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REVIEW ARTICLE

NMR methods for studying inclusion complexes focused on chiral hosts

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Abstract
Hosts, a key component of inclusion complexes, are cyclic oligomeric compounds containing a cavity in which another component of the complex is bound by non-covalent forces. Chiral hosts are particularly important and interesting because they allow the study of specific intermolecular interactions and molecular recognition. The most important classes of chiral hosts and their physicochemical properties are briefly reviewed. An important part of this Review is the description of selected concepts necessary to understand the properties and behavior of inclusion complexes studied by the most suitable analytical method for studying inclusion complexes—nuclear magnetic resonance.

Keywords Chiral inclusion complexes · Cyclodextrins · Crown ethers · Calixarenes · Cucurbiturils · Pillarenes

Introduction

Over the past few decades, there has been a growing interest in compounds (hosts) that would be able to bind molecules smaller than themselves (guests) in their interior and then, under altered conditions, release the guest. Hosts are cyclic compounds with a toroid, a crown or a bowl shape. The binding of the guest inside the host occurs as a result of the interplay of different types of intermolecular interactions and is further controlled by the ability of the guest to match the shape and size of the host's interior. Macrocyclic compounds play a major role in supramolecular chemistry, especially in the recognition of chirality and molecular encapsulation. Analytical techniques such as spectroscopy and chiral chromatography are used to determine their configuration and enantiomeric excess. These compounds, known for their diverse inclusion patterns and potential applications, exhibit unique chiral properties necessary for selective recognition and molecular binding, helping to design molecules for specific functions such as enantioselective catalysis and chiral separation. Different classes offer distinct structural features valuable for understanding molecular recognition, designing functional materials and developing therapeutic agents. The review highlights their role in the development of fields such as materials science, supramolecular chemistry, and drug delivery systems, underscoring the versatility of macrocycles as molecular scaffolds across scientific disciplines.

The history of discovering the precursors of compounds used today as hosts often dates back to the late 19th and early twentieth centuries. Some of the compounds that are used as hosts today were discovered by accident in the past and were described through the meticulous patience of researchers. Solving their structures took several decades and did not involve NMR, which only emerged as an analytical method in the 1960s. Others of today's hosts were also obtained long ago, but their structures were described relatively recently. It was only after the "host" ability of these compounds was discovered, regardless of the history of their discovery, that hundreds of variants in each group of these compounds were obtained in subsequent years in search of greater selectivity and greater binding strength. In parallel, new types of compounds began to be synthesized, the shape and size of the interior of which expanded the possibility of binding ligands of different sizes and more complex structures.

The first discoveries of cyclic hosts were accidental. Cyclodextrins simply crystallized separately (0.3%) in the

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process of dextrin investigation. The cyclic structure of the first among them was established at the turn of the twentieth century by chemical, optical and X-ray methods [1–11]. The use of them as hosts came half a century later. The first cyclic crown ethers were accidentally derived from aromatic vicinal diols in 1967 by Pedersen [12, 13]. NMR was already one of the methods used to determine the structure of this compound. The calixarenes were consciously synthesized based on previously obtained cyclic polymers of p-alkylphenols with formaldehyde [14, 15]. Their structures and conformational equilibria were monitored with ^{1}H NMR. The first cucurbituril was easily obtained in the third quarter of the twentieth century, repeating an experiment conducted eight decades earlier, but this time describing the product using NMR and X-ray [16, 17]. The pillararenes obtained in the early 2000s have already been intentionally introduced as key players in supramolecular chemistry [18]. Their synthesis was supported by the use of ^{1}H, ^{13}C and variable-temperature ^{1}H NMR.

A broad range of supramolecular systems is stabilized by several non-covalent forces which are largely electrostatic in origin. Among them there are inclusion complexes, proteins binding ions, small organic molecules, or peptides, protein–protein and protein-oligonucleotide complexes, and many others. All these systems are of great importance in many different areas of science and technology including chemistry, biology, pharmaceutical, medical and life sciences. In general, methodologies used in the investigations of the mentioned systems are similar independently of the size of those complexes. Among all classes of supramolecular systems one has to distinguish between macrocyclic compounds per se and the compounds able to incorporate other molecules. Not all macrocycles can be hosts in inclusion complexes specific for the mutual spatial arrangement of components. One of the complex components (guest) is partially or fully hidden in the cavity of the second one (host). The current research on the inclusion complexes is concerned with the determination of stoichiometry and association constants, the various modes and depths of the inclusion into the host cavity, the kinetics of exchange and the enantiomeric differentiation named also chiral recognition. Chirality was recognized as a necessary part of synthetic receptor molecule design and function. Such systems can be efficiently studied by nuclear magnetic resonance (NMR) techniques. Thomas J. Wentzel wrote in preface to his book [19]: *Nuclear magnetic resonance (NMR) spectroscopy represents one of the most common methods employed for the analysis of chiral compounds*.

A number of physicochemical methods are used for investigating the formation of inclusion complexes: microcalorimetry (ITC, DSC), UV–VIS absorption spectroscopy, fluorescence, circular dichroism (CD), Fourier transform infrared spectroscopy (FTIR), high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), ionization mass spectrometry (ESI–MS), and occasionally phase solubility diagrams, solid-phase microextraction, or volatilization [20, 21]. Obviously some methods are better suited to study such complexes than others, and among the non-separation methods NMR spectroscopy is one of the most efficient and widely used because it delivers a wealth of highly reliable quantitative information at the atomic resolution level providing several independent data sets for the evaluation of association constants K as well as an insight into the conformation of the inclusion complexes [22, 23]. Chemical shifts of magnetically active nuclei, especially those routinely detected (as ^{1}H and ^{13}C), constituting host molecules in general and chiral host molecules in particular should not be too broadly dispersed to avoid resonance superposition with NMR spectra of different guests.

Finally, hosts should not only be chiral but also they have to be easily available at high optical purity and not racemize. Among all classes of hosts used at present in supramolecular chemistry solely cyclodextrins and pillararenes are intrinsically chiral and solely the former are obtained in pure chiral configuration by biotechnological processes. The remaining invented host classes are derived by chemical synthesis and their chirality has to be introduced into molecules for a purpose.

The aim of this Review is to provide a general overview of the main concepts describing the formation of inclusion complexes, with particular emphasis on chirality recognition. The most important classes of compounds that are able to accommodate molecules in their interior are presented, with particular emphasis on their molecular symmetry.

Concepts in inclusion complex formation

Any branch of science requires unequivocal definitions of basic concepts and terminology to avoid confusion in communication among researchers. Terminology used in the studies of inclusion complexes is not always unequivocal. For that reason recollecting several essential definitions and terms seems to be useful. They are here supported with illustrative examples.

Host and guest molecules

Are indispensable constituents of inclusion complexes. Hosts contain a cavity or at least concave surface allowing them to accommodate another molecule called guest which fits spatially into the host cavity [24]. Often such a cavity exhibits lipophilic properties, while the outer surface is hydrophilic. Such host properties allow the host to accept partially or completely lipophilic guest molecules which facilitates its dissolution in water [25]. The reverse may also be true. The solubility of hydrophilic guest molecules can be

increased in organic solvents provided that the host cavity is hydrophilic and its outer surface lipophilic [26].

Inclusion complex

Is composed of host and guest molecules stabilized by non-covalent forces which include hydrogen bonding, ionic and dipole interactions, CH-π interactions, polar aromatic interactions, and dispersion forces of the van der Waals-London type [24, 27–29]. Commonly such complex is in a dynamic equilibrium with its free components in solution. The exchange between free and complex guest molecules is mostly fast on the NMR chemical shift time scale (vide infra). Therefore, the observed chemical shifts are the mole fraction weighted averages of the chemical shifts specific for free and complexed guest molecules. Guest and host will be further denoted *G* and *H*, respectively.

NMR titration

In the most common procedure one component of the inclusion complex is gradually added to the system containing a fixed concentration of another component while monitoring an NMR derived parameters (most often chemical shifts) or any other physical parameter that is sensitive to the interactions responsible for complex formation. Elaboration of such data allows the determination of binding constants of the complex [22, 23, 30]. In a chemical titration, the gradually added component with variable concentration, *titrant*, is added to the solution of constant concentration *analyte*. The terms titrant and analyte are not used, however, in NMR titration experiments. Therefore, it will be further assumed that guest concentration is maintained constant while host concentration is variable, except as otherwise indicated.

Stoichiometry

Of inclusion complexes depends on the nature of both guest and host molecules. It has to be determined in the course of the quantitative study of a given complex. Commonly inclusion complexes are built up of one guest and one host molecules resulting in stoichiometry 1:1. Other ratios as 1:2, 2:1, and 2:2 have also been reported [31–33]. Besides binary guest–host inclusion complexes ternary complexes have been observed with a third component that optimizes the fit of the guest in the host cavity [32, 33]. For many years determination of stoichiometry has been done using the continuous variation method [34]. At the end of the twentieth century it has been shown, however, that this method results in ambiguous results in the case of several competing reactions of complex formation [22, 31, 32]. It follows from the authors' experience that the superior approach is to fit titration data to different stoichiometry models and choose the best of them based on statistical tests [35–37]. Detailed discussion and comparison of several methods allowing to determine complex stoichiometry is given in Ref. [22].

Complex formation

Rate quantitatively describes the rate of decrease (increase) of concentration of the substrates (products). If the reaction of complex formation is given by the equation $G + H \rightarrow GH$ the reaction rate is expressed in terms of substrate concentrations $[G]$ and $[H]$: $-\frac{d[G]}{dt} = -\frac{d[H]}{dt} = k[G][H]$, where k is the reaction rate constant. For the reverse reaction of dissociation complex: $GH \rightarrow G + H$ a corresponding equation $\frac{d[GH]}{dt} = k_{-1}[GH]$ is valid with k_{-1}, the reverse reaction rate constant. The order of chemical reaction is defined as the sum of exponents at substrate concentrations. Therefore, the order of the forward reaction $G + H \rightarrow GH$ is equal to 2 while the reverse reaction has 1st order [38].

Binding constant

At equilibrium the rate of complex formation is equal to the complex dissociation and all concentrations $[G]$, $[H]$, $[GH]$ remain constant. Defining binding constant K as a quotient of product to substrate concentrations one obtains $K = [GH]/[G][H]$. This expression determines relation among concentrations of all species at equilibrium. Since $k[G][H] = k_{-1}[GH]$ the equation, $K = k/k_{-1}$ can be derived. Generally, if orders of forward and reverse reactions differ the binding constant is not dimensionless anymore. Its dimension is equal to the molarity (molar concentration) raised to the power equal to the difference of orders of reverse and forward reactions [22, 32, 33].

Binding constant—solvent correction and conversion to the mole fraction standard state

It should be pointed out that binding constants reported in the literature are mostly solvent uncorrected. That is why binding constants K are expressed in units $(\mathrm{mol/dm^3})^n$ where n stands for the difference in orders of reverse and forward reactions. When a complex of 1: 2 stoichiometry is formed, $n = -2$. Solvent correction becomes essential in the case of the interpretation of binding constants in terms of thermodynamic quantities [32, 33]. For dilute solutions the following relation between uncorrected constants K and solvent-corrected ones K_x holds: $K_x = KM_s^{-n}$ where M_s is solvent molarity. M_s may be calculated from the molar mass—M and density—d of a solvent. For instance, $M(\mathrm{D_2O}) = 20.027$ g/mol and $d(\mathrm{D_2O@25°C}) = 1104.4$ g/dm^3 results in $M_s = 55.15$ mol/dm^3. It is noteworthy that K_x is dimensionless.

Stepwise and overall binding constants

If the stoichiometry of the complex is, for example, G: $H = 1{:}2$ the binding constant is given as $K = [GH_2]/[G][H]^2$. Formation of the final complex, however, is a two-step process described by two successive reactions. Appropriate binding constants are: $K_1 = [GH]/[G][H]$ and $K_2 = [GH_2]/[GH][H]$. It is obvious that $K = K_1K_2$. K_1 and K_2 are stepwise binding constants, while K is an overall binding constant [22, 32, 33].

Macroscopic and microscopic binding constants

At the molecular level many guest molecules are too large to be completely included within a host cavity, so the guest may possess two (or more) nonequivalent binding sites. In order to distinguish two possible isomeric 1:1 complexes the notation *GH* and *HG* will be used and the 1:2 complex described *HGH* rather than GH_2. The corresponding binding site scheme is shown in Fig. 1A. The four equilibrium constants κ_i are named microscopic binding constants. They are not independent since $\kappa_1\kappa_3 = \kappa_2\kappa_4$. The complex formation can be alternatively described with three macroscopic binding constants K, K_1 and K_2. The relations among macroscopic and microscopic binding constants are given by: $K = \kappa_1\kappa_3 = \kappa_2\kappa_4$, $K_1 = \kappa_1 + \kappa_2$, and $K_2 = \kappa_3\kappa_4/(\kappa_3 + \kappa_4)$. If the host–guest complex is at a fast exchange regime the microscopic binding constants cannot be determined directly [22, 32, 33]. However, if separate signals of free and bound species can be observed (slow exchange regime) the information retrieved from experimental data allows to determine microscopic binding constants [39] from a single sample with known component concentrations.

Cooperativity

Let us define dimensionless constant $c = \kappa_3/\kappa_2 = \kappa_4/\kappa_1$ Then the scheme shown in Fig. 1A can be rearranged to the scheme given in Fig. 1B. Constant c is named the cooperativity coefficient. Cooperativity characterizes the interaction between the guest binding sites. The binding of a host molecule to one binding site changes the affinity of the other binding sites to the host by induction of a conformation change at the other binding sites. The cooperativity coefficient equal to one points out to non-cooperative binding. Coefficient greater than one indicates positive cooperativity, while coefficient less than one indicates negative cooperativity or anti-cooperativity [22, 32, 33, 40]. It can be determined from microscopic binding constants. However, the cooperativity coefficient can be estimated from the macroscopic binding constants using inequality $c \geq 4K_2/K_1$ [40].

Bimodal binding

Bimodal binding results in the formation of two different complex geometries characterized by different association constants, K_1 and K_2, and two different complexation-induced shifts, $\Delta\delta_{1\max}$ and $\Delta\delta_{2\max}$ ($\Delta\delta_{\max}$ definition–see Complexation induced chemical shift). NMR titration in the fast exchange regime does not allow for the separation of characteristic quantities/parameters of both parallel processes. This situation reminds the case of macroscopic vs. microscopic association constant determination [32, 33]. For 1:1 stoichiometry apparent K_{app} and $\Delta\delta_{app,max}$ resulting from the analysis of NMR titration data are given as:

$$K_{app} = K_1 + K_2$$

$$\Delta\delta_{app,\max} = (K_1\Delta\delta_{1,\max} + K_2\Delta\delta_{2,\max})/(K_1 + K_2)$$

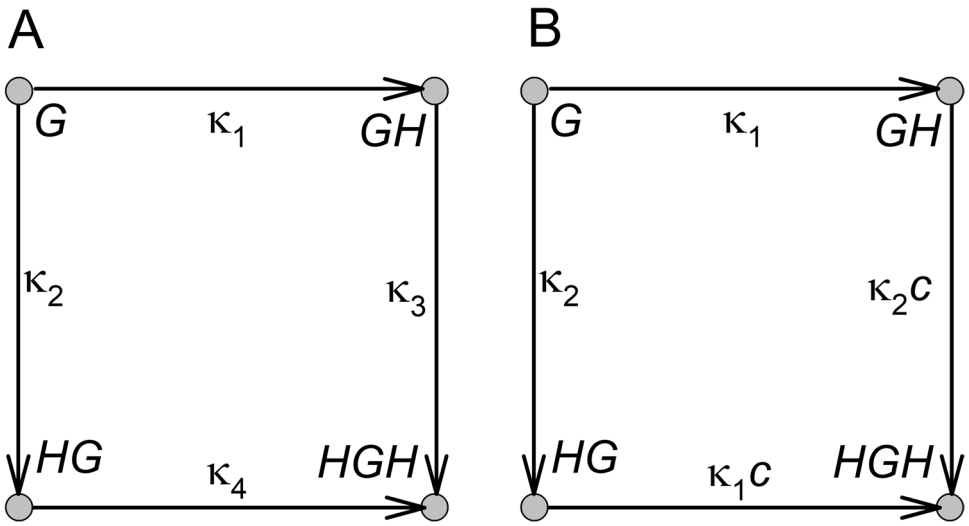

Fig. 1 Pathways of complex formation for guest possessing two nonequivalent binding sites. **A** scheme of microscopic binding constants κ_i; **B** introduction of the cooperativity coefficient c

In the unfavorable case of opposite signs of complexation induced shifts the changes of apparent chemical shifts in the NMR titration experiment can be partially compensated or fully cancelled out. The use of titration data for resonances of one side of bimodally bound guest molecules for the determination of K_1 association constant and next, the data for resonances of other side of guest for the determination of K_2 points out to the incomprehension of a competing binding mechanism. Even if complexation-induced shifts are strictly separated, what hardly ever takes place, two types of complexes always exist in solution and their concentrations are interrelated. It must not be assumed that complexes with different geometries can be treated independently. K_{app} rather than K_1 and/or K_2 is always determined from the titration data.

Chemical exchange and chemical shift time scale

Chemical exchange refers to the kinetic processes, that change the magnetic environment of nuclear spins. Such process or processes may influence parameters of NMR spectra: chemical shifts, scalar coupling constants, and line widths. When chemical shifts of nuclei are affected by such a process, a visible effect depends on the relation between the process rate k and the difference in resonance frequencies Δf corresponding to the chemical shift change resulting from the discussed process. If the relation $k >> \Delta f$ holds the observed chemical shift is a population-weighted average of chemical shifts in the individual species and such a process is called fast on the chemical shift time scale. On the contrary, separate NMR spectra are observed for each species if $k << \Delta f$ and the process is called slow on the chemical shift time scale. For intermediate rates ($k \approx \Delta f$) exchange-broadened signals appear in the NMR spectra [31, 41, 42]. The two most frequent cases of chemical exchange that happen in inclusion complex studies are association/dissociation dynamic process during guest–host formation or/and conformational motion(s) within one or both components of the complex. Since the rates of inclusion complex formation and its dissociation are frequently fast on the chemical shift time scale (often misleadingly named NMR time scale), the apparent chemical shifts during titration experiment are the mole fraction weighted averages of the chemical shifts specific for free and complexed molecules. On the other hand, separate set of signals of free and bound host or guest molecules can be observed at slow exchange regime. Such behavior was reported for different host classes: cyclodextrins [39, 43], crown ethers [44], cucurbiturils [45, 46], and pillararenes [47]. If the assumption of rapid equilibrium is not valid and the exchange rate is at the intermediate regime, an analysis of the total lineshape becomes indispensable [48]. The slow exchange limit begins to fail when the integration of free and complexed signals is disrupted, making it impossible to accurately determine the relevant concentrations. Numerical values of the exchange rate k at which the fast exchange limit becomes invalid, depend not only on the relationship between k and Δf, but also on several spectral parameters: the population and transverse relaxation rate of the free and bound complex component. Simple guidelines for such limits are unreliable. In case of any doubts, it is better to rely on the total lineshape analysis, which avoids systematic errors in the determination of binding constant. In the case of conformational motions, many hosts belonging to calixarenes [49] or pillararenes [50] display conformational flexibility. Rotational motions of chiral host units, substituted aryl fragments, about methylene bridges result in the interconversion between host enantiomers leading to their racemization and spoiling their ability to chiral discrimination of guests. Conformational flexibility of the calixarenes and pillararenes increases with increasing ring size and decreases with increasing size of substituents placed at a macrocycle rim (refer to appropriate sections in selected classes of chiral host molecules). It is noteworthy that the chemical shift time scale can depend on the magnetic field of a spectrometer. A difference in resonance frequencies for a given chemical shift difference can increase by one order of magnitude due to the change of magnetic field, e.g. from 2.3 T ($f_H = 100$ MHz, fast process) to 23.5 T ($f_H = 1$ GHz, intermediate process).

Complexation induced chemical shift (CIS)

Is defined as: $\Delta\delta = \delta_f - \delta_{obs}$ where δ_f and δ_{obs} denote chemical shift in free complex component and observed chemical shift is a population-weighted average of chemical shifts, respectively [31]. Depending on the relative concentrations of guest and host molecules $\Delta\delta$ varies within the following limits: $0 \le \Delta\delta \le \delta_f - \delta_c = \Delta\delta_{max}$, where δ_c is a chemical shift in the complex. *CIS* can be observed either for guest, host, or both components of a complex. One should mention, however, that the complex formation is not always accompanied by measurable *CIS* values.

Limits of binding constants in NMR titration

It has been commonly accepted that the upper limit of binding constant values, K, determined by NMR titration is *ca.* 10^5 dm^3/mol [22, 23]. In further analysis of this statement the following consideration is strictly valid for 1:1 stoichiometry. It has to be noticed that the shape of the titration curve depends rather on the dimensionless factor F_K defined as a product of the initial, fixed concentration of guest $[G]_0$ and binding constant K than the binding constant itself, $F_K = G_0 \cdot K$. Therefore, identical F_K values and shapes of titration curves can be obtained from different G_0 and K combinations. This observation allows to determine the upper limit

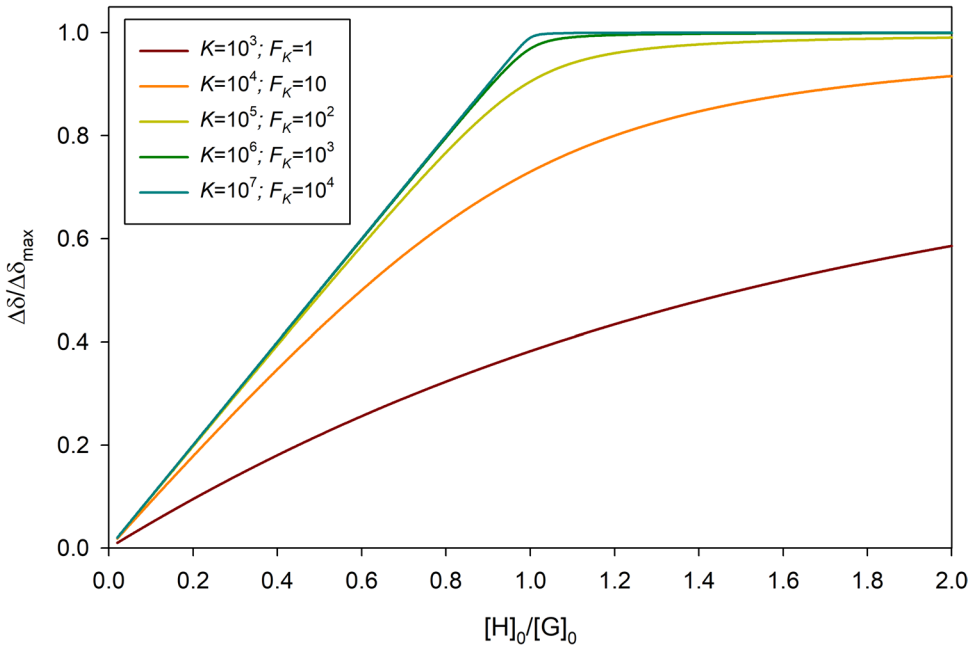

Fig. 2 Titration curves calculated for the stoichiometry 1:1 and $[G_0]=1$ mmol/dm^3. Different curves correspond to the range of binding constants K [dm^3/mol] and appropriate dimensionless factors F_K

of binding constants more formally. Titration curves shown in Fig. 2 were calculated assuming constant guest concentration $G_0=10^{-3}$ mol/dm^3 and subsequently increasing binding constants. The titration curve obtained for $K=10^5$ dm^3/mol ($F_K=100$) can be distinguished from other curves differing in F_K values. On the other hand, curves characterized by larger F_K values, $F_K=1000$ ($K=10^6$) and $F_K=10{,}000$ ($K=10^7$) are practically identical from an experimental standpoint. One can safely assume that $F_K=100$ is a limiting value for NMR titration. Recently NMR sensitivity has significantly increased due to technical progress in NMR equipment making feasible studies of very diluted NMR solutions. At present, acceptable NMR spectra can be measured for concentrations as low as 10^{-6} mol/dm^3 in favorable conditions. This value makes possible the determination of binding constant $K=10^8$ dm^3/mol with satisfactory accuracy.

The lower limit of binding constants, K, determined by NMR titration depends mainly on the solubility of host compounds in order to access sufficiently wide range of chemical shift changes (Fig. 3). Binding constants $K<1$ dm^3/mol were reported in the literature [51, 52].

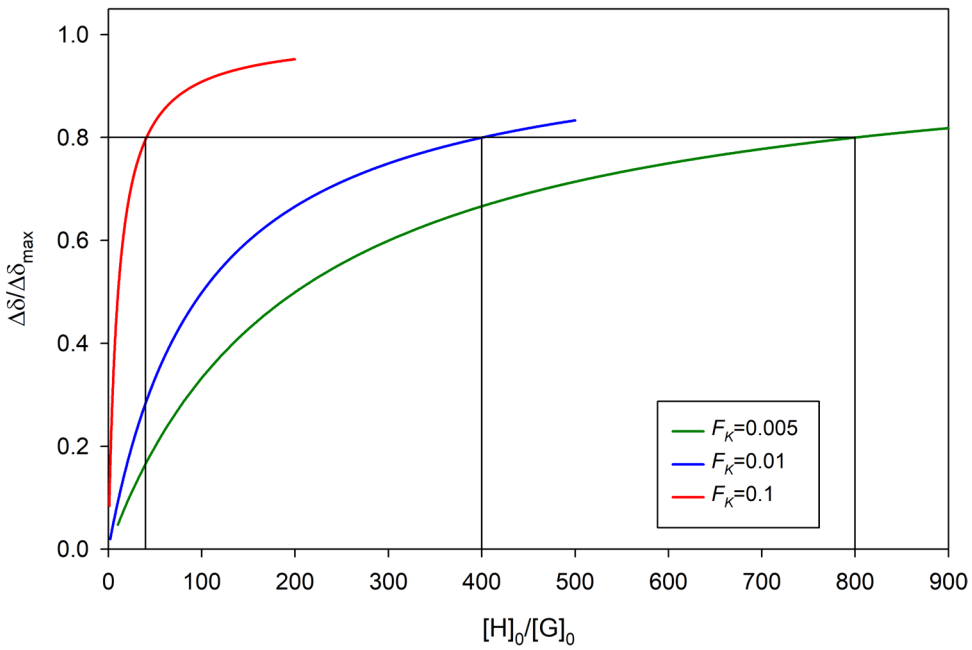

Fig. 3 Titration curves were calculated assuming guest concentration $G_0=10^{-2}$ mol/dm^3. Curve $F_K=0.005$ corresponds to the $K=0.5$ dm^3/mol. In this case a prerequisite of sufficiently large chemical shift changes would require as high a host concentration as 8 dm^3/mol

Competitive binding

Competitive binding can be used as a means of extending the upper limit of binding constant values available for NMR techniques [22, 23, 53]. The experiment is set up so that two guest molecules, studied and auxiliary, compete for binding to a host. One of the nascent complexes, named the reference system, has to be fully characterized. Its binding constant K_{ref}, chemical shift(s) in the uncomplexed guest $\delta_{f,ref}$ and chemical shift(s) in the complex $\delta_{c,ref}$, have to be determined in a separate titration experiment. Such a procedure allows to flattening of the titration curve and, thus, separation of titration curves with large F_K factors resulting in the increased accuracy binding constant determination (Fig. 4). The competitive binding can also be applied when two host molecules compete for a guest. Competitive binding based determination of binding constants has been introduced for the first time in studies of inclusion complexes with crown ethers [44] and cucurbiturils [45].

It should be kept in mind that the use of competitive binding requires the absence of interaction between competitive species. Concentrations of competing compounds and stabilities of studied and reference complexes should not to differ too much. Otherwise, negligible chemical shift variations are obtained, leading to high uncertainty of binding constants. This limitation imposes the necessity of the sequence of competitive experiments in order to determine a very large binding constant. It has been the case of tricyclo(3.3.1.13,7)decane derivative and cucurbituril CB[7] complex for which $K = 2 \cdot 10^{12}$ dm^3/mol has been determined in five subsequent competitive experiments [47]. It has to be mentioned that almost all the literature reports of competitive measurements present data for the systems exchanging slowly on chemical shift scale.

Chirality and chiral recognition

Chirality describes the geometric property of a rigid molecule which cannot be superimposed on its mirror image. Such mirror images are called enantiomers. In terms of symmetry elements a molecule is chiral if it lacks an improper, also called rotation-reflexion, axis. It can, however, possess a proper rotation axis/axes [38, 54]. NMR spectra of enantiomers in achiral media are identical because enantiotopic groups are isochronous, i.e., they display the same chemical shifts [55, 56]. Chirality has to be distinguished from optical activity. An equimolar (racemic) mixture of two enantiomers does not show a macroscopic optical activity.

The definition of chirality given above is fully complete. However, the concept of chirality has been artificially split into subgroups depending on specific chirality elements as chirality centre (e.g. an atom bearing four different substituents not placed in the same plane), chirality axis (e.g. substituted allenic moieties or spiro compounds), or planar chirality (e.g. monosubstituted paracyclophanes). Since the mentioned above chirality types do not include all possible chiral structures the concept of inherent chirality has been introduced in order to describe the chirality of calixarenes and other large synthetic molecules [57]. The most general definition reads "inherent chirality arises from the

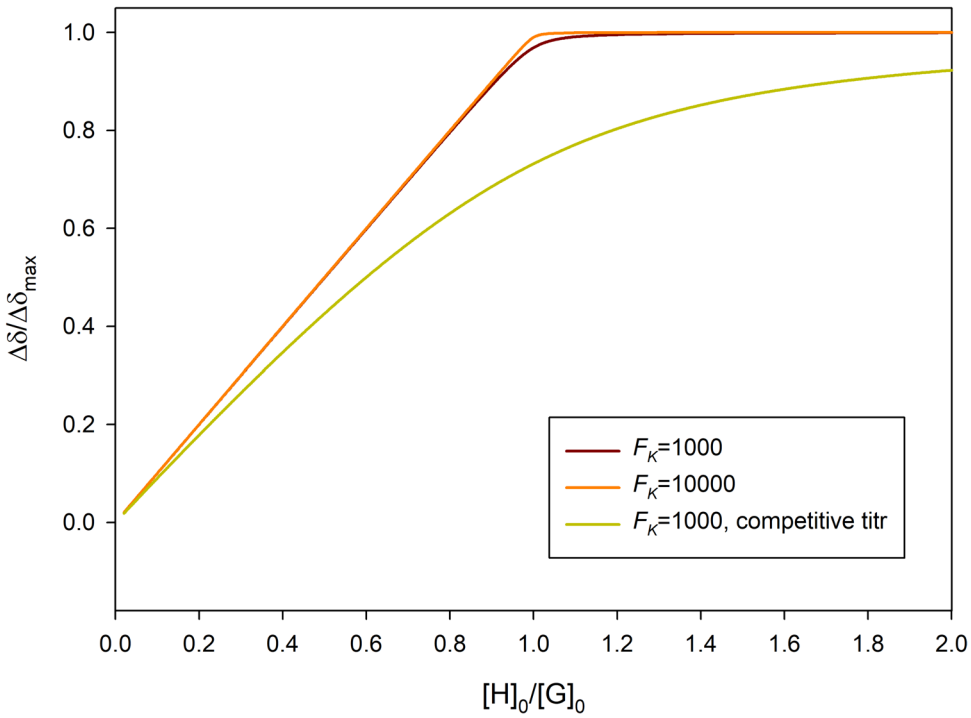

Fig. 4 Regular titration curves were calculated using the stoichiometry 1:1, $[G_0] = 1$ mmol/dm^3, and $F_K = 1000$ ($K = 10^6$) or $F_K = 10{,}000$ ($K = 10^7$). Competitive titration was obtained in the presence of the auxiliary guest: stoichiometry 1:1, $[G_0] = 10$ mmol/dm^3, and $K = 10^4$ dm^3/mol

introduction of a curvature in an ideal planar structure that is devoid of perpendicular symmetry planes in its bidimensional representation" [58].

Diastereomers are those stereoisomers which are not enantiomers. There are always only two enantiomers while a given molecule may have many diastereomers [38, 54]. NMR spectra of diastereomers in achiral media can differ [55].

Chiral recognition refers to the ability of one chiral molecule to recognize the chirality of another molecule. The use of a chiral host converts the mixture of guest enantiomers into a mixture of two diastereoisomeric inclusion complexes. Diastereoisomers may be distinguished by NMR spectroscopy because the resonances (of certain diastereotopic nuclei) are anisochronous [55, 56]. Differences in binding constants and complexation induced shifts (*CIS*) for diastereomeric complexes formed by enantiomeric components describe the phenomenon of chiral recognition. Separation of the appropriate NMR resonances at a single [G]/[H] ratio is merely a qualitative observation of chiral recognition. Measurement of resonance nonequivalence solely is not very informative and sometimes can be misleading as shown in Fig. 5. It is a full titration of such diastereomeric mixture which enables to determine binding constants and their difference characterizing chiral recognition more precisely [59].

Selected classes of chiral host molecules

Selected classes of host molecules of inclusion complexes are briefly presented. Two of them, cyclodextrins and pillararenes, are intrinsically chiral, while the introduction of chirality into the other hosts, crown ethers, cyclophanes, calixarenes, and cucurbiturils, requires the deliberate introduction of chiral element into the molecule. For each class, the spatial structures, their physicochemical properties and the characteristic features of their NMR spectra are discussed. Such a comparative overview of the different classes of hosts allows for optimal selection of the appropriate host to study complexes formed with the target guest, as different classes of supramolecular hosts exhibit different, though sometimes complementary, binding properties for different classes of guests.

Cyclodextrins

Cyclodextrins (CDs) are macrocyclic oligosaccharides composed of a number of glucopyranoside units bound together by α-1,4 bonds. The naturally occurring α-, β- and γ-cyclodextrins (αCD, βCD, and γ CD) consist of six, seven, and eight monosaccharides, respectively (Fig. 6).

They are obtained by enzymatic starch degradation [60–62]. CDs, whose shape remains a truncated cone, contain a lipophilic central cavity and a hydrophilic outer surface. CDs are intrinsically chiral since each glucopyranoside unit is naturally chiral. The basic dimensions of natural CDs are given in Table 1, however, the numbers differ slightly in various Refs. [25, 60, 63–65]. The size

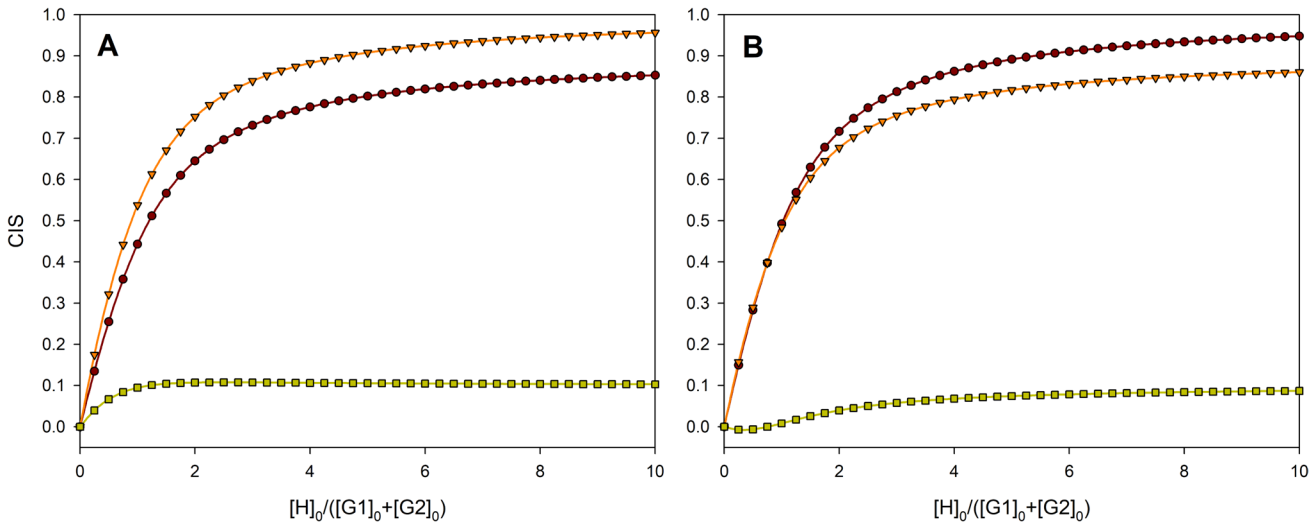

Fig. 5 Simulation of titration curves for two enantiomeric guests complexed with chiral host. Assumed stoichiometry 1:1. **A** guest 1 (circles): $K_1 = 1000$ dm^3/mol, $\Delta\delta_{1max} = 0.9$ ppm, guest 2 (triangles): $K_2 = 1200$ dm^3/mol, $\Delta\delta_{2max} = 1.0$ ppm, CIS2-CIS1 (squares). **B** guest 1: $K_1 = 1000$ dm^3/mol, $\Delta\delta_{1max} = 1.0$ ppm, guest 2: $K_2 = 1200$ dm^3/mol, $\Delta\delta_{2max} = 0.9$ ppm, CIS1-CIS2 (squares)

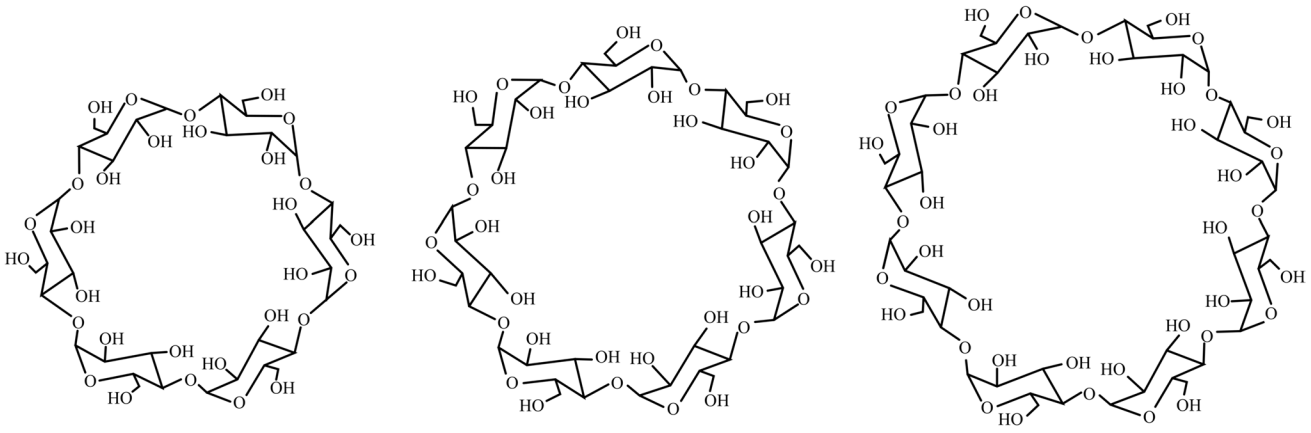

Fig. 6 Structures of natural cyclodextrins

Table 1 Dimensions of natural cyclodextrins and their solubility in water

Height of cone—0.79 nm	αCD	βCD	γCD
Inner diameter of wide rim [nm]	0.53	0.65	0.83
Inner diameter of narrow rim [nm]	0.47	0.60	0.75
Solubility in H_2O [mM/dm^3@25 °C][a]	132.7	16.2	191.5
Solubility in D_2O [mM/dm^3@25 °C][a]	86.0	10.5	169.2

[a]Ref. [68]

of the CD cavity allows for accommodating many low and medium molecular weight compounds (approximately ≤ 1000 daltons). α- and γ-cyclodextrins dissolve well in water in contrary to βCD exhibiting an order of magnitude smaller solubility. Solubility increases as the temperature increases [62, 66, 67]. It is also noteworthy that the solubilities of all three CDs in D_2O are considerably diminished in comparison with those in H_2O [68] (cf. Table 1). CDs are insoluble in most organic solvents but soluble in some polar aprotic solvents such as dimethylsulfoxide or dimethylformamide [62, 69].

Besides αCD, βCD, and γ CD larger cyclodextrins built up of dozens of glucopyranose units exist [70, 71]. One has to be aware, however, that large cyclodextrins display strong internal mobility of macrocycle [72] resulting in their irregular shape [64, 73–75] and are prone to the macrocycle ring opening owing to hydrolysis of glycosidic bond not only under acidic conditions [71, 76] but also at room temperature and neutral pH. This makes questionable the use of large CDs as host molecules.

Four axial protons of glucopyranose unit are located on opposite sides of the monosaccharide ring. In the CD macrocycle H3 and H5 hydrogens and endocyclic oxygens

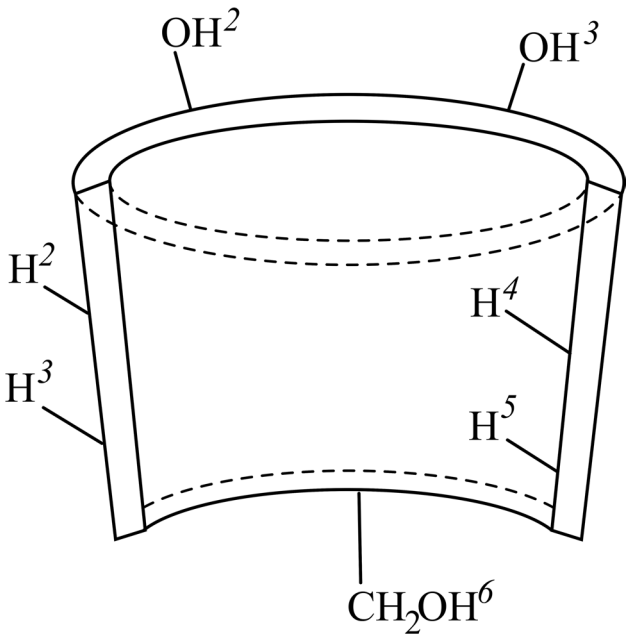

Fig. 7 Scheme of the proton distribution in the cyclodextrin surfaces

suitable for entrapping nonpolar molecules are located on the inner surface while H2 and H4 are on the outer surface. Intermolecular correlations observed in NOESY or ROESY spectra among guest protons and H3/H5 CD protons allow for unequivocal confirmation of inclusion complex formation and direct determination of its geometry [31, 77]. CDs contain also three hydroxyl groups in each glucopyranose unit. C6-OH primary groups are located at the narrow rim of the macrocycle. Two remaining, secondary groups, C2-OH and C3-OH, are situated at the wide rim (Fig. 7). It opens the broad possibilities to

Table 2 ^{1}H and ^{13}C chemical shifts in natural cyclodextrins

	Solvent	H1	H2	H3	H4	H5	H6,H6′
α-CD	D_2O[a] [83]	4.96	3.53	3.91	3.49	3.77	–
	D_2O[b] [72]	5.05	3.63	3.97	3.58	3.83	3.89
	DMSO[c] [84]	4.79	3.29	3.78	3.40	3.59	3.65
β-CD	D_2O[a] [83]	4.96	3.55	3.83	3.49	3.72	–
	D_2O[b] [72]	5.06	3.65	3.96	3.58	3.86	3.87
	DMSO[c] [84]	4.82	3.29	3.64	3.34	3.59	3.64
γ-CD	D_2O[a] [83]	5.02	3.56	3.86	3.50	3.80	–
	D_2O[b] [72]	5.11	3.65	3.93	3.58	3.86	3.87
	DMSO[c] [84]	4.89	3.32	3.65	3.36	3.56	3.65
	Solvent	C1	C2	C3	C4	C5	C6
α-CD	D_2O[d] [85]	102.2	72.6	74.2	82.1	72.9	61.4
	D_2O[b] [72]	104.1	74.4	76.0	83.9	74.7	63.2
	DMSO[e] [84]	103.0	73.2	74.3	83.2	73.3	61.2
β-CD	D_2O[d] [85]	102.6	72.7	73.9	81.9	72.9	61.2
	D_2O[b] [72]	104.5	74.8	75.8	83.8	74.5	63.0
	DMSO[e] [84]	103.0	73.6	74.2	82.8	73.2	61.2
γ-CD	D_2O[d] [85]	102.4	73.2	73.8	81.3	72.9	61.2
	D_2O[b] [72]	104.3	75.0	75.6	83.1	74.5	62.9
	DMSO[e] [84]	102.8	73.8	74.0	82.1	73.3	61.2

[a]T = 298 K, reference: δ(HOD) = 4.67 [83]; [b]T = 300.6 K, reference: external DSS-*d*4 [48]; [c]T = 333 K, reference: TMS [84]; [d]T = 323 K, reference: external TMS [85]; [e]T = 333 K, reference: external TMS [84]

the chemical modifications of CDs. Such modifications of native CDs change the size, shape, and physical properties of the CD macrocycles, affecting their solubility, and influencing their binding and selectivity of interaction with guest molecules.

The recent reviews describe numerous CD-derived molecules as well as their chemistry and applications [78–82]. Cyclodextrins can be covalently linked resulting in dimers or higher oligomers. They can also be combined with other macrocycles as crown ethers or calixarenes resulting in modified host properties [82].

^{1}H and ^{13}C chemical shifts reported for cyclodextrins in the literature differ depending on the solvent and the temperature of measurement. Errors in assignments and chemical shift referencing cannot be precluded (Table 2). It has to be pointed out that the resonances of chemically modified cyclodextrins can appear in other spectral regions than those listed in Table 2.

Crown ethers

Crown ethers are simple but very versatile macrocyclic compounds. The first systematic study of the synthesis of crown ether and the formation of their complexes was done by Pedersen [12, 13]. Crown ethers consist of a cyclic array of repeating ethyleneoxy unit $–CH_2–CH_2–O–$ and are universal hosts for both metallic cations (alkali, transition, and rare earth metals) and organic cations [86]. The simplest crown ethers are obtained by oligomerization of ethylene oxide. Their names incorporate the number of *n* atoms in the macrocycle and the number of *m* atoms of oxygen or other heteroatoms: *n*-crown-*m*. Oxygen atoms are in many cases replaced by nitrogen atoms. Contrary to the divalent oxygen atom nitrogen is trivalent, thus allowing the introduction of new substitution reactions to the macrocycle [19, 87]. It is possible to synthesize many nitrogen analogues of crown ethers, such as tetraaza-12-crown-4 or hexaaza-18-crown-6

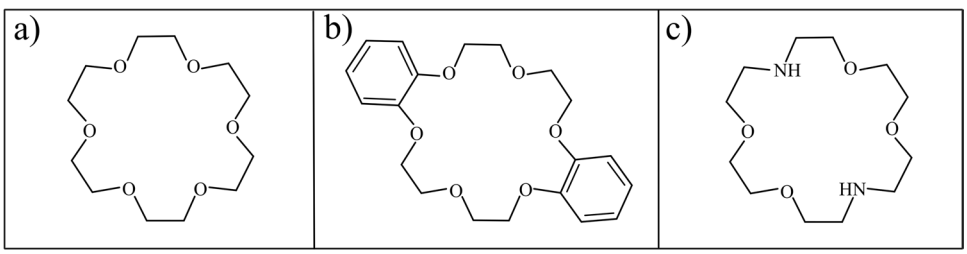

Fig. 8 Terminology of simple crown ethers. **a** 18-crown-6, **b** dibenzo-18-crown-6, **c** diaza-18-crown-6

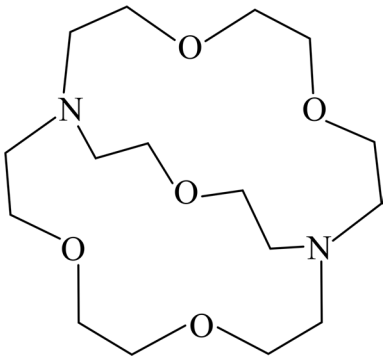

Fig. 9 [2,2,1] cryptand—the figures describe the numbers of ether oxygens in the chains

[88–90]. Lariat ethers consist of a crown ether with a side chain or side chains containing one or more additional coordinating sites. Lariats bind much more strongly than the corresponding aza crowns without side chains [91, 92]. A range of sulphur [93], selen [94], and phosphorus [95] analogues of crown ethers have also been described and shown to form complexes. The examples in Fig. 8 explain the nomenclature of simple crown ethers. Approximate cavity diameters of several crown ethers can be found in Refs. [12, 13] and [96].

Organic cations and neutral molecules can also be complexed by crown ethers commonly with 1:1 stoichiometry. Larger crowns could give 1:2 complexes such as that formed between dibenzo-24-crown-8 and two equivalents of potassium thiocyanate [97]. Alternatively, benzo-15-crown-5 with potassium iodide gives a 2:1 complex [98] in which the potassium ion is sandwiched between two crown ethers. The uncomplexed crown ethers are flexible and frequently do not have the same steric structure as the complexed form. Host–guest ion interactions cause the macrocycle to rearrange and shape the complex.

Cryptands are bicyclic or oligocyclic analogues of crown ethers (Fig. 9) with a well-defined three-dimensional cavity. Therefore, a guest could be encapsulated entirely within a cryptand. Such complex is called a cryptate. The binding of guests by cryptands is much stronger than their crown

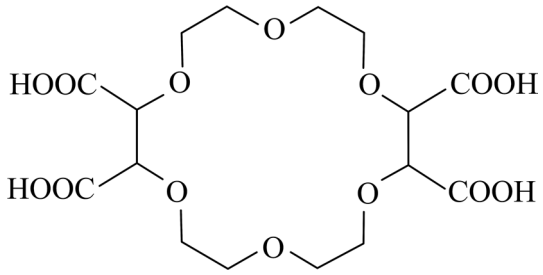

Fig. 11 18-crown-6 with chirality introduced by two (*R*,*R*)-(+)-tartaric acid units

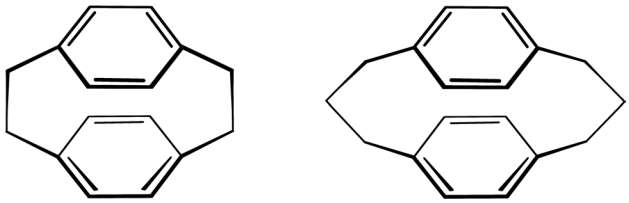

Fig. 12 [2,2′]-paracyclophane (left), [3,3′]-paracyclophane (right)

analogues. The possible topology of different cryptands has been discussed by Lehn [99].

Crown ethers are not naturally chiral and a chiral substituent(s) has to be incorporated into the macrocycle in order to create its chirality. A good example of such an approach is the use of sterically twisted 1,1′-binaphthyl (Fig. 10) and 2,2′-disubstituted-l,1′-binaphthyl unit(s) [100]. Such modified chiral crown ethers were used for chiral recognition of chiral guest molecules [26, 100]. Binaphthyl units can be replaced with numerous other chiral constituents; eg, tartaric acid (Fig. 11) or its derivatives [101–104]. The D-mannopyranoside unit incorporated in 18-crown-6 resulted in a chiral host displaying noticeable chiral recognition of amino acids [105].

Crown ethers could be well soluble in water or organic solvents. For example the solubility of basic crown ethers (12-crown-4, 15-crown-5, 18-crown-6) or aza-crown ethers in water is excellent. On the other hand, benzo- or

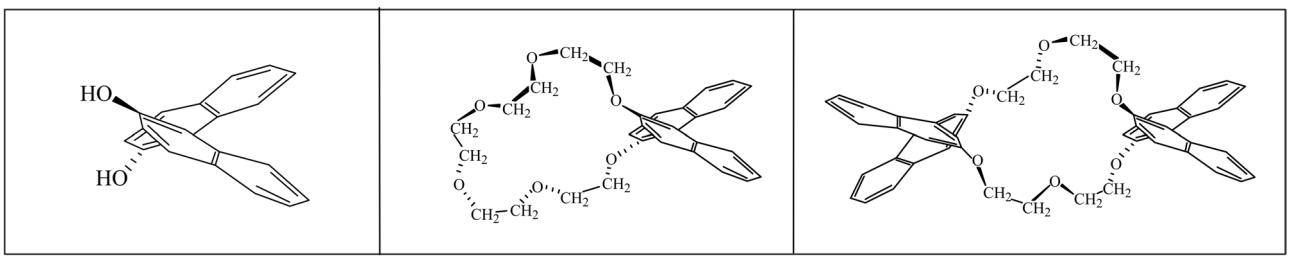

Fig. 10 Schemes of crown ethers with chirality introduced by one or two binaphthyl units

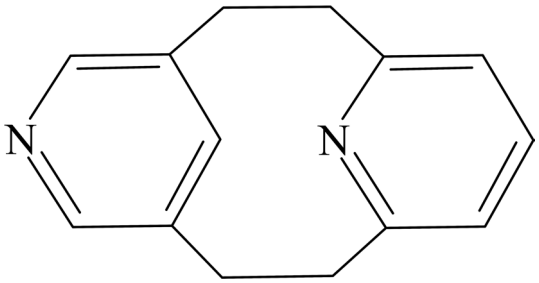

Fig. 13 [2,2′]-heterocyclophane

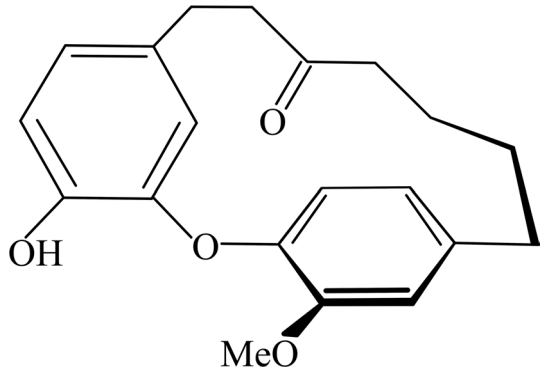

Fig. 15 Phenolic ketone, galleon

naphtho-crown ethers are only slightly soluble in water. Their water solubility can be improved by the substitution of oxygen with sulphur (thioethers) and hydroxylation [106] or sulphonation of aromatic moieties [107].

Cyclophanes

The simplest cyclophanes are compounds whose backbone is made up of an aromatic ring with a chain connecting its *meta* or *para* positions. But this class also includes very wide variety of complicated compounds with two or more aromatic rings bridged by chains. Chains of different length containing different atoms, functional groups or even compounds are used as linkers (Fig. 12). Aromatic hydrocarbons or aromatic compounds containing other heteroatoms in the ring are used as the aromatic core (Fig. 13). As a result, cyclophanes form an extremely diverse group of compounds schematically shown in Fig. 14 [82].

The first synthetic cyclophanes, polysalicylides, were obtained in 1892 by treating salicylic and homo-salicylic acids with phosphorus chlorides. The resulting tetrameric compounds were used to purify chloroform from phosgene, as it formed the crystalline complexes, $[O(C_6H_4)CO]_4$*2$CHCl_3$ and $[O(CH_3C_6H_4)CO]_4$*2$CHCl_3$, with them [109]. In 1909 through dehydration of *o*-thymotic acid two more complicated cyclophanes were obtained. Namely, *cis*-di-o-thymotide and tri-o-thymotide with 8- and 12-membered rings [110–112]. Their structures were assigned in 1952 [113]. Soon, cyclophane with a twelve-membered ring was also shown to form optically active crystalline complexes with several solvents. Two enantiomorphic forms of this compound are possible. However, in solution, the optical activity of these complexes disappeared due to racemization [114]. Regardless of this disappearance, this is the first case of detecting optical activity due to enantiomorphic configurations of molecules of this type. For some chiral solvents, chiral recognition of guest molecules in clathrates of the aforementioned cyclophane yielded enantiomeric excesses reaching up to 50% [115]. In the case of 2-bromobutane, the excess was 35% [116, 117].

Among the first isolated natural cyclophanes [118] was optically active phenolic ketone galeon (Fig. 15), which was extracted from the stems of the shrub, *Myrica gale* L. [119]. It is known to possess cytotoxicity against A549 cell lines, anti-tubercular activity, and moderate topoisomerase inhibitory activity [120]. In the following decades, cyclophanes have been found in a wide range of organisms with very different structures, often having a three-dimensional structure and a related biological activity [121].

The energy difference between cyclophane enantiomers is usually estimated at several kcal/mol [114, 122], and is attributed to the hindrance of free rotation around single bonds caused by steric obstructions. This conversion can be completely hindered by the introduction of a large group or

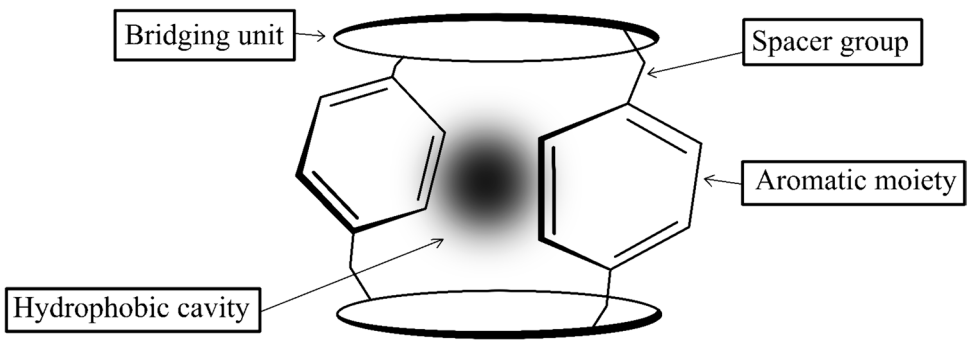

Fig. 14 Generalized scheme of cyclophanes (after ref. [108])

a suitable aromatic core, allowing pure enantiomeric forms to be obtained [123, 124]. The chirality of the cyclophane macrocycle can be enforced by the use of substituted allene bridges [124, 125]. In some cases, chiral enantiomerically pure macrocycles form selectively under the conformational tendency of the reacting components [126]. A number of methods have been developed to synthesize cyclophanes possessing planar chirality [127].

"Classical" cyclophanes are not water soluble. The attachment of hydrophilic groups, such as ammonium, sulfonium, carboxylic or viologen groups, to/in the chain or to the aromatic ring makes cyclophane water-soluble and allows it to be used as a host for hydrophobic guests [128]. Generally, 1:1 inclusion complexes are formed, whose stability constants in some cases are comparable to those of cyclodextrin complexes [129–131]. Importantly, the size of the hydrophobic cyclophane cavity can be easily modified.

Many spectacular cyclophanes were synthesized including those with bent aromatic core and very large nonplanar multicyclophanes [132]. Disilane-briged cyclophanes possessing planar chirality due to their chiroptical properties might serve as a host material in multilayered organic light-emitting devices [133]. Some cyclophanes were designed for the selective recognition of various biomolecules: DOPA [134], α-amino acid derivatives [135] sugars [136], glycosides [137], and nucleotides [138]. Two rigid macrocyclic cyclophane skeletons can be linked by four bridging segments to form chiral cage-type cyclophanes. When chiral amino acid residues are used for bridging, hydrophobic internal helical cavities are formed and very strong binding of enantiomeric guests is observed in aqueous media [139]. Many classes of dedicated chiral cyclophanes displayed chiral recognition in complexes with diverse clases of chiral guests [140–142].

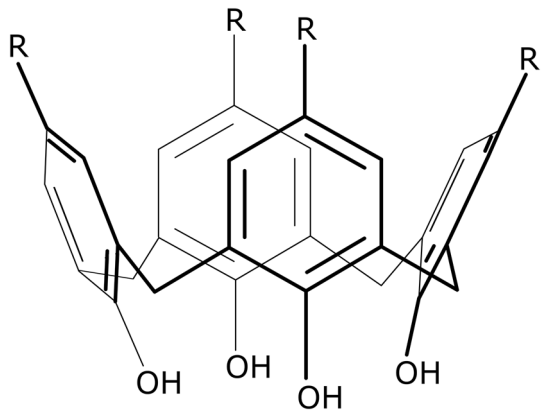

Fig. 16 Structure of calix[4]arene

Calixarenes and related compounds

Calixarenes are obtained in the condensation reaction of formaldehyde and *p*-substituted phenols [49, 143]. The more detailed name, calix[*n*]arene ($4 \geq n \geq 20$), shows that the macrocycle contains *n* aromatic moieties. OH groups are located at a narrow rim often called the lower or *endo* and R substituents at a wide (upper or *exo*) rim (Fig. 16). Gutsche divided calixarenes into three groups: *major*, readily available (n = 4, 6, 8) *minor*, less readily available (n = 3, 5) and remaining *large* calixarenes [49]. The molecular scaffold of calixarenes can be extensively used in the construction of functionalized host molecules. They can be modified on the narrow rim, wide rim, meta position, bridging methylene, and outer surface [144]. Calixarenes are virtually insoluble in water and slightly soluble in some organic solvents. The solubility of calixarenes in water can be increased by introducing sulphonate groups or other electron-withdrawing moieties [145–147].

Calixarenes are conformationally mobile systems since the aryl group rotates around the sp^2–sp^3 bonds. The simplest calix[4]arene exists in four basic conformations in which R substituents are in up/down orientations: u-u-u-u, u-u-u-d, u-d-u-d, and u-u-d-d [148]. It has to be stressed that larger calixarenes possess a greater number of possible conformations. Conversion among them result in the cone inversion [49]. Generally, such cone inversion is fast on the chemical shift time scale at room temperature. Conformational flexibility of the calixarenes increases with increasing ring size and decreases with increasing size of substituent R [149].

Calixarene scaffold is achiral provided that R substituents are achiral too. The introduction of *acquired* chirality into the calixarene framework can be done by attaching chiral substituent(s) at one of the rims or bridging methylene substituent [144]. It is noteworthy that cone inversion spoils the inherent chirality of calixarenes by changing the chiral molecule in its mirror image but has no effect on the acquired chirality. Prevention of macrocycle inversion can be achieved by increasing the substituent size at the narrow rim. Hydroxyl proton needs to be replaced by a more bulky group, usually by etherification or esterification [150]. In a similar way calixarene can be made *inherently* chiral [151] by forcing the absence of an improper rotation axis in the molecule as a whole. However, this approach requires a longer, stepwise synthesis [152]. Recent reviews summarize the achievements concerning preparation of chiral calixarenes [144, 153–155].

A large variety of modified calixarenes have been synthesized so far. One possibility comprises modification of $–CH_2–$ bridge(s). Oxacalixarenes, azacalixarenes, thiacalixarenes and silacalixarenes contain heteroatoms such as oxygen, nitrogen, sulfur or a dimethylsilyl group in place

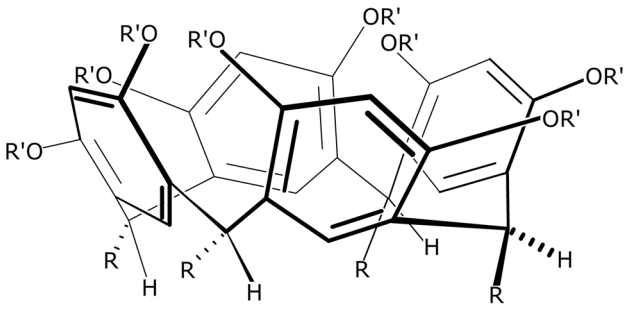

Fig. 17 Scaffold of calix[4]resorcinarenes

of methylene groups as bridging moieties [49]. Calixarenes in which one or more aryl moieties are directly connected are referred to as norcalixarenes [49, 156] while those with longer bridges between the aryl moieties as homocalixarenes [49, 157].

Resorcin[*n*]arenes (resorcinol-derived calixarenes, calix[*n*]resorcinarenes) are prepared using resorcinol (*m*-dihydroxybenzene) instead of *p*-substituted phenols and an aldehyde, preferentially forming a compound with four resorcinol units (Fig. 17) [158]. The use of α-naphthol leads to another calix compound, calixnaphthalene [159].

A number of heterocalixarenes: calixfurans, calixthiophenes, calixpyrroles (Fig. 18), calixindoles, calixpyridines and mixed heterocalixarenes have been obtained as well [49]. Replacement of methylene bridges with nitrogen or oxygen ones provides a new group of calixarenes [160].

Cucurbiturils

To date, no compound of natural origin has been found for this group of macrocycles. The structure of the first synthetic cucurbituril was determined in 1981 although the compound was obtained in 1905 [17]. Cucurbit[*n*]urils, pumpkin-shaped macrocyclic compounds, denoted Q[*n*]

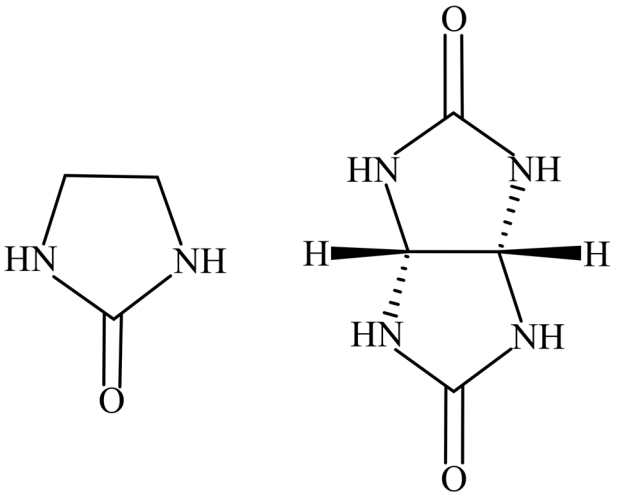

Fig. 19 Molecules of 2-imidazolidine (left) and glycoluril (right)

[161] or CB[*n*] [162], are prepared by acid catalyzed condensation of glycoluril (Fig. 19) and formaldehyde.

N glycoluril units are connected by double methylene bridges. The Q[*n*] family comprises five members with $n = 5, 6, 7, 8, 10$. Another cucurbituril, *t*-Q[14] is irregular and twisted taking the shape of a Möbius strip [163]. Shapes of regular cucurbiturils resemble an open barrel (Fig. 20). Since the glycoluril molecule is not planar the diameter of Q[*n*] is larger at the *equator* than at both identical rims [164] (Table 3) and all methine protons of glycoluril units are located on the outer surface of a macromolecule. The central cavity of the cucurbituril is hydrophobic and readily binds non-polar guest molecules. The guest can enter the cavity through one of two identical holes located on opposite sides of the host molecule. Both opposite holes are framed by negatively charged carbonyl oxygens.

Besides regular Q[*n*] molecules two inverted compounds, *i*-Q[6] and *i*-Q[7], were obtained [166]. Both

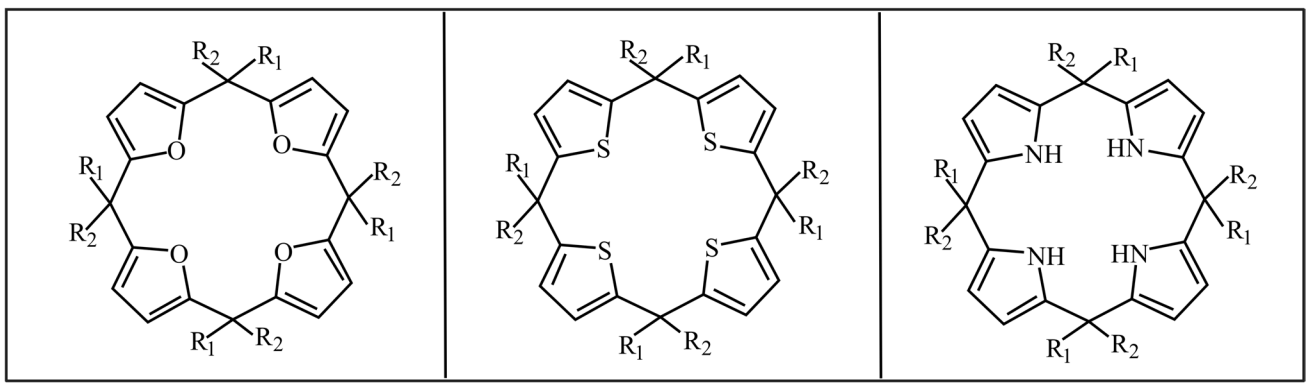

Fig. 18 General structures of calix[4]furan, calix[4]thiophene, and calix[4]pyrrole

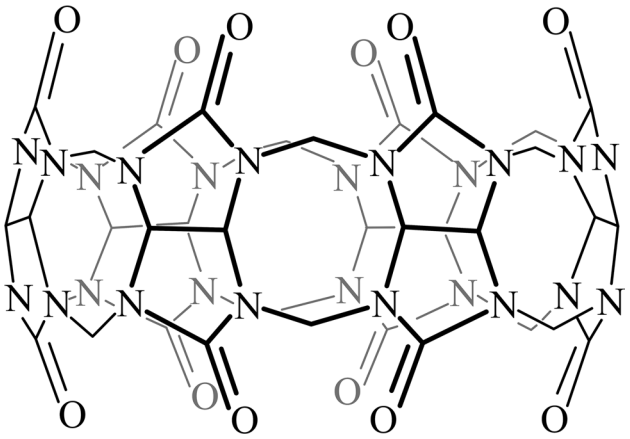

Fig. 20 Structure of Q[6]. Equatorial methine protons are not shown in the figure

Table 3 Dimensions of selected cucurbiturils and their solubility in water [161, 162, 164]

Height—0.91 nm	Q[5]	Q[6]	Q[7]	Q[8]
Inner diameter of rim [nm]	0.24	0.39	0.54	0.69
Inner *equatorial* diameter [nm]	0.44	0.58	0.73	0.88
Solubility in H_2O [mmol/dm^3]	20–30	0.018[a]	20–30	< 0.01[a]

[a]CB[6] and CB[8] have poor solubility in H_2O at pH 7. In the presence of alkaline metal salts their solubility appreciably improves. For instance, the solubility of CB[6] in 0.2 mol/dm^3 aqueous solution of Na_2SO_4 equals to 66 mmol /dm^3 [165].

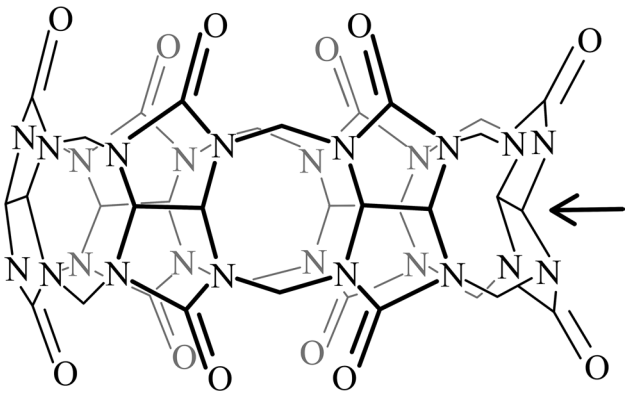

Fig. 21 Structure of *i*-Q[6]. The inversely oriented glycoluril unit is shown by the arrow

inverted cucurbiturils contain one glycoluril unit whose convex side and methine hydrogens point into the cavity (Fig. 21). Q[*n*] compounds lacking one or more methylene bridges are known as *nor-seco*-cucurbit[*n*]urils (*ns*-Q[*n*]) [167, 168].

Some cucurbiturils are extremely poorly soluble in water and organic solvents (Table 3). However, many cucurbituril

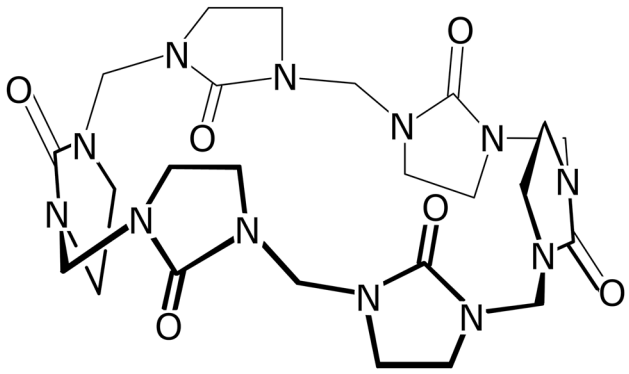

Fig. 22 Structure of hemicucurbituril HQ[6]

derivatives show significant increases in solubility. Derivatives such as permethyl-Q[*n*] (Me_{2n}Q[*n*]), perhydroxy-Q[*n*] (Q[*n*](OH)$_{2n}$), or derivatives with cyclohexyl groups at all equatorial positions (Cy_nQ[*n*]) display substantial improvement of solubility in water. Solubility of Cy_5Q[5] is tenfold larger than that of Q[5] while solubility of Cy_6Q[6] increases 4 orders of magnitude [169, 170].

Modified cucurbiturils can be obtained using substituted glycolurils as substrates. DecaQ[5] was synthesized by substituting glycoluril with dimethylglycoluril in a condensation reaction [171]. A monosubstituted cucurbituril in the methylene-bridged position was also synthesized by introducing new aldehydes, e.g. 3-phenylpropionaldehyde to the reaction mixture [172].

A severe drawback of cucurbiturils is the lack of chirality. Induction of chirality in achiral cucurbiturils can be achieved by their complexation with a chiral auxiliary ligand. Such chiral complexes can discriminate other chiral molecules after forming ternary complexes [173]. A supramolecular chiral complex was observed between the *heptakis*-(6-amino)-(6-deoxy)-β-cyclodextrin hydrochloride (AβCD^{+7}) and Q[6] and Q[7] having a 2:1 stoichiometry, stabilized by strong electrostatic interactions, but these complexes were not used for complexation with chiral guests [174]. Nor-*sec*-Q6 differs from Q6 by a lack of single methylene bridge. The removal of another methylene bridge results in (±)-bis-nor-*sec*-Q[6] (bis-*ns*-Q[6]), the first announced intrinsically chiral cucurbituril [175].

Hemicucurbiturils (HQ) constitute a subgroup of the cucurbituril class. They are prepared by condensation of 2-imidazolidone (ethylene urea) (Fig. 19) and formaldehyde. At first two compounds HQ[6] and HQ[12] were synthesized and identified [176] (Fig. 22).

The use of *cis*-octahydro-2H-benzimidazol-2-one in place of etylene urea resulted in a new group of macrocycles, hemicyclohexylcucurbiturils CyHQ[*n*]) (Fig. 23) [177]. Owing to the *cis* conformation of methine protons

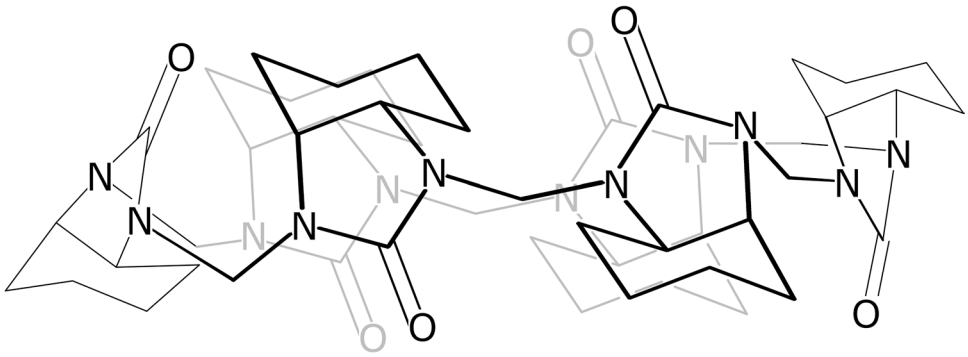

Fig. 23 Structure of chiral CyHQ[6]

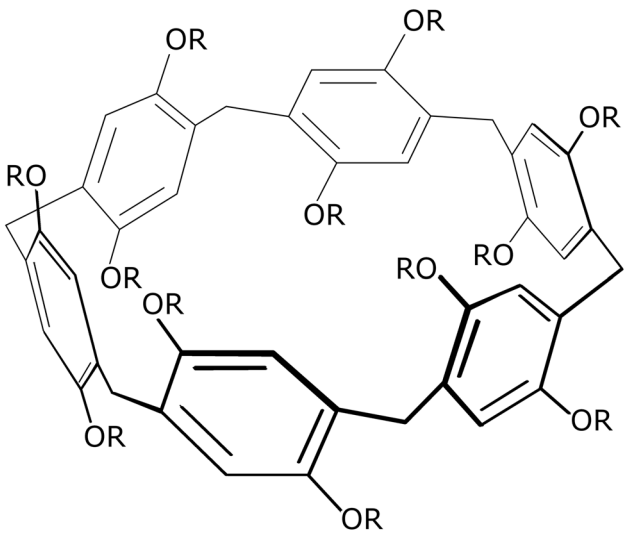

Fig. 24 Steric structure of 1,4-dialkoxypillar[6]arene. R—alkyl substituents of variable length

the reported CyHQ[6] was *meso* compound and, therefore, achiral.

Nevertheless, hemicyclohexylcucurbiturils provide the opportunity to obtain chiral host molecules using enantiomerically pure (*R*,*R*)- or (*S*,*S*)-*trans*-octahydro-2H-benzimidazol-2-one. Two hemicyclohexylcucurbiturils have been obtained so far; CyHQ[6] [178] and CyHQ[6] [179]. The ability of both hemicyclohexylcucurbiturils to form diastereomeric complexes with chiral guests was confirmed experimentally [178–180].

Pillararenes

The first pillararene, the symmetric 1,4-dimethoxypillar[5]arene (DM-P[5]) was obtained with in high yields by acid catalyzed condensation of 1,4-dimetoxybenzene and formaldehyde [181, 182]. The pillar[6]arene can be efficiently obtained and reversibly converted to the Pillar[5]arene [183]. Larger homologs, pillar[n]arenes have also been synthesized (n = 8–10) [184] or obtained by conversion of Pillar[5]arene (n = 6–15) [185]. Single crystal structures of P[8], P[9], and P[10] have exhibited that two of the methylene groups are orientated inwardly. Such an arrangement causes the formation of two cavities in contrast to P[5] and P[6] displaying a single rigid cavity [184]. Methods for the preparation and isomerisation of pillarenes of different sizes and their partial and full functionalization is described in detail, and the properties of these prism-shaped macrocyclic molecules as hosts, (Fig. 24) denoted P[*n*], are discussed in extensive reviews [186, 187].

Compounds synthesized from 1,2,4,5-tetramethoxybenzene, rather than 1,4-dialkoxybenzene, and paraformaldehyde closely remind pillararenes. The main difference relies on the substitution of benzene rings. They are fully, symmetrically substituted and as a result the intrinsic planar chirality of pillararenes is lost. These macrocycles have been named asararenes (1,2,4,5-tetramethoxybenzene = asarol methyl ether) and can be obtained in a single step with 6–12 aromatic units [188].

Owing to their electron-rich hydroquinone rings, the cavities of pillararenes are able to form strong complexes with positively charged molecules. The stiffened pillarene molecules should exhibit planar chirality. However, the macrocyclic rings of the pillararenes are not rigid. The dialkoxybenzene groups can rotate 180° around the methylene bridges [189]. As a result of this process, the protons of the methylene bridges of DM-P[5] show a singlet in the ^{1}H NMR spectrum at 25 °C indicating rapid macrocycle inversion. The rotation of the dialkoxybenzene groupings leads to inversion of planar chirality and results in racemisation of the macrocycle. Temperature NMR studies have shown that the racemisation process can be slowed down by the introduction of large linear alkoxy groups. However, even the introduction of two n-dodecanoxyl groups cannot prevent the racemisation of P[5] at ambient temperature [189]. This effect can only be achieved by introducing oxy(methyl(cyclohexane)) groups. The rotation barrier is then high enough to allow the separation of P[5] enantiomers by chiral column chromatography [190]. However,

even the size of the oxy(methyl(cyclohexane)) groups is not sufficient to inhibit the racemization in P[6] [191]. It thus becomes evident that the substituents at the periphery and the number of [n] units significantly affect the conformational mobility of the pillararenes. The latter also determines the number of possible conformers.

Generally, Pillar[5]arenes have eight conformers differing in the relative orientation of alkoxy units. All of them are chiral and can be grouped into four diastereomeric pairs of enantiomers [192]. Larger pillar[6]arenes have five diastereomeric pairs of enantiomers and three *meso* conformers [191]. X-ray single crystal studies revealed that the conformations of P[5] and P[6] molecules displayed C_5 and C_6 symmetries, respectively. Besides the intrinsic planar chirality of pillararene scaffold, molecular dissymmetry could also be introduced with chiral substituents attached to the pillararene rims. 2(*S*)-methylbutoxy [193], β-D-galactose [194] or alanine [195] were used for this purpose. The pillararene—guest complexes, their composition, stoichiometry and association constants have been discussed in a comprehensive review [196].

Summary and outlook

Cyclodextrins, crown ethers, cyclophanes, calixarenes, cucurbiturils, and pillararenes, all discussed in this review, are the most important classes of macrocyclic hosts and have been extensively studied in many aspects of supramolecular chemistry.

There are a number of important features that must characterize macromolecules making them effective and useful hosts. First and foremost, the production of hosts should be simple and inexpensive. Additionally, given the enantiomeric purity of chiral microcycles, the task becomes even more challenging. Currently, cyclodextrins are a unique class meeting all the conditions mentioned above. The stabilizing interaction between the inner cavity of the host and the poorly soluble guest, together with the good solubility of the host at the same time, usually requires differentiation of the physicochemical properties of the inner cavity and the outer surface of the host. The size of the inner cavity is important and can usually be adjusted by changing the number of component units in the macrocyclic host.

Macrocyclic molecules can be divided into two types according to their conformational mobility: conformationally fixed or conformationally flexible. This important aspect relates to their conformational, physicochemical, and host–guest properties. Cyclodextrins, cryptands, and cucurbiturils are conformationally fixed. Cucurbiturils due to the double bridging between constituent units and cryptands, due to their bicycling or multicycling structure, retain their absolute configuration and do not racemize. Their unique aspect as a molecular receptor is their structural rigidity. They cannot easily conform to the shape of incorporated small molecules. This leads to specificity in complexation and thus provides an opportunity to systematically study the factors involved in non-covalent binding. In the other classes, there is conformational freedom. The calixarenes contain methylene bridges in the *meta* position of the phenolic rings, while pillararenes are built from *para* substituted aromatic units. Consequently, calixarenes are bowl shaped molecules, while pillararenes are prisms. Nevertheless, all three classes of macrocycles including cyclophanes are conformationally mobile because the phenolic units rotate around the sp^2–sp^3 bonds. Their configuration can be stabilized by bulky substituents at one or both rims of the macromolecule. Nevertheless, there still appears to be great potential in the design and synthesis of new classes of hosts exhibiting both conformational rigidity and intrinsic chirality. A recent study confirming this statement is work describing the synthesis of mirror-image cyclodextrins, compounds that allow deep insights into the mechanism of chiral interactions between chiral guests and both cyclodextrins enantiomers [197].

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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