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Well-defined cyclopropenone-masked dibenzocyclooctyne functionalized polymers from atom transfer radical polymerization

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ABSTRACT

Two functional atom transfer radical polymerization (ATRP) initiators (**I-2** and **I-3**) were developed bearing a cyclopropenone-masked dibenzocyclooctyne group. ATRP was then explored on three main kinds of monomers for radical polymerization including acrylates, styrenics, and methacrylates based on these novel initiators. By a standard ATRP protocol, the polymerization behavior demonstrated the living characteristics for all three cases and the corresponding well-defined cyclopropenone-masked dibenzocyclooctyne end or middle functionalized polymers were produced conveniently. Since UV irradiation of the cyclopropenone-masked dibenzocyclooctynes could quantitatively release the dibenzocyclooctynes widely used in strain promoted azide-alkyne cycloaddition bioorthogonal click reaction, these novel ATRP initiators and the resultant well-defined polymers should play an important role in the preparation of topological polymers and bio-synthetic polymer conjugates and many other related fields.

1. Introduction

Bioorthogonal reactions are unique click reactions which neither interact nor interfere with a biological system [1,2]. The term was firstly coined by Bertozzi and co-workers [3], in which the reactive groups must be inert to biological moieties, must be selectively reactive with each other under biocompatible conditions, and must be nontoxic to cells and organisms for in vivo applications [2]. This endows bioorthogonal reactions with a crucial role played in modern life science. Although several click reactions have demonstrated the bioorthogonal properties including the Staudinger ligation of azides and triarylphosphines [4,5], Diels–Alder reaction of tetrazines with *trans*-cyclooctyne [6,7], and strain promoted azide-alkyne cycloaddition (SPAAC) [8–21], the SPAAC is seriously attracting researchers' attention as one of the most successful bioorthogonal reaction candidates.

The history of SPAAC can be traced back to 1961 when Wittig and Krebs reported that cyclooctyne reacted with phenyl azide like an explosion [8]. However, it was Bertozzi and co-workers who recognized the potential of cyclooctyne for bioconjugation in 2004 [9]. Although the rate of SPAAC reactions is relatively slow between the regular cyclooctyne and azide groups [9,10], it can be significantly enhanced by structural modification of cyclooctyne group, such as by introducing electron-withdrawing fluorine atoms at the propargylic positions [10,11] or fusing with two aryl rings [12–15]. Following significant contributions from Bertozzi [9–11], Boons [12] and others' research groups [14,15], SPAAC between cyclooctyne derivatives and azide has become an ideal bioorthogonal reaction and has been widely used in biology field [12,16–21], especially for preparing bio-synthetic polymer conjugates [22–26] comprised by synthetic polymer segments and biological entities including polynucleotides, polysaccharides, and proteins.

By combining the advantages of both biological and synthetic constituents, research studies on these biohybrid polymers have become one of the hottest topics in recent material and life science. For the formation of bio-synthetic polymer conjugates, one of the most important prerequisites lies in the preparation of well-defined polymers end functionalized with bioorthogonal reaction groups.

Recently, by designing a dibenzocyclooctyne functionalized atom transfer radical polymerization (ATRP) initiator **I-1** (Fig. 1), we successfully prepared well-defined dibenzocyclooctyne end-functionalized polymethacrylates and polystyrenics from a standard ATRP technique [27,28]. The SPAAC click reactivity of dibenzocyclooctyne end group was further demonstrated by successfully reacting with azide functionalized polymers to form block and

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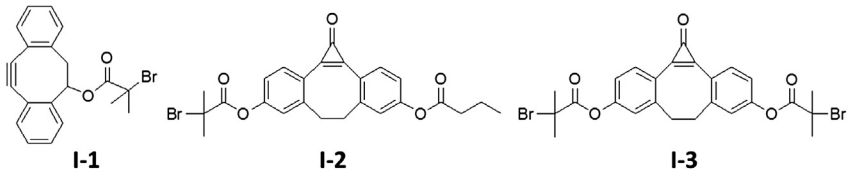


Fig. 1. Dibenzocyclooctyne functionalized ATRP initiator **I-1** and cyclopropenone-masked dibenzocyclooctyne functionalized ATRP initiators **I-2** and **I-3**.

brush copolymers. For acrylate monomers, however, the polymerization did not hold the living characteristics, which may be caused by the propagating acrylate radical addition onto the dibenzocyclooctyne group during the polymerization [27].

As a continuous contribution in this research topic herein, we developed updated functional ATRP initiators **I-2** and **I-3** (Fig. 1) with a cyclopropenone-masked dibenzocyclooctyne group which can quantitatively generate the corresponding dibenzocyclooctyne upon irradiation. By these novel initiators, we achieved the living polymerization behavior for polymerizing acrylates by a standard ATRP protocol. In addition, the well-defined polymethacyrlates and polysyrenics could be conveniently produced as well by ATRP from these initiators.

2. Experimental

2.1. Materials

Triphenylphospine, 3-methoxybenzylchloride, 3-methoxy benzaldehyde, potassium *tert*-butoxide (*t*-BuOK), Pd on charcoal (10%), aluminum chloride ($AlCl_3$), tetrachlorocyclopropenone, borontribromide (BBr_3), *n*-butyryl chloride, 4,4′-Dinonyl-2,2′-bipyridine (dnbpy), 2-bromo-2-methylpropanoyl bromide, triethyl amine (TEA), methyl methacrylate (MMA), styrene (St), *n*-butyl acrylate (*n*BA), *tert*-butyl acrylate (*t*BA), tribromophosphine (PBr_3), methanesulfonyl chloride (MsCl), poly(ethylene glycol) monomethylether (M_n = 350, corresponding to DP = 8) (PEO_8-OH), sodium azide (NaN_3), copper(I) bromide (CuBr), pentamethyldiethylenetriamine (PMDETA), sodium chloride (NaCl), sodium bicarbonate ($NaHCO_3$), alkaline alumina (Al_2O_3), magnesium sulfate ($MgSO_4$), hexane, methanol, acetone, toluene, petroleum ether, ethyl acetate, diethyl ether, benzene, dichloromethane (DCM), tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF) were purchased as regent grade from Alfa Aesar, Aldrich, Acros, J&K Chemical, or Beijing Chemical Reagent Co. and used as received unless otherwise noted. MMA and St were dried over calcium hydride overnight and distilled under the reduced pressure. *t*BA and *n*BA were filtered by the alkaline alumina column to remove the inhibitor. TEA was dried over KOH. CuBr was washed by acetic acid and ethanol three times respectively, and then dried under vacuum. For making dry solvents: DCM was refluxed over calcium hydride; THF was distilled from sodium/benzophenone. PEO_8-N_3 was prepared from PEO_8-OH according to our previous publication [27].

2.2. Characterization

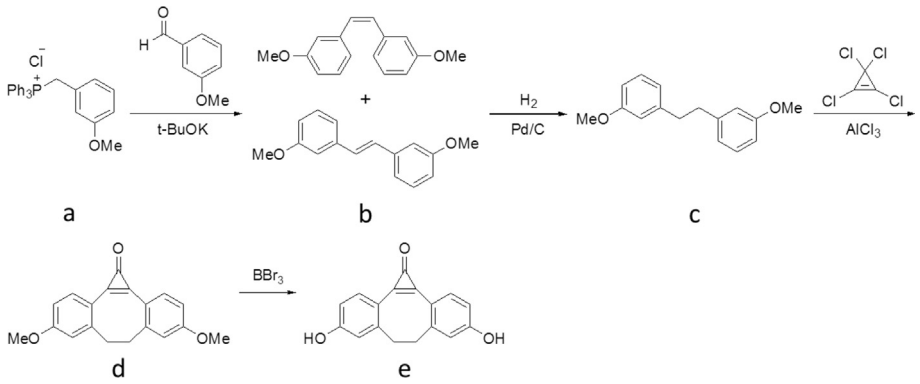
^{1}H NMR spectra were recorded on a Bruker Avance 400 spectrometer at room temperature.

Ultraviolet Spectra were recorded using a TU-1901 Ultraviolet Spectrophotometer.

Gel permeation chromatography (GPC) in THF was performed using four Waters Styragel columns (HT 2, HT 3, HT 4, and HT 5), a Waters 1515 isocratic HPLC pump, and a Waters 2414 RI detector. THF was used as the eluent at a flow rate of 1.0 mL/min. Polystyrene standards were used for the calibration.

2.3. Preparation of compound **e**

Compound **e** was synthesized according to the literature [29,30] and detailed as follows.



2.3.1. Compound ***a***

3-Methoxybenzylchloride (5.04 g, 32.12 mmol) and triphenylphosphine (8.40 g, 32.12 mmol) were heated to 80 °C for 12 h. A white precipitate was formed and the mixture was suspended in 250 ml of diethyl ether. The precipitate was filtered and dried to afford white solid **a** (12.96 g, 96.4% yield). ^{1}H NMR ($CDCl_3$), δ (ppm): 8.35–7.48 (m, 19H), 5.35 (s, 2H), 3.75 (s, 3H).

2.3.2. Compound ***b***

Compound **a** (12.34 g, 29.45 mmol) was dissolved in dry THF (65 mL) under N_2 and cooled to 0 °C. *t*-BuOK (3.57 g, 31.87 mmol) was added and the mixture was stirred for 90 min at 10 °C. 3-Methoxybenzaldehyde (3.34 g, 24.5 mmol) in dry THF (12 mL) was dropwised at 0 °C. After stirring for 5 h at 0 °C, the reaction mixture was quenched with 1 N HCl (100 mL), and extracted with

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