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Review

Inclusion complexation, encapsulation interaction and inclusion number in cyclodextrin chemistry

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ABSTRACT

In this paper, the inclusion complexation between host and guest in cyclodextrin (CD) chemistry is carefully compared with the coordination interaction between central ion (M^{x+}) and ligands in coordination chemistry. In view of the importance of the concept of the coordination number (CN) of M^{x+} in coordination compounds, the inclusion number (IN) is first defined to evaluate the nature of inclusion complexation between host and guest in CD supramolecular inclusion complexes. The similarities and differences between CN and IN are also discussed. The changes of the number and forms of water molecules both in CD hydrates and in CD crystal inclusion complex hydrates are reviewed. Moreover, this paper emphasizes the distinction between the two forms of CD-guest inclusion phenomenon, i.e., inclusion complexation and encapsulation interaction. Furthermore, the present work indicates that though chemical stoichiometric ratio can be used to characterize the inclusion phenomena, IN can better reveal the essence of inclusion phenomena in cyclodextrin chemistry.

1. Introduction

Supramolecules are complex and ordered molecular aggregates associated with two or more molecules, ions or coordination compounds through intermolecular interaction, which have particular functions [1,2]. Examples of host molecules in supramolecular chemistry include crown ethers, crypates, calixarenes, cyclodextrins (CDs), etc. [1,3,4]. As the typical host of the second generation in supramolecular chemistry, CDs are macrocyclic compounds with several D-glucopyranoses linked by α-1,4-glycosidic bonds. α-, β- and γ-CD are the most common CDs, which have six, seven and eight glucose units, respectively. Their structures are shown in Fig. 1 [5,6].

Because of the $^4C_1$ chair conformation of each glucopyranose unit, the whole molecule has the shape of a hollow truncated cone. The interior of the cavity is composed of hydrogen atoms of C-3, C-5 and oxygen atoms of the glycosidic linkage, which make the intracavity hydrophobic while the exterior of the cavity is hydrophilic due to assembling large numbers of alcoholic hydroxyl groups. CDs can form host–guest inclusion complexes by weak intermolecular interaction with a wide variety of guests including organic molecules, inorganic ions, coordination compounds and even rare gases [7–9].

CDs have been extensively studied in connection with many fields such as enzyme simulation, solubilization and modification of drug, food, spice, cosmetic, agriculture, catalysis, organic syn-

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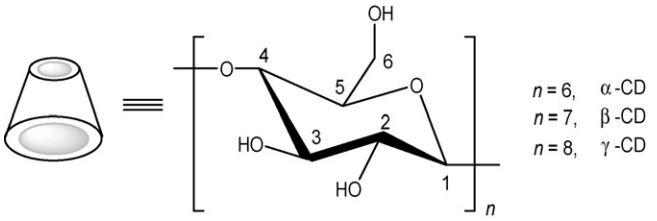

Fig. 1. Molecular structures of CDs.

thesis, etc. [10–12]. Cyclodextrin chemistry has become one of the most active research areas in supramolecular chemistry [13,14].

With the development of research in cyclodextrin chemistry, some important concepts need to be clearly defined and identified. They involve inclusion complexation and encapsulation interaction; molecular recognition and molecular discrimination; free CD, complexed CD and recovered CD (after removal of guest); complexation energy and interaction energy, etc. An accurate understanding of these concepts will benefit research in host–guest chemistry as well as promote the development of supramolecular chemistry.

According to this, we reported the structural transformations of free CD, complexed CD and recovered CD [15]. Here we will try to compare the similarities and differences between inclusion complexation in cyclodextrin chemistry and coordination interaction in coordination chemistry. Moreover, this study will reveal the distinction between two inclusion phenomena by concrete examples and give the concept of inclusion number (IN) of molecule–molecule or molecule–ion interaction between CD and guests. Furthermore, details about the number and forms of water molecules both in crystal CD hydrates and in hydrates of CD crystal inclusion complexes will be presented. In addition, the relationship between chemical stoichiometric ratio (CSR) and IN will be described.

2. A comparison between coordination interaction in coordination chemistry and inclusion complexation in cyclodextrin chemistry

In coordination chemistry, coordination interactions between central ion (M^{x+}) and ligands (molecules or ions) are accomplished by forming coordination compounds with certain stoichiometries and spatial configurations by the aid of coordination bonds through accepting or donating lone-pair electrons or π-electrons. If coordination interactions occur, the M^{x+} must have empty valence orbitals to accept lone-pair electrons or π-electrons from the ligands. The process of the formation of coordination compounds in aqueous solution can be considered as the process of replacement of coordinated water molecules of M^{x+} by ligands, as shown in Fig. 2A.

In cyclodextrin chemistry, inclusion complexation is accomplished by the intermolecular interaction between CD and guest, which leads to the penetration of the guest molecule partly or completely into the cavity of the CD. Contrarily, if some guest molecules only reside in the packing interstice of CD, an encapsulation interaction occurs. In other words, inclusion phenomena involve these two different intermolecular interactions. Undoubtedly, inclusion complexation is the main driving force of inclusion phenomena between CD and guest. Fig. 2B describes the process components of a representative embodiment of a 1:1 CD inclusion complex forming in aqueous solution [5]. As can be seen, the guest molecule is fully accommodated within the cavity of CD in a certain direction and then remains in the cavity driven by the inclusion complexation between CD and guest.

The inclusion complexation between CD and organic compounds with low polarity has been studied for several decades [7–9]. Much past research has indicated that the process of inclusion complexation between CD and guest is driven by electrostatic forces, van der Waals forces, hydrophobic interactions, hydrogen bonding, release of conformational strain and so on [5,16–19]. It is interesting that the driving forces always coexist or have a synergistic effect. The relative strength of each force is usually related to a certain inclusion system. More specifically, the size of the CD cavity and the nature of modified groups of CD; the shape, volume, polarity, number and character of substituting groups of guest, as well as reaction medium, temperature, ionic strength and other factors will affect the form and relative strength of these forces [20,21].

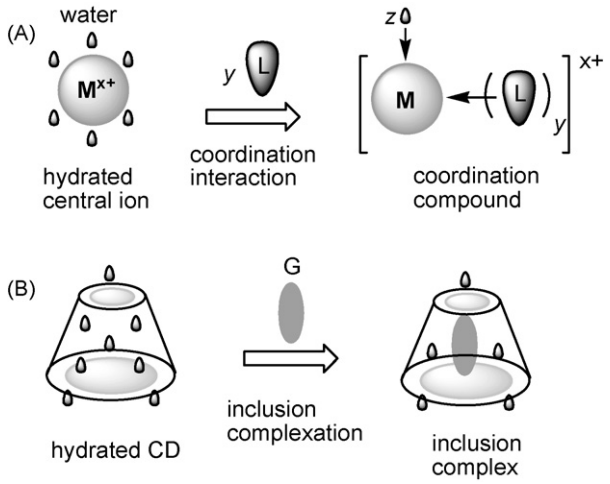

Fig. 2. A schematic drawing depicting the comparison between coordination interaction (A) and inclusion complexation (B). L and G represent ligand and guest, respectively.

Comparison between Fig. 2A and B shows that though there are some apparent similarities between inclusion complexation and coordination interaction in aqueous solution, the differences between them are more significant.

The similarities mean that in aqueous solution, an M^{x+} ion exists in the form of a hydrate. When ligands are added, the coordinated water molecules may be partly or completely replaced forming $[M(L)_y{\cdot}(H_2O)_z]^{x+}$. Likewise, a CD molecule also exists in the form of a hydrate in aqueous solution and always accommodates several water molecules using its cavity as binding site. When guests are added into the system, water molecules included in the CD cavity may be partly or completely excluded from the cavity by the guests. A hydrate of a CD inclusion complex, such as CD-G·$(H_2O)_n$, is formed due to the binding behavior of CD to guest and water molecules [20,22].

The differences are as follows: Firstly, a coordination compound between M^{x+} and ligands is formed by coordination bonds, while an inclusion complex between CD and guests is formed by intermolecular interaction. Secondly, although both M^{x+} and CD exist in the form of a hydrate, water molecules usually encircle the M^{x+} in a specific configuration while they are distributed both inside and outside the CD cavity in an uncertain form and quantity. Thus water molecules in a CD hydrate exist in two different environments. Even in the solid or crystalline state, α-, or β-CD can crystallize in several different ways, depending on the position and quantity of water molecules distributed inside and outside of the CD cavity [5,9,23–25]. Thirdly, M^{x+} can simultaneously interact with one or more ligands and form a coordinate unit. The coordination units always possess a certain conformation such as tetrahedron, square and octahedron, etc. [26,27] resulting also in isomerism [27] which exists widely in coordination compounds. However, few examples of isomeric inclusion complexes of CD with the same guest have been reported. For example, the 1:1 complex of β-CD with methyl-

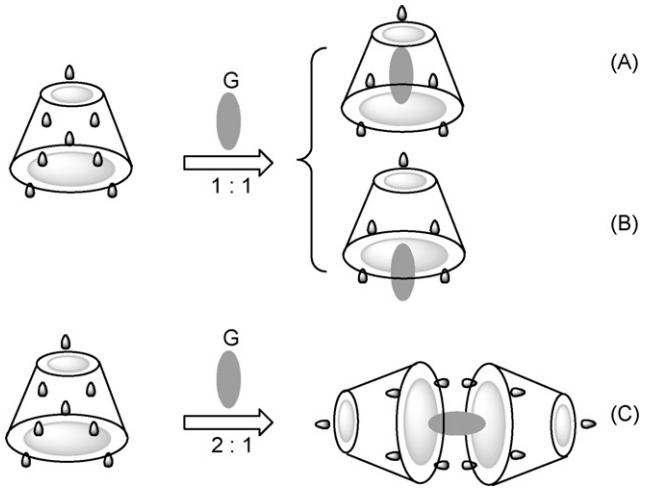

Fig. 3. Schematic sketches describing three kinds of the most common inclusion complexations between CD and guests.

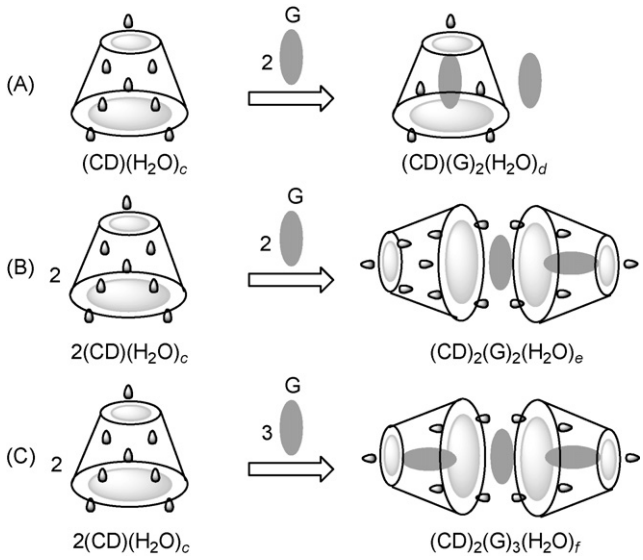

Fig. 4. Schematic sketches describing three kinds of encapsulation interaction accompanying inclusion complexations between β-CD and guests.

paraben occurs in different crystalline forms with different modes of guest inclusion [28]. In this regard, the isomerism of inclusion complexes is quite different from that of coordination compounds, such as number and structure of isomers. Furthermore, the interaction between CD and several different guests, such as G_1, G_2 and G_3, will cause a dynamic equilibrium in solution, and then several different supramolecules, i.e., CD-G_1, CD-G_2 and CD-G_3, with various different compositions, are formed [29–31]. The specific structure of the CD allows a guest with asymmetric construction to penetrate into the cavity of CD from one of two entrances in solution, potentially causing the formation of several complexes with different structures [32–34]. However, in fact, only one inclusion complex with the most stable structure, i.e., with the lowest stabilization energy is formed based on comparison between the results of theoretical calculation and nuclear magnetic resonance spectroscopy [34,35].

According to concepts in inorganic chemistry, supramolecular chemistry and host–guest chemistry as well as cyclodextrin chemistry may be all considered as extensions of coordination chemistry. CD and guests are seen to play the role of M^{x+} and ligands, respectively. However, the mode of the interaction between CD and guest is entirely different from that between M^{x+} and ligand.

3. Definition of inclusion complexation and encapsulation interaction in cyclodextrin chemistry

In solution, there is a dynamic equilibrium between inclusion and exclusion [5,20]. As for a 1:1 CD inclusion complex, the guest tends to stick in a certain site of the cavity based on nuclear magnetic resonance data [36,37]. In characterizing the formation of a complex by nuclear magnetic resonance titration, the current consensus is that the chemical shift changes of the protons (3-H or 5-H) inside are apparently larger than those of the protons (2-H or 4-H) outside the cavity [38,39].

When an inclusion complex is a single crystal, the relative position of CD and guest can be easily obtained by the determination of crystal structure [9,40,41].

The three most common modes of inclusion complexations are shown in Fig. 3A–C, corresponding to the values of CSR of 1:1, 1:1 and 2:1, respectively [5,42–47].

Recent research has revealed that in a few CD inclusion systems some of the guests have been incorporated in the sandwich structure formed by intermolecular hydrogen bonds between two CD molecules [48,49] or stay completely out of the cavity [50,51]. To the best of our knowledge, this can most likely happen in the case of β-CD inclusion complexes. The guest molecules lying outside the CD cavity may be able to change the spectroscopic properties of CD or the physical properties of the guests themselves. Since there is no actual inclusion complexation between CD molecules and the guest molecules, this kind of interaction is defined as an encapsulation interaction in this paper.

Fig. 4 displays three kinds of encapsulation interaction in the inclusion systems of β-CD and guests. Inclusion complexation and encapsulation interactions coexist in the inclusion phenomena shown in Fig. 4.

A typical example in Fig. 4A is the supramolecule formed by β-CD and iodide ions with a CSR value of 1:2. The crystal structure confirms that one iodide ion penetrates into the cavity of β-CD while the other is located outside the cavity [51].

In Fig. 4B, two β-CD molecules and two guest molecules form an inclusion complex with a CSR value of 2:2. One representative example is the crystalline state product formed by β-CD and salicylic acid [52]. As shown in the figure, two β-CD molecules form a head-to-head dimer by a net of hydrogen bonds among the secondary hydroxyl groups. One salicylic acid molecule lies horizontally in one of the cavities of the two β-CD molecules, and the other is located vertically between the wider rims of the cavities of two β-CD molecules. These correspond, respectively, to inclusion complexation and encapsulation interaction.

X-Ray diffraction data show that CSR is 2:3 in the inclusion complex of β-CD and 1,10-phenanthroline [48]. As shown in Fig. 4C, each of two 1,10-phenanthroline molecules is respectively included into one of two β-CD cavities, while the third one appears in the interstitial region formed by the wider rims of the cavities of two β-CD molecules, which is somewhat similar to the encapsulation interaction between β-CD and salicylic acid. Clearly, the third 1,10-phenanthroline molecule serves as a bridge, and there is no actual inclusion complexation. Similar examples were found in the complexes of β-CD with 8-nitroquinoline [49], 1-propanol [53] and 4-iodophenol [53], where CSR is also 2:3.

As shown in Figs. 3 and 4, the difference between inclusion complexation and encapsulation interaction consists in whether a guest is included in the cavity of CD or not. We argue that inclusion complexation occurs when at least one part of the guest is

accommodated in the cavity. In other words, it is the inclusion complexation that makes a guest molecule included in the cavity of CD to some degree rather than the encapsulation interaction that coexists with inclusion complexation in most cases. To associate molecule with molecule or ion between CD and guest only by a single encapsulation interaction can rarely be satisfactorily seen owing to the very weak intermolecular interaction of CD and the guest. Such examples appear when the nature of the CD cavity and the structure of the guest molecule or ion are incompatible, for example, in the inclusion systems of β-CD and simple inorganic salts such as calcium chloride [54].

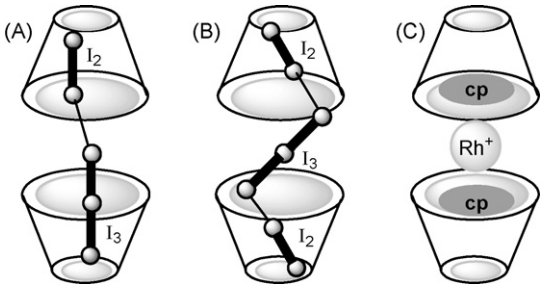

Fig. 5. Structural features of (A) α-CD–I_5^- [46], (B) β-CD–I_7^- [47] and (C) α-CD–$[Rh(cp)_2]^+$ [65].

4. The inclusion number in cyclodextrin chemistry and its influencing factors

In coordination chemistry, the coordination number (CN) is used to define the number of ligating atoms attached to the central metal ion. While in cyclodextrin chemistry, CSR is often used for expressing the stoichiometric relationship between CD and guest [9,17,38,55–57]. When an encapsulation interaction occurs with the inclusion complexation between CD and guest, it can only indicate the formation information of the inclusion complexes, but does not reveal the type of inclusion phenomenon or elucidate the structure of those complexes. Here, we attempt to define IN to express whether the inclusion complexation occurs between CD and guest, that is to say, *the value of IN is the ratio of the number of the guest molecules (not including solvent molecules) in the cavities of CDs to the number of CD molecules that have accommodated the guest molecules with their respective cavities.* In consideration of most inclusion complexes formed in aqueous solution, the quantitative determination of the IN value of a complex only depends upon the number of the nonaqueous guest molecules taking part in the inclusion complexation. Where the inclusion complexation only occurs between water molecules and CD, water molecules are regarded as a special kind of guest and the IN value is the number of them included in the cavity of each CD. According to the definition, the IN values of the three kinds of common inclusion complexes of CD shown in Fig. 3A–C are 1, 1, and 0.5, respectively. Also, the IN values of the CD complexes drawn in Fig. 4A–C are all 1. Based on reported data, for most organic guest molecules whether they are chain or cyclic structures, most are inclined to form one-to-one complexes with the IN value of one when they interact with the three common parent CDs.

One hundred and one representative inclusion complexes formed by organic or inorganic guest molecules or ions with α-, β-, γ-CD and modified CD, as well as their CSR values, IN and the number of crystal water (CRW), are listed in Table 1 .

The CSR values can be obtained by spectroscopic titration, nuclear magnetic resonance measurement, element analysis, X-ray crystal analysis, etc. The CRW values depend on the characterization of solid inclusion complexes. The IN values can be calculated based on the data from either nuclear magnetic resonance titration in solution or X-ray crystal structure in the crystalline state. As shown in Table 1, most of the IN values in the CD inclusion complexes are 1, and some are 0.5. Other numbers such as zero are very rare.

The present work indicates that inclusion complexes of different IN values are not formed when intermolecular force occurs between the same CD and several isomeric guest molecules which have subtle conformational differences between them. For example, the IN values of the inclusion complexes formed by β-CD with the isomers of aminobenzoic acid, i.e., 2-aminobenzoic acid, 3-aminobenzoic acid and 4-aminobenzoic acid [58], the IN values of those of α- or β-CD with the monosubstituted isomers of phenol such as 2-chlorophenol, 3-chlorophenol and 4-chlorophenol [59], and the IN values of α- or β-CD with the disubstituted isomers of phenol, such as 2,4-chlorophenol, 2,6-chlorophenol and 3,4-chlorophenol [59], are all one.

Moreover, for short-chain alkyl guests, the IN values of their inclusion complexes formed with the same CD are the same, such as the complexes of β-CD with formic acid and acetic acid [60] as well as those of β-CD with ethylene glycol and glycerol [61]. However, the inclusion complexes with an IN value of 1 are not be formed when the guest molecules have a longer chain, such as the complex of α-CD and decanoic acid [62] with an IN value of 0.5. This may be because the structural requirement of decanoic acid can only be fulfilled by the inclusion complexation between one decanoic acid molecule and two α-CD molecules.

Interestingly, guest molecules having longer branch chains than decanoic acid molecule can be bound by more CD molecules. For instance, poly(iminooligomethylene) [63] and poly(ethylene glycol) [64], can thread through a channel formed by the cavities of 40 β-CD molecules and 20 α-CD molecules, respectively. In this manner, they form stable inclusion complexes with CDs, and the IN values are 0.025 for the β-CD complex and 0.05 for the α-CD complex.

CD can also form inclusion complexes with an IN value of 0.5 with some inorganic ions with a chain structure or some sandwich π-coordination compounds. In the complex of I_5^- and α-CD [46], α-CD molecules are stacked to form columns in the channel type by head-to-head or tail-to-tail adjustment, and I_5^- ions are located in the columns formed by the α-CD cavities (see Fig. 5A) and nearly linearly arranged in the direction of the columns.

Fig. 5B displays the crystal structure of the inclusion complex of I_7^- and β-CD with an IN value of 0.5 [47]. The I_7^- is arranged in a zigzag fashion with the two ends completely inserted in the cavities.

In Fig. 5C, each of the two planar ligands of $[Rh(cp)_2]^+$ ion [65] is respectively included in one of the two α-CD molecules cavities in the inclusion complex of α-CD with an IN value of 0.5.

The inclusion complex of α-CD and ferrocene [66] is similar to that of α-CD and $[Rh(cp)_2]^+$ ion, with an IN value of 0.5 (see Fig. 6A).

The IN values of the two inclusion complexes of ferrocene with β-CD and γ-CD are both one, that is, one ferrocene molecule is fully included in the respective cavities [67] but they differ in the orientation of the ferrocene molecule (see Fig. 6B and C).

Some inclusion complexes have different IN values in different states, such as the complex of 4-hydroxybenzaldehyde with β-CD, implying that the inclusion complexation between CD and guest varies with the change of the state of an inclusion complex [97].

As a whole, the formation, structure and IN values of CD inclusion complexes are influenced by many factors, such as the chain length of the organic guests, the longitudinal extension of inorganic guests, the state of inclusion complexes, the size of the CD cavity etc. As a result, IN values vary with different inclusion systems.

Table 1
CSR, IN and CRW values in CD inclusion complexes

Host	Guest	State[a]	Method[b]	CSR	IN	CRW	Ref.[c]
α-CD	Eugenol	AQ	NMR	1:1	1	–	[38]
α-CD	Acetonitrile	SC	XRD	1:1	1	6	[44]
α-CD	$Cd_{0.5}I_5$	SC	XRD	2:1	0.5	27	[46]
α-CD	Iodine-iodide lithium salt(LiI_5)	SC	XRD	2:1	0.5	8	[46]
Hexakis(3-*O*-Acetyl-2,6-di-*O*-methyl)-α-CD	Butyl acetate	SC	XRD	1:2	1	–	[50]
α-CD	3-Aminobenzoic acid	AQ	NMR	1:1	1	–	[58]
α-CD	4-Aminobenzoic acid	AQ	NMR	1:1	1	–	[58]
α-CD	2-Chlorophenol	AQ	NMR	1:1	1	–	[59]
α-CD	3-Chlorophenol	AQ	NMR	1:1	1	–	[59]
α-CD	4-Chlorophenol	AQ	NMR	1:1	1	–	[59]
α-CD	2,4-Chlorophenol	AQ	NMR	1:1	1	–	[59]
α-CD	2,6-Chlorophenol	AQ	NMR	1:1	1	–	[59]
α-CD	3,4-Chlorophenol	AQ	NMR	1:1	1	–	[59]
α-CD	Decanoic acid	SC	XRD	2:1	0.5	25	[62]
α-CD	Polyethylene glycol	PO	XRD, NMR	20:1	0.05	–	[64]
α-CD	$Rh(cp)_2PF_6$	SC	XRD	2:1	0.5	8	[65]
α-CD	Ferrocene	SC	XRD	2:1	0.5	9	[66]
α-CD	Hydroquinone	SC	XRD	1:1	1	6	[68]
α-CD	Methanol	SC	XRD	1:1	1	5	[69]
α-CD	Nitromethane	SC	XRD	1:1	1	5	[70]
α-CD	4-Chlorophenol	SC	XRD	1:1	1	5	[71]
α-CD	4-Cresol	SC	XRD	1:1	1	6	[71]
α-CD	Syringic acid	AQ	NMR	1:1	1	–	[72]
α-CD	2-Methoxyphenol	AQ	NMR	1:1	1	–	[73]
α-CD	Benzyl alcohol	SC	XRD	1:2	1	6	[74]
α-CD	1-Phenylethanol	SC	XRD	1:1	1	4	[75]
α-CD	4-Fluorophenol	SC	XRD	1:1	1	6	[76]
α-CD	4,4′-Biphenyldicarboxylic acid	SC	XRD	2:1	0.5	28	[77]
α-CD	4,4′-Biphenyldicarboxylic acid	SC	XRD	1:0.5	0.5	9.5	[77]
Hexakis(2,6-di-*O*-methyl)-α-CD	Acetonitrile	SC	XRD	1:1	1	2	[78]
Hexakis(2,6-di-*O*-methyl)-α-CD	Acetone	SC	XRD	1:1	1	–	[79]
Hexakis(2,6-di-*O*-methyl)-α-CD	Iodine	SC	XRD	1:1	1	–	[80]
Hexakis(2,6-di-*O*-methyl)-α-CD	1-Propanol	SC	XRD	1:1	1	–	[80]
Hexakis(2,3,6-tri-*O*-mehtyl)-α-CD	1,7-Dioxaspiro[5.5]undecane	SC	XRD	1:1	1	2.7	[81]
Hexakis(2,3,6-tri-*O*-mehtyl)-α-CD	4-Nitrophenol	SC	XRD	1:1	1	1	[82]
β-CD	Desloratadine	AQ	NMR	1:1	1	–	[29]
β-CD	Eugenol	AQ	NMR	1:1	1	–	[38]
β-CD	Ethanol	SC	XRD	1:1	1	12	[45]
β-CD	Iodine-iodide potassium salt (KI_7)	SC	XRD	2:1	0.5	9	[47]
β-CD	1,10-Phenanthroline	SC	XRD	3:2	1	18.5	[48]
β-CD	Calcium chloride	SC	XRD	1:2	0	11.25	[54]
β-CD	2-Aminobenzoic acid	AQ	NMR	1:1	1	–	[58]
β-CD	3-Aminobenzoic acid	AQ	NMR	1:1	1	–	[58]
β-CD	4-Aminobenzoic acid	AQ	NMR	1:1	1	–	[58]
β-CD	2-Chlorophenol	AQ	NMR	1:1	1	–	[59]
β-CD	3-Chlorophenol	AQ	NMR	1:1	1	–	[59]
β-CD	4-Chlorophenol	AQ	NMR	1:1	1	–	[59]
β-CD	2,4-Chlorophenol	AQ	NMR	1:1	1	–	[59]
β-CD	2,6-Chlorophenol	AQ	NMR	1:1	1	–	[59]
β-CD	3,4-Chlorophenol	AQ	NMR	1:1	1	–	[59]
β-CD	Acetic acid	SC	XRD	1:0.4	1	7.7	[60]
β-CD	Formic acid	SC	XRD	1:0.3	1	7.7	[60]
β-CD	Ethylene glycol	SC	XRD	1:1	1	8	[61]
β-CD	Glycerol	SC	XRD	1:1	1	7.2	[61]
β-CD	Poly-(iminooligomethylene)s	AQ	NMR	40:1	0.025	–	[63]
β-CD	Ferrocene	PO	XRD,EA,NMR	1:1	1	–	[67]
β-CD	Syringic acid	AQ	NMR	1:1	1	–	[72]
β-CD	2-Methoxyphenol	AQ	NMR	1:1	1	–	[73]
β-CD	2,7-Dihydroxy-naphthalene	SC	XRD	1:1	1	4.6	[83]
β-CD	*trans*-cinnamic acid	SC	XRD	1:1	1	10.9	[84]
β-CD	1,4-Butanediol	SC	XRD	1:1	1	6.25	[85]
β-CD	Benzamide	SC	XRD	1:1	1	6	[86]
β-CD	1,12-Dodecanediol	SC	XRD	2:1	0.5	29	[87]
β-CD	4-Bromophenol	SC	XRD	1:1	1	5	[88]
β-CD	4-Nitrobenzoic acid	SC	XRD	2:2	1	28.5	[89]
β-CD	Methanol	SC	XRD	1:1	1	6.5	[51]
β-CD	4-*tert*-butyltoluene	SC	XRD	1:1	1	17	[90]
β-CD	Dimethysulfoxide	SC	XRD	1:0.5	1	7.35	[91]
β-CD	2-Methoxyphenol	PO	XRD, NMR	1:1	1	6	[92]
β-CD	Cyclizine	SC	XRD	4:3	1.33	50	[93]
β-CD	Naringin	AQ	NMR	1:1	1	–	[94]
β-CD	Naringin dihydrochalcone	AQ	NMR	1:1	1	–	[94]
β-CD	Desloratadine	AQ	NMR	1:1	1	–	[95]
β-CD	Metoprolol tartrate	AQ	NMR	1:1	1	–	[96]

Table 1 (*Continued*)

Host	Guest	State[a]	Method[b]	CSR	IN	CRW	Ref.[c]
β-CD	4-Hydroxybenzaldehyde	AQ	NMR	1:1	1	–	[97]
β-CD	4-Hydroxybenzaldehyde	SC	XRD	2:4	2	–	[97]
β-CD	Ferrocene	SC	XRD	4:5	1	–	[98]
β-CD	Ethyl 4-hydroxylbenzoate	AQ	NMR	1:1	1	–	[99]
β-CD	1,5-Naphthalenediamine	AQ	NMR	1:1	1	–	[99]
β-CD	1,8-Naphthalenediamine	AQ	NMR	1:1	1	–	[99]
β-CD	Niflumic acid	AQ	NMR	1:1	1	–	[100]
β-CD	Cesium salt of niflumic acid	SC	XRD	2:4	2	22	[100]
β-CD	Squaric acid	SC	XRD	1:1	1	6.65	[101]
β-CD	4-Bromoacetanilide	SC	XRD	1:1	1	13.5	[102]
β-CD	Acetaminophen	SC	XRD	1:1	1	13.3	[103]
β-CD	Monosulfonated triphenylphosphine	AQ	NMR	1:1	1	–	[104]
Heptakis(2,6-di-*O*-methyl)-β-CD	4-Iodophenol	SC	XRD	1:1	0	2	[105]
Heptakis(2,6-di-*O*-methyl)-β-CD	4-Nitrophenol	SC	XRD	1:1	0	2	[106]
Heptakis(2,6-di-*O*-methyl)-β-CD	Acetic acid	SC	XRD	1:1	1	3	[107]
Heptakis(2,3,6-tri-*O*-methyl)-β-CD	Indole-3-butyric acid	SC	XRD	1:1	1	0.37	[107]
Heptakis(2,3,6-tri-*O*-methyl)-β-CD	2,4-Dichlorophenoxyacetic acid	SC	XRD	1:1	1	2	[108]
Heptakis(2,3,6-tri-*O*-methyl)-β-CD	1-Iodophenol	SC	XRD	1:1	1	4	[109]
γ-CD	Ferrocene	PO	XRD,EA,NMR	1:1	1	–	[67]
γ-CD	Syringic acid	AQ	NMR	1:1	1	–	[72]
γ-CD	2-Methoxyphenol	PO	XRD, NMR	1:1	1	8	[92]
γ-CD	1-Propanol	SC	XRD	1:1	1	17	[110]
γ-CD	12-Crown-4-LiSCN	SC	XRD	1:1:1/3	1	7.7	[111]
γ-CD	12-Crown-4-KCl	SC	XRD	1:1:1/3	1	9	[111]
γ-CD	Bis(naphthylacetyl)polyethylene glycol	AQ	NMR	4:1	0.25	–	[112]
γ-CD	Fullerenes (C_{60})	PO	XRD, NMR	2:1	0.5	–	[113]

[a] SC, AQ and PO represent single crystal, aqueous solution and powder, respectively.
[b] XRD, NMR and EA represent X-ray diffraction, ^{1}H nuclear magnetic resonance and elemental analysis.
[c] Ref. represents references.

According to Table 1, the IN values of inclusion complexes of α-CD with whether large guest molecules, such as hydroquinone [68], eugenol [38] and 1-phenylethanol [75], or small guest molecules, such as acetonitrile [44], methanol [69] and nitromethane [70], are all one (see Table 1). Similarly, β-CD also forms inclusion complexes with an IN value of one with either large guest molecules, such as 1,10-phenanthroline [48], or small guests, such as methanol [51] and ethanol [45]. Additionally, similar examples also exist in the complexes of γ-CD with 1-propanol [110] and metal coordination compounds of 12-crown-4 [111]. Although the sizes of the two guests differ very much from each other, their complexes with γ-CD have the same value of IN. The inclusion complexes of γ-CD with 12-crown-4-M^+ (Li^+, K^+) are schematically depicted in Fig. 7. They have a very special structure which leads to different binding behavior [111]. As 12-crown-4 and 12-crown-4-M^+ are regarded as guests, the CSR and IN values in their inclusion complexes with γ-CD are 1:1, 1 and 3:1, 0.5, respectively.

Thus, variations in cavity volumes or the size of guest molecules do not greatly influence the IN values. A large CD molecule, such as γ-CD, and a small organic guest such as 1-propanol are not bound to form a complex with a value of IN larger than one. Contrarily, a smaller CD molecule, such as β-CD, and a large organic guest, such as 2,7-dihydroxy-naphthalene [83] and desloratadine [29], can also form an inclusion complex with an IN value of one, in which the large guest molecule cannot be fully included into the cavity of CD, but one or more groups of them can be accommodated by the cavity. These observations are very different from the association behavior between M^{x+} and ligands, because the CN values in many transition metal coordination compounds have a close relationship with the size of both M^{x+} and ligands.

An IN value of zero mainly occurs between native CDs and inorganic salts, such as in the crystal inclusion complex of β-CD with calcium chloride [54]. Neither calcium ion nor chloride ion is included in the β-CD cavity. They stay in the crystal interstice. At the same time, an energetically unfavorable situation obviously occurs when some of the water molecules are included in the hydrophobic cavity. A similar situation also appears in the inclusion complex of β-CD with copper chloride [114]. These results illustrate that inorganic ions possessing small size and strong hydrophilicity avoid the hydrophobic cavity of β-CD when compared with neutral water molecules. Since only an encapsulation interaction occurs, the crystal inclusion complexes are regarded as encapsulated products.

An IN value of zero also appears in inclusion complexes formed by modified β-CD with a few organic guests as shown in Table 1.

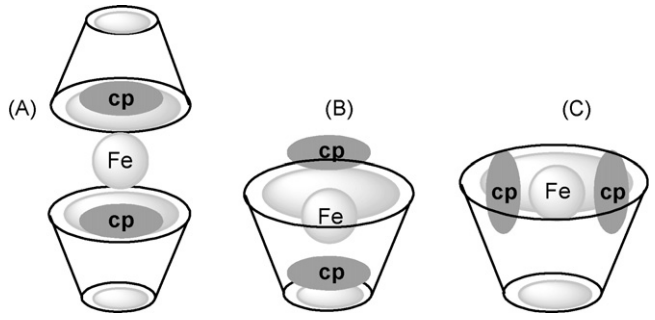

Fig. 6. Structural features of the inclusion complexes of ferrocene with (A) α-CD [66], (B) β-CD [67] and (C) γ-CD [67].

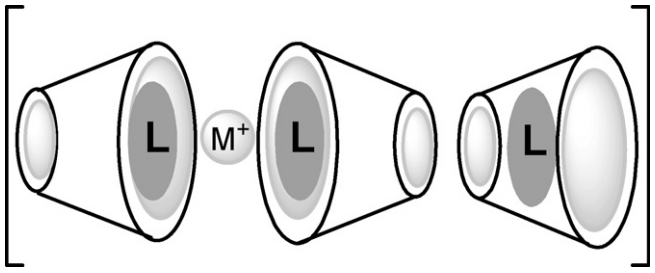

Fig. 7. A structural sketch of the inclusion complexes of γ-CD with 12-crown-4-M^+. M^+ represents K^+ and Li^+, and L represents 12-crown-4 [111].

For example, although 4-iodophenol [105] and 4-nitrophenol [105] are both hydrophobic organic guests, they can form inclusion complexes of heptakis(2,6-di-*O*-methyl)-β-CD with IN equal to zero.

5. Complexed water molecules and crystal-lattice water molecules in cyclodextrin hydrates

Crystal water (CRW) exists in two different forms, namely, the water molecules located in the cavity as complexed water (COW) and the others lie outside of the cavity of CD as crystal lattice water (see Table 2). Hydrates of the same CD can exist in different crystal forms (CF), dependent on the method of preparation [24,25,115–117].

The α-CD hydrates demonstrate three kinds of crystal form. The CRW values of crystal forms I and II [24,115,116] are both 6, but the CRW value of crystal form III [25] is 7.57. However, the COW values of crystal forms I, II and III are 2, 1 and 2.5 respectively, indicating that the values of COW in the crystal forms are different from each other. Thus the crystal form has an important effect on the distribution of the water molecules.

The β-CD hydrates have two crystal forms. The CRW values of crystal forms I and II [9,117] are 12 and 11, respectively, while the COW values of forms I and II are 7.3 and 6.3, respectively (Table 2). The hydrate of γ-CD has one crystal form, with CRW and COW of 14.1 and 7.1, respectively [118].

The CRW values of modified CD hydrates and their inclusion complexes, shown in Table 2, are obviously lower than those of the same native CDs and their complexes in crystals, respectively (see Tables 1 and 2). This change can be caused by the introduction of hydrophobic groups at the rim of CD cavity.

From Table 2, it is clear that the number of crystal forms decreases with the increase of the number of glucose units. Moreover, there is a large difference in COW values both between the different crystal forms of the same CD and between the same crystal forms of different CDs. Obviously, the diameter of the cavity of CD, the size and shape of the interior conformation of macrocycle, and the packing form of the CD molecules in a crystal structure have an effect on the distribution of the water molecules of three common CDs [9,117].

Interestingly, although the values of CRW and COW increase with the increase of volume of CD cavities as expected, the values of COW decrease sharply when the number of glucose units exceeds nine, for instance, COW decreases markedly from 8.75 of δ-CD [122], 6 of ε-CD [123] to 1 of ι-CD [124]. At the same time, CRW increases first and then decreases, which is rather irregular.

According to the definition of IN, the values of IN and COW are the same in CD hydrates. Both can directly reflect the occupancy of the solvent water molecules as guest in the CD cavity and indicate inclusion complexation between CD and water molecules. Conversely, the large differences between CRW and COW imply that the encapsulation interaction exists commonly in CD hydrates. Thus a CD hydrate may be regarded as kind of mixture between the inclusion complex and the encapsulation product of CD with water.

Table 2
The values of CRW and COW in CD hydrates

Host	CF	CRW	COW	Ref.
α-CD	I	6	2	[24,115,116]
α-CD	II	6	1	[24,115,116]
α-CD	III	7.57	2.57	[25]
β-CD	I	12	6.3	[9,117]
β-CD	II	11	7.3	[9,117]
γ-CD	I	14.1	7.1	[118]
Hexakis(2,6-di-*O*-methyl)-α-CD	I	0	0	[119]
Hexakis(2,6-di-*O*-methyl)-α-CD	II	1	1	[119]
Hexakis(2,6-di-*O*-methyl)-β-CD	I	0	0	[120]
Heptakis(2,3,6-tri-*O*-methyl)-β-CD	I	1	0	[121(a)]
Heptakis(2,3,6-tri-*O*-methyl)-β-CD	II	0	0	[121(b)]
Heptakis(2,3,6-tri-*O*-methyl)-β-CD	III	3	0	[121(b)]
δ-CD	I	13.5	8.75	[122]
ε-CD	I	19	6	[123]
ι-CD	I	9	1	[124]

6. Hydrates of cyclodextrin inclusion complexes in the crystal state

Having a structural advantage, the shape, size and polarity of most organic guest molecules even in aqueous solution fit the cavity of CD through inclusion complexation [58,71] better than water molecules. The inclusion complexes are then surrounded by many water molecules [58,59]. In the solid state, whether single crystal [45,90,91] or crystalline powder [92], the complexes contain several crystal water molecules with some embedded in the cavities as COW and the others inserted in the interstice of CD-G.

The solid inclusion complexes of β-CD with several structurally similar guests, such as ethylenediamine, diethylenetriamine and triethylamine, which were prepared and dried under the same condition, can be used to evaluate the change of CRW of β-CD before and after inclusion. In the complex: (β-CD)$_3$·triethylamine·21H$_2$O, [125] the triethylamine molecule with a small molecular volume is arranged in a trifurcate tree structure with each branch devoted to one of the cavities of three β-CD molecules, The remaining space in the cavities is large enough so that the CRW value is as high as 21, which is close to the total number of CRW of 24 in three hydrates of free β-CD. However, CRW obviously decreases in the other two complexes with different CSR values, i.e., (β-CD)$_2$·(ethylenediamine)$_5$·4H$_2$O [125] and β-CD·diethylenetriamine·H$_2$O [125], indicating that the CRW values may have a relationship with the CSR values of CD to guest in inclusion complexes of a set of similar guest molecules.

Moreover, the CRW values for the complexes with a CSR value of 1:1, such as the complexes of α-CD with hydroquinone [68] or methanol [69], are not only equal to each other approximately, but also close to the CRW value of 6 in hydrates of free α-CD [24]. Thus the volume and polarity of guest molecules have little effect on CRW values for CD inclusion complexes with the same CSR of 1:1. However, CRW increases rapidly for complexes with CSR of 2:1 formed by CD with a long chain guest, such as the complex of α-CD and decanoic acid with a CRW value of 25 [62]. This phenomenon can be attributed to a large increase of the free space in crystal interstice of supramolecular structure with CSR of 2:1.

With different cations, such as Li^+ and Cd^{2+}, the inclusion complexes formed by α-CD and the same inorganic anion, such as I_5^-, show quite different values of CRW, for example, in the complex of α-CD with LiI_5, CRW is 8 [46], but CRW in the complex of α-CD with $Cd_{0.5}I_5$ is 21 [46] (Table 1).

Furthermore, the CRW values of inclusion complexes formed by β-CD with guests are usually greater than those of the complexes of α-CD with the same guests. This phenomenon is quite similar to the behavior of the hydrates of free α-CD and β-CD (see Table 2). There is a big difference in CRW values among the complexes, with the same CSR, formed by β-CD and different guests. In addition, the CRW values of the hydrates of γ-CD inclusion complexes are usually large, especially when the molecular volumes of guest molecules are not big enough. For instance, the CRW value of 17 in the complex formed by γ-CD and 1-propanol [110] is significantly larger than those (CRW < 10) of the complexes of γ-CD with 2-methoxyphenol [92] and 12-crown-4 complexes of K^+ or Li^+ ion [111]. This observation can be attributed to the fact that 2-methoxyphenol and 12-crown-4 complexes have a much bigger size than 1-propanol. As described in section four, the inclusion

complexation between α-CD and inorganic anions is involved with inorganic cations. Similarly, in the inclusion complexes of γ-CD and 12-crown-4 complexes of different inorganic ions, the CRW values vary with different inorganic salts in an inclusion system even though the inclusion complexes have similar or the same crystal structures.

Therefore, the CRW values in CD inclusion complexes apparently have a direct connection with the cavity diameter of the parent CD molecules (Table 1).

7. The relationship between chemical stoichiometric ratio and inclusion number of cyclodextrin inclusion complexes

When inclusion phenomena occur only in the form of inclusion complexation, information about inclusion behavior between CD and guest is based on the value of IN. An IN value of one is the most common according to Table 1. Clearly, inclusion complexes possessing the same IN value do not mean that they also have the same value of CSR. For example, the CSR value of 1:2 appears in the inclusion complex of β-CD with iodide ion [51] as well as the complex of hexakis(3-*O*-acetyl-2,6-di-*O*-methyl)-α-CD with butyl acetate [50]. A CSR value of 2:3 appears in the complex of β-CD with 1,10-phenanthroline [48] or 8-nitroquinoline [49]. However, the four inclusion complexes described above have the same value of IN of 1 (Fig. 8).

Table 1 shows that β-CD with acetic acid [60] and formic acid [60] form inclusion complexes with CSR values of 1:0.4 and 1:0.3, respectively. Although the occupancy factors of the two guests in the cavity of β-CD are different from each other, the IN values in the two complexes are one, implying that unlike water molecules, small organic molecules, such as acetic acid and formic acid, cannot be spread all over the cavity of CD. Instead, they can occupy only a fraction of the cavity in the crystallization conditions as reported. Apparently, the polarity and hydrophilicity of the small organic guests are lower than those of water molecules. Theoretically, they are more appropriate to the environment of the CD cavity than water molecules, but most sites in the cavity are still occupied by water molecules. This phenomenon indicates that both hydrophobic interaction and structural fitness may not play an important role in the formation of CD inclusion complexes of small organic guests. A similar situation also occurs in β-CD complex of dimethylsulfoxide [91].

An inclusion complex with an IN value of 0.5 is usually formed by parent CD and a guest molecule with a special structure [46,47,62], and usually corresponds to a CSR value of 2:1 as reported in Table 1. Furthermore, an IN value of zero means that no inclusion complexation actually occurs, no matter what the CSR values are. Until recently, solely encapsulation interaction in inclusion systems have been limited to the inclusion behavior either between parent CDs and inorganic salts [54,114] or between some modified CDs and a few organic guests [105].

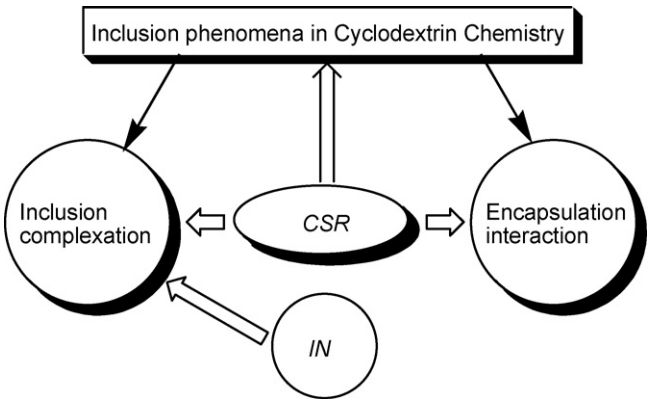

Fig. 8. The correlation among the inclusion phenomena, CSR and IN.

Although the CD inclusion complexes listed in Table 1 are but a selection of the many that have been reported, they are representative of the most common types. Table 1 presents fifteen types of CSR value. According to our definition of IN, there are eight types of IN values. Although in many cases, an IN value of 1 corresponds to a CSR value of 1:1, there is an uncertain relationship between CSR and IN. This difference between CSR and IN is somewhat similar to that between the number of ligands and CN.

When a CSR value is used to characterize inclusion phenomena, it can elucidate the stoichiometric relationship between CD and the guest that participated in the molecule–molecule chemical reaction or in the cocrystallization. Also, while an IN value is used to describe inclusion phenomena, it can reveal that the intermolecular interaction is inclusion complexation rather than encapsulation interaction. Therefore, the intermolecular interaction can be better reflected by the values of IN.

If the values of both CSR and IN are provided to describe the formation of CD inclusion complexes, especially inclusion complexes in the solid state, we can conveniently obtain information about whether guests are all included in the CD cavities.

8. Conclusion

The inclusion complexation in cyclodextrin chemistry is compared with the coordination interaction in coordination chemistry in this paper. The inclusion complexation and encapsulation interaction in CD-G systems are defined clearly. IN is proposed to reveal the type of inclusion phenomenon. The differences and similarities between CN of M^{x+} in coordination chemistry and IN of CD in cyclodextrin chemistry are discussed. At the same time, the factors which influence IN, and the differences between IN and CSR in characterizing CD inclusion complexes are also evaluated. The changes of the number and form of water molecules both in CD hydrates and in hydrates of crystal inclusion complexes of CD are reviewed.

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