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Review Article:

Cucurbituril: Supramolecular Perspectives for an Old Ligand

P. CINTAS
Department of Organic Chemistry, Faculty of Sciences, University of Extremadura, E-06071 Badajoz, Spain.

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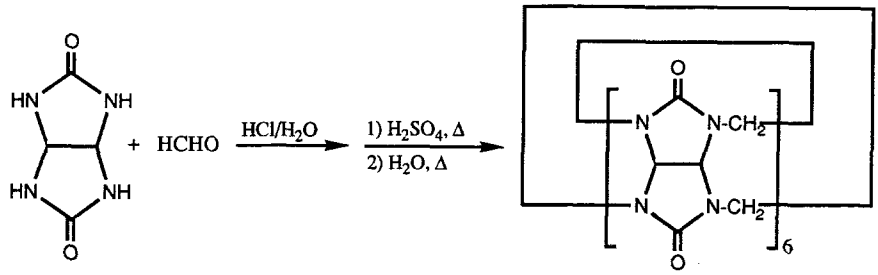
Abstract. This report deals with the preparation and inclusion properties of the synthetic receptor cucurbituril. Although its synthesis dates back to the beginning of the century, complex formation with this ligand has not been studied until quite recently. The most important feature of this macropolycyclic structure is the presence of an internal cavity with a diameter comparable to that of α-cyclodextrin. The rigid cavity of cucurbituril constitutes a rather apolar, lipophilic region, but the portals to the interior contain carbonyl groups as binding sites for ions. Bifunctional and amphiphilic substances can be successfully encapsulated. Similar to other cavitands, inclusion may be interpreted in terms of hydrophobic interactions by displacing solvent water molecules upon complexation, and of ion-dipole attractions with the urea moieties. Further profitable uses of cucurbituril as well as the preparation of attractive analogs are currently under research.

Key words: Cucurbituril, glycoluril, host-guest complexes, inclusion compounds, self-assembly, molecular cavities.

1. Introduction

By the end of this century, it should not be necessary to underline the importance of processes whereby simple building blocks are assembled into large molecules, which often have properties strikingly different from those of their precursors. Structures and properties are determined by noncovalent interactions such as hydrogen bonding, metal-ligand binding, van der Waals, and π-π interactions. Perhaps one of the major triumphs of so-called supramolecular chemistry is the design of imaginative, unnatural, macromolecular assemblies which have an enzyme-like activity, considered in terms of substrate selectivity and stereochemical control. These artificial molecules that Nature does not need, or possibly cannot make, open fascinating perspectives and constitute an exciting challenge to chemists to beat Nature at her own game.

The preparation and properties of cucurbituril illustrate the basic principles of host-guest chemistry, and represent another case of serendipity in chemistry. German chemists who prepared cucurbituril at the beginning of this century by the simple reaction of glycoluril (**1**) with formaldehyde (Scheme 1), did not suspect they had synthesized a novel macromolecular ring [1]. Acidic condensation of glycoluril with an excess of formaldehyde yielded an amorphous precipitate,



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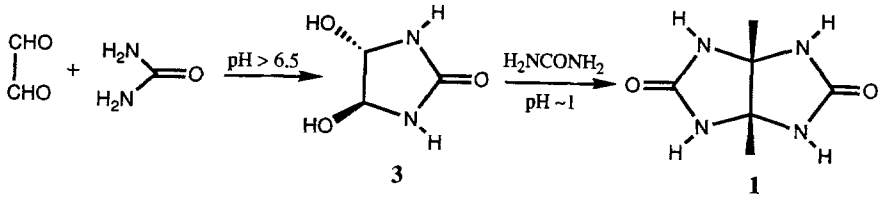
Scheme 1. Synthesis of cucurbituril.



3 1

Scheme 2. Preparation of glycolurils.

insoluble in all common solvents, which suggested a cross-linked, aminal-type polymer. Behrend and his associates [1] treated this solid with hot, concentrated sulfuric acid which dissolved the precipitate. The resulting solution was diluted with cold water and then refluxed, before being allowed to cool to give a crystalline solid (**2**). The authors characterized this compound as $C_{10}H_{11}N_7O_4.2H_2O$, in reasonable agreement with the elemental analysis of **2** as a hydrate.

The starting material, glycoluril, is readily accessible by reaction of glyoxal with urea under acidic conditions (Scheme 2), and alternatively compound **2** could also be obtained from such substances and formaldehyde. The transient monocyclic intermediate (**3**) is only stable at neutral and basic pH values, but at acid pH adds more urea to give the corresponding glycoluril (**1**). By using 1,3-disubstituted ureas (or thioureas), substituted glycolurils can be easily isolated, which constitutes a general route for this type of compounds [2–4].

In the absence of stuctural data for **2**, Behrend *et al.* [1] reported the preparation of crystalline addition products with a variety of metal salts such as potassium permanganate, potassium bromide, ammonium chloride, silver(I) nitrate, chromic acid, potassium dichromate, and dihydrogen hexachloroplatinate(IV), among others. Remarkably, compound **2** proved to be very stable toward such potent reagents, and with a few exceptions, all products were obtained as hydrates according to elemental analyses.

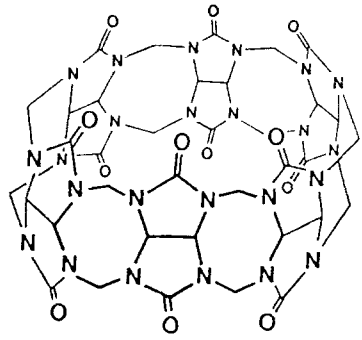


Fig. 1. Tridimensional array of the pumpkin-like structure of cucurbituril, a hollow molecule with two external carbonyl portals.

2. Structure and Self-Assembly

Seventy-six years later, Freeman *et al.* [5] reinvestigated this exciting subject, elucidated the structure of **2**, and recognized that its crystalline complexes with metal salts were indeed inclusion complexes. In following the experimental procedure reported by German chemists, they obtained **2** without difficulty. Spectroscopic data (IR, ^{1}H NMR spectra), along with elemental analysis, were in agreement with a stoichiometry $(C_6H_6N_4O_2)_n.2nH_2O$. The compound, however, was insufficiently volatile for MS molecular weight determination and suitable crystals for X-ray diffraction analysis could not be obtained. Fortunately, satisfactory crystals of the calcium bisulfate complex were obtained from sulfuric acid solution. The material had the composition $(C_6H_6N_4O_2)_3.CaSO_4.H_2SO_4.(H_2O)_{6.5}$.

The organic moiety (**2**) of this complex is a cyclic hexamer of dimethanoglycoluril (Figure 1), as evidenced by further details of the crystal structure [6]. All of its rings are held together entirely by aminal linkages, formed on the constituents formaldehyde, glyoxal, and urea. In the calcium complex, the metal ion is octacoordinated to oxygen atoms of ureido groups, to water, and to sulfate ligands.

Freeman *et al.* [5] proposed the name cucurbituril for the ligand because of a resemblance of **2** in any shape to a gourd or pumpkin, fruits of the family *Cucurbitaceae*, and order *Cucurbitales*. This trivial name has been widely accepted since the proper nomenclature (Chemical Abstracts index) of the macrocycle is too complicated for practical use.

The self-assembly of **2** is still a matter of controversy, although Freeman and his associates [5] reasoned that the condensation of glycoluril with formaldehyde must form a macromolecular product, which would then undergo an acid-induced, thermodynamically controlled rearrangement. It is noteworthy that glycoluril acts as a chemical template rather than as a simple reagent [7, 8]. Glycoluril directs the formation of the product and participates in the macroscopic geometry, although in this case, the template is an integral part of the structure it helps to form.

The authors [5] noted the most remarkable feature of **2**: its internal cavity of $\sim$ 5.5 Å diameter, which is accessible from the exterior by two carbonyl-fringed portals of $\sim$ 4 Å diameter. The cavity within cucurbituril has dimensions equivalent to that of α-cyclodextrin ($\sim$ 5.7 Å). Similar to cyclodextrins, the interior of cucurbituril is a hydrophobic region and therefore a site for possible entrapment of hydrocarbon molecules. Furthermore, the inner cavity is surrounded by carbonyl dipoles which constitute a cation binding site, to which a charged moiety may coordinate, with additional stabilization of dipole interactions by hydrogen bonding to the urea carbonyls. The optimum size of the inner cavity enables the encapsulation of a *para*-disubstituted benzene ring or another guest of comparable size. The *para*-substituted derivatives are able to adapt to the cavity, whereas the *ortho*- and *meta*-substituted counterparts are not bound significantly [9]. Aromatic substituents, however, must be oriented toward the carbonyl portals. These results suggest that cucurbituril is an effective receptor for aliphatic residues, even of rather large molecules, which can adopt shape complementarity with the ligand. Bulky substrates and larger six-membered aromatic molecules cannot be accommodated without some distortion, which results in higher dissociation constants of the complexes.

A second and unique aspect of cucurbituril, compared with cyclodextrins and other macrocycles, is its structural rigidity. This polycyclic assembly cannot conform itself to the shape of guests, and therefore it is expected that complexation occurs with exceptional specificity and with high association constants. The system should be particularly important in the study of hydrophobic effects and other factors of noncovalent binding.

3. Host-Guest Complexes and Molecular Recognition

Cucurbituril belongs to a series of macrocyclic ligands having an inner cavity, and therefore with a potential host-guest binding capacity [10]. According to Cram, this type of compound can be denoted appropriately as cavitands [11]. Similar to other inclusion compounds, the formation of cucurbituril complexes can be detected by various methods. When a guest is included within the cucurbituril cavity, its absorption, fluorescence, or NMR spectra usually change. These spectral changes, induced by the ligand, suggest that the chromophore of the guest is transferred from an aqueous environment to the apolar cavity.

The very low solubility of cucurbituril in water and the uncertainty of its hydration constitute additional problems. It may be recrystallized from dilute acid solutions. Material so obtained has the approximate composition of a tetradecahydrate [12]. Drying leads to variable dehydration depending on temperature [13]. Elemental analysis is in agreement with a decahydrate at room temperature, and FAB-MS analysis suggests a protonated ligand [14].

It is possible to prepare saturated aqueous solutions of cucurbituril at 25 °C, but the solubility cannot be easily determined. Spectral variations are better detected

in aqueous acid solutions. Thus, NMR spectra can be recorded in D_2O/DCl or in 1 : 1 (v/v) D_2O-85% formic acid solution [12]. The latter is an appropriate solvent system and 10% solutions of cucurbituril may be obtained. Moreover, this bulk mixture has a lipophobicity comparable to that of pure water [15, 16].

3.1. ALKYLAMMONIUM IONS

In the preliminary report by Freeman *et al.* [5], they noted that aliphatic amines undergo upfield shifts of 0.6–1.0 ppm in the presence of 1 molar equiv. of cucurbituril (**2**) in acid solution. The authors suggested that this was indicative of formation of inclusion complexes wherein the cationic head of the alkylammonium ion associates with the negative ends of the carbonyl dipoles of **2**, and in which the hydrocarbon chain of the guest penetrates within the cavity.

Seemingly, the interior of cucurbituril comprises a proton-shielding region with respect to the acidic aqueous environment of the bulk solvent, and guest protons located in the internal cavity are expected to exhibit large variations upon complexation. These induced shifts may be attributed to magnetic anisotropy effects of the twelve ureido groups of the host, each of which shows a face to the interior of the cavity.

In further studies, Mock and Shih described in detail the interactions between **2** and alkylammonium ions [9, 12, 15]. Experiments were performed in dilute formic acid solutions, the preferred solvent for cucurbituril. The formation of inclusion compounds was appropriately monitored by ^{1}H-NMR and UV spectroscopies. Addition of increasing amounts of **2** to a solution of an alkylammonium ion causes a diminution of its proton resonances, with a concomitant appearance of new signals. A 1 : 1 stoichiometry was deduced by NMR integration of appropriate peaks of host and guest.

Remarkably, any exchange between free and bound guests is slow on the NMR time scale, since signals from both species can be seen with an excess of alkylammonium ion. This feature enables the measurement of relative binding constants by the competitive complexation method, that is, by allowing two different alkylammonium ions to compete for a limited amount of **2**. Binding efficiencies of a large number of alkylammonium ions were estimated by correlating their dissociation constants to the 4-methylbenzylammonium ion, the reference guest for which the absolute K_d value is known. Thus, a dramatic perturbation in the UV spectrum of an acid solution of 4-methylbenzylamine is observed in the presence of an excess of cucurbituril [12]. Results suggest the encapsulation of the aryl ring within the cavity, and are also supported by NMR data. The spectral changes, induced by cucurbituril, are similar to those observed when the guest is dissolved in a less polar solvent (e.g. cyclohexane), suggesting that the chromophore of the guest is transferred from an aqueous environment to the apolar host cavity. Interestingly glycoluril, which has no cavity, does not induce appreciable UV spectral variations of the aromatic amine in acidic solution, even at a large excess.

TABLE I. Dissociation constants for host-guest complexes of alkylammonium ions with cucurbituril in aqueous formic acid solution.[a]

Guest	K_d	Guest	K_d
$CH_3(CH_2)_2NH_2$	8.2×10^{-5}	$(2\text{-}C_4H_3S)CH_2NH_2$	4.3×10^{-6}
$CH_3(CH_2)_3NH_2$	1.0×10^{-5}	$(2\text{-}C_4H_3O)CH_2NH_2$	8.8×10^{-6}
$(CH_3)_2CH(CH_2)_2NH_2$	2.8×10^{-5}	$H_2N(CH_2)_4NH_2$	6.5×10^{-6}
$(CH_3)_3C(CH_2)_2NH_2$	5.7×10^{-2}	$H_2N(CH_2)_5NH_2$	4.1×10^{-7}
$c\text{-}(CH_2)_3CHCH_2NH_2$	2.7×10^{-6}	$H_2N(CH_2)_6NH_2$	3.6×10^{-7}
$c\text{-}(CH_2)_4CHCH_2NH_2$	3.0×10^{-6}	$H_2N(CH_2)_7NH_2$	2.3×10^{-5}
$c\text{-}(CH_2)_5CHCH_2NH_2$	not bound[b]	$CH_3(CH_2)_3NHCH_3$	9.0×10^{-6}
$C_6H_5NH_2$	1.9×10^{-4}	$CH_3(CH_2)_3N(CH_3)_2$	1.3×10^{-3}
$C_6H_5CH_2NH_2$	3.7×10^{-3}	$H_2N(CH_2)_2S(CH_2)_2NH_2$	2.4×10^{-6}
$o\text{-}CH_3C_6H_4CH_2NH_2$	not bound[b]	$c\text{-}(CH_2S)_2CHCH_2NH_2$	1.7×10^{-6}
$m\text{-}CH_3C_6H_4CH_2NH_2$	not bound[b]	$CH_3NH(CH_2)_6NHCH_3$	5.8×10^{-7}
$p\text{-}CH_3C_6H_4CH_2NH_2$	3.1×10^{-3}	$H_2N(CH_2)_4NH(CH_2)_3NH_2$	7.4×10^{-7}

[a] Taken in part from references [9] and [12]. Reproduced with permission. Copyright 1983 and 1986, respectively, by the American Chemical Society.
[b] Amines mentioned as not bound had greater K_d values, and were not measurable by competitive binding.

Unfortunately, the competitive spectrometric method could not be applied in all cases. Thus, NMR spectra of certain guests were too complicated to assign separated resonances for free and complexed species. On the other hand some alkylammonium ions, such as ethyl- or n-propylammonium ions, exhibited very fast exchange rates and only averaged NMR spectra were observed. Finally in the absence of the characteristic NMR induced shifts, the authors concluded that guests were not bound significantly [9]. The latter is plausible in view of the strict size requirements of cucurbituril. However, weak binding for bulky guests could be determined by indirect evidence, by competing such a guest with a weaker inclusion complex [12].

Table I summarizes the complexing capability of cucurbituril toward a variety of alkylammonium ions. The data suggest, in general, an extremely high affinity between **2** and the corresponding amines, as revealed by the low dissociation constant values. Amines mentioned in the text as not binding have greater K_d values, which cannot be measured with accuracy. It is to be understood that the protonated form of the neutral amines is bound to **2**.

Some factors have a profound influence on the affinity of such ions for **2**, and support a structural model for host-guest complexation. In relation to the guest size, cucurbituril can successfully accommodate substituted polymethylene chains having diameters larger than 5 Å across. Among the straight-chain aliphatic monoamines, the n-butylammonium ion seems to be bound more tightly than its higher or lower n-alkyl analogs.

The strong binding of cucurbituril with α,ω-alkanediammonium ions, with the lowest K_d value at six carbons, should be noted. In the extended conformation of 1,6-hexanediamine, the interatomic distance between nitrogens is coincidental with the axial distance between carbonyl oxygens through the cavity, indicating an optimum NH^+---O=C interaction.

By considering branched and cyclic amines, complexation appears to be effective with an isobutyl group and aliphatic rings up to five carbon atoms. The *tert*-butyl group is too large to be encapsulated, and thus the neohexylammonium ion is bound relatively weakly (K_d 5.7×10^{-2}). Methyl substitution does not alter significantly the stability of complexes except for longer guests. Chain length seems to be therefore a crucial factor. Binding affinity follows a Gaussian-like tendency, with enhancement as the chain length of the guest increases until a maximum is reached followed by diminution (Figure 2). Thus for the n-alkylamines the order of complex stability is $n = 1 < 2 < 3 < 4 > 5 > 6 > 7$, with n-butylamine forming the most stable complex. The result is easly understandable since a chain of four carbon atoms fills approximately the cavity of cucurbituril. Longer guests extend out through the second portal and affect the local solvation of the polar carbonyl groups. There is a similar pattern in the case of alkanediamines, and the maximum is reached with a hydrocarbon chain length of five or six carbon atoms. As mentioned previously the stabilization must be attributed to the simultaneous coordination of both ammonium ions to the carbonyl portals, whereas this possibility is difficult with longer guests. Notably, a short derivative such as propanediamine has a weaker binding (higher K_d value), and this fact presumably indicates that it coordinates externally to a single carbonyl portal without appreciable penetration within the cavity.

Small cyclic hydrocarbons can be encapsulated without difficulty with an optimal complexation for the five-membered ring of the cyclopentanemethylammonium ion. Its inclusion complex is approximately 3.5-fold more stable than is the n-butylammonium ion complex. The insertion of a methylene group between the ring and the ammonium ion of the guest increases significantly the stability of the complex. Thus, cycloalkylmethylamines are more stable than cycloalkylamines of comparable ring size. In the latter case the ammonium cation is displaced toward the center of the cavity of **2** and away from the polar carbonyl groups.

Cyclohexylamine is too bulky to be encapsulated, but a planar benzene ring with van der Waals dimensions somewhat larger than the inner cavity of **2**, forms an inclusion complex. The aromatic ring seems to be the upper limit to the binding capacity of cucurbituril. As previously noted (Section 2) a *para*-disubstituted benzene ring can be accommodated within the cavity, but not the *ortho* and *meta* isomers due to steric hindrance. Even in the case of a *para*-disubstituted benzene derivative, crystallographic data reveal a clear distortion in the cage structure of the host [6]. Complexes with most arylamines are therefore weak (relative to the reference guest 4-methylbenzylamine), with the exception of some five-membered

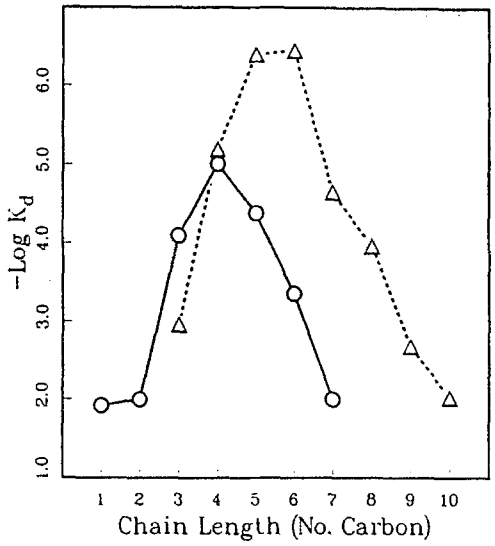


Fig. 2. Dependence of strength of binding to cucurbituril upon chain length for *n*-alkylammonium ions (O-O) and *n*-alkanediammonium ions (Δ---Δ). Reproduced with permission from ref. [12]: W.L. Mock and N.-Y. Shih: *J. Org. Chem.* **51**, 4440 (1986). Copyright 1986 by the American Chemical Society.

aromatic heterocycles such as thiophenemethylamine and furanmethylamine. This can be attributed to a better fit of guests to the cavity.

In stark contrast to cycloalkylamines, the insertion of methylene groups between the benzene ring and the ion decreases the stability of complexes, since the aromatic ring fully occupies the cavity and the chain elongation moves the ammonium cation away from the carbonyl portal.

Inclusion processes with cucurbituril seem to be very sensitive to the nature of alkyl substituents at the aromatic ring. Benzenoid binding is not only specific for *para* isomers, but also for methyl substituents. Thus, no evidence for inclusion was observed in the cases of 4-ethylbenzylamine, 4-ethyl-, and 4-isopropylaniline [12]. Probably, larger alkyl substituents affect more the solvation of carbonyl groups surrounding the cavity than does a methyl group. This extreme specificity of cucurbituril contrasts with those of other cavitands such as cyclodextrins, for which the arene substituent pattern has little influence on binding strength.

The incorporation of additional NH groups at both ends and the center of the hydrocarbon moiety, results in a strong affinity of adducts as a consequence of cumulative interactions of cations with carbonyl groups. The biological polyamine bases spermine and spermidine, have very low dissociation constants.

Apparently, nitrogenated heterocycles do not form inclusion complexes as evidence eperiments with pyrrolidine and pyridine. The protonated nitrogens would reside within the cavity away from carbonyl groups. This result, however, should

be analyzed in terms of competitive binding with a reference guest having a weak association with cucurbituril.

Factors affecting the hydrophobicity of the guest are expected to have a major effect upon strength of binding. Thus an alkylamine containing a thioether linkage associates more strongly than its oxygen counterpart, but less strongly than the alkylamine itself. The authors attribute this result to the greater hydrophobicity of a methylene compared to a thioether group, and the greater hydrophilicity of oxygen relative to sulfur [12]. Interestingly, sulfur-containing five-membered rings have strong association constants with **2**. The greater size of sulfur and the greater C-S bond length with respect to a C-C bond indicate that such heterocycles must have a diameter intermediate between that of a cyclopentane and a benzene ring, which would result in a better accommodation within the cavity.

Numerous thermodynamic and kinetic data have been analyzed to estimate the nature of noncovalent interactions between cucurbituril and alkylammonium ions [12, 15, 17, 18]. Hydrocarbon substituents on the ammonium ion with a proper size, no greater than a *para*-disubstituted benzene, will enter the cavity of cucurbituril displacing solvent water molecules and participating in the noncovalent binding. The hydrophobic effect must contribute to the stabilization of the complexes. The second contribution to the noncovalent interactions is due to the ion-dipole attraction between the ammonium cation and the electronegative oxygens of the urea carbonyls, which surround each portal of the cavity. It should be emphasized that this attraction is largely electrostatic in nature, although hydrogen bonding may also contribute to stabilization of the complex. Thus, the replacement of a terminal hydrogen of an alkylamine with another amino group enhances greatly the association constant, whereas the replacement by a hydroxyl group does not stabilize the complex, although the alcohol function is a good hydrogen-bonding group. Obviously, an alcohol and an alkylammonium ion may be hydrogen bonded with the host that would compete with the polar aqueous medium. The specificity of binding of ammonium ions rests on the fact that they are charged molecules.

It would be plausible to anticipate a tripodal hydrogen-bonding interaction of the ammonium ion with the portal, because there are six carbonyl groups in each portal and therefore hydrogens of the ammonium cation could be bound with alternate oxygen atoms. Probably, this situation is true for small guests such as ammonia or methylamine. For larger guests which fill the inclusion capacity of the host, symmetrical hydrogen bonding forces the rest of the molecule to adopt conformations that perturb host-guest interactions. According to a structural model (Figure 3), only two protons on nitrogen must interact with oxygens and the third lies on the outside. This could be confirmed by substitution experiments. No variations in binding were detected by changing one hydrogen site by a methyl group, while substitution of two N-H bonds diminished the association constant to a large extent.

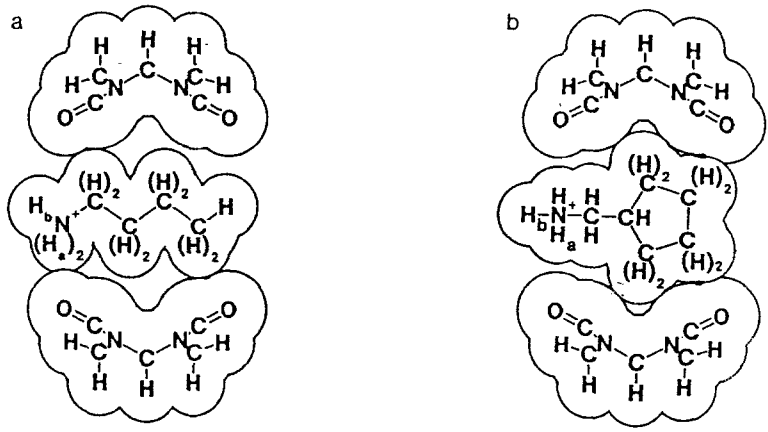


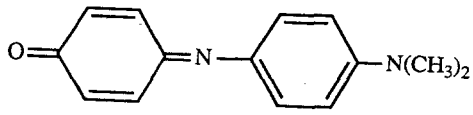
Fig. 3. Conjectured cross-sectional representations of host-guest complexes between cucurbituril and (a) n-butylammonium ion and (b) cyclopentanemethylammonium ion. Reproduced with permission from ref. [12]: W.L. Mock and N.-Y. Shih: *J. Org. Chem.* **51**, 4440 (1986). Copyright 1986 by the American Chemical Society.

3.2. Dyes and Other Organic Complexands

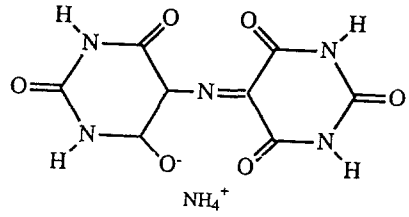
Guests other than alkylammonium ions have been little studied. These cations are indeed excellent ligands for cucurbituril in view of the critical charge-dipole attractions, and provide strong binding constants. However, to date, the complexes have been mostly studied by NMR spectrometry and association constants determined by competitive binding. NMR techniques provide a very useful evaluation of the nature and extent of modifications of the guest, but in contrast, they require appreciable concentrations (usually in the range of millimole) to visualize complexation-induced shifts. This is often hampered by the low solubility of some hosts and guests in water. Inclusion of guests having low association constants with cucurbituril has been observed using UV and fluorescence spectrophotometries, and electrochemical methods [19].

As previously noted, inclusion of benzene derivatives takes place with a considerable distortion of the host structure and gives rise to strained complexes. Five-membered hydrocarbons without ammonium ion substituents would form more stable complexes. Indeed, cyclopentane, tetrahydrothiophene, tetrahydrofuran, and methylcyclopentane showed induced NMR shifts in the presence of cucurbituril, with the higher affinity for the former, although no quantitative K_d values were given [12].

Numerous dyes of appropriate size form stable inclusion complexes with cucurbituril [20–24]. Similar to cyclodextrins, the encapsulation of dyes and pharmaceutical drugs leads to the stabilization of such molecules in an aqueous environment, which constitutes a subject of considerable importance.



Phenol Blue **4**



Murexide **5**

Most dyes are normally rather hydrophobic, and therefore these molecules, or parts of them, can establish stronger interactions with the apolar host cavity. Non-linear dye molecules have to adapt to the rigid cavity of cucurbituril and this pre-organization must cause favorable enthalpic and entropic changes, which increase the stability of complexes. Thus phenol blue (**4**), a linear dye molecule, forms a more stable complex with cucurbituril ($K_a \sim 93\ M^{-1}$) than does β-cyclodextrin (K_a $1.3\ M^{-1}$). The dye decomposes readily in acid solution to *p*-benzoquinone and a *para*-disubstituted aniline. Encapsulation within cucurbituril stabilizes considerably the guest and the rate of decomposition in 0.1 M hydrochloric acid solution is very slow. Consequently, the half-life of phenol blue in that acid solution increases to more than 7 h, while in the absence of any host the dye is destroyed after 3 min, and with β-cyclodextrin after 7 min. In contrast, some dyes are rather polar molecules, relatively soluble in aqueous media. A typical example is murexide (**5**), an ammonium salt with four highly charged oxygen atoms in the middle of the molecule. There is probably some interaction with the polar carbonyl portals of cucurbituril, however, no stabilization of the murexide molecule against acid hydrolysis was observed. This fact rules out the penetration of the dye within the hydrophobic host cavity [24].

Complexation of dyes with cucurbituril has also a technical importance in certain aqueous processes, especially in the textile industry [20–23]. Cucurbituril is effective for removal of dissolved, dispersed, or emulsified dyes from waste waters. The removal of dyes is possible even if the solid ligand is used. This process enables the separation of some dyes, which in solution form only weak or soluble complexes. Interestingly, the complexing agent can be attached to insoluble

TABLE II. Stability constants (log K, M^{-1}) for the complexation of cations with different ligands in water.[a]

Cation	Cucurbituril	18-Crown-6	(2,2,2)-Cryptand
Na	3.69	0.8	3.98
K	3.96	2.03	5.47
Rb	4.41	1.56	4.24
Cs	4.82	0.99	1.47
Ca	4.57	0.48	4.5
NH_4	3.97	1.23	
H	3.02	1.28	9.71

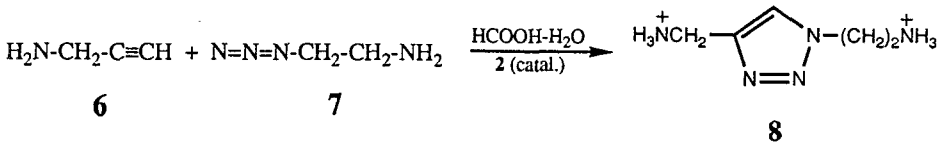
[a] Taken in part from ref. [14]: H.-J. Buschmann, E. Cleve and E. Schollmeyer: *Inorg. Chim. Acta* **193**, 93 (1992). Reproduced with permission. Copyright 1992 by Elsevier Sequoia.

supports such as alumina, silica, or kieselguhr for easy recovery. A complete removal of dye color is usually achieved.

3.3. Metal Ions

The ability of cucurbituril to bind cations has been known since the initial report by Behrend *et al.* [1], who described the formation of crystalline complexes with numerous metal salts. This is now evident in view of the two carbonyl-fringed portals of the macrocyclic structure. This outstanding feature enables the simultaneous complexation of a metal ion and inclusion of an organic molecule within the cucurbituril cavity. In spite of this, there are no detailed studies on the interactions of cucurbituril with metal ions. Recently, Buschmann *et al.* [14] reported the complexation of alkaline cations and other cations in aqueous solutions. Owing to the low solubility of cucurbituril in pure water, a saturated solution of ligand was employed and higher concentrations of metal chlorides. Data from solubility measurements are in accordance with a 1 : 2 host-metal stoichiometry. Because both metal ion binding sites are separated by the rigid cavity, the complexation of the first cation should not influence the binding of the second one, and the values of K_1 and K_2 should be quite similar.

Since the urea carbonyl group is an excellent σ-donor for charge-dense cations, stronger interactions with cations are expected to occur with cucurbituril than with ligands possessing ether oxygen donor atoms such as crown ethers. Furthermore, the rigidity of cucurbituril impedes conformational changes during the complexation, and all donor atoms are located in a plane toward the cavity. Finally, the higher polarity of the carbonyl bond compared with an ether linkage must favor stronger interactions as well. This is true by comparing the stability constants of cations with cucurbituril and 18-crown-6 (Table II).



6 7 8

Scheme 3. Cucurbituril-catalyzed 1,3-dipolar cycloaddition of alkynes with alkyl azides.

On comparing the complexation ability of cucurbituril with the (2,2,2)-cryptand [25], a bicyclic ligand with nitrogen donor atoms, the stability constants are of the same order of magnitude with the exception of the proton and potassium. The ionic radius of the latter nearly matches the cavity radius of the cryptand, thus enhancing the strength of interactions.

4. Catalytic Intermediacy

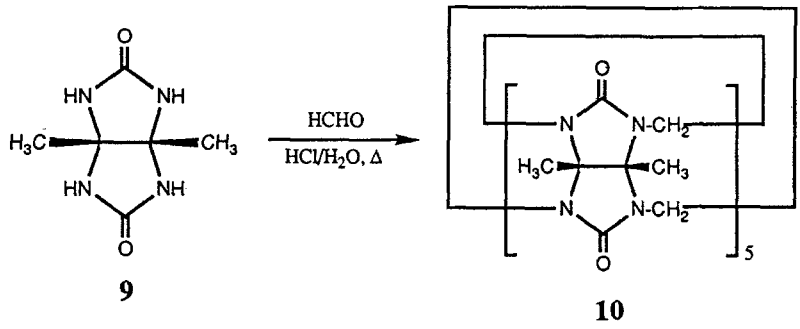
A current challenge of modern chemistry involves the preparation of artificial receptors having an enzyme-like activity. It is well known that cyclodextrins can act as enzyme mimics because they exhibit many of the properties of enzymes, such as molecular recognition in the formation of inclusion complexes and accelerated reactions from these complexes. The cavity of cyclodextrins constitutes a particular microenvironment wherein noncovalent catalyses can be accomplished [26]. It should be possible to anticipate these properties for other cavitands with similar dimensions and hydrophobicity. Cucurbituril is no exception, although only a preliminary study has been carried out on this exciting subject.

Based on the exceptional specificity of cucurbituril for ammonium ions, Mock and his associates [27] performed 1,3-dipolar cycloaddition of alkynes with alkyl azides, both of them substituted with a terminal ammonium group (Scheme 3).

While the cycloaddition reaction proceeds slowly in dilute formic acid to give the triazole **8** plus a regioisomer, the addition of a catalytic amount of cucurbituril (**2**) causes a considerable rate enhancement and renders the reaction regiospecific. The result was attributed to the formation of a transient ternary complex between curcurbituril and compounds **6** and **7**. The apolar moieties of both substrates should penetrate within the cavity facilitating the cycloaddition, and having the ammonium group coordinated to each carbonyl portal.

Interestingly, this host-mediated cycloaddition follows an enzyme-type kinetics, and exhibits substrate inhibition as well. The reaction becomes independent of substrate concentration with sufficient amounts of **6** and **7**, while high concentrations of **6** retard the process.

The data of stability constants seem to suggest that the cavity of cucurbituril is too small to accommodate both substrates without strain. This fact presumably gives rise to the kinetic acceleration rather than the appropriate orientation of reactants within a confined cavity. The authors pointed out an interesting feature of this biomimetic catalysis: despite the fact that both substrates exceed the binding



9 10

Scheme 4. Synthesis of decamethylcucurbit[5]uril.

capacity of cucurbituril, the transition state of the cycloaddition has dimensions comparable to those of an ideal guest for **2**.

5. Future Pursuits: Cucurbit[n]urils

For chemists engaged in supramolecular architecture and for those interested in the potential perspectives of host-guest chemistry, the long-awaited point of this article is the assessment of cucurbiturils as a broad family of ligands well suited to form inclusion compounds.

As noted in Section 1, the substitution of glycolurils enables the preparation of novel and often fascinating cyclic systems. Similar to the preparation of cucurbituril, Mock and Shih reported the condensation of dimethylglycoluril with formaldehyde under acidic conditions [13], but the exact structure of the compound could not be elucidated. The authors suggested a cyclic pentamer or tetramer based on the elemental analysis, and on the absence of inclusion complexes with alkylamines, which would indicate a smaller cavity. In a recent and detailed reinvestigation, Stoddart *et al.* [28] found that the reaction product from dimethylglycoluril (**9**) was indeed a cyclic pentamer (Scheme 4).

Crystals obtained from dilute nitric acid were suitable for X-ray diffraction analysis. Data indicate that, in the solid state, compound **10** deviates slightly from D_{5h} symmetry with a small amount of strain. The diameters of the inner cavity and of the carbonyl portals are about 6 Å and 2.5 Å, respectively. The inclusion of a molecule of nitric acid within the cavity suggests that the oxygen portals can expand allowing the penetration of the guest. Again, electrostatic and hydrogen bonding interactions with oxygen and carbon atoms of two different carbonyl groups must stabilize the inclusion compound.

The authors proposed the name decamethylcucurbit[5]uril for **10**, which resembles the nomenclature system proposed for calixarenes [29]. The number of glycolurils or substituted glycolurils is indicated by the number inside the square brackets; and the number of alkyl or aryl substituents at the ring junction between the two five-membered rings of glycoluril is denoted by a Greek prefix.

In addition to cucurbit[n]uril receptors, other cyclic systems which have no cavity, can also be synthesized from glycolurils [30, 31]. Although this topic lies beyond the scope of this review, the importance of these molecular clefts arises from their description as *supramolecular surfaces*. These relatively rigid and concave molecules can bind guests by means of hydrogen bonding and other simultaneous noncovalent interactions.

In summary, this review illustrates the advantages of the macropolycyclic receptor cucurbituril. The close juxtaposition of hydrophobic and hydrophilic regions in cucurbituril enhances the specificity that is not ordinarily available in other receptors. Likewise, a less rigid host which can more easily accommodate itself to a guest should not be expected to exhibit such a specificity.

The combination of a hydrocarbon moiety along with urea carbonyl groups converts cucurbituril to a unique miniature enzyme model, resembling proteins which contain hydrocarbon side chains and carboxamide dipoles.

Finally, cucurbituril can do more than form inclusion complexes, it can catalyze as well. It is expected that these promising considerations will stimulate an increasing interest in this old ligand that enjoys a new renaissance.

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