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Synthesis and Investigation of Host-[2]Rotaxanes That Bind Metal Cations

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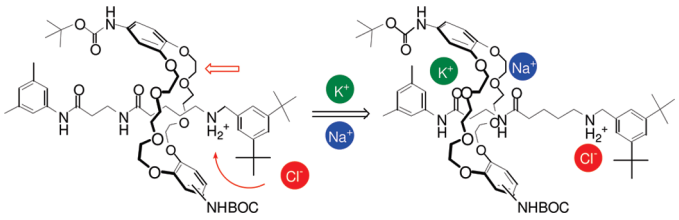

Materials that bind metal cations are highly sought after for new devices. In this report, we show that rotaxanes can transfer metal cations with picrate, perchlorate, or chloride counterions from an aqueous solution into chloroform. The rotaxanes contain a dibenzyl-24-crown-8 ether as the wheel with either a benzyl-18-crown-6 ether (CEBG-R1−3) or a 3,5-dimethylbenzyl moiety (ArBG-R) as one blocking group. Alkali and alkaline picrate salts were efficiently extracted from an aqueous solution, presented in the millimolar range, into chloroform. Large association constants were derived for the complexes in chloroform, especially for the divalent cation Mg^{2+}. Switching the counterion to chloride greatly diminished the amount of salt extracted. To explore the transfer mechanism of the rotaxanes, a comparison was made in the amount of $NaClO_4$, $KClO_4$, NaCl, and KCl extracted by CEBG-R1, ArBG-R, benzyl-18-crown-6 ether (B18C6), and two model compounds, which were used to represent the crown-ether blocking group and the axle of a rotaxane. Two-dimensional NMR analysis was performed on the rotaxane−cation complexes in $CDCl_3$. We found that the host rotaxanes transfer the perchlorate salts poorly when compared to B18C6, but they transfer chloride salts from 1 M salt solutions, whereas B18C6 does not. The transfer of chloride salts appears to rely on an allosteric type relationship between the binding of the chloride ion and metal cation to a rotaxane. Accordingly, when chloride binds to the dialkylammonium ion of the axle, the wheel moves along the axle and forms a binding site for a metal cation. In this report we demonstrate that host rotaxanes can bind metal cations, change their geometries upon cation and anion association, and operate through allosteric mechanisms, making them promising candidates for molecular devices.

Introduction

New industrial and medical applications, such as artificial enzymes or sensors, could arise with the creation of materials that house metal cations in chemically active pockets.[1−5] One of the many challenges in designing such hosts is to arrange the functional groups in the correct spatial arrangement to bind a metal cation, ostensibly by pointing their dipole moments toward the complexation site.[6] Proteins use a complex arrangement of side chains to efficiently extract (i.e., low concentration of the host and salt) metal cations out of aqueous solutions, making them useful model systems to

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design hosts. Alkaline cations, e.g., Ca^{2+} and Mg^{2+}, are generally bound within pockets composed of essentially two domains. An inner shell contains carboxylates of several Asp or Glu residues that coordinate with a cation. Mg^{2+} also binds at least one water molecule.[7,8] The outer shell is composed of hydrophobic side chains.[9] Alkali cations (Na^+ and K^+), on the other hand, tend to reside at protein surfaces and bind to the oxygen atoms of carbonyl amides.[10] Coordination sites for Li^+ are similar to the sites for Mg^{2+}.[11] To construct protein mimetics that bind cations, crown ethers appear to be an ideal building block. Crown ethers come in a variety of sizes. To specifically bind or extract a metal cation, a crown ether is chosen by simply matching its volume to the size of the metal cation.[12−14] Extensive investigations by Bartsch showed that the ability of crown ethers to selectively extract metal cations can be improved by derivatizing them with functional groups (e.g., carboxylic acids, phosphonic acid monoesters, carboxamides, and carboxylic esters) that provide additional favorable interactions with a cation.[15−20] Another option is to combine crown ethers with other synthetic hosts, such as calixarenes.[21]

Mechanically interlocked molecules, such as catenanes and rotaxanes,[22−27] are likely candidates to enhance the binding properties of crown ethers and, for this study, to make them more protein-like. Their components are commonly assembled around metal cations or dialkylammonium ions, and many contain crown ethers. Rotaxanes comprise a linear molecule (axle) threaded through a circular molecule (wheel) with bulky molecules (blocking groups) on the ends of the axle to keep the wheel threaded. The nature of the wheel is one advantage the rotaxanes has over other hosts. It can slide along the axle in response to internal cation production or external cation presentation to give a host−guest

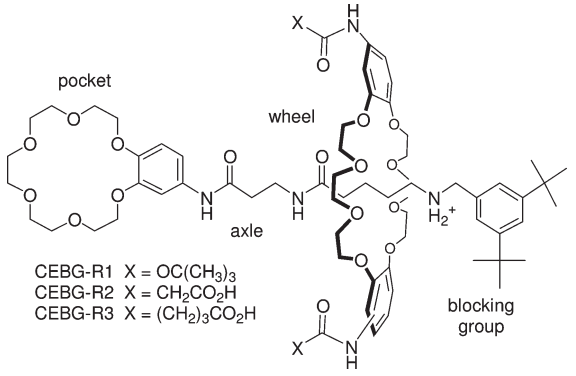

FIGURE 1. Host-rotaxanes that were constructed to bind and transport metal cations.

complex. For example, Li recently reported on an impressive rotaxane sensor that operates in response to the binding of Li^+ and Zn^{2+}.[28] Other recent applications include a bipyridine based rotaxane[29] whose ^1H NMR spectrum is highly sensitive to the presence of Li^+, Na^+, K^+, Mg^{2+}, and Ca^{2+} and molecular switches that operate through changes in the position of the wheel caused by the association of an alkali cation to an oligo(ethylene glycol) axle[30] or Zn^{2+} binding to a pyridine containing axle.[31] In a similar manner to the latter study, Chiu demonstrated a switch of PF_6^- counterion to Cl^- resulted in the wheel being repositioned on the axle though tight ionic bond formation to the dialkylammonium ion of the axle.[32]

Our research group initially created host rotaxanes to bind aromatic guests and deliver materials into cells.[33−36] Host-rotaxanes are rotaxanes with at least one blocking group being a pocket for guest recognition (Figure 1).[37,38] Additional groups for guest binding are attached to the wheel. These groups can assemble with the pocket to envelop a guest in a manner similar to protein pockets. Since the components of the binding site are split between the pocket and the wheel and the wheel can pirouette and slide along the axle, the structure of the pocket can readily change.[36] This is advantageous for strong guest association since the pocket can adjust its geometry to maximize the binding free energy. Additionally, rotaxanes can undergo the structural changes required for protein-like functions and the workings of future devices. These new materials not only may become new devices with a wide range of applications but could

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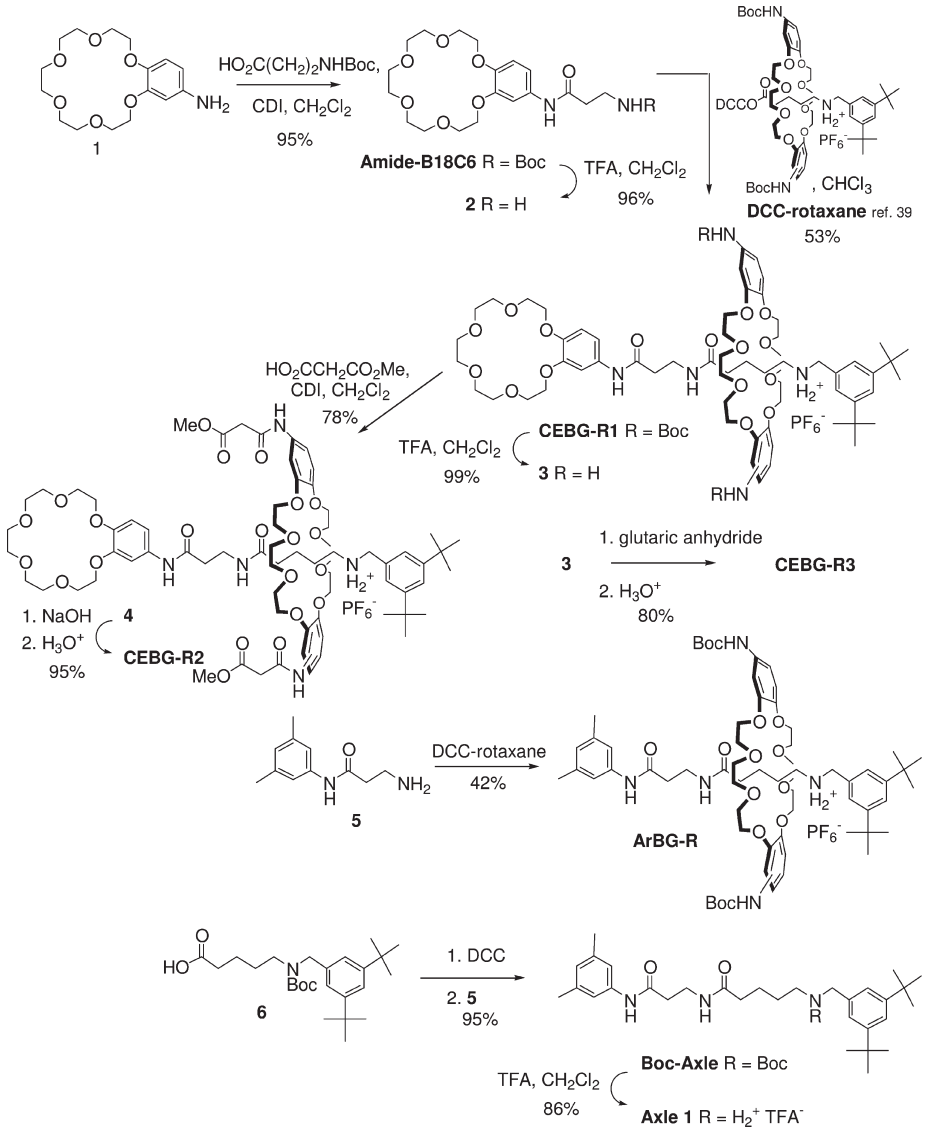
SCHEME 1



potentially operate within cells. In this report, we describe the synthesis and properties of the first host-rotaxanes designed to bind metal cations.

Results

Design and Synthesis of the Rotaxanes. As discussed previously, protein pockets that house metal cations contain hydrophilic and hydrophobic domains. These first generation rotaxanes were designed to mimic the inner shell. A $CHCl_3$ solution was used to represent the hydrophobic shell. Benzyl-18-crown-6 (B18C6) ether was chosen for the preformed recognition pocket and attached to the rotaxanes as a blocking group. It binds alkali cations, with K^+ being its preferred guest. Carbonyl or carboxylic acid moieties were attached to the wheel to bind the exposed portion of alkaline and alkali cations, respectively, when housed within the crown ether blocking group. The crown ether-blocking group-rotaxanes (CEBG-Rs) and aromatic ring-blocking group-rotaxane (ArBG-R) were readily synthesized using methods previously developed for the construction of host-rotaxanes (Scheme 1).[37,39] For the host-[2]rotaxanes, their synthesis began with the known amino-benzyl-18-crown-6-ether **1**.[40] Boc-β-alanine was linked to the crown ether to provide an attachment site for the DCC-rotaxane,[39] once it was deprotected. The DCC-rotaxane contains a Boc-protected diamino-B24C8 ether as the wheel. CEBG-R1 was deprotected, and the wheel was derivatized with monomethylmalonate to give CEBG-R2 (once the ester was hydrolyzed) or with glutaric anhydride to give CEBG-R3.

Although rotaxane synthesis is facilitated by the readily formed amide bonds and the attraction between the oxygen atoms of the wheel and the dialkylammonium ion of the axle, the presence of these functional groups could provide for more than one binding site for a metal cation. Metal cations could bind to the B18C6-blocking group or one or more of the carbonyl oxygen atoms. Because dibenzyl-24-crown-8 ether (DB24C8) can complex two Na^+ or two K^+,[41,42] the

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wheel could be a binding site for a metal cation as well, even though it is threaded onto the axle, which contains a dialkylammonium ion. Another possibility is that the wheel could be positioned near the B18C6-blocking group, creating a single binding pocket composed of two crown ethers. To help elucidate the coordination sites, model compounds were constructed and investigated as well (Scheme 1). Amide-B18C6 contains the crown ether pocket and the two amide moieties of the axle. It serves as a model for the portion of the axle attached to the B18C6-blocking group. ArBG-R contains the axle and wheel of the CEBG-R1, but not the B18C6-blocking group. Instead it has a 3,5-dimethylbenzenoid ring as one blocking group. Axle-1 was investigated to determine the ability of the axle's amides to bind metal cations. ArBG-R was readily synthesized by coupling the DCC-rotaxane with the commercially available 3-amino-*N*-(3,5-dimethylphenyl)propanamide **5**. The coupling of **5** with the Boc-protected axle **6** gave Axle-1 after deprotection. We postulated that the investigation of a potential binding pocket—isolated and in combinations—would lead to the identification of the coordinating site and the functional groups necessary to strongly and selectively bind metal cations.

Association Constants Obtained from Extraction Assays. Two-phase extraction assays (ions(aq)/$CHCl_3$) were performed to obtain transfer efficiencies and a measure of the binding affinities.[43] Extraction constants (K_e) were determined from the known concentration of the components and the concentration of picrate ion extracted into the $CHCl_3$ (chl) layer by a host, which is measured using UV−vis absorption spectroscopic analysis. The distribution constants (K_d) were taken from the literature.[40,44] Association constants for the binding of the metal cation by a host in $CHCl_3$ are the ratio of K_e/K_d. The percentage of metal cation extraction (%T) is equal to the ratio of the concentration of the picrate ion in the chloroform layer versus the total amount of picrate ion measured in the chloroform and aqueous layers. We found that all hosts used in this study existed predominantly in the $CHCl_3$ layer (>93%). Since the concentration of the host is approximately 30-fold greater than the concentration of the metal cation, the complexes are likely in a 1:1 ratio of host to guest. Additionally, the amount of picrate ion extracted in $CHCl_3$ by the hosts, which was determined through UV−vis analysis, was compared to the amount of Na^+ and K^+ extracted as determined through atomic absorption analysis (see below). Plotting the concentrations in $CHCl_3$ of Pic^- versus the alkali cations produced a correlation coefficient of 0.94. The amount of Mg^{2+} and picrate extracted by the rotaxanes was found to be in a 1:2 ratio. These findings are consistent with a 1:1 ratio of a host to a picrate salt in the $CHCl_3$ layer and a picrate salt being extracted instead of counterion exchange occurring between Pic^- and TFA^-.

$$K_e = [\text{Host}\cdot M^{n+}\cdot n\text{Pic}^-]_{chl}/[\text{Host}]_{chl}[M^{n+}]_{aq}[\text{Pic}^-]^n_{aq}$$

$$K_d = [M^{n+}\cdot n\text{Pic}^-]_{chl}/[M^{n+}]_{aq}[\text{Pic}^-]^n_{aq}$$

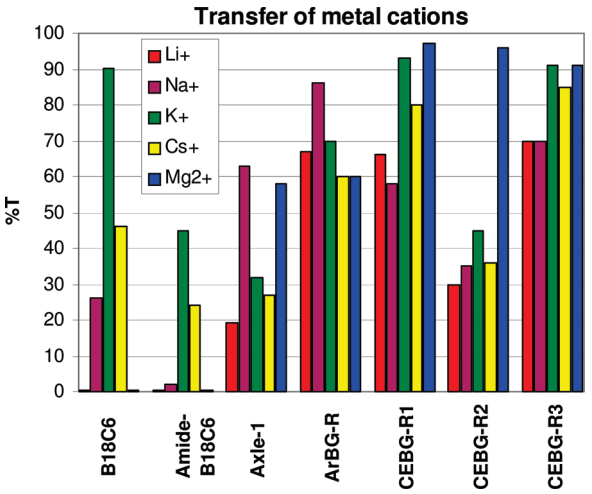

FIGURE 2. Percent of picrate ion in $CHCl_3$ versus the total concentration of picrate ion after extraction from an aqueous phase into $CHCl_3$ by a host (uncertainty %T ≤ 10%). Experimental conditions are given in Table 1 and %T values are given in Supporting Information.

TABLE 1. Association Constants ($K_a \times 10^{-6}$, M^{-1}) for Host−Metal Cation Complexes in $CHCl_3$ As Derived from Extraction Experiments of Metal Cation Picrate Salts (% Transfer Values Shown in Figure 2)[a]

	Li^+	Na^+	K^+	Cs^+	Mg^{2+}
B18C6	ND[b]	2.0	35	1.6	ND
Amide-B18C6	ND	0.12	3.2	0.58	ND
Axle-1	1.6	9.8	1.8	0.68	7.9×10^3
ArBG-R	14	35	9.1	2.8	9.0×10^3
CEBG-R1	14	7.9	52	7.4	2.6×10^6
CEBG-R2	3.0	3.1	3.2	1.0	1.4×10^6
CEBG-R3	16	13	40	11	2.7×10^5

[a][Host] = 2 mM, [picric acid] = 70 μM, and [M^+OH^-] = 50 mM or [$Mg(OH)_2$] = 20 mM, stirred for 30 min at 25 °C, uncertainty in K_a's ≤ 10%, [b]ND means not determined since %T < 1%.

$$K_a = K_e/K_d$$

$$\%\text{transfer (\%T)} = [\text{Pic}^-]_{chl}/([\text{Pic}^-]_{chl} + [\text{Pic}^-]_{aq})\cdot 100\%$$

The transfer efficiencies (%T) and the association constants (K_a) in $CHCl_3$ of the hosts interacting with picrate salts are given in Figure 2 and Table 1, respectively. As expected, B18C6 ether preferentially extracts K^+ and shows the following trend $K^+ > Cs^+ > Na^+ \gg Li^+ \approx Mg^{2+}$. Amide-B18C6 shows the same trend for cation binding as B18C6, but its transfer efficiencies and attraction for cations in $CHCl_3$ are diminished. Derivatizing the aromatic ring of B18C6 with an amide and/or the existence of the additional amide on the tether reduces the ability of the crown pocket to bind cations. These results further show that the oxygen atoms of the amides do not provide a stable binding pocket for a metal cation. Combining a rotaxane wheel with Amide-B18C6 to give CEBG-R1 results in a dramatic change in the observed strength and preference of cation binding. CEBG-R1 transfers all picrate salts into $CHCl_3$ with a slight preference for Mg^{2+} and K^+ ($Mg^{2+} > K^+ > Cs^+ > Li^+ > Na^+$). The amount of K^+ extracted is greater than seen for Amide-B18C6 and approximately the same as obtained with B18C6. CEBG-R1 either diminishes the negative effect of the amide moieties on the crown pocket or contains a different binding pocket. The

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transfer percentage increases from approximately 1% for Amide-B18C6 to 66%, 58%, and 97% for Li^+, Na^+, and Mg^{2+}, respectively for CEBG-R1. There is also a modest improvement in the transport of Cs^+, as well. This dramatic increase in the transfer of most metal cations by CEBG-R1, as compared to Amide-B18C6, indicates an additional binding pocket exists in the rotaxane, which most likely involves the wheel.

To find the other binding pocket(s) and to determine whether the wheel or axle is part of this pocket, the properties of ArBG-R and Axle-1 were determined and compared to the other hosts. Axle-1 can extract all of the metal cations tested, preferring Na^+ and Mg^{2+} ($Na^+ \approx Mg^{2+} > K^+ \approx Cs^+ > Li^+$). This result is surprising considering Amide-B18C6 extracts only K^+ and Cs^+. Both Axle-1 and Amide-B18C6 contain the two amides, but Amide-B18C6 has the known crown ether binding pocket. ArBG-R shows a preference for Na^+ ($Na^+ > K^+ \approx Cs^+ \approx Mg^{2+} \approx Li^+$) and outperforms Axle-1, except in the extraction of Mg^{2+}. This shows that the wheel contributes to the transfer process, likely through the formation of a new binding pocket. Cobbling all the pieces together: B18C6 ether, wheel, and axle produces CEBG-R1. It demonstrates a greater extraction of the metal cations than Amide-B18C6, which was also observed with ArBG-R. CEBG-R1, however, outperforms ArBG-R in the extraction of Mg^{2+}, K^+, and Cs^+, giving it a unique preference for metal cations ($Mg^{2+} \approx K^+ > Cs^+ > Li^+ \approx Na^+$). Surprisingly, CEBG-R1 demonstrates a nearly quantitative transfer of Mg^{2+} and forms a very stable complex with Mg^{2+} in $CHCl_3$ ($\Delta G^\circ = -17$ kcal·mol^{-1}). Its extraction of K^+ is similar to the level displayed by B18C6, which suggests that the presence of the B18C6-blocking group of CEBG-R1 is responsible for improved extraction of K^+ and likely Cs^+ as well when compared to ArBG-R. ArBG-R extracts only Na^+ better than CEBG-R1. The binding pocket for Na^+ available in ArBG-R appears not to exist in CEBG-R1. A comparison of the experimental results for the hosts shows that the components B18C6-blocking group, wheel, the amide(s) of the axle, and even the aromatic blocking group can enhance or diminish the binding of picrate salts, which depends on the number of binding pockets that assemble and how they combine.

To potentially obtain a single binding site and more stable complexes, the wheel of the rotaxane was derivatized with carboxylic acids. We envisioned the carboxylates extending outward and covering the B18C6 blocking group in a fashion similar to protein binding sites. Since the rotaxane can adopt a variety of conformations, linkers with different lengths were used in CEBG-R2 and CEBG-R3 to attach the carboxylic acid to the wheel. The wheel tends to reside over the dialkylammonium ion of the axle in $CHCl_3$ or in an apolar environment, whereas in an aqueous environment, the wheel resides closer to a hydrophobic end of an axle.[36] Metal cation extraction from an aqueous solution into $CHCl_3$ will likely involve the wheel being positioned on the axle to maximize the favorable binding free energy. The carboxylic acid of CEBG-R2 or CEBG-R3 could be better positioned depending on which step, aqueous sequestration of the cation or cation complexation in $CHCl_3$, drives the transfer event. Attaching a carboxylic acid to the wheel unfortunately does not significantly improve the ability of a CEBG-rotaxane to bind or transfer metal cations. CEBG-R3 displays similar properties as CEBG-R1, whereas the short chain variant CEBG-R2 extracts alkali cations less efficiently than CEBG-R1. On the other hand, CEBG-R2 does show a clear preference for Mg^{2+} over the other metal cations.

Effect of Counter Ion on Transfer Efficiencies. The extraction of the metal cations is likely aided by the presence of the picrate counterion(s). According to the hydrophobic effect,[45] the aromatic ring of a picrate ion will favorably associate with the hydrophobic groups of a host at the interface between the $CHCl_3/H_2O$ layers. Once in the $CHCl_3$ layer, the strength of this interaction is diminished. Considering the large magnitude of the K_a values (Table 1), the free energy for association in $CHCl_3$ is driven by cation−host interactions. The key step is the plucking of the metal cation from bulk water. Transfer experiments were performed for metal cations with ClO_4^- and Cl^- counterions to discover the importance of the counterion. The percent transfer values (%T) for these experiments were calculated by dividing the concentration of a metal cation detected in the $CHCl_3$ layer by the concentration of the host ($\%T = [M^+]_{chl}/[Host]_{chl}$). Atomic absorption spectroscopy was used to determine the concentration of K^+ and Na^+ in the $CHCl_3$ layer after the extraction experiments.[46] The measured absorbance values were converted to concentrations using calibration curves, which were constructed from the analysis of solutions that contained a known amount of metal cations. Extraction assays were also performed without salt and host to account for any solvent effect on the absorption. The very low concentration of free cations in $CHCl_3$, i.e., unbound cations, were undetectable using this assay. The carboxylic acids of CEBG-R2 and CEBG-R3 were deprotonated using Me_4NOH. Being a large cation, Me_4N^+ should not compete with the metal cations for the binding sites.

We found the hosts do not extract NaCl or KCl at the same concentration used in the picrate assay (2 mM), which shows the importance of the picrate ion in the transfer of metal picrates. To more fully investigate the effect of the counterion, the concentration of the model hosts, ArBG-R, and CEBG-R1 were raised to 20 mM and extraction assays were performed with $NaClO_4$ and $KClO_4$ at 100 mM or with NaCl and KCl at 1 M. We note that the maximum solubility of $KClO_4$ in water is around 100 mM, and metal cation transfer was not observed from aqueous solutions containing 100 or 200 mM chloride salts. Because of the differences in the concentrations of the components, only the trends of %T will be compared and discussed. Switching the counterion from picrate to a perchlorate produces small differences in the preference of K^+ over Na^+ for B18C6 and for Amide-B18C6 (Figure 2 and Table 2). A much greater effect on %T is seen for Axle-1, ArBG-R, and CEBG-R1 upon switching the counterion. Whereas these hosts outperformed B18C6 and Amide-B18C6 in the %T of NaPic and in some cases KPic, this advantage is lost with the perchlorate salts. Axle-1, ArBG-R, and CEBG-R1 either did not extract the perchlorate salts or performed as well as Amide-B18C6. This result is consistent with the ability of picrate to interact favorably with the aromatic surfaces of the hosts, which drives host−guest association in an aqueous environment. Because Axle-1,

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TABLE 2. Percent of Host Bound to a Metal Chloride Salt in $CHCl_3$ Obtained through Extraction Experiments[a]

	KCl (1 M)	NaCl (1 M)	KCl or NaCl (0.2 M)	$KClO_4$ (0.1 M)	$NaClO_4$ (0.1 M)	$KClO_4$ (0.1 M); KCl (0.1 M)	$NaClO_4$ (0.1 M); NaCl (0.1 M)
B18C6	ND[b]	ND	ND	60	40	52	13
Amide B18C6	ND	5	ND	26	9	22	ND
Axle-1	ND	ND	ND	ND	ND	ND	ND
ArBG-R	74	32	ND	ND	7	17	12
CEBG-R1	40	14	ND	22	ND	65	ND

[a][Host] = 20 mM, stirred for 24 h at 25 °C, uncertainty in %T is 3−10%. [b]ND not detected (%T < 1%).

ArBG-R, and CEBG-R1 contain a greater number of aromatic rings than B18C6 and Amide-B18C6, they should be more greatly affected by a switch to a nonaromatic counterion. The fact that Amide-B18C6 and CEBG-R1 extract $KClO_4$ approximately in the same amount (26% Amide-B18C6·K^+ and 22% CEBG-R1·K^+), whereas Axle-1 and ArBG-R do not detectably transfer $KClO_4$, suggests that K^+ resides in the ether pocket of the B18C6-blocking group when it carries a ClO_4^- counterion. $NaClO_4$ is not extracted by Axle-1 or CEBG-R1, and only a small amount is extracted by Amide-B18C6 and ArBG-R. The inability of Axle-1 to transfer $NaClO_4$ indicates that a crown ether, either free or as a wheel, is required for these hosts to extract $NaClO_4$. CEBG-R1 does not transfer Na^+ as well as ArBG-R independent of whether the counterion is perchlorate or picrate.

Because of a large desolvation penalty, the transfer of chloride salts from water into $CHCl_3$ is a very unfavorable process. This explains the lack of observable extraction of KCl or NaCl from a 1 M aqueous solution into $CHCl_3$ by B18C6, Amide-B18C6, and Axle-1, except for the 5% of Amide-B18C6 bound to Na^+ (Table 2). Considering the poor performance of the rotaxanes in the extraction of the perchlorate salts, we were surprised to find that they extract chloride salts. KCl is extracted preferably over NaCl. Seventy-four percent of ArBG-R and 40% of CEBG-R1 are bound to K^+ in $CHCl_3$, assuming a 1:1 complex of cation per host. The percentage of bound host is approximately halved in the extraction of NaCl. Interestingly, CEBG-R1 is not as efficient in extracting KCl as ArBG-R, even though it contains the B18C6-binding pocket. This fact combined with the observation that B18C6, Axle-1, and Amide-B18C6 do not noticeably extract KCl suggests that the binding pocket of the host rotaxanes for K^+ and Na^+ is constructed from the axle's amides and the wheel. Competition assays were performed to determine whether Na^+ and K^+ bind to the same pocket or different pockets. Presenting CEBG-R1 to KCl (1 M) and NaCl (1 M) resulted in 24% of the host being bound to K^+ and 10% bound to Na^+ in the $CHCl_3$ layer. This is a reduction in the amount of both cations being extracted when presented separately (40% CEBG-R1·K^+ and 14% CEBG-R1·Na^+). This is consistent with the cations binding to the same site on the rotaxane, with K^+ being selected over Na^+. Presenting ArBG-R to NaCl (1 M) and KCl (1 M), however, resulted in an increase in the amount of Na^+ extracted and a modest reduction in the amount of K^+ extracted (57% ArBG-R·K^+ and 54% ArBG-R·Na^+; salts presented separately gave 74% ArBG-R·K^+ and 32% ArBG-R·Na^+). Apparently, Na^+ and K^+ bind to different pockets of ArBG-R. The binding of K^+ enhances the association of Na^+, giving an allosteric type relationship for cation binding and a concomitant loss of preference for K^+.

The importance of the chloride ion for the transfer event is realized upon comparing %T of perchlorate salts versus chloride salts. A switch in preference occurs for ArBG-R from Na^+ to K^+ with a switch from ClO_4^- to Cl^- (7% ArBG-R·Na^+/ND ArBG-R·K^+ for ClO_4^- to 32% ArBG-R·Na^+/70% ArBG-R·K^+ for Cl^-). CEBG-R1 demonstrates a smaller preference for K^+ over Na^+ with a switch of ClO_4^- to Cl^- (>22-fold preference for $KClO_4$ over $NaClO_4$ to a 3-fold preference for KCl over NaCl). To obtain a direct measure of the effect of Cl^- on the transfer of metal cations, extraction assays were performed with a mixture of NaCl (100 mM)/$NaClO_4$ (100 mM) or KCl (100 mM)/$KClO_4$ (100 mM). The total cation concentration of 200 mM was chosen because we found that Na^+ and K^+ are not noticeably extracted from an aqueous solution containing chloride salts at 200 mM. An enhancement in the %T under these conditions, as compared to the perchlorate salts alone at 100 mM, would show that Cl^- is not only actively participating in the transfer event by binding to a host, but its binding results in an allosteric type of phenomenon, giving improved cation binding. There is a slight decrease in the amount of K^+ extracted when 100 mM of Cl^- is added to an aqueous solution of $KClO_4$ for B18C6 and Amide-B18C6. A large reduction in the amount of Na^+ extracted by these hosts occurs using the mixed aqueous solution (NaCl/$NaClO_4$) as compared to the $NaClO_4$ solution. Contrarily, the rotaxanes extract a significantly greater amount of K^+ with the addition of 100 mM KCl to the aqueous solution containing 100 mM $KClO_4$ (22% without Cl^- to 65% with Cl^- of bound host for CEBG-R1 and ND without Cl^- to 17% with Cl^- of bound host for ArBG-R). Only ArBG-R extracts a greater amount of Na^+ from the mixed aqueous solution of NaCl and $NaClO_4$ (7% without Cl^- to 12% with Cl^- of bound host). As seen with the other extraction assays, CEBG-R1 extracts less Na^+ under these conditions than ArBG-R.

^{1}H NMR Analysis of the Coordination Sites of the Host Rotaxanes. To further investigate the coordination sites for the metal cations and the counterions, 1D and 2D ^{1}H NMR analyses were performed on solutions containing CEBG-R1 and ArBG-R with and without the various salts. The "metal-cation-free" condition is defined as the state of the host obtained from HPLC purification. Because the eluent contained 0.1% TFA, we assume the dialkylamines of the rotaxanes are protonated with TFA^- counterions. Extraction assays were performed, and the materials in the chloroform layer were analyzed via ^{1}H NMR spectroscopy. Substantial changes were observable in the ^{1}H NMR spectra of the hosts (Figure 3). The effect of sodium salts on the ^{1}H NMR spectra of ArBG-R is shown in Figure 4 as an example. A few general trends observed in the plots are that the aromatic signals (C, F and G, H) and the axle

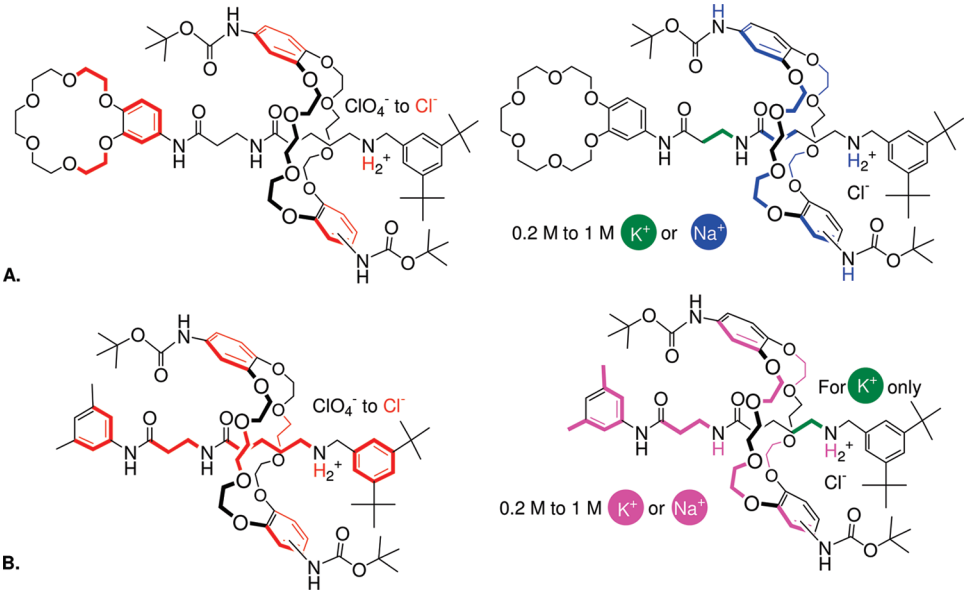
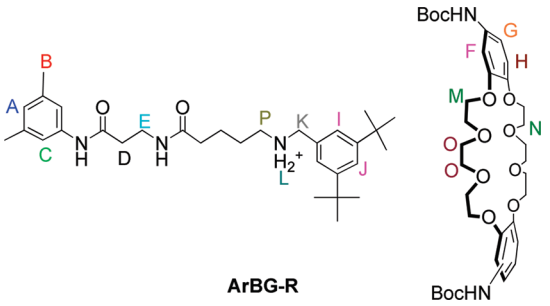


FIGURE 3. Changes to the ^{1}H NMR spectra of hosts after the extraction assays. (A) Red bonds highlight the protons that show a change in their chemical shift (> 0.05 ppm) in the spectra of CEBG-R1 after it is extracted with ClO_4^- (Na^+ or K^+) at 100 mM compared to when it is extracted with Cl^- (Na^+ or K^+) at 200 mM. Also shown are the differences in the chemical shifts for CEBG-R1 after extracting it with a low concentration of Cl^- (Na^+ or K^+ at 200 mM) compared to after extracting with a higher concentration of KCl (green) or NaCl (blue) at 1 M. (B) The same comparisons were made for ArBG-R.

protons O become more separated and the protons of amide linker (D, E) converge when the plots are viewed starting from TFA and going up to 1 M NaCl. The dialkylammonium ion protons L collapse and are positioned upfield with Cl^- as the counterion instead of ClO_4^- or TFA^-. A greater separation is clearly seen for protons N for the 1 M NaCl extraction as compared to the other conditions. 2D ^{1}H NMR spectra of the hosts are available in Supporting Information.

The hosts were extracted with 100 mM $NaClO_4$ or 100 mM $KClO_4$. At this concentration, ArBG-R transfers Na^+, albeit poorly (7% of host bound), but does not transfer K^+ (not detected (ND)), whereas CEBG-R1 transfers K^+ (22% of host bound) but not Na^+ (ND). Substantial changes are observable in the ^{1}H NMR spectra of the hosts after the extraction assays (Supporting Information), which suggest that TFA^- was replaced with ClO_4^-. Unexpectedly, the chemical shifts of the dialkylammonium protons of the axle (7.6 ppm, 7.7 ppm for ArBG-R and 7.2 ppm, 8.1 ppm for CEBG-R1) are unchanged after the extraction assay. A change in counterion should produce a change in the chemical shift of these protons. This unexpected result can be explained with the observation that similar chemical shifts and coupling pattern are observed for the pseudorotaxane with the PF_6^- counterion (7.5 ppm, 7.7 ppm). This indicates the wheel is over the dialkylammonium ion with either TFA^-, ClO_4^-, or PF_6^- as the counterion. The spectra of each host after extracting with $NaClO_4$ or $KClO_4$ appear to be identical (Supporting Information). Thus, changes to the spectra that occur with a change in counterion (TFA^- to ClO_4^-) are independent of the nature of the cation. Either the geometry of a host is unchanged when bound to a cation with perchlorate as the counterion or the amount of host bound to a cation is too low to produce an observable change in the spectra.

^{1}H NMR analysis was performed on the hosts after they were extracted with the chloride salts at a concentration where cation extraction does not occur (200 mM) to determine if Cl^- binds to them without concomitant cation binding. Observed changes include the protons of the dialkylammonium group of CEBG-R1 and ArBG-R, which are shifted downfield to 7.9 and 8.2 ppm, respectively. A chemical shift of 9.3 ppm is observed for these protons when the axle is protonated with HCl. At least a portion of the hosts had Cl^- as the counterion, and the wheel is off the dialkylammonium ion. The spectra of hosts with Cl^- as the counterion were compared to the corresponding host with ClO_4^- as the counterion to potentially discover how Cl^- aids in the transfer of the cations. As discussed previously, the chemical shifts of these spectra are not influenced by a metal cation. For CEBG-R1, shifts were observed in the Ar-H's of the wheel, B18C6-blocking group, and the dialkylammonium protons (Figure 3). Changes to the aromatic environments suggest that the wheel is positioned closer to the B18C6-blocking group with Cl^- as the counterion. Cl^- forms a tight ion pair with the dialkylammonium ion in $CHCl_3$, which forces the wheel off the dialkylammonium ion. This is why pseudorotaxane formation (wheel threaded onto axle) requires a swap of Cl^- for PF_6^-, which forms a weak or loose ion pair. For ArBG-R, substantial changes are not only observed for the Ar-H protons of both blocking groups (CEBG-R1 changes occurred with only the 18C6-blocking group) and the wheel, but changes are also observed for the protons of the axle and several of the ether linkages of the wheel. Apparently, the wheel shifts a greater distance away from the dialkylammonium ion of ArBG-R, as compared to CEBG-R1, with a swap of Cl^- for ClO_4^-. Most protons affected by the swap of Cl^- for ClO_4^- also show different chemical shifts when the ^{1}H NMR spectra of the hosts with TFA^- as the counterion are compared to hosts after



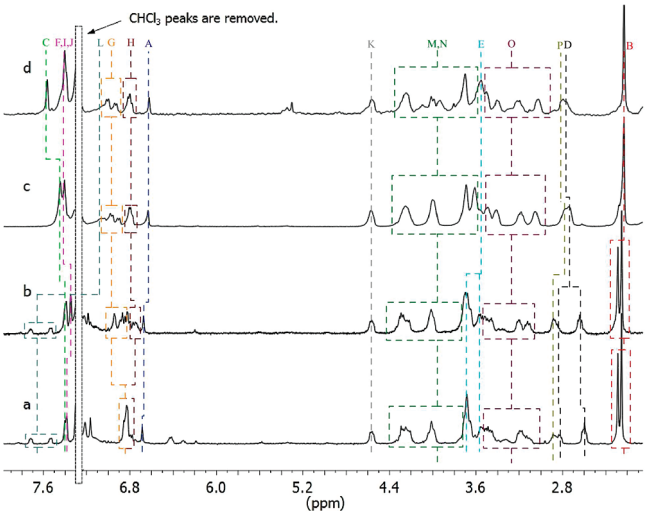


FIGURE 4. Partial ^{1}H NMR spectra in $CDCl_3$ for ArBG-R (a) as the TFA^- salt and after extracting with an aqueous solution containing (b) 100 mM $NaClO_4$, (c) 200 mM NaCl, and (d) 1 M NaCl.

extracting with Cl^- (Na^+ or K^+) at 200 mM (Supporting Information). This not surprising considering that ClO_4^- and TFA^- form weaker contact ion pairs than Cl^- in $CHCl_3$.

^{1}H NMR analysis was performed on the hosts after extracting them with a high concentration of salt (1 M NaCl or KCl), where metal cation binding occurs, to discover the nature of the coordinating site for Na^+ or K^+ with chloride as the counterion. These spectra were compared to the spectra of the corresponding salt presented at the lower concentration of 200 mM. In the case of CEBG-R1 binding to K^+, there is very little change in the conformation of the host except for the axle protons as indicated in green (Figure 3). Thus, the host appears to be optimized for binding to K^+ with Cl^- present. Binding to Na^+, however, produces substantial changes in the chemical shifts of the wheel's protons, protons of the dialkylammonium ion, and a couple of protons of the axle. This suggests that either the wheel shifts its position upon Na^+ binding and/or the wheel binds to Na^+. A different pattern is seen for the binding of Na^+ and K^+ to ArBG-R. Binding of K^+ or Na^+ produces the changes in the chemical shifts of the wheel as seen with CEBG-R1; however, changes are also observed for the 3,5-dimethylbenzyl blocking group and the portion of the axle that contains the amides. Furthermore, nearly identical spectra are observed for ArBG-R bound to Na^+ as K^+, except for one unique axle proton (shown in green) seen with the binding of K^+.

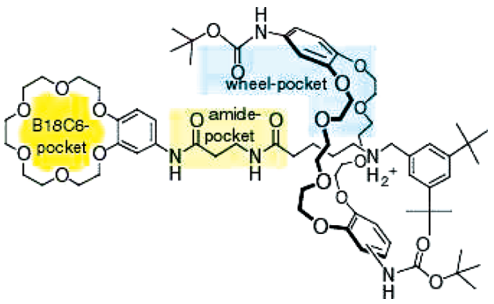


FIGURE 5. Proposed binding pockets for a metal cation are shown combined in CEBG-R1.

Discussion

The hosts were designed to bind cations in performed pockets, e.g., the B18C6-blocking group, with the wheel providing additional contacting groups. We did not design a binding site for a counterion. The counterion would play the traditional role of enhancing the solubility of a salt in chloroform with the order of picrate > perchlorate ≫ chloride. As expected, picrate salts are extracted at a lower concentration of components than the other salts. For B18C6 and Amide-B18C6, the predicted solubility trend continues with perchlorate salts being extracted more efficiently than the chloride salts. The rotaxanes, however, break from the pattern of the other hosts, showing the ability to transfer chloride salts from modest to high levels. Advantages for the rotaxanes include more oxygen atoms to bind a cation and more aromatic surfaces to remove water molecules from the oxygen atoms, which reduces the desolvation penalty that occurs with transfer. The trick is to get these components to work together to bind a metal cation, which is not a trivial endeavor. For example, we found that not all oxygen atoms embedded within a rotaxane contribute to cation binding, and in some cases, their presence lowers the amount of a metal cation that is extracted. To find which coordination sites are responsible for cation transfer, the properties of the hosts were compared. For this discussion, we will refer to the potential coordination sites for the cations as the B18C6-pocket, the amide-pocket, and the wheel-pocket (all pockets are shown in CEBG-R1, Figure 5). These sites were chosen on the basis of the known binding properties of crown ethers and proteins.

Aromatic surfaces clearly aid in the transfer of picrate salts, likely through the formation of stacking interactions between the aromatic rings of a host with the picrate. Bartsch found Pic^- stacks in a face-to-face orientation with DB24C8 ether in the crystallographic structure of DB24C8−NaPic complexes.[47] Aromatic interactions should be the strongest during the transfer event from water to chloroform, but once in $CHCl_3$, the favorable charge-dipole interactions between a cation and the oxygen atoms of a host will provide the majority of the binding free energy. Binding modes were constructed to explain the observed results for the extraction of picrate salts by placing a cation in one of the three pockets while maintaining stacking aromatic interactions (Supporting Information). Axle-1 contains only the amide-pocket. Thus,

(47) Talanova, G. G.; Elkarim, N. S. A.; Hanes, R. E.; Hwang, H. S.; Rogers, R. D.; Bartsch, R. A. *Anal. Chem.* **1999**, *71*, 672–677.

the cation likely binds to this pocket and its picrate ion interacts with the aromatic surface of a blocking group. For the binding of $MgPic_2$, each picrate ion likely interacts with one of the aromatic blocking groups. The addition of an aromatic crown ether, i.e., the B18C6-blocking group, to a host does not guarantee that it will extract a greater amount of salt into chloroform. For example, linking B18C6 to Axle-1, giving Amide-B18C6, diminishes the ability of the resulting host to transfer Na^+, Li^+, and Mg^{2+}. Although Amide-B18C6 contains an aromatic blocking group, aromatic interactions between this blocking group and the picrate counterion are probably weak. The crown ether moiety of Amide-B18C6 forms favorable interactions with water molecules, and their presence diminishes the hydrophobic effect afforded aromatic surfaces. Amide-B18C6 shows the same transfer trend as B18C6, suggesting that K^+ and Cs^+ bind to its B18C6-pocket and not the amide-pocket.

ArBG-R contains the amide-pocket and the wheel-pocket. Unlike the combination of B18C6-pocket and amide-pocket (i.e., Amide-B18C6), this combination produces more efficient transfer of all the alkali cations than the amide-pocket alone (i.e., Axle-1). This suggests that the amide-pocket and the wheel-pocket can converge to make a favorable binding site. The wheel can slide over the amide-pocket, giving a convergent arrangement of functional groups, in a manner similar to protein binding sites. The similar level of Mg^{2+} extracted by ArBG-R and Axle-1 is consistent with the requirement that both picrates need to form aromatic interactions with a host for Mg^{2+} to be efficiently extracted into $CHCl_3$. Dual stacking interactions between ArBG-R and the picrate ions likely forces the wheel to move away from the amide-pocket. Not only are aromatic interactions important in the efficient transfer of picrate salts by these hosts, but these interactions can also control which coordination site a metal cation will bind to.

CEBG-R1 and CEBG-R3 contain all three binding pockets and outperform ArBG-R in the transfer of K^+, Cs^+, and Mg^{2+}. The improved extraction of K^+ and Cs^+ and the availability of the B18C6-pocket, which extracts these cations, suggest that K^+ and Cs^+ bind in this pocket of the hosts. Because CEBG-R1 and -R3 extracts these cations to a greater extant than Amide-B18C6, the wheel must be involved in the process, likely through favorable interactions between the picrate ion and an aromatic ring of a wheel. In the extraction of Mg^{2+}, the cation could bind in the amide-pocket in a fashion similar to the predicted coordination site of ArBG-R. CEBG-R1 and -R3, however, transfer Mg^{2+} better than ArBG-R, which suggests Mg^{2+} also binds in the B18C6-pocket. The wheel must be part of the coordinating site since Amide-B18C6 does not transfer Mg^{2+}. The binding site must also accommodate both aromatic rings of $MgPic_2$, which appears to be necessary for the observed high %T of Mg^{2+}. We propose that Mg^{2+} is housed within the B18C6-pocket and its picrate ions interact with both aromatic rings of the wheel by one being positioned above and the other positioned below the plane of the crown ether. CEBG-R2 transfers Mg^{2+} as well as CEBG-R1 and -R3, but it transfers alkali cations less efficiently than these hosts. Its short $-CH_2-$ linker, which attaches the carboxylic acid to the wheel, appears to be the reason for its poorer performance. CEBG-R3, which contains longer $-(CH_2)_3-$ linkers, performs as well as or better than CEBG-R1. The 2:1 ratio of picrate to Mg^{2+} in $CHCl_3$ suggests that a carboxylate of CEBG-R2 and CEBG-R3 does not replace a picrate from Mg^{2+}. A possible reason for the inability of a carboxylate to remove picrate and for the poorer performance of CEBG-R2 is that the carboxylic acids remain protonated in the $CHCl_3$ layer, even though 2 equiv of base was added to the aqueous phase. The close proximity of a carboxylic acid of CEBG-R2 to a cation binding site could result in H-bond formation between the carboxylic acid proton and an oxygen atom or atoms used to bind the metal cations, e.g., in the B18C6-pocket, amide-pocket, or even the wheel-pocket. This H-bond would compete with a metal cation for the binding domain. Mg^{2+} apparently does not bind to the functional group or pocket that interacts with the carboxylic acid of CEBG-R2. The picrate ions could force the wheel away from the amide-pocket and B18C6-pocket to maximize aromatic interactions, which would reduce the negative effect of the carboxylic acid.

Perchlorate salts were extracted less efficiently into $CHCl_3$ than the picrate salts. The perchlorate ion cannot form aromatic interactions with a host and is less hydrophobic than the picrate ion. The importance of aromatic interactions is clearly seen with the inability of Axle-1 to transfer either $NaClO_4$ or $KClO_4$. Furthermore, Amide-B18C6 outperforms ArBG-R and CEBG-R1 in the transfer of $NaClO_4$ and $KClO_4$, whereas these rotaxanes transfer NaPic and KPic to a greater extent than Amide-B18C6. The only useful binding site for the perchlorate salts appears to be the B18C6-pocket. Hosts with this pocket transfer $KClO_4$ around 25% of bound host, except for B18C6, which shows 60% of bound host. ArBG-R, which contains the amide-pocket and wheel-pocket, does not transfer $KClO_4$ but does transfer $NaClO_4$, albeit weakly. Surprisingly, CEBG-R1, which contains all three pockets, does not transfer $NaClO_4$. Unlike the picrate ions, ClO_4^- does not bind to the rotaxanes in a manner that promotes metal cation transfer.

The transfer of NaCl and KCl from a 1 M aqueous phase could be simply a result of the high concentration of alkali cation, which is possible for assays with chloride salts. In this case, Cl^- would just go along with the cation into $CHCl_3$ as the counterion. Another possibility is that Cl^- binds to a host, and this association results in an allosteric-like relationship promoting the binding of a cation. Although Pic^- aids in the extraction of picrate salts, it likely stays associated with the metal cation and the entire salt binds as a single unit. An allosteric relationship of proteins involves at least two binding sites and the binding of an agent to one site alters the protein's conformation in such a manner to promote the binding of the second agent. The results of the experiments presented herein are consistent with Cl^- and K^+ or Na^+ binding to different sites on the host rotaxanes and the binding of Cl^- promotes the binding of the metal cation through a conformational change. Replacing TFA^- or ClO_4^- with Cl^- results in significant changes to its ^1H NMR spectra to a host. The likely binding site for Cl^- is the dialkylammonium ion of the axle since this will form a stable, tight ion pair and anions are known to bind to the side chains of proteins that are positively charged or form strong H-bonds.[48] Since the changes to the ^1H NMR spectra are not localized at the dialkylammonium ion, the binding of

(48) Kubik, S. *Chem. Soc. Rev.* **2009**, *38*, 585–605.

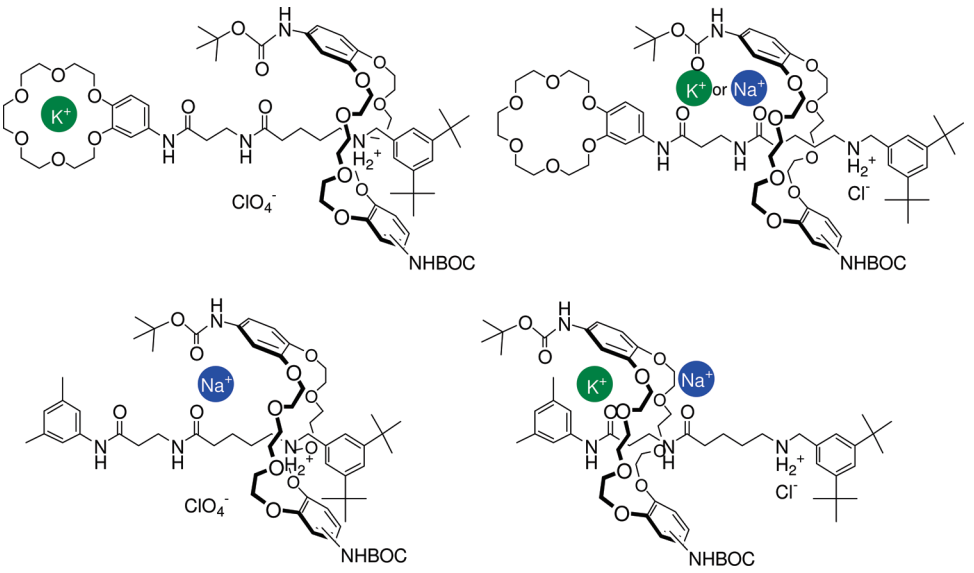


FIGURE 6. Proposed binding modes of the host rotaxanes with the perchlorate and chloride salts. For ArBG-R·Cl^-, K^+, and Na^+ can be bound simultaneously within the crown ether-amide pocket, but not necessarily in the positions shown.

Cl^- produces a global change in a host's conformation most likely through a repositioning of the wheel. Evidence for a cation binding in a site being separate from the Cl^- site is obtained by the observation that different protons are affected in the ^1H NMR spectra when Cl^- replaces TFA^- as compared to when both a M^+ and Cl^- bind. The last piece of the allosteric puzzle is the fact that the binding of Cl^- promotes that association of a metal cation, which was observed in extraction assays of mixed Cl^-/ClO_4^- solutions.

We postulate that the binding of Cl^- to the dialkylammonium ion of the axle forces the wheel to shift toward the amide-pocket, as shown in Figure 3. This establishes the binding site of the metal cation, which is a combination of the wheel-pocket and the amide-pocket. Even though the binding site exists, complexation requires either a high concentration of a metal cation in the aqueous phase (available with 1 M NaCl or 1 M KCl) or the presence of a salt that is more soluble in $CHCl_3$, e.g. a perchlorate salt. ClO_4^-, on the other hand, does not form a tight ion pair. The wheel either stays on the dialkylammonium ion of the axle or slides rapidly along the axle, but in either case, the binding site for a metal cation is not formed. The coordinating sites of CEBG-R1 and ArBG-R formed by the chloride ion are not equivalent. First, Na^+ is bound more favorably by ArBG-R than CEBG-R1 independent of the counterion. A second difference was observed in the competition assay. Na^+ and K^+ bind to the same site in CEBG-R1, whereas Na^+ and K^+ can bind simultaneously to different sites of ArBG-R and the binding of K^+ promotes the binding of Na^+. Finally, ^1H NMR analysis revealed that the wheel is positioned further away from the dialkylammonium ion for ArBG-R than CEBG-R1. On the basis of these findings, binding modes were constructed as shown in Figure 6. The wheel-pocket was positioned on the edge of the amide-pocket for CEBG-R1, according to the ^1H NMR analysis. Possibly, the B18C6-pocket keeps the wheel away from the amide-pocket through steric hindrance or repulsion between the electron-rich crown ethers. K^+, being larger, appears to fit between the amides of the amide-pocket better than Na^+. It would not require the wheel as much for binding as Na^+, resulting in K^+ being the preferred guest. The binding site of ArBG-R for alkali metals of chloride salts was drawn with the wheel-pocket sitting over the amide-pocket. Both amides of the amide-pocket can combine with the wheel to produce a binding site that can house K^+, Na^+, or both cations simultaneously. K^+ is the preferred guest, but once bound, it may help to "lock" the wheel promoting the binding of Na^+, producing the observed allosteric relationship in the extraction assay.

Conclusion

The goal of this research project was to create synthetic mimetics of protein binding domains that combine their functional groups in an appropriate arrangement to extract metal chloride salts from aqueous solutions into chloroform. Rotaxanes can perform this extraction, albeit it requires a high concentration of NaCl or KCl in the aqueous phase. The rotaxanes contain a variety of coordination sites for a cation and aromatic surfaces to reduce the desolvation penalty that occurs upon transfer. To obtain efficient transfer, the various pockets need to be organized to bind a particular salt. The extraction of picrate salts benefits from the favorable interactions with aromatic surfaces of a host, whereas the extraction of chloride salts require a host to present an apolar pocket containing a convergent arrangement of oxygen atoms. The interlocked nature of rotaxanes enables the wheel to adjust its position along the axle to accommodate the various salts. For picrate salts, the wheel appears to provide an aromatic surface to bind to the picrate ion of alkali cations and possibly both picrates of $MgPic_2$ when the cation binds to the B18C6-pocket or amide-pocket. In the extraction of NaCl and KCl, the wheel likely combines with the amide-pocket to bind Na^+ and K^+. Formation of this binding site, however, requires tight binding of Cl^- to the rotaxane. Since ClO_4^- does not bind tightly to a rotaxane and thus position its wheel, the wheel does not participate favorably in the binding of its cation. In our search for hosts

that bind cations, we constructed hosts that not only bind cations but also can form a tight ion pair with Cl^- in chloroform, giving an allosteric relationship that drives cation binding. Allosteric relationships between cations and anions have recently been found to exist with some ligand-gated ion channels.[49] The next generation of rotaxanes is being designed to further investigate allosteric relationships and to selectively bind targeted cations. Materials that operate through allosteric relationships could become integral components in future protein mimetics, cation sensors, or mechanical devices.

Experimental Section

General Experimental. Solvents, reagents, and materials used to create the materials were purchased. Moisture-sensitive reactions were carried out under positive argon pressure. All organic solvents were freshly distilled under vacuum over a suitable drying agent. Some rotaxanes were purified via HPLC using a C18 reversed phase column with water (0.1% TFA)/CH_3CN as the eluent. Concentrations of metal ions were determined using an atomic absorption spectrometer. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ or DMSO-d_6 using a spectrometer operating at 400.14 MHz for proton and 100.23 MHz for carbon nuclei. Chemical shifts are in ppm and are referenced against an internal TMS standard.

Determining Association Constants and %T for Host and Metal Picrate Complexes. Stock solutions were made of the hosts (2.0×10^{-3} M) in $CHCl_3$ and the metal hydroxides or metal oxides (5.0×10^{-2} M) with picric acid (7.0×10^{-5} M) in water. Extraction assays were performed by combining 1.0 mL of each solution in a vial and then vigorously stirring the solutions for 2 h. We determined the system had reached equilibrium within 2 h. A small aliquot of each $CHCl_3$ layer (0.10 mL) was carefully removed, and the $CHCl_3$ was removed in vacuo. The resulting material was dissolved in CH_3CN (1.0 mL), according to the procedure developed by Cram,[43] and the absorption of the solution at 380 nm was measured via UV−vis spectroscopy. The concentrations of the metal picrates were determined by solving the Beer−Lambert equation using these absorption values and the known extinction coefficients. The concentrations of the picrate ion in the aqueous phases were also determined using the same method to verify their concentrations. Each experiment was performed three times, and the observed absorbance values were averaged. K_d values were taken from the literature.[40,44] K_a and %T values were obtained by solving the equations presented earlier in the paper.

%T Experiments for Metal Chloride salts, Metal Perchlorate Salts, and Metal Chloride/Perchlorate Salts. Stock solutions were made for the hosts (5 mM) in $CHCl_3$, the metal chloride salts (200 mM or 1.0 M) in distilled water, the metal perchlorate salts (100 mM) in distilled water, and the metal chloride/perchlorate saltes (100 mM/100 mM) in distilled water. For hosts with carboxylic acids, 2 equiv of $(Me)_4NOH$ was added from a stock solution. Extraction assays were performed by combining 0.20 mL of a host solution and 0.20 mL of a guest solution in a vial and then vigorously stirring the solution for 24 h. A small aliquot of each $CHCl_3$ layer (0.10 mL) was carefully removed, extracted with 1.0 mL of 0.1 N HCl for 2 h, and finally diluted with distilled water to 10 mL. The amount of metal ion in this final solution was determined by atomic absorption spectroscopy. The absorbance maxima were read at 589 and 766 nm for Na^+ and K^+, respectively. These assays were duplicated. Any solvent effects were eliminated by subtracting background levels of absorbance obtained from assays performed without the presence of a host or metal cation. The absorbance values were converted to concentrations using a series of calibration curves, which were constructed prior to the assays. Percent transfer (%T) was determined by solving the following equation. The values give the percentage of hosts that contained a metal cation.

$$\%T = \frac{[\text{metal cation}]_{CHCl_3,\, t=24h}}{[\text{host}]_{CHCl_3,\, t=24h}} \times 100\%$$

Procedure for Determining the Effect of a Salt on the ^1H NMR Chemical Shifts of a Host. Stock solutions were made of CEBG-R1 and ArBG-R (20 mM) in $CHCl_3$, the metal chloride salts (200 mM or 1.0 M) in distilled water, and the metal perchlorate salts (100 mM) in distilled water. Extraction assays were performed by combining 0.20 mL of a host solution and 0.20 mL of a guest solution in a vial and then vigorously stirring the solution for 24 h. The $CHCl_3$ layer was carefully removed and evaporated. The residue was dissolved in 0.4 mL $CDCl_3$ and its 1D and 2D (COSY and ROESY) ^1H NMR spectra were recorded.

Synthesis of Materials. Amide-B18C6. Boc-β-alanine (1.0 g, 5.3 mmol) and 1,1′-carbonyldiimidazole (1.0 g, 6.1 mmol) were added to CH_2Cl_2 (15 mL). The reaction mixture was refluxed for 3 h and then exposed to NH_2-benzyl-18-crown-6 ether **1**[43] (1.73 g, 5.25 mmol) dissolved in CH_2Cl_2 (5 mL). The reaction mixture was refluxed for 0.5 h and then stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was extracted with EtOAc/H_2O. The organic layer was collected, dried with $MgSO_4$, and evaporated under vacuum. The crude material was separated by flash chromatography on silica gel with EtOAc as the eluent. Amide-B18C6 (2.5 g, 5.0 mmol) was obtained as a white solid in a 95% yield. ^1H NMR ($CDCl_3$): δ 1.43 (9H, s), 2.56 (2H, t), 3.46 (2H, t), 3.62−3.80 (12H, m), 3.89 (4H, m), 4.12 (4H, m), 5.32 (1H, s), 6.75 (1H, d), 6.92 (1H, d), 7.33(1H, s), 8.24 (1H, s). ^{13}C NMR ($CDCl_3$): δ 168.9, 155.2, 147.8, 144.1, 131.5, 113.6, 111.4, 105.9, 78.5, 69.7, 69.6, 69.5, 68.6, 68.4, 67.7, 35.9, 35.5, 27.3. MS: found 499.2730, calcd for $C_{24}H_{39}N_2O_9$ [M + H^+] 499.2656.

β-Alanine-amide-benzyl-18-crown-6 Ether 2. Amide-B18C6 (2.5 g, 5.0 mmol) was dissolved in 1:4 TFA/CH_2Cl_2 (15 mL). After the above solution was stirred for 2 h, the volatile materials were removed under reduced pressure. The residue was separated by flash chromatography on silica gel with 99:5 CH_2Cl_2/MeOH as the eluent. β-Alanine-amide-benzyl-18-crown-6 ether **2** (1.9 g, 4.8 mmol) was obtained as a pink oil in a 96% yield. ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.50 (1H,s), 2.66 (2H, t), 3.09 (2H, t), 3.41−3.65 (12H, m), 3.74 (4H, m), 4.35 (4H, s), 6.87 (1H, d), 7.10 (1H, d), 7.30 (1H, s), 7.87 (1H, s). ^{13}C NMR (DMSO-d_6): δ 168.9, 147.9, 143.4, 135.2, 113.3, 112.9, 105.6, 72.3, 71.9, 71.6, 71.5, 71.1, 68.5, 37.0, 34.0. MS: found 399.2186, calcd for $C_{19}H_{31}N_2O_7$ [M + H^+] 399.2131.

CEBG-R1. To a solution containing DCC-[2]rotaxane[39] (0.64 mmol in 1 mL $CHCl_3$) cooled to 0 °C was rapidly added β-alanine-amide-benzyl-18-crown-6 ether **2** (26 mg, 0.64 mmol) dissolved in 1:1 DMSO/$CHCl_3$ (1 mL). The reaction mixture was brought to room temperature and stirred overnight. The solvent was removed under vacuum. CH_3CN (20 mL) was added to the solution, and the resulting precipitated dicyclohexylurea (DCU) was removed by filtration. After the solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (1 mL). Diethyl ether (20 mL) was added to remove *N*-(3,5-di-*tert*-butylbenzyl)valerolactam, a byproduct, as a precipitate. After decanting the ether layer, the precipitation

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procedure was repeated. The ether layers were collected and dried over $MgSO_4$. After the solvent was removed in vacuum, the crude material was separated via column chromatography with 95:5 CH_2Cl_2/MeOH as the eluent.. CEBG-R1 **3** (470 mg, 0.34 mmol) was obtained as a yellow glass in a 53% yield. Note: to be consistent with the other rotaxanes, CEBG-R1 was subjected to HPLC conditions prior to performing extraction assays. ^{1}H NMR ($CDCl_3$): δ 1.30 (18H, s), 1.50 (18H, s), 1.51−2.00 (10H, m), 2.01−2.20 (12H, m), 2.30−2.40 (4H, m), 2.80−2.95 (2H, m), 3.00−3.5 (10H, m), 3.52−3.78 (16H, m), 3.80 (24H, s), 3.81−4.15 (16H, m), 4.59 (2H, s), 6.40 (8H, s), 6.60−6.65 (2H, m), 6.80−6.85 (2H, m), 7.01−7.10 (2H, m), 7.23−7.46 (5H, m). ^{13}C NMR ($CDCl_3$): δ 172.5, 171.5, 162.2, 153.3, 151.2, 151.5, 147.5, 142.9, 142.7, 133.8, 133.5, 131.7, 124.4, 123.2, 118.6, 115.5, 113.1, 111.6, 104.9, 79.9, 70.3, 70.2, 70.0, 69.7, 69.0, 68.8, 68.5,68.1, 53.5, 45.8, 45.4, 34.7, 33.9, 31.3, 28.2, 27.8, 25.6, 22.0. MS: found 1378.7896, calcd for $C_{73}H_{112}N_5O_{20}^+$ [M+ H^+] 1378.7943.

NH_2-CEBG-R 3. CEBG-R1 (150 mg, 0.11 mmol) was dissolved in a solution of 1:5 TFA/CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 2 h. After the solvent was removed in vacuum, NH_2-CEBG-R **3** was obtained as a yellow glass in a 99% yield. ^{1}H NMR ($CDCl_3$): δ 1.09 (18H, s), 1.43−1.78 (8H, m), 3.02−3.31 (12H, m), 3.38−3.89 (24H, m), 4.00−4.23 (10H, m), 4.60 (2H, s), 6.88−6.97 (3H, m), 6.98−7.09 (4H, m), 7.10−7.41 (5H, m). ^{13}C NMR (DMSO-d_6): 174.2, 170.4, 154.9, 152.0, 150.1, 149.4, 148.9, 148.0, 132.6, 126.5, 126.0, 125.3, 124.3, 116.9, 115.9, 114.0, 110.2, 109.2, 71.7, 71.4, 71.1, 70.7, 70.5, 70.3, 70.1, 69.5, 55.9, 49.6, 46.8, 35.7, 34.5, 33.7, 32.0, 26.5, 22.9. MS: found 1178.6954, calcd for $C_{63}H_{96}N_5O_{16}^+$ [M + H^+] 1178.6847.

MeO_2C-CEBG-R 4. Monomethylmalonate potassium salt (32 mg, 0.20 mmol) and 1,1′-carbonyldiimidazole (33 mg, 0.20 mmol) were dissolved in CH_2Cl_2 (15 mL). The reaction mixture was refluxed for 3 h and then treated with a solution of NH_2-CEBG-R **3** (120 mg, 0.10 mmol) in DMSO (2 mL). The reaction mixture was refluxed for 20 min and then stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure, and the crude material was extracted with EtOAc/H_2O. The organic layer was collected and dried with $MgSO_4$, and then the solvent was removed under vacuum. The residue was separated by flash chromatography on silica gel using 8:92 MeOH/CH_2Cl_2 as the eluent. MeO_2C-CEBG-R **4** (110 mg, 0.080 mmol) was obtained as a yellow oil in a 78% yield. ^{1}H NMR ($CDCl_3$): δ 1.17 (18H, s), 1.22−1.44 (6H, m), 1.80−1.93 (2H, m), 3.18−3.82 (44H, m), 3.92−4.19 (20H, m), 4.57 (2H, s), 6.29−6.45 (2H, m), 6.5−6.62 (2H, m), 6.79−6.94 (2H, m), 7.11−7.42 (6H, m). ^{13}C NMR ($CDCl_3$): δ 170.4, 168.7, 157.9, 154.6, 151.6, 148.7, 147.5, 144.0, 137.0, 134.9, 132.7, 131.7, 130.3, 124.4, 123.4, 121.1, 117.2, 112.3, 107.4, 105.8, 70.7, 70.6, 70.0, 69.7, 69.4, 68.7, 68.5, 68.3, 52.6, 52.5, 49.0, 41.3, 40.9, 36.4, 34.9, 31.4, 26.6, 25.3, 21.8. MS: found 1397.7711, calcd for $C_{71}H_{106}N_5O_{23}^+$ [M + H_2O^+] 1397.7357.

CEBG-R2. MeO_2C-CEBG-R **4** (110 mg, 0.080 mmol) was dissolved in MeOH (20 mL), and $(CH_3)_4NOH\cdot 5H_2O$ (40 mg, 0.2 mmol) was added. The reaction mixture was stirred overnight at 50 °C. The solvent was evaporated under reduced pressure, and the residue was extracted with EtOAc/1 N HCl. The organic layer was collected, dried with $MgSO_4$, and evaporated under vacuum. The residue was separated by HPLC to yield CEBG-R2 (105 mg, 0.076 mmol) as an orange foam in a 95% yield. ^{1}H NMR ($CDCl_3$): δ 1.17 (18H, s), 1.22−1.45 (6H, m), 1.81−1.94 (2H, m), 3.32−3.58 (8H, m), 3.62−3.87 (38H, m), 3.93−4.21 (14H,m), 4.58 (2H,s), 6.51−6.63 (2H,m), 6.66−6.81 (2H,m), 6.88−7.05 (2H,m), 7.13−7.43 (6H,m). ^{13}C NMR ($CDCl_3$): δ 171.1, 169.9, 157.8, 154.5, 151.0, 148.7, 143.9, 142.7, 136.4, 136.1, 135.4, 133.5, 130.9, 122.2, 121.8, 117.1, 116.5, 115.0, 111.7 106.3, 71.1, 71.0, 70.4, 70.2, 70.0, 69.6, 68.8, 66.4, 55.5, 49.4, 47.2, 40.9, 34.8, 34.7, 33.7, 31.4, 24.9 23.1. MS: found 1369.8661, calcd for $C_{69}H_{102}N_5O_{23}^+$ [M + H_3O^+] 1369.8547.

CEBG-R3. NH_2-CEBG-R **3** (120 mg, 0.10 mmol) was dissolved in 1:1 CH_2Cl_2/DMSO (15 mL). To this solution was added glutaric anhydride (23 mg, 0.20 mmol) followed by Et_3N (15 μL, 0.11 mmol). The reaction mixture was stirred overnight at room temperature. After the solvent mixture was removed under reduced pressure, the residue was separated by HPLC to yield CEBG-R3 (110 mg, 0.04 mmol) as a yellow oil in a 80% yield. ^{1}H NMR ($CDCl_3$): δ 1.14 (18H, s), 1.31−1.51 (2H, m), 1.74−1.85 (6H, t), 2.21−2.35 (8H, m), 3.08 (8H, m), 3.17−3.35 (4H, m), 3.36−3.7 (30H, m), 3.71−3.89 (8H, m), 3.98−4.2 (10H, m), 4.57 (2H, s), 6.84−7.01 (3H, m), 7.04−7.16 (3H, m), 7.15−7.27 (2H, m), 7.30−7.36 (2H, m) 7.4−7.51 (2H, m) . ^{13}C NMR ($CDCl_3$): δ 175.7, 172.8, 171.9, 169.9, 151.9, 148.2, 148.1, 144.7, 144.4, 134.9, 134.8, 134.1, 132.88, 125.3, 124.1, 113.2, 112.7, 112.5, 106.0, 105.4, 71.5, 71.1, 70.9, 70.5, 69.7, 69.6, 69.1, 67.9, 53.4, 49.6, 47.0, 37.2, 36.7, 36.5, 34.7, 34.4, 32.6, 32.4,26.8 22.0. MS: found 1406.7620, calcd for $C_{73}H_{110}N_5O_{23}^+$ [M + H_3O^+] 1406.7487.

Boc-Axle. 5-[*tert*-Butoxycarbonyl(3,5-di-*tert*-butylbenzyl)-amino]pentanoic acid **6**[38] (0.92 g, 2.2 mmol) was combined with DCC (0.87 g, 4.2 mmol) in $CHCl_3$ (5 mL). The resulting solution was stirred for 2 h at room temperature. 3-Amino-*N*-(3,5-dimethylphenyl) propanamide **5** (0.40 g, 2.1 mmol) was added to the solution, which was stirred overnight. $CHCl_3$ was partially evaporated under reduced pressure. DCU was precipitated with the addition of CH_3CN, which was removed by filtration. The mother liquor was removed in vacuum, and the residue was purified via flash chromatography on silica gel with 3:97 MeOH/CH_2Cl_2 as the eluent. Boc-Axle (1.24 g, 2.10 mmol) was obtained as a white glass in a 95% yield. NMR ($CDCl_3$): δ 1.31 (18H, s), 1.45 (9H, s), 1.68 (2H, m), 1.78 (2H, m), 2.26 (6H, s), 2.48 (2H, t), 2.58 (2H, t), 3.21 (2H, t), 3.57 (2H, t), 4.60 (2H, s), 6.73 (1H, s), 7.03 (2H, s), 7.19 (2H, s), 7.30 (1, s), 8.22 (1H, s), 8.47 (1H, s). ^{13}C NMR ($CDCl_3$): δ 172.6, 168.9, 155.1, 150.0, 137.5, 135.1, 125.0, 121.0, 120.4, 120.2, 116.7, 78.7, 49.4, 46.2, 36.2, 33.8, 32.9, 31.4, 30.5, 27.5, 23.9, 22.0, 20.4. MS: found 616.4095, calcd for $C_{36}H_{55}N_3O_4Na^+$ [M + Na^+] 616.4091.

Axle-1. Boc-Axle (1.4 g, 2.1 mmol) was treated with 1:4 TFA/CH_2Cl_2 (15 mL) for 2 h. After the volatile materials were removed via evaporation under reduced pressure, the material was separated via column chromatography using a 2:98 MeOH/CH_2Cl_2 as the eluent. Axle-1 (0.89 mg, 1.8 mmol) was obtained as a colorless oil in an 86% yield. ^{1}H NMR ($CDCl_3$): δ 1.28 (18H, s), 1.63 (2H, m), 1.76 (2H, m), 2.14 (1H, s), 2.23 (6H, s), 2.60 (2H, t), 2.86 (2H, t), 3.32 (2H, t), 3.51 (2H, t), 4.61(2H, s), 6.75 (1H, s), 7.10 (2H, s), 7.22 (2H, s), 7.36 (1, s), 8.90 (1H,s), 9.00 (1H, s). ^{13}C NMR ($CDCl_3$): δ 172.5, 170.9, 152.1, 138.7, 137.2, 134.9, 126.7, 123.9, 121.8, 118.5, 51.5, 47.5, 36.1, 34.8, 33.1, 31.4, 31.2, 25.2, 24.6, 21.2. MS: found 494.3734, calcd for $C_{31}H_{48}N_3O_2^+$ [M + H^+] 494.3747.

ArBG-R. ArBG-R was synthesized and purified following the methods used to obtain CEBG-R1 except that 3-amino-*N*-(3,5-dimethylphenyl)propanamide (38 mg, 0.20 mmol) was used as the starting material. ArBG-R (99 mg, 0.084 mmol) was obtained as a colorless oil in a 42% yield. Note: to be consistent with the other rotaxanes, ArBG-R was subjected to HPLC conditions prior to performing extraction assays. ^{1}H NMR: 1.27 (18H, s), 1.50 (18H, s), 1.71−2.03 (6H, m), 2.56−2.69 (2H, m), 2.79−2.96 (3H, m), 3.08−3.27 (3H, m), 3.28−3.83 (15H, m), 3.95−4.13 (3H, m), 4.16−4.42 (4H, m), 4.57 (2H, m), 6.69 (1H, m), 6.85 (2H, m), 6.87 (1H, m), 7.17 (1H, m), 7.22 (2H, m), 7.30 (2H, m), 7.39 (1H, m), 7.40 (1H, m), 7.56 (1H, m), 7.74 (1H, m), 8.06 (1H, s), 8.35 (2H, s), 8.37 (1H, m). ^{13}C NMR:

171.6, 169.1, 167.0, 156.2, 150.2, 146.3, 142.0, 137.2, 137.1, 132.1, 127.7, 124.5, 123.3, 122.2, 116.6, 112.2, 110.5, 79.2, 69.3, 68.9, 68.7, 51.6, 47.6, 35.9, 35.4, 34.1, 33.7, 31.4, 30.3, 27.2, 24.8, 23.1. MS: found 1172.7792, calcd for $C_{65}H_{98}N_5O_{14}^+$ $[M + H^+]$ 1172.7111.

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Supporting Information Available: 1D and 2D NMR spectra, postulated binding modes, chemical shift differences for hosts with TFA^- versus Cl^- as counterions, %T values. This material is available free of charge via the Internet at http://pubs.acs.org.