Crown Ethers: Sensors for Ions and Molecular Scaffolds for Materials and Biological Models

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1. Introduction to Crown Ethers

Crown ethers are heterocycles that, in their simplest form, are cyclic oligomers of dioxane. The essential repeating unit of any simple crown ether is ethyleneoxy, i.e., $-CH_2CH_2O-$, which repeats twice in dioxane and six times in 18-crown-6. There is no formal definition of the transition between heterocycle and heteromacrocycle. The nine-membered ring 1,4,7-trioxonane (9-crown-3) is often named as a crown and can certainly interact with cations. Macrocycles of the $(-CH_2CH_2O-)_n$ type in which $n \geq 4$ are generally referred to as crown ethers rather than their systematic names. This is partly because they comprise a special group of heterocycles that bind cations, many examples of which have appeared in the literature.[1,2] Complexation by 9-crown-3 (often two molecules per cation) is known but less common. Of course, the heterocycles dioxane and tetrahydrofuran (THF) are known to serve as donors for metal ions. Typically, several molecules of THF provide multiple binding sites whereas several heteroatom donors are typically present in each crown ether. Thus, distinctions at this level may be convenient but are largely artificial.

In the mid-1960s, Charles Pedersen, a chemist working at DuPont, was trying to prepare a complexing agent for divalent cations.[3] His strategy was to link two catechols through one hydroxyl on each molecule. This would give him a compound that could partially envelop the cation and, by ionization of the phenolic hydroxyls, neutralize the bound dication. He was surprised to isolate a byproduct that bound or complexed with potassium cation but had no ionizable hydroxyl group, Figure 1.

Pedersen called the new material dibenzo-18-crown-6; it is shown with the intended complexing agent that was also isolated.[4] Pedersen realized that the polyethers represented a new class of complexing agents that were capable of binding alkali-metal cations.[5] The challenge to do so with a neutral complexer was significant at that time, and such compounds were highly desirable. The fields of

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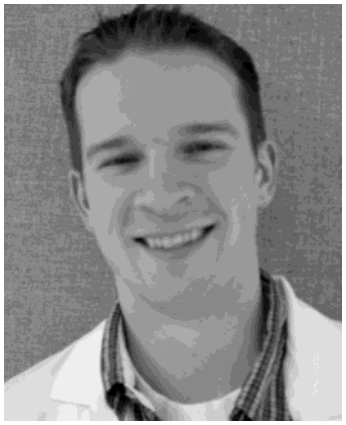

W. Matthew Leevy was born in Decatur, IL, in August of 1978. He obtained his B.S. degree in bioengineering from the University of Illinois at Urbana/Champaign with minors in chemistry and math in May of 2000. Presently, he is pursuing his Ph.D. degree in biophysics at Washington University at Saint Louis under the guidance of Professor George W. Gokel. His thesis involves the application of synthetic hydraphile channels to living systems as antimicrobial agents.

anionic synthetic reagents, phase-transfer catalysis, biological ion transport, and other emerging disciplines benefited profoundly from the discovery of crown ethers.

The origin of the crown ether name lies primarily in the complexity of organic nomenclature. One systematic name for dibenzo-18-crown-6 is 6,7,9,10,-17,18,20,21-octahydro-5,8,11,16,19,22-hexaoxa-dibenzo[a,j]cyclooctadecene. Such a name is conducive neither to common nor repetitive use. Pedersen examined molecular models of dibenzo-18-crown-6 and felt that the interaction between receptor and guest ion was such that the host "crowned" the cation.[6] He used a nomenclature in his pioneering papers that assumed crowns would have repeating ethyleneoxy units. Thus, a cycle comprised of five repeating ethyleneoxy units was called 15-crown-5. He named his first crown (see above) "dibenzo-18-crown-6", but the unresolved problem of designating

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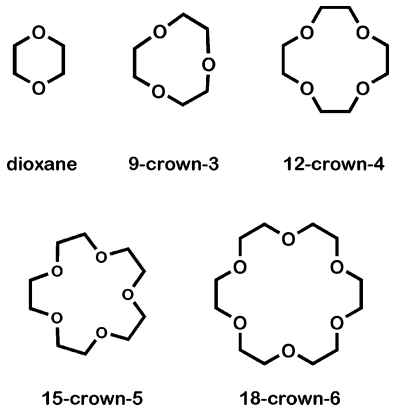

Figure 1. Cyclo-oligomers of ethylene oxide, from dioxane to 18-crown-6.

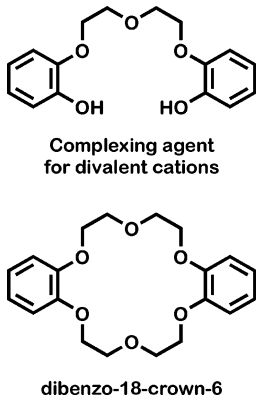

Figure 2. (Top) Pederson's complexing agent for divalent cations. (Bottom) Dibenzo-18-crown-6.

isomers in which the benzene rings are positioned differently will be obvious to the reader, Figure 2.

1.1. Out–In Bicyclic Amines and Cryptands

Simmons in the United States[7] and Lehn in France[8] both recognized the potential of "enveloping" heteromacrocycles. Simmons used two nitrogen atoms as the points of attachment for three hydrocarbon chains. He called these structures "out−in bicyclic

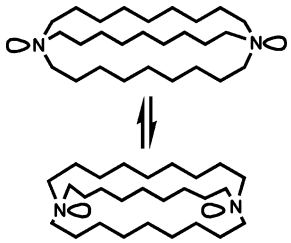

Figure 3. Out−in bicyclic amines: the out−out (top) and in−in (bottom) conformations.

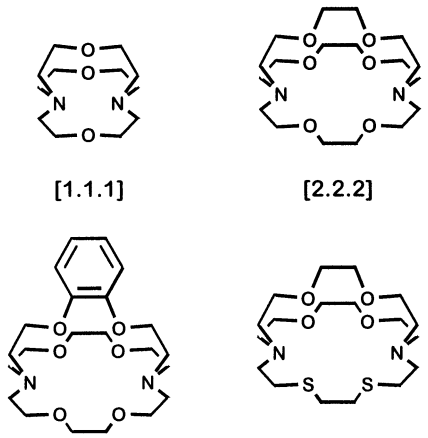

Figure 4. Structures of (top) [1.1.1]-, [2.2.2]-cryptands. (Bottom) Two [2.2.2]-cryptands (left) having one chain substituted by a benzo group and (right) having one chain incorporating two sulfur atoms.

amines". The "out−in" designation referred to the orientation of the nitrogen lone pairs relative to the interior. The compounds reported first by Lehn and Sauvage used two nitrogen atoms as the anchor or pivot atoms, but the connecting strands were ethyleneoxy units. The result was a family of compounds that had the three-dimensionality of Simmons's amines but also multiple donor groups.[9] The compounds designated in shorthand as [9.9.9]amine out,-out and in,in are shown in Figure 3.

Like the crown ethers, the cryptands suffer from complexity in nomenclature. Lehn used an expanded version of the nomenclature applied to bicyclic hydrocarbons to name them. Like Pedersen, he assumed that unless otherwise specified, the chains would be ethyleneoxy units and that they would be connected to nitrogen atoms. Rather than expressing the total number of atoms, the cryptands were named according to the presence of donors. Thus, the three chains in the first structure of Figure 4 each have one oxygen atom, and the compound is called [1.1.1]. Likewise, the top right structure is called [2.2.2]-cryptand or simply [2.2.2]. This is clearly preferable in conversation to 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane. Like the informal crown ether nomenclature, the two examples in the bottom panel show how quickly ambiguity intercedes.

1.2. Lariat Ethers

In a sense, lariat ethers are a blend of crowns and cryptands.[10] They were designed to have the three-dimensionality of cryptands while retaining the faster

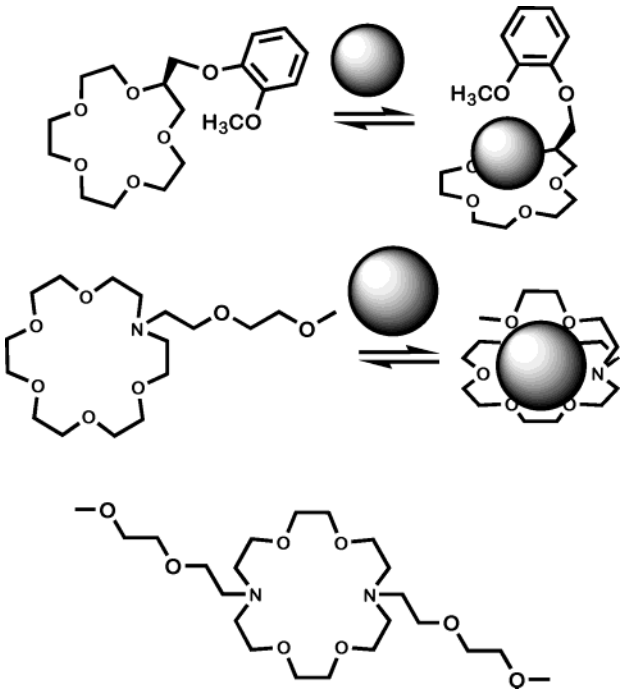

Figure 5. Folded (top) and extended (bottom) conformations for lariat ethers.

complexation dynamics of crown ethers.[11] Lariat ether sidearms are most commonly attached to the macroring at nitrogen, which is invertable and permits the sidearm maximum flexibility. Attachment of a sidearm at macroring oxygen is not a stable arrangement, as it would involve an oxonium ion. In principle, a sidearm could radiate from a macroring sulfur atom in its sulfonium salt state, but stability issues would attend this arrangement as well. An alternative is to replace an ethylene glycol ($HOCH_2$-CH_2OH) fragment with a glycerol ($HOCH_2CHOHCH_2$-OH).[12] When two of glycerol's adjacent hydroxyl groups are incorporated into a heteromacrocycle, the ring possesses a pendant hydroxymethyl group, $-CH_2OH$. This can be elaborated into a sidearm for the crown ether. Unlike attachment at nitrogen, however, the $-CH_2OR$ substituent will reside on one or the other side of the macroring, which will no longer be equivalent with respect to it. The stereochemistry is indicated in the top panel of Figure 5 for the lariat ether having an *o*-methoxyphenyl sidearm.

Figure 5 shows a lariat ether in both the extended and folded conformations (middle panel). It is known to adopt the latter when binding a suitable guest. The related, two-armed or bibracchial lariat ether[13] (bottom panel, Figure 5) can fold as well. It can contribute donors from the same or opposite sides of the macroring depending on the ring, the sidearms, and the guest. Some of these issues are discussed in the section on complexation.

2. Variations in Crown Structures

Enormous variety is known in the structures of crown ethers. A monograph by one of the present authors recorded thousands of the structures known by 1982. A review in 1989[14] and a monograph[15] in

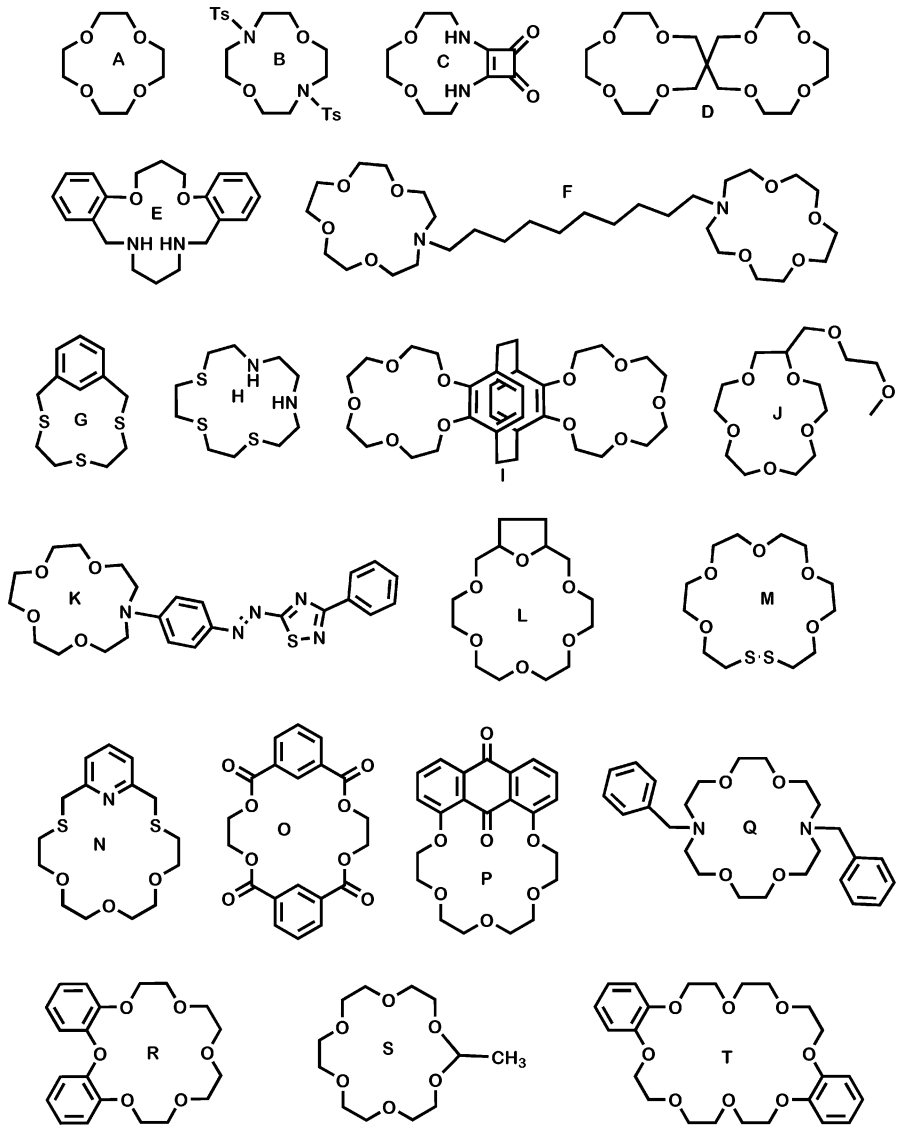

Figure 6. Twenty crown ether structures that suggest the large variations possible in this group of heterocycles.

1993 by Bradshaw and co-workers described a like number of additional compounds. It is probable that the number of examples of different macrocycles that have been prepared approaches 10 000. A short review such as this one can only hint at this huge variety. We have attempted to do so in Figure 6, which shows 20 structures (labeled A−T).

Macrocycles are known in essentially all ring sizes from 9 to at least 60. 12-Crown-4 (A) is an example of a small, unadorned structure. Variations of it are B, C, D, and E. When nitrogen is present in a crown macroring, it is secondary unless it is substituted. The nitrogen atoms of C and E are secondary, even though the macrocycles themselves are substituted. Compound B is a two-nitrogen analogue of 12-crown-4. Two isomeric structures are possible for diaza-12-crown-4, those in which the nitrogen atoms occupy adjacent positions (C) and those that are on opposite sides of the ring, as shown in B. In B, toluenesulfonyl (tosyl) groups protect the nitrogen atoms from further substitution. Tosyl groups have been used extensively in the preparation of azacrown derivatives, but they are more difficult to remove than are benzyl groups (see structure Q). The nitrogen atoms are tertiary in F and K and serve as sidearm attachment points.

Sulfur has also proven to be a common replacement heteroatom for oxygen.[16] All of the oxygen atoms have been replaced in G and H; each has three sulfur heteroatoms. Trithiaaza-15-crown-5 (1,4,7-trithia-10,-13-diazacyclopentadecane, H) contains both sulfur and secondary nitrogen atoms. Sulfur is also present in M but as a disulfide bridge. This link was formed by the cyclization of $HS(CH_2CH_2O)_5CH_2CH_2SH$ under oxidative conditions.[17]

Benzene rings have proved to be common substituents in crown ethers. The first crown isolated by Pedersen was dibenzo-18-crown-6, the structure of which is shown above. In terms of possible isomers, this is the analogue of compound T, a larger 24-crown-8 macrocycle. Dibenzocrown R is an isomer of the Pedersen compound that incorporates a diphenyl ether unit. Three isomers of dibenzo-18-crown-6 are possible. We may distinguish them informally as *pseudo-ortho* (R), *pseudo-meta* (not shown), and *pseudo-para* (see above). The latter is the common isomer. The structure shown as T corresponds to the *pseudo-para* isomer. We might also refer to compounds O and Q as *pseudo-para* isomers.

In addition to ethyleneoxy units, chains having 1, 3, 4, or more carbons are known. When the chains connecting heteroatoms are longer than ethylene, the structure is subjected to conformational interactions not apparent in the ethyleneoxy-derived compounds. Compound E incorporates three different types of three-carbon chains. One $(CH_2)_3$ chain is terminated by two oxygens and one by two nitrogen atoms. The third three-carbon chain in E is fused to the *ortho*-positions of a benzene ring. In this situation, benzene serves as a conformationally inflexible part of the spacer chain.

Benzene may also be present as a subcyclic unit that contributes no heteroatom to the macrocycle but does not otherwise alter the essential $(O-C-C)_n$ crown ether framework. Compound O, for example, has an 18-membered macroring, but a benzene CH occupies two sites that would be heteroatoms if the structure were 18-crown-6. This has three obvious effects on the structure. First, replacement of $OCH_2CH_2OCH_2CH_2O$ by $OCH_2C-CH-CCH_2O$ rigidifies the macrocycle. Second, each replacement results in the loss of a donor group relative to diethyleneoxy. Third, CH is larger than O and intrudes into the binding cavity. In compound O, only four donor groups are available to bind a cation within the macroring. The four ester carbonyl groups are turned outward and therefore of little utility in the binding context. The binding cavity (central hole) of the macroring is also reduced in volume relative to, for example, 18-crown-6. This is shown in Figure 7, which presents CPK molecular models of (a) 18-crown-6, (b) compound O, and (c) pyrido-18-crown-6. The latter structure is identical to structure N except that it contains five oxygen atoms in the macroring rather than three oxygen and two sulfur atoms.

Divalent sulfur atoms are significantly larger than oxygen. Compound G is drawn as a crown ether, but in fact, a calculated molecular structure shows that the benzene ring is turned upward relative to the ring and the sulfurs turn outward. That the sulfurs prefer an exocyclic conformation is known from a number of X-ray crystallographic studies.[16a]

Heterocyclic subunits such as tetrahydrofuran (structure L) or pyridine (structure N and panel c of Figure 7) are well accommodated in crown ethers. Numerous examples are known that incorporate heterocycles such as 2,5-methylenedioxyfuran, 2,5-methylenedioxythiophene, 2,6-methylenedioxypiperidine, etc. Nonheterocyclic units that also possess donors, such as 9,10-anthraquinone, may be successfully incorporated into a crown ether framework. In this case, one of the carbonyl donor groups protrudes directly into the cavity, changing both its size and symmetry relative to 18-crown-6.

Compounds M and S represent special situations in terms of the macroring structure. The disulfide link of M is rare but known[18] in macrocycles. Its sensitivity to reduction presents an obvious stability problem. There are also relatively few examples of macrocyclic acetals, due in large measure to their acid lability.[19] Gold and co-workers demonstrated, however, that cation complexation stabilized such macrocycles.[20] Even so, there are relatively few examples of this structural type.

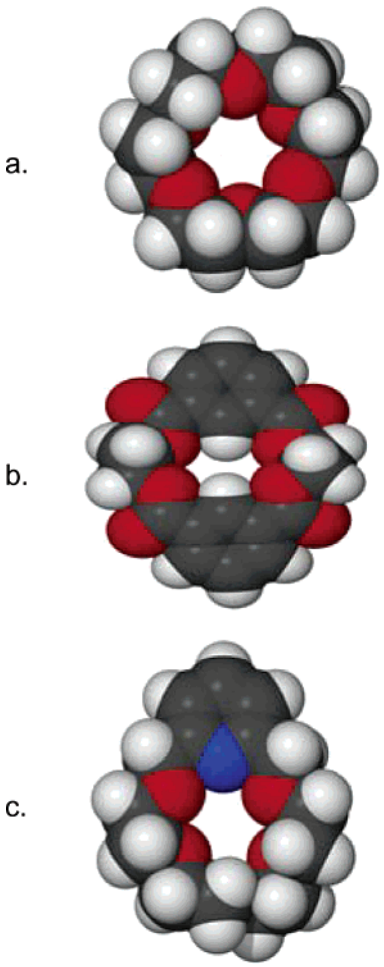

Figure 7. CPK representations of the isomers of dibenzo-18-crown-6.

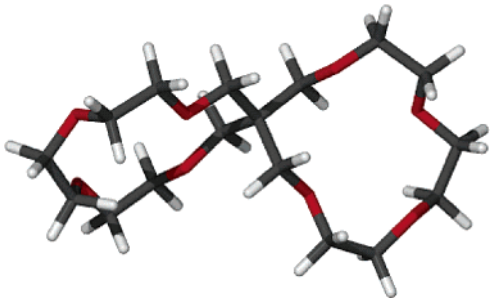

Figure 8. A linked crown ether containing a spiro center.

Macrocycles may be linked in a variety of ways. Three of the structures in Figure 6 hint at the possibilities. Two aza-15-crown-5 molecules are linked in F to form a bridged bis(crown). Several examples are known of this compound type, and they have been investigated in the author's lab.[21] Such compounds are often referred to as bola-amphiphiles or simply "bolytes". They form stable aggregates when sonicated in aqueous suspension. Two 13-crown-4 molecules are linked through a quaternary carbon in structure D. In principle, this provides eight aliphatic donor oxygen atoms to coordinate a cation. The spiro center, however, forces the molecule into a poor binding conformation (Figure 8). This is not true of structure F, the dodecyl chain of which could fold so that the two crowns could form a sandwich. Another example of an interesting structure that contains two

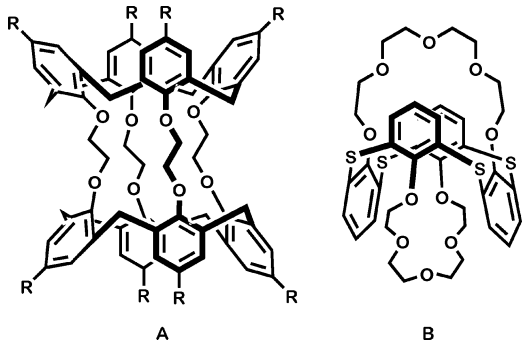

Figure 9. Structures of a calixarene-based tube (A) and a calixcrown (B).

crowns that cannot cooperate is I. In this case, two benzo 15-crown-5 structures are bridged by ethylene units into a [2.2]-paracyclophane derivative. The latter's rigidity prevents any intramolecular cooperation between the two macrocycles.

For a broad range of examples, the reader is referred to monographs on crown ether syntheses[22] and previously cited references.[1,2,15]

2.1. Calixarenes and Calixcrowns

Calixarenes are macrocycles formed by cyclooligomerization of phenol and formaldehyde. They are now known in a rich variety of ring sizes and substitution patterns. Their ability to complex cations, anions, and neutral molecules has made them a standard among supramolecular host molecules. Calixarenes have been hybridized to crown ethers, with the resulting formation of calixcrowns.[23] Calixcrown hosts have been elaborated to include azacrowns[24] and thiacrowns[25] attached to the calix. As with crown ethers, a combination of solution and crystal structure studies has defined the binding properties of these compounds. Calixcrowns have proved to be useful vehicles for the study of hydrogen-bonding and electrostatic interactions as well as cation−π interactions that occur when ions are complexed by these hosts.

The principal applications of calixcrowns have thus far mostly been in ion sensing and recognition. Cesium cation has been a particular target,[26] owing to its presence in radioactive wastes. Additionally, crown ether-based calixarenes have been designed for use as ionophores in ion-selective electrodes for various cations, including alkali metals,[24d,27] transition metals,[26e,28] heavy metals,[24b,29] and lanthanides,[30] as well as alkylammonium ions.[31]

2.2. Calixtubes

Calixtubes (left panel of Figure 9) are cryptand-like molecules that are three-dimensional hybrids of calixarenes and crown ethers. Beer and co-workers, who were the first to report a calixtube system selective for K^+ over other alkali and alkaline earth metals, developed much of this area.[32] On the basis of early work utilizing calixcrowns,[33] Williams et al. demonstrated that the rate of K^+ complexation by the calixtube shown in Figure 9 can be tuned by structural modifications at the calixarene "upper rim". They also propose that the preferred route of entry for K^+ into the calixtube is the axial route (through the calixarenes) rather than through the ethyleneoxy chains.

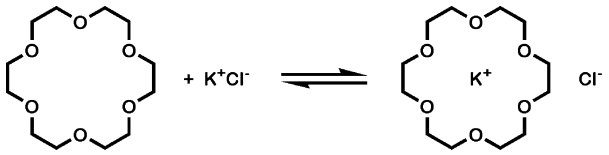

Figure 10. Potassium complex formation for 18-crown-6.

Extensions of this work have led to calixtubes that "shuttle" ions rather than binding them.[25a,34] Lee et al. reported the syntheses of several calixtube shuttles that are based on thiacalix[4]crowns (see Figure 9, right panel). The presence of sulfur diminished the binding to hard cations, resulting in rapid ion exchange through the tube.

3. Cation Binding by Heteromacrocycles

Crown compounds possess numerous remarkable attributes, but their most important property is the ability to complex cations. It was this property that Pedersen, Lehn, and Cram, who shared the 1987 Nobel Prize, all sought and exploited.

The complexation of a cation by a crown ether is simple to conceptualize but more complicated in its details. A typical complexation reaction is shown in Figure 10. 18-Crown-6 has 6 oxygen donor groups that are turned inward in the D_{3d} or binding conformation. Solid-state structures show that crowns typically crystallize in a parallelogram arrangement in the absence of a guest such as a cation. This can be seen in panel a of Figure 11, which is the crystal structure of uncomplexed 18-crown-6.[35] The illustration was made from data in the Cambridge Structural Database (CSD Structure code: HOXOCD). Thus, a conformational reorganization step probably precedes the equilibrium shown. In any event, a host−guest complex forms between the crown and K^+. Again, solid-state structures show that this is a symmetrical complex that has K^+ in the center. Panel d of Figure 11 shows the structure of an 18-crown-6 complex of $KMoO_4$ (CSD: HOXOMK).[36] There are two different potassium−crown complexes in the unit cell. In one case, the six crown ether oxygens and one water molecule bind potassium. Binding of the other potassium cation is similar except that an oxygen atom that is part of the MoO_4 anion replaces the water molecule. Several molecules of water also occupy space in the unit cell.

Figure 11b shows another common crown ether binding situation. In this case, the anion and the cation complex are completely separate. Two tetrahydrofuran (THF) molecules occupy the crown complex's axial positions. The $W(CO)_6$ anion, adjacent to the cation but not shown, occupies almost as much space as does the crown complex. It is interesting to compare the KNO_3 complex of 18-crown-6, shown in panel c of Figure 11.

3.1. Cryptands and Lariat Ethers

Crown ethers form essentially two-dimensional complexes as seen in the structures of Figure 11. In

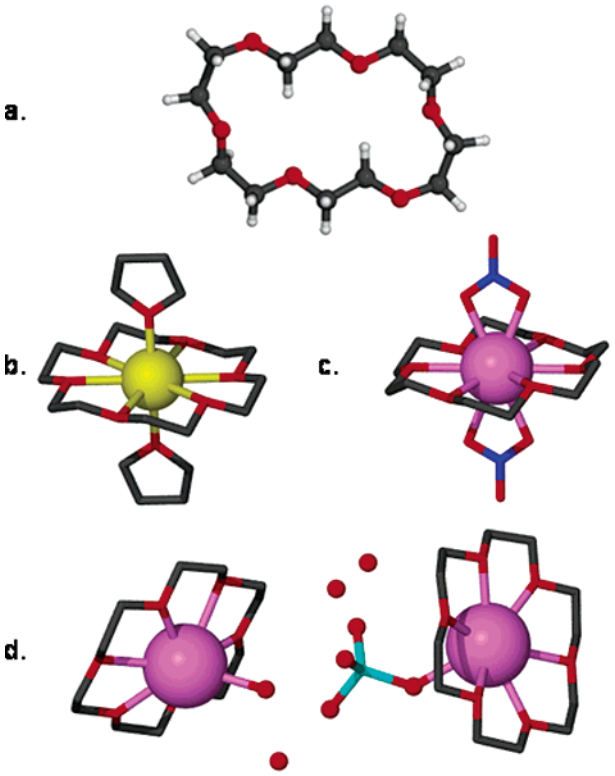

Figure 11. (a) Crystal structure of the parallelogram arrangement of uncomplexed 18-crown-6. (b and c) Conformation change of 18-crown-6 upon cation binding.

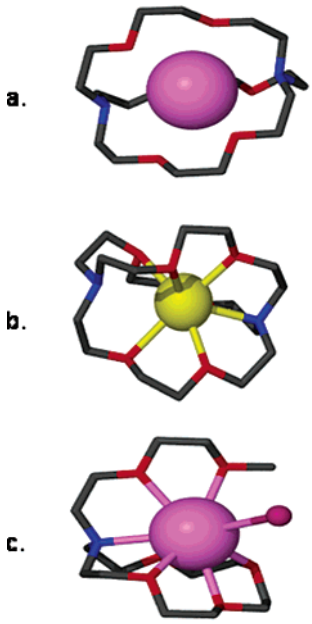

Figure 12. (a) Potassium complex of [2.2.2]. (b) Distortion of the sodium complex of [2.2.2]. (c) Coronate complex of a lariat ether.

contrast, cryptands and lariat ethers form enveloping complexes in which the cation is solvated by all donors more evenly than is typically the case in crown ether complexes. Usually, but not always, solvents and anions are excluded from the solvation sphere.

Panel a of Figure 12 shows a potassium complex of [2.2.2].[37] The donors are symmetrically distributed within the host and about the guest. The cation is completely inside the enveloping structure. Sodium ion is smaller than potassium,[38] and the host is distorted to fit the shorter Na^+-O bond distances. Even so, the ability of the cryptand to form an enveloping cryptate complex is apparent in panel b. In the bottom panel (c) of Figure 12, the coronate[39] complex of a lariat ether is shown. The macrocycle is aza-18-crown-6, and the sidearm, attached at nitrogen, is $(CH_2CH_2O)_2CH_3$. This open-chained ether has the same number of donors as [2.2.2], although they are present as one nitrogen and seven oxygen atoms rather than two N and six O. The structure shows that the K^+ ion is enveloped, but the iodide counterion is still close enough to interact directly.

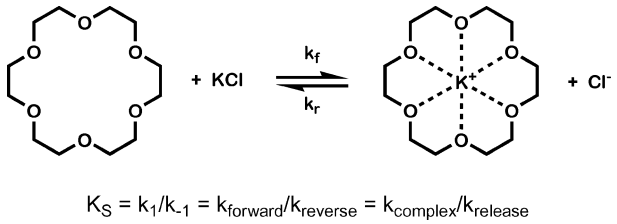

Figure 13.

3.2. Dynamics of Complexation

The complexation of cations by crown ethers has been extensively studied. Several reviews[40] and monographs[1] have appeared on the subject. The details will not be recounted, but some general principles are worth noting as they affect the use of crowns as scaffolds and as materials.

Complexation is illustrated in Figure 13 for the reaction of KCl with 18-crown-6. The process shown is illustrated in two dimensions and without solvent. Both of these are important issues to consider. We showed above that the crown complex might also involve a direct interaction of the anion with the ring-bound cation, interaction of the cation with solvent, or both. One common arrangement is for a water of solvation to coordinate to the ring-bound cation and then hydrogen bond to the anion. Solvent and/or the anion provide apical solvation to the otherwise two-dimensionally coordinated cation.

The structure of the complex is essentially a static, structural issue. Complexation typically occurs in a solvent from which the complex may crystallize. The position of the equilibrium (at a given temperature) depends on the relative stability of the crown, the salt, and the complex in the solvent. The equilibrium constant for the complexation reaction, K, is usually recorded as K_S, the stability constant. It is generally observed that the stability or equilibrium constant for the same crown and salt will be higher in low, rather than in high, polarity solvents. This is apparent in Figure 14, which shows data for the reaction between 15-crown-5 and NaCl.[41] The increase in K_S is dramatic from about 80% methanol to pure methanol. Binding is typically higher in lower polarity solvents such as $CHCl_3$, but dissolving salts in these solvents in the absence of the crown makes determining binding constants difficult in some cases. In addition, the potential for H-bonding may be very different in solvents that have similar dielectric

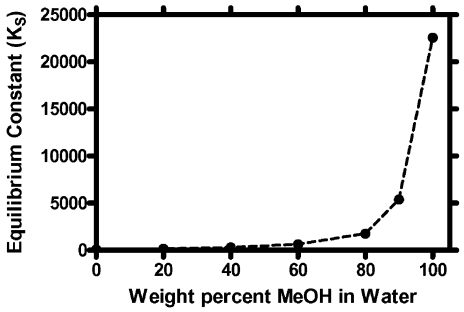

Figure 14. Plot of K_S for the reaction of 15-crown-5 with NaCl at 25 °C in methanol−water mixtures.

Table 1. Binding Data for Simple Crown Ethers

			log K_S	
compound	solvent	dielectric, ϵ	Na^+	K^+
12-crown-4	methanol	33	1.7	1.3
15-crown-5	methanol	33	3.24	3.43
18-crown-6	dioxane	2	4.55	
18-crown-6	methanol	33	4.35	6.08
18-crown-6	acetonitrile	37	4.8	5.7
18-crown-6	water	80	1.8	2.06

constants. Acetonitrile and methanol, for example, have similar dielectric constants, but only the latter is a strong H-bond donor. It may therefore be difficult to assess binding strengths and to compare the experimental values obtained.

A huge number of binding constants have been measured. Strong cation binders, such as 18-crown-6, have complexation constants with K^+ in methanol that are $>10^6$. The complexation constants will be even higher in lower polarity media. This huge range of values has led complexation equilibria to be expressed as the decadic logarithm of the constant, i.e., log K_S. Table 1 shows complexation constants for Na^+ and K^+ cations in various solvents. The equilibrium constants are expressed as log K_S.

It should be kept in mind that the equilibrium constant is the ratio of the binding and release rates, i.e., $K_S = k_1/k_{-1}$. An important property of crown ethers is that they complex and release cations rapidly in the polar solvents in which these rate constants have been measured. The complexation (k_1) and release (k_{-1}) rates for 18-crown-6 reacting with KCl in H_2O are 4.8×10^8 M^{-1} s^{-1} and 3.7×10^6 s^{-1}. The ratio ($4.8 \times 10^8/3.7 \times 10^6$) is the binding constant ($K_S =$) 115 M^{-1} (log $K_S = 2.06$).

An interesting and important difference between crown ethers and cryptands is that the latter typically have higher binding constants and slower binding dynamics. Thus, [2.2.2]-cryptand reacts with KCl in water with $k_1 = 7.5 \times 10^6$ M^{-1} s^{-1} and releases the cation with a rate $k_{-1} = 38$ s^{-1}. Note that the release rate is 10^5-fold slower than for 18-crown-6. The ratio k_1/k_{-1} is the binding constant in water, so $K_S = 2.0 \times 10^5$ M^{-1} (log $K_S = 5.3$). Complexation of the cation by the cryptand to form the cryptate complex is slower than for 18-crown-6, but release of the bound cation is even slower. This is because the cation is enveloped three-dimensionally by the cryptand in the complex and access of solvent is limited compared to a two-dimensional crown ether complex (a Coronate).

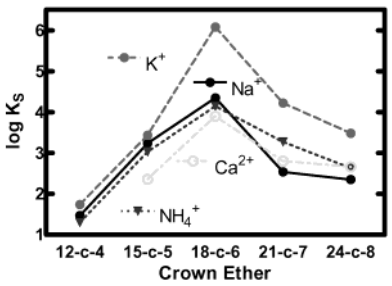

Figure 15. Binding constants (log K_S) for 3*n*-crown-*n* ($n = 4-8$) compounds with Na^+, K^+, Ca^{2+}, and NH_4^+ determined in CH_3OH at 25 °C.

3.3. Hole Size Relationship

It seems intuitively reasonable that when the crown ether's interior cavity ("hole") is about the same size as a given cation, binding will be optimal. Out of this intuition was born the so-called "hole size relationship". A problem in the crown ether area has often been the lack of comparative data obtained under identical conditions. Ideally, comparisons should be made for systems in similar solvents; cations should be paired with identical anions. When such a study was conducted for the family of simple crowns (12-crown-4 to 24-crown-8) in methanol, it was found that K^+ (counterion: chloride) binding was better for all crowns irrespective of ring size.[42] Further, K^+, Na^+, Ca^{2+}, and NH_4^+ were all bound more strongly by 18-crown-6 than by any of the other macrocycles. There may be cases in which the selectivity of a system may be understood on the basis of hole size correspondence, but the idea is not a principle that can be applied universally, Figure 15.

3.4. Lariat Ethers, Complexation, and Binding Dynamics

It was noted above that crown ethers form two-dimensional complexes. The rates for both the formation and release of ions by crowns are fast. Cryptands, in contrast, complex more slowly than do crowns, and they release bound ions far more slowly. The result is that cryptands have good ion selectivity, but they are not very useful for ion transport. Ionophores such as valinomycin are highly flexible and possess multiple donors. Valinomycin is a cyclododecadepsipeptide, that is, a cyclic compound formed from amino acids and hydroxy acids. It is a 36-membered ring that does not bind K^+, for which it is selective, in an interior hole. Instead, it folds over into what has been called a "tennis ball seam" arrangement and thus envelops the K^+ ion.

Lariat ethers were modeled on valinomycin complexation and designed to be flexible and dynamic when unbound and enveloping when a guest is complexed. This is illustrated for aza-18-crown-6 in which the sidearm is substituted by $(CH_2CH_2O)_2CH_3$ in Figure 16. It is compared structurally there with [2.2.2]-cryptand. Both are enveloping complexes, but the greater accessibility is apparent from the solid-state structure shown in panel c of Figure 12.

The participation of the sidearm in complexation that is clear from the solid-state structures was confirmed in solution. Binding constant studies

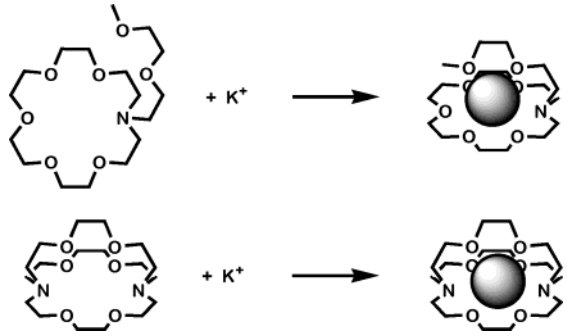

Figure 16. Potassium complexes of cryptands.

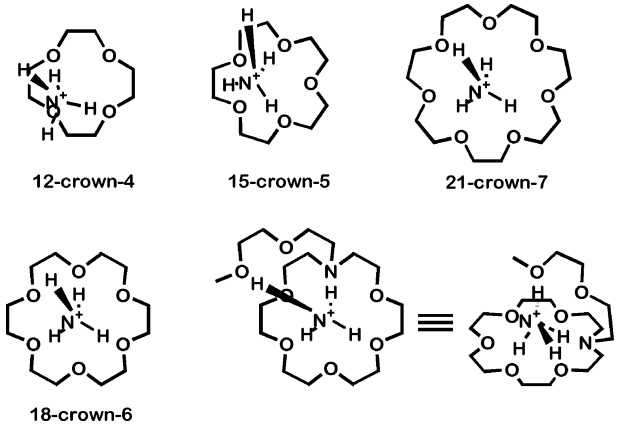

Figure 17. Ammonium ion binding in crown ethers.

showed clearly that when the sidearms had donors placed appropriately for binding, the measured equilibrium constants for complex formation were significantly higher than for other steric arrangements. One particular study involved the use of ammonium ion complexation. The NH_4^+ ion differs from alkali metals by the presence of directionality. Three of the four H-bonds coordinate nicely to an 18-crown-6 ring as shown in the lower left panel of Figure 17. The fit is not as good with larger crowns (e.g., 21-crown-7), and smaller crowns (e.g., 12-crown-4, 15-crown-5) cannot bind more than two of the three NH bonds. Ammonium ion complexation was studied with several lariat ethers having different ring sizes and different sidearm lengths. The highest binding measured for any of these complexes in CH_3OH solution is the structure shown in two views in the bottom center and right panels of Figure 17. In this complex, there was good complementarity between alternate ring oxygens and the ammonium ion's NH bonds. In addition, the second oxygen in the ethyleneoxy side chain was positioned appropriately to H-bond with the fourth NH, which is directed perpendicular to the plane of the macrocycle.

4. Heteromacrocycles as General Complexing Agents

The ability of crown ethers to bind metallic cations is documented in hundreds of papers. Binding is understood for many macrocycles and cations in considerable detail. There are so many cations and macrocycles that a brief survey cannot possibly encompass them all. Further, solvent plays a role in binding, which multiplies the complexity of the

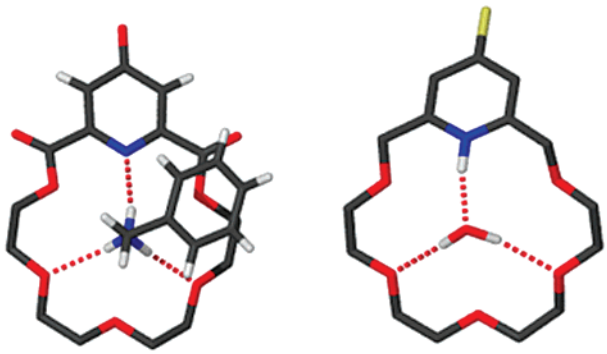

Figure 18. Hydrogen-bond interactions in crown complexes with benzylammonium (left) and water (right).

landscape. Understanding the details of metal cation complexation by heteromacrocycles, therefore, remains a worthwhile pursuit. In recent years, however, more attention has been focused on the exploration of supramolecular interactions between crowns and organic compounds. Some background is presented in the following section.

4.1. Crown Complexation of Molecular Species

Although the majority of complexation studies conducted with crown ethers involve metal ions, many other guest species have been examined. Ammonium ion, NH_4^+,[43] and primary alkylammonium ions, RNH_3^+ are particularly appropriate for crown complexation[44] and amenable to study.[45] As noted in section 3.4, three N−H···O hydrogen bonds can form to alternating oxygen atoms in 18-crown-6 compounds. The D_{3d} conformation of 18-crowns turns alternating oxygen electron pairs up, and the other three are tilted downward. The result is an excellent correspondence of electron pairs to ammonium ion hydrogens, making the complexes stable.

Flexible rings larger than 18-membered can still, in principle at least, adapt and interact with an ammonium ion's NH bonds. Water, which has only two H-bond donors but similar angles, may also complex within a macrocycle.[46] When the ring is smaller than 18-membered, only two H-bonds are possible. These conclusions are based on solution studies between crowns and alkylammonium ions[47] and on solution calorimetric measurements.[48] The preferred binding arrangement of an ammonium ion and 18-crown-6 ethers has been confirmed by solid-state structures.

Figure 18 shows the X-ray structures of a benzylammonium cation complex (left)[49] and a complexed water molecule (right).[50] In both cases, a dashed line connecting the appropriate atoms identifies the H-bond interactions. The water and ammonium ion complexes exhibit similar steric situations. Water has only two OH donors available for H-bonding. These are shared (right structure) in two O−H−O bonds, indicated by dotted lines. Water's oxygen atom is a Lewis base and H-bond acceptor, and it coordinates to the NH bond in the piperidinethione ring. The trigonal binding arrangement for water can also be achieved by protonation to give hydronium ion. The latter's coordination by 18-crown-6 was detected by infrared[51] and other spectroscopic techniques. Solid-

state structures confirm this 3-fold symmetrical arrangement,[52] and mass spectrometry has been used to assess its stability.[53] Crown complexation of many protonated molecular species, such as hydrazinium cation,[54] have also been reported.

4.1.1. Crystallization of Crown Ethers with Neutral Molecules

Crown ethers are cyclic and contain an internal hole or cavity. As such, their internal molecular void may be penetrated by various molecular species in addition to the ions mentioned above. Of course, small molecules fill the interstitial spaces of many crystals, and the "complexation" may actually be cocrystallization or solvation.

Early preparations of 18-crown-6 produced an oil that was troublesome to purify. Liotta discovered that the impure compound formed a solvate with acetonitrile that permitted effective purification.[55] Subsequently, numerous other materials were found to be included in crystals containing 18-crown-6.[56] Examples include nitromethane, dimethyl carbonate, and dimethyl oxalate. In some cases, specific, stabilizing interactions were identified between the crown and the "partner" molecule, such as urea.[57] Such inferences could best be drawn from solid-state structure analysis[58] and often could not be confirmed in solution. Multiple element complexes, for example, involving thiourea and potassium iodide,[59] have also been reported.

4.1.2. Diazonium and Other Cylindrical Cations

One guest molecule that gave clear evidence for insertion within a crown in solution was benzenediazonium ion ($Ar-N\equiv N^+BF_4^-$). Diazonium ions are quite reactive, thermally and photochemically. In addition, they undergo a variety of nucleophilic and radical reactions. In solution, arenediazonium ions are complexed[60] and stabilized.[61] Stability has also been assessed in the gas phase.[62] The original study was done with 18-crown-6, but a survey of crown sizes concluded that 21-crown-7 was the best fit for the arenediazonium ion's nitrogen atoms. The influence on stability of both steric and electronic factors has been studied in detail.[63] An especially interesting manifestation of this stabilization is that the Schiemann reaction of arenediazonium tetrafluoroborates, which gives aryl fluorides, is slowed by crowns.[64] Benzoyl and nitrosyl cations are also complexed by crown ethers,[65] although crowns containing aromatic subunits are prone to reaction with the cation, Figure 19.

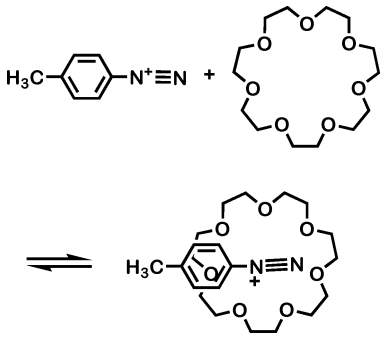

Figure 19. Benzenediazonium ion insertion with a crown in solution.

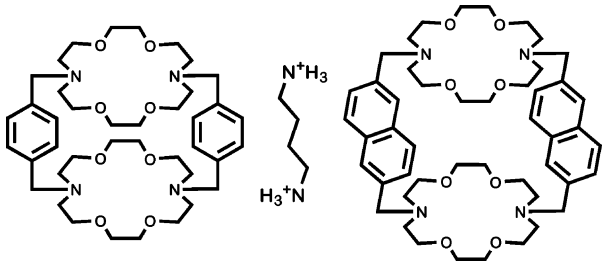

Figure 20. Ditopic complexation of diammonium salts.

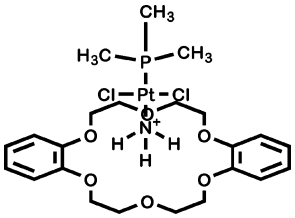

Figure 21. Metal ammonium salt complexation by dibenzo-18-crown-6.

4.1.3. Diammonium and Second-Sphere Complexes[66]

Receptors have been explicitly developed[67] to study the complexation of diammonium cations and mixed molecular and cationic species. At the left in Figure 20 is shown a ditopic receptor reported by Sutherland and co-workers intended to bind diammonium salts, $H_3N^+(CH_2)_nN^+H_3$. The aromatic spacers influence the NMR spectra of ammonium ions bound within the receptor. The optimal diammonium salts that correspond in size to the cavity can thus be identified by solution studies. The structure at the right was devised by Lehn and co-workers, who reported solid-state structures of the resulting complexes.[68] The Lehn lab developed macrotri- and pentacyclic ditopic receptors[69] as well as molecular co-receptor structures.[70] Shinkai and co-workers developed bis(crowns) connected by azo linkages that can be switched to bind and release diammonium ions under photochemical control.[71]

Positively charged $-NH_3^+$ groups are present in metal complexes that include amine ligands. Stable 1:1 complexes were formed between several crown ethers and various metal complexes.[66] These were dubbed "second-sphere" complexes because the primary role of NH_3 was to solvate the metal ion and because the crown was in the metal ion's second coordination shell. An example is shown in Figure 21. In this case,[72] when the amine was $H_2NCH_2CH_2NH_2$, a coordination polymer resulted that was isolated and characterized by X-ray analysis.[73]

4.1.4. Chiral Recognition of Ammonium Cations

Early in the development of crown ethers, Cram recognized that selective complexation of chiral ammonium salts could be achieved.[74] His approach was to use the orderly three-point binding of ammonium ions to 18-crown-6 arrays that incorporated a chiral barrier. The barrier would exert steric pressure within the complex, favoring the receptor's chiral complement rather than its enantiomer.

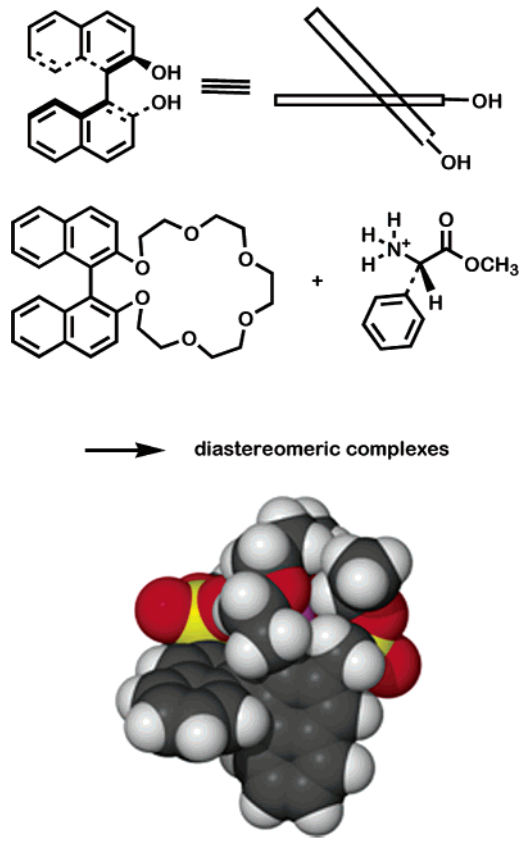

Figure 22. Chiral complexation of crown ethers. (top) Chiral binaphthyl in two representations. (center) Equation shows complexation between phenylglycine methyl ester and dibinaphthyl-20-crown-6. (bottom) X-ray structure of the complex.

β,β′-Dihydroxy-α,α′-binaphthyl can be resolved into its antipodes and then incorporated into a macrocycle such as shown in Figure 22. The two naphthalene rings are attached at the α-positions, so the two *peri*-hydrogens cannot easily pass each other. This creates a chiral barrier. The crystal structure shown is a potassium rather than an amine complex. It illustrates the barrier presented by the single *peri*-hydrogen to the second naphthalene ring. The two rings will be more or less hindering to phenylglycine in one configuration than in the other. Thus, one diastereomeric complex will be favored over the other. In principle, diastereomeric complexes can form from a racemic crown mixture and a stereochemically pure ammonium salt or vice versa. In most of Cram's studies the crown ethers were chiral and used to resolve ammonium salts such as phenylethylamine[75] or, as shown, phenylglycine methyl ester. Other examples of chiral recognition have been reviewed.[76]

Cram and co-workers enhanced the chiral recognition ability of binaphthyl by placing two of these subunits within the same macrocycle. In addition, they augmented the steric barrier presented by each binaphthyl by adding a methyl group at the 3-position. This resulted in a macrocycle that is formally a 22-crown-6, shown in Figure 23. The crystal structure of this molecule is shown complexing phenylglycine. The amino group of phenylglycine is protonated, and the perchlorate counterion has been omitted for clarity. The structure was taken from the coordinates in the CSD recorded as GACVIP. The orientation of

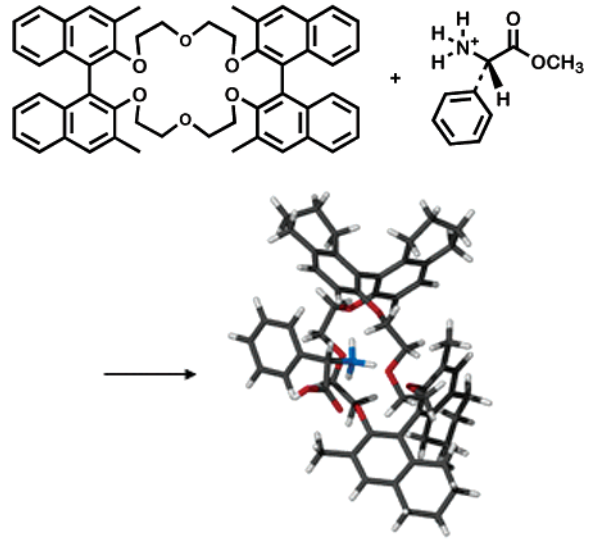

Figure 23. Chiral recognition of phenylglycine by dibinaphthyl-22-crown-6 shown as a chemical drawing and in its X-ray structure.

the three amino group hydrogens toward the macrocycle's oxygens is apparent in the center of the structure. The benzene ring, the largest of the substituents on the α-carbon atom, is turned away from the naphthalene rings to minimize unfavorable steric interactions.

4.1.5. Molecular Complexes

A catenane is a molecule that has interlocking rings. Many examples of catenanes exist in nature. They include interlocked or knotted DNA, many examples of which are found in bacteria and viruses.[77] Although such synthetic structures were long imagined, the first example did not appear until the 1960s, when Frisch and Wasserman[78] described a workable synthetic route. Generally, the formation of interlocking rings could be accomplished by "threading" a linear component into a ring, followed by the chemical closing of the second ring. The first interlocking ring system was synthesized by Harrison and Harrison in 1967.[79]

Interest in such systems peaked again in the early 1980s, when Sauvage and co-workers synthesized the first system of interlocked macrocycles obtained by complexation to a metal.[80] Using a crown ether macrocycle and a diphenyl phenanthroline, complexation by Cu^+ resulted in the interlocked ring system composed of two 30-atom rings about a central copper atom. Demetalation of the complex with potassium cyanide then gave the knotted system, termed a *catenand*, shown in Figure 24 (structure taken from the coordinates in the CSD recorded as CUFHEQ). NMR studies of the first catenand showed significant conformational changes, consistent with the ability of one ring to glide freely through the other. Subsequent work quickly began incorporating bulky sidearms. Several isomeric catenanes were developed. Sauvage and Mitchell reported the first synthesis of a topologically chiral catenand in 1988.[81]

In 1987, Stoddart and co-workers recognized that a complex formed between paraquat ($CH_3^+NC_5H_4-C_5H_4N^+-CH_3$) and bis(paraphenylene) crown ethers.

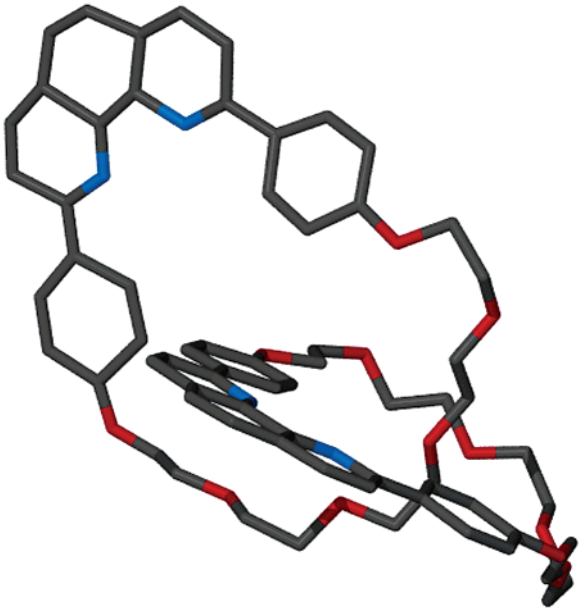

Figure 24. A catenand. The first example of a knotted crown ether system synthesized via a metal template.

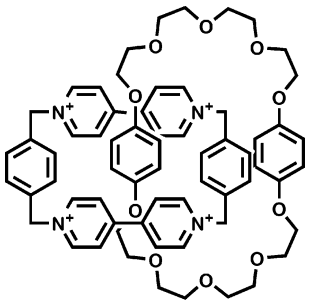

Figure 25. A [2]catenane.

A specific example was the inclusion complex formed by bisparaphenylene-34-crown-10.[82] The formation of this complex comprised catenane formation; the specific [2]catenane that resulted is shown in Figure 25. The driving forces for complexation are charge transfer or π-acid to π-base interactions between the electron-deficient paraquat and the electron-rich phenylenedioxy residues as well as the formation of CH hydrogen bonds.

Shortly after this complex was isolated, it was recognized that paraquat and methyl viologen are the same compound. The latter is well-known as an electrochemically switchable residue, meaning that it can undergo reversible electron transfer. Thus, it could function as an electrochemical switch. Kaifer, who worked extensively with viologens, joined forces with Stoddart to demonstrate the potential of this idea and these complexes.[83] In later work, the basic framework for these catenanes has been elaborated into rotaxanes, pseudorotaxanes,[84] molecular knots, a molecular shuttle,[85] and even a "molecular abacus".[86] The original "paraquat" box was also found to complex amino acids that have electron-rich side chains.[87]

A variation on the basic catenane structure was reported in 1993, where a gold electrode was used for surface attachment of an organosulfur macrocycle.[88] The approach taken by Lu et al. was to exploit

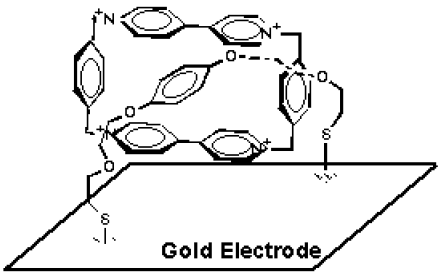

Figure 26. Surface attachment of an organosulfur macrocycle.

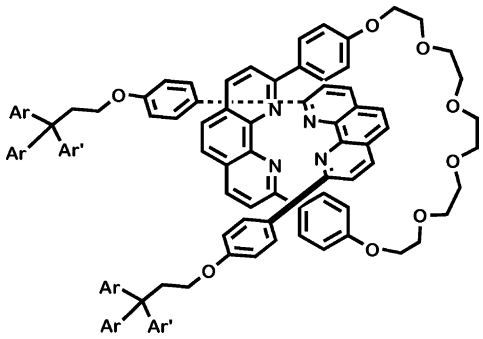

Figure 27. A [2]rotaxane.

charge-transfer interactions between π-donors and π-acceptors. The charge-transfer complex between the cyclophane and a bis(thiol) hydroquinol formed with $K_{assoc} = 253\ M^{-1}$. The terminating thiol groups were subsequently attached to the gold surface to close the catenane, and the cyclophane was irreversibly attached to the gold surface (Figure 26).

The first template-directed synthesis of a [2]rotaxane (Figure 27) was reported by Gibson and coworkers.[89] Similar to catenanes, rotaxanes are composed of a macrocycle and a dumbbell-shaped component. The linear portion of the dumbbell is encircled by the macrocycle in such a way as to be under thermodynamic control. The dumbbell component contains two bulky substituents that serve as stoppers; although they are not covalently linked, the two components cannot dissociate from each other.[90] The bulky aryl groups on the linear component of the rotaxane prevent that piece from coming out of the macrocycle, yet are distanced far enough apart to allow some rotational flexibility of the phenanthroline group.

Synthesis of these types of compounds has been accomplished primarily via metal templating (reviewed in ref 91). By exploiting the properties of transition metals, independent pieces can be positioned so as to induce an inter- or intramolecular reaction. For the templated-directed synthesis of catenanes and rotaxanes to occur, it is required that the pieces gather and thread together via coordination to the metal. Among others, Fe^{3+}, Ni^{+}, and Cu^{2+} have been used as transition-metal templates. In one particularly interesting example from Sauvage and co-workers, a [2]catenane was synthesized using a Cu^{+} template.[92] Upon oxidation of the metal center, the gliding of one ring within the other is observed. Subsequent reduction back to Cu^{+} triggers a second motion of the complex (Figure 28).

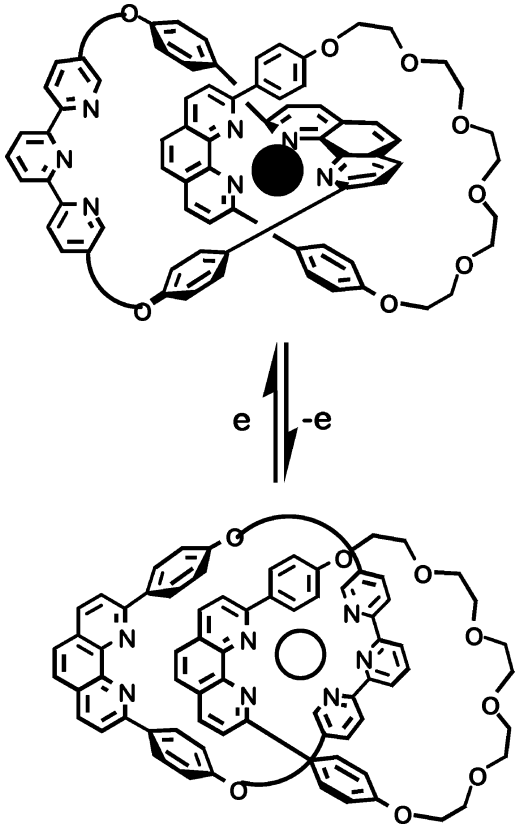

Figure 28. Use of redox switching to form an interlocked ring system.

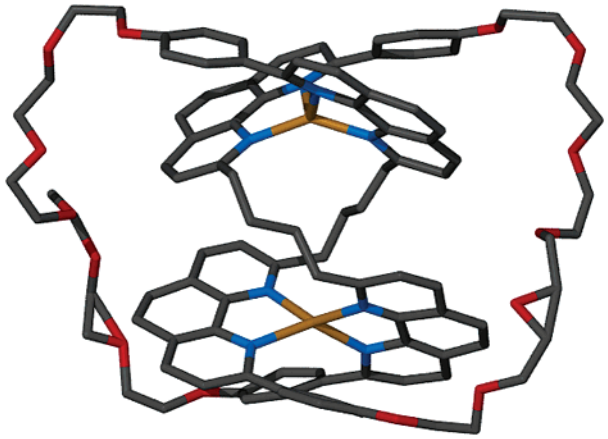

Figure 29. Crystal structure of the trefoil knot reported by Dietrich-Buckecker and Sauvage.

A challenging compound of this type was reported by Dietrich-Buchecker and Sauvage in 1989.[93] The crystal structure of the trefoil knot is shown in Figure 29 (CSD: KICHAF). Synthesized in a 3% yield, the knot consists of a single 86-membered ring and two Cu^+ ions, complexed by the phenanthroline groups. An interesting note about this knot is that it undergoes spontaneous resolution upon crystallization, and thus, the crystal structure contains only one enantiomer. NMR studies[94] on the demetalated knot were used to examine the molecular motion of the compound. At room temperature, ^1H NMR gives only broad signals; upon warming to 366 K, the proton resonances sharpen up considerably. The motion of the knot has been described as "wormlike"[95] and as "molecular reptation". On the basis of the NMR data, it was estimated that at room temperature it takes about 2 s for one full molecular reorganization cycle to take place. Subsequent work has involved variations in ring sizes and substituents, but yields have remained disappointing.[96]

4.2. Anion Binding

The potential of heteromacrocycles to bind anions as well as cations was recognized early. Park and Simmons[97] demonstrated by NMR analysis that the chloride ion was bound by [9.9.9.]- and [10.10.10]-amines under acidic conditions. Lehn showed that when protonated, a macrobicyclic, bis-tren cryptand could include linear azide ion within it. The complex was stabilized by H-bond interactions involving the bridgehead nitrogen atoms at either end of the cryptate's internal cavity.[98] The field of anion recognition by many synthetic receptor molecules is now a flourishing one that has recently been reviewed.[99]

4.3. Alkalides and Electrides

The ability of heteromacrocycles to complex cations permitted the observation of two novel anionic species—sodides and electrides. The first sodide (Na^-) was prepared from a saturated solution of Na^+ in $EtNH_2$ in the presence of a cryptand. Shiny, gold crystals were obtained that proved to be a complex of encapsulated (cryptated) Na^+ and the sodide anion. The crystal structure confirmed the analysis.[100] In a related effort, Dye obtained a crystalline compound, $Cs^+(18\text{-crown-}6)_2.e^-$, that was shown by a variety of techniques including ESR, NMR, and magnetic susceptibility to be the first crystalline electride. An electride is the simplest anion.[101]

5. Molecular Switches

The property of crown ethers that has engendered the greatest attention historically is their ability to bind cations. Almost as soon as their range of complexation abilities was outlined, efforts were made to control complexation strength and selectivity by using a variety of techniques.

The concepts of molecular switching and sensing evolved more or less simultaneously in the crown ether field. Molecular switching involves changes in charge state, conformation, or structure that enable or prevent cation complexation in a host structure that previously could not or could, respectively, bind a guest. Crowns are an integral part of many sensors as they provide the binding scaffold for the guest, the presence of which is detected by a change in some detectable property.

In sensor molecules that involve crown binding sites, the complexation process takes place to a greater or lesser extent. There has been considerable variation in the extent to which the putative complexation-responsive residue reflects binding. Obviously, not all strategies work equally well. In some cases, however, control experiments or comparison experiments with potential interferants are lacking. This is not the case for the examples reviewed.

5.1. Azobenzenes and Photochemical Switching

Among the earliest examples of molecular switching were those involving azobenzenes. Studies in the

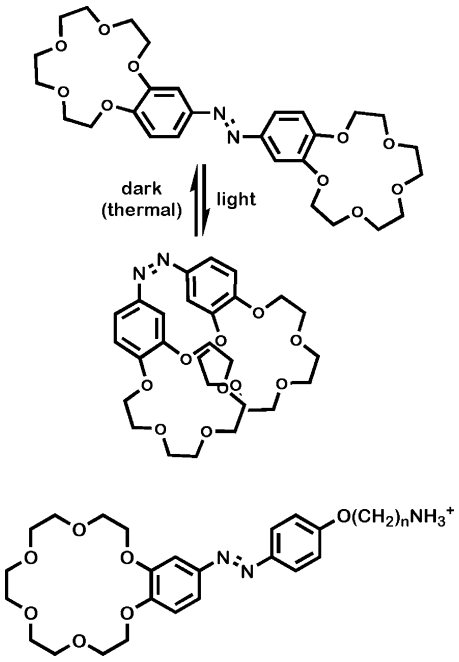

Figure 30. Photochemical switching of crown ether systems.

Shinkai laboratory demonstrated the broad capabilities of this subunit as a photoresponsive switch.[102] The normal geometry of the N=N bond in azobenzene is trans (*E*). When irradiated at the appropriate wavelength, the double-bond geometry changes from trans to cis (*E* to *Z*). An example is shown in Figure 30. The azo linkage has been used to join the aromatic rings of two benzo-15-crown-5 molecules. When the bis(crown) is irradiated, azobenzene undergoes a light-induced *E* to *Z* isomerization. The two macrorings are remote in the former isomer and proximate in the latter. A cation may be bound in the space created by the cooperation of two rings, while two molecules of the *E*-isomer would be required to form a sandwich complex with a large cation.[103] This principle was further demonstrated with a molecule containing a crown, an ammonium ion, and azobenzene to serve as the conformational switch. When the methylene chain was butylenes ($n = 4$), aggregates were detected in solution before or after irradiation. When $n = 6$ or 10, only monomers were detected, suggesting intramolecular crown−ammonium ion complexation.[104]

5.2. Redox and Electrochemical Switching

Shinkai and co-workers also recognized the versatility of redox chemistry in making crowns and in switching between species that had intrinsically different binding abilities. An example of the formation of a macrocycle from a disulfide is illustrated as structure M in Figure 6. In 1985, Shinkai and coworkers prepared a benzo 19-crown having five oxygen atoms and a disulfide bridge.[18] This group also demonstrated the oxidative coupling to give a disulfide-linked podand having 8-hydroxyquinoline residues at the terminus.[105] In these two cases, the redox chemistry of thiols is used to fix the structure in a binding arrangement. The increased organization affords enhanced complexing power. Thus, the

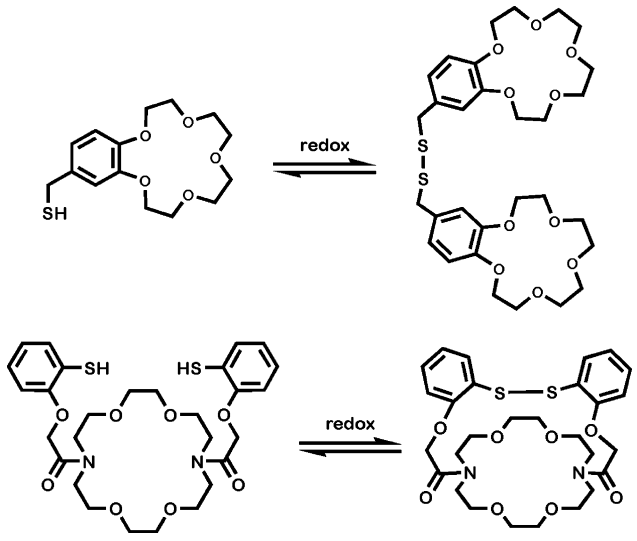

Figure 31. Redox switching of crown ether systems.

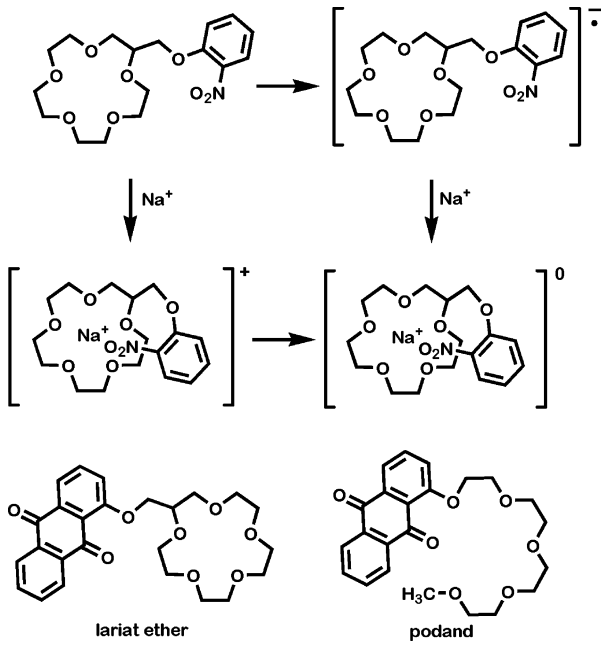

Figure 32. Electrochemical redox switching of crown ethers.

conformation or structure is "switched" from a low-binding to a high-binding state, Figure 31.

Redox switching by electrochemical methods was pioneered in lariat ethers by Echegoyen, Kaifer,[106] Gokel, and their co-workers.[107] The phenomenon was demonstrated first using 15-membered ring lariat ethers having nitrobenzene-terminated sidearms. The sidearms were attached to carbon of the macroring. Such lariat ethers are usually referred to as C− or carbon-pivot lariats. Figure 32 illustrates the concept. The crown may undergo either reduction of the nitroaromatic residue or complexation of Na^+ by the macroring. Reduction affords the radical anion, which is delocalized onto the nitro group oxygen atoms. The increased electron density makes the nitro group a better donor for the ring-bound cation. If complexation of Na^+ occurs first, coordination of the nitroaromatic ring with the Lewis acidic cation will make the arene more reducible. In either case, the ultimate complex (lower right of the figure) is

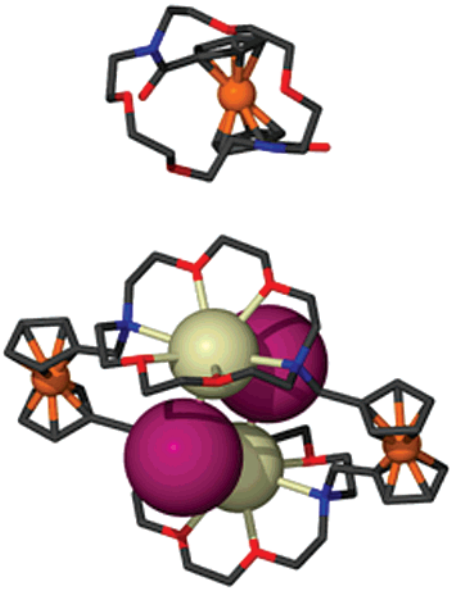

Figure 33. Sandwich complexes of ferrocenes and crown ethers.

neutral. In subsequent studies, nitrogen-pivot lariat ethers were shown to function similarly and even more effectively.[108]

A shortcoming of nitroaromatic radical anions is that they are rapidly quenched by water. This is not a drawback with anthraquinones, the radical anions of which are stable in aqueous solution in the absence of oxygen. Anthraquinone may be incorporated into lariat ethers as a redox-switchable sidearm element (shown in the bottom panel of Figure 32).[109] The stability of the anthraquinone residue, when attached to an open-chained (podand) complexing element, permitted electrochemically controlled transport of Li^+ ion through membranes.[110]

5.3. Ferrocene

Hall and co-workers combined ferrocene with a variety of macrocycles to afford cryptands in which the sandwich complex comprised one of the spans.[111] The structures were investigated extensively by NMR and other methods, but the use of ferrocene as a switch to alter properties was accomplished first by Saji.[112] Reduction of Hall's ferrocenylamide cryptands gave molecules that were excellent binders and redox-switchable.[113] Gokel, Kaifer,[106] and their co-workers exploited these properties to develop binders in which the ferrocenyl iron was shown to serve as a donor for bound alkali-metal cations.[114] Figure 33 shows a ferrocenyl bis(amide) crown (top)[115] and a RbI complex of a bis(ferrocenyl) cryptand (CSD: YURFUM).[116] A limitation of the ferrocenylamides was that the carbonyl groups are strong donors, but they are turned outward. The lower structure in this figure shows an interesting two cation−two anion array within the bis(ferrocene) structure. Redox-switchable ferrocenes have also proved to be general binders for diamines.[117]

5.4. Viologen–Catenane Switches

The catenane−paraquat system described above can be controlled by redox chemistry of the viologen moiety. Extensive work by Kaifer and Stoddart[118] demonstrated the potential of such a system. The concept was elaborated to "molecular shuttles"[119] and to the concept of simple machines.[120]

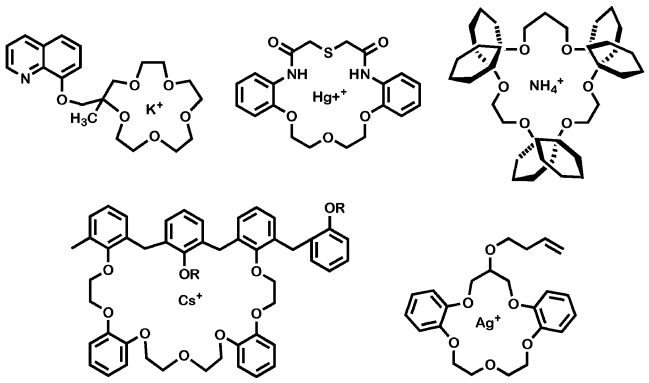

Figure 34. Crown-based ion sensors.

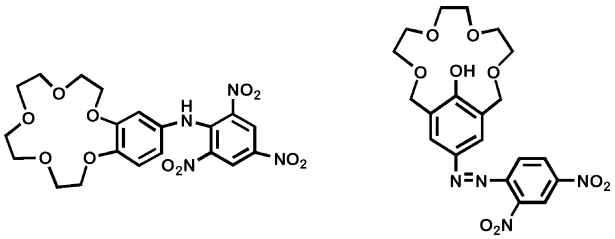

Figure 35. Crown-based dyes for spectrophotometric detection.

6. Crown Ethers as Sensors

There are numerous examples in the literature of crown ethers used as sensors for a broad range of inorganic ions. Their selective receptor properties in conjunction with the relative ease of synthesis and structural modification make crown ethers attractive targets as ionophores. Several recent examples of ionophores and the metals they complex can be seen in Figure 34.

Although many crown-based sensors are developed for use in ion-selective electrodes (ISEs), including those shown in Figure 34, there are many other applications. In the late 1970s, several reports appeared regarding crown ether dyes (for a review, see ref 121). The first compounds reported[122] were 4′-picrylamino-substituted derivatives of benzo-15-crown-5. These dyes, most of which are nearly insoluble in aqueous solvents, can efficiently extract cations at the organic/aqueous interface. This extraction is accompanied by a color change that can be detected spectrophotometrically. The 15-crown-5 derivative shown in the left panel of Figure 35 turns from orange to red when bound to K^+ or Rb^+. The host is unable to bind either Li^+ or Na^+. Studies on this compound have shown it to bind in a 2:1 ligand:metal complex with the large cations. Similar compounds utilizing 18-crown-6 bind in 1:1 ligand:metal complexes but show much less selectivity in binding. Such dyes have been designed to incorporate aza-crowns[123] and lariat ethers[124] to alter cation selectivity, water solubility, and pH dependence but still extract ions efficiently.

Kaneda and co-workers[125] prepared a crown ether dye that incorporates a phenolic hydroxyl group as

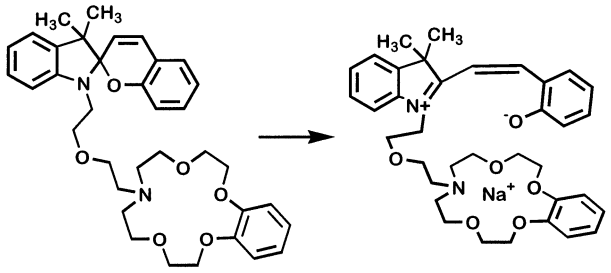

Figure 36. Changes in the spirobenzopyran-based crown ether for ion sensing.

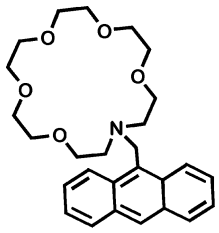

Figure 37. De Silva's anthracenylmethyl lariat ether for fluorescence signaling.

part of the crown ether backbone (Figure 35, right panel). Addition of LiCl and excess pyridine to the ligand results in a color change from purple to red. This effect was not observed upon addition of other metal cations. Sensing of Li^+, down to 25−250 ppb, has been achieved with this compound in $CHCl_3$/DMSO solvent mixtures. Several other chromogenic receptor molecules have been developed by Misumi,[126] Shono,[127] Bartsch,[128] Vaidya,[129] Biernat,[130] Kimura,[131] Kubo,[132] and others.[133] Vicens and co-workers recently reported a chromogenic calix−crown system that gives K^+-selective transport.[134] Shinkai and coworkers recently reviewed much of this effort.[135] Several of these examples of chromogenic crowns involve the spirobenzopyran subunit, which has been widely used in developing photochromic sensors. Figure 36 shows how the structural and photophysical changes correlate to permit ion sensing. This methodology has also been used in tandem with mass spectrometric analysis.[136]

De Silva and co-workers pioneered the use of crown-based ionophores for fluorescence sensing. This is a technology that is beginning to find wide-ranging application[137] (for reviews see ref 138). Such sensors integrate a receptor, in this case a crown ether, and a fluorophore for detection. Photoinduced electron transfer (PET) is the most common fluorescence technique used in these systems, whereby fluorescence is quenched by a partial charge, typically the free lone pair of electrons on a nitrogen atom. Binding of the species of interest results in an interaction for the lone pair, turning off the PET and turning on the fluorescence.

The first molecule[139] of this type that was studied is shown in Figure 37. It is an anthracenylmethyl lariat ether derived from aza-18-crown-6. Potassium demonstrated excellent 'off−on' fluorescence signaling in this system, and the binding constant of the cation with the fluorescent macrocycle was nearly identical to that with the free macrocycle. Variations of this work have appeared throughout the literature with time. One noteworthy example is the development of a fluorophore that can bind γ-aminobutyric acid (GABA) zwitterions via a guanidinium moiety incorporated into the fluorophore,[140] giving a valuable approach to tracking the neurotransmitter.

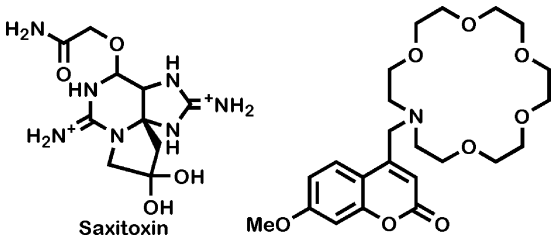

Figure 38. Saxitoxin (left) and a saxitoxin sensor (right).

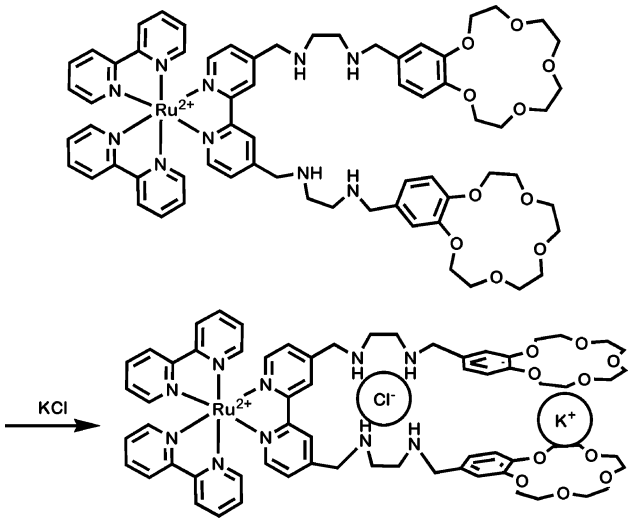

Figure 39. Luminescent sensor for ion pairs.

This fluorescent sensor and a related coumarin-based[141] macrocycle have been used as chemosensors for the marine toxin saxitoxin.[142] Saxitoxin is a bis(guanidinium) ion, and crown ethers are known to bind guanidinium ions.[60b] Incorporation of a fluorophore onto the crown structure then allows for fluorescence upon binding via PET, Figure 38.

Beer and Dent developed a hybrid 2,2′-bipyridyl−crown ether system to complex and sense ion pairs.[143] One bipyridyl subunit was incorporated into the scaffold terminated by bis(macrocycles). The fluorescent unit (the ruthenium tris(bipyridyl) complex) was then formed by treatment with two additional 2,2′-bipyridine units. Alternately, a corresponding bipyridyl ruthenium tetracarbonyl unit could be prepared. The former is shown in the adjacent figure (Figure 39). When treated with KCl in DMSO, an ion pair complex (shown) formed. It is proposed that the cation is bound in a sandwich complex involving the two 15-crown-5 residues at the side of the molecule opposite the ruthenium complex lumiphore. It is further proposed that chloride anion is complexed by four amide NH residues as shown in the figure.

Stability constants for binding chloride were determined by ^1H or ^{13}C NMR titrations. It was found, for example, that the host had a constant of 190 M^{-1} when titrated with Bu_4NCl. Addition of two equivalents of KPF_6 increased the apparent binding constant to 660 M^{-1}. This suggested the coordination of chloride ion as shown in the illustration.

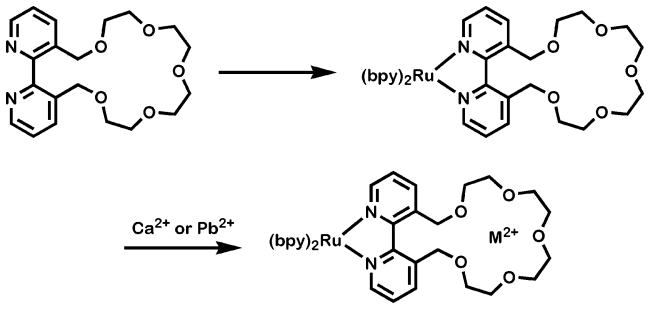

Figure 40. Luminescent sensor for divalent cations.

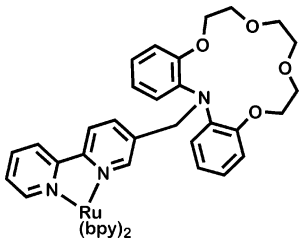

Figure 41. Crown ether sensor using ruthenium tris-(bipyridyl) as the lumiphore.

The emissive characteristics in CH_3CN of ruthenium tripipridyl complexes have been used for ion sensing in conjunction with crown ethers. Quantum yields were determined for the Ru(bipyridyl) complex shown in Figure 40 using $Ru(bpy)_3^{2+}$ as the standard. When either divalent calcium or lead was added to the 19-crown-5, emission increased by about 4-fold. The response of the crown was smaller when either Mg^{2+} or Na^+ was added. When the analogous crown-6 compound was studied, high ion concentrations were required to elicit smaller responses.[144]

Another recent strategy uses the ruthenium tris-(bipyridyl) lumiphore attached to a dibenzoaza-15-crown-5, Figure 41.[145] Both electrochemical and photophysical properties were examined. The crown−bpy host molecule (shown) exhibited a strong absorption band at 288 nm when irradiated in degassed CH_3CN at ambient temperature. Emission bands were observed at 450 and 625 nm. The effects of various cations on both the electrochemical and photochemical processes have been reported. Luminescence from the metal complex was enhanced particularly by the presence of lithium cations and protons. In particular, it was noted that "cation binding serves to decrease the rate of reductive quenching of the triplet state of the metal complex, thereby increasing the extent of fluorescence".

6.1. Mass Spectrometry of Heteromacrocycles

The complexation of a cation with a crown ether produces a positively charged molecular ion that can be detected by mass spectrometry under appropriate conditions. Mass spectrometric methods have been used extensively to characterize novel receptor structures, but a number of physical chemical studies were required to calibrate the technique.[53,146] Generally, low-energy ionization methods have proved to be the most successful for analytical purposes, and uses of supramolecular chemistry in the gas phase have been thoroughly reviewed recently.[147] Electrospray ionization (ESI) methodologies have been used widely to evaluate binding selectivities of crown ether ligands with a variety of different hosts, including alkali,[146i,148] transition,[148c] and heavy[149] metals, π-complexes,[150] and ammonium-based[148b] guests. Additionally, chiral recognition can be achieved in the gas phase, and many applications, especially those utilizing amino acid recognition, have recently appeared in the literature.[151]

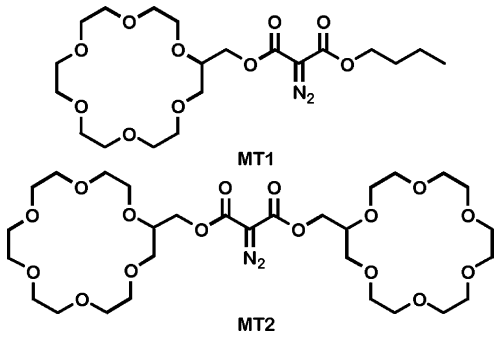

Figure 42. Molecular mousetrap sensors for ESI-MS.

6.2. Molecular Mousetraps

The ability of crown ethers to bind the positively charged side chains of lysine or arginine has long been known.[44,146i,152] Julian and Beauchamp exploited this recognition property by developing a family of receptors that they call "molecular mousetraps:" crown-based compounds that utilize the strong interaction between 18-crown-6 and protonated primary amines.[153] Compounds (MT1 and MT2, Figure 42) complex the cations in solution. The mixture is then subjected to electrospray ionization mass spectrometry (ESI-MS).

Beauchamp and co-workers showed that 18-crown-6 is a sensitive chemical probe of molecular structure. Their initial MS experiments with cytochrome *c* and bovine pancreatic trypsin inhibitor (BPTI) suggested that 18-crown-6 could be used to afford information about surface functional groups of folded proteins. Cytochrome *c* contains 19 lysine residues, 11 of which are surface exposed. When 18-crown-6 is added to a methanol/water solution (80:20) of cytochrome *c*, ESI-MS shows four complexed crowns. However, of the 11 exposed lysines, 7 are known to be tied up in salt bridges, leaving only the 4 available to complex the crown. When cytochrome *c* is partially denatured, 11 crown ethers are found attached to the protein. Similar results were obtained with BPTI, giving some indication about the folded vs unfolded structures of these proteins. It should also be noted that 18-crown-6 prevents the well-understood refolding of cytochrome *c*, as nearly identical spectra were obtained 2 days after denaturing.

Expanding their original work with lysine and 18-crown-6, Julian et al. also examined the molecular recognition of arginine by dibenzo-30-crown-10, the effect of nitrogen substitution on lysine recognition utilizing aza-18-crown-6 ether, and incorporation of diazo groups for controlled activation for molecular recognition. ESI-MS experiments show that dibenzo-30-crown-10 has a higher affinity for the protonated guanidinium side chain of arginine than does the

previously reported 27-crown-9. The combination of dibenzo-30-crown-10 and 18-crown-6 can be used to determine whether a peptide of unknown sequence contains lysine or arginine. In conjunction with the denaturing experiments, such techniques can give insight into the structural positioning of lysine and arginine residues in a protein of unknown structure. In an extension of this work, Beauchamp found that the proton affinity of aza-18-crown-6 was significantly higher than that of 18-crown-6.[154] The greater protonation diminished aza-18-crown-6's ability to recognize lysine. When the nitrogen atom was incorporated as an amide, the ability of aza-18-crown-6 to form a lysine complex was rescued but still showed weaker affinity for lysine than did 18-crown-6.

The design of MT1 and MT2 incorporated a reactive diazo group that can be converted to a carbene via collision-activated dissociation (CAD) in the gas phase. ESI-MS experiments using these compounds showed the loss of 28 Da in the gas phase, which is presumably the loss of the diazo group. Further fragmentation of the host occurred without loss of the guest, providing evidence that an intermolecular reaction had occurred between host and guest via CH insertion of the carbene. The derivatization of 18-crown-6 was done to introduce specific functional groups that can couple the host to target molecules. This "molecular mousetrap" approach offers a useful adjunct to traditional mass spectral analyses of biological substrates.

7. Biological Model Systems

The cells and organelles that are the fundamental macroscopic elements of living systems are dauntingly complex. The common chemical structures such as proteins, RNA, and DNA strands are simpler but incredibly complicated at the chemical level. Chemists have worked long and hard to dissect and study individual elements of complex biological structures. One approach is to prepare structures that are designed to mimic or probe specific chemical interactions thought to be involved in biological function. A different approach involves the preparation of simplified models that function in the same way as a biologically important structure. An example is the formation of liposomes from one or two kinds of phospholipid monomers. The resulting vesicles are usually smaller and simpler than cells, but they enclose space and are bounded by a phospholipid membrane barrier. Crown ether compounds have played a role in both approaches. Moreover, some simple crown ethers exhibit biological activity.

Some biologists feel that no model system is sufficiently sophisticated to provide useful information about the complex activity observed in nature. This is undoubtedly true in some cases. The issue is not a simple one, however. Site-directed or random mutagenesis in a protein may replace only one or just a few amino acids in a large protein. The influence of one or a few changes in amino acid sequence may have profound consequences on structure, properties, activity, selectivity, or all of these.

Relatively simple molecular structures that mimic biological function offer many advantages. Typically such models are of sufficiently low molecular weight that they can be fully characterized in the chemical sense. This includes detailed spectroscopic analysis and, in many cases, an X-ray crystal structure. Structural modifications in a functioning model can be directly assayed, and any change in the molecular arrangement can be determined precisely. The key issue, of course, is that the model must be functional. A compound designed to be an ion channel may, for example, have a tubular shape. Unless it can insert into a bilayer and transport ions, however, it is little more than a sculpture. Chemists are increasingly designing and synthesizing chemical structures that either function as do more complex chemical structures or permit a detailed analysis of interactions that are thought to be important in biology.

7.1. Receptors for Cation–π Interactions

One interaction that has been of particular interest in our own laboratory is the cation$-\pi$ interaction of alkali-metal cations. Three of the 20 common amino acids have a side chain aromatic donor group that could serve as a π-donor for an alkali-metal cation. Such interactions have not been widely recognized in biology for at least two reasons. First, convincing structural evidence for alkali-metal π interactions between either Na^+ or K^+ and the neutral side chains of phenylalanine, tyrosine, or tryptophan has been lacking. The arenes in question are benzene, phenol, and indole. Sodium and potassium cations are relevant because they are the most abundant metal cations in cells. Second, protein structures that could clearly identify cation$-\pi$ interactions often lack the resolution required. Additionally, water and sodium have similar scattering factors. When the X-ray data are modeled, the structural biologist is more likely to interpret the electron density as water rather than as sodium even though the latter might be more appropriate to the context.

The lariat ethers are almost ideal candidates for use in such a study. The crown can bind the cation in its macrocyclic hole, but the cation's apical positions will not be solvated intramolecularly unless the sidearms participate.

An example of the problem and approach may be found in the solid-state structure of bis(cyanomethyl)-diaza-18-crown-6 complexed by RbI.[155] This compound has two sidearms that, in principle, could serve as apical donors to a ring-bound cation. Unfortunately, neither sidearm interacts in this way. Our own studies using diaza-18-crown-6 ethers having allyl, propargyl, cyanomethyl, and benzyl sidearms also failed to show solid-state evidence of the cation$-\pi$ interaction.[156] A problem in the cyanomethyl case was also the propensity of the nitrile groups to function as σ donors, leading to coordination polymers, Figure 43.[157]

Subsequent studies revealed that bibracchial (two-armed) lariat ethers were appropriate receptors for these studies,[158] so long as the arenes were placed two carbons from nitrogen rather than just one. Studies with diaza-18-crown-6 having 2-phenylethyl,[159] 2-(4-hydroxyphenyl)ethyl,[160] and 2-(3-indolyl)-ethyl[161] sidearms all formed cation$-\pi$ complexes of

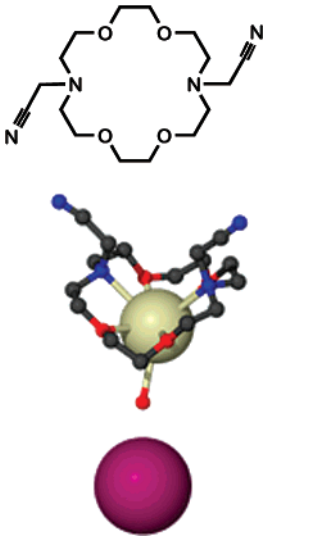

Figure 43. Two-armed lariat ether that shows no cation−π interaction with a ring-bound cation.

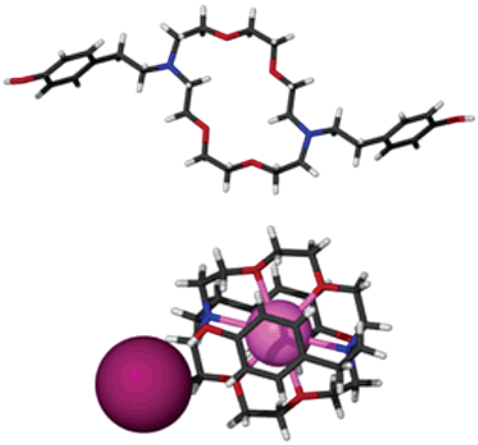

Figure 44. Demonstration of cation−π complex formation by diaza-18-crown-6 derivatives.

the type shown in Figure 44. In the absence of a cation (top), the crowns adopted the typical "parallelogram" shape in which two methylenes were turned inward toward the center of the ring. When complexed, however, the cation was bound in the center of the macroring (Figure 44, bottom) and both of the cation's apexes were solvated by the arenes. The emphasis of these studies[162] was the arenes noted above, as they are present in phenylalanine, tyrosine, and tryptophan. Although not among the 20 common amino acids, double[163] and triple bonds[164] were both shown to serve as π-donors to Na^+ and K^+ ions.

The question of cation−π interactions is especially important in biology, where 1 in every 11 amino acids has an aromatic side chain. The interaction of a neutral arene is expected to be strongest within a low-polarity medium such as in a membrane. The abundance of both sodium and potassium cations in organisms suggests that nature has evolved an application for this interaction.

7.2. Crown Ethers as Amphiphiles for Membrane Formation

Chains of poly(ethylene glycol) attached to hydrocarbons are detergents. Indeed, surface-active properties are well-known for poly(ethylene glycol)s (PEGs) and their various mono and diethers. It is not surprising that crowns exhibit similar properties. Kuwamura,[165] Okahara,[166] and their respective coworkers recognized the potential amphiphilicity of alkyl-substituted crown ethers. Both groups demonstrated the formation of aggregates from a variety of crown compounds.

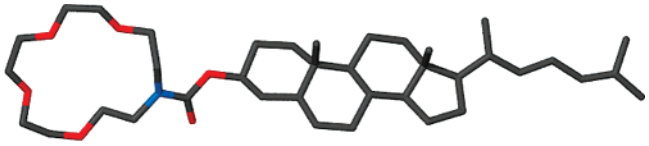

Figure 45. X-ray structure of a cholesteryl lariat ether.

Cholesterol is an important component of most mammalian plasma membranes and is thought to help organize or "rigidify" the bilayer. When cholesterol was linked to an aza-15-crown-5 residue, it fostered crystallization, making possible the solid-state structure shown in Figure 45. The combination of hydrophobic tail and polar crown headgroups permitted the formation of stable vesicles when the monomers were sonicated in water.[167] The vesicles resulting from these monomers proved to be remarkably rigid, suggesting a high level of organization within the bilayer.[168] Substituted cryptands also form stable aggregates when sonicated in aqueous suspension.[169]

A broad range of crown ethers was eventually shown to form aggregates generally or liposomes in particular. These included two- and three-armed diazacrowns[170] in addition to the previously known single-armed macrocycles. When two crowns are connected by a hydrocarbon chain, the so-called bola-amphiphiles may also form stable vesicles[171] or other aggregates. Bola-amphiphile "F", shown among the structures in section 2 (Figure 6), forms stable vesicles. When the chain connecting the two aza-15-crown-5 residues is $(CH_2)_{16}$ rather than $(CH_2)_{12}$, micelles are formed instead of liposomes. Fuhrhop and co-workers studied crown ether bola-amphiphiles as ion transporters for cobalt.[172] Fyles and co-workers recently showed that certain crown bola-amphiphiles function as "membrane disruptors".[173]

7.3. Ion Channel Model Systems

Membrane-spanning proteins play critical roles in regulating cell processes such as ion balance, cell signaling, and the uptake of organic molecules. Protein channels that conduct ions, rather than neutral molecules, through membranes have been of particular interest. This is important because it is challenging to move a charged species through the approximate 30 Å thickness of low dielectric (∼2−3) membrane hydrocarbons. Further, organisms rigorously maintain cellular salt concentrations, which indicates the importance of ion conductance mechanisms. Although ion channels have been studied for decades, the structural details of this process are only beginning to emerge.[174] Their importance is obvious from the award of the 2003 Nobel Prize in chemistry for this structural work. During the past two decades, the preparation of synthetic ion channels has been undertaken in an attempt to model protein channels and to develop therapeutic agents.

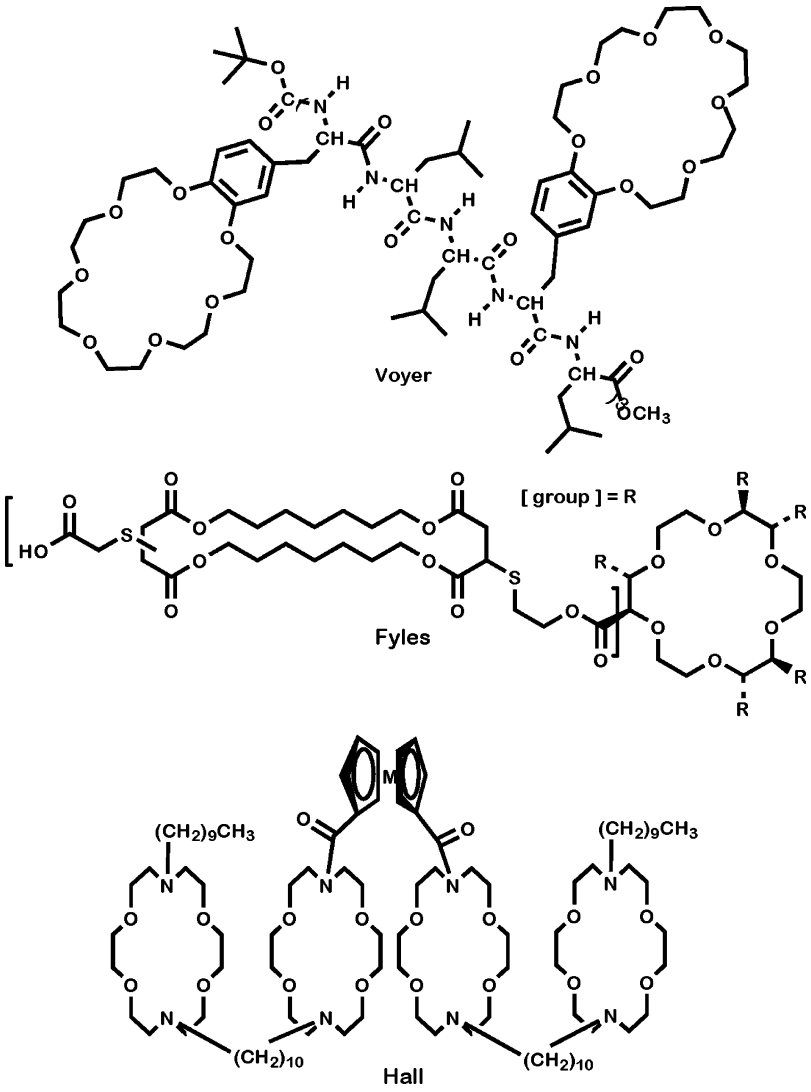

Figure 46. Synthetic model ion channel systems.

Numerous examples of synthetic channels have been reported, including the pioneering tetrachained cyclodextrin channel of Tabushi.[175] Although a number of synthetic channels have been reported, we focus here on the crown-based systems. The reader is directed to a recent review for a discussion of the broad range of abiotic channels.[176] Notable among the crown ether-based channels are the "chundles" reported by Lehn,[177] the bola-amphiphiles of Fyles,[178] Nolte's polymerized isonitriles,[179] Voyer's crown-substituted peptides,[180] the redox-switchable systems of Hall,[181] and the steroid-substituted crowns of Pechulis, Frye, et al.[182] Figure 46 shows the channel systems developed by Voyer (top), Fyles (middle), and Hall (bottom). These are noted particularly as conductance data have been acquired for them, either in planar bilayers or as patches,[183] that show the classic open−shut behavior of protein channels.[184]

Recent reports of ion-conducting channel have garnered considerable interest.[185] Voyer's approach to channels used the De Grado peptide backbone, to which is attached a benzo-21-crown-7 at every fourth residue. This peptide is thought to form an α-helix in the membrane, which then aligns the crown ethers to form a tube through the bilayer.[186] These channels have shown Cs^+ transport activity comparable to that of gramicidin in vesicles[187] and have demonstrated single-channel behavior in bilayer patch studies.[188]

The synthetic hydraphile channels developed in the author's lab[189] are represented by the structure shown in Figure 47. Two distal crown ethers extend to form the entry and exit portals of the pore. These terminal moieties are also thought to act as headgroups for pore stabilization, based on evidence that alkyl-substituted crown ethers can form stable vesicles.[170] Each headgroup is connected to a hydrophobic spacer chain that is, in turn, linked to a central crown ether. This middle unit was specifically designed to stabilize a cation in transit through the membrane,[190] as chemical intuition suggested a charged particle would not pass the entire hydrophobic core of the bilayer without some polar stabilization. Sidearms anchor the crown headgroup in the membrane and are of utmost importance for producing our most active ion-conducting compounds.[191]

The overall length of the compound shown in Figure 47 is about 42 Å, which is the approximate distance needed to span the membrane hydrocarbon insulator regime. The arrangement of the compound in the bilayer in the figure is based on extensive structural and fluorescence studies.[192] These experiments place the crown headgroups about 14 Å from

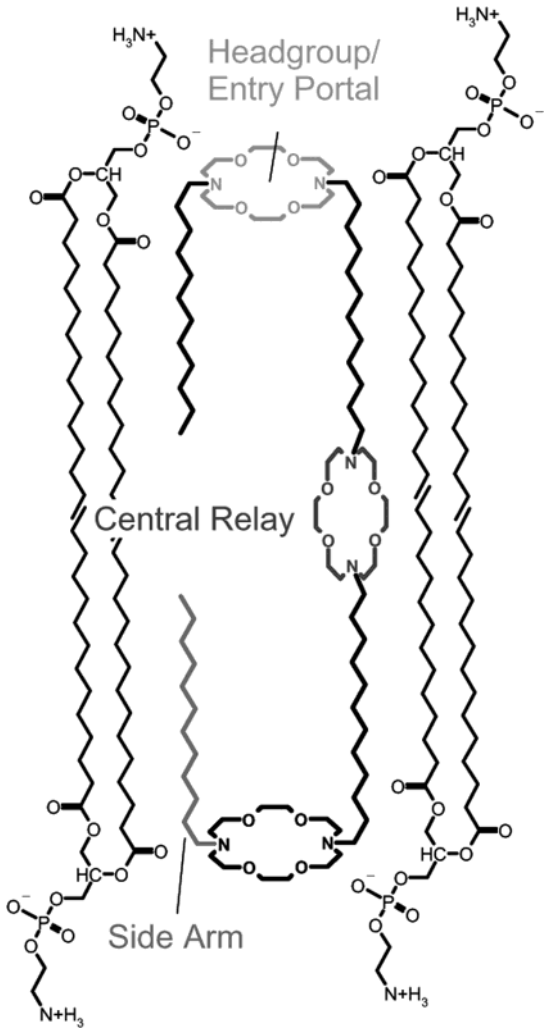

Figure 47. Synthetic hydraphile channels of Gokel and co-workers as they align in the membrane.

the center of the bilayer, in an environment of polarity equal to about (dielectric constant, ϵ) 25. These data are consistent with the distal crowns being located in the glyceryl ester midpolar regime of the bilayer.[193] In addition, NMR and biological studies have shown that channel activity is dependent on the length of the hydrocarbon spacer chain.[194] Furthermore, a conformationally restricted tunnel compound that has four diazacrowns connected by four 12-carbon spacers is the most active channel synthesized to date.[195] Taken together, these findings suggest the channel conformation shown in Figure 47.

Hydraphile channels have demonstrated activity in several systems including ^{23}Na NMR vesicle experiments,[190] sodium release from liposomes monitored with ion-selective electrodes, bilayer patch clamp studies,[196] and biological systems.[197] Recent results show that these channel compounds are active at similar levels across organisms. For example, a hydraphile possessing benzyl sidearms transports Na^+ in NMR experiments at 5 μM, inhibits the growth of *Escherichia coli* at 5 μM, and causes a 50% release of Na^+ from liposomes at 5 μM. Transport of ions in bilayer membranes clearly showed ion transport at picomolar (pM) levels. Indeed, the hydraphiles show remarkable consistency, and they

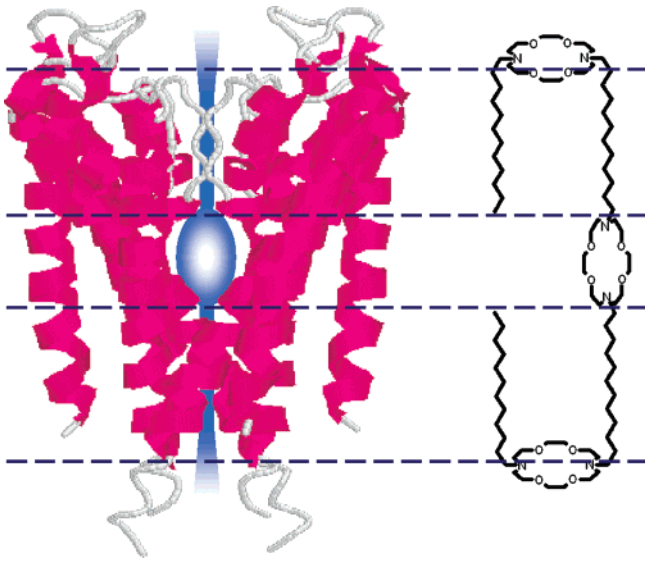

Figure 48. Natural KcsA K^+channel from *Streptomyces lividans* (left) compared with the synthetic hydraphile (right).

have proven themselves as models for ion transport across membranes.

Figure 48 compares the KcsA K^+ channel crystal structure[174] with the dodecyl-side chained hydraphile and demonstrates this point. Both channels have entry and exit portals connected by hydrophobic links to a "central relay" functionality. It is especially important to note that the "central relay", called a "water and ion filled capsule" in the biological community, was not known to be present prior to the first crystal structure. Thus, the design of a model system revealed an important requirement for channels not previously appreciated.[198] While our understanding of hydraphile channels continues to grow, models have already provided structural and functional insights into ion transport across membranes.

7.4. Biological Activity of Crown Ethers

Crown ethers are being used in applications across the spectrum of science. Beyond their traditional place in chemistry, their applications in biology include, inter alia, the ability to regulate enzyme activity, interact with and cleave DNA, and act as antimicrobial agents. Functionalized crowns have been synthetically designed to achieve these functions; however, the basic heterocycles themselves yield beneficial biological interactions as well.

Simple crown compounds such as 18-crown-6 and 15-crown-5 have the ability to interact with enzymes. This interaction boosts the activity of enzymes when used in organic solvents. The increase is noteworthy as enzymes may be utilized for biocatalysis of reactions where traditional synthetic chemistry is laborious. Numerous enzymes exist that benefit from the presence of crown ethers, including lipases,[199] the enzyme subtilisin Carlsberg,[200] and α-chymotrypsin.[200b] Reinhoudt investigated each of these enzymes and proposed that crowns principally interact with lysine ammonium groups. These complexes decrease the formation of inter- and intramolecular salt bridges, affording a more thermodynamically stable and

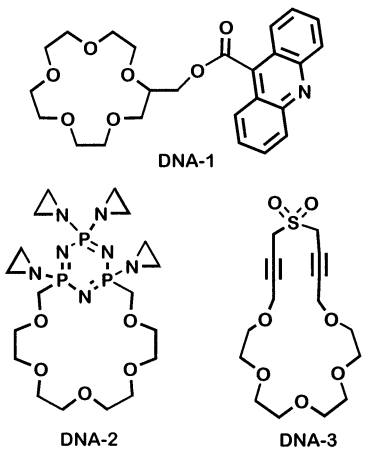

Figure 49. Crown ether DNA mimics.

catalytically active enzyme. A separate but contributing mechanism may be lyoprotection of the enzyme, since washing out the macrocycles leaves an enzyme that remains partially activated. Though the mechanism of activation is only beginning to be resolved, the impact of crown ethers in enzymology is significant, with potential applications in both biological science and industry.

Crown ether compounds have been designed and synthesized to interact with DNA, the double-stranded oligonucleotide helix that encodes life. DNA binding[201] and intercalation[202] studies have been performed with crown compounds possessing various sidearms. Intercalation experiments have utilized molecules similar to that shown as DNA-1 in Figure 49. In these studies, the acridine subunit binds DNA while the crown binds cations which interact with the phosphate backbone,[202b] thus stabilizing the complex. The binding is cation sensitive and has a *K* value approximately equal to 3000. While examples exist for DNA binding, other crowns have been designed to cleave DNA. Both Kerwin and Brandt developed compounds that can not only cleave DNA, but also halt the growth of cancer cells.[203] These lytic crown ethers are shown Figure 49. Compound DNA-2 is proposed to act through a mechanism by which the 1-aziridinyl groups form carbocations that interact with and cleave DNA. The DNA damage halts cell proliferation, making DNA-2 a cytostatic drug.

Macrocycle DNA-3 (Figure 49) is involved in an electrophilic alkylation reaction with the DNA phosphate backbone that leads to strand cleavage. Both DNA-2 and DNA-3 have been tested against cancer cell lines to assay their ability to inhibit growth in tissue culture. DNA-3 was screened against 57 different cancer cell lines; its typical activity was in the 10−50 μM range. Interestingly, DNA-2 was highly active against two AIDS-related lymphoma (ARL) cell strains at concentrations of 0.64 and 1.79 μM. The latter compound was adopted for testing by the Biological Evaluation Committee of the National Institute of Health, National Cancer Institute.

Crown ether systems have recently demonstrated function as antimicrobial agents. The toxicity of simple crown ethers such as 18-crown-6 has been studied[204] and, for the most part, found to be no more poisonous than aspirin.[205] Nevertheless, crowns may be synthesized to inhibit cell proliferation as shown above, and new systems are being exploited to kill microbial organisms. The synthetic hydraphile channels discussed above have long been employed as models for ion transport across membranes[190] but recently were shown to be highly lethal to *E. coli*.[197] To be sure, an open, unregulated ion channel will cause a rapid dissipation of cellular ion gradients, leading to physiological and osmotic stress for the organism. This toxicity mirrors the activity of natural ionophores such as the cecropins, valinomycin, and gramicidin, all of which are antimicrobial agents.[206] Benzyl channel (shown in Figure 50) kills all *E. coli* cells at 10 μM, while the most active hydraphile compound kills at 2 μM. While these antimicrobial studies are in their infancy, the potential impact remains large. They are active in the concentration range of known antibiotics,[181b] and other novel channel compounds have already been shown to cure infections in mice.[207] The demand for new and effective antimicrobial agents is increasing with the rise in bacterial resistance to conventional antibiotics.[208]

Hydraphile channels are advantageous owing to their demonstrated lethality. Their abiotic structure may prevent the development of microbial resistance. Further, hydraphiles possess unparalleled synthetic flexibility for channel compounds. As shown below, any of the four major components of the hydraphile may be synthetically altered. The hydrophobic spacer and sidearm, for example, may be tailored to fit the membrane length and other special properties (surface charge, lipid content) of the target organism. The use of hydraphiles as lethal, channel-forming toxins in bacteria provides yet another example of crown ether utility in biology.

The interest in crown ethers in both biological science and industry is keen and growing. Crowns have demonstrated significance in the catalysis of

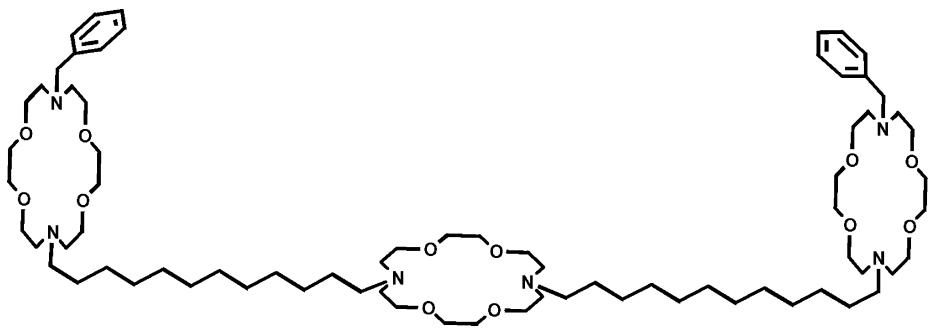

Figure 50. Synthetic hydraphile, benzyl channel.

reactions that use enzymes in organic solvents. Functionalized crowns have also been synthesized to bind and cleave DNA and have led to investigative drug studies in cancer research. Furthermore, crown compounds are being developed to fight microbial resistance. Without question, crown ethers have a firm foundation in biological science and industry that will produce new and innovative applications with future generations of compounds.

8. Crown Ether Polymers

Given the great current interest in nanoscience and materials science, it is not surprising that crown ethers have found their place in such systems. Numerous novel structures based on crowns have been prepared. These range from nanotubes[209] to light-emitting devices (LEDs)[210] based on crown ether templates. Numerous polymeric systems incorporating crown ethers were reported in the early 1970s.[211] Many of these had limited application beyond examining the polymer's ability to bind cations selectively or at all. As the field has developed, the applications of crown ether polymer systems have expanded greatly. Crowns have been integrated with other structural units and technologies, resulting in an array of novel compounds and materials.

First reported more than two decades ago,[212] dendrimers are polymers that spread like the branches of a tree. Dendrimers or arborols have many potential applications including uses as gels and films. Crown ether dendrimers offer the possibility of using metal-based templates for self-assembly.

Dykes and Smith recently reported an interesting application of crown ethers in dendrimer chemistry.[213] They used crown ether-functionalized dendritic branches to exploit the interactions between crowns and protonated amines for assembly of dendrimer superstructures via a template module. The addition of their branches to ditopic ammonium cation guests results in dendrimer assembly, the binding of two hosts to each ditopic guest. Subsequent addition of potassium results in disassembly of the dendrimer. Such a system holds forth the potential to encapsulate a template molecule within a dendrimer superstructure, modify its behavior, and then release it to solution. Disassembly can be accomplished by adding base, which will release the template in its nonprotonated form. Alternately, the ammonium template can be removed by competitive binding to added potassium, which has a binding constant at least 100-fold higher than the NH_3^+-functionalized templates. Dykes et al. monitored the dendrimer assembly and disassembly process by NMR, which gave clear evidence of cation binding and release of the ammonium template. The system illustrated in Figure 51 achieves the controlled release of the template into solution by reversible encapsulation of the functional species, Figure 51.

Stoddart and co-workers synthesized several examples of dendrimers that work by "slippage methodology", which is important in bridging the gap between kinetically stable interlocked compounds and those supramolecular assemblies that are kinetically labile. Dibenzo-24-crown-8 and dibenzylammonium ion form a rotaxane-like system[214] that is stabilized by a combination of hydrogen bonds and $\pi-\pi$ stacking interactions. At ambient temperature, this system does not self-assemble. However, after heating at 40 °C, complex formation was observed by NMR (Figure 52). This work was subsequently expanded to mechanically bonded dendrimers that could be controlled by rotaxane-like slippage.[215] The system was established using the same dibenzo-24-crown-8 ring in conjunction with Frechet-type[216] benzyl ether wedges coupled to a dialkylammonium salt as the dendrons. After heating, complex formation was observed. Once slippage kinetics had slowed, the mixture was separated and the dendrimer product isolated without undergoing dissociation. The authors project that the process of dendritic assembly via slippage may be made more efficient, and they express a goal to develop these systems for biomedical applications.

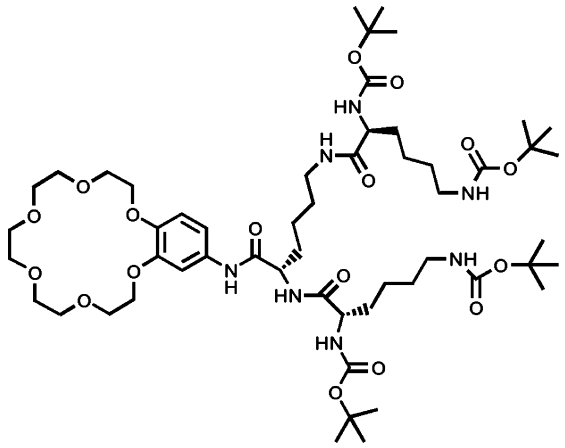

Figure 51. Subunit for dendrimer assembly via ammonium guest interactions.

Techniques to measure small enantiomeric excesses (% ee) for natural L-amino acids and D-sugars have long been difficult, owing generally to insufficient sensitivity of the available methodology. Nonokawa and Yashima recently reported a crown ether-based polymer that may have sufficient sensitivity to measure enantiomeric excesses $\leq 0.005\%$. Using both aza-18-crown-6[217] and aza-15-crown-5[218] ethers as pendants, the authors used induced circular dichroism (ICD) to assay complexed L-amino acids, which form polymeric, one-handed helices (Figure 53). Amplification of the amino acid chirality using these polymers occurs via a cooperative nonbonding interaction. The chirality of the amino acid is transferred to the polymer backbone, which can then be detected by ICD. Molecules that induce this helicity include unprotected amino acids (natural and unnatural), chiral amines, and amino alcohols in organic solvents as well as in water. These polymers may be used as probes both to assign optical purity and to determine absolute configuration for biological samples.

8.1. Crown Ethers in Chromatography

Chromatography is a process by which complex mixtures are separated, and it is of immense importance in both chemistry and biology. Chromatography

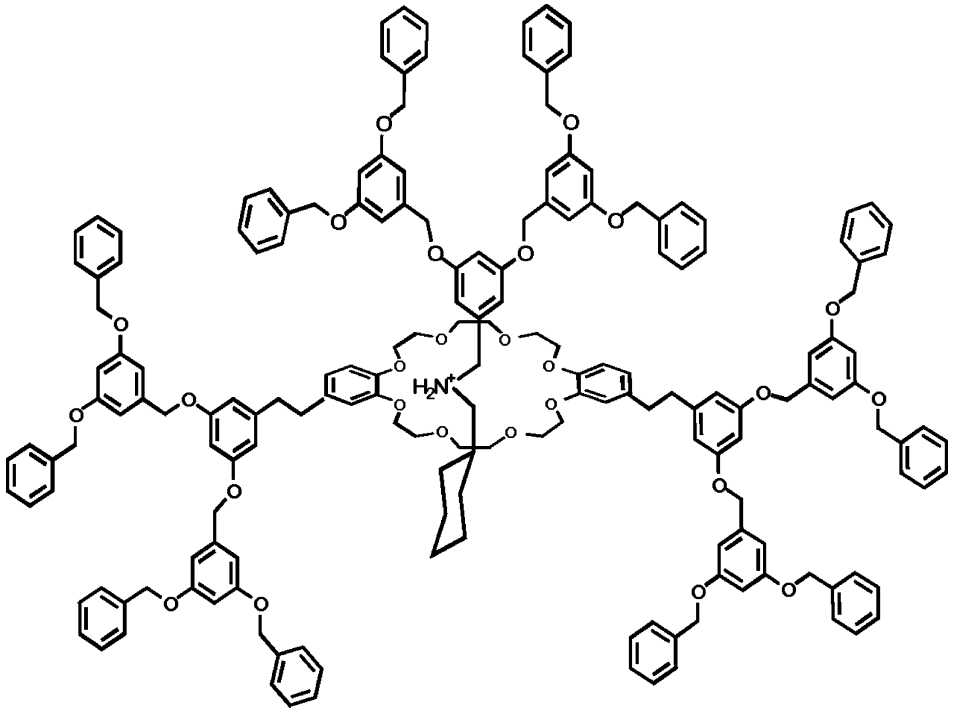

Figure 52. Dendrimer assembly via slippage methodology.

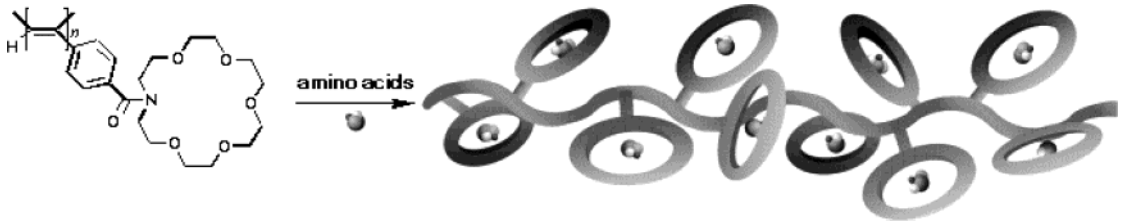

Figure 53. Helix formation by lariat crown ethers for enantiomeric excess (% ee) measurements.

is utilized to purify drugs,[219] proteins,[220] ions,[221] racemic mixtures,[222] and numerous other organic molecules.[223] Several clever techniques have been developed to accomplish each of these separations, including the use of crown ether compounds.

Cram and co-workers reported the first example of chiral crown ethers attached to silica[224] and a polymer resin[225] in the late 1970s. This work led to numerous examples of crown ethers incorporated as a stationary phase in chromatography. Hyun demonstrated crown-based separation of enantiomeric compounds that possess a primary amino group.[220] In one case, a diphenyl-substituted 1,1′-binaphthyl crown ether bonded to silica gel (Figure 54, top panel) separated fluoroquinolone enantiomers (gemifloxacin shown at bottom left) by HPLC.[226] This chiral crown was pioneered by Shinbo in 1992[227] and is commercially available today from Chiral Technologies.[228] Complexation of the free amine by the crown ether macroring is essential in the differentiation of these compounds.[229] Chiral crown ethers bound to a silica gel matrix have been used to separate D,L-amino acids and drug enantiomers[230] and other racemic organic ammonium salts.[231]

Crowns have been used for other types of chromatography as well. Addition of 15-crown-5 or 18-crown-6 to a $|\equiv Si\sim NH_3^+$ column alters the anion exchange selectivity as a result of the amine−crown complexation described above.[232] Crown ether resins

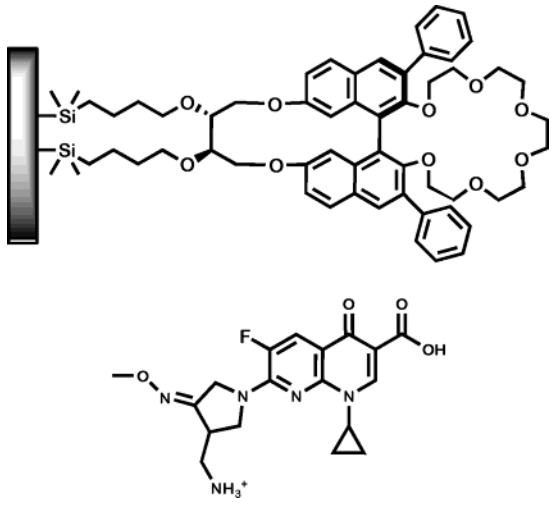

Figure 54. Solid support for chiral separation (top) and gemifloxacin (bottom).

have also been used as the stationary phase in capillary electrophoresis for chiral compounds possessing a primary amine.[229,233] Crown ethers may increase the resolution of ion chromatographic separations of alkali-metal cations, based on the well-known ability of crowns to complex these cations.[234] Crowns have been applied in stationary and mobile phases for ion chromatography and proven very effective.[235] The use of crown ethers in chromatog-

raphy is clearly increasing. As this technology develops, crown ether chromatography will likely lead to more efficient and less expensive chemical separations.

9. Conclusions

It is now nearly four decades since Pedersen began his effort to develop a complexing agent for divalent cations. Heteromacrocycle chemistry has gone through several phases during the ensuing years. At the early stage of the effort, numerous compounds were prepared so that the range of structural types possible could be outlined. This next but overlapping phase involved structural and physical studies undertaken to understand interactions in the solution and solid state. In many ways, these fundamental studies became the basis for supramolecular chemistry. Once the field had a reasonable underpinning of structural and physical chemistry, novel applications for heteromacrocycles emerged in many other areas of chemistry and biology. The application of these remarkable compounds shows no obvious limit, and novel applications abound.

10. Acknowledgments

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