Sulfate anion-templated assembly of a [2]catenane†

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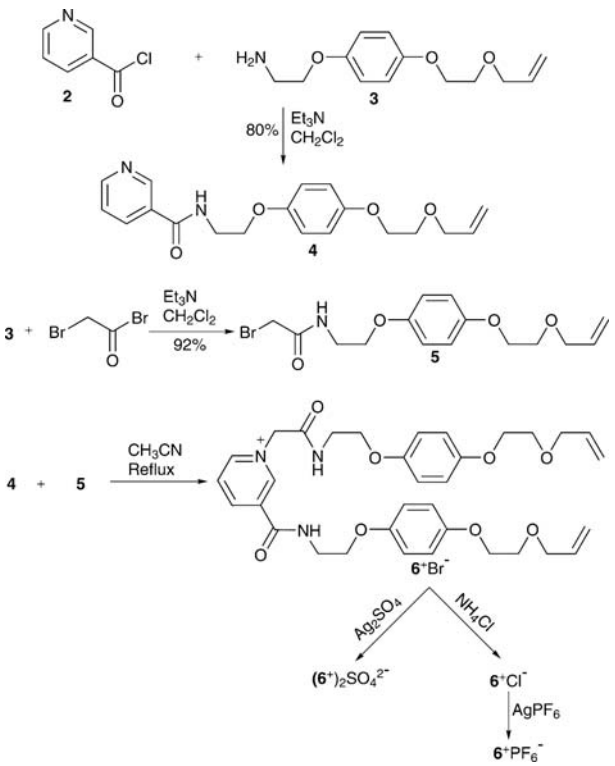
The sulfate anion's templating role in catenane formation is demonstrated for the first time; a novel bis-pyridinium nicotinamide [2]catenane is prepared in a remarkable high yield and is shown to exhibit selectivity for sulfate, the templating anion.

The strategic use of anions as potential templating reagents for the designed assembly of molecular architectures remains in its infancy,[1] which is somewhat surprising given the rapid growth in the field of anion supramolecular chemistry in recent years.[2] Rare examples, where specific inorganic anions have been demonstrated to play a templating role in the synthesis of organic-based systems, have been largely restricted to expanded porphyrins,[3] polypyrrolic,[4] hexaurea[5] and peptidic[6] macrocycles. During the past few years, we have developed a general method of using the chloride anion to template the formation of a range of interpenetrated and interlocked assemblies.[7] With a view to discovering other potential anion templating species for mechanical bond formation, we have recently demonstrated that the sulfate anion is capable of templating the formation of a pseudorotaxane assembly between two neutral components.[8] Encouraged by this observation, we now report the unprecedented templating role of sulfate in the synthesis of a [2]catenane structure. In fact, to the best of our knowledge, no examples of the sulfate anion-templated synthesis of interlocked molecular architectures exist in the literature. The novel bis-pyridinium nicotinamide [2]catenane, $\mathbf{1}^{2+}$, is obtained in a remarkably high yield *exclusively* with this oxodianion, and its unique interlocked binding domain is shown to exhibit selectivity for sulfate, the templating anion.

Influenced by Sauvage *et al.*'s imaginative exploitation of the tetrahedral directing nature of the copper(I) cation for catenane formation,[9] in an analogous fashion, the sulfate dianion is an attractive potential template for the orthogonal assembly of two monocationic positively-charged components.[10] With this in mind, the acyclic bis-vinyl pyridinium nicotinamide cation $\mathbf{6}^{+}$ was initially prepared as a precursor for subsequent sulfate anion-templated double ring-cyclized formation of the target catenane.



Scheme 1

Condensation of nicotinic acid chloride **2** with vinyl-functionalised amine derivative **3**[11] gave amide **4** in 80% yield. The reaction of **3** with bromo acetyl bromide afforded bromomethylene-functionalised amide compound **5** in 92% yield. The alkylation of **4** with **5** in refluxing acetonitrile solution produced the acyclic bis-vinyl pyridinium nicotinamide derivative $\mathbf{6}^{+}$ as its bromide salt. Anion exchange using silver sulfate, ammonium chloride and silver hexafluorophosphate gave the respective acyclic pyridinium nicotinamide salts, $(\mathbf{6}^{+})_2SO_4^{2-}$, $\mathbf{6}^{+}Cl^{-}$ and $\mathbf{6}^{+}PF_6^{-}$ (Scheme 1).

The simple addition of Grubbs' second generation RCM catalyst to a dichloromethane solution of $(\mathbf{6}^{+})_2SO_4^{2-}$ at room temperature, followed by purification using preparative silica TLC, gave the target [2]catenane, $\mathbf{1}^{2+}SO_4^{2-}$, in a remarkable yield of 80% (Scheme 2). It is noteworthy that analogous RCM-catalysed reactions with the chloride, bromide or hexafluorophosphate salts of $\mathbf{6}^{+}$ failed to produce any catenane. This highlights the crucial templating role of sulfate where, in addition to favourable electrostatic interactions, the orthogonal arrangement of four amide hydrogen bond-donating groups from two molecules of $\mathbf{6}^{+}$ complements the anion's tetrahedral shape.

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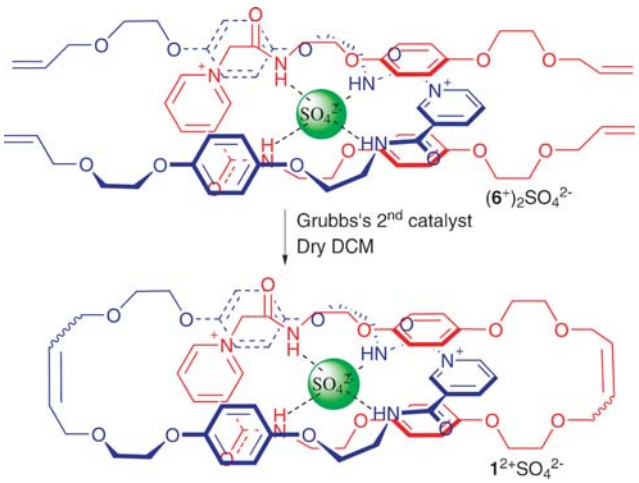
† Electronic supplementary information (ESI) available: Synthesis and characterisation data for compounds **1** and **6**, general procedures for ^{1}H NMR titration and supporting molecular dynamic simulations. See DOI: 10.1039/b808094a



Scheme 2 Sulfate-templated catenation.

Removal of the sulfate-templating anion from the catenane was achieved *via* exchange with chloride upon the addition of $BaCl_2$, followed by silver hexafluorophosphate conversion to $\mathbf{1}^{2+}(PF_6^-)_2$. All the catenane salts were characterised by ^{1}H NMR, ESI-MS and elemental analysis (see ESI†). Fig. 1 compares the ^{1}H NMR spectra of $\mathbf{6}^+PF_6^-$, $\mathbf{1}^{2+}Cl^-PF_6^-$ and $\mathbf{1}^{2+}SO_4^{2-}$. Upon sulfate-templated catenation, amide protons j, p and *ortho*-pyridinium nicotinamide proton k are significantly shifted downfield by $\Delta\delta$ = 2.15, 2.12 and 2.02, respectively, which indicates strong anion binding in the catenane cavity. The hydroquinone protons split into four doublets and move upfield, indicative of π–π stacking interactions.

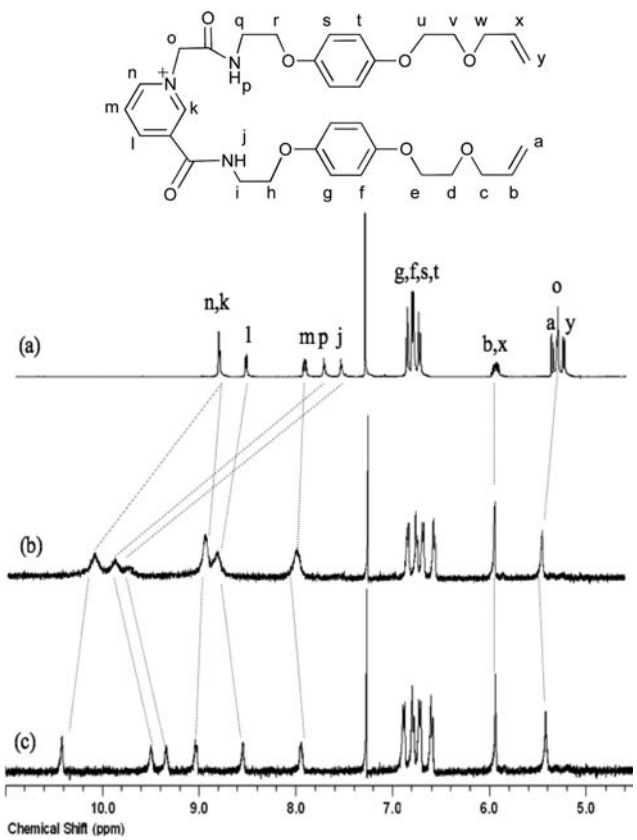


Fig. 1 ^{1}H NMR spectra ($CDCl_3$, 298 K) of (a) $\mathbf{6}^+PF_6^-$, (b) $(\mathbf{1}^+)_2SO_4^{2-}$ and (c) $\mathbf{1}^{2+}Cl^-PF_6^-$.

Table 1 Association constants ($/M^{-1}$) for $\mathbf{1}^{2+}(PF_6^-)_2$ and $\mathbf{6}^+PF_6^-$ with SO_4^{2-}, Cl^-, Br^- and OAc^- at 298 K in 1 : 1 *d*-chloroform/d_4-methanol[a]

	SO_4^{2-}	Cl^-	Br^-	OAc^-
$\mathbf{1}^{2+}(PF_6^-)_2$	2200	780	55	0
$\mathbf{6}^+PF_6^-$	1120	100	0	1850

[a] Errors less than 10%, determined by monitoring the *ortho*-pyridinium proton k.

ESI-MS revealed an intense doubly-charged molecular ion at m/z = 592.23, corresponding to $\mathbf{1}^{2+}$, for all the catenane salts and a singly-charged ion at m/z = 1219.65 for the chloride complex $\mathbf{1}^{2+}Cl^-$.

Proton NMR anion titration studies of the catenane $\mathbf{1}^{2+}(PF_6^-)_2$ were undertaken in a 1 : 1 $CDCl_3/CD_3OD$ solution, along with the acyclic pyridinium nicotinamide derivative $\mathbf{6}^+PF_6^-$ for comparison purposes. Both the amide and *ortho*-pyridinium protons of the catenane shifted significantly downfield upon addition of sulfate and chloride anions.

Interestingly, by way of contrast, with acetate and bromide, modest perturbations were seen, suggesting weak binding. Job plot and WinEQN MR[12] analysis of the titration data enabled association constants for 1 : 1 complexes to be determined. Table 1 shows that the catenane strongly and selectively binds sulfate in preference to chloride, bromide and acetate, where the latter two anions are very weakly bound. In stark contrast, the acyclic receptor $\mathbf{6}^+PF_6^-$ forms the strongest complex with acetate, followed by sulfate, chloride and bromide. No doubt, the topologically-constrained, unique catenane binding pocket complements the tetrahedral geometry of sulfate, which accounts for the observed selectivity trend. The non-complementary trigonal planar acetate anion presumably is unable to penetrate the catenane's anion binding domain. With $\mathbf{6}^+PF_6^-$, as commonly found for acyclic receptor systems, the oxobasicity of the coordinating anion dictates the strength of binding.[2]

Further insights into catenane structure and selectivity trends were gained by molecular dynamic simulations using AMBER9[13] software and the general amber force field (GAFF)[14] by following the experimental procedure described in the ESI.† Determination of the lowest energy co-conformations of several species studied was performed *via* gas phase simulated annealing procedures.

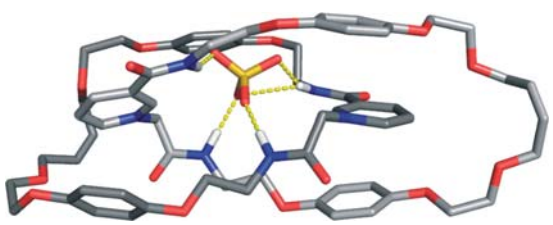


Fig. 2 Lowest energy structure of $\mathbf{1}^{2+}SO_4^{2-}$, obtained by gas phase simulated annealing molecular dynamics. Hydrogen bonds are shown as yellow dashes. Non-interacting hydrogens have been omitted for clarity.

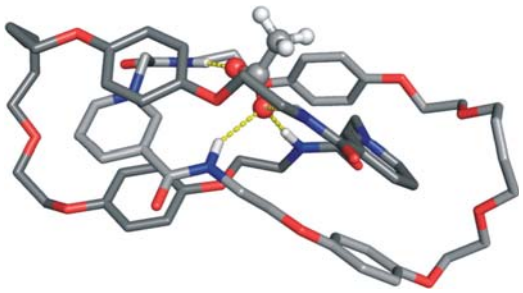


Fig. 3 Lowest energy structure of $\mathbf{1}^{2+}CH_3CO^{2-}$, obtained by gas phase simulated annealing molecular dynamics. Details as in Fig. 2.

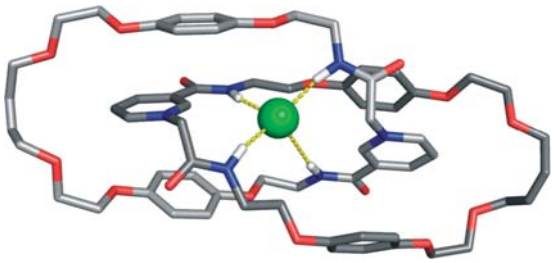


Fig. 4 Lowest energy structure of $\mathbf{1}^{2+}Cl^{-}$, obtained by gas phase simulated annealing molecular dynamics. Details as in Fig. 2.

The lowest energy structure obtained for $\mathbf{1}^{2+}SO_4^{2-}$ presents, as expected from the experimental data, the anion within the catenane binding pocket, establishing multiple hydrogen bonds to the amide hydrogens of the catenane chains (Fig. 2). It is interesting to note that the pyridinium rings are almost coplanar, rather than being arranged in a perpendicular fashion relative to each other, as depicted in Scheme 2. Nonetheless, the former disposition allows for the simultaneous establishment of six hydrogen bonds, with distances ranging from 1.69 to 2.43 Å, whereas the latter disposition would only allow four. The two sets of staggered stacking rings (each formed by a pyridinium and hydroquinone unit) are consistent with π–π interactions, despite the offset of one set of rings, which are dislocated from the stacked position due to the size of the anion and the spatial disposition adopted by the amides. A similar co-conformation was encountered for $\mathbf{1}^{2+}CH_3CO_2^{-}$ (Fig. 3), in which three hydrogen bonds are present (N–H···O distances of 1.79, 1.83 and 2.09 Å), and the relative disposition of the aromatic rings resembles that of $\mathbf{1}^{2+}SO_4^{2-}$. However, as suggested by the solution titration studies, the acetate anion is not included in the catenane cavity. The effect of the nature of the anion on the spatial organization of the catenane is quite remarkable when the anion is Cl^{-}. The relatively small size of chloride (compared to the stereoelectronic requirements of acetate and sulfate) allows for complete staggered stacking of the aromatic rings, along with π–π interactions, and thus the adoption of an overall elongated co-conformation, having N–H···Cl^{-} distances ranging from 2.14 to 3.35 Å. Furthermore, an almost perpendicular disposition of the pyridinium rings relatively to each other is adopted (Fig. 4).

The dynamic behaviour of the previously described co-conformations was evaluated in a solution of 1 : 1 $CH_3OH/CHCl_3$ using conventional molecular dynamics. The results obtained show that $\mathbf{1}^{2+}SO_4^{2-}$ was stable during the entire course of the simulation (10 ns), having the anion encapsulated within the catenane cavity, with average distances between the four oxygen atoms and N–H binding sites ranging from 1.87 to 2.13 Å (calculated using a cut off of 2.5 Å). Also, an average of 4.69 hydroxyl hydrogens from methanol, were found to be oriented towards and within 3.4 Å of the sulfate oxygens, thus completing the anion's first coordination shell and stabilizing its negative charge.

In contrast, for $\mathbf{1}^{2+}Cl^{-}$, only 1.14 hydroxyl hydrogens were found within the same distance of the chloride, clearly indicating that this anion was now highly enclosed by the catenane, hindering its contact with the outer solvent medium. In this case, average N–H···Cl^{-} distances ranging from 2.35 to 2.68 Å were obtained, using a 3.0 Å cut off. Interestingly, despite the more compact association of the catenane with chloride, the calculated relative binding free energies of SO_4^{2-} and Cl^{-} to $\mathbf{1}^{2+}$ at 300 K unambiguously indicate the former to be favoured by 12.93 kcal mol^{-1}, corroborating the experimental anion titration results. The association process was found to be enthalpy driven, with an entropic contribution of $T\Delta S = -26.01$ kcal mol^{-1}. In summary, the sulfate anion has been demonstrated as a highly efficient templating motif for catenane formation.

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