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Enhancement of Anion Recognition Exhibited by a Halogen-Bonding Rotaxane Host System

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Abstract: We report the first use of solution-phase halogen bonding to control and facilitate the assembly of an interlocked structure through the bromide anion-templated formation of a rotaxane based upon an iodotriazolium axle. The incorporation of a halogen atom into the rotaxane host cavity dramatically improves the anion-recognition capabilities of the interlocked receptor, giving unusual iodide selectivity in a competitive aqueous medium.

Halogen bonds are formally noncovalent interactions formed between polarized halogen atoms functioning as electrophilic centers (Lewis acids) toward neutral or anionic Lewis bases. These attractive interactions arise from the terminal positive polarization of a covalently bonded halogen atom along the direction of the R−X bond, which concomitantly produces a perpendicular "belt" of negative electron density around the halogen.[1] The polarization effect is most prominent in the less electronegative halogens (Br and I) and is further enhanced by their covalent bonding to electron-withdrawing groups. Halogen bonds are largely underexploited in solution-phase supramolecular chemistry,[2] which is surprising given their analogy to ubiquitous hydrogen bonding[3] and their increasing manipulation in the crystal engineering of magnetic and conducting materials[4] and liquid-crystal phases.[5]

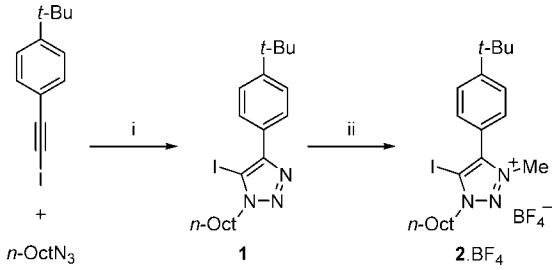
Inspired by the pervasive roles negatively charged species play in a range of chemical, biological, medical, and environmental processes, the design of host systems for anion-recognition applications is an ever-increasing field of research.[6] The plethora of positively charged and neutral acyclic and macrocyclic synthetic anion receptors reported to date utilize almost exclusively electrostatic, hydrogen-bonding, Lewis acid−base, and anion−π interactions for their efficacy of operation in polar organic and aqueous solvent media. In view of their stringent linear directionality and strength comparable to hydrogen bonds, it is surprising that the incorporation of halogen bonding into anion receptor design has remained largely dormant.[7]

We have exploited anion templation in the construction of three-dimensional interlocked anion host molecular frameworks that display a high degree of selectivity for the templating anion.[8] In a significant step forward for highlighting the potential importance of halogen bonding in anion supramolecular chemistry, herein we demonstrate the first use of solution-phase halogen bonding to control and facilitate the anion-templated assembly of an interlocked structure. Importantly, we then show that the incorporation of a halogen atom into the rotaxane host cavity dramatically improves the anion-recognition capabilities of the interlocked receptor.

We recently described the first example of the use of solution halogen bonding to facilitate the chloride anion-templated assembly of a 2-bromo-functionalized imidazolium-threading pseudorotaxane.[9] This discovery, together with recent advances in the preparation of 5-iodo-1,2,3-triazoles by a novel copper(I)-catalyzed azide−alkyne cycloaddition reaction,[10] prompted us to investigate the possibility of utilizing 5-iodo-1,2,3-triazolium groups for the anion-templated assembly of interpenetrated and interlocked systems.

The 5-iodo-1,2,3-triazole **1** was prepared from 1-*tert*-butyl-4-(iodoethynyl)benzene and 1-*n*-octylazide using a modified literature procedure with a copper(I)−tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)-methyl]amine (TBTA) catalyst.[10] Subsequent methylation of **1** with trimethyloxonium tetrafluoroborate gave **2**·BF_4 in high yield (Scheme 1).

Scheme 1. Synthesis of 5-Iodo-1,2,3-triazolium Tetrafluoroborate[a]



[a] Reagents, conditions and yields: (i) 5% CuI, 5% TBTA, THF, RT, N_2, 87%; (ii) $(Me_3O)BF_4$, CH_2Cl_2, RT, N_2, 94%.

Anion exchange of dichloromethane solutions of **2**·BF_4 with excess ammonium chloride, bromide, and iodide solutions provided the corresponding halide salts in quantitative yield. Crystals of **2**·Cl, **2**·Br, and **2**·I suitable for X-ray structural analysis[11] were obtained, and significant halogen bonding was observed in all three salts, as the distance between the iodine of the 5-iodo-1,2,3-triazolium motif and the halide anion is 79−84% of the sum of the van der Waals radii while the C−I···X^- angle is very close to the expected linear arrangement arising from the terminal polarization of the iodine atom. Full crystallographic details for the three structural determinations are given in the Supporting Information (SI).

Halogen-bond anion-templated pseudorotaxane assembly studies with **2**·X (X = Cl, Br, I, BF_4) and macrocycle **3** were undertaken by ^{1}H NMR titration experiments via the addition of increasing amounts of the 5-iodo-1,2,3-triazolium salt to a solution of the macrocycle in $CDCl_3$. Significant perturbations in the ^{1}H NMR spectra of **3** were observed upon the addition of each of the halide salts of **2**. Downfield shifts for the interior and exterior isophthala-

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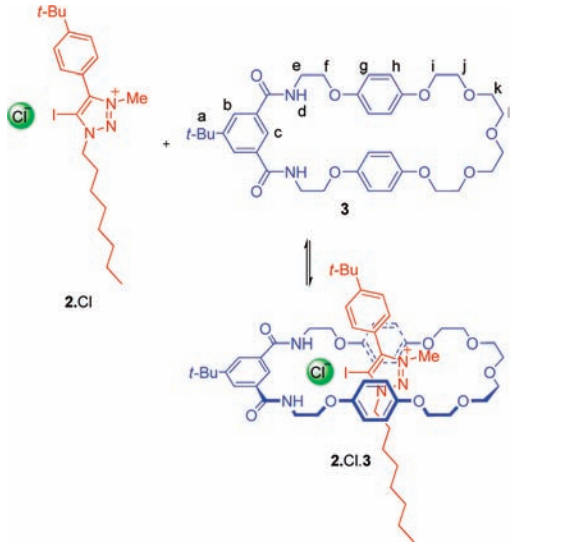
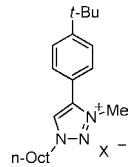
Scheme 2. Halogen-Bond Halide Anion-Templated Pseudorotaxane Formation



mide protons and the amide protons were observed, with simultaneous upfield shifting and splitting of the hydroquinone protons. The splitting and upfield shift of the hydroquinone protons is diagnostic of pseudorotaxane formation, as it corresponds to the interaction of the electron-deficient triazolium heterocycle with the electron-rich hydroquinone counterparts (Scheme 2). Pseudorotaxane assembly association constants (K_a) were calculated from monitoring of the exterior (b) and interior (c) isophthalamide resonances and the hydroquinone resonances (g and h) using WinEQNMR2[12] with 1:1 binding stoichiometry (Table 1 and the SI). The association constant values determined from the titration data for the interior isophthalamide (c) and upfield hydroquinone (h) resonances were in good agreement, importantly indicating that both the halide anion and the iodotriazolium thread are simultaneously bound by the macrocycle.

Table 1. Association Constants K_a for Pseudorotaxane Formation between Triazolium Salts and Macrocycle **3** in $CDCl_3$ at 293 K



4·X

ion pair	K_a (M^{-1})[a]
2·Cl	538(17)
2·Br	1188(93)
2·I	392(24)
2·BF_4	29(19)
4·Cl	490(38)
4·Br	610(31)
4·I	232(8)

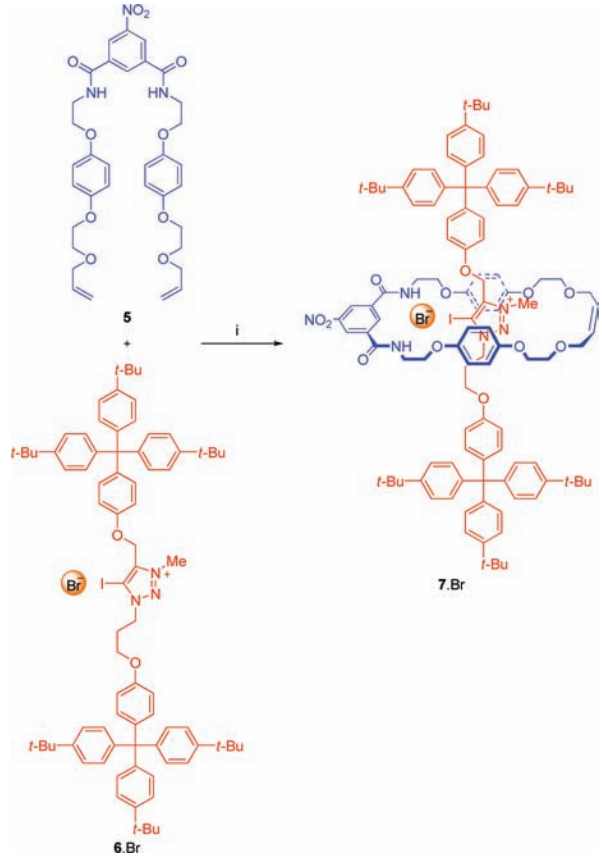
[a] Obtained from hydroquinone proton g. Errors in parentheses.

The iodotriazolium bromide thread **2**·Br forms the strongest pseudorotaxane assembly association, followed by the chloride and iodide salts. It is noteworthy that **2**·BF_4 exhibits a very weak association with macrocycle **3**, which serves to highlight the crucial importance of the iodine−halide halogen-bond templation mechanism for interpenetrative assembly. To contrast the efficacy of halogen bonding relative to hydrogen bonding for pseudorotaxane formation, the corresponding hydrogen-bonding threads **4**·X (X = Cl, Br, I) were prepared and investigated analogously to the threads **2**·X. Table 1 shows that the association constant values of the halogen-bonding ion pairs are significantly larger than their hydrogen-bonding counterparts. Interestingly, as observed with the iodo-functionalized triazolium systems, the most stable pseudorotaxane assembly is formed with the bromide salt **4**·Br.

Halogen-bonding templated threading was confirmed by ^{1}H NMR ROESY spectroscopy for a 1:1 mixture of **2**·Br and **3** in $CDCl_3$ (see the SI).

After it was established that iodotriazolium halide salts are capable of forming anion-templated interpenetrative assemblies, the synthesis of a halogen-bonding rotaxane was undertaken (Scheme 3).

Scheme 3. Synthesis of Rotaxane **7**·Br[a]



[a] Reagents and conditions: (i) 10 wt % Grubbs' II catalyst, CH_2Cl_2, RT, N_2.

Reaction of an equimolar mixture of bisvinyl-functionalized derivative **5** and iodotriazolium axle **6**·Br with Grubbs' II catalyst in CH_2Cl_2 solution followed by purification using preparative-plate thin-layer chromatography gave rotaxane **7**·Br in 15% yield. The isolated rotaxane was characterized by ^{1}H, ^{13}C{^{1}H}, and ^{1}H ROESY NMR spectroscopy and high-resolution electrospray ionization mass spectrometry (ESI-MS). Analysis of the ^{1}H NMR spectrum of **7**·Br revealed significant upfield shifts and splitting of the hydroquinone protons, diagnostic of the interaction of the electron-deficient iodotriazolium heterocycle of the axle with the electron-rich hydroquinone macrocycle counterparts. A significant downfield shift and broadening was observed for the interior isophthalamide ArH proton and the amide protons. ^{1}H ROESY NMR spectroscopy revealed a number of through-space cross-peaks between the axle and the macrocycle (see the SI). The pivotal importance of the

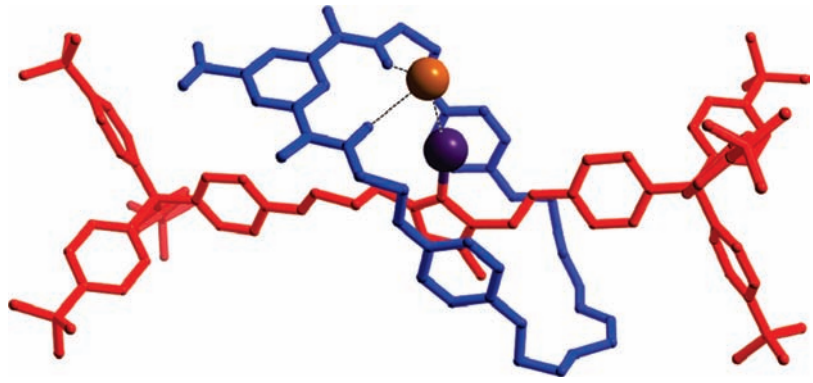


Figure 1. X-ray crystal structure of **7**·Br. Nonacidic hydrogens and minor components of disordered residues have been omitted for clarity.

bromide anion template to the rotaxane synthesis was further emphasized by the lack of ESI-MS or ^{1}H NMR evidence for the interlocked structure when the synthesis was repeated with **6**·BF_4.

Crystals of **7**·Br suitable for structural analysis were grown from toluene by a thermal-gradient method,[13] permitting the collection of diffraction data using synchrotron radiation (Figure 1). The structure unambiguously confirms the interlocked nature of the system and the vital role played by halogen-bonded anion templation in its assembly. The bromide anion is coordinated by both the triazolium iodine atom and the amide protons. The halogen bond is lengthened slightly [3.127(4) vs 3.0927(4) Å] and bent [165.07(15) vs 177.74(9)°] relative to the iodotriazolium bromide salt **2**·Br, an effect due to competitive hydrogen bonding with the bromide anion. The assembly is further stabilized by charge-assisted $\pi-\pi$ stacking and secondary hydrogen bonding between the triazolium methyl group and the polyether chain of the macrocycle.

Repeated washings with aqueous NH_4PF_6 removed the bromide anion template to give rotaxane **7**·PF_6. Preliminary ^{1}H NMR bromide anion titration experiments with **7**·PF_6 in 1:1 $CDCl_3$/CD_3OD gave a WinEQNMR2-determined association constant of $>10^4$ M^{-1}, which is remarkably at least an order of magnitude larger than that for the hydrogen-bonded triazolium rotaxane analogue (K_a = 970 M^{-1}).[14] Analogous halide anion titration experiments of **7**·PF_6 in 45:45:10 $CDCl_3$/CD_3OD/D_2O using tetrabutylammonium salts provided further evidence of the superior anion-recognition capabilities of this halogen-bonding rotaxane host system. Bromide and iodide are both bound strongly by **7**·PF_6 in this competitive aqueous solvent mixture, with a selectivity preference for the larger halide anion (Table 2), in contrast to the protic triazolium analogue, which was bromide-selective.[14] This preference for iodide may be attributed to the accessibility of the binding site to larger anions (Figure 1) and weaker competition for the more lipophilic halide by the aqueous solvent medium.

Table 2. Association Constants K_a for Anion Binding by Rotaxane **7** in 45:45:10 $CDCl_3$/CD_3OD/D_2O at 293 K

anion	K_a (M^{-1})[a]
Cl^-	457(4)
Br^-	1251(10)
I^-	2228(171)

[a] Obtained from exterior isophthalamide proton b using tetrabutylammonium salts. Errors in parentheses.

In summary, we have demonstrated the utility of the halogen-bonding 5-iodo-1,2,3-triazolium group for the halide anion-templated formation of interpenetrated assemblies and the bromide anion-templated synthesis of the first halogen-bonding interlocked host system. Anion-binding investigations revealed that the iodine halogen-bond donation by the iodotriazolium axle significantly enhances the rotaxane's anion-recognition properties in comparison with the hydrogen-bonding analogue, providing unusual selectivity for iodide. The fabrication of halogen-bond donor motifs into molecular and interlocked anion host structural design is continuing in our laboratories.

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Supporting Information Available: Full details of syntheses and characterization, ^{1}H NMR binding studies, and crystallography (including CIFs). This material is available free of charge via the Internet at http://pubs.acs.org.

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