 25 °C) 160.9, 147.6, 140.2, 133.1, 126.6. ESI⁺ HRMS: calc. for C₉H₉N₅O₄·H⁺: 252.0732, found: 252.0739. EA calc. for C₉H₉N₅O₄·1.1 H₂O: %C 39.89, %H 4.17, %N 25.84, found %C 40.25, %H 3.79, %N 25.53. Mp 183-185 °C. The inclusion of water is confirmed by the crystal structure (see below).

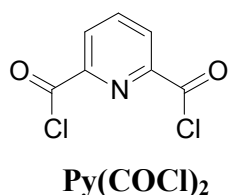
Macrocycle 1: A sodium hydride suspension (85.3 mg, 60% in mineral oil, 2.1 mmol, 2.8 equiv.)



Was washed with hexanes under argon, and suspended in dry DMF (12 mL) under argon. **4** (191 mg, 0.761 mmol) was then added and the yellow suspension stirred for an hour at room temperature. 2,6-Bis(bromomethyl)-pyridine (202 mg, 0.761 mmol, 1.0 equiv.) was then added at once. The yellow solution was stirred for 24 hours at room temperature. water (20 mL) was poured and the resulting light yellow precipitate was collected and purified by column chromatography (silica gel, 100:5 CH₂Cl₂ / MeOH, first fraction, R_f = 0.17)

to give 156 mg (0.441 mmol, 58%) of macrocycle **1** as a white solid. ¹H NMR (CDCl₃*, 500 MHz, 25°C) 10.63 (d, ³J = 10 Hz, 2 H), 8.48 (d, ³J = 7.5 Hz, 2 H), 8.11 (t, ³J = 7.5 Hz, 1 H), 7.86 (d, ³J = 10 Hz, 2 H), 7.75 (t, ³J = 7.5 Hz, 1 H), 7.31 (d, ³J = 7.5 Hz, 2 H), 5.29 (s, 4 H). ¹³C NMR (CDCl₃ with 2 drops of CD₃OD, 150 MHz, 25 °C) 162.6, 155.6, 148.0, 138.9, 138.1, 135.2, 127.3, 122.2, 76.1. Mp 200 °C (dec.). ESI⁺HRMS: calc. for C₁₆H₁₄N₆O₄·H⁺: 355.1154, found: 355.1151. EA calc. for C₁₆H₁₄N₆O₄·2.55 H₂O: %C 48.01, %H 4.81, %N 21.00; found %C 48.17, %H 4.61, %N 20.80.

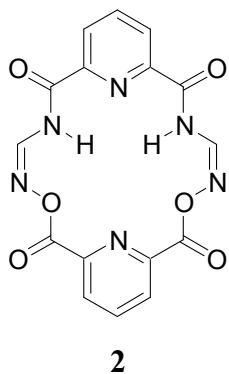
2,6-Pyridinedicarboxylic acid chloride (Py(COCl)₂): The acyl chloride was synthesized from dipicolinic acid using thionyl chloride under reflux condition. Thionyl chloride (20 mL, 0.28



mol, 28 equiv.) was added to pre-dried dipicolinic acid (2.1 g, 0.01 mol) and the reaction mixture was refluxed under argon for 13 h. The excess thionyl chloride was distilled off, purged with argon and dried under membrane pump to give pyridine-2,6-dicarbonyl dichloride (**Py(COCl)₂**), 2.5 g) as a pinkish solid in 96% yield.

Macrocycle 2:

a) Non-template reaction: To a solution of **4** (166.0 mg, 0.66 mmol) in anhydrous DMF (9.0 mL) under argon, was added 4-dimethylaminopyridine (DMAP, 161 mg, 1.32 mmol, 2.0 equiv.), and the mixture was stirred at room temperature for 30 min. 2,6- Pyridinedicarboxylic acid chloride (135.0 mg, 0.66 mmol, 1.0 equiv.) was then added at 0 °C. The mixture was stirred for 10 min at 0 °C and then allowed to warm to room temperature, and stirred overnight. The resulting white precipitate was filtered, and washed with diethyl ether to and purified by chromatography on silica gel, to yield macrocycle **2** (117 mg, 46% yield) as a white powder.



A single crystal was obtained by slow diffusion of diethyl ether into a solution of **2** in a mixture of chloroform and methanol to form colorless cube-like crystals (see crystal data below). ^1H NMR (CDCl_3^* with 3-4 drops of CD_3OD , 600 MHz, 25 °C) 12.9 (d, $^3J = 9.3$ Hz, 2 H), 8.56 (d, $^3J = 7.8$ Hz, 2 H), 8.46 (d, $^3J = 7.8$ Hz, 2 H), 8.27 (s, 2 H), 8.20 (t, $^3J = 7.8$ Hz, 2 H), 8.12 (t, $^3J = 7.8$ Hz, 2 H). ^{13}C NMR (CDCl_3^* with 3-4 drops of CD_3OD , 150 MHz, 25 °C) 163.0, 160.9, 147.5, 146.6, 140.3, 140.1, 139.4,

130.6, 128.2. ESI⁺-HRMS: calc. for $\text{C}_{16}\text{H}_{10}\text{N}_6\text{O}_6$: 382.2874; found: 383.0749 $[\text{M}\cdot\text{H}]^+$, 405.0541 $[\text{M}\cdot\text{Na}]^+$, 787.1257 $[2\text{M}\cdot\text{Na}]^+$. Mp ~220 °C (dec.). EA calc. for $\text{C}_{16}\text{H}_{10}\text{N}_6\text{O}_6$ 1.5 CH_3OH : %C 48.84, %H 3.75, %N 19.53; found %C 48.81, %H 3.50, %N 19.52.

b) Template reaction (LiCl): To a solution of **4** (50.0 mg, 0.20 mmol) in anhydrous DMF (4.0 mL) under argon, was added 4-dimethylaminopyridine (DMAP, 48.6 mg, 0.4 mmol, 2 equiv.) and lithium chloride (8.4 mg, 0.2 mol, 1 equiv.). The mixture was stirred for 30 min. 2,6-Pyridinedicarboxylic acid chloride (40.6 mg, 0.20 mmol, 1.0 equiv.) was then added at 0 °C. The mixture was stirred for 10 min at 0 °C and then allowed to warm to room temperature, and stirred overnight. The resulting white precipitate was filtered, and washed with diethyl ether and purified by chromatography on silica gel, to yield **2** (46.0 mg, 61 % yield) as a white powder.

A.5. Preparation of the complexes

Ba(1-2 H⁺): Macrocyclic **1** (7.7 mg, 0.0218 mmol) and barium triflate (14.8 mg, 0.0218 mmol, 1.0 equiv.) were dissolved into a 3:2 $\text{MeOH}/\text{CH}_2\text{Cl}_2$ mixture (0.8 mL). A tetramethylammonium hydroxide solution (0.218 mmol, 10 equiv.) was then added and the solution was fully mixed. A white precipitate gradually appeared and was collected by centrifuge after 20 minutes. The collected white solid was washed with a small amount of methanol and chloroform, and dried to give 3.2 mg of pure Ba.**1** as white powder (30%). ^1H NMR ($\text{DMSO}-d_6$, 25 °C, 400 MHz): 8.15 (d, $^3J = 7.7$ Hz, 2 H), 8.01 (t, $^3J = 7.7$ Hz, 1 H), 8.01 (s, 2 H), 7.87 (t, $^3J = 7.5$ Hz, 1 H), 7.37 (d, $^3J = 7.8$ Hz, 2 H), 5.29 (s, 4 H). ESI-MS (+ mode; sample prepared *in situ* by mixing **1**, $\text{Ba}(\text{OTf})_2$, 1.0 equiv., and tetramethylammonium hydroxide, 2.0 equiv., in DMSO): 355 (1.H^+), 491 ($[\text{1-2H}^+, \text{Ba}]\cdot\text{H}^+$). EA calc. for $\text{C}_{16}\text{H}_{12}\text{N}_6\text{O}_4\text{Ba}\cdot 0.4 \text{CHCl}_3\cdot 0.3 \text{CH}_3\text{OH}$: %C 36.67, %H 2.51, %N 15.36; found %C 36.86, %H 2.12, %N 15.02.

Ca(1-2 H⁺): Macrocycle **1** (5.0 mg, 0.0141 mmol) and calcium triflate (4.77 mg, 0.0141 mmol, 1.0 equiv.) were dissolved in a 1:1 mixture of CHCl₃*:CH₃OH (0.6 mL) to give a clear solution. Tetramethylammonium hydroxide (25.52 mg, 0.141 mmol, 10 equiv.) was dissolved in 1.0 mL of the same solvent to give a clear solution of concentration 0.141 mol/L. The above TMAH solution (500 µL) was added to the prepared solution of **1** and Ca(OTf)₂ to give a white precipitate. After centrifugation, the white precipitate was re-dispersed in 1:1 CHCl₃*:CH₃OH (1.0 mL), sonicated and centrifuged again. Such dispersion-sonication-centrifugation procedure was repeated. The final white precipitate was dried under reduced pressure to give 3.7 mg of a white powder (67%). ¹H NMR (*d*₆-DMSO, 500 MHz, 25 °C) 8.21 (d, ³*J* = 7.6 Hz, 2 H), 8.16 (s, 2 H), 8.12 (t, ³*J* = 7.6 Hz, 1 H), 7.93 (t, ³*J* = 7.7 Hz, 1 H), 7.40 (d, ³*J* = 7.8 Hz, 2 H), 5.31 (s, 4 H). ESI-MS (– mode; sample prepared *in situ* by mixing MH, Ca(OTf)₂, 1.0 equiv., and tetramethylammonium hydroxide, 2.0 equiv., in DMSO): 427 ([**1**-2 H⁺)Ca. Cl]⁺), 591 ([**1**-2 H⁺)Ca. OTf]⁺), 819 ([**1**-2 H⁺)Ca]₂. Cl⁺), 933 ([**1**-2 H⁺)Ca]₂.OTf⁺). EA calc. for C₁₆H₁₂N₆O₄Ca. 0.3 CHCl₃.0.2 CH₃OH: %C 45.60, %H 3.04, %N 19.34; found %C 45.99, %H 2.97, %N 18.94.

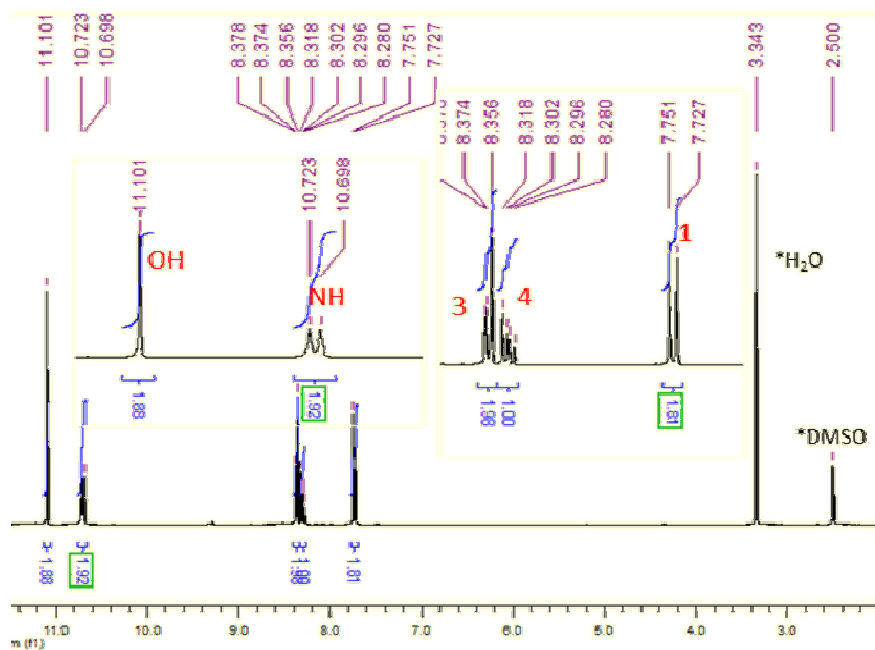
References:

- [1] Weiwen Zhao, Ruiyao Wang, Nicholas Mosey, Anne Petitjean, *Org. Lett.* **2011**, *13*, 5160-5163.
- [2] Weiwen, Zhao, Ruiyao Wang, Anne Petitjean, *Org. Biomol. Chem.* **2011**, *9*, 7647-7651.

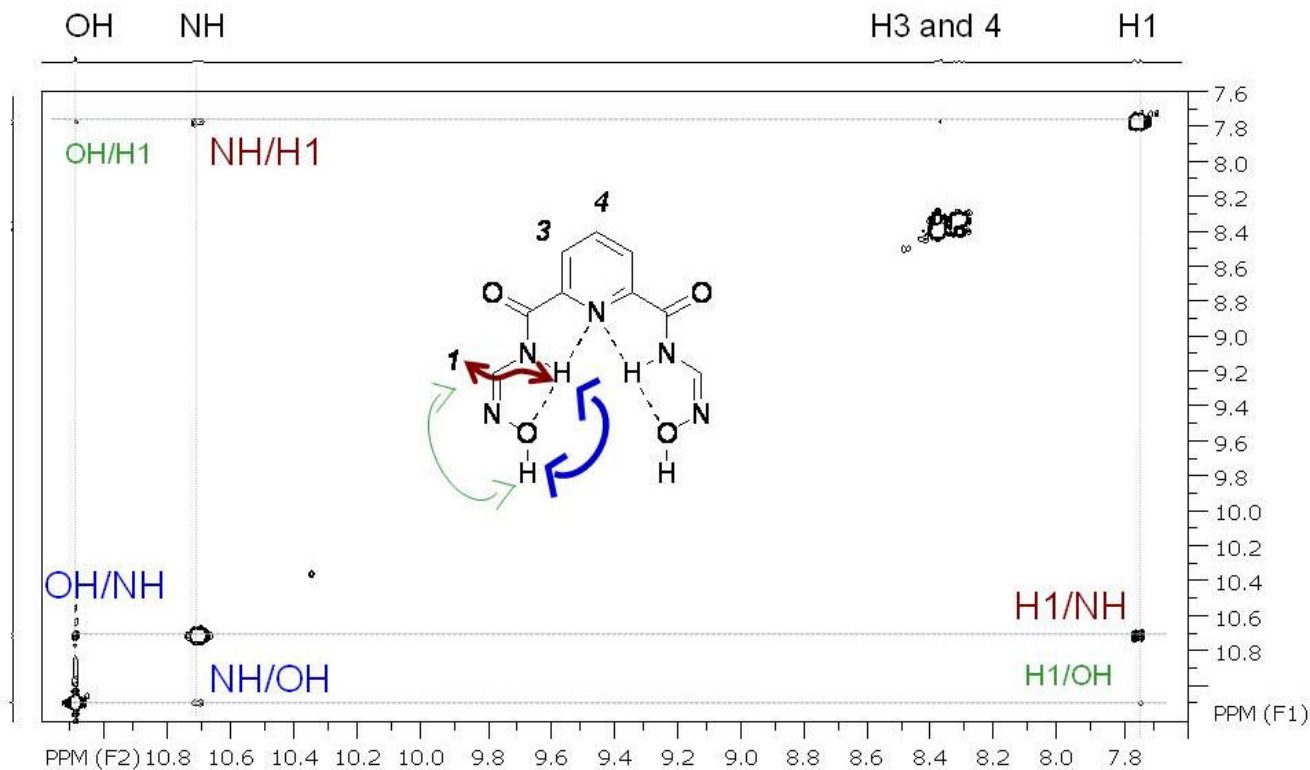
B. NMR (and Mass Spectrometry) data for new compounds

Curved precursor 4

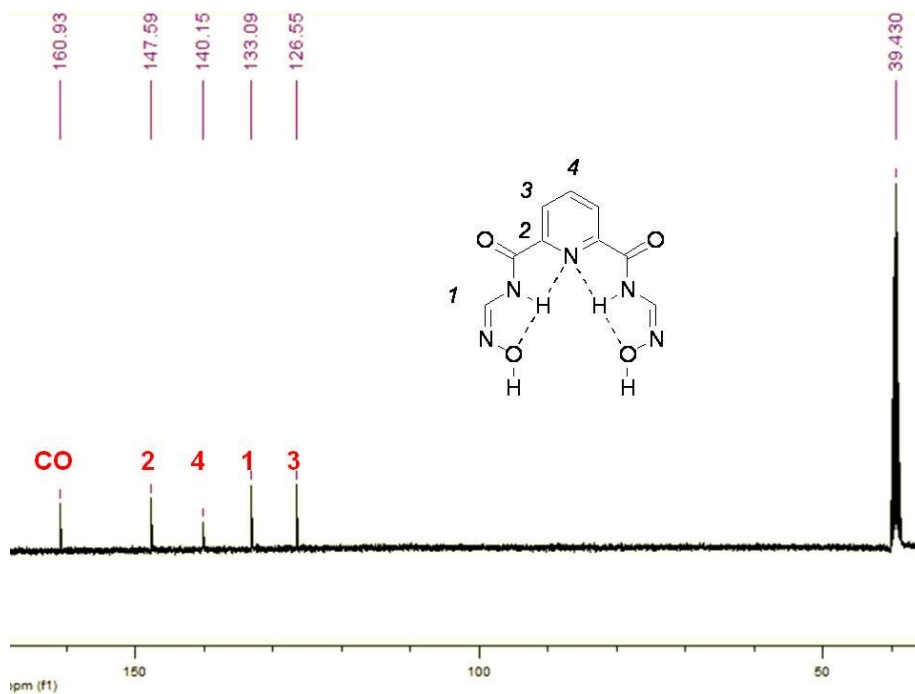
^1H NMR (DMSO- d_6 , 400 MHz, 25°C)



^1H - ^1H NOESY NMR of 4 (DMSO- d_6 , 500 MHz, 25°C)

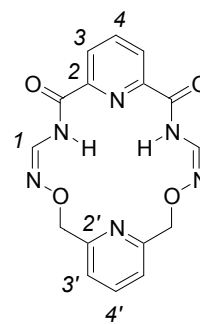
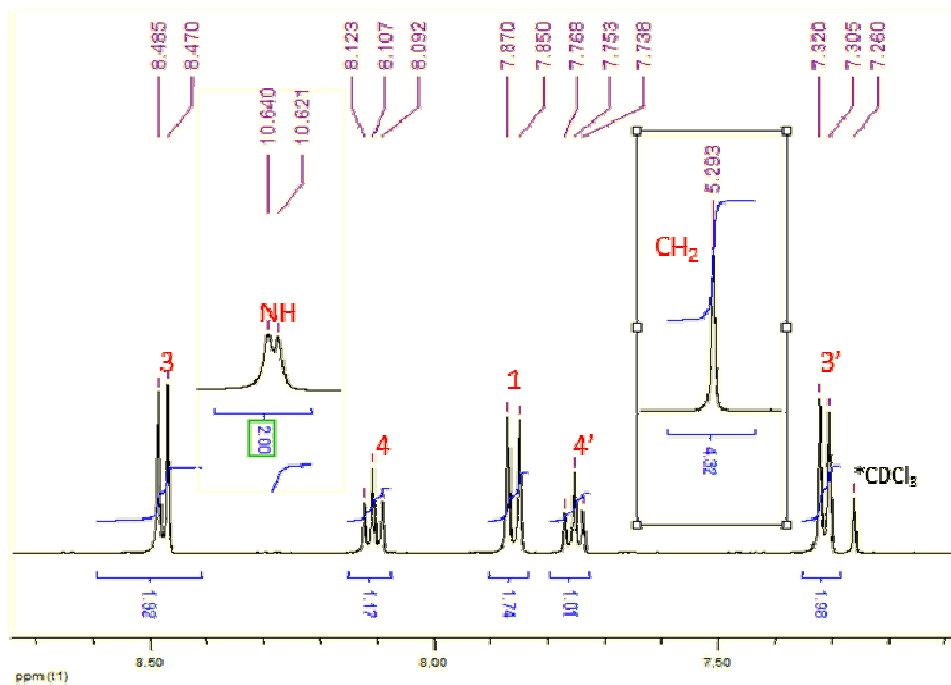


^{13}C NMR of **4** (DMSO- d_6 , 100 MHz, 25°C)



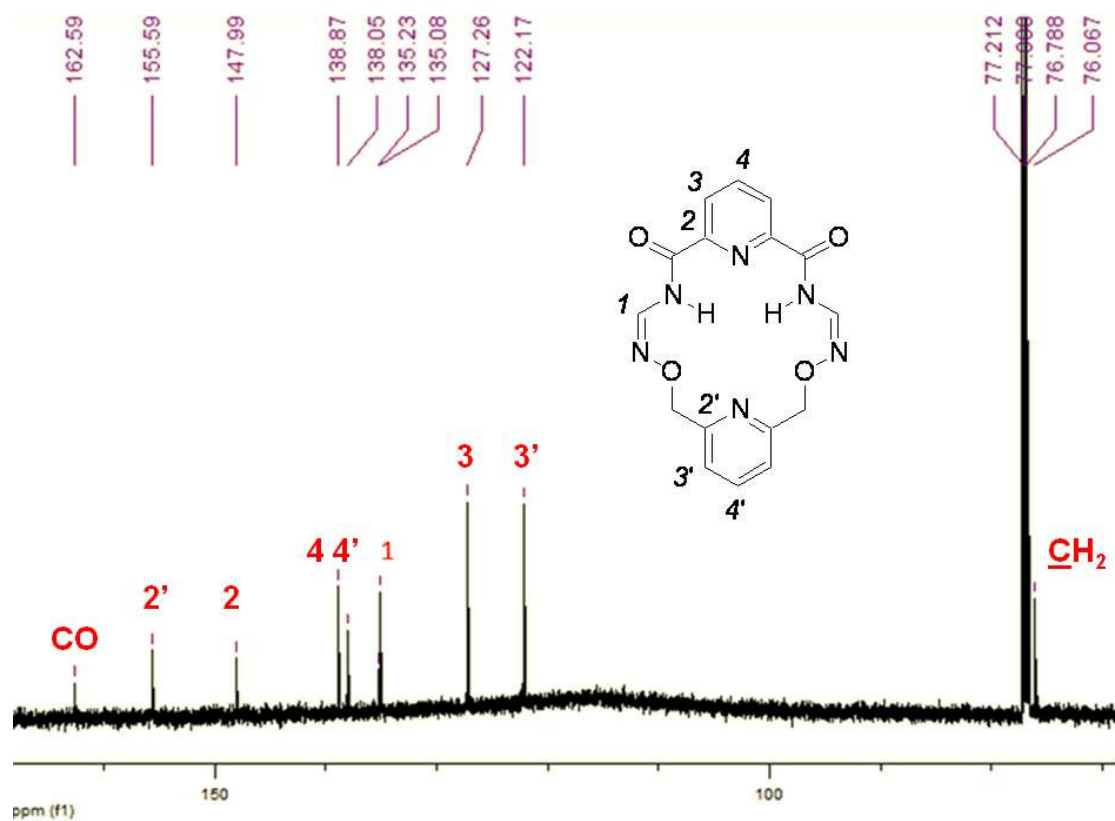
Macrocycle 1

^1H NMR (CDCl $_3$ *, 500 MHz, 25°C)

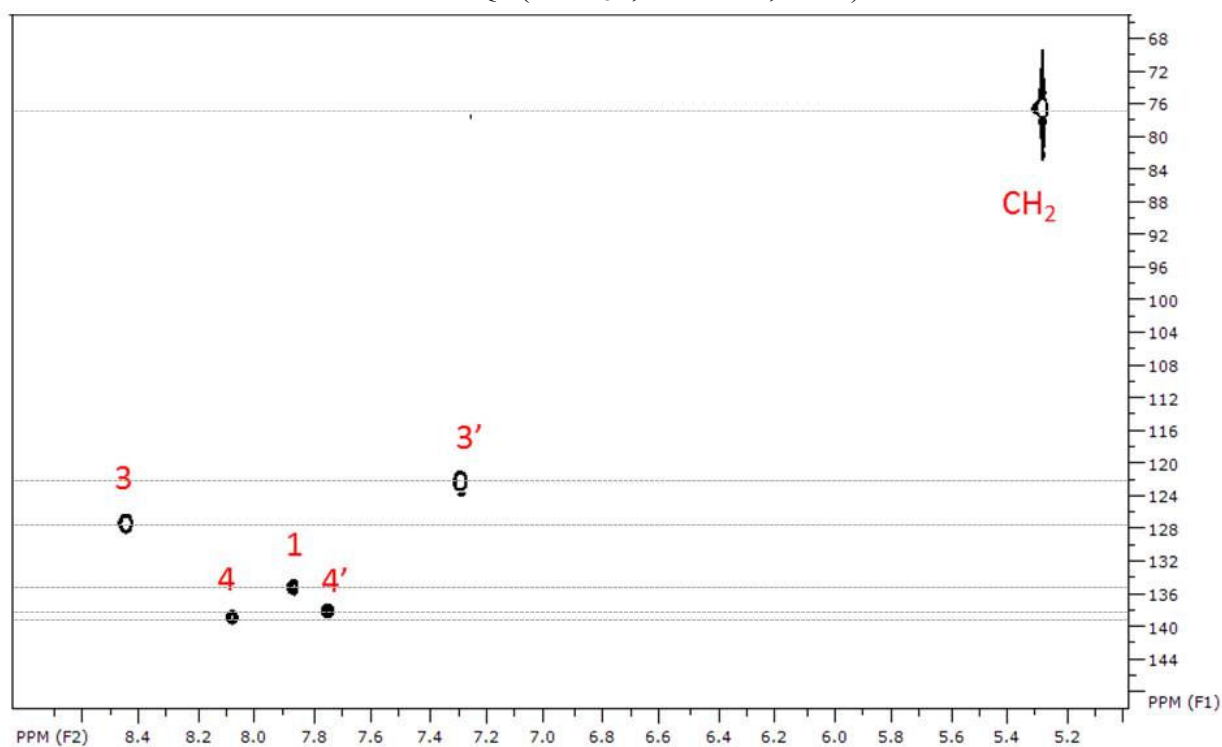


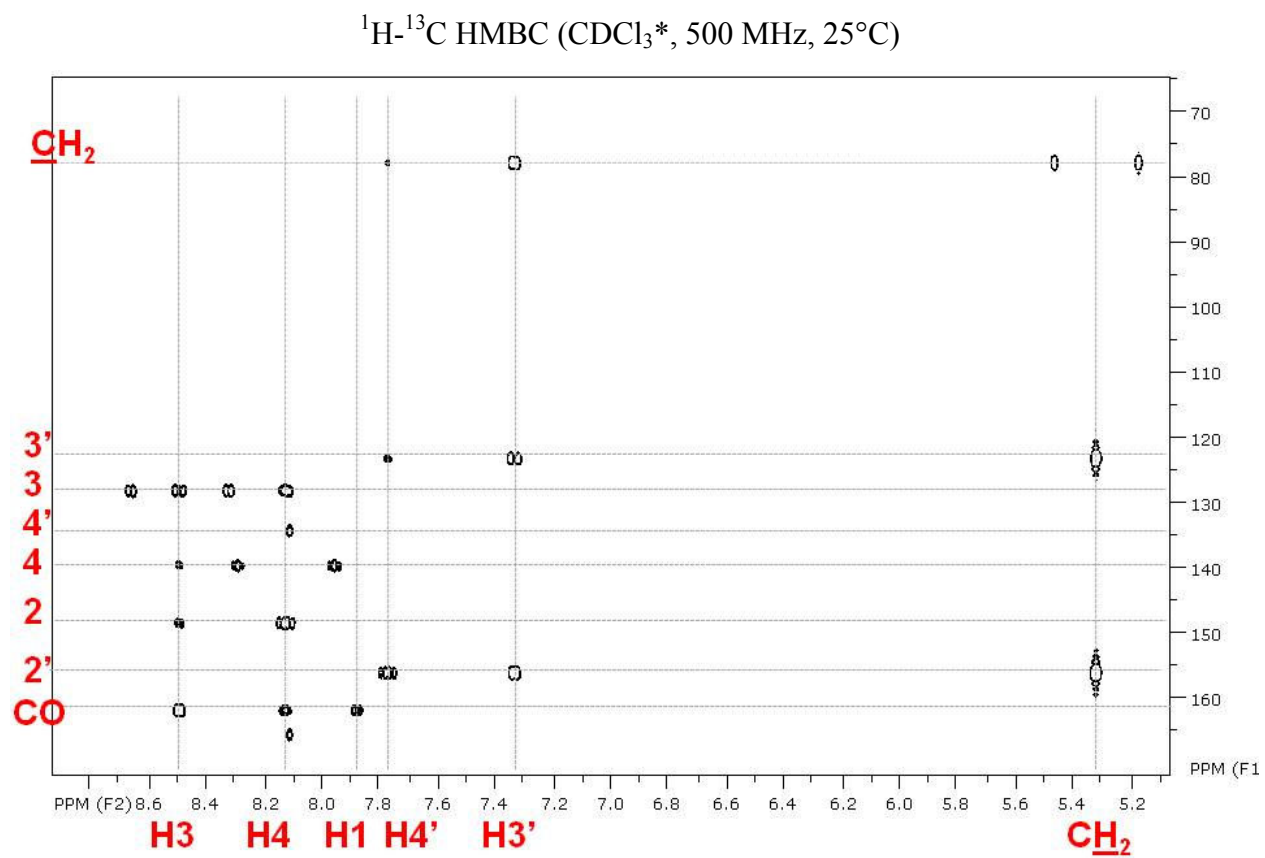
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^{13}C NMR (CDCl_3 with 3-4 drops of CD_3OD , 150 MHz, 25°C)

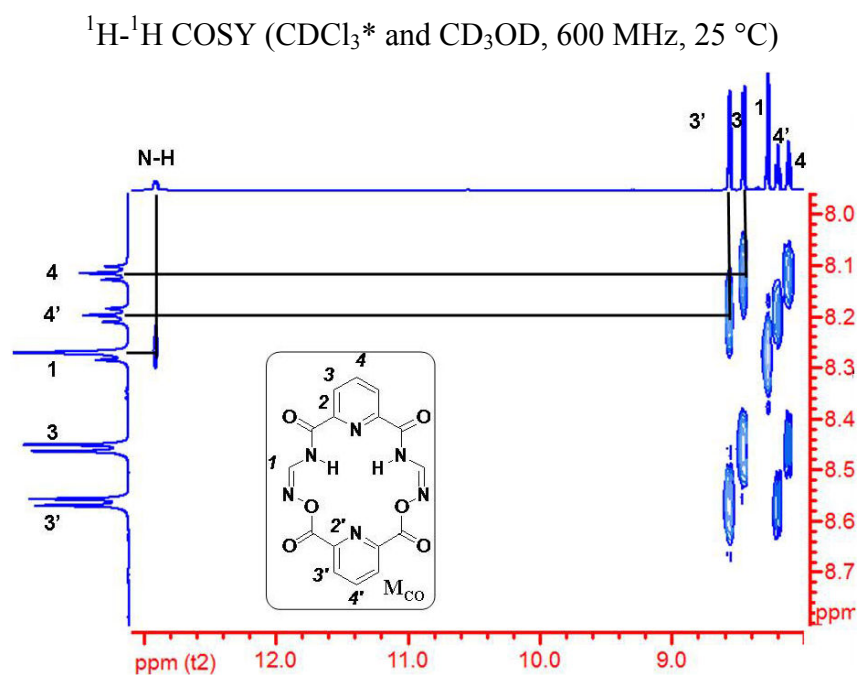
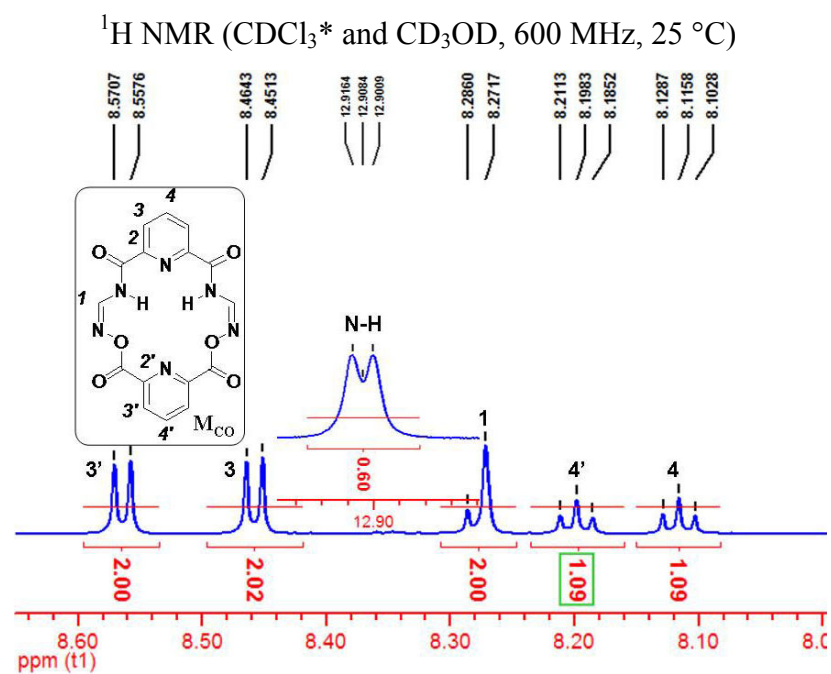


^1H - ^{13}C HSQC(CDCl_3^* , 600 MHz, 25°C)

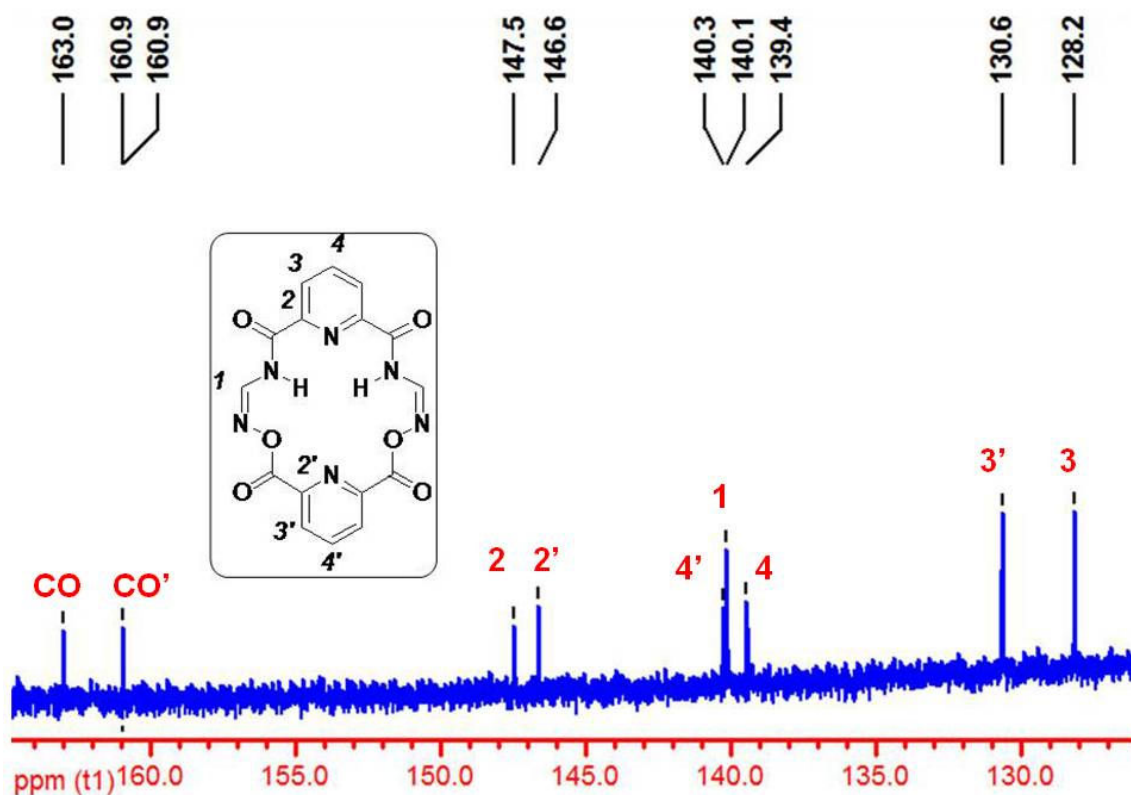




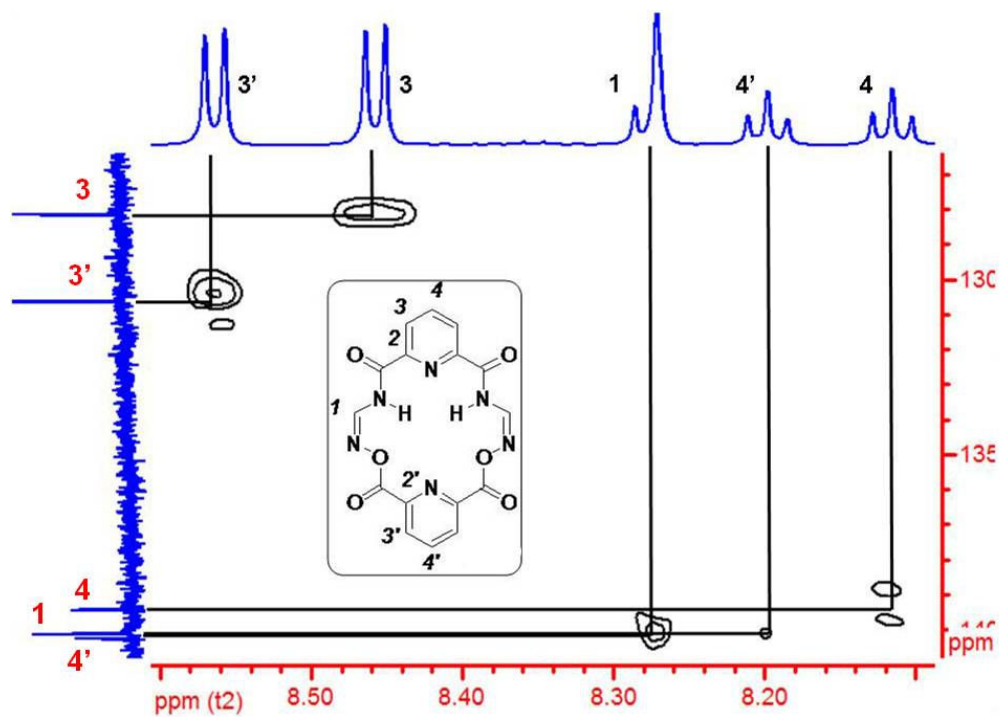
Macrocycle 2:



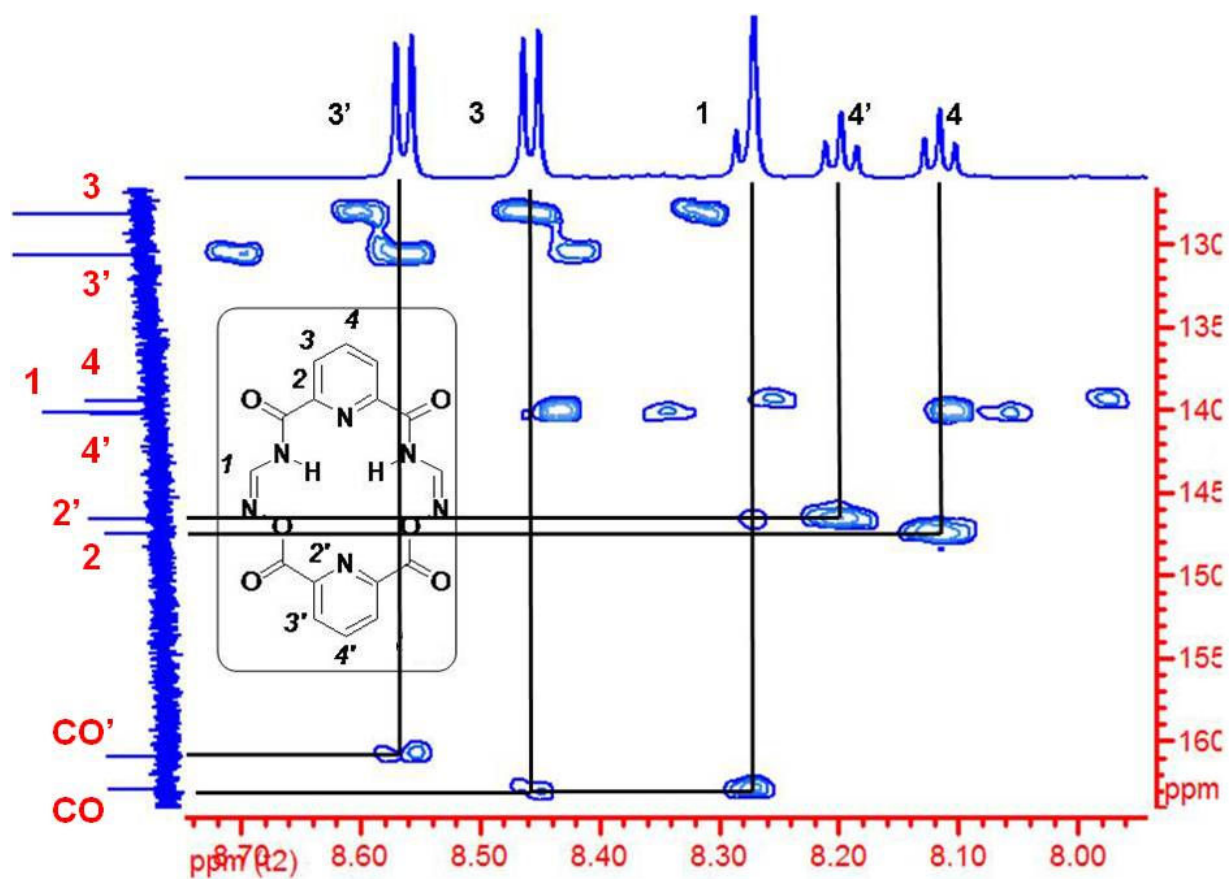
^{13}C NMR (CDCl_3^* and CD_3OD , 150 MHz, 25 °C)



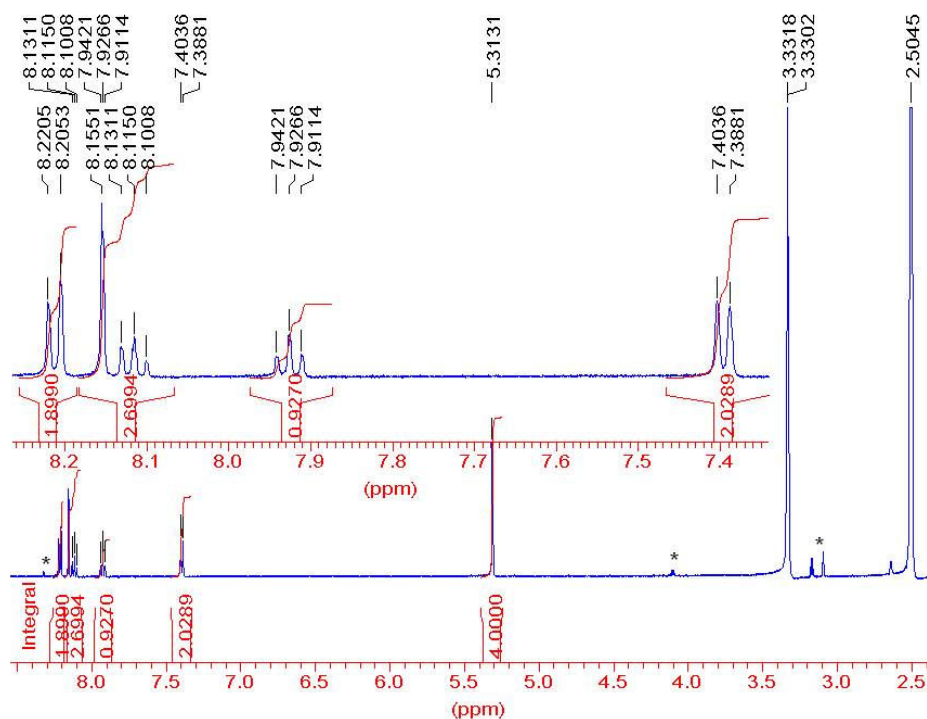
^1H - ^{13}C HSQC (CDCl_3^* and CD_3OD , 600 MHz, 25 °C)



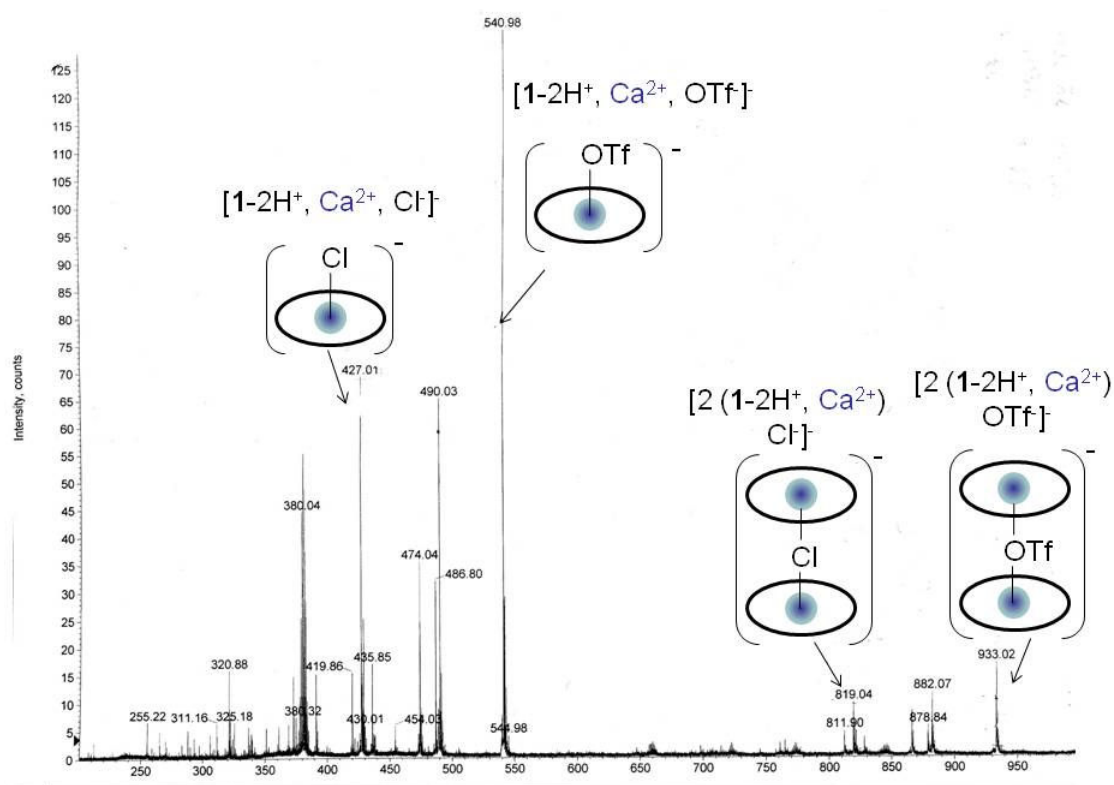
^1H - ^{13}C HMBC (CDCl_3^* and CD_3OD , 600 MHz, 25 °C)



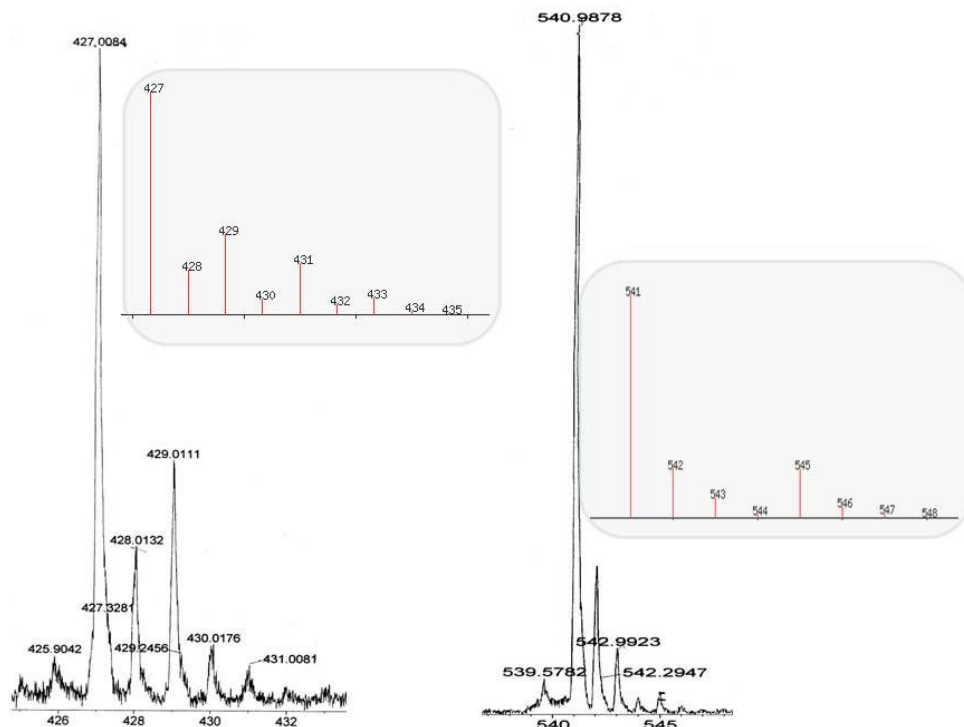
Ca(1-2H⁺)



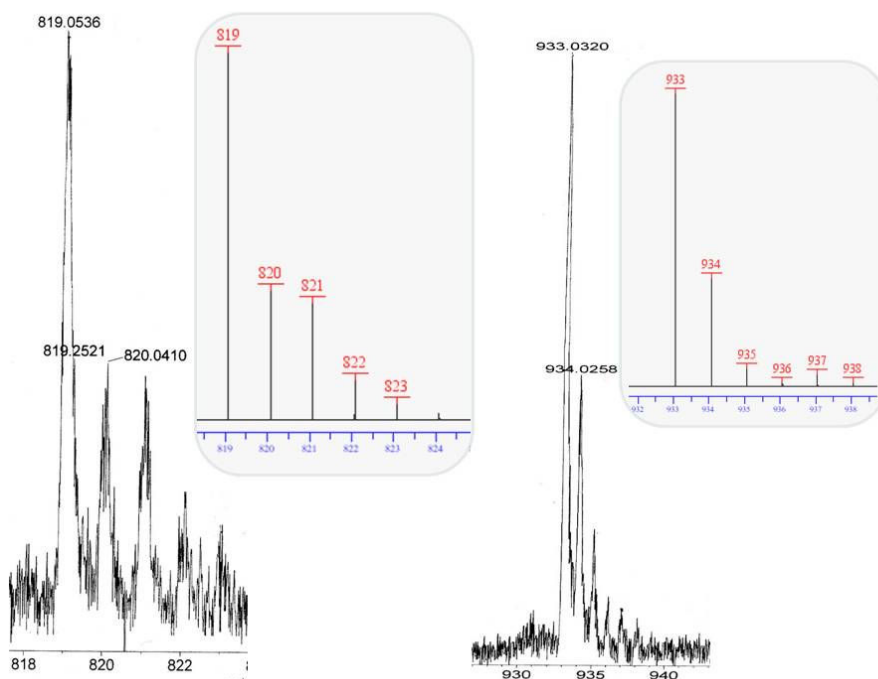
¹H NMR of isolated Ca(1-2H⁺) (DMSO-d₆, 25 °C, 500 MHz, ‘*’ signifies solvent residues, CHCl₃ at 8.32 ppm, and CH₃OH at 3.16 and 4 ppm).



ESI-MS (- mode) Ca(1-2 H⁺): full spectrum.

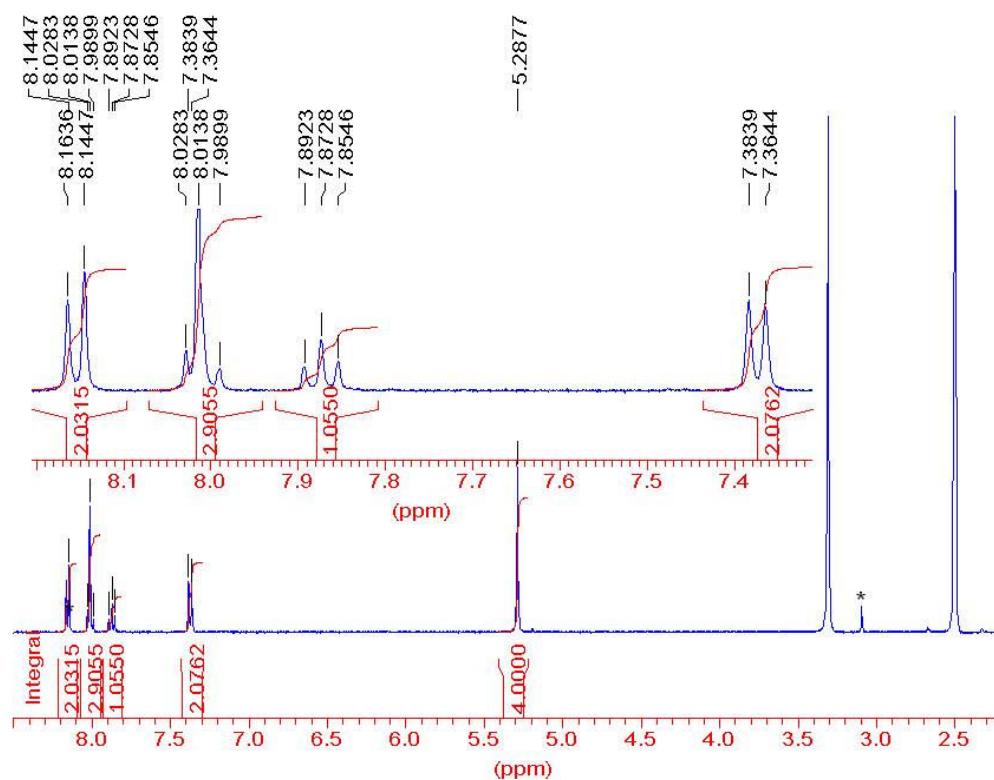


ESI-MS (- mode) $\text{Ca}(\mathbf{1-2} \text{H}^+)$: zoom on experimental and simulated (insert) isotope patterns at m/z 427 and 541 for $[\text{Ca}(\mathbf{1-2} \text{H}^+)]\cdot\text{Cl}^-$ and $[\text{Ca}(\mathbf{1-2} \text{H}^+)]\cdot\text{OTf}$ respectively.

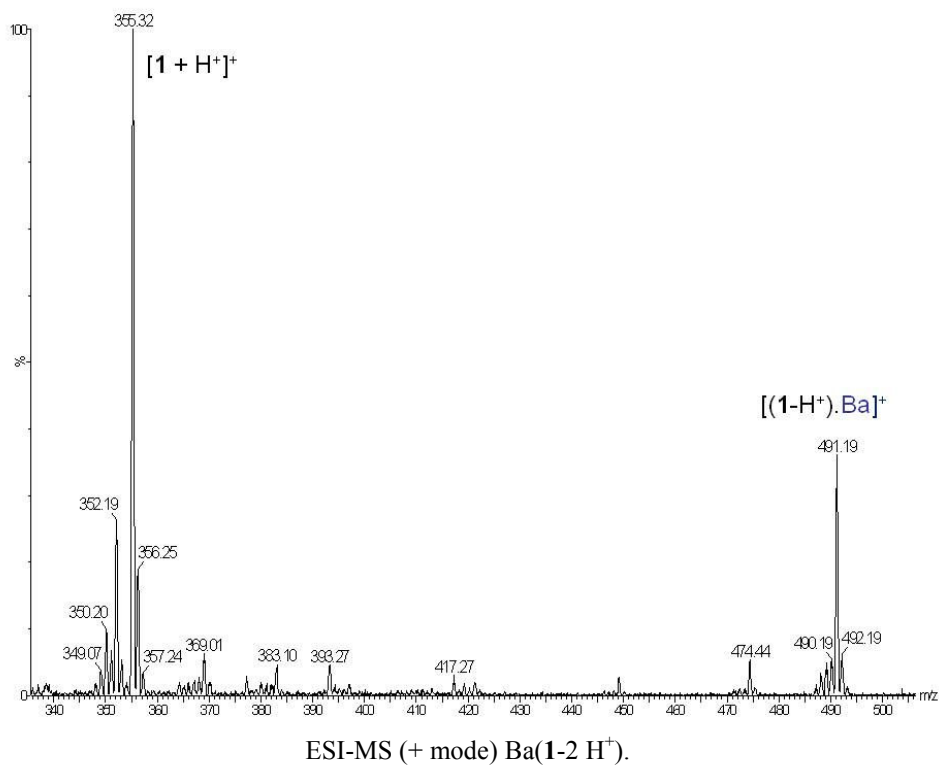


ESI-MS (- mode) $\text{Ca}(\mathbf{1-2} \text{H}^+)$: zoom on experimental and simulated (insert) isotope patterns at m/z 819 and 933 for $[\text{Ca}(\mathbf{1-2} \text{H}^+)]_2\cdot\text{Cl}^-$ and $[\text{Ca}(\mathbf{1-2} \text{H}^+)]_2\cdot\text{OTf}$ respectively.

Ba(1-2 H⁺)



¹H NMR of isolated Ba(1-2 H⁺) (DMSO-d₆, 25 °C, 400 MHz).

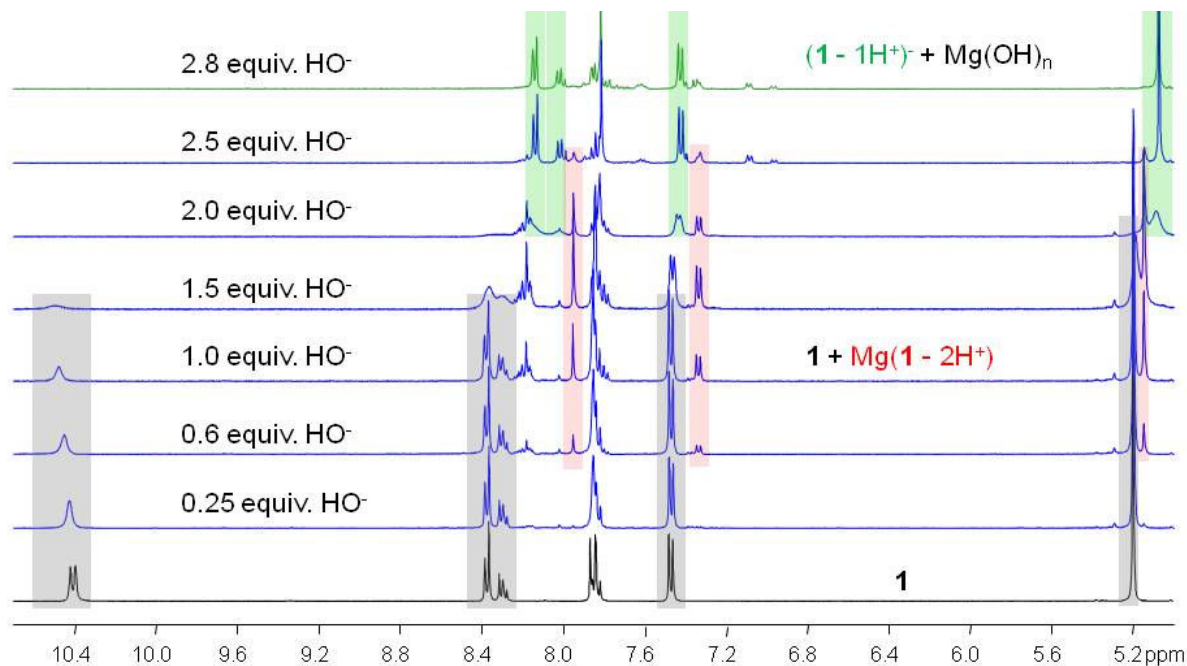


ESI-MS (+ mode) Ba(1-2 H⁺).

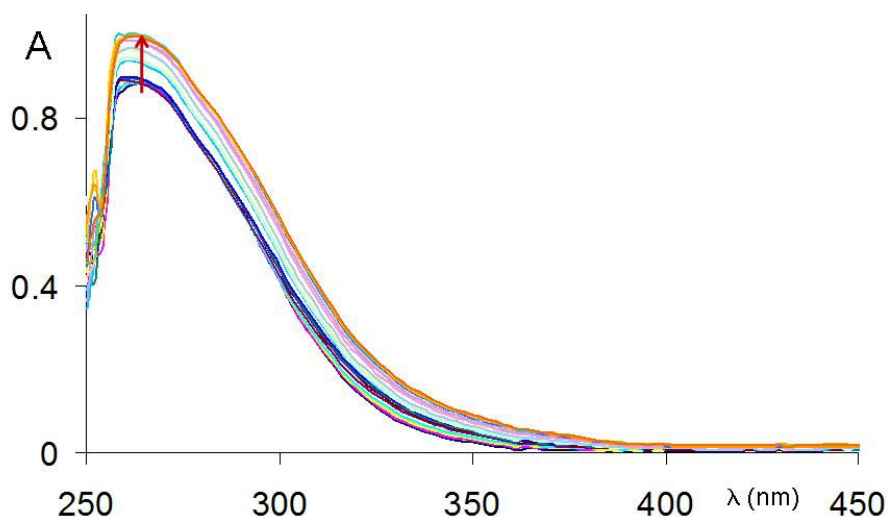
C. Binding studies

C.1: Base triggered coordination

a) Base-induced **magnesium** complexation (macrocycle **1**).

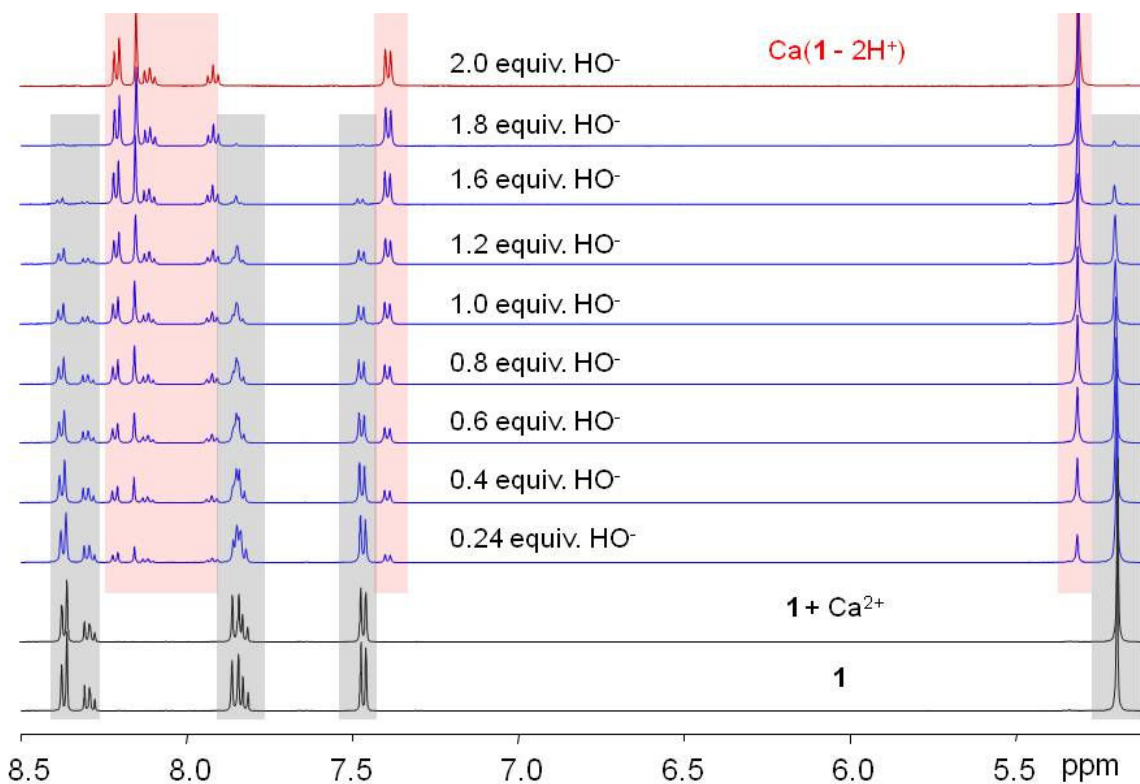


^1H NMR monitoring of base-induced complexation of Mg^{2+} by **1** (up to 2 equiv. HO^-), followed by decomplexation via competition with HO^- (DMSO-d_6 , 500 MHz, 25°C).

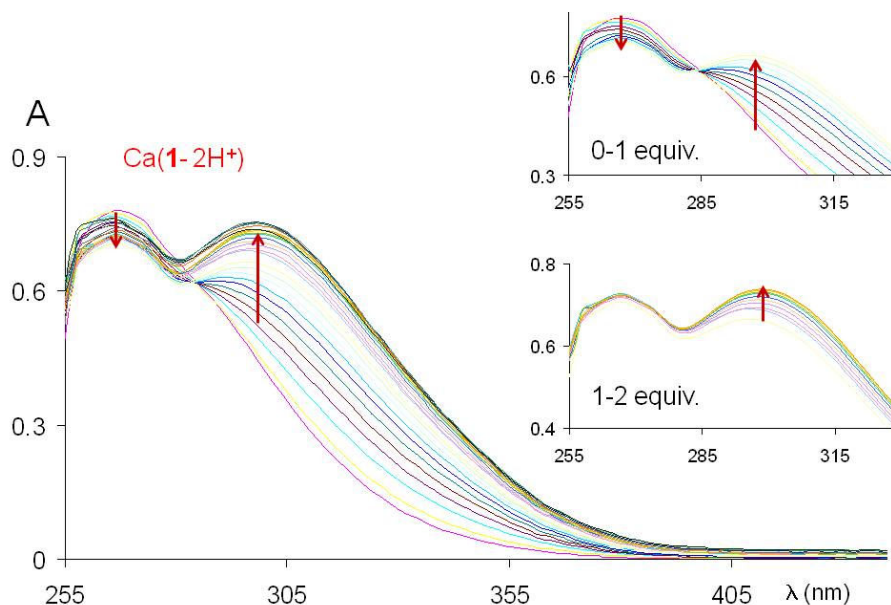


UV-vis monitoring of the base titration of hydroxide base to a 1:1 mixture of **1** and $\text{Mg}(\text{OTf})_2$ (titration of 0 to 2.0 equiv. of NMe_4HO in DMSO , 3.8×10^{-5} M).

b) Base-induced **calcium** complexation (macrocycle **1**).

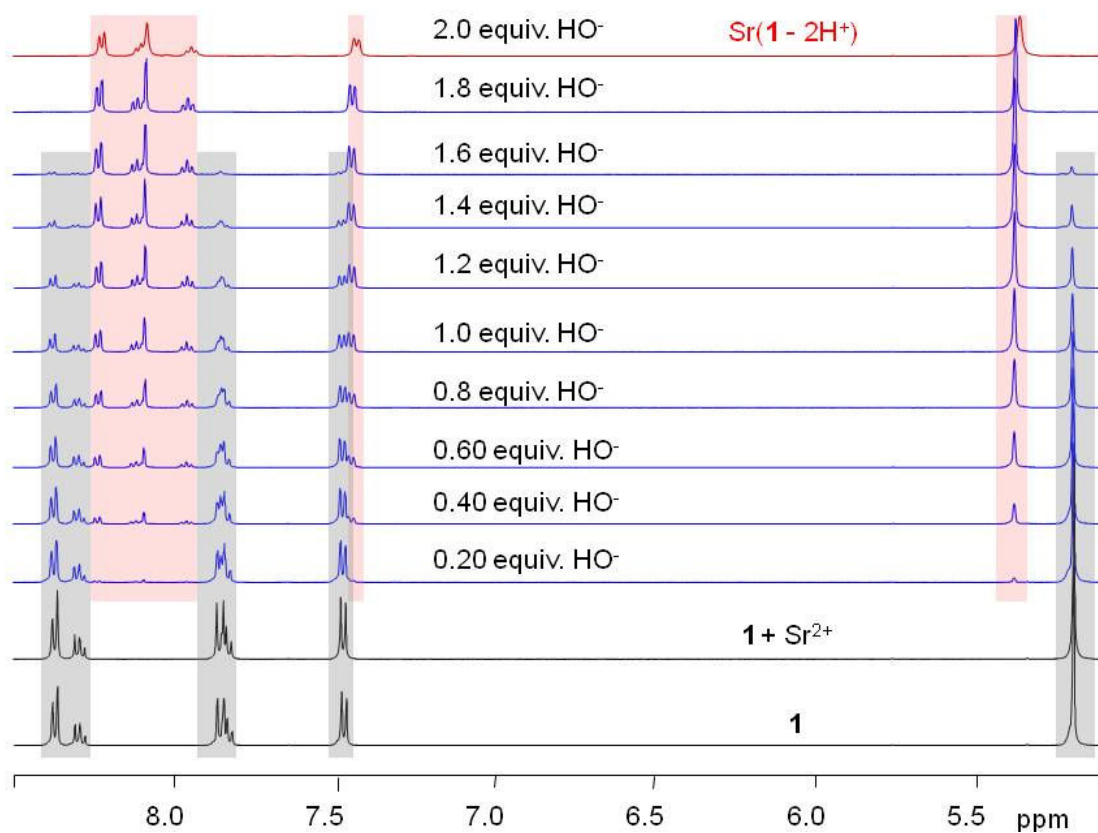


^1H NMR monitoring of base-induced complexation of Ca^{2+} by **1** (up to 2 equiv. HO^-) in DMSO-d_6 (500 MHz, 25°C).

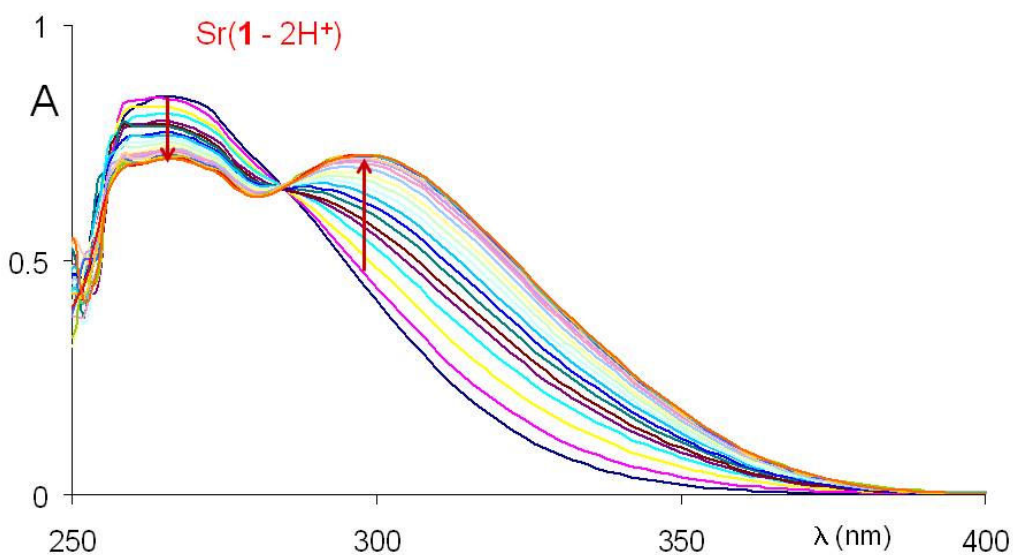


UV-vis monitoring of the base induced calcium binding by **1** in DMSO (1:1 mixture of $\text{Ca}(\text{OTf})_2$ and **1** in DMSO, 3.8×10^{-5} M); left: full titration, from 0 to 2.0 equiv. of NMe_4HO ; right: spectral response split into two regimes (0 to 1 and 1 to 2 equiv. of base).

c) Base-induced **strontium** complexation (macrocycle **1**).

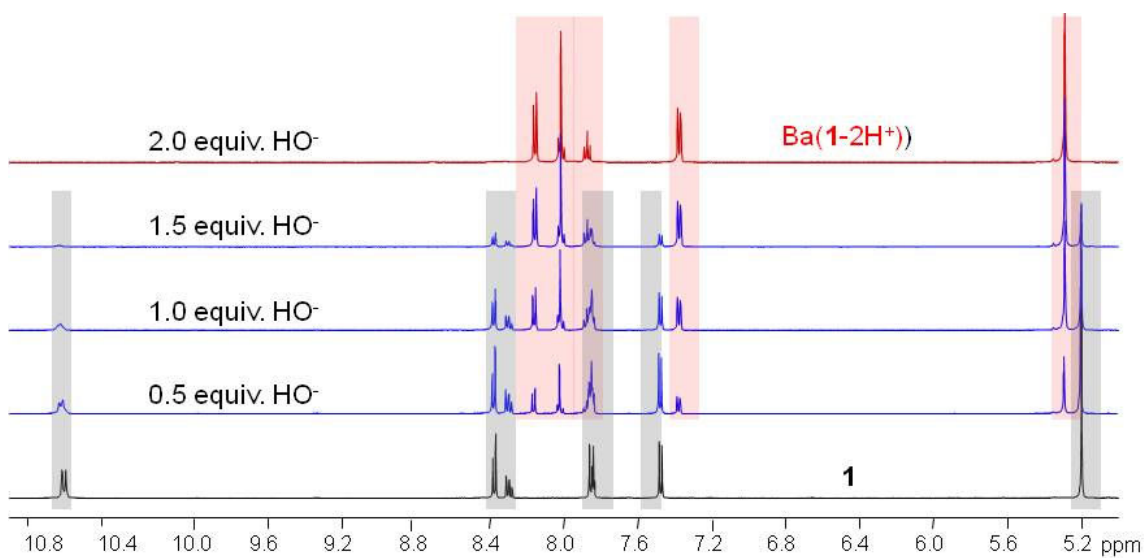


^1H NMR monitoring of base-induced complexation of Sr^{2+} by **1** (up to 2 equiv. HO^-) in DMSO-d_6 (500 MHz, 25°C).

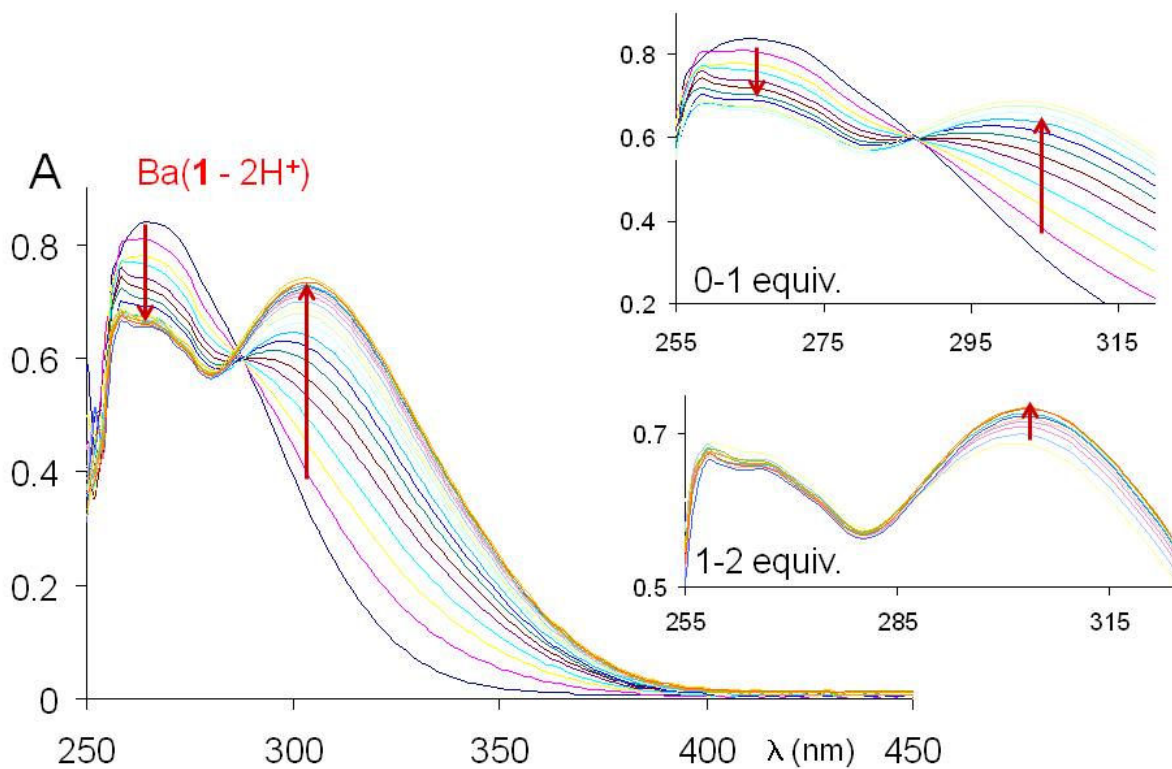


UV-vis monitoring of the base induced strontium binding by **1** (titration of 0 to 2.0 equiv. of NMe_4HO into a 1:1 mixture of $\text{Sr}(\text{OTf})_2$ and **1** in DMSO , $3.8 \times 10^{-5} \text{ M}$).

d) Base-induced **barium** complexation (macrocycle **1**).

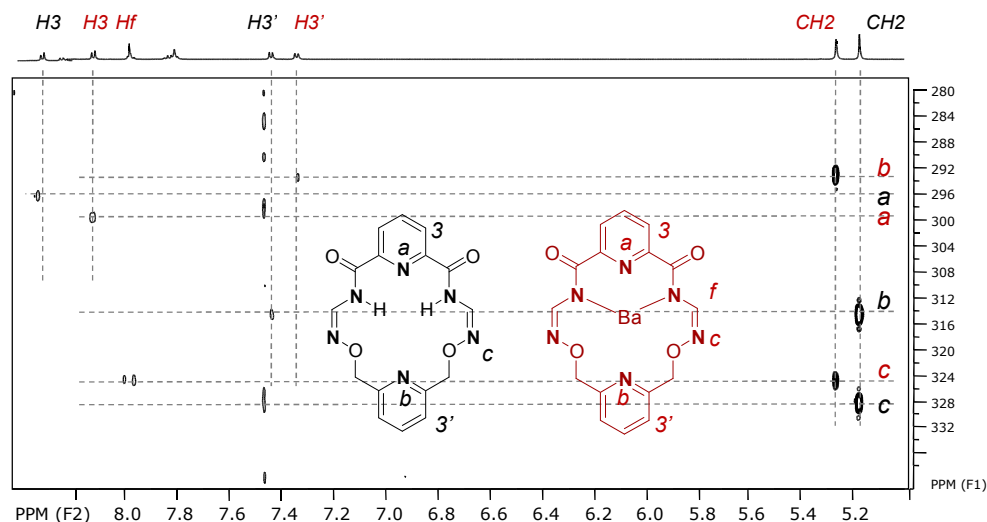


^1H NMR monitoring of base-induced complexation of Ba^{2+} by **1** (DMSO-d_6 , 500 MHz, 25°C).



UV-vis monitoring of the base induced barium binding by **1** in DMSO (1:1 mixture of $\text{Ba}(\text{OTf})_2$ and **1** in DMSO, 3.8×10^{-5} M); left: full titration, from 0 to 2.0 equiv. of NMe_4HO ; right: spectral response split into two regimes (0 to 1 and 1 to 2 equiv. of base).

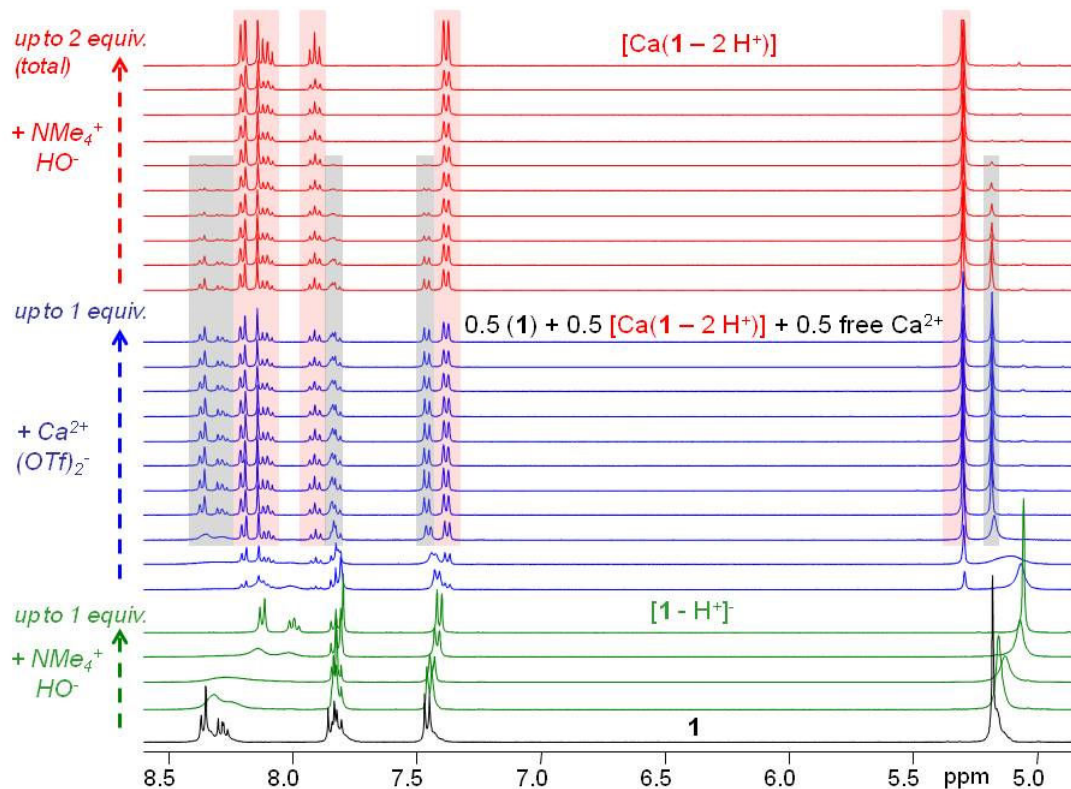
C.2: Effect of metal binding on ^{15}N NMR illustrated with the $[\text{Ba}(\mathbf{1}-2\text{H}^+)]$ complex.



^1H - ^{15}N HMBC of a 1:1 mixture of **1** and $[\text{Ba}(\mathbf{1}-2\text{H}^+)]$ in $\text{DMSO}-d_6$ (600 MHz, 25°C). Note the major shift from the alkoxyamine pyridyl fragment (^{15}N labeled 'b'). For ^{15}N chemical shift variations upon cation complexation, see H.

G. Förster, J. D. Roberts, *J. Am. Chem. Soc.* **1980**, *102*, 6984-6988.

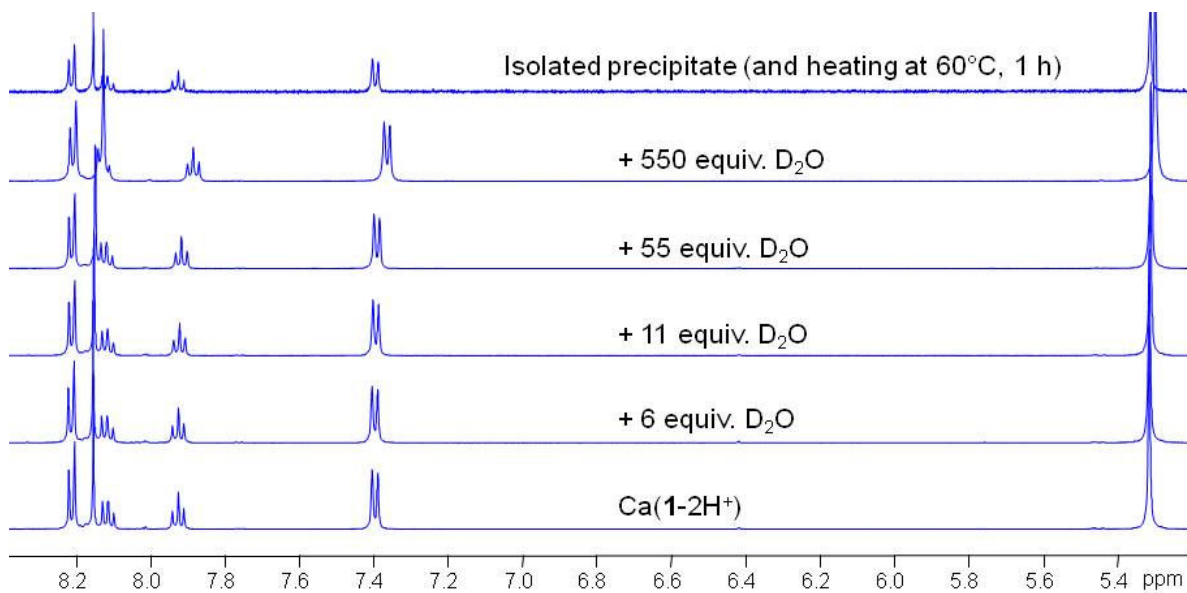
C.3: Disproportionation of monoanionic $[\mathbf{1}-\text{H}^+]^-$ into neutral **1** and bisanionic $[\mathbf{1}-2\text{H}^+]^{2-}$ induced by Ca^{2+} .



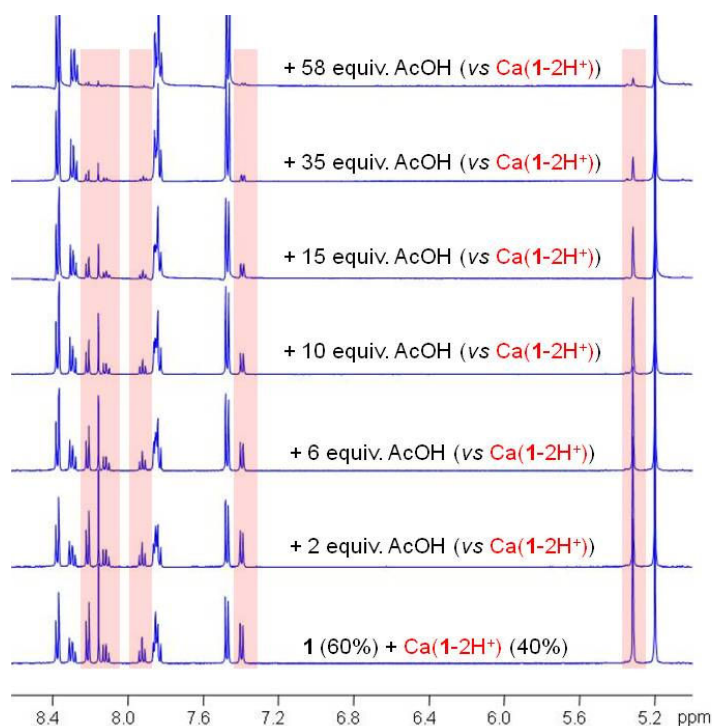
^1H NMR evidence of the disproportionation of monodeprotonated $[\mathbf{1}-\text{H}^+]^-$ into **1** and $[\text{Ca}(\mathbf{1}-2\text{H}^+)]$ induced by Ca^{2+} (**1** in grey, $[\text{Ca}(\mathbf{1}-2\text{H}^+)]$ in pink), followed by completion of the $[\text{Ca}(\mathbf{1}-2\text{H}^+)]$ complex by deprotonation of remaining **1** (400 MHz, $\text{DMSO}-d_6$, 25°C).

D. Stability and reversibility studies

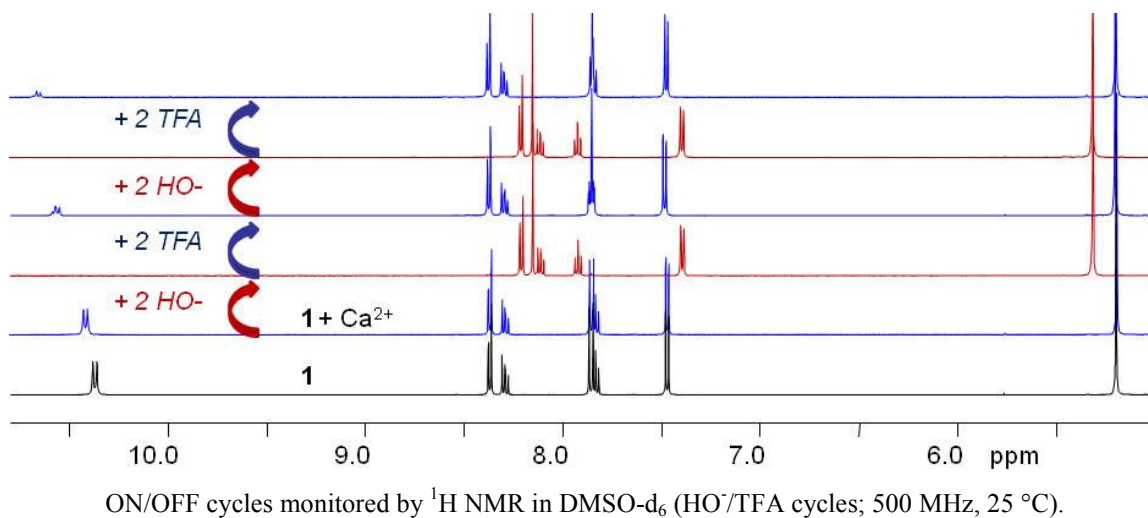
D.1. Stability of calcium complex to water



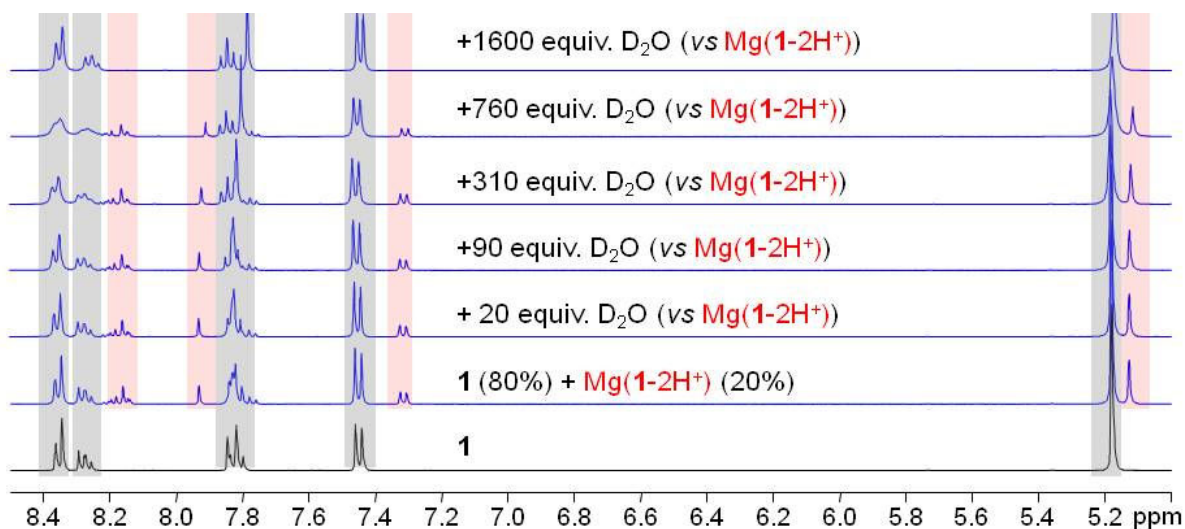
D.2. Stability of Calcium complexes to acetic acid



D.3. Reversibility: base/acid cycles (Calcium complex $\text{Ca}(\mathbf{1}-2\text{H}^+)$)

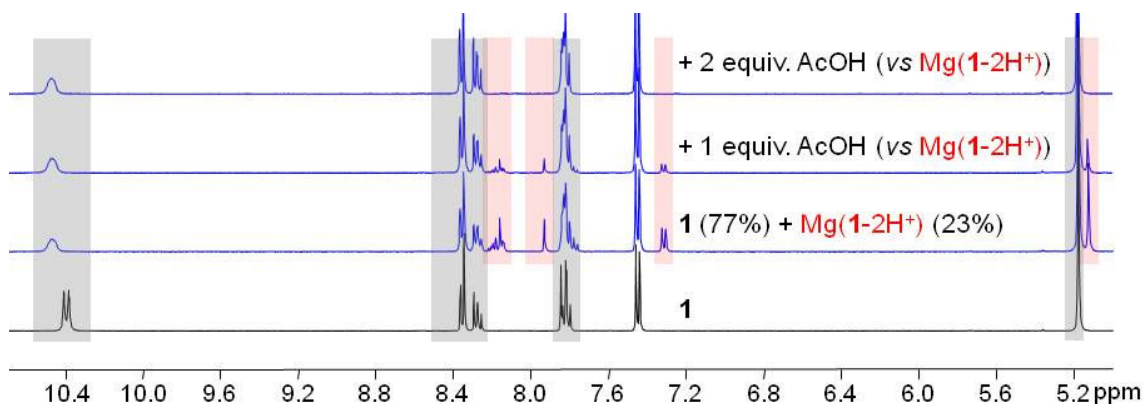


D.4. Stability of Magnesium complex to water



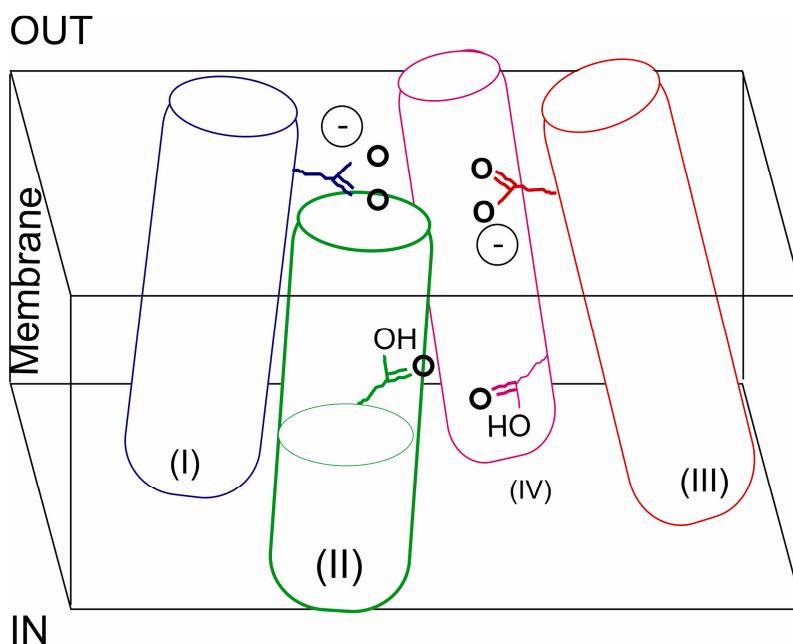
^1H NMR monitoring of $\text{Mg}(\mathbf{1}-2\text{H}^+)$ in DMSO-d_6 upon addition of D_2O $\text{Mg}(\mathbf{1}-2\text{H}^+)$. The signals from $\text{Mg}(\mathbf{1}-2\text{H}^+)$ are highlighted in pink; those of $\mathbf{1}$ in grey.

D.5. Stability of Magnesium complex to acetic acid



^1H NMR monitoring of decomplexation of $\text{Mg}(\mathbf{1-2H}^+)$ from a ~8:2 mixture of **1** and $\text{Mg}(\mathbf{1-2H}^+)$ in DMSO-d_6 upon addition of AcOH (400 MHz, 22 mM, 25 °C; signals of $\text{Mg}(\mathbf{1-2H}^+)$ in pink; those of **1** in grey).

E. Cartoon representation of the selectivity filter for voltage dependent calcium channels



Conserved glutamates involved in the selectivity filter of voltage dependent calcium channels (note the deprotonated glutamates involved in the selection of the entering cation, on helices I and III).

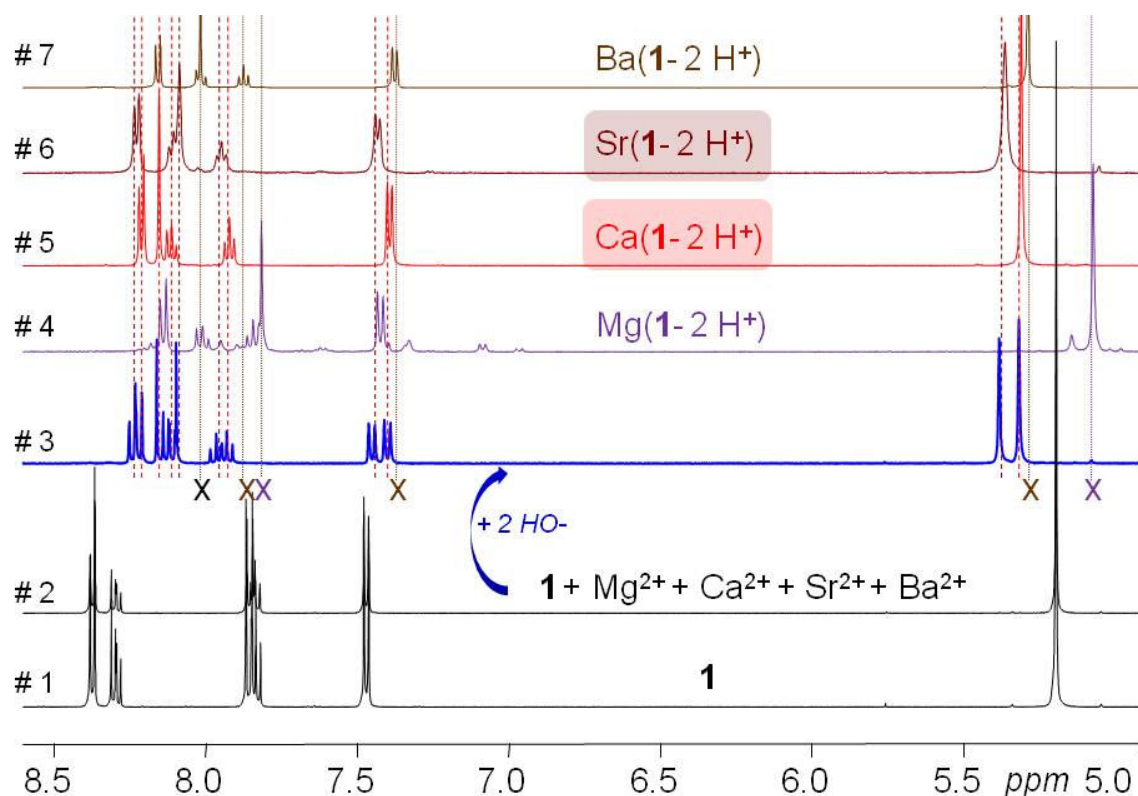
Adapted from ref: G. Varadi, M. Strobeck, Sheryl Koch, L. Caglioti, C. Zucchi, G. Palyi, *Crit. Rev. Biochem. Molec. Biol.* **1999**, 34, 181-214.

F. Selectivity studies

F.1. Exchange reactions: Sr(**1**-2 H⁺) was first prepared *in-situ* by mixing **1** (1.0 equiv.), strontium triflate (1.0 equiv.) and base (2.0 equiv.). The competing ion was added portion-wise, and the mixture allowed to stabilize (24-120 h) at 25° C (as per constant integration). Several points were taken and the exchange

constant calculated for each by the ratio of the integration of the well-resolved CH ₂ signals.	Sr/Ca ratio	$K_{\text{exchange}} = \frac{K_{\text{binding}}(\text{Ca})}{K_{\text{binding}}(\text{Sr})}$	Sr/Ba ratio	$K_{\text{exchange}} = \frac{K_{\text{binding}}(\text{Ba})}{K_{\text{binding}}(\text{Sr})}$
	1:0.75	4.1	1:30	3.8×10^{-4}
	1:1	3.1	1:60	3.5×10^{-4}
	1:1.25	2.6	1:120	2.4×10^{-4}

F.2. Selection experiments: macrocycle **1** (1.0 equiv.) was mixed with all four alkaline earth ions (1.0 equiv. each), in DMSO-d₆ (concentration of each component: 17 mM). Tetramethylammonium hydroxide (2.0 equiv.) was added and the signals compared to reference spectra.



¹H NMR monitoring of cation selection by **1** upon deprotonation (DMSO-d₆, 500 MHz, 25 °C). #1: **1** alone, #2: **1** after addition of Mg(OTf)₂ (1.0 equiv.), Ca(OTf)₂ (1.0 equiv.), Sr(OTf)₂ (1.0 equiv.) and Ba(OTf)₂ (1.0 equiv.); #3: same mixture after addition of NMe₄HO (2.0 equiv.); #4-7: reference spectra of Mg(**1**-2 H⁺), Ca(**1**-2 H⁺), Sr(**1**-2 H⁺) and Ba(**1**-2 H⁺) respectively. Color-coded 'X' signify the absence of peaks in spectrum #3, highlighting the absence of the Ba²⁺ and Mg²⁺ complexes among the selected ones. Faint vertical lines have been added to guide the eye.

G. Modeling and Calculations

G.1. DFT methods: Electronic structure calculations were performed using density functional theory in conjunction with the B3LYP hybrid exchange correlation functional.^[1] A 6-31G(d,p) basis set was used for all atoms except Sr and Ba, which treated with the LANL2DZ effective core potential/basis set combination.^[2] The calculations were performed using the integral equation formalism polarizable continuum model^[4] to represent the effects of the species being solvated by dimethylsulfoxide. Geometries of all structures were characterized as minima through frequency calculations. All calculations were performed using the Gaussian 09 software package.

References: [1] Becke, A.D., *J. Chem. Phys.* **1993**, 98, 5648.

[2] (a) Hay, P.J.; Wadt, W.R. *J. Chem. Phys.*, **1985**, 82 270, (b) Wadt, W.R.; Hay, P.J. *J. Chem. Phys.*, **1985**, 82 284, (c) Hay, P.J.; Wadt, W.R. *J. Chem. Phys.*, **1985**, 82 299.

[3] Tomasi, J.; Mennucci, B.; Cammi, R., *Chem. Rev.*, **2005**, 105, 2999.

[4] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, *Gaussian 09, Revision C.01*; Gaussian, Inc., Wallingford CT., 2010.

G.2. DFT structures for complexes of **1** with Mg^{2+} , Ca^{2+} , Sr^{2+} and Ba^{2+} (distances in Å)

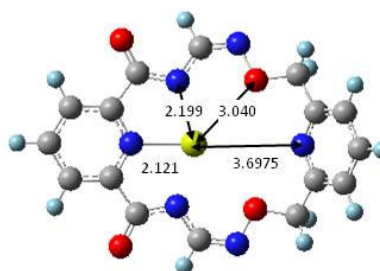
Complex

Calculated structures

$\text{Mg}(\mathbf{1-2} \text{ H}^+)$



side

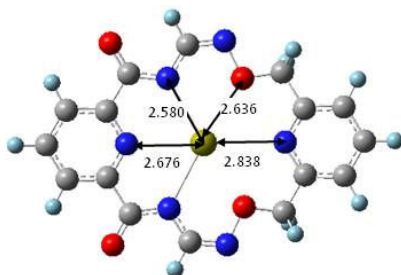


top

Ca(1-2 H⁺)

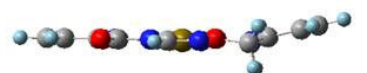


side

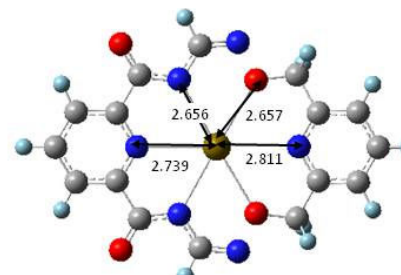


top

Sr(1-2 H⁺)

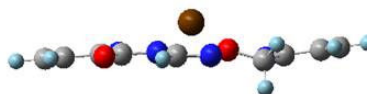


side

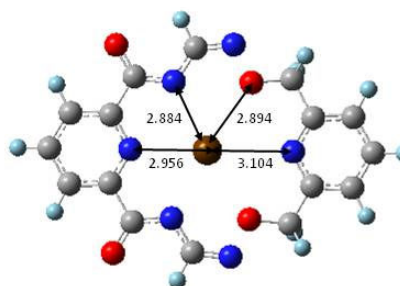


top

Ba(1-2 H⁺)

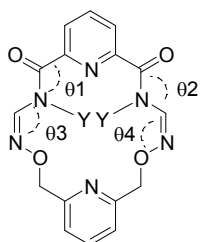


side



top

The cation / macrocycle fit is translated in the distances, as indicated above, and bond angles as detailed below. In Mg(1-2 H⁺) in particular, contraction of the $\theta 2$ angle and expansion of the $\theta 3$ angle reflect poor affinity.



Y = H in **1**

YY = M²⁺ in others

	1	Mg(1-2 H ⁺)	Ca(1-2 H ⁺)	Sr(1-2 H ⁺)	Ba(1-2 H ⁺)
$\theta 1$ (°)	116.3	113.96	114.1	114.5	114.5
$\theta 2$ (°)	120.9	112.6	114.1	115.8	115.4
$\theta 3$ (°)	126.5	128.7	126.5	127.2	127.6
$\theta 4$ (°)	120.6	111.15	109.8	110.4	110.7

H. Crystallographic data

H.1. Curved precursor 4 [CCDC 876656]

A crystal of the compound (colorless, needle-shaped, size $0.06 \times 0.10 \times 0.30$ mm) was mounted on a glass fiber with grease and cooled to -93 °C in a stream of nitrogen gas controlled with Cryostream Controller 700. Data collection was performed on a Bruker SMART APEX II X-ray diffractometer with graphite-monochromated Mo K_{α} radiation ($\lambda = 0.71073$ Å), operating at 50 kV and 30 mA over 2θ ranges of $4.30 \sim 52.00^{\circ}$. No significant decay was observed during the data collection. Data were processed on a PC using the Bruker AXS Crystal Structure Analysis Package:^[1] Data collection: APEX2 (Bruker, 2010); cell refinement: SAINT (Bruker, 2009); data reduction: SAINT (Bruker, 2009); absorption correction: SADABS (Bruker, 2008); structure solution: XPREP (Bruker, 2008) and SHELXTL (Bruker, 2000); structure refinement: SHELXTL; molecular graphics: SHELXTL; publication materials: SHELXTL. Neutral atom scattering factors were taken from Cromer and Waber.^[2] The crystal is monoclinic space group $P2_1/c$, based on the systematic absences, E statistics and successful refinement of the structure. The structure was solved by direct methods. Full-matrix least-square refinements minimizing the function $\sum w (F_o^2 - F_c^2)^2$ were applied to the compound. All non-hydrogen atoms were refined anisotropically. All H atoms attached to C and N were placed in geometrically calculated positions, with C-H = 0.95 (aromatic) and N-H = 0.88 Å, and refined as riding atoms, with $U_{iso}(H) = 1.2 U_{eq}C$ or N. The H atoms on water or OH groups were located from difference Fourier maps, and refined without restraints. There are two molecules in the asymmetric unit. Each is hydrogen bonded to one water molecule.

Convergence to final $R_1 = 0.0410$ and $wR_2 = 0.0856$ for 3426 ($I > 2\sigma(I)$) independent reflections, and $R_1 = 0.0655$ and $wR_2 = 0.0969$ for all 4754 ($R(int) = 0.0430$) independent reflections, with 375 parameters and 0 restraints, were achieved.^[3] The largest residual peak and hole to be 0.196 and -0.225 e/Å³, respectively. Crystallographic data, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, torsion angles and hydrogen bond information are given in Table S1 to S7. The molecular structure and the cell packing are shown in Figures S1 and S2.

[1] Bruker AXS Crystal Structure Analysis Package: Bruker (2000). SHELXTL. Version 6.14. Bruker AXS Inc., Madison, Wisconsin, USA; Bruker (2008). SADABS. Version 2008/1. Bruker AXS Inc., Madison, Wisconsin,

USA; Bruker (2008). XPREP. Version 2008/2. Bruker AXS Inc., Madison, Wisconsin, USA; Bruker (2009). SAINT. Version 7.68A. Bruker AXS Inc., Madison, Wisconsin, USA; Bruker (2010). APEX2. Version 2010.3-0. Bruker AXS Inc., Madison, Wisconsin, USA. [2] Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, UK, 1974; Vol. 4, Table 2.2 A.

$$[3] \quad R_1 = \sum ||Fo| - |Fc|| / \sum |Fo|$$

$$wR_2 = \{ \sum [w(Fo^2 - Fc^2)^2] / \sum [w(Fo^2)^2] \}^{1/2}$$

$$(w = 1 / [\sigma^2(Fo^2) + (0.0435P)^2 + 0.4373P], \text{ where } P = [\text{Max}(Fo^2, 0) + 2Fc^2] / 3)$$

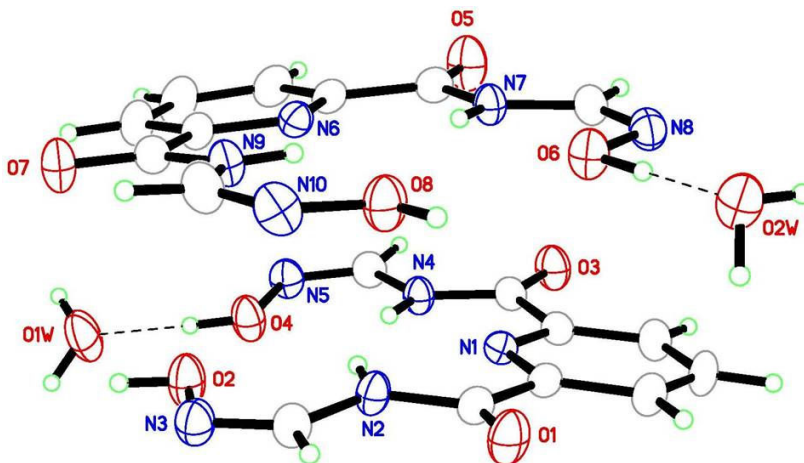


Figure S1. Molecular Structure (displacement ellipsoids for non-H atoms are shown at the 50% probability level and H atoms are represented by circles of arbitrary size).

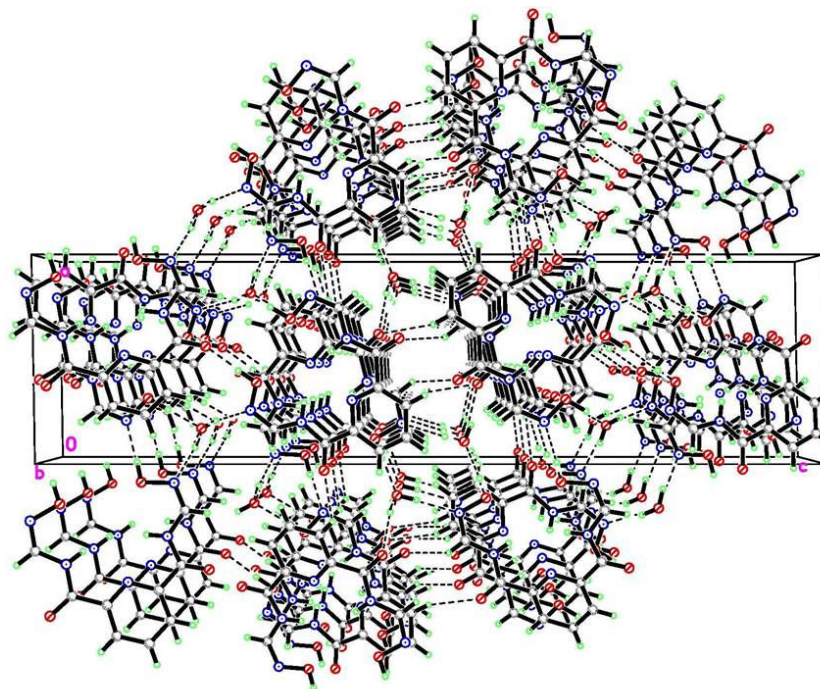


Figure S2. Unit cell packing.

Table S1. Crystal data and structure refinement for ap32

Identification code	ap32	
Empirical formula	C ₉ H ₁₁ N ₅ O ₅	
Formula weight	269.23	
Temperature	180(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.48230(10) Å	α = 90°.
	b = 7.17710(10) Å	β = 90.9590(10)°.
	c = 35.7292(6) Å	γ = 90°.
Volume	2431.22(6) Å ³	
Z	8	
Density (calculated)	1.471 Mg/m ³	
Absorption coefficient	0.122 mm ⁻¹	
F(000)	1120	
Crystal size	0.30 x 0.10 x 0.06 mm ³	
Theta range for data collection	2.15 to 26.00°.	
Index ranges	-11 ≤ h ≤ 11, -8 ≤ k ≤ 8, -44 ≤ l ≤ 32	
Reflections collected	17514	
Independent reflections	4754 [R(int) = 0.0430]	
Completeness to theta = 26.00°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9927 and 0.9643	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4754 / 0 / 375	
Goodness-of-fit on F ²	1.019	
Final R indices [I > 2σ(I)]	R1 = 0.0410, wR2 = 0.0856	
R indices (all data)	R1 = 0.0655, wR2 = 0.0969	
Largest diff. peak and hole	0.196 and -0.225 e.Å ⁻³	

Table S2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for ap32. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	5584(1)	7979(2)	2353(1)	36(1)
O(2)	9480(2)	7594(2)	1553(1)	37(1)
O(3)	3860(1)	11836(2)	597(1)	36(1)
O(4)	8634(1)	10092(2)	668(1)	36(1)
O(5)	4083(1)	7086(2)	340(1)	44(1)
O(6)	3220(1)	5653(2)	1598(1)	34(1)
O(7)	9963(1)	3148(2)	1264(1)	36(1)
O(8)	6030(1)	3555(2)	2041(1)	36(1)
N(1)	5177(1)	9871(2)	1442(1)	23(1)
N(2)	7081(2)	8070(2)	1866(1)	27(1)
N(3)	9424(2)	7040(2)	1930(1)	33(1)
N(4)	6026(1)	10704(2)	752(1)	26(1)
N(5)	7919(2)	10678(2)	342(1)	31(1)
N(6)	6798(2)	5112(2)	904(1)	24(1)
N(7)	4109(2)	6154(2)	946(1)	26(1)
N(8)	2230(2)	6476(2)	1354(1)	30(1)
N(9)	7800(2)	3468(2)	1520(1)	26(1)
N(10)	7284(2)	2604(2)	2132(1)	34(1)
C(1)	4793(2)	9491(2)	1792(1)	24(1)
C(2)	3508(2)	10040(3)	1939(1)	30(1)
C(3)	2591(2)	11028(3)	1712(1)	34(1)
C(4)	2959(2)	11420(3)	1348(1)	30(1)
C(5)	4256(2)	10809(2)	1224(1)	25(1)
C(6)	5830(2)	8449(2)	2032(1)	26(1)
C(7)	8206(2)	7315(3)	2062(1)	29(1)
C(8)	4677(2)	11167(2)	830(1)	26(1)
C(9)	6620(2)	10957(3)	406(1)	28(1)
C(10)	6238(2)	5884(2)	594(1)	25(1)
C(11)	7000(2)	6224(3)	274(1)	32(1)
C(12)	8419(2)	5781(3)	278(1)	36(1)
C(13)	9016(2)	4957(3)	593(1)	32(1)
C(14)	8165(2)	4632(2)	897(1)	25(1)
C(15)	4712(2)	6427(2)	607(1)	27(1)

C(16)	2751(2)	6671(3)	1030(1)	28(1)
C(17)	8753(2)	3688(2)	1238(1)	26(1)
C(18)	8111(2)	2652(3)	1856(1)	31(1)
O(1W)	11238(2)	10016(3)	414(1)	55(1)
O(2W)	1841(2)	5302(2)	2230(1)	37(1)

Table S3. Bond lengths [Å] and angles [°] for ap32.

O(1)-C(6)	1.220(2)	N(9)-C(17)	1.371(2)
O(2)-N(3)	1.404(2)	N(9)-H(9B)	0.8800
O(2)-H(2H)	0.90(2)	N(10)-C(18)	1.271(2)
O(3)-C(8)	1.227(2)	C(1)-C(2)	1.392(2)
O(4)-N(5)	1.4014(19)	C(1)-C(6)	1.495(2)
O(4)-H(4H)	0.91(3)	C(2)-C(3)	1.374(3)
O(5)-C(15)	1.213(2)	C(2)-H(2A)	0.9500
O(6)-N(8)	1.4032(19)	C(3)-C(4)	1.382(3)
O(6)-H(6H)	0.98(3)	C(3)-H(3A)	0.9500
O(7)-C(17)	1.213(2)	C(4)-C(5)	1.385(2)
O(8)-N(10)	1.405(2)	C(4)-H(4A)	0.9500
O(8)-H(8H)	0.93(3)	C(5)-C(8)	1.492(3)
N(1)-C(1)	1.336(2)	C(7)-H(7A)	0.9500
N(1)-C(5)	1.342(2)	C(9)-H(9A)	0.9500
N(2)-C(6)	1.362(2)	C(10)-C(11)	1.382(3)
N(2)-C(7)	1.376(2)	C(10)-C(15)	1.500(2)
N(2)-H(2B)	0.8800	C(11)-C(12)	1.382(3)
N(3)-C(7)	1.271(2)	C(11)-H(11A)	0.9500
N(4)-C(8)	1.355(2)	C(12)-C(13)	1.384(3)
N(4)-C(9)	1.381(2)	C(12)-H(12A)	0.9500
N(4)-H(4B)	0.8800	C(13)-C(14)	1.384(3)
N(5)-C(9)	1.272(2)	C(13)-H(13A)	0.9500
N(6)-C(10)	1.340(2)	C(14)-C(17)	1.495(2)
N(6)-C(14)	1.342(2)	C(16)-H(16A)	0.9500
N(7)-C(15)	1.361(2)	C(18)-H(18A)	0.9500
N(7)-C(16)	1.379(2)	O(1W)-H(1WA)	0.90(3)
N(7)-H(7B)	0.8800	O(1W)-H(1WB)	0.86(3)
N(8)-C(16)	1.272(2)	O(2W)-H(2WA)	0.91(3)
N(9)-C(18)	1.366(2)	O(2W)-H(2WB)	0.93(3)

N(3)-O(2)-H(2H)	100.9(16)	N(2)-C(6)-C(1)	114.77(16)
N(5)-O(4)-H(4H)	102.6(17)	N(3)-C(7)-N(2)	125.07(18)
N(8)-O(6)-H(6H)	103.6(14)	N(3)-C(7)-H(7A)	117.5
N(10)-O(8)-H(8H)	102.2(16)	N(2)-C(7)-H(7A)	117.5
C(1)-N(1)-C(5)	117.41(15)	O(3)-C(8)-N(4)	122.94(18)
C(6)-N(2)-C(7)	122.08(16)	O(3)-C(8)-C(5)	122.20(16)
C(6)-N(2)-H(2B)	119.0	N(4)-C(8)-C(5)	114.86(15)
C(7)-N(2)-H(2B)	119.0	N(5)-C(9)-N(4)	123.48(17)
C(7)-N(3)-O(2)	111.14(15)	N(5)-C(9)-H(9A)	118.3
C(8)-N(4)-C(9)	123.57(15)	N(4)-C(9)-H(9A)	118.3
C(8)-N(4)-H(4B)	118.2	N(6)-C(10)-C(11)	123.37(17)
C(9)-N(4)-H(4B)	118.2	N(6)-C(10)-C(15)	116.71(16)
C(9)-N(5)-O(4)	110.75(15)	C(11)-C(10)-C(15)	119.91(16)
C(10)-N(6)-C(14)	117.46(15)	C(10)-C(11)-C(12)	118.27(17)
C(15)-N(7)-C(16)	124.28(16)	C(10)-C(11)-H(11A)	120.9
C(15)-N(7)-H(7B)	117.9	C(12)-C(11)-H(11A)	120.9
C(16)-N(7)-H(7B)	117.9	C(11)-C(12)-C(13)	119.38(18)
C(16)-N(8)-O(6)	110.27(15)	C(11)-C(12)-H(12A)	120.3
C(18)-N(9)-C(17)	123.99(15)	C(13)-C(12)-H(12A)	120.3
C(18)-N(9)-H(9B)	118.0	C(14)-C(13)-C(12)	118.36(17)
C(17)-N(9)-H(9B)	118.0	C(14)-C(13)-H(13A)	120.8
C(18)-N(10)-O(8)	109.64(15)	C(12)-C(13)-H(13A)	120.8
N(1)-C(1)-C(2)	123.25(17)	N(6)-C(14)-C(13)	123.11(17)
N(1)-C(1)-C(6)	116.92(15)	N(6)-C(14)-C(17)	116.65(15)
C(2)-C(1)-C(6)	119.82(17)	C(13)-C(14)-C(17)	120.23(16)
C(3)-C(2)-C(1)	118.32(18)	O(5)-C(15)-N(7)	123.14(17)
C(3)-C(2)-H(2A)	120.8	O(5)-C(15)-C(10)	122.53(17)
C(1)-C(2)-H(2A)	120.8	N(7)-C(15)-C(10)	114.31(15)
C(2)-C(3)-C(4)	119.46(17)	N(8)-C(16)-N(7)	123.16(17)
C(2)-C(3)-H(3A)	120.3	N(8)-C(16)-H(16A)	118.4
C(4)-C(3)-H(3A)	120.3	N(7)-C(16)-H(16A)	118.4
C(3)-C(4)-C(5)	118.40(17)	O(7)-C(17)-N(9)	122.88(17)
C(3)-C(4)-H(4A)	120.8	O(7)-C(17)-C(14)	122.97(16)
C(5)-C(4)-H(4A)	120.8	N(9)-C(17)-C(14)	114.15(15)
N(1)-C(5)-C(4)	123.15(18)	N(10)-C(18)-N(9)	124.61(17)

N(1)-C(5)-C(8)	116.85(15)	N(10)-C(18)-H(18A)	117.7
C(4)-C(5)-C(8)	120.00(16)	N(9)-C(18)-H(18A)	117.7
O(1)-C(6)-N(2)	122.32(17)	H(1WA)-O(1W)-H(1WB)	105(2)
O(1)-C(6)-C(1)	122.91(16)	H(2WA)-O(2W)-H(2WB)	105(2)
N(2)-C(6)-C(1)	114.77(16)		

Table S4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for ap32. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	34(1)	50(1)	25(1)	5(1)	8(1)	8(1)
O(2)	28(1)	53(1)	31(1)	7(1)	7(1)	8(1)
O(3)	28(1)	45(1)	34(1)	7(1)	-3(1)	8(1)
O(4)	26(1)	54(1)	27(1)	5(1)	-1(1)	6(1)
O(5)	37(1)	63(1)	31(1)	13(1)	-2(1)	13(1)
O(6)	31(1)	42(1)	30(1)	4(1)	3(1)	6(1)
O(7)	22(1)	47(1)	38(1)	5(1)	2(1)	9(1)
O(8)	31(1)	47(1)	30(1)	3(1)	8(1)	3(1)
N(1)	22(1)	22(1)	26(1)	-2(1)	0(1)	-1(1)
N(2)	25(1)	33(1)	23(1)	2(1)	5(1)	6(1)
N(3)	28(1)	43(1)	27(1)	0(1)	2(1)	5(1)
N(4)	22(1)	32(1)	23(1)	4(1)	0(1)	4(1)
N(5)	28(1)	40(1)	25(1)	3(1)	0(1)	3(1)
N(6)	25(1)	25(1)	23(1)	-1(1)	1(1)	2(1)
N(7)	22(1)	32(1)	26(1)	3(1)	0(1)	4(1)
N(8)	25(1)	31(1)	34(1)	1(1)	1(1)	1(1)
N(9)	20(1)	36(1)	23(1)	4(1)	1(1)	2(1)
N(10)	31(1)	41(1)	30(1)	6(1)	0(1)	-2(1)
C(1)	23(1)	23(1)	25(1)	-3(1)	3(1)	-1(1)
C(2)	28(1)	34(1)	30(1)	-2(1)	7(1)	2(1)
C(3)	22(1)	39(1)	40(1)	-5(1)	8(1)	8(1)
C(4)	24(1)	31(1)	37(1)	2(1)	0(1)	6(1)
C(5)	21(1)	21(1)	32(1)	-2(1)	0(1)	-1(1)
C(6)	26(1)	25(1)	27(1)	-3(1)	4(1)	0(1)
C(7)	27(1)	35(1)	26(1)	1(1)	0(1)	4(1)
C(8)	22(1)	25(1)	30(1)	-1(1)	-2(1)	1(1)
C(9)	29(1)	33(1)	22(1)	3(1)	-1(1)	2(1)

C(10)	28(1)	24(1)	23(1)	-2(1)	1(1)	3(1)
C(11)	39(1)	32(1)	24(1)	4(1)	4(1)	6(1)
C(12)	40(1)	42(1)	28(1)	7(1)	15(1)	8(1)
C(13)	27(1)	41(1)	29(1)	0(1)	7(1)	6(1)
C(14)	23(1)	26(1)	26(1)	-2(1)	4(1)	2(1)
C(15)	30(1)	26(1)	26(1)	0(1)	-1(1)	1(1)
C(16)	22(1)	31(1)	32(1)	1(1)	0(1)	2(1)
C(17)	23(1)	28(1)	26(1)	-3(1)	1(1)	0(1)
C(18)	26(1)	38(1)	30(1)	6(1)	-1(1)	2(1)
O(1W)	25(1)	103(2)	36(1)	-10(1)	4(1)	0(1)
O(2W)	36(1)	47(1)	28(1)	2(1)	-1(1)	10(1)

Table S5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$)
for ap32.

	x	y	z	U(eq)
H(2H)	10380(30)	7310(30)	1500(7)	64(8)
H(4H)	9540(30)	10040(30)	593(8)	79(9)
H(6H)	2710(30)	5530(30)	1833(7)	68(8)
H(8H)	5510(30)	3400(40)	2255(8)	73(8)
H(2B)	7172	8316	1627	32
H(4B)	6552	10216	932	31
H(7B)	4620	5613	1123	32
H(9B)	6935	3877	1481	32
H(2A)	3270	9739	2189	37
H(3A)	1711	11439	1806	40
H(4A)	2337	12093	1186	36
H(7A)	8060	6973	2315	35
H(9A)	6028	11361	205	34
H(11A)	6560	6748	58	38
H(12A)	8979	6040	66	44
H(13A)	9985	4623	600	39
H(16A)	2176	7198	837	34
H(18A)	9010	2080	1886	37
H(1WA)	11470(30)	9660(40)	180(9)	91(10)
H(1WB)	11980(30)	10580(40)	499(8)	79(10)
H(2WA)	2200(30)	6010(40)	2421(9)	90(10)
H(2WB)	990(30)	5880(40)	2162(8)	78(9)

Table S6. Torsion angles [°] for ap32.

C(5)-N(1)-C(1)-C(2)	-0.8(3)	C(14)-N(6)-C(10)-C(11)	-0.9(3)
C(5)-N(1)-C(1)-C(6)	-179.85(15)	C(14)-N(6)-C(10)-C(15)	-179.52(15)
N(1)-C(1)-C(2)-C(3)	-0.3(3)	N(6)-C(10)-C(11)-C(12)	-1.5(3)
C(6)-C(1)-C(2)-C(3)	178.70(17)	C(15)-C(10)-C(11)-C(12)	177.16(17)
C(1)-C(2)-C(3)-C(4)	1.0(3)	C(10)-C(11)-C(12)-C(13)	2.3(3)
C(2)-C(3)-C(4)-C(5)	-0.5(3)	C(11)-C(12)-C(13)-C(14)	-1.0(3)
C(1)-N(1)-C(5)-C(4)	1.3(3)	C(10)-N(6)-C(14)-C(13)	2.4(3)
C(1)-N(1)-C(5)-C(8)	-177.98(15)	C(10)-N(6)-C(14)-C(17)	-177.12(15)
C(3)-C(4)-C(5)-N(1)	-0.7(3)	C(12)-C(13)-C(14)-N(6)	-1.4(3)
C(3)-C(4)-C(5)-C(8)	178.61(17)	C(12)-C(13)-C(14)-C(17)	178.01(17)
C(7)-N(2)-C(6)-O(1)	-7.3(3)	C(16)-N(7)-C(15)-O(5)	-3.2(3)
C(7)-N(2)-C(6)-C(1)	172.36(16)	C(16)-N(7)-C(15)-C(10)	175.36(16)
N(1)-C(1)-C(6)-O(1)	-177.93(16)	N(6)-C(10)-C(15)-O(5)	-177.82(17)
C(2)-C(1)-C(6)-O(1)	3.0(3)	C(11)-C(10)-C(15)-O(5)	3.5(3)
N(1)-C(1)-C(6)-N(2)	2.4(2)	N(6)-C(10)-C(15)-N(7)	3.6(2)
C(2)-C(1)-C(6)-N(2)	-176.68(16)	C(11)-C(10)-C(15)-N(7)	-175.11(16)
O(2)-N(3)-C(7)-N(2)	-0.6(3)	O(6)-N(8)-C(16)-N(7)	-1.0(2)
C(6)-N(2)-C(7)-N(3)	-175.27(18)	C(15)-N(7)-C(16)-N(8)	-176.82(18)
C(9)-N(4)-C(8)-O(3)	0.8(3)	C(18)-N(9)-C(17)-O(7)	1.0(3)
C(9)-N(4)-C(8)-C(5)	-178.92(16)	C(18)-N(9)-C(17)-C(14)	-179.67(16)
N(1)-C(5)-C(8)-O(3)	172.23(16)	N(6)-C(14)-C(17)-O(7)	178.28(17)
C(4)-C(5)-C(8)-O(3)	-7.1(3)	C(13)-C(14)-C(17)-O(7)	-1.2(3)
N(1)-C(5)-C(8)-N(4)	-8.1(2)	N(6)-C(14)-C(17)-N(9)	-1.0(2)
C(4)-C(5)-C(8)-N(4)	172.63(16)	C(13)-C(14)-C(17)-N(9)	179.47(16)
O(4)-N(5)-C(9)-N(4)	0.0(3)	O(8)-N(10)-C(18)-N(9)	-1.6(3)
C(8)-N(4)-C(9)-N(5)	173.52(17)	C(17)-N(9)-C(18)-N(10)	172.64(18)

Table S7. Hydrogen bonds for ap32 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2H)...N(8)#1	0.90(2)	1.93(3)	2.831(2)	174(2)
O(4)-H(4H)...O(1W)	0.91(3)	1.74(3)	2.644(2)	175(3)
O(6)-H(6H)...O(2W)	0.98(3)	1.66(3)	2.641(2)	179(2)
O(8)-H(8H)...O(1)#2	0.93(3)	1.78(3)	2.7060(19)	176(2)
O(1W)-H(1WA)...N(5)#3	0.90(3)	1.98(3)	2.873(2)	170(3)
O(1W)-H(1WB)...O(3)#1	0.86(3)	2.03(3)	2.875(2)	169(3)

O(2W)-H(2WA)...N(10)#4	0.91(3)	2.01(3)	2.921(2)	172(3)
O(2W)-H(2WB)...N(3)#5	0.93(3)	1.88(3)	2.807(2)	169(3)

Symmetry transformations used to generate equivalent atoms:

#1 $x+1, y, z$ #2 $-x+1, y-1/2, -z+1/2$ #3 $-x+2, -y+2, -z$
 #4 $-x+1, y+1/2, -z+1/2$ #5 $x-1, y, z$

H.2. **Macrocycle 1.CH₃OH** [CCDC 874203]

A crystal of the compound (colorless, block-shaped, size $0.20 \times 0.15 \times 0.12$ mm) was mounted on a glass fiber with grease and cooled to -93 °C in a stream of nitrogen gas controlled with Cryostream Controller 700. Data collection was performed on a Bruker SMART APEX II X-ray diffractometer with graphite-monochromated Mo K $_{\alpha}$ radiation ($\lambda = 0.71073$ Å), operating at 50 kV and 30 mA over 2θ ranges of $3.76 \sim 52.00^\circ$. No significant decay was observed during the data collection. Data were processed on a PC using the Bruker AXS Crystal Structure Analysis Package:^[1] Data collection: APEX2 (Bruker, 2006); cell refinement: SAINT (Bruker, 2005); data reduction: SAINT (Bruker, 2005); structure solution: XPREP (Bruker, 2005) and SHELXTL (Bruker, 2000); structure refinement: SHELXTL; molecular graphics: SHELXTL; publication materials: SHELXTL. Neutral atom scattering factors were taken from Cromer and Waber.^[2] The crystal is monoclinic space group $P2_1/n$, based on the systematic absences, E statistics and successful refinement of the structure. The structure was solved by direct methods. Full-matrix least-square refinements minimizing the function $\sum w (F_o^2 - F_c^2)^2$ were applied to the compound. All non-hydrogen atoms were refined anisotropically. The H atom of OH from MeOH was located from difference Fourier maps. All of the other H atoms were placed in geometrically calculated positions, with C-H = 0.95 (aromatic), 0.99(CH₂), and 0.88(N-H) Å, and refined as riding atoms, with Uiso(H) = 1.2 Ueq(C or N). The methyl group of MeOH was refined with AFIX 137, which allowed the rotation of the methyl group whilst keeping the C-H distances and X-C-H angles fixed. Convergence to final $R_1 = 0.0405$ and $wR_2 = 0.0933$ for 2336 ($I > 2\sigma(I)$) independent reflections, and $R_1 = 0.0681$ and $wR_2 = 0.1084$ for all 3451 ($R(\text{int}) = 0.0357$) independent reflections, with 259 parameters and 0 restraints, were achieved.^[3] The largest residual peak and hole to be 0.157 and -0.146 e/Å³, respectively. Crystallographic data, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement

parameters, torsion angles and H-bonding information are given in Table S8 to S14. The molecular structure and the cell packing are shown in Figure S3.

[1] Bruker AXS Crystal Structure Analysis Package: Bruker (2000). SHELXTL. Version 6.14. Bruker AXS Inc., Madison, Wisconsin, USA; Bruker (2005). XPREF. Version 2005/2. Bruker AXS Inc., Madison, Wisconsin, USA; Bruker (2005). SAINT. Version 7.23A. Bruker AXS Inc., Madison, Wisconsin, USA; Bruker (2006). APEX2. Version 2.0-2. Bruker AXS Inc., Madison, Wisconsin, USA.

[2] Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, UK, 1974; Vol. 4, Table 2.2 A.

[3]
$$RI = \sum ||Fo| - |Fc|| / \sum |Fo|$$

$$wR_2 = \{ \sum [w (Fo^2 - Fc^2)^2] / \sum [w (Fo^2)^2] \}^{1/2}$$

$$(w = 1 / [\sigma^2(Fo^2) + (0.0476P)^2 + 0.134P], \text{ where } P = [\text{Max}(Fo^2, 0) + 2Fc^2] / 3)$$

Figure S3. a) molecular Structure (displacement ellipsoids for non-H atoms are shown at the 50% probability level and H atoms are represented by circles of arbitrary size. The solvent molecules and the anions are omitted for clarity); b) crystal cell packing.

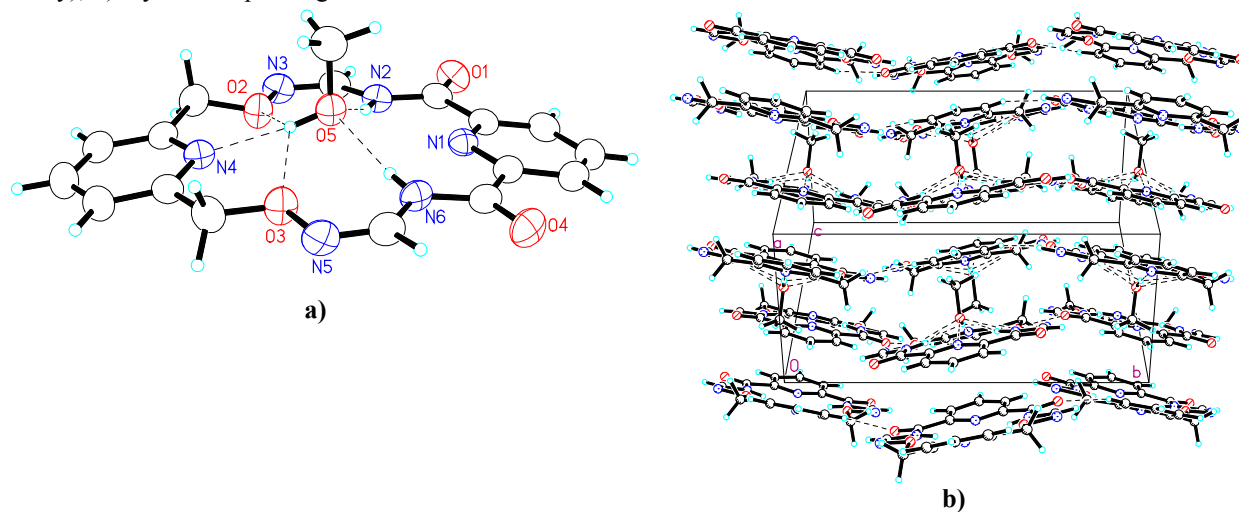


Table S8. Crystal data and structure refinement for ap19

Identification code	ap19	
Empirical formula	C17 H18 N6 O5	
Formula weight	386.37	
Temperature	180(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 7.5319(8) Å	$\alpha = 90^\circ$.
	b = 15.1775(19) Å	$\beta = 98.919(3)^\circ$.
	c = 15.610(2) Å	$\gamma = 90^\circ$.
Volume	1762.8(4) Å ³	
Z	4	
Density (calculated)	1.456 Mg/m ³	
Absorption coefficient	0.110 mm ⁻¹	
F(000)	808	
Crystal size	0.20 x 0.15 x 0.12 mm ³	
Theta range for data collection	1.88 to 26.00°.	
Index ranges	-9<=h<=8, -18<=k<=14, -17<=l<=19	
Reflections collected	9428	
Independent reflections	3451 [R(int) = 0.0357]	
Completeness to theta = 26.00°	99.5 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9869 and 0.9782	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3451 / 0 / 259	
Goodness-of-fit on F ²	1.038	
Final R indices [I>2sigma(I)]	R1 = 0.0405, wR2 = 0.0933	
R indices (all data)	R1 = 0.0681, wR2 = 0.1084	
Extinction coefficient	0.0046(8)	
Largest diff. peak and hole	0.157 and -0.146 e.Å ⁻³	

Table S9. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for ap19. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	3292(2)	6998(1)	157(1)	49(1)
O(2)	446(2)	6474(1)	2615(1)	44(1)
O(3)	-690(2)	3508(1)	2582(1)	44(1)
O(4)	1296(2)	2481(1)	30(1)	50(1)
O(5)	1716(2)	4809(1)	2243(1)	40(1)
N(1)	2134(2)	4759(1)	408(1)	35(1)
N(2)	2023(2)	6349(1)	1228(1)	37(1)
N(3)	1023(2)	7281(1)	2291(1)	43(1)
N(4)	-758(2)	5054(1)	3411(1)	36(1)
N(5)	-745(2)	2644(1)	2226(1)	44(1)
N(6)	807(2)	3322(1)	1174(1)	37(1)
C(1)	2082(2)	3990(1)	-19(1)	36(1)
C(2)	2544(2)	3909(1)	-840(1)	44(1)
C(3)	3085(3)	4644(1)	-1245(1)	47(1)
C(4)	3169(2)	5442(1)	-811(1)	43(1)
C(5)	2693(2)	5468(1)	9(1)	36(1)
C(6)	2718(2)	6336(1)	473(1)	37(1)
C(7)	1753(2)	7141(1)	1623(1)	41(1)
C(8)	50(3)	6625(1)	3455(1)	45(1)
C(9)	-918(2)	5854(1)	3771(1)	36(1)
C(10)	-1893(3)	5992(1)	4434(1)	42(1)
C(11)	-2759(3)	5288(1)	4748(1)	48(1)
C(12)	-2637(3)	4470(1)	4378(1)	44(1)
C(13)	-1635(2)	4378(1)	3719(1)	36(1)
C(14)	-1488(3)	3470(1)	3345(1)	43(1)
C(15)	14(3)	2638(1)	1552(1)	42(1)
C(16)	1385(2)	3198(1)	396(1)	38(1)
C(17)	3408(3)	4695(1)	2763(1)	55(1)

Table S10. Bond lengths [Å] and angles [°] for ap19.

O(1)-C(6)	1.227(2)	C(2)-H(2A)	0.9500
O(2)-C(8)	1.409(2)	C(3)-C(4)	1.385(3)
O(2)-N(3)	1.4189(18)	C(3)-H(3A)	0.9500
O(3)-C(14)	1.417(2)	C(4)-C(5)	1.382(3)
O(3)-N(5)	1.4221(18)	C(4)-H(4A)	0.9500
O(4)-C(16)	1.227(2)	C(5)-C(6)	1.502(2)
O(5)-C(17)	1.411(2)	C(7)-H(7A)	0.9500
O(5)-H(5H)	0.90(3)	C(8)-C(9)	1.503(2)
N(1)-C(1)	1.342(2)	C(8)-H(8A)	0.9900
N(1)-C(5)	1.344(2)	C(8)-H(8B)	0.9900
N(2)-C(6)	1.363(2)	C(9)-C(10)	1.374(2)
N(2)-C(7)	1.380(2)	C(10)-C(11)	1.380(3)
N(2)-H(2B)	0.8800	C(10)-H(10A)	0.9500
N(3)-C(7)	1.270(2)	C(11)-C(12)	1.379(3)
N(4)-C(13)	1.349(2)	C(11)-H(11A)	0.9500
N(4)-C(9)	1.350(2)	C(12)-C(13)	1.375(2)
N(5)-C(15)	1.272(2)	C(12)-H(12A)	0.9500
N(6)-C(16)	1.365(2)	C(13)-C(14)	1.507(2)
N(6)-C(15)	1.375(2)	C(14)-H(14A)	0.9900
N(6)-H(6A)	0.8800	C(14)-H(14B)	0.9900
C(1)-C(2)	1.385(3)	C(15)-H(15A)	0.9500
C(1)-C(16)	1.498(3)	C(17)-H(17A)	0.9800
C(2)-C(3)	1.375(3)	C(17)-H(17B)	0.9800
		C(17)-H(17C)	0.9800
C(8)-O(2)-N(3)	108.15(12)	O(2)-C(8)-H(8B)	109.4
C(14)-O(3)-N(5)	107.49(12)	C(9)-C(8)-H(8B)	109.4
C(17)-O(5)-H(5H)	109.9(16)	H(8A)-C(8)-H(8B)	108.0
C(1)-N(1)-C(5)	116.93(16)	N(4)-C(9)-C(10)	122.88(16)
C(6)-N(2)-C(7)	120.12(15)	N(4)-C(9)-C(8)	118.99(16)
C(6)-N(2)-H(2B)	119.9	C(10)-C(9)-C(8)	118.11(16)
C(7)-N(2)-H(2B)	119.9	C(9)-C(10)-C(11)	119.15(18)
C(7)-N(3)-O(2)	110.15(14)	C(9)-C(10)-H(10A)	120.4
C(13)-N(4)-C(9)	117.11(16)	C(11)-C(10)-H(10A)	120.4
C(15)-N(5)-O(3)	109.86(14)	C(12)-C(11)-C(10)	118.78(19)

C(16)-N(6)-C(15)	119.85(15)	C(12)-C(11)-H(11A)	120.6
C(16)-N(6)-H(6A)	120.1	C(10)-C(11)-H(11A)	120.6
C(15)-N(6)-H(6A)	120.1	C(13)-C(12)-C(11)	119.06(17)
N(1)-C(1)-C(2)	123.05(17)	C(13)-C(12)-H(12A)	120.5
N(1)-C(1)-C(16)	117.87(16)	C(11)-C(12)-H(12A)	120.5
C(2)-C(1)-C(16)	118.97(16)	N(4)-C(13)-C(12)	123.01(17)
C(3)-C(2)-C(1)	119.19(18)	N(4)-C(13)-C(14)	119.28(16)
C(3)-C(2)-H(2A)	120.4	C(12)-C(13)-C(14)	117.70(16)
C(1)-C(2)-H(2A)	120.4	O(3)-C(14)-C(13)	110.74(14)
C(2)-C(3)-C(4)	118.69(19)	O(3)-C(14)-H(14A)	109.5
C(2)-C(3)-H(3A)	120.7	C(13)-C(14)-H(14A)	109.5
C(4)-C(3)-H(3A)	120.7	O(3)-C(14)-H(14B)	109.5
C(5)-C(4)-C(3)	118.57(18)	C(13)-C(14)-H(14B)	109.5
C(5)-C(4)-H(4A)	120.7	H(14A)-C(14)-H(14B)	108.1
C(3)-C(4)-H(4A)	120.7	N(5)-C(15)-N(6)	129.08(17)
N(1)-C(5)-C(4)	123.54(17)	N(5)-C(15)-H(15A)	115.5
N(1)-C(5)-C(6)	117.41(16)	N(6)-C(15)-H(15A)	115.5
C(4)-C(5)-C(6)	119.00(16)	O(4)-C(16)-N(6)	122.33(17)
O(1)-C(6)-N(2)	122.83(17)	O(4)-C(16)-C(1)	120.50(17)
O(1)-C(6)-C(5)	120.25(17)	N(6)-C(16)-C(1)	117.14(15)
N(2)-C(6)-C(5)	116.88(15)	O(5)-C(17)-H(17A)	109.5
N(3)-C(7)-N(2)	128.60(17)	O(5)-C(17)-H(17B)	109.5
N(3)-C(7)-H(7A)	115.7	H(17A)-C(17)-H(17B)	109.5
N(2)-C(7)-H(7A)	115.7	O(5)-C(17)-H(17C)	109.5
O(2)-C(8)-C(9)	111.20(14)	H(17A)-C(17)-H(17C)	109.5
O(2)-C(8)-H(8A)	109.4	H(17B)-C(17)-H(17C)	109.5
C(9)-C(8)-H(8A)	109.4		

Table S11. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for ap19. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	54(1)	38(1)	58(1)	12(1)	14(1)	-4(1)
O(2)	64(1)	26(1)	47(1)	-2(1)	19(1)	-9(1)
O(3)	60(1)	24(1)	50(1)	-2(1)	15(1)	-5(1)
O(4)	62(1)	33(1)	54(1)	-10(1)	5(1)	5(1)
O(5)	46(1)	32(1)	43(1)	-2(1)	10(1)	-3(1)

N(1)	32(1)	34(1)	38(1)	2(1)	2(1)	4(1)
N(2)	39(1)	28(1)	43(1)	6(1)	5(1)	-2(1)
N(3)	50(1)	26(1)	54(1)	2(1)	8(1)	-7(1)
N(4)	38(1)	30(1)	40(1)	0(1)	4(1)	0(1)
N(5)	50(1)	25(1)	57(1)	-4(1)	8(1)	-4(1)
N(6)	41(1)	26(1)	42(1)	-4(1)	3(1)	0(1)
C(1)	31(1)	38(1)	39(1)	-3(1)	-1(1)	7(1)
C(2)	40(1)	46(1)	44(1)	-8(1)	1(1)	6(1)
C(3)	42(1)	60(1)	39(1)	2(1)	5(1)	6(1)
C(4)	37(1)	48(1)	44(1)	10(1)	5(1)	4(1)
C(5)	30(1)	37(1)	41(1)	8(1)	2(1)	5(1)
C(6)	32(1)	35(1)	43(1)	9(1)	1(1)	1(1)
C(7)	43(1)	27(1)	53(1)	4(1)	6(1)	-5(1)
C(8)	55(1)	36(1)	46(1)	-7(1)	11(1)	-7(1)
C(9)	38(1)	33(1)	36(1)	-2(1)	0(1)	1(1)
C(10)	48(1)	38(1)	41(1)	-4(1)	4(1)	4(1)
C(11)	54(1)	49(1)	42(1)	1(1)	15(1)	3(1)
C(12)	48(1)	41(1)	44(1)	7(1)	12(1)	-1(1)
C(13)	34(1)	33(1)	38(1)	6(1)	2(1)	1(1)
C(14)	49(1)	32(1)	50(1)	4(1)	15(1)	-2(1)
C(15)	46(1)	27(1)	51(1)	-4(1)	4(1)	-2(1)
C(16)	34(1)	34(1)	43(1)	-4(1)	-3(1)	8(1)
C(17)	49(1)	61(1)	53(1)	8(1)	6(1)	3(1)

Table S12. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for ap19.

	x	y	z	U(eq)
H(5H)	860(40)	4881(16)	2582(17)	84(9)
H(2B)	1747	5852	1465	44
H(6A)	942	3838	1433	44
H(2A)	2488	3352	-1121	53
H(3A)	3395	4605	-1811	57
H(4A)	3546	5962	-1071	52
H(7A)	2168	7650	1360	50
H(8A)	-707	7159	3451	54

H(8B)	1181	6731	3858	54
H(10A)	-1970	6564	4672	51
H(11A)	-3427	5367	5211	57
H(12A)	-3237	3977	4576	52
H(14A)	-753	3090	3779	52
H(14B)	-2700	3205	3210	52
H(15A)	37	2084	1272	50
H(17A)	3788	5252	3053	82
H(17B)	4291	4515	2398	82
H(17C)	3319	4240	3199	82

Table S13. Torsion angles [°] for ap19.

C(8)-O(2)-N(3)-C(7)	166.09(16)	O(2)-C(8)-C(9)-N(4)	22.2(2)
C(14)-O(3)-N(5)-C(15)	-177.77(15)	O(2)-C(8)-C(9)-C(10)	-159.54(16)
C(5)-N(1)-C(1)-C(2)	-1.1(2)	N(4)-C(9)-C(10)-C(11)	-0.3(3)
C(5)-N(1)-C(1)-C(16)	-177.33(15)	C(8)-C(9)-C(10)-C(11)	-178.50(18)
N(1)-C(1)-C(2)-C(3)	0.0(3)	C(9)-C(10)-C(11)-C(12)	-0.9(3)
C(16)-C(1)-C(2)-C(3)	176.25(16)	C(10)-C(11)-C(12)-C(13)	1.1(3)
C(1)-C(2)-C(3)-C(4)	0.7(3)	C(9)-N(4)-C(13)-C(12)	-1.0(2)
C(2)-C(3)-C(4)-C(5)	-0.5(3)	C(9)-N(4)-C(13)-C(14)	-179.49(16)
C(1)-N(1)-C(5)-C(4)	1.4(3)	C(11)-C(12)-C(13)-N(4)	-0.1(3)
C(1)-N(1)-C(5)-C(6)	178.68(15)	C(11)-C(12)-C(13)-C(14)	178.38(18)
C(3)-C(4)-C(5)-N(1)	-0.6(3)	N(5)-O(3)-C(14)-C(13)	-174.88(14)
C(3)-C(4)-C(5)-C(6)	-177.90(16)	N(4)-C(13)-C(14)-O(3)	-11.7(2)
C(7)-N(2)-C(6)-O(1)	7.3(3)	C(12)-C(13)-C(14)-O(3)	169.74(15)
C(7)-N(2)-C(6)-C(5)	-170.31(15)	O(3)-N(5)-C(15)-N(6)	0.1(3)
N(1)-C(5)-C(6)-O(1)	176.77(16)	C(16)-N(6)-C(15)-N(5)	-173.08(18)
C(4)-C(5)-C(6)-O(1)	-5.8(3)	C(15)-N(6)-C(16)-O(4)	-3.2(3)
N(1)-C(5)-C(6)-N(2)	-5.5(2)	C(15)-N(6)-C(16)-C(1)	174.56(15)
C(4)-C(5)-C(6)-N(2)	171.88(16)	N(1)-C(1)-C(16)-O(4)	179.44(16)
O(2)-N(3)-C(7)-N(2)	-0.7(3)	C(2)-C(1)-C(16)-O(4)	3.0(3)
C(6)-N(2)-C(7)-N(3)	175.14(18)	N(1)-C(1)-C(16)-N(6)	1.6(2)
N(3)-O(2)-C(8)-C(9)	168.52(14)	C(2)-C(1)-C(16)-N(6)	-174.80(15)
C(13)-N(4)-C(9)-C(10)	1.2(3)		
C(13)-N(4)-C(9)-C(8)	179.40(16)		

Table S14. Hydrogen bonds for ap19 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(5)-H(5H)...N(4)	0.90(3)	1.93(3)	2.827(2)	174(2)
O(5)-H(5H)...O(2)	0.90(3)	2.44(2)	2.7935(17)	103.7(18)
O(5)-H(5H)...O(3)	0.90(3)	2.39(2)	2.7864(17)	106.8(18)
N(2)-H(2B)...O(5)	0.88	2.00	2.8523(19)	164.0
N(6)-H(6A)...O(5)	0.88	1.97	2.8273(18)	164.2

H.3. **Macrocycle 2.CH₃OH** [CCDC 874204]

A crystal of the compound (colorless, prism-shaped, size 0.15 × 0.20 × 0.25 mm) was mounted on a glass fiber with grease and cooled to -93 °C in a stream of nitrogen gas controlled with Cryostream Controller 700. Data collection was performed on a Bruker SMART APEX II X-ray diffractometer with graphite-monochromated Mo K α radiation (λ = 0.71073 Å), operating at 50 kV and 30 mA over 2 θ ranges of 3.86 ~ 52.00°. No significant decay was observed during the data collection. Data were processed on a PC using the Bruker AXS Crystal Structure Analysis Package:^[1] Data collection: APEX2 (Bruker, 2010); cell refinement: SAINT (Bruker, 2009); data reduction: SAINT (Bruker, 2009); absorption correction: SADABS (Bruker, 2008); structure solution: XPREP (Bruker, 2008) and SHELXTL (Bruker, 2000); structure refinement: SHELXTL; molecular graphics: SHELXTL; publication materials: SHELXTL. Neutral atom scattering factors were taken from Cromer and Waber.^[2] The crystal is monoclinic space group C2/m, based on the systematic absences, *E* statistics and successful refinement of the structure. The structure was solved by direct methods. Full-matrix least-square refinements minimizing the function $\sum w (F_o^2 - F_c^2)^2$ were applied to the compound. All non-hydrogen atoms were refined anisotropically. For the hydrogen bonded MeOH, the H atoms of the -OH group were located from difference Fourier maps, and refined as riding atoms with Uiso(H) = 1.2 UeqO, while the H atoms of the methyl group were not added. No H atoms on the disordered lattice MeOH were added. All other H atoms were placed in geometrically calculated positions, with C-H = 0.95 (aromatic), and N-H = 0.88 Å, and refined as riding atoms, with Uiso(H) = 1.2 UeqC or N. The -O-N=C-N- part of the molecule and the hydrogen bonded -OH group are disordered. Shelx commands, PART, SAME and SADI were applied to resolve the disorder. Convergence to final R_1 = 0.0484 and wR_2 = 0.1498 for 1608 ($I > 2\sigma(I)$) independent reflections, and R_1 = 0.0537 and

$wR_2 = 0.1617$ for all 1864 ($R(\text{int}) = 0.0175$) independent reflections, with 197 parameters and 2 restraints, were achieved.^[3] The largest residual peak and hole to be 0.568 and $-0.213 \text{ e}/\text{\AA}^3$, respectively. Crystallographic data, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, torsion angles and the hydrogen bonding information are given in Tables S15 to S21. The molecular structure and the cell packing are shown in Figure S4.

[1] Bruker AXS Crystal Structure Analysis Package: Bruker (2000). SHELXTL. Version 6.14. Bruker AXS Inc., Madison, Wisconsin, USA; Bruker (2008). SADABS. Version 2008/1. Bruker AXS Inc., Madison, Wisconsin, USA; Bruker (2008). XPREP. Version 2008/2. Bruker AXS Inc., Madison, Wisconsin, USA; Bruker (2009). SAINT. Version 7.68A. Bruker AXS Inc., Madison, Wisconsin, USA; Bruker (2010). APEX2. Version 2010.3-0. Bruker AXS Inc., Madison, Wisconsin, USA.

[2] Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, UK, 1974; Vol. 4, Table 2.2 A.

[3] $R_1 = \sum ||Fo| - |Fc|| / \sum |Fo|$
 $wR_2 = \{ \sum [w(Fo^2 - Fc^2)^2] / \sum [w(Fo^2)^2] \}^{1/2}$
 $(w = 1 / [\sigma^2(Fo^2) + (0.1054P)^2 + 0.7778P], \text{ where } P = [\text{Max}(Fo^2, 0) + 2Fc^2] / 3)$

Figure S4. a) Molecular Structure (Displacement ellipsoids for non-H atoms are shown at the 50% probability level and H atoms are represented by circles of arbitrary size).

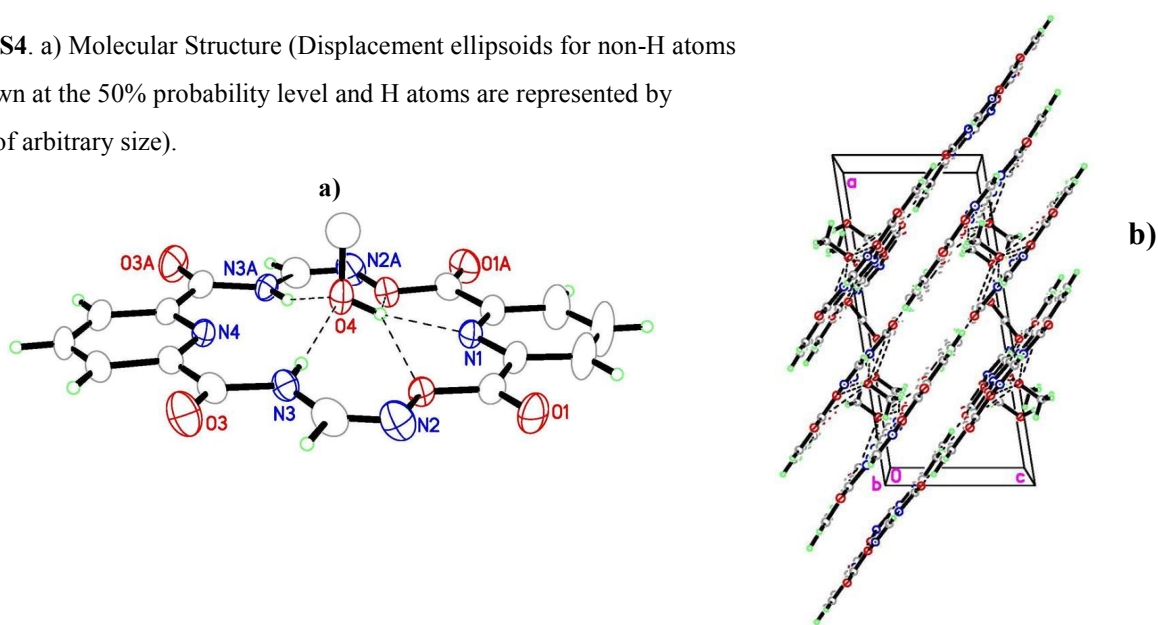


Table S15. Crystal data and structure refinement for ap33b

Identification code	ap33b	
Empirical formula	C _{17.50} H ₁₅ N ₆ O _{7.25}	
Formula weight	425.36	
Temperature	180(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/m	
Unit cell dimensions	a = 17.5387(3) Å	α = 90°.
	b = 13.3386(2) Å	β = 99.1200(10)°.
	c = 7.87380(10) Å	γ = 90°.
Volume	1818.72(5) Å ³	
Z	4	
Density (calculated)	1.553 Mg/m ³	
Absorption coefficient	0.124 mm ⁻¹	
F(000)	880	
Crystal size	0.25 x 0.20 x 0.15 mm ³	
Theta range for data collection	1.93 to 26.00°.	
Index ranges	-12 ≤ h ≤ 21, -16 ≤ k ≤ 16, -9 ≤ l ≤ 9	
Reflections collected	4940	
Independent reflections	1864 [R(int) = 0.0175]	
Completeness to theta = 26.00°	99.2 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9816 and 0.9697	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	1864 / 2 / 197	
Goodness-of-fit on F ²	1.083	
Final R indices [I > 2σ(I)]	R1 = 0.0484, wR2 = 0.1498	
R indices (all data)	R1 = 0.0537, wR2 = 0.1617	
Extinction coefficient	0.0035(13)	
Largest diff. peak and hole	0.568 and -0.213 e.Å ⁻³	

Table S16. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for ap33b. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	1873(1)	2634(1)	-3773(2)	48(1)
O(3)	4860(1)	2630(1)	2320(2)	55(1)
O(5)	0	0	0	124(4)
N(1)	2121(1)	0	-3304(2)	31(1)
N(4)	4636(1)	0	1830(2)	31(1)
C(1)	807(2)	0	-5787(5)	82(1)
C(2)	1139(1)	893(2)	-5180(3)	62(1)
C(3)	1797(1)	855(1)	-3931(2)	37(1)
C(4)	2144(1)	1833(1)	-3277(2)	35(1)
O(2)	2804(6)	1771(8)	-2099(17)	28(1)
N(2)	3093(11)	2674(11)	-1480(18)	48(3)
C(5)	3672(9)	2541(10)	-330(20)	42(2)
N(3)	3971(13)	1733(11)	463(17)	31(2)
O(2A)	4050(20)	1718(18)	490(30)	38(5)
N(2A)	3725(15)	2737(16)	-140(30)	37(3)
C(5A)	3180(20)	2620(20)	-1520(50)	49(6)
N(3A)	2743(18)	1580(20)	-2010(50)	37(4)
C(6)	4610(1)	1826(1)	1778(2)	37(1)
C(7)	4970(1)	855(1)	2434(2)	34(1)
C(8)	5650(1)	894(2)	3630(2)	43(1)
C(9)	5991(1)	0	4215(3)	47(1)
C(10)	2608(2)	0	1290(3)	47(1)
C(11)	575(5)	0	-717(14)	104(3)
O(4)	3084(1)	0	-21(2)	38(1)

Table S17. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for ap33b.

O(1)-C(4)	1.2096(19)	C(5)-H(5A)	0.9500
O(3)-C(6)	1.210(2)	N(3)-C(6)	1.405(19)
O(5)-C(11)	1.232(13)	N(3)-H(3A)	0.8800
O(5)-C(11)#1	1.232(13)	O(2A)-C(6)	1.31(3)
N(1)-C(3)#2	1.3339(19)	O(2A)-N(2A)	1.52(4)
N(1)-C(3)	1.3339(19)	N(2A)-C(5A)	1.33(4)
N(4)-C(7)	1.3348(18)	C(5A)-N(3A)	1.60(5)

N(4)-C(7)#2	1.3348(18)	C(5A)-H(5AA)	0.9500
C(1)-C(2)	1.379(3)	N(3A)-H(3AA)	0.8800
C(1)-C(2)#2	1.379(3)	C(6)-C(7)	1.496(2)
C(1)-H(1A)	0.9500	C(7)-C(8)	1.399(2)
C(2)-C(3)	1.393(2)	C(8)-C(9)	1.380(2)
C(2)-H(2A)	0.9500	C(8)-H(8A)	0.9500
C(3)-C(4)	1.495(2)	C(9)-C(8)#2	1.380(2)
C(4)-O(2)	1.366(12)	C(9)-H(9A)	0.9500
C(4)-N(3A)	1.37(3)	C(10)-O(4)	1.426(3)
O(2)-N(2)	1.367(19)	O(4)-H(4H)	0.90(4)
N(2)-C(5)	1.26(2)	O(4)-H(4HA)	0.91(5)
C(5)-N(3)	1.31(3)		
C(11)-O(5)-C(11)#1	180.0(11)	C(6)-O(2A)-N(2A)	110.6(17)
C(3)#2-N(1)-C(3)	117.55(19)	C(5A)-N(2A)-O(2A)	110(2)
C(7)-N(4)-C(7)#2	117.42(18)	N(2A)-C(5A)-N(3A)	123(3)
C(2)-C(1)-C(2)#2	119.6(2)	N(2A)-C(5A)-H(5AA)	118.3
C(2)-C(1)-H(1A)	120.2	N(3A)-C(5A)-H(5AA)	118.3
C(2)#2-C(1)-H(1A)	120.2	C(4)-N(3A)-C(5A)	104.3(19)
C(1)-C(2)-C(3)	118.07(18)	C(4)-N(3A)-H(3AA)	127.9
C(1)-C(2)-H(2A)	121.0	C(5A)-N(3A)-H(3AA)	127.9
C(3)-C(2)-H(2A)	121.0	O(3)-C(6)-O(2A)	123.9(11)
N(1)-C(3)-C(2)	123.33(16)	O(3)-C(6)-N(3)	122.7(6)
N(1)-C(3)-C(4)	119.45(14)	O(2A)-C(6)-N(3)	4(2)
C(2)-C(3)-C(4)	117.22(15)	O(3)-C(6)-C(7)	122.38(15)
O(1)-C(4)-O(2)	121.3(5)	O(2A)-C(6)-C(7)	113.5(11)
O(1)-C(4)-N(3A)	131.9(12)	N(3)-C(6)-C(7)	114.9(6)
O(2)-C(4)-N(3A)	12.1(14)	N(4)-C(7)-C(8)	123.41(16)
O(1)-C(4)-C(3)	122.83(15)	N(4)-C(7)-C(6)	118.66(14)
O(2)-C(4)-C(3)	115.8(4)	C(8)-C(7)-C(6)	117.91(15)
N(3A)-C(4)-C(3)	105.1(12)	C(9)-C(8)-C(7)	118.10(17)
C(4)-O(2)-N(2)	114.5(8)	C(9)-C(8)-H(8A)	121.0
C(5)-N(2)-O(2)	110.0(12)	C(7)-C(8)-H(8A)	121.0
N(2)-C(5)-N(3)	132.3(14)	C(8)#2-C(9)-C(8)	119.5(2)
N(2)-C(5)-H(5A)	113.8	C(8)#2-C(9)-H(9A)	120.2
N(3)-C(5)-H(5A)	113.8	C(8)-C(9)-H(9A)	120.2

C(5)-N(3)-C(6)	119.4(12)	C(10)-O(4)-H(4H)	117(3)
C(5)-N(3)-H(3A)	120.3	C(10)-O(4)-H(4HA)	117(4)
C(6)-N(3)-H(3A)	120.3	H(4H)-O(4)-H(4HA)	126(6)

Symmetry transformations used to generate equivalent atoms: #1 -x,-y,-z #2 x,-y,z

Table S18. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for ap33b. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	50(1)	39(1)	53(1)	11(1)	-2(1)	14(1)
O(3)	49(1)	48(1)	62(1)	-18(1)	-6(1)	-15(1)
O(5)	203(14)	115(8)	51(4)	0	15(6)	0
N(1)	28(1)	34(1)	28(1)	0	-1(1)	0
N(4)	26(1)	44(1)	23(1)	0	0(1)	0
C(1)	72(2)	74(2)	78(2)	0	-52(2)	0
C(2)	57(1)	55(1)	61(1)	8(1)	-28(1)	8(1)
C(3)	34(1)	43(1)	31(1)	5(1)	-4(1)	6(1)
C(4)	34(1)	36(1)	34(1)	7(1)	3(1)	8(1)
O(2)	30(2)	13(3)	40(2)	6(2)	-2(2)	0(2)
N(2)	41(4)	38(5)	64(4)	-5(3)	4(3)	0(2)
C(5)	43(3)	19(5)	62(3)	-11(3)	5(3)	-5(3)
N(3)	30(3)	30(4)	31(4)	-8(3)	0(2)	-5(2)
O(2A)	36(8)	30(6)	47(8)	0(5)	0(4)	-4(4)
N(2A)	45(5)	9(7)	54(6)	-5(4)	-2(4)	-5(4)
C(5A)	41(9)	17(6)	87(13)	-15(6)	3(7)	-1(5)
N(3A)	42(5)	16(8)	51(6)	3(5)	0(3)	-9(5)
C(6)	32(1)	45(1)	33(1)	-9(1)	5(1)	-11(1)
C(7)	28(1)	50(1)	24(1)	-5(1)	3(1)	-7(1)
C(8)	30(1)	70(1)	29(1)	-7(1)	2(1)	-11(1)
C(9)	24(1)	87(2)	27(1)	0	-5(1)	0
C(10)	50(1)	36(1)	53(2)	0	5(1)	0
C(11)	71(5)	113(7)	108(8)	0	-49(5)	0
O(4)	36(1)	34(1)	39(1)	0	-11(1)	0

Table S19. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for ap33b.

	x	y	z	U(eq)
H(1A)	351	0	-6619	98

H(2A)	926	1517	-5600	74
H(5A)	3942	3140	33	50
H(3A)	3774	1139	173	37
H(5AA)	3041	3186	-2236	59
H(3AA)	2861	984	-1572	44
H(8A)	5871	1518	4028	52
H(9A)	6457	0	5015	56
H(4H)	2840(30)	0	-1120(60)	45
H(4HA)	3610(30)	0	340(80)	45

Table S20. Torsion angles [°] for ap33b.

C(2)#2-C(1)-C(2)-C(3)	-1.4(6)
C(3)#2-N(1)-C(3)-C(2)	0.7(3)
C(3)#2-N(1)-C(3)-C(4)	-179.54(11)
C(1)-C(2)-C(3)-N(1)	0.3(4)
C(1)-C(2)-C(3)-C(4)	-179.4(3)
N(1)-C(3)-C(4)-O(1)	-178.96(16)
C(2)-C(3)-C(4)-O(1)	0.8(3)
N(1)-C(3)-C(4)-O(2)	2.5(6)
C(2)-C(3)-C(4)-O(2)	-177.7(6)
N(1)-C(3)-C(4)-N(3A)	-3.3(14)
C(2)-C(3)-C(4)-N(3A)	176.5(14)
O(1)-C(4)-O(2)-N(2)	3.6(14)
N(3A)-C(4)-O(2)-N(2)	-150(10)
C(3)-C(4)-O(2)-N(2)	-177.9(9)
C(4)-O(2)-N(2)-C(5)	176.0(12)
O(2)-N(2)-C(5)-N(3)	-9(3)
N(2)-C(5)-N(3)-C(6)	-176.8(17)
C(6)-O(2A)-N(2A)-C(5A)	177(3)
O(2A)-N(2A)-C(5A)-N(3A)	18(5)
O(1)-C(4)-N(3A)-C(5A)	-13(3)
O(2)-C(4)-N(3A)-C(5A)	18(8)
C(3)-C(4)-N(3A)-C(5A)	172(2)
N(2A)-C(5A)-N(3A)-C(4)	169(3)
N(2A)-O(2A)-C(6)-O(3)	-3(3)
N(2A)-O(2A)-C(6)-N(3)	68(26)

N(2A)-O(2A)-C(6)-C(7)	-178.3(15)
C(5)-N(3)-C(6)-O(3)	6.4(18)
C(5)-N(3)-C(6)-O(2A)	-104(26)
C(5)-N(3)-C(6)-C(7)	-172.3(12)
C(7)#2-N(4)-C(7)-C(8)	1.1(3)
C(7)#2-N(4)-C(7)-C(6)	179.83(11)
O(3)-C(6)-C(7)-N(4)	176.69(16)
O(2A)-C(6)-C(7)-N(4)	-8.4(14)
N(3)-C(6)-C(7)-N(4)	-4.6(8)
O(3)-C(6)-C(7)-C(8)	-4.5(2)
O(2A)-C(6)-C(7)-C(8)	170.4(14)
N(3)-C(6)-C(7)-C(8)	174.2(8)
N(4)-C(7)-C(8)-C(9)	-0.1(3)
C(6)-C(7)-C(8)-C(9)	-178.88(15)
C(7)-C(8)-C(9)-C(8)#2	-0.9(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y,-z #2 x,-y,z

Table S21. Hydrogen bonds for ap33b [$\text{\AA}$ and $^\circ$].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(4)-H(4H)...O(2)	0.90(4)	2.481(17)	2.871(10)	106.5(11)
O(4)-H(4H)...N(1)	0.90(4)	1.97(4)	2.855(2)	168(4)
N(3)-H(3A)...O(4)	0.88	1.93	2.780(16)	160.6
O(4)-H(4HA)...O(2A)	0.91(5)	2.42(3)	2.84(3)	108.2(14)
N(3A)-H(3AA)...O(4)	0.88	1.79	2.64(3)	160.5

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y,-z #2 x,-y,z