Deep Eutectic Solvents for Next-generation Cyclodextrin Science

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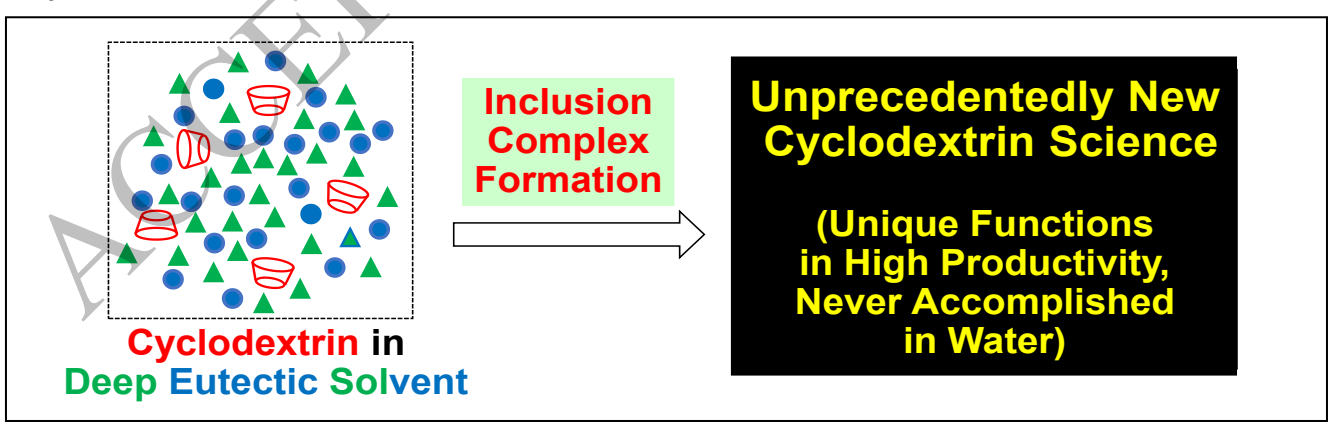
Makoto Komiyama received his Ph.D. from The University of Tokyo in 1975. After spending four years at Northwestern University as a postdoctoral fellow, he became an assistant professor at The University of Tokyo, and then an associate professor at University of Tsukuba. In 1991, he was promoted to a professor of The University of Tokyo, and became a professor emeritus in 2012. Then, he spent four years at University of Tsukuba, and two years at the National Institute for Materials Science, Tsukuba. In 2016-2019, he was a visiting professor of Ocean University of China.

Abstract

In cyclodextrin science, water has been almost exclusively employed as solvent, and this imposes non-negligible limitations to the scope of applications. Accordingly, deep eutectic solvents, constructed from hydrogen-bonding donors and acceptors, have been attracting much interest as important substitutes of water. This review comprehensively covers chemical and physicochemical features of cyclodextrins in these eco-friendly solvents. In one category, cyclodextrins or their derivatives are dissolved as solutes in conventional deep eutectic solvents. All of α-, β-, and γ-cyclodextrins efficiently form inclusion complexes with various guest molecules, exactly as observed in water. Notably, chemically modified cyclodextrins (e.g., 2-hydroxypropyl-cyclodextrins) form still more stable inclusion complexes than native cyclodextrins. Alternatively, deep eutectic solvents are prepared by combining cyclodextrins with other hydrogen-bonding components. The cyclodextrin units in these mixtures also form inclusion complexes with guest molecules. It has been proposed that enhanced flexibility of cylindrical structures of cyclodextrins allows effective induced-fit to stabilize inclusion complexes. The applications of these systems widely range from catalysis for organic synthesis to extraction, analysis, pharmaceutics, and many other fields. High solubilities of CDs and various chemicals in these solvents guarantee high productivity of target transformation, and unprecedentedly novel functions are promising for these unique systems.

Keywords: cyclodextrin, deep eutectic solvent, inclusion complex, modified cyclodextrin

Graphical abstract



1. Introduction

Cyclodextrins (CDs) are cyclic oligomers of D-glucose, which have donut-like shapes and are soluble in water (Figure 1a). Internal diameters of the cavities of α-, β-, and γ-CDs (6, 7, and 8 glucose units) are about 4.5-6.0, 6.0-8.0, and 8.0-9.5 Å, respectively. These cavities are surrounded by a ring of C-H groups, a ring of glycosidic oxygens, and another ring of C-H groups, and provide apolar microenvironments in aqueous solutions. The most important characteristic of CDs is formation of inclusion complexes in which various guest molecules are accommodated in the apolar cavity.[1-12] The stability of inclusion complex fairly corelates with both the hydrophobicity of guest and the fitness of guest size to the cavity size. Through the inclusion complex formation, the physicochemical properties of guest molecules are significantly modulated. For example, water-insoluble guest molecules are solubilized in water. Highly volatile compounds are stably trapped for a long time, while unstable molecules are protected from undesired degradation. Furthermore, CDs show unique catalysis for various reactions, since reagents and catalysts are placed in mutual proximity in inclusion complexes to promote the reactions.[10] The size and shape of products (and substrates) are strictly regulated by steric restriction of the cavity. Importantly, all these specific functions of CDs are further improved by chemical modifications in which desired functional groups are selectively introduced to predetermined sites. In terms of these advantageous characteristics, CDs and their derivatives have been widely and usefully employed in our daily lives (pharmaceutics, cosmetics, foods, biotechnology, medicine, agriculture, catalysis, nanotechnology, and many other fields).[13-30] In addition to native α-, β-, and γ-CDs, variously modified CDs (e.g., methylated-CDs and 2-hydroxypropyl-CDs) are currently manufactured in industry, and commercially available at reasonable prices for many attractive applications (Figures 1b and 1c).[31-34]

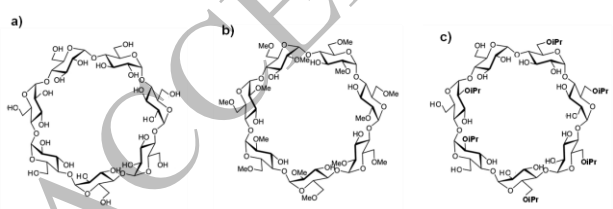


Fig. 1. Molecular structures of (a) native β-CD, (b) heptakis(2,6-di-O-methyl)-β-CD (Me = -CH_3), and (c) 2-hydroxypropyl-β-CD (iPr = -$CH_2CH(OH)CH_3$), which are commercially available. Note that the numbers and positions of substituents in modified CDs, as well as their physicochemical properties, are dependent on their preparation conditions (and thus on commercial source).

For a long time, it has been believed that CDs form inclusion complexes only in water. Thus, water was exclusively employed as the solvent for CD science (DMSO and DMF were exceptionally employed as substitutes).[1-8,12] This water-biased property is highly appropriate for many applications of CDs in our daily lives (food additives, medicines, cosmetics, and many others). However, there exist also many other applications, in which the use of water solvent imposes notable limitations (e.g., industrial applications, material science, and others). First, the solubility of CDs in water is rather low. For example, only 18 g of β-CD can be dissolved in 1 L of water at room temperature ([β-CD] = 16 *mM*). Accordingly, huge reactor vessels are necessary to produce (or transform) large amount of target chemicals. This factor should be also troublesome to fabricate CD-based materials. Secondarily, the chemicals employed for these applications must be sufficiently water-soluble and insensitive to water. Unfortunately, however, many practically important chemicals and drugs are often poorly soluble in water and/or unstable there (even in the presence of CDs). Thirdly, large amount of waste water is released from these applications, and must be purified to avoid environmental pollutions. Enormous cost and energy are required for this post-processing.

In order to solve these problems and develop still more advanced CD science for next-generation, the use of deep eutectic solvents (DESs) has been recently attracting interest as a promising strategy (Figure 2).[35-70] These artificial solvents are produced by mixing two (or more) components which possess hydrogen-bonding activity. Because of an enormous amount of melting point depression, the mixtures retain liquid states at wide range of temperatures, and conveniently employed as media for various chemical transformations. As described more in detail in Section 3, the properties of DESs can be modulated through appropriate choice of components and their compositions, widening the scope of practical applications.

Fig. 2. Use of deep eutectic solvents (DESs), in place of water, for next-generation CD science.

This review comprehensively covers the findings in the CD science using DESs as media. Most importantly, DES systems satisfactorily fulfill both of two critically important requirements for the successes of CD science; (i) high solubility of CDs and their derivatives and (ii) efficient inclusion complex formation with guest molecules. Furthermore, sufficiently high solubilities of various chemicals in DESs are advantageous for effective and economical applications. All the experimental procedures are very simple and easy, and virtually the same as those for CD science in water solvent. The green characters of these systems are also big advantages for environmental protection. Throughout this review, unique features of CD science in DESs, which are difficult to accomplish by using water as solvent, will be emphasized.

2. Two types of DES systems involving CDs

Current CD science in DESs is mainly divided into the following two categories (Figure 3).

(1) *Category I: CD-in-DESs* (left-hand side of Figure 3)
CDs (or their derivatives) are simply solubilized as solutes in conventional DESs, and allow to exhibit their functions in these non-aqueous media.
(2) *Category II: CD-derived-DESs* (right-hand side)
CDs (or their derivatives) are directly combined with other hydrogen bonding components to construct novel DESs, and the resultant CD-derived-DESs are employed for specific functions.

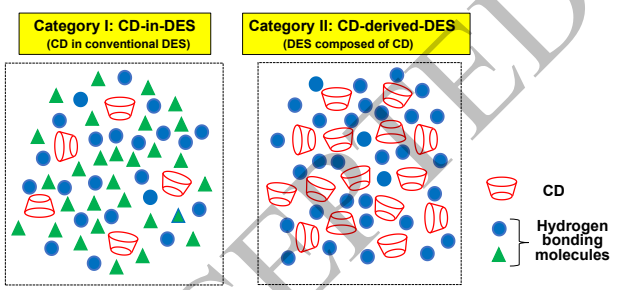


Fig. 3. Schematic views of two types of CD science in DESs. In category I, CDs are simply dissolved in conventional DESs. In category II, however, novel DESs are fabricated by using CDs as the primary components. In both systems, the CD units satisfactorily exhibit unique functions through inclusion complex formation.

Both of these DES systems are characterized by high thermal stabilities, low vapor pressures, nontoxicity, and biodegradability, which are highly suitable for green chemistry and promising for variety of applications.[35] As expected, their unique functions are primarily ascribed to inclusion complex formation of the CD units with reagents and catalysts. In this review, these two categories are described in detail in Sections 4 and 5, respectively. The evidence for inclusion complex formation in DESs is presented, together with the corresponding thermodynamic and kinetic characteristics. Various chemical transformations using these non-aqueous solvents are also described. In Section 6, "flexibilization-promoted induced-fit mechanism" is proposed as the primary driving force for the inclusion complex formation of CDs in DESs. For the readers who are not very familiar with this field, general introduction of conventional DESs is presented in Section 3.

3. Brief survey of previous studies on conventional deep eutectic solvents (DESs)

DESs are prepared from two (or more) components which are in general a hydrogen bond donor and a hydrogen bond acceptor, and conveniently employed as the media for various purposes.[40-59] Both components (at least one of them) are solid at room temperature. Upon the mixing of these components, however, they strongly interact each other through hydrogen bondings (also through electrostatic forces and van der Waals interactions). As the result, the self-assembly of each component is suppressed. When the combinations and compositions are appropriate, the melting point of the whole system is lowered down to sufficiently low temperatures to provide DESs as convenient solvents (detailed arguments were made in elegant reviews[40,48]). Representative components for DES preparation are presented in Figure 4. Note that so many other components are available, and the scope of DES is almost unlimited. Compared with conventional organic solvents and ionic liquids (composed of a cation and an anion)[71], DESs are usually less expensive.[38,40,72]

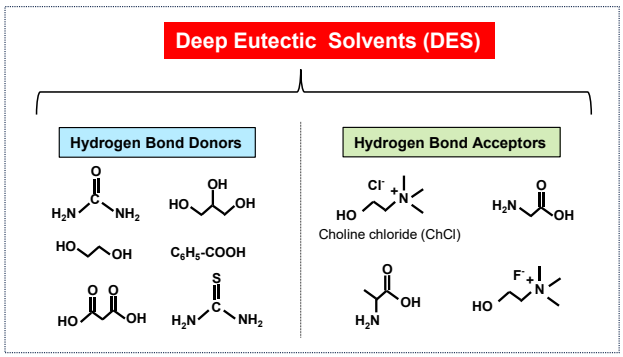


Fig. 4. Representative components to produce DESs. Many other compounds are also available, so that DESs of desired properties can be prepared through their appropriate combinations and compositions.

The studies in this new field started about 20 years ago, when Abbott et al. discovered an abnormally deep melting point depression upon the mixing of hydrogen bond donors and acceptors.[74,75] For example, the combination of (2-hydroxyethyl)trimethylammonium chloride (choline chloride: ChCl) with urea in 1:2 mole ratio provided a viscous liquid at room temperature (choline chloride is a solid and decomposes at 302 °C, whereas urea melts at 133°C). The liquid state of this ChCl-urea (1:2) mixture was maintained down to 12 °C. In the resultant DES, complicated hydrogen-bonding networks are formed between the two components.[76,77] The interactions of chloride ions with urea also prevail, playing significant roles for DES formation. This ChCl-urea (1:2) DES is named as "reline", and the most widely used for many applications. After these reports, many other DESs were prepared by using variety of combinations of hydrogen bonding components.[75] Of course, their physicochemical properties are strongly dependent on the molecular structures of components and their compositions, and thus freely designable according to the needs. The DESs composed of bio-based compounds such as sugars, organic acids, and amino acids are especially eco-friendly, and sometimes termed as natural deep eutectic solvents (NADES).[78] More recently, new kinds of DESs were prepared by using CDs as one of the components and combining them with citric acid, lactic acid, tartaric acid, evulinic acid, dimethylurea, and others, as described in Section 5 of this review.[42]

These DESs successfully dissolve various organic and inorganic compounds, even when they are only poorly soluble in water.[79] As expected from hydrogen bond-rich structures of DESs,[80] hydrogen-donating or hydrogen-accepting compounds are especially well soluble.[74] In ChCl-urea (1:2) DES, for example, the solubility of benzoic acid is 0.82 *M* (the value in water = 0.02 *M*).[80] Even virtually water-insoluble AgCl is solubilized up to 0.66 *M*. Highly hydrophobic danazol (a testosterone derivative for endometriosis treatment) dissolves up to 0.14 *mM*. Gases (CO_2 and SO_2) are also successfully absorbed by the DES.[81-84] Hydrogen-bonding solvents (e.g., water, methanol, and ethanol) are miscible with this DES. On the other hand, acetone, acetonitrile, acetophenone, dichloroethane, diethyl ether, ethyl acetate, hexane, propylene carbonate, and toluene are immiscible with this DES, and construct biphasic systems. This DES is far more viscous (552 mPa·s at 30 °C) than water (1 mPa·s).[85] However, its viscosity notably decreases with increasing temperature (46 mPa·s at 70 °C). Addition of small amount of water is also effective to decrease the viscosity. The density, the surface tension, and the refractive index are 1.25 g·cm^{-3}, 52 mN·m^{-1}, and 1.504, respectively (the values of pure water are 1.0 g·cm^{-3}, 73 mN·m^{-1}, and 1.333). On the other hand, the density of DES formed from ChCl and D-glucose (1:1 ratio) is 1.30 g·cm^{-3}, and its refractive index is 1.666.[86] The pH of this DES, evaluated by using a conventional pH meter, is around 7, and decreases with increasing temperature (6.3 at 80℃).[87] The readers who need more detailed information on conventional DESs should refer to the review articles.[40-42]

In some literatures, DESs are occasionally called as "low-melting mixture solvents". In a strict sense, these two concepts are not exactly identical with each other.[73] In this manuscript, however, the term "DES (deep eutectic solvents)" is always used, since this terminology seems to be more easily understandable for many readers.

4. Addition of CDs and their derivatives as solutes to conventional DESs ("CD-in-DES")

As described in previous section, conventional DESs intrinsically exhibit a number of excellent characteristics. However, their properties are further improved by combining with CDs, and unprecedently new functions can be accomplished. In CD-in-DESs (category I), CDs or their derivatives are added as solutes to conventional DESs, which are prepared from hydrogen-bonding donors and hydrogen-bonding acceptors. The most important concerns are (i) whether CDs are satisfactorily dissolved in these DESs, and (ii) whether CDs form inclusion complexes with guest molecules in these non-aqueous media.

4.1 Solubilities of CDs in conventional DESs

In many cases, CDs and their derivatives are well dissolved in conventional DESs.[42,88] In ChCl-urea (1:2) DES which is the most widely employed, for example, the solubilities of α-, β-, and γ-CDs at room temperature are >500, >1000, and >1000 g·L^{-1}, respectively.[89] These solubilities are much higher than the corresponding values in water (130, 18, and 249 g·L^{-1}). Especially, the increase of solubility of β-CD in this DES is highly attractive, since this CD is the cheapest among the three native CDs but its poorest solubility in water often hampers still wider applications. According to a small angle X-ray scattering study on β-CD solution of ChCl-urea (1:2) DES,[90] the β-CD molecules exist completely in their monomeric state without mutual aggregation (at least up to the concentration of 800 g·L^{-1}). Both the ChCl and the urea are hydrogen bonding with the hydroxyl groups of β-CD, and the dispersion force between β-CD and urea further mitigates the self-assembling of β-CD molecules. Chemically modified CDs (e.g., 2-hydroxypropyl-β-CD and methylated β-CD) are also satisfactorily dissolved in ChCl-urea (1:2) DES (>1000 g·L^{-1}).[91]

The solubilities of CDs in DESs strongly depend on their components and compositions, as expected. Thus, appropriate DES should be carefully chosen

according to the needs. Furthermore, physicochemical properties of DES solutions of CDs are notably changed upon the addition of small amount of water.[92-95] The solubility of CD is generally increased by the addition of water, whereas the viscosity of mixture decreases through partial rupture of the hydrogen bonds between the constituents (including CDs).[94]

4.2 Inclusion complex formation of CDs in conventional DESs

4.2.1 Evidence for inclusion complex formation

It has been well recognized that the addition of CDs to DESs increases the solubilities of hydrophobic substrates. Furthermore, the activities of DESs as extraction agents are also enhanced by the addition of CDs. These phenomena indicate that the CDs in the DESs interact with hydrophobic guest molecules. More direct and concrete evidence for inclusion complex formation in DESs was obtained by NMR experiments. For example, a specimen was prepared by adding aniline or toluene to the ChCl-urea (1:2) DES containing β-CD.[96] Small amount of water was added to decrease the viscosity of specimen and obtain high-resolution spectrum.[97] In the ^{1}H-^{1}H rotating-frame Overhauser spectroscopy (ROESY), clear nuclear Overhauser effects were observed between the protons of β-CD (H3′ and H5′) and the aromatic protons of the guests (at 2, 3, 5, and 6 positions) (Figure 5). However, no nuclear correlation was detected between the other protons of β-CD (H2′ and H6′) and the guest protons. The H3′ protons are located inside the cavity of β-CD, and form a ring near the secondary hydroxyl side, as depicted in the right-hand side of Figure 5. Similarly, the H5′ protons in the cavity form a ring near the primary hydroxyl side. Thus, these nuclear Overhauser effects show that, in the DES, the aromatic ring of aniline deeply penetrates into the cavity to place its protons near these intra-cavity protons. Concrete evidence for the inclusion complex formation of β-CD in the DES has been obtained (similar methodology has been widely employed to analyze the inclusion complexes in water). In terms of similar nuclear Overhauser effects, the formation of inclusion complexes of β-CD with two kinds of tricyclic drugs (amitriptyline and cyclobenzaprine) in ChCl-urea (1:2) DES was firmly evidenced.[98]

In order to analyze inclusion complex formation of a variety of guests in DESs, static headspace gas chromatography has been conveniently employed.[91-100] In a hermetically sealed vial containing a DES, predetermined amounts of CD and guest are incubated at constant temperature, and the vapor phase of equilibrium mixture is subjected to gas chromatography. When an inclusion complex is formed in the DES, the peak area of guest should accordingly decrease in a magnitude which reflects the amount of inclusion complex in the DES. This method is very useful to analyze many inclusion complexes systematically (see Table 1).

As is well known, UV/visible spectroscopy has been mostly employed for CD science in water. The spectra of chromophoric guests change upon the inclusion complex formation, reflecting the difference of chemical environments between aqueous phase and the inside of CD cavity. However, this method is not very successful for CD science in DESs. For example, the spectral change of methyl viologen on the inclusion complex formation with β- and γ-CDs in ChCl-urea (1:2) DES was too small, and inappropriate for detailed analysis.[89,91] The chemical circumstances inside the CD cavity are not much different from those in the DES phase to induce sufficiently large spectral change.

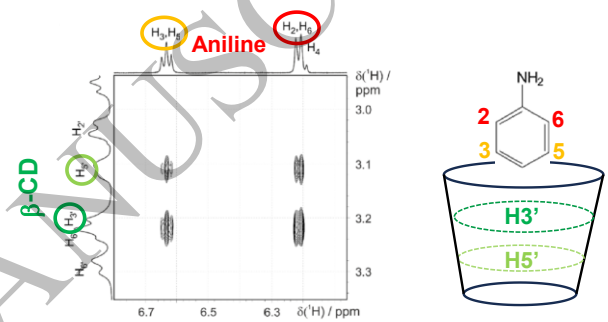


Fig. 5. Selected regions of ^{1}H-^{1}H ROESY spectra showing intermolecular correlation between the H3′ and H5′ protons of β-CD (vertical dimension) and the aromatic protons of aniline (horizontal dimension) in ChCl-urea (1:2) DES. The H3′ and H5′ are located inside the cavity, as depicted in the right-hand side. Reproduced from ref. 96 with permission (Copyright 2019 American Chemical Society).

4.2.2 Formation constants K of inclusion complexes in DES

In ChCl-urea (1:2) DES, the formation constants K of inclusion complexes of CDs and their derivatives were determined with the use of static headspace gas chromatography (Table 1).[91] For all the guests employed here (toluene, t-butylcyclohexane, limonene, and methyl orange), the CD/guest ratio in inclusion complexes is 1:1. In general, inclusion complexes of β-CD are more stable than the complexes of α-CD and γ-CD, as usually observed in water. Thus, β-CD, which is the most widely employed in water, is also very useful in the DES, at least for these guests. Furthermore, it is noteworthy that γ-CD forms rather stable inclusion complexes in this DES. Due to the large-sized cavity, this CD intrinsically shows many unique features which are not found with α-CD and β-CD. For example, two or more guest molecules can be simultaneously included in a cavity, leading to specific bimolecular reactions. Unfortunately, however, its weak guest-binding activity has often hampered still wider

applications. Thus, the use of γ-CD in DESs can be an important solution to this problem.

For the purpose of comparison, the K values for the inclusion complex formation in water are shown in the parentheses in Table 1. For all the guests and the CDs, the inclusion complexes in the DES are considerably less stable than those in water. Fortunately, however, the solubilities of CDs in the DES are very high, as described above. Thus, by using high concentrations of CDs, sufficient amounts of inclusion complexes can be successfully obtained in the DES. For example, about 90% of toluene (K = 11 M^{-1}) forms inclusion complex with β-CD in the DES, when [β-CD] = 1000 g·L^{-1} (0.88 *M*). With α-CD (500 g·L^{-1}) or γ-CD (1000 g·L^{-1}), about 75% of toluene is forming the inclusion complex in the DES.

Interestingly and significantly, in ChCl-urea (1:2) DES, 2-hydroxypropyl-β-CD (HP-β-CD; degree of substitution = 5.6) and partially methylated β-CD (CRYSMEB; degree of substitution = 4.9) form more stable inclusion complexes than native β-CD. These two β-CD derivatives are commercially obtainable at reasonable prices, and thus can be employed for various purposes in DESs. Furthermore, these results strongly indicate that the guest-binding activity in DESs can be promoted by appropriate modification of native CDs. Fortunately, the methods for precise modification of CDs have been already firmly established.[101-104] Highly advanced CD science is promising with the use of DESs.

Table 1. Formation constants K (M^{-1}) of CD inclusion complexes in ChCl-urea (1:2) DES, determined by static headspace gas chromatography [a,b]

Guest Molecule	α-CD	β-CD	γ-CD	HP-β-CD	CRYSMEB
Toluene	6 (38)	11 (142)	4 (33)	66 (163)	25 (165)
t-Butylcyclohexane	0 (248)	11 (4092)	4 (18)	20 (2036)	42 (5577)
Limonene	2 (1289)	14 (3162)	7 (116)	80 (2787)	34 (3668)
Methyl orange	-	70 (2500)	-	141 (5373)	-

a. The K values in water are presented in parentheses for the purpose of comparison. CRYSMEB = partially methylated β-CD (degree of substitution = 4.9). b. Ref. 91

4.2.3 Kinetics and thermodynamics of inclusion complex formation in DESs

By electron paramagnetic resonance study, kinetic parameters of inclusion complex formations of β-CD and γ-CD in ChCl-urea (1:2) DES were determined (Table 2).[105-107] As the probe, benzyl-*tert*-butyl nitroxide ($C_6H_5CH_2N(-O\cdot)C(CH_3)_3$) was employed. Because of shorter timescale of this method than NMR, free and included species provide separated signals, and thus the equilibrium constant (K) for the inclusion complexes, as well as the rate constants of host-guest association (k_{on}) and of host-guest dissociation (k_{off}), are directly determined. When β-CD is used as the host, k_{on} in the DES (2.3 x 10^7 M^{-1}s^{-1}) is more than 100 fold smaller than the value in water (2.5 x 10^9 M^{-1}s^{-1}). The inclusion of guest into the cavity of β-CD is enormously suppressed in the DES, probably because of its high viscosity. On the other hand, the dissociation process is less affected, and k_{off} in the DES (2.1 x 10^6 s^{-1}) is only 4.3 fold smaller than k_{off} in water (9.0 x 10^6 s^{-1}). Accordingly, the formation constant K (= k_{on}/k_{off}) of β-CD inclusion complex in the DES is 25 times (= 277 M^{-1}/11 M^{-1}) as small as the value in water. With the use of γ-CD as host, however, the rate constant of guest inclusion (k_{on}) in the DES is 34 fold (= 9.3 x 10^8/2.7 x 10^7) smaller than the value in water. On the other hand, the dissociation of inclusion complex (k_{off}) is 44 fold (= 4.4 x 10^7/1.0 x 10^6) slower in the DES than in water. As the result, the K value of γ-CD inclusion complex in the DES (27 M^{-1}) is 1.3 fold larger than the value in water (21 M^{-1}). Thus, γ-CD efficiently forms inclusion complex in the DES, mainly because its dissociation is notably slow. Apparently, some factor stabilizes this inclusion complex in the DES in a notable amount. As discussed more in detail in Section 6, "flexibilization-promoted induced-fit" of γ-CD cavity should be responsible for this stabilization. Furthermore, high viscosity of DES induces rather small retardation on the inclusion process due to its large-sized cavity.

Table 2. Rate constants k_{on} of the inclusion complex formation of benzyl-*tert*-butyl nitroxide with β-CD or γ-CD in ChCl-urea (1:2) DES, as well as the values of its dissociation (k_{off}).[a]

	Temp/℃	Solvent	$k_{on}/M^{-1}s^{-1}$	k_{off}/s^{-1}	K/M^{-1}
β-CD	90	water	2.5 x 10^9	9.0 x 10^6	277
		DES	2.3 x 10^7	2.1 x 10^6	11
γ-CD	70	water	9.3 x 10^8	4.4 x 10^7	21
		DES	2.7 x 10^7	1.0 x 10^6	27
	90	DES	8.8 x 10^7	3.8 x 10^6	23

CD + Guest $\underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}}$ CD-Guest inclusion complex

a. Ref. 105

In Table 3, thermodynamic parameters for the inclusion complex formation in the 7:3 (wt%) mixture of ChCl-urea (1:2) DES with water were directly compared with the values in pure water.[108] In both solvents, verbenone (4,6,6-trimethylbicyclo[3.1.1]hept-3-en-2-one) forms 1:1 complex with β-CD. In the 7:3 DES/water mixture, the inclusion process is driven by large negative ΔH (-3.3 kcal mol^{-1}), which is close to the corresponding ΔH in water (-4.4 kcal mol^{-1}). In both solvents, the TΔS terms show only minimal contributions. On the other hand, camphor (1,7,7-trimethylbicyclo[2.2.1]heptan-2-one) dominantly forms 1:2 complex with α-CD under the conditions employed.[109] In both solvents, the ΔH term is the primary driving force, and the TΔS term shows a

smaller contribution. In conclusion, the inclusion complex formation of CD in the DES-water mixture is primarily enthalpy-driven, in the same way as the complex formation in water is. Important roles of van der Waals interactions are indicated. The driving force of inclusion complex formation in DESs will be further discussed in Section 6.

Table 3. Thermodynamic parameters (kcal mol^{-1}) for the inclusion complex formation of β-CD with verbenone (and of α-CD with camphor) in water and in the mixture of ChCl-urea (1:2) DES and water (7:3 wt%) [a]

1:1 Verbenone/β-CD Complex				
Solvent	K (M^{-1})	ΔG	ΔH	TΔS
Water	1096	- 4.1	- 4.4	- 0.26
DES-water	253	- 3.3	- 3.3	+ 0.02
1:2 Camphor/α-CD Complex				
Solvent	K (M^{-2})	ΔG	ΔH	TΔS
Water	70300	- 8.0	- 13.6	- 5.6
DES-water	13800	- 5.6	- 11.2	- 5.6

a. Ref. 108.

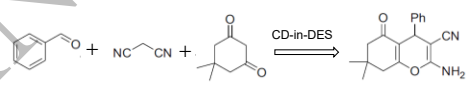
4.3 Applications of CD-in-DESs

4.3.1 Catalysts for organic synthesis

The catalysis by CDs in water is characterized by enormously high specificities with respect to the size, shape, chirality, and other features of both substrates and products.[1,6,7,10] In DESs, CDs also successfully exhibit unique catalysis, since they efficiently form inclusion complexes as described above.[67,110] In Table 4, a practically useful chemical (2-amino-4*H*-benzo[*b*]pyran) was synthesized by one-pot reaction in ChCl-urea (2:1) DES with the use of various types of CDs.[111] To this DES, benzaldehyde, malononitrile, and 5,5-dimethyl-1,3-cyclohexanedione (0.5 *M* each), as well as CD (5 mol%), were added, and incubated at 60 ℃ for 15 min. With this simple one-pot reaction, 2-amino-4*H*-benzo[*b*]pyran was successfully prepared. In the presence of γ-CD in the DES, the yield was 98 mol% which was far larger than the value (27%) in the corresponding aqueous solution of γ-CD. α-CD and β-CD were also effective in the DES, although slightly less active. Without CDs, however, the yield of target product was only 14%, confirming essential roles of CDs for the synthesis in this non-aqueous medium. In this one-pot synthesis, arylidenemalononitrile is first produced by Knoevenagel condensation between benzaldehyde and malononitrile, and then reacts with 5,5-dimethyl-1,3-cyclohexanedione. The resultant Michael-type adduct cyclizes, tautomerizes, and is finally converted to the final product 2-amino-4*H*-benzo[b]pyran. These reactions are very effective, because hydrophobic cavity of CD acts as microvessel to accommodate benzaldehyde, malononitrile and 5,5-dimethyl-1,3-cyclohexanedione. Accordingly, γ-CD of large-sized cavity is the most effective (note that γ-CD forms stable inclusion complexes in this DES, as described above). Furthermore, the reaction intermediates are protected by CD from undesired side-reactions, and straightforwardly employed for the next step. These roles of CDs in the DES are virtually identical with their roles in water solvent.[1,6,7,37,112-115] In this DES, the urea could further function as acid/base catalyst to promote the reaction. This one-pot synthesis was also successful in another DES formed from sorbitol, urea, and ammonium chloride (7:2:1). By replacing the malononitrile with ethyl acetoacetate ($CH_3C(O)CH_2C(O)OC_2H_5$), 1,4-dihydropyridines were also efficiently obtained by one-pot reaction in ChCl-urea (2:1) DES using γ-CD as catalyst.

Table 4. One-pot synthesis of 2-amino-4*H*-benzo[*b*]pyran using CD-in-DESs [a,c]

Additive	Solvent	Yield of Product(%)
-	ChCl-urea(1:2)	14
α-CD	ChCl-urea(1:2)	75
β-CD	ChCl-urea(1:2)	82
γ-CD	ChCl-urea(1:2)	98
	H_2O	27
	Sorbitol-urea-NH_4Cl(7:2:1) [b]	68



a. [benzaldehyde] = [malononitrile] = [5,5-dimethyl-1,3-cyclohexanedione] = 0.5 *M* at 60 ℃ for 15 min in the presence of 5 mol% of CD. b. At 70℃. c. Ref. 111

Organic syntheses in DESs are very advantageous from the viewpoint of practical applications, in that large amounts of products are preparable in a reaction vessel of predetermined size. By using DESs, the reactions can be accomplished at very high concentrations of both CDs and reagents, which are hardly attainable in water. With the use of γ-CD in ChCl-urea (1:2) DES, for example, about 140 g of 2-amino-4H-benzo[b]pyran are obtained in 1 L reaction mixture (as calculated from the data in the 4th row of Table 4). Furthermore, CDs are easily recovered and reused. After the first synthetic run, hot water was added to the reaction mixture, and the crude product was filtered out. The ChCl-urea-CD catalytic systems were recovered by evaporation of water, and directly used for the next run without noticeable deterioration. Advantages of DESs as solvents for organic synthesis are apparent. Note that target product can be also synthesized by mixing the reagents and CD in the absence of solvent.[116,117] However, this solvent-free synthesis would be very convenient only to produce a target chemical in small amount, and inappropriate for large-scale production.

Through the polymerization in a DES, CD-based polymeric materials were prepared.[118] Into the DES formed from choline chloride and citric acid, β-CD was added together with sodium hypophosphite

monohydrate (catalyst). In the mixture, many β-CD units were covalently connected with citric acid. Polymeric composite gels containing CDs were also constructed.[119] With the use of methacrylic acid as a DES component, magnet-responsive β-CD composites were prepared to separate proteins efficiently.[120] Molecular imprinting methodology was useful to improve the binding selectivity toward target chemical.[121-123]

4.3.2 CD-in-DESs as eminent solvents

DESs are intrinsically featured by superb solubilization of various chemicals (Section 3), but their solubilizing activities are further increased by the addition of CDs. Variety of water-insoluble chemicals are successfully dissolved in CD-in-DESs. Volatile chemicals are stably retained through encapsulation in the cavity.[124] Alternatively, microbial whole-cell asymmetric biosynthesis in DESs was accelerated by adding methylated β-CD through the improvements of both the solubility of substrates and the rates of mass transfer.[125,126] Extraction of natural products (e.g., polyphenols) by CD-in-DES from various natural sources is practically significant, and employed in industry.[64,127-136]

CD-in-DESs are also useful in environmental science. Hazardous substances such as aromatic compounds and antibiotics were efficiently captured from water.[96,137,138] Furthermore, poisonous chemicals in wastewater are concentrated by CD-in-DESs to facilitate their analytical monitoring.[129,139,140] The detection limit of tetracycline by HPLC was lowered down to mg L^{-1} level,[129] when ChCl-ethylene glycol (1:2) DES containing β-CD was used for dispersive liquid-liquid microextraction[141] (extraction solvent = thymol-octanoic acid DES). Applications of CD-in-DESs to pseudo-stationary phase in capillary electrophoresis are also significant.[142-151] To proline-urea (1:3) DES containing 20% of water, β-CD was added, and employed for conventional capillary electrophoresis. Furthermore, CD-in-DESs are very powerful as chiral separators, since the enantiomers bind to the chiral cavity of CD units with different binding strengths. For example, the enantiomers of adrenaline or noradrenaline were clearly separated by using ChCl-urea (2:1) DES containing 2-hydroxylpropyl-β-CD.[143]

5. "CD-derived-DES" constructed by combining CD with other hydrogen-bonding components (category II)

In Section 4, CDs were added as solutes into conventional DESs for various applications, and showed eminent functions in these non-aqueous media (category I). In this Section, however, novel DESs are constructed by using CDs as one of the primary components and combining them with other hydrogen-bonding components (category II). The resultant "CD-derived-DESs" are highly abundant in CD units, and bind guest compounds through both the inclusion complex formation and hydrogen bondings.[31,152-154]

5.1 Formation of CD-derived-DESs

The first CD-derived-DES was reported in 2014.[155] Without the use of any other solvents, β-CD was mixed with *N,N'*-dimethylurea at weight ratio 3:7 by using a mortar and pestle, and the mixture was then heated until a clear homogenous liquid was formed. Above around 90 ℃, the resultant DES was a highly viscous liquid (the viscosity was 1165 mPa·s at 90 ℃). The melting point of *N,N'*-dimethylurea is 104 ℃, whereas β-CD decomposes at >250 ℃. Notable freezing point depressions were also observed, when β-CD was replaced by either α-CD or γ-CD. 2-Hydroxypropyl derivatives of α-, β-, and γ-CDs, as well as randomly methylated β-CD, are also available to prepare DES with *N,N'*-dimethylurea. However, no DES was obtained with the use of heptakis(2,3,6-tri-*O*-methyl)-β-CD, in which all the hydroxyl groups are methylated. Apparently, hydrogen bondings of dimethylurea with the hydroxyl groups of CDs are necessary to form these DESs. Like conventional DESs described in Section 3, these CD-derived-DESs are non-volatile, non-flammable, biodegradable, non-toxic, and highly promising for green chemistry.

Later, more easy-to-use CD-derived-DESs of lower melting temperatures were prepared by mixing chemically modified CDs with levulinic acid (HOOC-CH_2CH_2-C(=O)CH_3).[156] This short-chain fatty acid (melting point = 33-35 °C) is economically prepared from biomass, and biodegradable to allow widespread commercial use.[157,158] For example, 2-hydroxypropyl-β-CD (degree of substitution = 5.6) was stirred with levulinic acid in weight ratio 1:2.5 (mole ratio 1:32) at 60 ℃. The mixture was liquid even at room temperature. At high temperatures, the viscosity is sufficiently low for many applications (< 80 mPa·s at 60 °C), although most of CD-derived-DESs are highly viscous. Heptakis(2,6-di-*O*-methyl)-β-CD also provided a DES with levulinic acid. According to X-ray scattering experiments,[159] the heptakis(dimethyl)-β-CD units are homogeneously distributed in the mixture without mutual aggregation. In most of the hydrogen bonds, the COO<u>H</u> of levulinic acid is hydrogen-bond donor, and the glycosidic <u>O</u>, the primary <u>O</u>CH_3, and the secondary <u>O</u>H of heptakis(dimethyl)-β-CD are hydrogen-bond acceptors. Other types of hydrogen bonds (levulinic acid as hydrogen-bond acceptor and heptakis(dimethyl)-β-CD as hydrogen-bond donor) are rarely formed. Randomly methylated β-CD (degree of substitution = 12.9) was also available for DES preparation with levulinic acid. When unmodified β-CD (native α- and γ-CDs also) was combined with levulinic acid, however, no DESs of sufficiently low melting points were obtained. Apparently, the density and flexibility of hydrogen bond network in the mixtures must be carefully controlled to prepare eminent DESs.

With the use of native α-, β-, or γ-CD as one component, CD-derived DESs were prepared by using formic acid, glacial acetic acid, or propionic acid as the counterpart component (e.g., mole ratio = 3:1). At 30 ℃, CDs were mixed with these organic acids under vigorous stirring for 5-10 min, until transparent homogeneous liquid was formed. These DESs are very easily preparable, and are employed for the industrial desulfurization of fuel oil (see Section 5.3).[160]

It should be noted that CD-derived-DESs usually contain considerable amount of water (a few percents in weight or more), since commercially obtainable CDs always bear some hydration water molecules.[160] These water molecules in DESs perturb the hydrogen bonding networks, resulting in notable changes in their physicochemical properties (viscosity, solubility of chemicals, and others). Thus, sufficient care should be paid to the water content, when CD-derived-DESs of desired physicochemical properties are prepared according to the literatures.

5.2 Inclusion complex formation of the CD unit in CD-derived-DESs

Direct evidence for inclusion complex formation of CDs in CD-derived-DESs was obtained by ^{1}H-NMR, as was the case for CD-in-DESs (see Section 4.2.1).[161] Into the DES prepared from randomly methylated-β-CD (degree of substitution = 12.9) and levulinic acid (3:7 weight ratio), *trans*-anethole (CH_3O-C_6H_4-CH=CH-CH_3) was added as the guest molecule. The specimen contained 2.5 wt% of water. Nuclear Overhauser correlations between the protons of *trans*-anethole and the protons of randomly methylated-β-CD were analyzed. In ROESY spectrum (Figure 6), the aromatic protons of *trans*-anethole strongly correlated with the H3′ and the H5′ protons of methylated-β-CD, which are located inside the cavity (see Figure 5). The methoxy protons of methylated-β-CD, which are hanging at the periphery of cavity, also correlated with the aromatic protons of *trans*-anethole. Apparently, in this CD-derived-DES, the phenyl group of *trans*-anethole is placed inside the cavity of methylated-β-CD to form inclusion complex.

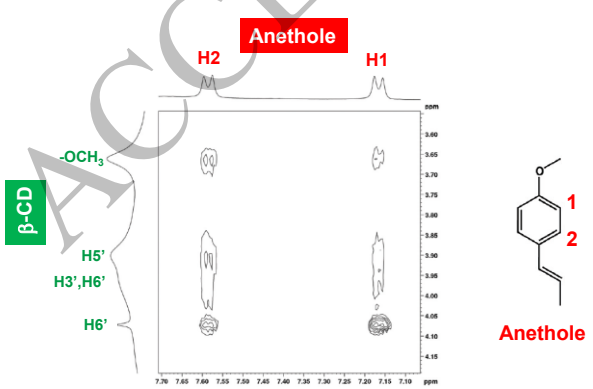


Fig. 6. ^{1}H-^{1}H ROESY spectra showing intermolecular correlation between the protons of β-CD (vertical dimension) and anethole (horizontal dimension) in the DES composed of randomly methylated-β-CD and levulinic acid (3:7 weight ratio). Reproduced from ref. 161 with permission (Copyright 2020 Royal Society of Chemistry).

5.3 Practical applications of CD-derived-DES

5.3.1 Solvents for organic synthesis

CD-derived-DESs successfully dissolve various chemicals and catalysts, and are very convenient as the solvents for variety of reactions.[161,162] Their non-volatility, nontoxicity, and thermal stability are significant advantages over conventional organic solvents. In the DESs formed from β-CD (or its derivatives) and *N,N′*-dimethylurea (3:7 weight ratio), Rh(acac)$(CO)_2$/(*m*-sulfonatophenyl)phosphine catalyzed hydroformylation of 1-decene to the aldehyde under 1:1 CO-H_2 mixture (50 bar).[153,163,164] The DES formed from randomly methylated β-CD was especially eminent, since the viscosity is low because of limited density of hydrogen bondings. The reaction rapidly proceeded in biphasic systems (1-decene was insoluble in the DES), and almost completed within 1 h. Similarly, Pd$(OAc)_2$/(*m*-sulfonatophenyl)phosphine in this DES catalyzed the cleavage of allylcarbonates with diethylamine (Tsuji–Trost reaction).[161] For Suzuki and Heck couplings, a DES was prepared from β-CD and N-methylurea (3:7 weight ratio).[165] The catalyst was β-CD-capped Pd^0 nanoparticles, which were obtained by treating Na_2PdCl_4 with $NaBH_4$ in the presence of β-CD. Catalytic amounts of K_2CO_3 and water were added. At 85 ℃ under air, target reactions (e.g., coupling of bromobenzene and phenylboronic acid to biphenyl) were efficiently accomplished without the use of any toxic ligands and organic solvents. Furthermore, DESs composed of CDs and natural acids (citric acid and malic acid) were heated to 80 ℃ to provide new materials showing unique adhesion properties and excellent processability.[166] Up to now, the number of researches on organic synthesis in CD-derived-DESs has not yet been abundant. However, successful inclusion complex formation, as well as many other unique features, indicates strong possibility of future developments.

5.3.2 Desulfurization of fuel oil

In oil industry, desulfurization process is inevitably necessary to avoid the exhaust of poisonous SO_x in the combustion gas.[167,168] Among various types of sulfur compounds in oil, dibenzothiophene derivatives are especially stable, and hardly removable by traditional hydrodesulfurization processes. In order to remove them efficiently, "extraction combined with catalytic oxidation desulfurization" method is useful and attractive, since ultra-deep desulfurization is achievable under mild conditions.[169] In this method,

aromatic sulfur compounds are first extracted from fuel oil to appropriate solvent, and catalytically oxidized to sulfones there. Recently, it was reported that CD-derived-DESs are powerful as both extractants and catalysts for these processes. In Figure 7, a DES was prepared from methylated-β-CD and formic acid (in 1:3 mole ratio).[159] According to infrared spectroscopy, the COOH group of formic acid is hydrogen-bonding donor, whereas the OH (or OCH_3) of methylated-β-CD is acceptor. When a model fuel oil (n-octane containing dibenzothiophene (DBT), benzothiophene, and 4,6-dimethyldibenzothiophene) was treated with this DES containing H_2O_2 (oxidant), these aromatic sulfur compounds in the oil were efficiently oxidized and removed. Under the optimal conditions (T = 30 ℃, the H_2O_2/DBT ratio = 3), the DBT was almost completely removed. In the DES phase, the formic acid as its major component is converted by H_2O_2 into its peroxide ($HOO\text{-}CH(OH)_2$), which is the active species for the oxidation process. Into this DES phase, the DBT, benzothiophene, and 4,6-dimethyldibenzothiophene are extracted from the oil due to their inclusion complex formation with methylated-β-CD.[170] Their fair solubilities in the DES are also favorable for this extraction process. In the DES phase, the aromatic sulfur compounds are strongly hydrogen bonding with the components of CD-derived-DES, and chemically activated through the distortion of their planar structure.[171,172] Accordingly, the peroxide of formic acid promptly oxidizes these otherwise less reactive aromatic sulfur compounds to the corresponding sulfones, which are accumulated in the DES phase. As the result, chemically stable aromatic sulfur compounds can be efficiently removed from the oil. The desulfurization efficiency of methylated-β-CD-derived DES was higher than those of α-, β-, and γ-CD-derived DESs, probably reflecting the strong affinity of aromatic sulfur compounds to the cavity of this modified β-CD for their efficient extraction from the oil to the DES phase. As the partner of CD for DES formation, formic acid is more appropriate than glacial acetic acid and propionic acid. The DESs can be readily recovered and recycled. The addition of carbon quantum dots to DESs was effective to promote the desulfurization efficiency.[173]

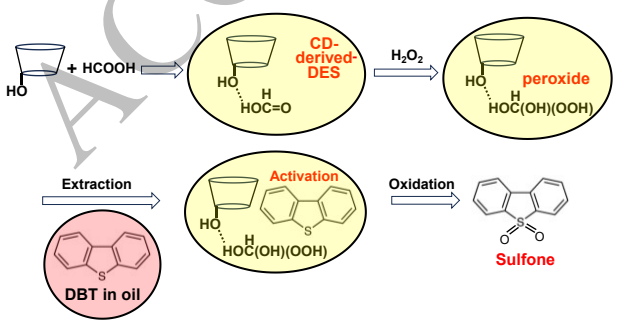


Fig. 7. Removal of dibenzothiophene (DBT) from fuel oil through "extraction combined with catalytic oxidation desulfurization method" with the use of H_2O_2 in the DES composed of methylated-β-CD and formic acid (1:3). Ref. 159.

5.3.3 Other applications

CD-derived-DESs are very attractive as green solvents showing high solubilities of variety of chemicals.[42] Poorly water-soluble pharmaceutical ingredients (e.g., steroids) were successfully dissolved in the DES composed of sulfobutylether-β-CD (degree of substitution = 6.5) and levulinic acid (3:7 weight ratio).[174] Furthermore, various practical applications have been widely attempted. For example, volatile and poisonous organic compounds (acetaldehyde, dichloromethane, and thiophene) were efficiently trapped through the encapsulation by CD units.[175-177] These chemicals were easily desorbed by increasing temperature. Various contaminants (pesticides, antibiotics, metal ions, and others) in foods were precisely analyzed by concentrating them in CD-derived-DESs through extraction pretreatments.[178] Furthermore, the DES prepared from sulfated-β-CD and citric acid was effective as chiral selector in capillary electrophoresis.[179,180] With the network of β-CD cavity and/or high viscosity of DES, the enantiomers of amphetamine, nefopam, and cathinone derivatives were clearly separated.

Alternatively, the DESs composed of CD derivatives (e.g., randomly methylated-β-CD) and levulinic acid (or citric acid and lactic acid) are useful as vehicles for drug delivery.[152,181-184] For example, the solubility of ketoprofen (a non-steroidal anti-inflammatory drug) in methylated-β-CD-levulinic acid (1:27 mole ratio) DES is 190 mg/mL, which is 1600 times as large as the value (0.12 mg/mL) in water.[182] Furthermore, unstable drugs are stabilized by the inclusion complex formation with CD units. Volatile flavors were kept shelf-stable during long-term storage.[183] Of course, non-toxicity and environmental friendliness of CD-derived-DESs are essential for all these applications.

The DESs composed of CDs and monoethanolamine (1:3 mole ratio) eminently absorb CO_2 at 80℃.[83] The CO_2 absorption is primarily ascribed to hydrogen bonding of the amino group with CO_2, which leads to the formation of carbamate intermediate via a zwitterion ($-NH_2^+COO^-$). The absorption rate was not much changed above 80℃, indicating that the viscosity of media hardly affected the process. The absorbed CO_2 was efficiently released by increasing temperature, since the carbamate in the DES is unstable. The absorption-desorption cycle was repeated without significant deterioration, reflecting high thermal stability of the CD-derived DES.

6. Why CDs can effectively form inclusion complexes in DESs?

As described in Introduction section, it has been long believed that CDs form inclusion complexes only in water.[1-8] Inclusion complexes are efficiently formed there, primarily because guest molecules prefer the apolar cavity of CDs to aqueous medium, and this preference is the main impetus for the transfer of guest into the cavity. Accordingly, apolar guests, which fit the cavity tightly, form more stable inclusion complexes. In the cavity, van der Waals interactions occur between the guest and the cavity wall, leading to enthalpy-driven formation of inclusion complexes (more details are described elsewhere [1,2,9-11]). Thus, it was rather surprising that CDs effectively form inclusion complexes in DESs, since the following two factors should be unfavorable for inclusion processes. First, many guest molecules are fairly soluble in DESs, and do not necessarily prefer the accommodation in the cavity of CDs. Secondarily, the components of DESs (hydrogen-bonding donors and acceptors) should be, at least to some extent, bound by the cavity, and competitively suppress the inclusion complex formation of target guest compound. In order to form CD inclusion complexes successfully in DESs, these two unfavorable factors must be satisfactorily compensated by some other factor(s). However, no detailed mechanistic arguments have not yet been made on this critical issue.

As the primary driving force for efficient inclusion complex formation in DESs, the present author should like to propose "flexibilization-promoted induced-fit mechanism". Here, DESs enormously facilitate induced-fit of CDs upon guest-binding, compared with the process in water. In water, CD takes a firmly stabilized cylindrical structure, since the secondary hydroxyl groups consecutively form hydrogen-bonds with the adjacent glucose units to construct an intramolecular ring of hydrogen bonds at the rim of cavity.[1,10,185,186] When a guest molecule is accommodated in this rigid CD cavity to form inclusion complex, notable gaps should be formed between the guest and the internal wall of the cavity, as schematically depicted in the upper part of Figure 8. Accordingly, van der Waals interactions between the host and the guest can never be maximized. In DESs, however, the components of DESs, which are hydrogen bonding donors and acceptors (see Section 3), should form hydrogen bonds with these hydroxyl groups of CDs, and suppress the formation of intramolecular ring of hydrogen bonds. As the result, CD molecules are made more flexible, and can alter the structures to fit the guest molecule more tightly. In other words, the shape of cavity can be changed, when necessary, to fill up the gaps between the guest and the cavity wall as much as possible (see the lower part of Figure 8). The resultant increase of van der Waals interactions compensates the two unfavorable factors which should suppress the inclusion complex formation in DESs ((i) high solubilities of guests and (ii) competitive inhibition by the DES components). Thus, CD inclusion complexes can be efficiently formed as enthalpy-driven processes even in these non-aqueous media.

All these arguments are supported by several findings. First, γ-CD, which is a rather poor host molecule in water, can form sufficiently stable inclusion complexes in DESs (see Tables 1 and 2). The cavity of this CD is too large and less hydrophobic to form highly stable inclusion complexes in water. In DESs, however, the intramolecular ring of hydrogen bonds at the rims of cavity is partially destroyed through competitive hydrogen-bonding of the DES components. As the result, the cylindrical structure of γ-CD, which is intrinsically more flexible than those of α- and β-CDs, is further flexibilized to change the structure adequately to strengthen van der Waals interactions with this guest. The second support of proposed mechanism is that both 2-hydroxypropyl-β-CD and partially methylated β-CD (CRYSMEB) form more stable inclusion complexes in DESs than native β-CD. In these chemically modified β-CDs, the intramolecular ring of hydrogen bonds is incomplete even in water (some of the substitutions occur at the secondary hydroxyl groups). Thus, their intramolecular rings of hydrogen bonds are destroyed in DESs still more drastically to fit the guest for strong binding through induced-fit.

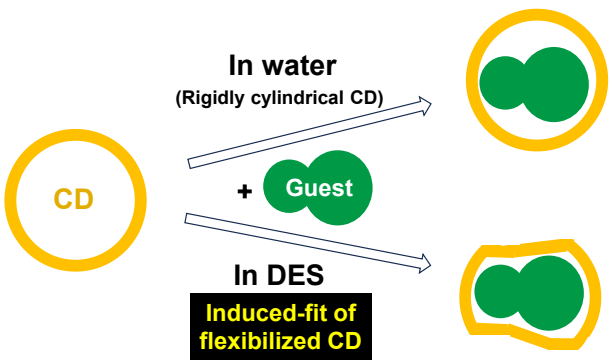


Fig. 8. Schematic view of "flexibilization-promoted induced-fit mechanism" (the lower part), proposed for efficient inclusion complex formation of CDs in DESs. The cylindrical structure of CD is more flexible in DESs, and can be distorted according to the needs to fit the guest tightly. For the purpose of comparison, inclusion of a guest into rigidly cylindrical cavity of CD in water is presented in the upper part.

Furthermore, the proposed mechanism is consistent with previous X-ray crystallography on the crystals of chemically modified CDs, prepared from aqueous solutions. For example, permethylated α- and β-CDs, in which all the hydroxyl groups are methylated

and cannot form hydrogen bonds with the adjacent glucose units, take highly distorted non-cylindrical structures.[187] Each of the 2,3,6-tri-O-methyl-D-glucose units is orienting almost independently from the other units. Even in the crystal of hexakis(2,6-di-O-methyl)-α-CD, each of the dimethyl-D-glucose units inclines with considerably different tilt-angle, making the cavity less symmetrical.[188] Although hydrogen bonds are consecutively formed between the $0^{(3)}\underline{H}$ and the $\underline{0}^{(2)}(CH_3)$, the resultant intramolecular ring cannot sufficiently maintain the canonical cylindrical structure of native α-CD. In order to obtain more straightforward evidence for the "flexibilization-promoted induced-fit mechanism" proposed for the inclusion complex formation in DESs, quantitative analysis by NMR (e.g., nuclear Overhauser effects and relaxation time) should be useful. Structural analysis on the crystals of inclusion complexes, prepared from DES solutions, should also provide valuable information.

7. Conclusions and Prospects

DESs are constructed from hydrogen-bonding donors and acceptors, and have been attracting much interest as green solvents. Quite interestingly, CDs and their derivatives efficiently form inclusion complexes with various guest molecules in conventional DESs (CD-in-DESs). The solubilities of CDs in DESs are usually far higher than the values in water, and thus large amounts of inclusion complexes can be formed therein. It is noteworthy that chemically modified CDs (e.g., 2-hydroxypropyl- and methyl-CDs) form more stable inclusion complexes than native CDs. In another approach, DESs are directly prepared by combining CDs with other hydrogen-bonding components (CD-derived-DESs). The CD units therein also successfully form inclusion complexes with guest compounds. It has been proposed that the molecular flexibility of CD is increased in DESs to promote induced-fit for efficient inclusion complex formation. These DES systems are freely designable in terms of the structures of both DESs and CDs. Chemical modifications of CDs are one of the most important approaches. Thus, most of the excellent features of CDs, observed in water, are satisfactorily accomplished in DESs. Still more importantly, the productivities of transformations in DESs can be enormously high, compared with the reactions in water, mainly due to higher solubilities of CDs and reagents. Furthermore, inclusion complexes in DESs could take novel and unique structures, and thus are expected to show unprecedentedly sophisticated functions, which are never accomplishable in water. Variety of practical applications (catalysis, extraction, analysis, medicine, environmental science, and many others) are promising.

In order to develop still more advanced CD science in DESs, detailed physicochemical studies should be highly required. The most important information is "apparent" pK_a values of various functional groups (amine, carboxylic acid, and others) in DESs. They should be considerably different from the values in water, and strongly dependent on the kind of DES. With the use of these "apparent" pK_a values, the amounts of acidic form of a functional group and its conjugate-base in DESs are precisely evaluated, and used to logically design eminent functional systems for various applications (including superb catalytic systems). The most appropriate functional group(s) for desired function can be connected to CDs covalently or noncovalently, while the most suitable DESs can be fabricated through appropriate combination of hydrogen-bonding components. In addition to these physicochemical studies, the use of ordered assemblies of multiple CDs should be also highly attractive for further developments of CD science in DESs. As evidenced previously in water solvent, multiple CD units in ordered assemblies successfully cooperate each other to show complicated and elaborate functions which are not achievable with monomeric CDs.[10] By extending these findings to DES systems, entirely novel CD world should be opened. The researches on CD-in-DESs and CD-derived-DESs are rather new and still premature, but should grow rapidly soon in terms of their unique and practically attractive features.

Conflict of interest statement. None declared.

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