Anion Induced and Inhibited Circumrotation of a [2]Catenane

Supporting Information

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Experimental

All commercial-grade chemicals were used without further purification unless stated otherwise. Tetrabutylammonium (TBA) salts, ammonium hexafluorophosphate, silver triflate and Grubbs’ first-generation catalyst were stored prior to use under vacuum in a desiccator that contained phosphorus pentoxide and self-indicating silica gel. Triethylamine was distilled from and stored over potassium hydroxide. Thionyl chloride was distilled from triphenyl phosphite and used immediately. Dry solvents were obtained by degassing with nitrogen and then passing through a column of activated alumina by using Grubbs apparatus. Elemental analyses were carried out by the service at the Inorganic Chemistry Laboratory, University of Oxford. Mass spectra were obtained by using a Micromass LCT (ESMS) instrument. NMR spectra were recorded by using a Varian Mercury-VX 300 or a Varian Unity Plus 500 spectrometer, in which the solvent serves as the lock and internal reference.

Synthesis of catenane precursor 2 and 3

The pyridinium macrocycle 2 was prepared via a multi-step synthesis as depicted in Scheme S1.

Scheme S1 Synthesis of pyridinium macrocycle 2.
2-(4-Hydroxyphenoxy)acetonitrile S1: Hydroquinone (10.76 g, 97.6 mmol), chloroacetonitrile (1.54 ml, 24.4 mmol) and potassium carbonate (3.71 g, 26.8 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 hydroquinone and the di-substituted by-product through silica column chromatography (9:1 chloroform : methanol) to obtain a white solid (2.13 g, 58.5 %).

$^1$H NMR (500 MHz, CDCl$_3$, 298 K): $\delta$ = 6.906 (2H, d, $J$ = 8.1 Hz, ArH), 6.832 (2H, d, $J$ = 8.1 Hz, ArH), 4.707 (2H, s, OC$_2$H$_2$); positive ESI-MS: [C$_8$H$_8$NO$_2$ + H]$^+$ m/z: observed 150.01, calc 150.06.

S2: 2-(4-hydroxyphenoxy)acetonitrile S1 (3.00 g, 20.1 mmol), tetraethylene glycol-di-p-tosylate (5.03 g, 10.0 mmol) and potassium carbonate (2.86 g, 20.7 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 colourless oil (3.84 g, 83.7 %).

$^1$H NMR (500 MHz, CDCl$_3$, 298 K): $\delta$ = 6.931 (2H, d, $J$ = 9.3 Hz, ArH), 6.891 (4H, d, $J$ = 9.3 Hz, ArH), 4.697 (4H, s, OC$_2$H$_2$CN), 4.074 (4H, t, $J$ = 4.6 Hz, ArOCH$_2$CH$_2$O), 3.830 (4H, t, $J$ = 4.8 Hz, ArOCH$_2$CH$_2$O), 3.679-3.719 (8H, m, OC$_2$H$_2$C$_2$H$_2$O); positive ESI-MS: [C$_{24}$H$_{28}$N$_2$O$_7$ + Na]$^+$ m/z: observed 479.18, calc 479.18.

$\cdot$2HCl: To a 1 M solution of borane in THF (50 ml) at 70 °C was added dropwise a solution of S2 (3.53 g, 7.7 mmol) in dry THF. After 4 hour of reflux the mixture was cooled to room temperature and methanol was added under the release of hydrogen. Subsequently concentrated hydrochloric acid was added and after co-evaporation with methanol the protonated product was filtered, washed with small amount of cold methanol and dried in a desiccator overnight to give a white solid (2.58 g, 62.3 %).

$^1$H NMR (500 MHz, CD$_3$OD, 298 K): $\delta$ = 6.867-6.955 (8H, m, ArH), 4.151 (4H, t, $J$ = 4.7 Hz, NH$_2$CH$_2$CH$_2$O), 4.052 (4H, t, $J$ = 4.7 Hz, ArOCH$_2$CH$_2$O), 3.802 (4H, t, $J$ = 4.7 Hz, ArOCH$_2$CH$_2$O), 3.654-3.709 (8H, m, OCH$_2$CH$_2$OCH$_2$CH$_2$O), 3.303 (4H, t, $J$ = 1.5 Hz, NH$_2$CH$_2$CH$_2$O); positive ESI-MS: [C$_{24}$H$_{36}$N$_2$O$_7$ + H]$^+$ m/z: observed 465.26, calc 465.26; elemental analysis (%) calcd for C$_{24}$H$_{38}$N$_2$O$_7$Cl$_2$•H$_2$O (found): C 51.89 (51.75), H 7.26 (7.00), N 5.04 (4.55).

Pyridine macrocycle S4: pyridine-3,5-dicarbonyl dichloride (0.76 g, 3.72 mmol) and S3$\cdot$2HCl (2.00 g, 3.72 mmol) were each dissolved in dry dichloromethane (250 ml) in two dropping funnels. The reactants were added over 3 hours to a solution of triethylamine (5 ml) in dry dichloromethane (1 L) and stirred for 12 hours. After which the volume of solvent was 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 (456 mg, 20.6 %).

\[ ^1H \text{ NMR} \ (500 \text{ MHz, CDCl}_3, 298 \text{ K}): \delta = 9.184 \ (2H, \text{s, ortho-}H \text{ of pyridine}), 8.253 \ (1H, \text{s, para-}H \text{ of pyridine}), 6.716-6.760 \ (8H, \text{m, hydroquinone }H), 3.972-4.051 \ (8H, \text{m, NHCH}_2\text{CH}_2\text{O and ArOCH}_2\text{CH}_2\text{O}), 3.760-3.836 \ (8H, \text{m, NHCH}_2\text{CH}_2\text{O and ArOCH}_2\text{CH}_2\text{O}), 3.632-3.662 \ (8H, \text{m, OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}); \text{positive ESI-MS: } [C_{31}H_{37}N_3O_9 + Na]^+ \ m/\z \text{: observed 618.20, calc 618.24; elemental analysis } (%) \text{ calcd for C}_{31}H_{37}N_3O_9\cdot\text{H}_2\text{O (found): } C 60.67 \ (60.36), \ H 6.41 \ (6.20), \ N 6.85 \ (6.65). \]

Pyridinium iodide macrocycle 2: S4 (735 mg, 1.23 mmol) was refluxed in iodomethane for 12 hours. The solvent was then evaporated, the residue filtered and washed with small amount of chloroform to afford a bright yellow solid (580 mg, 63.9 %).

\[ ^1H \text{ NMR} \ (500 \text{ MHz, CD}_3\text{CN, 298 K): } \delta = 9.431 \ (1H, \text{s, para-}H \text{ of pyridinium}), 9.251 \ (2H, \text{s, ortho-}H \text{ of pyridinium}), 8.236 \ (2H, \text{br, s, NH}), 6.936 \ (4H, \text{d, } J = 9.0 \text{ Hz, hydroquinone }H), 6.857 \ (4H, \text{d, } J = 9.1 \text{ Hz, hydroquinone }H), 4.442 \ (3H, \text{s, N}^+\text{CH}_3), 4.199 \ (4H, \text{t, } J = 4.9 \text{ Hz, ArOCH}_2\text{CH}_2\text{O}), 4.028 \ (4H, \text{t, } J = 4.7 \text{ Hz, NHCH}_2\text{CH}_2\text{O}), 3.750-3.856 \ (8H, \text{m, NHCH}_2\text{CH}_2\text{O and ArOCH}_2\text{CH}_2\text{O}), 3.615-3.660 \ (8H, \text{m, OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}); \text{positive ESI-MS: } [C_{32}H_{40}N_3O_9]^+ \ m/\z \text{: observed 610.26, calc 610.28; elemental analysis } (%) \text{ calcd for C}_{32}H_{40}N_3O_9\cdot\text{CHCl}_3\text{MeOH (found): } C 45.94 \ (45.70), \ H 5.10 \ (4.89), \ N 4.73 \ (4.84). \]

The phenolic synthon 3 was prepared from the condensation of 5-hydroxyisophthaloyl dichloride with a vinyl appended amine motif S5 reported elsewhere.\(^{1,2}\) (Scheme S2)
3: To a dichloromethane solution of S5 (450 mg, 1.41 mmol) and triethylamine (4 ml) at 0 ºC was added 5-hydroxyisophthaloyl dichloride (153 mg, 0.70 mmol). The reaction mixture was stirred for 12 hours, washed with 1 M HCl solution (2 × 100 ml), water (2 × 100 ml) and purified by column chromatography (6:4 ethyl acetate : dichloromethane) to give a white solid (270 mg, 54.4 %).

1H NMR (300 MHz, CDCl₃, 298 K): δ = 8.345 (1H, s, O-H), 7.568 (1H, s, para- H of phenol), 7.374 (2H, s, ortho- H of phenol), 6.978 (2H, s, NH), 6.669-6.787 (8H, m, hydroquinone H), 5.764-5.894 (2H, m, C=CH₂), 5.187 (2H, d, J = 17.2 Hz, trans-CH=CH₂), 5.096 (2H, d, J = 10.3 Hz, cis-CH=CH₂), 3.945-3.976 (12H, m, NHCH₂CH₂O, ArOCH₂CH₂O and OCH₂CH=CH₂), 3.749-3.793 (8H, m, NHCH₂CH₂O and ArOCH₂CH₂O), 3.673-3.692 (4H, m, polyether H), 3.581-3.600 (4H, m, polyether H); positive ESI-MS: [C₃₈H₄₈N₂O₁₁ + Na]⁺ m/z: observed 731.33, calc 731.32; elemental analysis (%) calcd for C₃₈H₄₈N₂O₁₁•½MeOH (found): C 63.80 (63.78), H 6.95 (6.65), N 3.86 (3.90).

Synthesis of catenane 1⁺Cl⁻

![Scheme S3 Synthesis of catenane 1⁺Cl⁻ and 1⁺PF₆⁻](image)

1⁺Cl⁻: To a well stirred mixture of 2 (30 mg, 0.041 mmol), 3 (28.8 mg, 0.041 mmol) and TBA chloride (11.3 mg, 0.041 mmol) in dry dichloromethane 1st Generation Grubbs’ catalyst (3 mg, 10% by weight) was added. The reaction was left to stir under N₂ overnight followed by column chromatography on 85:15 dichloromethane : methanol to elute the catenane as a yellow solid (20 mg, 37.0 %).

1H NMR (500 MHz, 1:1 CDCl₃ : CD₃OD, 298 K): δ = 9.451 (1H, s, para-H of pyridinium), 9.269 (2H, s, ortho-H of pyridinium), 8.236 (2H, br, s, NH of pyridinium), 7.812 (2H, s, NH of phenol), 7.505 (1H, s, para-H of phenol), 7.387 (2H, s, ortho-H of phenol), 6.544-6.666 (12H, m, hydroquinone H), 6.453 (4H, m, hydroquinone H), 5.544 (1.5H, s, trans-HC=CH), 5.441 (0.5H, s, cis-HC=CH), 4.357 (3H, s, N⁺CH₃), 3.536-4.035 (52H, m, polyether H), 13C
NMR (125.7 MHz, 1:1 CDCl₃ : CD₃OD, 298 K): \( \delta = 167.907, 161.286, 161.180, 157.841, 153.316, 153.120, 152.562, 152.524, 146.795, 146.609, 140.909, 135.371, 133.652, 129.013, 128.790, 118.150, 116.436, 116.389, 115.498, 115.463, 115.229, 115.074, 95.003, 71.008, 70.845, 70.782, 70.631, 70.606, 70.053, 69.993, 69.899, 69.801, 69.766, 68.192, 67.857, 66.712, 66.670, 66.605, 66.259; \) positive ESI-MS: \([C_{68}H_{84}N_5O_{20}]^+ \) \( m/z: \) observed 1290.35, calc 1290.57, \([C_{68}H_{84}N_5O_{20} + Na]^2+ \) \( m/z: \) observed 656.75, calc 656.78.

Anion exchange from \( 1^- \text{Cl}^- \) to \( 1^- \text{PF}_6^- \)

The anion exchange was conducted with a published procedure² through a triflate intermediate.

\( 1^- \text{OTf}^- : 1^- \text{Cl}^- \) (28 mg, 0.021 mmol) was stirred with silver triflate (11 mg, 0.042 mmol) in 1:1 methanol : dichloromethane overnight. The solution was filtered through celite and purified by column chromatography (4:1 dichloromethane : methanol) to obtain \( 1^- \text{OTf}^- \) quantitatively.

\( 1^- \text{PF}_6^- : \) To a solution of \( 1^- \text{OTf}^- \) (30 mg, 0.021 mmol) in methanol was added a saturated solution of NH₄PF₆ (236 mg, 1.45 mmol) dissolved in 1:1 methanol : water. The solution was well stirred prior to addition of chloroform (100 ml) and washed with water (3 \times 100 ml). The solvent was removed in vacuo to afford \( 1^- \text{PF}_6^- \) (16.3 mg, 54 %).

\( 1^- \text{PF}_6^- \) : To a solution of \( 1^- \text{OTf}^- \) (30 mg, 0.021 mmol) in methanol was added a saturated solution of NH₄PF₆ (236 mg, 1.45 mmol) dissolved in 1:1 methanol : water. The solution was well stirred prior to addition of chloroform (100 ml) and washed with water (3 \times 100 ml). The solvent was removed in vacuo to afford \( 1^- \text{PF}_6^- \) (16.3 mg, 54 %).

\( 1^- \text{OTf}^- \) : 1, 2-Hydroquinone (28 mg, 0.021 mmol) was stirred with silver triflate (11 mg, 0.042 mmol) in 1:1 methanol : dichloromethane overnight. The solution was filtered through celite and purified by column chromatography (4:1 dichloromethane : methanol) to obtain \( 1^- \text{OTf}^- \) quantitatively.

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1H NMR Titrations

All titration results were acquired by a Varian 500 MHz NMR spectrometer and performed with the starting concentration of $1^{+}\text{PF}_6^{-}$ or $1^{+}\text{Cl}^{-}$ at $2.5 \times 10^{-3}$ M and the addition of appropriate aliquots of titrant with a microsyringe in steps of 0.2 equivalent. The titration for ring circumrotation was ceased when 1 equivalent of base was added, followed by the addition of 1 molar equivalent of trifluoroacetic acid. In the case for chloride association studies the titration was continued until a 10-fold excess of TBACl was reached.

Anion binding studies with TBACl

The para-pyridinum proton $H_c$ was followed during the course of the titration. The data was fitted and analysed to give an association constant of $K_a = 520 \pm 8$ M$^{-1}$ in 1:1 CDCl$_3$:CD$_3$OD using the program EQNMR. Binding stoichiometries were confirmed to be 1:1 host : guest by the use of Job Plots.

Figure S1 Experimental data and fitted binding curves for the $^1$H NMR titration of $1^{+}\text{PF}_6^{-}$ with TBACl.

Ring circumrotation studies

The phenolate induced ring circumrotation of $1^{+}\text{PF}_6^{-}$ was studied in 9:1 $d$-chloroform:$d_6$-DMSO, CD$_3$CN, $d_6$-DMSO and CD$_3$NO$_2$. Downfield shift of the pyridinium proton $c$ and amide proton $d$ were observed in all cases. The shift is indicated by solid lines connecting the peaks in Figure S2 – S4. In CD$_3$CN, $d_6$-DMSO and CD$_3$NO$_2$ the peaks reverted back to their original positions after adding 1 molar equivalent of trifluoroacetic acid (TFA), indicating the reversible nature of the rotation.
Figure S2  $^1$H NMR (500 MHz, 9:1 $d$-chloroform:$d_6$-DMSO, 298 K) of $1$PF$_6^-$ upon addition of 0, 0.2, 0.4, 0.6, 0.8 and 1.0 molar equivalent of P1 base.
Figure S3  $^1$H NMR (500 MHz, $d_6$-DMSO, 298 K) of 1$^+$/PF$_6^-$ upon addition of 0, 0.2, 0.4, 0.6, 0.8 and 1.0 molar equivalent of P1 base and thereafter 1 molar equivalent of TFA.

Figure S4  $^1$H NMR (500 MHz, CD$_3$NO$_2$, 298 K) of 1$^+$/PF$_6^-$ upon addition of 0, 0.2, 0.4, 0.6, 0.8 and 1.0 molar equivalent of P1 base and thereafter 1 molar equivalent of TFA.
The effect of chloride on the rotational motion was investigated by first titrating TBACl into 1⁻PF₆⁻, followed by the addition of phosphazene base P₁. (Figure S5) Typical downfield shifts of the anion recognizing protons c, d, g and f were observed upon addition of chloride. Subsequent addition of phosphazene base P1, however, did not result in any significant change in the spectrum.
Figure S5  $^1$H NMR (500 MHz, 9:1 $d$-chloroform:$d_6$-DMSO, 298 K) of 1$^{+}$PF$_6^-$ upon addition of 0, 0.2, 0.4, 0.6, 0.8, 1.0 molar equivalent of TBACl and thereafter addition of 0.2, 0.4, 0.6, 0.8, 1.0 molar equivalent of P1 Base.
ROESY studies

All ROESY spectra was acquired in 9:1 \(d\)-chloroform : \(d_6\)-DMSO at 298 K with a Varian Unity Plus 500 spectrometer (500 MHz). Through space proton-proton correlations provided evidence for the interlocking nature of \(1^{+}\text{PF}_6^-\) and \(1^{+}\text{Cl}^-\), in a conformation containing a tetrahedral anion binding pocket (in which the chloride is bound for \(1^{+}\text{Cl}^-\)). The addition of phosphazene base \(P_1\) to \(1^{+}\text{PF}_6^-\) led to the disappearance of these correlation signals, which is explained by the rotation of the pyridinium moiety to the phenolate station. The presence of chloride in the binding cavity, however, inhibits the rotation and preserves the correlation signals.

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Figure S6  ROESY spectrum of \(1^{+}\text{PF}_6^-\) showing the correlations of pyridinium proton \(b\).
Figure S7  ROESY spectrum of \(1^{+}\text{PF}_6^-\) showing the correlations of phenolic proton \(e\).
Figure S8  ROESY spectrum of \(1^{+}\text{PF}_6^-\) after addition of 1 molar equivalent of base.
Figure S9  ROESY spectrum of \(1^{+}\text{Cl}^-\).
Figure S10 ROESY spectrum of \(1^{+}\text{Cl}^-\) after addition of 1 molar equivalent of base.
Figure S6  ROESY spectrum of $1^+\text{PF}_6^-$ showing the correlation between the pyridinium proton $b$ with the hydroquinones and polyethers on the phenolic macrocycle.
Figure S7  ROESY spectrum of $\text{I}^+\text{PF}_6^-$ showing the correlation between the phenolic proton $e$ with the hydroquinones and polyethers on the pyridinium macrocycle.
Figure S8  ROESY spectrum of $\mathbf{1}^+\text{PF}_6^-$ after addition of 1 molar equivalent of phosphazene base $\mathbf{P_1}$. 
Figure S9  ROESY spectrum of $\text{I}^+\text{Cl}^-$ showing the important correlations of protons $b$ and $e$. 
Figure S10  ROESY spectrum of $1^+\text{Cl}^-$ after addition of 1 molar equivalent of phosphazene base $P_1$. 
Supporting Figures

Figure S11  Lowest energy MM structure of 4, with both bisamide units adopting a *syn* disposition. Hydrogen bonds (cyan dashes) between the phenolate oxygen and both pyridinium bisamide N-H binding sites, as well as between a polyether oxygen and both phenolate N-H binding sites are indicated. Only the hydrogen atoms of the bisamide clefts are shown for clarity.
**Experimental for Molecular Dynamic (MD) Simulations**

Conventional Molecular Dynamic (MD) simulations were carried out with the AMBER9 software package. Parameters for $\text{I}^+$, $\text{4}$ and $\text{4}\cdot\text{Cl}^-$ were taken from GAFF whereas parameters for $\text{Cl}^-$ were taken from reference 6; acetonitrile was described using a full atoms model. Partial RESP fitted charges, for the individual macrocycles of the [2]catenanes, were obtained from HF/6-31G* level calculations using Gaussian03.

Starting models of $\text{I}^+$, $\text{4}$, were obtained through assembly of the adequate individual macrocycles. Insertion of $\text{Cl}^-$ into the cavity of $\text{4}$ yielded the starting binding arrangement for $\text{4}\cdot\text{Cl}^-$. Subsequently, these were submitted to gas phase simulated annealing, consisting on the heating of the structures to 500 K followed by slow cooling to 0 K during 250 ps, thus yielding their lowest energy conformations. No bond or angle parameters between $\text{Cl}^-$ and the [2]catenane N-H binding sites were applied, for what the attractive interactions were primarily electrostatic. The obtained lowest energy conformations were then immersed in separated cubic boxes (typically 44 Å in size after equilibration) containing approximately 1000 molecules of acetonitrile. MD simulations of the several systems started with an initial solvent and solute relaxation, followed by 50 ps NVT heating to 300K and 500 ps NPT equilibration periods. The final densities of the equilibrated boxes were in close agreement with the experimental density of the pure solvent, and remained constant during, at least, the final 300 ps of the NPT simulation. The SHAKE algorithm was employed in all condensed phase simulations to constrain all hydrogen involving bonds, thus allowing the usage of 2fs time steps. Non-bonded van der Waals interactions were restrained to a 12 Å cutoff, while the particle mesh Ewald method was used to describe the long range electrostatic interactions. The temperature of the systems was controlled by the Langevin thermostat, using a collision frequency of 1.0 ps$^{-1}$. 

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References: