Anion Templation

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Exploiting the 1,2,3-Triazolium Motif in Anion-Templated Formation of a Bromide-Selective Rotaxane Host Assembly**

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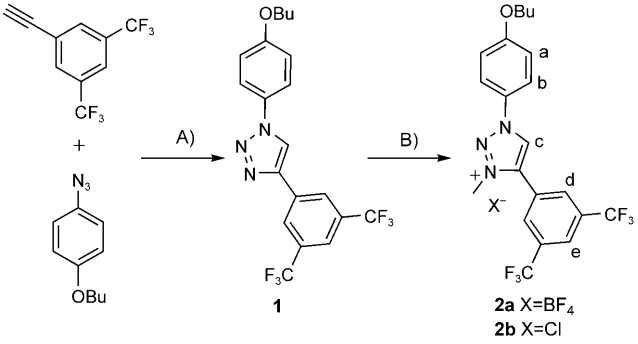
Stimulated by the efficacy of copper(I) catalyzed Huisgen-type 1,3-dipolar cycloaddition of terminal alkynes and organic azides to generate 1,4-disubstituted 1,2,3-triazole derivatives, the importance of "click" chemistry in the synthesis of organic and biological molecular systems is ever increasing.[1] The mild reaction conditions have also led to this reaction gaining favor in the construction of interlocked molecular architectures.[2–4] In the majority of cases however, the triazole group simply serves as a covalent linkage with no function in the resulting organic molecular framework. More recently a renewed interest has emerged in the transition-metal coordination chemistry of triazole ligands.[3,5,6] In addition, novel aryl macrocyclic and acyclic triazole based oligomers have been shown to recognize halide anions through cooperative triazole C^5–H···anion hydrogen bonds.[7] In light of this, it is surprising that the potential anion-binding affinity of the positively charged triazolium motif has not, with one notable exception,[8] been investigated. With the objective of manipulating the unique topological cavities of mechanically bonded molecules for anion recognition purposes, we have developed general methods of using anions to template the formation of interpenetrated and interlocked structures.[9–13] Herein we report the first examples of exploiting the 1,2,3-triazolium group in the anion templated formation of pseudorotaxane and rotaxane assemblies. In an unprecedented discovery, the bromide anion is shown to be a superior templating reagent to chloride in the synthesis of a novel [2]rotaxane incorporating a triazolium axle. Furthermore, the resulting rotaxane interlocked host system exhibits the rare selectivity preference for bromide over chloride.

To assess the anion binding properties of simple acyclic triazole and triazolium thread derivatives, the triazole compound **1** was synthesized, by utilizing a modified literature procedure (Scheme 1).[5] Subsequent alkylation of **1** with trimethyloxonium tetrafluoroborate afforded the triazolium receptor **2a** in quantitative yield.

^{1}H NMR titration experiments in [D_6]acetone were initially undertaken to assess the binding of chloride to **1** and **2a**.



Scheme 1. Synthesis of simple triazole and triazolium threads for anion-binding studies. Reagents and conditions: A) $CuSO_4$, sodium ascorbate, tris(benzyltriazolylmethyl)amine (TBTA), MeOH, *t*BuOH, H_2O, 24 h, 50 °C, N_2, 91 %; B) $(Me_3O)^+(BF_4)^-$, dry CH_2Cl_2, N_2, 2 days, room temperature, 82 %.

No significant changes occurred in the ^{1}H NMR spectra upon addition of tetrabutylammonium (TBA) chloride to a solution of triazole derivative **1**, indicating no anion binding. However, for **2a**, addition of chloride resulted in significant downfield shifts in the triazolium CH proton c, and the aromatic protons d and b indicating strong anion binding in the triazolium CH cleft of the molecule (Figure 1). Analogous titration experiments were carried out using Br^-, I^-, and $H_2PO_4^-$, and the respective 1:1 stoichiometric association constants were calculated using WinEQNMR[14] (Table 1 and Figure S1 in the Supporting Information). Chloride and bromide bound strongly to the triazolium derivative, with iodide and dihydrogen phosphate displaying more modest binding strengths.[15]

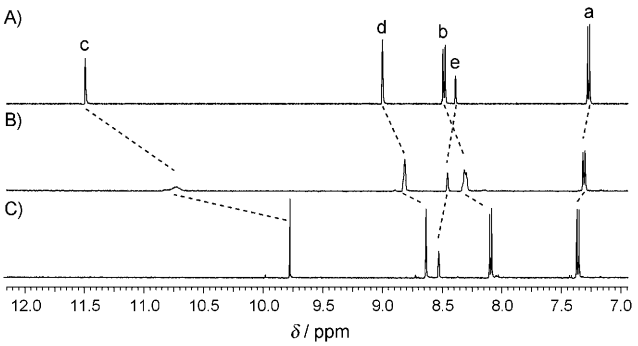


Figure 1. ^{1}H NMR spectra for solutions in [D_6]acetone: A) triazolium receptor **2a** plus 10 equivalents of TBACl; B) triazolium receptor **2a** plus 1 equivalent of TBACl; C) triazolium receptor **2a**.

X-ray structural analysis of crystals obtained by slow diffusion of diisopropyl ether into a 1:10 solution of **2a** and

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Table 1: Association constants K_a for the binding of various anions to triazolium receptor **2a** in [D_6]acetone at 293 K.

Anion	K_a [M^{-1}][a]
Cl^-	1120
Br^-	1060
$H_2PO_4^-$	270
I^-	105

[a] Errors < 15 %.

TBACl in acetone confirms 1:1 stoichiometric binding of chloride to the receptor in the solid state. The halide anion is situated within a cleft of the receptor stabilized by a hydrogen bond (2.37 Å) with the triazolium proton and slightly longer contacts with nearby phenyl protons on either side (2.85 Å and 2.74 Å). There is also contact with a methyl hydrogen on the opposite side of an adjacent molecule (2.59 Å), thus forming an infinite chloride-linked chain structure (Figure 2).

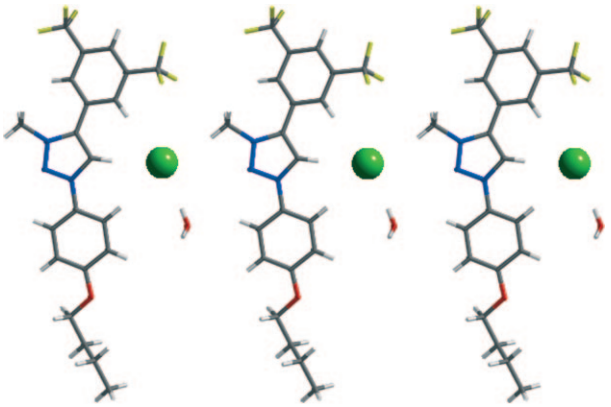
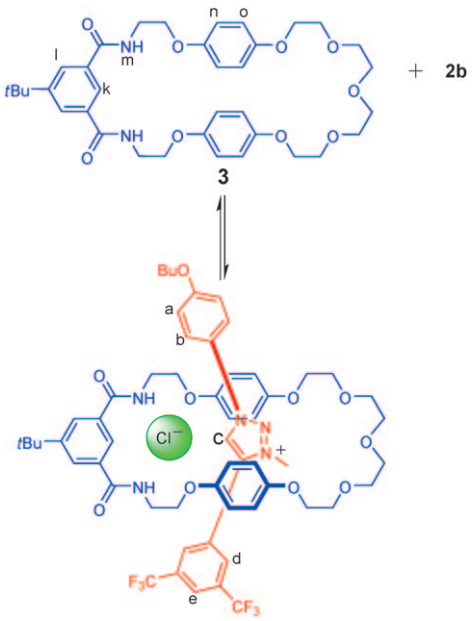


Figure 2. X-ray crystal structure of triazolium thread **2a** plus TBACl. Disorder in CF_3 groups omitted for clarity.

We have previously demonstrated the use of chloride and sulfate anions to template the formation of a range of pseudorotaxanes, rotaxanes and catenanes.[10–13] Encouraged by the fact that the triazolium motif of receptor **2a** associated strongly with chloride (Table 1), it was envisioned that pseudorotaxane formation with isophthalamide macrocycle **3**[12] could be facilitated by chloride anion templation.

Initial evidence of pseudorotaxane formation came from the changes in chemical shift in the ^{1}H NMR spectrum of **3** and the chloride anion ion pair triazolium compound **2b** in an equimolar mixture in [D_6]acetone (Scheme 2, Figure 3). Large downfield shifts in the macrocycle amide protons m ($\Delta\delta = 0.94$ ppm), and isophthalamide protons k ($\Delta\delta = 1.06$ ppm) were observed, indicating complexation of chloride to the macrocycle. Importantly, upfield shifts of the triazolium CH proton c and aromatic protons d and a were observed due to a combination of favorable donor–acceptor π–π stacking interactions between the positively charged triazolium thread and the electron-rich hydroquinone aromatic groups of the macrocycle, and polarization of the chloride anion towards the amide hydrogen-bond donors of the macrocycle. Significant upfield shifts of the macrocycle hydroquinone protons n and o ($\Delta\delta = 0.39$ and 0.41 ppm, respectively) owing to π–π stacking interactions between the thread and macrocycle were also observed.



Scheme 2. Anion-templated pseudorotaxane formation between the isophthalamide macrocycle and triazolium thread.

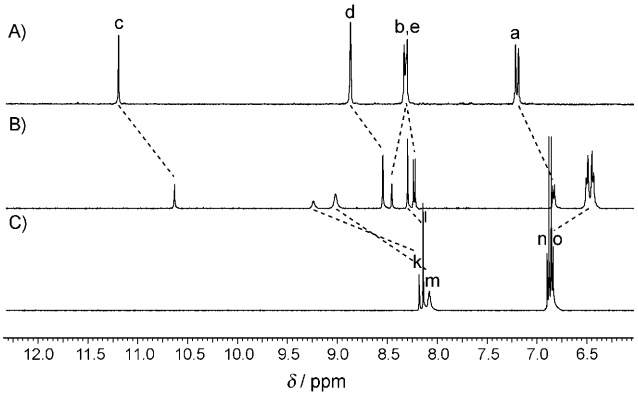


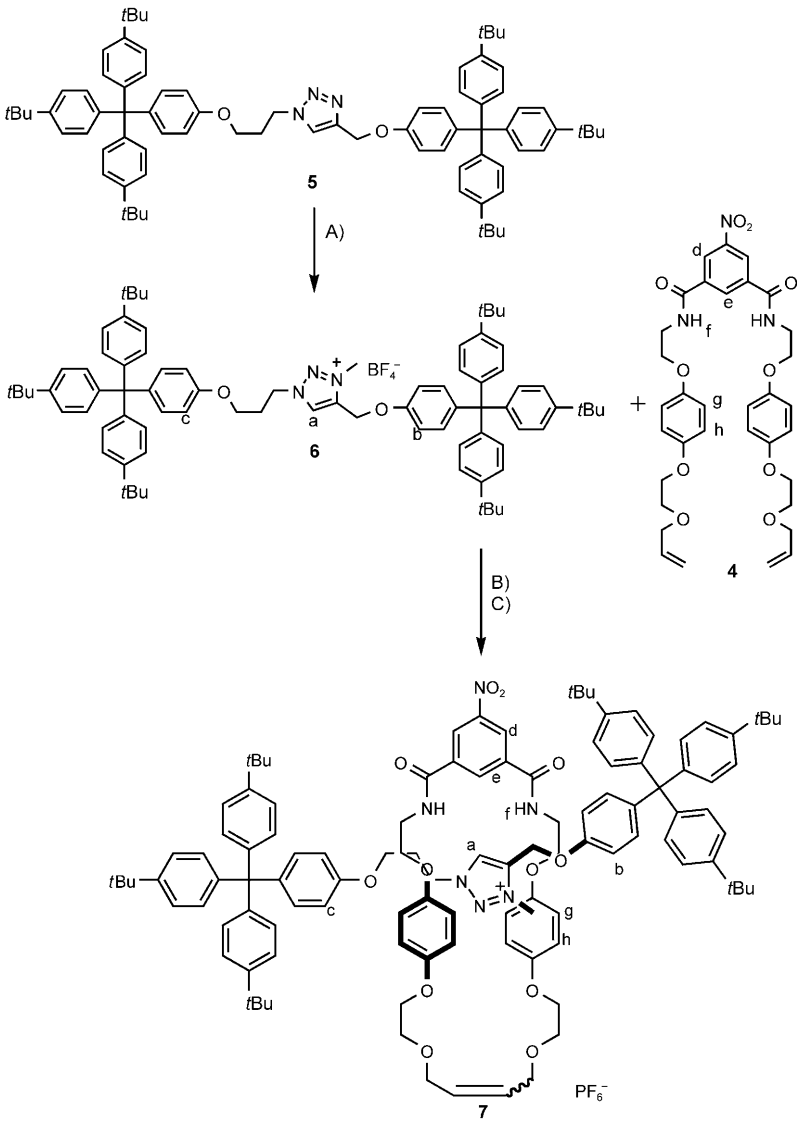
Figure 3. ^{1}H NMR spectra for solutions in [D_6]acetone: A) triazolium receptor **2b**; B) triazolium receptor **2b** plus 1 equivalent of macrocycle **3**; C) macrocycle **3**.

Further evidence of pseudorotaxane formation was provided by the ROESY spectrum of a 1:1:1 mixture of macrocycle **3**, triazolium thread **2a**, and TBACl in [D_6]acetone. Through-space interactions between the hydroquinone protons and the triazolium CH proton c, and the aromatic protons b and d were detected, suggesting that the triazolium thread interpenetrates through the annulus of the macrocycle in the presence of chloride (see the Supporting Information, Figure S3).

Similar perturbations of chemical shifts were detected when TBABr was added to an equimolar mixture of **2a** and macrocycle **3** in [D_6]acetone indicating that pseudorotaxane formation was possible using Br^- as a template. Notably, no evidence of pseudorotaxane formation was detected with an

equimolar solution of **2a** and macrocycle **3** in [D_6]acetone alone, or in the presence of TBAI, or $TBAH_2PO_4$, which highlights the importance of complementary size and shape of potential templating anions in the pseudorotaxane assembly process.

Having demonstrated chloride anion templated pseudorotaxane formation, an attempt to synthesize the first triazolium rotaxane by ring-closing metathesis (RCM) clipping of a bis-vinyl appended acyclic precursor around a stoppered triazolium axle in the presence of a chloride anion template, mediated by Grubbs′ catalyst, was undertaken. Alkylation of the stoppered triazole axle **5**[4] with trimethyloxonium tetrafluoroborate afforded **6** in quantitative yield. The rotaxanation reaction was undertaken by the addition of Grubbs' second-generation RCM catalyst to a solution of **4**,[13] **6**, and one equivalent of TBA chloride in dichloromethane at room temperature (Scheme 3).



Scheme 3. Synthesis of a triazolium [2]rotaxane. Reagents and conditions: A) $(Me_3O)^+(BF_4)^-$, dry CH_2Cl_2, N_2, 2 days, room temperature, 61%; B) TBACl, Grubbs' second generation catalyst, dry CH_2Cl_2, 3 days, room temperature, N_2; C) 0.1 M NH_4PF_6(aq), 21%.

The desired [2]rotaxane $\mathbf{7}^+Cl^-$ was obtained following purification by preparative silica thin layer chromatography. Removal of the chloride anion template from the [2]rotaxane cavity was achieved by repeated washings with aqueous NH_4PF_6 to give rotaxane $\mathbf{7}^+(PF_6)^-$ in an overall 21% yield, characterized by ^{13}C and ^1H NMR spectroscopy and ESI mass spectrometry ($[M]^+$: m/z 1766.8600). The partial ^1H NMR spectrum of $\mathbf{7}^+(PF_6)^-$ in [D_6]acetone is displayed in Figure 4.

As noted in the pseudorotaxane studies, the hydroquinone protons of the rotaxane were shifted upfield significantly relative to the macrocycle, owing to favorable π-π stacking interactions between the triazolium axle and the macrocycle. Likewise the triazolium CH proton a displayed upfield shifts from $\delta = 9.12$ ppm in the triazolium axle alone to $\delta =$ 8.85 ppm in the rotaxane.

^1H NMR anion titration studies of rotaxane $\mathbf{7}^+(PF_6)^-$ were undertaken initially in [D_6]acetone. The triazolium CH proton a, the macrocycle isophthalamide proton e and NH proton f were shifted significantly downfield upon addition of chloride (Figure 4). WinEQNMR[14] analysis of the titration data gave an association constant of greater than $10^4\,M^{-1}$ for the binding of chloride to the rotaxane $\mathbf{7}^+(PF_6)^-$, which is significantly higher than that calculated for the triazolium axle **6** ($K_a = 880\,M^{-1}$), confirming that the strength of anion binding is enhanced greatly owing to the cooperative binding effects of both the triazolium axle and isophthalamide macrocycle within the unique highly preorganized three-dimensional cavity afforded by the rotaxane interlocked host structure.

Preliminary chloride and bromide anion-titration experiments with rotaxane $\mathbf{7}^+(PF_6)^-$ were also undertaken in the more competitive 1:1 $CDCl_3$/MeOD solvent mixture, and the respective association constants were calculated using WinEQNMR.[14] The rotaxane complexed bromide ($K_a = 970\,M^{-1}$) approximately an order of magnitude more strongly than chloride ($K_a = 90\,M^{-1}$), which is surprising as isophthalamide macrocycle–pyridinium axle rotaxane host systems are known to selectively bind chloride in the same mixed solvent system.[10,12,13,16]

The rotaxane synthesis was then repeated using bromide as the templating anion. As was predicted, given the stronger binding affinity the rotaxane exhibits towards bromide, the yield of rotaxane isolated as $\mathbf{7}^+(PF_6)^-$ increased significantly, from 21 to 31% overall yield. These results suggest the unique interlocked triazolium axle and isophthalamide macrocycle hydrogen bonding cavity of rotaxane $\mathbf{7}^+(PF_6)^-$ is of a more complementary size and shape match for the larger bromide anion guest species.

In summary, we have shown that the ubiquitous click triazole forming reaction can

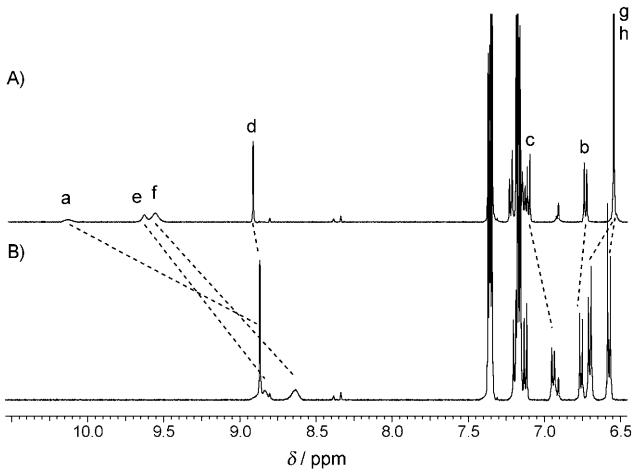


Figure 4. ^{1}H NMR spectra for solutions in [D_6]acetone: A) triazolium [2]rotaxane $\mathbf{7}^+(PF_6)^-$ plus 1 equivalent of TBACl; B) triazolium [2]rotaxane $\mathbf{7}^+(PF_6)^-$.

be used not only as a covalent linker in the preparation of interlocked architectures, but can be further transformed into a new class of potent triazolium anion receptors by alkylation. In the presence of chloride and bromide templating anions, the triazolium motif formed pseudorotaxanes with a neutral isophthalamide macrocycle, and this interaction was utilized in the preparation of the first triazolium-based [2]rotaxane. Preliminary anion binding studies revealed that this rotaxane host system exhibits the rare selectivity preference for bromide over chloride,[17] with the larger halide anion also proving to be a more efficient templating reagent for the rotaxane synthesis.

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