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The Design of Molecular Hosts, Guests, and Their Complexes

DONALD J. CRAM
Department of Chemistry and Biochemistry, University of California at Los Angeles, Los Angeles, CA 90024, U.S.A.

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Origins

Few scientists acquainted with the chemistry of biological systems at the molecular level can avoid being inspired. Evolution has produced chemical compounds exquisitely organized to accomplish the most complicated and delicate of tasks. Many organic chemists viewing crystal structures of enzyme systems or nucleic acids and knowing the marvels of specificity of the immune systems must dream of designing and synthesizing simpler organic compounds that imitate working features of these naturally occurring compounds. We had that ambition in the late 1950's. At that time, we were investigating π-complexes of the larger $[m \cdot n]$paracyclophanes with $(NC)_2C{=}C(CN)_2$, and envisioned structures in which the π-acid was sandwiched by two benzene rings. Although no intercalated structures were observed [1, 2], we recognized that investigations of *highly structured complexes* would be central to simulation of enzymes by relatively simple organic compounds.

In 1967, Pedersen's first papers appeared [3, 4] which reported that alkali metal ions bind crown ethers to form highly structured complexes. We immediately recognized this work as an entrée into a general field. The 1969 papers on the design, synthesis, and binding properties of the cryptands by J.-M. Lehn, J.-P. Sauvage, and B. Dietrich [5, 6] further demonstrated the attractions and opportunities of complexation chemistry. Although we tried to interest graduate students in synthesizing *chiral crown ethers* from 1968 on, the efforts were unsuccessful. In 1970 we insisted that several postdoctoral co-workers enter the field. During 1973, we published five communications on the subject [7–11]. In 1974 with Jane M. Cram, we published a general article entitled 'Host-Guest Chemistry', which defined our approach to this research [12].

Aeschylus, the Athenian Poet-Dramatist, wrote 2500 years ago, "Pleasantest of all ties is the tie of host and guest" [13]. Our research of the past 17 years had dealt with the pleasant tie between host and guest at the organic molecular level. The terms *host*, *guest*, *complex*, and their binding forces were defined in 1977 as follows [14]:

> Complexes are composed of two or more molecules or ions held together in unique structural relationships by electrostatic forces other than those of full covalent bonds . . . molecular complexes are usually held together by hydrogen bonding, by ion pairing, by π-acid to π-base interactions, by metal to ligand binding, by van der Waals attractive forces, by solvent reorganizing, and by partially made and broken covalent bonds (transition

> states) . . . high structural organization is usually produced only through multiple binding sites . . . a highly structured molecular complex is composed of at least one host and one guest component . . . a host-guest relationship involves a complementary stereoelectronic arrangement of binding sites in host and guest . . . the host component is defined as an organic molecule or ion whose *binding sites converge* in the complex . . . the guest component is defined as any molecule or ion whose *binding sites diverge* in the complex . . .

In these definitions, hosts are synthetic counterparts of the receptor sites of biological chemistry, and guests, the counterparts of substrates, inhibitors, or co-factors. These terms and concepts have gained broad international acceptance [15]. A new field requires new terms which, if properly defined, facilitate the reasoning by analogy on which research thrives.

From the beginning, we used Corey-Pauling-Koltun (CPK) molecular models [16], which served as a compass on an otherwise uncharted sea full of synthesizable target complexes. We have spent hundreds of hours building CPK models of potential complexes, and grading them for desirability as research targets. Hosts were then prepared by my co-workers to see if they possessed the anticipated guest-binding properties. Crystal structures of the hosts and their complexes were then determined to compare what was anticipated by model examination with what was experimentally observed. By the end of 1986, Drs. K. N. Trueblood, C. B. Knobler, E. F. Maverick, and I. Goldberg, working at UCLA, had determined the crystal structures of over 50 complexes, and those of another 25 hosts. These crystal structures turned our faith into confidence. Chart I traces the steps involved in linking the structures of *biotic complexes* of evolutionary chemistry with our *abiotic complexes* designed with the aid of CPK molecular models [17].

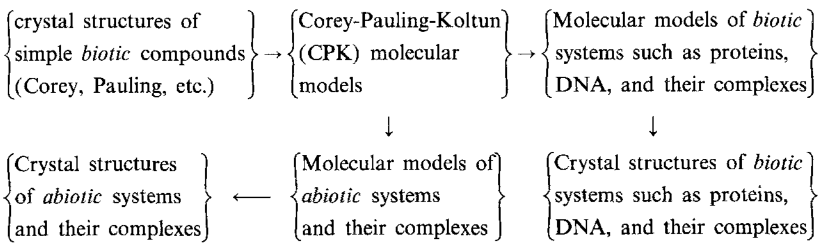


Chart I. Crystal structures of abiotic compounds are correlated with those of biotic compounds through CPK models.

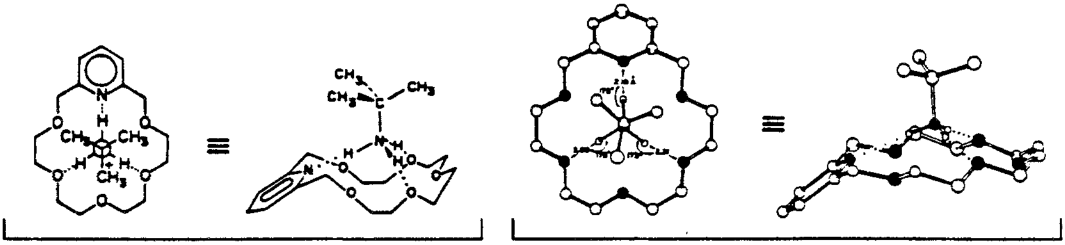
In molecular modeling, we made extensive use of the self-evident principle of complementarity: "to complex, hosts must have binding sites which cooperatively contact and attract binding sites of guests without generating strong nonbonded repulsions" [18]. Complexes were visualized as having three types of common shapes: (1) perching complexes, resembling a bird perching on a limb, an egg protruding from an egg cup, or a scoop of ice cream sitting on a cone; (2) nesting complexes, similar to an egg resting in a nest, a baby lying in its cradle, or a sword sheathed in its scabbard; (3) capsular complexes, not unlike a nut in its shell, a bean in its pod, or a larva in its cocoon. Chart II provides a comparison of CPK models of the three types of complexes (**1**, **2**, and **3**) and their actual crystal structures [19, 20].

Principle of Preogranization

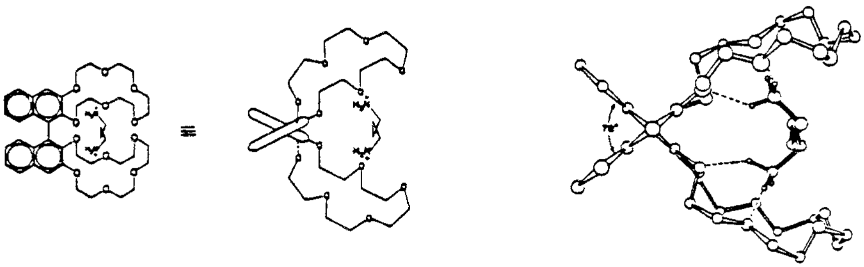
Crystal structures of Pedersen's 18-crown-6 [21] and Lehn's [2.2.2]cryptand [22, 23] show that in their uncomplexed states, they contain neither cavities nor convergently-arranged

Molecular model structures Crystal structures

Perching complex (**1**)



Nesting complex (**2**)



Capsular complex (**3**)

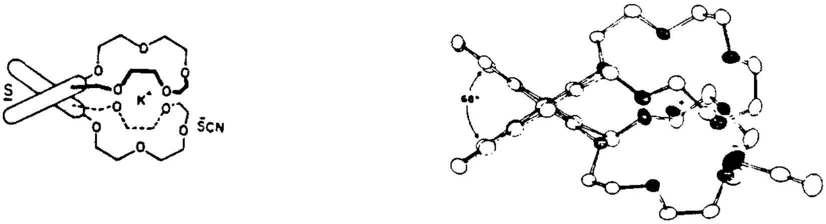
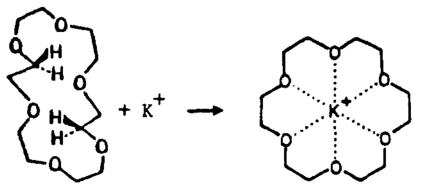


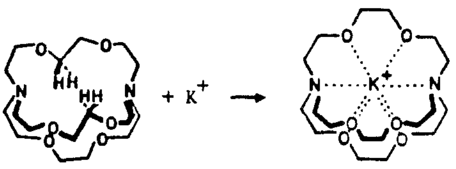
Chart II. Three types of complexes.

binding sites. Comparisons of the crystal structure of host **4** with that of its K^+ complex **5**, and of host **6** with that of its K^+ complex **7** indicate that the complexing act must be accompanied by host reorganization and desolvation.

With the help of CPK molecular models, we designed ligand system **8**, whose oxygens have no choice but to be octahedrally arranged around an enforced spherical cavity complementary to Li^+ and Na^+ ions. We have given the family name, *spherand*, to completely preorganized ligand systems, and the name, *spheraplex*, to their complexes, which like **7**, are capsular [24]. The syntheses and crystal structures of **8**, **9**, and **10** have been reported [25]. As expected, the crystal structure of **11** contains a hole lined with 24 electrons, which are shielded from solvation by six aryl and six methyl groups. The snowflake-like structures of **11** and of spheraplexes **12** and **13** are nearly identical. Thus **8** is the first ligand system



4 5



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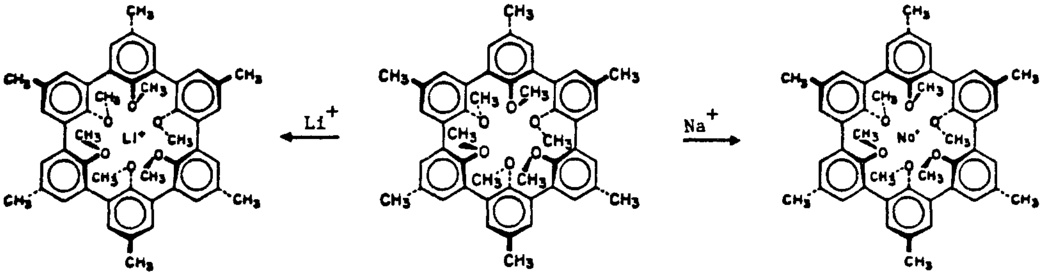
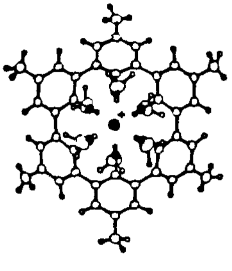
to be designed and synthesized which was completely organized for complexation during synthesis, rather than during complexation.

A method was developed of determining the binding free energies of lipophilic hosts toward guest picrate salts of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$. The guest salts were distributed between $CDCl_3$ and D_2O at 25°C in the presence and absence of host. From the results, K_a (mol^{-1}) and $-\Delta G^0$ values (kcal mol^{-1}) were calculated



9 8 10



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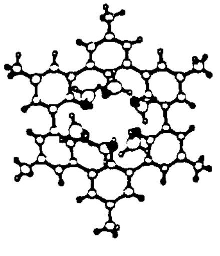

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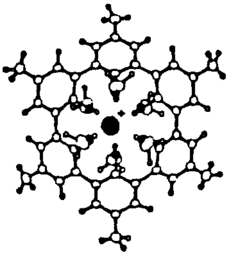

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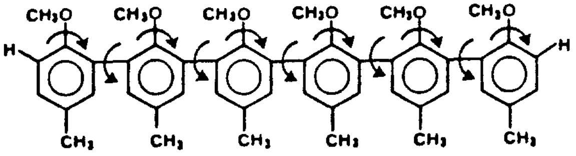


14

(equations (1)). This method was rapid and convenient for obtaining

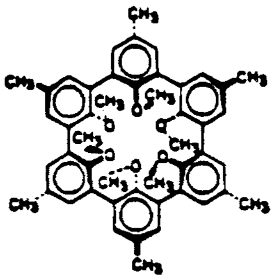
$$\mathrm{H} + \mathrm{GPic} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{H} \cdot \mathrm{G} \cdot \mathrm{Pic} \qquad K_a = k_1/k_{-1} \qquad \Delta G^0 = -RT \ln K_a \tag{1}$$

$-\Delta G^0$ values at 25°C ranging from about 6 to 16 kcal mol^{-1} in $CDCl_3$ saturated with D_2O [26]. Higher values (up to 22 kcal mol^{-1}) were obtained by equilibration experiments between complexes of known and those of unknown $-\Delta G^0$ values [18, 27, 28]. Others were determined from measured k_{-1} and k_1 values, all in the same medium at 25°C [18]. Spherand **8** binds LiPic with $-\Delta G^0 > 23$ kcal mol^{-1}, NaPic with a value of 19.3 kcal mol^{-1}, and totally rejects the other standard ions, as well as a wide variety of other di- and trivalent ions [18]. The open-chain counterpart of **8**, podand **14**, binds LiPic and NaPic with $-\Delta G^0 < 6$ kcal mol^{-1} [29]. *Podand* is the family name given to acylic hosts [15].

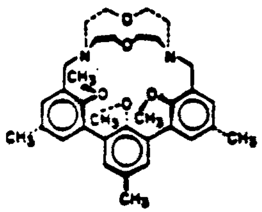
Podand **14** differs constitutionally from spherand **8** only in the sense that **14** contains two hydrogen atoms in place of one Ar—Ar bond in **8**. The two hosts differ radically in their conformational structures and states of solvation. The spherand possesses a single conformation ideally arranged for binding Li^+ and Na^+. Its oxygens are deeply buried within a hydrocarbon shell. The orbitals of their unshared electron pairs are in a microenvironment whose dielectric properties are between those of a vacuum and a hydrocarbon. No solvent can approach these six oxygens, which remain unsolvated. The free energy costs of organizing the spherand into a single conformation and of desolvating its six oxygens were paid for during its synthesis. Thus spherand **8** is preorganized for binding [30]. The podand, in principle, can exist in over 1000 conformations, only two of which can bind metal ions octahedrally. The free energy for organizing the podand into a binding conformation and desolvating its six oxygens must come out of its complexation free energy. Thus the podand is not preorganized for binding, but is randomized to maximize the entropy of mixing of its conformers, and to maximize the attractions between solvent and its molecular parts.

The difference in $-\Delta G^0$ values for spherand **8** and podand **14** binding Li^+ is >17 kcal mol^{-1}, corresponding to a difference in K_a of a factor of $>10^{12}$. The difference in $-\Delta G^0$ values for **8** and **14** binding Na^+ is >13 kcal mol^{-1}, corresponding to a difference in K_a of a factor of $>10^{10}$. These differences are dramatically larger than any we have encountered that are associated with other effects on binding power toward alkali metal ion guests. We conclude that *preorganization is a central determinant of binding power.* We formalized this conclusion in terms of what we call the principle of preorganization, which states that "the more highly hosts and guests are organized for binding and low solvation prior to their complexation, the more stable will be their complexes." Both enthalpic and entropic components are involved in preorganization, since solvation contains both components [29]. Furthermore, binding conformations are sometimes enthalpically rich. For example, the benzene rings in spherand **8** and spheraplexes **9** and **10** are somewhat folded from their planar structures to accommodate the spacial requirements of the six methoxyl groups [30]. The anisyl group is an intrinsically poor ligand [31, 32]. That **8** is such a strong binder provides an extreme example of the power of preorganization.

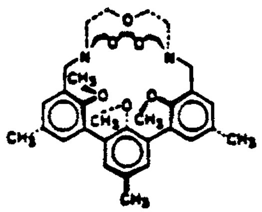
Families of hosts generally fall into the order of their listing in Chart III when arranged according to their $-\Delta G^0$ values with which they bind their most complementary guests: spherands > cryptaspherands > cryptands > hemispherands > corands > podands. Corand is the family name given to modified crown ethers [33]. Spheraplex **8** · Li^+ provides a $-\Delta G^0$ value of >23 kcal mol^{-1}. Cryptaspheraplexes **15** · Na^+, **16** · Na^+, and **17** · Cs^+ [34] give values of 20.6, 21.0, and 21.7 kcal mol^{-1}, respectively [27]. Cryptaplexes **18** · Li^+, **19** · Na^+, and **6** · K^+ give respective values of 16.6, 17.7, and 18.0 kcal mol^{-1} [27].



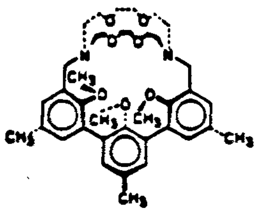
8, spherand



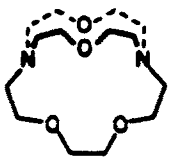
15, cryptaspherand



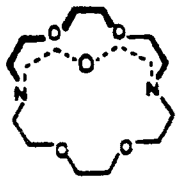
16, cryptaspherand



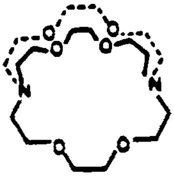
17, cryptaspherand



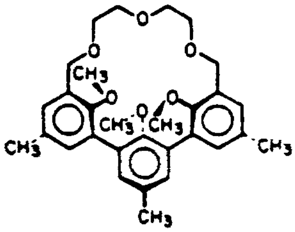
18, cryptand



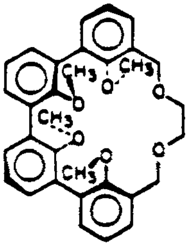
19, cryptand



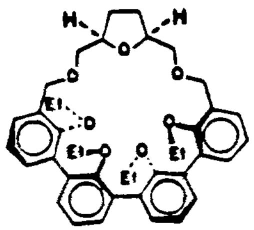
6, cryptand



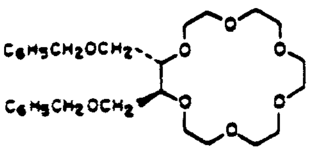
20, hemispherand



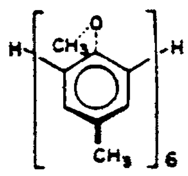
21, hemispherand



22, hemispherand



23, corand



14, podand

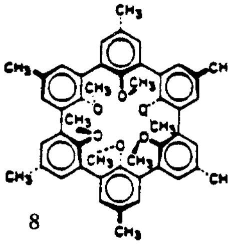
Chart III. Host structures arranged in the order of decreasing $-\Delta G^0$ values for binding their most complementary guest picrate salts at 25°C in $CDCl_3$ saturated with D_2O.

Hemispheraplexes **20** · Na^+, **21** · Na^+, and **22** · K^+ are bound by 12.2, 13.5, and 11.6 kcal mol^{-1} [35, 36]. Coraplex **23** · K^+ has a $-\Delta G^0$ value of 11.4 [26, 37] and podaplexes **14** · M^+ values of <6 kcal mol^{-1} [29]. Although the numbers of binding sites and their characters certainly influence these values, the degree of preorganization appears to be dominant in providing this order.

Structural Recognition

Just as preorganization is the central determinant of binding power, complementarity is the central determinant of structural recognition. The binding energy at a single contact site is at most a few kilocalories per mole, much lower than that of a covalent bond. Contacts at several sites between hosts and guests are required for structuring of complexes. Such contacts depend on complementary placements of binding sites in the complexing partners.

The most extensive correlations of structural recognition with host-guest structure involve the K_a values with which the spherands, cryptaspherands, cryptands, and hemispherands associate with the various alkali metal picrate salts at 25°C in $CDCl_3$ saturated with D_2O. Chart IV lists the $K_a^A/K_a^{A'}$ ratios for various hosts binding two alkali metal ions A and A' that are adjacent to one another in the periodic table [33]. Notice that factors as high as $>10^{10}$ are observed for the spherands binding Na^+ better than K^+. Cryptaspherand **15** provides a factor of 13,000. The highest factors for hosts binding K^+ better than Na^+ are observed for cryptaspherand **17** (11,000) and hemispherand **22** (2,000). The highest factors for a host binding Li^+ over Na^+ are found for cryptand **18** (4,800). These particular selectivities are important because of the physiological importance of these ions. These hosts, or modifications of them, are being developed for commercial use in the medical diagnostics industry.



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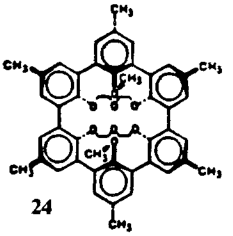
Li^+/Na^+	Na^+/K^+
>600	$>10^{10}$



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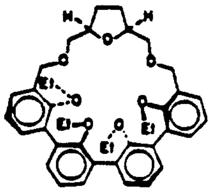
Na^+/Li^+	Na^+/K^+
125	$>10^9$



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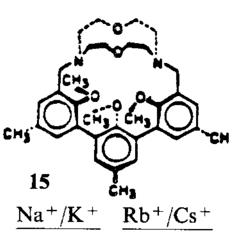
K^+/Na^+	Rb^+/Cs^+
2,000	5



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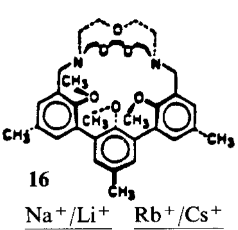
Na^+/K^+	Rb^+/Cs^+
13,000	134



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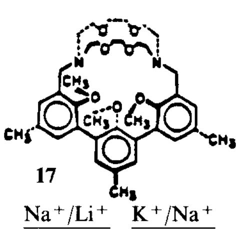
Na^+/Li^+	Rb^+/Cs^+
420,000	900



17

Na^+/Li^+	K^+/Na^+
440	11,000

Chart IV. Structural recognition measured by $K_a^A/K_a^{A'}$ values for alkali metal picrates at 25°C in $CDCl_3$ saturated with D_2O.

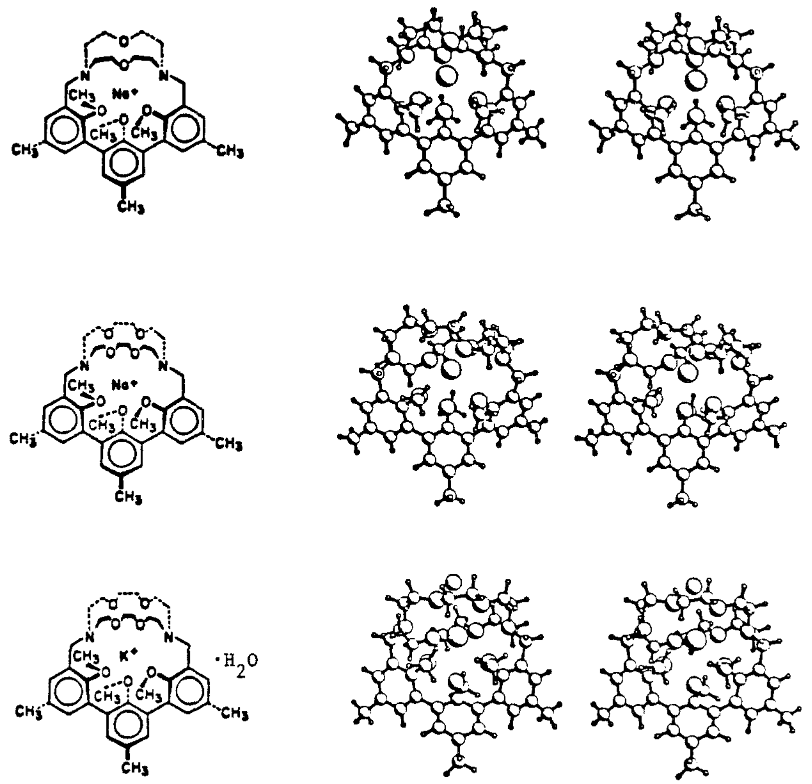
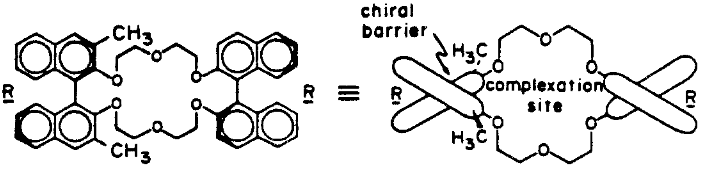


Chart V. Stereoviews of crystal structures of cryptaspheraplexes.

Chart V provides stereoviews of crystal structures of capsular complexes **15** · Na$^+$, **17** · Na$^+$, and **17** · K$^+$. Notice that in **15** · Na$^+$ and **17** · K$^+$ the metal ions contact all of the heteroatoms, whereas in **17** · Na$^+$, the Na$^+$ ion does not. Here is a visual example of complementarity vs. noncomplementarity. The $K_a^A/K_a^{A'}$ ratio for **17** · K$^+$/**17** · Na$^+$ = 11,000 [34].

Arrangement of the classes of hosts in decreasing order of their ability to select between the alkali metal ion guests provides spherands > cryptaspherands ~ cryptands > hemispherands > corands > podands. This order is similar but less rigidly followed than that for host preorganization. In some cases, rather small changes in structure provide a substantial spread in $-\Delta G^0$ values for binding under our standard conditions [33].

Chiral recognition in complexation is a fundamental aspect of structural recognition in complexation in the biotic world. We synthesized host **25** in an enantiomerically pure form to study its ability to distinguish between enantiomers in complexation of amino acids and ester salts in solution. We were careful to design a system containing at least one C_2 axis of symmetry, a tactic that made the hosts *nonsided* with respect to perching guests. A $CDCl_3$ solution of (*R*,*R*)-**25** in $CDCl_3$ at 0°C was used to extract D_2O solutions of racemic amino acid or ester salts. As predicted in advance by CPK molecular models, the (*D*)-enantiomers were extracted preferentially into the organic layer. Chiral recognition factors ranged from a high of 31 for $C_6H_5CH(CO_2CH_3)NH_3PF_6$ to a low of 2.3 with $CH_3CH(CO_2H)NH_3ClO_4$. These factors represent free energy differences between diastereomeric complexes of 1.9 kcal mol^{-1} and 0.42 kcal mol^{-1}, respectively. Other



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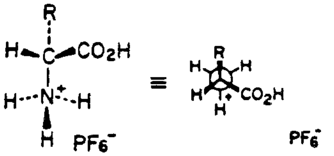
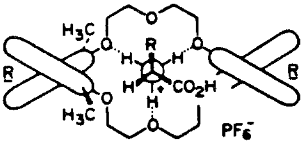




26

STABLER COMPLEX

amino acid and ester salt guests ranged between these values. We interpreted these results in terms of the complementarity between host and guest of the (*R*,*R*)-(*D*)-configurations as visualized in the complex **26**, and the lack of complementarity in those of the (*R*,*R*)-(*L*)-configurations, which were designed not to form [38, 39].

An amino acid and ester resolving machine was designed, built, and tested, which is pictured in Figure 1. It made use of chiral recognition in transport of amino acid or ester salts through lipophilic liquid membranes. From the central reservoir of the W-tube

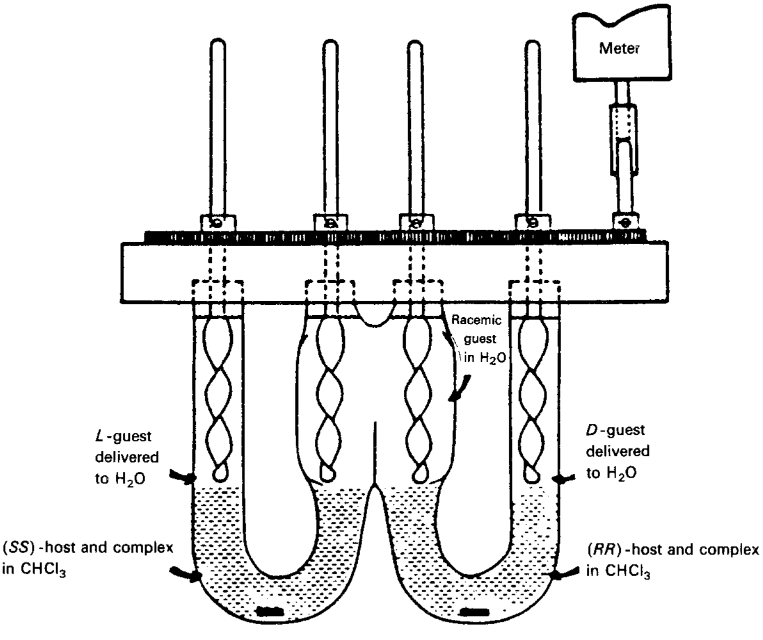
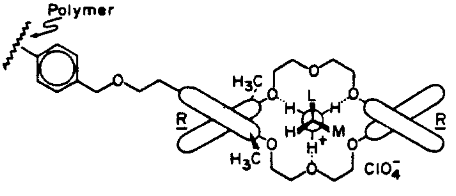


Fig. 1. Enantiomer resolving machine.

containing an aqueous solution of racemic salt, the (*L*)-enantiomer was picked up by (*S*,*S*)-**25** in the left hand chloroform reservoir and delivered to the left hand aqueous layer, while the (*D*)-enantiomer was transported by (*R*,*R*)-**25** in the right hand chloroform reservoir and delivered to the right hand aqueous layer. The thermodynamic driving force for the machine's operation involved exchange of an energy-lowering entropy of dilution of each enantiomer for an energy-lowering entropy of mixing. To maintain the concentration gradients down which the enantiomers traveled in each arm of the W-tube, fresh racemic guest was continuously added to the central reservoir, and (*L*)- and (*D*)-$C_6H_5CH(CO_2CH_3)NH_3PF_6$ of 86–90% enantiomeric excess were continuously removed from the left and right hand aqueous reservoirs, respectively [40].

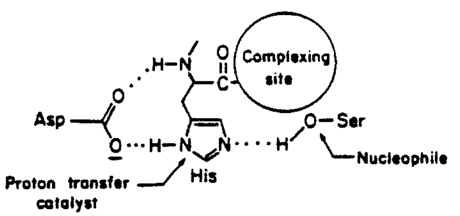
In another experiment, we covalently attached the working part of (*R*,*R*)-**25** at a remote position of the molecule to a macroreticular resin (polystyrene-divinylbenzene) to give immobilized host of ~ 18,000 mass unit per average active site. This material (the host part of **27**) was used to give complete enantiomeric resolution of several amino acid salts. The behavior in the chromatographic resolution paralleled that observed in the extraction and transport experiments, and was useful both analytically and preparatively. Separation factors ranged from 26 to 1.4, the complexes of the (*R*,*R*)-(*D*)- or (*S*,*S*)-(*L*)-configurations always being the more stable. The structure envisioned for the more stable complex is formulated in **27** [41].



27

Partial Transacylase Mimics

The design and synthesis of enzyme-mimicking host compounds remains one of the most challenging and stimulating problems of organic chemistry. We chose to examine transacylase mimics first because the mechanism of action of these enzymes had been so thoroughly studied.



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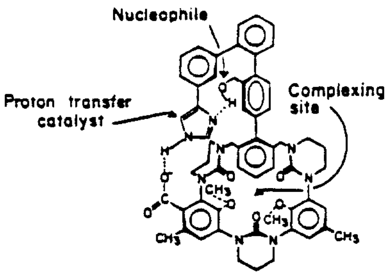
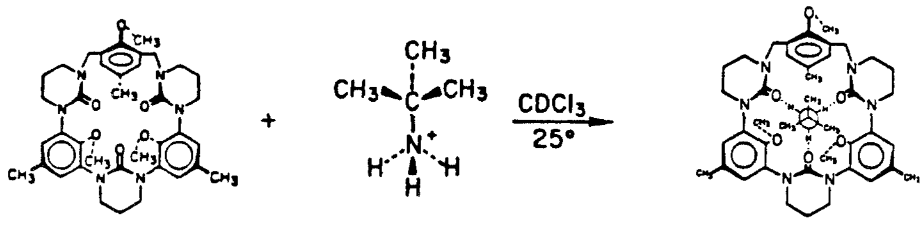


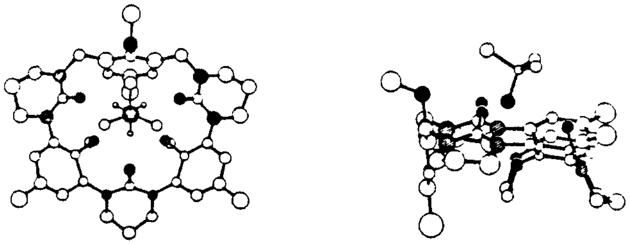
29

The active site of chymotrypsin combines a binding site, a nucleophilic hydroxyl, an imidazole, and a carboxyl group in an array preorganized largely by hydrogen bonds as indicated in **28**. With the help of molecular models, we designed **29** as an 'ultimate target' host possessing roughly the same organization of groups as that of **28**.

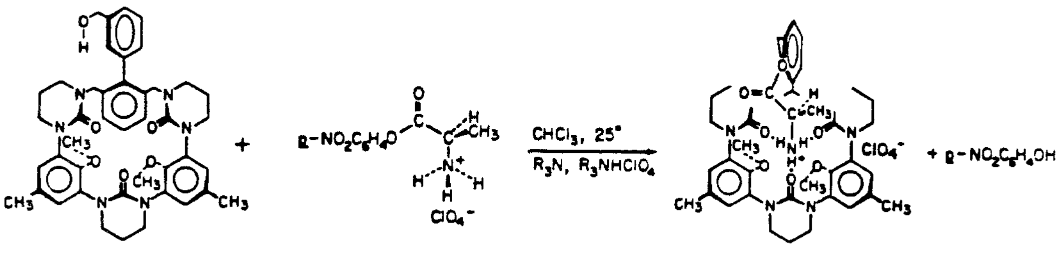
Compound **29** is much too complicated to synthesize without getting encouragement from simpler model compounds. An incremental approach to **29** was employed. We first prepared **30**, and found that it binds *t*-BuNH$_3$Pic in CDCl$_3$ saturated with D$_2$O with $-\Delta G^0 = 13.2$ kcal mol^{-1}. The complex, **30** · (CH$_3$)$_3$CNH$_3^+$, had the expected crystal structure [42]. Accordingly, **31** was prepared, and found to bind CH$_3$NH$_3$Pic and NaPic under our standard conditions with $-\Delta G^0 = 12.7$ and 13.6 kcal mol^{-1}, respectively [43]. Host **31** was acylated by **32** to give **33** and *p*-nitrophenol. The kinetics of formation of **33** were measured in CHCl$_3$, and found to be first order in added Et$_3$N/Et$_3$NHClO$_4$ buffer ratio. Thus the alkoxide ion is the nucleophile. The rate constant for acylation of **31** by **32** was calculated to be ~10^{11} higher valued than the rate constant for the noncomplexed model



30 **30** · (CH$_3$)$_3$CNH$_3^+$



30 · (CH$_3$)$_3$CNH$_3^+$

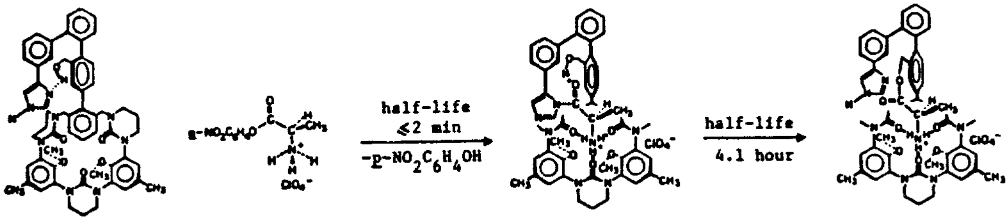


31 **32** **33**

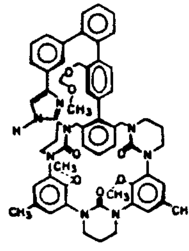
compound, 3-phenylbenzyl alcohol [44]. This high factor demonstrates that collecting and orienting reactants through highly structured complexation can result in an enormous rate acceleration. When $NaClO_4$ was added to the medium, the acylation rate of **31** was depressed by several powers of ten. Thus the acylation of **31**, like that of the serine esterases, is subject to competitive inhibition.

A thirty-step synthesis of **34** was then devised, and about 0.5 g of the compound prepared [45]. This compound combines the binding site, the nucleophilic hydroxyl, and the imidazole proton-transfer agent in the same molecule, lacking only the carboxyl group of final target compound **29**. Compound **34** complexed CH_3NH_3Pic and NaPic with respective $-\Delta G^0$ values of 11.4 and 13.6 kcal mol^{-1} in $CDCl_3$ saturated with D_2O at 25°C. In pyridine-chloroform, amino ester salt **32** instantaneously acylated the imidazole group of **34** to give **35**, which more slowly gave **36**. In $CHCl_3$, in the absence of any added base, the observed rate constant for acylation of **34** by **32** was higher by a factor of 10^5 than that for acylation of an equal molar mixture of noncomplexing model compounds **39** or **40** under the same conditions. The same ratio was obtained when **37** was substituted for **34**. Thus the imidazole groups of **34** and **37** are the sites of acylation. Introduction of $NaClO_4$ into the medium as a competitive inhibitor of complexation destroyed much of the rate acceleration. When **32** added to **38** was substituted for **34**, the resulting complex acylated imidazole **40** with a 10 rate-constant factor increase. Thus complexed **32** is a better acylating agent than **32** alone.

The disadvantages of comparing rate constants for reactions with different molecularities are avoided by referring to uncomplexed **34** or **37**, noncomplexing imidazole **40**, and uncomplexed acylating agent **32** as standard starting states, and the rate-limiting transition states for transacylation as standard final states. This treatment introduces K_a into the second order rate constant expression when complexation precedes acylation. The resulting second order rate constants for **32** acylating **34** or **37** are higher by factors of 10^{10} or 10^{11} than the second order rate constant for **32** acylating **40**. This work clearly demonstrates that complexation of the transition states for transacylation can greatly stabilize those



34 32 35 36



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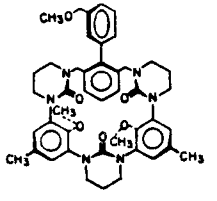

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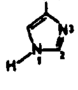

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transition states to produce large rate factor increases over comparable noncomplexed transition states [46]. Others have shown that the imidazole of chymotrypsin is acylated first by esters of nonspecific substrates [47].

These investigations demonstrate that totally synthetic systems can be designed and prepared which mimic the following properties of enzymes: the ability to use complexation to vastly enhance reaction rates and the sensitivity to competitive inhibition. In a different, chiral system, we demonstrated that a synthetic host was capable of distinguishing between enantiomeric reactants [48, 49]. We anticipate that as the field matures, many of the other remarkable properties of enzyme systems will be observed in designed, synthetic systems. Our results illustrate some of the strategies and methods that might be applied in this expanding field of research.

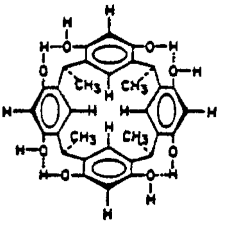
Cavitands – Synthetic Molecular Vessels

Although enforced cavities of molecular dimensions are frequently encountered in enzyme systems, RNA, or DNA, they are almost unknown among the seven million synthetic organic compounds. In biological chemistry such cavities play the important role of providing concave surfaces to which are attached convergent functional groups which bind substrates and catalyze their reactions. If synthetic biomimetic systems are to be designed and investigated, simple means must be found of synthesizing compounds containing enforced concave surfaces of dimensions large enough to embrace simple molecules or ions. We applied the name *cavitand* to this class of compound [50].

Cavitands designed and studied include compounds **42–45**, many of which were prepared from **41**. The structure and conformational mobility of **41** had been established by A. G. S. Högberg [51]. The substance is prepared in good yield by treatment of resorcinol with acetaldehyde and acid. We rigidified **41** and its derivatives by closing four additional rings to produce **42–45** [50, 52].

As anticipated by molecular model examinations, **42–45** crystallize only as solvates because these rigid moelcules taken alone are incapable of filling their voids either intermolecularly or intramolecularly. They are shaped like bowls of differing depth supported on four methyl 'feet'. Compound **42** forms crystallates with SO_2, CH_3CN, and CH_2Cl_2, molecules to which it is complementary (molecular model examination). Cavitand **43**, whose cavity is deeper, crystallizes with a mole of $CHCl_3$. Crystal structures of **42** · CH_2Cl_2 and **43** · $CHCl_3$ show they are caviplexes, as predicted [53]. Cavitand **44** is vase-shaped. It crystallizes with one mole of $(CH_3)_2NCHO$, which is just small enought to fit into the interior of **44** in models. Although the amide cannot be removed at high temperature and low pressure, it is easily displaced with $CHCl_3$, one and one-half moles of which appear to take the place of the $(CH_3)_2NCHO$ in the crystallate [50].

Treatment of octol **41** with R_2SiCl_2 gave a series of cavitands, of which **45** is typical. In molecular models, **45** has a well-shaped cavity, defined by the bottoms of four aryls and by four inward-turned methyl groups. In molecular models, this well is complementary to small, cylindrical molecules such as $S{=}C{=}S$, $CH_3C{\equiv}CH$, and $O{=}O$, but not to larger compounds such as $CDCl_3$ or C_6D_6. Cavitand **45** and its analogues when dissolved in $CDCl_3$ or C_6D_6 complex guests such as those mentioned above, whose external surfaces are complementary to the internal surface of the host cavity. Association constants were determined for **45** and its analogues binding $S{=}C{=}S$. Values of $-\Delta G^0$ as high as 2 kcal mol^{-1} have been observed. A crystal structure of **45** · CS_2 shows that CS_2 occupies the well in the expected manner. Compound **45** in $CDCl_3$ was also shown to bind dioxygen reversibly [52]. Dissolution of **45** in solvents such as $CDCl_3$ or C_6D_6 is the equivalent of



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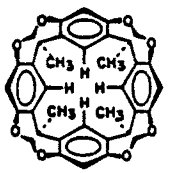

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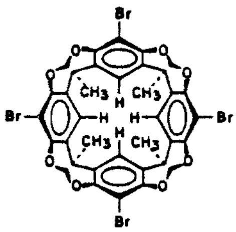

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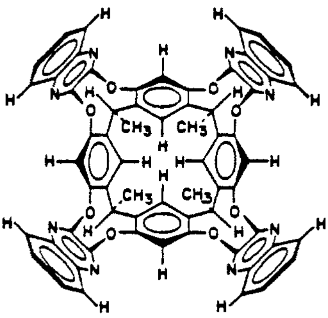

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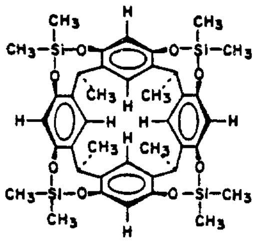

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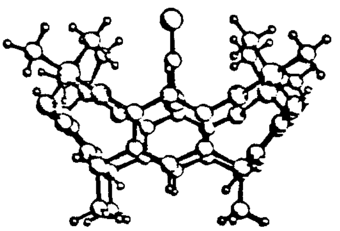
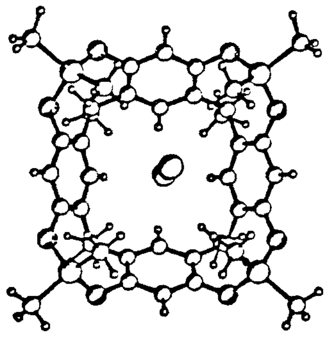


45 · CS_2 (side view)



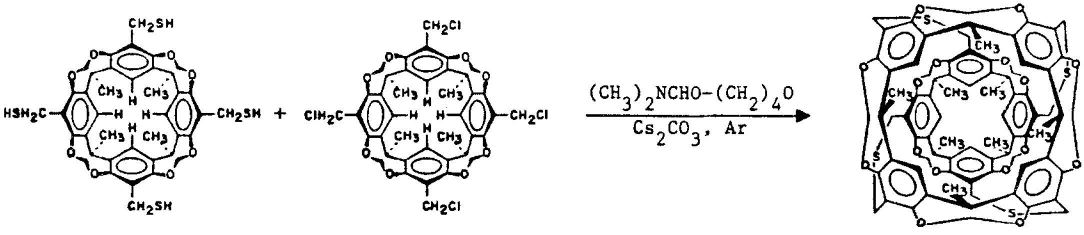
45 · CS_2 (top view)

dissolving 'holes' in a medium into which appropriately shaped solutes fall. The discrimination shown by the holes for the guests exemplifies the principle of complementarity as applied to cavitand complexation.

The next steps in research on these cavitands is to append to them water-solubilizing and catalytic groups. The former will provide them with hydrophobic driving forces to complex nonpolar guests, and the latter to catalyze reactions of such guests.

Carcerands – Synthetic Molecular Cells

Absent among the millions of organic compounds hitherto reported are closed-surface hosts with enforced interiors large enough to imprison behind covalent bars, guests the size of ordinary solvent molecules. After much thought and molecular model examination, we chose **48** as the target for synthesis of the first molecular cell. The term *carcerand* was applied to this class of compound. The synthesis involved treating Cs_2CO_3 with a solution in $(CH_3)_2NCHO—(CH_2)_4O$ of equal molar amounts of cavitands **46** and **47** under an atmosphere of argon. The first question to be answered was: what guest compounds would be trapped inside during the shell closure? This question is akin to asking whether two soup bowls closed rim-to-rim under the surface of a kettle of stew would net any stew. The answer was that **48** 'contained' essentially every kind of component of the medium present during shell closure [54].



46 **47** **48**

The product (**48** and guests) was very insoluble in all media, and was purified by extracting it with the most powerful solvents of each type. The remaining material was subjected to elemental analysis for C, H, S, O, N, Cl, and Cs. Nitrogen analysis and an IR spectrum of the substance revealed that $(CH_3)_2NCHO$ had been entrapped. The presence of equivalent amounts of Cs and Cl demonstrated that one or the other ion or both had to be encapsulated in the host.

A fast atom bombardment mass spectrum of **48** · G showed the presence of the following host-guest combinations, the species trapped in the interior of **48** being enclosed by parentheses:

48 · no guest; **48** · $(Cs^+) \cdot Cl^-$; **48** · $((CH_3)_2NCHO))$: **48** · $(Cs^+ + H_2O) \cdot Cl^-$;
48 · $((CH_2)_4O + H_2O)$; **48** · $((CH_3)_2NCHO + Cs^+) \cdot Cl^-$; **48** · $(Cs^+ + Ar) \cdot Cl^-$;
48 · $(Cs^+ + H_2O + Cs^+) \cdot 2Cl^-$; **48** · $(Cs^+ + Cl^-)$, and
48 · $(Cs^+ + Cs^+ + Cl^-) \cdot Cl^-$.

No peaks were found at molecular masses above that of the last carcaplex listed. None were observed that could not be interpreted in terms of appropriate host-guest combinations. When highly dried **48** was boiled with D_2O, the **48** · $(Cs^+ + H_2O)$ peak was substantially replaced by a **48** · $(Cs^+ + D_2O)$ peak. Models suggest that **48** has two small portals lined with methyl groups through which molecules as small as H_2O can pass.

Molecular models of **48** show that its interior surface is complementary to the outer surface of anti-$ClCF_2CF_2Cl$. Shell closure of **46** and **47** in the presence of this Freon resulted in entrapment of a small amount of this gas in the interior of **48**.

The FAB-MS coupled with the elemental analyses indicated that about 5% of the mixture was noncomplexed **48**, about 60% encapsulated Cs^+, about 45% encapsulated $(CH_3)_2NCHO$, 15% encapsulated $(CH_2)_4O$, but only 1–2% encapsulated Cl^-. Thus Cs^+

49

was mainly inside and Cl^- mainly outside the carcaplex. Models show that if the final covalent bond leading to **48** · G involves an intramolecular S_N2 linear transition state as in **49**, any Cs^+ ion-paired to the S^- is trapped inside the cavity and the Cl^- must be external to the cavity [54].

We anticipate that unusual physical and chemical properties will provide unusual uses for carcaplexes, particularly when their design renders them soluble and separable.

We warmly thank the following co-workers for carrying out the research described here. L. A. Singer, R. H. Bauer, M. G. Siegel, J. M. Timko, K. Madan, S. S. Moore, T. L. Tarnowski, G. M. Lein, J. L. Toner, J. M. Mayer, S. P. Ho, M. P. de Grandpre, S. P. Artz, G. D. Y. Sogah, S. C. Peacock, L. A. Domeier, H. E. Katz, I. B. Dicker, J. R. Moran, and K. D. Stewart as graduate students; E. P. Kyba, L. R. Sousa, K. Koga, R. C. Helgeson, G. W. Gokel, D. M. Walba, J. M. Cram, T. Kaneda, S. B. Brown, K. E. Koenig, P. Stückler, G. D. Y. Sogah, G. R. Weisman, Y. Chao, F. C. A. Gaeta, M. Newcomb, P. Y. S. Lam, S. Karbach, A. G. S. Högberg, Y. H. Kim, and M. Lauer as postdoctoral fellows. The crystal structure work of colleagues K. N. Trueblood, C. B. Knobler, E. F. Maverick and I. Goldberg was indispensable.

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