Bis(polypseudorotaxane)s Formed by Multiple Metallo-Bridged \(\beta\)-Cyclodextrins and the Thermodynamic Origin of Their Molecular Aggregation

Yu Liu,* Yun Song, Hao Wang, Heng-Yi Zhang, and Xue-Qing Li

State Key Laboratory of Functional Polymer Materials for Adsorption and Separation, Department of Chemistry, Nankai University, Tianjin 300071, P. R. China

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ABSTRACT: Bis(polypseudorotaxane)s possessing the bridged bis(\(\beta\)-cyclodextrin)s with multicoordinated metal centers are prepared, in which \(\beta\)-cyclodextrin (\(\beta\)-CD) acts as the host structure, amino-terminated polypropylene glycol (PPG; MW = 2000) as the guest, and nickel(II) complexes as templating moieties. The assembly behavior is comprehensively studied by NMR spectroscopy, gel permeation chromatography (GPC), end group assay, static light scattering, thermogravimetric (TG), differential thermal analysis (DTA), and scanning tunneling microscopy (STM). The obtained results indicate that not only could the two PPG molecules be respectively threaded into metallo-bridged bis(\(\beta\)-CD)s forming the double-strand structure, but they also could play a stabilizing role in the molecular aggregation. The fluorescence titrations are performed in a mixture of acetonitrile/water to calculate the effective binding constants and thermodynamic parameters for the threading process of 2 onto PPG. The results reveal that the assembly process as being driven by favorable entropic contributions accompanied by a large positive enthalpic change. The present investigations provide a simple way to prepare multicomponent nanometer-scale organic supermolecules with multiple CD dimers coordinated metal centers.

Introduction

Structural supramolecular aggregations in nanoscale sizes created by synthetic receptors have attracted extensive attention in recent years because of their potential applications in material science.\(^1\) Among them, a system of current interest is the molecular assembly formed by cyclodextrins (CDs) and modified CDs.\(^5\) Therefore, a lot of effort has been devoted to the design and synthesis of such molecular assemblies in order to reveal the molecular aggregation mechanism and assembly function, including polypseudorotaxanes composed of CDs as the host structures and amino-terminated polymer chains as the guest molecules.\(^9\) Molecular tubes constructed by cross-linking adjacent CDs units in a polypseudorotaxane,\(^10\) molecular tubes linked by the inclusion complexation between \(\beta\)- or \(\gamma\)-CDs and diphenylhexatrienes,\(^11\) and conjugated polypseudorotaxanes that can be used as building blocks to form insulated wires threading \(\alpha\)- or \(\beta\)-CDs.\(^12\) In a somewhat different manner, inclusion complexes of CDs with organometallic coordination compounds have been used to produce porous metal–silica hybrid materials.\(^13\) Recently, CD-based molecular machines, such as molecular shuttles, motors, and necklaces, have been well reviewed.\(^6,14\) However, to the best of our knowledge, the construction of bis(polypseudorotaxanes) by \(\beta\)-CD dimers possessing multiple coordinated metal centers has not been reported thus far. In particular, there has been no investigation of the thermodynamic origin of molecular aggregation on chain guests threaded into the multihydrophobic cavities of CD dimers, though these studies are very important to the understanding of the driving force in the formation of nanosized supermolecules by molecular assembly and controlled aggregation behavior. In this context, the molecular assembly behavior of bis(polypseudorotaxane)s has been comprehensively studied using the GPC analysis, end group assay, 1D and 2D NMR spectrometry, static light scattering, TG, DTA, STM, and fluorescence titration. Here, we report our investigation of the synthesis of novel nanosized organic supermolecules with multiple coordinated metal centers and the thermodynamic origin of their molecular aggregation process.

Results and Discussion

Synthesis. Bis(polypseudorotaxanes) possessing multicoordinated metal centers are prepared according to the procedure shown in Scheme 1. Metallo-bridged bis(\(\beta\)-CD)s 2 are synthesized by the reaction of Ni(NO\(_3\))\(_2\)-6H\(_2\)O with N,N′-bis(2-aminoethyl)-2,2′-biqunoline-4,4′-dicarboxamide-bridged bis(\(\beta\)-CD)s (1).\(^15\) The stoichiometry of the complex 1 and metal ion is determined as 2:3 by conductometric titrations. Subsequently, amino-terminated PPG (MW = 2000) is added to the saturated clear aqueous solution of metallo-bridged bis(\(\beta\)-CD)s 2. With addition of 2,4-dinitrofluorobenzene, the aqueous solution turned turbid and a gray precipitate formed. A control experiment is performed under the same conditions, verifying that the product of PPG with 2,4-dinitrofluorobenzene is a liquid. Therefore, we can preliminarily conclude that metallo-bridged bis(\(\beta\)-CD)s 2 are successfully threaded onto amino-terminated PPG, and then the inclusion complexes (ICs) are precipitated from the resultant mixture by adding 2,4-dinitrofluorobenzene.

Analysis and Characterization. Two-dimensional NMR spectroscopy has recently become an essential method for the study of the inclusion complexation behavior of CD derivatives. If the PPG moiety threads into the \(\beta\)-CD cavity, the NOE correlations between the protons of the PPG molecule and the protons (H-3, H-5, or H-6) of the \(\beta\)-CD will be observed. A 2D ROESY experiment of ICs was performed in DMSO-\(d_6\). As shown in Figure 1, a strong cross-peak (peak A) was

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observed, in which we do not rule out the possibility of the cross-peak arising from the NOE of PPG molecule itself. However, on one hand, pure PPG is liquid and soluble in acetone, but the resulting ICs are solid after washed thoroughly with acetone. Therefore, there should be no free PPG molecules in the resulting ICs. On the other hand, the methyl proton peaks of PPG, both shifting downfield from $\delta = 0.835$ ppm (free PPG) to $\delta = 0.983$ ppm and turning broader, are shown in the $^1$H NMR spectrum of the resulting ICs, indicating that the methyl protons of PPG must be located in the cavities of CDs. Consequently, the correlation between H-3/H-5 of CD and the methyl protons of PPG is inevitable; i.e., the cross-peak labeled “A” must include an NOE between the methyl protons of PPG and the internal CD protons of 2.

The results of gel permeation chromatography (GPC) of 2/PPG blend show a multiple elution pattern, and the polydispersity is ca. 4.72. However, the polydispersity of commercially available PPG (MW = 2000) is determined to be ca. 3.86. In sharp contrast, ICs show a unimodal elution pattern at the time of 30.8 min, and the polydispersity is ca. 1.49. All these results can be interpreted as positive evidence for the occurrence of a single species rather than of a physical mixture of PPG and compound 2. Additionally, $^1$H NMR spectra of amino-terminated PPG and ICs are recorded in DMSO-$d_6$. As shown in Figure 2, not only do the methyl proton peaks of the polymer chain in ICs shift downfield because of the interaction between the PPG units and the cavity of the $\beta$-CDs, but they also turn broader than those of pure PPG because the movements of the molecules are restricted, which is consistent with the results reported by Harada et al.16 These results further confirm that amino-terminated PPG must be threaded into the hydrophobic cavities of the multiple metallo-bridged bis($\beta$-CD)s 2. From the $^1$H NMR spectrum of ICs, we calculate the average number of metallo-bridged bis($\beta$-CD)s 2 in ICs to be ca. 4 by comparing the integral of the peak of 2 (C-1 H) and that of the methyl protons on amino-terminated PPG. The molecular weight of the ICs is determined to be $3.3 \times 10^4$ g mol$^{-1}$ by the end group assay method,17 indicating that four units of 2 are assembled together by amino-terminated PPG and then precipitated from the resultant mixture by 2,4-dinitrofluorobenzene. Additionally, we also perform a static light scattering experiment to validate the weight-average molecular weight of ICs. Since the molecular weight of ICs is considered to be relatively low and its angular dependence is consequently poor, we make Debye plots at 90° using a value of $(\Delta n/\Delta c) = 0.0771$, giving the weight-average molecular weight of ICs as $3.4 \times 10^4$ g mol$^{-1}$, which is consistent with the results obtained from the $^1$H NMR spectrum and the end group assay. However, under the control experiment, the scattering intensities of the DMF solution of 2/PPG
blend are much weaker than that of ICs under the identical conditions, which is beyond the molecular weight detected lower limit of the instrument.

To compare the thermal stabilities of 2 and ICs, the thermogravimetric (TG) and differential thermal analyses (DTA) are performed. The TG data show that the decomposition point of ICs is higher than that of the metallo-bridged bis(β-CD)s. The decomposing temperatures of ICs and 2 are shown to be 251 and 202 °C, respectively. Simultaneously, DTA show exothermic peaks at 315 °C for 2 and at 331 °C for ICs, which indicates that PPG plays a thermal stabilizing role in ICs.

The detailed structure of ICs is obtained from scanning tunneling microscopy (STM) data. For the purpose of comparison, the STM image of dimeric CD 1 is shown in Figure 3. Extended analogical linear arrays appear in Figure 3a, in which one elliptical bright dot is in fact composed of two smaller dots, as illustrated in Figure 3b. From the size and shape of the two adjacent smaller bright dots, it is straightforward to conclude that one elliptical bright dot corresponds to one dimeric CD 1 (Figure 3c). The height of the dimer unit is about 1.8 nm (Figure 3d), which is consistent with the actual external diameter of 1.54 ± 0.04 nm for β-CD. From previous reports by Kunitake et al., Miyake et al., and our present study, we can conclude that a dimeric CD 1 is located on the hydrophobic surface of HOPG along its apolar outside wall and self-assembled to form regular linear arrays. This is due to intermolecular hydrogen-bonding interactions arising from the hydroxyl groups on the secondary side of the CD. Furthermore, a control experiment is performed to obtain the STM image of metallo-bridged bis(β-CD)s (see Supporting Information), which shows four bright dots and an array in a random fashion. Interestingly, a typical STM image of ICs clearly shows double-line-like arrays (Figure 4a), indicating that the bis(polyseoporotaxane) is successfully fabricated from the metallo-bridged bis(β-CD)s 2 and two amino-terminated PPG chains. To visualize the detailed structure, a sectional picture in 3D mode is also shown in Figure 4b. It can be easily observed that four bright dots represent a block of metallo-bridged bis(β-CD)s 2, and furthermore four such blocks are lined in regular double alignment to form bis(polyseoporotaxane). The length and width of bis(polyseoporotaxane) are ca. 20 and 8 nm, respectively. One of the possible schematic structures is shown in Figure 4c.

**Thermodynamic Origin.** To quantitatively investigate the binding behavior of 2 with amino-terminated
PPG, the effective binding constants and thermodynamic parameters are determined using titration fluorimetry. As shown in Figure 5, the fluorescence intensity of 2 gradually decreases with increasing amino-terminated PPG concentration. The effective aggregation constants ($K_S$) for molecular aggregation of PPG and 2 are calculated by using a nonlinear least-squares method.\(^{18}\)

To gain insight into the molecular assembly behavior of 2 with amino-terminated PPG from the thermodynamic point of view, fluorometric titrations are performed at the temperatures of 20, 25, 30, 35, 40, and 45 °C, which facilitate the calculation of the effective aggregation constants ($K_S$) and the Gibbs free energy changes ($-\Delta G^\circ$). The obtained results indicate that the assembly stability constants ($K_S$) and Gibbs free energy changes ($-\Delta G^\circ$) are enhanced with increase in temperature, which is consistent with the reported results.\(^{19}\) On the basis of van’t Hoff Equation, plots of log $K_S$ values as a function of the inverse of temperature should give good linear relationships. A plot for 2 with amino-terminated PPG is shown in Figure 6. The enthalpic
change ($\Delta H^\circ = 54 \text{ kJ mol}^{-1}$) and entropic change ($T \Delta S^\circ = 82.8 \text{ kJ mol}^{-1}$) of the assembly formation are obtained from the value of slope and intercept of the temperature dependence on the equilibrium constant ($K_S$). As can be recognized easily from the thermodynamic parameters, the threading process of 2 with amino-terminated PPG is entirely endothermic ($\Delta H^\circ$) and gives a large positive entropic gain ($T \Delta S^\circ$), indicating that the aggregation process is entropy driven. Thermodynamically, strong hydration of free CD and PPG is expected to occur in bulk water through hydrogen-bonding interactions. Under such circumstances, the aggregation process breaks up the strong hydrogen bonding to give a highly positive value of $\Delta H^\circ$. Simultaneously, the entropic loss arising from the structural freezing upon PPG threading into the CD cavities is compensated by the gain of entropy from the accompanying extensive loss of the hydration shell order, which is destroyed upon binding, resulting in a net favorable entropy term. On combining the present and reported thermodynamic quantities of self-aggregation of mono-modified CDs, we conclude that the assembly process occurs due to a stronger hydrophobic interaction accompanying the extensive dehydration effect. The results obtained by us not only reveal the thermodynamic origin of the process of molecular assembly but also enhance our further understanding of molecular aggregation behavior by CDs.

Conclusion

We have demonstrated that novel bis(polypropylrotaxanes) can be successfully constructed by threading amino-terminated PPG chains through bridged bis(β-CD)s possessing multicoordinated metal centers. The bis(polypropylrotaxanes) are characterized by NMR, GPC, end group assay, static light scattering, TG, DTA, and STM experiments. Furthermore, thermodynamic investigations of the threading process of metallo-bridged bis(β-CD)s onto the polymer chain reveal that the formation of bis(polypropylrotaxane) is absolutely driven by favorable entropic contributions, which will serve our further understanding of the molecular assembly mechanism and control the aggregation behavior of CDs. Our present studies afford a general method to construct sophisticated and highly ordered supermolecular assemblies through simple inclusion complexation with metallo-bridged bis(β-CD)s.

Experimental Section

Materials. Amino-terminated PPG (MW = 2000) is purchased from Aldrich. Bridged bis(β-CD) 1 is prepared from monod-$6$-(2-aminoethylamino)-6-deoxy)-β-CD with 2,2'-biquinoline-4,4'-dicarboxylic dichloride according to our previous report.15 The nickel(II) complex of bridged bis(β-CD) is 2 prepared by the reaction of 1 and Ni(NO$_3$)$_2$$\cdot$6H$_2$O in aqueous solution.

Measurements. 1D and 2D NMR spectra are obtained in DMSO-$d_6$ on a Varian VINOVA 300 spectrometer at room temperature. GPC analysis is carried out with a HPLC workstation and a Waters 410 differential refractometer equipped with PL gel permeation columns. DMF is used as an eluent at a flow rate of 0.8 mL min$^{-1}$ at 40 °C. Polystyrene standards are used to obtain a calibration curve. A Brookhaven Instruments BI-200MS goniometer and a BI9000AT correlator are used in static light scattering experiments for vortially polarized light at $\lambda_0 = 514.5$ nm and an (Innova 304) Ar$^+$ ion laser. The experiment is performed at 25 °C in DMF by using toluene as the standard reference. The laser power is maintained at 173 mW, and the scattering angle is fixed at 90°. The TG-DTA experiments are recorded with a Rigaku standard type spectrometer. The samples are heated at 10 °C min$^{-1}$ from room temperature to 600 °C. For the analysis of the conformation of bridged bis(β-CD)s 1, metallo-bridged bis(β-CD)s 2, and the ICs, STM experiments on a freshly prepared highly ordered pyrolytic graphite (HOPG) substrate are performed using an EASYSCAN STM system fabricated by Nanosurf AG of Switzerland. The samples are dissolved in water at the concentration of 1 $\times$ 10$^{-3}$ M, which are diluted enough to enable observation of an isolated structures of the compounds. A drop of the sample is spotted on a freshly cleaved HOPG substrate, followed by evaporating the liquid for at least 2 h in air. Fluorescence titration experiments are performed at 20.0, 25.0, 30.0, 35.0, 40.0, and 45.0 °C using a conventional quartz cell (10 $\times$ 10 $\times$ 45 mm) on a Jasco FP-750 spectrofluorometer with excitation and emission slits 10 nm wide and the excitation wavelengths at 350 nm.

Preparation. N,N'-Bis(2-aminoethyl)-2,2'-bicuinoine-4,4'-dicarboxamide-bridged bis(β-CD) (1).15,22 $2\times$ 2,2'-Biquinoline-4,4'-dicarboxylic dichloride$^{22,23}$ (0.3 g, 0.8 mmol) was dissolved in dry DMF (30 mL) containing dilcyclohexylcarbodiimide (0.7 g, 34 mmol), to which dry 6-(2-aminoethylamino)-6-deoxy-β-CD$^{24}$ (3.0 g, 2.55 mmol) and dry pyridine (25 mL) were added. The resultant mixture was stirred for 20 h in an ice bath and for an additional 2 days at room temperature. The precipitate formed was then removed by filtration. The filtrate was evaporated under reduced pressure to a completely dry state. The residue was dissolved in water, and the aqueous solution was poured into acetone (200 mL) to give a red precipitate. The crude product obtained was dried and purified by column chromatography over Sephadex G-25 with distilled deionized water as an eluent to give pure bis(β-CD) 1 in 35% yield as a red solid. $\text{H}$ NMR (300 MHz, DMSO-$d_6$ TMS): $\delta$ 3.0–4.0 (m

Figure 5. Fluorescence spectral changes of a bis(CD) unit (7.4 x 10$^{-6}$ mol dm$^{-3}$) and nonlinear least-squares analyses (inset) of differential intensities ($\Delta I$) to calculate the complex stability constant ($K_S$) upon addition of the amino-terminated PPG (0–5.92 x 10$^{-6}$ mol dm$^{-3}$ from a to l) in a mixed solvent (acetonitrile:water = 0.02:100 v/v) at 25 °C.

Figure 6. Plot of log $K_S$ vs 1/$T$ in fluorimetric titration of amino-terminated PPG with host compound 2 at 20, 25, 30, 35, 40, and 45 °C.


References and Notes


