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MICROENCAPSULATION BY CYCLODEXTRINS

Molecular encapsulation has attracted much attention in a broad area of science and technology, particularly in chemistry, biology and pharmacy. Natural as well as synthetic nanometer–sized supramolecular aggregations are widely used for host guest complexation, influencing the properties of the mostly organic guest molecules.

Generally, molecules interact with each other, depending on their size, their shape, the complementarity of their molecular surfaces and their electrostatic potentials. The inclusion of small or medium–sized compounds by proper host molecules or larger biomolecules results from such interactions. These forces lead to less specific solvation, to more specific host guest interactions and at least to very highly specific ligand biomolecule interactions.

Host guest complexation occurs between many different molecules or ions with larger molecular assembles with more or less pronounced cavities, possessing a broad variety of physico–chemical properties.

The host compounds might be flexible to some extent, to enable conformational changes with respect to the molecular shape of the guest molecule or might be rather rigid leading to a higher specification of molecular recognition. Many molecular receptors have been investigated in the past, like crown ethers, calixarenes, cucurbituril, cyclic peptides and cyclodextrins. A highly important inorganic system for host guest inclusion has been found in zeoliths, where organic molecules are absorbed at an inorganic matrix.

Particularly cyclodextrins (CDs) have been used for a broad variety of applications, especially in pharmacy, environmental and technical chemistry, because these type of compounds are very convenient due to their great variability of molecular shape and molecular properties. Stereospecific separations of diastereomers and optical isomers, protection of unstable compounds (e.g. light–, temperature– or oxidation–sensitive substances), emulsification of apolar compounds, catalytic activity and support in organic syntheses are topics which make CDs to an undispensable excepient in many scientific disciplines. A not underestimated property of most CDs should be mentioned here, the low toxicity for humans, which enables the application in a wide field of pharmacy and pharmaceutical technology e.g. masking of odour or taste, solubility enhancement and increase of bioavailability and efficiency of the active substance and the permission of its controlled release. A very interesting and important application possibility of CDs is the isolation of biologically active compounds e.g. from plant extracts.

Cyclodextrins are cyclic macromolecules obtained by the degradation of starch [a(1→4) linked polyglucose] by α–1,4–glucan–glycosyltransferases. Depending on the respective transferase, different types of CDs result, consisting of 6 (α–CD), 7 (β–CD) or 8 (γ–CD) α(1→4) linked glucose units. The molecular shape of CDs resembles that of cones. They have a hydrophobic cavity with an average diameter of 5 Å (α–CD), 6.2 Å (β–CD) and 7.9 Å (γ–CD), respectively, and a thickness of 8 Å. There are also existing larger CDs, as delta, epsilon and i–CDs with 9, 10, and 14 glucose residues. In these CDs the macrocyclic ring does not form well–defined molecular cavities despite the formation of intramolecular hydrogen bonds.

The molecular structure of CDs and some CD–guest complexes has been elucidated by X–ray and neutron diffraction. Structural elucidation of various CDs and the related complexes is also supported by molecular modeling studies. As a consequence of the size of these molecular systems molecular mechanics studies on the conformations of CDs and the inclusion complexes were reported mainly, but also Dynamic Monte Carlo simulations have been performed including solvation shells. The geometry of inclusion complexes was also treated by semiempirical methods, and, more recently by ab initio and density functional theory methods.

The inclusion of guests can also be monitored by various spectroscopic methods. If the guest absorbs in UV range, its inclusion can be observed by titration with CD. In a similar way the change of circular dichroism

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can be used, even if the guest is achiral, due to the fact that upon inclusion the complex shows an induced circular dichroism. Also NMR spectroscopy offers excellent possibilities for the characterization of CD–guest complexes and has particularly been used to study preferential inclusion of enantiomeric compounds.

THEORETICAL BACKGROUND

The large number of experiments on CD–guest complexes together with many physicochemical and theoretical investigations give some insight into the nature of the forces which are responsible for the association of the CDs and guest molecules. Several driving forces for the complexation process have been suggested:

– Electrostatic interactions

– Van der Waals interactions

– Hydrophobic interactions

– Hydrogen bonding between polar groups of the "guest" and the hydroxyl groups of the "host"

– Relaxation by release of high–energy water from the CD cavity upon substrate inclusion

– Relief of the conformational strain in a CD–water adduct

– Induced fit (CDs undergo significant conformational changes upon complex formation to optimise opportunities for other modes of interactions

The elementary reaction steps of the overall binding of a guest molecule to the host in an polar solvent can be grouped to the following processes:

– desolvation of the guest

– internal desolvation of the host

– host – guest binding

– reorganization of the solvent around and inside the cavity

The different forces, responsible for the affinity between host and guest molecules can be separated by molecular calculations. Particularly, prediction models for the free energy of complexation between various CDs and guest molecules (mostly drugs) were developed, based on linear and nonlinear correlation analysis (multiple linear regression and partial least squares). In these investigations experimentally determined free energies of complexation were correlated with theoretically calculated molecular descriptors.

The predictive abilities of some models are good, reflected in high predictive r^2_{cv} values at different leave–out levels and good de novo predictions. Introducing explicitly nonlinearities into the model generation leads to a significant improvement of their predictive abilities. The regression equations, together with molecular modeling studies, give insight to the complexation mechanisms, which appear to be different for the three types of cyclodextrins.

In the case of α–CD the predictive power of the models is relatively low. Together with the observation that in none of the models the volumina of the guest molecules correlate significantly with the free energy of complexation, it can be concluded that the complexes are not well defined. It seems, that the guest molecules are included only partially or not at all, if their volumina are too large. Most of associations occur at the external, also hydrophobic part of the cyclodextrin.

The predictive abilities of the models for β– and γ–CDs is fairly high. The fact that in both cases steric parameters do have weighty contributions to the complexation energy, suggest the importance of Van der Waals forces for both, β– and γ–CDs. However, for β–CD it appears that hydrophobic interactions are additionally crucial for host–guest complexation hydrophilicity of the molecular surface. The hydrogen bond donor capacity of the guests appears to have little contribution to the stabilization of the complexes. Generally in β–CD structure of the rim is rigid, as it is stabilized by intramolecular hydrogen bonds, and does not allow a broad steric variety of the guest.

In contrast, for γ–CD, the most important stabilizing contribution stems – besides the van der Waals interactions – from the hydrogen bond donor and acceptor capacity of the guest molecule. The molecule is rather flexible and adapts its structure to much higher extent to the molecular shape of the guest molecule.

As another example for the influence of the encapsulation on molecules by CDs the change of the environment sensitive intramolecular proton transfer equilibrium in Mannich bases can be used to characterize the interaction forces. In these molecular systems naphthol as proton donor is bound via a methylene bridge to aliphatic amines like piperidine or morpholine. An intramolecular hydrogen bond is formed in these compounds and depending on the strength of the proton donor and the proton acceptor proton transfer between the hydroxyl group and the nitrogen atom of the amine may take place. This proton transfer equilibrium is rather sensitive to changes of the solvent, as the polarity of both reaction partners is significantly different. Encapsulation of these compounds by CDs changes the proton transfer equilibrium in a such a way, that the zwitter ionic structure is not stabilized by the mostly hydrophobic cavity of CDs. Comparisons with measurements in various dioxane water mixtures show that the proton transfer equilibrium in piperidinomethyl–2–naphthol is similarly shifted by an amount of 20% dioxane as by complexation with β–CD in aqueous solution. Moreover, the influence of the cavity of various CDs on the proton transfer equilibrium is different, which can be used to characterize the cavity.

The thermodynamic parameters are of high interest for a detailed investigation of CDs host–guest inclusion complexation, as the give some insight about the importance of the contribution of the reaction enthalpy and the reaction entropy to the overall energy profile of the association process. Generally, from

measurements of the thermodynamics of many hundreds of compounds no clear correlations could be found, although in many cases a somewhat linear correlation between the reaction enthalpy and the reaction seems to be a common principle. Moreover, enthalpy–entropy compensation is observed very often.

In detailed studies (e.g. on the solubility enhancement of triflumizole, a systemic fungicide) it was found, that the association constant of this compound with β–CD and dimethyl–β–cylcodextrin (DM–β–CD) is very similar, but the temperature dependence of the equilibrium constant differs significantly, indicating that the reaction enthalpy and entropy CD values are completely different for both host molecules. An analogous behaviour was observed for spironolacton, a compound with large complexation constants for both CDs.

INDUSTRIAL APPLICABILITY

Many application possibilities exist for CDs in many branches of industrial uses. As some examples the enhancement of the bioavailability of poorly soluble drugs should be mentioned. This phenomenon is caused by the increase of the solubility of such drugs in water, connected with an increase of the dissolution rat. Moreover, a more complete and faster absorption after oral application can be achieved. The improved bioavailability offers the possibility of lower dose administration with comparable therapeutic effect and of diminished dose–related side effects. There exist also some technological advantages in the formulation of oral drugs: Liquid compounds can be transformed into crystalline form suitable for tabletting. Incompatible compounds can be mixed and used together in complexed form. Extended release formulations can be prepared. Similar advantages are valid for liquid drug formulations, as stable aqueous solutions of water insoluble drugs can be prepared without using organic cosolvents. Generally, CDs can be applied as binder, resulting in tablets of suitable properties.

Another application of CDs widely used is the isolation of biologically active compounds from natural mixtures. The extraction of scilliroside from dried urginea maritime is an example of a more efficient isolation than solute–solute extraction. On the other hand the removal from contaminents from gases, from waste groundwater or from soil is an important contribution for a more clean environment.

Although the applicability of CDs is tremendous high, the development of new possibilities techniques is in fast progress, also because of the syntheses of new products and the increasing importance of the use of CDs as carriers in nanotechnology.

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