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Iodo-imidazolium Salts: Halogen Bonding in Crystals and Anion-Templated Pseudorotaxanes

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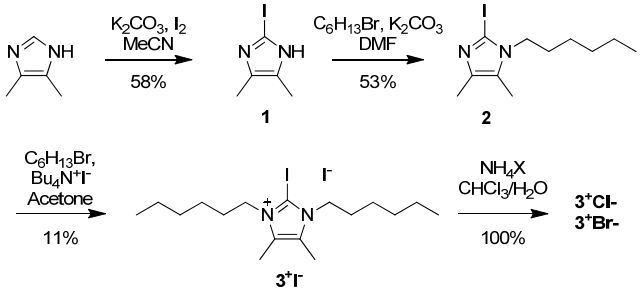
Synthesis and Characterisation

General Information:

Commercially available materials were used without any pre-treatment unless otherwise stated. Dry solvents were obtained by purging with N_2 and then passing through an MBraun MPSP-800 column. H_2O was de-ionised and microfiltered using a Milli-Q® Millipore machine. Triethylamine was dried and stored over potassium hydroxide. All other solvents and commercial grade reagents were used without further purification. Routine NMR spectra were recorded on a Varian Mercury 300 spectrometer with ^{1}H NMR operating at 300 MHz, ^{13}C{^{1}H} at 75.5 MHz. ^{1}H NMR titrations and ROESY spectra were recorded on a Varian Unity Plus 500 spectrometer with ^{1}H operating at 500 MHz. Routine mass spectra were recorded on a Micromass LCT Premier XE spectrometer and accurate masses determined to four decimal places using Bruker micrOTOF and Micromass GCT spectrometers. Melting points were recorded on a Gallenkamp capillary melting point apparatus and are uncorrected.



Scheme S1 Synthesis of iodoimidazolium threads.

2-Iodo-4,5-dimethyl-1H-imidazole (1)

4,5-Dimethyl-1H-imidazole (0.46 g, 4.79 mmol) and K_2CO_3 (0.80 g, 5.75 mmol) were dissolved in CH_3CN (125 mL). Iodine (1.34 g, 5.29 mmol) was added and the mixture was heated to 60 °C and stirred for 12 hours under a N_2 atmosphere. The reaction mixture was then filtered and the solvent removed *in vacuo*. EtOAc (100 mL) and water (100 mL) were added and the organic layer extracted. Further extraction of the organic layer was carried out with EtOAc (2x 50ml) and the combined organic layers dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified *via* silica gel column chromatography (EtOAc) tp give the product as a white solid (0.621g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ; 2.11 (6H, s, -C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 130.8, 77.6, 9.8; HRMS (FI +ve) *m/z*: 222.9728 (M^+, $C_5H_7IN_2^+$, requires 222.9727); mp 162 °C

2-Iodo-1-hexyl-4,5-dimethyl-1H-imidazole (2)

2-Iodo-4,5-dimethyl-1H-imidazole (0.37 g, 1.65 mmol), 1-bromohexane (0.30 g, 1.82 mmol), K_2CO_3 (2.28 g, 16.5 mmol) and dry DMF (15 mL) were added to a reaction flask and the mixture heated to 100 °C and stirred for 4 hours under a N_2 atmosphere. The residue was filtered, washed with DMF (10 mL) and the solvent removed *in vacuo*. The resulting residue was re-dissolved in CH_2Cl_2 (50 mL) and washed with 10% $NaOH_{(aq.)}$ (25 mL) and water (25 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting crude product was suspended in a 1:1 solution of EtOAc (50 mL) and hexane (50 mL), and filtered through a silica plug to give the product as a yellow oil (0.27 g, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ; 3.68 (2H, t, ^3J = 7.9 Hz, -NC*H*$_2$), 2.12 (3H, s, -C*H*$_3$), 2.07 (3H, s, -C*H*$_3$), 1.51-1.61 (2H, m, -NCH$_2$C*H*$_2$), 1.18-1.26 (6H, m, -C*H*$_2$CH$_3$, -C*H*$_2$CH$_2$C*H*$_3$, -C*H*$_2$CH$_2$CH$_2$CH$_3$), 0.83 (3H, t, ^3J = 6.2 Hz, -C*H*$_3$); HRMS (FI +ve) *m/z*: 307.0672 ($[M]^+$, $C_{11}H_{20}IN_2$, requires 307.0666); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ:137.4, 126.3, 47.3, 31.3, 30.4, 26.3, 22.5, 14.0, 12.9, 9.6.

2-Iodo-1,3-dihexyl-4,5-dimethyl-1H-imidazol-3-ium iodide (3^+I^-)

Procedure 1: Compound **2** (0.18 g, 0.59 mmol) and 1-bromohexane (0.09 g, 0.59 mmol) were dissolved in acetone (15 mL) before adding TBAI (0.27 g, 0.73 mmol). The mixture was refluxed for 4 hours, then cooled to room temperature before removing the solvent *in vacuo*. Silica gel column chromatography (9:1 $CHCl_3$:EtOH) gave the product as a yellow oil (33.0 mg, 11%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.02 (4H, t, ^3J = 8.2 Hz, -C*H*$_2$NR$_2$), 2.22 (6H, s, -C*H*$_3$), 1.63-1.70 (4H, m, -NCH$_2$C*H*$_2$), 1.22-1.34 (12H, m, -C*H*$_2$CH$_3$, -C*H*$_2$CH$_2$CH$_3$, -C*H*$_2$CH$_2$CH$_2$CH$_3$), 0.84 (6H, t, ^3J = 7.0 Hz, -C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 128.3, 49.9, 32.3, 31.3, 30.0, 26.2, 22.5, 14.0, 9.9; HRMS (FI +ve) *m/z*: 391.1595 ($[M - I]^+$, $C_{17}H_{32}IN_2$, requires 391.1605).

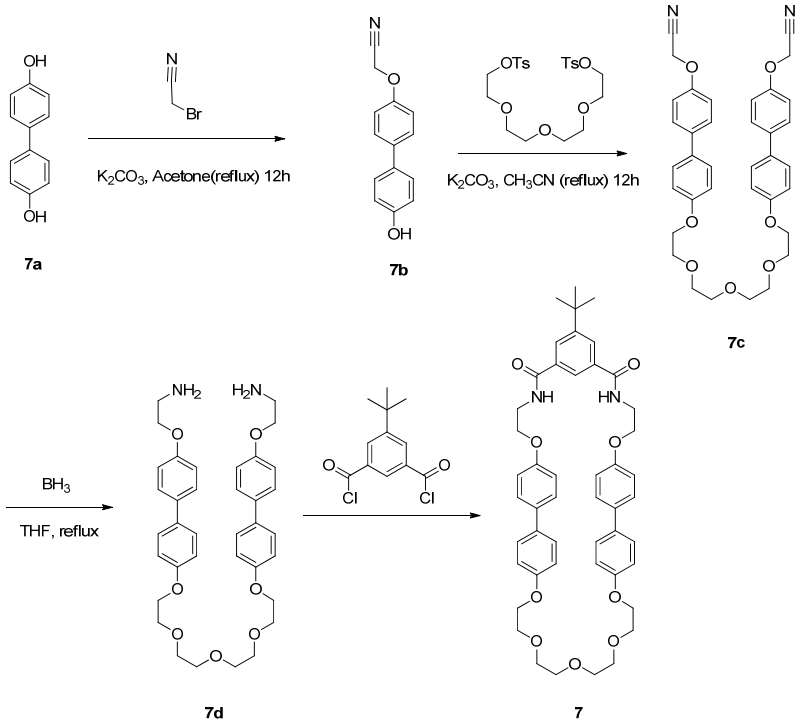
Procedure 2: Compound **2** (0.20 g, 0.90 mmol) was dissolved in CH_3CN (100 mL). K_2CO_3 (1.24 g, 9.00 mmol) was added to the solution and stirred at room temperature for five minutes. Five equivalents of TBAI (1.66 g, 4.50 mmol) were added to the mixture, followed by 1-bromohexane (0.59 g, 3.60 mmol) and the mixture stirred under reflux for 12 hours. Iodine (0.34 g, 1.35 mmol) was added and the reaction left to stir under reflux for another 2 hours. The crude product mixture was filtered, the solvent removed *in vacuo* and then purified *via* silica gel column chromatography (9.5:0.5 $CHCl_3$:EtOH) to give the product as a yellow oil (33.0 mg, 7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.02 (4H, t, ^3J = 8.2 Hz, -C*H*$_2$NR$_2$), 2.22 (6H, s, -C*H*$_3$), 1.63-1.70 (4H, m, -NCH$_2$C*H*$_2$), 1.22-1.34 (12H, m, -C*H*$_2$CH$_3$, -C*H*$_2$CH$_2$CH$_3$, -C*H*$_2$CH$_2$CH$_2$CH$_3$), 0.84 (6H, t, ^3J = 7.0 Hz, -C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 128.3, 49.9, 32.3, 31.3, 30.0, 26.2, 22.5, 14.0, 9.9; HRMS (FI +ve) *m/z*: 391.1595 ($[M - I]^+$, $C_{17}H_{32}IN_2$, requires 391.1605).

Procedure 3: Compound **2** (0.33 g, 1.09 mmol) and 1-iodohexane (0.18 g, 1.18 mmol) were dissolved in CH_3CN (20 mL) and stirred for 12 hours at 50 °C. The solvent was removed *in vacuo* and the product isolated *via* silica gel column chromatography (95:05 $CHCl_3$:EtOH) as a

yellow oil (23.0 g, 4%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.02 (4H, t, ^3J = 8.2 Hz, -NCH_2), 2.22 (6H, s, -CH_3), 1.63-1.70 (4H, m, -NCH$_2$CH_2), 1.22-1.34 (12H, m, -CH_2CH$_3$, -CH_2CH$_2$CH$_3$, -CH_2CH$_2$CH$_2$CH$_3$), 0.84 (6H, t, ^3J = 7.0 Hz, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 128.3, 49.9, 32.3, 31.3, 30.0, 26.2, 22.5, 14.0, 9.9; HRMS (FI +ve) *m/z*: 391.1595 ([M – I]$^+$, $C_{17}H_{32}IN_2$, requires 391.1605).

General Anion Exchange Procedure

Imidazolium receptor **3$^+$I$^-$** (0.033 g, 0.09 mmol) was dissolved in $CHCl_3$ (50 mL) and stirred vigorously with saturated $NH_4X_{(aq.)}$ (X = Cl, Br) (50 mL) for 20 minutes. The aqueous layer was decanted off and the procedure repeated five more times to exchange the counter ion from I^- to X^- (X = Cl, Br). The resulting organic solution was dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give the product as a yellow oil in quantitative yield.



Scheme S2 Synthesis of macrocycle **7**.

2-((4'-hydroxy-[1,1'-biphenyl]-4-yl)oxy)acetonitrile (7b)

4,4′-Biphenol (3 g, 16.1 mmol), bromoacetonitrile (1.11 ml, 15.9 mmol) and potassium carbonate (4.44 g, 32.2 mmol) were refluxed in acetone for 12 hours. The solvent was then removed *in vacuo* and chloroform (500 ml) was added. The resultant mixture was filtered and the filtrate washed with 1 M HCl solution (3 × 100 ml) and water (100 ml). The mono-substituted compound was separated from excess ,4′-biphenol and the di-substituted by-product through silica column chromatography (9:1 chloroform : methanol) to obtain a white solid (1.62 g, 45 %). ^{1}H NMR (300 MHz, DMSO, 298 K): δ = 9.49 (1H, s), 7.54 (2H, d, ^3J = 9 Hz), 7.42 (2H, d, ^3J = 9 Hz), 7.08 (2H, d, ^3J = 9 Hz), 6.80 (2H, d, ^3J = 9 Hz), 5.17 (2H, s); ^{13}C NMR (75.5 MHz, DMSO, 298 K); δ = 156.8, 155.1, 134.7, 130.3, 127.5, 127.3, 116.7, 115.7, 115.3, 53.6; ESI-MS: [$C_{14}H_{11}NO_2$ - H]$^-$ *m/z*: observed 224.08, calc 224.08; m.p. 141ºC.

Bis(nitrile) 7c

Acetonitrile derivative **7b** (1.5 g, 6.7 mmol), tetraethylene glycol-di-*p*-tosylate (1.67 g, 3.3 mmol) and potassium carbonate (4.62 g, 26.7 mmol) were refluxed in acetonitrile for 12 hour. The solvent was then removed *in vacuo* and chloroform (250 ml) was added. The resultant mixture was filtered and purified by silica column chromatography (3:1 ethyl acetate : hexane) to afford a white solid (1.73 g, 85 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.51 (4H, d, ^3J = 9 Hz), 7.42 (4H, d, ^3J = 9 Hz), 7.02 (4H, d, ^3J = 9 Hz), 6.97 (4H, d, ^3J = 9 Hz), 4.79 (4H, s), 4.15 (4H, t, ^3J = 5 Hz), 3.87 (4H, t, ^3J = 5 Hz) 3.69-3.75 (8H, m) ;^{13}C NMR (75.5 MHz, CDCl3, 298 K); δ = 158.2, 155.5, 135,9, 132.9, 128.1, 127.8, 115.3, 114.9, 70.8 70.7, 69.7, 67.5, 53.7; ESI-MS: [$C_{36}H_{36}N_2O_7$ + H]$^+$ *m/z*: observed 609.25, calc 609.25; m.p. 90ºC.

Bis(amine) 7d

To a refluxing 1 M solution of borane in THF (50 ml) at 70 ºC was added dropwise a solution of **7c** (1.5 g, 2.5 mmol) in dry THF. After 4 hours of reflux the mixture was cooled to room temperature and methanol was added to release hydrogen. Subsequently concentrated hydrochloric acid was added and the mixture was evaporated to 75% of the initial volume. The mixture was then neutralized with NaOH 10M. precipitating a white solid (0.8 g, 52 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.38 (8H, d, ^3J = 9 Hz), 6.88 (4H, d, ^3J = 9 Hz), 4.08 (4H, t, ^3J = 5 Hz), 3.94 (4H, t, ^3J = 5 Hz), 3.81 (4H, t, ^3J = 5 Hz) 3.68-3.68 (8H, m), 3.01 (4H, t, ^3J = 5 Hz) ;^{13}C NMR (75.5 MHz, DMSO, 298 K); δ = 157.8, 157.6, 132.3, 132.2, 127.2, 127.1, 114.9, 114.8, 72.3, 69.9, 69.8, 69.7, 67.2, 60.5, 40.8; ESI-MS: [$C_{36}H_{44}N_2O_7$ + H]$^+$ *m/z*: observed 616.31, calc 616.31; m.p. 150ºC decomp.

Macrocycle 7

5-tert-butylbenzene-1,3-dioyl dichloride (0.21 g, 0.8 mmol) and **7b** (0.5 g, 0.8 mmol) were each dissolved in dry dichloromethane (250 ml) in two separate dropping funnels. The reactants were added dropwise over 3 hours to a solution of triethylamine (5 ml) in dry dichloromethane (1 L) and stirred for 12 hours. The volume of solvent was then reduced to 250 ml and the solution washed with 1 M HCl solution (2 × 100 ml) and water (2 × 100 ml). The solvent was then evaporated leaving a brown oil that was purified by gradient elution column chromatography (switching from 7:3 acetone : dichloromethane to acetone) to afford a white solid (0.218 g, 20 %). Although it is possible that larger macrocycles were also produced in this reaction, none could be isolated from the reaction mixture. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 8.13 (2H, s), 7.73 (1H, s), 7.36 (4H, d, ^{3}J = 9 Hz), 7.30 (4H, d, ^{3}J = 9 Hz), 6.90 (4H, d, ^{3}J = 9 Hz), 6.86 (4H, d, ^{3}J = 9 Hz), 4.16 (4H, t, ^{3}J = 5 Hz), 4.09 (4H, t, ^{3}J = 5 Hz), 3.90-3.92 (8H, m), 3.72-3.75 (8H, m), 1.34 (9H, s); ^{13}C NMR (75.5 MHz, DMSO, 298 K); δ = 167.2, 158.0, 157.3, 153.1, 134.3, 134.0, 133.0, 128.5, 127.7, 127.6, 120.4, 114.8, 114.7, 70.8, 70.7, 69.7, 67.6, 66.9, 39.5, 35.1, 31.15; ESI-MS: $[C_{48}H_{54}N_2O_9 + H]^+$ *m/z*: observed 802.38, calc 802.38; m.p. 170ºC decomp.

Crystallography

Single crystal X-ray diffraction data were collected either using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) on a Nonius KappaCCD diffractometer, or (for **4b**) using Cu Kα (λ = 0. 1.54180 Å) on an Oxford Diffraction SuperNova diffractometer. Both diffractometers were equipped with a Cryostream N_2 open-flow cooling device,[1] and the data were collected at 150(2) K.

If using the Nonius machine, series of ω-scans were performed in such a way as to collect every independent reflection to a maximum resolution of 0.77 Å, aiming for 99.5 % completeness. Cell parameters and intensity data (including inter-frame scaling) were processed using the DENZO-SMN package.[2]

When using Cu radiation, ω-scans were performed aiming for 99.5 % completeness at 0.98 Å resolution. Cell refinement, data reduction, and scaling were performed using the CrystalClear package.[3]
The structures were solved by direct methods using the SIR92 software,[4] or by charge flipping using Superflip.[5] The structures were refined using full-matrix least-squares on F^2 within the CRYSTALS suite.[6] All non-hydrogen atoms were refined with anisotropic displacement parameters, unless specified otherwise. Disordered portions were modelled using refined partial occupancies. Geometric and vibrational restraints were applied where appropriate to ensure physically reasonable models. The H atoms were usually located in the difference map, but those attached to carbon atoms were repositioned geometrically. Protic H atoms which could not be located in the difference map were positioned to satisfy hydrogen bonding requirements. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularise their geometry (C-H in the range 0.93-0.98 Å, N-H in the range 0.86-0.89 Å, and O-H = 0.82 Å and isotropic displacement factors in the range 1.2-1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints.

After the construction of a stable, physically reasonable, and complete model, the weights were optimised,[7, 8] anomalous reflections were omitted, and absent high-angle data (in the case of poorly diffracting samples) was pruned using the Wilson plot. This generally led to convergence of the refinement, giving the final structure.

IUCr CheckCIF/PLATON[9] was used to validate the structures, and warnings were dealt with as appropriate or justified using validation reply forms. The crystal structures in CIF format have also been supplied.

Graphics were created using the CrystalMaker package version 2.6.2.

^{1}H NMR Titration and ROESY Data

In previous pseudorotaxane titrations with macrocycle **6**,[10, 11] the change in chemical shift of the macrocycle hydroquinone proton *d* has been used to calculate the strength of pseudorotaxane assembly (K_{app}) since the observed perturbation is directly attributable to threading. However, because of overlapping of signals corresponding to protons *d* and *g* in macrocycle **7**, and a characteristic solvent peak, macrocyclic proton *b* was followed instead. Fig. S1 shows a series of titration binding isotherm curves monitoring the macrocyclic proton *b* on both macrocycles.

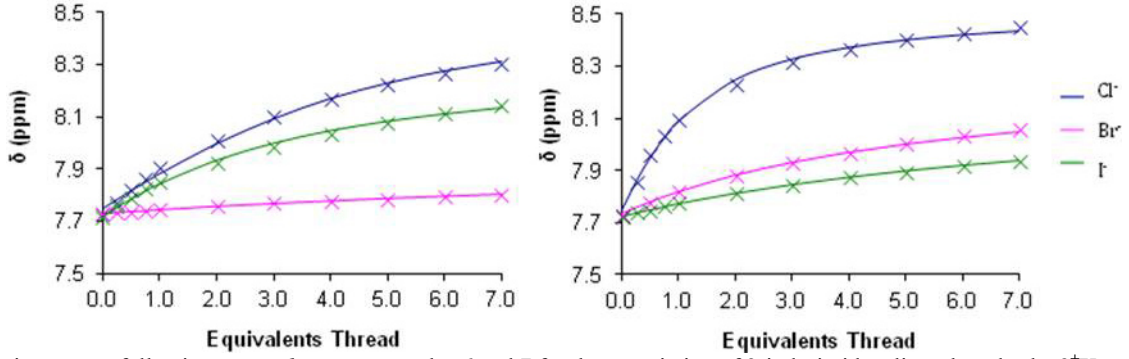


Fig. S1 Titration curves following proton *b* on macrocycles **6** and **7** for the association of 2-iodo-imidazolium thread salts $\mathbf{3}^{+}\mathbf{X}^{-}$, recorded in $CDCl_3$ at 293 K. Symbols represent experimental data points; lines represent calculated titration curves.

WinEQNMR program analysis of the titration data[12] determined apparent association constant values, shown in Table 1 (main text).

Further evidence for pseudorotaxane formation by macrocycle **6** and thread **3**$^{+}$**Cl**$^{-}$ was provided by a ^{1}H ROESY spectrum of a 1:1 mixture of the two components in $CDCl_3$ (Fig. S2). Through space interactions between the 2-iodo-imidazolium thread and the macrocycle were observed, most notably those between methyl imidazolium protons *β* and macrocycle hydroquinone protons *d*, *e*, and polyether chain protons. These through space interactions in particular not only confirm penetration of the thread **3**$^{+}$**Cl**$^{-}$ through the macrocycle **6**, but also the orientation of the thread 2-iodo-imidazolium motif which is consistent with halogen bonding to the macrocycle's isophthalamide bound chloride anion.

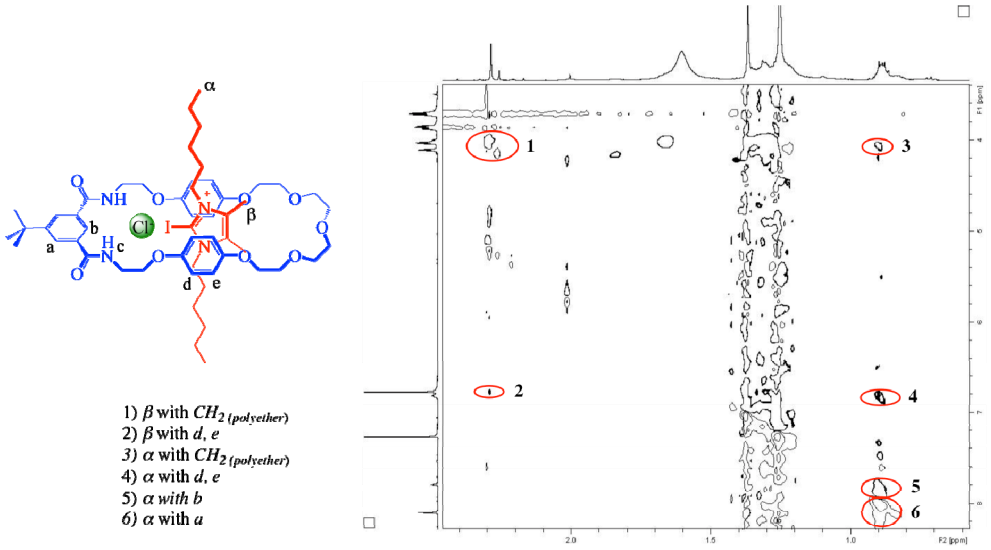


Fig S2 ^{1}H ROESY spectrum (500 MHz, $CDCl_3$, 293 K) of a 1:1 mixture of macrocycle **6** and thread **3**$^{+}$**Cl**$^{-}$.

Similarly, further evidence for pseudorotaxane formation with macrocycle **7** was provided by a ROESY spectrum of a 1:1 mixture of macrocycle **7** and thread **3**$^{+}$**Cl**$^{-}$ in $CDCl_3$ (Fig. S3). Once again, through space interactions between the 2-iodo-imidazolium thread and the macrocycle were observed. Importantly, interactions indicative of thread **3**$^{+}$**Cl**$^{-}$ penetration through macrocycle **7** and hence pseudorotaxane assembly are shown to occur between thread methyl imidazolium protons *β* and macrocycle biphenyl protons *d*, *e*, *f* and *g*.

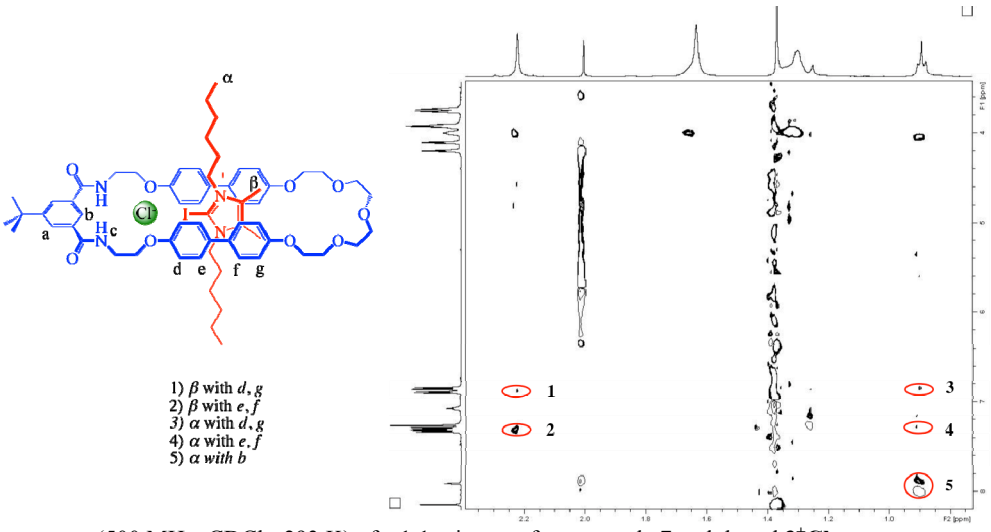


Fig S3 ^{1}H ROESY spectrum (500 MHz, $CDCl_3$, 293 K) of a 1:1 mixture of macrocycle **7** and thread **3**$^{+}$**Cl**$^{-}$.

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