

Cavitands: Organic Hosts with Enforced Cavities

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Several million organic compounds with a wide variety of shapes, sizes, and properties have been synthesized. Some of these compounds are rigid at ordinary temperatures in their nonsolid states, but the majority are capable of assuming a variety of shapes through rotations of their various parts around covalent single bonds. Because chemical bonds radiate outward from nuclei, most organic

and H₂ is about 2 by 2.5 angstroms. The interior surfaces of cavitands can have spherical, hemispherical, ellipsoidal, oblong, collar, or any other designable and synthesizable shapes.

The cyclodextrins are the most studied of the naturally occurring compounds that contain rigid cavities. They are cyclic oligomers of the 1,4-glucopyranoside unit. They are torus-shaped and have

Summary. Organic hosts are now being designed and synthesized which contain enforced cavities large enough to complex and even surround simple inorganic or organic guest compounds.

compounds have convex surfaces composed of hydrogen atoms bound to carbon, oxygen, or nitrogen. A few simple compounds such as benzene and cyclobutane have flat or nearly flat surfaces. Like stones, very few organic compounds have concave surfaces of any size. If organic compounds that contain enforced (rigid) cavities are to be designed and prepared, they must be composed of units that are concave on parts of their surfaces. The virtual nonexistence of such units until recently is related to the nonexistence of cavity-containing compounds.

I use the class name cavitands for synthetic organic compounds that contain enforced cavities of dimensions at least equal to those of the smaller ions, atoms, or molecules. Among the latter, Li⁺ has a diameter of about 1.48 angstroms, He a diameter of 2.6 angstroms,

cavities that are enforced by the rigidity of the six, seven, or eight monosaccharide units. Their internal dimensions are large enough to embrace aryl units. Much interesting enzyme modeling has been done with cyclodextrins and their derivatives (*1*). Other important cavities in the biological world include the binding sites of enzymes and the troughs in the helices of RNA and DNA, which thus far have no counterparts in synthetic organic chemistry.

Why should cavitands interest scientists? One of the supreme challenges to the organic chemist is to design and synthesize compounds that simulate the properties of the working parts of evolutionary chemistry. Complexation between substrate and enzyme, or between inhibitor and receptor site, is a central feature in catalysis and regulation of biological processes. Cooperativity between catalyzing functional groups in enzyme systems is possible only if those groups are held in positions that con-

verge on a substrate-binding site, usually located in a cavity. The design, synthesis, and study of cavity-containing organic compounds is a principal theme in what we term host-guest complexation chemistry.

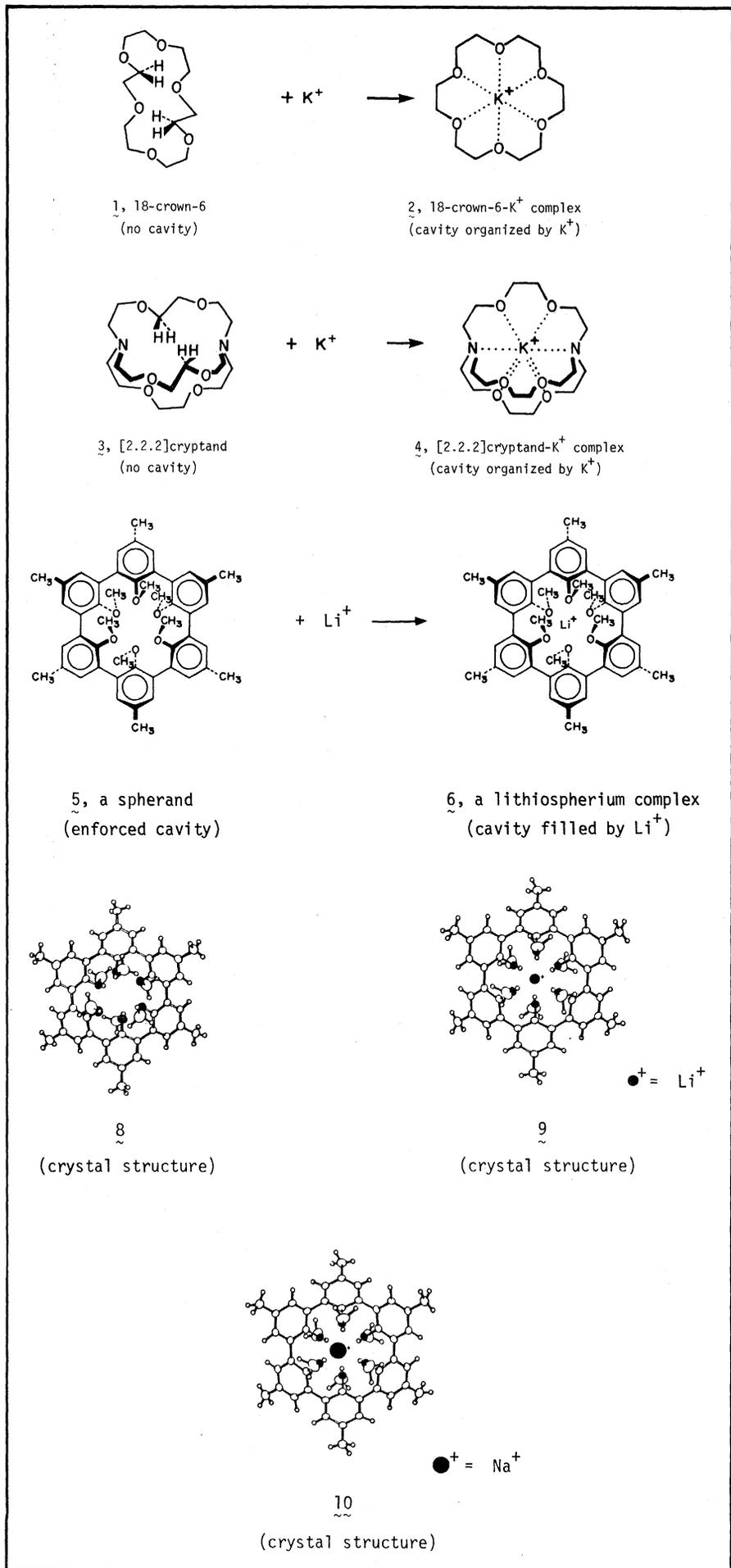
A host is a compound with binding sites arranged to converge on the same point, line, or surface. A guest is a compound or ion with binding sites that diverge from a point, line, or surface. When a host and a guest have complementary binding sites and steric requirements, complexation occurs. A complex is composed of two or more distinct molecules held together by noncovalent forces in a definable structural relationship. The binding can result from any combination of hydrogen bonding, ion pairing, metal ion to ligand attractions, π -acid to π -base attractions, van der Waals attractions, and solvent-liberation driving forces. Hosts can contain cavities that are rigid or that are developed by reorganization of the hosts during the process of complexation. Thus cavitands are particular kinds of hosts—those whose cavities are enforced and exist prior to complexation.

The first section of this article describes a cavitand whose rigid organization vastly enhances its ability to bind guests with high selectivity. The second describes larger cavitands that contain moving parts. The third section traces the evolution of an approach to another family of cavitands whose syntheses are in progress, and the fourth describes a saddle-shaped cavitand containing two clefts of substantial size. The final section indicates how cavitands might be chemically manipulated to produce desired physical and chemical properties.

Importance of Preorganization of Hosts to Their Complexing Powers

Among hosts that bind metal cations, the most thoroughly investigated have been Pedersen's chorands (or crowns) (2), particularly 18-crown-6 (**1**) and its derivatives. The crystal structures of **1** and other chorands (**3**) show that they do not contain cavities because one or two methylene groups turn toward the gener-

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al center of the molecule to fill potential intramolecular voids. The crystal structure of 18-crown-6- K^+ (2) shows that the complex contains a cavity formed and filled by the potassium ion during complexation. Other chorands behave similarly (3).

Although less conformationally mobile than the chorands, Lehn's cryptands (4) also fill their own cavities when not complexed, and are reorganized by the guest during complexation. The complexation of [2.2.2]cryptand (3) with K^+ provides an example. Crystal structures reveal that two inward-turned CH_2 groups fill the cavity in free host 3 that is occupied by K^+ in 4 (3).

Unlike the chorands or cryptands, whose cavities are developed by the complexing guest, the spherands contain cavities in their uncomplexed state which become filled upon complexation (3, 5). Thus the spherands are rigidly organized for complexation during their synthesis rather than during their complexation. In spherand 5, the six oxygens are octahedrally arranged with their 24 unshared electrons lining a cavity enforced by the rigidity of the benzene rings and by the spatial requirements of the methoxy groups. The ring system inhibits all but small rotations about the aryl-aryl bonds. The cumulative effect of three methyls protruding from each face of the best plane of the macroring, coupled with the flanking benzene rings, prevents all but small rotations about the Ar-O bonds (3, 5). In projection, formulas 5 and 6 are shaped like snowflakes.

Host 5 readily complexes Li^+ and Na^+ and is the strongest known binder of these ions (6). Other ions such as K^+ , Rb^+ , Cs^+ , Mg^{2+} , and Ca^{2+} are completely rejected by 5. Since no electron pairs on the oxygens of 5 can turn outward, ions are either fully complexed by encapsulation or not complexed at all. Thus 5 shows very high structural recognition in complexation. The crystal structures of 5, 6, and sodiospherium complex 7 (not shown) are drawn in 8, 9, and 10, respectively. Clearly visible are the enforced cavity in 8 and the filled cavities in 9 and 10 (5). The cavity diameter in 8 is 1.62 Å, the Li^+ -filled cavity diameter of 9 is 1.48 Å, and the Na^+ -filled cavity diameter of 10 is 1.75 Å. Thus when 5 becomes complexed to form 6 or 7, very little reorganization occurs. In Corey-Pauling-Koltun (CPK) molecular models (7), the metal ions of 6 and 7 are barely visible because they are buried in a skin of C-H bonds.

A measure of the importance of preorganization to complexation is found in a comparison of the binding free energies

of spherand **5** with those of its unorganized open-chain relative **11**. Compound **11** differs constitutionally from **5** only in the sense that two hydrogen atoms terminate the chain of **11** at the point where an aryl-aryl bond completes the ring system of **5**. Whereas spherand **5** has a single conformation organized for binding, compound **11** has 1024 conformations, only two of which provide the octahedral arrangement of oxygens needed for fully cooperative binding. In chloroform at 25°C, spherand **5** binds sodium picrate by > 13 kilocalories per mole more, and lithium picrate by >> 16 kilocalories per mole more than does **11** (6). Normally, the anisyl unit of **5** and **11** is regarded as a poor ligand for binding metal ions.

Larger Cavitands That Contain Moving Parts

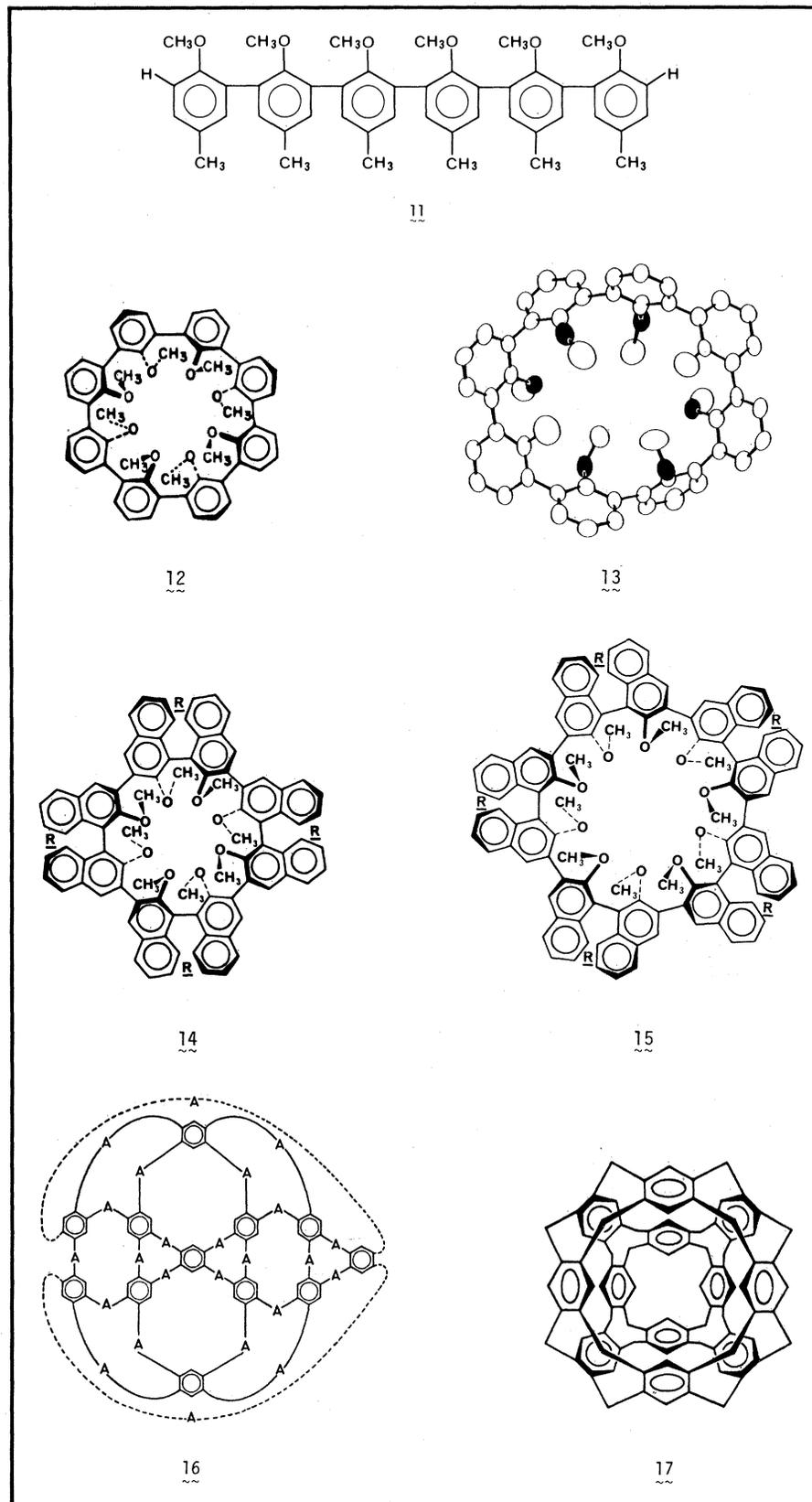
Collar-shaped cavitands have been prepared whose enforced cavities have variable shapes and sizes because they contain inward-directed, mobile substituents. The most studied example is spherand **12**, whose eight oxygens have an enforced, square antiprismatic arrangement. The methyl groups of **12** are much less congested than the corresponding methyls of its smaller analog, **5**. As a result, each methyl in **12** can turn inward toward the center of the cavity, or away from the center between the oxygens (as in the drawing of **12**), thus extending the cavity. In molecular models of **12** with all eight methyl groups turned inward, the cavity is cylindrical and is lined by the hydrogens of the eight methyl groups. The cylinder has a diameter of about 3 Å and a length equal to that of diacetylene (~ 8 Å), whose model just fits into the cylinder. With all the methyl groups facing outward, the molecular model of **12** has a cavity just large enough to accommodate a model of chair cyclohexane. A sphere with the diameter of Cs⁺ (3.4 Å), when inserted in this model of **12**, barely reaches the eight oxygens when the aryl-aryl dihedral bond angles are minimized (8).

The crystal structure of **12** is shown in **13** (9). As expected, the eight oxygens have an alternating up-down arrangement. Of the eight methyl groups, two that are adjacent and the two that are opposite these extend inward, two others opposite one another turn upward, and the remaining two, which are also opposite, turn downward. The resulting cavity is egg-shaped, ~ 4 Å in its longer and ~ 2.5 Å in its shorter dimension (9).

At room temperature, the proton nuclear magnetic resonance spectrum of **12** shows a singlet for its methyl protons, which indicates that the methyls rapidly equilibrate between their possible positions. Such flexibility allows this host, while rigidly maintaining a cavity, to

vary the size, shape, and lining of that cavity, depending on the size, shape, and surface polarity of the guest.

Spherand **12** complexes cesium picrate in chloroform with a binding free energy of 11.8 kcal mole⁻¹. This is 4 kcal mole⁻¹ greater than the binding free energy ob-



served for **12** complexing potassium picrate and 6 kcal mole⁻¹ greater than for **12** complexing lithium picrate. Probably all eight oxygens ligate Cs⁺ simultaneously but cannot reach the smaller ions (9).

Spherands **14** and **15** have also been prepared (10). They are composed of chiral binaphthyl units and possess *D*₄ and *D*₅ symmetry, respectively. In molecular models, **14** resembles **12** except that the dihedral angles within the binaphthyl units of **14** must be substantially greater than those within the biphenyl units of **12** (3). Consequently, the enforced cavity of **14** must be larger than that of **12**, which explains why **12** binds cesium picrate less well (by 3.5 kcal mole⁻¹) than does **14**. Host **14** crystallizes with 1 mole of cyclohexane (10). A molecular model of cyclohexane neatly occupies the cavity of a model of **14**.

However, a crystal structure of the complex is not yet available.

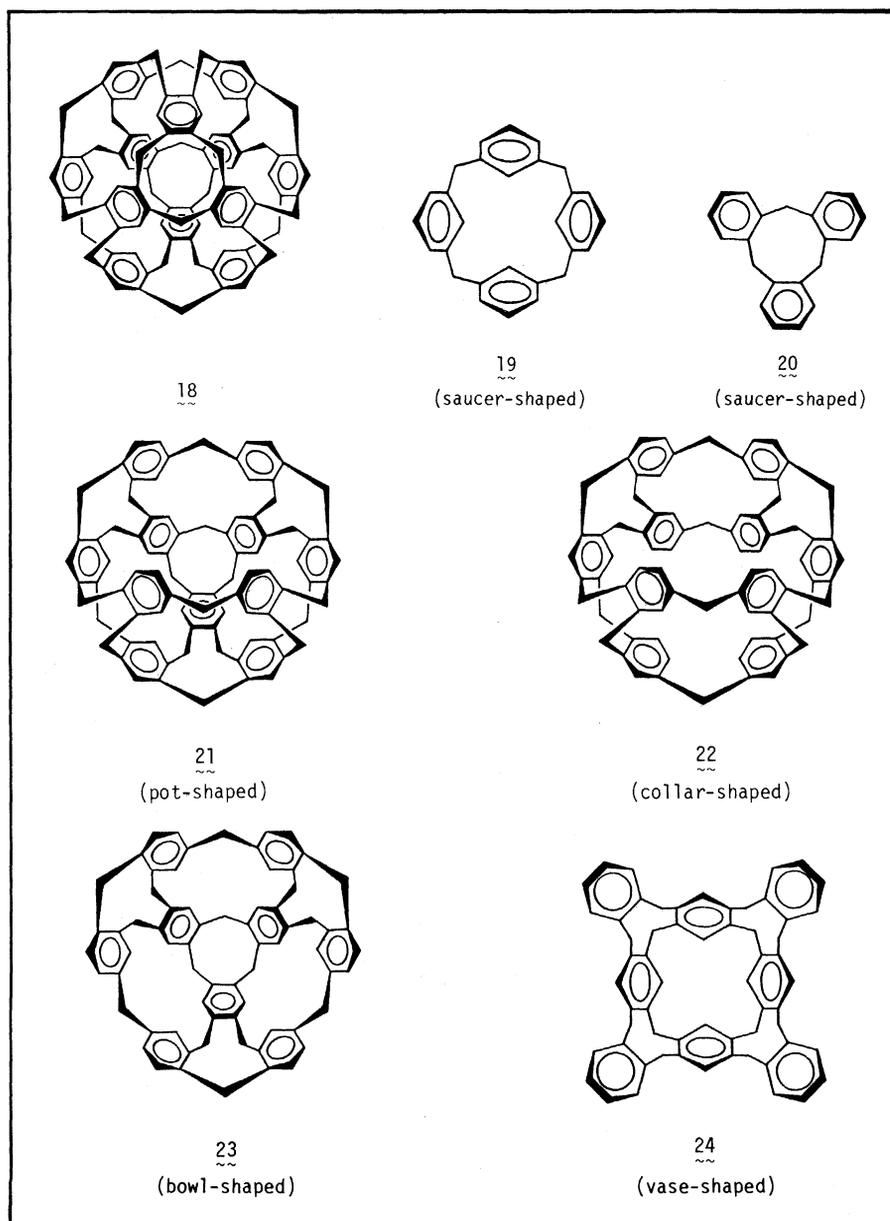
In models, larger spherand **15** possesses an enforced arrangement of oxygens complementary to the ten hydrogens of ferrocene. With all the methyl groups of the host turned outward, a model of ferrocene beautifully fills the minimum cavity available, with each of the ten guest hydrogens touching an oxygen of the host. The model dimensions of the cavity of this conformation range from about 6 by 8 Å to about 7.2 by 8.4 Å, depending on the aryl-aryl dihedral angles. With all of the methyl groups in the model turned inward, the cylindrical cavity is about 4.8 Å in diameter and 7.2 Å in length. A model of chair cyclohexane nicely fills this cavity. The complexing properties of **15** have not yet been examined.

Approaches to a New Family of Cavittands

Hosts are yet to be prepared whose cavities can imprison simple organic compounds. These hosts suggest a variety of interesting questions. (i) Can the closing of the shells of such cavittands be templated by solvent or by solvated ion pairs? (ii) When organic (or inorganic) guests are encapsulated by such cavittands, how do the physical properties of the complex differ from those of the host and guest taken separately? (iii) What kinds of organic reactions can be carried out on encapsulated guests? (iv) Can cavittands be prepared with "pores" in their "skins" that allow the entrance and departure of certain guests from their interior, but forbid passage to others? In other words, can cavittands be made that resemble cells? (v) What types of synthetic strategies are required to bring such cavittands to hand and to make their solubility properties manipulable?

Examination of many possible structures by use of molecular models led us to prototype structure **16**, in which A stands for simple bridging groups such as CH₂, O, S, NH, C=O, CH₂-CH₂, O-CH₂-O, *o*-C₆H₄, *m*-C₆H₄, and *p*-C₆H₄. Such compounds are close to being spherical, and their parts are rigidly distributed in three dimensions. In order to show their bonding sequences, we resort to Mercator projection formulas such as **16**. Gerhardus Mercator was a Flemish geographer who in the 16th century invented the Mercator projection maps of the world for navigation. The spirit of our use of a drawing such as **16** is that it is useful for molecular navigation.

A model of **16**, in which each A is a CH₂ group, is almost strain-free. The model is spherical in shape, about the size of a small melon, and has a cavity about the size of a large orange. It contains 12 benzene rings and 24 CH₂ groups, and each benzene ring has two hydrogens *para* to one another. Formulas **17** and **18** are different representations of this hypothetical compound, which is composed of two kinds of concave units (**19** and **20**) that repeat on the surface of the sphere. Unit **19** is composed of four *meta*-attached benzenes, and **20** of three *ortho*-attached benzenes, each linked through CH₂ groups. In **17**, the viewer looks into the sphere through the center of an expanded **19** unit; in **18**, through the tiny opening of a greatly expanded **20** unit. In models of the structure, these two different kinds of holes in the skin of the sphere are very small. Only those described by the **19** units are



large enough to allow passage of the smallest of chemical entities, such as e^- , H^+ , H_2 , or Li^+ .

Removal of one or more benzene units with their attached CH_2 groups from models of **18** (or **17**) produces simpler cavitands, with ample room for entrance to and escape from the cavities by guests. For example, omission of the benzene located at 12 o'clock in the drawing of **18** along with its four attached CH_2 groups gives a pot-shaped entity. Formula **21** represents the resulting structure, with the viewer looking into the "pot" off center from its top. Omission of the benzene located at 6 o'clock and its four CH_2 groups from **21** gives **22**, which is shaped like a collar. Elimination of the top three benzene rings and their attached CH_2 groups from **18** results in **23**, which is bowl-shaped. If the top four benzene rings and their attached CH_2 groups are subtracted from **17**, vase-shaped **24** is produced. Extension of such processes ultimately produces **19** or **20**, which in their concave conformations are saucer-shaped.

Formally, we have shown how hypothetical molecules with the shapes of spheres, pots, collars, bowls, or vases can be constructed from assemblies of saucers, which in turn are constructed from three or four benzene rings and methylene groups. How close have organic chemists come to preparing these compounds or ones like them?

Derivatives of simple units **19** and **20** have been reported, and are easily prepared. For example, Gutsche *et al.* (11) reported that treatment of 4-*tert*-butylphenol with formaldehyde and base gave **25**. The compound equilibrates between a number of different conformations, only the saucer-shaped one of which has been formulated. The other conformations have been eliminated by converting all of the aryl-OH to aryl-OSi(CH₃)₃ groups, which are too large to pass through the center of the ring (12). The authors call such compounds calixarenes (11, 12).

Following the lead of Erdtman *et al.* (13), Högberg (14) reported that resorcinol and acetaldehyde in an appropriately acidic medium produced stereoisomerically pure **26** in 57 percent yield. This compound was found to exist as an equilibrating mixture of two conformations, only one of which has been formulated (14). By treating **26** with bromine and the tetrabromide product with base and $ClCH_2Br$, we closed four rings to give **27**, which was converted to **28** through metallation and carbonation (15). Both **27** and **28** can exist only in the shallow bowl conformation shown be-

cause of the constraints of the multiple ring systems.

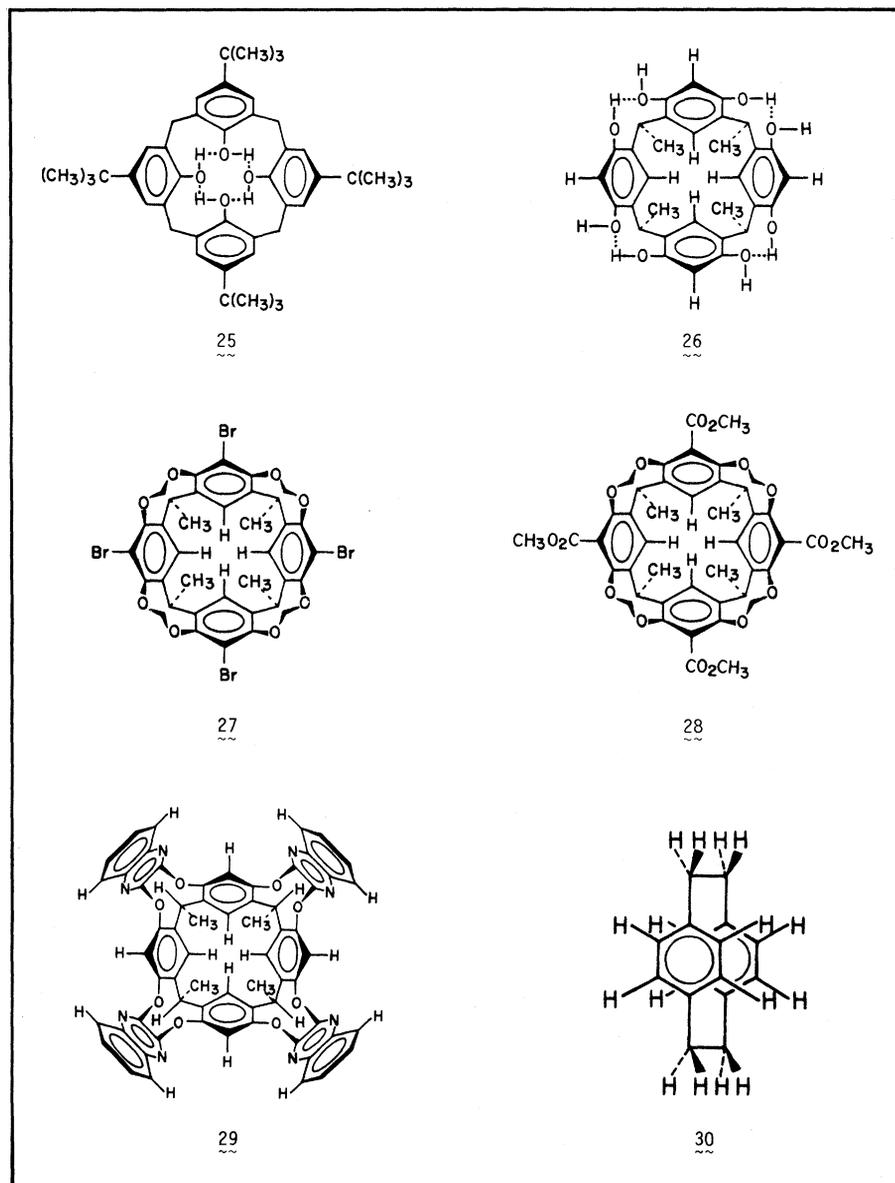
Compound **26** also served as our starting material for the construction of the tall, vase-shaped compound **29**. When mixed with four equivalents of 2,3-dichloro-1,4-diazanaphthalene and excess potassium hydroxide, **26** was converted to **29** by closing four new rings (15).

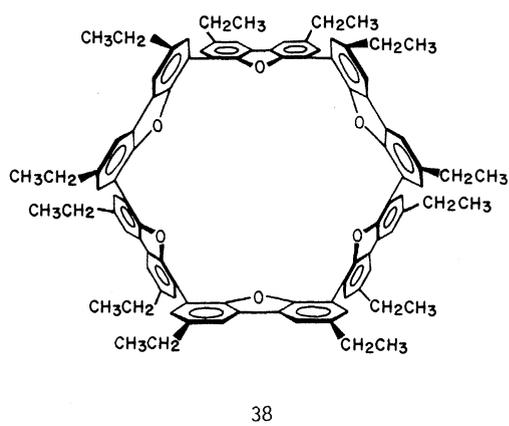
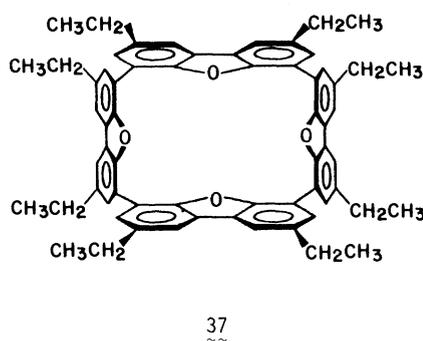
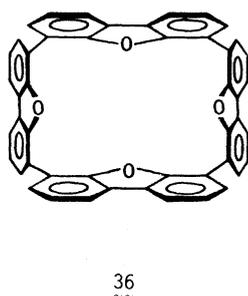
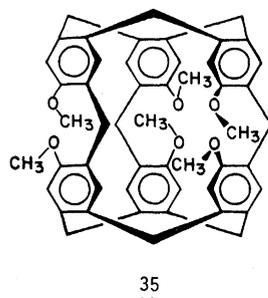
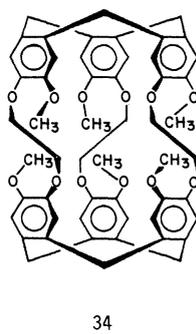
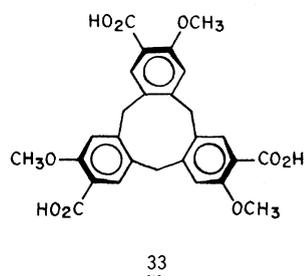
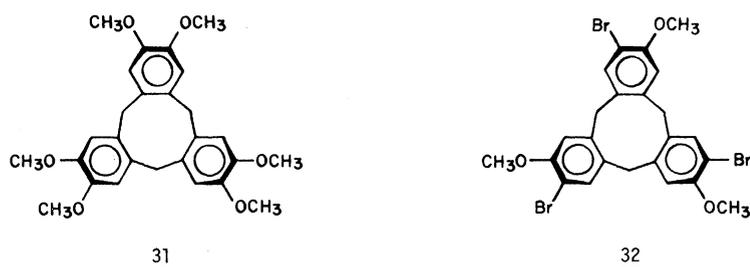
Molecular models and proton nuclear magnetic resonance spectral measurements indicate that **29** exists in either the compact structure drawn or an extended structure. At 25°C and above, **29** is exclusively in the compact structure in which the four diazanaphthalene groups occupy planes perpendicular to the plane of the eight oxygens. At -100°C and below, the compound exists exclusively in the extended structure in which the four diazanaphthalene groups occupy planes more closely parallel to the plane of the eight oxygens. As a result of their

drastic differences in shape, the two structures have different numbers and kinds of solvent-solute interactions, and consequently their relative stabilities are very temperature-dependent. The molecular model of the compact structure has a cavity of sufficient size to contain one model of [2.2]paracyclophane or 12 models of water (15).

The hexamethoxy derivative of **20**, cyclotrimeratrylene (**31**), has been identified by Erdtman *et al.* (13) and Lindsey (16), and several studies have shown that the ring system of **31** exists only in the saucer conformation drawn (16). The compound is made by treating veratrole with formaldehyde and acid (16). We have found that treatment of 3-methoxy-4-bromobenzyl alcohol with acid produces analog **32**, which on metallation and carbonation gives **33** (17).

These three saucer-shaped units and their analogs provide good starting





points for the syntheses of a variety of cavitands. An example is cavitand **34**, whose elegant synthesis has just been reported by Gabard and Collet (18). Compound **31** is chiral and has D_3 symmetry. One of our target cavitands is **35**, which in molecular models must be chiral and has D_3 symmetry.

The sizes of the cavities and perforations in molecular models of **34** and **35** provide interesting comparisons. Experimentally, cavitand **34** crystallizes with one molecule of chloroform, which escapes while a mass spectrum is being taken (18). In models, the gaps in the skin of **34** are just barely large enough in the most advantageous conformations to allow entrance or egress of a single molecular model of chloroform. Up to six molecules of water (in models) can be inserted with ease into the cavity of a model of **34**. The cavity of a model of **35** can contain only one molecular model of water. The largest organic compound whose model can be encapsulated by **35** is CH_4 . The holes in the skin of a model of **35** are too small to allow either H_2O or CH_4 to enter or depart from cavity without severe strain. However, models of H_2 , H-F , or LiF can enter and depart without much difficulty.

Cavitands with Rectangular or Hexagonal Cross Sections

Examination of molecular models of possible cavitands containing rigid clefts led to the design of compound **36**. It is composed of four dibenzofuran units bound directly to one another in a cycle. Since these units are rigid and planar, the model has only a low order of conformational freedom, which can be exercised by rotating the aryl groups a few degrees around all of the aryl-aryl bonds in concert with one another. The largest cavity in models of **36** has a rectangular or square cross section. The compound belongs to the point group D_{2d} . The overall shape of the model is that of a high western saddle, and it contains two long, cleft-shaped cavities approximately 10.8 Å long, 3.4 Å wide, and 4.3 Å deep. Attempts to prepare **36** led to material that, although sublimable at very high temperatures, was essentially insoluble even under severe conditions in all solvents tried. To increase the solubility we prepared compound **37**, whose eight ethyl groups made it subject to dissolution and purification (19). The compound has been characterized.

Cavitand **38** was obtained as a by-product of **37**. In spite of its high molecular weight (1332), the compound was

easily purified and characterized by ordinary techniques. In molecular models the substance has a sizable enforced cavity whose shape depends somewhat on the dihedral angles between the planes of the attached aryl rings. These six angles vary in concert with one another in a way similar to those in a collapsible wine rack. The largest cavity in models of **38** has a hexagonal cross section. The compound belongs to point group D_{3d} , since it contains a C_3 axis, three C_2 axes, and three mirror planes. The dimensions of the cavity are approximately 11 by 7 by 7 Å. It neatly embraces molecular models of seven benzene rings, one lying in the plane of the six oxygens, three stacked in planes perpendicular to one side of the first benzene, and three similarly stacked on the other side. Alternatively, molecular models of two molecules of *p*-CH₃C₆H₄C₆H₄CH₃-*p* completely occupy the cavity.

The cavity of **38** can partially collapse. Total collapse is inhibited by two sets of oxygens of the dibenzofuran units running into one another. The resulting minimum cavity has an irregular hexagonal cross section. Its dimensions are 11 by 9 by 3.5 Å. This cavity snugly embraces models of four benzenes stacked in specialized ways. The orientations of the ethyl groups affect the cavity sizes in only minor ways. They tend to line the cavity surfaces in the areas not lined by aromatic rings.

Unlike the other characterized cavitands, **37** and **38** are more soluble in toluene and xylene than in chloroform. Molecular model fitting indicates that the space in cavitands **37** and **38** can be more thoroughly occupied by aromatic solvent molecules whose bulk is distributed largely in two dimensions than by those whose bulk is distributed largely in three dimensions, such as chloroform. It will

be interesting to discover whether a general correlation exists between solubility and complementarity in shapes of cavities and solvents. Preliminary results show that both **37** and **38** complex a variety of solvents in the crystalline state.

Envisioned Modifications of Cavitands

Some of the kinds of cavitands whose structures have been suggested here are potential hosts for binding and orienting guests. Others are hydrocarbons that offer only π -electron or relatively weak van der Waals forces to attract possible guests. Complexations involving such hosts are expected to be greatest with water as the solvent and with guests that are also lipophilic. Many of the suggested cavitands could be rendered water-soluble by introduction of several ArSO₃⁻ or ArCH₂N⁺(CH₃)₃ groups appropriately placed in the compounds so that micelle formation is avoided. For example, introduction of eight CH₂CH₂N⁺(CH₃)₃ groups into the framework of **37** in place of the eight CH₂CH₃ groups should provide water solubility as well as opportunities for ion pairing with appropriate guests. Water solubility opens the way for use of hydrophobic binding (solvent liberation driving forces for complexation). Thus both solubility and binding site manipulation are subject to molecular design.

One of the incentives for the exploration of host-guest complexation chemistry is the expectation that organic catalysts of the future will combine binding and orientation with cooperativity between catalytic functional groups. Many of the cavitands suggested here have aryl-hydrogen bonds that are potentially substitutable with catalytic groups such as carboxyl, hydroxyl, amino, or imid-

azole. The direct attachment of such functional groups to aryl rings tends to make their location relatively free of conformational mobility. I believe that structural recognition in complexation and catalysis will depend on the availability of hosts whose cavity sizes and shapes and catalytic sites are subject to a minimum of ambiguity.

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20. I thank the U.S. Public Health Service for grant GM 12640 and the National Science Foundation for grant NSF CHE 81-09532, which supported this research. This article is dedicated to H. Erdtman on the occasion of his 80th birthday.