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Review Article

The Driving Forces in the Inclusion Complexation of Cyclodextrins

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Abstract

The driving forces leading to the inclusion complexation of cyclodextrins were reviewed, which included the electrostatic interaction, van der Waals interaction, hydrophobic interaction, hydrogen bonding, release of conformational strain, exclusion of cavity-bound high-energy water, and charge–transfer interaction. It was shown that except for the release of conformation strain and exclusion of cavity-bound water, the other interactions were indeed contributive to the complex formation. However, it was concluded that the enthalpy and entropy changes of the complexation were not good criteria to be used in judging whether a particular driving force was present or important, mainly because of the occurrence of enthalpy-entropy compensation. On the other hand, the multivariate quantitative structure-activity relationship analyses usually could illustrate which driving forces were important in certain inclusion complexation systems.

Introduction

The understanding of non-covalent interactions is of paramount importance in supramolecular chemistry and in biological chemistry [1]. Towards this goal, the molecular recognition of many simple host molecules, such as crown ethers, cyclodextrins, and calixarenes, have been extensively studied [2]. Unlike the natural systems, the synthetic host–guest complexes have better defined conformations and therefore can be analyzed experimentally and theoretically in more detail.

Cyclodextrins (CDs) are among the most frequently used host molecules in supramolecular chemistry [3]. They are macrocyclic oligomers of α-D-glucose, and shaped like truncated cones with primary and secondary hydroxyl groups crowning the narrower rim and wider rim, respectively [4]. Four species of CDs are known with rings comprising from 6 to 9 glucose units: α-CD (6 units), β-CD (7 units), γ-CD (8 units), and δ-CD (9 units) (Figure 1). As they have a hydrophobic cavity of appropriate dimension, they can bind with various guest molecules to form inclusion complexes [5]. This property has enabled CDs to be widely used in pharmaceutical science [6], catalysis [7], separation technology [8] and other areas [9]. Furthermore, the CD inclusion complexation has been considered an ideal model mimicking the enzyme-substrate interactions [10].

Apparently, the quantification of the driving forces involved in the molecular recognition of CDs is fundamentally important not only for CD chemistry but also for supramolecular chemistry as a whole. As a result, a large number of studies have been done on this topic, which have been repeatedly summarized in several review articles. Nevertheless, it is still often claimed that the driving forces leading to CD complexation remain unclear or controversial.

Here we present a new review focusing on the topic, in which the former studies are surveyed in more detail and very recent progress is covered [11]. It is noteworthy that in the present review only the interactions between the substrates and the cavity wall of CDs are considered. Therefore, the interactions between the substrates and the substituent groups of the substituted CDs will not be discussed.

Possible driving forces

Electrostatic interaction

The electrostatic interaction energy is the energy of interaction between the undistorted charge distributions of the two molecules interacting with each other. It includes all electrostatic forces between permanent charges, dipoles and higher multipoles present in the system. Usually, three types of electrostatic interactions are the most important, i.e., ion–ion interaction, ion–dipole interaction, and dipole–dipole interaction.

Apparently, as CDs are neutral molecules, the ion–ion interaction does not occur in CD complexation, unless the CD is appropriately substituted [12].

On the other hand, the ion–dipole interaction is expected to take place in CD complexation for the apparent reason

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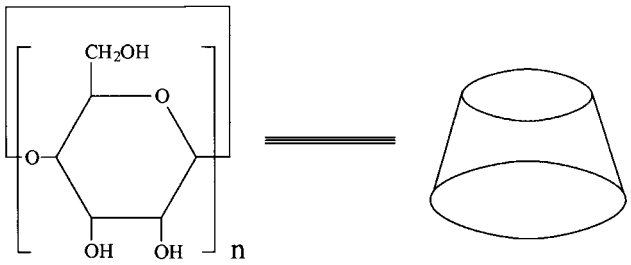

Figure 1. Structure of cyclodextrin (n = 6(α-CD), n = 7(β-CD), n = 8(γ-CD), n = 9(δ-CD)).

that CDs are polar molecules. Unfortunately, the occurrence of this interaction is difficult to show. For example, as the ion–dipole interaction should be enhanced when the charge of the ion increases, it can be expected that dianions such as SO_4^{2-} and CO_3^{2-} will bind more tightly with CDs than anions such as ClO_4^- and NO_3^-. However, though the complexation of CD with ClO_4^- and NO_3^- have been observed experimentally, no complex formation can be detected for SO_4^{2-} or CO_3^{2-} [13]. In fact, any strong ion-dipole interaction is not necessarily favorable for the CD complexation in aqueous solution because under this condition the interaction between the substrate and water will also be strong [14]. Nevertheless, it should be mentioned that recently the complexes of CDs with the molecular ions of many species have been observed in the gas phase with mass spectrometry [15]. Apparently, in these systems the ion–dipole interaction should play a crucial role.

In 1987, Chujo *et al.* calculated the dipole moments of CDs based on published X-ray crystal structures with the CNDO/2 method, and obtained very large values in the range of 10–20 D [16]. Thus, it was believed that the CD cavity is highly polarized. Later, several other authors performed the study again, and found that the dipole moments of CDs are highly susceptible to the influence of chemical environment [17]. Usually, smaller dipole moments in the range of 2–4D were obtained for the CD molecules optimized by various theoretical methods, especially in a recent *ab initio* calculation [18].

Nevertheless, it is true that CDs have modestly large dipole moments, and this property of CDs must play a role in their complexation. In 1988, Chujo *et al.* used the CNDO/2 method to model the complexation of α-CD with several substituted benzenes such as benzoic acid, *p*-hydroxybenzoic acid, and *p*-nitrophenol [19]. It was found that in the complexes, the dipoles of the guest molecules are antiparallel to that of the host. Interestingly, as the magnitude of the guest dipole increases, so does the value of the CD dipole but in the opposite direction. Thus, the authors concluded that the dipole–dipole interaction plays an essential role in stabilizing the complex as well as determining its orientation.

The importance of the dipole–dipole interaction in CD complexation can also be shown with the free energy relationship analyses. For example, the correlation has been studied between the binding constants of α-CD with 4-substituted benzoic acids and the Hammett σ constants of the substituents [20]. In the system, as the —COOH group always stays at the positive end of the dipole of the host [21], it is readily understandable that the binding is enhanced by electron release from the *para* substituent. However, in the complexation of α-CD with 4-substituted benzoate anions, it is the electron-withdrawing *para* substituents that favor the binding [20]. This is again caused by the dipole–dipole interaction, because in the anion complexes the —COO^- group stays at the negative end of the dipole of the CD.

The above behaviors are also observed in α-CD complexation with 4-substituted phenols, phenolate anions, and anilines [22]. As in these complexes the *para* substituent stays at the positive end of the dipole of the host [23], the stability of the complexation roughly increases in order of increasing Hammett σ substituent constant.

Later, based on a correlation analysis, Davies *et al.* also pointed out the importance of dipole–dipole interaction in CD complexation [24]. In their study, the Hammett σ values were chosen to reflect the electronic effects of the substituents in 1,4-disubstituted benzenes. It was found that for neutral 1,4-disubstituted benzenes, the group with a larger σ value is bound in the narrower end of the α-CD cavity because of the favorable dipole–dipole interaction energy. The conclusion has been successfully applied to a number of systems [25], and it was found that the several exceptions to the rule such as the complexation of α-CD with *para*-substituted aromatic sulfides, sulfoxides, sulfones, and ketones are caused by steric hindrance [26].

The above results can also be shown from other studies. For instance, Hamai *et al.* studied the effect of CD complexation on the acidities of several phenol derivatives such as 4-nitrophenol, 4-cyanophenol, 4-bromophenol, and 4-methoxyphenol [27]. It was found that except for 4-methoxyphenol, the acidities of phenols are enhanced as a result of CD complexation. The behaviors were thought to be due to the dipole moments of the phenols, which are usually directed from the hydroxyl group to the *para* substituent, except for 4-methoxyphenol. Thus, the dipole–dipole interaction was concluded to be important in CD complexation. Similar results were also obtained in our recent study. Though 4-nitrobenzoic acid or 4-nitrobenzaldehyde was found to have smaller binding constants with β-CD than benzoic acid or benzaldehyde, the binding of β-CD with 4-nitrophenol or 4-nitroaniline is much stronger than that with phenol or aniline. [28] Obviously, the direction of the dipole of the guest compound and the dipole–dipole interaction between the host and guest cause the above behaviors.

In addition, Yasuda *et al.* recently performed scanning tunneling microscopy observations on self-assembled α-CD inclusion complexes on HOPG for the guest compounds of water, methanol, and 4-nitrophenol [29]. The observed structures of α-CD-water and α-CD-methanol complexes were different from the structure of the α-CD-4-nitrophenol complex. It was believed that the difference reflected the important role of the dipole–dipole interaction in CD complexation.

Van der Waals interaction

As pointed out by Connors [11d], in spite of the ambiguity attached to the term van der Waals force, workers in the CD field when mentioning van der Waals force mostly seem to mean either the induction and dispersion forces combined or the dispersion force alone. Herein, the induction force, or dipole-induced dipole interaction, is the interaction of an induced dipole moment of one molecule with the permanent dipole moment of another molecule. On the other hand, the dispersion force, or London-Eisenschitz force, is caused by the synchronization of the electronic motion in the two molecules, which results in momentary dipole moments oriented so as to produce an attraction between the molecules.

The presence of the two forces in CD complexation is reasonable. As CDs have modestly large dipole moments, it is not unexpected that the induction force could be strong in CD complexation. In fact, as early as in the 1960s, Casu and Rava mentioned that the induction force could be the major driving force of CD complexation [30]. However, the importance of the dispersion force is hard to show without any ambiguity, because the dipole-induced dipole interaction is always present even in the best illustrative examples of the dispersion force such as CD complexes of xenon and krypton [31]. Thus, to avoid complication, we will use the term van der Waals interaction instead of induction or dispersion force in the following discussion.

Many authors have claimed the involvement of van der Waals interaction in CD complexation, but the arguments of some of them are in fact weak. For example, as it is generally believed that the hydrophobic interaction between two nonpolar molecules is with a positive enthalpy, the observation of a negative enthalpy change in CD complexation is often considered to indicate the dominance of van der Waals interaction instead of the hydrophobic interaction [32]. However, as CD complexation is a complicated process, the above argument is not always correct, which will be shown in the following section.

Nevertheless, one reasonable method to show the involvement of van der Waals interaction in CD complexation is the correlation analysis between the strength of binding and the structural features of the substrates. For instance, both the induction and dispersion forces depend on polarizability, which in turn is related to molecular size and electron density, and so to the correlation variables molar refraction, molecular volume, surface area, molecular weight, the parachor, and so on so forth. Thus, the correlation between the strength of binding and the above parameters is at least indicative of the importance of van der Waals interaction in CD complexation [33].

The involvement of van der Waals interaction in CD complexation can also be shown by the structures of the complexes. In fact, numerous studies have revealed that bulky guest molecules are in close van der Waals contact with the CD cavities [34]. Interestingly, sometimes van der Waals interaction might be so strong that the hydrophobic but bulky side of the guest molecule can enter the CD cavity. For example, inclusion from the sulfonate side was observed in the CD complexation with azo dyes [35]. Moreover, the fact that CDs can form stable complexes with the guest molecules in pure organic solvents such as DMF, DMSO, and even heptanes evidently demonstrates that van der Waals interaction is essentially important [36].

Another method to show the involvement of van der Waals interaction in CD complexation is molecular modeling [37], which is usually performed with molecular mechanic and molecular dynamic calculations. In the calculations, the magnitude of van der Waals interaction is usually estimated on the basis of the Lennard–Jones 6-12 potential, while the magnitude of the electrostatic interaction is estimated on the basis of the charges of the atoms. It should be mentioned that most calculations on CD complexation were performed in the gas phase, so that the solvation effect plays no role in the results. Nevertheless, the results of the calculations are still valuable. First, from the calculations many authors concluded that van der Waals interaction makes the major contribution to the formation of CD complexes [38]. This conclusion is not unexpected, because in the calculation the energetic contributions from the dehydration and hydration of the host, guest and their complex, and from the reorganization of the solvent molecules were not taken into consideration. Therefore, the above conclusion should be modified, i.e., from the calculation it could be concluded that the magnitude of the van der Waals interaction is large between CD and the substrates, but whether or not van der Waals interaction plays a major role in CD complexation in solution remains unclear. Interestingly, most calculations revealed that the electrostatic interaction makes a minor or negligible contribution to complex stability. The conclusion was drawn either from the small magnitude of the calculated electrostatic interaction [39], or from the fact that the binding energies calculated at different dielectric constants were almost identical [40]. The result is not difficult to understand, because the dipole–dipole interaction is the most important of the electrostatic interactions between CD and the substrates. As known, the larger and more complicated a complex, the less does the presence or absence of a dipole–dipole force matters to the interaction energy.

In addition, it should be mentioned that van der Waals interactions also exist between the solvent molecules and the substrates of CD. Thus, in the CD complexation the substrate is exchanging one set of van der Waals interaction (with the solvent molecules) for another set (with the CD cavity). In fact, this type of exchange is the reason why the ion–dipole interaction is not significant in CD complexation as mentioned before. However, as the polarizability of water is much lower than that of the organic components lining the CD cavity, it is expected that van der Waals interaction should be stronger between CD and the substrates than between water and the substrates. As a result, van der Waals interaction has a positive contribution to complex stability. This effect can be shown by the complexation of CDs with inorganic ions such as ClO_4^- and NO_3^- [41]. Apparently, the hydrophobic interaction cannot make a contribution in these systems. As the ion–dipole interaction might be stronger between water and the ions than between

CD and the ions, the only possible driving force leading to the complex formation is van der Waals interaction.

Hydrophobic interaction

The role of the hydrophobic interaction in CD complexation is a controversial problem. This is not strange, because the subject of hydrophobic interaction itself also remains controversial [42].

Traditionally, hydrophobicity was considered to be the result of the enhanced structure of the water molecules in the near vicinity of the non-polar solute, which would bring about a usually large entropy loss during the hydration [43]. Sometimes, this explanation was even overemphasized, resulting in the postulation of the iceberg- or clathrate-like structures of the hydrophobic hydration shell [44]. According to the model, the destructive overlap of the hydrophobic hydration shell, which is entropically favorable due to the release of the structured hydration water, constituted the driving force for the aggregation of nonpolar solutes in aqueous solution [45]. This driving force is usually named the hydrophobic interaction.

However, the above microscopic picture of the hydrophobic interaction was greatly challenged recently. Neither the neutron scattering measurements nor the computer simulations indicated any evidence that the structure of the hydration water close to a nonpolar solute was more ordered than that of water in the bulk [46]. In consequence, researchers are beginning to develop completely new theories of hydrophobic interaction [47].

Nevertheless, in the experimental studies, the association of nonpolar molecules in water is usually found to be with positive enthalpy and positive entropy changes. This has long been taken as the experimental signature of the hydrophobic interaction. According to it, the fact that most of the experimental enthalpy and entropy changes of CD complexation are negative [48] seems to indicate that the hydrophobic interaction is not an important driving force in CD molecular recognition.

The above conclusion is annoying to some extent. As the interior of CD cavities is higher nonpolar, it is hard to understand why the hydrophobic interaction does not significantly contribute to the complexation. Sometimes, it was suspected that the above experimental observation was not representative enough, possibly because all the guest molecules that had been used were not sufficiently hydrophobic. Thus, the α-CD complexation with 1-adamantanecarboxylate was studied, and the observed positive entropy was believed to settle the problem [49]. Unfortunately, a reinvestigation of the system showed that the entropy change is still negative [50].

In fact, the above problem can be settled if we notice that in CD complexation many interactions other than the hydrophobic interaction are also involved [51]. For example, unlike that in the aggregation of two small nonpolar molecules, the van der Waals interaction between CD and the substrate is quite strong (10–20 kcal/mol according to the theoretical calculations) in their association. As the interaction is attractive in nature and it tends to restrict the conformation freedom of the complex, it is possible that the total enthalpy and entropy of the complexation are both negative in spite of the presence of the hydrophobic interaction. However, the total negative enthalpy and entropy do not indicate that the van der Waals interaction is more important than the hydrophobic interaction, because interactions such as the exclusion of high-energy water from CD cavities also contribute negative enthalpy and entropy to the complexation. Nevertheless, the only possible source of the positive entropy is the hydrophobic interaction. As a result, it seems valid to claim the importance of the hydrophobic interaction if the total entropy change of the complexation is indeed positive [52]. Moreover, it is well known that the transfer of nonpolar gases into water is associated with a large positive heat capacity change. Therefore, the fact that CD complexation is often accompanied with a large negative heat capacity change also demonstrates that the hydrophobic interaction is important in the association [53].

In addition to using the thermodynamic criteria, there are several other methods to show the involvement of the hydrophobic interaction. In CD chemistry, the most compelling evidence in favor of the presence of the hydrophobic interaction is the repeated observation that in the CD complexes the most nonpolar portions of the guest molecules are usually enclosed in CD cavities. In fact, this structural feature of CD complexes has enabled CDs to be applied to many physical organic studies, in which a nonpolar microenvironment in bulk aqueous solution is needed [54]. The above structural feature of CD complexes is also consistent with the fact that the CD can markedly affect the tautomeric equilibrium of the guest molecule by preferentially binding with the less polar tautomer [55].

The involvement of the hydrophobic interaction in CD complexation can also be shown by the correlation analyses, as in general increasing the hydrophobicity of the substituent of the guest molecule enhances the complexation [56]. Parameters of hydrophobicity including the partition coefficient log P [57] and the hydrophobic surface area [58] are frequently chosen. Sometimes, the correlation between the binding strength and the number of the carbon atoms of a homologous series of substrates is also taken as evidence of the hydrophobic interaction [59]. As an increment of $\sim$3.0 kJ/mol in the standard free energy of complexation for each methylene group is observed, which is close to the value in the transfer of homologous organic compounds from water to hydrocarbon solvents, it is repeatedly suggested that the binding mechanism of CD is of a hydrophobic nature [60].

Another evidence of the hydrophobic interaction is that the strength of CD complexation is usually weakened upon the addition of organic cosolvent [61]. Likewise, the presence of urea also decreases the binding constants, which usually indicates the importance of the hydrophobic interaction [62]. On the other hand, the addition of inorganic salts tends to strengthen the binding, simply because it makes the bulk solution more polar [63]. However, sometimes when the salt can also form complexes with CD, its competition with the guest compound will lower the strength of binding

of the guest [64]. Interestingly, the binding constants of CD also increase when D_2O is used as the solvent instead of H_2O [65], which might be caused by the fact the hydrophobic interaction is stronger in D_2O than in H_2O [66].

Hydrogen bonding

The hydrogen bond is typically an interaction involving an electronegative donor X, a hydrogen, and a electronegative acceptor Y: $R - X - H \cdots Y - R'$. Though many authors claim that the fundamental nature of the hydrogen bond remains somewhat obscure, great emphasis has been placed on interpreting the bond on a purely electrostatic basis.

In CD chemistry, the important role of hydrogen bonding in the complexation has been well established for the complexes in the solid state [67]. A number of crystal structures of CD complexes have clearly shown the well-defined hydrogen bonds between the substrates and the hydroxyls of CDs [68]. Computational studies also showed the energetic advantage of adopting a hydrogen-bonded conformation in the complexation [69]. Usually, the host–guest hydrogen bonding is restricted to the primary O(6)—H groups of CDs because they are flexible and can rotate about the C(5)—C(6) bond in contrast to the secondary O(2) and O(3) atoms which are rigid due to the preferred $^4C_1$ form of the glucose units. However, it should be mentioned that sometimes there are also C—H$\cdots$O [70], C—H$\cdots$N [71], and C—H$\cdots\pi$ [72] interactions between the cavity walls of CDs and the guest molecules, whose energy has been recently estimated with *ab initio* calculations to be 0.7–1.1 kcal/mol. Though the value is far below the value of conventional hydrogen bonding, it is appreciably above the energies of van der Waals contact [73].

On the other hand, the role of hydrogen bonding in CD complexation in aqueous solution is still controversial. Apparently, the primary reason for the problem is that water can compete with CDs to form the hydrogen bonds with the substrate molecules [11a]. For example, molecular dynamic calculations on the complexation of α-CD with *p*-chlorophenol and *p*-hydroxybenzoic acid in water clearly indicated that the hydrogen bond is rarely formed between CD and the substrates [74]. Thus, it was concluded that hydrogen bonding plays a minor role in the complexation. Besides, it has been demonstrated that although in the solid complex of α-CD with 4-fluorophenol the OH group of phenol is hidden inside the CD cavity [75], in aqueous solution the F group remains inside and OH outside the CD cavity [76]. The behavior has been reproduced with our semiempirical molecular orbital calculations, which indicated that though the OH of 4-fluorophenol can be hydrogen-bonded to the glycosidic oxygen of CD in the solid state, in aqueous solution it is more likely to form a hydrogen bond with water in the bulk [77].

Nevertheless, examples of hydrogen bonding in CD complexation in aqueous solution have been shown by some authors. For instance, in the study of the complexation of γ-CD with pamoic acid, the large observed binding constants were thought to indicate the occurrence of hydrogen bonding between the carboxylate of the guest and a secondary OH of CD [78]. Likewise, the fact that the binding constants of β-CD are in the following order: 4,4′-dihydroxydiphenyl > 2,2′-dihydroxydiphenyl > *p*-hydroxydiphenyl > diphenyl indicates that the hydrogen bonding provides an important contribution to the binding [79]. A similar argument has been used to show the importance of hydrogen bonding in the study of CD complexation with guest compounds such as ammonia [80].

Sometimes, the occurrence of hydrogen bonding in CD complexation can be detected with spectroscopic methods. For example, in 1986, Takahashi *et al.* used the ^1H and ^{15}N NMR techniques to study the interaction of aspartame with β-CD in aqueous solution. It was concluded that the amide part of aspartame was hydrogen-bonded to the C(2) or C(3) hydroxyl groups of the CD [81]. Likewise, several spectroscopic studies later also suggested the occurrence of hydrogen bonding in CD complexation in aqueous solution [82]. Interestingly, in 1992 Hamai studied the complexation of heptakis(2,3,6-tri-*O*-methyl)-β-CD (TMβ-CD) with *p*- and *m*-chlorophenol in organic solvents such as cyclohexane with various spectroscopic methods, and it was concluded that the phenolic OH is hydrogen bonded to the ether oxygen of the host [83].

Recently, Chen *et al.* studied the pH dependence of the complexation of 3-hydroxynaphthalene-2-carboxylic acid with β-CD [84]. It was found that with increasing pH (pH < 11), the binding constant decreases probably because the deprotonated substrate is more hydrophilic. However, at pH > 11 the binding constant increases as the pH value rises. The behavior was thought to be due to the hydrogen bonding between the deprotonated secondary OH of CD and the hydroxyl group of the substrate at the pH range. Interesting, after β-CD is permethylated into TMβ-CD, the binding constant at pH > 11 changes little with increasing pH value, presumably because TMβ-CD cannot be deprotonated under the same condition. Thus, it was concluded that hydrogen bonding plays an important role in the CD complexation.

Relief of conformational strain

Calculations have shown that the geometry of a CD molecule in the crystalline state does not correspond to the global energy minimum in the gas phase, and presumably in solution either [18]. This result is consistent with the fact that the conformation of a CD in the solid state is usually less symmetrical than that in solution [85]. Possibly, the crystalline packing and the presence of water molecules in the solid state lead to the above behavior.

In the 1970s, it was assumed that the deviation from the symmetrical conformation of the CDs in the solid state constitutes a store of energy, whose relief upon complexation is a driving force of the process [86]. Unfortunately, the point of view has been criticized later [11d, 87]. In fact, the above postulation is not relevant to the complexation of CDs in solution. Though it is possibly true that a CD in the solid state has a higher conformational energy than that in solution, the thermodynamics of the CD complexation in solution does not involves the energy of a solid state CD.

Thus, relief of conformational strain is not a driving force of CD complexation in solution.

However, the idea of "induced fit" in CD complexation derived from the above postulation is basically correct [88]. As shown by many authors, the CD molecules usually undergo a significant conformational change upon complex formation, whose primary role in the complexation is apparently to optimize opportunities for other modes of interactions. Nevertheless, it should be emphasized that the "induced fit" mechanism is an experimental behavior, not a driving force in CD complexation.

Exclusion of cavity-bound high-energy water

As the CD cavities are nonpolar, it is not unexpected that the water molecules included in CD cavities should lack the complement of stabilizing hydrogen bonds that would be available to them in the bulk aqueous solution [89]. Thus, the water molecules in CD cavities are at higher level of energy than those in bulk solution, whose release upon the CD complexation with the guest molecules was postulated as a driving force leading to the complex formation [90].

However, some authors disagreed with the above postulation [91]. In fact, though the cavity-bound water molecules are at a higher energy, or in other words, they are "enthalpy-rich", they should have more conformational freedom than the water molecules in the bulk solution because of the lack of hydrogen bonding. Thus, although the exclusion of the cavity-bound water is accompanied with a negative enthalpy change, the free energy change of the process is not necessarily negative. As shown below, the reorganization of solvent molecules is actually a process of enthalpy-entropy compensation without any free energy contribution. As a result, the exclusion of cavity-bound water is not a driving force of the complexation.

Charge–transfer interaction

Charge–transfer interaction is in fact a type of van der Waals interaction [92]. However, as in the field of CD chemistry the term van der Waals interaction usually refers to the combination of induction and dispersion forces, it seems necessary to discuss the role of charge–transfer interaction separately. As known, unlike the induction force in which the electron distribution of a molecule involved in the interaction is distorted within the molecule itself, in charge–transfer interaction the electrons of the higher-lying occupied molecular orbitals of one molecule are transferred into the low-lying unoccupied molecular orbitals of another molecule.

In CD chemistry, in addition to the charge–transfer interaction between the substitution groups of CDs and the guest compounds [93], charge–transfer interaction directly between the CD skeleton and the substrate has also been observed [94]. However, the involvement of charge–transfer interaction as a driving force in CD complexation was only mentioned recently in our study [95]. As known, the complex α-CD-4-nitrophenolate is much more stable than α-CD-4-nitrophenol, which, however, cannot be explained on the basis of the consideration of hydrophobic or electrostatic interaction. Though Connors explained the above behavior in a phenomenological way that the electron density at the substrate binding site is larger in the first complex [96], our calculation showed that the stronger interaction in α-CD-4-nitrophenolate might be due to the fact that 4-nitrophenolate is a better electron donor than 4-nitrophenol. Thus, charge–transfer interaction is influential to CD complexation.

In fact, the role of charge–transfer interaction in CD complexation can also be shown by the facts that: (1) the binding constant of the α-CD complex of the 1,4-dicyanobenzene radical anion is 45 times larger than that of the neutral 1,4-dicyanobenzene complex [97]; (2) the binding constant of the β-CD complex of neutral 10-methylphenothiazine is 35 times smaller than that of the 10-methylphenothaizine radical cation complex [98]; (3) the binding of α-CD with the singlet xanthone is much more stable than that with the triplet one [99]; etc. Though sometimes an explanation based on dipole–induced dipole interaction was proposed, the distortion of the electrons within the substrate molecule itself is not sufficient to account for the above behaviors. That is why charge–transfer interaction should be paid attention to, but in fact the interaction is nothing new but one type of van der Waals interaction.

Relations between different driving forces

The detailed thermodynamic steps in CD complexation

As anticipated, the detailed mechanism of CD inclusion complexation is quite complicated. However, it is still possible to break the binding process into several steps, which is helpful in illustrating the driving forces of the complexation.

In 1978, Tabushi *et al.* presented a comprehensive model of the inclusion process of α-CD [100], in which the binding was broken into the following steps: (1) Release of two water molecules from the CD cavity into the gas phase. The step accompanies losses of van der Waals interaction and hydrogen bonding between the two water molecules, gains of motional freedom of the two water molecules, and a change in conformation energy of the host. (2) Transformation of the extruded gaseous water molecules into a liquid phase, which is apparently accompanied with a negative enthalpy and entropy change. (3) Transfer of a nonpolar guest molecule from water to an ideal gaseous state leaving a structured cavity behind, which collapses with redistribution of the water molecules. (4) Binding of the guest molecule by the host, accompanied by the turning on of the host–guest intermolecular interaction and a change in the conformation energy of the host. On the basis of the model, the authors calculated the binding energy of α-CD with benzene, *p*-iodoaniline and methyl orange. The results are modestly close to the experimental values.

The results from the above calculation are interesting. Firstly, it was found that van der Waals interaction between CD and the guest is very important because it provides a large negative enthalpy. This enthalpy is to some extent

compensated by the freezing of the motional freedom of the guest molecule in the complex formation, but not completely. Therefore, van der Waals interaction is a driving force of the complexation. However, it was shown that the release of the cavity-bound water molecules is also accompanied by a large negative enthalpy. Thus, the experimental negative enthalpy cannot be used to demonstrate the dominance of van der Waals interaction in CD complexation.

Secondly, it was found that the conformation energy of the host molecule increases from the hydrate to an inclusion complex. Apparently, instead of relief of the conformational strain, the inclusion complexation leads to a more strained conformation of CD with higher conformation energy. Presumably, by changing the conformation of the host, the complex can optimize the interactions between the host and guest and lower its energy. Nevertheless, it is clear that the relief of conformation strain is not a driving force in CD complexation.

It should be mentioned that the above calculation overlooked an important interaction in the inclusion complexation, i.e., the interaction between the free guest molecule and the water molecules around it. Though the collapse of the structured cavity left by the guest molecule gives a positive entropy change, the enthalpy change of the process is also positive and in fact compensates the entropy. Thus, the hydrophobic effect does not merely rely on the redistribution of the cavity water molecules, and the interaction between the solute and water is also very important.

The above model is also flawed by an erroneous estimate of the change in the number of vibrational degrees of freedom during the complexation process. As a result, the release of the cavity-bound water was calculated to give a positive entropy change, because of the gains of motional freedoms of the water molecules as to translation and three-dimensional rotation. This source of positive entropy has been used to argue that positive entropy does not necessarily indicate hydrophobic interaction [101]. However, if the release of the cavity-bound water really produces a negative enthalpy and positive entropy, in an equilibrium of CD aqueous solution the water cannot stay in CD cavity at all.

Later, Wojcik also presented a statistical thermodynamic model of CD binding [102]. In the model, the enthalpy and entropy of the complexation were not considered, and the free energy change of the complexation was separated into five contributions, i.e., contributions from translational motion, rotational motion, vibrational motion, electronic motion, and solvation.

Apparently, the model is strict in terms of thermodynamics. Its only problem lies in the evaluation of every contribution of the free energy. According to the separation, the translational contribution contains only the masses of the species involved and can be evaluated easily. The rotational contribution can also be evaluated without much difficulty as the principal moments of inertia of the species involved can be reasonably estimated. The consideration of vibrational contribution in the paper is interesting, because Tabushi *et al.* did not take into account the additional six vibrational modes gained during the complex formation [100]. However, the estimation of the vibration contribution is not an easy task because it requires an accurate calculation of the host-guest interaction energy as a function of the six vibration coordinates. The same problem was also encountered in the estimation of the electronic contribution, which was roughly evaluated based on the van der Waals and electrostatic interaction between the host and guest molecules. The contribution from solvation could be theoretically estimated on the basis of the fact that the solvation free energy of a species can be calculated from the equilibrium constant for the process: solute in gas $\rightarrow$ solute in solution. However, as the solvation equilibrium constants are not available, the solvation contribution had to be estimated from the difference between the known experimental free energy of complexation and those of the other several contributions.

The results of the evaluations are interesting. As expected, the transitional and rotational contributions are not favorable for the complexation, because three translational and three rotational modes are lost on complex formation. However, the vibrational contribution and the electronic contribution are favorable for the complexation, which constitute the driving forces of the complexation. The solvation contribution is, on the other hand, unfavorable to the complexation. This fact does not mean that the hydrophobic effect is absent in CD complexation, because the calculated values of the hydrophobic interaction could still be favorable for complexation according to Ben-Naim's definition of the hydrophobic effect.

Enthalpy-entropy compensation

Enthalpy-entropy compensation is the phenomenon in which the change in enthalpy is offset by a corresponding change in entropy resulting in a smaller net free energy change [103]. Though it has been widely observed in many fields of chemistry and biophysics, the details and origin of the compensation effect remain poorly understood [104]. Nevertheless, it is generally believed that enthalpy-entropy compensation plays an important role in the reactions in solution.

In CD chemistry, the occurrence of enthalpy-entropy compensation was observed early and has been well documented [105]. In particular, Inoue *et al.* have conducted a systematic study on the behavior [106], and it has been suggested that the slope and intercept of the enthalpy-entropy ($\Delta H - T\Delta S$) plot could be quantitative measures of the conformational change and extent of desolvation upon complexation.

However, there remains some controversy concerning the enthalpy-entropy compensation in CD complexation. First, it remains unknown whether or not the observed compensation is a fact or an artifact. As known, the correlation between the enthalpies and entropies obtained from the van't Hoff plots could be an artifact because the experimental errors of the two quantities tend to be dependent on each other [107]. Nevertheless, most of the enthalpy and entropy data of CD complexation were obtained from calorimetric measurements, and it has been shown recently on the basis of computer simulations that the compensation between them should be a real one [108].

The other problem concerning the enthalpy-entropy compensation is the physical origin of such an effect. Although a number of theories have been proposed [109], most are not applicable to CD chemistry. Nevertheless, Grunwald recently proposed a theory of enthalpy-entropy compensation, in which the solvent reorganization was suggested to be the physical origin of the compensation [110]. Interestingly, it turns out that this theory can successfully explain the enthalpy-entropy compensation in many real systems [111] including CD inclusion complexation [112].

In the theory it is firstly assumed that there are certain amounts of CD and substrate in aqueous solution. Thus there are seven distinguishable species in equilibrium [113], i.e., X/w, Y/w, XY/w, W/x, W/y, W/xy, and W/w. The capital letters stand for the water molecules (W), cyclodextrin (X), substrate (Y), and their complex (XY). The lower-case letters immediately following describe the environmental constraint sensed by the species. For example, W/w represents a water molecule in bulk aqueous solution and hence surrounded solely by water, while W/x represents the water molecules in the hydration shell of a CD molecule and hence contacting that molecule. The enthalpy of the solution can be written as

$$\begin{aligned} H &= N_{X/w}h_{X/x} + n_{Y/w}h_{Y/w} + n_{XY/w}h_{XY/w} \\ &\quad + n_{W/w}h_{W/w} + n_{W/x}h_{W/x} + n_{W/y}h_{W/y} \\ &\quad + n_{W/xy}h_{W/xy}, \end{aligned} \tag{1}$$

where h represents the partial molar enthalpy, and n the quantities of the species.

Considering that the CD complexation undergoes a sequence of quasistatic process, thus

$$\Delta H = \int dH. \tag{2}$$

In each quasistatic process, the enthalpy change (dH) is caused by the changes in the partial molar enthalpies and the amount of the solution species, i.e., dh_i and dn_i (herein i represents X/w, Y/w, XY/w, W/x, W/y, W/xy, and W/w, respectively). Therefore,

$$\begin{aligned} dH &= n_{X/w}dh_{X/w} + h_{X/w}dn_{X/w} + n_{Y/w}dh_{Y/w} \\ &\quad + h_{Y/w}dn_{Y/w} + n_{XY/w}dh_{XY/w} \\ &\quad + h_{XY/w}dn_{XY/w} + n_{W/w}dh_{W/w} + h_{W/w}dn_{W/w} \\ &\quad + n_{W/x}dh_{W/x} + h_{W/x}dn_{W/x} + n_{W/y}dh_{W/y} \\ &\quad + h_{W/y}dn_{W/y} + n_{w/xy}dh_{w/xy} \\ &\quad + h_{w/xy}dn_{w/xy}. \end{aligned} \tag{3}$$

According to Gibbs–Duhem's equation, the changes in the partial molar enthalpy obey the following equation

$$\begin{aligned} n_{X/w}dh_{X/w} &+ n_{Y/w}dh_{Y/w} + n_{XY/w}dh_{XY/w} \\ &+ n_{W/w}dh_{W/w} + n_{W/x}dh_{W/x} \\ &+ n_{W/y}dh_{W/y} + n_{W/xy}dh_{W/xy} = 0. \end{aligned} \tag{4}$$

On the other hand, as the amount of solvent is invariant, $dn_{W/x} + dn_{W/y} + dn_{W/xy} + dn_{W/w} = dn_W = 0$. Therefore,

$$\begin{aligned} dH &= h_{W/w}(-dn_{W/x} - dn_{W/y} - dn_{W/xy}) \\ &\quad + h_{X/w}dn_{X/w} + h_{W/x}dn_{W/x} + h_{W/y}dn_{W/y} \\ &\quad + h_{Y/w}dn_{Y/w} + h_{W/xy}dn_{W/xy} + h_{XY/w}dn_{XY/w} \\ &= (h_{X/w}dn_{X/w} + h_{Y/w}dn_{Y/w} + h_{XY/w}dn_{XY/w}) \\ &\quad + [(h_{W/x} - h_{W/w})dn_{W/x} + (h_{W/y} - h_{W/w})dn_{W/y} \\ &\quad + (h_{W/xy} - h_{W/w})dn_{W/xy}]. \end{aligned} \tag{5}$$

In consequence,

$$\begin{aligned} \Delta H &= \int dH = \int (h_{X/w}dn_{X/w} + h_{Y/w}dn_{Y/w} \\ &\quad + h_{XY/w}dn_{XY/w}) + [(h_{W/x} - h_{W/w})dn_{W/x} \\ &\quad + (h_{W/y} - h_{W/w})dn_{W/y} \\ &\quad + (h_{W/xy} - h_{W/w})dn_{W/xy}]. \end{aligned} \tag{6}$$

Similarly, the entropy and free energy changes in the complexation are

$$\begin{aligned} \Delta S &= \int dS = \int (s_{X/w}dn_{X/w} + s_{Y/w}dn_{Y/w} \\ &\quad + s_{XY/w}dn_{XY/w}) + [(s_{W/x} - s_{W/w})dn_{W/x} \\ &\quad + (s_{W/y} - s_{W/w})dn_{W/y} \\ &\quad + (s_{W/xy} - s_{W/w})dn_{W/xy}] \end{aligned} \tag{7}$$

and

$$\begin{aligned} \Delta G &= \int dG = \int (\mu_{X/w}dn_{X/w} + \mu_{Y/w}dn_{Y/w} \\ &\quad + \mu_{XY/w}dn_{XY/w}) + [(\mu_{W/x} - \mu_{W/w})dn_{W/x} \\ &\quad + (\mu_{W/y} - \mu_{W/w})dn_{W/y} \\ &\quad + (\mu_{W/xy} - \mu_{W/w})dn_{W/xy}], \end{aligned} \tag{8}$$

where s and μ represent the partial molar entropy and chemical potential, respectively.

Interestingly, since the solution remains in a thermodynamic equilibrium during every quasistatic process, the following chemical potentials are always equal

$$\mu_{W/w} = \mu_{W/x} = \mu_{W/y} = \mu_{W/xy}. \tag{9}$$

Therefore, the last three terms in the free energy change actually disappear, i.e.,

$$\begin{aligned} \Delta G &= \int dG = \int (\mu_{X/w}dn_{X/w} + \mu_{Y/w}dn_{Y/w} \\ &\quad + \mu_{XY/w}dn_{XY/w}). \end{aligned} \tag{10}$$

This means that the corresponding three terms in the enthalpy and entropy changes compensate each other, i.e.,

$$\begin{aligned} &\int [(h_{W/x} - h_{W/w})dn_{W/x} + (h_{W/y} - h_{W/w})dn_{W/y} \\ &\quad + (h_{W/xy} - h_{W/w})dn_{W/xy}] \\ &= \int [(s_{W/x} - s_{W/w})dn_{W/x} + (s_{W/y} - s_{W/w})dn_{W/y} \\ &\quad + (s_{W/xy} - s_{W/w})dn_{W/xy}]. \end{aligned} \tag{11}$$

As the three compensation terms correspond to the reorganization of the solvent molecules, it could be concluded that

solvent reorganization is the physical origin of the compensation effect. In fact, on the basis of the extent of solvent reorganization compared to the host-guest interaction, it was predicted that good enthalpy-entropy compensation should take place in the complexation of CDs with hydrophobic compounds, while poor or no enthalpy-entropy compensation should take place in the complexation of CDs with relatively hydrophilic compounds [112]. Interestingly, the prediction has been confirmed by the experimental observations [112].

Multivariate QSAR analyses and the relative importance of every driving force

Apparently, in CD complexation the several driving forces often function simultaneously [114]. Thus, many theoretical models of CD complexation were proposed on the basis of multivariate quantitative structure–activity relationship (QSAR) analyses. These models are usually useful in predicting the binding constants of the complexation and illustrating which driving force is the most important in certain complex systems. However, it should be mentioned that to date no single QSAR model has been successful in predicting the binding constants of all the CD complexes. Therefore, all the conclusions drawn from the multivariate QSAR studies are more or less system-dependent, and incautious application of any conclusion drawn from one system to the other might cause controversy. In addition, it should be mentioned that in some QSAR studies on CD complexation, regression parameters such as spectroscopic properties and molecular connectivity index were used. Though such QSAR models may be useful in predicting the binding constants, they are not very informative concerning with the mechanism of CD complexation [115].

In 1979, Matsui *et al.* studied the complexation of α- and β-CD with a variety of alcohols [116]. The binding constants (K_a) were analyzed in connection with the partition coefficients (P_e) of the alcohols in a diethyl ether-water solvent system, which indicated that hydrophobic interaction played a significantly important role in the complexation due to the high positive correlation between the log K_a and log P_e values. Interestingly, when the Taft's steric substituent constant (E_s) was also considered in the correlation, the coefficient of E_s was positive in sign for the α-CD complexes and negative for the β-CD complexes. The difference might indicate that a bulky alcohol was subject to van der Waals repulsion by the small α-CD cavity and to van der Waals attraction by the relatively larger β-CD cavity.

Later, Connors studied the complexation of α-CD with sym-1,4-disubstituted benzenes [117]. Good correlations were found between the binding constants and log S_0 (solubility) and μ (group dipole moment) or between the binding constants and ΔH_f^0 (heat of fusion) and log P (n-octanol/water partition coefficient) of the substrates. The results might be interpreted that electrostatic interaction, van der Waals force, and hydrophobic interaction were all important to the complexation.

In 1985, on the basis of previous work [118], Matsui *et al.* described the multivariate free energy relationships in CD complexation with alcohols, substituted bicyclic phosphates, substituted phenyl acetates, and substituted phenols [119]. Different regression variables including the partition coefficient log P, Taft's steric substituent constant E_s, the substituent hydrophobic constant π, the substituent molar refractivity MR, and the Hammett σ constant were used, and fair to excellent correlations were observed. The results indicated that van der Waals force and the hydrophobic interaction constitute the major driving forces of CD complexation. Likewise, Lopata *et al.* studied the QSAR in α- and β-CD complexation with barbituric acid derivatives [120]. The variation in the binding constant was partly accounted for by the molar refractivity and hydrophobicity of the substituent group of the barbiturate ring, indicating the importance of van der Waals force and hydrophobic interaction. In addition, in the QSAR study of β-CD complexation by Buvari *et al.* using the molar mass, molar refraction, dipole moment, and water solubility of the guest molecule as regression parameters, it was demonstrated that besides several other factors, if hydrogen bonding were possible with the hydroxyls of CD, the binding constant would be increased [121].

Sanemasa *et al.* have done a systematic study of the CD complexation with polynuclear aromatic hydrocarbons, halobenzenes, dihalobenzenes, and volatile nonelectrolytes [122], in which they compared the free energy of CD complexation ($\Delta G_{\text{complex}}$) with the free energy for the substrate to be transferred from water to gaseous phase (ΔG_{dehyd}). As $-\Delta G_{\text{complex}} \gg -\Delta G_{\text{dehyd}}$, it was concluded that the hydrophobic interaction could not be a significant driving force. The conclusion was not necessarily correct, because usually the free energy for the substrate to be transferred from water to an organic solution is used to describe the hydrophobicity of the compound. Nevertheless, the conclusion in the study that van der Waals force is a significant driving force on the basis of the linear plot of log K_a vs. the total surface area of the substrate should be fully correct.

In 1994, Park *et al.* studied the β-CD complexation with a number of organic solutes in aqueous solution [123]. Types and relative strengths of various intermolecular forces between CD and the guests affecting the stability of the complexes were studied on the basis of the linear solvation energy relationship (LSER), in which the molecular volume V_1, dipolarity/polarizability π^*, and hydrogen bond acceptor basicity β of the guest molecules were taken as the regression parameters. The regression (Equation (12)) is remarkably successful, as the guest molecules are quite different from each other in their physicochemical properties.

$$\log K_a = -1.40 + 7.62V_1/100 - 0.90\pi^* - 1.27\beta \quad (n = 20, r = 0.972). \tag{12}$$

Interestingly, from the signs of the coefficients, it could be concluded that van der Waals force and the hydrophobic interaction are the major driving forces of the complexation because increasing guest molecular size stabilizes the complex. However, increasing guest dipolarity and hydrogen

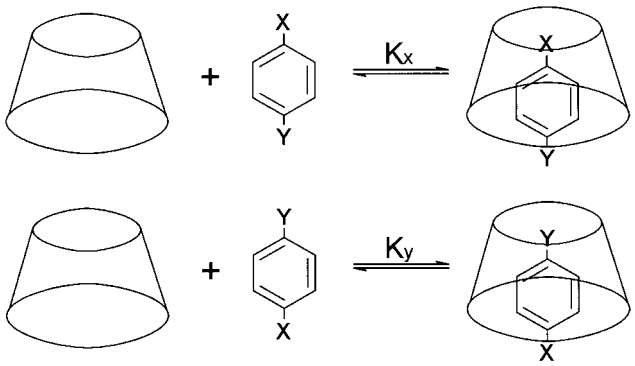

Figure 2. Inclusion complexation of α- and β-cyclodextrin with 1,4-disubstituted benzene in different orientation.

bond acceptor basicity leads to a decrease in the stability of the complex, which indicates that hydrogen bonding between the guests and water is stronger than that between the guests and CD.

Recently, we studied the α- and β-CD complexation with *mono*- and 1,4-disubstituted benzenes. The substituent parameters including molar refraction R_M, Hansch hydrophobicity π, and Hammett σ constants were used in the QSAR analyses, which reflect the volume and polarizability, hydrophobicity, and electronic properties of the guest molecules, respectively. Mathematical methods including multiple linear regression [124], artificial neural network [125], and genetic algorithm [126] were employed. It was found that such models could fairly well predict the binding constants in general. In fact, similar regression models can also be found in the studies of other CD complex systems such as α-CD complexation with substituted acetic acids [127] and β-CD complexation with phenolic compounds [128].

However, as it is quite obvious from our work that the artificial neural network is always superior to multiple linear regression in predicting the binding constants, [124, 125], we realized that in CD complexation usually more than one binding modes or complexation orientations might be involved so that the corresponding free energy relationship should be nonlinear. Thus, we developed a nonlinear free energy relationship model for the α- and β-CD complexation with 1,4-disubstituted benzenes (X-C_6H_4-Y) [129]. According to the model, two modes of complexation should be considered (Figure 2). In consequence, binding of X-C_6H_4-Y with α- or β-CD can form two isomeric complexes, CD·X-C_6H_4-Y and CD·Y-C_6H_4-X, according to which substituent is located in the cavity. Based on this concept, we developed corresponding nonlinear free energy relationship models. After several steps of mathematical deduction, the final equations (Equations (13) and (14)) were digitalized with the help of genetic algorithm optimization.

$$K_a(\alpha - \mathrm{CD}) = e^{0.166R_{mX}+0.139\pi_X+1.44\sigma_X-1.27\sigma_Y+2.51} + e^{0.166R_{mY}+0.139\pi_Y+1.44\sigma_Y-1.27\sigma_X+2.51}. \quad (13)$$

$$K_a(\beta - \mathrm{CD}) = e^{0.073R_{mX}+0.640\pi_X+0.507\sigma_X-0.506\sigma_Y+4.02} + e^{0.073R_{mY}+0.640\pi_Y+0.507\sigma_Y-0.506\sigma_X+4.02}. \quad (14)$$

Though they look complicated, they are in fact quite simple in that the equations are symmetric in nature. Moreover, it is interesting that from the above two equations much knowledge could be learned concerning CD complexation. At first, the above equations might be very useful in estimating the binding constants of α- and β-CD complexation with *mono*- and 1,4-disubstituted benzenes. The correlation coefficients between the predicted and experimental binding constants are 0.92 for 56 α-CD complexes and 0.94 for 46 β-CD complexes, respectively. Secondly, the models can well predict the preferred binding mode of the complex. For instance, from the model it is straightforward that in most 4-substituted benzoic acids, it is the COOH group that should be located inside the CD cavity. Remarkably, such predictions of complexation orientation are mostly consistent with the experimental observations. Finally and most importantly, from the above nonlinear free energy relationship model, it could be concluded that van der Waals force, hydrophobic interaction, and electrostatic interaction are all significant in CD complexation. In fact, the signs of the coefficients of R_M are positive, indicating that increasing the volume and polarizability of the guest substituent can increase the stability of the complex due to stronger van der Waals interaction. The signs of the coefficients of the π constant are also positive so that a more hydrophobic substituent will result in a larger binding constant. Interestingly, the signs of the coefficients of σ_X are positive whereas the signs of the coefficients of σ_Y are negative. Thus, an electron-withdrawing substituent X and an electron-donating substituent Y favor the binding, simply because the narrower end of the CD cavity is at the positive end of its dipole moment and the wide end at the negative one.

Conclusion

The driving forces leading to the inclusion complexation of cyclodextrins should include the electrostatic interaction, van der Waals interaction, hydrophobic interaction, hydrogen bonding, and charge–transfer interaction. However, due to enthalpy-entropy compensation, release of conformational strain and exclusion of cavity-bound high-energy water are not energetically contributive to the complex formation, and the enthalpy and entropy changes of the complexation are not good criteria to be used in judging whether a particular driving force is present or important. Nevertheless, the multivariate quantitative structure-activity relationship analyses not only are useful in predicting the binding constants of the inclusion complexation, but also can illustrate which driving forces are important in particular complexation systems. Usually, it is found that van der Waals interaction and hydrophobic interaction constitute the major driving forces for cyclodextrin complexation, whereas electrostatic interaction and hydrogen bonding can significantly affect the conformation of a particular inclusion complex.

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