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Self-assembly behavior of phenyl modified β-cyclodextrins

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Abstract The self-assembly behavior of mono(6-phenolic-6-deoxy)-β-cyclodextrin (**1**) both in solution and the solid state is comparatively studied by X-ray crystallography and ^{1}H NMR spectroscopy. The results obtained show that the phenolic groups in the crystal **1** can successively penetrate into the adjacent β-cyclodextrin cavities from the secondary side to form head-to-tail linear polymeric supramolecule with a 2-fold screw axis. The self-assembly behavior also can be determined in D_2O solution, giving a self-association constant of 240 mol^{-1}·L. Using the present and previous structures reported for the relevant β-cyclodextrin derivatives, *i.e.*, mono(6-anilino-6-deoxy)-β-cyclodextrin (**2**), mono(6-phenylselenyl-6-deoxy)-β-cyclodextrin (**3**), and mono(6-phenylthio-6-deoxy)-β-cyclodextrin (**4**), we further reveal the factors governing the formations of supramolecular assemblies.

Keywords: crystal structure, cyclodextrin, pivot atoms, self-assembly, supramolecule.

Cyclodextrins (CDs), a cyclic oligosaccharides composed of 6, 7, or 8 α-1,4-linked D-glucopyranose units, are able to form supramolecular complexes with a wide range of guest molecules by the inclusion complexation within the hydrophobic cavities, and therefore have been received much attention in the fields of molecular recognition and molecular assembly.[1-4] The conformations of many modified CDs have been carefully studied both in solution and the solid state, and most studies show that the formation of self-inclusion complexes or supramolecular assemblies mainly depend on the spatial size-fit and/or geometric complementarily between the substituents and CD cavities.[5-10] We have recently reported systematical studies on the binding behaviors of mono-modified β-CDs both in solution and the solid state. The obtained results indicated that the assembly modes of polymeric supramolecules might be governed through the precise control of structures and chemical properties of substituents.[8a] In the present study, we wish to report the self-assembly behavior of mono(6-phenolic-6-deoxy)-β-cyclodextrin (**1**) both in solution and the solid state by means of X-ray crystallography and ^{1}H NMR. Using the present and previous structures reported for the relevant β-CD derivatives (Fig. 1), *i.e.*, mono(6-anilino-6-deoxy)-β-CD (**2**),[8b] mono(6-phenylselenyl-6-deoxy)-β-CD (**3**),[8a] and mono(6-phenylthio-6-deoxy)-β-CD (**4**),[10b] the factors governing the formations of supramolecular assemblies are further discussed. It is of our particular interest to investigate how the slight difference of pivot heteroatoms, through which the aromatic substituent is tethered to β-CD, affects the binding behavior of modified β-CDs with phenyl substituents both in solution and the solid state.

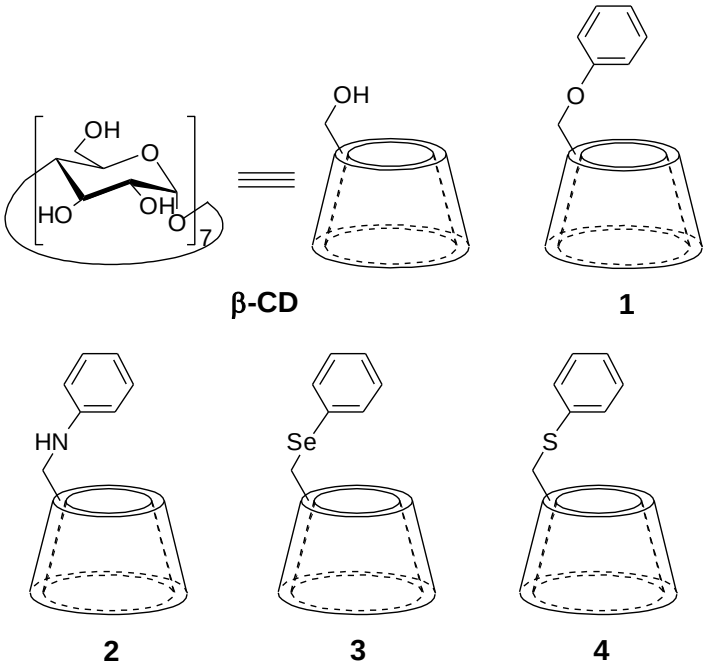


Fig. 1. The schematic representation of the compounds **1**-**4**.

1 Experimental

1.1 Materials and instruments

Analytically pure phenol is used without further purification. β-CD of reagent grade (Shanghai Reagent Factory) is recrystallized twice from water and dried in vacuo at 95 ℃ for 24 h prior to use. *N*,*N*-Dimethylformamide (DMF) is dried over calcium hydride for two days and then distilled under a reduced pressure and 40 °C prior to use. Mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin (6-OTs-β-CD) is prepared by the reaction of *p*-toluenesulfonyl chloride with β-CD in alkaline aqueous solution.[11]

The X-ray intensity data are collected on a standard Siemens SMART CCD Area Detector System equipped with a normal-focus molybdenum-target X-ray tube (λ = 0.071073 nm) operated at 2.0 kW (50 kV, 40 mA) and a graphite monochromator at T = 293(2) K. The structures are solved by using direct method and refined, employing full-matrix least squares on F^2 (Siemens, SHELXTL, version 5.04). Elemental analysis is performed on a Perkin-Elmer 2400C instrument. 2D NMR spectrum is recorded in D_2O on a Bruker AV600 spectrometer. The self-association constant of mono(6-phenolic-6-deoxy)-β-CD **1** is determined in D_2O by the ^1H NMR titration experiments on a Varian Mercury VX300 spectrometer, using the concentration-dependent chemical shifts of aromatic protons. The

concentration range is spanned from the detection limit of the NMR instrument at the low end to the solubility limit of the compound at the high end.

1.2 Synthesis of mono(6-phenolic-6-deoxy)-β-CD **1**[12]

To a solution of phenol (0.4 g, 4 mmol) in DMF (10 mL) is added anhydrous K_2CO_3 (0.56 g, 4 mmol). The mixture is stirred for 2 h at room temperature under nitrogen, after which 6-OTs-β-CD (1.9 g, 1.5 mmol) in dry DMF (20 mL) is added dropwise with stirring, and then the whole solution is heated at 80 ℃ for 24 h. The resultant solution is evaporated under reduced pressure to give a yellow powder, which is dissolved in a minimum amount of hot water, and then the solution is poured into acetone (200 mL). The crude product obtained is purified on a Sephadex G-25 column, recrystallized twice from water, and then dried in vacuo to give a pure sample of **1.** Yield 20 %. Anal. Calcd. (%) for $C_{48}H_{73}O_{35}\cdot 5H_2O$: C 44.34, H 6.43; found (%): C 44.21, H 6.46. ^{1}H NMR (600 MHz, D_2O, TMS): δ 3.42-4.28 (m, 42H), 4.91-5.02 (m, 7H), 6.92-6.97 (m, 3H), 7.21-7.26 (m, 2H). UV-vis (H_2O) λ_{max} (ε) = 269 nm (1.3×10^3 $mol^{-1}\cdot L\cdot cm^{-1}$).

1.3 Preparation of crystal **1**

A small amount of the compound **1** is dissolved in hot water to make a saturated solution, which is then cooled to room temperature. After the precipitates are removed by filtration, the resultant solution is kept at room temperature for several weeks. The crystal formed is collected along with its mother liquor for X-ray crystallographic analysis.

2 Results and discussion

2.1 Self-assembly structure in the solid state

The crystal structure of modified β-CD **1** is orthorhombic system with the space group $P2_12_12_1$, Z = 4, and the unit cell parameters a = 1.4652(3) nm, b = 1.7715(4) nm, c = 2.9234(7) nm. The crystal data, experimental and refinement parameters of **1** are shown in Table 1, and its molecular structure is shown in Fig. 2. In the molecular structure, each glucose residue of β-CD has a $^4C_1$ chair conformation, and the secondary hydroxyl groups of β-CD form the well-documented successive intra- and inter-glucose hydrogen bond network circling the rim

of CD. The seven glycosidic oxygen atoms (O4) of β-CD are coplanar with a mean deviation of 0.01 nm to form a heptagon. The side length and the radius of the heptagon are in the range of 0.433-0.444 nm and 0.494-0.513 nm, which suggest that the heptagon composed of glycosidic oxygen atoms is essentially regular. In other words, each β-CD moiety in **1** has an approximate 7-fold axis and maintains a round shape of the macrocycle, indicating that the introduction of a phenolic group does not significantly alter the original skeleton of native β-CD. The phenolic group of **1** is located just above the GIU(1) glucose residue and the dihedral angle of the aromatic ring and the heptagon (or GIU(1)) of β-CD is 119.1° (or 51.7°). Interestingly, the substituent attached to β-CD extends outside the β-CD ring and stretches straight along the sidewall of the β-CD, facilitating the formation of head-to-tail helical columnar superstructure described below.

Table 1. The crystal data, experimental and refinement parameters of **1**.

	Crystal **1**
Molecular formula	$C_{48}H_{96.50}O_{46.25}$
M_r (g mol^{-1})	1413.75
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Z	4
a (nm)	1.4652(3)
b (nm)	1.7715(4)
c (nm)	2.9234(7)
α (°)	90
β (°)	90
γ (°)	90
V (nm^3)	7.588(3)
ρ_{calcd} (g cm^{-3})	1.238
F (000)	3018
T (K)	293(2)

μ (M_o K_α) / mm^{-1}	0.112
Crystal dimensions (mm)	0.34 × 0.24 × 0.20
Range scanned θ (°)	1.80~25.05
Index range	$-14 \le h \le 17$, $-18 \le k \le 21$, $-31 \le l \le 34$
No. of reflections collected	43378
No. of unique reflections	13160
R_{int}	0.0552
R_1 (I > 2σ (I))	0.1114
wR_2 (all data)	0.2746

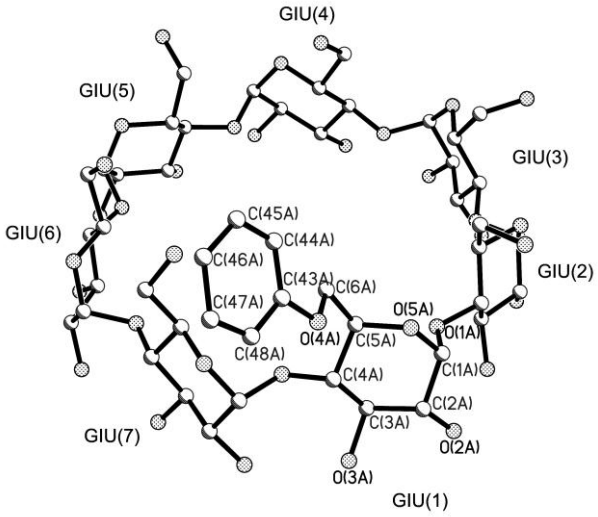


Fig. 2. The molecular structure of crystal **1**.

It is well known that mono-modified CDs crystallize in three types: self-inclusion, layer-type packing, and one-dimensional self-assembly,[5a] and the 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. As shown in Fig. 3, the packing structure of modified β-CD **1** belongs to the one-dimensional self-assembly. The molecules in the crystal **1** are arranged along a 2-fold screw axis to form a head-to-tail linear polymeric supramolecule in which the phenolic groups successively penetrate into the adjacent β-CD cavities from the secondary side, thus a single molecule act as both guest and host. The phenolic groups of **1** are spirally

aligned in one direction through the column of compiled β-CDs and function as joints to bind the β-CD rings (125.1° of dihedral angle and 0.0434 nm of centroid separation between the plane of aromatic ring and the heptagon composed of seven glycosidic oxygen atoms in the adjacent β-CD). It can also be seen that, along with the aromatic ring insetting into an adjacent CD cavity, a 6-site hydroxyl group of the β-CD and a 3-site hydroxyl group of the adjacent β-CD cavity form a hydrogen bond ($d_{O14B\cdots O33A}$ = 0.298 nm), which fix the position and orientation of the linear polymeric supramolecule. On the other hand, the self-assembled structure of **1** further extends to a more complicated level, since the columns or channels associate with each other through hydrogen bond interactions along the *a* and *b* axes. As can be seen from Fig. 4, many water molecules fill the lattice space, and thus the hydrogen bond interactions occur either through direct association of the primary and secondary hydroxyl groups of β-CD or through intervening water molecules.

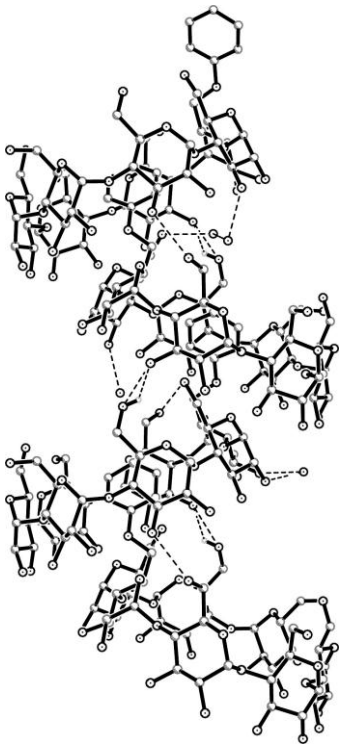


Fig. 3. The stereoviewing of the one-dimensional arrangement of **1** related by the screw axes 2_1.

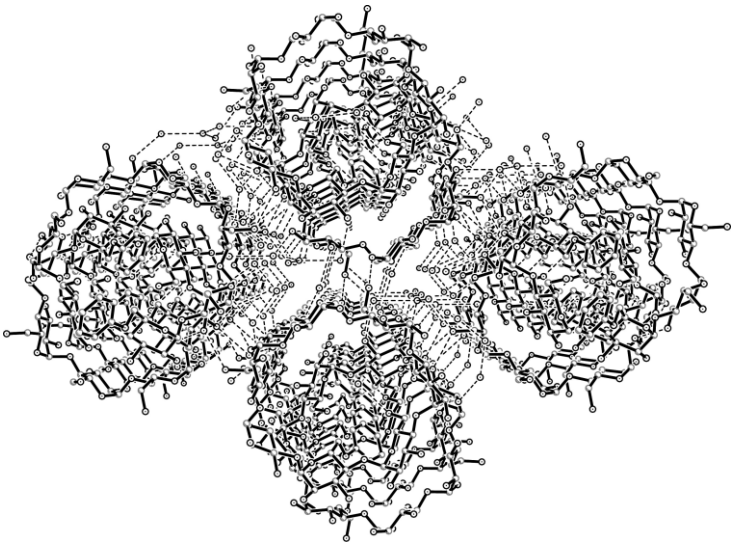


Fig. 4. The three-dimensional helical columnar structure of **1**.

Combining the present and previous structures reported for the relevant β-CD derivatives **2**-**4**, 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 (orthorhombic system) with a 2-fold axis, while those with an *S*- or *Se*-pivot give head-to-tail helices (tetragonal system) with a 4-fold axis. The dihedral angles between the plane of aromatic ring and the heptagon composed of seven glycosidic oxygen atoms in the crystals **1** and **2** are about 2-fold as compared with these of crystals **3** and **4**. The contrasting 2- and 4-fold helical structures may be accounted for in terms of the larger atomic radius and lower electronegativity of *S* and *Se* atoms compared to those of *N* and *O* atoms.[8a] Comparison of the present results with the previous reports reveals that the packing mode of **1** may be analogous to that of the relevant complexes reported previously, but the depth of penetration is appreciably different. Comparative data of crystal structures **1**-**4** are summarized in Table 2. In close relation, mono-modified β-CDs with aliphatic substituents, *e.g.* 1-propylamino,[5b] 2-hydroxypropyl,[5c] 6-aminohexylamino,[9] and *tert*-butylthio,[10a] also adopt the 2-fold helical structure, which are attributable to the conformationally flexible alkyl substituents. Thus, a flexible, slim aliphatic substituents can adjust its conformation to maximize the van der Waals contacts with the inside wall of β-CD, while the rigid, planar aromatic substituents have 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. These results indicate that we can use different pivot atom as

an additional convenient and reliable tool for designing and constructing desired supramolecular structures.

Table 2 Comparative data for the crystal structures **1**-**4**.

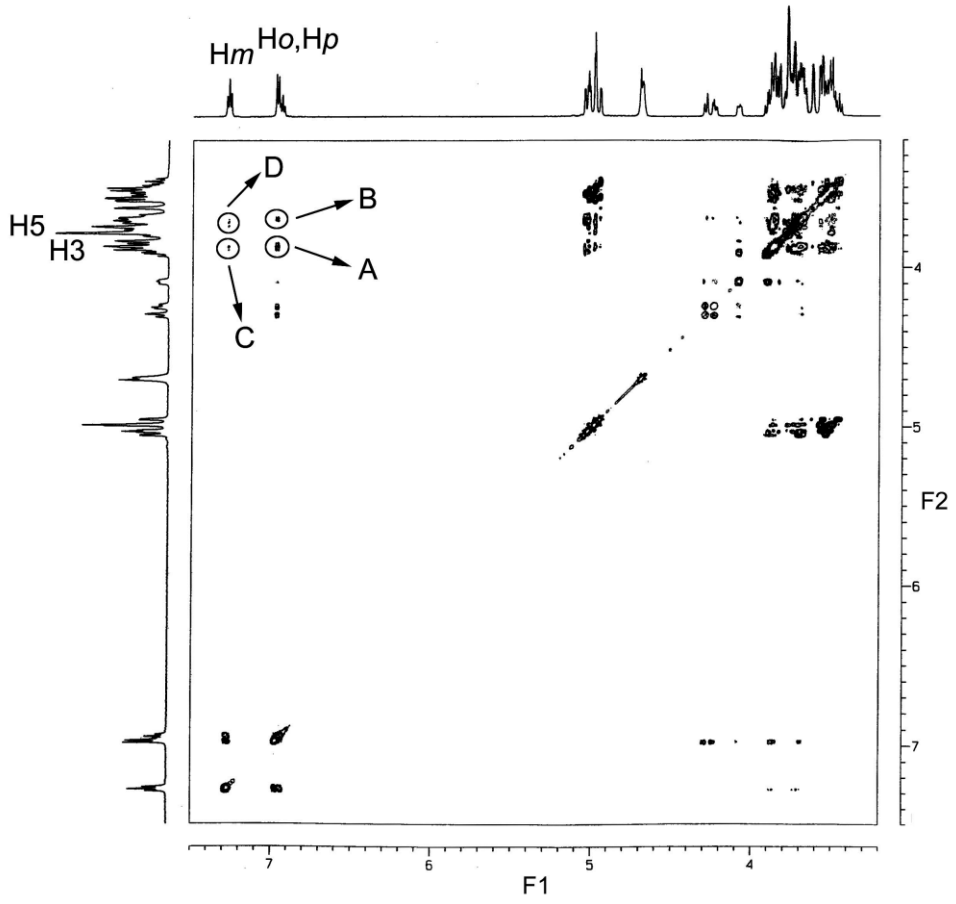
Crystal	Crystal system	Space group	Pivot atom	Screw axis	Coplanarity of heptagon (nm)	Dihedral angle of aromatic ring and heptagon (°)
1	Orthorhombic	$P2_12_12_1$	*O*	2-fold	0.010	119.1
2	Orthorhombic	$P2_12_12_1$	*N*	2-fold	0.013	117.4
3	Tetragonal	$P4_12_12_1$	*Se*	4-fold	0.006	51.6
4	Tetragonal	$P4_12_12_1$	*S*	4-fold	0.021	53.0

2.2 Self-assembly behavior in solution

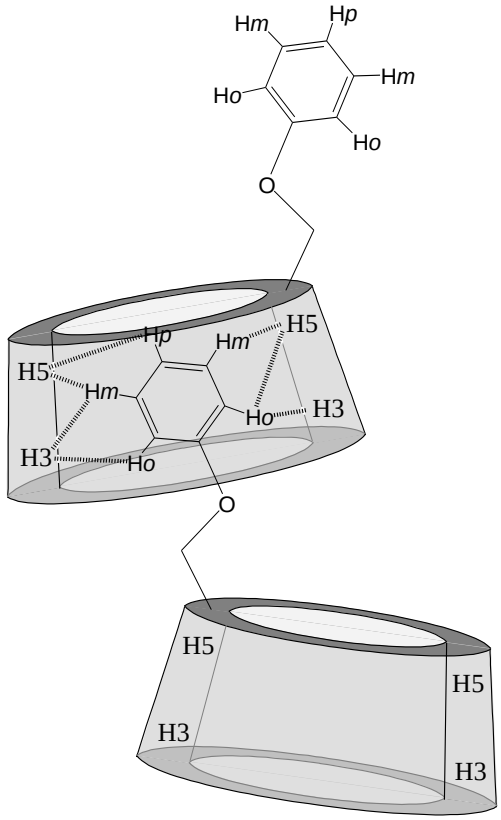
2D NMR spectroscopy has recently become an important method for the investigation of the conformation of modified CDs, since the NOE cross-peaks between the protons that are closer than 0.4 nm in space will be observed in NOESY or ROESY spectrum and the relative intensities of these cross-peaks depend on the spaces between the corresponding protons.[13] 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 solution, as the mutual weak interactions are often perturbed by the solute-solvent interactions in solution. To get insights into the conformation of the mono-modified β-CD in solution, the 2D NMR spectrum of **1** is performed in D_2O.

As can be seen from Fig. 5a, the ROESY spectrum of **1** shows clear NOE cross-peaks of H3 and H5 of β-CD with the aromatic protons, demonstrating that the phenyl substituent of **1** is included in the β-CD cavity. Furthermore, strong correlations of H3/H5 with ortho/para protons (H*o*/H*p*) of the aromatic ring (peaks A and B), as well as the relatively weak cross-peaks between H3/H5 and meta protons (H*m*) (peaks C and D), unequivocally indicate that the phenyl substituent of **1** is accommodated in the β-CD cavity from the secondary side to form a head-to-tail inclusion complex. A possible inclusion mode is shown at Fig. 5b.

In aqueous solution, it is demonstrated that the mono-substituted β-CD **4** with *S* pivot atom can form the dimers or higher complexes by intermolecular interaction, which is similar to that of its crystal structure.[10b] In contrast, modified β-CDs **2**[8b] and **3**[8a] behave somewhat differently, forming the self-inclusion complexes in solution, the aromatic moiety of which is shallowly embedded in own β-CD cavity. Therefore, the difference of conformation in aqueous solution may be attributed to the diversity of pivot heteroatoms in **1**-**4**.



(a)



(b)

Fig. 5. (a) ^{1}H ROESY spectrum (600 MHz) of **1** (5.0×10^{-4} mol dm^{-3}) in D_2O at 293.2 K with a mixing time of 200 ms, (b) plausible complex structure of **1** in solution.

It is very significant to reveal the stability of aggregation in solution, because it involves not only the formation of the certain structure in the solid state but also how to design versatile building units for supramolecular self-assembly. In order to quantitatively study the self-assembling behavior of modified β-CD **1** in solution, the ^{1}H NMR titration experiments are performed in D_2O at 293.2 K to give the self-association constant (K_a) of **1** by equation (1):[8a,14]

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

where C_{tot} refers to the total concentration of modified β-CD **1**, δ_{obs} are the observed chemical shifts, and δ_{mon} and δ_{agg} represent the extrapolated values of the monomer and aggregate, respectively. By substituting aggregation number (n) with 2 in equation (1), we obtain the equation for monomer-dimer equilibrium (2):[15]

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

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

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

The NMR chemical shifts of **1** at various concentrations are plotted against the concentration, giving the self-association constant (K_a) and relevant parameters by the parametric fitting (Fig. 6). A 1.08×10^{-3} mol·L^{-1} solution of **1** in D_2O is sequentially diluted to a final concentration of 0.11×10^{-3} mol·L^{-1}, and the chemical shift of the *meta* proton in aromatic ring is monitored. The self-association constant K_a is calculated to be 240 mol^{-1}·L, indicating that the β-CD **1** can form dimer in the determined concentration range, which further reveals that the dimerization of β-CD **1** is the key step for the formation of higher head-to-tail linear polymeric supramolecules.

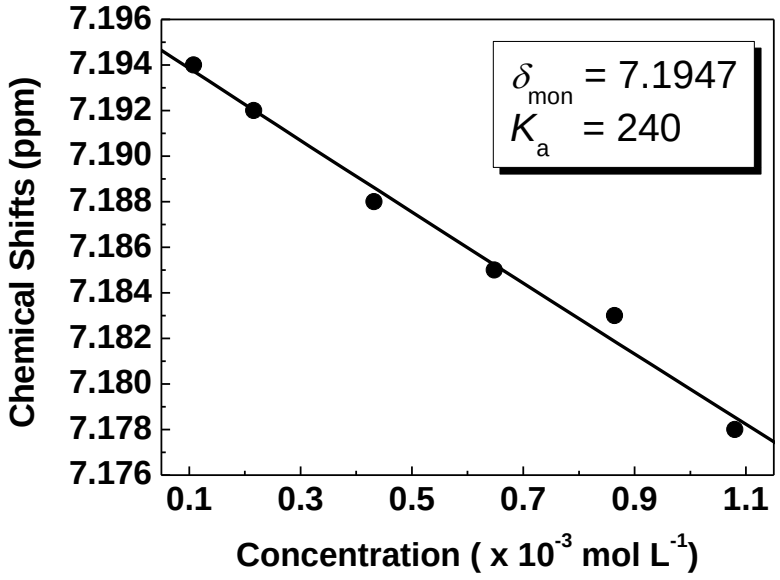


Fig. 6. Plot from ^{1}H NMR data of **1** as a function of total concentration to determine the aggregation equilibrium constant. The solid circles are the experimental data points, and the line is the theoretical curve based on the calculated values from equation 3.

3 Conclusions

From the comparative studies on phenyl modified β-CDs **1**-**4** both in solution and the solid state, we elucidated the factors and mechanisms that govern supramolecular helical- and

columnar channel-structure formation of phenyl modified β-CDs with different pivot heteroatoms (*O*, *N*, *Se*, and *S*). The crystallographic studies show that the phenyl modified β-CDs could form the head-to-tail helical superstructure with a 2- or 4-fold axis. Furthermore, the modified β-CDs **1**-**4** in solution reveal different binding behaviors, *i.e.*, the self-inclusion modes for **2** and **3** and the dimer or higher complexes for **1** and **4**. 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 functional materials.

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