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# SYNTHESIS OF FUNCTIONALIZED β-CYCLODEXTRINS BY "CLICK CHEMISTRY"

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**Abstract** – Two new β-cyclodextrins (β-CDs) modified with chromophore were synthesized in high yields through Huisgen 1,3-dipolar cycloaddition. The amount of Cu catalyst was demonstrated to be a key factor that determines the yield of the 1,3-dipolar cycloaddition when applied to CD derivatization. While a catalytic amount of Cu-catalyst is commonly required in conventional click chemistry, more than a half equivalent of Cu catalyst was desirable for obtaining the modified CDs in satisfactory yields.

"Click chemistry" is a chemical philosophy introduced by Sharpless in 2001, which allows reactive molecular building blocks to "click" together selectively and covalently.[1] Among the several reaction types that are regarded as "click chemistry," the Cu-catalyzed 1,3-dipolar cycloaddition of azide to alkyne is one of the most reliable reactions and therefore frequently used in various areas of science and technology, such as organic chemistry,[2] molecular biology,[3] materials science,[4] and biochemistry.[5] Recently, this click reaction was employed as a convenient, efficient tool for constructing supramolecular assemblies.[6]

Cyclodextrins (CDs), a series of cyclic oligosaccharides, have been widely used as supramolecular hosts for molecular recognition,[7] nano-sized reaction containers,[8] and building blocks of supramolecular assemblies.[9] Especially interesting is the modified cyclodextrins with an appropriate light-absorbing (chromophoric) group(s).[10] However, in order to utilize their versatile functions in practical applications,

chemical modifications of CDs are indispensable. Although a large number of modified CDs have already been reported, efficient and selective derivatization of CDs still remains a difficult challenge for chemists. In this context, click chemistry is expected to provide a promising route to the efficient modification of CDs, in view of the ready access to 6-azido-6-deoxy-β-CD[11] and the high reactivity and regioselectivity of the azide-alkyne 1,3-dipolar cycloaddition. By using $(Ph_3P)_3$•CuBr and $(EtO)_3P$•CuI as catalysts soluble in organic solvent, a click reaction has been applied to CD peracetates,[12] which are however insoluble in water and has only limited application in supramolecular chemistry. No efforts other than our recent work[13] have been made to modify native CDs through a click chemical approach.

In this paper, we wish to show that click chemistry provides a convenient direct access to the preparation of β-CD derivatives with aromatic chromophores, which are applicable to supramolecular sensing and photosensitization. The factors affecting the Cu-catalyzed 1,3-dipolar cycloaddition of aryl alkynes to 6-azido-6-deoxy-β-CD were elucidated in detail and optimized.

6-Azido-6-deoxy-β-CD (Figure 1) was synthesized by reacting 6-TsO-β-CD with $NaN_3$ in hot water, and then purified by recrystallization from water. In the first attempt, commercially available phenylacetylene was chosen as starting material for studying the 1,3-dipolar cycloaddition reaction with 6-azido-6-deoxy-β-CD. The 1,3-dipolar cycloaddition was conducted in a mixed solvent of $H_2O$ and THF (1:1 v/v) in the presence of Cu(I) catalyst prepared *in situ* from $CuSO_4$ and sodium ascorbate. However, the reaction of phenylacetylene with 6-azido-6-deoxy-β-CD in the presence of 10 to 20 molar percent of $CuSO_4$ at room temperature did not give an appreciable amount of aimed adduct **1** after the typical work-up procedures reported by Sharpless et al.[1b] Further efforts to promote the reaction by elongating the reaction time up to several days, raising the temperature up to 60 °C, increasing the amount of $CuSO_4$, and replacing the solvent with DMF, DMSO, ethanol, methanol, and acetone proved unsuccessful. The very rigid rod-like structure of phenylacetylene and the bulky size of CD may be jointly responsible for the failure.

We consequently attempted to synthesize compound **2** by reacting propargyl bromide with 6-azido-6-deoxy-β-CD, because **2** is frequently used as a versatile intermediate that can be readily converted to a variety of useful functionalities through nucleophilic substitution. Indeed, the addition reaction did occur, when an equimolar amount of $CuSO_4$ was used. After 2 days of reaction, no trace of 6-azido-6-deoxy-β-CD was detected in the reaction mixture by electrospray ionization (ESI) mass spectral examinations. However, the ESI-MS also gave no signal that is assignable to the aimed adduct **2**. Instead, an intense molecular ion peak was observed at *m/z* 1338, which is tentatively assigned to the secondary product **3** [$+Na^+$] derived from the coupling of initially formed **2** with another propargyl bromide.

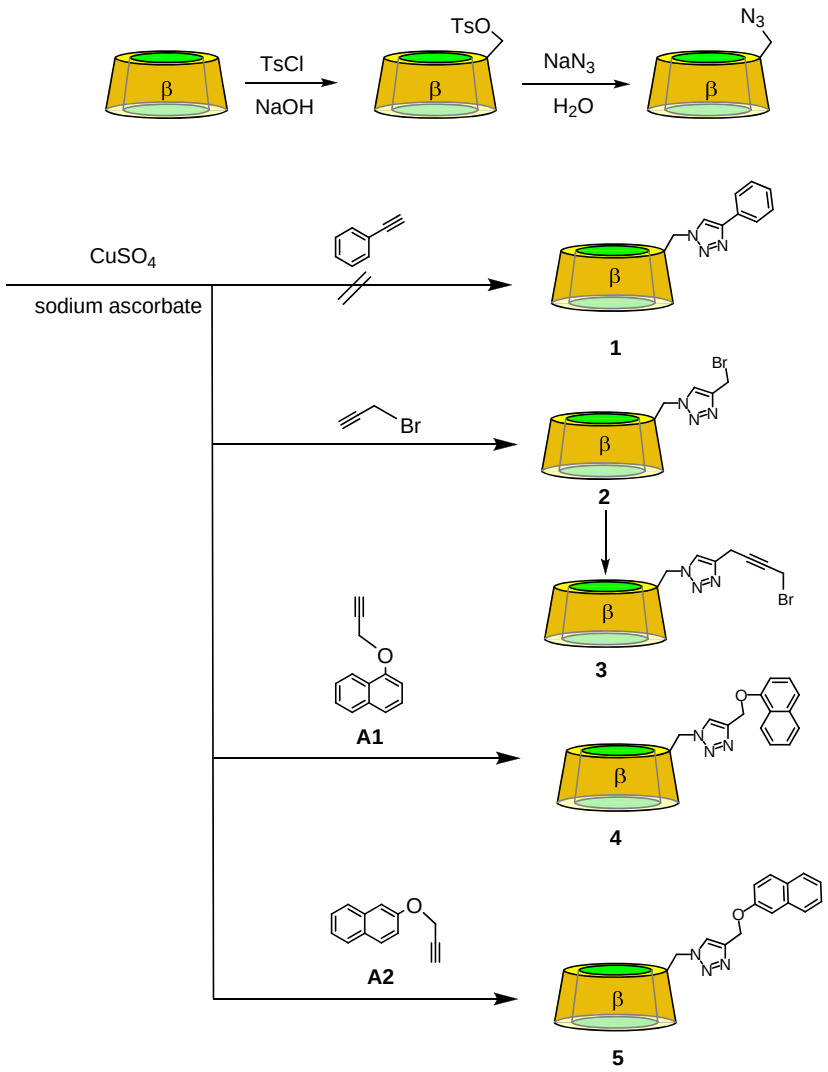


**Figure 1**. Syntheses of β-cyclodextrin derivatives **1**-**5**

Based on the above results, we decided to use 1- and 2-naphthyl propargyl ethers **A1** and **A2**[14] as chromophoric alkynes that are feasible to cycloadd to 6-azido-6-deoxy-β-CD. **A1** and **A2** were prepared by the reaction of propargyl bromide with 1- and 2-naphthol in acetone in the presence of $K_2CO_3$. The 1,3-dipolar cycloaddition 6-azido-6-deoxy-β-CD was examined under a variety of conditions. The consumption of starting material was monitored by ESI-MS, and the adduct yield was determined after separation by column chromatography. As shown in Table 1, the amount of $CuSO_4$ catalyst is crucial for the click reaction, and there appears to be a critical amount to start the reaction smoothly. Thus, the use of 0.1-0.4 equivalent of $CuSO_4$ resulted in no conversion even after 2 days at 60 °C. However, by using 0.5 equivalent of $CuSO_4$, the cycloaddition proceeded to give adduct **4** in 20% yield.[15] Interestingly, a slight increase in the amount of $CuSO_4$ to 0.55 equivalent led to a dramatic leap of the yield to 72%, and the yield was further improved up to 84% by using 0.8 equivalent of $CuSO_4$. In comparison to the conventional click reaction that normally completes within 12-24 h at room temperature with a catalytic

amount of Cu(I), the present cases need much longer period of time and higher temperature to obtain the adduct in satisfied yields, indicating that the activation energy is higher in the click reaction of azido-CD. It is noteworthy to mention that the 1,3-dipolar addition has been demonstrated to proceed smoothly with compounds bearing a single glucose unit in the presence of catalytic amount of Cu(I) catalyst.[16] Thus, we speculate the reason of lower reactivity in the present system is mainly due to the hydroxyl groups of CD, particularly those on the secondary rim that weakly coordinate to Cu,[17] as well as the steric bulkiness of the cyclodextrins[18] that jointly operates in hindering the access of Cu(I) to the azido group.

**Table 1.** Syntheses of β-CD derivatives *via* click chemistry

| alkyne | $CuSO_4$/eq[b] | temperature/°C | reaction time/h | yield[c]/% |
|---|---|---|---|---|
| phenylacetylene | 0.2 | 60 | 48 | *d* |
| | 1.0 | 60 | 48 | *d* |
| propargyl bromide | 0.2 | 60 | 48 | *d* |
| | 1.0 | 60 | 48 | *d,e* |
| **A1** | 0.1 | 60 | 48 | *d* |
| | 0.3 | 60 | 48 | *d* |
| | 0.4 | 60 | 48 | *d* |
| | 0.5 | 60 | 48 | 20 |
| | 0.55 | 60 | 48 | 72 |
| | 0.55 | r.t. | 48 | 41 |
| | 0.8 | 60 | 48 | 84 |
| | 1.0 | 60 | 24 | 65 |
| | 1.5 | 60 | 24 | 73 |
| **A2** | 0.55 | 60 | 48 | 73 |

[a] The 1,3-dipolar cycloaddition were carried out by reacting 6-azido-6-deoxy-β-CD with corresponding organic alkynes in a 1:1 mixture of $H_2O$ and THF. [b] Molar ratio of $CuSO_4$ to 6-azido-6-deoxy-β-CD. [c] Isolated yield; average of two independent runs. [d] No aimed adduct was obtained. [e] Secondary product, presumably **3**, was detected by ESI-MS.

In conclusion, we developed a new efficient method for introducing a functional/chromophoric group to the primary rim of β-CD through Cu-catalyzed 1,3-dipolar cycloaddition of aromatic alkynes to 6-azido-6-deoxy-β-CD. Although a much larger amount of Cu catalyst, longer reaction period, and higher temperature are needed as compared with the conventional click reaction, the β-CD adducts were obtained in satisfactory yields via the crick chemistry of CDs.

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14 To an acetone solution (20 mL) of 1- or 2-naphthol (1.0 g, 7 mmol) was added $K_2CO_3$ (1.5 g) with stirring at rt. Propargyl bromide solution (1.5 g, 80 wt. % in toluene) was then added dropwise to the mixture to yield a brown solution. After stirring for 12 h at rt, the deposit formed was removed by filtration and the filtrate was evaporated in *vacuo*. The residue was subjected to silica gel chromatography to give white solid. **A1**: yield: 91%, $^1$H NMR (300MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.81 (d, 1H), 7.39-7.54 (m, 4H), 6.97 (d, 1H), 4.91 (t, 2H), 2.57 (s, 1H). **A2**: yield: 90%, $^1$H NMR (300MHz, $CDCl_3$): δ 7.75-7.80 (m, 3H), 7.43 (t, 1H), 7.36 (t, 1H), 4.82 (d, 1H), 4.91 (t, 2H), 2.57 (d, 1H).

15 6-Deoxy-6-azido-β-CD was prepared according to the literature procedure.[11] An aqueous solution (20 mL) of 6-deoxyl-6-azido-β-CD (2.0 g, 1.4 mmol) was added to a THF solution (20 mL) of **A1** or **A2**

(380 mg, 2.1 mmol) with stirring. To the resulting mixture was added an aqueous solution (15 mL) containing $CuSO_4 \cdot 5H_2O$ (360 mg) and sodium ascorbate (850 mg). After stirring for 48 h at 60 $^oC$, the reaction mixture was cooled down and the solvent was removed under a reduce pressure. The residue was dissolved in DMF (20 mL) and filtered. The filtrate was added dropwise to 300 mL of acetone to obtain a precipitate, which was collected and recrystallized twice from a 4:1 mixture of water and acetone (v/v) to give the final product as a light yellow solid.

**4**: $^1$H NMR (300MHz, DMSO-$d_6$): δ 8.29 (s, 1H), 8.11 (d, 1H), 7.87 (d, 1H), 7.51 (m, 4H), 7.19 (d, 1H), 5.93-5.66 (m, 14H), 5.30 (s, 2H), 5.06-4.80 (m, 7H), 4.66-4.33 (m, 6H), 3.67-3.58 (m, 14H), 3.47-2.89 (m, 28H); ESI-MS: 1364.63 $[M+Na]^+$.

**5**: $^1$H NMR (300MHz, DMSO-$d_6$): δ 8.24 (s, 1H), 7.85 (bs, 3H), 7.51 (bs, 2H), 7.37 (s, 1H), 7.20 (s, 1H), 5.92-5.74 (m, 14H), 5.22-4.36 (m, 15 H), 4.02-3.63 (m, 14H), 3.38-2.73 (m, 28H); ESI-MS: 1365.09 $[M+Na]^+$.

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