Polymer 78 (2015) 31–36

Contents lists available at ScienceDirect

Polymer

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

Molecularly imprinted polymers by reversible chain transfer catalysed polymerization

Marc Bompart [a], Atsushi Goto [b], Olivier Wattraint [c], Catherine Sarazin [c], Yoshinobu Tsujii [b, ***], Carlo Gonzato [a, *], Karsten Haupt [a, **]

[a] Sorbonne Universités, Université de Technologie de Compiègne, CNRS Laboratory for Enzyme and Cell Engineering, CS60319, 60203 Compiègne Cedex, France
[b] Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan
[c] CNRS Laboratory for Enzyme and Cell Engineering, University of Picardie Jules Verne, 80039 Amiens Cedex, France

ARTICLE INFO

Article history:
Received 16 July 2015
Received in revised form
21 September 2015
Accepted 23 September 2015
Available online 28 September 2015

Keywords:
Molecularly imprinted polymer
Reversible chain-transfer catalysed polymerization
Living radical polymerization

ABSTRACT

Molecularly imprinted polymers (MIPs) are tailor-made biomimetic receptors obtained by polymerization in the presence of molecular templates. They contain binding sites for target molecules with affinities and specificities on a par with those of antibodies, hormone receptors or enzymes. Mainly synthesized *via* radical polymerization of vinyl monomers, MIPs have also recently taken advantage of the introduction of modern methods of controlled/living radical polymerization (CRPs). In this paper, we report for the first time the use for MIP synthesis of a recently developed CRP method based on an iodide-transfer polymerization with a reversible activation mechanism, referred to as *Reversible chain-Transfer Catalysed Polymerization* (RTCP). Using S-propranolol as model template, we show that this technique is a convenient method for the synthesis of MIPs, both in the format of bulk polymers and nanoparticles, yielding polymers with reactive chain ends for an easy surface functionalization.

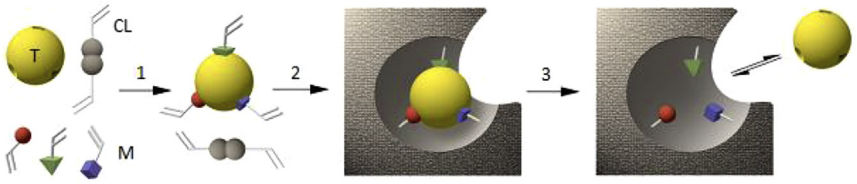
1. Introduction

Molecularly imprinted polymers (MIPs) are tailor-made, biomimetic receptors that contain binding sites for target molecules with affinities and specificities on a par with those of natural receptors such as antibodies, hormone receptors, or enzymes [1–4]. The target molecule, or a derivative thereof, acts as a template around which functional and cross-linking monomers are copolymerized to form a cast like shell. Upon template removal, binding sites are revealed that are complementary to the template in terms of size, shape, and position of chemical functionality (Scheme 1).

So far, molecular memories have been created in a variety of scaffolds including sol–gel matrices [5], polyurethanes [6], polyamides [7]. Nevertheless a great majority of MIPs is nowadays fabricated *via* radical polymerization of vinyl monomers. This can be ascribed to the remarkable flexibility of this polymerization approach in terms of choice of monomers and solvents, tolerance for functional groups and reagent purity, variety of experimental setups, accessibility of different physical forms of the material, easy nanostructuring, etc. [8]. During last decades, the versatility of these materials has even been pushed further, with the introduction of modern methods for controlled/"living" radical polymerization (CRP), allowing to couple the above mentioned advantages with the possibility of a precise control over molecular weight, molecular weights distribution and macromolecular architecture. Methods such as nitroxide mediated radical polymerization (NMP) [9], atom transfer radical polymerization (ATRP) [10], iniferter (standing for *ini*tiator-trans*fer* agent-*ter*minator) radical polymerization [11] and reversible addition–fragmentation chain transfer radical polymerization (RAFT) [12–14], just to cite the most popular, have literally transformed polymer chemistry, affording to unprecedented degrees of control for radical processes. Indeed, as many other areas of polymer science, MIPs have also taken advantage of CRPs [8], often affording improved binding properties (i.e. increased binding affinities and capacities) compared to equivalent MIPs obtained by conventional free-radical polymerization (FRP). These improved features were mainly associated to

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: tsujii@scl.kyoto-u.ac.jp (Y. Tsujii), carlo.gonzato@utc.fr (C. Gonzato), karsten.haupt@utc.fr (K. Haupt).

http://dx.doi.org/10.1016/j.polymer.2015.09.060
0032-3861/



Scheme 1. Schematic representation of molecular imprinting strategy. Functional monomers (M), cross-linker (CL), template molecule (T); 1: formation of a prepolymerization complex, 2: polymerization, 3: extraction. Reproduced form Ref [4] with permission. Copyright (2003) American Chemical Society.

the development of more homogenous networks during the macromolecular growing step, resulting in more homogeneously distributed cross-liking points [15–17]. However, in the context of MIPs, the most important benefit of using CRP lies in the presence of living chain-ends, which allow for an easy post-functionalization and a fine-tuning of the MIP architecture and properties. Applications of the living character of CRPs in the imprinting field deal for instance with the synthesis of brushes for improved water compatibility [18], for steric stabilization or improved barrier toward the unspecific absorption of proteins [19], or with the possibility of switching the zeta-potential on particles' surface [20].

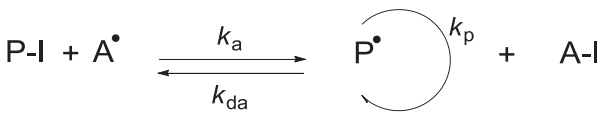
Among the different CRPs, iodide transfer polymerization (ITP) [21], and in particular its improved version based on a reversible chain transfer catalysis mechanism, referred to as *reversible chain transfer catalysed polymerization* (RTCP) [22,23], has shown to be a convenient and robust method to synthesize polymers in terms of safety, absence of metal species and range of polymerizable monomers and catalysts [24]. As for RAFT, RTCP is based on a chain transfer process (Scheme 2), and the generally low exchange frequency of iodine shown by alkyl-iodides and leading to poor control over molecular weight distribution is compensated by the use of germanium, tin and phosphorous-based catalysts acting as chain transfer agents [22].

Herein, we report for the first time the synthesis of MIPs by RTCP. We use *N*-iodosuccinimide (NIS) as the catalyst, and apply the technique to the synthesis of both bulk polymer monoliths and micro-spheres, using the beta-antagonist drug S-propranolol as the target molecule and model template for the MIP. We demonstrate in particular the convenience of using RTCP by restarting the polymerization to grow poly(ethylene glycol methacrylate phosphate) p(EGMP) brushes on the surface of the original polymeric nanoparticles.

2. Experimental

2.1. Materials

Ethylene glycol dimethacrylate (EGDMA) (98%), methacrylic acid (MAA) (99%), ethylene glycol phosphate methacrylate (EGMP), N-iodosuccinimide (95%), iodine (≥99.8%), (S)-propranolol hydrochloride (≥98%), [^{3}H]-(RS)-propranolol, anhydrous acetonitrile and anhydrous sodium thiosulphate $Na_2S_2O_3$ (99%) were purchased from Sigma–Aldrich (St-Quentin Fallavier, France) and used as received. 2,2'-azobis-(2,4-dimethylvaleronitrile) (ABDV, Vazo-52) was from DuPont Chemicals (Wilmington, USA). Toluene,



Scheme 2. Schematic representation of the reversible chain transfer catalysed mechanism: an alkyl-iodide (P–I) is reversibly activated by A˙ to give a propagating radical (P˙) and a chain transfer agent (A-I, i.e. *N*-iodosuccinimide in this work).

methanol and acetic acid of analytical grade were purchased from VWR International (Strasbourg, France). Chloroform-d ($CDCl_3$) (99.80% D) was from euriso-top (St-Aubin, France). (S)-propranolol hydrochloride was converted into the free base by extraction from a sodium carbonate solution at pH 9 into chloroform.

2.2. Synthesis of alkyl iodide CP-I

Iodine (4.50 g, 17.7 mmol) and ABDV (4.50 g, 18.1 mmol) were mixed in toluene (100 mL) and reacted at 85 °C for 4 h using a reflux apparatus under a nitrogen atmosphere. Upon cooling down to room temperature, anhydrous $Na_2S_2O_3$ was added to the solution and the dispersion was stirred until the red colour disappeared (the colour changed to yellowish-brown). After filtration of the $Na_2S_2O_3$ excess, the solution was passed through basic alumina to give a pale yellow solution. The solvent was then evaporated under reduced pressure (60 mm Hg) at room temperature to give 2-cyanopropyl iodide (CP–I) as a pale yellow liquid. The obtained CP-I was considered pure enough for RTCP. Since CP-I is sensitive to light, the purification, handling and storage was done in the dark.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 2.21 (s, 3H), 2.0 (dd, 1H), 1.85 (3, 1H), 1.69 (dd, 1H), 1 (m, 6H).

2.3. Polymer synthesis

Bulk polymers by RTCP were synthesized as follows. The template molecule S-propranolol (0.04 mmol), the alkyl iodide CP-I, the catalyst NIS (0.4 μmol), the radical initiator ABDV, the cross-linking monomer EGDMA (1.6 mmol), and the functional monomer MAA (0.32 mmol) were dissolved in 350 μL of anhydrous acetonitrile in a glass tube. Upon purging with nitrogen, the polymerization was carried out in an incubator at 60 °C for 12 h. The bulk polymers were then ground in a mortar, transferred to microcentrifuge tubes and crushed with 2.8 mm-diameter zirconia beads in the presence of methanol using a Precellys 24 homogeniser (Bertin Technologies, Montigny le Bretonneux, France). The template was extracted by three incubations in methanol/acetic acid 4/1 (v/v) for 1 h, followed by three incubations in methanol. The crushed particles were then dried under vacuum and stored at ambient temperature until use. Non-imprinted, control polymers (NIP) were synthesized under identical conditions in the absence of the template molecule. Polymers by conventional FRP were synthesized using the same protocol, except that NIS and CP-I were omitted.

Polymeric spheres were synthesized by precipitation polymerization, by using the same recipes as described above for RTCP and FRP bulk polymers, except that the monomer concentrations were set to 1–2% (v/v). The prepolymerization solutions were degassed by bubbling nitrogen for 15 min while cooling on ice.

PEGMP brushes were grown from the surface of polymeric nanoparticles by using reference NIP particles obtained by precipitation polymerization as a macromolecular alkyl iodide; in a glass vial, NIP nanospheres (0.1 g, 1 μmol of iodide) were dispersed in acetonitrile (2 mL), and mixed with EGMP (40 μL, 0.50 mmol) and