ATRP technique in glycopolymer synthesis

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Abstract
Glycopolymers: synthetic sugar containing macromolecules are of great interest not only as simplified models of biodegradable polymers but also in biological, biochemical and biomedical uses. This review summarizes the state of art in the synthesis of linear glycopolymers by Atom Transfer Radical Polymerisation (ATRP). Particular emphasis is placed on initiators and ligands used in the synthesis of glycopolymers by ATRP. Monomers, initiators and ligands have been described using Figures.

Keywords: glycopolymer, atom transfer radical polymerisation, block copolymer, biopolymers

1. Introduction

Synthetic carbohydrate-containing macromolecules or glycopolymers have attracted increasing attention in various fields of science with particular interest to the biological sciences due to their recognition properties [1–3]. Advances in synthetic chemistry allow for the preparation of well defined and multi-functional glycopolymers in a relatively facile manner [4]. The carbohydrate units critically control the specific biological functions of cells and also play an important role in cell–cell recognition [5,6]. It is desirable to be able to control the chain length, composition and topology of the glycopolymer since these factors determine the location and distance between the carbohydrates on the polymer chain [7,8]. Importantly, precise recognition properties can be achieved by an absolute control over the microstructure of the glycopolymer

Although free radical polymerisation is most widely studied and used polymerisation techniques for glycopolymers it is impossible to control the polydispersity index (PDI) and terminal functionalities of the resulting polymers. Meanwhile, advances in controlled radical polymerizations have provided the synthetic polymer chemists with an improved technique for the synthesis of polymers with controlled molecular weights, PDI and terminal functionalities. Recent developments in controlled radical polymerisation such as atom transfer radical polymerization (ATRP)[9], nitroxide-mediated polymerisation (NMP)[10] and reversible addition-fragmentation chain transfer (RAFT) polymerization[11,12] have enabled the syntheses of glycopolymers with well-defined architectures and functionalities. ATRP polymerisation of protected sugars which lead to linear polymers will be dealt in detail in this review.

2. General mechanism for ATRP

Atom transfer radical polymerization (ATRP, Figure 1) is a controlled radical polymerization technique that was developed independently by the research groups headed by Sawamoto [13] and Matyjaszewski [14] in 1995. An ATRP system contains a halogenated organic compound (initiator) R–X, a transition metal M^n, which can increase its oxidation number, a complexing ligand L to stabilize the metal, and monomer M. Initiation involves abstraction of the initiator's halogen atom by the metal complex, which simultaneously undergoes a single electron oxidation.

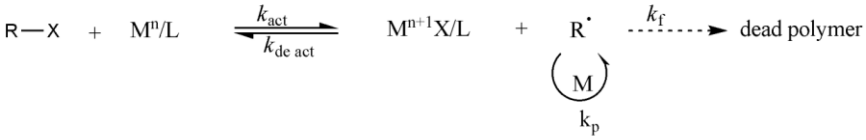

Figure 1. General mechanism for the atom transfer radical polymerisation

This gives an organic radical R• and a new metal complex $M^{n+1}X/L$ in which the metal's oxidation number has increased by 1. The radical can add monomer units, thereby initiating chain growth, before abstracting the hydrogen atom from the metal complex and restoring its dormant state P*n*–X. This halogen-capped polymer chain assumes the same role that the initiator occupies in the initiation step; it remains in its dormant state until activated by the metal complex to reform the radical P*n*•, which can then add a few more monomer units before being deactivated. These atom transfer equilibria lie heavily toward the dormant species, which reduces the effective radical concentration and thereby limits bimolecular termination. Termination still occurs but is greatly suppressed, imparting living characteristics on the polymerization process.

Atom transfer radical polymerization has been successfully performed using a variety of transition metals, but copper (Cu) complexes have proven to be the most efficient and versatile. The choice of ligand influences the relative rates of activation and deactivation and, therefore, the degree of control over the polymerization. Nitrogen-containing multidentate ligands are commonly employed for Cu-mediated ATRP, and those relevant to glycopolymer synthesis are shown in Figure 2. Figure 3 shows the initiators relevant to the present review. For simplicity, the bold code will be used in text to refer to each ligand and initiator, rather than including its full or abbreviated name.

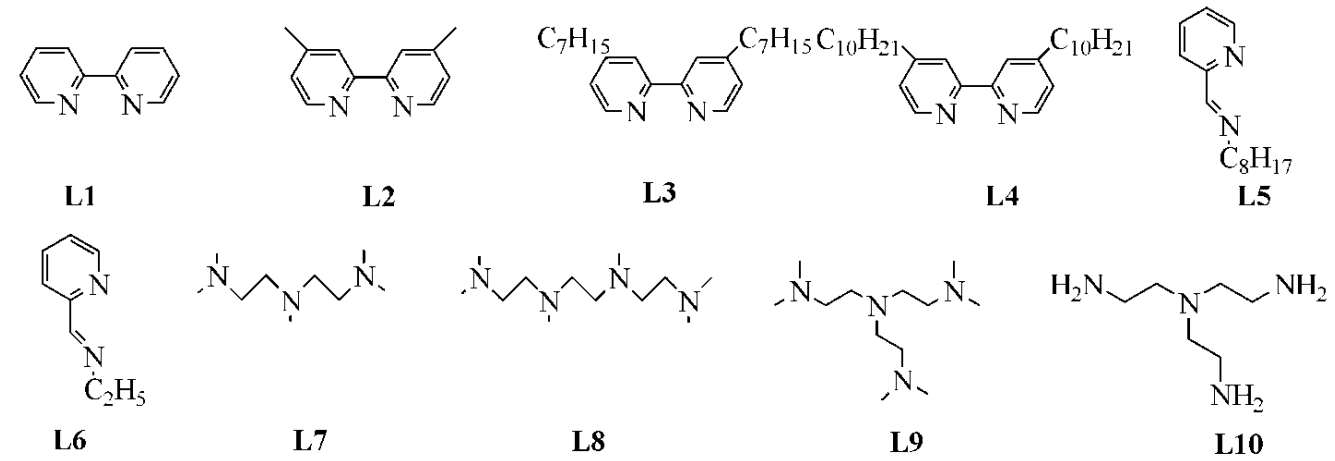

Figure 2. Ligands used in the synthesis of glycopolymers by ATRP

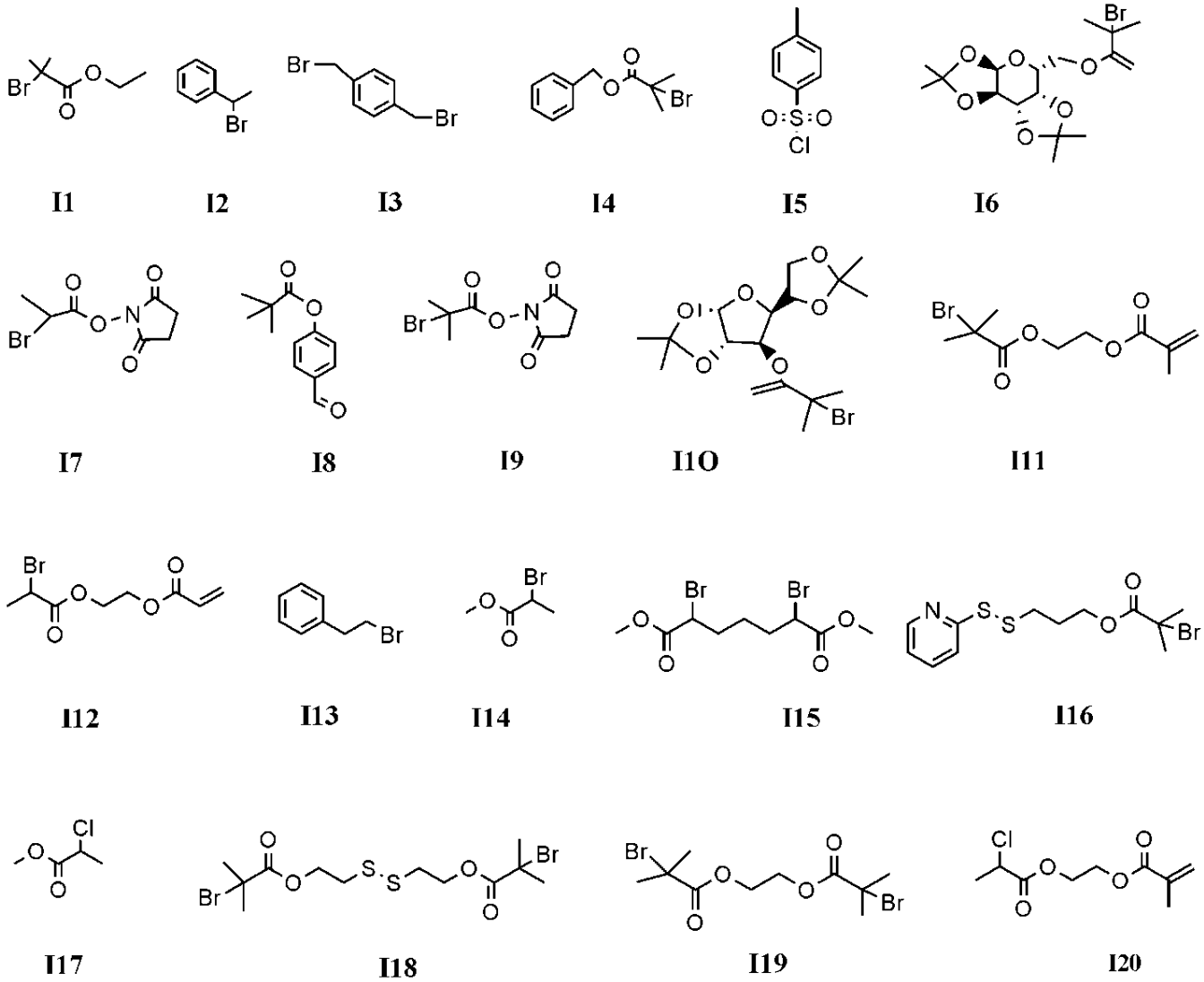

Figure 3. Initiators used in the synthesis of glycopolymers by ATRP

3. Synthesis of glycopolymers using protected glycomonomers

Ohno et al. from Kyoto University reported the first ATRP of a sugar monomer by polymerizing 3-*O*-methacryloyl-1,2:5,6-di-*O*isopropylidine-d-glucofuranose **M1**(MAIpGlc)

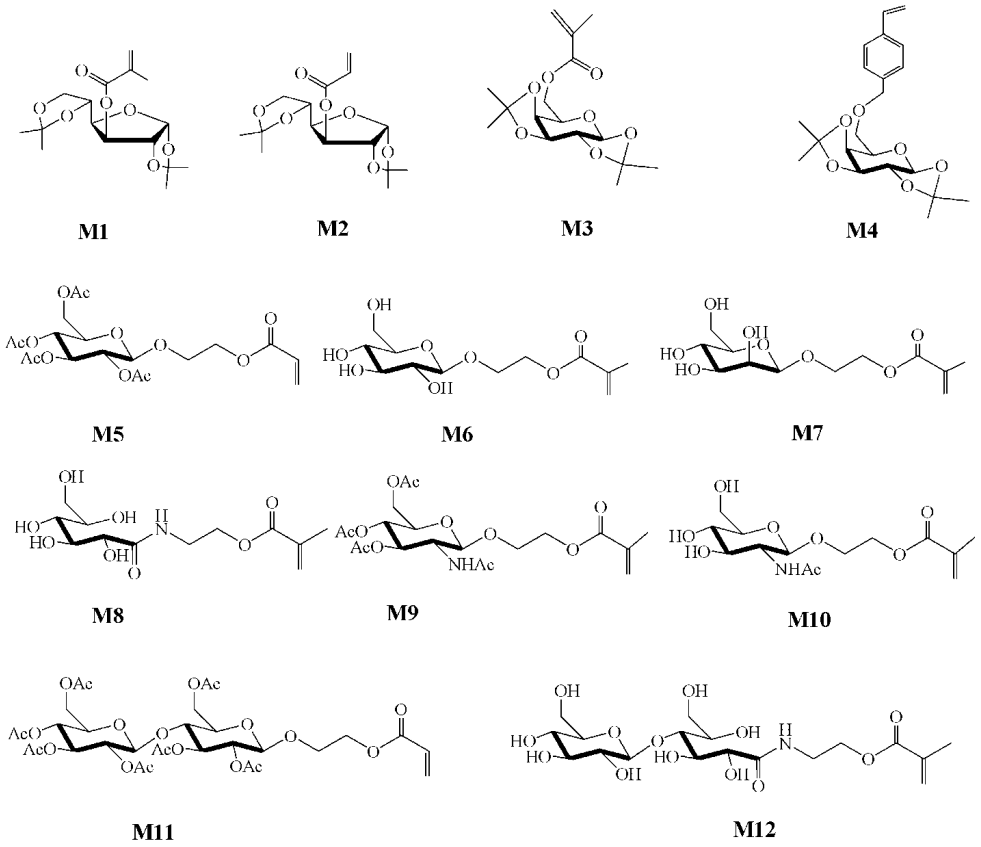

Figure 4: Selected examples of glycomonomers polymerized using ATRP

using a CuBr/**L3** catalyst in veritrole containing **Ethyl 2-isobutyrate** as initiator at 80ºC [15]. The first-order kinetic plots for the polymerizations of MAIpGlc were approximately linear, which means that the system obeys first-order kinetics with respect to monomer concentration. However, a twofold increase in the initiator concentration (holding all else constant) had a negligible effect on the rate of polymerization r_p, whereas a doubling of the activator concentration increased r_p by a factor of 3. Previous studies using styrene indicated that r_p is first order with respect to both the dormant alkyl halide concentration and the activator concentration [16]. Despite these unexpected kinetic features, the polydispersity index (PDI) of the resulting glycopolymers was less than 1.30, indicating that the polymerizations were reasonably controlled. Li et al. achieved the controlled polymerization of glycomonomers (Figure 4) via ATRP.[17-23] The controlled polymerization of protected 2-(2',3',4',6'-tetra-*O*-acetyl-β-Dglucopyranosyloxy) ethyl acrylate (AcGEA) **M5** (Figure 4) by ATRP in chlorobenzene at 80°C using 2,2'-bipyridine as a ligand was reported.[17,18] After deprotection with sodium methoxide, the unprotected polymer was obtained, which exhibited a low polydispersity (PDI < 1.4). The authors also reported the synthesis of the well-defined PEO-*b*-PAcGEA (PDI = 1.12) by ATRP in chlorobenzene at 80°C using PMDETA as a ligand. [19-21,23] Studies on the self-aggregation and interaction with concanavalin A were carried out by turbidity and fluorescence measurements. The 6-*O*-methacryloyl-1,2:3,4-di-*O*-isopropylidene D-galactopyranose (MAIPGal) **M3** (Figure 4) was polymerized at 60°C via ATRP by the use of ethyl 2-bromoisobutyrate, methyl 2-bromoisobutyrate or a macroinitiator (PEO-Br) as the initiators and bipyridine or PMDETA as the ligand. Chain extension of the polymer by ATRP with methyl methacrylate as the second monomer was carried out, and the diblock copolymer P(MAIPGal)-*b*-P(MMA) was obtained. Functional polymers were obtained after removal of the protecting groups. The polymers exhibited a PDI lower than 1.4.[20] 6-*O*-(4-vinylbenzyl)- 1,2:3,4-di-*O*-isopropylidene-D-galactose **M4** (Figure 4) was polymerized as well as copolymerized via ATRP by the use of poly(ε-caprolactone)-bromide as the macroinitiator and bipyridine as the ligand.[22]

Ohno and co-workers used ATRP to polymerize 3-*O*-methacryloyl-1,2:5,6-di-*O*isopropylidene- D-glucofuranose (MAIpGlc) **M1** (Figure 4) at 80°C in *o*-dimethoxybenzene, using an alkyl halide/copper complex system.[24] The polymerization proceeded in a controlled way and yielded polymers with predictable molecular weights and low polydispersities (PDI ≤ 1.5). The authors also synthesized poly(styrene)-*b*-PMAIpGlc diblock copolymers under similar conditions. The graft polymerization of the same monomer on SiO2/Au/Cr-coated glass plate was also achieved by ATRP. The initiator, 2-(4-chlorosulfonylphenyl)ethyltrimethoxysilane, was immobilized onto a glass plate by the Langmuir-Blodgett technique.[25]

Armes and co-workers synthesized the glycomonomers 2-gluconamidoethyl methacrylate (GAMA) **M8** (Figure 4) and 2-lactobionamidoethyl methacrylate (LAMA) **M12** (Figure 4) via ring opening of either glucono- or lactobiono-lactone with 2-aminoethyl methacrylate. Polymerization of these monomers was performed in MeOH/H_2O using the CuBr/bipy catalyst system with either a PEGylated or aldehyde-functionalized initiator. [26-28] Block copolymers of the monomers with 2-(diethylamino) ethyl methacrylate (DEA) were also synthesized by ATRP in methanol. These glycopolymers displayed predictable pH dependent aqueous solution properties, and spontaneously self-assembled into micelles of 29 nm average diameter above pH 7, as measured by dynamic light scattering.[26] Copolymers of **M12** (Figure 4) with DEA and poly(propylene oxide) (PPO) were prepared and both were found to be stimuliresponsive; the former was found to have pH-reversible micelle-forming properties while the latter showed thermoresponsive surface activity.[27]

Müller and co-workers reported the polymerization of the glycomonomers 3-*O*-methacryloyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **M1** (Figure 4) and its acryloyl analogue**.** Homopolymerization of **M1** and its acryloyl derivative with ethyl 2-bromoisoburate as the initiator and CuBr/PMDETA as a catalyst system in ethyl acetate resulted in glycopolymers having controlled molecular weights and narrow polydispersities (PDI < 1.2).[29,30] Cylindrical glycopolymer brushes with poly(3-*O*methacryloyl-α,β-D-glucopyranose) side chains were prepared using the "grafting-from" approach via ATRP of the protected monomer **M1**. Well-defined brushes with a narrow length distribution were formed. The deprotection of the isopropylidene groups resulted in water soluble cylindrical glycopolymer brushes.[31]

Vazquez-Dorbatt and co-workers used ATRP to prepare the biotinylated glycopolymers that bind to the protein streptavidin. In their work, poly(methacrylate)s with pendent *N*-acetyl-D-glucosamine were synthesized by polymerizing the protected monomer 2-(*O*-methacryloyl) ethyl 2-acetamido-2-deoxy-β-D-glucopyranoside **M9** (Figure 4), followed by deprotection. Alternatively, the unprotected monomer was directly polymerized. Both paths provided well-defined glycopolymers with narrow polydispersities (PDI = 1.07–1.23). The polymers were synthesized using a biotin-functionalized initiator for ATRP.[32]

A new glycopolymer-polypeptide triblock copolymer, poly(L-glutamate)-poly(2-acryloyloxyethyllactoside)-poly(L-glutamate), was synthesized by Chaikof and coworkers.[33,34] 2-*O*-Acryloyloxyethyl-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside **M11** (Figure 4) was polymerized by ATRP using the dibromoxylene/CuBr/bipy system. The polymer chain ends were transformed into diamino groups and the glycopolymer was used as a macroinitiator for the ring-opening polymerization of β-benzyl-L-glutamate *N*-carboxyanhydride. The triblock copolymers were proved to have defined architectures, controlled molecular weights, and low polydispersities (PDI < 1.45). FTIR of the triblock copolymers showed that the α-helix/β-sheet ratio increased with the poly(benzyl-L-glutamate) block length.

Amphiphilic ABA triblock as well as star copolymers composed of poly(methacrylate) bearing a galactose fragment and poly(ε-caprolactone) were reported by Wulff and coworkers. The ring-opening polymerization (ROP) of ε-caprolactone and the ATRP of 6-*O*methacryloyl-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose **M3** (Figure 4) led to the block copolymers with low polydispersities (PDI < 1.25).[35]

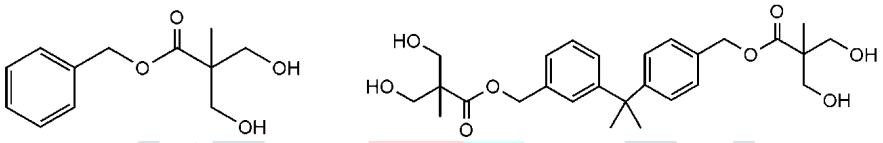

Figure 5 Initiators used for ring opening polymerisation of ε-caprolactone

Finn and co-workers reported a new glycopolymer obtained via ATRP of methacryloyloxyethyl-*O*-glucoside **M6** (Figure 4) with an azide-containing initiator, and CuBr/bipy system in MeOH/H_2O. The well-defined glycopolymer (Mn = 13,000, PDI = 1.3) possessing a single azide-terminated chain end was reacted with a fluorescein dialkyne to generate a glycopolymer-alkyne. The glycopolymer-alkyne was then condensed with an azide-labeled virus to generate a virus-polymer conjugate.[36]

The synthesis and characterization of a series of *N*-(hydroxy)succinimidyl ester-terminated glycopolymers obtained via ATRP have been described by Haddleton and co-workers. Glucofuranoside **M1** (Figure 4) and galactopyranoside **M3** (Figure 4) were used as glycomonomers. The system CuBr/*N*-(*n*-octyl)-2-pyridylmethanimine was applied for the polymerization, and *N*-succinimidyl- 2-bromopropionate was employed as the initiator. The corresponding polymers featured a relatively narrow polydispersity (PDI = 1.10–1.31) and Mn between 4,500 and 10,200. The protecting groups were removed by treatment with formic acid.[37]

4. Conclusion

Well defined glycopolymers architectures have been successfully synthesized with atom transfer radical polymerisation. It has proven a more versatile technique for the synthesis of glycopolymer architectures with poly(acrylate) and poly(methacrylate) backbone: Multi-block copolymers, graft copolymers, multi-arm stars, hyperbranched polymers as well as cylindrical brushes have been successfully prepared by ATRP. Furthermore, Armes *et al.* extended its applicability to unprotected monomers in aqueous or aqueous/alcoholic media [26,27,28], while Fukuda and co. successfully grafted well-defined glycopolymer brushes onto a silicon substrate [25]. In spite of this, several drawbacks to the use of ATRP in glycopolymer synthesis persist:
(i) functional groups likely to deactivate the catalyst (e.g., acid functions) need to be protected during the polymerization process [38]
(ii) achieving a good degree of control in aqueous media is challenging due to the occurrence of several side reactions involving the catalytic system [39]. For instance, in water the CuI-based ATRP activator may disproportionate; the Cu^{II}-based deactivator is likely to lose its halide ligand; and the alkyl halide initiator may hydrolyze or react with the monomer if it contains basic or nucleophilic groups. In this case, better results are obtained by adding an organic co-solvent (e.g., methanol or DMF) and (or) a Cu^{II} halide complex to the catalyst.

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