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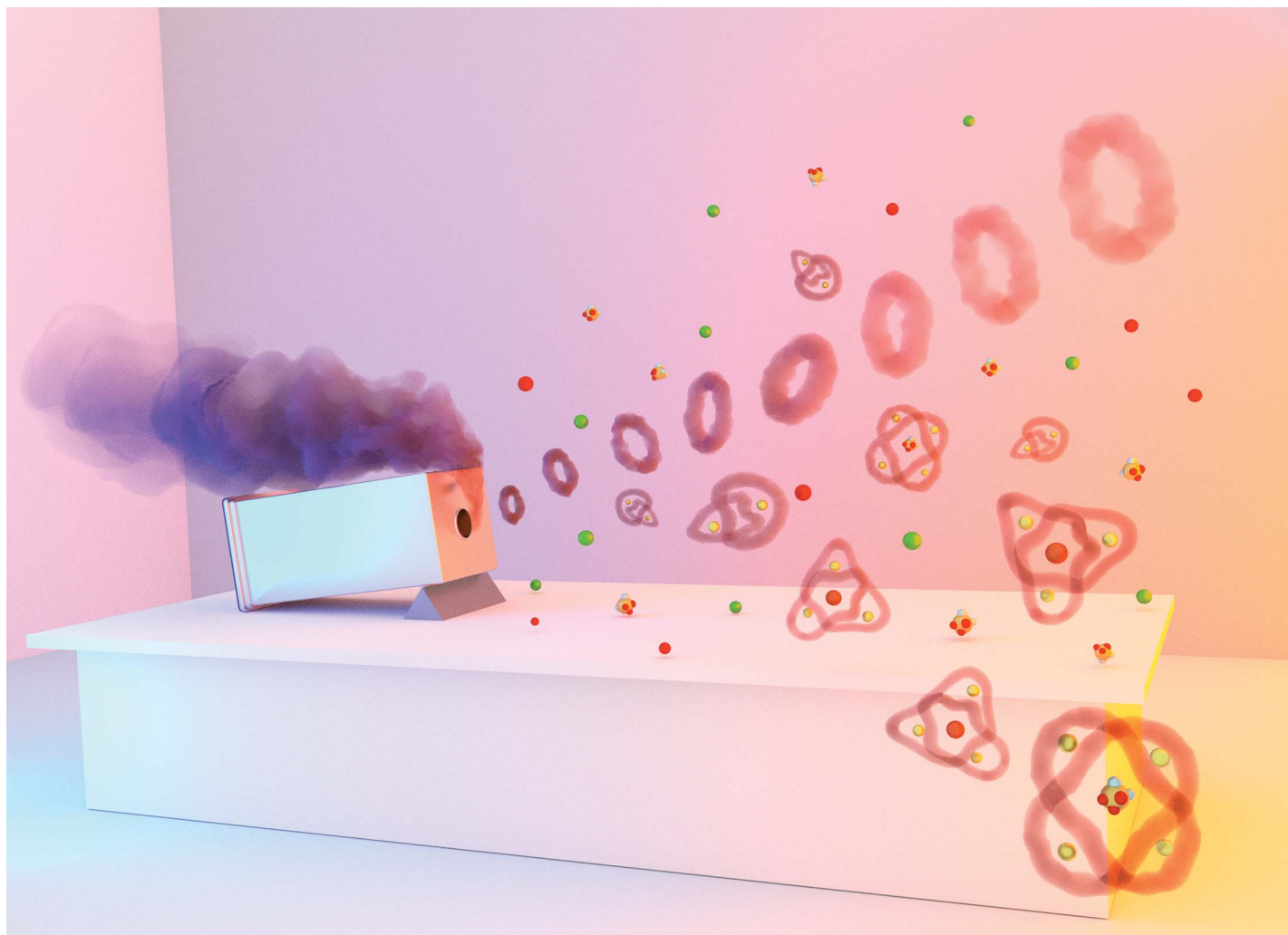
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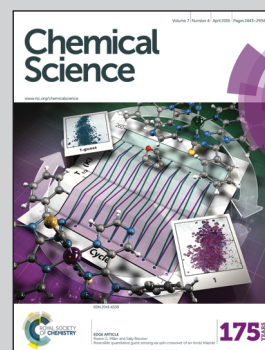


Showcasing research from Ali Trabolsi's laboratory, New York University Abu Dhabi, Abu Dhabi, United Arab Emirates.

Title: [C–H⋯anion] interactions mediate the templation and anion binding properties of topologically non-trivial metal–organic structures in aqueous solutions

In the Trabolsi group, three topologically non-trivial structures can be prepared in one pot: a [2]catenane, a trefoil knot and a Solomon link. The outcome of the reaction could be controlled either by temperature or the use of an anionic template. The trefoil knot was found to accommodate monovalent anions of different sizes and shapes with a relatively high binding affinity. The image was produced by Miss Khulood Alawadi at NYUAD.

As featured in:



See Mourad Elhabiri,
Ali Trabolsi *et al.*,
Chem. Sci., 2016, 7, 2524.



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[C–H⋯anion] interactions mediate the templation and anion binding properties of topologically non-trivial metal–organic structures in aqueous solutions†

Rana A. Bilbeisi,^a Thirumurugan Prakasam,^a Matteo Lusi,^a Roberto El Khoury,^a Carlos Platas-Iglesias,^b Loïc J. Charbonnière,^c John-Carl Olsen,^d Mourad Elhabiri^{*e} and Ali Trabolsi^{*a}

Two synthetic approaches—temperature variation and anion templation—allowed for the selective formation of a [2]catenane ([2]C⁴⁺) or a trefoil knot (TK⁶⁺), or for the enhanced formation of a Solomon link (SL⁸⁺), all from a simple set of starting materials (Zn(II) acetate, diformylpyridine (DFP) and a diamino-2,2'-bipyridine (DAB)) in mixed aqueous solutions. The catenane formed exclusively at 90 °C in a 1 : 1 mixed solvent of D₂O and MeOD. In the presence of bromide ion as template, TK⁶⁺ formed exclusively at 50 °C in the same solvent. In the solid state, TK⁶⁺ hosts two bromide ions in its central cavity by forming six C_{sp}²–H hydrogen bonds. In D₂O, TK⁶⁺, which was originally prepared as a trifluoroacetate (TFA) salt, was found to exchange two TFA counterions for two monovalent anions of different sizes and shapes, which lodged within the knot's central cavity. In contrast to bromide, the larger triflate anion (CF₃SO₃[−]) promoted the formation of SL⁸⁺, which was characterized by ¹H NMR spectroscopy and mass spectrometry. Two dimensional heteronuclear ¹⁹F-¹H-HOSEY NMR experiments detected CH⋯F interactions inside the cavity of SL⁸⁺. Thus, the product distribution of this dynamic link forming system is sensitive to temperature and the size and shape of the anion template, and one of the products, TK⁶⁺, is capable of binding a variety of monovalent anions in D₂O with high affinity (with log β₂ values of 4 to 6 being typical).

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Introduction

During the past 15 years, many small synthetic molecules displaying a variety of structural motifs have been developed for binding anions in organic or aqueous solvents.^{1–6} The most challenging goal, and the one with the greatest potential rewards in terms of practical applications, is the selective recognition of anions in water.^{1,2,7} Not surprisingly, a survey of natural anion receptors provides impressive benchmarks for

comparison and emulation. For example, the sulfate-binding and transport protein of *Salmonella typhimurium* sequesters sulfate in water with a dissociation constant, *K*_D, of 20 μM.⁸ The phosphate binding protein of *Escherichia coli* binds phosphate selectively with a *K*_D of 0.7 μM.^{9–12} Recent achievements involving the recognition of anions in water by synthetic receptors include the sensitive detection of pollutants,^{13–18} the transportation of ions across membranes, and the sensing of biologically relevant anions *in vivo*.^{19–25} Gale and co-workers have published comprehensive reviews of these applications and other recent highlights in the field.^{26–28}

Previously, we reported a one-pot synthesis of a set of topologically non-trivial, Zn(II)-templated complexes that were isolated as trifluoroacetate (TFA) salts: a [2]catenane, [2]C(TFA)₄; a trefoil knot, TK(TFA)₆, and a Solomon link, SL(TFA)₈.²⁹ By relying on reversible imine and metal–ligand bond formation (ref. 30) we were able to form all three complexes simultaneously from a simple pair of chelating ligands: diformylpyridine (DFP) and a diamino-2,2'-bipyridine (DAB).³⁰ The [2]catenane was fully characterized by NMR spectroscopy, mass spectrometry and X-ray crystallography. The more complex structures, TK(TFA)₆ and SL(TFA)₈, initially resisted full

^aNew York University Abu Dhabi (NYUAD), Experimental Research Building (C1), Saadiyat Island, Abu Dhabi, UAE. E-mail: ali.trabolsi@nyu.edu

^bCentro de Investigaciones Científicas Avanzadas (CICA) and Departamento de Química Fundamental, Universidade de Coruña, Campus da Zapateira, Rúa da Fraga 10, 15008 A Coruña, Spain

^cLaboratoire d'Ingénierie Moléculaire Appliquée à l'Analyse, IPHC, UMR 7178 CNRS/ Uds, ECPM, 25 rue Becquerel, 67087 Strasbourg, France

^dSchool of Sciences, Indiana University Kokomo, Kokomo, IN 46904, USA

^eLaboratoire de Chimie Bioorganique et Médicinale, UMR 7509 CNRS/Uds, ECPM, 25 rue Becquerel, 67087 Strasbourg, France. E-mail: elhabiri@unistra.fr

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characterization. We could not grow X-ray quality crystals of $\text{TK}(\text{TFA})_6$ and could only detect SL species by mass spectrometry at early stages of the reaction. We now report (i) the solid state characterization of a bromide containing trefoil knot complex, $\text{TK}(\text{TFA})_4\text{Br}_2$, (ii) quantitative studies in D_2O of the exchange of two TFA anions of the $\text{TK}(\text{TFA})_6$ complex for various other monovalent anions and (iii) the effects of temperature and anion size and shape on the product distribution of the templation reaction itself. We demonstrate that different monovalent anions can be used to favor formation of either TK^{6+} or SL^{8+} in mixed aqueous solvents. A notable feature of this system is the cooperative effect of both cationic and anionic templates. The zinc(II) cation is necessary for complex formation, whereas the anion template influences complex topology.

We would also like to call attention to the relatively rare structural motif by which TK^{6+} and SL^{8+} bind anions within their central cavities: multiple weak but cooperative $\text{C}_{\text{sp}^2}\text{-H}$ hydrogen bonds. This motif is present in small anion binders such as the bisimidazoliums of the Maeda group,³¹ as well as the triazole-containing macrocycles and podands reported by Flood and coworkers.^{32–34} Previous examples of topologically interesting complexes in which this feature is present include Leigh's pentafoil knot,^{35–37} which is templated, in part, by a central chloride ion; and the chloride and nitrate-binding rotaxanes^{38,39} of the Beer group. Nevertheless, measurements of the anion binding affinities of molecular links and knots have rarely been reported.^{38,40} It is particularly remarkable that the C–H hydrogen bonding of the TK^{6+} and SL^{8+} complexes are effective in D_2O , one of the most competitive solvents. We believe that the results described below, in particular, the anion binding studies of TK^{6+} are a unique contribution to the field of aqueous anion receptor chemistry.

Results & discussion

Solid state structure of TK^{6+}

Single crystals containing $\text{TK}(\text{TFA})_4\text{Br}_2$ and suitable for X-ray diffraction were isolated by slow vapor diffusion of *n*-butylether into a trifluoroethanol solution of $\text{TK}(\text{TFA})_6$ that contained a small amount of tetrabutyl ammonium bromide. Tri-bladed propeller-shaped cationic complexes of TK^{6+} crystallized as a racemic mixture in the trigonal $P\bar{3}$ space group. The crystal structure presented in Fig. 1b, depicts the C_3 symmetry of the knotted Zn_3L_3 complex (where L represents the condensed DAB + DFP organic ligands). Three equivalent L strands are held together by three Zn(II) ions located 13.3 Å apart. Each zinc cation is coordinated to five nitrogen atoms (two from the 2,2'-bipyridine and three from the 2,5-diiminopyridine) and has a distorted octahedral geometry, with its coordination sphere being completed by one trifluoroacetate anion. The bipyridines of the ligand strand are located between phenoxy substituents that are attached to the imine moieties. The shortest distance between phenoxy and bipyridyl rings is ~ 3.5 Å, which is at the upper limit associated with effective π - π stacking interactions. An adduct composed of two tetrahedral $[\text{ZnBr}(\text{CF}_3\text{COO})_3]^{2-}$ complexes that are hydrogen-bonded by water molecules is co-crystallized with the cationic knot (Fig. 1c). The presence of

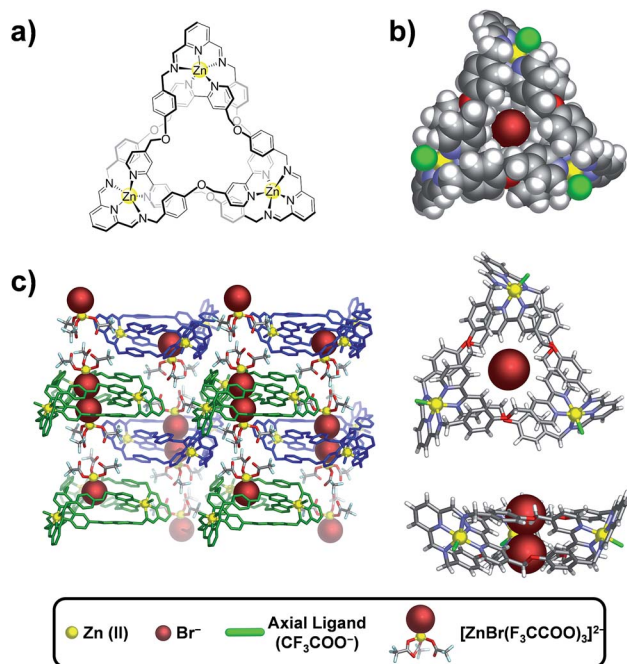


Fig. 1 Single crystal structure of the Zn(II)-based trefoil knot. (a) Molecular structure of TK^{6+} . (b) Space-filling (top) and stick-figure (bottom) views of $[\text{TK}(\text{TFA})_3\text{Br}_2]^+$. (c) Crystal packing of $[\text{TK}(\text{TFA})_3]^{3+}$ and the adduct $[\text{ZnBr}(\text{CF}_3\text{COO})_3]^{2-}$.

bromide anions was confirmed (Fig. S1†) by EDAX analysis of the single crystal used in the XRD experiment as well as by mass spectrometry in the gas phase. In the solid state, two bromide ions were found to occupy the central cavity of TK^{6+} and seem to be essential for crystallization, as all attempts to crystallize TK^{6+} from bromide-free solutions failed.

TK^{6+} cations and adducts alternate regularly in such a way (Fig. 1c) that the bromides of two adducts reside in the center of TK^{6+} and are each fixed by at least three $\text{CH}\cdots\text{Br}^-$ charge-assisted hydrogen bonds that range in length from 2.92 to 2.98 Å. The strength of binding between the TK^{6+} cation and the adduct also likely facilitates crystallization of the knot.

The average diameter and average depth of the TK^{6+} cavity, as deduced from the crystal structure, are 5.86 Å and 4.06 Å, respectively. In the solid state, this cylindrical pocket hosts two bromide anions by establishing $\text{CH}\cdots\text{anion}$ interactions.^{32,41–42}

Computational modeling of TK^{6+}

Due to the large size of the TK^{6+} complex, semi-empirical PM6 calculations were used to determine a theoretically optimal geometry. The PM6 algorithm had reproduced fairly well (see ESI†) the experimentally determined geometry of $[\text{C}]^{4+}$.²⁹ Subsequent single-point calculations on the PM6-generated TK^{6+} structure were performed using density functional theory (DFT) at the B3LYP/6-31G(d) level to determine the electrostatic potential at the surface of the knot. The electrostatic potential over the surface of TK^{6+} , depicted in Fig. 3a, was calculated in aqueous solution as defined by an isodensity surface of 0.001 electrons bohr^{-3} .⁴³ Regions with the highest positive



electrostatic potential are located on the aromatic C_{sp^2} -H hydrogens that point toward the center of the cavity.

The optimized geometry of TK^{6+} presents a nearly undistorted C_3 symmetry, where the symmetry axis passes through the center of the central cavity. However, the helical arrangement of the three pyridyl units of the supramolecular assembly results in a sizeable dipole moment directed along the C_3 axis, which at the B3LYP/6-31G(d) level amounts to 2.77 D in the gas-phase and 4.97 D in aqueous solution (Fig. 3a).

Two centroids are defined by the three methylene protons that point to each side of the central cavity. These centroids delimit the cavity's height, which measures 6.57 Å. The radius of the base is 2.93 Å and is estimated from the distances between the methylene protons and the centroid that they define. Thus, assuming the simultaneous binding of two anions, the size of the TK^{6+} cavity ($\sim 130 \text{ \AA}^3$) is suited for the recognition of two anions of relatively small radius ($\leq 2.5 \text{ \AA}$).

The favorable distribution of positive charge in TK^{6+} and its demonstrated ability to firmly host two bromide anions within its central cavity in the solid state inspired us to explore the knot's anion recognition properties in solution. There are few examples of molecular links that have pre-organized cavities capable of aromatic hydrogen bonding,^{40,44,45} and to the best of our knowledge quantitative anion binding studies involving knotted structures in aqueous media have not been reported.

The binding of monovalent anions of different size and shape to TK^{6+} was initially evaluated computationally, using semi-empirical PM6 calculations. This computational study provided insight into possible binding modes and stoichiometries. The geometry optimized $[TKBr_2]^{4+}$ complex (Fig. S2†) is in reasonably good agreement with the X-ray structure. Energy-minimized models of complexes of TK^{6+} with linear (thiocyanate), trigonal planar (nitrate) and tetrahedral (tetrafluoroborate) anions are presented in Fig. 2. The anions are held within the knot's central cavity by multiple non-classical aromatic $CH \cdots$ anion hydrogen bonds.

Measurement of anion exchange and binding

Initially, TK^{6+} was prepared as its trifluoroacetate salt in isopropanol and characterized in methanol.²⁹ After discovering that $TK(TFA)_6$ is soluble and stable in water, we designed experiments to assess the knot's anion binding ability in this highly competitive medium. Preliminary 1H - ^{19}F HOESY NMR

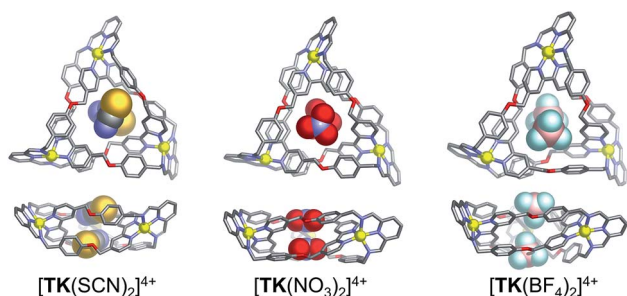


Fig. 2 Top and side views of PM6-optimized geometries of host-guest complexes involving TK^{6+} and, from left to right, SCN^- , NO_3^- and BF_4^- .

spectroscopy experiments (SI) gave no indication of interactions between the fluorines of TFA and the hydrogens of the organic framework of TK^{6+} ; hence, the mode of association of TFA with TK^{6+} could not be determined.

The binding of bromide ion in water was evaluated in titration experiments monitored by 1H NMR spectroscopy. Incremental amounts of aqueous tetrabutylammonium bromide were added to a D_2O solution of $TK(TFA)_6$ at room temperature. The spectra show (Fig. 3c) the gradual spectral shifts of TK^{6+} resonances that occur as the result of the knot's interaction with bromide ions in solution. These continuous spectral changes are characteristic of an exchange process that is fast on the NMR timescale. The signal that corresponds to the H_j protons exhibits the largest downfield shift, from 8.18 ppm (before addition of Br^-) to 9.10 ppm (upon saturation with the anion). Its change as a function of bromide ion concentration is illustrated in Fig. 3c. The signals that correspond to the diastereotopic H_g protons are significantly split apart as the concentration of bromide increases. The signal of the H_e protons displays a small shift, and the signals that correspond to the H_a , H_b , H_c , and H_d protons are only slightly affected by bromide ion binding.

These spectroscopic results are consistent with the relative positions of the TK^{6+} protons and bromide ions in the crystal structure of the knot, which shows, for example, that the H_a , H_b , H_c , and H_d protons point away from the knot's cavity and that the H_g and H_j bipyridyl protons point toward its center and are involved in hydrogen bonding with bromide.

The shift data was processed and found to fit with good agreement to a 1 : 2 ($TK^{6+} : Br^-$) binding model, indicating that two bromides bind within the cavity of TK^{6+} in D_2O . (A 1 : 1 binding model, and others, were not consistent with the data.) Mass spectrometry experiments (see ESI†) provided strong evidence for the existence of the 1 : 2 complex in the gas phase. A series of m/z fragments corresponding to $[TK(TFA)_2(Br)_2]^{2+}$, $[TK(TFA)_3Br]^{2+}$, and $[TK(TFA)_4]^{2+}$ were detected by ESI-HRMS, with no evidence for complexes containing more than two bromide ions.

From the solid state and solution studies, we infer that two TFA anions located outside the TK^{6+} cavity are exchanged for two bromides that lodge within the cavity. The process is facilitated by electrostatic attraction between the positively charged host cavity and the negatively charged bromides. Multiple $CH \cdots$ anion interactions are formed in the host-guest complex, even in the aqueous solvent. The process is dynamic, with bound bromides being exchanged continuously with bromides free in solution.

The first (K_1) and second (K_2) association constants (which can be considered to be binding constants) were calculated and found to be $4.4(0.5) \times 10^2 \text{ M}^{-1}$ and $2.3(0.3) \times 10^3 \text{ M}^{-1}$, respectively. Interestingly, the $TK(TFA)_4Br_2$ complex is significantly more stable than the monobromide complex, $TK(TFA)_5Br$, which suggests that the binding of two anions is a cooperative process. The ratio of the calculated binding constants (K_2/K_1) is approximately five which indicates positive cooperativity and suggests that binding of the first bromide ion



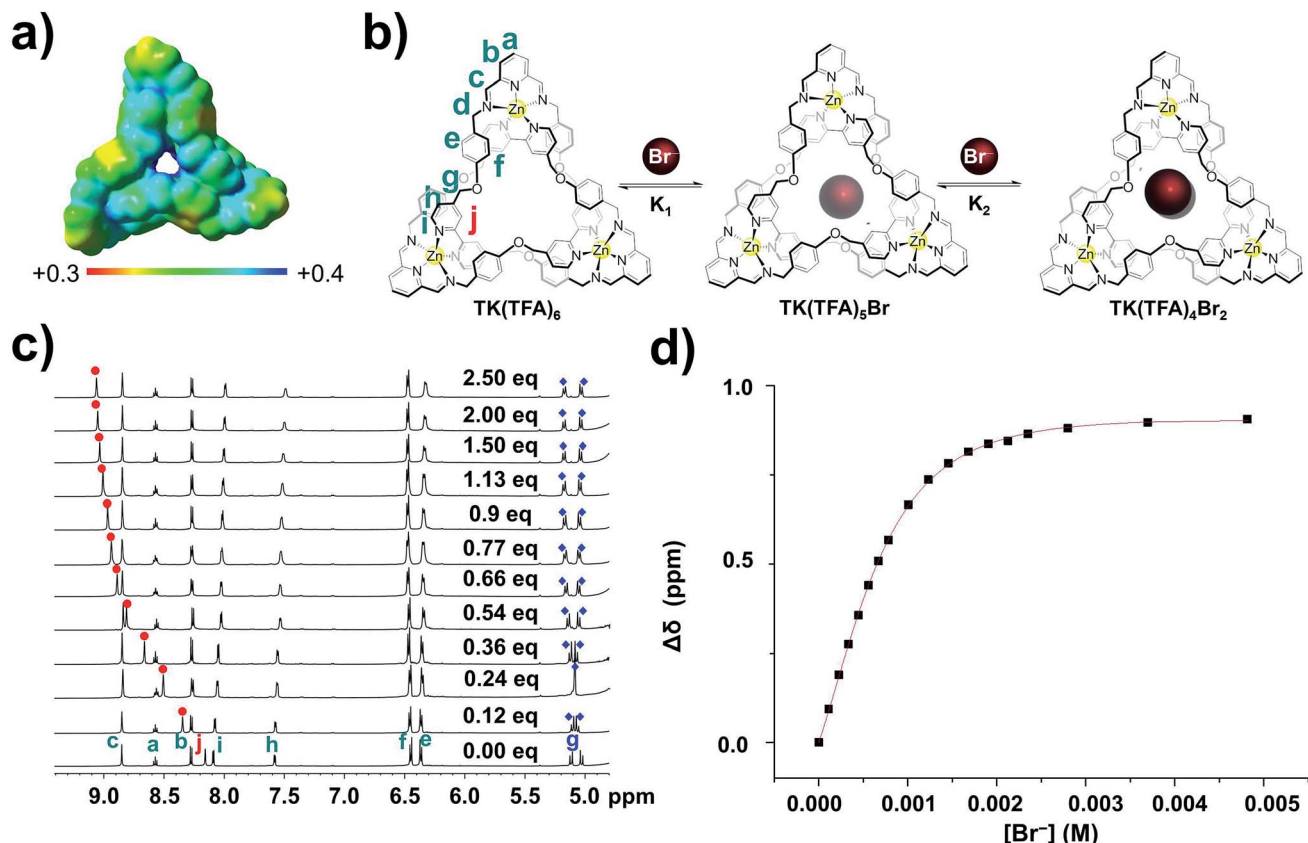


Fig. 3 Measurement of the bromide ion binding constants of TK⁶⁺ complexes by titration. (a) Computed B3LYP/6-31G(d) electrostatic potential of TK⁶⁺ on the molecular surface defined by the 0.001 electrons bohr⁻³ contour of the electron density (b) schematic representation of bromide ion binding. (c) Stacked plots of ¹H NMR (600 MHz, 298 K) spectra of 1.87 mM solutions of TK⁶⁺ in D₂O titrated with, bottom to top, increasing amounts of tetrabutylammonium bromide. (d) Binding isotherm obtained by plotting H_j signal shift versus bromide ion concentration. In most cases, addition of more than two equivalents of anion precipitated the knot and prevented further measurements.

causes conformational changes in the host's framework that facilitate binding of the second.^{46–51}

The same general pattern of spectral shifts occurred during titrations of the knot with other monovalent anions of different size (ionic radii, *r*, of 1.7 to 2.4 Å) and shape (Fig. S3–S7†) including I⁻, N₃⁻, SCN⁻, and NO₃⁻ (Fig. S3–S6†).^{1,32,52}

The pattern was somewhat different with BF₄⁻ (Fig. S7†). The H_j signal was shifted, indicating an interaction between the anion and the interior surface of the knot's cavity, but the direction of the shift was upfield rather than downfield. A sample containing the knot and BF₄⁻ was further analyzed in a ¹H-¹⁹F HOESY experiment. The resulting spectrum (Fig. S8†) shows NOE interactions between the fluorine atoms of BF₄⁻ and the H_g and H_j protons, which confirms the close proximity of the anion and the walls of the knot's central cavity. Thus, all of the selected anions, including BF₄⁻, bind within the cavity, though BF₄⁻ may extend beyond it, as suggested by computational modelling (Fig. 2, right).

The shift of the H_j signal that occurred during the titrations was used to calculate the association constants, K₁ and K₂, for all anions except BF₄⁻, whose association constants were deduced from the shift of the H_h signal. A global binding constant, log β₂, and a cooperativity parameter, K₂/

K₁, were also calculated for each anion. The results are listed in Table 1. Regardless of size and shape, all of the selected anions were found to bind with the same 1 : 2 (TK⁶⁺ : anion) stoichiometry. In the case of BF₄⁻, this stoichiometry was supported by an ESI-HRMS analysis (see ESI†) that revealed a series of *m/z* fragments corresponding to the complexes [TK(TFA)₂(BF₄)₂]²⁺, [TK(TFA)₃BF₄]²⁺, and [TK(TFA)₄]²⁺, and no evidence for complexes involving more than two BF₄⁻ anions.

As compared to other small-molecule receptors, TK⁶⁺ exhibits high affinities for the selected anions in water.^{1,2} However, the cooperativity of the two binding events associated with each anion type varied. For the spherical and linear anions, the K₂/K₁ ratio was always significantly larger (1.0 < K₂/K₁ < 23.0) than 0.25, indicating positive cooperativity.⁵¹ A comparison of the data for the two spherical anions investigated, Br⁻ (*r* = 1.82 Å) and I⁻ (*r* = 2.06 Å), revealed that I⁻ binds with a slightly higher global binding affinity, but with lower cooperativity (log β₂ = 6.1, K₂/K₁ = 3.3), than Br⁻ (log β₂ = 6.0, K₂/K₁ = 5.2). These results suggest that I⁻ fits better in the cylindrical cavity of TK⁶⁺ but that the smaller size of Br⁻ minimizes anion–anion repulsion. Of the two linear anions, SCN⁻ (length = 2.13 Å) and N₃⁻ (length = 1.71 Å), the larger one, SCN⁻, displays



Table 1 Successive (K_1 and K_2) and global ($\log \beta_2$) binding constants determined from ^1H titrations of TK^{6+} with monovalent anions at room temperature in D_2O . Binding constants were deduced from ^1H chemical shifts measured as a function of anion concentration. H_j protons were monitored in all cases except the BF_4^- titration, for which the H_h protons were monitored. Standard deviations are shown in parentheses

Anion	K_1 (M^{-1})	K_2 (M^{-1})	$\log \beta_2$	K_2/K_1
Br^-	$4.4(0.5) \times 10^2$	$2.3(0.3) \times 10^3$	6.0	5.2(0.8)
I^-	$6.5(0.6) \times 10^2$	$2.2(0.3) \times 10^3$	6.15	3.3(0.6)
N_3^-	$9.8(1.7) \times 10^2$	$9.3(7.8) \times 10^2$	5.96	1.0(0.8)
SCN^-	$1.5(0.3) \times 10^2$	$3.4(2.0) \times 10^3$	5.72	22.5(2.5)
NO_3^-	$5.2(0.2) \times 10^2$	$6.7(2.5) \times 10^1$	4.54	0.13(0.05)
BF_4^-	$1.0(0.2) \times 10^3$	$2.2(0.7) \times 10^2$	5.34	0.21(0.08)

a comparable global binding constant but a higher cooperativity value ($\log \beta_2 = 5.72$, $K_2/K_1 = 22.5$) than N_3^- ($\log \beta_2 = 5.96$, $K_2/K_1 = 1.0$). The unexpectedly higher cooperativity of SCN^- is consistent with the negative charge of this anion being more localized on the nitrogen atom, a property that leads to a more directed interaction with TK^{6+} and results in structural adaptation that facilitates the binding of the second SCN^- anion. Considering the calculated structure of $[\text{TK}(\text{SCN})_2]^{4+}$ illustrated in Fig. 2, we hypothesize that the two SCN^- anions are bound in a staggered configuration that minimizes anion–anion repulsion and therefore increases binding affinity and cooperativity. Also, we suspect that resonance delocalization of the negative charge of N_3^- likely weakens this anion's interaction with TK^{6+} and fails to induce the conformational changes that would enhance binding cooperativity.

In contrast to the positively cooperative binding behavior of the spherical and linear anions, the binding of the larger trigonal planar (NO_3^-) and tetrahedral (BF_4^-) anions was negatively cooperative, with both K_2/K_1 values being lower than 0.25. In these cases, the first anion to bind hinders the second from binding due to increased steric and electronic repulsions. The K_2/K_1 ratio of 0.21 for BF_4^- indicates statistically negative cooperation which can be attributed to the anion's relatively large ionic radius; however, BF_4^- was found to bind to TK^{6+} with relatively high overall affinity ($\log \beta_2 = 5.34$).

The larger trifluoromethylsulfonate (triflate, OTf^-) anion was titrated as its tetrabutylammonium salt, and no signal shifting in the knot's ^1H NMR spectrum was observed (Fig. S9†). This result indicates that OTf^- binding (to any part of the knot) is relatively weak under the experimental conditions and is likely due to the non-coordinating nature of the anion and its relatively large size which prevents entry into the knot's central cavity.

Binding experiments with Cl^- , CN^- , OCN^- and ClO_4^- were also attempted, but all of these anions caused TK^{6+} to precipitate from solution, which prevented accurate measurements. In addition to binding to the central cavity of TK^{6+} , these anions might also be replacing TFA anions that coordinate axially to the $\text{Zn}(\text{II})$ metal centers and in this way causing reduced solubility and precipitation of the complexes in aqueous media.

Using variable temperature NMR spectroscopy, we studied and compared the binding of Br^- with that of BF_4^- . At 298 K, the H_g and H_j signals are sharp in a spectrum (Fig. S15†) of a solution of the knot and Br^- measured at 298 K, which indicates that exchange of Br^- is relatively fast at room temperature. At 268 K, the H_g and H_j peaks are considerably broader, which reflects a slower exchange with respect to room temperature. In contrast, at 298 K, the H_g and H_j signals are broad in a spectrum (Fig. S16†) of a solution containing BF_4^- and the knot, whereas they are sharp when the temperature is 333 K. Thus, for any given temperature, exchange of BF_4^- is slower.

Controlling $[\text{2}]C^{4+}$, TK^{6+} and SL^{8+} populations in solution

The trifluoroacetate salt of the DAB ligand that was previously used²⁹ for the synthesis of the three links was replaced by the corresponding neutral DAB molecule (see ESI† for synthetic details). Use of the neutral ligand prevented precipitation of the complexes in the mixed aqueous solvent and allowed us to monitor their simultaneous formation under different reaction conditions.⁵³

Mixing neutral DAB with DFP and zinc(II) acetate in a 1 : 1, $\text{D}_2\text{O} : \text{MeOD}$ solvent mixture, at temperatures ranging from 50 °C to 90 °C, lead to the formation of TK^{6+} and $[\text{2}]C^{4+}$ in various proportions. When the reaction was carried out at 90 °C, $[\text{2}]C^{4+}$ was formed exclusively, whereas, at 50 °C, a significant amount (63%) of TK^{6+} was formed. We found that the $\text{TK}^{6+} : [\text{2}]C^{4+}$ ratio was dependent on both temperature and solvent. There were no signs of SL^{8+} formation under any of these conditions. The fact that a greater proportion of $[\text{2}]C^{4+}$ formed at higher temperatures substantiates previous findings²⁹ of ours that suggested that $[\text{2}]C^{4+}$ is the thermodynamic product of the reaction and that TK^{6+} is a kinetic product.

We had postulated that bromide was responsible for significant stabilization of the X-ray structure of the knot. This hypothesis was supported by an NMR investigation of the ability of Br^- to template the formation of TK^{6+} in solution. In the absence of a Br^- template, DFP, DAB and $\text{Zn}(\text{OAc})_2$ afforded a mixture of 63% $\text{TK}(\text{TFA})_4\text{Br}_2$ and 37% $[\text{2}]C(\text{TFA})_4$ in a 1 : 1, $\text{D}_2\text{O} : \text{MeOD}$ solution at 50 °C. However, the mole fraction of the knot increased to 77% upon addition of one equivalent (relative to the stoichiometry of the starting materials) of tetrabutylammonium bromide, and addition of two equivalents of bromide resulted in an even greater proportion (85%) of the knot (Fig. S19†).

In a 1 : 1 : 1 mixture of CD_3OD , D_2O and CD_3CN the bulky triflate anion gave rise to an additional set of resonances in the spectrum of the reaction mixture (Fig. 4) that matched neither those of TK^{6+} nor $[\text{2}]C^{4+}$. Further NMR and mass spectrometric analysis allowed us to assign the new set of peaks to SL^{8+} (Fig. S20†). SL^{8+} is much larger than TK^{6+} and has a large central cavity that may be able to accommodate the triflate anion. The size of the cavity was estimated with the aid of PM6 calculations. The optimized geometry of SL^{8+} (Fig. S21†) presents a nearly undistorted C_2 symmetry with a cylindrical cavity having a height of ~ 5.90 Å (6.57 Å for the TK^{6+}) and bases of *ca.* 4.52 Å



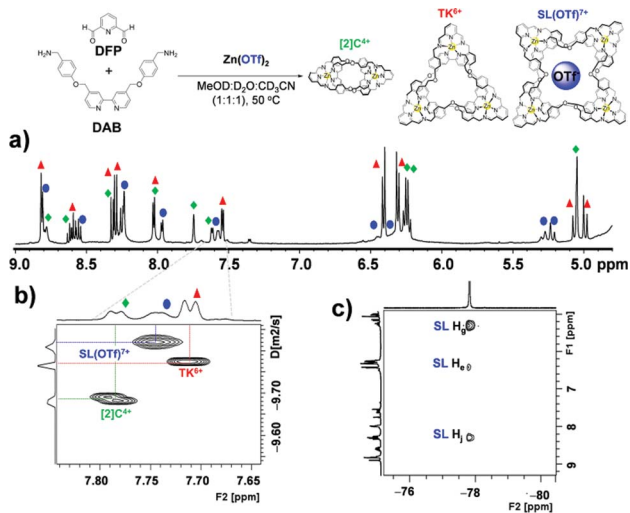


Fig. 4 NMR spectroscopic evidence for the formation of SL^{8+} . (a) ^1H NMR, (b) DOSY and (c) HOESY spectra of a solution ($\text{MeOD} : \text{D}_2\text{O} : \text{CD}_3\text{CN}$, 1 : 1 : 1) of $[\text{2C}]^{4+}$, TK^{6+} and $[\text{SL}(\text{OTf})]^{7+}$ at 500 MHz and 298 K.

radius (*versus* 2.39 Å for TK^{6+}). Thus, the central cavity of SL^{8+} is significantly wider than that of TK^{6+} .

The ESI-HRMS spectrum of the reaction mixture in which triflate was used as a templating anion confirmed the presence of the three links. In addition to peaks characteristic of the catenane and the trefoil knot, the spectrum reveals two major peaks (Fig. S20†) with maxima at m/z 1036.44 and 1629.13, which are consistent with the cations $[\text{SL}(\text{OTf})_5]^{3+}$ (calculated $m/z = 1036.45$) and $[\text{SL}(\text{OTf})_6]^{2+}$ (calculated $m/z = 1629.16$).

Diffusion ordered ^1H NMR spectroscopy (DOSY) of reaction mixtures that included OTf^- as a template produced spectra (Fig. 4b) that confirmed the presence of the three complexes. The diffusion coefficients of $[\text{2C}]^{4+}$, TK^{6+} and SL^{8+} complexes were found to be $1.98(0.01) \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$, $1.62(0.01) \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ and $1.460(0.005) \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$, respectively. The corresponding hydrodynamic radii of the complexes were calculated to be 1.35, 1.65 and 1.83 nm, respectively (see ESI† for calculations). Moreover, ^1H - ^{19}F heteronuclear NOESY (HOESY) experiments revealed through-space interactions between the aromatic protons of SL^{8+} 's cavity and the fluorine nuclei of the triflate anion. Fig. 4c shows three cross peaks that indicate correlations between the fluorines and the H_e , H_g and H_j protons of the Solomon link. These correlations confirm the close proximity of the protons and fluorines and provide evidence for triflate's role as a template. The H_g and H_j protons seem to be involved in stronger coupling interactions, as indicated by the greater signal intensities of their cross peaks. PM6 calculations performed on the $[\text{SL}(\text{OTf})]^{7+}$ system provided (Fig. S21†) an optimized geometry in which triflate is held inside the cavity of the host by $\text{CH}\cdots\text{O}$ and $\text{CH}\cdots\text{F}$ interactions involving H_g and H_j , and H_e protons, respectively, and which is in good qualitative agreement with the experimental measurements.

Conclusions

Anion templating and temperature variation were used to control the product distribution of a dynamic library of zinc(II)-based molecular knots and links ($[\text{2C}]^{4+}$, TK^{6+} and SL^{8+}). Electrostatic forces, including weak non-covalent $\text{CH}\cdots\text{anion}$ interactions that operated in the $\text{MeOD}/\text{D}_2\text{O}$ solvent mixtures mediated the topological outcome of the reaction. In the solid state, the electropositive central cavity of TK^{6+} was found to accommodate two bromide anions with multiple CH hydrogen-bonds. These $\text{CH}\cdots\text{anion}$ interactions occur between bipyridinyl units and bromide anions and are a major stabilizing feature in the packed crystal. In D_2O , TK^{6+} preserved its anion binding properties: monovalent anions of various shapes and sizes were found to bind to TK^{6+} in 1 : 2 (TK^{6+} : anion) stoichiometries and with high affinities, with $\log \beta_2$ values typically in the range of 4 to 6.

Thermodynamic control over the library's product distribution was possible by varying the temperature of the reaction and/or by changing the anion template. Catenane $[\text{2C}]^{4+}$, being the most thermodynamically stable complex, was formed exclusively when the reaction was carried at 90 °C. Lowering the temperature to 50 °C caused $[\text{2C}]^{4+}$ and TK^{6+} to form simultaneously in 37% and 63% chemical yields, respectively. Addition of two equivalents of bromide ion to the reaction at 50 °C resulted in a much greater proportion of TK^{6+} (85%). Addition of the bulkier triflate anion (OTf^-) allowed for formation and characterization of a Solomon link, SL^{8+} . The presence of $\text{CH}\cdots\text{F}$ interactions inside the cavity of the SL^{8+} were supported by 2D heteronuclear ^{19}F - ^1H -HOESY NMR experiments.

An analogous system in which both cations and anions influence the distribution of several metallocsupramolecular products by templating has been described by Nitschke and coworkers.⁵⁴ In that system a set of cages, helicates and prisms were formed. To our knowledge, ours is the first such library involving knots and links.

With further development, anion binding within the topologically unique cavities of these molecular complexes could find application in areas such as anion-sensing and anion-assisted catalysis. For example, incorporation of fluorogenic substituents into TK^{6+} could allow for the sensing of specific anions.⁴¹ Furthermore, it might be possible to fabricate ion selective electrodes by modifying the surfaces of the electrodes with molecular knots and links.

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