ORIGINAL ARTICLE

A di(thio-1,2-dicyane ethylenylthio)ethane-tethered β-cyclodextrin dimer as a molecular carrier of ferrocene in DMF solution

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Abstract A new β-cyclodextrin dimer bridged with di(-thio-1,2-dicyane ethylenylthio)ethane moiety has been synthesized and shown unusual electrochemical effect upon complexation with ferrocene in DMF solution, which suggests some structural specificity of the novel cyclodextrin dimer host.

Introduction

Recently, cyclodextrin (CD) dimers, of which the two molecular cavities show characteristic specificity and therefore give access to controllable selectivity, have been extensively investigated [1]. The variety of bridged moieties make it possible to create unique specificity and functions in addition to that of the monotonous cavity of original CDs [2]. Here we report two unique dimeric CDs (compounds **2** and **5**, in Scheme 1) and the electrochemical behavior of their inclusion compounds with ferrocene (Fc) in DMF solution.

Ferrocene and its derivatives are well-known guests for complexation by CDs [3]. They are suitable for the hydrophobic cavities of CDs (especially β-CD), and exhibit simple electrochemical behavior, which is favorable to this study. As is shown in Fig. 1a, the effects of CDs on the electrochemical properties of Fc and its derivatives have been extensively investigated, since the Fc/Fc$^+$ (ferrocenium) redox couple is a suitable redox system for testing biomimetic models, which involve a one-electron-transfer step [4].

Material and methods

Physical measurements and materials

A Bruker IFS66V FT-IR spectrophotometer was used, and the measurements were made by the KBr disk method. The UV spectra were recorded on a Shimadzu UV-3100 spectrometer. All ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AVANCE-300 spectrometer in DMSO-d_6 solution at 15 °C. Elemental analyses were determined by a Perkin–Elmer 240C elemental analyzer. Electrochemical measurements were performed on an Autolab PGSTAT-30 digital potentiostat/galvanostat, (Eco Chemie BV, Utrecht, Netherlands), conventional three-electrode system was used with the glassy carbon electrode as working electrode, a platinum wire as auxiliary electrode, and a saturated calomel electrode (SCE) as reference against which all potentials were measured. The CD spectra were recorded on JASCO J-810 Circular dichroism spectrometer. Ethanol, 1,2-dibromide ethane (BrC$_2$H$_4$Br) were of analytically pure grade. DMF was distilled under reduced pressure in N$_2$ atmosphere before use. 2-Butene-dinitrile-2,3-dimercapto disodium salt (Na$_2$mnt), 6-Ots-β-CD, and 6-mnt-β-CD (compound **2** in Scheme 1) were synthesized according to the methods described in the literatures [5–7]. MALDI-TOF-MS analyses were performed

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Scheme 1 Syntheses of the proposed β-CD dimers
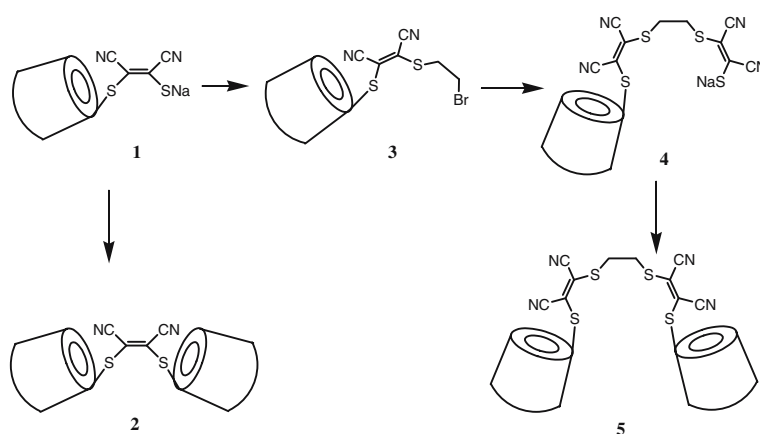
Fig. 1 Cyclic voltammograms of Fc (DMF, 0.50×10^{-3} M, 0.1 M $(Et)_4NClO_4$, 0.100 V/s, 20 °C) in the presence of β-CD (a), β-CD dimers **2** (b) and **5** (c). Curves a to g refer to the molar ratio of guest and host at 1:0 (i), 1:2 (ii), 1:4 (iii), 1:8 (iv), 1:15 (v), 1:30 (vi), 1:50 (vii), respectively
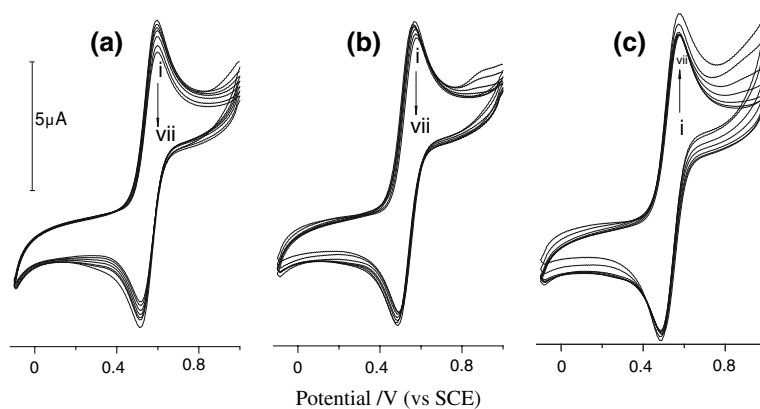
employing delayed extraction in positive ion mode on a time-of-flight mass spectrometer (Voyager- DE STR, Applied Biosystems, Framingham, MA, USA) with a 2.0-m flight tube. Desorption/ionization was obtained by using a 337-nm nitrogen laser with a 3-ns pulse width. Available accelerating potential is in the range of +20/–20 kV. The spectral data shown generally represent the sums of 300 laser shots.

Synthesis of CD-mnt-CD (**2**)

To a solution of 6-OTs-β-CD (**1**) (1.0 g, 0.78 mmol) in water (20 ml) was added 6-mnt-β-CD (1.2 g, 0.94 mmol), and the solution was stirred at 80 °C for 3–4 h, After cooling to room temperature, the yellow solution was concentrated under reduced pressure. The dark-red residue (about 3–4 mL) was then added dropwise to stirred methanol (120 mL) to precipitate crude CD-mnt-CD (0.8 g, 80%) as yellow deposits. The crude product was dissolved in 2 mL of water, and was then added dropwise to stirred methanol (50 mL). After standing overnight, the final product precipitated from the methanol solution as a light yellow powder. UV: λ_{max} nm (DMF): 374 (logε 4.07). IR (v, cm^{-1}): 2210.3 (w). ^{1}H-NMR (288K, DMSO-d_6): δ, 4.87

(s, 7H, C1–H), 3.52–3.67 (m, 28H, C3,5,6-H), 3.31–3.44 (m, 14H, C2,4-H) ppm. ^{13}C-NMR (288K, DMSO-d_6): δ 102.11, 81.62, 73.27, 72.43, 72.18, 60.02, 121.51 ppm. MALDI-TOF MS: 2397.8 [CD-mnt-CD + Na$^+$], 2415.9 [CD-mnt-CD + H$_2$O + Na$^+$].

Synthesis of 6-[Br-mnt]-β-CD (**3**)

To a vigorously stirred solution of 6-mnt-β-CD (**1**) (2.0 g, 1.36 mmol) in water (30 mL) was added BrC$_2$H$_4$Br (1.0 g, 5.32 mmol), and the mixture was stirred at room temperature for 3–4 h. After standing overnight, the precipitate formed was collected by filtration and washed with water and ethanol to give product **4** as yellow deposits (1.8 g, 90%). Anal. Calc. for C$_{48}$H$_{73}$O$_{34}$BrN$_2$S$_2$·10H$_2$O: C, 37.28; H, 6.06; N, 1.81. Found: C, 37.38; H, 6.20; N, 1.77. UV: λ_{max} nm (DMF): 343.5 (logε 3.98). IR (v, cm^{-1}): 2212.6 (w). ^{1}H-NMR (288K, DMSO-d_6): δ, 4.82 (s, 7H, C1–H), 3.71–3.84 (m, 4H, methylene), 3.55–3.63 (m, 28H, C3,5,6-H), 3.30–3.45 (m, 14H, C2,4-H) ppm. ^{13}C-NMR (288K, DMSO-d_6): δ 102.07, 81.63, 73.16, 72.48, 72.14, 60.01, 56.19 ppm. MALDI-TOF MS: 1389.7 [6-[Br-mnt]-β-CD + Na$^+$].

Synthesis of 6-(mnt)$_2$-β-CD (**4**)

The mixture of 6-[Br-mnt]-β-CD (**4**, 1.0 g, 0.732 mmol) and Na$_2$mnt (0.4 g, 2.15 mmol) was allowed to react in DMF with stirring at 60 °C for 2–4 h. The dark-red solution was filtrated and concentrated under reduced pressure to 3–4 mL, then poured into alcohol to precipitate crude 6-(mnt)$_2$-β-CD (**5**). The crude product was dissolved in 3–4 mL of water and then added dropwise to stirred alcohol. After standing overnight, the final product precipitated from the alcohol solution as a light yellow power (0.8 g, 80%). Anal. Calc. for C$_{52}$H$_{73}$O$_{34}$N$_4$NaS$_4$·10H$_2$O: C, 38.33; H, 5.75; N, 3.44. Found: C, 38.46; H, 5.87; N, 3.28. UV: λ_{max} nm (DMF): 382 (logε 3.84), 346 (logε 3.76). IR (v, cm^{-1}): 2186.4 (w). ^{1}H-NMR (288K, DMSO-d_6): δ 4.83 (s, 7H, C1–H), 3.71–3.85 (m, 4H, methylene), 3.55–3.63 (m, 28H, C3,5,6-H), 3.31–3.45 (m, 14H, C2,4-H) ppm. ^{13}C-NMR (288K, DMSO-d_6): δ 102.06, 81.62, 73.15, 72.48, 72.14, 60.01, 56.19 ppm. MALDI-TOF MS: 1450.2 [6-mnt$_2$-β-CD + Na$^+$].

Synthesis of CD-mnt-C$_2$H$_4$-mnt-CD (**5**)

The way is similar to the process **4.2** and the yields is 50%. UV: λ_{max} nm (DMF): 370 (logε 3.98). IR (v, cm^{-1}): 2212.5 (w). ^{1}H-NMR (288K, DMSO-d_6): δ 4.87 (s, 7H, C1–H), 3.53–3.63 (m, 28H, C3,5,6-H), 3.33–3.45 (m, 14H, C2,4-H) ppm. ^{13}C-NMR (288K, DMSO-d_6): δ 101.96, 81.59, 73.07, 72.43, 72.05, 60.00 ppm. MALDI-TOF MS: 2567.8 [CD-mnt-C$_2$H$_4$-mnt-CD + Na$^+$].

Results and discussion

The synthetic strategy has been shown in Scheme 1. The ^{1}H and ^{13}C NMR of these compounds have shown satisfactory agreement with the expected structures. The electronic spectra of compounds **2**, **3**, **4** and **5** show quite a reasonable absorption of the maleonitriledithiolate (mnt) moiety, from which the ionized and non-ionized mnt parts have been seen at 374, 382 and 370 nm in **2**, **3** and **5**, and at 346 nm in **4**, respectively (See the "Materials and methods"). Moreover in these spectra, the molar absorption coefficients are roughly proportional to the number of chromophors in the molecule. IR spectra of the compounds also support the existence of non-ionized mnt group in **2** (2,208.3 cm^{-1}), **3** (2,212.6 cm^{-1}), **5** (2,212.5 cm^{-1}), ionized mnt group in **4** (2,186.4 cm^{-1}), which can be confirmed by the shifts of v_{CN}.

Figure 1a shows the changes observed in the typical cyclic voltammetric response of Fc upon addition of β-CD in DMF solution. The presence of the host (β-CD) hardly shifts the apparent half-wave potential of Fc, but causes a considerable decrease on the currents associated with the Fc/Fc$^+$ wave. It has been well documented that after complexation, the inclusion complex exhibits a lower diffusion coefficient relative to that of the uncomplexed Fc [4]. Therefore, the substantial reduction of the peak currents in Fig. 1 can be interpreted by the fact that much of the guest (Fc) exists as the more slowly diffusing inclusion complex. And the minor shifts (from i to vii) of the potential suggest no more pronounced CD-induced stabilization of Fc compared to that experienced by Fc$^+$ in DMF solution.

Compound **2** is a β-CD dimer with the thio-1,2-dicyane ethylenylthio group as a connecting bridge. The effect of dimer **2** on the electrochemical behavior of Fc is demonstrated in Fig. 1b, where the reversible, one-electron oxidation of Fc is clearly visible on the current-potential curve as is the case of that in Fig. 1a. The presence of dimer **2** decreases the apparent diffusion coefficient of Fc, suggesting that complexation takes place in this case in DMF solution. Thus, the inclusion complex of **2** with Fc hinders the electron-transfer process, indicating the β-CD cavities encapsulate the electroactive guests. Obviously, the dimer **2** bridged by the connecting group cannot do favor to the transfer process of Fc to the electrode surface.

As is the case with **2**-Fc pair in Fig. 1b, the voltammetric behavior of the compound **5**-Fc pair in Fig. 1c can also be characterized by the reversible oxidation of Fc group. But, the effect of dimer **5** on the electroactive guest is not as the case for all the Fc-CD pairs reported [4]. It is evidently observed that upon addition of **5**, the peaks retain their reversible shape and a unusual increasing of peak currents is recorded. Considering the longer connecting group, dimer **5** would not excel **2** in benefiting the diffusion coefficient of Fc upon complexation. So, the experimentally increasing in current intensity in Fig. 1c can only be attributed to other factors. Owing to the more flexible bridge compared with that in dimer **2**, dimer **5** could adopt various possible conformational changes rather than the rigid structure of **2** proposed in Scheme 1, where the two CD cavities maybe interplay with each other.

The expected structural specificity or structural priority has been revealed in Scheme 2. Although β-CD cavity is transparent and the bridged group itself achiral, dimer **2** and its precursor (6-mnt-β-CD, compound **1** in Scheme 1) have shown visible signals in the circular dichroism (c.d.) spectra (Fig. 2a). It is well known that the rules of Harata [8] and Kodaka [9] can be successfully applied in the case that a chromophoric achiral substitute linking up with a chiral host, such as CDs, produces induced circular dichroism (ICD) signals around its corresponding transition bands. That is, if the substitute is located inside the CD cavity, its electronic transition moment parallel to the CD symmetric axis gives a positive ICD signal, whereas the

Fig. 2 Circular dichroism spectra (top) and absorption spectra (bottom) of (**a**) compounds **1** (—, 1.05×10^{-4} M) and **2** (·····, 1.15×10^{-4} M), and (**b**) compounds **4** (—, 0.92×10^{-4} M) and **5** (·····, 1.10×10^{-4} M)
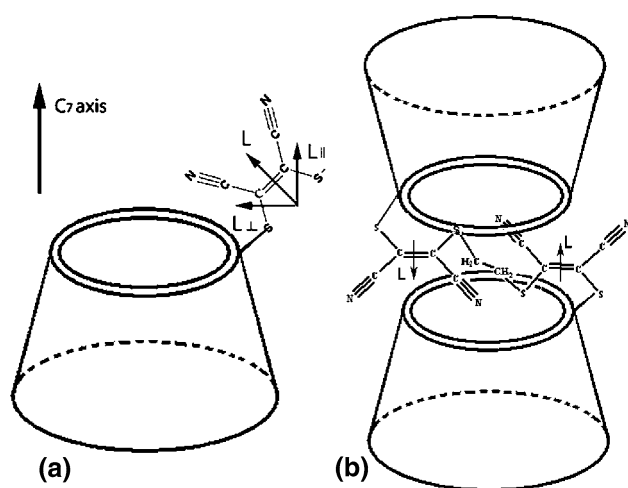
Scheme 2 Proposed conformations of compounds **1** and **5**

perpendicular transition moment gives a negative signal, but this situation is reversed for a guest located outside the CD cavity. As the Fig. 2 shows, complexes **1**, **2**, **4** and **5** displayed different ICD signals. The circular dichroism spectrum of **1** showed a positive Cotton-effect peak at 351 nm and a negative Cotton-effect peak at 403 nm. According to the conformation of compound **1** (Scheme 2a), the transition moment of mnt moiety (L) could be equivalently divided into two components, one parallel ($L_{\parallel}$) and the other perpendicular ($L_{\perp}$) to the CD symmetric axis (C_7 axis in Scheme 2), which respectively resulted in the positive and negative Cotton-effect peaks in the circular dichroism spectrum. In the case of compound **2**, the circular dichroism spectrum also showed a positive Cotton-effect and a negative Cotton-effect peak. Because the relatively small acclivitous angle between the transition moment of mnt moiety (L) and the CD symmetric axis, we deduced that $L_{\parallel}$ should be stronger than $L_{\perp}$, which consequently rationalized the stronger negative ICD of **2**.
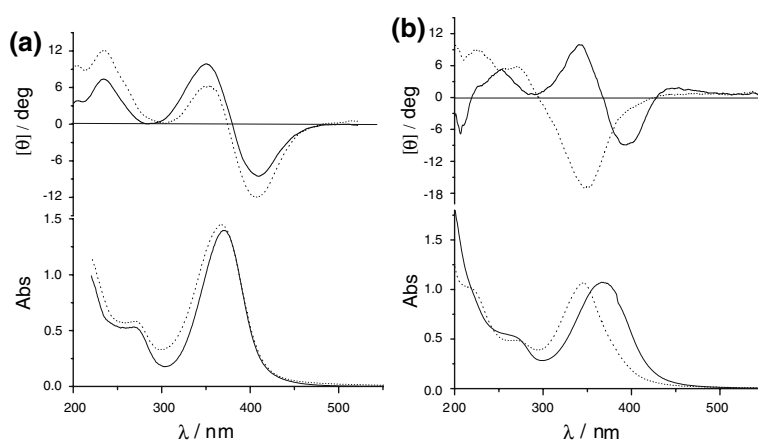
Compared with compound **1**, there is a long distance between the CD host and the attached mnt moiety in compound **4**, so the ICD spectrum of **4** is similar as that of compound **1**. In that of the CD dimer **5**, there must be a strong interaction between two CD cavities so that the transition moment of mnt moiety (L) is nearly parallel to the CD symmetric axis (Scheme 2b). For whatever reason, these two CD cavities have a dramatic preference to corporate with each other, which is favored by the flexibility of the linker. This maybe results in the evidently intensive negative-Cotton-effect-peak in the ICD spectrum of compound **5** compared to that of compound **4**. And if it's true, the linker in compound **2** is too rigid to favor the corporation of those two CD cavities. Therefore, when compared with compound **1**, there are no obvious ICD signals shifts observed in the spectra of compound **2**.

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