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Supramolecular Self-Assemblies of β-Cyclodextrins with Aromatic Tethers: Factors Governing the Helical Columnar versus Linear Channel Superstructures

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A series of 6-*O*-(*p*-substituted phenyl)-modified β-cyclodextrin derivatives, i.e., 6-*O*-(4-bromophenyl)-β-CD (**1**), 6-*O*-(4-nitrophenyl)-β-CD (**2**), 6-*O*-(4-formylphenyl)-β-CD (**3**), 6-phenylselenyl-6-deoxy-β-CD (**4**), and 6-*O*-(4-hydroxybenzoyl)-β-CD (**5**), were synthesized, and their inclusion complexation behavior in aqueous solution and self-assembling behavior in the solid state were comparatively studied by NMR spectroscopy, microcalorimetry, crystallography, and scanning tunneling microscopy. Interestingly, (seleno)ethers **1**−**4** and ester **5** displayed distinctly different self-assembling behavior in the solid state, affording a successively threading *head-to-tail* polymeric helical structure for the (seleno)ethers or a mutually penetrating *tail-to-tail* dimeric columnar channel structure for the ester. Combining the present and previous structures reported for the relevant β-CD derivatives, we further deduce that the pivot heteroatom, through which the aromatic substituent is tethered to β-CD, plays a critical role in determining the helix structure, endowing the 2-fold and 4-fold axes to the *N*/*O*- and *S*/*Se*-pivoted β-CD aggregates, respectively. This means that one can control the self-assembling orientation, alignment, and helicity in the solid state by finely tuning the pivot atom and the tether length. Further NMR and calorimetric studies on the self-assembling behavior in aqueous solution revealed that the dimerization step is the key to the formation of linear polymeric supramolecular architecture, which is driven by favorable entropic contributions.

Introduction

Synthetic nanometer-sized supramolecular assemblies have recently attracted much attention in a broad area of science and technology.[1,2] In this field, not only the construction of supramolecular architecture but also the relationship between the structure and property/function are the subjects of recent studies on the molecular receptors, employing crown ethers,[3] calixarenes,[4] and cucurbituril[5] and so on. Of our particular interest are linear polymeric supramolecular architechtures,[6−14] which are created upon inclusion complexation and self-assembling of native and modified cyclodextrins (CDs). It is sensible therefore that an enormous amount of effort has been devoted to the studies of conformation,[15] homo-[16,17] and heterodimeric/polymeric complexation,[18] binding ability,[19−22] and supramolecular assembly[6−14,23] of CDs to

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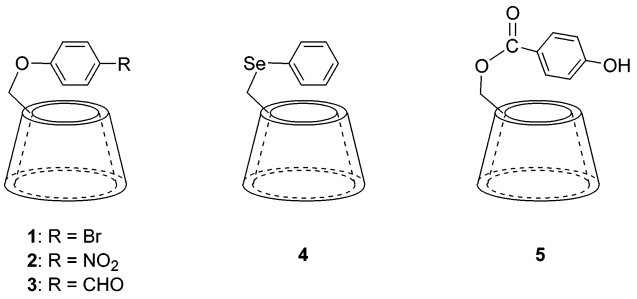
elucidate the mechanism and general rule that govern the molecular aggregation and self-assembling processes. Indeed, the inclusion complexation studies of chemically modified CDs in aqueous solution show that the chromogenic substituent appended to CD is either self-included in its own cavity to form an intramolecular complex or penetrates into the other CD's cavity to give a dimer complex. On the other hand, the crystallographic studies show that monomodified CDs crystallize in three different ways: self-inclusion, packed layer, and one-dimensional self-assembly.[9] Close examinations of the crystal structures of a variety of inclusion complexes[24−30] and assemblies[6−14] reveal that the geometrical complementarity, or size/shape matching, of host and guest is certainly one of the most important factors that determine the molecular conformation and packing in the crystal. However, the crystal structure is affected also by other factors, such as the type, length, and nature of substituent, tether, and linker atom. This in turn implies that the supramolecular crystal structure of the CD derivative is designable through the precise control of interactions of the substituent with the other CD unit. Nevertheless, no structure-based systematic approach has been employed in the attempts to understand and control the inclusion and packing mode of supramolecular self-assembly based on the molecular recognition mechanism. In this context, it is essential to systematically investigate the complexation and self-assembling behavior of structurally related β-CD derivatives comparatively in solution and in the solid state.[13b]

CHART 1



1: R = Br
2: R = NO_2
3: R = CHO

4 **5**

In the present study, we prepared a series of modified β-CDs with simple aromatic substituents **1**−**5** (Chart 1) and systematically investigated the supramolecular association behavior both in solution and in the solid state by means of crystallography, NMR spectroscopy, microcalorimetric titration, and STM (scanning tunneling microscopy) technique. It is of our particular interest to elucidate the key step and the general rule that govern the supramolecular association of β-CD derivatives that possess different aromatic substituents, tether groups, and pivot atoms. These studies will serve our understanding of the mechanism and structure of supramolecular aggregation and may further contribute to the prediction of supramolecular structures of a wide variety of chemically modified β-CDs.

Experimental Section

Materials. Reagent grade β-CD (Shanxi Biochemical Reagent Works) was recrystallized twice from water and dried in vacuo at 95 °C for 24 h prior to use. *N*,*N*-Dimethylformamide (DMF) and pyridine were dried over calcium hydride for 2 d and then distilled under a reduced pressure prior to use. K_2CO_3 (Shanghai Reagent Works) was dehydrated by heating at 200 °C in an oven. 6-Phenylselenyl-6-deoxy-β-CD (**4**) was synthesized according to the reported procedures.[22a]

6-*O*-(4-Bromophenyl)-β-CD (1) was prepared from 6-(*p*-toluenesulfonyl)-β-CD and 4-bromophenol. To a solution of 4-bromophenol (0.52 g, 3 mmol) in DMF (10 mL) was added anhydrous K_2CO_3 (0.4 g, 3 mmol). The mixture was stirred for 2 h at room temperature under nitrogen, to which 6-(*p*-toluenesulfonyl)-β-CD (1.9 g, 1.5 mmol) in dry DMF (20 mL)

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TABLE 1. Crystal Data for the Compounds 1−5

	1	2	3	4	5
empirical formula	$C_{48}H_{83}BrO_{40}$	$C_{48}H_{81}NO_{41}$	$C_{49}H_{80}O_{40}$	$C_{48}H_{80}O_{37}Se$	$C_{49}H_{90}O_{45}$
formula weight	1380.05	1328.14	1309.13	1328.08	1399.21
temp/K	293(2)	293(2)	293(2)	273(2)	293(2)
wavelength/ Å	0.71073	0.71073	0.71073	0.71073	0.71073
crystal system	orthorhombic	orthorhombic	orthorhombic	tetragonal	monoclinic
space group	*P*2(1)2(1)2(1)	*P*2(1)2(1)2(1)	*P*2(1)2(1)2(1)	*P*4(1)2(1)2	*C*2
cell constants					
a/Å	13.401(3)	13.207(4)	13.204(5)	22.074(15)	19.21(2)
b/Å	19.157(5)	18.993(5)	19.146(7)	22.074(15)	24.62(3)
c/Å	28.489(7)	28.563(8)	28.835(12)	28.61(4)	15.707(19)
β/deg					109.97(3)
volume/Å^3	7313(3)	7165(3)	7290(5)	13938(23)	6982(14)
Z	4	4	4	8	4
calcd density/kg/m^3	1.253	1.231	1.193	1.266	1.331
F(000)	2904	2816	2776	5584	2976
reflns collected/unique	30316/12899	24886/10339	30174/12876	49515/12273	14524/11747
parameters	812	839	803	755	831
final *R* indices	0.1135	0.1165	0.1416	0.1257	0.1248

was added dropwise with stirring, and then the whole solution was heated to 80 °C for 24 h. The resultant solution was evaporated under a reduced pressure to give yellow powder, which was dissolved in a minimum amount of hot water, and then the solution was poured into acetone (200 mL). The crude product obtained was purified on a Sephadex G-25 column, recrystallized twice from water, and then dried in vacuo to give pure **1** (15% yield). ^{1}H NMR (D_2O, TMS, ppm) δ 3.4−4.4 (m, 42H), 4.9−5.1 (m, 7H), 6.8−6.9 (d, 2H), 7.3−7.4 (d, 2H). UV−vis (H_2O) λ_{max} (ϵ) 279 nm (1170 M^{-1} cm^{-1}). Anal. Calcd for $C_{48}H_{73}O_{35}Br\cdot 6H_2O$: C, 41.77; H, 6.06. Found: C, 41.57; H, 6.35.

6-*O*-(4-Nitrophenyl)-*β*-CD (2) was synthesized by the reaction of 6-(*p*-toluenesulfonyl)-*β*-CD with 4-nitrophenol in dry DMF according to a similar procedure described above for **1**. After the crude product was purified on a Sephadex G-25 column, the residue was recrystallized from acetone−water (2:1, v/v), and then dried in vacuo to give pure **2** in 36% yield. ^{1}H NMR (D_2O, TMS, ppm) δ 3.4−4.2 (m, 42H), 4.8−4.9 (m, 7H), 6.9−7.0 (d, 2H), 7.9−8.1 (d, 2H). UV−vis (H_2O) λ_{max} (ϵ) 314 nm (1.20 × 10^4 M^{-1} cm^{-1}). Anal. Calcd for $C_{48}H_{73}NO_{37}\cdot 5H_2O$: C, 42.83; H, 6.21; N, 1.04. Found: C, 42.61; H, 6.48; N, 1.35.

6-*O*-(4-Formylphenyl)-*β*-CD (**3**) was synthesized in 30% yield by the reaction of 6-(*p*-toluenesulfonyl)-*β*-CD with 4-hydroxybenzaldehyde in dry DMF according to a similar procedure described above for **1**.[13b] ^{1}H NMR (D_2O, TMS, ppm) δ 3.6−4.2 (m, 42H), 5.2−5.3 (m, 7H), 7.3−7.4 (d, 2H), 8.0−8.1 (d, 2H), 9.9 (s, H). UV−vis (H_2O) λ_{max} (ϵ) 283 nm (1.45 × 10^4 M^{-1} cm^{-1}). Anal. Calcd for $C_{49}H_{74}O_{36}\cdot 6H_2O$: C, 43.69; H, 6.43. Found: C, 43.87; H, 6.38.

6-*O*-(4-Hydroxybenzoyl)-*β*-CD (5). *β*-CD (2.8 g, 2.5 mmol) and 4-hydroxybenzoic acid (0.28 g, 2 mmol) were dissolved in 200 mL and 50 mL of dry DMF, respectively. The two solutions were mixed after being cooled in an ice bath under nitrogen. To the solution of DCC (0.41 g, 2 mmol) was added 100 mL of freshly distilled pyridine. The mixture was stirred for 24 h in the presence of 4 Å molecular sieves under ice bath and another 12 h at room temperature. Then the mixture was heated to 60 °C for 12 h with stirring. The resulting solution was evaporated under reduced pressure to give a yellow powder, which was dissolved in a minimal amount of hot water and then poured into acetone (150 mL). The precipitate was collected by filtration and purified by recrystallization from 4:1 ethanol−water mixture to give crystals, which were chromatographically on a Sephadex G-25 column. The product was recrystallized from water to give pure **5** (yield 8%). ^{1}H NMR (DMSO-d_6, TMS) δ 3.2−4.5 (m, 47H), 4.8−4.9 (m, 7H), 5.7−5.8 (m, 15H), 6.8−6.9 (d, 2H), 7.7−7.8 (d, 2H), 10.4 (s, H). UV−vis (H_2O) λ_{max} (ϵ) 257 nm (1.20 × 10^4 M^{-1} cm^{-1}). Anal. Calcd for $C_{49}H_{74}O_{37}\cdot 8H_2O$: C, 42.06; H, 6.48. Found: C, 42.01; H, 6.30.

Crystals of modified *β*-CDs **1**−**5** were obtained from aqueous solution. A small amount of the compound was dissolved in hot water to make a saturated solution, which was then cooled to room temperature. After the precipitates were removed by filtration, the resultant solution was kept at room temperature for several weeks. The crystal formed was collected along with its mother liquor for X-ray crystallographic analysis.

Instruments and Measurements. Self-association constants of the CD derivatives were determined by the ^{1}H NMR titration experiments on a Varian Mercury VX300 spectrometer, using the concentration-dependent chemical shifts of aromatic protons. The concentration range spanned from the detection limit of the NMR instrument at the low end to the solubility limit of each compound at the high end. Microcalorimetric titrations were performed with an isothermal calorimeter Microcal VP-ITC. In the crystallographic study, the X-ray intensity data were collected on a standard Siemens SMART CCD Area Detector System equipped with a normal-focus molybdenum-target X-ray tube operated at 2.0 kW (50 kV, 40 mA) and a graphite monochromator. The structures were solved by using direct method and refined by full-matrix least-squares method (Siemens SHELXTL, version 5.04). STM experiments were performed by using a DS-89S instrument equipped with a W tip, and the STM images were taken at a sample bias voltage of +300 mV and a tunneling current of 2.10 nA. Aqueous solutions of samples (10^{-5} M) were prepared and dripped onto a freshly prepared, highly ordered pyrolytic graphite (HOPG) surface at room temperature, and then the samples were dried in vacuo for 30 min.

Results and Discussion

Crystal Structures. The crystallographic data for modified *β*-CDs **1**−**5** are listed in Table 1, and the crystal structures are illustrated in Figure 1.

The apparently trivial difference between (seleno)ether **1**−**4** and ester **5** leads to a dramatic change in crystal structure. In (seleno)ether **1**−**4**, the substituent attached to CD stretches straight along the side wall of the CD, facilitating the formation of the one-dimensional helical columnar superstructure in which the substituent group successively penetrates into the adjacent CD cavity. In sharp contrast, two molecules of **5** face each other and the substituent group is mutually penetrating into the facing CD cavity. It is highly plausible that this *tail-to-tail* dimer structure is made possible by the longer, flexible ester linkage in **5** rather than the (seleno)ether linkage in **1**−**4**, as the substituent group is more easily

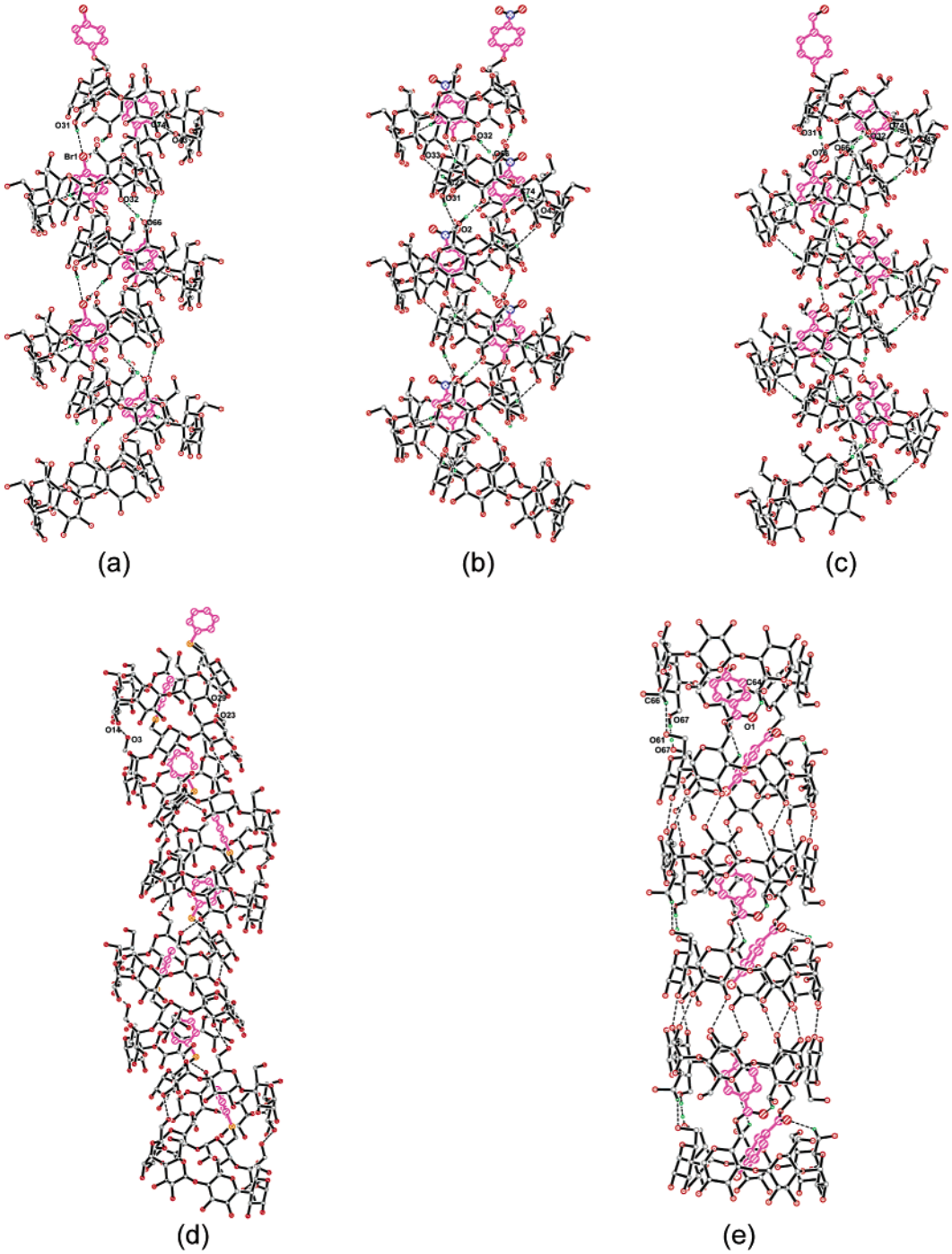

FIGURE 1. Stereoview of the one-dimensional arrangement of the compounds (a) **1**, (b) **2**, (c) **3**, (d) **4**, and (e) **5**.

directed inward to take a conformation appropriate for the mutual penetration. The C−H···O interactions[31] ($d_{C63-H63B\cdots O1}$ = 2.632 Å; $d_{C64-H64B\cdots O1}$ = 2.432 Å) of benzoyl's carbonyl oxygen with one of facing CD's H6, as well as the hydrogen bonding interactions of two primary hydroxyls of facing CDs, fix the orientation of the hydroxyphenyl group and reinforce the dimer structure. Both ends of the dimer complex are connected successively to the adjacent dimers by nine hydrogen bonds of the CD's secondary hydroxyls to form the columnar channel architecture of crystalline **5**.

Self-Assembling Behavior in the Solid State. It is well-known that monomodified β-CDs crystallize in three types: self-inclusion, layer-type packing, and one-dimensional self-assembly.[9] As can be seen from Figure 1, the packing structures of modified β-CDs **1**−**4** belong to the one-dimensional self-assembly. The aromatic rings with the different substituents penetrate deeply into the hydrophobic cavity of the adjacent β-CD, and align along the screw axis to form *head-to-tail* helical columnar superstructures. Comparing the present results for **1**−**4** with those reported for 6-phenylthio-6-deoxy-β-CD[11b] and

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TABLE 2. Parameters for Hydrogen-Bonding Interaction Observed in 1−5

compd	interaction[a]	distance (Å)[b]	angle (deg)
1	O31B−H31···Br1A	2.749	174.0
	O66B−H66···O32C	1.997	178.0
	C74A−H74···O43C	2.533	165.3
2	O31C−H31···O2B	2.420	169.3
	O66A−H66···O32C	1.997	179.4
	C12A−H12···O26C	2.557	140.9
	C27A−H27···O33C	2.574	150.3
	C74B−H74···O43A	2.459	169.3
3	O31B−H31···O76A	1.980	176.9
	O66C−H66···O32B	1.989	179.7
	O27C−H27···O33B	2.513	168.3
	C74A−H74···O43C	2.444	179.6
4	O23A−H23···O29B	2.115	151.0
	O23A−H23···O30B	2.469	133.3
	O29B−H29···O23A	2.080	179.2
	O3AA−H3···O14B	1.974	169.8
	O14B−H14···O3AA	1.993	162.1
5	O67A−H67···O67B	1.972	175.9
	O67B−H67···O67A	1.972	175.9
	C64B−H64···O1A	2.426	132.6
	C64A−H64···O1B	2.426	132.6
	C66A−H66···O61B	2.571	119.4
	C66B−H66···O61A	2.571	119.4

[a] A, B, and C denote the monomer serial number in the arrangement of these compounds. [b] Heavy atom to H atom.

6-anilino-6-deoxy-β-CD,[13a] one can readily recognize that modified β-CDs, tethering the aromatic group through an *N*- or *O*-pivot, afford *head-to-tail* helical columnar superstructures with a 2-fold axis, while those with an *S*- or *Se*-pivot give *head-to-tail* helices with a 4-fold axis. The contrasting 2- and 4-fold helical structures may be accounted for in terms of the larger size and lower electronegativity of S and Se atoms compared to those of N and O atoms. In close relation, monomodified β-CDs with aliphatic substituents, e.g. *tert*-butylthio,[11a] 1-propylamino,[12a] 2-hydroxypropyl,[12b] and 6-aminohexylamino,[14] also adopt the 2-fold helical structure, which is attributable to the conformationally flexible alkyl substituent. Thus, a flexible, slim aliphatic substituent can adjust its conformation to maximize the van der Waals contacts with the inside wall of β-CD, while the rigid, planar aromatic substituent has much less freedom in finding the optimal position in the cavity, critically depending on the angle and length of the tether as well as the pivot atom. In the literature,[9] one-dimensional self-assembly is the most frequently observed structure, in which the substituent group successively penetrates into the next CD cavity from the secondary side to form an extended linear polymeric complex. The precise control of position and orientation of the penetrating group at the center of the β-CD cavity is achieved in **1**−**3**, most probably because of the substituent introduced at the para-position of the aromatic group. As can be seen from Figure 1a−c, the aromatic group pierces through the adjacent CD cavity and the *p*-bromo, -nitro, or -formyl substituent attached to the phenyl reaches one of the secondary hydroxyls of the third β-CD molecule to form a hydrogen bond (Table 2). At the same time, the glucosyl O atom accepts one of the aromatic hydrogens. These two independent hydrogen-bonding interactions fix the position and orientation of the substituent of **1**−**3** in the self-assembling structure. The crystal structures of **1**−**3** may be regarded as helical rotaxane analogues, in which each β-CD residue acts as both "wheel" and "stopper". However, the "wheels" in the rotaxane analogues do not freely rotate around the axis due to the hydrogen-bonding interaction between the adjacent β-CD molecules. Comparison of the present results with the previous report[9] reveals that the packing mode of **1**−**4** may be analogous to that of the relevant complexes reported previously, but the depth of penetration is appreciably different. This indicates that we can use the para-substituent as an additional convenient and reliable tool for designing and constructing desired supramolecular structures and functions.

It is somewhat surprising and therefore intriguing that the crystal structure of **5** is entirely different from those of most monomodified CDs ever reported and possesses a unique C2-symmetric *tail-to-tail* dimer unit, in which the substituent interpenetrates into the cavity of the facing CD from the primary side. The C−H···O interaction of benzoyl carbonyl with H6 not only stabilizes the dimer structure but also fixes the *p*-hydroxyphenyl group in the partner CD cavity. The dimer complex unit further self-assembles to form a linear supramolecular channel structure through the extensive hydrogen-bond network of the secondary hydroxyls, as shown in Figure 1. It is likely that the dramatic switching of supramolecular architecture from the *head-to-tail* helical chain to the *tail-to-tail* channel structure originates in the very initial stages of aggregation in the solid state or even in the solution phase. Thus, the initial dimer-forming process is extremely important in elucidating the origin and mechanism of the completely different types of supramolecular aggregation.

Self-Assembling Structure of Modified β-CDs in Aqueous Solution. The (self-)inclusion behavior of a substituent attached to CD and the resulting complex structure are not necessarily the same in the solid state and in aqueous solution, as the mutual weak interactions are often perturbed by the solute−solvent interactions in solution.[5c] To get insights into the conformation of the monomodified β-CDs in aqueous solution, **1**−**5** were subjected to the 2D NMR measurements.[32]

As can be seen from Figure 2, parts a and c, the ROESY spectra of **2** and **5** show clear NOE cross-peaks of H3 and H5 of CD with the aromatic protons, demonstrating that the phenyl substituents of **2** and **5** are included in the CD cavity. In the case of **2**, strong correlations of H3 with meta protons (H_m) and of H5 with ortho protons (H_o) of the nitro group, as well as the relatively weak cross-peaks between H5 and H_m and between H3 and H_o, unequivocally indicate that the nitrophenyl group of **2** is accommodated in the cavity of other CD from the secondary side to form a *head-to-tail* dimer (Figure 2b). For **5**, strong correlations of H3 and H5 with H_o and of H5 with H_m of the phenolic hydroxyl group were observed, indicating that the hydroxyphenyl group penetrates into the cavity of other CD from the primary side to form a *tail-to-tail* dimer (Figure 2d). The ROESY spectra of **1**−**3** and of **5** reveal that they share the same self-assembling behavior in solution and in the solid state. In contrast, modified β-CD **4** behaves somewhat differently, forming a self-inclusion complex in

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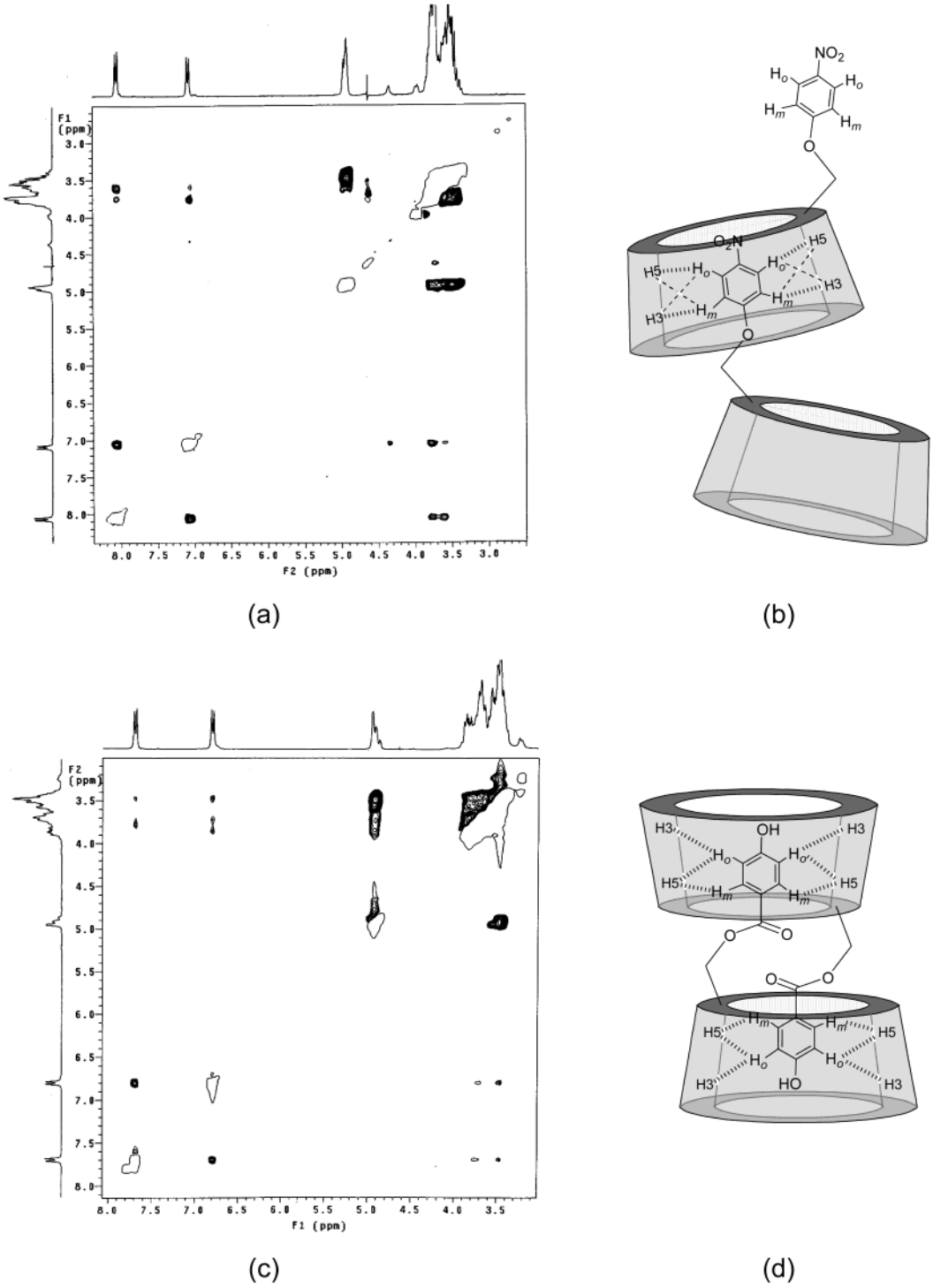

FIGURE 2. ^{1}H ROESY spectra (300 MHz) of (a) **2** ([**2**] = 1.0×10^{-3} M) with a mixing time of 600 ms and (c) **5** ([**5**] = 1.0×10^{-3} M) with a mixing time of 800 ms in D_2O at 298 K, and plausible complex structures of (b) dimeric **2** and (d) dimeric **5**. Hashed and dashed dashes indicate strong and relatively weak NOEs, respectively.

solution, the aromatic moiety of which is shallowly embedded in the hydrophobic cavity.[22a] This result may be related to the unique self-assembling behavior of this host in the solid state.

Quantitative Self-Assembling Behavior of Modified *β*-CDs in Aqueous Solution. The NMR titration is a convenient method for determining the self-association constant K_a and aggregation number n of modified β-CDs by eq 1:[13b,17,32]

$$\ln(\delta_{mon} - \delta_{obs})C_{tot} = n \ln(\delta_{obs} - \delta_{agg})C_{tot} + \ln k_a + \ln n - (n-1)\ln(\delta_{mon} - \delta_{agg}) \quad (1)$$

where C_{tot} refers to the total concentration of modified β-CD and δ_{mon} and δ_{agg} the extrapolated values of the monomer and aggregate, respectively. By substituting n with 2 in eq 1, we obtain the equation for monomer−dimer equilibrium:[33]

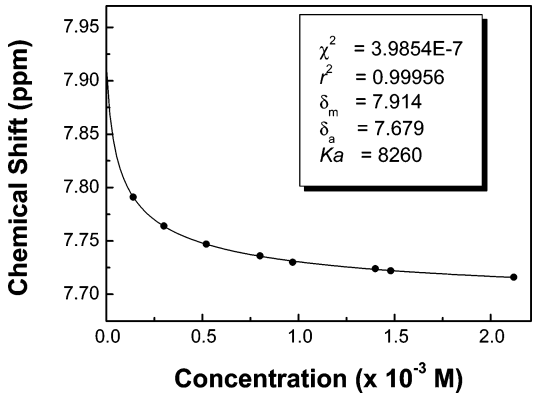

FIGURE 3. Plot from ^{1}H NMR data of **5** as a function of total concentration to determine the aggregation equilibrium constant. The solid circles are the experimental data points, and the line is the theoretical curve based on the calculated values from eq 3.

$$\delta_{obs} = \delta_{dimer} + \{(\delta_{mon} - \delta_{dimer})[-1 + (1 + 8K_{dimer}C_{tot})^{1/2}]/(4K_aC_{tot})\} \quad (2)$$

For easy plotting, the above equation was modified to eq 3:

$$\delta_{obs} = \delta_{mon} + f_{dim}(\delta_{dim} - \delta_{mon}) = \delta_{mon} + (\delta_{dim} - \delta_{mon})\frac{(1 + 8K_aC_{tot})^{1/2} - 1}{(1 + 8K_aC_{tot})^{1/2} + 1} \quad (3)$$

In Figure 3 the NMR chemical shifts of **5** at various concentrations are plotted against the concentration; the parametric fitting, assuming a dimeric complex,[13b,17] gave the self-association constant (K_a) and relevant parameters. The K_a values of **1**−**3** and **5** are listed in Table 3, along with the complex stability constants (K_s) of native β-CD with the guests equivalent to the substituent groups of **1**−**3** and **5**. The K_a values for **1**−**3**, as well as the general tendency, nicely coincide with those of K_s obtained for the complexation of native β-CD with 4-bromoanisole, 4-nitroanisole, and 4-methoxybenzaldehyde. This result is compatible with the idea that the substituent appended to β-CD penetrates into the cavity of the partner CD in the dimer complex, while the substituent of the penetrated CD does not positively participate in the complexation process. In contrast, the K_a value for **5** is much greater than the K_s of the inclusion complex of methylparaben with β-CD, and also than the K_a's of **1**−**3**. These contrasting results indicate that the aggregation behavior, and aggregate structure, of **5** are completely different from those of **1**−**3**, which could be attributed to the extended spacer and/or the interaction through the hydrogen-bonding phenol group, resulting in a better self-association. Combining the results from the NMR titration and the ROESY spectrum, we conclude that the mutually penetrating *tail-to-tail* dimer of **5** is formed in aqueous solution as is the case with the crystals.

Heterodimer Stability of Modified β-CD in Aqueous Solution. Obviously there is a competition between self-association and guest binding, and hence the self-association constant (K_a, the bimolecular aggregate stability constant of modified β-CD in solution) of modified β-CD should be different from its heterodimerization constant (K_s, the complex stability constant between modified β-CD and native CD) with native β-CD. To compare the binding behavior of the self-association and heterodimerization, microcalorimetric titration (ITC) was performed at 25 °C in aqueous solution to give the heterodimerization constants (K_s) and the relevant thermodynamic parameters for the inclusion complexation of **1**−**5** with β-CD. As can be seen from Table 4, the K_s values obtained for **1**−**3** are comparable to the self-association constants K_a of **1**−**3** determined by NMR titration (Table 3). In contrast, the heterodimerization K_s of **5** is much weaker than the self-association K_a or even than the heterodimerization K_s of **1**−**3**. This high K_a value (8260 M^{-1}) for self-association of **5**, almost amounting to the square of the K_s value (110 M^{-1}), further confirms that the extraordinarily strong homodimerization of **5** is ascribable to the cooperative mutual inclusion of the substituent. Intriguingly, **4** did not produce any heat upon addition of β-CD, suggesting that no appreciable interaction occurs between **4** and native β-CD, probably as a consequence of the strong self-inclusion of the substituent group. Therefore, the thermodynamic parameters obtained upon inclusion complexation of **1**−**3** with β-CD may be taken as a measure of the aggregation of **1**−**3**. Thermodynamically, the penetration of the substituent of **1**−**3** into the β-CD cavity to form inclusion complex is driven primarily by favorable entropy changes with additional minor enthalpic contribution, giving the moderate binding constant. These high entropic gains may be attributed to the desolvation around the CD and the penetrating substituent due to the hydrophobic effect.

TABLE 3. Self-Association Constants (K_a) of 1−3 and 5 and Binding Constants (K_s) for Inclusion Complexation of β-Cyclodextrin with the Guests Equivalent to the Substituents in 1−3 and 5 in Aqueous Solution at 25 °C

guest/host	K_a (K_s)/M^{-1}	log *K*	method	ref
1	485	2.69	NMR	*a*
2	1060	3.02	NMR	*a*
3	345	2.54	NMR	*b*
5	8260	3.92	NMR	*a*
4-bromoanisole + β-CD	464 ± 57	2.67	cal	*a*
4-nitroanisole + β-CD	680 ± 64	2.83	cal	*a*
4-methoxybenzaldehyde + β-CD	526 ± 16	2.72	cal	*a*
methylparaben + β-CD	627 ± 10	2.80	cal	*a*

[a] This work. [b] Reference 13b.

STM Observation. To further characterize or visualize the supramolecular assembly structure, STM experiments were performed. As shown in Figure 4, parts a and b, a zigzag structure and a straight array are observed for the assemblies of modified β-CDs **2** and **5** on graphitic surface, respectively. From the images obtained, the dimension of each bright dot measures ca. 1.5 nm long and 0.75 nm wide for **2** (Figure 4a) and ca. 1.45 nm long and 0.72 nm wide for **5** (Figure 4b). It is well-known that the diameter of β-CD is about 1.54 ± 0.04 nm and the height of torus is about 0.79 ± 0.01 nm.[34] Therefore, we may conclude that each bright dot corresponds to one β-CD unit. It is also worth noting that the

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TABLE 4. Binding Constants (K_s) and Thermodynamic Parameters (in kJ/mol) for 1:1 Inclusion Complexation of Modified β-CDs with β-CD at 25 °C in Aqueous Solution

guest/host	[modified β-CD]/mM	[β-CD]/mM	N[a]	K_s/M^{-1}	$-\Delta G°$	$-\Delta H°$	$T\Delta S°$
1+β-CD	0.60	13.0	2	490 ± 28	15.34 ± 0.14	2.55 ± 0.09	12.79 ± 0.23
2+β-CD	0.62	13.0	2	458 ± 52	15.17 ± 0.29	1.67 ± 0.10	13.50 ± 0.39
3+β-CD	0.44	13.4	2	315 ± 14	14.26 ± 0.11	2.63 ± 0.12	11.63 ± 0.01
4+β-CD	0.79	13.2	1	*b*			
5+β-CD	0.81	13.0	3	110 ± 17	11.62 ± 0.39	1.22 ± 0.20	10.40 ± 0.59

[a] Number of microcalorimetric titration experiments performed. [b] Equilibrium constant was not determined, because the enthalpy change observed was too small.

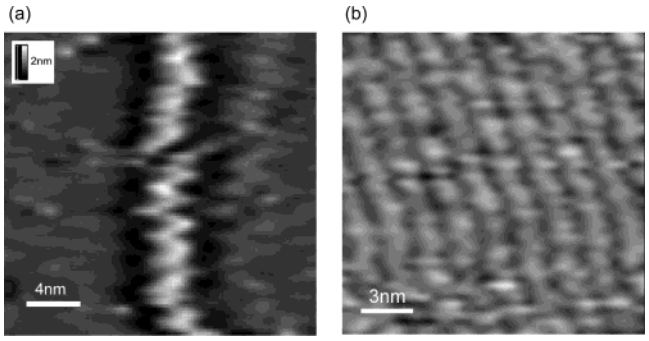

FIGURE 4. STM images of (a) **2** and (b) **5**.

zigzag chain of **2** is regularly arranged in a herringbone fashion and forms nanometer-sized aggregates, which resemble the helical columnar structure in crystal. On the other hand, compound **5** displays a nanometer-sized linear structure in good agreement with the crystal structure. It should be noted, however, that the aggregation is a slow dynamic process and the STM images are fairly time-dependent.[35] In Figure 5, the Ostwald ripening process is shown as a series of STM images taken at ca. 0, 9, 16, and 24 min after sample preparation. These results may indicate that more ordered linear polymeric supramolecular structures of modified β-CD, as observed in the solid state, could also be constructed in solution.

Conclusion

Two distinct types of linear polymeric supramolecular structures, forming helix and channel, were constructed from monomodified β-CDs **1**−**5**. From the comparative studies in solution and in the solid state, we elucidated the factors and mechanisms that govern this particular supramolecular helical- and columnar channel-structure formation of modified β-CDs **1**−**5**. The crystallographic studies showed that the modified β-CDs tethering aromatic groups through the ether-type single-heteroatom pivot form the *head-to-tail* helical superstructure with a 2- or 4-fold axis, while modified β-CD **5**, tethering a 4-hydroxyphenyl group through an ester linkage, affords the rare *tail-to-tail* channel superstructure. Further investigations of the binding behavior of modified β-CDs **1**−**5** in solution, particularly of the self-association and

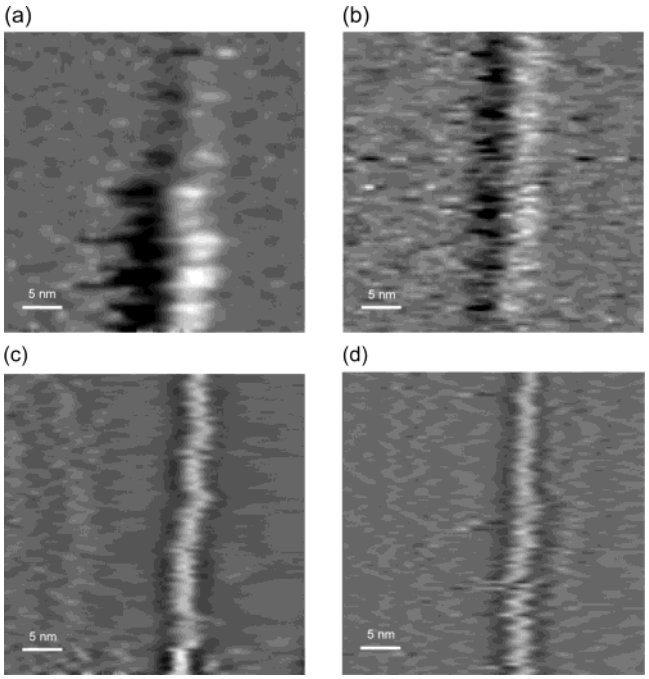

FIGURE 5. Series of STM images of compound **2** at (a) 0, (b) 9, (c) 16, and (d) 24 min illustrating Ostwald ripening. I_t = 2.1 nA, V_b = 300 mV.

complexation with native β-CD, reveal that the initial dimerization process determines the fate of the subsequent supramolecular aggregation to the helical or channel structure. Thermodynamically, the supramolecular aggregation of modified CDs is driven by favorable entropy changes, but contains a kinetically slow process. These new observations and empirical rules elucidated are useful not only for globally understanding the supramolecular aggregation phenomena but also for designing tailored building blocks for versatile supramolecular aggregates and materials.

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Supporting Information Available: The molecular structures of modified cyclodextrins **1**−**5** and the dimeric structure of **5**; the plot from ^{1}H NMR data of **2**; and ITC titration data of CD with **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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