European Polymer Journal 55 (2014) 9–16

Contents lists available at ScienceDirect

European Polymer Journal

journal homepage: www.elsevier.com/locate/europolj

Macromolecular Nanotechnology

# Facile Williamson etherification of hyperbranched polyglycerol and subtle core-dependent supramolecular guest selection of the resulting molecular nanocapsule

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ARTICLE INFO

*Article history:*
Received 12 January 2014
Received in revised form 8 March 2014
Accepted 11 March 2014
Available online 19 March 2014

*Keywords:*
Williamson etherification
Supramolecular chemistry
O-alkylation
Host–guest
Polyglycerol
Dimethyl sulfoxide

ABSTRACT

O-alkylation of highly polar polyglycerol with alkyl bromides, promoted just by sodium hydroxide in dimethyl sulfoxide (DMSO), is reported. Zimmermann–Dathe type Williamson etherification, which can be carried out by a mild base in DMSO, is very useful in preparing ethers. However, it is always limited to alkyl chlorides or methyl halides due to the elimination reaction. In this contribution, this reaction is promoted to alkyl bromides and iodides just by decreasing the reaction temperature and then it is further applied in preparing a series of O-alkylated hyperbranched polyglycerol (PG). It is found per-alkylation of PG is possible regardless of its dense hydroxyl groups. In addition, the modified method shows selectivity over the halogen species. The resulting core–shell amphiphilic macromolecules (CAMs) can be used for dye encapsulation and they show core-dependent selection over the dye species. For example, the ether-based CAM **1b** (PG–O–$(C16)_{0.61}$, 61% of OH groups are O-alkylated by cetyls) is with limited difference from the ester-based CAM **2a** (PG–COO–$(C16)_{0.60}$), but they show very different guest selection. Controlled release is also available by core design of the CAMs.



## 1. Introduction

Williamson etherification [1] is a well-known organic reaction regarding the O-alkylation of a small alcohol with a halide, but is less successful when applied to polyol macromolecules. A classic Williamson etherification reaction is conducted under rigorous conditions (typically NaH, alkyl halide, excess ROH), and is typically featured by by-reactions and a moderate yield. In 1960, Cram et al. [2] showed that if a polar aprotic solvent, such as dimethyl sulfoxide (DMSO), was used in place of the excess ROH (acts as solvent besides reactant), both the reaction rate and yields could be significantly enhanced. However, a strongly reductive and hazardous base, such as NaH, was needed. In 1965, Zimmermann and Dathe [3] further optimized the Cram system by replacing the rigorous base with a much milder one, such as sodium hydroxide (NaOH). And in their system, the rigorously anhydrous condition was no longer necessary too. However, Zimmermann–Dathe reaction was limited to chlorides, such as alkyl chlorides and active allyl chlorides. When bromides were used as reactant, the elimination reaction would dominantly occur and the aimed substituted product (ether) was hardly available [4].

At the same time, the etherification of biomass polyol carbohydrates, such as cellulose, has long been a hot topic and much effort has been devoted in [5–12], and the

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http://dx.doi.org/10.1016/j.eurpolymj.2014.03.012
0014-3057/

structural analysis of polyol molecules is possible only through the peralkylated derivative. However, until 1984, Ciucanu and Kerek [13] successfully developed a satisfactory way for permethylation of polyol molecules, in which a route similar to Zimmermann–Dathe type reaction was adopted using methyl iodide because no elimination can occur for a methyl halide. After nearly 50 years development, Zimmermann–Dathe type etherification reaction has evoked limited interest even with so much convenience. Compared with the extensively studied phase transfer catalysis (PTC) method to prepare polyethers, Zimmermann–Dathe reaction is limited to chlorides and the reaction has to be conducted at a rather high temperature. However, the catalyst in PTC may meet other problems such as cost, recycle and separation [14]. In this regards, if the Zimmermann–Dathe reaction can be extended to more alkyl halide species and the reaction can take place under milder conditions, it will be attractive. Up to now, this is realizable only through specially combined media of $SO_2$/amine/DMSO [15].

Hyperbranched polyglycerol (PG) [16] has become a representative hyperbranched polymer with high density of functional groups of hydroxyls. It can be used as a scaffold of a variety of amphiphilic polymers [17–27]. O-alkylated derivatives of PG are stable against acidic or basic conditions and are good candidates for these applications. However, PG is poorly soluble in conventional apolar solvents and the classic Williamson reaction is unsatisfactory for O-alkylation of PG unless through PTC system [27,28].

Here, with our continuous effort on supramolecular selection through core engineering of a nanocapsule [29,30], we would like to know if O-alkylation of PG can be conducted in a controllable way so that the multifunctional PG core of a nanocapsule is further designable. In detail, we want to clarify the following issues: (1) Can Zimmermann–Dathe type etherification reaction be conducted under a milder condition (?). (2) If (1) is possible, can the etherification be proceeded in a controllable way so that full or part of O-alkylation of hydroxyls is possible. (3) Can the reaction be selective in terms of the halides so that more derivatives based on PG are possible (?). (4) Can the selectivity of the supramolecular encapsulation be designable through core engineering of the O-alkylated PG? On the other hand, the guest release from a host nanocapsule can be controlled by core engineering of the host nanocapsule [31]. In this paper, the Zimmermann–Dathe etherification reaction is promoted to prepare amphiphilic O-alkylated PG and the gained core–shell amphiphilic macromolecules (CAMs) are used in the guest encapsulation. The subtle influence of the core structure on guest encapsulation and release is also studied.

## 2. Experimental

### 2.1. Materials

PG was synthesized on literature [18]. $M_n = 2.59 \times 10^4$, $M_w/M_n = 1.77$ (GPC data with water as eluent). All dyes, such as Rose bengal (RB), cationic pure blue GB (GB), congo red (CR), bromophenol blue (BB), and cetyl bromide, ethyl iodide, 1-bromo-4-chloro-butane were purchased from SCRC (China).

### 2.2. Synthesis

The synthetic route of O-alkylation of PG was shown in Scheme 1. General procedure: To a solution of PG (1.50 g, 20.2 mmol of OH groups) in DMSO (5.0 mL), halides (2–4 equiv. of OH) and NaOH (3.23 g, 4 equiv. of OH) were added and the mixture was stirred at 25–50 °C for certain time. Water (80 mL) and chloroform (80 mL) were added. After vigorous shaking and followed standing, a clear oil phase was formed. The chloroform layer was separated and washed with water. After drying over sodium sulfate, the chloroform solution was dialyzed against fresh chloroform (spectro/por, molecular weight cut off (MWCO): 8000–14,000) for 24 h with the chloroform refreshed every 12 h.

**1a.** To a solution of PG (5.00 g, 67.6 mmol of OH groups) in DMSO (25 mL), cetyl bromide (41.00 g, 134.4 mmol) and NaOH (18.70 g, 467.5 mmol) were added and the mixture was stirred at 50 °C for 3 days. Water (200 mL) and chloroform (300 mL) were added. The work-up was similar to the general procedure. Yield: 30.00 g (61.4%). $^1$H NMR (400 MHz, $CDCl_3$, δ): 0.88 (t, 3H, $CH_3$), 1.26 (s, 26H, $CH_2$), 1.58 (m, 2H, $OCH_2\mathbf{CH_2}$), 3.55 (s, 2H, $OCH_2$), 3.33–3.65 (m, 2.1H, PG). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 14.10 ($CH_3$), 22.69 ($CH_3\mathbf{C}H_2$), 25.75 ($OCH_2CH_2\mathbf{C}H_2$), 29.36 ($CH_3CH_2(\mathbf{C}H_2)_{11}$), 31.93 ($OCH_2CH_2\mathbf{C}H_2$), 70.89 ($OCH_2$); signals due to PG: 63.03, 65.00, 71.66, 72.98. **1b**–**1d** were synthesized with the same workup but different reaction time to get different etherification ratios. **1e** was synthesized following the general procedure but purified by repeated washing with ethanol. Elemental analysis: found (**1a**), C 75.01, H 13.10; (**1b**), C 73.31, H 11.98; (**1c**), C 71.89, H 12.10; (**1d**), C 61.85, H 10.30; (**1e**), C 75.10, H 12.88.

The functional degree of **1a**–**1e** could be derived from $^1$H NMR by the equation: $6I_{0.88}/(3I_{3.3-3.8}-I_{0.88})$, where $I_{0.88}$ and $I_{3.3-3.8}$ represented the signal intensity at 0.88 and that between 3.3 and 3.8 ppm, respectively (similar for the following equations). Or from elemental analysis by the equation: (74C-36)/(192-224C), where C was the mass fraction of carbon.

**1f.** To a solution of PG (0.15 g, 2 mmol of OH groups) in DMSO (5 mL), ethyl iodide (13.00 g, 83.3 mmol) and NaOH (0.31 g, 7.75 mmol) were added and the mixture was stirred at 25 °C for 7 days. The residual work-up was similar to **1a**. Yield: 0.21 g (100%). $^1$H NMR (400 MHz, $CDCl_3$, δ): 1.19 (t, 3H, $CH_3$), 3.33–3.65 (m, 7 H, PG and $CH_2$ of ethyl). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 15.42, 66.71 (signals other than PG). Elemental analysis: found (**1a**), C 58.7, H 9.89. The functional degree could be derived from $^1$H NMR by the equation: $6I_{1.19}/(3I_{3.3-3.8}-I_{1.19})$, or from elemental analysis by the equation: (74C-36)/(24-28C).

**1g.** To a solution of PG (0.69 g, 9.3 mmol of OH groups) in DMSO (8 mL), 1-Br-4-Cl-butane (12.24 g, 72 mmol) and NaOH (1.90 g, 47.5 mmol) were added and the mixture was stirred at 25 °C for 5 days. The residual work-up was similar to **1a**. Yield: 1.43 g (96%). $^1$H NMR (400 MHz, $CDCl_3$, δ): 1.71 (t, 2H, $CH_2C$–O–), 1.86 (t, 2H, $CH_2C$–Cl), 3.30–3.65 (m, 9.15 H, PG, $CH_2O$ and $CH_2Cl$). $^{13}$C NMR (100 MHz,