FACILE SYNTHESIS OF MONO- AND POLYTOPIC
β-CYCLODEXTRIN AROMATIC ALDEHYDES
BY CLICK CHEMISTRY

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GRAPHICAL ABSTRACT

Abstract The first examples of mono-, di-, and trimeric β-cyclodextrin aromatic aldehyde derivatives 5, 10, and 11 were designed and conveniently synthesized by using the CuI-catalyzed azide–alkyne cycloaddition reaction of mono-6-azido-cyclodextrin (CD) with aromatic aldehyde alkynyl derivatives. The reaction proceeded under mild conditions, and the yields were as high as 75%. The ultraviolet–visible complexation experiments suggested they had good binding properties for dyes and the more CDs units were achieved greater association constants.

Keywords Aromatic aldehyde; click chemistry; cyclodextrin; synthesis

INTRODUCTION

In recent years, cyclodextrins (CDs) have been extensively used in many research fields such as food chemistry, analytical chemistry, biology, and pharmacy because of their appealing unique binding properties.1–7 However, the binding properties of native CDs are generally limited and the more elaborated structures

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are often needed for binding guests effectively. To construct the new supramolecular systems of CDs, various functional groups and unique structural units were introduced into CDs to obtain novel CDs derivatives with interesting binding properties.\textsuperscript{[1–7]} However, because of the difficulties of selective modifications of the hydroxyl groups on CDs, the varieties and amounts of CDs derivatives are far fewer than that of other organic supramolecules, such as crown ethers and calixarenes. One pathway to solve this problem is to synthesize efficiently CDs intermediate derivatives containing active-terminal functional groups, which can react easily with other molecules to construct novel CDs derivatives. For example, the CDs derivatives with terminal amino-group prepared by reacting mono-6-tosyl-β-CD with corresponding amine, were applied to synthesize some CDs derivatives by addition reaction or ammonolysis reaction, etc.\textsuperscript{[8–10]} It is well known that the aldehyde group is an important active functional group, which could be conveniently transformed to other derivatives by reduction, oxidation, addition, or condensation reactions. Thus, the first CD aliphatic aldehyde derivative was reported by oxidation of hydroxyl group as early as in 1994.\textsuperscript{[11]} Subsequently, several different oxidizing methods for hydroxyl groups of CDs were applied to prepare the CDs aliphatic aldehyde derivatives.\textsuperscript{[12–14]} Also, by the further addition and oxidizing reaction of these aldehyde derivatives, some interesting CDs derivatives were obtained.\textsuperscript{[15–18]} No condensation reaction, such as Schiff-base condensation, was reported due to the unstable and reversible condensation process of aliphatic aldehyde. If the aromatic aldehyde group is introduced into CDs, the obtained CDs aromatic aldehyde derivative would possess better reaction activities and could be transformed effectively to all kinds of CDs derivatives based on the stable aromatic conjugate structure comparing with the aliphatic aldehyde. However, no CD aromatic aldehyde derivative has been described up to now. On the other hand, it was well known that the Cu\textsuperscript{I}-catalyzed click chemistry, which reacts easily the azide group with alkynyl group, had been used to prepare CDs derivatives effectively.\textsuperscript{[19–25]} Considering the significance of CDs aromatic aldehyde derivative as the synthetic platform to construct other CDs derivatives, in this article, we report the first synthesis of CDs aromatic aldehyde derivatives via a facile click reaction and their preliminary ultraviolet–visible (UV-vis) complexation properties for dyes.

Initially, we tried to prepare the CDs aromatic aldehyde derivative by the nucleophilic substitution reaction of CD derivative 2 with 4-hydroxybenzaldehyde as shown in Scheme 1. However, this reaction failed to afford any product under all kinds of reaction systems, such as K\textsubscript{2}CO\textsubscript{3}/H\textsubscript{2}O, K\textsubscript{2}CO\textsubscript{3}/DMF, K\textsubscript{2}CO\textsubscript{3}/MeCN, NaOH/DMF, NaOH/THF, NaOH/H\textsubscript{2}O, etc. The reason might be attributed to the unfavorable influences of the strong hydrogen bonding between the phenolate and the multiple hydroxyl groups of CD. Alternately, click chemistry was chosen as the linking reaction for aromatic aldehyde with CD because the click reaction had been confirmed as a useful reaction mode in introducing other functional groups on CDs.\textsuperscript{[19–25]}

Scheme 2 illustrates the synthetic route of cyclodextrin aromatic aldehyde derivative 5 via click chemistry. The mono-6-azido-β-CD 3 was obtained from the readily available mono-6-tosyl-β-CD according to previous methods.\textsuperscript{[26,27]} Also, 4-(prop-2-ynyloxy)benzaldehyde 4 was prepared in yield of 87% by reacting 4-hydroxybenzaldehyde with 3-bromoprop-1-yne under K\textsubscript{2}CO\textsubscript{3}/MeCN system according to literature reports.\textsuperscript{[27,28]} Once the reactants had been prepared, the coupling reaction of β-CD azido derivative 3 and compound 4 was accomplished by click chemistry of
the Huisgen [2 + 3] cycloaddition reaction. The molar ratio of compounds 3 and 4 was 1:1.1, and 1.1 equiv. CuSO$_4$·5H$_2$O and 2.4 equiv. sodium ascorbate (with respect to the CD) were used as catalysts. This procedure was carried out at room temperature in dimethylformamide (DMF) solution in 15 h. The first example of CD aromatic aldehyde derivative 5 was obtained conveniently after simple purifying procedure of recrystallization in DMF/acetone and the yield was as high as 80%.

Inspired by the successful synthesis of mono CD aromatic aldehyde derivative 5, we designed the synthetic routes of dimeric and trimeric CD aromatic aldehyde derivatives 10 and 11 as shown in Scheme 3. According to literature methods,[25,26] 3,4-bis(prop-2-ynyloxy)benzaldehyde 7 and 3,4,5-tris(prop-2-ynyloxy)benzaldehyde 9 were easily prepared by treating 3,4-dihydroxybenzaldehyde 6 or 3,4,5-trihydroxybenzaldehyde 8 with 3-bromoprop-1-yn in K$_2$CO$_3$/MeCN system in
yields of 86% and 80%, respectively. Few modifications were required to carry out the click reaction of compounds \(7\) and \(9\) with compound \(3\). It takes more time and needed higher reaction temperatures for the synthesis of dimeric CD \(10\) and trimeric CD \(11\). The reaction temperatures were enhanced to 90 °C and the reaction times were prolonged to 48 h and 60 h, respectively, to achieve complete conversion of the di- or trialkyne linkers, probably because of the steric hindrance between the bulky CD interfering with the formation of the terminal alkyne-CuI species. It is interesting that, unlike the method in the literature,\(^{[28]}\) no excess CD derivative \(3\) was needed for these click reactions (molar ratios were 2:1 and 3:1 for compounds \(10\) and \(11\), respectively). As a result, compounds \(10\) and \(11\) could be easily separated and purified by recrystallization in DMF/acetone without column chromatography, which was required in most cases for the separation of CD dimers and trimers.\(^{[28,29]}\) Compounds \(10\) and \(11\) were obtained as yellowish-white powders and the yields were as high as 78% and 75%, respectively. It is worth noting that the simple separating procedures and good yields for compounds \(10\) and \(11\) are ideal in comparison with the synthetic procedures of other CD dimers and trimers.\(^{[27–29]}\) Moreover, these

Scheme 3. Synthetic routes of dimeric and trimeric CD aromatic aldehyde derivatives \(10\) and \(11\). (a) \(K_2CO_3/\text{CH}_3\text{CN}, 86\%\); (b) \(K_2CO_3/\text{CH}_3\text{CN}, 86\%\); (c) \(\text{CuSO}_4\), sodium ascorbate, DMF, 78\%; and (d) \(\text{CuSO}_4\), sodium ascorbate, DMF, 75\%.
results are also very favorable for using them as new synthetic platform to construct other novel CD derivatives.

The novel mono-, di-, and trimeric CD aromatic aldehyde derivatives 5, 10, and 11 were characterized by elemental analysis, FT-IR, electrospray ionization–mass spectrometry (ESI-MS), and NMR spectra. The IR spectra of compounds 5, 10, and 11 exhibited strong absorption peaks at 1670 cm\(^{-1}\) approximately, indicating the existence of C=O of aromatic aldehyde groups (Figures 1, 5, and 9 of the supporting information). The Fermi doublet was not observed due to the overlapping of the strong peaks of other C-H bonds in these compounds. Their ESI-MS spectra showed the corresponding molecular ion peaks at 1342.3 (MNa\(^+\)), 2556.4 (MNa\(^+\)), and 3774.3 (MNa\(^+\)), respectively, and no other peak appeared obviously (Figures 2, 7 and 11 of the supporting information). In their \(^1\)H NMR spectra, the characteristic peaks were assigned well for triazole proton and phenyl proton (Figures 3, 6 and 10 of the supporting information). For example, in the \(^1\)H NMR spectrum of mono CD aromatic aldehyde derivative 5, the characteristic peaks were observed clearly (a pair of doublet for ArH at 7.23 and 7.87 ppm, a singlet for triazole proton at 8.20 ppm, and a singlet for the proton of CHO at 9.88 ppm). On the other hand, as generally observed for substituted CDs, especially for polytopic CDs, the proton signals at sugar units were hardly exploitable due to overlapping and broadening.\(^{27,28}\) This phenomenon suggested a modification of the conical CD structures leading to nonequivalent glucopyranose units.\(^{27,28}\) As a result, complete signal assignment was therefore difficult for CD units of compounds 10 and 11. By contrast, in their \(^{13}\)C NMR spectra, the characteristic signals were detected distinctly for the aromatic aldehyde group and triazole cycle (Figures 4, 8, and 12 of the supporting information). For instance, the \(^{13}\)C NMR spectrum of mono-CD aromatic aldehyde derivative 5 showed the signals of carbon atoms for aldehyde and triazole cycle at 191, 163, and 142 ppm, respectively. The results of elemental analysis were also in accordance with their structures. Based on all these characteristic results of IR, ESI-MS, NMR, and elemental analysis, the structures of novel mono-, di-, and trimeric CD aromatic aldehyde derivatives 5, 10, and 11 were confirmed as shown in Schemes 2 and 3.

The formation of inclusion complexes between cyclodextrin unit and guests, such as dyes, were reported widely for the potential application on sensors and probes studies.\(^{30,31}\) Thus, the preliminary binding properties of compounds 5, 10, and 11 for two normal dyes of orange I and neutral red were investigated by UV-vis spectroscopy. The results are shown in Fig. 1. Moreover, based on the absorbance at maximal absorption wavelength, the association constants and correlation coefficients were calculated by Benesi–Hildebrand equation, which was usually used to study the complexation behaviors of host–guest.\(^{32}\) The calculated formula was as follows:

\[
\frac{1}{\Delta A} = \frac{1}{K_s \Delta \varepsilon [H]} \frac{1}{[G]} + \frac{1}{\Delta \varepsilon [H]}
\]

where \(H\) is host; \(G\) is guest; \(n\) is the ratio of complexation; \([H]\) and \([G]\) are the concentration of host and guest, respectively; \(K_s\) is association constant; \(\Delta \varepsilon\) is molar absorption coefficient; and \(\Delta A\) is the change of absorbance at maximal absorption wavelength.
The calculated results are summarized in Table 1. It could be seen that the correlation coefficients ($R^2$) were close to 1 when the values of the ratio of complexation ($n$) were 1. These results indicated the formation of 1:1 host–guest complexes for Table 1.

Table 1. Association constants ($K_s$) and correlation coefficients ($R^2$) for the complexation behaviors of compounds 5, 10, and 11 with two dyes

| Dyes | $n$ | 5 $R^2$ | $K_s$ | 10 $R^2$ | $K_s$ | 11 $R^2$ | $K_s$ |
|------|-----|--------|------|----------|------|----------|------|
| OI   | 1   | 0.985  | $2.4 \times 10^4$ | 1   | 0.964  | $3.4 \times 10^4$ | 1   | 0.986  | $4.8 \times 10^4$ |
| NR   | 1   | 0.965  | $4.4 \times 10^4$ | 1   | 0.987  | $5.6 \times 10^4$ | 1   | 0.956  | $6.7 \times 10^4$ |

Figure 1. UV-vis spectra of compounds 5, 10, and 11 ($1 \times 10^{-4} \text{ M}$) in the presence of orange I and neutral red in H$_2$O solution. The concentrations of dye were from the top: 0.0, 0.2, 0.4, 0.6, 0.8, 1.0, and 2.0 ($\times 10^{-6} \text{ M}$).
compounds 5, 10, and 11 with dyes. The associations constants were greater than $10^4$ and exhibited the trends of compound 5 $<$ compound 10 $<$ compound 11. These results indicated that the more CD units were favorable for complexation based on the cooperation action of polytopic CD units, which were in accordance with other reports.\textsuperscript{[27–29]}

In conclusion, the design and synthesis of the first examples of novel mono-, di-, and trimeric CD aromatic aldehyde derivatives 5, 10, and 11 were accomplished by highly efficient CuSO$_4$–sodium ascorbate–catalyzed cycloaddition. The synthetic processes were simple with mild conditions and the yields were 75%. Their structures were confirmed by elemental analysis, FT-IR, ESI-MS, and NMR spectra. The preliminary UV-vis complexation experiments of compounds 5, 10, and 11 for orange I and neutral red suggested they had good binding properties for dyes. The more CDs units gave greater associations constants. It is expected that they are used as novel building platforms to construct new CD derivatives with special structures and unique properties based on the various reactions of the aromatic aldehyde group, such as addition and condensation reaction, which will be further investigated in the following work.

EXPERIMENTAL

All chemicals were purchased from commercial suppliers and used without further purification. The other organic solvents and inorganic reagents were purified according to standard anhydrous methods before use. Distilled water was used in all experiments. Thin-layer chromatographic (TLC) analysis was performed using pre-coated glass plates. IR spectra were recorded on a Perkin-Elmer PE-983 infrared spectrometer as KBr pellets with absorption in cm$^{-1}$. $^1$H NMR spectra was recorded in DMSO-d$_6$ on a Bruker-ARX 600 instrument at 30°C. Chemical shifts are reported in parts per million (ppm), using tetramethylsilane (TMS) as internal standard. ESI-MS spectra were obtained from DECAX-30000 LCQ Deca XP mass spectrometer. Elemental analyses were performed on a Vario EL III elemental analyzer. 4-(Prop-2-ynyloxy)benzaldehyde 4, 3,4-bis(prop-2-ynyloxy)benzaldehyde 7, and 3,4,5-tris(prop-2-ynyloxy)benzaldehyde 9 were conveniently prepared by reacting 4-hydroxybenzaldehyde, 3,4-dihydroxybenzaldehyde, or 3,4,5-trihydroxybenzaldehyde with 3-bromoprop-1-ynyl under K$_2$CO$_3$/MeCN system in yields of 87%, 86%, and 80%, respectively.\textsuperscript{[27]}

**Syntheses of Mono-CD Aromatic Aldehyde Derivative 5**

Compound 4 (0.16 g, 1 mmol) with compound 3 (1.16 g, 1 mmol) was carried out in DMF (35 mL) in the presence of CuI generated by the reduction of copper sulfate (0.28 g, 1.1 mmol) with sodium ascorbate (0.48 g, 2.4 mmol). The mixture was stirred at room temperature for 15 h. TLC detection indicated the disappearance of materials of compounds 3 and 4. After reaction, most of the solvent was evaporated under reduced pressure and 20 mL of distilled water was added with vigorous stirring at room temperature. The mixture was stored in the refrigerator overnight and then the precipitate was collected by filtration. The precipitate was further purified by recrystallization in DMF/acetone three times. Compound 5 was obtained as a gray-white solid in yield.
of 80%. Compound 5: IR/cm$^{-1}$: 3387, 2927, 1679, 1599, 1509, 1157, 1031, 756; $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm: 2.78−4.10 (m, 40H, CH and CH$_2$), 4.25−4.68 (8H, OH and NCH$_2$), 4.69−5.10 (m, 7H, CH), 5.23 (s, 2H, CH$_2$O), 5.53−5.99 (m, 14H, OH), 7.24 (d, $J = 8.0$ Hz, 2H, ArH), 7.88 (d, $J = 8.0$ Hz, 2H, ArH), 8.22 (s, 3H, NCH), 9.87 (s, 1H, CHO). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ ppm: 191.9, 163.5, 142.4, 132.3, 130.3, 126.2, 115.6, 102.6, 101.7, 83.9, 82.5, 82.1, 81.4, 73.7, 73.6, 73.4, 73.1, 72.9, 72.6, 72.2, 70.5, 61.8, 60.4, 60.0, 59.5, 50.5. MS m/z (%): 1342.3 (MNa$^+$, 100). Anal. calcd. for C$_{52}$H$_{77}$N$_3$O$_{36}$: C, 47.31; H, 5.88; N, 3.18; found: C, 47.38; H, 5.82; N, 3.22%.

**Syntheses of Dimeric CD Aromatic Aldehyde Derivative 10**

Compound 7 (0.107 g, 0.5 mmol) with compound 3 (1.16 g, 1 mmol) was carried out in DMF (35 mL) in the presence of CuI generated by the reduction of copper sulfate (0.28 g, 1.1 mmol) with sodium ascorbate (0.48 g, 2.4 mmol). The mixture was stirred at 90°C for 48 h. TLC detection indicated the disappearance of materials of compounds 3 and 7. After reaction, most of the solvent was evaporated under reduced pressure and 20 mL of distilled water was added with vigorous stirring at room temperature. The mixture was stored in the refrigerator overnight, and then the precipitate was collected by filtration. The precipitate was further purified by recrystallization in DMF/acetone three times. Compound 10 was obtained as a gray-white solid in yield of 78%. Compound 10: IR/cm$^{-1}$: 3387, 2926, 1661, 1594, 1504, 1154, 1082, 756; $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm: 2.68−3.98 (m, 114H), 4.18−4.67 (m, 6H), 4.68−4.99 (m, 6H), 5.48−6.05 (m, 16H), 7.24−8.28 (m, 5H, ArH and NCH), 9.88 (s, 1H, CHO). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ ppm: 195.4, 165.2, 143.1, 134.1, 131.1, 128.4, 127.1, 118.3, 102.4, 100.4, 84.2, 81.9, 81.8, 81.1, 73.6, 73.5, 73.3, 73.1, 72.8, 72.5, 72.3, 70.2, 61.7, 60.6, 60.3, 51.1. MS m/z (%): 2556.4 (MNa$^+$, 100). Anal. calcd. for C$_{97}$H$_{148}$N$_6$O$_{71}$: C, 45.97; H, 5.89; N, 3.32. Found: C, 46.02; H, 5.82; N, 3.26%.

**Syntheses of Trimeric CD Aromatic Aldehyde Derivative 11**

Compound 9 (0.090 g, 0.34 mmol) with compound 3 (1.16 g, 1 mmol) was carried out in DMF (35 mL) in the presence of CuI generated by the reduction of copper sulfate (0.28 g, 1.1 mmol) with sodium ascorbate (0.48 g, 2.4 mmol). The mixture was stirred at 90°C for 60 h. TLC detection indicated the disappearance of materials of compounds 3 and 9. After reaction, most of the solvent was evaporated under reduced pressure and 20 mL of distilled water was added with vigorous stirring at room temperature. The mixture was stored in the refrigerator overnight and then the precipitate was collected by filtration. The precipitate was further purified by recrystallization in DMF/acetone three times. Compound 11 was obtained as a gray-white solid in yields of 75%. Compound 11: IR/cm$^{-1}$: 3393, 2925, 1664, 1589, 1286, 1153, 1032, 758; $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm: 2.80−3.99 (m, 171H), 4.37−4.68 (m, 9H), 4.69−4.92 (m, 9H), 5.39−5.98 (m, 24H), 7.89 (m, 5H, NCH and ArH), 9.89 (s, 1H, CHO). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ ppm: 188.2, 161.1, 143.5, 131.8, 130.0, 127.5, 126.3, 117.2, 103.2, 101.8, 101.4, 100.8, 83.3, 82.4, 81.0, 72.8, 72.6, 72.3, 71.9, 71.7, 71.4, 71.1, 70.6, 61.4, 60.7, 60.2, 50.4.
MS $m/z$ (%): 3774.3 (M$\text{Na}^+$, 100). Anal. calcd. for $\text{C}_{142}\text{H}_{219}\text{N}_9\text{O}_{106}$: C, 45.50; H, 5.89; N, 3.32. Found: C, 45.56; H, 5.83; N, 3.25%.

UV-Vis Spectra Studies of Complexation Experiments

All UV-vis experiments were performed in H$_2$O solution by adding aliquots stock solution of respective dyes. The stoichiometry of the complexes was determined by the Job method of continuous variations. The association constant was calculated by Benesi–Hilderbrand formula with nonlinear curve fitting procedure.\cite{32}

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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