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A pyridine-*N*-oxide catenane for cation recognition†

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The rapid preparation of a pyridine-*N*-oxide containing [2]catenane is described. The [2]catenane was characterized by NMR spectroscopy, mass spectrometry and X-ray single crystal structure determination. ¹H NMR titration experiments reveal the [2]catenane may be reversibly protonated, as well as an ability to bind lithium cations more strongly than sodium cations.

Introduction

Hydrogen bonding – often augmented with other non-covalent interactions – has been widely used in the templated synthesis of mechanically interlocked molecules (MIMs)¹ such as catenanes² and rotaxanes.³ Examples of MIMs prepared by hydrogen bonding templation strategies,^{4,5} have been explored as nanotechnological components such as molecular switches⁶ and rotors,⁷ as well as catalysts⁸ and receptors for anionic guests.⁹

Pyridine-*N*-oxides (PNOs) are hydrogen bond acceptors and as such have been used in the construction of several hydrogen bond templated MIMs,¹⁰ as well as MIMs prepared using other non-covalent interactions.¹¹ When included in MIMs, the PNO motif may offer the potential of protonation¹² and/or metal ion coordination.¹³

The development of molecular receptors capable of the selective binding and/or sensing of lithium cations¹⁴ is of relevance to society, due to the increased extraction of lithium to support lithium ion-battery technology – activity which risks mobilizing toxic levels of lithium salts into the environment.¹⁵ Only a handful of MIMs have been prepared by lithium cation templation^{16,17} or shown to bind lithium cations.¹⁸

Here we report on the *rapid* synthesis of a rare example of a PNO containing [2]catenane^{13c} capable of binding of cationic guests. The catenane was characterized by NMR spectroscopy, mass spectrometry and X-ray crystallography. ¹H NMR titrations were then undertaken to assess the solution phase cationic guest recognition ability of the [2]catenane. These titrations revealed both reversible protonation and the binding of

alkali metal cations – notably lithium more strongly than sodium.

Results and discussion

PNO [2]catenane: design, synthesis and characterization

To prepare a PNO [2]catenane, we proposed to use our previously reported hydrogen bond templation synthetic methodology,⁵ⁿ but substituting the central CH₂OCH₂ unit of the glycol chain for a 2,6-pyridyl unit. Oxidation of pyridyl group(s) of the pyridyl [2]catenane would then furnish a PNO [2]catenane.

The pyridyl [2]catenane **2** (Scheme 1) was thus prepared. Simultaneous addition of previously reported dimethanamine **1** (preparable in two steps)^{5j} and commercially available isophthaloyl chloride into a solution of triethylamine in dichloromethane under pseudo-high dilution conditions led to the formation of the desired pyridyl [2]catenane **2** and non-interlocked macrocycle **3**. Upon aqueous workup and purification by column chromatography, [2]catenane **2** was isolated in a 15% yield (a yield broadly in line with our previously reported [2]catenane⁵ⁿ). The novel catenane was characterized by ¹H and ¹³C NMR spectroscopy and mass spectrometry (see ESI, pp. S2 and S3†).

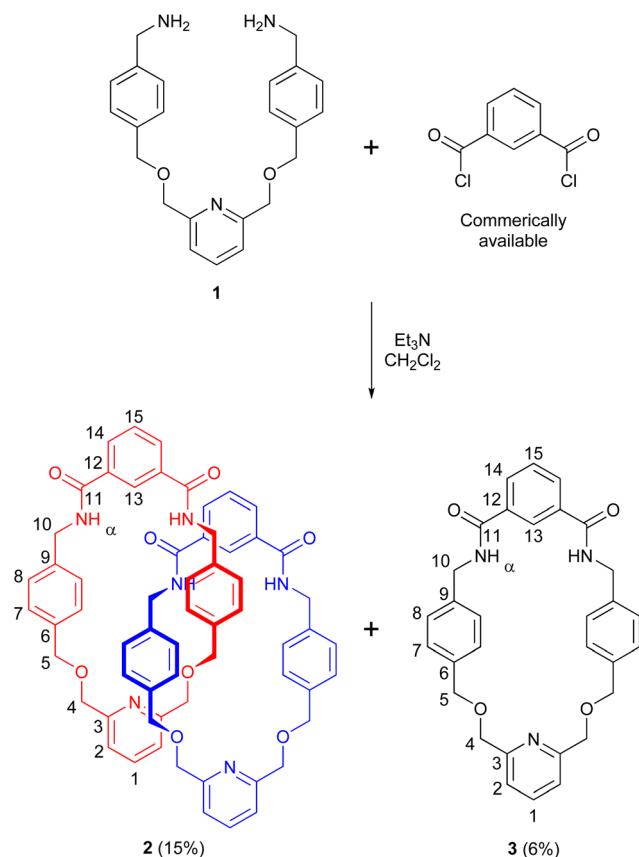
The PNO [2]catenane **4** was then synthesized by reacting [2]catenane **2** with an excess of *m*-chloroperoxybenzoic acid (*m*CPBA) to achieve oxidation of the two pyridine units within the catenane (Scheme 2).¹⁹ After aqueous workup and column chromatography, PNO [2]catenane **4** was afforded in 82% yield, and characterized by ¹H and ¹³C NMR spectroscopy and mass spectrometry (see Fig. 1 and ESI, pp. S6 and S7†).

Evidence for the interlocked structures of [2]catenanes **2** and **4** may be found by comparison of their ¹H NMR spectra with macrocycle **3** (Fig. 1). Large downfield shifts in amide protons *α* and internal isophthalamide proton *13* for [2]catenane **2** compared to macrocycle **3** is indicative of inter-ring hydrogen bonding in the catenane. The upfield shift of protons *7* and *8* are consistent with the threading of one

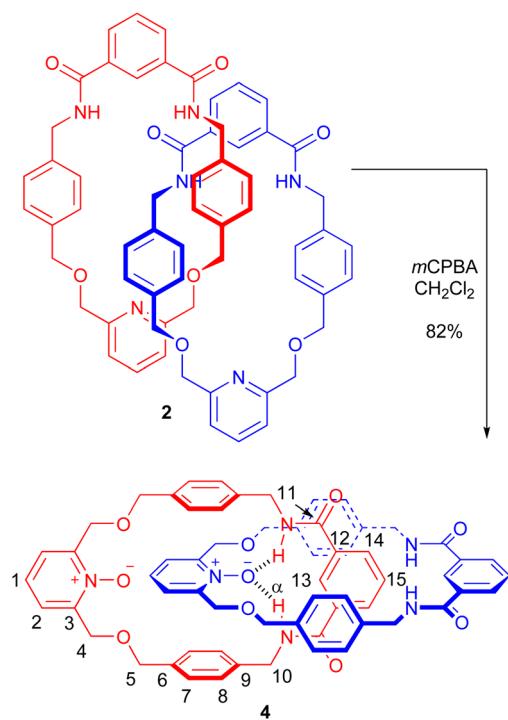
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†Electronic supplementary information (ESI) available: Copies of characterization data; further data and protocols for titrations and NMR spectra. CCDC 2305367 and 2305368 for **4** and **2**. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4ob00176a>

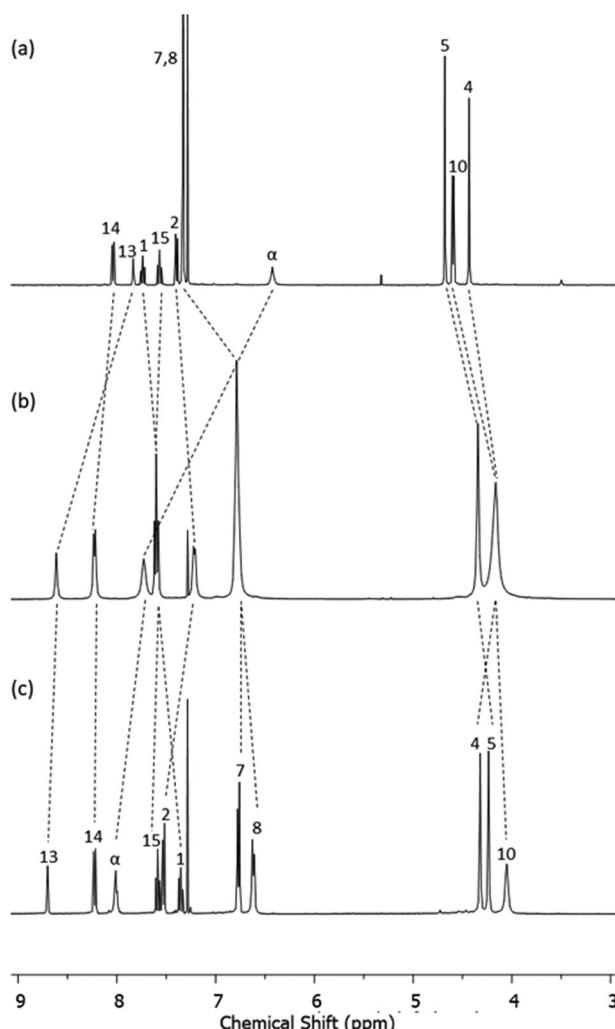




Scheme 1 Synthesis of [2]catenane 2.



Scheme 2 Synthesis of target PNO [2]catenane 4.

Fig. 1 ^1H NMR spectra of (a) macrocycle 3, (b) [2]catenane 2 and (c) PNO [2]catenane 4 (CDCl_3 , 400 MHz, 298 K). For atom labels, see Schemes 1 and 2.

macrocyclic ring through the other. Upon oxidation to PNO [2] catenane 4, there is a further downfield shift in the amide protons α , attributed to hydrogen bonding now being possible to the negatively charged oxygen atom of the PNO.

Unequivocal evidence for the interlocked structures of both pyridyl [2]catenane 2 and PNO [2]catenane 4 were provided by X-ray structure determination using single crystals grown by slow evaporation of separate chloroform solutions. As depicted in Fig. 2a, the amide N-Hs of the left-hand macrocycle of [2] catenane 2 are participating in hydrogen bonds with the carbonyl oxygen of the right-hand macrocycle ($\text{N-H}\cdots\text{O}=\text{C}$ distances: 2.15(2) Å and 2.29(2) Å). When oxidized to PNO [2]catenane 4 (Fig. 2b), these hydrogen bonding events are retained ($\text{N-H}\cdots\text{O}=\text{C}$ distances: 2.14(2) Å and 2.36(4) Å), and in addition the pyridine-*N*-oxide oxygen of the macrocycle on the left-hand ring participates in intramolecular hydrogen bonding events with the isophthalamide N-Hs of the right-hand macrocycle ($\text{N-H}\cdots\text{O}=\text{N}^+$ distances: 2.06(0) Å and 2.25(3) Å).



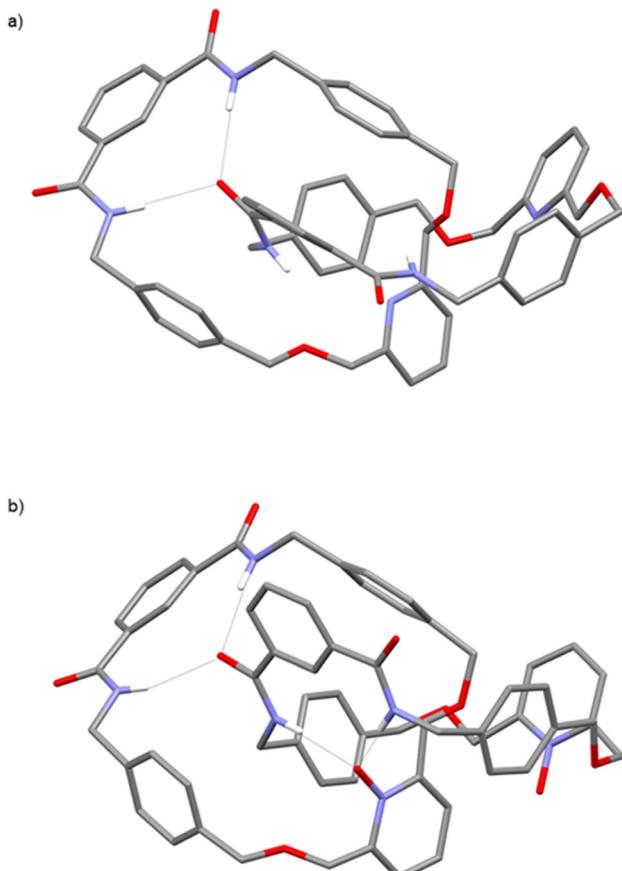


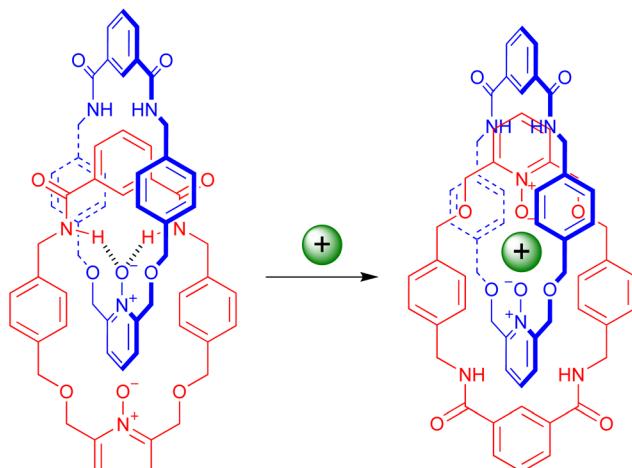
Fig. 2 X-ray crystal structures of (a) pyridyl [2]catenane 2 and (b) PNO [2]catenane 4. Hydrogen atoms (except N-Hs) are omitted for clarity.

PNO [2]catenane: ^1H NMR titration binding studies

With PNO [2]catenane 4 in hand, attention turned to investigating whether it could act as a host for positively charged guest species. It was hypothesized that a single atom cation may bind within the central cavity of the catenane, coordinated by both pyridine-*N*-oxide units, achieved by pirouetting of the interlocked rings (Scheme 3).²⁰ ^1H NMR titration studies were undertaken in conjunction with BindFit²¹ to determine association constants.

An initial titration study was undertaken with aliquots of trifluoroacetic acid (TFA) being added to [2]catenane 4 in CDCl_3 (Fig. 3 & ESI, pp. S9–S11†).^{22–24} Several perturbations in the aromatic protons are observed, indicating the coordination of the proton by [2]catenane 4. For example, proton 13 experiences an upfield shift, consistent with reduction in hydrogen bonding arising from protonation inducing pirouetting of the catenane rings.²⁵ Furthermore, the protonation event could be reversed upon addition of base (d_5 -pyridine) resulting in a restoration of the initial proton signal shifts in the ^1H NMR spectrum.

We then proceeded to study if [2]catenane 4 could act as a host for alkali metal cations.^{26,27} Due to the poor solubility of alkali metal salts in neat CDCl_3 , a solvent system of 4 : 1 $\text{CDCl}_3/\text{CD}_3\text{CN}$ was used in the titration studies. Upon addition of LiClO_4 to [2]catenane 4, shifts in several resonances are



Scheme 3 Potential binding motif of [2]catenane 4 with a cationic guest.

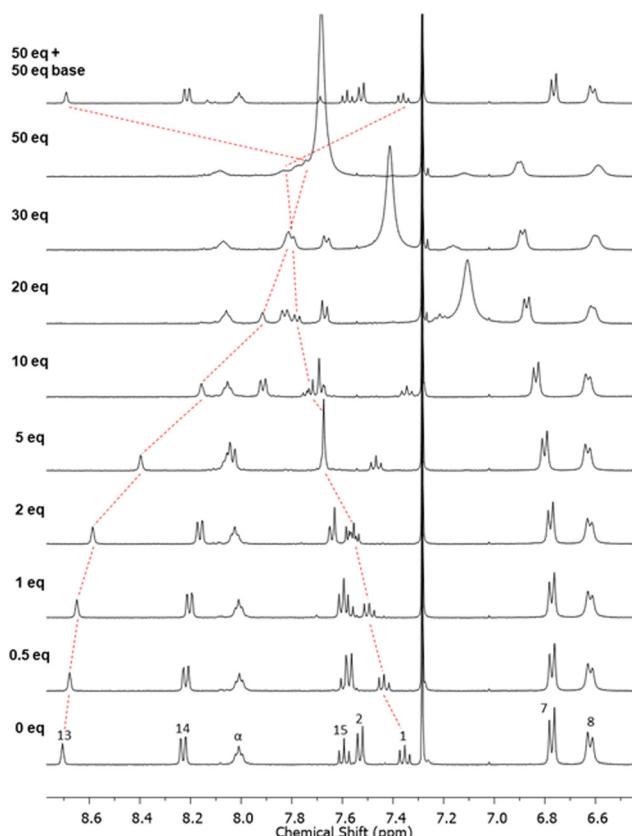


Fig. 3 Partial ^1H NMR spectra and highlighted chemical shifts of diagnostic proton resonances of PNO [2]catenane 4 with set equivalent additions of TFA followed by reversal with the addition of d_5 -pyridine (CDCl_3 , 400 MHz, 298 K). NB: The large peak that appears in spectra for 20, 30 and 50 eq. of TFA is protic O–H.

observed (Fig. 4). The most obvious is the upfield shift for isophthalamide proton 13, which is consistent with coordination of the Li^+ cation to the PNO oxygen atom once again disrupt-

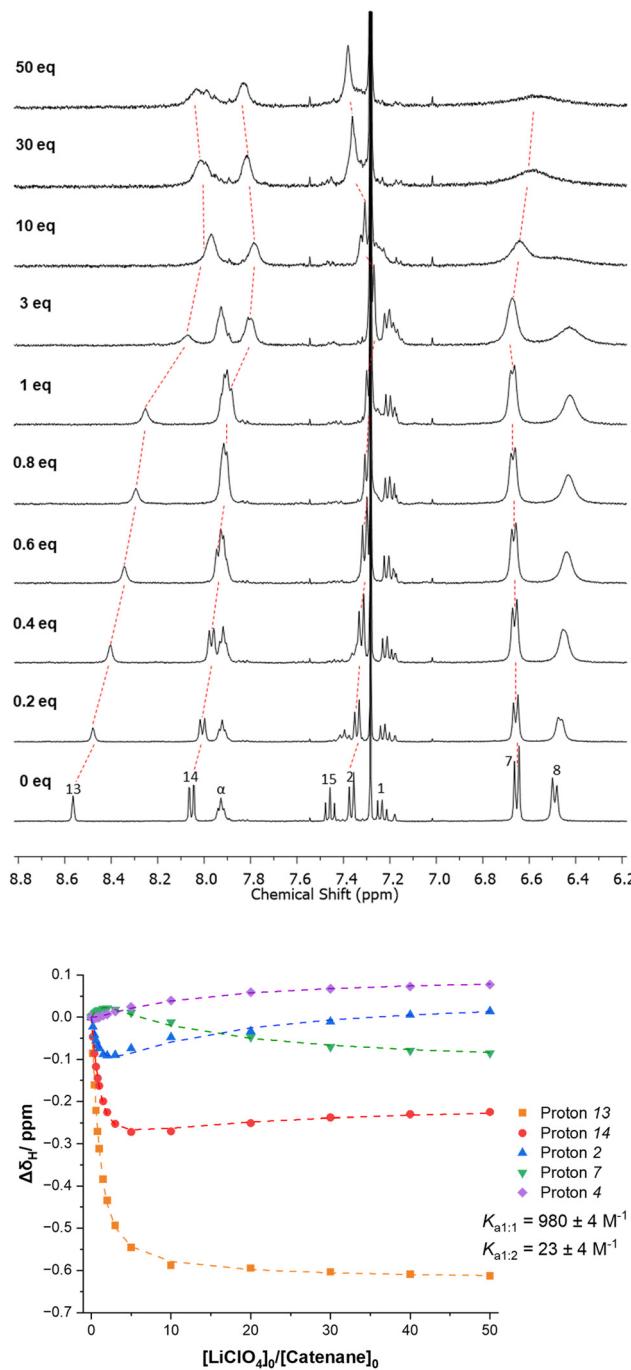


Fig. 4 Partial ^1H NMR spectra and highlighted chemical shifts of diagnostic proton resonances of PNO [2]catenane 4 with set equivalent additions of LiClO_4 (4 : 1 $\text{CDCl}_3/\text{CD}_3\text{CN}$, 400 MHz, 298 K) and globally fitted data (by BindFit) for a 1 : 2 binding isotherm using change in peak positions against a ratio of initial cation and catenane concentration.

ing inter-ring hydrogen bonding. Beyond 1 equivalent, there is a reverse in shift direction – implying a second binding mode occurring. BindFit analysis of non-overlapping resonances of catenane protons 2, 4, 7, 13 and 14, determined 1 : 2 stoichiometric host–guest associations constants of $K_{1:1} = 980 \text{ M}^{-1}$ and $K_{1:2} = 20 \text{ M}^{-1}$ respectively.²⁸

The addition of NaBArF to a fresh sample of [2]catenane 4 showed smaller perturbations of the diagnostic protons (Fig. 5). Furthermore, there is no evidence of a second binding event upon addition of excess NaBArF . BindFit analysis affords a 1 : 1 stoichiometric association constant for Na^+ of $K = 80 \text{ M}^{-1}$.²⁹ The observed differences in binding of Li^+ and Na^+ may be attributed to the higher charge density of the Li^+ cation

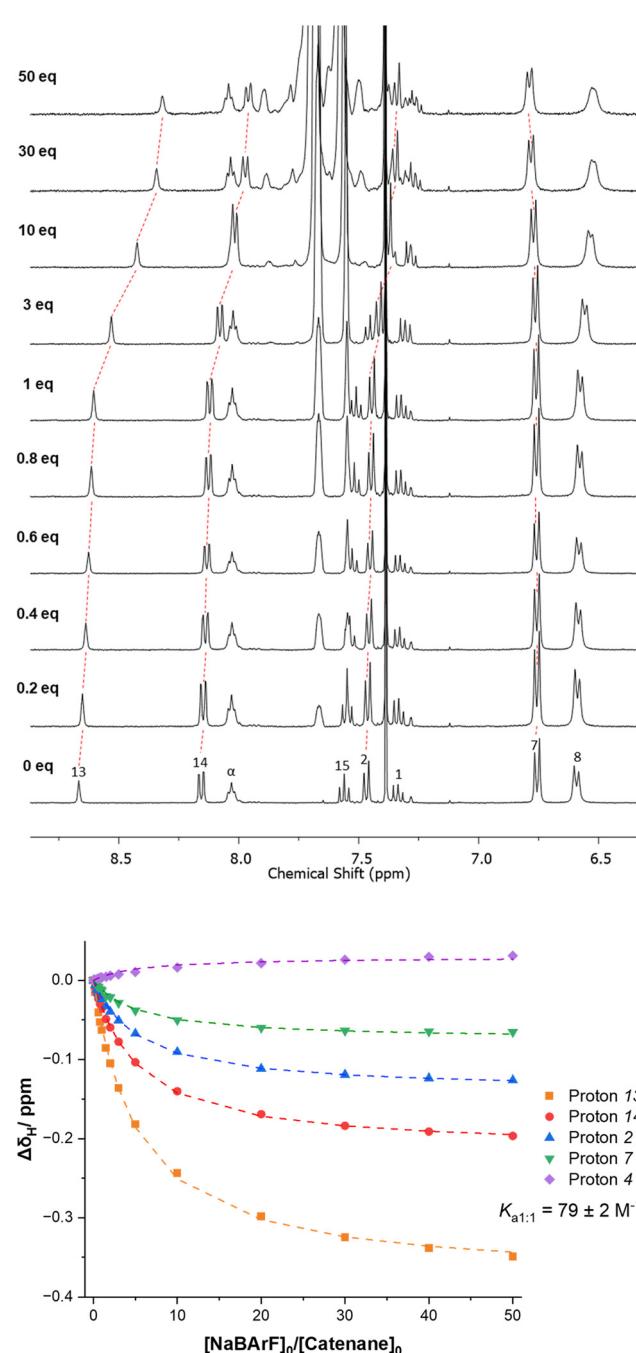


Fig. 5 Partial ^1H NMR spectra and highlighted chemical shifts of diagnostic proton resonances of PNO [2]catenane 4 with set equivalent additions of NaBArF (4 : 1 $\text{CDCl}_3/\text{CD}_3\text{CN}$, 400 MHz, 298 K) and globally fitted data (by BindFit) for a 1 : 1 binding isotherm using change in peak positions against a ratio of initial cation and catenane concentration.

compared to that of the Na^+ cation and better size complementarity with the small cavity available within [2]catenane **4**.

Conclusions

The rapid synthesis and characterization of a pyridine-*N*-oxide [2]catenane was undertaken. A series of ^1H NMR titrations were undertaken with cationic guests. Addition of acid leads to protonation and pirouetting of the interlocked rings, which could be reversed with the addition of base. The PNO [2]catenane also showed a strong binding affinity for the Li^+ cation (compared to Na^+). To the best of our knowledge this paper represents the first reported quantitative study of alkali metal cation binding by a PNO containing interlocked molecule.³⁰ Future work will be focused on enhancing the selectivity of such catenanes for Li^+ and other alkali metal cation guests. In general, the use of the pyridine-*N*-oxide motif in mechanical bond formation and investigations into MIMs capable of ion binding are continuing in our laboratory.

Experimental section

General information

All reagents and solvents were used as obtained from commercial suppliers, unless otherwise stated. Dry solvents and Et_3N were purchased dry and stored under an inert atmosphere. Deionised water was used in all cases. All aqueous solutions are saturated unless otherwise stated.

Silica gel with a 60 Å particle size was used as the stationary phase for column chromatography. Analytical TLC was used to monitor the progress of column chromatography, with analytical TLC plates examined under short wavelength (254 nm) UV light or staining with potassium permanganate and phosphomolybdic acid solutions as appropriate.

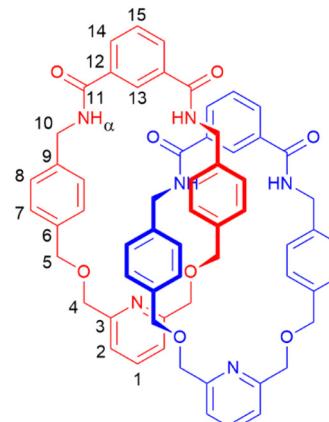
IR spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. NMR spectra were recorded on a Bruker AVANCE III 400 at 298 K (unless otherwise stated). Mass spectra were recorded on Shimadzu LCMS-8040, Shimadzu LCMS IT ToF and Bruker Compact ToF coupled to an Agilent 1260 Infinity LC. Melting points were recorded on a Gallenkamp capillary melting point apparatus and are uncorrected.

Bis-amine **1** was synthesized by adaptation of a previously reported procedure.^{5j}

Experimental procedures

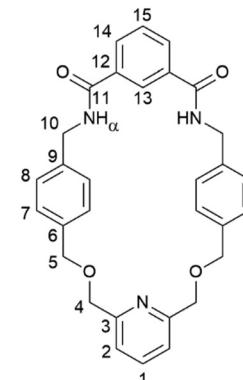
Pyridyl [2]catenane 2. To a three-neck flask containing Et_3N (0.83 mL, 6.00 mmol) in dry CH_2Cl_2 (100 mL) under Ar (g) was added a solution of bis-amine **1** (907 mg, 2.40 mmol) in dry CH_2Cl_2 (50 mL) and a solution of isophthaloyl chloride (487 mg, 2.40 mmol) in dry CH_2Cl_2 (50 mL) in simultaneous dropwise addition. After the addition was complete, the reaction mixture was stirred for a further 20 h, then washed with 1 M HCl (aq) (2 × 50 mL) and brine (1 × 50 mL). The organic layer was then dried (MgSO_4) and concentrated *in vacuo*. The crude material was puri-

fied by silica gel column chromatography (9 : 1 EtOAc/ CH_2Cl_2) to afford the *title product* **2** (364 mg, 15%) as a colourless solid.



R_f : 0.31 [EtOAc/ CH_2Cl_2 9 : 1]; mp: 111–113 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 3321 (N–H), 2857 (C–H), 2365 (C–H), 1647 (C=O), 1522 (C–O), 1079 (C–O); δ_{H} (400 MHz, CDCl_3): 8.61 (2H, s, H¹³), 8.22 (4H, d, J = 7.5 Hz, H¹⁴), 7.72 (4H, br s, H^a), 7.60 (4H, app. t, H¹ & H¹⁵), 7.21 (4H, d, J = 6.9 Hz, H²), 6.84–6.70 (16H, m, H⁷ & H⁸), 4.34 (8H, s, H⁵), 4.22–4.09 (16H, m, H¹⁰ & H⁴); δ_{C} (100 MHz, CDCl_3): 166.1 (C¹¹), 157.0 (C³), 137.5 (C¹⁵ or 1), 136.8 (C⁹), 135.9 (C⁶), 133.4 (C¹²), 131.7 (C¹⁴), 128.8 (C⁷ or 8), 128.6 (C¹ or 15), 128.4 (C⁸ or 7), 124.9 (C¹³), 121.1 (C²), 72.7 (C⁵), 71.5 (C⁴), 44.3 (C¹⁰); MS (ESI +ve) m/z : 1037.4258 ([M + Na]⁺ $\text{C}_{62}\text{H}_{58}\text{N}_6\text{NaO}_8$ requires 1037.4208).

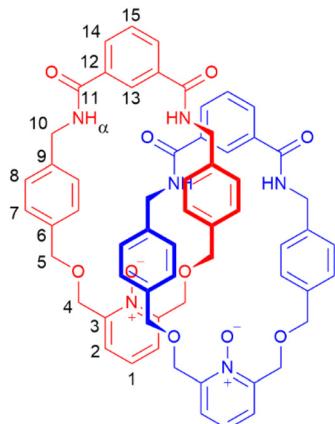
Macrocyclic 3. Macrocyclic 3 was isolated from the above catenation reaction upon purification of the crude reaction mixture by silica gel column chromatography as a colourless solid (60 mg, 6%).



R_f : 0.40 [EtOAc/ CH_2Cl_2 4 : 1]; mp: 130–132 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 3296 (N–H), 2864 (C–H), 1643 (C=O), 1537 (C–H), 1090 (C–O); δ_{H} (400 MHz, CDCl_3): 8.04 (2H, dd, J = 7.8, 1.7 Hz, H¹⁴), 7.84 (1H, s, H¹³), 7.74 (1H, t, J = 7.8 Hz, H¹), 7.56 (1H, t, J = 7.7 Hz, H¹⁵), 7.40 (2H, d, J = 7.7 Hz, H²), 7.33 (8H, s, H⁷ & H⁸), 6.44 (2H, bs, H^a), 4.67 (4H, s, H⁵), 4.59 (4H, d, J = 5.6 Hz, H¹⁰), 4.43 (4H, s, H⁴); δ_{C} (100 MHz, CDCl_3): 166.5 (C¹²), 157.4 (C³), 137.5 (C⁶ or 9), 137.1 (C¹), 134.8 (C¹²), 130.7 (C¹⁴), 129.3 (C¹⁵), 129.0 (C⁷ or 8), 128.7 (C⁷ or 8), 124.0 (C¹³), 120.1 (C²), 72.2 (C⁵), 71.3 (C⁴), 44.2 (C¹⁰); MS (ESI +ve) m/z : 530.2067 ([M + Na]⁺ $\text{C}_{31}\text{H}_{29}\text{N}_3\text{NaO}_4$ requires 530.2050).



PNO [2]catenane 4. To a solution of pyridyl [2]catenane 2 (50 mg, 0.04 mmol) in CH_2Cl_2 (5 mL) was added *m*CPBA (35 mg, 0.14 mmol, 72% mixture in water). The reaction mixture was stirred for 18 h then NaHCO_3 (aq) (10 mL) was added. The aqueous layer was then extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (98 : 2 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$) to afford the *title product* 4 (42 mg, 82%) as a colourless solid.



R_f: 0.31 [$\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98 : 2]; **mp**: 121–122 °C; **IR ν_{max} / cm⁻¹ (neat)**: 3295 (N–H), 3062 (C–H), 2860 (C–H), 1729 (C=O), 1649 (N–H), 1537 (N–O); δ_{H} (400 MHz, CDCl_3): 8.70 (2H, s, H^{13}), 8.22 (4H, dd, $J = 7.9$ Hz & 1.4 Hz, H^{14}), 8.01 (4H, br s, H^{α}), 7.58 (2H, t, $J = 7.9$ Hz, H^{15}), 7.52 (4H, d, $J = 7.8$ Hz, H^2), 7.35 (2H, t, $J = 7.8$ Hz, H^1), 6.77 (8H, d, $J = 7.8$ Hz, H^7), 6.61 (8H, d, $J = 7.8$ Hz, H^8), 4.32 (8H, s, H^4), 4.23 (8H, s, H^5), 4.05 (8H, br s, H^{10}); δ_{C} (100 MHz, CDCl_3): 166.1 (C^{11}), 148.7 (C^3), 137.9 (C^9), 135.7 (C^6), 133.8 (C^{12}), 131.5 (C^{14}), 129.3 (C^7), 128.9 (C^{15}), 128.3 (C^8), 126.4 (C^1), 124.6 (C^{13}), 123.7 (C^2), 73.0 (C^5), 65.4 (C^4), 43.4 (C^{10}); **MS (ESI +ve) m/z**: 1047.4245 ([M + H]⁺ $\text{C}_{62}\text{H}_{59}\text{N}_6\text{O}_{10}$ requires 1047.4287).

Author contributions

NHE proposed the study. SRB conducted the synthesis, characterization (with contribution from NRH) and analysis of all materials. NHE supervised SRB. SRB and NHE wrote the manuscript. All authors discussed and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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of Chemical Industry. High resolution mass spectrometry data of 2 and 3 were recorded by Mr Karl Heaton at the University of York. High resolution mass spectrometry data of 4 was recorded by Mr Harry Mills (Lancaster University). We thank Dr Rebecca Spicer (Lancaster University) for the recording of low resolution mass spectrometry data and for useful discussions regarding analysis of the ¹H NMR titration data. Underlying data for this paper are provided in the Experimental Section and ESI[†]. Electronic copies of NMR spectra (including fid files) will be available upon publication from: DOI:10.17635/lancaster/researchdata/640.

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19 Initial attempts to oxidize the pyridine motif with Oxone®, were thwarted by the poor solubility of [2]catenane **2** under the reaction conditions.

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25 Considering the rapid rotation of the identical rings of uncomplexed [2]catenane **4**, a ^1H – ^1H ROESY NMR experiment will not unambiguously reveal whether pirouetting has occurred upon cation coordination.

26 LiClO₄ was used as the source of Li⁺ and NaBArF as the source of Na⁺. Different non-coordinating counter-anions were used due to issues with maintaining solubility in appropriate solvent systems for the determination of association constant data.

27 Due to the insolubility of the oxidized analogue of macrocycle **3**, it was not possible to undertake titrations to ascertain the alkali metal cation binding properties of the non-interlocked rings of catenane **4**.

28 Fitted titration data for **4** with LiClO₄ can be found under <https://app.supramolecular.org/bindfit/view/29ae08eb-c98c-4e4a-8538-d83822d473a7> (accessed 22nd June 2023).

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