Placido Neri · Jonathan L. Sessler
Mei-Xiang Wang *Editors*

Calixarenes and Beyond

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Foreword

In the Spring of 1970 I became, by default, the chairman of the Department of Chemistry at Washington University in St Louis. It was not a happy time to be a chairman; the United States was mired down in a disastrous war in Vietnam, the federal and private support for science was declining, the faculty was dispirited, and the mood of the country was one of anger and despair. It was in this time of national and private discontent that calixarene chemistry was born. Seeking to restore my own faltering research funding I embarked on a quest to build enzyme mimics, focusing on a group of macrocyclic compounds that had come to my attention through an association with the Petrolite Corporation. These were thought at the time to be cyclic tetramers formed by the condensation of formaldehyde and *para*-substituted phenols whose basket-like shape promised to provide interesting mimics for the active site contour of an enzyme. Enthused by this prospect, I sought first to find a simple designation for these compounds to complement the very extended name assigned by *Chemical Abstracts*. Using the word "calix" (from the shape of a Greek vase called a "calix crater") as the prefix and "arene" (denoting the presence of aryl residues in the cyclic array) as the suffix, the word "calixarene" was coined. This proved to be a felicitous choice which, along with the subsequent demonstration of how to make calixarenes of various sizes in good yields, brought these compounds to the attention of the chemical world and set in motion the creation of what is now called "calixarene chemistry". The impressive size to which the field has grown is a nice example of the power of an apt name coupled with a readily accessible source of the materials in question. During the almost half century since the scarcely noticed birth of calixarene chemistry, the efforts of hundreds of talented and devoted researchers have spawned several thousand journal articles, many book chapters, a handful of books and 13 international conferences. This great effort has created a sturdy platform that now provides the basis for the next advances that will take us "***beyond*** calixarene chemistry" into new

and even more exciting territories. To quote Alfred Lord Tennyson, “All experience is an arch wherethrough gleams that untraveled world whose margin fades forever and forever as I move.”

Seattle, WA, USA C. David Gutsche
February 2016

Preface

The word *calixarene* was coined by C. David Gutsche, and appeared in print in 1974, to define the cup-shaped molecules obtained from the condensation of *p*-substituted phenols with formaldehyde. ***Beyond*** this early meaning, the term was then extended to define the carbonious macrocyclic skeleton of [1_n] metacyclophanes independent of their starting materials. In this way, several other macrocycles obtained from different phenolic compounds and different aldehydes came to be included under the calixarene umbrella. In particular, the Högberg macrocycles, obtained from resorcinol and alkylaldehydes, started to be viewed as differently substituted "calixarenes". These compounds are now referred to as *calixresorcinarenes*, *resorcinarenes*, or *resorcarenes*. Similarly, their analogues derived from pyrogallol are now called *pyrogallolarenes*.

Beyond the carbonious skeleton, calixarene-like macrocycles containing sulpur atoms as bridges (*thiacalixarenes*) were also synthesized. They were then quickly followed by others containing oxygens (*oxacalixarenes*), nitrogen (*azacalixarenes*), or other heteroatoms (*heteracalixarenes*). A further addition came with the advent of macrocycles containing more than one bridging atom (*homocalixarenes*, *homooxacalixarenes*, or *homoheteracalixarenes*). ***Beyond*** the benzenoid rings, several others aromatic and heteroaromatics rings, such as naphthalene, pyrrole, pyridine, etc., were also used to construct macrocycles that bear resemblance to calixarenes giving rise to *calixnaphthalenes*, *calixpyrroles*, *calixpyridines*, etc.

Beyond the *meta*-bridging emblematic of calixarenes ([1_n]metacyclophanes), the community now embraces related macrocycles having different bridging positions. These include systems where *ortho*- and *para*-bridging were also used to construct, respectively, *cyclotriveratrilenes* ([1_3]orthocyclophanes) and *pillararenes* ([1_n]paracyclophanes).

As suggested by the title, *Calixarenes and Beyond* aims to give an update on the chemistry of this ever-growing family of macrocycles, including related compounds ***beyond*** any strict or rigorous definition. In addition to their ostensibly similar structural features, the *fil-rouge* connecting the macrocycles discussed in

this book is their chemical relationship, particularly as it relates to their complementary supramolecular properties. With the exception of the newer members, the basic chemistry of this family has been thoroughly investigated, leading to solid and well-established preparative procedures and functionalization methods. However, since the turn to the third millennium, there has been a steady shift to go from synthesis and analysis of basic recognition features to an exploitation of their supramolecular properties in an increasing number of applications that span an increasing broad array of fields.

The present multi-author book, *Calixarenes and Beyond*, provides a forum for summarizing the current state-of-the-art in calixarene-related research. Given the present trends, much of the focus is on properties and applications. However, advances in the synthetic chemistry of calixarenes and related systems are also included. This preparative effort has reached a very high level of sophistication targeting more subtle and specific modifications or syntheses that are more difficult than previously considered tenable. The basic molecular recognition studies have moved from the classical cation and anion binding to an exploitation of these features, and those involving neutral substrates, towards the creation of well-defined multi-molecular assemblies. Many of these latter are endowed with very peculiar switching abilities and provide tantalizing glimpses of a future fully populated with interpenetrated architectures and molecular machines. Investigations in the biomedical field have reached an impressive level of precision and efficiency and provide a window into future real-life applications. A wealth of new materials with smart and marvelous properties has emerged with possible technological applications. As editors we have tried to give a complete picture of this scenario. Of course, we recognize that it is impossible to have a comprehensive coverage in a single medium-size volume. Therefore, we apologize in advance knowing full well that, from a combination necessity and our own shortcomings, some topics have been neglected or not appropriately treated.

The 39 chapters of this book are written by highly active, world-renowned authors who hail from dozens of countries. Their expertise and first-hand understanding of the field provides a wealth of perspectives, while giving specific overviews of particular topics that is second to none. Moreover, the authors' passion for the field and their enthusiasm for their own contributions permeates every page of the book. We thus like to think that *Calixarenes and Beyond* will provide a timely summary of the field—one that is both vibrant in its youth and solid in its maturity—while setting forth a full spectrum of opportunities that will take the field of calixarenes ***beyond*** the limits of our current imagination. Personally, we believe the best is yet to come. This book, we hope, will be the steppingstone to that bright future.

Salerno, Italy — Placido Neri
Austin, TX, USA — Jonathan L. Sessler
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February 2016

Contents

Chapter 1
Introduction and History

David N. Reinhoudt

The 'lock-and-key' concept formulated more than a Century ago by Emil Fischer has guided chemists and biologists to understand molecular interactions, enzyme reactivity and material properties. The same concept has inspired synthetic chemists in their design of synthetic receptors and catalysts.

Building blocks for synthetic receptors that have a rigid 3-D structure play an important role in the synthesis of molecular receptors and enzyme models. Inside the confined space of these rigid building blocks the shape and functionality is very precisely defined.

In this book the chemistry of Calixarenes, rigid vase-like molecules, is described. For their widespread use in supramolecular chemistry, two aspects are crucial. First, their large scale synthesis is relatively simple from cheap starting materials. Second, they can be selectively functionalized at different positions which render them attractive starting materials from a synthesis point of view.

The members of the cyclodextrin family (**1**) are the prototype of building blocks that have a molecular cavity and that can be prepared on large, industrial scale. They are reported in the literature for the first time in 1891 by Villiers [1] as crystalline products that are formed by enzymatic degradation of starch. Schardinger [2] identified the cyclic structure and the enzyme that is responsible for the formation of cyclodextrins from starch, but it was only in 1938 that Freudenberg characterized them as cyclic structures of α-1,4-linked glucose units [3]. In 1965 the first X-ray structure was published of an α-cyclodextrin salt complex that revealed the rigid molecular cavity [4]. The outer rims of the cyclodextrins are decorated with hydroxyl groups which render them more or less soluble in water (Fig. 1.1).

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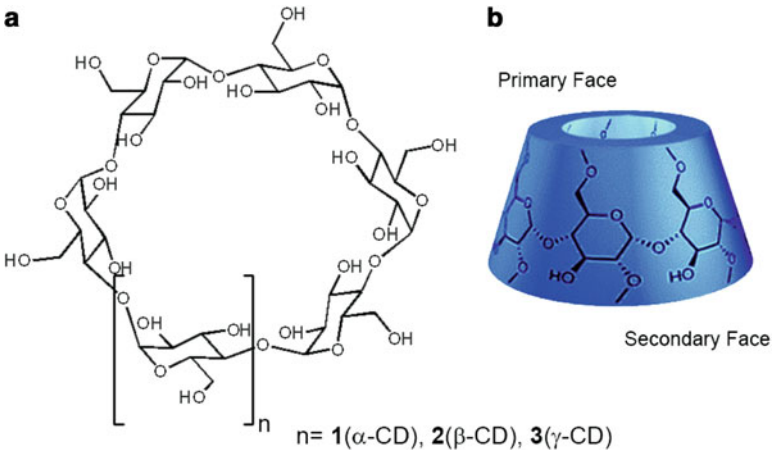


Fig. 1.1 Structures of cyclodextrins (**1**)

In the cyclodextrins the rigid non-polar cavity is formed by the carbon atoms of the glucose units with the hydrogen atoms at C(3) and C(5) pointing into the cavity. The cavity volumes of the α-, β-, and γ-cyclodextrins are 176, 346, and 510 $Å^3$, respectively. In these rigid cavities organic guests can be complexed, the driving force being the hydrophobic interaction between host and guest and the liberation of water molecules from the cavity.

A family of *synthetic* molecules that have a rigid, apolar cavity are the Cucurbiturils (**2**). The history of these condensation products of glycoluril and formaldehyde goes back to 1905 when Behrend and coworkers [5] described that under strongly acidic conditions a product was obtained that was slightly soluble in aqueous acids or bases [6]. Decades later in 1981 Bill Mock and his group reinvestigated this work and isolated and characterized a complex of calcium bisulfate and a cyclic molecule that is composed of 6 glycoluril units linked by 12 methylene bridges [6]. They proposed the name cucurbituril because of the pumpkin (Cucurbitaceae)-like structure. Almost 20 years later Kim and his group in Korea isolated and characterized three other members of the cucurbituril family, CB(5), -(7), and -(8). More recently even higher members of this family have been reported [7] (Fig. 1.2).

There are several similarities between the cyclodextrins and the cucurbiturils. They both come in different ring sizes; they have an apolar cavity and rims lined with polar moieties that render them slightly soluble in aqueous solutions. Second they both have structures with a high degree of symmetry which makes selective functionalization, other than mono or complete, difficult. The most important similarity is that they both can complex organic molecules in their apolar cavity with size- and structure -dependent selectivity. The latter is the main reason that these molecules have become the most important receptors for supramolecular chemistry *in water*, with many practical applications.

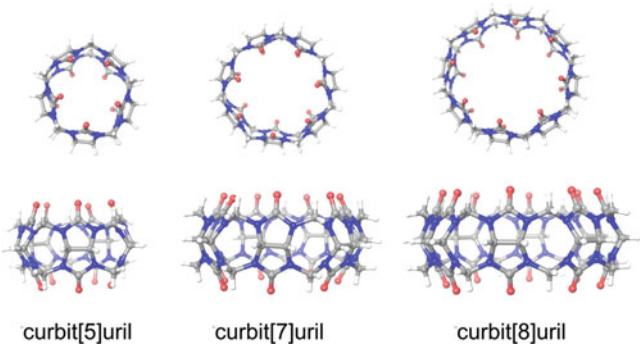


Fig. 1.2 Structures of cucurbiturils (**2**)

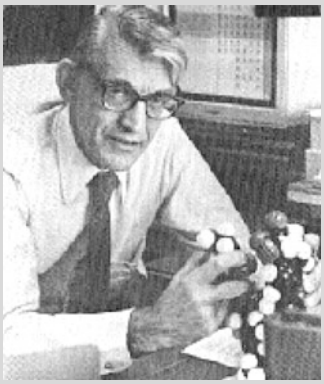
A similar cyclo-condensation reaction as between glycoluril and formaldehyde that gives rise to the cucurbiturils is the basis of a third class of basket-like molecules. In 1872 Baeyer reported the formation of resinous material from the reaction of formaldehyde and phenol which was the basis for the work of Baekeland's discovery of the first synthetic plastic that had practical application, Bakelite [8].

In 1940 a *cyclic* tetrameric structure was proposed by Niederl and Vogel [9] for the acid-catalyzed reaction products of resorcinol with aldehydes. The structural evidence was based only on molecular weight determinations which pointed to a 4:4 adduct of resorcinol and the aldehyde. It took until 1968 before the X-ray analysis by Erdtman, Högberg, and coworkers definitely proved the structure [10]. These molecules became available in larger quantities by the work of Högberg et al. [10].

Soon after the publication of Niederl and Vogel, it was Zinke in 1944 who isolated from a reaction of a *para*-substituted phenol, viz. *p*-1,1,3,3-tetramethylbutyl phenol and formaldehyde a compound that had a molecular weight of 876 in agreement with a *cyclotetrameric* structure [11]. Not much later Cornforth and his coworkers at the Shell – Laboratories in the UK found that the product reported by Zinke was not a single compound but a mixture of cyclic reaction products [12].

This apparent controversy was resolved by the seminal work of David Gutsche who developed reproducible synthetic procedures for the family of vase-like compounds, which in 1975 he called Calixarenes. David became interested in the chemistry of the Zinke compounds because he was a consultant to the Petrolite Corporation that produced surfactants for the oil industry. One of their products was a linear oligomer obtained from reaction of *p-tert*-butylphenol and formaldehyde. Problems in the production process led to a detailed study of the reaction and during the more detailed investigations the Petrolite team rediscovered the crystalline Zinke compound. David's personal interest in these macrocyclic molecules was their possible use as platforms for enzyme mimics, in particular the Aldolase catalysis. Although he never realized such an artificial enzyme, David devoted

most of his academic career to the chemistry of the calixarenes. For a more detailed history of this chemistry the reader is referred to the books published by David Gutsche [8].



The first time I met David Gutsche was in my laboratory in Twente in the 1980s, when he was making a lecture tour in Europe. I had followed the story of the calixarenes since the early 1970s when my colleague at Shell, Sir John Cornforth, gave me samples of the LBC and HBC products that he had obtained from the condensation of p-tert-butylphenol and formaldehyde. David told me about his Petrolite connection and how he became involved. We discussed his ideas on synthetic enzyme mimics of aldolase based on the cone conformer of calix[4]arene and our urease mimic based on uranyl salenophenes. Since that first meeting we have been in close contact. During this period David and Alice moved several times. First from Washington University in St. Louis to TCU in Fort Worth as the Robert A. Welsh Professor of Chemistry, then to the University of Arizona in Tucson, and finally to retire in Seattle. He published many important research papers and several books and book chapters. David is beyond any doubt the godfather of modern Calixarene chemistry who made the major members of the calix family available on large laboratory scale. A condition for the work by many others. In 2002 he received the Izatt Christensen Award in Macrocyclic Chemistry. During the 13th International Conference on Calixarenes, the first David Gutsche Award in Calixarene Chemistry was presented to another pioneer of the field, Rocco Ungaro of the University of Parma.

The ultimate structure proof came in the case of calix[4]arene from the Parma group of Rocco Ungaro, Andrea Pochini an Giovani Andreetti [13] (Fig. 1.3).

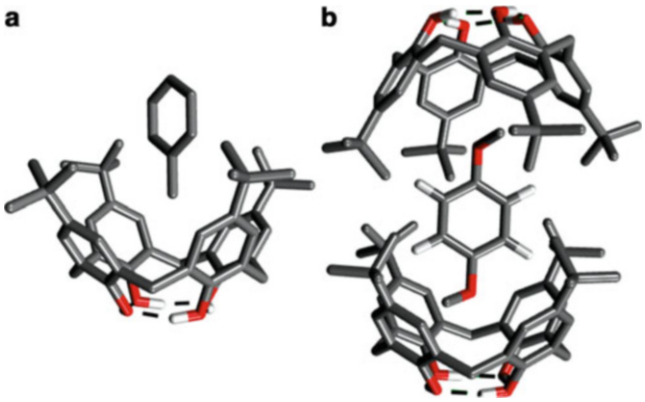


Fig. 1.3 X-ray crystal structures of the *p-tert*-butylcalix[4]arene and (**a**) toluene 1:1 complex and (**b**) anisole 2:1 complex (the two statistically equivalent OCH_3 anisole groups are shown)

Rocco Ungaro was born in the South of Italy, in Anzi. He studied chemistry at the University of Parma where he graduated with Professor Giuseppe Casnati in 1968. He worked with Johannes Smid at the State University of New York in Syracuse (NY) as a post-doctoral research fellow. When he returned to Parma he started in collaboration with Andrea Pochini and Giovanni Andreetti a study on the reactions of the metal templated cyclo-oligomerization of phenols and formaldehyde. In 1979 the Parma group made a seminal contribution to the emerging field of Calixarene Chemistry. The resolution the X-ray structure not only definitely proved the cyclic structure for calixarenes, but also showed the presence of toluene as a guest molecule. My collaboration with Rocco began in 1985 when we were interested in kinetically stable complexes of radioactive Rb^+ ions for the study of renal blood flow. He played a prominent role in establishing the first European network in Supramolecular chemistry.

Many years before Gutsche found effective synthetic procedures for the various calixarenes, Hayes and Hunter [14] reported a stepwise preparation of calixarenes. This method was many years later investigated in Mainz by Herman Kämmerer and by Volker Böhmer [15]. Their method comprises the tedious synthesis of linear precursors and their subsequent cyclisation.

Now there are a number of classes of molecules that are structurally related to the calixarenes, like the oxa-, aza-, and thiacalixarenes, the chemistry of which is described in Chaps. 13–15.

Calix[*n*]arenes have been synthesized by one-step procedures from $n = 4$ to 20 in good to very poor yields. From a practical point of view only the synthesis of the smaller members of this family of macrocycles has been optimized. *p-tert*-Butylcalix[4]arene can be prepared in bulk quantities according what Gutsche has described as the *Modified Zinke-Cornforth Procedure* [16], by reaction of *p-tert*-butylphenol and formaldehyde in the presence of small quantities of NaOH at 110–120 °C. The yield of the cyclic tetramer can be as high as 60 %. At higher concentration of base, under the same conditions, the cyclic hexamer becomes the predominant and even the only product in 65 % yield. This *p-tert*-butylcalix[6]arene can be synthesized in even higher yield (80–85 %) from what Gutsche calls the *Modified Petrolite Procedure*. Through a slightly different *Standard Petrolite Procedure* the *p-tert*-butylcalix[8]arene can be prepared in 60–65 % yield. Two other members of this family ($n = 5$ and 7) have been prepared in modest yields of 10–20 %, the other larger calixarenes up to $n = 20$ have been isolated and characterized but in low yields.

As already mentioned, the step-wise procedures reported by Haynes and Hunter in 1956, were extensively explored in Mainz by Kämmerer [17] and later by Volker Böhmer [18] (Fig. 1.4). In time these multistep syntheses actually preceded the work of Gutsche but never became of practical importance.

Confusion about the stereochemistry of the calix[4]- and [8]arenes already played a role in the work of Cornforth et al. mentioned above. They attributed the different physical properties of the high and low melting fractions (HBC and LBC, respectively) to different conformers of the cyclic tetramer (a calix[4]arene), because on the basis of their space filling molecular models they believed that the phenolic OH groups could not rotate through the annulus. And this could give rise to four different rotational diastereoisomers (Fig. 1.5).

However, Kämmerer showed later by temperature-dependent ^{1}H NMR spectroscopy of what was definitely a cyclic tetramer, that the nonequivalent protons of the bridging methylene groups at room temperature, became equivalent at 60 °C. This was first interpreted by Kämmerer in terms of conversion of two of the Cornforth's diastereoisomers but a few years later [19] correctly interpreted as the mirror image conformational interconversion of the cone structure (Fig. 1.5). In 1985 Gutsche et al. [20] proved that the HBC fraction of Cornforth was the cyclic octamer.

Calix[4]arenes can exist in four different conformations, the cone, partial cone, 1,2-, and 1,3-alternate (Fig. 1.5), which differ in thermodynamic stability. With larger substituents at the phenolic oxygens the interconversion of the different conformers is no longer possible, and different stable conformers can be

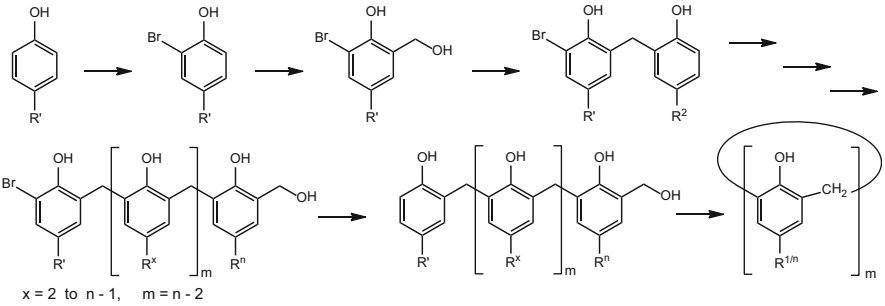


Fig. 1.4 The Kämmerer-Böhmer stepwise synthesis of Calixarenes

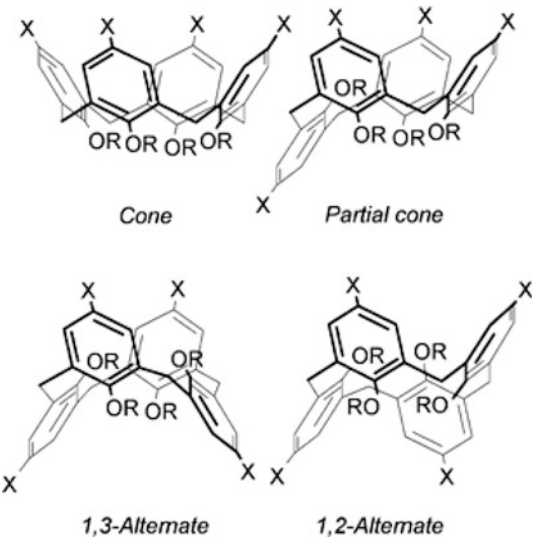


Fig. 1.5 The four different conformers of Calix[4] arenes

synthesized. The larger calixarenes are more flexible and the energy barriers for interconversion become lower.

The stereochemistry of the related calix[4]resorcinarenes is, for the parent compounds derived from condensation of resorcinols with formaldehyde, similar to the calix[4]arenes. In the NMR spectra the bridging methylene groups show up as an AB quartet at low temperature which coalesces at higher temperatures. When they are obtained from higher aldehydes, the stereochemical outcome of the reaction is much more complex. The conformation of the macrocyclic ring can adopt five extreme conformations, the crown, boat, chair, diamond, and saddle. The

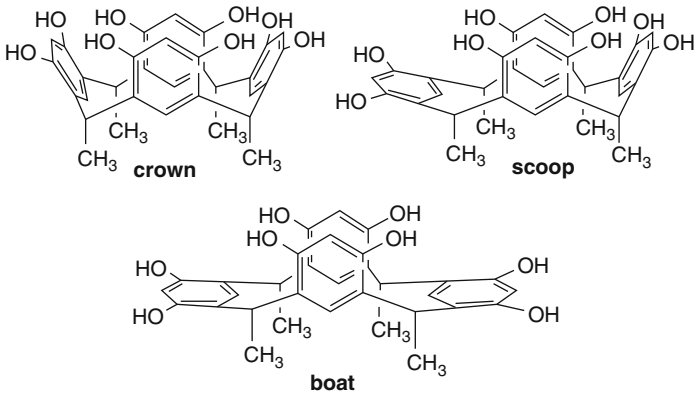
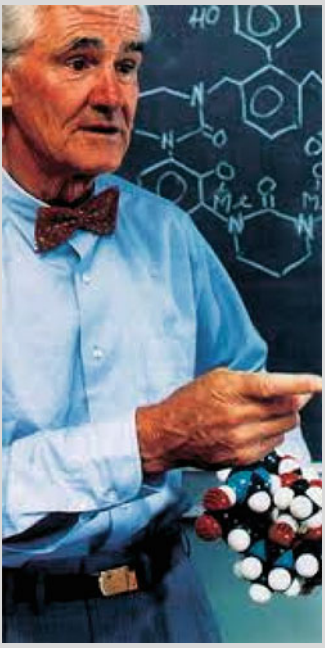


Fig. 1.6 Representative examples of conformations of calix[4]recorcinarenes

relative configuration of the substituents at the methylene bridges can be ccc, cct, ctt, and tct and the substituents can be axial or equatorial. However, in practice only a few isomers have been isolated [21]. Representative examples are given in Fig. 1.6.

In general an efficient synthesis of the vase-like molecules from simple building blocks results in highly symmetrical molecules with a high degree of functional degeneracy. In order to convert them in useful, selectively functionalized building blocks, their symmetry will have to be broken in a selective way. In this respect the calix[4]arenes are unique because they have been functionalized selectively, mainly by alkylation of the lower rim phenolic hydroxyl groups, or selective dealkylation of the *para*-alkyl groups. This ability to modify the chemistry at both rims render them useful building blocks for incorporation in complex chemical structures. Other calixarenes are more difficult to functionalize, although calix[6] arene has been selectively alkylated in the 1,3,5-positions [22]. Functionalization of calix[4]recorcinarenes starts with the selective electrophilic substitution, like bromination, at the four positions in between the hydroxyl groups [23]. Subsequent bridging with bromochloromethane gives the cavitands, highly rigid molecules that have a crown-like conformation with a C_{4v} symmetry. This bridging can also be partly to give useful building blocks for further synthesis (vide infra). This chemistry has been extensively developed by Donald Cram for their use in the synthesis of (hemi)carcerands and cavitands. This field is described in detail by Bruce Gibbs in Chap. 9.



My first meeting with Don Cram was at a conference in Louvain-la Neuve, organized by Leon Ghoseh and Gunther Viehe in the early 1970s. He gave a very inspiring talk, perhaps one of his first on host-guest chemistry. At the diner he played his guitar and sang country and western songs. He accepted to come to visit my labs at Shell and the University of Twente. For me Don became a great source of inspiration and scientific mentor. Many times I visited and lectured at UCLA and at his marvelous home in the canyons we could play with CPK models till late at night. The Nobel Prize in 1987 was not only a personal recognition but was felt also as a recognition for a new field of host-guest chemistry and chemistry beyond the molecule. Cram's contributions are many, but in the framework of this book it is his extensive use of recorcinarenes as the building blocks for molecular containers in which small guestmolecules can be incarcerated.

As mentioned above rigid vase-like molecules are interesting because of their rigid 3-D structure that defines precisely the space inside the cavity. The cavity of the cone of calix[4]arene is small but it can be enlarged by the covalent combination with other components that deepen or close the cavity. In this ways compartments are formed in which guest species can be confined. The calix–crown ether combinations [24] can complex potassium or cesium ions with remarkable selectivities. Combined with terphenyls, 1,3-dialkylcalix[4]arenes give the calixspherands that can complex alkali cations with very high kinetic stability [25]. Combination of

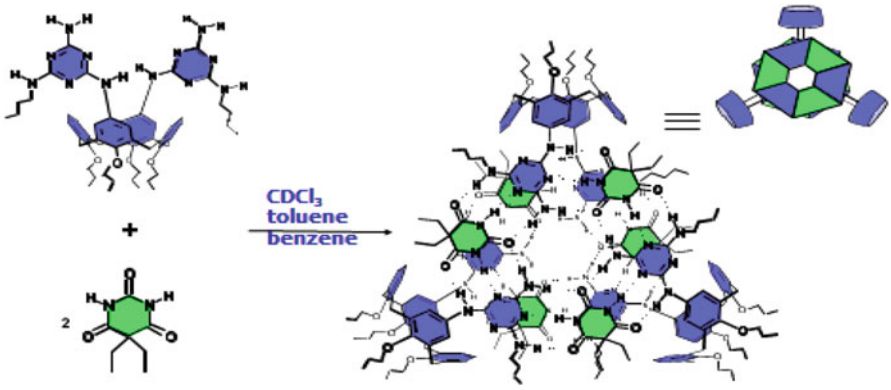


Fig. 1.7 Assembly of calixarenes and barbiturates via H-bonding

calix[4]arene with the recorcinarenes building block resulted in both the 1:1 and 2:2 product, respectively. The latter is a molecule that has a rigid cavity in which solvent molecules are complexed. In the cavity of the first a solvent molecule is incarcerated during the synthesis [26].

Not only the covalent combination of calixarenes with other building blocks leads to products with precisely defined molecular cavities. Julius Rebek and his group at Scripps were the first to explore the non-covalent assembly of calix[4] arenes to dimeric capsules in which small guest molecules can be complexed [27]. Together with the group of Volker Böhmer they have explored this self-assembly in great detail [28]. This chemistry is described by Aragay and Ballester in Chap. 32.

In another strategy aimed at the self-assembly of calixarenes in noncovalent capsules that can complex larger guests, our group at Twente has used the so-called rosette motif that was originally introduced by George Whitesides. By decorating (poly) calix[4]arenes with melamine residues and addition of complementary barbiturates or cyanurates, large H-bonded assemblies with high kinetic stabilities were formed quantitatively [29] (Fig. 1.7). In the inner space of these assemblies discrete trimers of alizarins could be encapsulated [30]. Hexameric complexes of calix[4]resorcinarenes and their (molecular recognition) properties are dealt with by Cohen et al. in Chap. 31.

Another way to assemble calixarenes into defined capsules that have well-defined intramolecular space, is via ionic interactions [31].

Calixarenes have used for many different purposes that are the subject of several of the following chapters of this book. The original motivation of David Gutsche for developing the calixarene chemistry was their use as a concave platform for aldolase mimics and this idea has also been explored extensively by others. Part of this chemistry is described by Casnati et al. in Chap. 26 and by Yilmaz in Chap. 27.

Application areas where calixarenes have had a large impact are sensing and membrane separation technologies, and materials chemistry.

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Chapter 2
Chiral Calixarenes and Resorcinarenes

Michał Wierzbicki, Hanna Jędrzejewska, and Agnieszka Szumna

2.1 Introduction

Differentiation between enantiomers is the immanent feature of biological receptors, most frequently achieved by surrounding of a guest molecule within a well-organized chiral binding site. Calixarenes, the *meta*-substituted cyclophanes (including also resorcinarenes, oxacalixarenes and homocalixarenes), have well-defined, modifiable hydrophobic cavities, that appear to be ideal platforms for the elaboration of artificial receptors. Therefore, the natural consequence of initial studies on host-guest interactions of achiral calixarenes was synthesis and complexation studies of chiral calixarenes. Since the earliest synthesis of chiral calixarene reported by Gutsche in 1979 [1] the field has expanded enormously and evolved in diverse directions. Effective chiral receptors based on calixarenes contributed to a better understanding of biological systems, have found applications in recognition of chiral guests in solution, as chromatography stationary phases, [2, 3] enantioselective membrane carriers [4, 5] and as catalysts [6]. Their potential has also been demonstrated in interactions with biological molecules, [7, 8] protein recognition, [9, 10] formation of gels [11] and antimicrobial activity [12]. A new direction that arose as a result of simultaneous development of nanotechnology and synthetic methodology involves application of chiral calixarenes as building blocks for construction of nanoscale based objects.

The variety of types of chiral calixarenes is exceptionally broad. We will discuss here the main strategies for obtaining chiral calixarenes involving classic approach via attachment of auxiliary/ies with stereogenic centers. We will also focus on

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unique features of calixarenes that enable formation of chiral structures in a non-classic way – through generation of inherent chirality and supramolecular chirality. Many additional examples of chiral calixarenes, particularly peptidocalixarenes and glycocalixarenes can be also found in other chapters of this book.

2.2 Chiral Substituents

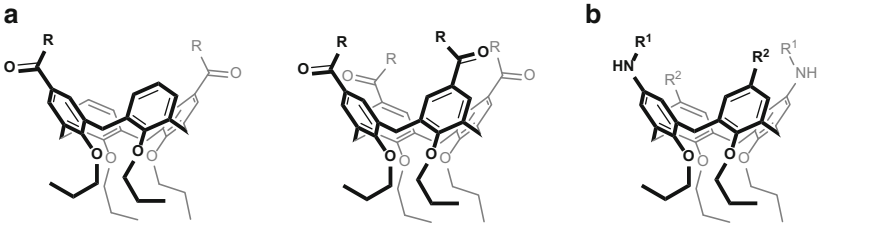
Attachment of chiral substituents to calixarene skeleton is the first, the most straightforward and still the most popular way to construct chiral calixarenes. In 1979 Gutsche reported the synthesis of the first chiral calixarene by attaching camphorosulfonyl group to *p*-*t*Bu-calix[8]arene [1]. Nowadays, attachment of virtually any chiral moiety at the selected position is synthetically feasible. However, some chiral groups, due to their availability and versatility, have been particularly widely exploited, for example amino acid derivatives, peptides, carbohydrates, chiral amines and axially chiral groups.

2.2.1 Amino Acid Derivatives and Peptides

Utilization of amino acids and peptides as chiral modifiers of calixarenes has many advantages: amino acids and peptides are biocompatible, they are natural and versatile sources of chirality and their derivatives are easily available. Additionally, amino acids and peptides have rich chemistry of non-covalent interactions (mostly hydrogen bonds, both in their backbones and side chains) and considerable conformational flexibility. Therefore, they can assist in the recognition processes by forming numerous attractive forces and by adaptation of a binding site by an induced-fit mechanism. On the other hand, the same features that constitute the strength of peptidocalixarenes, render such hosts extremely difficult to design. The non-covalent interactions often form intramolecularly and engage potential binding sites precluding effective guest complexation. When the non-covalent interactions form intermolecularly, they may cause non-specific aggregation that considerably reduces solubility. However, when properly designed, peptidocalixarenes form well-defined molecular cavitands and capsules that exhibit interesting complexation properties.

2.2.1.1 Cavitands and Semi-Open Structures

The direct connection of an amino acid or a peptide to a calixarene scaffold at the upper rim requires the presence of an acid or an amino functionality in a calixarene. Such an approach has been widely studied in the group of Ungaro (for review see ref. [13]). For example, calix[4]arene di- or tetracarboxylic acids have been used to



1a: R = -Ala-Ala-OMe
1b: R = -Ala-OMe
1c: R = -Ala-Ala-$NHNH_2$
1d: R = -Ala-$NHNH_2$

2a: R = -Ala-Ala-OMe
2b: R = -Ala-OMe
2c: R = -Ala-$NHNH_2$
2d: R = -Ala-OH

3a: R^1 = H-Ala-, R^2 = H-Ala-NH-
3b: R^1 = H-Phe-, R^2 = H-Phe-NH-
4a: R^1 = Ac-Ala-, R^2 = Ac-Ala-NH-
4b: R^1 = Ac-Phe-, R^2 = Ac-Phe-NH-
5a: R^1 = Bz-Ala-, R^2 = Bz-Ala-NH-
5b: R^1 = Bz-Phe-, R^2 = Bz-Phe-NH-
6a: R^1 = H-Ala-, R^2 = H
6b: R^1 = H-Phe-, R^2 = H
7a: R^1 = Ac-Ala-, R^2 = H
7b: R^1 = Ac-Phe-, R^2 = H

Fig. 2.1 Peptidocalixarenes: calixarenes modified at upper rims with peptides connected through: (**a**) the *N*-terminus; (**b**) the *C*-terminus

connect peptides through their *N*-termini forming *N*-peptidocalixarenes **1a**–**2d** (Fig. 2.1) [14]. Hydrazides **1c** and **1d** exhibited moderate binding properties towards short peptides, lauric acid and its derivatives and receptor **2b** towards ammonium salts. *C*-Peptidocalixarenes (with peptides connected via *C*-termini), for example **3a**–**7b**, on the contrary to *N*-peptidocalixarenes, display a pronounced tendency to aggregate and form self-complementary interactions [15]. Such tendency has a profound effect on recognition properties. For example, for the interaction of host **6a** with carboxylate anions a higher K_a was observed in DMSO (more polar solvent) than in $CDCl_3$ (less polar solvent) although both are very low. It was attributed to the formation of intramolecular hydrogen bonds in a less polar solvent ($CDCl_3$) that engaged binding sites that consequently hampered guest complexation.

A unique example of a chiral calix[4]arene functionalized at the upper rim with an amino acid is the aminophosphonic acid derivative **8** (Fig. 2.2). Its synthesis using Pudovik-type addition was reported recently by the group of Kalchenko [16]. The synthesis of **8** is a very rare example that utilizes diastereoselective pathways to achieve chiral calixarenes. In most cases chiral groups are simply attached to the macrocyclic ring. Here, the stereogenic centers were introduced on an imine-calixarene scaffold using a chiral auxiliary strategy.

Resorcin[4]arenes, the resorcinol analogs of calix[4]arenes (also called calix[4] resorcinols), were also modified at their upper rims with amino acids or peptides at two possible positions: either at oxygen atoms or at the *ortho* positions. Resorcinarenes substituted with amino acid amides at oxygen atoms have found applications as chiral stationary phases (CSP) in capillary gas chromatography [17]. In particular, exhaustive *O*-alkylation of resorcin[4]arene using L-valine

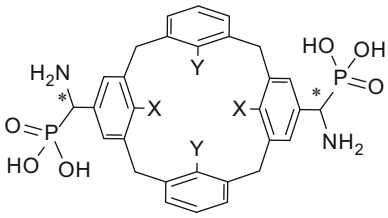


Fig. 2.2 Chiral aminophosphonic acid derivative of calix[4]arene

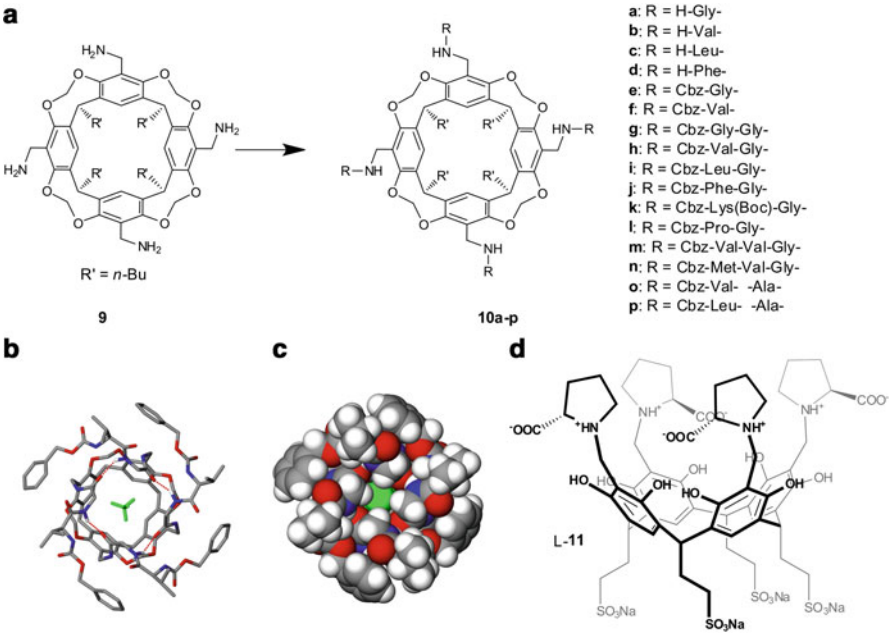


Fig. 2.3 (**a**, **d**) Resorcinarenes with amino acids and peptides attached at the upper rims; (**b**, **c**) suggested molecular structure of cavitand **10h** with complexed acetonitrile molecule (Based on NOE and molecular modeling, courtesy of prof. M. Feigel)

derivative and subsequent chemical bonding to a poly(hydro)dimethylsiloxane gave a chiral stationary phase, named Chirasil-Calix, having good thermal and long-term stability. The central *ortho* position of the resorcinol ring has also been used to attach peptides either using their *C*- or *N*-termini (Fig. 2.3). Simple amino acids, like proline [18] and variously substituted hydroxyprolines [19] were attached to resorcin[4]arenes using single step Mannich reaction to obtain water soluble chiral resorcin[4]arenes, for example L-**11**. Such derivatives were successfully used as NMR chiral resolving agents for chiral substrates possessing pyridyl, phenyl, and bicyclic aromatic rings in their structures. Peptidoresorcin[4]arenes **10g-l** were obtained by attachment of peptides through their *C*-termini to

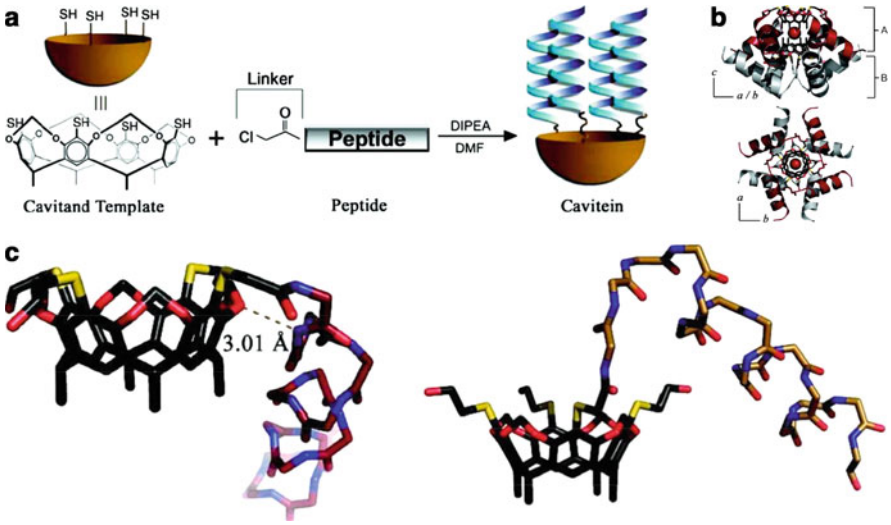


Fig. 2.4 (**a**) Design of caviteins – helical bundles of proteins above the cavitand; (**b**) the X-ray structure of cavitein with helices containing 16 amino acid residues; (**c**) *side* view showing position of a helix in respect to the cavitand (the remaining three of the helices were removed for clarity) (Reprinted with permission from [22]. Copyright 2009 American Chemical Society)

aminomethylated cavitand **9** using classical peptide chemistry (Fig. 2.3a) [20]. Such derivatives form complexes with acetonitrile molecules which are kinetically stable on the NMR timescale. Based on molecular modeling and NOE experiments, the authors suggest that the cavitands are closed at their upper parts by hydrogen bonds that restrict guest's release (Fig. 2.3b, c). Much longer amino acid sequences (up to 16 amino acid residues) attached to resorcinarenes were tested in the group of Sherman. The authors envisioned such peptidoresorcinarenes as a new family of *de novo* proteins called *caviteins* (from the combination of cavitand + protein, Fig. 2.4) [21]. Resorcin[4]arenes were expected to act as rigid organic scaffolds to organize peptide helical bundles or form β-sheets. However, for structures based on thioether linker and sequences promoting formation of α-helices such organization was not achieved. X-ray structure of a cavitein containing 16 amino acid residues at each arm shows the peptides wrapping independently downward around the cavitand bowl (Fig. 2.4b) [22].

Another approach to functionalize calixarenes and resorcinarenes with peptides consists in modification of lower rims. Such a modification requires introduction of all potential binding sites within substituents since derivatives do not take advantage of the inclusion properties of the calixarene hydrophobic cavity. Additionally, the lower rim is much more narrow than the upper rim, and, therefore peptides are arranged in close proximity. As a consequence, it is difficult to avoid adverse intramolecular non-covalent interactions. In fact, derivatives **12** and **13** exhibit

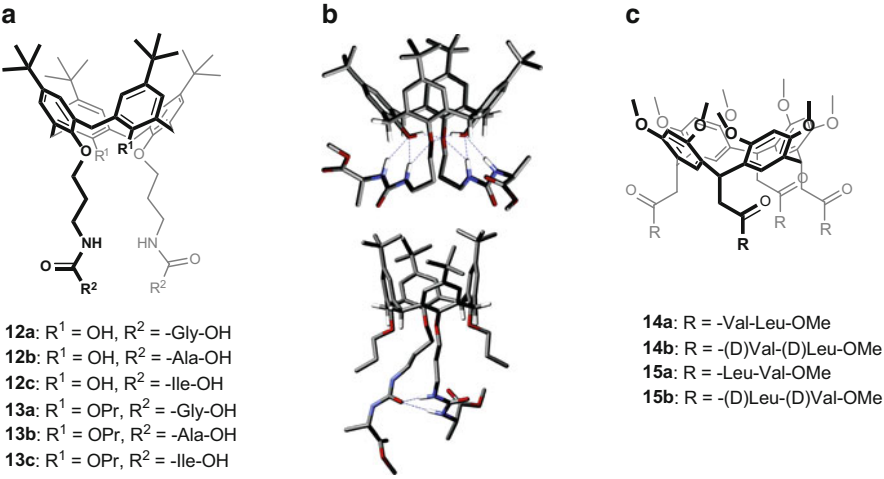


Fig. 2.5 (**a**, **c**) Peptidocalixarenes and peptidoresorcinarenes with peptides connected at the lower rim; (**b**) lowest energy conformations for **12b** and **13b** (Reprinted with permission from [23]. Copyright 2009 American Chemical Society)

intramolecular hydrogen bonding (Fig. 2.5) [23]. Therefore, **12** and **13** display only weak complexing properties towards anions of *N*-acetylated amino acids in $CDCl_3$, and again the K_a values were higher in a more polar solvent, which is a characteristic feature of breaking of the intramolecular hydrogen bonding system during complexation. Even though the association constants were not high, the host was able to recognize enantiomers of selected *N*-acetylated amino acids (max. $K_a(D)/K_a(L) = 4.1$ for **13b**). Resorcinarenes functionalized at their lower rim by amino acid derivatives were studied for their enantioselective guest binding both in solution [24] and in the gas phase (Fig. 2.5c) [25, 26]. Octamethyl resorcin[4]arene tetrafunctionalized at the lower rim with valyl-leucine and leucyl-valine methyl esters (**14** and **15** respectively) are capable of recognizing some dipeptides as guests, both in solution and in the gas phase. Association constants of 2030 and 186 M^{-1} ($CDCl_3$) were found for interaction of **14a** with trifluoroacetates of L-Val-L-LeuOMe and D-Val-D-LeuOMe respectively, indicating a substantial chiral recognition (one order of magnitude).

2.2.1.2 Capsules

Many examples of peptidocalixarenes and peptidoresorcinarenes show a natural tendency of peptidic backbones to form arrays of self-complementary hydrogen bonds that is often perceived as a disadvantage in construction of chiral receptors. However, such arrays, when rationally optimized, can be of great significance for formation of supramolecular aggregates of finite or infinite sizes. For example, calix[4]arenes **16**-**25** with two peptides mounted on the same scaffold using

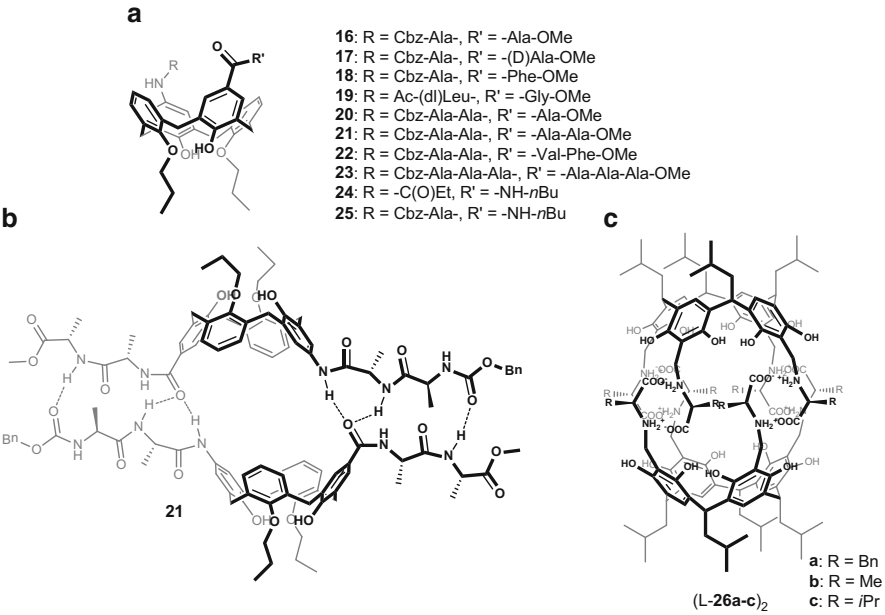


Fig. 2.6 Examples of peptidocalixarenes forming capsules

respectively *N*-terminus and *C*-terminus are able to dimerize by formation of an antiparallel β-sheet structure (for **21**–**23** $K_{dim} = 70–950\ M^{-1}$ in $CDCl_3$, Fig. 2.6b) [27]. Another example is the dimeric capsule (L-**26a**)$_2$ that is made of simple amino acids connected using the Mannich reaction to the resorcin[4]arene scaffold [28]. Capsule (L-**26a**)$_2$ utilizes self-complementarity of ionic hydrogen bonds between amine and carboxylate groups. Hydrophobic side chains of amino acids (e.g., of alanine or phenylalanine) are positioned at the outer surface of the capsule that renders the capsule hydrophobic. In hydrophobic environment, the ionic hydrogen bonds are strong and therefore the capsule is highly stable. Therefore, L-**26a** dimerizes quantitatively already in the reaction mixture and is isolated solely as a dimer (L-**26a**)$_2$. Capsular dimers (L-**26a**)$_2$ and (L-**26b**)$_2$ have two unique features: they are chiral and have all polar groups gathered in their interiors, which makes them very efficient in chiral recognition of small polar molecules [29, 30]. Chirality plays a crucial role in the recognition properties and also in the self-assembly process. For phenylalanine derivatives capsules made of two hemispheres having different chirality, i.e. (L-**26a**)(D-**26a**), are considerably more stable than capsules with two hemispheres of the same chirality, i.e. (L-**26a**)$_2$. However, for valine derivatives, due to the close proximity of branched side chains, homochiral capsules (L-**26c**)$_2$ are not formed at all, while heterochiral capsules (L-**26c**)(D-**26c**) are easily formed [31]. It has far-reaching consequences, requiring a "mutualistic approach" to the synthesis. The hemispheres, L-**26c** or D-**26c**, being constituents of the heterochiral capsules, cannot be simply obtained by chemical