Cyclodextrins and Their Complexes

Chemistry, Analytical Methods, Applications

Edited by Helena Dodziuk

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Contents

Preface

Cyclodextrins and their complexes constitute a fascinating subject that, due to its complexity, lacked an extended coverage in a monograph for long time. We are happy to bridge this gap with this book. The field has grown immensely, thus discussing or even mentioning many valuable works was not possible in the limited volume. However, we hope to have given an extensive description of all important aspects of research and applications involving cyclodextrins.

The creation of this book would not be possible without the assistance of several people deserving acknowledgement. They have helped by précising its content, choosing contributors, reviewing chapters, and in other ways. I am especially indebted to Prof. H. Ueda, Prof. R. Bilewicz and Prof. K. Harata for their involvement in the project. The critical remarks on specific chapters by Prof. A. Temeriusz, Prof. M. Kańska, Prof. J. Frelek, Prof. A. Holas, Prof. M. Jaszuński, Dr. R. Nowakowski and Dr. K. Chmurski are gratefully acknowledged. I would like also to thank Wacker, GmbH for a generous gift of cyclodextrins that helped me to carry out cyclodextrin experimental studies, and Oxford University that has enabled my literature research at Kebble College, leading to my deeper understanding of supramolecular complexes.

Warsaw, January 2006   *Helena Dodziuk*

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Molecules with Holes – Cyclodextrins

Helena Dodziuk

1.1
Introduction

Cyclodextrins, CyDs, are macrocyclic oligosugars most commonly composed of 6, 7, or **8** glucosidic units bearing the names α-**1**, β-**2** and γ-**3** CyD, respectively [1–3]. Other, usually smaller, molecules (called guests) can enter their cavity forming inclusion complexes with these hosts. α- and β-CyDs are believed to have been isolated for the first time at the end of nineteenth century [4] while their first complex seems to have been reported early in the twentieth century [5]. However, it took more than 50 years to establish and confirm the structure of CyDs. Today we take for granted the idea of inclusion complex formation by these macrocycles, but when it was suggested by Cramer in the 1940s the idea was not, to put it mildly, generally accepted. Cramer said later with considerable enjoyment [6]: ''When I presented my results for the first time at a meeting in Lindau, Lake Konstanz, I met fierce opposition from some parts of the establishment. One of my older (and very important) colleagues even stated publicly and bluntly in the discussion that he would try to remove a young man with such crazy ideas from the academic scene. But there was also a good number of supporters, so I finally made it.''

According to Stoddart [6], ''Cyclodextrins are all-purpose molecular containers for organic, inorganic, organometallic, and metalloorganic compounds that may be neutral, cationic, anionic, or even radical.'' They are usually built of glucopyranoside units in the $^4C_1$ conformation (Fig. 1.1). In most cases these host molecules have an average structure of a truncated cone with a cavity lined with H3 and H5 protons and lone pairs of glycosidic oxygen atoms lying in a plane thus endowing the cavity with hydrophobic character, while the bases formed by the primary and secondary OH groups bestow a hydrophilic character (Fig. 1.2). The great significance of CyDs both in research and applications lies in their ability to selectively form inclusion complexes with other molecules, ions, or even radicals. This phenomenon bears the name *molecular recognition* while the selectivity in the formation of complexes with enantiomeric species as guests is called *chiral recognition*. Complex formation changes the properties of both host and guest, allowing one to monitor the process by several experimental techniques. On the basis of X-ray
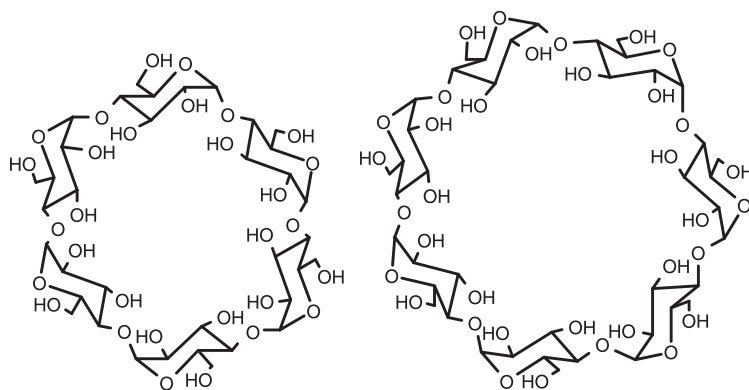
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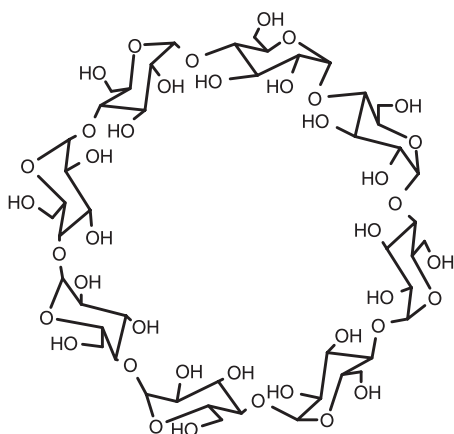
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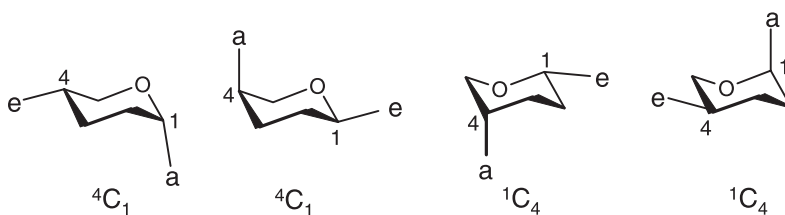
Fig. 1.1. Notation of conformations of the glucopyranoside ring.
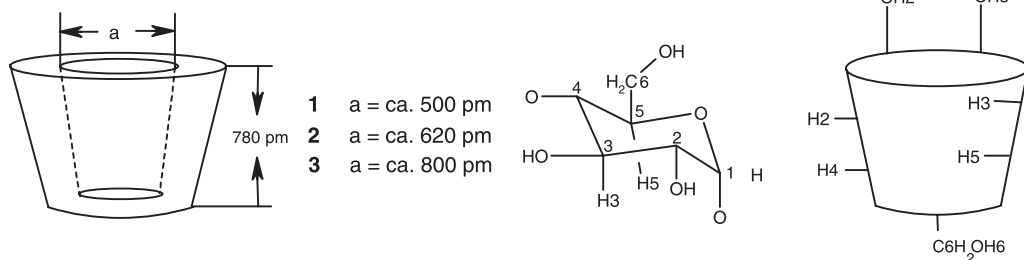
Fig. 1.2. Schematic view of the glucopyranoside ring with the atom numbering and native CyD sizes and the average orientation of the most important atoms and OH groups.

measurements, native CyDs **1–3** have for years been considered to possess a rigid, truncated-cone structure [7–9]. This view is inconsistent both with the CyDs' ability to selectively complex guests of various shapes and with several experimental and theoretical findings, discussed later in this chapter. These data reveal the amazing flexibility of the CyD macrocycles. The implications of the non-rigidity of CyDs for their complexing ability, and its influence on the results obtained using different experimental techniques, are also presented there. One of the most striking examples of this kind is provided by the different mode of entrance of the guest in the complex of nitrophenol **4** with permethylated α-CD **5** (R1 = R2 = R3 = Me) [10] in the solid state and in solution shown in Fig. 1.3.

The ability to predict recognition by CyDs would be of great practical value, especially for drug manufacturers. Consequently, several models of chiral recognition by CyDs have been proposed in the literature, neglecting the complexity of the complexation process involving very small energy differences between the complexes with enantiomeric species. The models critically reviewed later in this chapter are mostly based on very few experimental data and some of them contradict
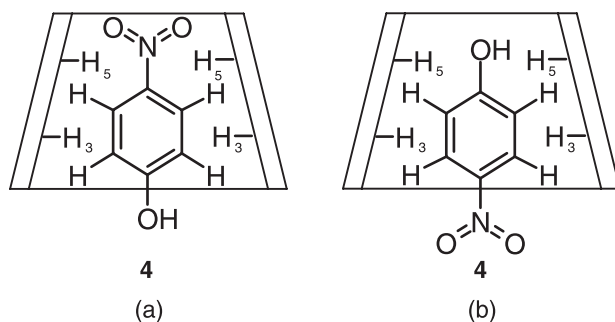
Fig. 1.3. A schematic view of the entrance of nitrophenol guest **4** in the cavity of **5** (R1 = R2 = R3 = Me) in solution (a) and in the solid state (b).
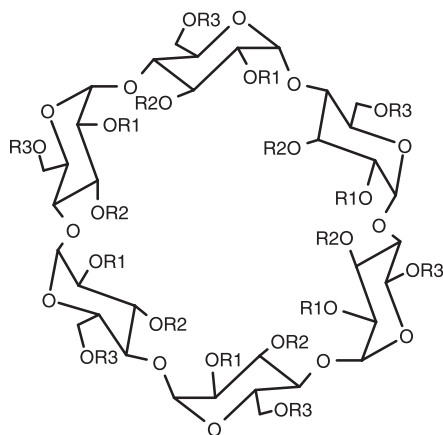
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the basic properties of three-dimensional space. For instance, the most often used 3-point Dalgleish model [11] is incompatible with the basic requirement of three-dimensional space that at least four points (not lying in a plane) are necessary for an object to be chiral [12, 13].

Numerous CyD derivatives have been synthesized with the aim of improving their complexing properties and to make them suitable for various applications, in particular to increase the bioavailability of a drug complexed with a particular CyD derivative. By appropriate choice of host and guest one can achieve a very high selectivity. For instance, **6** is complexed much more strongly by the dimeric host **7** than is **8** [14]. Numerous CyD derivatives mono- or polysubstituted in positions 2, 3 and/or 6 by alkyl groups **5**, **9** as well as modifications of hydroxyl groups
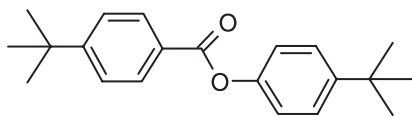
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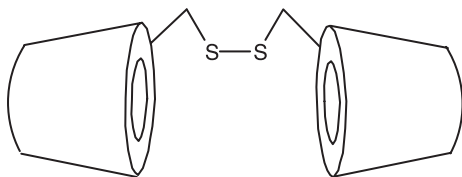
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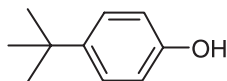
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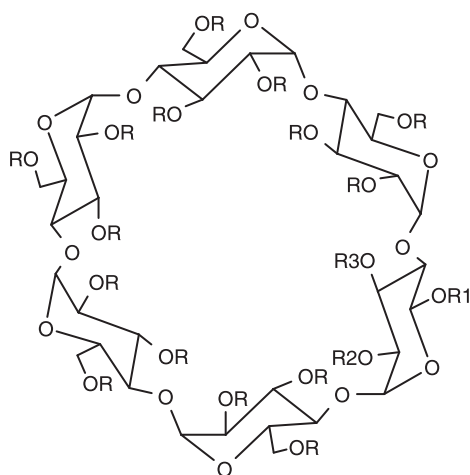
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to sulfopropyl, carboxymethyl, tosyl, aldehyde, silyl, and many other groups have been obtained [15, 16]. The reactivity of CyD and the plethora of exciting CyD structures developed, among other reasons, to enhance and modify their complexing ability will be shown in Chapter 2. Fascinating CyD structures include, among others, **10** [17], **11** [18], amphiphilic **5** (R1 = R2 = OH, R3 = CH$_2$S(CH$_2$)$_3$C$_6$F$_{13}$ [19], capped **12** [20], peptide appended **13** [21] and 2:2 complex **14** formed by the CyD dimer with porphyrin and zinc ion [22]. On the other hand, obtaining dimers

10

= β–Cyclodextrin

11

β-CyD
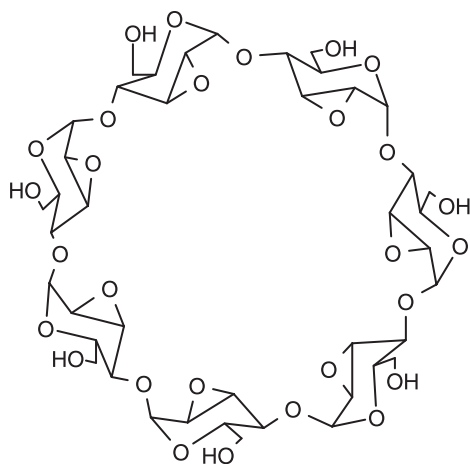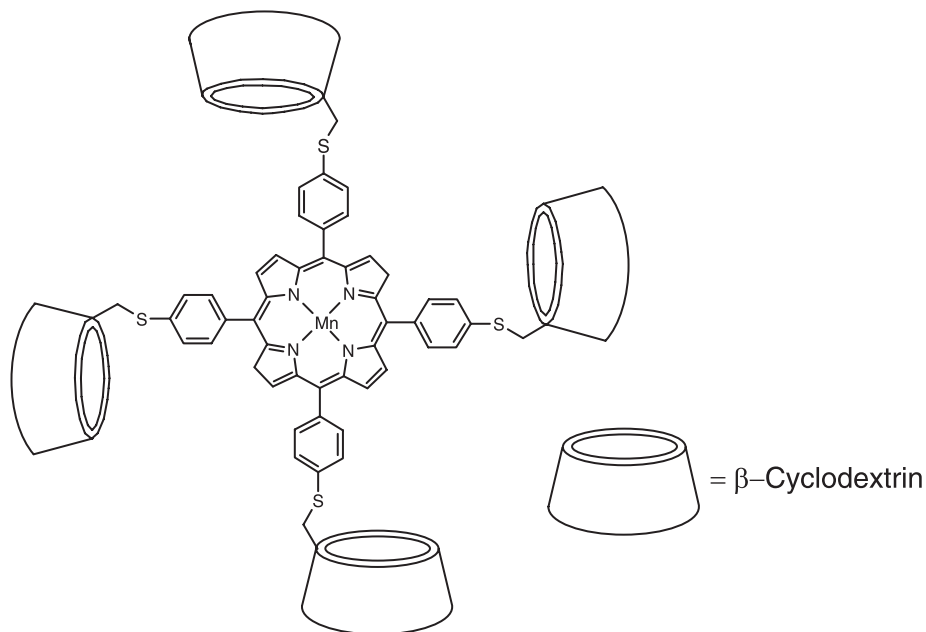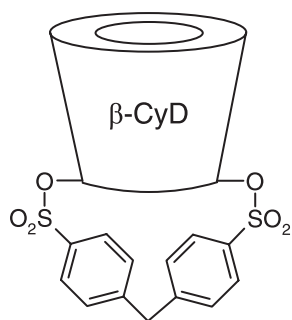
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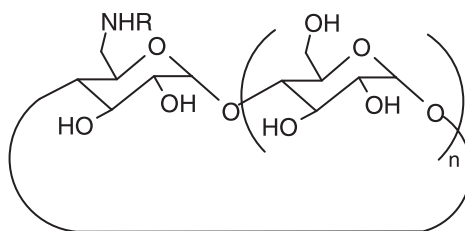
n = 6, 7   R = Glycyl-L-Phenylalanyl

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of isomeric naphthalenic acid, using an appropriately substituted γ-CyD template to exert control of the reaction's stereochemistry, shows a very elegant method making use of the encapsulation of two naphthyl-involving substituents on different glucopyranoside rings (Fig. 1.4) [23].

Exciting CyDs involving oligomers and polymers both covalently bound and self-assembled will be presented in Chapter 3 while their SPM observations and some
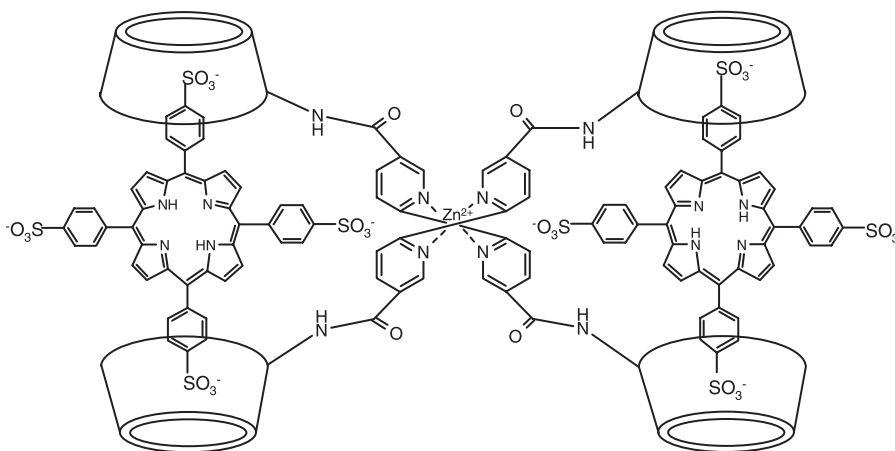
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polymers having catenane or rotaxane structures (Fig. 1.5) will be discussed in Section 10.6 and Chapter 12.

CyD catalysis, discussed in Chapter 4, and the application of CyDs as enzyme models constitute a fascinating field. The influence of a specific CyD on the stability of the included molecule can have, like the two-headed god Janus, contrasting consequences. Mostly, luckily for pharmaceutical applications, complexation with CyD usually stabilizes the guest. (However, it can also catalyze its decomposition as is the case with aspirin **16** [24] preventing its application in the form of a CyD complex.) CyDs are known to catalyze numerous reactions. Notably, the catalytic activity is usually not high, but (a) it can reach high values in a few cases as evidenced by the ca. 1.3 million-fold acceleration of the acylation of *β*-CyD **2** by bound *p*-nitrophenyl ferrocinnamate **17** [25] and (b) CyDs may impose limitations on the reaction's regioselectivity. Chlorination of anisole in the absence or presence of *α*-CyD illustrates this point [26] (Fig. 1.6) since it is known to produce only *para*-substituted isomers in the presence of *α*-CyDs while both *meta*- and *para*-isomers are obtained in its absence [27]. It should be stressed that, although the catalytic activity of CyD can achieve high levels [25, 28], these oligosaccharides are much more effective in inducing stereo- or regioselectivity than in genuine catalytic action. Another example of regioselectivity induced by *γ*-CyD was presented earlier in Fig. 1.4.

An exciting field of considerable importance related to CyD catalysis is their use as enzyme models by testing the reactivity of appropriately substituted CyDs [29–32]. For instance, to mimic the cleavage of RNA followed by cyclization of phosphate ester with subsequent hydrolysis using imidazole groups of Histidine-12 and Histidine-119 of ribonuclease A, isomeric diimidazole-substituted at C6 positions *β*-CyDs **18–20** were synthesized [29] and checked for their influence on the

a)

b)

c)

Obtained from 1,2- or 1,3 ring substitutions   Obtained from 1,4- or 1,5 ring substitutions

Yield: 80-92 %   Yield: 89-91 %
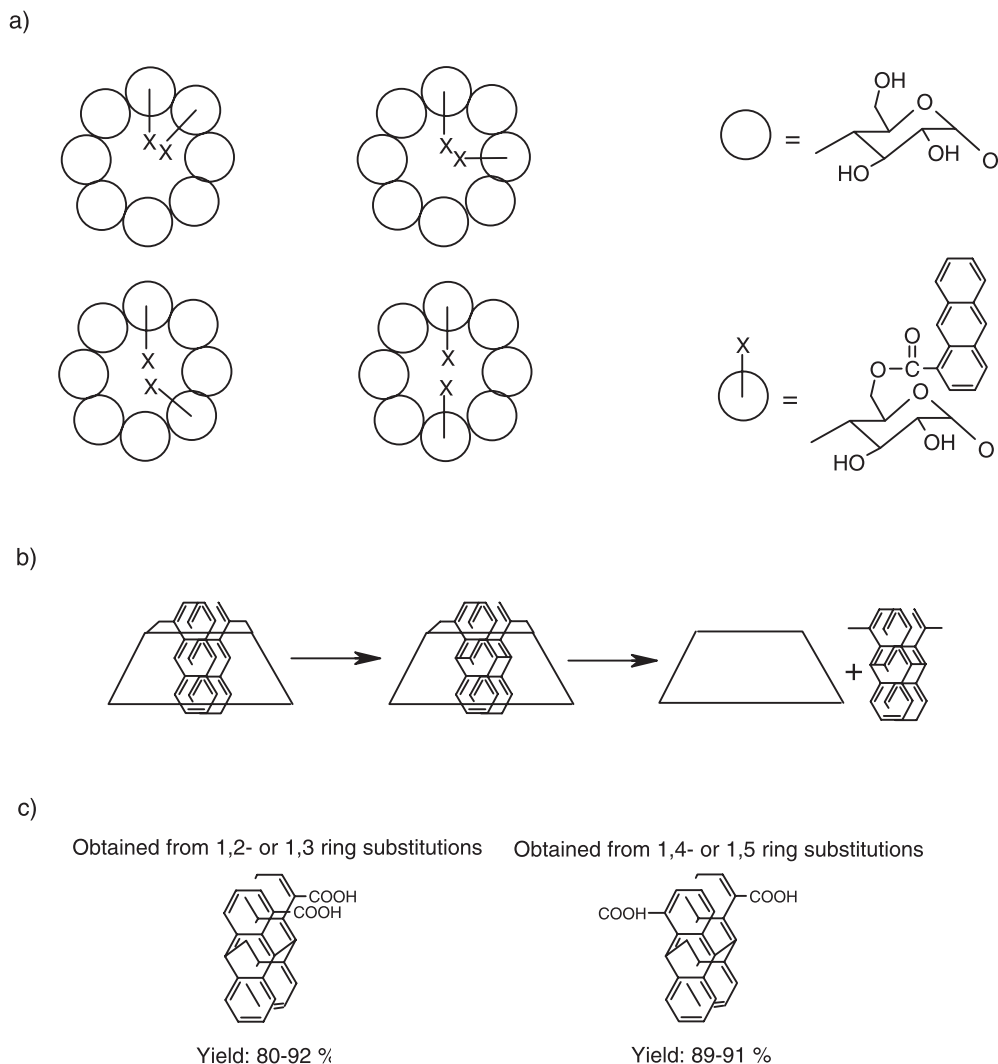
Fig. 1.4. Regioselectivity of the reaction of the included guest: schematic views of (a) disubstituted γ-CyDs, (b) the course of the reaction, (c) the product and yield of the reaction.

cleavage reaction. Interestingly, contrary to the classic mechanism proposed for this reaction, the close to linear arrangement of imidazole **21** groups in **20** did not lead to the most efficient catalysis, causing the abandonment of the mechanism commonly accepted in textbooks. The catalytic action of nuclease, ligase, phosphatase, and phosphorylase was also analyzed using more complicated CyD derivatives [33].
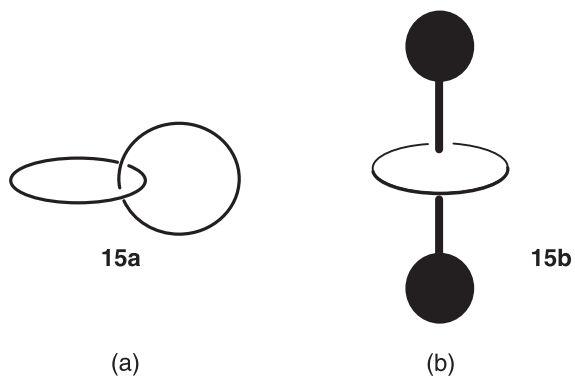
Fig. 1.5. Schematic catenane (a) and rotaxane (b) structures.

X = CH$_2$—N

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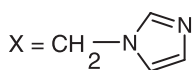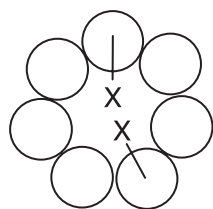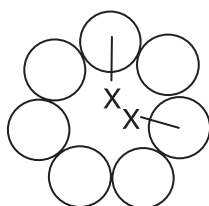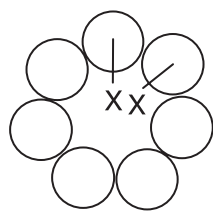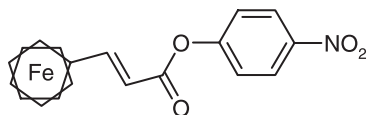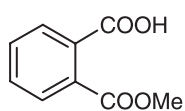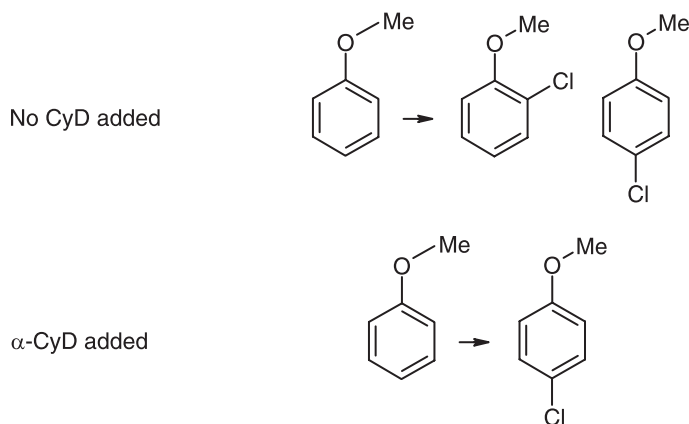
Fig. 1.6. Influence of α-CyD on anisole chlorination.

As mentioned before, CyDs and their complexes elicit a vivid interest as systems that allowing us to study the factors that drive the selective complexation known as molecular recognition. Particularly great interest is focused on the differentiation between enantiomers of guest molecules by their complexation with CyDs, i.e. on chiral recognition. This will be of great importance in future CyD applications, in particular in the pharmaceutical industry, since most drugs and the active sites in which they operate are chiral. As a consequence (remember a small child trying to put his foot into the other shoe?), enantiomers of several drugs have been found to exhibit different pharmacological activities [34]. The differences may go so far as to result in harming instead of healing. (The old thalidomide **22** tragedy, when pregnant women taking this drug in the racemate form later gave birth to babies with crippled extremities, was sometimes interpreted in terms of the teratogenic activity of its second enantiomer [35]. However, the recent revival of interest in thalidomide drug for various illnesses [36–38] should be acknowledged.

Chromatography is one of the most important methods for direct studies of molecular and chiral recognition by CyDs. Today it has split into several branches, e.g. gas chromatography, GC, high-performance liquid chromatography, HPLC, and capillary electrophoresis and other electromigration techniques, that enable us not only to detect the recognition but also to estimate the complex stoichiometry and formation constant and, consequently, the enthalpies and entropies of complex for-
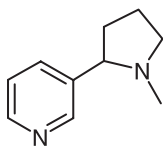
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mation. The amazing sensitivity of CyDs to the shapes of guest molecules or ions may be illustrated by the big difference among retention times of the complex of 1,8-dimethylnaphthalene **23h** with **2** on the one hand and those of other isomers **23a–23g** on the other, determined by gas–liquid chromatography (discussed in Chapter 4 in more detail) [39]. Such a big difference is most probably caused by a difference in the stoichiometry of these complexes. Namely, the latter complexes are of 1:1 stoichiometry while in the former one guest molecule is mostly embedded in a capsule formed by two host CyDs [40]. The striking change in elution order with temperature rise indicates the importance of the entropy factor and of CyD flexibility on the complex stability [41]. Similarly, the dependence of the elution order of the enantiomers of phenothiazines **24** complexed with γ-CyD **3** on the buffer used shows the complexity of the complexation process [42]. Molecular and chiral recognition by CyDs, as studied mainly by HPLC and GC, will be presented in Chapter 5 together with the application of this method for studying complex stoichiometries and stability constants while a wide range of chromatographic methods used for enantioseparations will be discussed in Chapter 6.
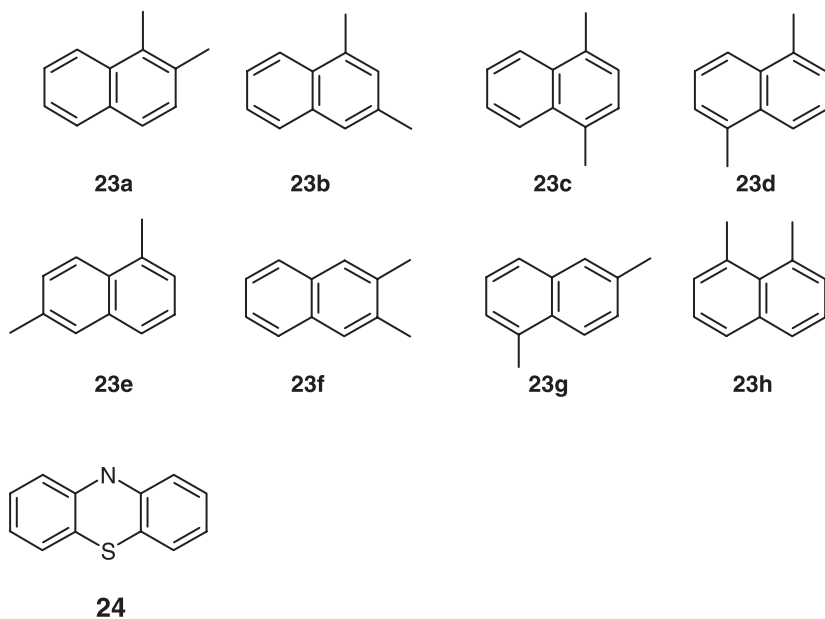
In most cases, CyD structures are elucidated on the basis of X-ray studies which will be presented in Chapter 7 together with the results of a few, but very interesting, neutron diffraction investigations. They include systems of O2H → O3 and O3H → O2 hydrogen bonds in β-CyD **2** rapidly interchanging at room temperature (Fig. 1.7) [43]. Freezing the process and accurately determining the positions of hydrogen atoms using neutron diffraction [9] allowed the determination of the
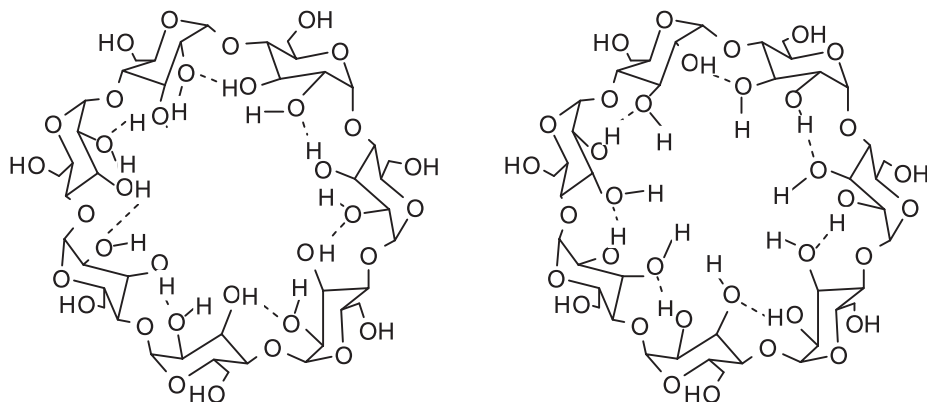
Fig. 1.7. Rapidly interconverting circular systems of hydrogen bonds in *β*-CyD **2** (flip-flop, HO2 → O3 simultaneously and reversibly changing to O3H → O2).

circular systems of the bonds shown in the figure. The mechanism of simultaneous change of directions of hydrogen bonds in **2** is called ''flip-flop''. Other fascinating examples of X-ray determined CyD structures are provided among others by [3] catenane-type CyDs **25** [44], the sixteenfold deprotonated *γ*-CyD dimer with Pb ions **26** [45], and the complex of an alkali ion buried inside a capsule formed by two crown ethers, in turn inserted in another capsule built of two *γ*-CyD molecules, the whole system resembling a Russian doll [46, 47].

The forces driving complexation by CyDs cannot be understood without a knowledge of the energy differences and barriers involved in the complexation. The calorimetric measurements, involving isothermal titration calorimetry and differential scanning calorimetry are discussed in Chapter 8. They give the most accurate thermodynamic data characterizing the complexes. In particular, these data provide further examples of the amazing enthalpy–entropy compensation that is not limited to CyD complexes [48]. Exciting studies of isotope effects on complex formation are also discussed there.

X-ray and neutron diffraction studies yield precise information on the CyD structure in the solid state. On the other hand, in addition to the information on the structure and dynamics of complexes in the solid state, NMR spectra allow elucidation of the structure in solution, which is of particular importance since most CyD applications take place in this state. (Even if we take a drug as a CyD complex in the form of a pill it dissolves in the stomach before acting.) NMR studies can give not only unequivocal proof of the complex formation in form of, usually small, chemical shifts but also, by studying the NOE effect [49], they can show how the organic guest molecule enters the host cavity in the solid state and in solution. The spectra are also sensitive to the dynamics of the complex and so they provide
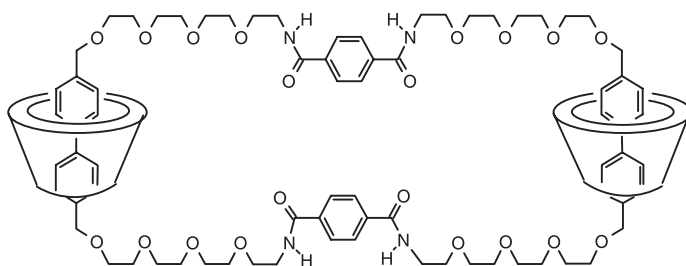
25a
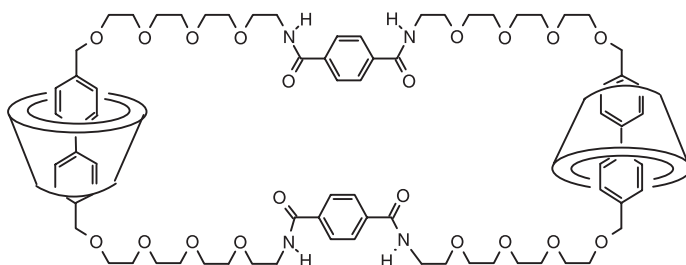
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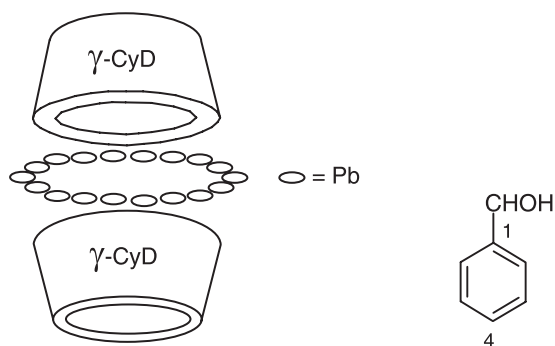
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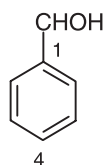
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information on the complex's nonrigidity showing the host and/or guest movement even in the solid state where, owing to positional and time averaging, X-ray results point to a single rigid structure. This is the case for the complex of benzyl alcohol **27** with **2** for which ^{2}H NMR spectra indicate a rapid flip of the aromatic ring around the C1C4 axis [50]. In addition to information on the complex's

28   **29**
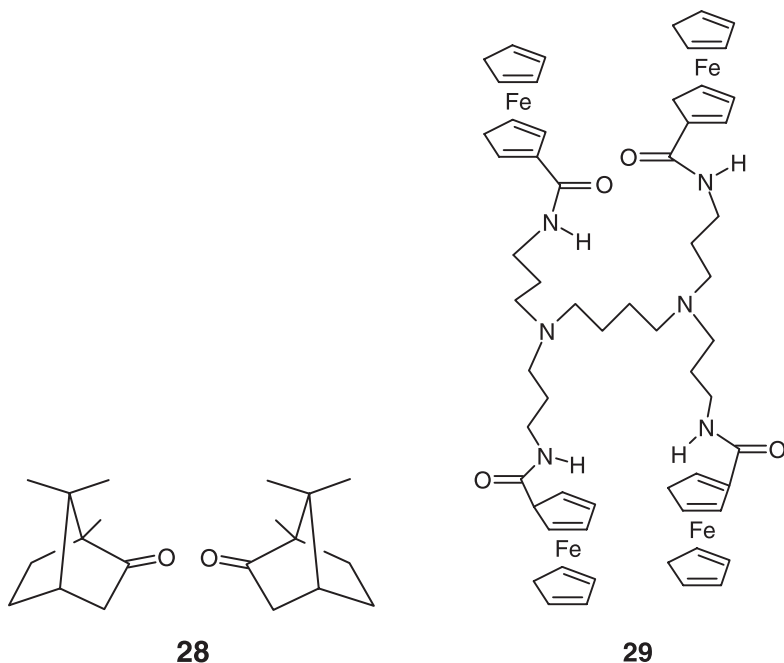
stoichiometry and stability constants, in favorable cases the study of relaxation rates in ^{1}H NMR spectra can show the orientation of the guest in the host cavity in solution, which no other technique can give, as shown for the complexes of camphor enantiomers **28** with **1** [51]. The kind of information on CyDs and their complexes that can be provided by NMR studies is discussed in Chapter 9 while Chapter 10 is devoted to the application of other physicochemical methods (UV, circular dichroism, mass spectroscopy, electrochemistry, AFM and STM, etc.) to the elucidation of the structure of CyDs and their complexes. Some of these methods are usually less sensitive to complex formation involving CyDs, but the effect can be considerable in specific cases and is of importance for applications in sensors and other devices. Although CyDs themselves do not have electroactive groups, electrochemical studies of their complexes form the basis of their future applications. Dendrimers with electroactive end groups like **29** [52] forming multiple CyD complexes are, probably, one of the most interesting examples in this area. Of course, mass spectra are most frequently used to prove the synthesis of a CyD derivative but, as shown in this chapter, they can be a source of valuable information on CyD complexes. New, rapidly developing AFM and STM techniques allowing the study of CyD aggregates on surfaces will also be presented there. They provide information on a single molecular aggregate or superstructures formed by

them. In particular, rotaxane-type structures **15b** (discussed in detail in Chapter 12) can be observed with atomic resolution by the latter method.

The possibility of predicting the molecular and chiral recognition ability of CyDs would be of great value, in particular for the pharmaceutical industry. The need for reliable theoretical treatment of CyD complexes is also reflected in several chapters in this book. Numerous studies applying quantum mechanics [53], molecular mechanics [54], and molecular dynamics [55] have been published by researchers fascinated by beautiful computer models and the ease of carrying out the calculations. The complexity of the complexation process and its consequences for the nonrigidity of CyDs, as well as the limited accuracy of the calculations, are neglected in most of these studies. Modeling of CyDs and their complexes and the dependence of the results of calculations on the assumed model and its parameterization are critically reviewed in Chapter 11.

The exciting catenanes, like **25** [44], and rotaxane molecular necklace **30** of 1:n stoichiometry incorporating $n = 20$–22 α-CyD macrocycles [56], respectively, falling into the realm of topological chemistry [57] will be shown in Chapter 12. These systems, also discussed in Chapters 10.6 and 16, form the basis of exciting applications. Large CyDs such as the 12-membered **31**, which differ dramatically from native CyDs in properties and, most probably, in complexing ability, will be discussed in Chapter 13. In particular, contrary to the structure of **1**–**3**, large CyDs do not have truncated-cone average structures with glycosidic oxygen atoms lying approximately in a single plane, but some of them are known to be twisted allowing for formation of hydrogen bonds between OH groups of distant glycosidic units [58].

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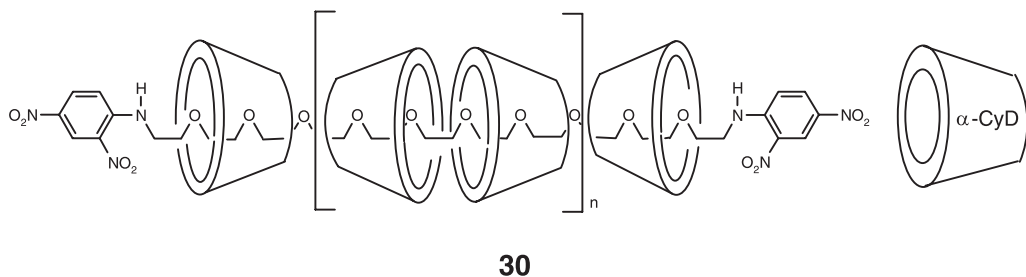
Chiral recognition by CyDs is of primary importance for the pharmaceutical industry since the second enantiomer of a drug, usually present as 50% impurity as the result of chemical synthesis, can be harmful. Therefore, an effective preparative separation of enantiomers is one of the important goals of applied CyD research since at present it has not reached the industrial scale. Today the main CyD application in the pharmaceutical industry is their use as drug carriers, since CyD containers in most cases stabilize and solubilize the included drugs (see, how-
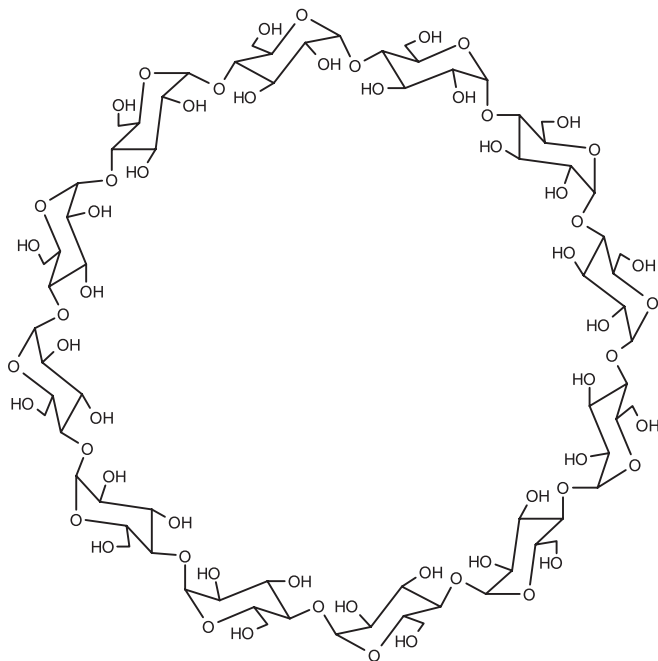
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ever, the aspirin case mentioned above). Moreover, the slow release of a drug from the complex results in its higher and more uniform content in the organism, allowing less frequent administration of the drug. Interestingly, CyD applications in drug delivery were considerably delayed by the erroneous determination of their toxicity at an early stage of development [59]. Today we know that they are not harmful in most cases by oral, parenteral, nasal, or skin administration [60]. CyD applications in the form of inclusion complexes in the pharmaceutical industry in general are presented in Chapter 14 with a detailed discussion of the ways in which various CyD types (hydrophilic, hydrophobic, or ionizable ones) affect the bioavailability of drugs by influencing their solubility and the rate of release from the CyD complex. A small section on site-specific drug delivery is also included. The even better therapeutic effect of drugs in the form of emulsions, micro-particles, nanoparticles, and higher aggregates is given in Chapter 15.

CyD applications are by no means restricted to the pharmaceutical industry. Several examples, mainly prospective ones, are scattered throughout this book. CyDs are used to remove unpleasant tastes, odors, or other undesirable components in the food industry, in agrochemistry, cosmetics, dying, cleaning, and in many other areas. To name just a few examples of numerous CyDs applications: grapefruit juice loses its unpleasant taste when its bitter component naringine is removed by complexation with β-CyD [61]; similarly, removal of phenylalanine and tyrosine

makes the food harmless for those suffering from phenylketonuria [62]. Garlic retains all its health benefits but lacks its annoying odor when applied in the form of a CyD complex. Similarly, other flavor components (such as apple, citrus fruits, and plums) and spices (cinnamon, ginger, horseradish, menthol, etc.) are marketed as β-CyD complexes characterized by high stability exhibited towards heating during industrial food processing [63–66]. The problems encountered by the use of CyDs for stabilization of mixtures has to be mentioned here since the components involved can be released at different rates, changing the taste or smell of the product. The creation and higher stability of foams used in both the food and cosmetic industries is also favored by the complexation. Interestingly, CyD applications should not only improve the properties of a marketed product but, consistently with modern trends, they are also aiming at creating new needs by producing new types of products with unheard of properties. A long-lifetime fragrance-releasing room-decorating paint is one example of such applications [67]. A few examples of numerous CyD applications in industries other than pharmaceuticals are briefly presented in Chapter 16, which concludes with the presentation of their thought-challenging prospective applications in molecular devices and machines.

The cyclodextrin field is rapidly expanding. According to information from the Cyclolab website, 3.9 articles per day on CyDs were published on average in 1995. This figure increased to 4.4 in 2004 (http://www.cyclolab.hu/literature_0.htm) and is still growing. The field is not only very large but also highly diversified. This is probably the reason why no general modern comprehensive monograph on CyDs has been available [1–3, 16, 68–71] for so long. We would like to bridge this gap, providing a survey of the whole exciting area with numerous references to help novices to enter this domain on the one hand and to give researchers in a specific field a broader insight into the whole area on the other. We apologize for not being able to mention, even briefly, numerous valuable works on CyDs but we hope to have given the picture of the whole CyDs field, illustrated by representative examples of the respective research and applications.

1.2
Cyclodextrin Properties

In the standard way, native CyDs **1–3** are obtained by enzymatic degradation of starch. First obtained in minute amounts and very expensive, in particular α- and γ-CyD, they now cost less than \$10/kg, making their large-scale industrial use feasible [72]. IUPAC names of these macrocycles are cumbersome; 5,10,15,20,25,30,35-heptakis-(hydroxymethyl)-2,4,7,9,12,14,17,19,22,24,27,29,32,34-tetradecaoxaoctacyclo[31.2.2.2.$^{3,\,6}$.2$^{8,\,11}$.2$^{13,\,16}$.2$^{18,\,21}$.2$^{23,\,26}$.2$^{28,\,31}$]nonatetracontane-36,37,38,39,40, 41,42,43,44,45,46,47,48,49-tetradecol for β-CyD makes the use of trivial names necessary. Lichtenthaler and Immel proposed a general system of naming macrocyclic oligosaccharides [73] but it has not been generally accepted and used. The chemical, physical, and biological properties of CyDs, and in particular their toxicity by various type of administration, are summarized in Ref. [60] while their stability when

Table 1.1. Some properties of native CyDs [60][a]

	α-CyD 1	*β*-CyD 2	2*γ*-CyD 3
Number of glucose units	6	7	8
Molecular weight	972	1134	1296
Approximate inner cavity diameter (pm)	500	620	800
Approximate outer diameter (pm)	1460	1540	1750
Approximate volume of cavity (10^6 pm^3)	174	262	427
$[\alpha]_D$ at 25 °C	150 ± 0.5	162.5 ± 0.5	177.4 ± 0.5
Solubility in water (room temp., g/100 mL)	14.5	1.85	23.2
Surface tension (MN/m)	71	71	71
Melting temperature range (°C)	255–260	255–265	240–245
Crystal water content (wt.%)*	10.2	13–15	8–18
Water molecules in cavity	6	11	17

[a] Some data on these and larger CyDs are also given in Tables 9.1 and
13.1.

treated by various enzymes is presented in Ref. [74]. Some of their properties are
given in Table 1.1.

As mentioned earlier, native CyDs are usually obtained by biochemical processes
[72]. However, a 21-step synthesis of **1** with 0.3% total yield [75] and that of **3** [76]
with 0.02% yield are worth mentioning. The macrocycle built of only five gluco-
pyranose rings **32** [77] (thought to be too strained to exist on the basis of model
calculations [78]) and probably thousands of CyD derivatives have been synthe-
sized [15, 16]. Several exciting CyDs have been presented earlier. Here CyDs hav-
ing glucopyranoside ring(s) in $^1C_4$ [79–81] or *skew* conformations [82], those incor-
porating other than glucopyranoside units [83] and large CyDs having from 9 to
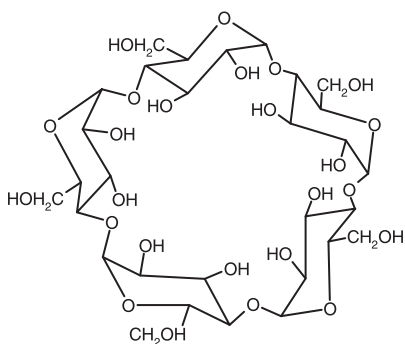
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more than 100 monosaccharide rings (discussed in Chapter 13) should be mentioned [58, 84, 85]. Interestingly, three unusual CyD derivatives have been found in nature [86].

As discussed in Chapter 7, native CyDs can form complexes with differing amounts of water. CyDs are seldom really empty. Even if they do not contain another guest there is usually at least one solvent molecule in their cavity. Almost all their applications involve inclusion complex formation when one or more molecules are at least partly immersed in the CyD cavity. The complexes can be obtained both in solution (sometimes requiring heating or the use of a cosolvent) or in the solid state, e.g. by cogrinding or milling [87]. In solution, they exist in a rapidly exchanging equilibrium of the free CyD host and guest. As mentioned before, CyD complexes of different stoichiometry are known. In addition to 1:1 complexes like **4@5** (R1 = R2 = R3 = Me) [10], the 1:2 ones like those of camphor enantiomers **28** embedded in a capsule formed by two α-CD **1** [51] and that of C_{60} buried in two γ-CyD molecules **3** in a similar way [88], 2:2 complex **14** [22] or even rotaxane molecular necklace **29** of 1:n stoichiometry involving $n = 20$–22 α-CyD macrocycles [56] are known. In spite of the years that have passed from the publication of the Szejtli review [89], his statement ''The 'driving force' of complexation, despite the many papers dedicated to this problem, is not yet fully understood.'' is still valid. The complexation process in a, mostly water, solvent is considered to involve a release of water molecule(s) from the relatively hydrophobic CyDs' cavity, removal of the polar hydration shell of the apolar guest molecule, entry of the guest into the empty CyD cavity where it is stabilized mainly by weak but numerous van der Waals attractive interactions, restoration of the structure of water around the exposed part of the guest, and integration of this with the hydration shell of host macrocycle. Thus, a change in both enthalpic and entropic contributions occurs in complex formation that depends on the host- and guest-induced fit [90], the solvent used, and numerous other factors. On the other hand, in the solid state the magnitude of the crystal forces is comparable with the forces keeping the complex together. Thus, as exemplified by **4@5** (R1 = R2 = R3 = Me) [10], they can influence the complex's structure and dynamics which is considerable even in the solid state. To summarize: CyD complexes are very difficult to study since (1) for poorly soluble species the complexation process can be much more effective for impurities (present in minute amount in the solution) than for the guest under investigation; (2) the process depends heavily on the experimental conditions (pH, cosolvent, temperature, etc.); (3) the complexes can involve species of different stoichiometries, e.g. dimethylnaphthalenes **23a–g** and **23h** [40], or an additional solvent molecule can enter the cavity as a second guest resulting in ternary complex formation [91, 92] (interestingly, complexes of even higher stoichiometry, involving two CyDs, one pyrene, and two cyclohexanol guest molecules [92] are known); (4) the experimental results for a CyD complex can depend on the technique used since the CyD complexes are held together by weak forces (one example of this kind was shown in Fig. 1.3 [10]); (5) Reliable theoretical studies for CyD complexes are extremely difficult to obtain since, as discussed in detail in Chapter 11, these large systems are characterized by energy surfaces exhibiting numerous very shal-

low local minima separated by low energy barriers [93, 94]. The size of the system and its *n*-fold degeneracy ($n = 6, 7, 8$ for α-, β-, or γ-CyD, respectively) also make it difficult to compare X-ray geometrical parameters for, for example, complexes with different guests. As discussed in detail in Section 1.4, one can either attempt to analyze the values of all internal parameters (e.g. of 126 bond lengths in α-CyD, etc.) in the series, which gives a very nontransparent picture, or compare the values of, for instance, the C2O2 bond length averaged over all saccharide rings, losing a lot of information by such an approach.

1.3
Cyclodextrin Nonrigidity [94, 95]

On the basis of X-ray studies [7–9], for tens of years CyDs structure was thought to resemble a rigid truncated cone of the high C_6, C_7, or C_8 symmetry for α-, β-, or γ-CyD, respectively, with a planar ring of glycosidic oxygen atoms [8, 96, 97]. Numerous experimental and theoretical data are incompatible with the concept of rigid CyDs. First of all, a general analysis of these systems shows that there is no physical reason for the rigidity, since the macrocycles are built of relatively rigid glucopyranose rings connected by ether C–O bonds, characterized by a low barrier to internal rotation of ca. 1 kcal mol^{-1} [98]. This reasoning was supported by model molecular mechanics calculations on α-CyD [93] showing that (a) the usually depicted structure with planar rings formed by glycosidic oxygen atoms does not correspond to the energy minimum and (b) the energy hypersurface exhibits several energy minima separated by low barriers. With regard to CyD complexes, they are held together by weak intermolecular interactions which somewhat limit the macrocycle's mobility but cannot endow the macrocycle with considerable rigidity.

It should be emphasized that a rigid structure for CyDs is also incompatible with the ease of formation of inclusion complexes of various shapes, since the latter implies an effective fitting of the host and guest to each other [90]. Most experimental proofs of the nonrigidity of CyDs come from NMR studies not only in solution but even in the solid state. If CyDs were not flexible then the spectra of complexes with aromatic guests in solution should exhibit several signals for, e.g. H3 CyD protons on different glucopyranose rings pointing into the cavity (Fig. 1.2). This is not the case [99]. Moreover, NMR studies in the solid state show that the rings included in the CyD cavity can exhibit a rapid flip around the C1C4 axis. One example is provided by **27@2** for which ^{2}H NMR spectra are incompatible with the rigid structure [50]; similar evidence has been obtained on the basis of ^{13}C NMR spectra [100, 101]. The rapid inversion of *cis*-decalin **33** in the complex with **2** at room temperature frozen at 233 K, observed in both ^{1}H and ^{13}C NMR spectra [102, 103], is also incompatible with CyD rigidity.

The very fast internal movement of native CyDs and of most of their derivatives, leading to the observation of averaged structures by most experimental techniques, is frequently overlooked. In addition to the temperature-dependent process of self-inclusion of substituent(s) [104–107], we were able to find only two studies of substituted CyDs in which movement of the macrocycles was at least partly frozen [104, 108]. Some other experimental results proving CyD flexibility using NMR