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Oligoether-Strapped Calix[4]pyrrole: An Ion-Pair Receptor Displaying Cation-Dependent Chloride Anion Transport

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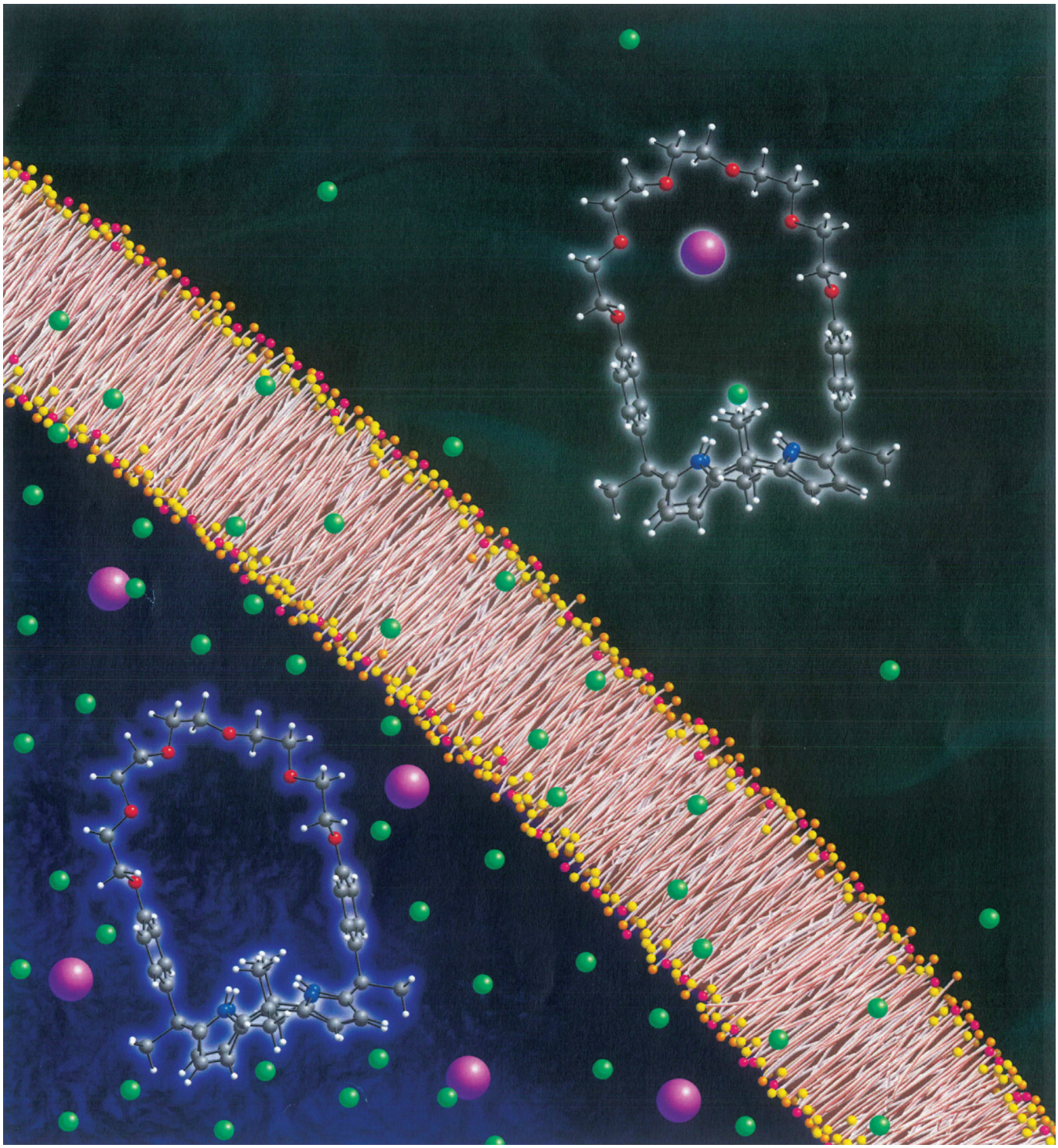

Abstract: A ditopic ion-pair receptor (**1**), which has tunable cation- and anion-binding sites, has been synthesized and characterized. Spectroscopic analyses provide support for the conclusion that receptor **1** binds fluoride and chloride anions strongly and forms stable 1:1 complexes ($[\mathbf{1}\cdot F]^-$ and $[\mathbf{1}\cdot Cl]^-$) with appropriately chosen salts of these anions in acetonitrile. When the anion complexes of **1** were treated with alkali metal ions (Li^+, Na^+, K^+, Cs^+, as their perchlorate salts), ion-dependent interactions were observed that were found to depend on both the choice of added cation and the initially complexed anion. In the case of $[\mathbf{1}\cdot F]^-$, no appreciable interaction with the K^+ ion was seen. On the other hand, when this complex was treated with Li^+ or Na^+ ions, decomplexation of the bound fluoride anion was observed. In contrast to what was seen with Li^+, Na^+, K^+, treating $[\mathbf{1}\cdot\mathbf{F}]^-$ with Cs^+ ions gave rise to a stable, host-separated ion-pair complex, [F·**1**·Cs], which contains the Cs^+ ion bound in the cup-like portion of the calix[4]pyrrole. Different complexation behavior was seen in the case of the chloride complex, $[\mathbf{1}\cdot Cl]^-$. Here, no appreciable interaction was observed with Na^+ or K^+. In contrast, treating with Li^+ produces a tight ion-pair complex, [**1**·Li·Cl], in which the cation is bound to the crown moiety. In analogy to what was seen for $[\mathbf{1}\cdot F]^-$, treatment of $[\mathbf{1}\cdot Cl]^-$ with Cs^+ ions gives rise to a host-separated ion-pair complex, [Cl·**1**·Cs], in which the cation is bound to the cup of the calix[4]pyrrole. As inferred from liposomal model membrane transport studies, system **1** can act as an effective carrier for several chloride anion salts of Group 1 cations, operating through both symport (chloride + cation co-transport) and antiport (nitrate-for-chloride exchange) mechanisms. This transport behavior stands in contrast to what is seen for simple octamethylcalix[4]pyrrole, which acts as an effective carrier for cesium chloride but does not operates through a nitrate-for-chloride anion exchange mechanism.

Keywords: binding sites · calixarenes · crown compounds · ion pairs · ion transport · structure-activity relationships

Introduction

The simultaneous recognition and binding of cationic and anionic guests by a single receptor, either as ion pairs or co-bound salts, is a recognized challenge in supramolecular chemistry. However, properly designed ion-pair receptors are attractive for use in selective extraction/transportation applications and for mimicking important biological functions, such as ion transport across cellular membranes. Although considerable effort has been devoted to the problem of designing ion-pair receptors, the number of available systems remains limited and the determinants of concurrent anion and cation recognition remain recondite.[1] Many of the reported studies have concerned spatially separated ditopic receptors that contain a cation complexation site combined with an amide-derived anion-binding site.[2] The use of thiourea groups[3] and macrocyclic phosphine oxide sites[4] for ion-pair recognition have been reported recently. Various other molecular frameworks have been developed for ion-pair recognition; however, it is rare that recognition takes place through formation of a contact ion pair. One of the essential, and still unanswered, questions in the area of ion-pair recognition is why different systems bind different combinations of anions and cations in different ways. Recently, we detailed three limiting binding modes for ion-pair recognition,[5] namely, contact ion pair, solvent-separated ion pair and dissociated ion pair, and have begun working to understand how the combination of anion and cation, combined with differences in receptor structure, favor one mode or another.[5,6]

An attractive approach to the design and synthesis of ion-pair receptors involves incorporating disparate binding sites into a properly preorganized scaffold in such a way that that the targeted anion and cation are held in close proximity without allowing significant interaction between the individual recognition subunits. Ion-pair receptors designed according to these principles are generally expected to display superior binding properties (e.g., higher affinities and greater selectivity) than linked systems that simply serve to bind pairs of dissociated ions, rather than associated ion pairs. Currently, the definition of associated ion pair is operational in the context of receptor design and can refer to constructs in which the anion and cation are 1) in close contact, 2) solvent separated, or 3) bound in a convergent fashion as the result of receptor-mediated interactions.[7]

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Results and Discussion

Recently, we described a calix[4]arene–calix[4]pyrrole hybrid system, in which all three of these limiting binding modes were observed within the same receptor depending on the choice of anion and cation.[5] Herein, we report the synthesis, characterization, and ion-pair-recognition properties of a new hybrid receptor (**1**; Figure 1) that contains both

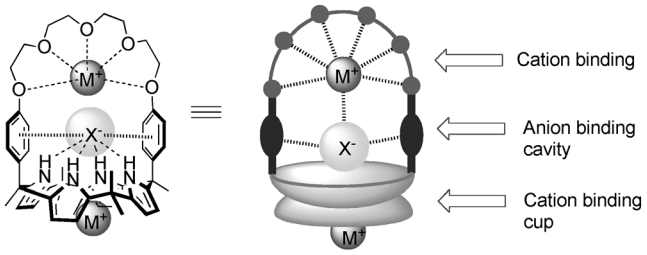


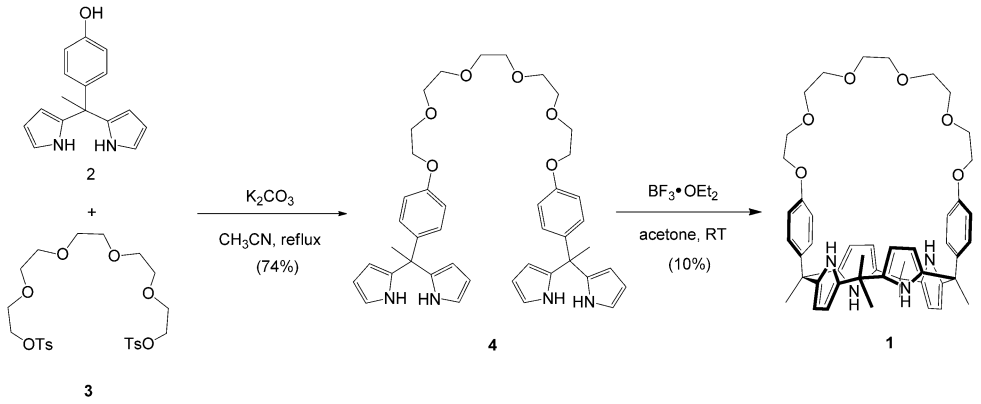
Figure 1. Schematic line drawing of crown-ether-strapped calix[4]pyrrole ion-pair receptor **1**.

an anion-binding site and a cation-binding site held in close proximity. This system, the first to our knowledge that is based on the direct strapping of a calix[4]pyrrole core with an oligoether, was found to form ion-pair complexes with halide anion salts, the nature and stability of which was found to depend on the choice of Group 1 counterion. As judged from through-liposomal and bulk U-tube type model membrane studies, this same system was found to be an effective carrier for chloride anions, the efficiency of which was again found to depend on the choice of counterion. Of particular note is that chloride anion transport was seen when NaCl, KCl, or CsCl was used as the chloride anion source, whereas chloride transport was only observed in the case of CsCl with simple octamethylcalix[4]pyrrole.[8] Based on the transport studies, it is inferred that system **1** can function both as a Group 1 cation+chloride anion symport carrier and a chloride-for-nitrate exchanger (antiport carrier).

The design of receptor **1** is based on two well-established recognition motifs, namely, a crown ether (oligoether) for cation binding and a calix[4]pyrrole for anion recognition. However, as has been demonstrated in several studies since 2005, the calix[4]pyrrole skeleton is not completely innocent as an anion binding agent;[9] in certain circumstances large cations can be accommodated in the pyrrole-derived cup present in the pyrrole-bound cone conformation (Figure 1). However, such in-cup cation complexation has not been observed in the case of smaller cations, such as K^+ and Na^+. Thus, points of interest are whether the combined use of a crown ether strap and a calix[4]pyrrole core would allow for ion-pair recognition of NaCl, KCl, and CsCl; whether the nature of the complex would differ (e.g., crown- or cup-based recognition of M^+ ($M^+ = Cs^+$, K^+, or Na^+)); and how these presumed recognition effects would translate into differences in transport phenomenon. In this latter context, we were particularly keen to see if the crown-strapped calix[4]pyrrole **1** could be used to effect the concurrent transport of K^+ and Cl^- or Na^+ and Cl^- in our standard liposomal model. Such cotransport is not observed with simple octamethylcalix[4]pyrrole, even in the presence of a good K^+ transporter, such as valinomycin.[10]

The synthesis of receptor **1** is summarized in Scheme 1. Tosylated pentaethylene glycol **3** was reacted with *meso*-(*p*-hydroxyphenyl-methyl)dipyrromethane **2** to give the corresponding podand-like dipyrromethane **4** in 74% yield. Lewis acid-catalyzed condensation of **4** with acetone (as the solvent) afforded receptor **1** in 10% yield.[11,12]

Receptor **1** was characterized by standard spectroscopic means. Although efforts to obtain a diffraction-grade single crystal of free host **1** were not successful, crystals of the CsCl complex of receptor **1** ([**1**·CsCl]) suitable for X-ray analysis could be obtained by slow evaporation from a mixture of chloroform and ethanol. The resulting structure revealed that in [**1**·CsCl] one molecule of ethanol forms a hydrogen bond with the bound cesium cation (Figure 2). The cesium ion is also complexed by four of the six oxygen atoms of the oligoether moiety, as inferred from the presence of $Cs^+ \cdots O$ contacts, the lengths of which vary from 3.052 to 3.438 Å. However, the bound chloride anion is hydrogen bonded to the four pyrrole NH protons as well as to a bound ethanol molecule. The separation between the chlo-



Scheme 1. Synthesis of receptor **1**.

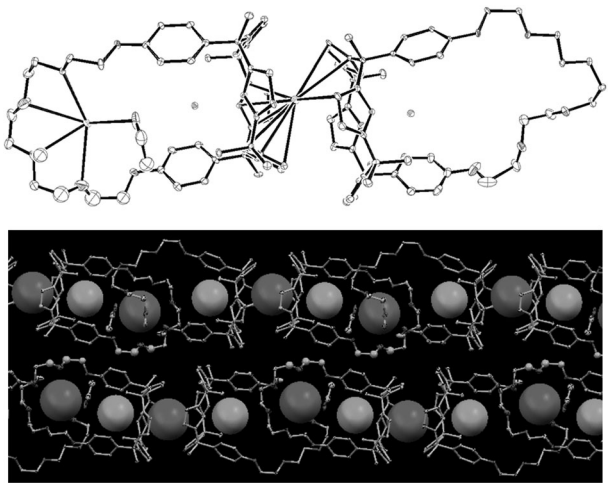


Figure 2. A) Single-crystal X-ray structure of the cesium chloride complex of receptor **1**. Hydrogen atoms have been removed for clarity and displacement ellipsoids are scaled to the 50% probability level. Note that two different complexation modes are seen for the two cesium cations. One of these involves complexation by the oligoether, whereas the other involves binding of the cation within the tetrapyrrolic "cup" present in the cone conformation of calix[4]pyrrole. B) The resulting extended framework (dark gray spheres: Cs^+, light gray spheres: Cl^-).

ride anion and the pyrrole nitrogen atoms is nearly constant (3.23 Å < $Cl^-\cdots N$ < 3.29 Å). The $Cl^-\cdots O$–Et separation was 3.143 Å, whereas the $Cs^+\cdots Cl^-$ separation was 5.407 Å. The relatively short contact between the Cl^- ion and the bound ethanol is consistent with the notion that for this particular salt, complexation of the anion and cation as a solvent-separated ion pair is energetically more favorable than binding the corresponding putative contact ion pair.[6]

In the structure of complex [**1**·CsCl], a cup-bound cesium ion is also seen. It interacts with a chloride anion bound in a neighboring calix[4]pyrrole. Because the crown-bound cesium ion also interacts with a neighboring crown ether moiety, an extended superstructure is produced in the solid state (see below).

Preliminary solution-phase anion-binding studies of receptor **1** were carried out in CD_3CN by using ^1H NMR spectroscopy. To check the interactions between Group 1 cations and the oligoether moiety, receptor **1** was subjected to titrations with various alkaline metal perchlorate salts (Li^+, Na^+, K^+, and Cs^+). However, no appreciable changes in chemical shifts were observed (see the Supporting Information). This finding provides support for the conclusion that the
oligoether moiety does not complex these metal cations in acetonitrile. In contrast to what was seen for PF_6^- cation salts, significant chemical shift changes were observed when receptor **1** was titrated with fluoride ions (as the tetrabutylammonium (TBA) salt). Titrations involving other anions also revealed changes in the calix[4]pyrrole chemical shifts characteristic of anion binding, with the extent of the changes at a given number of anion equivalents being found to depend on the specific anion employed. Quantitative studies of anion binding were made in acetonitrile by using isothermal titration calorimetry (ITC), a technique that has been applied extensively to the study of calix[4]pyrrole-based anion binding in recent years.[13] Table 1 summarizes the resulting association constants K_a, measured by ITC (all anions were studied as the corresponding TBA salts). On the basis of these studies, it is concluded that the fluoride anion interacts exceptionally well with receptor **1** ($K_a = 4.88\times10^8\,M^{-1}$). Although further study will be required to elucidate fully the determinants underlying this exceptionally high affinity, we ascribe it to a combination of hydrogen-bond interactions (as found in many fluoride anion receptors) and stabilizing anion–π interactions that are possible in the present instance as the result of the two phenyl groups present within the receptor. Evidence for a second binding event, characterized by $K_2 = 1.49\times10^5\,M^{-1}$, was also obtained when excess fluoride anion was added. These results provide support for the notion that receptor **1** provides relatively preorganized binding sites that allow for both cooperative hydrogen-bonding interactions with one or two fluoride anions (as a function of relative concentration) and anion–π interactions. In the event, it is important to underscore that receptor **1** binds the fluoride anion remarkably well, at least in acetonitrile.

Table 1. Association constants measured by ITC as determined from the titration of receptor **1** with various anions (all studies carried out by using the corresponding tetrabutylammonium salts) in CH_3CN. In these studies, [**1**] = 0.25 mM. Estimated errors are ≤10%.

	K_1 [M^{-1}]	K_2 [M^{-1}]
F^-[a]	4.88×10^8	1.49×10^5
Cl^-	9.70×10^4	
Br^-	2.09×10^3	
AcO^-	2.56×10^5	
$H_2PO_4^-$	3.89×10^3	
HSO_4^-	1.29×10^2	
NO_3^-	2.86×10^2	

[a] Treated mathematically as two separate and successive binding events.

The effect of the counterion was explored by treating preformed fluoride complex [**1**·**F**]$^-$ (TBA counterion) with various alkaline metal ion salts. A mixture of acetonitrile/methanol (9:1 v/v), which was chosen due to solubility considerations, was used for these studies. As shown in Figure 3, the spectrum of the fluoride-bound complex [**1**·**F**]$^-$ shows typical signal changes associated with slow complexation/decomplexation. Upfield shifts were seen for the Ar–H signal, a finding considered consistent with the presence of possible anion–π interactions.

Upon addition of Cs^+ (as the perchlorate salt), a slight downfield shift for the pyrrole-β-H protons was observed (Figure 3). Conversely, the pyrrole NH protons were observed to undergo a modest shift to higher field. Little discernable change in the signals ascribable to the oligoether moiety was observed. These results are consistent with the Cs^+ being bound to the cup of the calix[4]pyrrole in its cone conformation, thus forming a receptor-mediated ion-pair

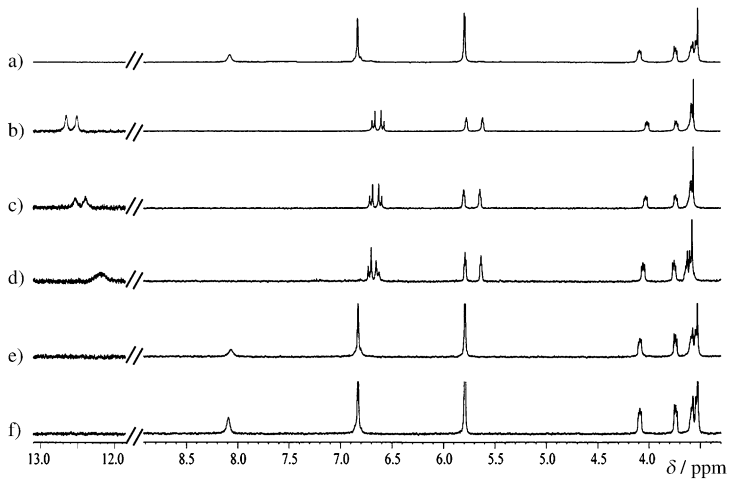


Figure 3. Partial ^{1}H NMR spectra of complex $[\mathbf{1}\cdot F]^-$ (TBA salt) observed upon treatment with various alkaline perchlorate salts. a) Free **1**, b) $[\mathbf{1}\cdot F]^-$ (**1** + TBAF (1.5 equiv)), c) $[\mathbf{1}\cdot F]^-$ + $CsClO_4$ (5 equiv), d) $[\mathbf{1}\cdot F]^-$ + $KClO_4$ (5 equiv), e) $[\mathbf{1}\cdot F]^-$ + $NaClO_4$ (5 equiv), f) $[\mathbf{1}\cdot F]^-$ + $LiClO_4$ (5 equiv) in CD_3CN/CD_3OD (9:1 v/v).

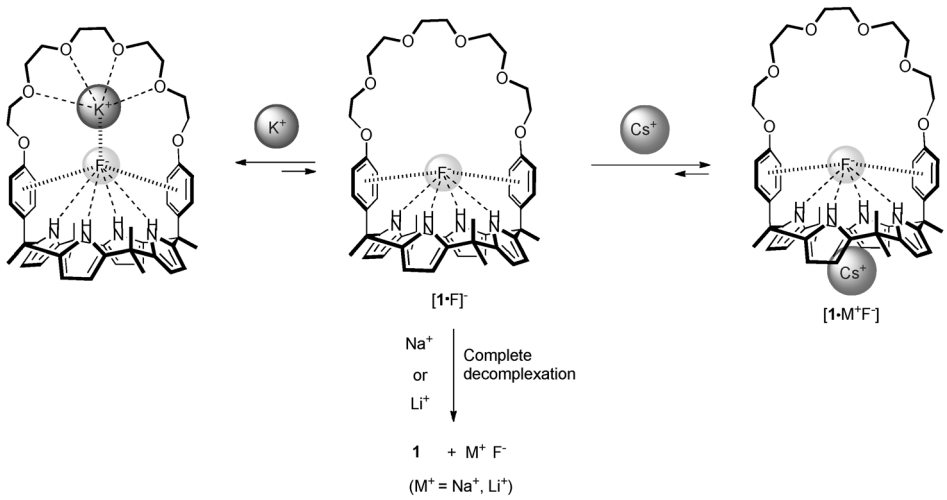
observed. Rather, a cavity-bound ion-pair complex containing both the Li^+ and Cl^- ions formed. Evidence for this complexation mode comes from the ^{1}H NMR spectra shown in Figure 4. The chemical shift of the pyrrole NH proton signal undergoes little appreciable change upon addition of Li^+ ions. Conversely, the chemical shift of the ether bridges was gradually shifted to lower field upon addition of Li^+ ion. These observations are most readily rationalized in terms of Li^+ ions binding to the oligoether moiety and the chloride remaining co-bound by the pyrrole NH protons; the net result is the formation of a cavity-bound ion-pair complex.

Preformed complex $[\mathbf{1}\cdot Cl]^-$ was also treated with different alkaline metal cations (as the perchlorate salts) under analogous solution-phase conditions. Again, the resulting changes in chemical shift allowed insights into the complexation behavior to be inferred. As can be seen from an inspection of Figure 5, the addition of one equivalent of Cs^+ to $[\mathbf{1}\cdot Cl]^-$ resulted in a significant downfield shift in the β-pyrrolic proton signals but little change in the NH proton signals.

complex. In the case of K^+, a significant downfield shift in the signals ascribed to the oligoether moiety was observed. Concomitantly, the resonance of the pyrrole NH protons was found to shift to higher field. These observations provide spectroscopic support for the conclusion that the ion pair $[K^+\cdot F^-]$ is bound within the receptor cavity.

The upfield shift seen for the pyrrole NH signal is consistent with the intuitively appealing conclusion that the hydrogen bonding between the pyrrole NH protons and the F^- ion become weaker as the interaction between the co-bound ions, K^+ and F^-, becomes stronger. On this basis, it is suggested that preformed complex $[\mathbf{1}\cdot F]^-$ forms two different kinds of ion-pair complex depending on whether the counterion is Cs^+ or K^+. In contrast, the addition of smaller cations, specifically Li^+ or Na^+, serves to break preformed complex $[\mathbf{1}\cdot F]^-$, as evidenced by a restoration of signals in the NMR spectrum originally seen for free **1**. Presumably, these cations mediate this effect by binding so tightly with the fluoride anion under these solvent conditions that they outcompete and thus rupture the N–H···F^- hydrogen-bonding interactions present in $[\mathbf{1}\cdot F]^-$. These varying cation-dependent processes are summarized in Scheme 2.

In contrast with the above, when preformed chloride complex $[\mathbf{1}\cdot Cl]^-$ (TBA salt) was treated with $LiClO_4$, no evidence of decomplexation of the bound chloride anion was



Scheme 2. Effect of treating complex $[\mathbf{1}\cdot F]^-$ (TBA salt) with perchlorate salts of various alkaline metal ions.

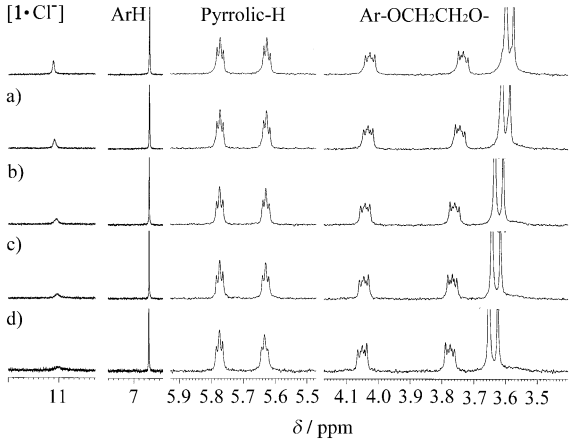


Figure 4. ^{1}H NMR spectral changes observed when complex $[\mathbf{1}\cdot Cl]^-$ (top trace) is treated with a) 1, b) 3, c) 5, and d) 10 equivalents of $LiClO_4$ in CD_3CN.

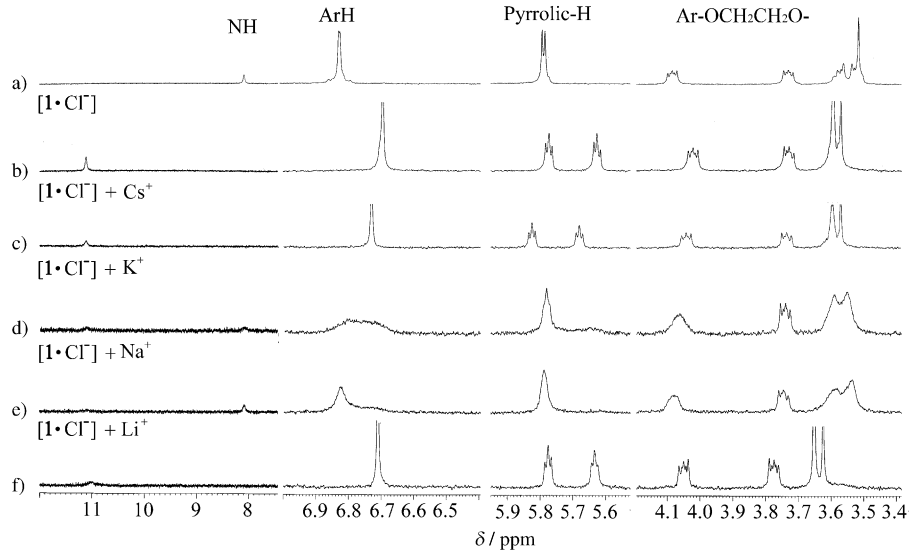
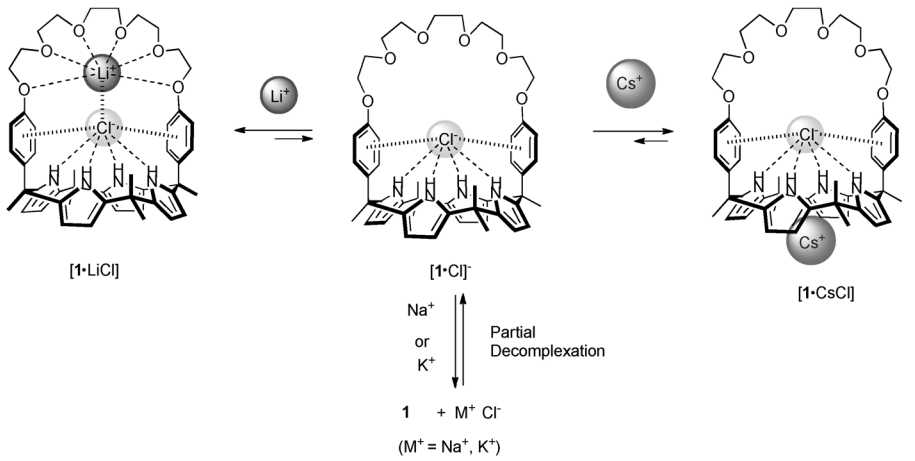


Figure 5. ^{1}H NMR spectra of a) free **1**, b) $[\mathbf{1}\cdot Cl]^-$ (TBA salt), c) $[\mathbf{1}\cdot Cl]^- + Cs^+$, d) $[\mathbf{1}\cdot Cl]^- + K^+$, c) $[\mathbf{1}\cdot Cl]^- + Na^+$, and d) $[\mathbf{1}\cdot Cl]^- + Li^+$ ($[M^+] = 5$ equiv, perchlorate salts) in CD_3CN.

This cation-induced behavior is ascribed to cation (Cs^+)–π(pyrrole ring) interactions. To an extent this assignment is correct, the observed chemical shifts are consistent with the cesium cation being bound to the cup of the calix[4]pyrrole moiety, rather than by the oligoether moiety as in the case of Li^+ (see above). Finally, addition of K^+ or Na^+ resulted in no appreciable change in the chemical shifts, although peak broadening was observed. This finding is interpreted in terms of partial decomplexation of the bound chloride anion occurring with these two cations.

Taken in concert, the cation-dependent ^{1}H NMR spectral changes are consistent with the nature of the prebound anion complex, $[\mathbf{1}\cdot\mathbf{Cl}]^-$ or $[\mathbf{1}\cdot\mathbf{F}]^-$ (both as the corresponding TBA salt), having a significant role in determining the chemical events that transpire upon subsequent treatment with an alkali cation (perchlorate salt) and the nature of the ion-pair complex (if any) that is ultimately formed. The chemistry occurring in the case of $[\mathbf{1}\cdot\mathbf{F}]^-$ is summarized in Scheme 2, whereas that proposed for $[\mathbf{1}\cdot\mathbf{Cl}]^-$ is shown in Scheme 3. In the case of the latter anion complex, it is inferred that only the upper, crown-like cavity of the chloride-bound receptor $[\mathbf{1}\cdot\mathbf{Cl}]^-$ can accommodate the Li^+ ion effectively, whereas the lower calix[4]pyrrole cup allows for effective Cs^+ complexation. Neither Na^+ nor K^+ bind well to either cation binding site and thus partial anion decomplexation occurs. When receptor **1** was mixed with equimolar quantities of various test anions (acetate, phosphate, chloride, and fluoride, as their corresponding tetrabutylammonium salts) in [D_3]acetonitrile/[D_4]MeOH (9:1), the fluoride anion complex was formed in preference and to the exclusion of the other possible complexes. Support for the suggestion that the fluoride complex is formed exclusively (within the limits of ^{1}H NMR spectroscopic analysis) comes from noting that under these conditions the pyrrole NH proton signal shifts to lower field and displays the ^{19}F–^{1}H splitting typical of a calix[4]pyrrole fluoride anion complex undergoing slow exchange.

Successive treatment of the preformed $[\mathbf{1}\cdot\mathbf{F}]^-$ complex with three equivalents of $LiClO_4$ resulted in complete decomplexation of the receptor-bound fluoride anion, as inferred from ^{1}H NMR spectral changes. These changes lead us to propose that under these solvent conditions (chosen to accommodate a wide range of anion salts) a combination of Coulombic interactions between Li^+ and F^- and solubilization by the relatively polar medium dominate over hydrogen-bonding interactions involving the pyrrolic NH protons and the F^- anion. As a result, decomplexation of the fluoride anion occurs. However, when the chloride complex $[\mathbf{1}\cdot\mathbf{Cl}]^-$ is treated with $LiClO_4$ under identical conditions, the cation (Li^+) binds to the oligoether moiety of the host molecule. As a result an ion pair complex is stabilized and decomplexation of the bound chloride anion does not occur. The cavity-bound ion-pair complex (Li^+Cl^-) is presumably



Scheme 3. Proposed cation-induced changes that occur when complex $[\mathbf{1}\cdot Cl]^-$ is treated with perchlorate salts of various alkaline metal ions in CD_3CN.

stabilized in part by the ditopic nature of the receptor, which allows for energetically favorable receptor-ion contacts with the co-bound ions, as well as favorable Li^+–Cl^- interactions.

When a mixture of acetate, chloride, and phosphate anions (containing no fluoride anions) was treated with receptor **1** under the above mixed-solvent conditions, the greatest spectral changes were seen in the case of the acetate anion. On this basis, we conclude that the acetate anion is bound in preference over the chloride and phosphate anions. When this mixture, containing the pre-formed acetate complex $[\mathbf{1}\cdot\mathbf{OAc}]^-$ as the dominant species, is treated with $LiClO_4$, decomplexation of the bound acetate anion occurs and is replaced by the chloride anion, which is bound in the form of the Li^+–Cl^- ion pair, as inferred from the nature of the ^{1}H NMR spectral signals observed. This cation-mediated control of anion recognition is a unique feature of receptor **1** that could find use in various applications involving, for example, anion separations.

Several modified calix[4]pyrroles, including certain strapped calixpyrroles, have previously been observed to function as chloride transporters across lipid bilayer membranes.[14] Accordingly, we studied the transport properties of receptor **1** by using the test alkali cation salts CsCl, RbCl, KCl, and NaCl. The most highly hydrated member of the series, LiCl, was excluded from this study. For these studies, unilamellar 1-palmitoyl-2-oleoylphophatidylcholine (POPC) vesicles were loaded with the salts in question and then suspended in an external solution containing either $NaNO_3$ or Na_2SO_4 buffered to pH 7.2 with 5 mM sodium phosphate salts. A sample of receptor **1** (4% molar carrier to lipid) was added in the form of a DMSO solution and the resultant Cl^- anion efflux was monitored using a chloride selective electrode. As discussed below, these studies revealed that receptor **1**, in contrast to simple calix[4]pyrrole,[13] is capable of transporting chloride from within liposomes containing sodium, potassium and rubidium chloride, with the fastest release being observed in the case of the larger Group 1 metal cations (Figure 6).

Two sets of conditions were used to assess the ability of receptor **1** to act as a chloride anion carrier. In the first the solution on the outside of the liposome was loaded with $NaNO_3$, whereas in the second Na_2SO_4 was used. The doubly negatively charged sulfate anion is highly hydrophilic ($\Delta G_{hydr}(SO_4^{2-}) = -1080\ kJ\,mol^{-1}$)[14] and was not expected to be soluble in the liposomal membrane. In contrast, the nitrate anion is much more hydrophobic ($\Delta G_{hydr}(NO_3^-) = -300\ kJ\,mol^{-1}$) and is able to diffuse through the liposomal barrier when transport is mediated by a carrier so as to maintain charge neutrality across the membrane. Thus, as detailed in previous reports,[15] the use of Na_2SO_4 in the extra-liposomal medium was expected to allow for an assessment of carrier function under conditions of cation+anion co-transport. In the specific case of experiments involving receptor **1**, an appreciable increase in chloride anion concentration outside of the vesicle as a function of time would only be expected if both the chloride anion and its counter

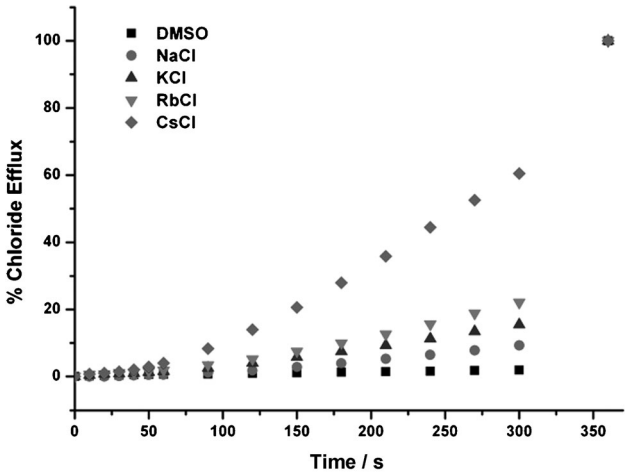


Figure 6. Chloride efflux promoted by receptor **1** (4 mol% with respect to lipid) from unilamellar POPC vesicles loaded with MCl (489 mM; M = Na, K, Rb or Cs) buffered to pH 7.2 with sodium phosphate salts. The vesicles were dispersed in Na_2SO_4 (167 mM) buffered to pH 7.2 with sodium phosphate salts (5 mM). Each point represents the average of three trials.

cation were being co-transported. On the other hand, when $NaNO_3$ is used, chloride anion transport would be expected via a chloride-for-nitrate exchange or "antiport" mechanism (as well as by default a cation+anion cotransport mechanism). Thus, by studying carriers using both conditions qualitative insights into the relative importance of these two limiting mechanisms may be obtained.

As can be seen from an inspection of Figures 6 and 7, receptor **1** can function as a carrier through a cation+anion cotransport mechanism and through anion exchange. As implied above, more effective transport was observed for the more lipophilic cations ($Cs^+ > Rb^+ > K^+ > Na^+$). However,

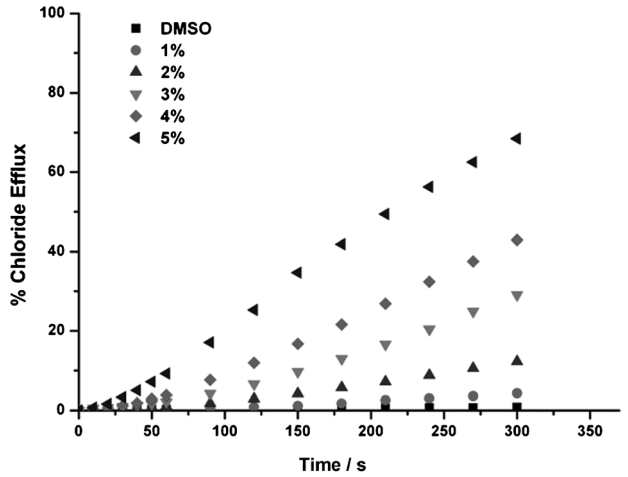


Figure 7. Chloride efflux promoted by 1–5 mol% of receptor **1** from unilamellar POPC vesicles loaded with NaCl (489 mM) buffered to pH 7.2 with sodium phosphate salts. The vesicles were dispersed in $NaNO_3$ (489 mM) buffered to pH 7.2 with sodium phosphate salts (5 mM). Each point represents the average of three trials.

even when the anion-exchange mechanism is not operative, a modest level of transport was seen in the case of NaCl (Figure 6). In accord with expectations, this latter transport rate increases when nitrate-for-chloride exchange processes are operative (Figure 7). Here, in accord for what is predicted for a carrier-based transport mechanism, the rate of transport increased as the concentration of the receptor within the membrane was increased. Control experiments confirmed, in agreement with prior studies involving elaborated calixpyrrole transport agents, that a test crown ether, alone or in conjunction with calix[4]pyrrole, did not act as an effective carrier for the chloride anion under NaCl-for-$NaNO_3$ exchange conditions (see the Supporting Information). On this basis, we conclude that receptor **1** is an effective carrier for the chloride anion and one that benefits, at least in part, from an ability to effect the co-transport of both an anion (chloride) and a cation (preferentially Cs^+, but also other alkali cations).

Qualitative support for the conclusion that receptor **1** functions as carrier through a cation+anion cotransport mechanism came from bulk membrane transport studies. These involved a U-tube setup in which a dichloromethane layer (10 mL) containing receptor **1** (1 mM) was used to separate two aqueous phases (5 mL each). The first of these two aqueous phases (Aq. 1) consisted of 0.5 M MCl (M = Cs, K, Na) in 20 mM phosphate buffer (pH 7), whereas the second (Aq. 2) consisted of either 0.5 M $NaNO_3$ or Na_2SO_4 in 20 mM phosphate buffer (pH 7).

The amount of chloride anion transferred to Aq. 2 was then monitored as a function of time by recording data points at regular intervals over a period of about 24 h (see Figures S17–S23 in the Supporting Information). It was found that if Aq. 1 contained either CsCl or KCl, the relative rate of chloride anion transport (roughly 50 and 40% increase in $[Cl^-]$ after 1 d for Cs^+ and K^+, respectively) was essentially independent of the salt ($NaNO_3$ or Na_2SO_4) in the receiving phase (see Figure S17 in the Supporting Information). In contrast, if Aq. 1 contained NaCl then roughly twice as much Cl^- was transferred if the receiving phase contained $NaNO_3$ rather than Na_2SO_4 (roughly 40 and 25% increase in $[Cl^-]$ after 1 d for NO_3^- and SO_4^{2-}, respectively). This observation is consistent with an antiport mechanism playing a major role for the more highly hydrated cation, Na^+, than for K^+ or Cs^+.

Conclusion

Oligoether-strapped ion-pair receptor **1**, which has both a strong anion-binding site and two possible cation recognition sites, has been synthesized and characterized by standard spectroscopic means, as well as by the single crystal X-ray diffraction analyses. The ^{1}H NMR spectroscopic analyses reveal that in solution in acetonitrile, receptor **1** forms a strong anion complex with fluoride and chloride anions. The receptor–fluoride complex $[\mathbf{1}\cdot\mathbf{F}]^-$ only forms an ion-pair complex with Cs^+ ions, in which the cesium ion binds to the cup of the calix[4]pyrrole moiety. Conversely, the K^+ forms a cavity-bound ion-pair complex. The bound fluoride anion in $[\mathbf{1}\cdot\mathbf{F}]^-$ is decomplexed upon addition of $NaClO_4$ or $LiClO_4$. The receptor–chloride complex $[\mathbf{1}\cdot\mathbf{Cl}]^-$, on the other hand, displays quite different cation-binding properties. The addition of $CsClO_4$ results in formation of an cup-bound ion pair. Support for this latter conclusion comes from a single crystal X-ray diffraction analysis of the CsCl complex of **1**, which revealed such a binding mode, along with an in-cavity Cs^+–Cl^- ion-pair binding. The Li^+ ion forms a cavity-bound ion-pair complex, whereas the addition of Na^+ and K^+ induces partial decomplexation (all cations were added as the corresponding perchlorate salts). This behavior stands in marked contrast to what was seen for the earlier system.[5] The advantages of the present receptor is that its ion-recognition properties can be modulated by an appropriate choice of both the anion and cation. These findings led to the consideration that receptor **1** could act as a versatile ion transporter, and liposomal model membrane studies revealed that could act as a chloride+cation co-transporter, as well as a chloride-for-nitrate ion exchanger. Support for these key conclusions came from U-tube bulk transport experiments.

Experimental Section

General methods and materials. ^{1}H NMR spectra were recorded by using a 300 or 400 MHz NMR spectrometer with TMS as the internal standard. Chemical shifts are reported in parts per million (ppm). Peak multiplicities are given as the following abbreviations: s, singlet; brs, broad singlet; d, doublet; t, triplet; m, multiplet. ^{13}C NMR spectra were proton decoupled and recorded by using a 100 MHz NMR spectrometer with TMS as the internal standard. High-resolution mass spectra were obtained by using a Voyager-DE STR MALDI-TOF mass spectrometer. The bulk membrane transport data were obtained by using Orion Ion-Selective Solid-State Combination Electrodes (Thermo Scientific). All other chemicals and solvents were purchased from commercial sources and were used as such, unless otherwise mentioned. Column chromatography was performed over silica gel. Compounds **2** and **3** were synthesized by using slightly modified procedures previously reported in the literature.[11,16] All titrations (UV/Vis, fluorescence and ITC) were performed by using HPLC-grade CH_3CN purchased from Aldrich.

Compound 4: A mixture of 5-(*p*-hydroxyphenyl)-5-methyldipyrromethane **3** (480 mg, 1.92 mmol), K_2CO_3 (1.27 g), and pentaethylene glycol ditosylate **2** (530 mg, 0.96 mmol) was dissolved in acetonitrile and heated at reflux for 12 h. After cooling, the solvent was removed in vacuo and the remaining solid was dissolved in methylene chloride, then washed with water and dilute acid. The solvent was removed in vacuo and the resulting solid was purified by column chromatography over silica gel (CH_2Cl_2/EtOAc 5:1) to give compound **4** as a white solid (yield 651 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.81 (brs, 4H), 6.99 (d, J = 8.64 Hz, 4H), 6.79 (d, J = 8.85 Hz, 4H), 6.63–6.62 (m, 4H), 6.15–6.13 (m, 4H), 5.95–5.93 (m, 4H), 4.07 (t, J = 4.84 Hz, 4H), 3.80 (t, J = 4.84 Hz, 4H), 3.69–3.67 (m, 4H), 3.65–3.63 (m, 4H), 3.62 (s, 4H), 1.99 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 157.8, 140.0, 138.17, 128.9, 117.3, 114.5, 108.6, 106.5, 71.2, 71.0, 70.1, 67.8, 44.5, 29.4 ppm; MS (MALDI-TOF): m/z calcd for $C_{42}H_{50}N_4O_6$: 706.37 $[M]^+$; found: 709.42 $[M+3H]^+$.

Oligoether(O-6) strapped calix[4]pyrrole 1: Compound **4** (1.4 mmol) was dissolved in acetone (150 mL) and $BF_3\cdot OEt_2$ (7.0 or 8.4 mmol) was added. The reaction mixture was stirred for 2 h at RT. The reaction was quenched by adding aqueous NaOH (1 N), then extracted several times

with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and the solvent was removed in vacuo, The residual solid was purified by column chromatography (silica gel; CH_2Cl_2/EtOAc4:1) to give **1** as a white solid (yield 0.110 g, 10%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.03$ (br s, 4H), 6.96 (d, $J = 8.85$ Hz, 4H), 6.83 (d, $J = 8.88$ Hz, 4H), 5.96–5.94 (m, 4H), 5.88–5.86 (m, 4H), 4.16 (t, $J = 5.02$ Hz, 4H), 3.88 (t, $J = 5.02$ Hz, 4H), 3.75–3.73 (m, 4H), 3.70–3.69 (m, 4H), 3.68 (s, 4H), 1.94 (s, 6H), 1.52 (s, 6H), 1.39 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta = 157.3$, 139.1, 137.3, 136.9, 128.3, 114.1, 104.9, 104.2, 70.9, 70.8, 70.7, 69.7, 67.5, 44.2, 35.5, 30.2, 29.1, 29.0 ppm; MS (MALDI-TOF): m/z calcd for $C_{48}H_{58}N_4O_6$: 786.44; found: 787.33 $[M+H]^+$.

Liposomal model membrane studies: POPC was supplied by Genzyme. Chloride concentrations during transport experiments were determined by using an Accumet chloride-selective electrode. Vesicles were prepared as follows: A lipid film of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) and cholesterol (0% or 30%) was formed from a solution in chloroform under reduced pressure and dried under vacuum for at least 6 h. The lipid film was rehydrated by vortexing with the metal chloride (MCl) salt solution in question (489 mM MCl, 5 mM phosphate buffer at pH 7.2). The lipid suspension was then subjected to seven freeze–thaw cycles and allowed to age for 30 min at RT before extruding 25 times through a 200 nm polycarbonate membrane. The resulting unilamellar vesicles were dialyzed against the external medium to remove unencapsulated MCl salts.

Unilamellar POPC vesicles containing MCl, prepared as described above, were suspended in 489 mM $NaNO_3$ or 162 mM Na_2SO_4 solution buffered to pH 7.2 with sodium phosphate salts. The lipid concentration per sample was 1 mM. A solution of the carrier molecule (10 mM) in DMSO was added to start the experiment and the chloride efflux was monitored by using a chloride-sensitive electrode. At 5 min, the vesicles were lysed with polyoxyethylene(8) lauryl ether (50 μL, 0.232 mM in 7:1 water/DMSO v/v) and a total chloride reading was taken at 7 min.

U-tube transport studies: U-tube studies were carried out according to procedures detailed previously.[17] Briefly, a U-shaped tube was used to separate two aqueous phases (Aq. 1 and Aq. 2; 5 mL each) from one another by means of an intervening dichloromethane layer (10 mL). Aq. 1 consisted of MCl (0.5 M, M = Na, K, Cs) in phosphate buffer (20 mM, pH 7). Aq. 2 contained either $NaNO_3$ or Na_2SO_4 (0.5 M) in phosphate buffer (20 mM, pH 7). The dichloromethane layer contained carrier **1** at a concentration of 1 mM. Transport was monitored by taking 2 mL aliquots from Aq. 2 at regular time intervals (typically every hour for several hours and one at around 24 h), testing the chloride anion concentration by means of a chloride-selective electrode, and returning the aliquot to Aq. 2. The electrode, which was calibrated before and after use, provides readout as mV, with lower numbers corresponding to greater chloride anion concentrations.

X-ray data for the CsCl complex of 1 ($C_{48}H_{58}N_4O_6$·CsCl·$CHCl_3$·0.5 C_2H_5OH): Crystals grew as colorless prisms by slow evaporation from chloroform and ethanol. The data crystal was cut from a larger crystal and had approximate dimensions 0.30×0.20×0.06 mm. The data were collected by using a Rigaku AFC12 diffractometer with a Saturn 724+ CCD equipped with a graphite monochromator with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). A total of 869 frames of data were collected by using ω-scans with a scan range of 1° and a counting time of 30 s per frame. The data were collected at 100 K by using a Rigaku XStream low-temperature device. Details of crystal data, data collection, and structure refinement are listed in Table S1 in the Supporting Information. Data reduction were performed by using Rigaku Americas Corporation's Crystal Clear v. 1.40.[18] The structure was solved by direct methods using SIR97[20] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms calculated by using SHELXL-97.[19] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2×Ueq of the attached atom (1.5×Ueq for methyl hydrogen atoms). The two molecules of chloroform were disordered. Portions of the ether linkages were also disordered. One of the Cs ions was π-bound to the pyrrole rings of an adjacent receptor molecule. This Cs ion, Cs2, was also disordered. Finally, the methyl group of the ethanol molecule was disordered. The disordered groups/ions were modeled in essentially the same fashion. For example, the site occupancy factor for Cs2 was assigned the variable x, whereas that of Cs2a was assigned to $(1-x)$. A common isotropic displacement parameter was refined while refining variable x. In this way, the site occupancy for Cs2 refined to 68(2)%. No geometric restraints were applied to the Cs ions. Geometric restraints were applied to the chloroform molecules such that the C–Cl bonds and the Cl-C-Cl bond angles were restrained to be equivalent. Similar geometric restraints were applied to the other disordered groups. H atoms on ethanol and chloroform were not included in the refinement model. The function $\Sigma w(|F_o|^2-|F_c|^2)^2$, in which $w = 1/[(\sigma(F_o))^2+(0.0752\times P)^2+(3.33\times P)]$ and $P = (|F_o|^2+2|F_c|^2)/3$, was minimized. $wR(F^2)$ refined to 0.180, with $R(F)$ equal to 0.0614 and a goodness of fit (S) of 1.58. Definitions used for calculating $R(F)$, $wR(F^2)$ and S are given below. The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[20] All X-ray structural figures were generated by using SHELXTL/PC.[21] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, and figures are given in the Supporting Information. CCDC-821894 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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