Progress in Polymer Science 39 (2014) 235–249

Contents lists available at ScienceDirect

Progress in Polymer Science

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

Complex macromolecular architecture design via cyclodextrin host/guest complexes

Bernhard V.K.J. Schmidt[a,b], Martin Hetzer[c], Helmut Ritter[c,**], Christopher Barner-Kowollik[a,b,*]

[a] *Preparative Macromolecular Chemistry, Institut für Technische Chemie und Polymerchemie, Karlsruhe Institute of Technology (KIT), Engesserstr. 18, 76128 Karlsruhe, Germany*

[b] *Institut für Biologische Grenzflächen, Karlsruhe Institute of Technology (KIT), Hermann-von-Helmholtz-Platz 1, 76344 Eggenstein-Leopoldshafen, Germany*

[c] *Lehrstuhl für Präparative Polymerchemie, Institut für Organische Chemie und Makromolekulare Chemie, Heinrich-Heine Universität, Universitätsstraße 1, Geb. 26.33.00, 40225 Düsseldorf, Germany*

ARTICLE INFO

Article history:
Received 25 March 2013
Received in revised form 3 September 2013
Accepted 5 September 2013
Available online 26 September 2013

Keywords:
Cyclodextrin
Macromolecular architecture
Supramolecular chemistry
Reversible-deactivation radical polymerization

ABSTRACT

The design of complex macromolecular architectures has driven macromolecular engineering over the past decades. The introduction of supramolecular chemistry into polymer chemistry provides novel opportunities for the generation of macromolecular architecture with specific functions. Cyclodextrins are attractive design elements as they form supramolecular inclusion complexes with hydrophobic guest molecules in aqueous solution affording the possibility to combine a large variety of building blocks to form novel macromolecular architectures. In the present critical review, the design of a broad range of macromolecular architectures driven by cyclodextrin host/guest chemistry is discussed, including supramolecular block copolymers, polymer brushes, star and branched polymers.

Contents

Abbreviations: AFM, atomic force microscopy; ATRP, atom-transfer radical polymerization; CD, cyclodextrin; ConA, concanavalin A; CuAAc, copper(I)-catalyzed azide–alkyne cycloaddition; DLS, dynamic light scattering; DMF, *N*,*N*-dimethylformamide; DNA, desoxyribonucleic acid; DOSY, diffusion-ordered NMR spectroscopy; Dox, doxorubicin; ECD, PEG-*b*-PCL-*b*-PDMAEMA; FT-IR, Fourier transform-infrared spectroscopy; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; ITC, isothermal titration calorimetry; LCST, lower critical solution temperature; MPEG, methoxy poly(ethylene glycol); NAS, *N*-acroyloxysuccinimide; NCCM, noncovalently connected micelle; NMP, nitroxide mediated radical polymerization; NMR, nuclear magnetic resonance; NOESY, nuclear Overhauser enhancement spectroscopy; OEGMA, oligo ethylene glycol methacrylate; PAA, poly(acrylic acid); PCL, poly(ε-caprolactone); PDEAAm, poly(*N*,*N*-diethylacrylamide); pDNA, plasmid DNA; PDMAAm, poly(*N*,*N*-dimethylacrylamide); PDMAEMA, poly(2-(dimethylamino)ethyl methacrylate); PEG, poly(ethylene glycol); PHEA, poly(hydroxyl ethylacrylate); PLA, poly(lactide); PMMA, poly(methyl methacrylate); PNIPAAm, poly(*N*-isopropylacrylamide); PPG, poly(propylene glycol); PSty, poly(styrene); RAFT, reversible addition-fragmentation chain transfer; ROESY, rotating frame nuclear Overhauser enhancement spectroscopy; ROP, ring-opening polymerization; siRNA, small interfering ribonucleic acid; SEC, size exclusion chromatography; SEM, scanning electron microscopy; SLS, static light scattering; TEM, transmission electron microscopy; TGA, thermo gravimetric analysis; XPS, X-ray photoelectron spectroscopy.

* Corresponding author. Tel.: +49 721 608 5641; fax: +49 721 608 5740.
** Corresponding author. Tel.: +49 211 81 14760; fax: +49 211 81 15840.
E-mail addresses: h.ritter@uni-duesseldorf.de (H. Ritter), christopher.barner-kowollik@kit.edu (C. Barner-Kowollik).

0079-6700/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.progpolymsci.2013.09.006

1. Introduction

Complex macromolecular architectures play a critical role in contemporary polymer science [1–3]. The control over polymer functionality, polymer composition and polymer topology provides an opportunity to prepare polymeric materials for a large variety of applications, e.g. microelectronic materials [4], drug/gene delivery [5], biomedical materials [6], supersoft elastomers [7] or hybrid materials [8]. Especially the development of reversible-deactivation radical polymerization techniques, e.g. nitroxide-mediated radical polymerization (NMP) [9,10], atom transfer radical polymerization (ATRP) [11,12], and reversible addition-fragmentation chain transfer (RAFT) polymerization [13–15], had a significant impact on the formation of complex macromolecular architectures, due to their convenient handling and functional group tolerance. Especially in connection with modular ligation chemistry it is possible to generate very complex building blocks with a large diversity due to the high tolerance of functional groups [16–19], e.g. via copper(I)-catalyzed azide-alkyne cycloaddition (CuAAc) [20], thiol-ene [21,22] or Diels–Alder reactions [23].

Concomitantly, supramolecular chemistry had significant impact on polymer science and especially on the formation of complex macromolecular architectures. Examples for supramolecular interactions that have been utilized in polymer chemistry are hydrogen bonding [24,25], metal complexes [26] as well as inclusion complexes [27–29]. Cyclodextrins (CDs) constitute an important building block for supramolecular systems, as they can form inclusion complexes with hydrophobic guest molecules primarily in aqueous solution. This ability has been utilized in polymer science in manifold applications, e.g. drug delivery [30], nano-structures [28], supramolecular polymers [31], self-healing materials [32], amphiphiles [33], bioactive materials [34] or in the solubilization of hydrophobic monomers or RAFT agents [35,36].

In recent years CD complexes have proven to be an elegant tool for the generation of complex macromolecular architectures. Almost every conceivable architecture has been described so far. Especially the development of reversible-deactivation radical polymerization techniques for the synthesis of end-functionalized polymers and modular ligation chemistry [17] had a very significant impact on the recent progress in the area.

Fig. 1 depicts a compilation of different architectures that were generated via CD host/guest complexes thus far. CDs have been utilized for the modification of polymer functionality, polymer composition and polymer topology. CD functionalized polymers are rather readily accessible via reversible-deactivation radical polymerization giving control of end chain and mid chain functionality. Diverse supramolecular polymer compositions can be obtained via incorporation of CD complexes at the interface between different blocks. To achieve more complex topologies, a combination of different functionalized building blocks is necessary, e.g. multi-CD functionalized polymer strands. In general, the control over polymer functionality gives rise to the formation of complex supramolecular polymer compositions and topologies. In the following, the structures depicted in Fig. 1 will be illustrated with several examples.

2. Common CD containing building blocks

Although CDs possess a large number of functional groups, the reactivity of the primary (at C-6) and secondary hydroxyl groups (at C-2 or C-3) differs significantly, providing an opportunity to exclude some of the hydroxyl groups in specific reactions (refer to Fig. 2) [37,38]. Nevertheless, at least six hydroxyl groups with the same reactivity exist in a CD molecule. To obtain mono functionalization, the reaction conditions have to be monitored carefully. The most commonly used intermediate is the mono tosylate at C-6, which can be synthesized in pyridine for all native CDs [39–41] or in aqueous NaOH solution for β-CD and α-CD [42,43]. The tosylate can be transformed into several useful building blocks, e.g. azide [40,41], thiol [44] or amine via nucleophilic substitution with a diamine [45]. The azide is available via a nucleophilic substitution of the tosylate with sodium azide [40–42], whereas the thiol is formed via a nucleophilic substitution with thiourea and subsequent hydrolysis [44,46]. The azide can be further converted into an amine via reduction [39–41]. With these 3 substituents a large variety of modern polymer conjugation reactions can be utilized, e.g. CuAAc [43,47] and thiol-ene reactions [48]. CD-functionalized polymerization mediators, e.g. for NMP [49], ATRP [50] or RAFT [51] have been described in the literature as well as post-polymerization conjugation reactions with CDs. [50,52] Mono functionalizations at C-2 are described in the literature as well [53,54], yet C-2 or C-3 derivatives are not utilized as frequent as the C-6 derivatives. Certainly an esterification of the hydroxyl groups is possible as well, yet the selectivities are usually low. Either full conversions are initially targeted or lower substitution grades are targeted and the obtained mixtures have to be purified in inconvenient procedures.