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Calix[4]pyrrole-Based Ion Pair Receptors

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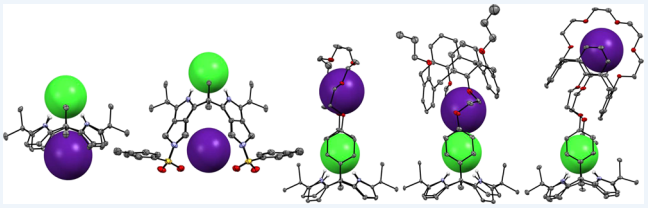
CONSPECTUS: Ion pair receptors, which are able to bind concurrently both a cation and an anion, often display higher selectivity and affinity for specific ion pairs than simple ion receptors capable of recognizing primarily either a cation or an anion. This enhancement in recognition function is attributable to direct or indirect cooperative interactions between cobound ions via electrostatic attractions between oppositely charged ions, as well as to positive allosteric effects. In addition, by virtue of binding the counterions of the targeted ion, ion pair receptors can minimize the solvation of the counterions, which can otherwise have a negative effect on the interactions between the receptors and the targeted ions. As a result of their more favorable interactions, ion pair receptors are attractive for use in applications, such as extraction and sensing, where control of the binding interactions is advantageous. In this Account, we illustrate this potential in the context of ion pair receptors based on the calix[4]pyrrole scaffold. Both simple ditopic ion pair receptors, containing sites for the recognition of a single anion and single cation, and so-called multitopic ion pair receptors will be discussed. The latter systems differ from conventional, so-called ditopic ion pair receptors in that they contain more than one binding site for a given targeted ion (e.g., a cation). This permits a level of selectivity and control over binding function not normally seen for simple ion or ion pair receptors containing one or two binding sites, respectively.



Calix[4]pyrroles are macrocyclic compounds consisting of four pyrrole units linked via fully substituted sp^3 hybridized meso carbon atoms. They are effective receptors for Lewis basic anions (e.g., halides) in typical organic media and under certain conditions will recognize ion pairs containing charge diffuse cations, such as a small alkylammonium, imidazolium, or cesium cations. The calix[4]pyrrole framework is further attractive in that it is relatively easy to modify. In particular, functionalization of the *β*-pyrrolic carbon and *meso*-carbon atoms with simple crown ethers or calix[4]arene crown ethers can produce heteromultitopic ion pair receptors containing more than two cation binding sites. This allows the interactions between receptors and ions to be manipulated on a higher level than can be achieved using simple ion receptors or heteroditopic ion pair receptors and has made these systems attractive for use in ion transport, recognition, and extraction. Recent progress in developing calix[4]pyrroles as both multitopic and more conventional ion pair receptors is summarized in this Account. The emphasis will be on our own work.

1. INTRODUCTION

Over the past several decades, considerable effort has been devoted to the development of ion receptors that are capable of binding either a cation or an anion with high affinity and selectivity.[1−7] More recently, increasing attention has been paid to more elaborate systems that are able to bind both a cation and an anion.[8−10] This emphasis reflects a growing appreciation that counterions play a critical role in modulating the selectivity and strength of the binding interactions occurring between simple ions and receptors designed to achieve their recognition. Typically, ion pair receptors contain two disparate binding sites, one for an anion and one for a cation. In many cases, ion pair receptors show enhanced affinities and selectivity for target ions as compared with analogous single ion receptors.[8−10] These improved ion recognition features are attributable to allosteric effects and enhanced electrostatic interactions between the cobound ions present in the ion pair complexes, as well as reductions in competing solvation effects as the result of concurrent ion binding within a receptor pocket or cavity.[8−10] This increased level of control has made ion pair receptors attractive for use in inter alia ion extraction, transmembrane ion transport, ion sensing, and logic gate design.[8−10]

Most ion pair receptors reported to date have been constructed on the basis of heteroditopoic systems, which consist of one cation binding domain and one anion binding site.[8−10] More recently, we demonstrated that more sophisticated systems, multitopic ion pair receptors having more than two cation binding sites with different ion selectivities and affinities, can be used to support ion pair recognition, selective extraction, and controlled cation release.[11−13] On this basis, we suggest that multitopic ion pair receptors may permit a greater level of control over the underlying interactions between ion pairs and receptors than can be achieved from simple ion receptors or heteroditopic receptors. We have worked to test this postulate using systems based on the calix[4]pyrrole framework.

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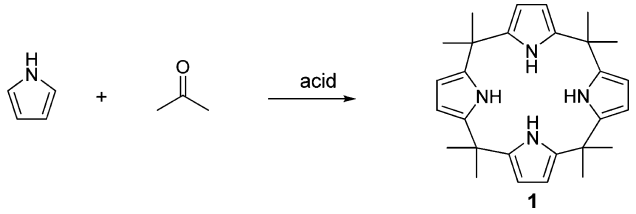
Calix[4]pyrroles are macrocyclic compounds consisting of four pyrrole units linked through their 2 and 5 positions via four fully substituted sp^3 hybridized meso carbon atoms. They are attractive frameworks for the construction of multitopic ion pair receptors because (1) they bind Lewis basic anions in organic media via pyrrole NH−anion hydrogen bonds, (2) after anion binding they adopt an organized cone-like structure that supports the further recognition of charge diffuse cations, and (3) they may be functionalized readily with various cation binding motifs, including crown ethers and calixarenes, via the meso carbons or β-pyrrolic carbons.[14−16]

The parent form of calix[4]pyrrole (**1**) was first synthesized by Baeyer in 1886 via the acid-catalyzed condensation reaction of pyrrole with acetone in the presence of HCl (see Scheme 1).[17] The structure was correctly characterized as a *meso*-octamethyl substituted tetrapyrrolic macrocycle by Chelintzev and Tronov in 1916.[18] In 1996, we found that calix[4]pyrrole **1** has the ability to bind halide anions efficiently as the result of hydrogen bonding interactions involving the pyrrolic NHs and the anions.[19] Since then, calix[4]pyrroles have attracted wide interest as anion receptors, and considerable effort has been dedicated to improving the binding affinity and selectivity for specific anions.[14−16] In 2005, we reported that calix[4]pyrrole **1** can form ion pair complexes with halide anion salts containing charge diffuse cations, such as the cesium and imidazolium cations.[20] In follow-up studies, the ion pair binding capability of calix[4]pyrroles has been exploited for use in two-phase, liquid−liquid ion extractions and in the transmembrane transport of cesium halide ion pairs.[21−23] More recently, a number of ion pair receptors based on functionalized calix[4]pyrroles have been developed for ion pair recognition and extraction.[11−13,24−29] These approaches to ion pair recognition are summarized in this Account.

Scheme 1. Synthesis of Calix[4]pyrrole 1



2. CALIX[4]PYRROLE

Unsubstituted calix[4]pyrrole **1** can exist in four limiting conformations, namely, the so-called cone, partial cone, 1,2-alternate, and 1,3-alternate conformations.[14−16] In noncompetitive solvents, these conformations are in fast equilibrium on the NMR time scale at room temperature.[14−16] In contrast, several crystal structures have served to reveal that calix[4]-pyrrole **1** adopts the 1,3-alternate conformation favorably in the solid state. In contrast, the cone conformation dominates for the anion-bound form, both in solution and in the solid state (Figure 1).[14−16]

Early evidence that calix[4]pyrrole **1** can function as an ion pair receptor came from single crystal X-ray diffraction analyses of complexes containing charge diffuse cations.[20] The structures of several cesium halide complexes of **1** revealed, for instance, that the halide anions are bound to all four pyrrolic NH protons via hydrogen bonds (Figure 2). Concurrently, the cesium countercations were found to be encapsulated by the

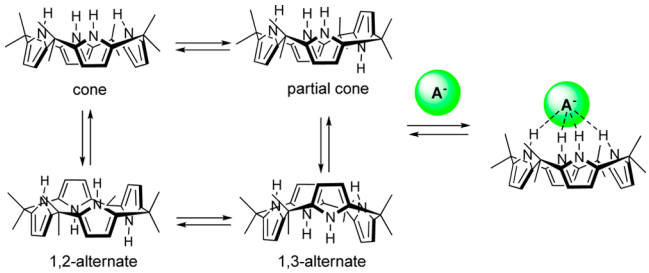


Figure 1. Four possible conformations of calix[4]pyrrole **1**. These are shown in schematic form, along with the equilibrium that serves to interconvert them in the absence of an anion. The cone conformation dominates for the anion bound form.

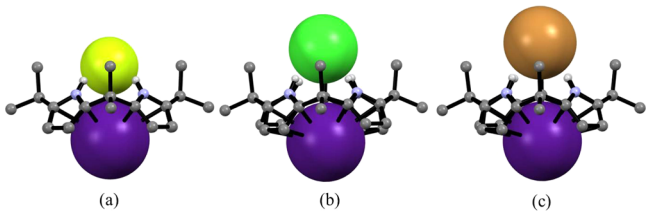


Figure 2. Single crystal X-ray diffraction structures of (a) the CsF, (b) CsCl, and (c) CsBr complexes of calix[4]pyrrole **1**. This and other X-ray figures were produced using data downloaded from the Cambridge Crystallographic Data Centre.

bowl-shaped electron-rich calix[4]pyrrole cavity that is produced when the macrocycle becomes fixed in the cone conformation as a result of anion binding (Figure 2). Based on the structural parameters, it was inferred that the cesium cation is held in place via a combination of π-cation complexation and dipole interactions. Further evidence for the proposed π−cation interactions came from ^{1}H NMR spectroscopic analyses using acetone-d_6 containing 2% D_2O as the solvent.[20] Specifically, upon the addition of $CsClO_4$ to the tetrabutylammonium chloride complex of calix[4]pyrrole **1**, the signal corresponding to the β-pyrrolic protons was found to undergo a significant downfield shift.

Two phase liquid−liquid extraction experiments using nitrobenzene and water provided direct support for the proposition that calix[4]pyrrole **1** can act as an effective ion pair receptor.[21] It was demonstrated by these extraction studies that calix[4]pyrrole **1** is able to extract cesium halide salts, such as CsCl and CsBr, but not $CsNO_3$, from an aqueous phase into a relatively polar organic phase consisting of nitrobenzene. Under conditions of extraction, an ion-paired 1:1:1 cesium/calix[4]pyrrole/halide complex (halide = chloride or bromide) is formed in the nitrobenzene phase. The process of solvent extraction was proposed to take places via three thermochemical steps (Figure 3). First, the cesium cations and the halide anions partition into the nitrobenzene phase from the water phase. The conformation of calix[4]pyrrole **1** then switches to the cone conformation as the result of halide anion binding. Finally, the cesium cation is encapsulated within the calix[4]-pyrrole cavity formed as a result of the conformational change occurring in the second step.[21]

Transmembrane transport experiments also served to demonstrate that calix[4]pyrrole **1** transports CsCl across phospholipid bilayers with high selectivity and efficiency relative to other alkaline chloride salts (Figure 4).[22,23] For this study, unilamellar POPC (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine) vesicles loaded with alkali metal chloride

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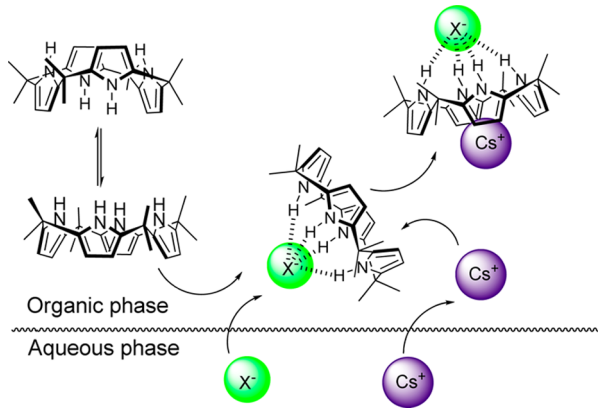

Figure 3. Proposed steps involved in cesium halide salt extraction.

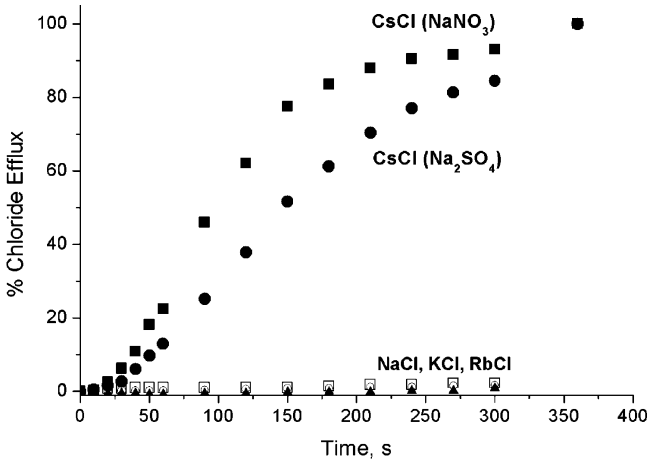

Figure 4. Chloride efflux promoted upon addition of **1** (2% molar carrier to lipid) to unilamellar POPC vesicles loaded with 488 mM CsCl (■), RbCl (○), KCl (▲), or NaCl (□), 5 mM phosphate buffer, pH 7.2, dispersed in 488 mM $NaNO_3$, 5 mM phosphate buffer, pH 7.2, and unilamellar POPC vesicles loaded with 488 mM CsCl (●), 5 mM phosphate buffer, pH 7.2, dispersed in 162 mM Na_2SO_4. Reproduced with permission from ref 22. Copyright 2008 Royal Society of Chemistry.

salts were prepared and suspended in an external $NaNO_3$ or Na_2SO_4 solution. Calix[4]pyrrole **1** (2% molar carrier to lipid) dissolved in DMSO was added, and the resulting alkali chloride anion efflux was monitored with a chloride selective electrode. Five minutes after the addition of the calix[4]pyrrole, the vesicles were lysed by addition of detergent, and the final reading of the electrode was used to calibrate 100% release of the chloride. Under these conditions, calix[4]pyrrole **1** engendered the selective and efficient transport of the CsCl ion pair (Figure 4).[22,23]

The anion-bound, cone-shaped calix[4]pyrrole cavity is also capable of interacting with certain organic cations, including imidazoliums, pyridiniums, and tetraalkylammoniums, thereby forming ion pair complexes.[20] This was revealed, for example, by single crystal X-ray structural analyses of the complexes formed between **1** and either 1-butyl-3-methylimidazolium chloride (**2**) or 1-butyl-3-methylimidazolium bromide (**3**); in both cases, the imidazolium cations were found to be included in the cone-shaped calix[4]pyrrole cavity. They are held in place via presumed CH−π interactions involving the acidic CH groups in the 4- and 5-positions of the imidazolium ring and the π-electron clouds of two of the four pyrrole rings that make up the calix[4]pyrrole cone (Figure 5).[20] Similar binding interactions were observed between calix[4]pyrrole **1** and 1-

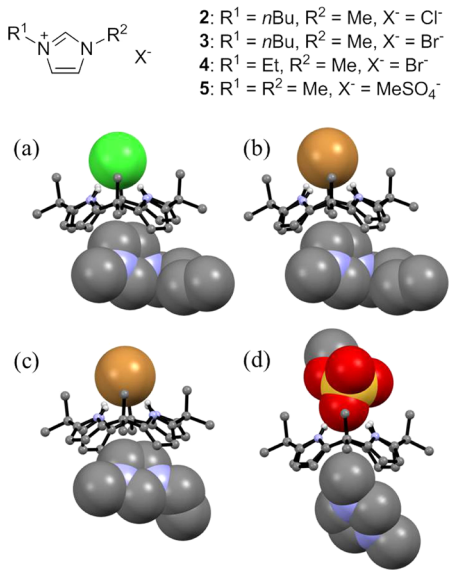

Figure 5. Single crystal X-ray diffraction structures of complexes (a) [**1**·**2**], (b) [**1**·**3**], (c) [**1**·**4**], and (d) [**1**·**5**].

ethyl-3-methylimidazolium bromide (**4**) (Figure 5). By contrast, in the case of the complex formed between calix[4]pyrrole **1** and 1,3-dimethylimidazolium methylsulfate (**5**), the methyl group is coordinated within the cone-shaped calix[4]pyrrole cavity via CH−π interactions while one oxygen atom of the methylsulfate anion is hydrogen bonded to the four NH protons (Figure 5). Proton NMR spectroscopic analyses, carried out in CD_2Cl_2, support the proposition that the imidazolium cations are bound to the calix[4]pyrrole cavity in the cone conformation. Specifically, upon addition of 1-butyl-3-methylimidazolium tetrafluoroborate to the chloride complex of **1**, the proton resonances of the imidazolium ring are shifted upfield, as would be expected for a species bound in a more shielded environment.[20]

3. β-SUBSTITUTED CALIX[4]PYRROLES

One of the more appealing strategies for constructing calix[4]pyrrole-based ion pair receptors is to introduce cation binding sites into β-pyrrolic positions of the parent calix[4]-pyrrole **1**.[26] The first β-octaalkyl substituted calix[4]pyrrole derivative **6** was synthesized by the reaction of *N*-tosylpyrrolidine pyrrole with acetone in the presence of 1.0 equiv of trifluoroacetic acid (TFA) (Scheme 2).[26]

The affinity of calix[4]pyrrole **6** for tetraalkylammonium halide ion pairs were determined by isothermal titration calorimetry (ITC) analyses in chloroform; the resulting values were found to be 2.4×10^6, 2.2×10^5, and 4.4×10^2 M^{-1} for TBACl, TBABr, and TBAI, respectively.[26] These values are considerably enhanced relative to what is seen for unsubstituted calix[4]pyrrole **1** (e.g., $<10^2$ M^{-1} for TBACl).[26] This enhancement is ascribed to the presence of additional stabilizing interactions between the tetraalkylammonium cations and the four tosyl groups as evidenced by the X-ray crystal structure of the TBACl complex, [**2**·TBACl] (Figure 6). In this case, the TBA^+ cation is encapsulated by the four tosyl groups, which are brought together in proximity as a result of chloride anion binding.[26] The presumed interaction between

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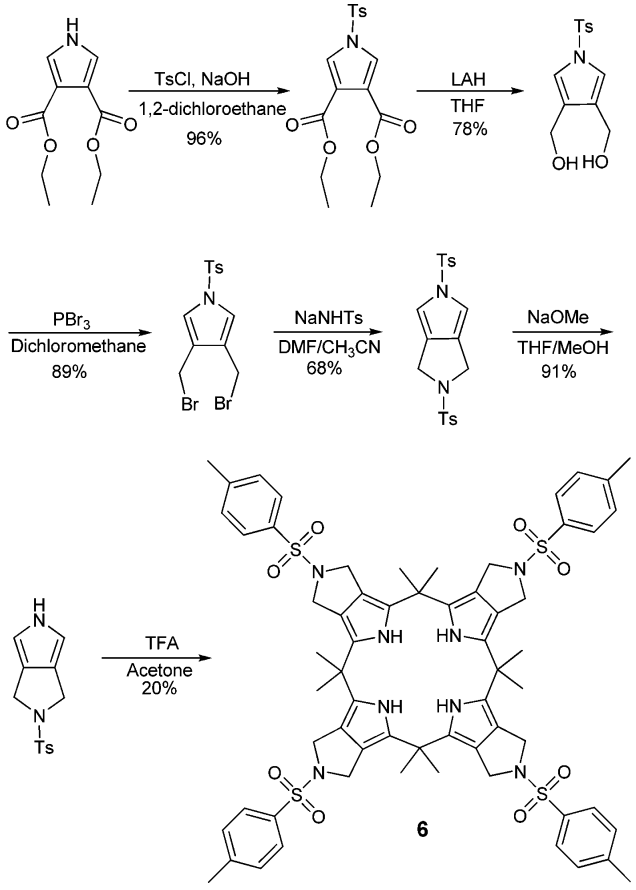
Scheme 2. Synthesis of β-Octaalkyl Substituted Calix[4]pyrrole 6



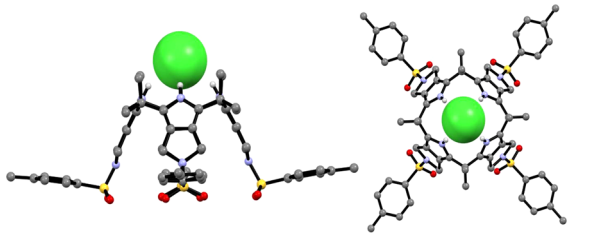


Figure 6. Two different views of the single crystal structure of **6**·TBACl. Most hydrogen atoms have been removed for clarity. The countercation, TBA^+, sitting in the cavity formed by four sulfonyl groups, is disordered and is not shown.

the tetraalkylammonium countercations and the four tosyl groups was further supported by ^{1}H NMR spectral studies of calix[4]pyrrole **6** carried out in $CDCl_3$. Specifically, it was found that in the presence of TEACl the proton resonances of the tetraethylammonium cation undergo an upfield shift.[26]

The hydrofuran ring-fused calix[4]pyrrole **7** was synthesized as a racemic mixture by condensing pyrrole with acetone (0.75 equiv) and hydroxyacetone (0.25 equiv) in the presence of 1.0 equiv of methanesulfonic acid in methanol.[27] Proton NMR spectroscopic analysis carried out in $CDCl_3$ revealed that calix[4]pyrrole (**7**) forms a strong complex with CsF. This receptor was also found to solubilize the otherwise insoluble cesium fluoride salt in chloroform.[27] The relatively strong binding of receptor **7** with CsF is ascribed to participation of the oxygen atom of the hydrofuran ring in the binding of the cesium cation as shown schematically in Figure 7. Support for

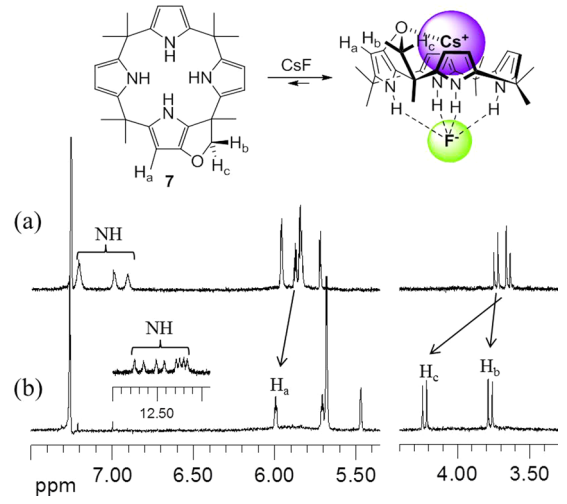


Figure 7. Putative binding mode of CsF with receptor **7** and partial ^{1}H NMR spectra recorded in room temperature in $CDCl_3$ (a) before and (b) after the addition of CsF (as solid).

this conclusion came from the observation that the pyrrolic proton H_a resonance is shifted to lower field upon contact with the cesium cation (Figure 7). Such a chemical shift change stands in marked contrast to what is seen with the relatively noncoordinating TBA^+ cation.[27]

4. CALIX[4]PYRROLES MODIFIED IN THE MESO POSITIONS WITH CATION RECOGNITION SITES

In an effort to create ion pair receptors with an improved ion binding property, simple crown ethers of different ring sizes

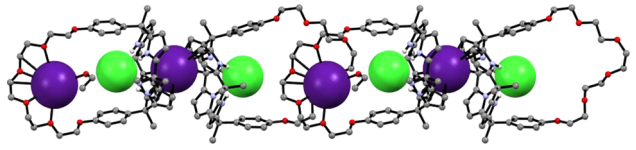


Figure 8. Single crystal X-ray structure of the cesium chloride complexes of receptor **8**. Most hydrogen atoms have been removed for clarity.

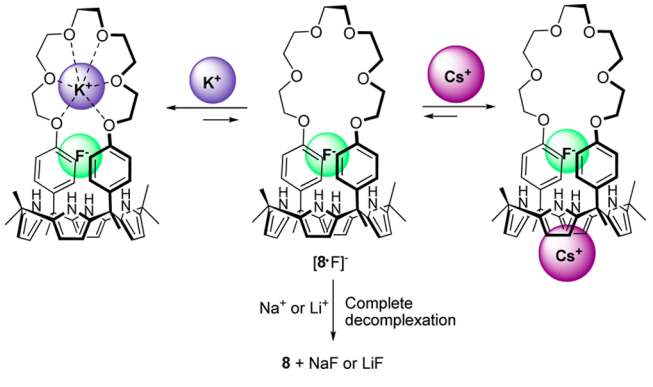


Figure 9. Schematic representation of the effect of treating complex [**8**·F^-] (TBA salt) with perchlorate salts of various alkali metal cations in 10% CD_3OD in CD_3CN.

have been linked to the *meso*-carbon atoms of the calix[4]-pyrrole framework. Examples include compounds **8** and **9**.[28,29]

Evidence that receptor **8** acts as an ion pair receptor came from a single crystal X-ray diffraction analysis of the CsCl

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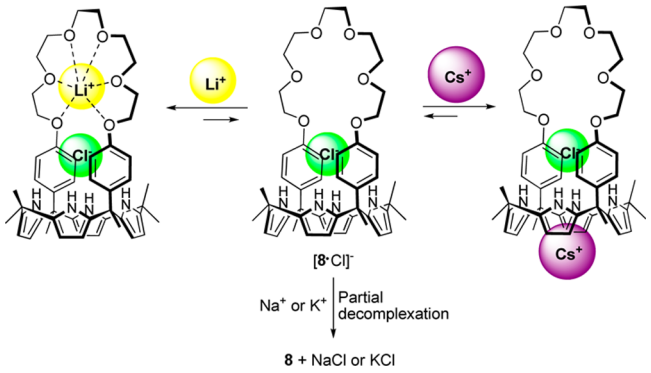


Figure 10. Schematic representation of the complexation and decomplexation events seen for [**8**·Cl$^-$] (TBA salt) upon exposure to various alkali metal cations (as perchlorate salts) in CD_3CN.

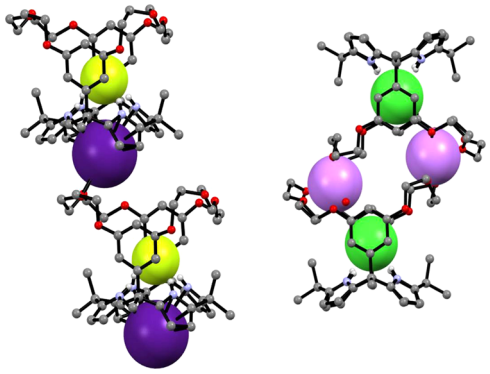
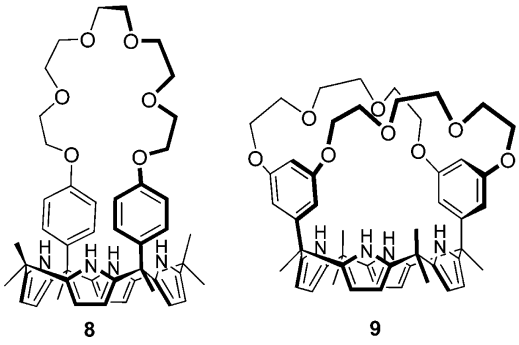


Figure 11. Single crystal X-ray diffraction structures of the CsF (left) and LiCl (right) complexes of receptor **9**.

complex of **8**. The resulting crystal structures revealed that receptor **8** interacts with CsCl in two different binding modes to form a 2:2 ion pair complex (Figure 8). One cesium ion is coordinated by four oxygen atoms of the crown ether ring, as well as by two oxygen atoms from a different molecule (Figure 8). The other cesium ion is sandwiched between two cone-shaped calix[4]pyrroles via apparent π–cation interactions (Figure 8). The chloride anions are hydrogen-bonded to the



NH protons of the two calix[4]pyrroles that make up the overall 2:2 complex (Figure 8).[28]

^{1}H NMR spectroscopic analyses in 10% CD_3OD in $CDCl_3$ provided evidence that receptor **8** is also able to bind alkali metal halide salts in solution. When the fluoride and chloride complexes of receptor **8** were treated with alkali metal ions (as their perchlorate salts), varying ion binding behavior, including ion pair complexation and anion decomplexation, was observed. In the specific case of fluoride, it was concluded that the cesium cation resides within the cone-shaped calix[4]pyrrole cavity, while the potassium cation is coordinated to the oxygen atoms of the crown ether ring (Figure 9). Finally, it was found that treatment of [**8**·F$^-$] with either a Li$^+$ or Na$^+$ cation source induces decomplexation of the prebound F$^-$ anion; this produces the ion-free receptor **8** and either LiF or NaF (Figure 9).[28]

Different behavior was seen upon the addition of akali metal cations to the chloride anion complex of receptor **8** ([**8**·Cl$^-$]; TBA salt). In contrast to what was seen with [**8**·F$^-$], the lithium cation is bound to the crown ether ring present in [**8**·Cl$^-$], forming an ion pair complex of [**8**·LiCl]. On the other hand, addition of the potassium cation causes partial decomplexation of the bound chloride anion (Figure 10). Liposomal model membrane transport studies using unilamellar POPC vesicles revealed that receptor **8** is able to function as an effective ion or ion pair transporter for alkali metal chloride salts, including NaCl, KCl, RbCl, and CsCl.[28]

In the case of the ion pair receptor **9**,[29] single crystal X-ray crystal structural analyses served to establish the formation of stable ion pair complexes with CsF and LiCl in the solid state

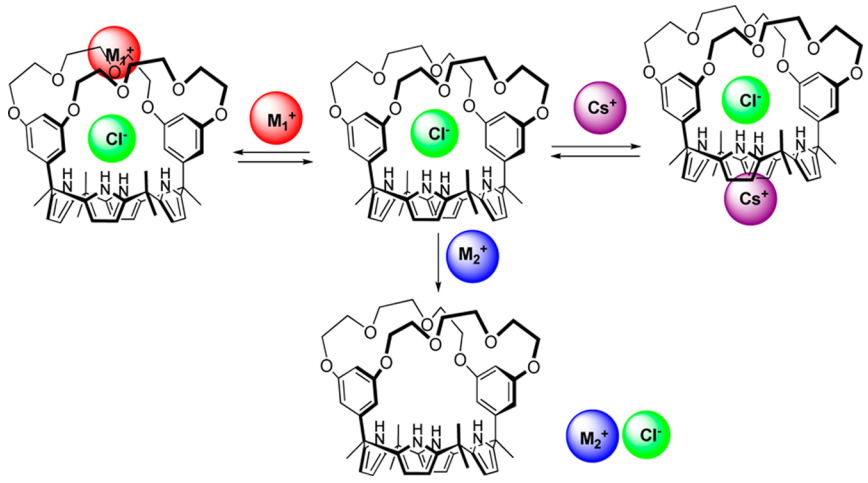


Figure 12. Schematic view of the varying complexation behavior seen for the chloride complex ([**9**·Cl$^-$]; TBA salt) upon exposure to various metal cation perchlorate salts in acetonitrile. M_1^+ = K$^+$ and Li$^+$; M_2^+ = Na$^+$, Mg^{2+}, and Ca^{2+}; M_2^+Cl$^-$ = NaCl, $MgCl_2$, and $CaCl_2$.

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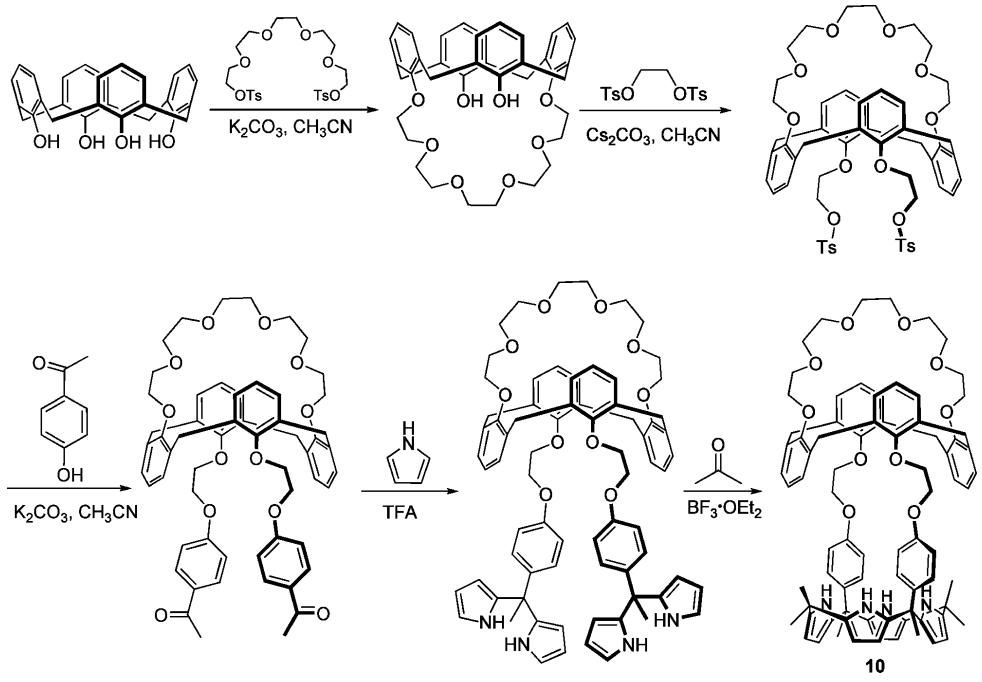
Scheme 3. Synthesis of the Calix[4]crown-6 Strapped Calix[4]pyrrole 10



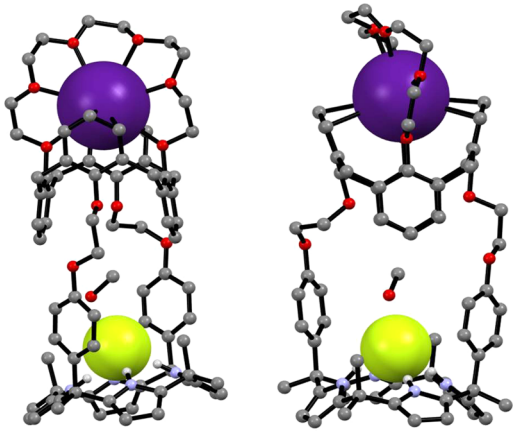


Figure 13. Two different views of the single crystal X-ray diffraction structure of [**10**·CsF·MeOH].

(Figure 11). Two different complexation modes were observed. CsF forms an ion pair complex wherein the cesium cation is held within the cone shaped calix[4]pyrrole cavity. It also interacts with two oxygen atoms of the crown ether ring of a different molecule (Figure 11). In contrast, LiCl forms a 2:2 ion pair complex with receptor **9** where two lithium cations are sandwiched by the crown ether rings from two different receptor molecules, while the chloride anions are hydrogen bonded to the pyrrolic NH protons (Figure 11). The bound Li^+ cation and Cl^- anion are separated by water molecules. The net result is a solvent-separated ion pair complex.[29]

In analogy to what was seen from receptor **8**, varying binding behavior is seen for the fluoride anion complex of receptor **9** in acetonitrile solution. Based on ^{1}H NMR spectral studies, it was concluded that the nature of these anion complexes varies depending upon the choice of akali or alkaline earth cation. When the fluoride complex of receptor **9** ([**9**·F^-]) was treated with the Li^+, Na^+, Mg^{2+}, or Ca^{2+} cations (as their respective perchlorate salts), decomplexation of the prebound fluoride

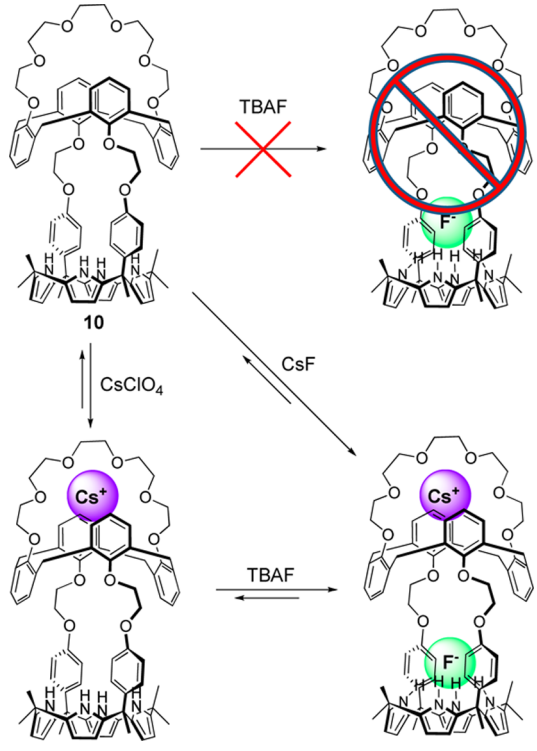


Figure 14. Binding modes for receptor **10** and various salts of Cs^+ and F^- that are proposed to be operative in methanol-d_4/chloroform-d (1/9, v/v).

anion was observed. In contrast, addition of the K^+ or Cs^+ cations to [**9**·F^-] led to formation of the ion pair complexes, [**9**·KF] and [**9**·CsF], wherein the cations are bound to the calix[4]pyrrole cavity.

Different interactions were observed when analogous studies were carried out using the chloride complex ([**9**·Cl^-]; TBA salt) and metal cations. When exposed to Li^+, K^+, and Cs^+ (as

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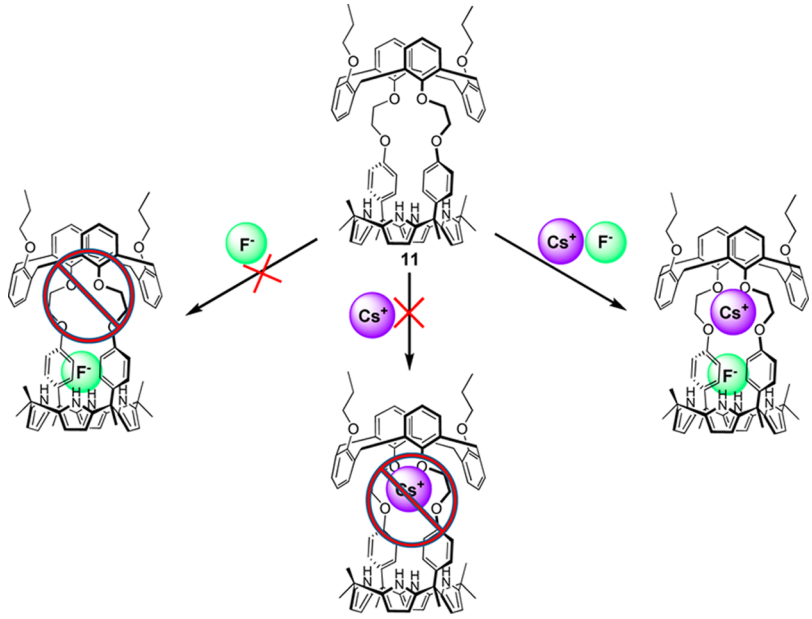

Figure 15. Proposed AND logic gate binding behavior exhibited by receptor **11** when exposed to the cesium cation, fluoride anion, or mixtures thereof in $CD_3OD/CDCl_3$ (1:9, v/v). In addition to CsF, the sources of the ions were TBAF and $CsClO_4$.

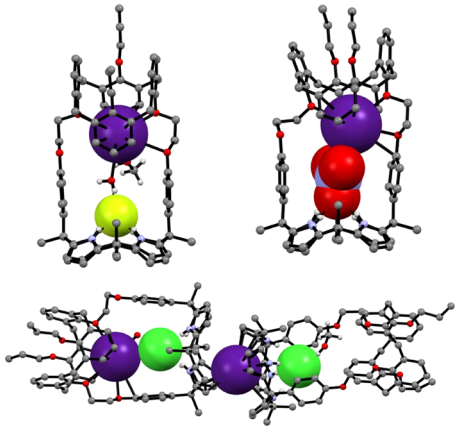

Figure 16. Single crystal X-ray structures of the CsF (top left), CsCl (bottom), and $CsNO_3$ (top right) complexes of receptor **11**.

the perchlorate salts) in acetonitrile, ion pair complexes are formed involving these cations. However, the actual nature of the ion pair complex depends on the choice of the cation. For example, the Li^+ and K^+ cations are bound within the crown ether of [**9**·Cl^-], whereas the cesium cation is coordinated with the calix[4]pyrrole cavity that is locked in the cone conformation as the result of chloride anion binding (Figure 12). In contrast to these cations, exposure of [**9**·Cl^-] (TBA salt) to sodium, magnesium, or calcium perchlorate salts induces decomplexation of the chloride anion.[29]

The 1,3-alternate calix[4]crown-6 subunit is recognized for its high selectivity and affinity for the Cs^+ cation.[30] It is a key component of **10**, a potentially multitopic ion pair receptor whose synthesis is shown in Scheme 3.[24] Initial evidence that receptor **10** forms a stable 1:1 complex with CsF came from a single crystal X-ray diffraction analysis. The resulting crystal structure revealed that the cesium cation is complexed within the calix[4]arene crown-6 ring, while the fluoride anion is hydrogen-bonded to the pyrrole NH protons of the calix[4]-pyrrole subunit. There is thus a large separation (ca. 10.92 Å) between the cobound cation (Cs^+) and anion (F^-). A methanol molecule also interacts with the bound fluoride anion (Figure 13).[24]

Proton NMR spectroscopic analysis performed in methanol-d_4/chloroform-*d* (1/9, v/v) provided support for the notion that complexation of the Cs^+ cation within the calix[4]arene crown-6 ring serves to enhance the F^- binding by the calix[4]pyrrole subunit. Specifically, when the cesium cation

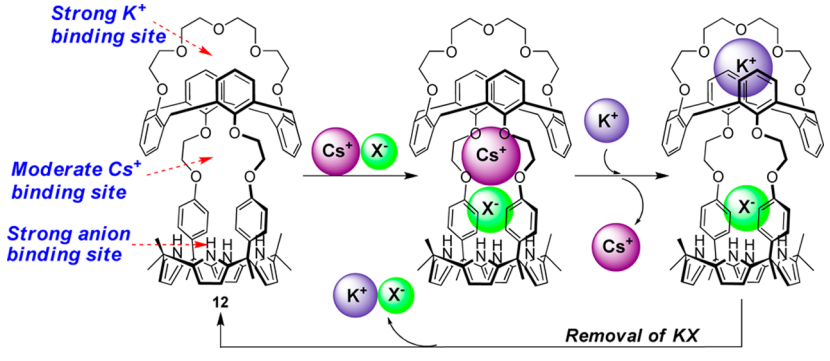

Figure 17. Design concept underlying ion pair receptor **12**.

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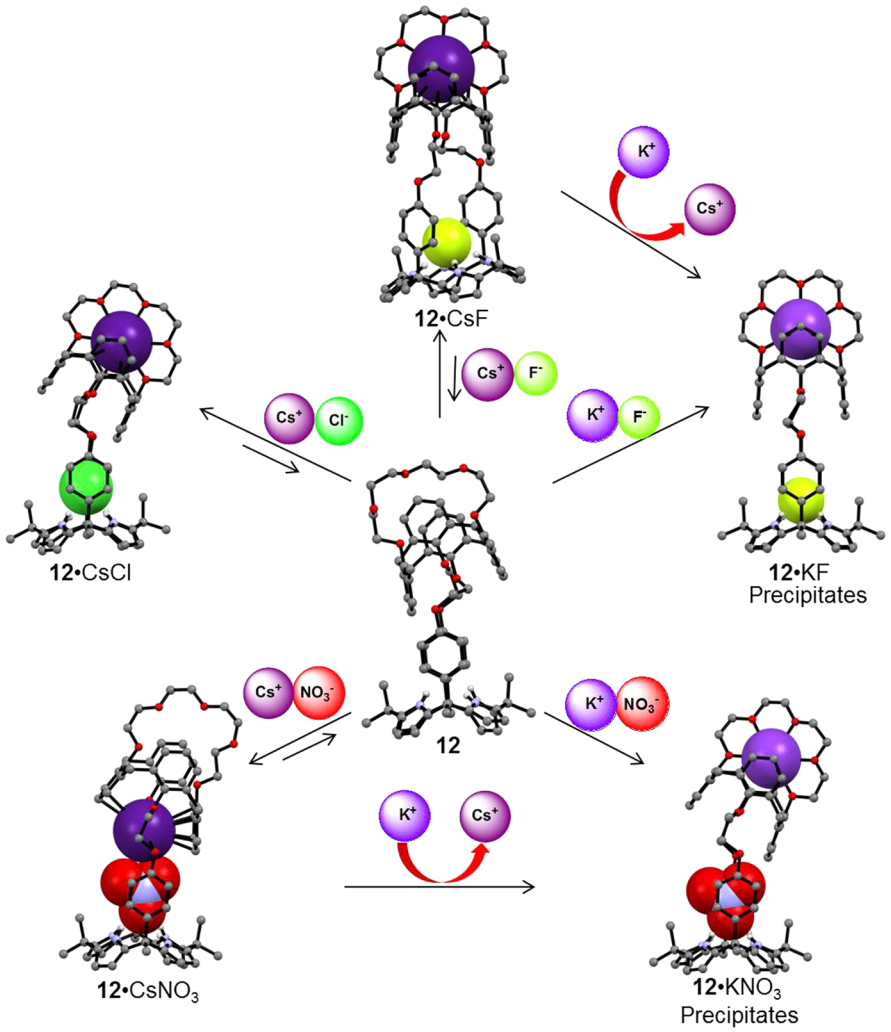

Figure 18. Proposed binding interactions involving receptor **12** and various K^+ and Cs^+ ion pairs as inferred from ^1H NMR spectroscopic studies carried out in $CD_3OD/CDCl_3$ (1/9,v/v). Also shown are the X-ray diffraction structures of the ion pair complexes in question as determined using single crystals grown from mixtures of chloroform and methanol or ethanol. Most hydrogen atoms and solvent molecules have been omitted for clarity.

is complexed within the calix[4]arene crown-6, the F^- binds to the receptor to form a CsF ion pair complex. Conversely, no fluoride binding is seen when Cs^+ is replaced by TBA^+ (Figure 14).[24] This observation is rationalized in terms of the presumption that with the less-coordinating TBA^+ cation, solvation of F^- by the protic solvent (methanol) present in the methanol-d_4/chloroform-*d* (1/9, v/v) mixture outcompetes complexation by the calix[4]pyrrole unit.

The crown-free ion pair receptor **11** was also synthesized.[25] In contrast to what was seen with **10**, in methanol-d_4/chloroform-*d* (1/9, v/v), receptor **11** fails to interact appreciably either F^- or Cs^+ when exposed to salts of these ions in the absence of one another (Figure 15). However, in the presence of CsF or a mixture of salts that provide a source of CsF *in situ*, it binds both Cs^+ and F^- to give rise to a stable 1:1 CsF ion pair complex (Figure 15). This CsF binding behavior thus follows the rules of an AND logic gate. Experimental support for this recognition behavior came from ^1H NMR spectroscopic analysis carried out in methanol-d_4/chloroform-*d* (1/9, v/v). Chemical shift changes were observed that were consistent with the conclusion that receptor **11** binds both the Cs^+ cation and the F^- anion and that recognition of the two ions occurs concurrently, rather than in the stepwise manner observed in the case of receptor **10**.[25]

Receptor **11** was also found to bind other cesium salts, such as CsCl, CsBr, and $CsNO_3$ in solution as well as in the solid state.[25] However, the nature of the ion pair complex was found to differ dramatically within this series of cesium salts highlighting a strong dependence on the specific choice of anion. For example, receptor **11** forms a solvent-separated ion pair complex with CsF in which the cation and anion are bridged by a water molecule (Figure 16). In contrast, the $CsNO_3$ is present as a contact ion pair within the receptor cavity (Figure 16). Moreover, an unusual 2:2 ion pair complex characterized by two different ion pair complexation modes is seen in the case of CsCl (Figure 16). In one complex, the cesium cation is encapsulated within the cavity of calix[4]arene directly contacting the chloride anion that is in turn hydrogen-bonded to the calix[4]pyrrole NH protons. The other cesium cation is held in a sandwich-like fashion between two cone-shaped, chloride anion bound calix[4]pyrroles. The net result is an unusual host-separated ion pair complex (Figure 16).[25]

The multitopic ion pair receptor **12** was also designed and synthesized in an effort to control cation binding and release by

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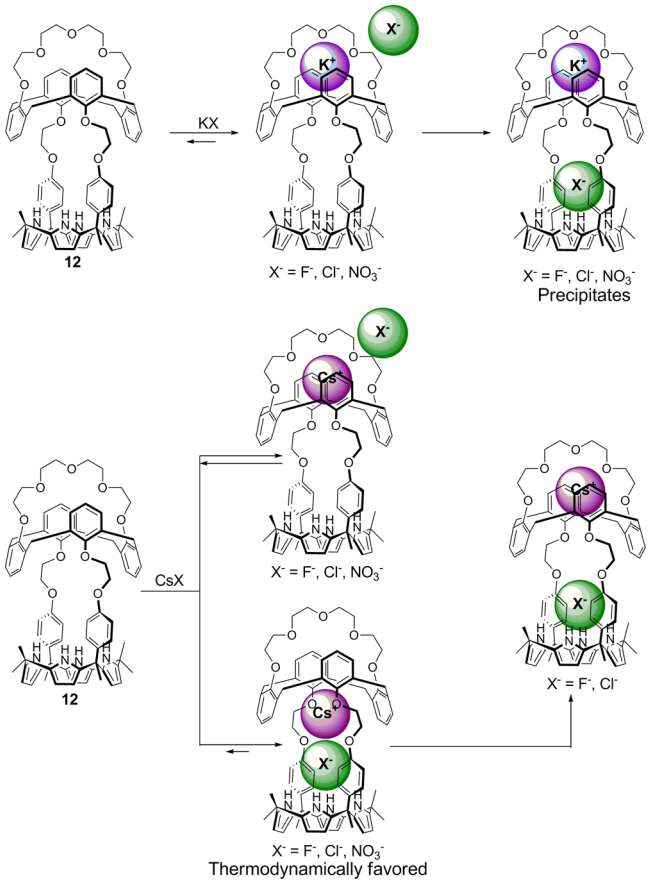

Figure 19. Binding modes of **12** proposed to exist in the absence and presence of various K^+ and Cs^+ salts as inferred from ^1H NMR spectroscopic studies carried out in $CD_3OD/CDCl_3$ (1/9, v/v).

cation metathesis (Figure 17).[11,12] This receptor consists of one anion binding site and three cation recognition sites having differing selectivities and affinities for different cations. For example, the 1,3-alternate calix[4]arene crown-5 subunit has an inherently high preference for the K^+ cation relative to the Cs^+ cation. This preference holds for other cation recognition sites within receptor **12**. Therefore, receptor **12** was expected to complex the Cs^+ cation in the absence of the K^+ cation but to release the Cs^+ cation if subsequently exposed to the K^+ cation (Figure 17).[11,12]

Single crystal X-ray diffraction analysis and ^1H NMR spectroscopic studies serve to demonstrate that ion pair receptor **12** has the ability to bind anions, cations, and various ion pairs containing the Cs^+ and K^+ cations. Various binding modes were found to be operative, both in solution and in the solid state (Figures 18 and 19). For example, this receptor binds KF, KCl, KNO_3, CsF, and CsCl to form 1:1 ion pair complexes where the cations are complexed within the calix[4]arene crown-5 subunit while the anions are bound to the calix[4]pyrrole NH protons (Figures 18 and 19).[11,12] While the overall geometries were similar in all cases, the binding kinetics and physical properties of these ion pair complexes proved to be significantly different. In the cases of KF, KCl, and KNO_3, it was found that receptor **12** binds the K^+ cation and the anions in a stepwise manner when studied in a solution of 10% methanol in chloroform (a mixture chosen for reasons of solubility). That is, the K^+ cation is complexed to the calix[4]arene crown-ring prior to the anions being bound to the calix[4]pyrrole moiety. Once the K^+ is associated with the receptor, anion binding to the calix[4]pyrrole moiety occurs to produce the three ion pair complexes [**12**·KF], [**12**·KCl], and [**12**·KNO_3] (Figure 19). All three complexes then precipitate.

Under the same solution phase conditions (i.e., $CD_3OD/CDCl_3$ (1/9, v/v)), receptor **12** was found to interact with CsF and CsCl to produce complexes characterized by two different binding modes. In one binding mode, the Cs^+ cation, but not the anion, is loosely bound to the calix[4]arene crown-5 ring; this gives a cation complex ([**12**·Cs^+]X^-, X^- = F^- or Cl^-) where the counteranions are not cobound (Figure 19).[11,12] These cation complexes are labile and exist in fast equilibrium with the unbound form on the NMR time scale. In the other identified binding mode, the Cs^+ cation and the anions (the F^- and Cl^-) are bound concurrently to the receptor (Figure 19). Based on detailed ^1H NMR spectroscopic analyses, it was further concluded that the Cs^+ cation is bound first to the ethylene glycol moieties but then moves to the crown-5 ring to form what is a more thermodynamically stable ion pair complex ([**12**·CsX], X^- = F^- or Cl^-) wherein the anion and cation are spatially separated from one another (Figures 18 and 19).

In analogy to what was seen with CsF and CsCl, receptor **12** also binds the $CsNO_3$ ion pair via two different binding modes. However, in this case, the Cs^+ cation remains complexed by the ethylene glycol spacers to form a contact ion pair (Figures 18 and 19). No evidence of a more thermodynamically stable binding mode involving Cs^+ complexation by the crown moiety is seen. This finding stands in marked contrast to what was observed from the KNO_3 complex of receptor **12** where the K^+ is coordinated within the crown-5 ring; presumably, this difference reflects the relative affinity of this latter binding site for the Cs^+ and K^+ cations (Figures 18 and 19).[11,12]

Receptor **12** was found to release Cs^+ when exposed to the K^+ as the result of cation metathesis. For instance, when $KClO_4$ dissolved in 10% CD_3OD in $CDCl_3$ was added to either the CsF or $CsNO_3$ ion pair complexes of **12** in the same solvent, precipitates were formed. This phase change is attributed to the formation of the insoluble ion pair complexes with KF and KNO_3 as a consequence of cation exchange, namely replacement of the prebound Cs^+ cation by the more strongly bound K^+ cation (Figure 18 and eqs 1 and 2).[11,12]

$$[\mathbf{12}] + CsX \rightarrow [\mathbf{12}\cdot CsX] \quad (1)$$

$$[\mathbf{12}\cdot CsX] + KClO_4 \rightarrow [\mathbf{12}\cdot KX] + CsClO_4 \quad (2)$$

where X = F or NO_3

Receptor **12** could be used to extract the Cs^+ cation from aqueous media into a nitrobenzene organic phase. It was found that the Cs^+ cation extracted in this way could be released and recovered by exposure to K^+ as shown schematically in Figure 20.[11] The actual experiments consisted of exposing receptor **12** in nitrobenzene-d_5 to an aqueous (D_2O) solution of $CsNO_3$ in the presence of excess $NaNO_3$. This exposure led to changes in the ^1H NMR spectrum of the organic phase that were ascribed to the selective extraction of $CsNO_3$ from the aqueous phase and its complexation by receptor **12** within the organic phase. A subsequent washing of the organic phase (containing the $CsNO_3$ complex, [**12**·$CsNO_3$]) with an aqueous D_2O solution of $KClO_4$ leads to release of $CsNO_3$ into the aqueous phase (Figure 20). This produces a new cation complex, [**12**·K^+]NO_3^-, in the organic phase as evidenced by ^1H NMR spectroscopy.[18] Contacting the nitrobenzene layer containing this potassium complex with excess chloroform (2×) and D_2O

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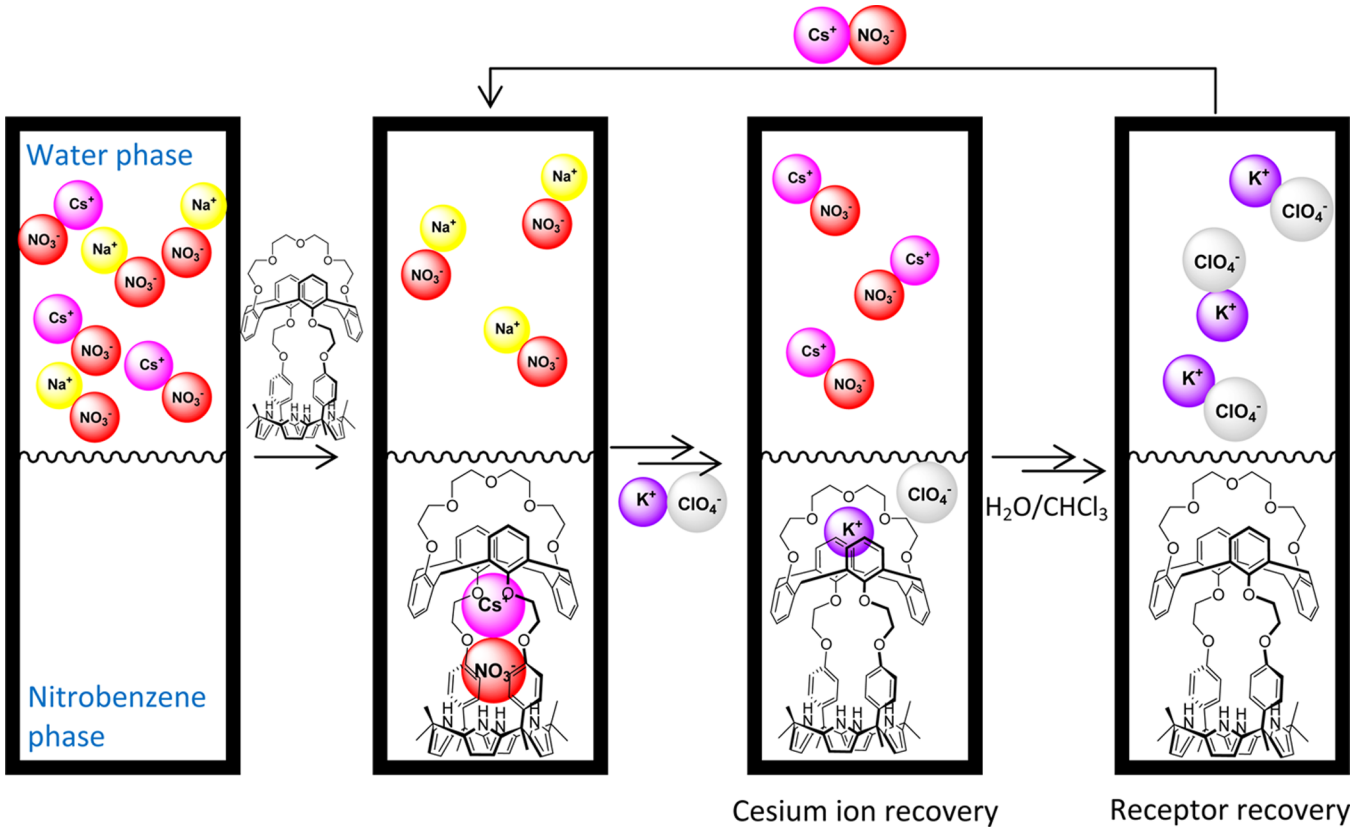

Figure 20. Schematic representation of a two-phase $CsNO_3$ extraction and recovery process that is based on ion pair receptor **12**. Cation metathesis allows for controlled removal of the cesium cation, while further contacting steps allow recycling of the receptor. Reproduced with permission from ref 11. Copyright 2012 American Chemical Society.

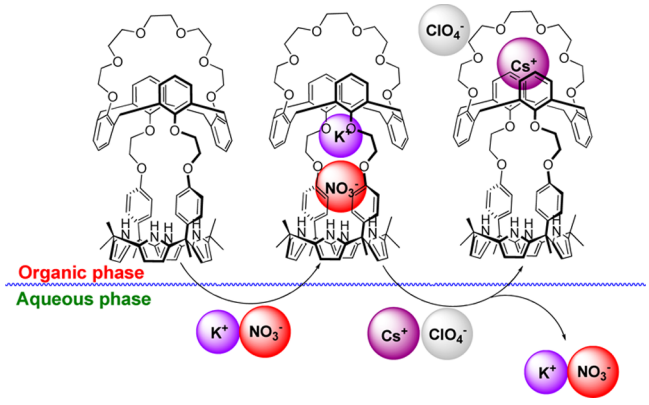

Figure 21. Schematic representation of a two-phase cation metathesis-based extraction and recovery process involving KNO_3 that is mediated by the ion pair receptor **10**.

serves to regenerate the ion-free form of receptor **12** in the organic phase (Figure 20).[11] In contrast, under these two-phase extraction conditions, binding and release of ions or ion pairs could not be accomplished effectively using either the unsubstituted calix[4]pyrrole (**1**), a simple calix[4]arene crown-6 in its 1,3-alternate conformation, or an equimolar mixture of these latter receptors.[12]

More hydrophilic ion pairs, including KNO_3, could be likewise extracted and recovered when the multitopic ion pair receptor **10** was used in lieu of **12**.[13] When exposed to a D_2O solution of KNO_3, receptor **10** complexes and extracts the KNO_3 to a nitrobenzene organic phase as shown in Figure 21. Washing the nitrobenzene phase (containing the KNO_3 complex of **10**) with an aqueous $CsClO_4$ solution serves to release the bound KNO_3 into the aqueous phase and leads to formation of a new cation complex, $[\mathbf{10}\cdot Cs^+]ClO_4^-$, in the organic phase (Figure 21).[13]

5. CONCLUSIONS

The calix[4]pyrrole framework has emerged as a useful platform for the construction of ion pair receptors. Unsubstituted calix[4]pyrroles (e.g., **1**) can function as ion pair receptors for several cesium salts, as well as ion pairs containing several large, charge diffuse organic cations, including the imidazolium, pyridinium, and tetraalkylammonium cations. Moreover, calix[4]pyrrole **1** is able to transport the CsCl ion pair across phospholipid bilayers selectively and can extract CsCl and CsBr from an aqueous phase into a nitrobenzene organic phase under two phase liquid−liquid extraction conditions. Modification and functionalization of the *β*-pyrrolic and *meso*-carbon atoms of the calix[4]pyrrole framework with various cation recognition sites can be used to produce more elaborate ion pair receptors. Strapping the calix[4]pyrrole framework with cation binding motifs that independently bind cations can be used to generate multitopic ion pair receptors. Some of these allow for the metathesis-based control of the underlying cation recognition and release processes. These latter systems are attractive as extractants since they allow for both the extraction and ion-triggered release of a targeted cation. The fundamental understanding that is developing through the study of both simple and complex calix[4]pyrrole-based ion pair receptors is expected to allow for the design and

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preparation of yet-improved systems, including those that may be used for the extraction and sensing of more complex ion pair combinations than have been considered to date. Furthermore, properly designed ion pair receptors are expected to find use in the construction of various self-assembled structures via ion pair recognition. They could also emerge as useful carriers capable of promoting the transport of ion pairs through cell membranes thereby inducing apoptosis. Studies of these new directions are currently in progress in our group.

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Notes

The authors declare no competing financial interest.

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Dr. Sung Kuk Kim received his Ph.D. from the University of Texas at Austin in 2011 under the supervision of Prof. Jonathan L. Sessler. He is currently a postdoctoral researcher in the same research group. His research interests are focused on the development of novel supramolecular systems involved in recognition and sensing of neutral guests and ionic species.

Prof Jonathan L. Sessler received his Ph.D. from Stanford University in 1982. After postdoctoral work with Profs. Jean-Marie Lehn and Iwao Tabushi, he began his academic career at The University of Texas at Austin in 1984, where he now holds the position of Pettit Centennial Chair. He is a cofounder of Pharmacyclics, Inc. (PCYC; Nasdaq) and the author of approximately 600 publications. His research interests include cancer drug development, ion recognition, supramolecular chemistry, sensing, expanded porphyrins, and electron transfer.

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