

Strong and Selective Anion Binding within the Central Cavity of Molecular Knots and Links

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S Supporting Information

ABSTRACT: A molecular pentafoil knot and doubly and triply entwined [2]catenanes based on circular Fe(II) double helicate scaffolds bind halide anions in their central cavities through electrostatic and CH...X⁻ hydrogen-bonding interactions. The binding is up to $(3.6 \pm 0.2) \times 10^{10} \text{ M}^{-1}$ in acetonitrile (for pentafoil knot [2·Cl](PF₆)₉), making these topologically complex host molecules some of the strongest synthetic noncovalent binders of halide anions measured to date, comparable in chloride ion affinity to silver salts.

In a classic series of experiments in the mid-1990s, Lehn and co-workers found that Fe(II) salts and tris(bipyridine) ligands with short spacers between the chelating groups assemble into double-stranded circular metal helicates.¹ The size of the circular helicate produced was often influenced by the counterion of the metal salt employed: for example, the use of FeCl₂ led to a pentameric cyclic helicate with a chloride anion at the center of the structure in the solid state.^{1a} Unlike the other counterions, this clearly strongly bound chloride ion was reported not to be exchanged upon washing with a saturated solution of hexafluorophosphate or triflate salts.^{1a} However, the strength and selectivity of the anion binding of these circular helicates were never quantified, perhaps because of the perceived difficulty of analyzing the substitution of one anion for another in the presence of other counterions.

We recently described the synthesis of a series of molecular knots² and links³ using different sized circular helicate scaffolds to control the number of crossings in the closed-loop ligand strand. Solomon link [1](PF₆)₈ (a doubly entwined [2]catenane) and pentafoil knot [2·Cl](PF₆)₉ are derived from tetrameric and pentameric circular helicates, respectively,^{4,5} and are assembled through reversible imine chemistry (Figure 1).⁶ The Star of David 6₂ link [3](PF₆)₁₂ (a triply entwined [2]catenane) is based on a hexameric circular helicate prepared from tris(bipyridine) ligands with the entwined complex covalently captured by olefin metathesis.⁷ Here we report on the binding affinities of the central cavities of knots and links [1](PF₆)₈, [2](PF₆)₁₀, and [3](PF₆)₁₂ (Figure 1) for various halide anions.⁸

Well-ordered anions are found associated with the central cavity in the X-ray crystal structures of salts of each of these links and knot: two PF₆⁻ anions in [1](PF₆)₈;⁴ one Cl⁻ anion in [2·Cl](PF₆)₉⁵ and one PF₆⁻ anion in [3·PF₆](Ph₄B)₁₁.⁷ The solid-state structures (Figure 2) show that in each case the H¹ aromatic protons (see Figure 1 for numbering scheme) line the walls of the

inner cavities of the circular helicates. The metal ions not only provide long-range attractive electrostatic interactions to any electron-rich moiety in the central cavity (the overall charge of the complex is, of course, neutral because of the other counterions) but also preorganize the binding pocket (through formation of the relatively rigid circular double helicate) and inductively activate the C–H¹ protons as hydrogen bond donors for a second sphere of coordination¹⁰ to electron-rich species.^{11–13}

The all-PF₆⁻ complexes of the Solomon link and Star of David catenane, [1](PF₆)₈ and [3](PF₆)₁₂, respectively, were isolated from the reactions used to form the interlocked architectures by washing with aqueous KPF₆.^{4,7} We found that the chloride anion could be removed from [2·Cl](PF₆)₉ by a two-stage procedure of salt metathesis,¹⁴ first using aqueous NH₄BF₄ and then aqueous NH₄PF₆ (see Supporting Information (SI)).¹⁵ Exchange of the chloride ion is accompanied by a ~1.4 ppm upfield shift in the H¹ protons as a consequence of their no longer being involved in strong CH...Cl⁻ hydrogen-bonding (Figure 3e). Addition of up to 1 equiv of Bu₄NCl¹⁶ to the “empty”¹⁷ pentafoil knot ([2](PF₆)₁₀) replaces just one of the 10 PF₆⁻ anions (electrospray ionization mass spectrometry (ESI-MS) shows a series of *m/z* fragments corresponding to [2(PF₆)_nCl]⁽⁹⁻ⁿ⁾⁺ but no evidence for complexes with more than one Cl⁻ anion). ¹H NMR spectroscopy (Figure 3c) confirms that the chloride anion is bound within the central cavity of the knot in solution (H¹, and to a lesser extent H⁶,¹⁸ are significantly shifted compared to [2](PF₆)₁₀; Figure 3c, cf. Figure 3e). Addition of less than 1 equiv of Bu₄NCl to [2](PF₆)₁₀ gives two distinct species in the ¹H NMR spectrum (Figure 3d), [2](PF₆)₁₀ and [2·Cl](PF₆)₉, indicating that the Cl⁻ anion bound in the cavity of the knot only undergoes slow exchange on the NMR time scale with others in bulk solution.¹⁹

With all three of the all-PF₆⁻ complexes ([1](PF₆)₈, [2](PF₆)₁₀, and [3](PF₆)₁₂) in hand, we measured the equilibrium constant (effectively a binding constant) for the exchange of one of the PF₆⁻ anions for a single halide anion in acetonitrile²⁰ (Scheme 1; Table 1). In every case (with the exception of Cl⁻ or Br⁻ with [3]):²¹ (i) ESI-MS showed the exchange of only one halide for a PF₆⁻ anion (i.e., no complexes with more than one halide) during addition of up to 1 equiv of the tetrabutylammonium salt;¹⁶ and (ii) ¹H NMR indicated halide binding only within the central cavity of the circular helicates (significant shifts in H¹ compared to the rest of the ¹H NMR spectrum, e.g., Figure 3).²² These results confirmed that the displacement of the first PF₆⁻

Received: June 18, 2015

Published: July 6, 2015

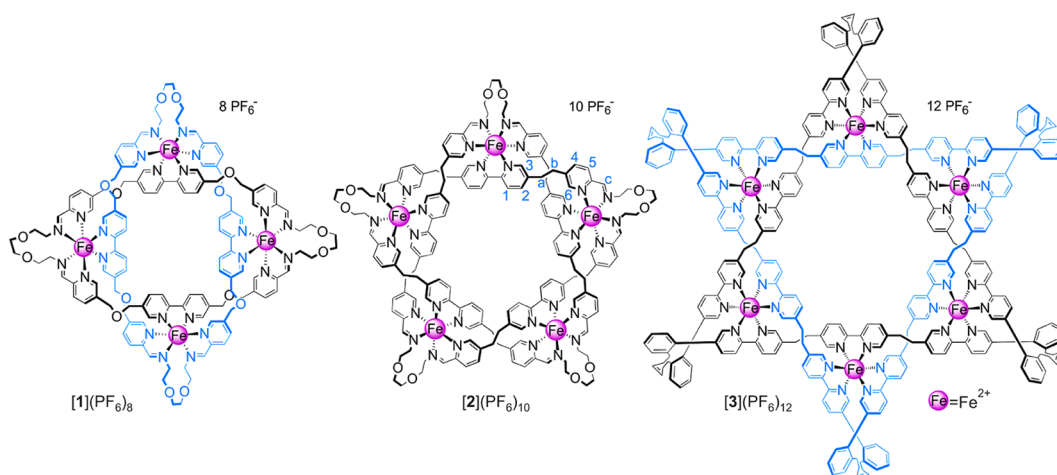


Figure 1. Chemical structures of Solomon link [2]catenane [1],⁴ pentafoil knot [2],⁵ and Star of David [2]catenane [3],⁷ shown as their PF_6^- salts.

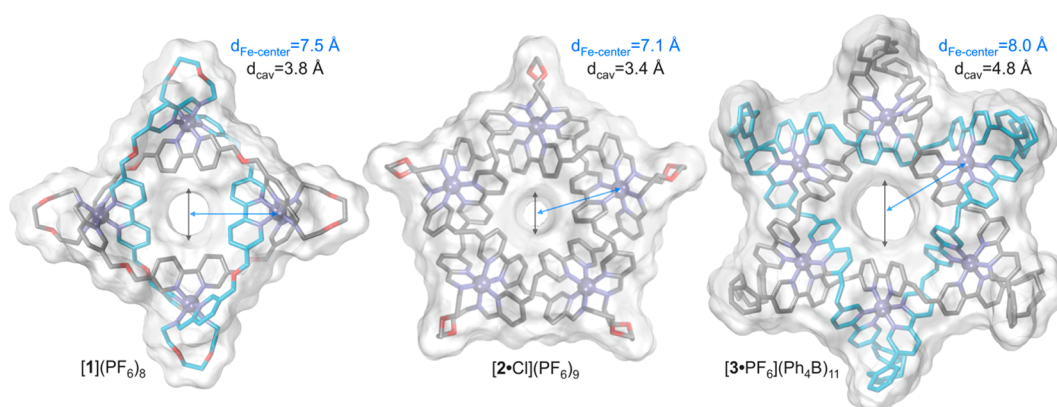


Figure 2. Single-crystal X-ray structures of Solomon link [1](PF_6)₈,⁴ pentafoil knot [2·Cl](PF_6)₉,⁵ and Star of David [2]catenane [3· PF_6](Ph_4B)₁₁.⁷ Solvent molecules, H-atoms, and counterions have been omitted for clarity. The solvent-accessible isosurface is shown as a semitransparent white surface. The distances between the centers of the inner binding pockets and the metal ions are shown by the blue double-headed arrows, and the diameters of the pockets (H¹ radius 1 Å, the typical value for hydrogen-bonding H-atoms⁹) are indicated by the black double-headed arrows.

anion, by a halide that binds within the central cavity, occurs in a very different binding strength regime to the exchange of the other PF_6^- counterions.

The strength of binding of each knot/link with iodide was sufficiently modest in acetonitrile that it could be measured by ¹H NMR titration experiments. In contrast, the affinity of the pentafoil knot for Cl^- or Br^- was so strong, even in acetonitrile, that it was determined by comparison with the affinity of AgPF_6 for the halide. The other binding constants were measured by competition experiments with a readily accessible calix[4]-bipyrrrole derivative for which (strong) halide binding constants had previously been determined (see SI).²³

The anion exchange experiments (Table 1) show that the links and knot each bind halide ions strongly in the central cavity in acetonitrile. The K_1 values given in Table 1 denote the preference for halide binding over PF_6^- association by the circular helicate and indicate that even the weakest halide host, Star of David catenane [3], binds I^- >10 000× stronger in the central cavity than it does PF_6^- . Pentafoil knot [2] binds a single Cl^- or Br^- ion with extremely high affinity (>10¹⁰ M^{-1}), 5 orders of magnitude stronger than I^- . To put this into context, 450 equiv²⁴ of AgPF_6 is required to remove all of the chloride ions from [2·Cl](PF_6)₉ in acetonitrile (see SI).²⁵ Unless in the presence of excess AgPF_6 , pentafoil knot [2](PF_6)₁₀ readily sequesters traces of Cl^- from its

environment, including solvents and glassware, re-forming [2·Cl](PF_6)₉.

Solomon link [1] also binds the two smaller halide anions strongly (Cl^- , $K_1 = (3.0 \pm 2.5) \times 10^8 \text{ M}^{-1}$; Br^- , $K_1 = (1.0 \pm 0.5) \times 10^7 \text{ M}^{-1}$), although notably weaker than the pentafoil knot. The Star of David [2]catenane [3] binds the first I^- ion exchanged for PF_6^- selectively within the catenane's central cavity ($K_1 = (1.2 \pm 0.1) \times 10^4 \text{ M}^{-1}$) in the manner observed for the smaller host molecules with each of the halides. However, unlike the other systems, a single PF_6^- anion is not exchanged for one Cl^- or Br^- ion preferentially before all of the others,²¹ nor are the Cl^- or Br^- ions bound exclusively within the central cavity (the resonances of several ligand protons, not just H¹, shift in the ¹H NMR spectrum). With each of the circular helicates, nonspherical anions did not show selective binding of solely a single exchanged anion.

The strength and binding preferences within the central cavities of the knot and links can be rationalized through consideration of the solid-state structures shown in Figure 2. The smallest cavity is actually that of the pentafoil knot [2], a circular pentameric helicate, which has a size ($d \approx 3.4 \text{ Å}$ at its narrowest) and hourglass cylindrical topography that allows the spherical Cl^- ($d = 3.6 \text{ Å}$ ²⁶) and Br^- ($d = 3.9 \text{ Å}$ ²⁶) anions to bind effectively to the inner ring of electron-poor H¹ protons. The Solomon link cavity is slightly larger ($d \approx 3.8 \text{ Å}$ at its narrowest) despite being based on a circular

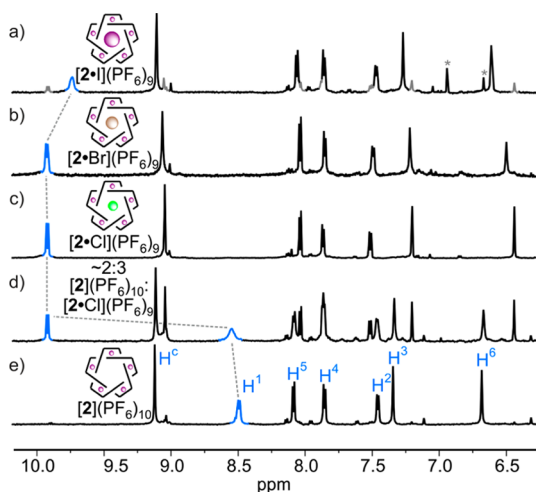
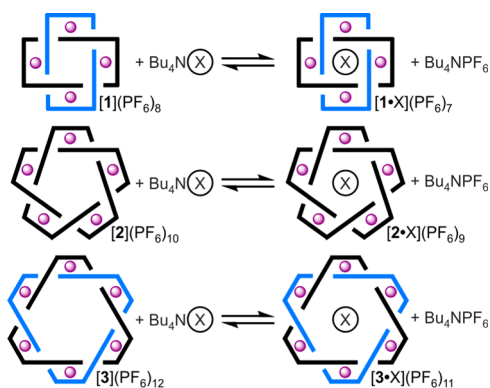


Figure 3. Partial ^1H NMR spectra (600 MHz, CD_3CN , 298 K) of the halide-complexed and “empty” 17 pentafoil knots: (a) iodide-complexed $[\mathbf{2}\cdot\text{I}](\text{PF}_6)_9$; (b) bromide-complexed $[\mathbf{2}\cdot\text{Br}](\text{PF}_6)_9$; (c) chloride-complexed $[\mathbf{2}\cdot\text{Cl}](\text{PF}_6)_9$; (d) $\sim 2:3$ mixture of $[\mathbf{2}](\text{PF}_6)_{10}$ and $[\mathbf{2}\cdot\text{Cl}](\text{PF}_6)_9$, showing that the bound halide is not in fast exchange; and (e) “empty” $[\mathbf{2}](\text{PF}_6)_{10}$. Note the large upfield shift in H^1 of $[\mathbf{2}](\text{PF}_6)_{10}$ compared to the other complexes in which H^1 is involved in $\text{CH}\cdots\text{X}^-$ hydrogen-bonding within the central cavity. The proton assignments correspond to those shown in Figure 1. The signals shown in gray are due to $[\mathbf{2}\cdot\text{Cl}](\text{PF}_6)_9$, formed during the experiment; * = impurity.

Scheme 1. Exchange of a Single PF_6^- Anion for a Halide (X^-) Anion in the Formation of $[\mathbf{1}\cdot\text{X}](\text{PF}_6)_7$, $[\mathbf{2}\cdot\text{X}](\text{PF}_6)_9$, and $[\mathbf{3}\cdot\text{X}](\text{PF}_6)_{11}$ from the Corresponding Knot or Link All- PF_6^- Salts with Tetrabutylammonium Halides (Bu_4NX , $\text{X}^- = \text{Cl}^-$, Br^- , or I^-) in Acetonitrile at 298 K



tetramer helicate, as a result of the ligand strand having extra O-atoms on either side of the bipyridine groups. The weaker halide affinity of the Solomon link is consistent with halide binding in the central cavity being based on 8 $\text{CH}\cdots\text{X}^-$ hydrogen bonds and slightly longer range ($\text{Fe}(\text{II})\cdots\text{X}^-$, 7.5 Å) electrostatic interactions with 4 $\text{Fe}(\text{II})$ ions, compared to 10 $\text{CH}\cdots\text{X}^-$ hydrogen bonds and 5 ($\text{Fe}(\text{II})\cdots\text{X}^-$, 7.1 Å) $\text{Fe}(\text{II})-\text{X}^-$ ion interactions in the pentafoil knot complexes.

The Star of David $[\mathbf{2}]$ catenane, based on a hexameric circular helicate, has a significantly larger diameter central cavity ($d \approx 4.8$ Å at its narrowest) than the other two host molecules studied. This is close to the diameter of an I^- anion ($d = 4.4$ Å 26), with which it forms a 1:1 complex (Table 1), but is too large for the other halide anions to be able to simultaneously form hydrogen bonds with all of the H^1 protons, which may account for why Cl^- and Br^- are not solely bound within the cavity.

Table 1. Equilibrium Constants (K_1 , M^{-1}) for the Exchange of One PF_6^- Anion for One Halide Anion for Complexes of Molecular Knot and Links $[\mathbf{1}]$, $[\mathbf{2}]$, and $[\mathbf{3}]$ (CD_3CN , 295 K) a

	Cl^- , $d = 3.6$ Å 26	Br^- , $d = 3.9$ Å 26	I^- , $d = 4.4$ Å 26
$[\mathbf{1}](\text{PF}_6)_8$	$(3.0 \pm 2.5) \times 10^8$ b,c	$(1.0 \pm 0.5) \times 10^7$ b,c	$(2.1 \pm 0.2) \times 10^5$ d
$[\mathbf{2}](\text{PF}_6)_{10}$	$(3.6 \pm 0.2) \times 10^{10}$ e	$(1.7 \pm 0.2) \times 10^{10}$ e	$(5.8 \pm 1.3) \times 10^5$ d
$[\mathbf{3}](\text{PF}_6)_{12}$	— f	— f	$(1.2 \pm 0.1) \times 10^4$ d

a Equilibrium constants are the average of several experiments (titrations or competition experiments). The errors given are intrinsic limits of the method or twice the standard deviation of the experimental data. b Determined by competitive binding against a calix[4]bipyrrrole derivative. 23 c Determined by competitive binding against $[\mathbf{2}](\text{PF}_6)_{10}$. d Determined by ^1H NMR titration. e Determined by competitive binding with AgPF_6 . f A single halide anion is not bound selectively within the central cavity. 21

In conclusion, molecular knots and links derived from circular metal double helicates of different sizes bind a single halide anion within their central cavities through multiple $\text{CH}\cdots\text{X}^-$ hydrogen bonds and long-range $\text{Fe}(\text{II})\cdots\text{X}^-$ electrostatic interactions. The size of the cavity and the number of hydrogen bonds and metal ions involved determine the strength and selectivity of halide binding. Pentafoil knot $[\mathbf{2}]$ is one of the strongest noncovalent binding synthetic hosts for Cl^- known, 27 with a chloride:hexafluorophosphate binding preference of $>10^{10}:1$ in acetonitrile and a chloride affinity comparable to that of silver salts.

The physical manifestation of knots and links at various length scales is increasingly being recognized in contexts as disparate as biopolymers, 28 colloidal clusters, 29 liquid crystals, 30 and soap films. 31 The exceptional strength and selectivity of the anion binding of $[\mathbf{1}]$, $[\mathbf{2}]$, and $[\mathbf{3}]$, and the fact that their binding pockets are topologically chiral, make metalated molecular knots and links an intriguing new class of host architectures for anion binding and recognition processes.

■ ASSOCIATED CONTENT

📄 Supporting Information

Synthesis, binding constant determinations, and NMR and MS data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06340.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Engineering and Physical Sciences Research Council (EPSRC) for funding, and the EPSRC National Mass Spectrometry Service Centre (Swansea, U.K.) for high-resolution mass spectrometry.

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(15) Salt metathesis of [2-Cl](PF₆)₉ with NH₄PF₆ does not exchange all of the Cl⁻ ions, even after exhaustive washings. It is necessary to first exchange all of the counterions of [2-Cl](PF₆)₉ for BF₄⁻ (with NH₄BF₄), forming [2](BF₄)₁₀, and then exchange the BF₄⁻ counterions for PF₆⁻ (with NH₄PF₆). This may be because the centrally bound Cl⁻ is less strongly held in an intermediate [2-Cl](BF₄)₉ complex.

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(17) The central cavities of the "empty" all-PF₆⁻ complexes of 1–3 are solvent and anion accessible (well-ordered PF₆⁻ anions are bound in the cavities of [1] and [3] in the X-ray crystal structures⁴⁷).

(18) H⁶ is in the shielding region of a pyridine ring (see Figure 2) and so is sensitive to minor structural changes in the circular helicates that occur upon binding.

(19) The slow kinetics of exchange of all of the halides (Figure 3), even relatively weakly bound I⁻, in complexes of the pentafoil knot, [2-X](PF₆)₉, suggests that the kinetic barrier to exchange may be due to slow release of a PF₆⁻ anion from [2](PF₆)₁₀ (a putative intermediate in the exchange process). The corresponding Solomon link and Star of David catenane complexes are all in fast exchange.

(20) In some solvents the halide–PF₆⁻ anion-exchange experiments significantly changed the solubility of the knot/link complexes. Acetonitrile proved to be a good solvent for comparing the binding constants across the range of different sizes of knots and links with each halide ion.

(21) The addition of Bu₄NCl or Bu₄NBr to [3](PF₆)₁₂ also produced ions corresponding to more than one halide-for-PF₆⁻ substitution.

(22) The bipyridyl CH protons on the outside of the circular helicates (H⁴ and H⁵) are also electron-poor as a result of metal coordination to the bipyridyl groups, and can also interact with anions. From the ¹H NMR spectra and by competition with calix[4]bipyrrole, these association constants are of the order ~10³ M⁻¹ (I⁻), ~10⁵ M⁻¹ (Br⁻), and ~10⁴ M⁻¹ (Cl⁻), typically several orders of magnitude less than halide binding associated with the central cavity of the knot or links.

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(25) The amount of AgPF₆ required to remove the chloride from [2-Cl](PF₆)₉ depends on the solubility product (K_{sp}) of AgCl in the solvent used. Only 1.2 equiv of AgPF₆ is required (1.4 × 10⁻⁴ M concentration of knot) in d₆-acetone (AgCl, log K_{sp} = -16.4) compared to 450 equiv of AgPF₆ in CD₃CN (AgCl, log K_{sp} = -12.4). AgCl solubility product values: Luehrs, D. C.; Iwamoto, R. T.; Kleinberg, J. *Inorg. Chem.* **1966**, *5*, 201.

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