Lariat Ethers: From Simple Sidearms to Supramolecular Systems

George W. Gokel
Department of Chemistry, University of Miami, Coral Gables, Florida 33124, U.S.A.

1 Conceptual Development of the Lariat Ethers

Until the 1960s, complexation of alkali and alkaline earth metal cations was problematic. Although such Ca^{2+} binders as ethylenediaminetetraacetic acid, EDTA, were well known, neutral compounds that bind these metals were not. This situation changed abruptly and dramatically when Pedersen reported the crown ethers.[1] Shortly thereafter, Lehn reported the cryptands,[2] and Cram began to study their use in selective complexation.[3] Pedersen, Cram, and Lehn shared the 1987 Nobel prize for their efforts.

As the crowns and cryptands became more familiar, the relationship of these synthetic substances to naturally occurring molecules became apparent. One of the best known K^+ complexing agents is the mitochondrial ionophore valinomycin.[4] It is a cyclododecadepsipeptide, that is, a macrocyclic peptide that alternates amino and hydroxy acids. Its structure contains repeating units of L-lactate (L-lac), L-valine (L-val), D-hydroxyisovalerate (D-hyv), and D-valine (D-val): (L-lac-L-val-D-hyv-D-val)$_3$. The molecule thus contains six amide and six ester carbonyl donor groups and a hydrophobic surface composed of nine isopropyl and three methyl groups.

The structural features of valinomycin are both interesting and revealing. The 36-membered ring, if planar (*i.e.* crown-like), is too large to accommodate K^+, for which it is quite selective. Instead, the molecule folds over to create a three-dimensional cavity. In so doing, the backbone assumes a 'tennis-ball-seam' geometry. The resulting conformation has the hydrophobic alkyl residues turned outward and a cavity that is the appropriate size for K^+. The amide donor groups are more polar than are the ester carbonyls but the latter bind the cation. This is for two reasons. First, the amides participate in transannular hydrogen bond formation that helps hold valinomycin in the binding conformation. Second, since the amides are involved in hydrogen bonds, they cannot bind to the cation. This is important because the polar amides would favour more charge dense cations like Ca^{2+} rather than the K^+ preferred by valinomycin.

The three-dimensionality of valinomycin's cavity is important for solvating the bound cation and excluding water. The isopropyl and methyl groups interact with the hydrophobic membrane during transport and their orientation outward may also play a conformational role in directing the carbonyl groups inward. The amide carbonyl groups play another role as well. Complexation of a cation by valinomycin would likely be difficult if the large macro-ring had to fold, turn the alkyl groups outward, and bind the cation all at once. The intra-annular hydrogen bonds that form when valinomycin folds, stabilize the binding conformation so that a smaller energy price must be paid upon complexation.[5] A recognition of some, but admittedly not all, of these properties of valinomycin led us to design the lariat ethers.

George Gokel was born in New York City in 1946 but moved as a child to Miami, where he was raised. He earned the B.S. in chemistry at Tulane University in New Orleans in 1968 and the Ph.D. at the University of Southern California in 1971 and then did post-doctoral work with D. J. Cram at U.C.L.A. He has held positions at Dupont's Central Research Department, the Pennsylvania State University, the University of Maryland and is currently Professor of Chemistry at the University of Miami. He has published books and research papers in the areas of ferrocene chemistry, phase transfer catalysis, crown and lariat ether chemistry, and molecular recognition.

2 Design and Syntheses of the Lariat Ethers

The paradox of membrane transport is that a carrier should optimally have different properties in each of the three, chemically-different regions (source phase, lipid membrane interior, receiving phase) encountered by the ionophore. At the membrane's source phase, binding should be fast and strong. Chemically speaking, this means that in the binding equation (1)

$$K_S = k_{complex}/k_{release} = k_1/k_{-1} \quad (1)$$

both K_S and k_1 should be large. Inside the hydrophobic membrane, the cation should be strongly bound, *i.e.*, K_S should be large. Finally, at the receiving or exit side of the membrane, K_S should be small and k_{-1} should be large. Obviously, these conflicting requirements cannot all be met. Thus, some compromise is apparent in the binding strengths and dynamics of each successful carrier.

When we decided to undertake an effort to study and mimic valinomycin, it was apparent that the cryptands had the required three-dimensionality but lacked dynamics. On the other hand, the crowns were dynamic but lacked both the capability to envelop a cation and the requisite binding strength, especially in water. Our solution to this problem was to explore crown ethers having sidearms. Each sidearm would contain one or more donor groups placed in a position appropriate to provide a third dimension of solvation to a ring-bound cation. The lariat ether idea is represented schematically in Figure 1. The schematic, the appearance of the molecular models, and the use of a lasso in the American west to 'rope and tie' an animal all suggested the name lariat.[6]

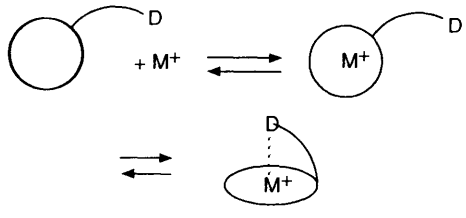


Figure 1 Schematic of the lariat ether complexation process.

2.1 Structural and Synthetic Considerations

In an article as short as this one, the design considerations can, at best, only be adumbrated. We chose to study macrocycles having the traditional $-CH_2CH_2O-$ subunits as the new properties of the lariat ethers would thus be more readily distinguished from those of the known crown ether relatives. Most of the design work was accomplished by a consideration of Corey–Pauling–Koltun (CPK) atomic models. It was apparent, for example, that if the sidearm was attached to the macro-ring at nitrogen, the best distance for interaction between a ring-bound cation and an apical donor group was three, rather than two, carbons. This required, however, a non-optimal conformation in the sidearm. Further, direct attachment of the sidearm to

an all-ethyleneoxy macrocycle (a carbon-pivot lariat) was difficult using a carbon–carbon bond and worse using a carbon–oxygen bond. In the latter case, an acetal would have been contained within the ring potentially leading to chemical instability. Thus, design plans were carefully made but compromises were required at an early stage.

The first attachment point chosen was the $-CH_2-O-$ unit, based upon glycerol ($HOCH_2CHOHCH_2OH$]. This afforded the carbon-pivot (C-pivot) lariats. The N-pivot lariats were accessible from the known azacrowns by *N*-alkylation or by preparing the crowns from the appropriately substituted diethanolamine derivative, $R-N(CH_2CH_2OH)_2$. Because $H(OCH_2CH_2)_4OH$ is readily available and $H(OCH_2CH_2)_5OH$ is not, the first C-pivots were 15-membered while both 15- and 18-membered N-pivots could be prepared fairly easily. Typical structures in each group are shown in Figure 2.

2.2 Syntheses of C- and N-pivot Compounds

Two families of molecules were prepared. The first family to be completed was that of the C-pivot compounds [(1—5) Figure 3] discussed below.[7] The N-pivot compounds were undertaken as well but had a lower priority for completion.[8] As envisioned, the carbon-pivot lariat ethers proved to be more chemically stable but less dynamic than the N-pivot counterparts. The greater flexibility of the latter is due to the facile inversion of the nitrogen atom, a property not shared by carbon.

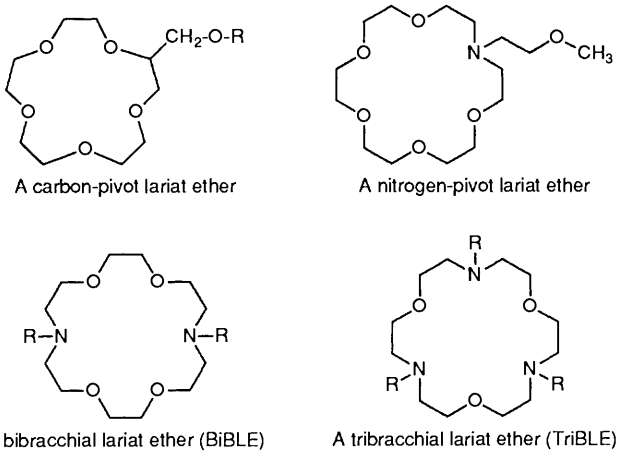


Figure 2 Carbon-pivot and nitrogen-pivot lariat ethers.

3 Confirmation of Sidearm Participation

Obviously, all research efforts in chemistry require imagination. When novel hosts are designed in the hope that they will bind to specific guests ('property-directed synthesis'[9]) one often imagines specific modes of interaction. The NMR spectrum of the complex may be consistent with the interactions envisioned, but this is often permissive evidence rather than proof. A vast array of structural techniques is available to the modern chemist. More than one of these should be used to confirm the structure of a non-covalently linked complex or, as Lehn has termed it, a supermolecule.[10] An arsenal of NMR techniques including relaxation time measurements and NOESY experiments are available to assess solution interactions. Solid state studies, if not directly applicable to the solution phase, are very important in this area as they involve the key molecules (host and guest). The structure may not correspond directly to solution but it certainly represent at least a local energy minimum. We determined at the outset to use whatever physical techniques were available to confirm the participation of the sidearm in cation binding.

We began with the preparation of a family of C-pivot lariats. The series of compounds obtained included examples that were expected to be good cation binders and those that were not. Once these compounds were in hand, it was important to assess whether or not the sidearm participated in the binding as designed. Several closely related structures were selected for study. All of the compounds studied were 15-crown-5 derivatives. The derivatives included compounds having no donor groups in the sidearms or no sidearm, different lengths of donor-group-containing sidearms, and a special pair of structures having isomeric sidearms in which one was thought to be sterically capable of interaction with a ring bound cation and the isomer was not. The well-known picrate extraction technique (see below) was used for this purpose. The compounds studied are shown in Figure 3.

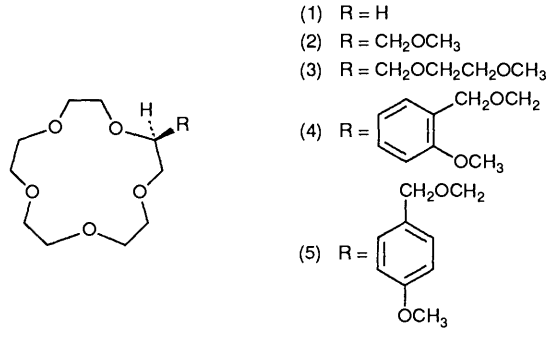


Figure 3 Compounds (1)—(5).

3.1 The Picrate Extraction Technique

A brief comment about the picrate extraction technique is in order here.[11] The method is straightforward and uses readily available UV–visible instrumentation. The principle is as follows. A two-phase mixture, usually of $CHCl_3$ and water is prepared. The ligand (crown, cryptand, lariat ether, *etc.*) is dissolved in $CHCl_3$ and a metal picrate salt is dissolved in H_2O. In the absence of a ligand, the yellow picrate salt remains in the aqueous solution. When shaken, the ligand extracts the metal cation and the yellow picrate anion accompanies it into the chloroform phase, which turns yellow. By using Beer's law and the extinction coefficient of picrate, one can assess how much of the available cation (assuming 1:1 M^+picrate$^-$) has been extracted. The extraction constant (%) is (moles of picrate in $CHCl_3$)/(moles of picrate corresponding to 100% extraction) × 100.

The problem with this method lies in the details. Sometimes, M^+picrate$^-$ is prepared by dissolving picric acid in an excess of M^+OH^-. In such a case, the ionic strength of the medium is quite different from an aqueous solution of M^+picrate$^-$. Other variables include solution temperature, relative solvent volumes, vigour of mixing, *etc.* Unless *all* variables are kept constant, results will not be comparable between studies.

3.2 Evidence for Sidearm Participation

Extraction constant data for five of the new lariats were particularly revealing. In these 15-crown-5 derivatives, the sidearms and percents of Na^+ extracted were: (1), H (7.6%); (2), CH_2OCH_3 (5.1%); (3), $CH_2OCH_2CH_2OCH_3$ (18%); (4), CH_2–2-methoxyphenyl (15.7%); and (5), CH_2–4-methoxyphenyl (6.4%). The most immediate conclusion drawn from these data is that the lariat ether concept was confirmed. Clearly, when the sidearm was too short to solvate a ring-bound cation [(2), CH_2OCH_3, 5.1%], Na^+ binding was low but when the sidearm was extended [(3), $CH_2OCH_2CH_2OCH_3$, 18%], extraction was much greater. Further, when the sidearm donor group was sterically inaccessible (5), binding was far lower (6.4%) than when it was appropriately placed [(4), 15.7%].

All of this seemed very satisfying. We then thought to compare our data with those obtained in other laboratories for somewhat related systems. Here the difficulties of the picrate extraction method became apparent. In some cases, the con-

ditions used in other laboratories were similar to ours, but in others, not even the two solvents were identical. We thus made the strategic decision to measure the equilibrium cation binding constants[12] (K_S for the equilibrium: $Cr + M^+ \rightleftharpoons [Cr \cdot M^+]$) in homogeneous solution so that our values could be compared with those obtained by others even if different techniques were used to obtain them.

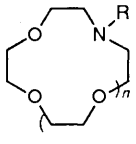
The change to a homogeneous system (anhydrous methanol) gave surprising and, frankly, distressing results. For compounds (1)—(4), the homogeneous binding constants, $\log_{10} K_S$ for compounds (1)—(5) are shown with the extraction values in parentheses: (1), 3.27 (7.6%); (2) 3.03 (5.1%); (3), 3.01 (18%); and (4), 3.24 (15.7%). Obviously one would draw different conclusions from these two sets of data but cation binding results obtained by these two distinctive methods are often considered to be interchangeable. Since none of the log K_S values for (2)—(4) exceeded that for (1), in which no sidearm was present, we felt the need to confirm ring-sidearm cooperation by other methods.

Two things were encouraging, however. Dilution of solutions containing (3) or (4) did not alter log K_S as would be expected if intermolecular interactions were involved. Second, although log K_S did not show dramatic binding enhancement when a sidearm was present, binding *was* improved by location of the methoxy group in the accessible *ortho*-position compared to the sterically inaccessible *para*-position.

4 Complexation: The Solution Phase

One difficulty with the conflicting data presented above is that none of the binding strengths shown is particularly large. This is primarily because compounds (2)—(5) are C-pivot lariat ethers. The CPK models of these derivatives seem relatively inflexible and we expected the C-pivots to have certain shortcomings as valinomycin models. We thus undertook our first detailed assessment of ring-sidearm cooperativity with the N-pivot structures.

A study of CPK models and results obtained by others[13] suggested that the tetrahedral ammonium (NH_4^+) cation would be well accommodated in an 18-membered macrocycle: it should form three $\equiv N-H\cdots O$ hydrogen bonds. The corresponding 15-membered ring could not, at least according to models, form more than two such bonds. When the sidearm was long enough [as in (6), $n = 2$], a fourth hydrogen bond could form which should stabilize the complex even further. We thus determined log $K_S(NH_4^+)$ for the family of 15- and 18-membered ring, N-pivot lariat ethers having $(CH_2CH_2O)_nCH_3$ sidearms. The prediction for this experimental test of ring–sidearm interaction was that NH_4^+ binding for all of the 15-membered ring compounds would be poor to modest regardless of sidearm length and that 18-membered rings should fare better. In the latter case, peak binding was expected to occur when the sidearm was $CH_2CH_2OCH_2CH_2OCH_3$ (7O + 1N = 8 total donors, see Figure 5).[14]



(6) $n = 1$, R = $(CH_2CH_2O)_3CH_3$
(7) $n = 2$, R = CH_3
(8) $n = 2$, R = $CH_2CH_2OCH_3$
(9) $n = 2$, R = $(CH_2CH_2O)_2CH_3$
(10) $n = 2$, R = $(CH_2CH_2O)_3CH_3$
(11) $n = 3$, R = CH_3
(12) $n = 3$, R = $CH_2CH_2OCH_3$
(13) $n = 3$, R = $(CH_2CH_2O)_2CH_3$
(14) $n = 3$, R = $(CH_2CH_2O)_3CH_3$

Figure 4 Nitrogen-pivot lariat ethers.

This experimental test was effective. The predictions made from molecular models were fully realized. Peak binding (log $K_S = 4.8$) occurred when eight total donors were present. Models suggested that four hydrogen bonds should be formed in the latter case. Thus, a value of ≈ 1.2 log units per hydrogen bond was established. In the 15-membered ring lariat ether cases expected to form a maximum of three hydrogen bonds, peak binding was nearly 3.6.

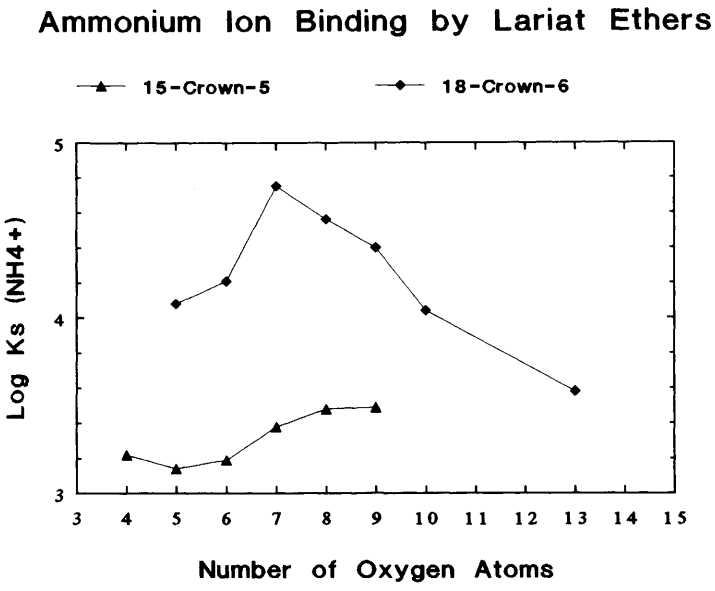


Figure 5 Ammonium ion binding.

A general study of cation binding was undertaken in order to see if the design goal of enhanced binding was actually realized. Cation binding constants for just a few compounds are shown in Table 1. All were determined in anhydrous methanol using ion selective electrode (ISE) methods. The ISE method is convenient and reliable but it has another advantage: K_S values can readily be determined at different temperatures. Determination of equilibrium constants at various temperatures permits application of the van't Hoff relationship and the calculation of thermodynamic parameters.

4.1 A Comment on the Hole–Size Relationship

The fact that (9) and (12) showed identical log $K_S(Na^+)$ values surprised us. Indeed, we found that throughout the range of compounds prepared, when an identical number of donor groups were present, the binding was nearly the same, no matter whether the macro-ring was 15 or 18-membered. This seemed to contradict the so-called 'hole–size' relationship. When we examined the literature to discover on what data the latter principle was based, we discovered that the idea has little more credibility than a rumour.

Cation binding data for cryptands correlate well with a relationship between cation diameter and cryptand cavity size. Such three-dimensional, enveloping ligands might well be expected to exhibit selectivity. The crown ethers are another matter, however. We surveyed Na^+, K^+, Ca^{2+}, and NH_4^+

Table 1 Cation binding for selected lariat ethers

Compound No.	Ring Size	Sidearm	log K_S	
			Na^+	K^+
(6)	12	$(CH_2CH_2O)_3CH_3$	3.64	3.85
(7)	15	CH_3	3.39	3.07
(8)	15	$CH_2CH_2OCH_3$	3.88	3.95
(9)	15	$(CH_2CH_2O)_2CH_3$	4.54	4.68
(10)	15	$(CH_2CH_2O)_3CH_3$	4.32	4.91
(11)	18	CH_3	3.93	5.33
(12)	18	$CH_2CH_2OCH_3$	4.58	5.67
(13)	18	$(CH_2CH_2O)_2CH_3$	4.33	6.07
(14)	18	$(CH_2CH_2O)_3CH_3$	4.28	5.81

binding by 12-crown-4, 15-crown-5, 18-crown-6, 21-crown-7, and 24-crown-8.[15] In short, 18-crown-6 bound all cations better than any of the other ligands and, in all cases, K^+ was bound more strongly than any other cation. The latter result is expected based on a consideration of cation solvation enthalpies. 18-Crown-6 probably was superior in this regard because it had sufficient (six) donors for effective complexation but is neither strained nor constrained to an unfavourable geometry for binding. Indeed, the idea that flexible systems can be effective binders regardless of the complement of ring size and sidearm length is in accord with our observations on lariat ether binding.

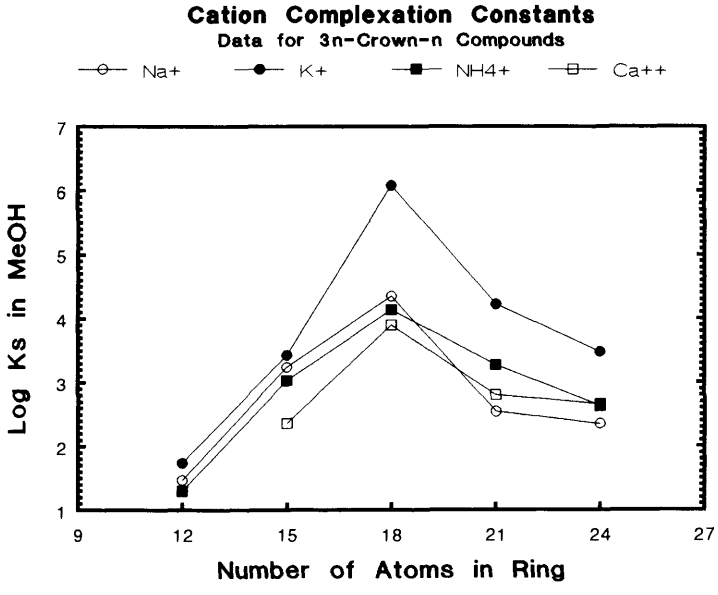


Figure 6 Graph: Hole–size relationship.

4.2 ^{13}C-NMR Relaxation Time Studies

Although the Author favours predictive experiments designed to test a specific point, there is much to be said for the application of general analytical techniques. Indeed, use of any method, instrumental or otherwise, is far superior to simply presuming that the hoped-for complex has formed. We thus undertook a series of spectroscopic studies to determine the nature of the lariat ether complexes in solution.

In collaboration with Echegoyen[16] we studied the molecular dynamics of several crown and lariat ethers and their cation complexes by measuring ^{13}C-NMR relaxation times. This technique permits a carbon-by-carbon (when resonances are resolved) assessment of host interactions with a bound cation. Such information permits inferences to be drawn concerning microstructural interactions in the complexes. Generally, the C-13 relaxation time varies with atom mobility: the greater the motion of the atom, the longer the relaxation time. For 15-crown-5 and 18-crown-6, T_1 values were determined in both 90% CH_3OD:D_2O and in $CDCl_3$. In the former solvent, T_1 values for 15C5 *versus* 18C6 were 2.14 and 1.28 s respectively. The smaller macrocycle thus appears more mobile. In chloroform, both molecules should be less encumbered by viscosity and hydrogen bonding so the T_1 values should be longer. For 18-crown-6, T_1 increases from 1.28 to 1.56 s. The same trend was observed for the lariat ethers.

Relaxation time studies demonstrated that the macro-rings in carbon-pivot systems participated strongly in the binding. The most interesting confirmation of sidearm participation could again be demonstrated by comparing (4) and (5). When the methoxy was *ortho* and well-positioned for binding Na^+, the CH_3 T_1 decreased 50% from 3.60 s for (4) to 1.80 s for (4)·Na^+. In *para*-methoxy lariat (5), the methyl group T_1 increased slightly from 4.30 s to 4.60 s in the presence of Na^+. The N-pivot compounds showed much less change in T_1 values on binding even though measured K_S values showed clearly that the sidearms were involved in binding. This suggested that binding was distributed more evenly over all donors in the N-pivots compared to the C-pivots in which the main interaction was the the ring. Indeed, when seven donors (6O, 1N) were present in the N-pivot system, log $K_S(Na^+)$ was identical and equal to 4.56 ± 0.02 irrespective of whether the donors resulted from a 15-membered ring and a $-CH_2CH_2OCH_2CH_2OCH_3$ sidearm or an 18-membered ring and a $-CH_2CH_2OCH_3$ sidearm.

4.3 Lanthanide Shift Reagents

This important technique provided additional confirmation of sidearm participation for (4) but not for (5). Experimental difficulties such as severe line broadening proved problematic but the limited conclusions that could be drawn corresponded to the findings described above.[17]

4.4 Complexation Kinetics

An important presumption about the lariat ethers was that they would be more dynamic than cryptands if less dynamic than crowns. Because complexation kinetics are generally rapid, an appropriate method was required. We were fortunate to find collaborators who could undertake such studies. Using the T-jump method, Eyring and Petrucci showed that complexation takes place in two steps. First, the cation is bound by the macro-ring and then a conformational change takes place in which the sidearm presumably folds over the ring. The kinetic parameters they determined for (9) binding Na^+ in methanol solution were as follows. For complexation of the cation by the macro-ring, $k_1 = 9.0 \times 10^{10}$ M^{-1} s^{-1}, $k_{-1} = 2.1 \times 10^8$ s^{-1}, and $K_1 = 429$ M^{-1}. For the second step, in which the sidearm moves into binding position, $k_2 = 1.2 \times 10^7$ s^{-1}, $k_{-2} = 1.5 \times 10^5$ s^{-1}, and $K_2 = 80$. $K_\Sigma = 3.47 \times 10^4$ M^{-1} ($\log_{10} K_S = 4.54$).[18]

Kinetic confirmation of the two-step mechanism along with the NMR data, binding data, and shift reagent studies placed the lariat ether concept on a firm footing. We still desired solid state structure data because details of interactions obtained from such a study are really not available using any other technique.

5 Complexation: The Solid State

Although it is correctly argued that interactions apparent in solution do not always correspond to those observed in the solid state, judicious use of solid state data is critical to understanding three-dimensional interactions. Indeed, the correspondence of solution and solid structures often proves to be excellent when both are known. While it may be acceptable to argue that the solid state structure does not guarantee an identical organization of atoms in solution, it is foolish to ignore its implications. Moreover, the effort to obtain solid state structures should be made with all vigour, especially when the design of supermolecules is the goal.

We were fortunate enough to obtain crystals of complexes between various lariat ethers and several different cations. In such an endeavour, one often must accept the crystals that form since not all complexes give crystals and those that do may fail to yield useful *X*-ray data. In fact, we have never been able to obtain crystals of a carbon-pivot lariat ether complex. The nitrogen-pivot studies have been more rewarding, however. In collaboration with Atwood, Fronczek, and Gandour, we have obtained numerous solid state structures in which both macro-ring and sidearm interactions were obvious.[19] Four structures are shown schematically in Figure 7.

It is interesting to note that the solid state structure work confirmed all that had been learned from solution studies. Indeed, certain subtleties that were not imagined became apparent from the structures. For example, the potassium cation, when complexed by (12), remained slightly below the mean plane of the macro-ring suggesting why the complexes are so dynamic.

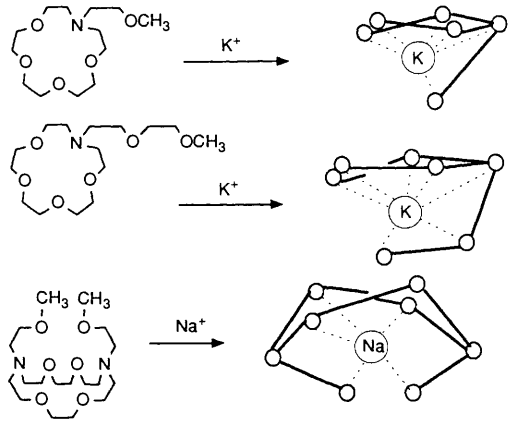


Figure 7 Solid state structures of lariat ethers.

The solid state work also made clear that when two sidearms were present, cation complexation could involve neither sidearm, both from the same side, or both from opposite sides of the macro-ring. No example of single sidearm participation was found in the BiBLE series. The only examples of non-participation were observed when the sidearms lacked heteroatom donors. When the cation was bound by both sidearms from the same side, the donor group array strongly resembled that of the corresponding cryptand.

6 Multi-Sidearmed Lariat Ethers

When more than one sidearm was present on the macrocycle, we used the Latin word *bracchium*, which means arm, to designate them. Thus, two-armed lariat ethers were *bib*racchial *l*ariat *e*thers, or BiBLEs. Three-armed structures were TriBLEs, *etc.* The syntheses of two-armed, nitrogen-pivot structures were undertaken and eventually methods were developed that could provide 4,13-diaza-18-crown-6 in a single step or other diaza-macrocycles in several steps.[20] The only tribracchial systems we have studied thus far are based upon symmetrical triaza-18-crown-6, prepared originally by Lehn and co-workers.[21]

Two issues concerning the BiBLEs were of particular interest to us. We wondered whether cation binding would involve one or both sidearms and, if the latter, whether they would bind from the same or opposite sides of the macro-ring. Second, allowing our presumption that both sidearms are involved in cation binding, we wondered if we could find evidence for π-complexation of a ring-bound alkali metal cation. The answer to the latter question has thus far been 'no,' but thereby hangs a tale which follows below.

The addition of a second, potentially cation-binding sidearm should alter cation binding. A simple comparison of binding strengths for one- and two-armed lariat ethers might tell whether one or both sidearms participate in complexation. The question then becomes which two or more compounds should be compared. Addition of a second sidearm in the N-pivot series requires replacement of O by N in the process. Complexation of an alkali metal cation is usually weakened by the change from O to N, so this fact complicates the assessment. Sodium and potassium cation binding data (determined in methanol at 25 °C) are shown in Table 2 for a small selection of lariat ethers. The problems are apparent. It appears, for example that an increase in ring size from 15 to 18 members, while keeping the sidearm constant improves potassium binding more than sodium binding. Alas, the number of donors has changed as well. A comparison of the second and fourth entries in the table suggests that Na^+ binding is enhanced but K^+ binding is not, if ring-size and sidearm identity remain constant. Of course, the number of nitrogen atoms is unequal in these two cases.

Solid state data permitted us to answer the question of sidearm participation (see Table 2). A survey of a broad range of

Table 2 Complexation by one- and two-armed lariat ethers

	No. of		log K_S	
Macrocycle	N's	O's	Na^+	K^+
Aza-15-crown-5–$CH_2CH_2OCH_3$	1	5	3.88	3.95
Aza-18-crown-6–$CH_2CH_2OCH_3$	1	6	4.58	5.67
Aza-18-crown-6–$CH_2CH_2OCH_2CH_2OCH_3$	1	7	4.33	6.07
Diaza-18-crown-6–$(CH_2CH_2OCH_3)_2$	2	6	4.75	5.46

structures showed that when no donor group was present in the sidearm, complexation was accomplished exclusively by the macro-ring and counterion.[19c] When donor groups were present in the macro-ring, they generally bound sodium from the same side (*pseudo*-crypt) and potassium from opposite sides (*anti*).[19d] In the absence of solution data, the solid state studies proved critical to understanding complexation in these systems.

6.1 π-Donor Sidearms and Thermodynamic Studies

It is synthetically difficult to incorporate unsaturation into a cryptand so we felt that bibracchial lariat ethers presented an ideal vehicle to explore π-participation in cation binding. We prepared diaza-18-crown-6 derivatives having n-propyl, allyl ($-CH_2CH{=}CH_2$), and propargyl ($-CH_2C{\equiv}CH$) sidearms. Crystals of complexes involving crowns having allyl sidearms were obtained but no evidence of any π-electron donation to an alkali metal could be discerned. Cation binding studies suggested otherwise, however. The diaza-18-crown-6 derivatives noted above had the following Na^+ and K^+ binding constants (log K_S, MeOH): n-propyl, 2.86, 3.77; allyl, 3.04, 4.04; and propargyl, 3.61, 4.99. Thus, both Na^+ and K^+ binding ascended with the potential for π-participation. An additional experiment altered the trend, however. The cyanomethyl group, $-CH_2C{\equiv}N$, is the isostere of and electronically similar to propargyl and was expected to act in a similar fashion to the latter. Log K_S values for this BiBLE were as follows: Na^+, 2.69; K^+, 3.91.

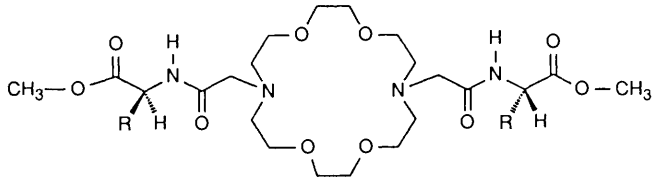
We realized that we would need to determine ΔH and $T\Delta S$ for these systems in order to understand the binding. Although extensive calorimetric studies had been undertaken and reviewed by Izatt and co-workers,[22] we did not have a calorimeter at our disposal. Since we could determine K_S, an equilibrium constant, at different temperatures, we could apply the van't Hoff relationship to these systems. We did so and found that ΔH for the Na^+ binding reaction increased in the order propyl < allyl < propargyl ($-$ 2.82, $-$ 3.56, $-$ 4.97 kcal/mole). The enthalpic contribution to binding for cyanomethyl, $-$ 4.87 kcal/mole, was identical to that for propargyl. The cation binding constants reflected an unfavourable entropy ($T\Delta S$) in the cyanomethyl case that diminished binding compared to the isostere. The thermodynamic information seemed to be in accord with π-participation. The corresponding enthalpies for K^+ binding were: propyl, $-$ 6.28; allyl, $-$ 7.34; propargyl, $-$ 4.97; cyanomethyl, $-$ 9.54 kcal/mole. Clearly the latter data set cannot be explained in terms of π-participation.[23]

An equally important lesson is that complexation is, to coin a phrase, complex. Organic chemists tend to think structurally (enthalpically) and build upon such data as are obtained in cation binding studies. When major changes in solvation are involved, the enthalpic terms may be identical and the entropic component of ΔG may completely alter the binding profiles. It is therefore important to assess ΔH and ΔS as well as the equilibrium constant in any binding, complexation, or supermolecule-forming reaction.

6.2 Calcium Binding Ionophores

The intriguing $-$(amide–ester)$_6-$ structure of valinomycin suggested a special possibility to us. In valinomycin, the more polar

amide donors are involved in hydrogen bonding to hold the 'tennis-ball-seam' conformation so that the less polar esters can bind K^+. We reasoned that if the amide donors were free to bind a cation, a more charge-dense cation than K^+, *e.g.* Na^+ or Ca^{2+}, would be favoured. We thus prepared diaza-18-crown-6 derivatives having –glycine–amino acid ester sidearms. Examples included Gly-Gly-OMe, Gly-Ala-OMe, Gly-Val-OMe, and Gly-Leu-OMe. Binding and selectivity results were disappointing when determined in methanol solution under our 'standard' conditions. Since calcium-selective electrodes cannot easily be used in methanol solution, we had developed a competitive method to determine Ca^{2+} binding in this solvent.[15] The method requires the determination of ligand binding to, for example, Na^+, in the absence and then presence of Ca^{2+}. The results proved inconclusive but suggested that Ca^{2+} complexation might be significant.



R = H (Gly-Gly); R = CH_3; (Gly-Ala);

R = $CH(CH_3)_2$ (Gly-Val); R = $CH_2CH(CH_3)_2$ (Gly-Leu)

Figure 8 Dipeptide lariat ethers.

If Ca^{2+} binding in methanol was so strong that it prohibited the competitive method from giving information, perhaps binding in water could be measured. Cation binding strengths of crowns and cryptands generally increase with decreasing polarity so water is rarely the best choice for a complexation study. The advantage in this case was that calcium selective electrodes could be used directly in water. When we measured the binding constants, we were gratified to find that log K_S for Ca^{2+} in water, for all four of the BiBLEs identified above were > 6 (*i.e.*, $K_S > 10^6$). In water, log $K_S(Na^+)$ is ≈ 2. Thus, the selectivity in water for one cation over a similarly sized cation proved to be an unprecedented 10^4—10^5.[24]

Why is the cation binding by the dipeptide BiBLEs so high? Several factors no doubt contribute. First, crown ethers generally are characterized by a selectivity profile that correlates with the inverse of cation solvation enthalpy. When the ether donor groups are altered to more polar residues such as carbonyl, amide, or carboxylate, the binding assumes a Coulombic profile. The normal, non-Coulombic cation binding order (log K_S in CH_3OH) is represented by either 15-crown-5 or 18-crown-6: $K^+ > Na^+ > Ca^{2+}$. A rigid system such as [2.2.2]-cryptand will favour K^+ over Na^+ because the cryptand's cavity and the cation are of a similar size. An ionizable system such as ethylenediaminetetraacetic acid (EDTA) will prefer Ca^{2+} over either Na^+ or K^+ because it is the most charge-dense of the three. The ester and particularly the amide donor groups of the dipeptide BiBLEs are quite polar. The amides exhibit resonance of the type $NH{-}C{=}O \leftrightarrow NH^+{=}C{-}O^-$. The partially charged oxygen donor favours more charge dense cations just as EDTA's carboxylate groups do.

A second factor is that these dipeptide BiBLEs may be able to fold into a solvent-excluded binding pocket that parallels the calcium binding loop arrangement in such peptides as lactalbumin.[25] Such proteins bind Ca^{2+} with high selectivity in the aqueous cellular milieu. Žinić has recently shown that these same dipeptide BiBLEs can also selectively transport protected amino acids. Thus the versatility of these small molecular systems may be great indeed.[23c]

6.3 Tribracchial Lariat Ethers

The three-armed lariat ethers are little studied thus far because the preparation of triaza-18-crown-6 has been difficult. We have recently solved the synthetic problems and prepared a few derivatives in the hope that the binding profiles would tell us whether the third sidearm enhances the binding.[21] The difficulties associated with such comparisons are noted above but the data, shown in Table 3, deserve at least brief consideration. When the sidearm is $CH_2COOCH_2CH_3$ there is little difference in the Na^+, K^+, and Ca^{2+} binding strengths between the di- and triaza-18-crown-6 derivatives. When the sidearm is $CH_2CH_2OCH_3$ the triaza binding is generally weaker than that for the corresponding diaza-18-crown-6 structures. This evidence is far from conclusive but it suggests what is obvious from molecular models: there really is not enough room in the solvation sphere for more sidearms. To date, we have been unsuccessful in obtaining solid state data that could confirm this conclusion.

Table 3 Comparison of two- and three-armed lariat ethers

		log K_S		
Crown Ether	Sidearms	Na^+	K^+	Ca^{2+}
Diaza-18-c-6	$CH_2CH_2OCH_3$	4.75	5.46	4.48
Triaza-18-c-6	$CH_2CH_2OCH_3$	4.19	4.93	4.07
Diaza-18-c-6	$CH_2COOCH_2CH_3$	5.51	5.78	6.78
Triaza-18-c-6	$CH_2COOCH_2CH_3$	5.13	5.87	6.70

7 Sidearms to Self-Assembly

The earliest concept of lariat ether chemistry was primarily to develop flexible, three-dimensional cation binders. This was accomplished, the structures developed have been fully characterized, and the lariat ether concept has been validated by several methods. Beyond the basic preparation and characterization of these systems, however, lay broader prospects that are described below.

7.1 Redox-switched Cation Binding

The paradox of membrane transport may be solved by compromise as noted in Section 2 or by switching. In the latter approach, a poor cation binder is altered in some way to make it a strong binder. Thus altered (switched on), it conducts a cation from the source side across a membrane whereupon it is returned (switched off) to its original, weak binding state. The weak binder readily yields its cation at the receiving side phase.

A number of switches have been developed including pH, thermal, and photochemical control. Our own approach, developed in collaboration with Echegoyen and Kaifer, utilized redox control.[26] In the systems studied, electrochemical reduction switched a weak binder to a much stronger one. Ultimately, oxidation converted the radical anion back to its original, neutral state. Examples of lariat ether sidearms that exhibited this switching characteristic are nitrobenzenes and anthraquinones. In recent work, the concept has been extended to ferrocene[27] which, as part of a cryptand structure, exhibits stronger binding when neutral but ejects the cation when oxidized. The nitrobenzene and anthraquinone lariats, and anthraquinone cryptand, and a ferrocenyl cryptand are shown in Figure 9.

7.2 Steroidal Lariat Ethers and Membranes

While the redox-switchable systems made possible controlled transport in membranes, the steroidal lariat ethers made possible the formation of novel membranes themselves. Cholesterol is present in many bio-membranes and provides organization to the system. We reasoned that a steroidal lariat ether might have

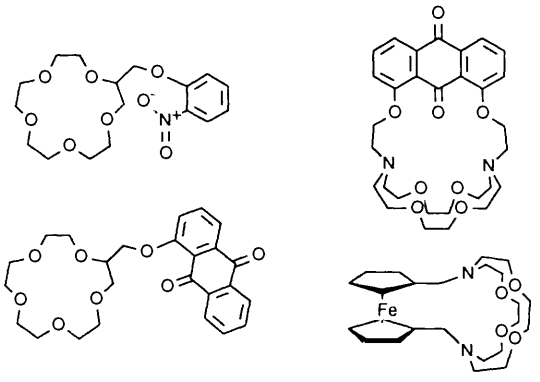


Figure 9 Redox-switchable lariat ethers and cryptands.

the appropriate balance of hydrophobicity and hydrophilicity, either in the neutral state or with a cation bound, to form a membrane. Indeed, nearly all of the systems examined showed a tendency to organize either into micelles or vesicles.

Aza-15-crown-5–CH_2COCl was treated with cholesterol or cholestanol to form the lariat ester. In principle, the carbonyl could serve as a donor group for a ring-bound cation, but that was not the intent in this case. Rather, the steroidal units were expected to self-assemble into an organized array. Indeed, the vesicles formed from the neutral aza-15-crown-5–CH_2CO–cholestanyl compound proved to be stable and similar in size to those formed from egg lecithin (phosphatidylcholine). An important difference between the lariat and pc vesicles was that the former were far more rigid. Indeed, using steroidal EPR probes, we found that the steroidal lariat niosomes were approximately 300-fold more rigid than the lecithin counterparts. This is not surprising in light of the steroid's natural tendency to aggregate and rigidify, but gratifying, nevertheless.[28]

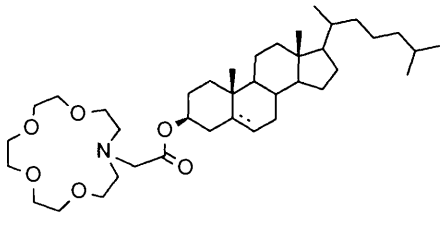


Figure 10 Cholesteryl lariat ether.

7.3 Nucleotide Bases as Sidearms

No group of molecules is more important or ubiquitous than the purine and pyrimidine bases of RNA and DNA. Cumulated base pairs are the archetype of the supermolecule. Incorporation of either purines or pyrimidines in crown ethers should lead to systems that could use base-pairing interactions to organize monomers into supermolecules. We have explored this possibility by preparing diaza-18-crown-6 derivatives having adenine or thymine sidearms at the end of short hydrocarbon chains. We represent these derivatives using the shorthand A–O–A to represent diaza-18-crown-6 having two adenine-terminated sidechains ($CH_2CH_2CH_2$ groups in this case). We have also prepared T–O–T, the complement of A–O–A. When A–O–A and T–O–T are dissolved together, evidence suggests that an aggregate, perhaps the dimer box shown in Figure 11, is formed.[29] Another interesting structure is a compound that might be represented as A–O–T–A. Preliminary evidence suggests that adenine folds back on thymine, an interaction consistent with π-stacking in $CDCl_3$ (or CD_3CN). The adenine in the stacked pair then forms a single hydrogen bond to the opposite adenine. Evidence for this is currently limited to an examination of CPK molecular models and detailed NOESY NMR experiments consistent with the structural possibility. Nevertheless, studies of such systems may lead to novel induced-fit receptors and to a better understanding of nucleotide base interactions in the megamolecules RNA and DNA.

7.4 A Cation-conducting Channel

Two main modes of cation transport exist in natural systems: cation carriers and cation channels. The former is exemplified in nature by valinomycin[5] and the latter by gramicidin.[30] Synthetic cation carriers based upon podands, crown ethers, cryptands, *etc.* are too numerous to catalogue and discussion of them may be found in reference 11. Several attempts have been made to design and synthesize small molecular (non-peptidic) cation-conducting channels. Notable among the attempts[31] is that of Fyles.[31e,f] It is based upon a central crown ether framework similar to that of Lehn[31d] but appears to be a more functional design.

Our own effort[32] to prepare cation-conducting channels was based upon our notion that Nature sets the structural stage for most biofunctional molecules with the primary amino acid sequence. Secondary and tertiary structure then afford the structural intricacies that lead to binding, catalysis, and other functions. The forces that accomplish this remarkable biological activity are, for the most part, feeble and include hydrogen bonding, π-stacking, conformational preferences, van der Waals interactions, and salt bridge formation. We felt that if we could construct a flexible framework having the appropriate elements for channel formation, biofunction would follow. We already knew that crowns could both bind cations and serve as polar head groups in micelle and bilayer formation. We therefore designed a system that had crowns as head groups held at a distance appropriate to be at opposite ends of a bilayer. A third crown ether served as the mechanical central point and perhaps as ion relay in residence near the bilayer's mid-plane. A stylized illustration of the concept is shown in Figure 12.

Efficacy in cation transport was established in egg lecithin (phosphatidyl choline) vesicles by ^{23}Na NMR. Using a dysprosium shift reagent, Na^+ inside and Na^+ outside the vesicles could be distinguished. The rate of transport could thus be assessed from the linewidths. By this method, it was shown that Na^+ was transported through the synthetic channel about 100-fold slower than through gramicidin but the kinetic order was interesting. The gramicidin channel is a dimer of two identical pentadecapeptides. Thus, transport is second order. A single molecule of our channel presumably spans the bilayer and, indeed, kinetics were found to be first order. Numerous other channel model compounds are under preparation in our group and we hope that much information concerning channels will soon be revealed as part of this effort.

8 Toward Supramolecular Assemblies

Crown ethers, cryptands, lariat ethers, and other variations on this theme[33] have proved to be the starting point for numerous, more complex molecular structures. The work has proved evolutionary and revolutionary as fairly simple structures have been adapted to remarkably complex tasks such as to mimic intricate biological functions. The work recorded here is just one thread of this multifarious fabric. It is hoped that the strand of development is apparent but perhaps more important is the lesson that structural analysis both in solution and in the solid state are required for all of the work to have a firm foundation. The field requires the efforts of designers, synthetic chemists, crystallographers, magnetic resonance experts, and many more. The author has benefited profoundly from interactions and collaborations with many talented individuals whose expertise was beyond his own in many areas. The author gratefully acknowledges these interactions and offers the following advice to any entering the field of supramolecular chemistry: Let your imagination go where it will but distinguish carefully between evidence that merely supports your conclusions and evidence that confirms it.

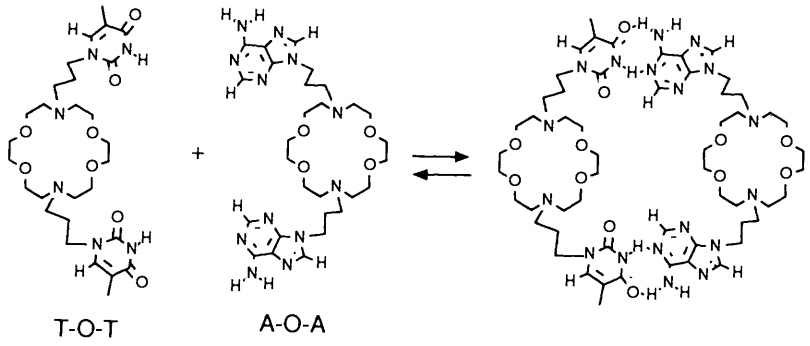


Figure 11 Nucleotide-based molecular box.

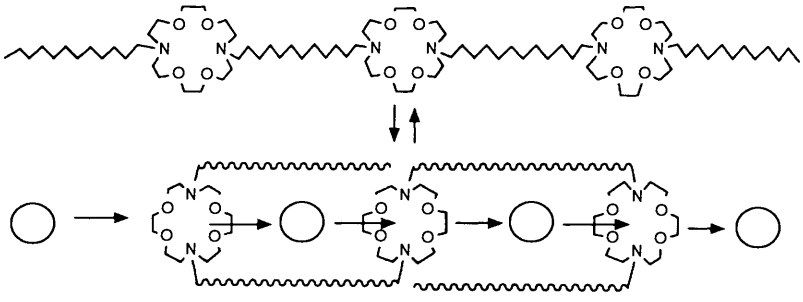


Figure 12 Cation-conducting channel.

Acknowledgments. The Author warmly thanks the NIH for support of this work by several grants, currently including GM 36262. The contributions of co-workers named on the cited references are gratefully acknowledged. In addition, collaboration with Professors J. L. Atwood, (the late) J. J. Christensen, L. A. Echegoyen, E. M. Eyring, F. R. Fronczek, R. D. Gandour, R. M. Izatt, A. E. Kaifer, (the late) M. Okahara, A. Nakano, S. Petrucci, and M. Žinić has proved invaluable.

9 Notes and References

1 (*a*) C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 6017. (*b*) C. J. Pedersen, *J. Inclusion Phenom.*, 1988, **6**, 337.
2 J. M. Lehn, *J. Inclusion Phenom.*, 1988, **6**, 351.
3 D. J. Cram, *J. Inclusion Phenom.*, 1988, **6**, 397.
4 E. Grell, T. Funck, and F. Eggers, in 'Membranes', ed. G. Eisenman, Marcel Dekker, New York, 1975, Vol. 3, p. 1.
5 (*a*) W. L. Duax, H. Hauptmann, C. M. Weeks, and D. A. Norton, *Science*, 1972, **176**, 911. (*b*) G. D. Smith, W. L. Duax, D. A. Langs, G. T. DeTritta, J. W. Edmonds, D. C. Rohrer, and C. M. Weeks, *J. Am. Chem. Soc.*, 1975, **97**, 7242.
6 G. W. Gokel, D. M. Dishong, and C. J. Diamond, *J. Chem. Soc., Chem. Commun.* 1980, 1053.
7 D. M. Dishong, C. J. Diamond, M. I. Cinoman, and G. W. Gokel, *J. Am. Chem. Soc.*, 1983, **105**, 586.
8 R. A. Schultz, B. D. White, D. M. Dishong, K. A. Arnold, and G. W. Gokel, *J. Am. Chem. Soc.*, 1985, **107**, 6659.
9 G. W. Gokel, J. C. Medina, and C. Li, *Synlett.*, 1991, 677.
10 J. M. Lehn, *Struct. Bonding*, 1973, **16**, 1.
11 For additional discussion of this and other binding techniques, see 'Cation Binding by Macrocycles', ed. Y. Inoue and G. W. Gokel, Marcel Dekker, New York, 1990.
12 (*a*) H. K. Frensdorff, *J. Am. Chem. Soc.*, 1971, **93**, 600. (*b*) D. M. Dishong and G. W. Gokel, *J. Org. Chem.*, 1982, **47**, 147. (*c*) K. A. Arnold, and G. W. Gokel, *J. Org. Chem.*, 1986, **51**, 5015.
13 D. J. Cram, and K. N. Trueblood, *Top. Curr. Chem.*, 1981, **98**, 43.
14 (*a*) R. A. Schultz, E. Schlegel, D. M. Dishong, and G. W. Gokel, *J. Chem. Soc., Chem. Commun.*, 1982, 242. (*b*) K. A. Arnold, J. Mallen, J. E. Trafton, B. D. White, F. R. Fronczek, L. M. Gehrig, R. D. Gandour, and G. W. Gokel, *J. Org. Chem.*, 1988, **53**, 5652.
15 G. W. Gokel, D. M. Goli, C. Minganti, and L. Echegoyen, *J. Am. Chem. Soc.*, 1983, **105**, 6786.
16 (*a*) L. Echegoyen, A. Kaifer, H. D. Durst, and G. W. Gokel, *J. Org. Chem.*, 1984, **49**, 688. (*b*) A. Kaifer, L. Echegoyen, H. Durst, R. A. Schultz, D. M. Dishong, D. M. Goli, and G. W. Gokel, *J. Am. Chem. Soc.*, 1984, **106**, 5100.
17 A. Kaifer, L. Echegoyen, and G. W. Gokel, *J. Org. Chem.*, 1984, **49**, 3029.
18 (*a*) G. W. Gokel, L. Echegoyen, M. S. Kim, E. M. Eyring, and S. Petrucci, *Biophys. Chem.*, 1987, **26**, 225. (*b*) L. Echegoyen, G. W. Gokel, M. S. Kim, E. M. Eyring, S. Petrucci, *J. Phys. Chem.*, 1987, 3854.
19 (*a*) F. R. Fronczek, V. J. Gatto, R. A. Schultz, S. J. Jungk, W. J. Colucci, R. D. Gandour, and G. W. Gokel, *J. Am. Chem. Soc.*, 1983, **105**, 6717. (*b*) F. R. Fronczek, V. J. Gatto, C. Minganti, R. A. Schultz, R. D. Gandour, and G. W. Gokel, *J. Am. Chem. Soc.*, 1984, **106**, 7244. (*c*) R. D. Gandour, F. R. Fronczek, V. J. Gatto, C. Minganti, R. A. Schultz, B. D. White, K. A. Arnold, D. Mazzocchi, S. R. Miller, and G. W. Gokel, *J. Am. Chem. Soc.*, 1986, **108**, 4078. (*d*) K. A. Arnold, L. Echegoyen, F. R. Fronczek, R. D. Gandour, V. J. Gatto, B. D. White, and G. W. Gokel, *J. Am. Chem. Soc.*, 1987, **109**, 3716. (*e*) B. D. White, F. R. Fronczek, R. D. Gandour, and G. W. Gokel, *Tetrahedron Lett.*, 1987, 1753.
20 (*a*) V. J. Gatto and G. W. Gokel, *J. Am. Chem. Soc.*, 1984, **106**, 8240. (*b*) V. J. Gatto, K. A. Arnold, A. M. Viscariello, S. R. Miller, C. R. Morgan, and G. W. Gokel, *J. Org. Chem.*, 1986, **51**, 5373.
21 S. R. Miller, T. P. Cleary, J. E. Trafton, C. Smeraglia, F. R. Fronczek, and G. W. Gokel, *J. Chem. Soc., Chem. Commun.*, 1989, 806.
22 (*a*) R. B. Davidson, R. M. Izatt, J. J. Christensen, R. A. Schultz, R. M. Dishong, and G. W. Gokel, *J. Org. Chem.*, 1984, **49**, 5080. (*b*) R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb, J. J. Christensen, and D. Sen, *Chem. Rev.*, 1985, **85**, 271.
23 (*a*) K. A. Arnold, L. Echegoyen, and G. W. Gokel, *J. Am. Chem. Soc.*, 1987, **109**, 3713. (*b*) K. A. Arnold, A. M. Viscariello, M. Kim, R. D. Gandour, F. R. Fronczek, and G. W. Gokel, *Tetrahedron Lett.*, 1988, 3025.
24 (*a*) B. D. White, J. Mallen, K. A. Arnold, F. R. Fronczek, R. D. Gandour, and L. M. B. Gehrig, *J. Org. Chem.*, 1989, **54**, 937. (*b*) J. E. Trafton, C. Li, J. Mallen, S. R. Miller, A. Nakano, O. F. Schall, and G. W. Gokel, *J. Chem. Soc., Chem. Commun.*, 1990, 1266. (*c*) M. Žinić, L. Frkanec, V. Skaric, J. Trafton, and G. W. Gokel, *J. Chem. Soc., Chem. Commun.*, 1990, 1726.
25 A. C. R. daSilva and F. C. Reinach, *Trends Biochem. Sci.*, 1991, **16**, 53.
26 A. E. Kaifer and I. Echegoyen, in 'Cation Binding by Macrocycles', ed. Y. Inoue and G. W. Gokel, Marcel Dekker, New York, 1990.

p. 363.
27 (*a*) J. C. Medina, T. T. Goodnow, S. Bott, J. L. Atwood, A. E. Kaifer, and G. W. Gokel, *J. Chem. Soc., Chem. Commun.*, 1991, 290. (*b*) J. C. Medina, I. Gay, Z. Chen, L. Echegoyen, and G. W. Gokel, *J. Am. Chem. Soc.*, 1991, **113**, 365.
28 G. W. Gokel and L. Echegoyen, *Bioorganic Chemistry Frontiers*, 1990, **1**, 116.
29 M. Kim, and G. W. Gokel *J. Chem. Soc., Chem. Commun.*, 1987, 1686.
30 (*a*) D. W. Urry, T. L. Trapane, and C. M. Venkatachalam, *J. Membr. Biol.*, 1986, **89**, 107. (*b*) B. A. Wallace, and K. Ravikumar, *Science*, 1989, **241**, 182. (*c*) D. A. Langs, *Science*, 1989, **241**, 188.
31 (*a*) I. Tabushi, Y. Kuroda, and K. Yokoto, *Tetrahedron Lett.*, 1982, 4601. (*b*) U. F. Kragton, M. F. M. Roks, and R. J. M. Nolte, *J. Chem. Soc., Chem. Commun.*, 1985, 1275. (*c*) J.-H. Fuhrhop, U. Liman, and H. H. David, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 339. (*d*) L. Julien, J.-M. Lehn, *Tetrahedron Lett.*, 1988, 3803. (*e*) V. E. Carmichael, P. J. Dutton, T. M. Fyles, T. D. James, J. A. Swan, and M. Zojaji, *J. Am. Chem. Soc.*, 1989, **111**, 767. (*f*) T. M. Fyles, *Bioorganic Chemistry Frontiers*, 1990, **1**, 71.
32 A. Nakano, Q. Xie, J. V. Mallen, L. Echegoyen, and G. W. Gokel, *J. Am. Chem. Soc.*, 1990, **112**, 1287.
33 G. W. Gokel, 'Crown Ethers and Cryptands', Royal Society of Chemistry, Cambridge, 1991.