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Effective syntheses of per-2,3-di- and per-3-*O*-chloroacetyl-β-cyclodextrins: A new kind of ATRP initiators for star polymers

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ABSTRACT

Selective chloroacetylations at per-2,3- and per-3-positions of β-cyclodextrin have been achieved via protection–deprotection methods. The reaction condition of pH >4 controlled by appropriate proton scavenger is essential for obtaining designed chloroacetylation degree under effective protection, as well as for high yield with less side-products. The β-cyclodextrin derivatives with 14 or 7 chloroacetyl groups are useful initiators for synthesizing star polymers with well-defined structure by atom transfer radical polymerization.

Star polymers are characterized as structures in which a number of arms radiate from a small-molar-mass core. In the past decade, they have received significant attention due to their notable properties and multiple applications. For example, star polymers can provide most of the properties of high molecular weight materials without the solution viscosity penalty of linear materials of similar molecular weight.[1] The star-like polymers can basically be synthesized using two different strategies: 'arm-first' and 'core-first'. The 'arm-first' approach consists of reacting preformed living linear polymers (arm) with a multifunctional quencher molecule that forms the core of the star. In contrast, the alternative 'core-first' method involves using a multifunctional initiator to initiate polymerization, which has emerged successfully to acquire well-defined stars with a precise number of arms. Meanwhile, living polymerization, including atom transfer radical polymerization (ATRP), has been demonstrated to be an efficient technique for synthesizing star polymers with well-defined structure, arm chain length in particular.[2,3]

The number of arms could significantly affect the morphology, solution behaviour, viscosity, precise control over the molecular weight and surface functionality of star polymers. Thus a multifunctional core with well-defined initiation sites is essential to prepare star polymers with a precise number of arms by the 'core-first' strategy. In order to utilize ATRP to synthesize star polymer, it is also necessary to introduce halogens into the multifunctional core. Cyclodextrins (CDs) are a series of cyclic oligosaccharides composed of six, seven or eight glucose units (α-, β- or γ-CD, respectively) linked by α-1,4-linkages. Due to their specific steric structure of truncated conical shape and 18–24 substitutable hydroxyl groups on their outside surface, CDs have often been modified into ATRP initiators to prepare star polymers.[3–6]

Chloroacetylated β-CD modified by chloroacetyl chloride (CAC) was first reported by Carpov et al.[7] The alkyl chlorine with carbonyl group on its α-carbon could be the potential ATRP initiation site according to the ATRP mechanism.[8] In Carpov's report, completely chloroacetylated β-CD (per-2,3,6-tri-*O*-chloroacetyl-β-CD, 21Cl-β-CD) was successfully synthesized in basic aprotic dipolar solvents, especially in *N*,*N*-dimethylacetamide (DMA), which acted both as CD solvating agent and as HCl acceptor.[7] However, the number and position of substituted chloroacetyl groups could not be further precisely controlled while substitution degrees were blow 21. In this work, based on the different reaction activities of hydroxyl groups at the 6-, 3- and 2-positions of β-CD providing the possibility for selective modifications,[9] we will report an efficient synthetic-route of preparing chloroacetylated β-CD with well-designed 14 or 7 ATRP initiation sites, which will be useful initiators for synthesizing and investigating the 'arm number-property' relationship of various functional star polymers. Although the chloroacetyl groups at 6-, 3- and 2-positions of β-CD may have different reactivities for ATRP, it is also applicable to synthesize star polymers with designed structure.[4,6]

The per-2,3-di-*O*-chloroacetyl-β-CD (14Cl-β-CD, compound **3**) and per-3-*O*-chloroacetyl-β-CD (7Cl-β-CD, compound **6**) are obtained in a three-step synthesis strategy by using *tert*-butyldi-

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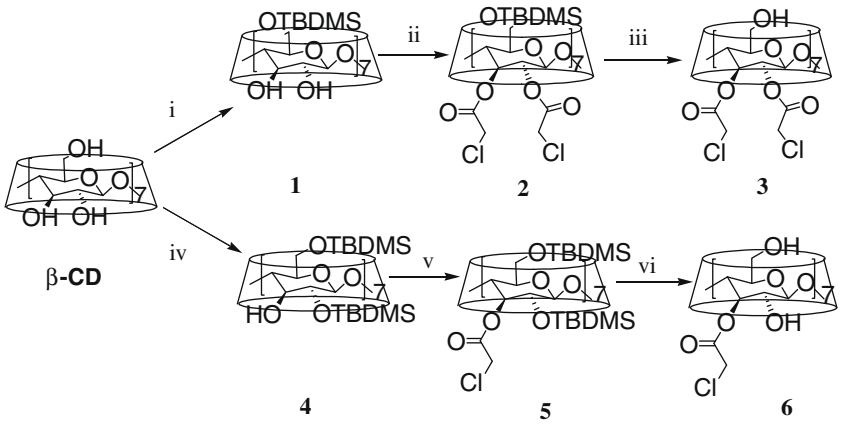

Scheme 1. Syntheses of per-2,3-di-*O*-chloroacetyl-β-cyclodextrin (14Cl-β-CD) and per-3-*O*-chloroacetyl-β-cyclodextrin (7Cl-β-CD). Reagents: (i) TBDMSCl, pyridine; (ii) CAC, imidazole, DMAP, DMA; (iii) $BF_3{\cdot}Et_2O$, CH_2Cl_2; (iv) TBDMSCl, DMAP, pyridine/DMF; (v) CAC, imidazole, DMAP, DMA; (vi) $BF_3{\cdot}Et_2O$, CH_2Cl_2.

methylsilyl chloride (TBDMSCl) as the regioselective protection reagent (Scheme 1).

The precursor **1** with protected groups on the primary face of β-CD is synthesized by Zhang's method,[10] which has modified the separation method of Fugedi[11] with a yield higher than 90%. In the next step of preparing the per-6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-chloroacetyl-β-CD (compound **2**), vacuum-dried compound **1** (1.94 g, 1 mmol) was dissolved in 30 mL anhydrous DMA and was cooled to 0 °C. Imidazole (28 mmol, 2 equiv per OH function) and dimethylaminopyridine (DMAP, 20 mg) were added to the solution under argon. CAC (24 mmol, 1.7 equiv per OH) dissolved in anhydrous DMA (15 mL) was then added dropwise to the mixture solution with magnetic stirring. The reaction was carried out at 0 °C for 2 h and then at 50 °C for 6 h (pH 8). After rotary evaporating of DMA from the slight yellow solution, the residue was redissolved in 40 mL methylene chloride and was washed successively with saturated $NaHCO_3$ aqueous solution (2×100 mL) and water (2×100 mL). The organic layer obtained was concentrated in vacuum and then recrystallized from $CHCl_3$/hexane (1:9, v/v) to obtain a white compound **2** (2.42 g, yield 80.2%). Its ^{1}H NMR ($CDCl_3$) peaks of the $Si(CH_3)_2$ (δ 0.05 ppm, 6H) and $C(CH_3)_3$ (δ 0.88 ppm, 9H) resonances are intact, which demonstrates that no deprotection has taken place at this step. The above-mentioned chloroacetylation reaction is accompanied by HCl release, which might result in the deprotection of TBDMS groups at high degree of temperature. We found that two main factors could affect the deprotection while chloroacetylating by CAC: pH and temperature of the reaction system (Table 1). Triethylamine (TEA), pyridine and imidazole were chosen as HCl acceptors at first. However, although TEA and pyridine could control the pH of the system, the severe side reactions between CAC and them resulted in viscous brown products. This phenomenon was also mentioned by Leduc and Chabrier[12] The side reaction almost exhausted the chloroacetylation reagent CAC, thus the substitution degree of the final pale product obtained by chromatographic separation (eluant trichloromethane/methanol, 7:1) was much lower than the designed value (14). Imidazole, which is a weaker nucleophilic reagent, could both avoid the side reaction and perform well as proton scavenger to control the pH.

Table 1
Effect of pH and temperature on the formation of CD derivative **2**

pH	Temperature	Remained protection groups (TBDMS) [a]	Chloroacetylation degree[b]
2	0	0	5.0
2	rt	0	16.0
2	50	1	16.5
4	0	7	4.9
4	rt	7	8.6
4	50	7	13.9
7	0	7	5.1
7	rt	7	8.9
7	50	7	13.8

[a] The initial number of TBDMS group is 7.
[b] Calculated as $DS = \frac{1935\times Cl\%}{35.5\times 100 - 76.5\times Cl\%}$ (the designed chloroacetylation degree for derivative **2** is 14).

Finally, the compound **2** was deprotected by treatment with $BF_3{\cdot}Et_2O$ in dry CH_2Cl_2[13] to yield the compound **3** (1.49 g, overall yield 60.3%): FTIR (KBr): 3393 cm^{-1} (ν_{O-H}), 2930 cm^{-1} (ν_{C-H}), 1751 cm^{-1} ($\nu_{C=O}$), 1154 (ν_{C-O-C}); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.35 (7H, H-3); 5.22 (7H, H-2); 4.85 (7H, H-1); 4.18 (28H, $-CH_2Cl$); 3.53–3.68 (28H, H-4, 5, 6, 6′). Anal. Calcd for $C_{70}H_{84}O_{49}Cl_{14}$: C, 38.12; H, 3.84; Cl, 22.5. Found: C, 38.80; H, 3.93; Cl, 22.4 (Schoniger's method[14]).

The per-6,2-di-*O*-*tert*-butyldimethylsilyl-β-CD (compound **4**) was synthesized according to the procedure described by Ashton et al.,[15] in which DMAP and pyridine/DMF were used as the catalyst and co-solvent, respectively. In the next step of chloroacetylation, due to the steric hindrance of the 3-position of the per-6,2-protected-β-CD, stronger reaction conditions were applied to realize the designed modification: (1) The molar ratio of CAC was increased to 2.0 equiv per OH; (2) the reaction was carried out at 60 °C for 72 h (pH 8). The resonances (^{1}H NMR) of the *tert*-butyldimethylsilyl groups on compound **5** exhibit no perturbation, which demonstrates no deprotection has taken place under above-mentioned stronger condition. After a deprotection treatment with $BF_3{\cdot}Et_2O$, the compound **6** was obtained (overall yield 28.6%) as: ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 5.23 (7H, H-3); 5.03 (7H, H-1); 4.45 (14H, $-CH_2Cl$); 3.50–4.10 (35H, H-2, 4, 5, 6, 6′). Anal. Calcd for $C_{56}H_{77}O_{42}Cl_7$: C, 40.24; H, 4.61; Cl, 14.88. Found: C, 40.47; H, 4.68; Cl, 14.14.

Current works are underway to prepare and investigate star polymers made from above-mentioned ATRP initiators. Preliminary experiments show that polymers growing from the same CD-core but with different 7, 14 and 21 arms are ideal models to study the effect of arm number on the properties and applications of star polymers, which will be discussed in several forthcoming publications.

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