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Selectivity/structure correlation in cyclodextrin chemistry

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Generally we can not fit a "guest" to a cyclodextrin (CD), but we can select (or even synthesize by modifying the CD-structure) a better fitting -host- for a given guest. For the majority of potential guests (the most appropriate) CD-(derivative) and the most adequate conditions can be found, which make it possible to distinguish the host/guest complex from other components in a multicomponent system. This distinction will then be embodied in the separation of a given guest (by chromatography, extraction, selective precipitation, etc.), in selective reactions (regio- and enantioselective reactions, catalytic effects, etc.), in specific biological responses (accelerated and improved absorption, toxicity or elimination of toxic effects, etc.), in selective modification of physical-chemical parameters (spectral characteristics, dissociation, electrochemical properties, etc.). Recent examples for such selective interactions and their practical utilizations in technologies and industrial products illustrate the significance of structure/selectivity correlation in the CD-chemistry.

INTRODUCTION

The total number of cyclodextrin-publications (including patent literature) in 1994 reaches the 10.000 mark, equivalent to about 50.000 printed pages (1). About 85% of this material is dedicated directly or indirectly to inclusion-type interactions of cyclodextrins (CDs) with a very large variety of guest molecules of very different structures. The differences in the structures of both host and guest result in selectivity. The structure of α-cyclodextrin is shown in Fig. 1. Selectivity/Structure correlation in CD-Chemistry means that *interactions* between CDs and reacting partners (not only guests!)

- differ both in their intensities and mechanisms depending on the structure of both partners:

→ selectivity in chemical and enzymic reactions of CDs
→ selectivity in inclusion complex formation

- depend on all parameters, which influence the fit of the guest in the CD-cavity: conformation, ionization/hydratation, i.e. steric and electronic properties of the partners:

→ possibility for modification of the selectivity
→ possibility to optimize the CD-structure for a given task

- by partial shielding of the included guests, selectivity is induced in their reactions:

→ selective synthetic reactions
→ CD-catalysis (or stabilizing effects), enzyme modelling.

In many cyclodextrin complexation reactions, selectivity is a crucial factor. When a single-component substance is

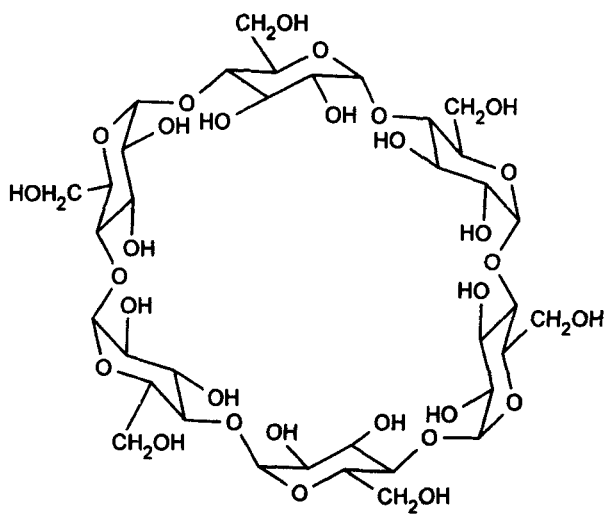

Figure 1 α-cyclodextrin.

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complexed-e.g. a drug-then the selectivity is irrelevant-only complex stability, complex solubility and the anti-catalytic (guest stabilizing) effect of the cyclodextrin play a significant role. In most cases however the cyclodextrins are reacting-in the presence of water-with multicomponent systems, where correlation between structure (both guest and host) and selectivity is a decisive factor. There are cases, when the technology is successful only, when the selectivity is fully suppressed. One such example is the production of stable flavor powders, i.e. the cyclodextrin-complexation of natural food flavors (which are always very heterogeneous multicomponent systems) when the complexation of all important characteristic components is required, in unaltered ratio (2). The other extreme is illustrated, when this multicomponent flavor substance is analysed by HPLC or GC using cyclodextrins to separate not only the individual compounds, but even their enantiomers. The selectivity/structure correlation forms the basis for

- Separation of mixtures using CDs:
  by chromatography
  by extraction
  by crystallization,
  by selective precipitation
- Selective synthesis in presence of CDs:
  chemical synthesis with regioselectivity
  chemical reactions with enantioselectivity
  photochemical reactions, etc.
- Enzyme modelling by CDs:
  catalysis with CDs
  synthesis and studies on prosthetic groups bearing CDs
- Biochemical reactions in the presence of CDs:
  enzymatic conversion in the presence of CDs, cell-membrane effects, etc.
- Selective modification of properties of the CD-included guest:
  ionization, reactivity and stability of the guest, spectral, electrochemical, hydrodynamic, etc. properties.

For illustration of the structure/selectivity correlation in cyclodextrin-complex chemistry, hundreds of examples have been published, and here only several recent characteristic examples, and several successful industrial applications will be discussed.

INFLUENCE OF GUEST STRUCTURE ON THE COMPLEX FORMATION

The fundamental works of CRAMER (3) and FRENCH (4) in the 50s already revealed that under identical conditions a given CD forms inclusion complexes of very different stability with various guest molecules. The term "stability" in this case means a shift of the association-dissociation equilibrium in solution. A higher degree of association results in a stronger modification of the reactivity of the included guest. If the complex is more soluble than the guest itself, it results in enhanced solubility. If the complex is less soluble than the CD itself, this is manifested in the precipitation of the complex in microcrystalline form. Correlation between the structure of the guest and complex stability has been studied by various methods and illustrated on series of structurally related guests, like steroids (2, 5), barbiturates (2, 6), fatty acids (7), homologous series of anionic surfactants (8) etc. It is now clear, that in the case of a given CD structural features of the guest, like geometric dimensions, and structure dependent properties like hydrophobicity, polarizability, etc. determine the stability of the complex.

A quite recent example which illustrates the significance of the geometric dimensions of the guest is CD-complexation of C60. On stirring the C60-Buckmisterfullerene with aqueous CD-solutions at room temperature, no interactions can be observed. Heating however, the mixture to 95°C for about 100 h, from the γCD solution the purple C60/γCD complex can be isolated. Its inclusion structure was evident from NMR, circular dichroism, and UV-VIS-spectrometry. The α- and β-CDs were shown to be too small for this bulky guest (9). The fact that steric and electronic factors play a more important role in the key-lock fitting, than the geometric factors is illustrated in the example of two bile acids. The molecular size of the stereoisomeric bile acids (taurocholic and tauroursodeoxycholic acids) is about 7 × 13 Å (width × length). The K_{ass} values at 25°C in aqueous solutions for the Na-taurodeoxycholate with α-, β- and γ-cyclodextrins are, 100, 2000 and 3000 M^{-1}, respectively, and for the Na-tauroursodeoxycholate are 100, 60000 and 40000 M^{-1}, respectively (10).

The interactions between bile acids and CDs delivered further interesting examples for the structure/selectivity correlation. Cardiovascular heart diseases and also the occurence of gallstones are believed to be associated-among others-with the consumption of highly digestible foods, with the strongly reduced bulk amount of digested and partially digested foods that enters the large intestines. The partially digested food components-mainly non-digested starch, pectins, etc. bind the bile acids, and facilitate their excretion and thus prevent their reabsorption. The liver replace this lost bile acid fraction by synthetising it from cholesterol, and this results in the reduction of blood cholesterol levels.

Cholestyramine (an ion-exchanger resin) is a synthetic sequestering agent, for bile acids which after oral administration binds strongly and removes the bile acids from the intestinal tract. A recent study, dedicated to the bile

acid sequestering capacity of various bile-acid chelators, revealed interesting structure/selectivity correlations.

The non-specific cholestyramine removed-both ^{14}C-chenodeoxycholate, and the ^{3}H-cholate (both administered intravenously) from mice-in a dose dependent manner. Orally administered βCD removed the ^{14}C-chenodeoxycholate with good effectivity, but not the cholate. γCD had no effect at all, very probably because of two reasons: its cavity is too "wide" for the bile acids, moreover it is rapidly degraded by the amylolytic enzymes in the small intestines. The αCD was not degraded, it is more resistant to the amylases and, similarly to cellulose, simply increased the amount of the faeces without sequestering bile acids. On a weight basis, the affinity of βCD for chenodeoxycholate is at least 200 fold greater than that of starch. βCD is only three times less effective (considering the necessary doses) than cholestyramine at eliminating chenodeoxycholate in mice. (11)

The cholate (3,7,12-tri-hydroxycholanic acid) is less hydrophobic than the chenodeoxycholate (3,7-dihydroxycholanic acid) this may explain, at least partly, the different affinities of these bile acids for the βCD-cavity.

Generally, we can not modify the structure of the guest, because the guest is given. It has to be protected, stabilized, transported, i.e. manipulated by CD-complexation. Even if a drug molecule-after a minor chemical modification forms a "better"-i.e. more soluble, more stable, or less bitter, etc. cyclodextrin complex, this way is not feasible, as it is already another drug, probably with significantly different pharmacological and toxicological effects. It means, that generally we can not fit the guest to the host, but we can look for a more appropriate host.

INFLUENCE OF THE HOST STRUCTURE ON THE SELECTIVITY

Looking for the most appropriate host for a given guest, CDs with various cavity diameters, with various axial cavity lengths, and with various CD-cylinder rim polarities are at our disposal. For slim aliphatic molecules e.g. fatty acids, the α-CD is the most appropriate. The α-CD readily forms insoluble complexes with fatty acids and this observation is utilized e.g. to remove the fatty acids from blood plasma in clinical diagnostic manipulations, or to remove detrimental free fatty acids from edible plant oils. The wider cavity of β- and γ-CD is not appropriate for these purposes. The unsaturated fatty acids because of their cis-double bonds-are not "slim" stretched roods, but folded e.g. horseshoe-shaped structures, which fit much better into the wider β-CD-cavity. Therefore when a mixture of saturated and unsaturated fatty acid-esters are complexed, the unsaturated fatty acids will form the more stable β-CD complexes, therefore they will be enriched significantly in the precipitated and isolated complex mixture (2).

Such selectivity may have very far-reaching consequences. E.g. in experimental rats, the hydroxypropyl-βCD administered directly into the brain (by a cerebral ischemia reperfusion technique) caused a significant increase in the content of cerebral mitochondrial membrane free fatty acids, the hydrolysis of polyunsaturated fatty acyl chains from phosphatidylcholine and posphatidyl ethanolamine. The preferred complexation of the polyunsaturated fatty acids through the apparent stimulation of brain mitochondrial membrane phospholiphase resulted in a polyunsaturated/saturated fatty acid ratio, significantly higher than normal. This enhanced free fatty acid level of altered composition is a potentially damaging factor to the brain energy metabolism, and the membranes in general (12). Fortunately, not only the orally, but also the intravenously administered CDs are unable to pass the blood/brain barrier.

Using the more soluble alkylated, hydroxyalkylated, branched (glycosylated) or ionic cyclodextrin-derivatives, a surprisingly high (up to 10000 fold or even more) and industrially suitable solubilizing effects can be attained. This makes possible the preparation of injectable aqueous solutions from drugs practically insoluble in water (like steroids). The possibilities for the chemical modification of cyclodextrins are far from being exhausted, as hundreds of further CD-derivatives can be synthetised.

These efforts may follow the following pathways:

- the substitution of hydroxyl group(s) of the CD-structure with other groups. Hydrophilicity/ hydrophobicity can be modified, the axial length of the cavity can be elongated, all this will affect the complex forming ability, i.e. may result in improved selectivities.

- Theoretically the cavity diameter could be enlarged (δ, ϵ etc. CDs), but they are too wide for any practically interesting guest and these oversized CDs contain too many water molecules, therefore the "driving force" for complex formation is negligible. Quite recently the synthesis of the 5-membered pre-αCD has been published (13). Its very narrow cavity certainly will be inutilizable for complexing e.g. drugs.

- CD's containing a heteroatom or a hetero-pyranose unit might be interesting, but actually very little is known about their complexing abilities, and even less about their toxicological properties.

The ultimate goal of the selectivity enhancing efforts is a CD-derivate which is quite soluble, forms-selectivity-

stable complexes with given guests (generally drug molecules), is stable upon storage, but will be decomposed rapidly in the biological milieu. The ring structure must be opened e.g. in the blood stream, after parenteral administration, otherwise cell-membrane effects can not be avoided. The rate of enzymic hydrolysis of α-1,4-glucosidic linkages of the CD-ring is generally slow, and a slight modification (substitution) further enhances the resistance of a CD-structure to enzymic degradation. If a CD-derivate does not react with cell-membrane components, with steroids, fatty acids, phospho- and neurolipids, than it certainly will not react satisfactorily either with drug molecules. It means, that a CD derivate is needed, which after fulfilling its task, solubilizing and carrying a poorly soluble drug to the required site, will be destroyed (by ring opening) and eliminated from the organism, without resulting in cumulating effects (e.g. in depletion of cholesterol in the kidneys).

REGIO- AND STEROSELECTIVE EFFECTS IN REACTIONS OF INCLUDED GUESTS

Many observations have been reported, and some reviews (2, 14, 15) have summarized the relevant literature. Quite recent publications have reported further typical examples. E.g. the synthesis of Naphthalenedicarboxylic acids from Naphthalenecarboxylic acid and CCl_4 is catalyzed by βCD in aqueous alkaline solution in the presence of copper powder. The yields of 2,6-DNA-2,7-DNA and 1,6-DNA were 58, 10 and 2,5 mol%, respectively. αCD was fully ineffective, γCD showed a low catalytic activity, as the yields of the above dicarboxylic acids were only 0,5, 0,7 and 0,2 mol%, respectively (16). In a similar reaction, the preparation of 4,4'-biphenyl dicarboxylic acid from 4-biphenyl carboxylic acid and CCl_4, only the βCD showed catalytic activity. In the presence of α- and γCD and without βCD no reaction took place (17).

The hydroxymethylation of indole with formaldehyde results in a 0.75:1 molar ratio of 3-(hydroxymethyl)-indole to 1,3-bis(hydroxymethyl)-indole. Performing the reaction in presence of 150 mM αCD or γCD or 15 mM βCD this ratio is 7.8, 6.7 or 1.5, respectively. Probably, the mono-hydroxylated product forms the most stable inclusion therefore it is protected from further substitution by complex formation (18).

Many examples have been reported for assymmetric induction in the presence of CDs, in homogeneous solutions, suspensions or the crystalline state. Production of keto-acids and norbornenones, halogenation, hydrohalogenation, oxidation of sulfides, epoxidation, sigmatropic rearrangements, Michael addition, Diels-Alder and Wittig reaction, photochemical rearrangements, etc. have been achieved in high optical yields using the combination of an achiral reagent and a prochiral substrate. Association constants alone are not enough to explain the assymetric induction, specific structure dependent orientation and mobility of the guest have to be considered, too (14).

Upon reacting with αCD, both the phenyl-group and the trans-double bond of trans-phenylethylenethioamide are shielded by the CD-cavity. In case of the cis-isomer, only the phenyl-moiety is included, correspondingly the K_{ass} value for the trans- and cis-isomers are 450 M^{-1} and 130 M^{-1}. On UV-irradiation, the trans-cis isomerization is retarded by the αCD-cavity, whereas the cis-trans transformation is facilitated. In the βCD complex of naphtylethylene thioamide only the naphtyl-moiety is included in the βCD-cavity, the trans-cis transformation is not influenced by the βCD, as probably the double bond remains outside the cavity, the K_{ass} is 270 M^{-1} (18).

Pirimidines in aqueous solutions are rather sensitive to UV-light e.g. the photoreduction of thymine proceeds rapidly on combined action of UV-light and hypophosphite. βCD in solution is an effective protector, it suppresses fully the photoreduction, while α- and γCDs are ineffective in this respect (20).

TERNARY COMPLEXES

Ternary CD-complexes may be true inclusion complexes containing, two (identical or different) guests or pseudo-ternary complexes, which contain only one included guest, while the third component modifies (through hydrogen-bond and/or salt formation) the structure of the host and/or guest in a non-covalent manner.

Until short time ago only a few examples were known of true ternary complexes. Also, the first examples of pseudo-ternary complexes have been published only quite recently. These structures deserve particular attention, because without chemical (covalent) modification of the host and/or guest unexpectedly high solubility enhancement effects have been attained, which can be very well utilized for practical purposes. For example to dissolve the 20 mg daily dose of Domperidone—which is a practically water-insoluble drug (its solubility is 0.005 mg/ml)—124,8 ml 10% HPBCD containing solution was needed (i.e. 12480 mg HPBCD). Forming a pseudo-ternary complex with 57,3 mg HPBCD and 6,9 mg L-tartaric acid only 0,6 ml (!) water is needed to obtain a clear injectable aqueous solution (21).

In such pseudo-ternary systems the solubility of the CDs also shows remarkable enhancement. E.g. the Cyclobenzaprine:βCD:citric acid in 1:1:1 molar ratio is quite soluble, the solubility of βCD increases to 20-fold and the solubility of Cyclobenzaprine is 44 mg/ml (this means a 366 fold solubility enhancement) (22).

The solubility of Terfenadine in water is only about 0,01 mg/ml which increases with increasing βCD concentration up to about 0,08 mg/ml, then reaching a plateau. This drug readily forms a Terfenadine/βCD 1:2 solid complex, as supported by the usual tests, while in solution the ratio of 1:1 and 1:2 complexes depends on the concentration of the components. In the presence of acids, the solubility of Terfenadine increases e.g. in HCl to 0,12 mg/ml, in tartaric acid solution to 0,45 mg/ml, i.e. to 12- and 45-fold, respectively. Combining these acids with βCD an unprecedented synergetic effect has been observed. Aqueous solutions of 30–50 mg/ml Terfenadine and 160–200 mg βCD concentrations could be prepared, i.e. the solubility enhancement factors for βCD and Terfenadine were about 10 and 3000–5000 fold, respectively. These hydroxyacids alone resulted only in a 2–3-fold solubility enhancement of βCD (23).

This type of solubility enhancement is very sensitive to minor structural differences both in the guest, and in the "pseudo-guest" carboxylic acid. E.g. D- and L-tartaric acids are more effective than the racemic D-, L-tartaric acid in enhancing the solubility of Astemizole (about 25 mg/ml with both pure enantiomers, and only 7 mg/ml with a racemic mixture).

EXAMPLES FOR PRACTICAL UTILIZATION OF THE STRUCTURE/SELECTIVITY CORRELATION

Separations on analytical scale

The literature on the application of CDs in analytical separations (which is the most direct utilization of the structure/selectivity correlation) by HPLC, TLC, GC, EKC, etc. is enormous. During the last 12 months (July 1993-June 1994) Cyclodextrin News published the abstracts of 206 such papers.

Separations on preparative scale

The number of papers on separations on a preparative scale, or on industrial scale are less abundant, than those on an analytical scale. Among these the separation of hydrocarbon isomers and the separation of cholesterol from butter and egg seem to be the most interesting. Earlier relevant literature has been summarized (2), and the possibilities can be illustrated on the separation of cresol isomers.

The boiling points of o-, p-, and m-cresols are 190.9, 201.9 and 202.2°C, respectively, therefore the separation of p- and m-cresols (on industrial scale) is impossible by distillation. On mixing the mixture of cresol isomers with aqueous alkaline αCD solution a precipitate is obtained which after isolation and decomposition delivers a significantly modified isomeric ratio. From an equimolar mixture of the three isomers a 7:69:24 ratio of o:p:m-cresols has been obtained (24).

A representative example: complexation of cholesterol with various cyclodextrins

Cholesterol/CD complexes deliver an excellent illustration for the practical utilization of CD-complexation in very different fields as well as for the effect of structural modifications of the host on the behavior of the complex and its utility.

The first observation on the interactions of cholesterol and βCD were rather discouraging. Parenteral administration of βCD to rats caused nephrotoxic effects. The symptoms were rather complex, but the main phenomen was the apparent formation of needle-like crystals in the kidneys. It was assumed, that the parenterally administered βCD forms a poorly soluble cholesterol complex which upon concentrating in the kidneys forms cell-destroying crystals. (25)

On synthetising hydroxypropyl-βCD this problem has been eliminated. Substituting several hydroxyl groups by hydroxypropyl groups had four important consequences:

- The solubility of βCD has been enhanced to extremely high levels
- The solubilizing capacity for many poorly soluble substances was strongly increased
- No crystalline complexes could be formed, because the HPBCD is a very heterogeneous, non-crystallizable substance
- Because of the strong hydrophilicity of HPBCD, its affinity toward the cholesterol has been reduced. Nevertheless, repeated i.v. administration of HPBCD to hypercholesterinemic Watanabe-rabbits led to a gradual increase in total cholesterol in circulation and even to a slight reduction of atheroschlerotic lesions in the thoracic aorta (26).

HPBCD—in acute treatments—can be injected even as 40% (w/w) solution, intraveneously, without any crystal formation provoking nephrotoxic consequences (long, lasting, chronic treatment with high HPBCD doses is not recommended: the HPBCD will be excreted through the kidneys, but the transported cholesterol is retained and cumulates in the kidneys). Hydroxypropyl-βCD probably will be approved soon by the appropriate Health Autorities as a parenteral drug carrier in short term treatments.

A second observation was not less discouraging: CDs exert a haemolytic effect on erythrocites. The probable mechanism is that the CDs sequester the cholesterol (and other vital cell-membrane lipids: phospholipids, lipoproteins) from the cell membrane, resulting in their rupture.

The sequestring capacity of various CDs for cell membrane components of both erythrocites and intestinal cell-membranes also showed a structure/selectivity correlation. While for the "slim" aliphatic chains containing phospholipids the effectivity sequence was $\alpha > \beta > \gamma$, for the cholesterol it was $\alpha > \beta > \gamma$.

It soon become obvious that the more liphophilic CDs (e.g. methylated CDs) show the strongest haemolytic effect, with decreasing lipophilicity, the haemolysing activity decreases rapidly. The hydroxypropyl-αCD and hydroxypropyl-βCD showed limited specificity toward phospholipids and cholesterol, respectively. On introducing ionic groups into the CD-structure, the immediate haemolytic effect can be supressed almost completely. Presently the sulfobutyl-βCD is the most promising such a CD-derivative (27).

The very high affinity of βCD for cholesterol means that in a lipid mixture the βCD will react preferably with cholesterol. Mixing butter with βCD in the presence of water, the βCD will form insoluble and easily separable complexes with cholesterol, and to some less extent with free fatty acids, D-vitamins, etc. The low-cholesterol butter in which the original 0,2% cholesterol content is reduced to about 0,02% already is produced and marketed in several countries. Similarly, the cholesterol can be removed from egg-yolk, and cholesterol-free eggs also are produced and marketed.

By immobilizing βCD on the surface of a quartz oscillator surface, the construction of a cholesterol specific sensor has been reported, which allegedly can be used for determination of cholesterol in the blood (28).

On feeding rats and hamsters with βCD or βCD derivatives (amino derivatives or polymers), a significant reduction in the blood cholesterol and triglyceride level has been observed (29, 30). The cholesterol level reduction was similar to that attained by cholestyramine. The enhanced removal of the bile acids stimulated the synthesis of bile acids from cholesterol. Considering that a very large number of compounds, all at very different concentration levels, are present in the intestinal tract (a full spectrum of degradation products of the consumed foods), a high selectivity of βCD for the cholesterol-derived bile acids is manifested in this observation.

The very strongly haemolysing methylated CDs also have found their practical applications. Five mg/ml clear aqueous cholesterol solutions are prepared as cholesterol standards. In aqueous solutions of cholesterol and other, otherwise poorly soluble, steroids such reactions (both chemical and enzymatic) can now be performed which earlier were not possible because of the very low solubility.

The microbial conversion of cholesterol to important steroid synthesis intermediates can be performed with excellent effectivity and selectivity in presence of CDs. (31) Androst-4-ene-3,17-dione and androst-1,4-diene are the synthesis precursors for most expensive steroid drugs. They can be produced by microbiological degradation of the side chains of cheap steroids, like cholesterol or sitosterol. Cholesterol degradation, however, occurs not only via side-chain cleavage, but also by sterolnucleus degradation. This diminishes the yield, and the removal of the non-desired by-products makes the technology more complicated and more expensive.

A further complicating factor is, that some microorganisms are sensitive to the products formed, i.e. product inhibition with the above mentioned side reactions reduces the yield and effectivity of the microbial conversion to about 40%. In presence of βCD these problems are eliminated, 95% of the cholesterol is converted to the desired products.

In the production of Δ^4-cholestenone from sitosterol, γCD was shown to be the most effective. βCD showed little effect, and αCD had no effect at all. For the production of Δ^4-cholestenone from cholesterol, again βCD was the best agent; γCD also was effective, but αCD was practically indifferent. It is generally believed that CDs are not very discriminating hosts. Like all such statements, also this one can be challenged because

—a CD cavity can accommodate only a guest, if its size and polarity is appropriate-i.e. the absolute majority of inorganic compounds, polymers, small or strongly hydrophilic molecules are excluded from CD-inclusion. Nevertheless the border between a "true inclusion complex" and "inclusion-like interaction" can not be clearly defined. E.g. electrospray ionization mass spectrometry showed that the 40 aminoacid containing synthetic β-amyloid polypeptide interacts with βCD, presumably through the aromatic aminoacid moieties. As a consequence of this interaction, the neurotoxic effect of this polypeptide in a cell-line (32) is substantially diminished.

—the reported $K_{1:1}$ association constants for complex-forming molecules are between 0.5 to about 80,000 M^{-1} for natural CDs, but a value as high as 10^6 M^{-1} has been reported for chemically modified CDs. Considering the enormous number of successful HPLC, GC and EKC separations with CDs or CD-derivatives (CD either in the mobile phase or in the stationary phase) it is clear, that CDs are very discriminating hosts, only the appropriate conditions have to be found.

CONCLUSIONS

Summarizing and evaluating our actual knowledge on selectivity/structure correlations and taking into consid-

eration the requirements of actual and potential users of CDs the following directions become apparent for the future:

1. Modifying the shape of the CD-cylinders: distorted, ellipsoid cavities are expected to show enhanced enantioselectivities. Eventually these efforts will make possible (also on preparative scale) a sharp resolution of enantiomers now only possible on an analytical scale.
2. Attaching substituents to the secondary and/or primary hydroxyl rims of CD-cylinders that will exert more selective effects on the included guest, either enhancing their reactivity (catalytic effects, enzyme modelling) or increasing selectivity for specific guests (sensors).
3. Preparing CDs which will decompose in the blood, releasing the carried drug, but which can not react with cholesterol or other lipids of the plasma or with cell-membranes.

The source of any toxic effect of CDs is associated with their interactions with the lipids either in cell-membranes or in the circulation. Chronic treatment of humans with larger doses of CD-derivatives will result unavoidably in cumulated effects in the kidneys and in the pancreas. These effects apparently are due to the intact ring. Therefore, it is not enough to substitute the hydroxyl groups. It is possible to prepare such CD-derivatives, which will have a rather low affinity for lipids, but they will have a low affinity also for poorly soluble, hydrophobic drugs. Therefore such derivatives do not seem to be promising as parenteral drug-carriers. We need CD-derivatives, which are highly soluble, good solubilizers for poorly soluble drugs, but will be destroyed shortly after getting into the circulation. Destruction in this case means the opening of the ring under physiological conditions.

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