Synthesis and Optical Properties of 6-Substituted-β-cyclodextrin Derivatives

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Abstract: β-Cyclodextrin derivatives with varying lengths of π-conjugated arms have been synthesized. Their structures have been confirmed by ^{1}H NMR, elemental analysis, mass spectrometry and X-ray crystal structure determination. Their self-inclusion properties are evaluated using Circular Dichroism, 1D and 2D ^{1}H NMR measurements. It is found that, when the length of the π-conjugated arm is extended from **4** to **5** and to **6**, the self-inclusion of the π-conjugated arm to the CD ring is enhanced. The effect of the self-inclusion on the optical properties of the CD-linked π-conjugated systems has been explored. Stronger inclusion leads to enhanced excitation-energy transfer.

Keywords: β-cyclodextrin, inclusion complex, π-conjugation, excitation energy transfer.

INTRODUCTION

Cyclodextrins (CDs) are among the most captivating molecules, not only due to their unique and appealing hollow truncated conical cylindrical structures, but also due to their ubiquitous molecular-encapsulation properties which have found broad applications as drug delivery systems, enzyme mimics, molecular receptors, and chemical and biological sensors [1-5]. More recently, CD rings have been used to encapsulate individual π-conjugated oligomers or polymers, leading to not only improved solubility in polar media but also a step closer to realize insulated molecular wires [6-11]. Inclusion occurs when a suitable hydrophobic guest molecule replaces the high-enthalpy water molecules from the CD's hydrophobic cavity [12]. Although inclusion-complex formation is usually favored thermodynamically, and in many cases the formed inclusion complexes can be isolated as stable crystalline substances [13-19], the formation and the dissociation of the inclusion complexes in solution is nonetheless a dynamic process. End-capping is thus required to prevent unthreading of the CDs from their inclusion complexes [6-11]. While a number of CD-threaded π-conjugated systems have been studied, very few have the π-system and the CD ring covalently linked [20]. In this paper, we report the synthesis and optical properties of three β-CD derivatives containing covalently linked short π-conjugated systems. Their self-inclusion phenomenon and optical properties have been studied.

RESULTS AND DISCUSSION

Synthesis

Scheme **1** shows the structures and synthesis of the three β-CD derivatives. 6-Deoxy-6-formyl-β-cyclodextrin was synthesized according to literature procedures [21, 22]. 3,5-Diethynylaniline (**2**) was prepared by the Sonogashira coupling of 3,5-diiodoaniline (**1**) with trimethylsilyl-acetylene, followed by desilylation, while compound (**3**) was synthesized by the coupling of **1** with ethynylbenzene. Targeted β-CD derivatives (**4**), (**5**) and (**6**) were realized by reductive amination of mono-6-formyl-β-cyclodextrin with their respective aniline derivatives in mixed solvents of methanol/water with 0.2 M acetate buffer (pH = 5) at room temperature. $Na(CN)BH_3$ was used as the reducing agent. The products were purified by reversed-phase column chromatography, eluting with water, followed by 10% aqueous methanol, and then 20% aqueous methanol. The yields are 20, 15, and 15%, for Compounds (**4**), (**5**) and (**6**), respectively. Single crystals suitable for X-ray diffraction analysis were grown in water by dissolving Compound (**4**) in hot water and letting the solution stand at room temperature for several days. Attempts in growing single crystals out of Comounds (**5**) and (**6**) have not been successful.

Structural Characterization

All three compounds are soluble in common polar solvents such as methanol, DMSO, DMF, etc. Compounds (**4**) and (**5**) are partially soluble in water while **6** is insoluble. The ^{1}H NMR spectra of **4** and **5** in DMSO-d_6 are shown in Fig. (**1**). The aromatic region of the ^{1}H NMR spectrum of **4** shows well-resolved one triplet (J = 1.2 Hz) at 7.10 ppm and one doublet (J = 1.2 Hz) at 6.99 ppm, which can be assigned to *para* and *ortho* aryl protons (in relation to the amino group), respectively. The rest of the spectrum resembles that of β-CD. The broad peak at 5.82 ppm is attributed to the secondary hydroxyl group and NH, while primary hydroxyl protons appear at 4.43 ppm. The protons linked to C1 (see Scheme **1** for labeling) give a relatively sharp signal at 4.81 ppm. Compound (**5**) gives two singlets in the aromatic region. A sharp singlet at 4.01 ppm is observed which can be attributed to the ethynyl protons. The rest of the signals can

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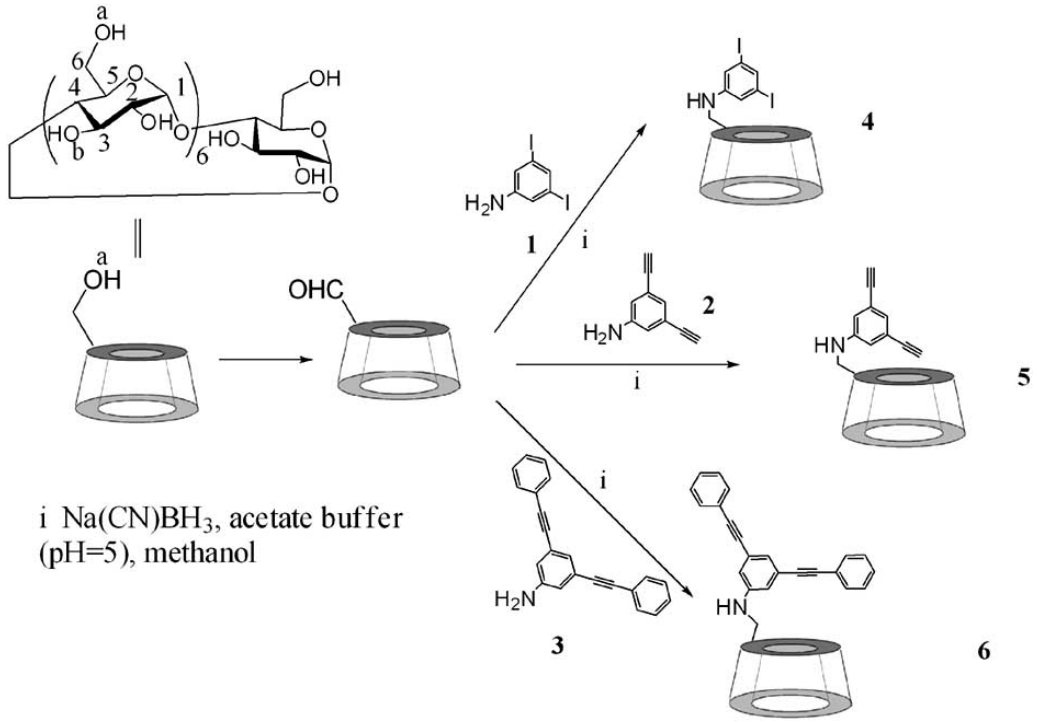

Scheme 1. Structures and synthesis of β-CD derivatives.

be assigned to protons associated with the CD ring. The ^{13}C NMR spectrum of **4** and **5** showed all the normal peaks of β-CD at around 60 (C_6), 72-73 (C_5, C_2, C_3), 81 (C_4), and 102 (C_1) ppm [23]. The substituted glucose of cyclodextrin gives ^{13}C signals at around 43, 69 and 83 ppm, which correspond to C6', C5' and C4', respectively. Four peaks for the 3,5-diiodoaniline moiety at 96.0, 119.9, 130.7 and 151.3 ppm are observed. For **5**, four aromatic carbon signals at 115.8, 121.9, 122.5, and 149.0 ppm and two alkyne carbons at 83.1 and 83.4 ppm are observed. These results are consistent with their structures. The structure of **4** was further confirmed by elemental analysis and *X*-ray crystal structure determination while the structure of **5** was confirmed by mass spectrometry measurements (see experimental section).

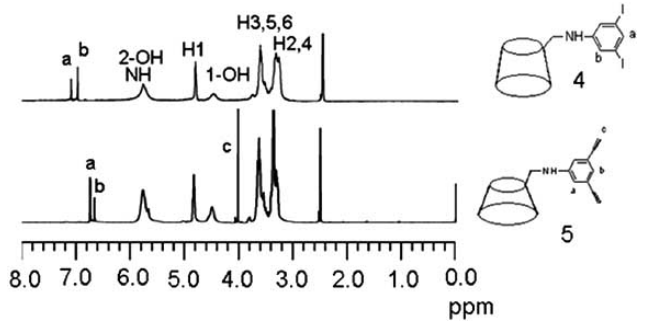

Fig. (1). ^1H NMR spectra of **4** and **5** in DMSO-d_6.

Fig. (**2**) shows the ^1H NMR spectrum of **6**, which is proximately the summation of the spectra of **3** and β-CD (both spectra are shown in Fig. (**2**) as well). Again, all signals are well resolved and can be unambiguously assigned. MALTI-TOF mass spectrometry of **6** gave a major peak at 1432.6 which corresponds to the ($M+Na^+$) (calculated M = 1409.5). These results validate the structure of **6**.

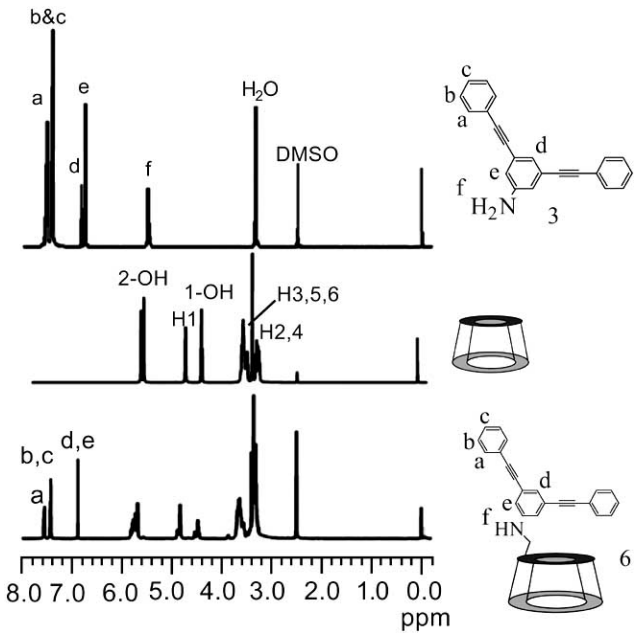

Fig. (2). ^1H NMR spectra of **3, 6** and β-CD in DMSO-d_6.

Conformational Analysis

Fig. (**3**) shows the UV/Vis absorption and circular dichroism spectra of the aqueous solutions of compounds (**4**), (**5**) and (**6**). Compound (**4**) shows one n-π* transition band at 311 nm and two π-π* transitions at 260 nm (^1L_b) and 230 nm (^1L_a). The same three types of transitions are also observed for **5** with moderate red-shifts, appearing at 340, 270 and 240 nm, respectively. From **5** to **6**, the π-π* transitions are significantly red-shifted while the n-π*

transition is only slightly so. The circular dichroism spectra of **4** show positive Cotton effect for all three bands. For **5**, the ^1L_b band gives a weak negative Cotton effect. For **6**, negative Cotton effects are observed for both the n-π* band and the major π-π* bands (at 301 and 285 nm). It is known that the sign of the induced circular dichroism signal of an achiral guest molecule depends mainly on its location and orientation in relation to the CD cavity [24, 25]. For a guest molecule located inside the CD cavity, its electronic transitions with transition dipole moments parallel to the CD axis (or the angle between the transition dipole and the CD axis is less than 30°) give positive induced circular dichroism signals while those transitions having a higher-than 30° angle with the CD axis give negative signals. The situation is reversed if the guest molecule is located outside but near the CD cavity. Thus, all positive Cotton effects observed on **4** indicate that the phenyl ring was located at the exterior of the CD cavity and is more or less parallel to the narrow CD rim. As shown in Fig. (**4a**), both ^1L_a and ^1L_b transitions have angles more than 30° in relation to the CD axis (α,β>30°) and thus give positive circular dichroism signals. If the angle β is less than 90°, the twisting of the phenyl ring will result in one iodo group closer to the CD cavity while the other pointing away which is confirmed by its crystal structure, described later.

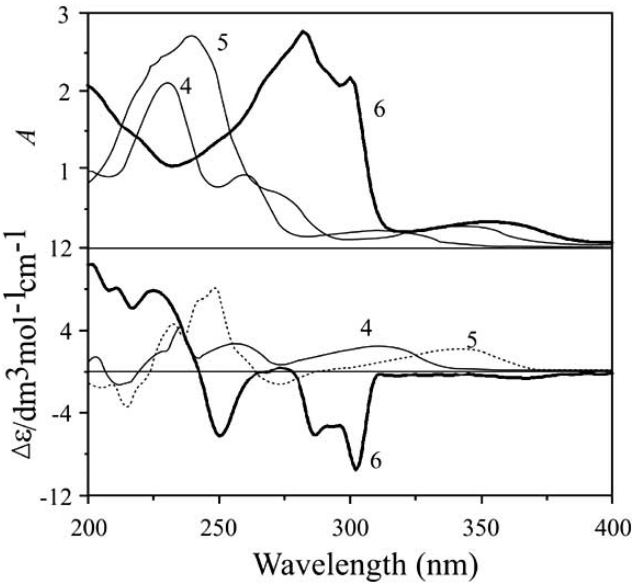

Fig. (3). UV/Vis absorption and circular dichroism spectra of **4-6** in aqueous solutions.

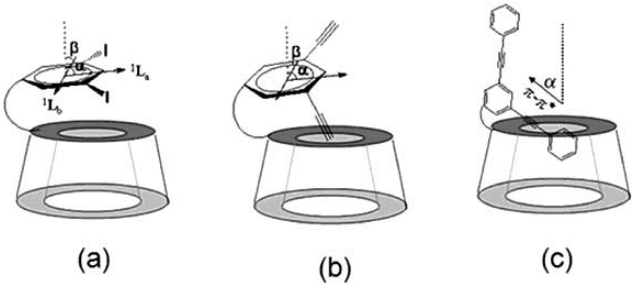

Fig. (4). Schematic structures of **4-6** deduced from circular dichroism spectra.

When the two iodo groups in **4** are converted to two ethynyl groups, compound (**5**) now possesses longer "hands" which may reach into the CD cavity. To facilitate this inclusion, the phenyl ring is now severely twisted with its axis now nearly perpendicular to the CD axis (β<30°, Fig. (**4b**)), resulting in a weak negative ^1L_b signal and a positive ^1L_a signal (^1L_a is still nearly perpendicular to the CD axis). For compound (**6**), one arm is now deeply included inside the CD cavity (**Fig.** (**4c**)). The phenylacetylene arm, however, is not included in the CD cavity in a straight-down fashion, but rather in a perched way (α>30°), presumably due to the short binding bridge between the conjugated π-system and the CD rim, resulting in negative Cotton effects for the major π-π* transitions (at 301 and 285 nm) associated with the partially included diphenylacetylene segment. Similar to **5**, the ^1L_a and ^1L_b transitions associated with the center phenyl ring give positive (225 nm) and negative signals (250 nm), respectively.

The structure of **4** deduced from the CD spectrum is confirmed by its crystal structure. Compound (**4**) crystallizes in the monoclinic space group $P2_1$. There are two crystallographically dependent but chemically equivalent CD molecules **A** and **B** in the asymmetric unit. For the sake of simplicity, only the structure of molecule **A** is shown in Fig. (**5**), which reveals that the CD skeleton maintains a round belt shape. The seven bridge oxygen atoms are nearly coplanar, forming a heptagon with edge lengths in the range of 4.241-4.423 Å for **A** and 4.189-4.510 Å for **B** and angles in the range of 123.8-134.6 ° for **A** and 124.3-132.3 for **B**, respectively. As seen in many mono-6-aryl-β-CDs, the introduction of 3,5-diiodophenyl substituent does not lead to significant geometrical changes for the CD skeleton [26-29]. The 3,5-diiodophenyl group bends inward towards the cavity with a dihedral angle C43A-N1A-C42A-C41A for **A** and C43B-N1B-C42B-C41B for **B** of *ca* 72° (72.1° and 72.2° for **A** and **B**, respectively). The angle between the C2 rotational axis of the phenyl ring and the normal of the CD ring for both **A** and **B** is around 76°. The phenyl ring is further twisted around its rotational axis, resulting in a dihedral angle between the phenyl ring and the CD ring of 43.8 and 45.8°, for **A** and **B**, respectively. One iodo group sits at the outskirts of the cavity of its own CD ring, while the other iodo group points away. The angle between the ^1L_a transition and the CD axis is thus 76°, while that between ^1L_b and the CD axis is around 44°. Both should give positive ICD signals, consistent with its CD spectrum.

The protruding iodo group is actually included into the cavity of an adjacent CD ring from the secondary hydroxyl side to form a one-dimensional quasi-columnar superstructure. As shown in Fig. (**6**), there are two sets of CD rings of **A** and **B**, each containing alternate parallel CD rings, in one moderately displaced columnar superstructure. The two sets of CD rings are horizontally offset by ca 2.50 Å. All CD rings are arranged nearly perpendicular to the columnar axis with a cross angle of 94°. The adjacent 3,5-diiodophenyl moieties are nearly orthogonal to each other (96° dihedral angle), forming a zigzag core. While similar columnar superstructures have been observed in many other mono-6-

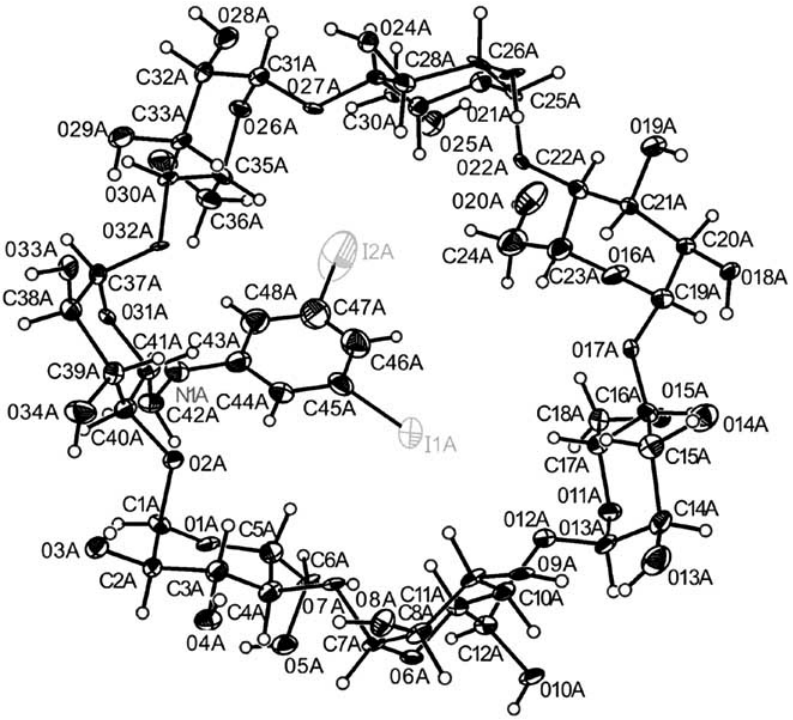

Fig. (5). Ortep (left, cavity view) and Rasmol (right, side view) representations of the molecular structure of **4**.

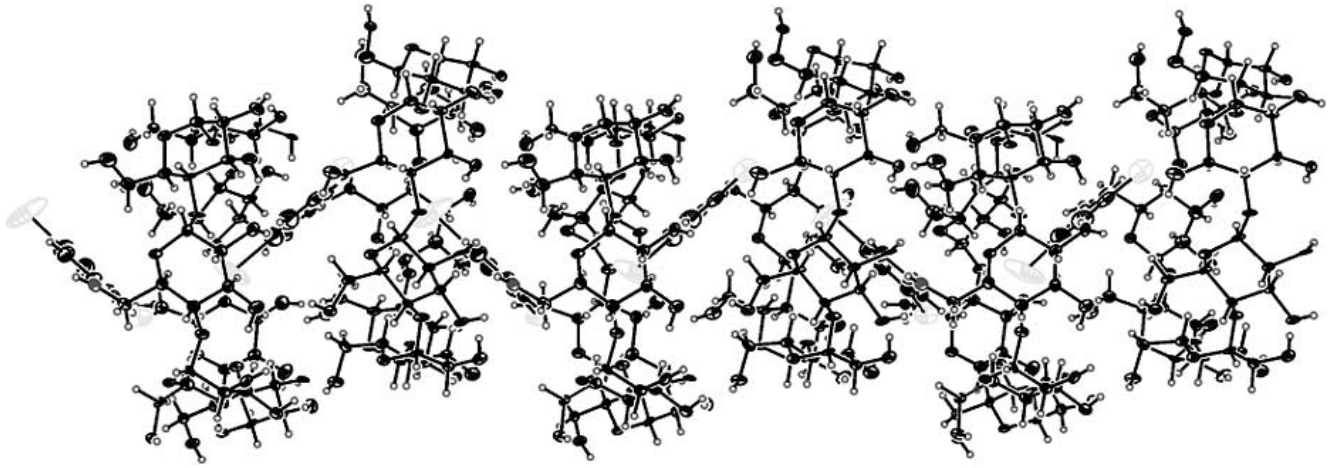

Fig. (6). Moderately displaced columnar superstructure formed by intermolecular encapsulation. Left, rasmol drawing of a side view of the columnar structure; right, top: side view of the core; right, bottom: cavity view of the column.

substituted-β-CDs [26-29], the CD rings in those superstructures are significantly tilted, resulting in less regular columnar structures.

While our efforts in growing single crystals suitable for X-ray crystallography were not fruitful for compound (**5**), its 1D and 2D ^{1}H NMR spectra do provide valuable information in regard to its conformation. In DMSO-d_6, the ^{1}H NMR spectrum of **5** shows only one signal corresponding to H_1 (Fig. (**7**)) and see Scheme **1** for proton labeling). In D_2O, however, the seven H_1 protons give five adequately dispersed signals in the range of 4.85~5.20 ppm with integration ratio of 1:1:1:2:2. The significant dispersion (over 0.3 ppm) of the anomeric signals reflects the reduction of the seven-fold symmetry due to self-inclusion into the CD cavity or fixation near the rim of the cavity by the covalently linked pendant [29-31]. The 2D ROESY spectrum (Fig. (**8**)) showed very weak interactions between aromatic protons and the CD protons. The fact that no cross peak is observed for proton b and the CD's H3 protons, indicates that the phenyl ring is not deeply included. Compared to proton b, proton a showed relatively stronger crosspeaks with CD's H5 protons. This result, coupled with the overall weak NOE correlations between protons a, b and CD's protons, yields a consistent picture that the phenyl ring sits over the CD's narrow rim with the phenyl ring significantly twisted so that one proton a is much closer to the CD rim than the proton b is.

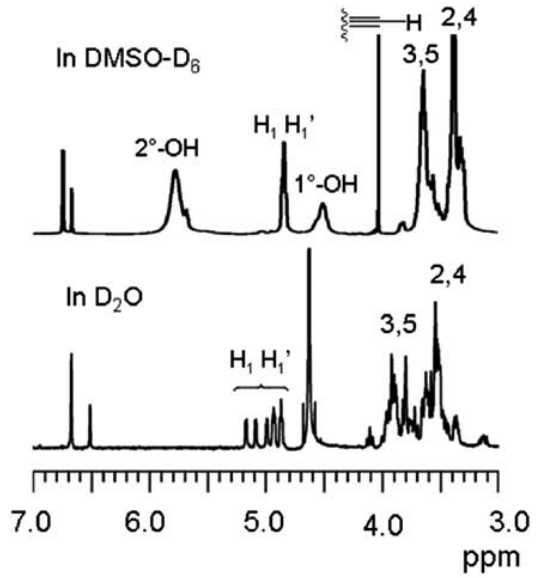

Fig. (7). ^{1}H NMR spectra of **5** in DMSO-d6 and D_2O.

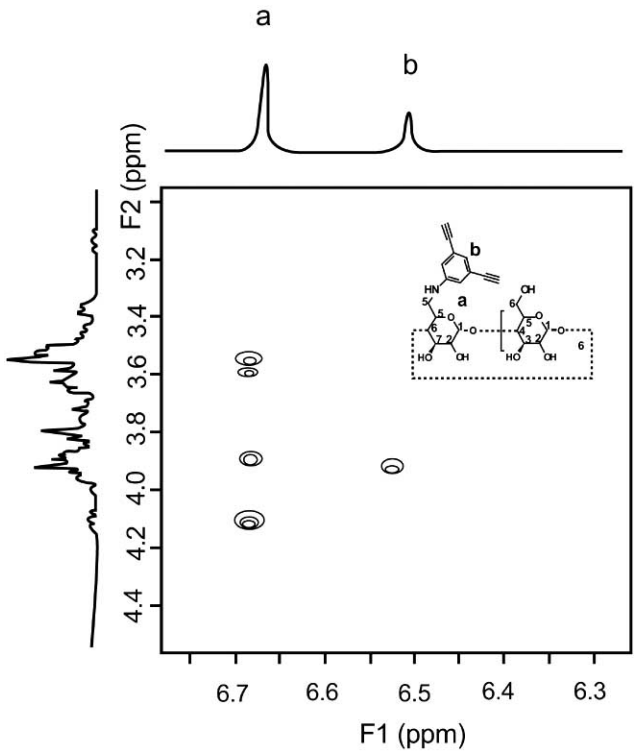

Fig. (8). Partial ^{1}H 2D ROESY spectrum of **5** in D_2O at 298 K.

Electronic Properties

Compounds (**1**), (**2**), (**4**), and (**5**) exhibit enough solubility in water so that their optical properties in DMSO and water can be compared. As shown in Fig. (**9**), all four compounds show two absorption peaks in DMSO, one at longer wavelengths and with lower intensity associated with the n-π* transition while the other due to the π-π* transition. In water, a new intense peak at shorter wavelengths appeared for all four compounds. Besides the new broad peaks at 224 nm and 230 nm for compounds (**1**) and (**2**), respectively, one can notice their n-π* transitions which are not only significantly suppressed in intensity, but also hypsochromically shifted by more than 20 nm (dotted curves), compared with those in DMSO (solid curves). The π-π* transition peaks shown in their DMSO solutions are also significantly blue-shifted and merged to the new broad peak. For **4** and **5**, however, one still observes the n-π* and π-π* transitions appearing at only slightly blue-shifted wavelengths in water versus their counter-peaks in DMSO. Apparently, by linking to β-CD, the aryl systems of **4** and **5** in water are able to at least partially maintain a hydrophobic environment similar to what they experience in DMSO, presumably due to the formation of inclusion complexes or self-inclusion.

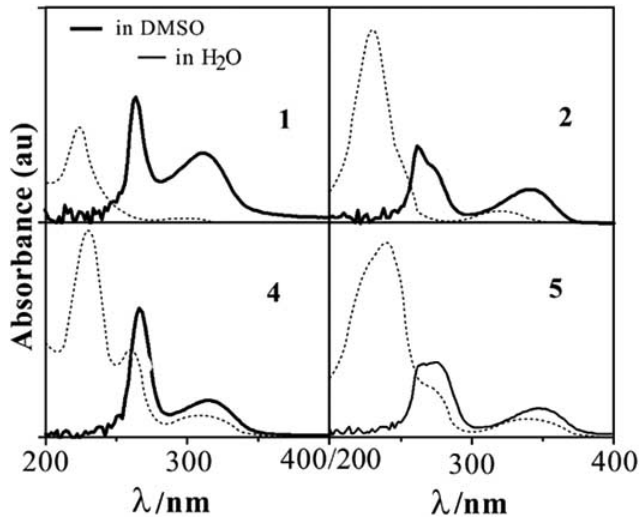

Fig. (9). Absorption spectra of **1,2,4** and **5** in DMSO and water.

Compounds (**2**) and (**5**) are highly fluorescent and thus their fluorescent emission properties were explored. The emission spectra of **2** and **5** were studied in both DMSO and H_2O, under different excitation wavelengths corresponding to their absorption peaks. As shown in Fig. (**10**), compound (**2**) shows nearly identical emission wavelengths whether in DMSO or in water and whether it was excited at the n-π* transition wavelength or the π-π* transition wavelength. The excitation wavelength-independent emission indicates energy transfer from the π-π* transition to the n-π* transition. The excitation spectra of **2** in both DMSO and water match their corresponding absorption spectra in terms of peak positions. By comparing the absorption spectra with the corresponding excitation spectra, one can estimate the π–π* to n-π* energy transfer efficiency to be 55% (at 271 nm) and 42% (at 233 nm) in DMSO and water, respectively. For compound (**5**), its fluorescence emission is again independent of the excitation wavelengths. The energy transfer efficiency from the π–π* to n-π* transition is markedly higher (67% at 276 nm) in DMSO than that of compound (**2**). The excitation spectra of **5** in water show three peaks, again matching its absorption spectra. At 276 nm, the excitation energy transfer efficiency in water is even higher at 75%.

As stated earlier, circular dichroism measurements indicate that the self-inclusion is much stronger in **6** than in **4**

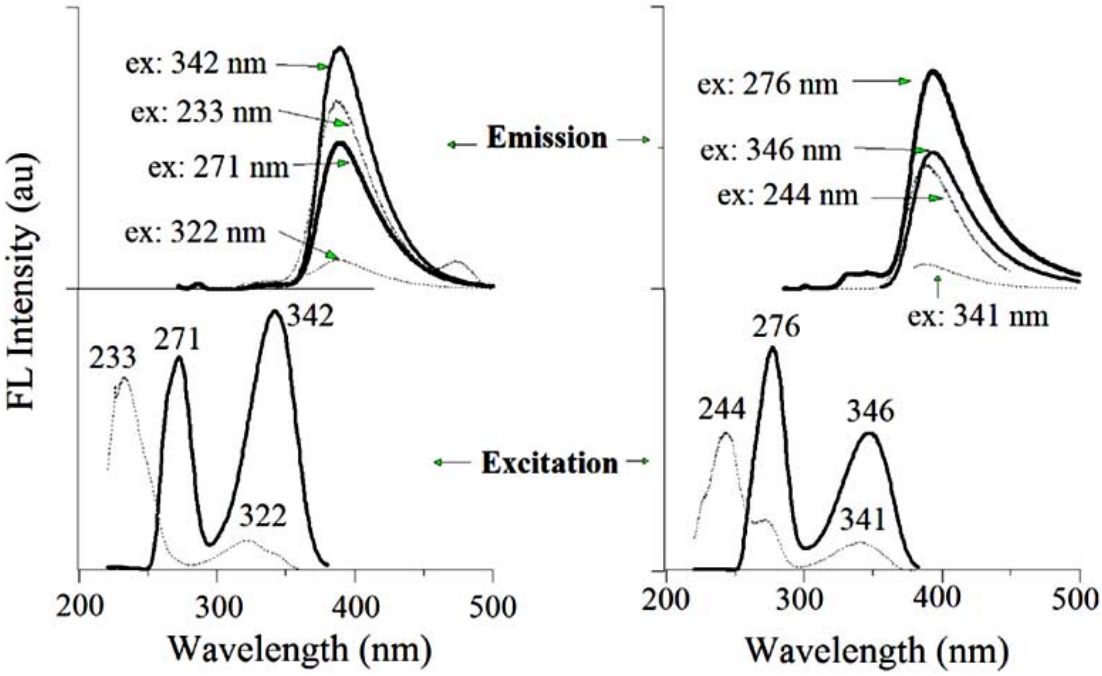

Fig. (10). FL emission and excitation spectra of **2** (left) and **5** (right) in DMSO (solid curves) and water (dotted curves).

and **5**. It would thus be interesting to see how the optical properties of **6** change in water versus DMSO, and how they compare with those of **3**. Unfortunately, **3** is totally insoluble in water. However, **6** shows enough solubility for absorption and fluorescence measurements. Fig. (**11**) shows the absorption, excitation and emission spectra of **6** in DMSO and water. The absorption spectrum shows that, similar to **4** and **5**, the n-π* transition of **6** in water is slightly blue-shifted. Its π-π* transitions, however, give nearly identical peaks in both DMSO and water. More significantly, the absorption spectrum of **6** in water shows no new peak around 230 nm, the one which was observed in all four other compounds (**1**,**2**,**4**,**5**). Overall, the difference between the two absorption spectra, one in water and one in DMSO, is much smaller in **6** than those observed in **4** and **5**, consistent with the previous suggestion that the aryl system is strongly included in **6**. The excitation spectrum of **6** in water matches very well with its absorption spectrum. The excitation energy transfer efficiency from the π–π* to n-π* transition is nearly quantitative (>98%). These results clearly indicate that self-inclusion of an aryl system into a CD cavity exhibits significantly beneficial effects on their optical properties [6, 32].

CONCLUSION

In conclusion, three β-CD derivatives with varying lengths of π-conjugated arms have been synthesized. Circular dichroism measurements indicate that when the π-conjugated arms are extended from **4** to **5** and to **6**, the self-inclusion of the π-conjugated arm to the CD ring is enhanced. The extent of inclusion results in very different solvent-dependent optical properties for these compounds. In aqueous solutions, stronger inclusion leads to enhanced excitation energy transfer.

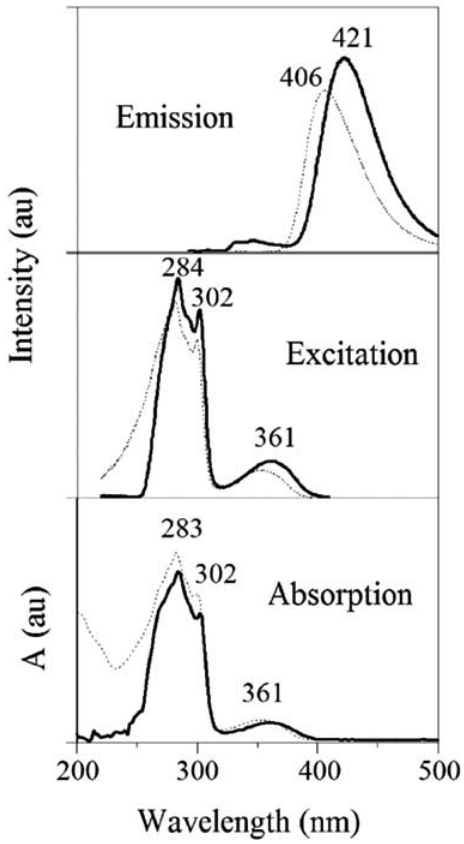

Fig. (11). Absorption, excitation and emission spectra of **6** in DMSO (solid curves) and water (dotted curves).

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded on a Varian 400-MHz spectrometer. The 2D ROESY spectra were recorded

on a Varian 400-MHz spectrometer by dissolving 6.0 mg of compound **5** in 1mL D_2O with scan per Inc 64, number of Inc 512, mixing time 200 ms, relaxation time 2 s at 298 K. Thin layer chromatography was performed on aluminum-backed silica gel plates with solvent system (n-butanol/ethanol /water, 5:4:3). Cyclodextrin compound was visualized by charring with 50% sulfuric acid in ethanol spray, whereas UV exposure revealed the aromatic substituted product. C18-Reversed phase, 24 %C silica gel was used for reverse-phase column chromatography.

6-Deoxy-6-formyl-6-β-cyclodextrin [22] and 1, 3-diiodo-aniline [33] were synthesized according to literature procedures. Water used for the purification was 18 MΩ Ultra pure water obtained from LABCONCO water purification system. All the other chemicals are purchased from either ACROS or Aldrich and used as received unless otherwise stated.

3,5-Diethynylaniline

To the solution of 3,5-diiodoaniline (3.45 g, 10 mmol) in THF (10 mL) and Et_3N (8 mL), $Pd(PPh_3)_2Cl_2$ (280 mg, 0.4 mmol) and CuI (152 mg, 0.8 mmol) were added at room temperature. The solution was degassed by bubbling N_2 through it. Trimethylsilylacetylene (2.94 g, 30 mmol) was then added and the mixture was stirred overnight. The resulting solution was filtered. The filtrate was concentrated and redissolved in CH_2Cl_2. The resulting solution was washed with water, dried over anhydrous $MgSO_4$ and concentrated to get crude product. The crude product was purified by flash column chromatography eluting with 4:1 (hexane/ethyl acetate) to yield 3,5-bis(trimethyl-silylethynyl)aniline. To the solution of this compound in CH_2Cl_2 (20 mL), *t*-butylammonium fluoride (22 mL, 22 mmol) was added. The reaction mixture was stirred for 20 min and was then poured into water. The aqueous solution was extracted with CH_2Cl_2. The organic layer was collected, dried over anhydrous $MgSO_4$, and the solvent was then evaporated. The resulting crude product was purified by flash column chromatography eluting with 4:1 hexane / ethyl acetate to give the title compound as light brown needle crystals (overall yield 1.23 g, 80%, m.p. 126-127 °C, lit 125-127 °C [34]). ^{1}H NMR (DMSO-d_6, TMS): δ 6.67 (d, *J* = 1.2 Hz, 2H, ArH), 6.64 (*t*, *J* = 1.2 Hz, 1H, ArH), 5.44 (s, 2H, NH_2), 4.07 (s, 2H, ≡CH). ^{13}C NMR (DMSO-d_6, TMS): δ 149.1, 122.5, 121.8, 117.2, 83.2, 80.0.

3,5-Bis(phenylacetylene)aniline

Triethylamine (8 mL) was added to a mixture containing 3,5-diiodoaniline (3.45 g, 10 mmol), phenylacetylene (2.55 g, 25 mmol), $Pd(PPh_3)_2Cl_2$ (280 mg, 0.4 mmol), CuI (152 mg, 0.8 mmol), and THF (10 mL) at r.t.. The resulting solution was stirred at r.t. overnight and was then filtered. The filtrate was concentrated and redissolved in CH_2Cl_2. The resulting solution was washed with water, dried over anhydrous $MgSO_4$ and the solvent was then stripped off. The crude product was purified by flash column chromatography eluting with 4:1 hexane / ethyl acetate. The title compound was obtained as a brown solid (2.30 g, 78%, m.p. 118-120 °C). ^{1}H NMR (DMSO-d_6, TMS): δ 7.55 (4H, m, ArH), 7.42 (6H, m, ArH), 6.85 (t, *J* = 1.2 Hz, 1H, ArH), 6.76 (d, *J* = 1.2Hz, 2H, ArH), 5.49 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, TMS): δ 149.4 , 131.5 , 128.9 , 128.8 , 123.1 , 122.3, 121.5 , 116.6, 89.2, 88.6.

Compound (4)

6-Deoxy-6-formyl-β-cyclodextrin (1 g, 0.88 mmol), and 3, 5-diiodoaniline (3.73 g, 10.81 mmol) were dissolved in mixed solvents containing an acetate buffer solution (NaOAc/AcOH, pH = 5) and methanol in a ratio of 1:2 at 25 °C. After stirring for 1 h, $Na(CN)BH_3$ (276 mg, 4.4 mmol) was added to the resulting solution. The mixture was stirred for 10 d, and then neutralized with 2 M sodium hydroxide. The solution was added dropwise to acetone (1 L). After being kept in the refrigerator for 2 h, the precipitate was collected and rinsed with acetone. Purification was accomplished utilizing reversed phase column chromatography, eluting with water (1.5 L), followed by 10% aqueous methanol (1 L), and then 20% aqueous methanol (2.5 L). The appropriate fractions were concentrated to 15 mL under vacuum and lyophilized to give the desired product as a colorless solid (250 mg, 20%. Decompose at 254 °C before melting). R_f 0.55 (n-butanol/ethanol /water, 5:4:3). The product was dissolved in hot water and the solution was allowed to stand at room temperature for several days, giving crystals suitable for X-ray analysis. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C, ppm): δ 7.10 (t, *J* =1.2 Hz, 1H), 6.99 (d, *J* = 1.2 Hz, 2 H), 5.82 (br, 15 H, 2°OH and NH), 4.81 (m, 7H), 4.43 (br, 6H), 3.90-3.05 (m). ^{13}C NMR (DMSO-d_6, 400 MHz, 25 °C, ppm): δ 42.9, 60.2, 69.0, 72.0, 72.4, 73.1, 81.4, 83.1, 96.0, 102.0, 119.9, 130.7, 151.3. Anal. Calc. for $C_{48}H_{73}I_2NO_{34}\cdot 9.5\ H_2O$: C, 35.30; H, 5.68; N, 0.86. Found: C, 35.03; H, 5.21; N, 0.92.

Compounds (**5**) and (**6**) were synthesized using the same approach and workup procedures as those of **4**.

Compound (5)

190 mg was obtained as light yellow powder (yield 15%, decomposed at 230 °C before melting). ^{1}H NMR (DMSO-d_6, TMS): δ 6.74 (s, 2H, ArH), 6.66 (s, 1H, ArH), 5.76 (br, 14H, 2°OH), 5.66 (t, 1H, *J* = 5.6 Hz, NH), 4.84 (br, 7H, H_1), 4.48 (br, 6H, 1°OH), 4.01 (s, 2H, ≡CH), 3.82 (m, 1H, $H_{6b'}$), 3.63 (m, 27H,H_3, H_5, H_6, H_{6a}'), 3.30 (m). ^{13}C NMR (DMSO-d_6, TMS): δ 43.2 (C_6'), 59.7(C_6), 59.9(C_6), 69.4(C'$_5$), 72.1(C_5), 72.2(C_5), 72.4(C_5), 73.0(C_5), 73.1(C_5), 79.9 (≡CH), 81.3(C_4), 81.4(C_4), 81.5 (C_4), 83.1(C'$_4$), 83.4(≡C), 101.9(C1), 102.2(C_1'), 115.8(C_c), 121. 9(C_f), 122.5(C_b), 149.0(C_a). MS (MALDI) calcd for $C_{52}H_{75}O_{34}N$: 1257.4, found 1280.1 (M + Na^+).

Compound (6)

208 mg was obtained as earth yellow powder (yield 15%, decomposed at 240 °C before melting). ^{1}H NMR (DMSO-d_6) δ 7.57 (m, 4H, ArH), 7.43 (m, 6H, ArH), 6.88 (s, 3H, ArH), 5.77 (m, 14H, 2°OH), 5.56 (t, *J* = 5.2 Hz, 1H, NH), 4.87 (m, 7H, C_1H), 4.63 (t, 1H, 1°OH), 4.47 (m, 5H, 1°OH), 3.82 (br, 1H, H_{6b}'), 3.66 (m, 27H, H_3, H_6, H6_a', H_5), 3.28 (m). ^{13}C NMR (DMSO-d_6, TMS): δ 43.2(C_6'), 59.9(C_6), 60.2(C_6), 70.0(C_5'), 72.1(C_5), 72.2(C_5), 72.5(C_5), 73.0(C_5), 73.1(C_5), 81.4(C_4), 81.6(C_4), 82.9(C_4'), 88.7 (≡C), 89.4(≡C), 102.0(C_1), 102.2(C_1'), 115.5(C_b), 121.6, 122.4, 123.1, 128.8,

131.5, 149.4. MS (MALDI) calcd for $C_{64}H_{83}O_{34}N$: 1409.5, found 1432.6 ($M + Na^+$).

X-Ray Single Crystal Structure Analysis

A colorless needle-shaped crystal of dimensions 0.40 x 0.08 x 0.06 mm was selected for structural analysis. Intensity data for this compound were collected using a Bruker APEX ccd area detector using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) [35]. The sample was cooled to 100(2) K. The intensity data were measured as a series of ω oscillation frames each of 0.3 ° for 60 sec / frame. Coverage of unique data was 99.8 % complete to 21.97 degrees in θ. Cell parameters were determined from a non-linear least squares fit of 7740 peaks in the range $2.36 < \theta < 22.87°$. A total of 33612 data were measured in the range $2.14 < \theta < 21.97°$. The data were corrected for absorption by the semi-empirical method giving minimum and maximum transmission factors of 0.6772 and 0.9393 [36]. The data were merged to form a set of 15478 independent data with R(int) = 0.0630.

The monoclinic space group $P2_1$ was determined by systematic absences and statistical tests and verified by subsequent refinement. The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 [37]. Hydrogen atom positions were initially determined by geometry and refined by a riding model. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atom displacement parameters were set to 1.2 (1.5 for methyl) times the displacement parameters of the bonded atoms. A total of 1698 parameters were refined against 1623 restraints and 15478 data to give $wR(F^2) = 0.2106$ and S = 1.035 for weights of $w = 1/[\sigma^2 (F^2) + (0.1270\ P)^2 + 24.9400\ P]$, where $P = [F_o^2 + 2F_c^2] / 3$. The final R(F) was 0.0795 for the 12733 observed, [$F > 4\sigma(F)$], data. The largest shift/s.u. was 0.001 in the final refinement cycle. The final difference map had maxima and minima of 1.677 and -1.078 e/Å^3, respectively. The absolute structure was determined by refinement of the Flack parameter [38]. The polar axis restraints were taken from Flack and Schwarzenbach [39]. CCDC-246676 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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