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Short communication

Trimerization of β-cyclodextrin through the click reaction

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ABSTRACT

Triprop-2-ynyl benzene-1,3,5-tricarboxylate (**A**) is synthesized by the reaction of 1,3,5-benzenetricarbonyl trichloride with propargyl alcohol and (**A**) is clicked with mono-6-deoxy-6-azido-β-cyclodextrin (N_3–β-CD) in the presence of copper(I) bromide catalyst. N_3–β-CD has been prepared from β-cyclodextrin (β-CD) on treatment with toluenesulfonyl chloride (TsCl) and then with sodium azide (NaN_3) in two consecutive steps. Further trimer of β-CD is characterized by ^{1}H NMR and FTIR studies. Solubility of β-cyclodextrin (β-CD) in water can be increased by increasing the number of alcoholic —OH functionalities and hydrophobic cavities in a molecule by the trimerization of β-CD.

1. Introduction

Cyclodextrins are able to form host–guest complexes with hydrophobic molecules because of the unique nature imparted by their structure, therefore, these molecules have found number of applications in various fields (Nasir et al., 2012) like drug delivery and pharmaceutical industry due to their complexation ability and other versatile characteristics. One of the most common pharmaceutical applications of cyclodextrin is to enhance the solubility, safety, stability and bioavailability of drug molecules (Rasheed et al., 2008). β-CD, one of the cyclodextrins, is a cyclic oligosaccharide consisting of 7-D (+)-glucopyranose units, with 7-primary and 14-secondary alcoholic —OH functional groups and can accommodate various guest molecules into its truncated cone-shaped hydrophobic cavity (Szejtli, 1998). Recently many works have been done based on β-CD star copolymers by using different techniques like ATRP (Gou et al., 2010; Storsberg et al., 2000) and RAFT (Kollisch et al., 2006). In those techniques, the alcoholic —OH functionalities are the active parts. There are few papers, in which dimerization of β-CD has been achieved through different linkages like sulfur linkage (Tang et al., 2005), terephthalic acid bridge (Ohga et al., 2005), ethylene diamine link (Tang et al., 2006), etc. and thus they have improved the solubility of β-CD.

In this paper, we have reported the synthesis of β-CD trimer by the utilization of click reaction (Huan et al., 2012; Nielsen et al., 2010). We have clicked triprop-2-ynyl benzene-1,3,5-tricarboxylate (**A**) with N_3–β-CD to synthesize β-CD trimer, having 18-primary, 21-secondary alcoholic —OH functional groups and 3-truncated cone-shaped hydrophobic cavities in one molecule to obtain better solubility in water.

2. Experimental

2.1. Materials

1,3,5-Benzenetricarbonyltrichloride (98%, Aldrich), propargyl alcohol (Avra, Hyderabad), p-toluenesulfonyl chloride (TsCl) (Spectrochem, Mumbai), sodium azide (NaN_3) (99.5%, SDFCL, Mubai), N,N,N′,N″,N″-pentamethyldiethylenetriamine (PMDETA) (99%, Aldich), tetrahydrofuran (THF) (≥99%, MERCK, Mumbai), dichloromethane (DCM) (≥99%, MERCK), sodium hydroxide (NaOH) (≥97%, MERCK, Mumbai) hydrogen chloride (HCl) (35–38%, MERCK, Mumbai), acetone (SDFCL, Mumbai) and N,N-dimethylformamide (DMF) (99.5%, SDFCL, Mumbai) were used as received. β-Cyclodextrin hydrate (β-CD) (Aldrich) and copper(I) bromide (CuBr) (98% HIMEDIA, Mumbai) were purified and the used.

2.2. Synthesis of triprop-2-ynyl benzene-1,3,5-tricarboxylate (*A*)

Propargyl alcohol (3.2 mL, 55 mmol) and triethylamine (697 μL, 5 mmol) were dispersed in 20 mL of THF in a 100 mL round bottom flask. The mixture was cooled to 0 °C in an ice-water bath. 1,3,5-Benzenetricarbonyl trichloride (982 μL, 5.5 mmol) was dissolved in 15 mL of THF and was introduced into the reaction mixture slowly over a period of 30 min. Further the mixture was stirred at 0 °C for

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1 h and then at 40 °C for 18 h. White precipitate obtained was then filtered out and filtrate was collected. The solvent was evaporated from the filtrate, under vacuum. The product obtained was redissolved in dichloromethane and then washed with 10% HCl, aqueous $NaHCO_3$ and finally twice with distilled water. Dichloromethane was subsequently removed by rotary evaporation and the crude product was purified by column chromatography (Chen et al., 2009). Yield 1.37 g, 75%.

2.3. Synthesis of mono-6-deoxy-6-(p-tolylsulfonyl)-β-cyclodextrin (TsO–β-CD) (**B**)

β-Cyclodextrin hydrate (12.5 g, 11 mmol) was dissolved in a solution which was prepared by dissolving 6.25 g of sodium hydroxide in 375 mL of water in 1 L round bottom flask. The mixture was cooled to 0–5 °C and stirred at same temperature in an ice-water bath while p-toluenesulfonyl chloride (5 g, 26.25 mmol) was being added in small portions. The reaction mixture was stirred vigorously for 2 h at 0–5 °C and then p-toluenesulfonyl chloride (7.5 g, 39.25 mmol) was added in small portions and the mixture was stirred at 0–5 °C temperature for 3 h further. The reaction mixture was filtered to separate unreacted tosyl chloride. Filtrate was cooled at 0–5 °C while 10% aqueous hydrochloric acid (87.5 mL) was being added. Resulting solution was stored for 8 h in a refrigerator at 0 °C, and then filtered. The product was dried to constant weight in a vacuum oven to yield a white solid of TsO–β-CD. Further the white solid was recrystallized three times by dissolving it in 40 mL of boiling water and then cooling to room temperature (Brady et al., 2000, 2004; Lovrinovic & Niemeyer, 2007). Yield 3.97 g, 28%.

2.4. Synthesis of mono-6-deoxy-6-azido-β-cyclodextrin (N_3–β-CD) (**C**)

A mixture of mono-6-deoxy-(p-tolylsulfonyl)-β-cyclodextrin (2.5 g, 2.0 mmol) and sodium azide (1.95 g, 30 mmol) in water (10 mL) was stirred at 80 °C for 3 days. The resulting solution was then concentrated to half of its volume and cooled to room temperature. Acetone (200 mL) was added to precipitate. Obtained white solid was redissolved in water (10 mL) and reprecipitated in acetone (200 mL). This process was repeated one more time. The white solid was dried under vacuum at 60 °C for 2 days (Muderawan et al., 2005). Yield 2.2 g, 96%.

2.5. Click reaction of (N_3–β-CD) with triprop-2-ynyl benzene-1,3,5-tricarboxylate (**D**)

Triprop-2-ynyl benzene-1,3,5-tricarboxylate (0.162 g, 0.5 mmol), N_3–β-CD (1.762 g 1.5 mmol) and PMDETA (0.209 mL, 1 mmol) were dissolved in DMF(20 mL). CuBr (0.143 g, 1 mmol) was introduced under the protection of nitrogen (N_2) gas flow. The reaction mixture was degassed by three freeze–pump–thraw cycles, placed in an oil bath thermostated at 60 °C and stirred for 3 days (Huan et al., 2012). The reaction mixture was exposed to air and evaporated to half of its volume. Then the mixture was precipitated in excess of acetone and the precipitate was washed several times with acetone. The crude product was dissolved in water and passed through a basic alumina column to remove CuBr. Further the mixture was precipitated by ethanol and the product was washed with ether to get a white solid. Yield 1.25 g, 65%.

3. Results and discussion

The above synthesized compounds **A**, **B**, **C** and **D** were confirmed by ^{1}H NMR and FTIR spectroscopies which are given in Figs. 1 and 2 respectively. Trimerization of β-CD was done by the click reaction of triprop-2-ynyl benzene-1,3,5-tricarboxylate (**A**) with N_3–β-CD (**C**). The detailed synthetic route for preparation of β-CD trimer is shown in Scheme 1.

Compound (**A**): In ^{1}H NMR, clear characteristic alkynyl signal is present at 2.55 ppm. The integration ratio of —C≡CH (δ = 2.56 ppm), phenyl protons (δ = 8.93 ppm) and —CH_2—C≡C— (δ = 4.99–4.98 ppm) was calculated to be 1:1:2, indicating the

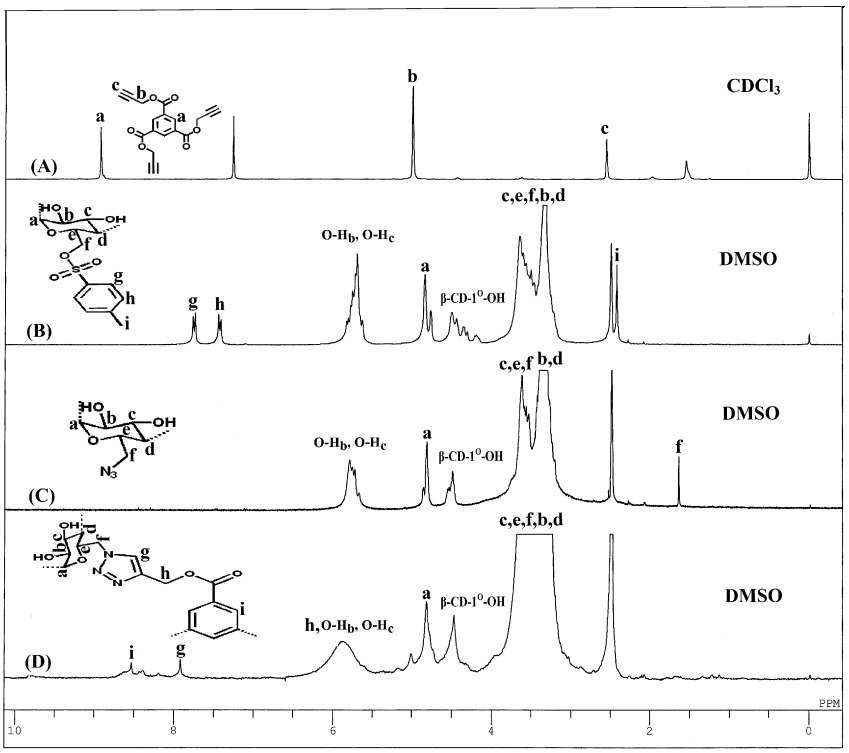


Fig. 1. ^{1}H NMR spectrum of purified compounds (**A**), (**B**), (**C**) and (**D**) (from top to bottom). Spectra were recorded at room temperature in $CDCl_3$ and DMSO as shown above.

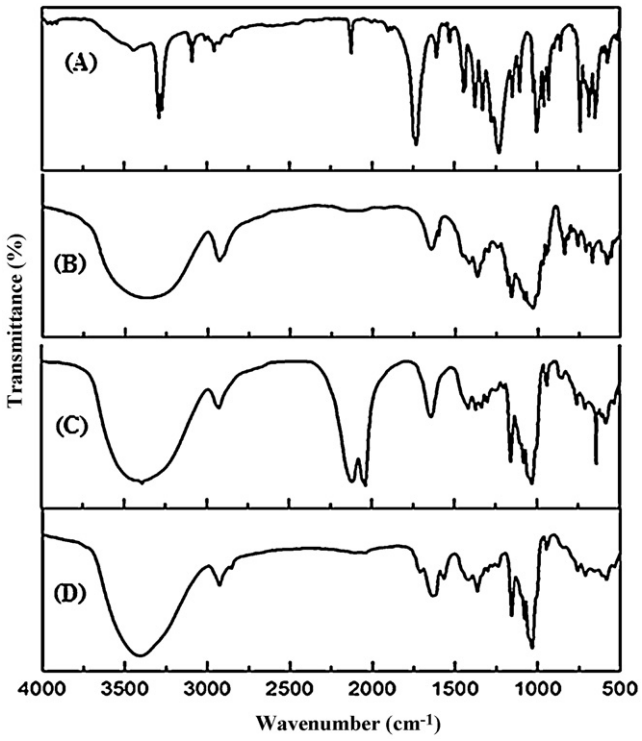
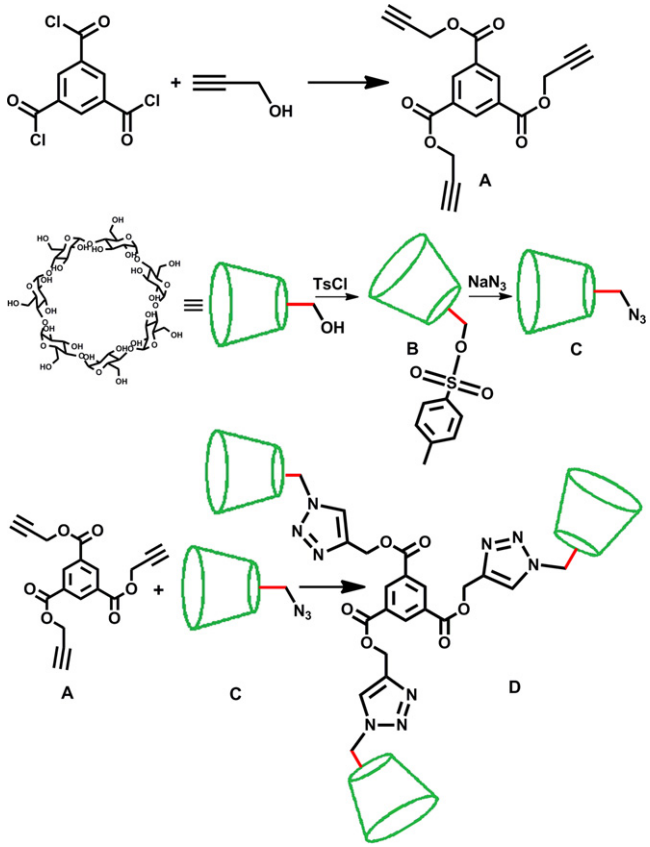


Fig. 2. FTIR spectrum of purified compounds (**A**), (**B**), (**C**) and (**D**). Spectra were recorded at room temperature in KBr pellet.



Scheme 1. Synthetic route for β-CD trimerization.

formation of the desired product (**A**). FTIR has the characteristics bands of≡C—H stretching at 3288 cm^{-1}, aromatic C—H stretching at 3008 cm^{-1}, —C≡C— stretching at 2124 cm^{-1}, C=O stretching at1732 cm^{-1}, aromatic C=C stretching at 1444 cm^{-1} and C—O stretching at 1230 cm^{-1}.

Compound (**B**): In ^1H NMR, characteristic peaks of toluenesulfonyl group appeared at $\delta = 7.76$ ppm (d), $\delta = 7.44$ ppm (d) and $\delta = 2.42$ ppm (s). The integration ratio of aromatic protons, —CH_3 protons of toluenesulfonyl group and β-CD primary —OH protons was found to be 2:2:3:6 which confirmed that only one β-CD primary —OH group was involved in reaction with TsCl and the remaining 6 —OH groups remained as such. In FTIR, along with β-CD signals, toluenesulfonyl group characteristic bands were present as aromatic C=C stretching at 1599 cm^{-1}, S=O stretching at 1366 cm^{-1} and S—O—Ar stretching at 836 cm^{-1}.

Compound (**C**): In ^1H NMR peaks of toluenesulfonyl group had disappeared, two —CH_2—N_3 protons signal was shifted to $\delta = 1.64$ ppm (s) and remaining —CH_2 protons of β-CD were present at $\delta = 3.62$–3.53 (m) along with all other proton signals of β-CD at their respective positions, which confirmed the formation of compound (**C**). Further it was confirmed by IR stretching frequency of —N_3 at 2120 cm^{-1} and the absence of toluenesulfonyl group signals.

Compound (**D**): In ^1H NMR, signals of aromatic protons at $\delta = 8.53$ ppm (s), =C—H proton of triazole ring at $\delta = 7.92$ ppm (s) and =C—CH_2—β-CD proton signals at $\delta = 5.98$ ppm along with other β-CD proton peaks were present and there was no signal of(C—H at $\delta = 2.56$ ppm, which confirms all 3 alkyne groups were involved in click reaction and formed triazole rings. Thus ^1H NMR study confirms the formation of β-CD trimer. In FTIR, signals for aromatic C=C stretching were present at 1568 cm^{-1}, N=N stretching of triazole ring at 2046 cm^{-1}, C=O stretching at 1709 cm^{-1}, H_2C—O—C— stretching at 1156 cm^{-1} and —N_3 characteristic peak disappeared. This confirms the formation of β-CD trimer.

It was observed that, β-CD gets soluble in water at higher temperature (40–70 °C) where as β-CD trimer is readily soluble in water, even at 1 °C. Solubility of β-CD in water is 18.5 mg/mL where as solubility of β-CD trimer is 580 mg/mL at room temperature. Thus trimerization of β-CD helped to increase the solubility.

4. Conclusions

Trimerization of β-CD was done successfully through click reaction. Further β-CD trimer was characterized and showed better solubility in water, even at room temperature. As β-CD trimer is having 18-primary and 42-secondary alcoholic —OH functional groups and 3-cone-shaped hydrophobic cavities it can show much better applications, than β-CD, in various fields.

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