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Graphical Abstracts

HFIP solutions of CDs act as a powerful tool to facilely prepare CD-assembled materials.

CD/HFIP solution

Evaporation of HFIP on a substrate

Electrospinning

Channel-type CD assemblies

CD crystalline solid

CD microfiber

Amorphous CD assemblies

Journal Name

COMMUNICATION

1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) as a novel and effective solvent to facilely prepare cyclodextrin-assembled materials

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We found that cyclodextrins (CDs) have a high solubility in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). Evaporating HFIP from CD solutions on a glass plate gave crystalline solids composed of channel-type CD assemblies, and electrospinning with an HFIP solution of CDs fabricated CD microfibers.

The subnanometer-sized cavity of cyclodextrins (CDs, Fig. 1) can incorporate a variety of guest molecules, including low- and high-molecular-weight compounds.[1] Due to this unique property, CDs are applicable to diverse fields, including food, cosmetic and pharmaceutical industries as well as analytical and separation science.[2] In the last decade, fabrication of supramolecular architectures and materials,[3] such as polyrotaxanes[4] and hydrogels,[5] utilizing the guest inclusion ability of CDs in solution has received much attention. Recently, unique supramolecular nano- and microstructures have also been constructed via the self-assembly of CDs by mixing CDs dissolved in good solvents with poor solvents.[6]

Although solvents play a key role in the formation of supramolecular CD materials and structures, the number of good solvent for CDs is rather limited. To date, suitable solvents for CDs include water, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), pyridine and ionic liquids.[7] Because all of these solvents have relatively high boiling points (100 °C or more) at normal pressure, completely removing these solvents from CDs is difficult. This is a serious drawback in the fabrication of supramolecular CD structures, which are normally sensitive to solvent contamination.[6a,8] On the other hand, the solubility of CDs in common organic solvents, which have lower boiling points and are easily separated from CDs, is very poor.[9] If an organic solvent possessing a relatively low boiling point as well as high dissolving ability for native CDs is discovered, the applications of CDs for material fabrication and organic syntheses would be largely extended. We report herein that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, Fig. 1), which has a low boiling point of 58 °C at normal pressure, works as a good solvent for CDs. HFIP solutions of CDs act as a powerful tool to facilely prepare CD-assembled materials, including CD microfibers. Although HFIP has been used to dissolve peptides and polymers that are insoluble in common organic solvents,[10] to the best of our

α-CD (n = 1), β-CD (n = 2), γ-CD (n = 3)
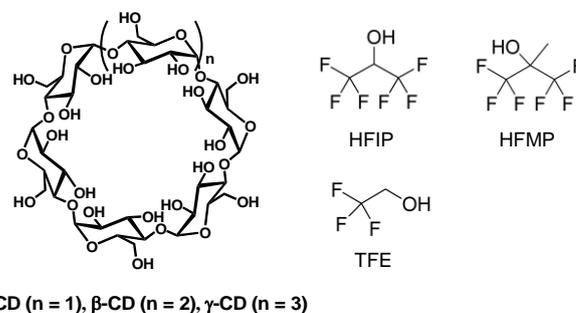
Fig. 1 Chemical structures of CDs and fluorinated alcohols.

knowledge, this is the first example using HFIP as a solvent for oligosaccharides, including CDs.

Table 1 shows the solubility of α-, β- and γ-CD in various fluorinated alcohols (Fig. 1) and water (g/100 mL) at 20 °C. HFIP exhibits a high dissolving ability towards these CDs, whereas the other two fluorinated alcohols, 1,1,1,3,3,3-hexafluoro-2-methyl-2-propanol (HFMP) and 2,2,2-trifluoroethanol (TFE), show only slight dissolution towards these CDs. These results suggest that the solubility of CDs in fluorinated alcohols may be affected by both the molecular size and acidity of the solvent (the pK_a values of HFIP, HFMP and TFE are 9.3, 9.6 and 12.4, respectively).[11] The ^{1}H NMR spectra of α-, β- and γ-CD regenerated by evaporating HFIP from

Table 1 Solubility of CDs in various fluorinated solvents and H_2O at 20 °C.

solvent	solubility (g/100 mL)		
	α-CD	β-CD	γ-CD
HFIP[a]	25	34	25
HFMP[b]	< 0.1	< 0.1	< 0.1
TFE[c]	< 0.1	< 0.1	< 0.1
H_2O[d]	14.5	1.8	23.2

[a]1,1,1,3,3,3-hexafluoro-2-propanol. [b]1,1,1,3,3,3-hexafluoro-2-methyl-2-propanol. [c]2,2,2-trifluoroethanol. [d]ref.12.
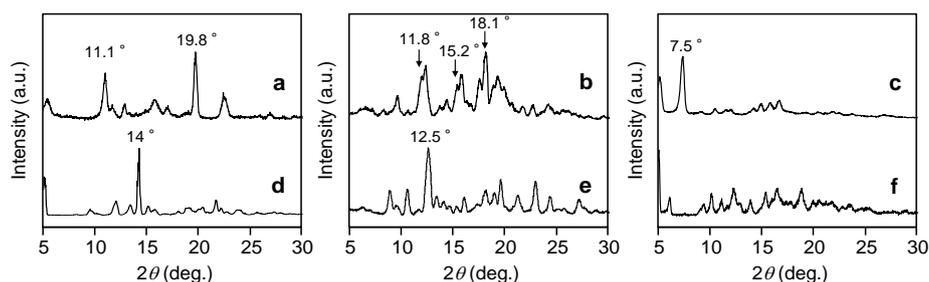
Fig. 2 XRD patterns of (a) α-, (b) β- and (c) γ-CD solids obtained after drying HFIP solutions on a glass plate and as-received (d) α-, (e) β- and (f) γ-CD.

the corresponding CD/HFIP solutions confirm that these CDs are dissolved in HFIP without damage (Fig. S1, ESI).

Interestingly, the solubility of β-CD in HFIP is higher than that of α- or γ-CD. This trend is contrary to when water is used as the solvent; the solubility of β-CD in water is much lower than that of α- or γ-CD[12] due to the strong intermolecular hydrogen bonding in the crystalline state of β-CD. These results imply that the interactions between β-CD and HFIP molecules work more effectively to break the intermolecular hydrogen bonds between β-CD molecules compared with those between β-CD and water molecules. A study on inclusion complex formation between CDs and HFIP in D_2O using an NMR titration method reveals that β-CD forms a 1:1 inclusion complex with HFIP in D_2O with an association constant of 110 ± 17 M^{-1}, whereas α- and γ-CD hardly form the inclusion complex with HFIP in D_2O (Fig. S2-S6, ESI). These results suggest that the inclusion complex formation between β-CD and HFIP as well as their hydrogen bonding interactions participates in the higher solubility of β-CD in HFIP.

Because HFIP has a relatively low boiling point, it is easily evaporated from the corresponding CD solution under mild conditions. We found that CD crystalline solids composed of channel-type assemblies of CDs form by evaporating HFIP from the CD/HFIP solutions (0.1 mol/L) on a glass plate at ambient temperature. Normally channel-type CD assemblies are formed from inclusion complexes between CDs and guest molecules.[13] On the other hand, there are only a few reports on the formation of channel-type assemblies from CD molecules in the absence of guest molecules.[14] Therefore, preparing channel-type CD assemblies without guest molecules remains a challenging subject. Figure S2 and S3 show photographs of the CD/HFIP solutions and the obtained CD crystalline solids, respectively (see ESI).

Figure 2 shows the X-ray diffraction (XRD) patterns of the resulting CD solids as well as those of the as-received CD powders. The XRD pattern of the obtained α-CD solid has two strong peaks, which are characteristic of an α-CD channel assembly ($2\theta = 11.1$ and 19.8°).[15] On the other hand, the peak characteristic of the cage-
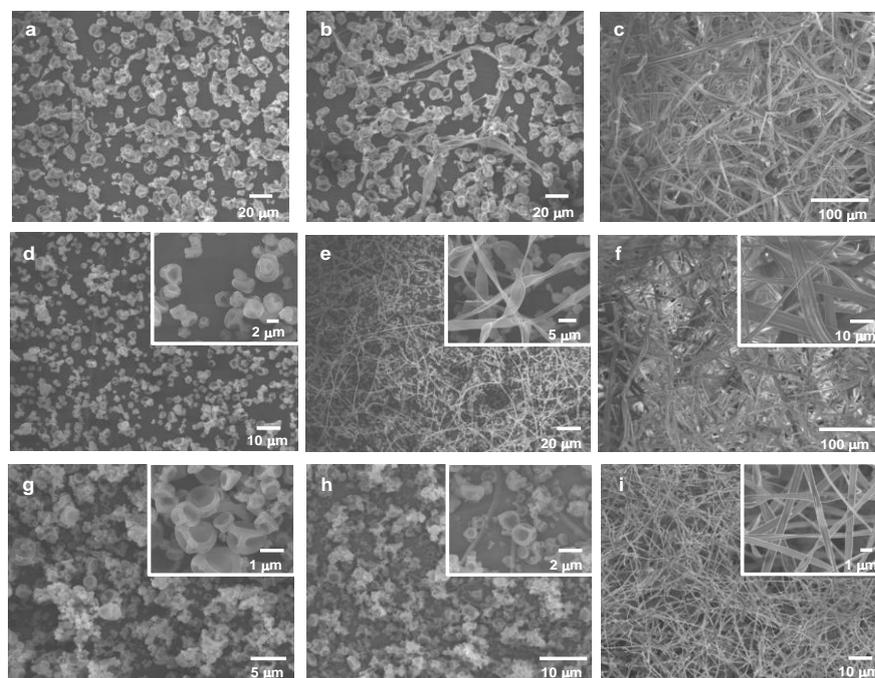
Fig. 3 SEM images of (a–c) α-, (d–f) β- and (g–i) γ-CD structures formed by electrospinning of HFIP solutions with various CDs concentrations. (a,e,i) 7.5 wt%, (b) 10 wt%, (c,f) 12.5 wt%, (d,h) 5.0 wt% and (g) 2.5 wt%. Insets show higher magnification images.

type assembly ($2\theta = 14°$)[16] in the as-received α-CD almost disappears. In sharp contrast to the as-received γ-CD composed of the cage-type assembly,[13] a strong peak characteristic of a channel-type assembly of γ-CD ($2\theta = 7.4°$)[13,14a] is observed in the resulting γ-CD solid. These observations indicate that the dissolution of α- and γ-CDs in HFIP and subsequent evaporation of HFIP from the solutions on a glass plate induce a remarkable change in the assembly mode of the CDs from a cage-type to a channel-type assembly. On the other hand, the XRD pattern of the obtained β-CD solid shows the original peaks corresponding to a cage-type assembly of the as-received β-CD ($2\theta = 12.5°$)[17] as well as a new set of peaks characteristic of a channel-type assembly ($2\theta = 11.8, 15.2, 18.1°$),[17] indicating that the resulting β-CD crystalline solid is composed of a mixture of cage-type and channel-type assemblies. Considering that HFIP can be incorporated within the cavity of β-CD, some HFIP molecules remaining in the β-CD cavity after the drying may prevent the complete conversion of the assembly mode from the cage-type to the channel-type assembly. In the XRD patterns of solid samples obtained by the freeze-drying of α-, β- and γ-CD/HPIC solutions (0.1 mol/L), only broad peaks were observed regardless of the type of CD, indicating that these solids are composed of amorphous CD assemblies (Fig. S9, ESI). These observations suggest that α-, β- and γ-CD hardly adopt definite packing modes in the 0.1 mol/L HFIP solutions. Hence, the evaporation of HFIP from the CD solutions on a glass plate should be a key process to prepare channel-type CD assemblies.

Furthermore, we fabricated CD fibers by electrospinning with an HFIP solution at ambient temperature, 25 kV voltage, a 10-cm tip-to-collector distance, and a speed of 0.16 mL/min. Normally high concentrations of polymeric materials are used for electrospinning because long molecular chains are required for the entanglements and overlapping between polymer chains to prevent fiber breakage.[18] On the other hand, there are only a few reports on electrospinning of low-molecular-weight molecules.[19] Although Uyar et al.[20] and Kim et al.[21] recently prepared nanofibers from native CDs by the electrospinning method, these works employed high concentrations of CDs (more than 60 wt%) in the solution. Thus, fabricating CD fibers using lower CD concentrations in solution remains a challenge.

Figure 3 shows the SEM images of the α-, β- and γ-CD structures formed by electrospinning of HFIP solutions with various CD concentrations. At CD concentrations less than 5.0 wt%, micrometer-sized beads form for all the CD types. On the other hand, increasing the concentration from 5.0 wt% up to 12.5 wt% forms microfibers, where the ratio of microfibers to beads increases as the CD concentration increases. At CD concentrations above 12.5 wt%, CD microfibers are predominantly formed. A comparison of the estimated diameters of β-CD fibers, which are formed from HFIP
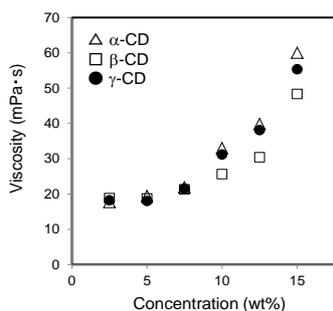
solutions with different β-CD concentrations (7.5 wt%, 10.0 wt% and 12.5 wt%), shows that the fiber diameter increases with an increase in the β-CD concentration (the β-CD fiber diameters are 2.3 ± 1.1 μm, 3.0 ± 1.5 μm and 5.3 ± 2.0 μm for 7.5 wt%, 10.0 wt% and 12.5 wt% β-CD concentrations, respectively) (Fig. 3e,f and Fig. S11, ESI). The dependence of CD fiber formation and CD fiber diameter on the concentration can be explained by considering that the number of CD assemblies in HFIP and/or the particle sizes increase as the CD concentration increases.

These behaviors are consistent with previous reports where the CD fibers are formed by electrospinning with aqueous NaOH solutions of α- and β-CD,[20a] DMSO/water solutions of γ-CD,[20b] and the 1-ethyl-3-methylimidazolium acetate (ionic liquid)/DMF solutions of β-CD.[21] On the other hand, the critical CD concentration in HFIP for the selective fiber formation is much lower than the previous cases, which required 150% (w/v) or higher concentrations of CDs for selective fiber fabrication. The exception was an ionic liquid/DMF solution that employed a 60 wt% β-CD concentration.[21] Thus, the CD/HFIP solution more effectively fabricates electrospun CD fibers compared to previous CD solutions. In particular, for the γ-CD/HFIP solution, bead-free fibers are formed at the lowest CD concentration (7.5 wt%).

The critical concentration for selective fiber formation shows that the spinnability increases in the following order: γ-CD > β-CD > α-CD (Fig. 3). The estimated diameters of α-, β- and γ-CD fibers, which are formed with the corresponding CD/HFIP solution (12.5 wt% for α- and β-CD, 7.5 wt% for γ-CD), are 8.3 ± 3.4 μm, 5.3 ± 2.0 μm and 0.75 ± 0.21 μm, respectively, based on the SEM images. Hence, the type of CD affects the fiber diameter as well as the fiber formation.

To understand the relationship between the formation of an electrospun fiber and the CD/HFIP solution property, the viscosities of HFIP solutions of α-, β- and γ-CD were measured as functions of concentrations (Fig. 4). In all cases, the viscosity increases as the CD concentration increases. It is noteworthy that the viscosity of the CD solutions used to fabricate the fiber is much lower compared to previous CD solutions,[20,21] suggesting that HFIP is more suitable to form an electrospun CD fiber than previous solvents. Typically, electrospinning of polymer solutions with a lower viscosity tends to produce thinner fibers.[22] Thus, the decreasing order in the CD fiber diameter (α-CD > β-CD > γ-CD) can be rationalized by considering the decreasing viscosity order of the corresponding CD solutions (α-CD > β-CD > γ-CD).

Fig. 4 Viscosity versus CD concentration in a HFIP solution (at 1 rpm shear rate, 20 °C).
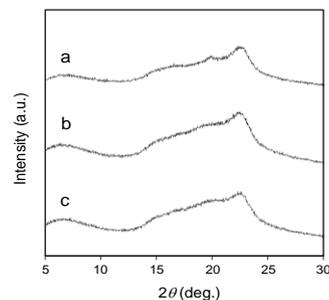
Fig. 5 XRD patterns of (a) α-, (b) β- and (c) γ-CD fibers obtained by electrospinning of HFIP solutions (12.5 wt% for α- and β-CD, 7.5 wt% for γ-CD).

However, a direct correlation between the viscosity of the CD/HFIP solution and the spinnability is not observed. Consequently, the reason that the spinnability differs between α-, β- and γ-CD/HFIP

solutions remains unclear. The electrospun CD fiber formation with the HFIP solution may be affected by the assembly mode of the CD molecules in the solution as well as the size and number of the CD assembly.

Figure 5 shows the XRD patterns of the resulting CD fibers. All the electrospun CD fibers exhibit broad peaks, indicating that these fibers are composed of amorphous CD assemblies, which differ from the as-received CDs that are composed of cage-type CD assemblies (Fig. 2d–f). The XRD patterns of the micrometer-sized beads, which are formed with the corresponding CD/HFIP solutions (2.5 wt%), show that these beads are also composed of amorphous CD assemblies (Fig. S10, ESI). These results reveal that dissolution into HFIP and the subsequent electrospinning process disrupt the crystalline structure of the as-received CDs. On the other hand, the dissolution of the as-received CDs into HFIP and the subsequent evaporation of HFIP from the solution on a glass plate induce a change in the CD assembly mode from cage-type to channel-type assemblies (Fig. 2). These findings suggest that supramolecular CD materials composed of different CD assemblies can be separately prepared by appropriately treating the HFIP solution of CDs.

In conclusion, HFIP is a novel and good solvent for α-, β- and γ-CD. CD crystalline solids composed of channel-type CD assemblies are easily fabricated by evaporating HFIP from an HFIP solution of CDs on a glass plate. Moreover, CD microfibers are successfully fabricated by electrospinning with an HFIP solution of CDs. HFIP has great potential to realize new CD applications.

Notes and references

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