Sulfate anion templated synthesis of a triply interlocked capsule†

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Sulfate templation has been used in the synthesis of a novel tris-urea-based triply interlocked capsule, whose structure has been verified by DOSY NMR, mass spectrometry and molecular modelling investigations.
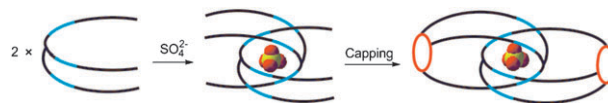
The efficient use of chemical templation has enabled the synthesis of mechanically interlocked architectures with increasingly sophisticated molecular topologies.[1] In particular metal ions have been utilised in the metal-directed assembly of a variety catenanes, rotaxanes, molecular knots and more recently Borromean rings.[2] In comparison, in spite of the fundamental roles played by negatively charged species in many biological, chemical and environmental processes,[3] the strategic use of anions as templating reagents, especially for mechanical bond formation, remains largely underdeveloped.[4] Sulfate is an attractive anion to use as a potential template due to its orthogonal tetrahedral coordination preference and strong binding capability as a consequence of its dinegative charge. Indeed sulfate anion templation of macrocycles, helicates and the very first example of an interlocked [2]catenane have recently been described.[5] Independent reports by Custelcean et al. and Wu et al. demonstrated that crystallisation of a simple acyclic tris(2-aminoethyl)amine (tren)-based tris-urea ligand functionalised with pyridyl metal coordinating groups with various metal sulfate salts such as magnesium and zinc afforded one-dimensional coordination polymers consisting of dimeric tren urea–sulfate hydrogen bonded capsule frameworks.[6] Inspired by this work we report herein the first sulfate anion templated synthesis of a mechanically bonded triply interlocked capsule.

It was envisioned that by synthesising suitably functionalised tren-based tris-urea ligands, subsequent covalently bonded capping reactions performed in the presence of a sulfate anion template would result in the formation of a novel permanently interlocked capsule (Scheme 1). The initial synthetic target was a tris-urea functionalised benzylic polyether tripodal ligand 2 which was prepared by the reaction of tris(2-aminoethyl)amine (tren)[7] with three equivalents of isocyanate 1 in dry dichloromethane in the presence of dibutyltin dilaurate (Scheme 2).

Scheme 1   General scheme for the sulfate templated synthesis of a triply interlocked capsule.

Scheme 2   Synthesis of polyether tripodal receptor 2.

The sulfate anion recognition properties of 2 were initially studied by ^{1}H NMR titration experiments with tetrabutylammonium (TBA) sulfate in CD_3CN–DMSO-d_6 = 5 : 1 solution (Fig. 1). Upon addition of one equivalent of sulfate significant deshielding of chemical shifts for the two urea NH protons ($\Delta\delta$ 1.90 ppm and $\Delta\delta$ 2.09 ppm) were observed which is indicative of anion binding. Interestingly, for hydroquinone proton H_d, the chemical shift of the proton resonance is observed to become more shielded upon addition of 0.5 equivalents of $(TBA)_2SO_4$. At higher equivalents of anion, however, significant deshielding perturbations were observed which indicates the assembly of a dimeric 2 : 1 complex at 0.5 equivalents of sulfate which dissociates at higher anion concentrations to form a 1 : 1 ligand–sulfate complex. Analogous ^{1}H NMR titrations with Cl$^-$, Br$^-$ and
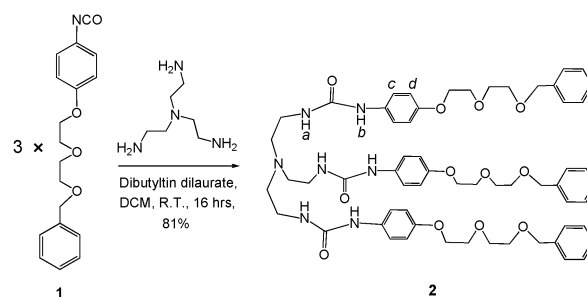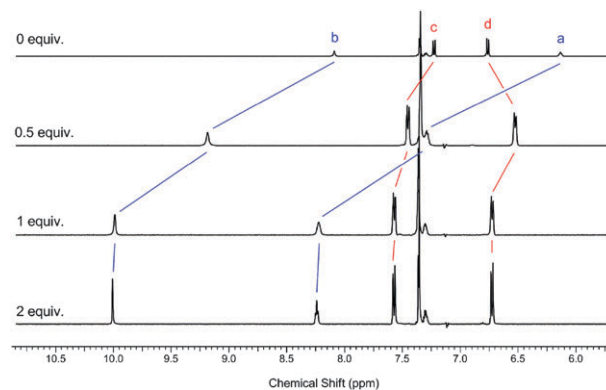
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Fig. 1 ^{1}H NMR titration spectra for the addition of $(TBA)_2SO_4$ to a solution of 2×10^{-3} M receptor 2 in CD_3CN–d_6-DMSO = 5 : 1 at 298 K.

benzoate induced only deshielding of the hydroquinone proton H_d resonance which suggests these anions exclusively form 1 : 1 complexes (see ESI† Fig. S1).

Furthermore negative-ion ESI-MS of a DMSO solution of ligand **2** and 0.5 equivalents of TBA$_2$SO$_4$ showed a doubly charged molecular ion peak at m/z 1133.7 corresponding to the dimeric $[2 \times 2 + SO_4]^{2-}$ complex.

Encouraged by the ^{1}H NMR evidence of **2** being capable of forming a 2 : 1 stoichiometric assembly with sulfate led to the attempted synthesis of a mechanically interlocked capsule being undertaken. In addition the strong 1 : 1 association of **2** with chloride was exploited in the halide templated formation of a cryptand-like macrobicyclic structure. Benzyl deprotection of **2** followed by reaction with tosyl chloride and subsequent reaction with sodium azide gave the tris-azide compound **3** (Scheme 3). Copper(I) catalysed Huisgen 1,3-dipolar cyclo-addition of **3** and 1,3,5-tris(prop-2-ynyloxy)benzene[8] in the presence of one equivalent of chloride as the template afforded the novel cryptand product **4**-Cl$^-$ in 32% yield. Chloride anion template removal *via* precipitation on addition of AgPF$_6$ afforded the anion free macrobicycle **4** which was characterised by ^{1}H NMR spectroscopy and accurate electrospray ionisation mass spectrometry (see ESI†). The ^{1}H NMR spectrum of **4**-Cl$^-$ in DMSO-d_6 reveals a signal for the triazole protons k at 8.11 ppm, the aromatic proton m at 6.35 ppm and the CH$_2$ proton l at 5.06 ppm indicating attachment of the 1,3,5-tris substituted benzylic capping group. The overall symmetry of the ^{1}H NMR spectrum also confirms formation of the macrobicycle (Fig. S3).†

Repeating the reaction with 0.5 equivalents of sulfate as the template gave the mechanically interlocked capsule **5**-SO$_4^{2-}$ in 21% yield following purification by column chromatography (Scheme 3). The ESI-MS analysis of **5**-SO$_4^{2-}$ gave the expected mass peak at m/z 1178.97 $[5 + SO_4]^{2-}$ indicating that one sulfate molecule is trapped inside the capsule. The ^{1}H NMR spectrum of **5**-SO$_4^{2-}$ is similar to that of **4**, however, the urea protons of **5**-SO$_4^{2-}$ are split which may indicate that urea protons are involved in hydrogen bonding with the sulfate anion to different extents, due to steric constraints (Fig. S3, ESI†). Interestingly the urea protons have lower chemical shift values than expected. This is presumably due to

the additional shielding by the adjacent hydroquinone moieties in a sterically hindered capsule structure that is not seen in the cage.

The click reaction of **3** and 1,3,5-tris(prop-2-ynyloxy) benzene was then repeated in the absence of any templating anion. Following purification by preparative TLC the macrobicycle **4** was isolated in 18% yield. Interestingly, even in the absence of sulfate, sufficient intermolecular hydrogen bonding is present to allow the triply interlocked capsule to be isolated in 9% yield. The isolated capsule however was found to have sulfate bound (presumably complexed during purification by preparative TLC) as evidenced by ESI-MS analysis which showed the $[5 + SO_4]^{2-}$ peak at 1178.96 and ^{1}H NMR spectrum which was identical to that obtained in the sulfate templated synthesis described above. In an attempt to remove the sulfate anion from the cavity a solution of capsule **5**-SO$_4^{2-}$ was stirred with either BaCl$_2$ or triflate Ba(OTf)$_2$ in a 45 : 45 : 10 CHCl$_3$–MeOH–H$_2$O solvent mixture. Unfortunately despite repeated attempts this was unsuccessful indicating that sulfate is very strongly complexed within the cavity of the interlocked capsule.

In order to further confirm that **5**-SO$_4^{2-}$ is in fact a triply interlocked capsule, NMR diffusion ordered (DOSY) experiments were performed. From such experiments diffusion coefficients can be obtained, and using the Stokes–Einstein equation the hydrodynamic radii of molecules can be calculated (see ESI†). DOSY spectra of solutions of **4**, **4**-SO$_4^{2-}$ and **5**-SO$_4^{2-}$ in DMSO-d_6 were obtained and the experimentally determined diffusion coefficients and hydrodynamic radii are shown in Table 1. The radii of **4** and **4**-SO$_4^{2-}$ are significantly smaller than that of **5**-SO$_4^{2-}$ suggesting the latter is in fact the larger triply interlocked capsule structure.

Further corroboration of these experimentally determined radii was provided by molecular dynamic simulations carried out on **4**, **4**-SO$_4^{2-}$ and **5**-SO$_4^{2-}$ (see ESI†). Initially, the lowest energy conformations in the gas-phase of these species were determined by conformational analysis as discussed in the ESI† (Fig. S4). Subsequently these lowest energy structures were immersed in DMSO cubic boxes in order to evaluate the stability of the binding arrangements described in the gas-phase and to estimate other relevant properties such as the diffusion coefficients.
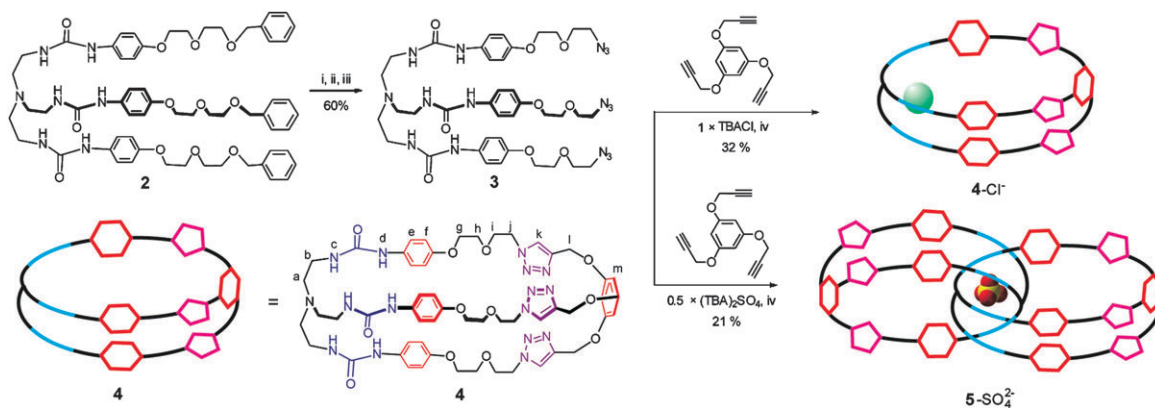
Scheme 3 Reagents and conditions for the synthesis of cage **4**-Cl$^-$ and interlocked capsule **5**-SO$_4^{2-}$, (i) Pd/C, H$_2$, 1 : 1 DCM–EtOH, 95%; (ii) tosyl chloride, Et$_3$N, DMAP, DCM, 71%; (iii) NaN$_3$, DMF, 89%; (iv) Cu(CH$_3$CN)$_4$PF$_6$, DIPEA, TBTA, DCM.

Table 1 Comparison of the experimentally determined diffusion coefficients (D_{exp}) and hydrodynamic radii (rs_{exp}) with the calculated ones (D_{calc}). Estimated hydrodynamic radii (rs), radius of gyration (R_g) and the maximal distance of an atom from the center of geometry (R_{max}) are also listed

System	$D_{exp} \times 10^{-10}/m^2 \, s^{-1}$	$rs_{exp}/\text{Å}$	$D_{calc} \times 10^{-10}/m^2 \, s^{-1}$	$rs/\text{Å}$	$R_g/\text{Å}$	$R_{max}/\text{Å}$
4	1.38	7.98	1.22	9.06	6.90	10.78
4 + SO_4^{2-}	1.23	8.90	1.10	10.03	6.50	10.48
5 + SO_4^{2-}	0.91	12.16	0.81	13.61	8.07	12.97
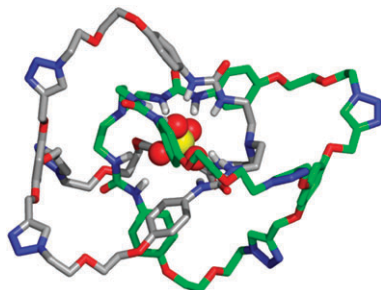
Fig. 2 Snapshot of **5**-SO_4^{2-} in DMSO solution taken after 20 ns of simulation, showing the sulfate anion inside of the interlocked structure. Only urea N–H hydrogen binding groups are shown for clarity. The DMSO solvent molecules are omitted.

The molecular dynamics simulations support entirely the formation and the thermodynamic stability of the interlocked structure as can be seen in Fig. S8 (ESI†), where the time evolution of the N–H···S distances for 20 ns of NPT data collection run are shown. All urea N–H protons are kept bonded to sulfate with N···S distances varying between 2.13 Å and 4.15 Å. Furthermore, the oxygen donors are shared with more than one urea group, leading to different urea···sulfate environments with weaker (shared) or stronger (not shared) interactions. A snapshot taken at the end of the simulation, illustrating **5**-SO_4^{2-} anion binding association, is shown in Fig. 2.

Evidence for the interlocked capsule formation (**5**-SO_4^{2-}) using the diffusion coefficients obtained from the DOSY NMR experiments can also be corroborated by the molecular dynamics simulations. The diffusion coefficients for **4**, **4**-SO_4^{2-} and **5**-SO_4^{2-} were estimated from the 10 ns trajectories of NVE simulations using the Einstein relation (see ESI† for details) and are given in Table 1. Although the diffusion coefficient (D_{calc}) calculated for **4** is slightly underestimated when compared with the experimental one, leading to a bigger value for the hydrodynamic radii (9.06 Å) when compared with the experimental one (7.98 Å), agreement can be considered to be good. The D_{calc} values obtained for **4**-SO_4^{2-} and **5**-SO_4^{2-} are also in close agreement with experimental values and, therefore, the calculated radii using the Stokes–Einstein relation compare well with the experimentally determined ones. Indeed, the ratio rs(**5**-SO_4^{2-})/rs(**4**-SO_4^{2-}) is 1.35 for the experimental values and 1.36 for the calculated ones, which is excellent. The calculated rs(**5**-SO_4^{2-}) 13.61 Å is only ~1.5 Å bigger than the experimental one (12.16 Å). We also decided to check whether the theoretical values for hydrodynamic radii are correlated or not with the radius of gyration (R_g) of the systems. The estimated values of R_g for **4** and **4**-SO_4^{2-} are very similar (~6 Å), but are smaller than the experimentally determined hydrodynamic radii (rs_{exp}), ~8 Å and ~9 Å, respectively. The R_g value for **5**-SO_4^{2-} is much

smaller (~8 Å) than the experimental one (12 Å). However, the value R_{max}, defined as the maximal distance of an atom from the center of geometry (see ESI† for more information), gives a better approximation for the hydrodynamic radius, namely for **5**-SO_4^{2-} (exp: 12.16 Å, calc: 12.97 Å). The values of R_{max} obtained for **4** and **4**-SO_4^{2-} are similar and are also slightly bigger than the experimental rs value of **4**.

In conclusion we have shown that anion templation can be used to synthesise a novel sulfate-encapsulated triply interlocked capsule. Structural assignment is aided by ^{1}H NMR, ESI-MS and DOSY spectra. The experimentally determined diffusion coefficients are in good agreement with molecular dynamic simulations confirming the formation of an interlocked structure with a hydrodynamic radius of ~12 Å. Further studies into the anion binding properties of **4** and **5** are continuing in our laboratories.

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