Perspective

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Recent Developments in the Synthesis of Biomacromolecules and their Conjugates by Single Electron Transfer–Living Radical Polymerization

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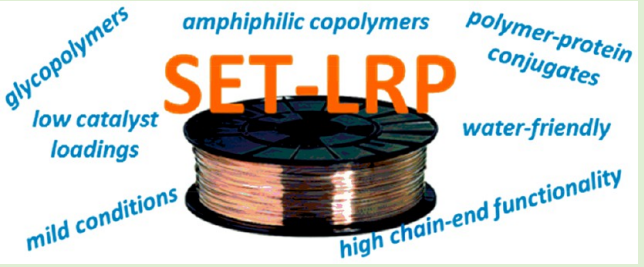
ABSTRACT: Single electron transfer–living radical polymerization (SET-LRP) represents a robust and versatile tool for the synthesis of vinyl polymers with well-defined topology and chain end functionality. The crucial step in SET-LRP is the disproportionation of the Cu(I)X generated by activation with Cu(0) wire, powder, or nascent Cu(0) generated in situ into nascent, extremely reactive Cu(0) atoms and nanoparticles and $Cu(II)X_2$. Nascent Cu(0) activates the initiator and dormant chains via a homogeneous or heterogeneous outer-sphere single-electron transfer mechanism (SET-LRP). SET-LRP provides an ultrafast polymerization of a plethora of monomers (e.g., (meth)-acrylates, (meth)-acrylamides, styrene, and vinyl chloride) including hydrophobic and water insoluble to hydrophilic and water soluble. Some advantageous features of SET-LRP are (i) the use of Cu(0) wire or powder as readily available catalysts under mild reaction conditions, (ii) their excellent control over molecular weight evolution and distribution as well as polymer chain ends, (iii) their high functional group tolerance allowing the polymerization of commercial-grade monomers, and (iv) the limited purification required for the resulting polymers. In this Perspective, we highlight the recent advancements of SET-LRP in the synthesis of biomacromolecules and of their conjugates.



1. INTRODUCTION

The roots of single electron transfer–living radical polymerization (SET-LRP) began to grow during the development of a metal-catalyzed living radical polymerization (LRP) of vinyl chloride (VC).[1] At that time, it was reported that even the most active Cu(I)X complexes failed to polymerize VC under atom transfer radical polymerization (ATRP) due to the inert nature of -CHClX end groups of poly(vinyl chloride) (PVC).[2] In addition, chain transfer to polymer is the most dominant process through the free radical polymerization of VC, whereas bimolecular termination is negligible.[2] This prevents the establishment of the persistent radical effect (PRE)[3] in which a small extent of bimolecular radical termination accumulates $Cu(II)X_2$ deactivator leading to a shift of the dormant/radical equilibrium toward the dormant species. In addition when X = I, CuI_2 can not act as a deactivator because CuI_2 does not exist.[4] However, it was discovered that various Cu(0) species showed remarkable activity for reinitiation of -CHClX chain-ends of PVC compared to that of Cu(I)X species.[1] By exploiting the disproportionation of Cu(I)X into Cu(0) and $Cu(II)X_2$ in water and in polar media in the presence of specific ligands, these studies further evolved into single-electron transfer–degenerative transfer living radical polymerization (SET-DTLRP) mediated by Cu(0)/tris(2-aminoethyl)amine (TREN), Cu(0)/branched poly(ethylene imine), or $Na_2S_2O_4$.[4,5] In SET-DTLRP, both activation and deactivation steps are controlled by a competition between the SET from Cu(0) or $Na_2S_2O_4$ and degenerative chain transfer mechanisms and by $Cu(II)X_2$/L generated by the disproportionation of Cu(I)X without the need for PRE. In water, protic, dipolar aprotic, and other polar solvents, and in the presence of N-ligands that stabilize $Cu(II)X_2$ such as tris(2-(dimethylamino)-ethyl)amine (Me_6-TREN), TREN, and branched poly(ethylene imine),[6,7] when activation and deactivation are faster than the degenerative chain-transfer, the DT part of SET-DTLRP is eliminated, and the newly elaborated LRP becomes SET-LRP.[8] A successful SET-LRP process is dependent on the disproportionation of the in situ-generated Cu(I) to extremely reactive nascent Cu(0) activator and $Cu(II)X_2$/L deactivator.[9] In this self-regulated mechanism, the disproportionation of Cu(I)X maintains the equilibrium between the active and dormant species. The crucial function of nascent Cu(0) nanoparticles in the activation step of SET-LRP has been studied in depth by our laboratory.[10−14] Note that early work on Cu(0)- and Cu(I)-mediated "most probably a living" radical polymerization was reported, as discovered recently,[9] in 1954

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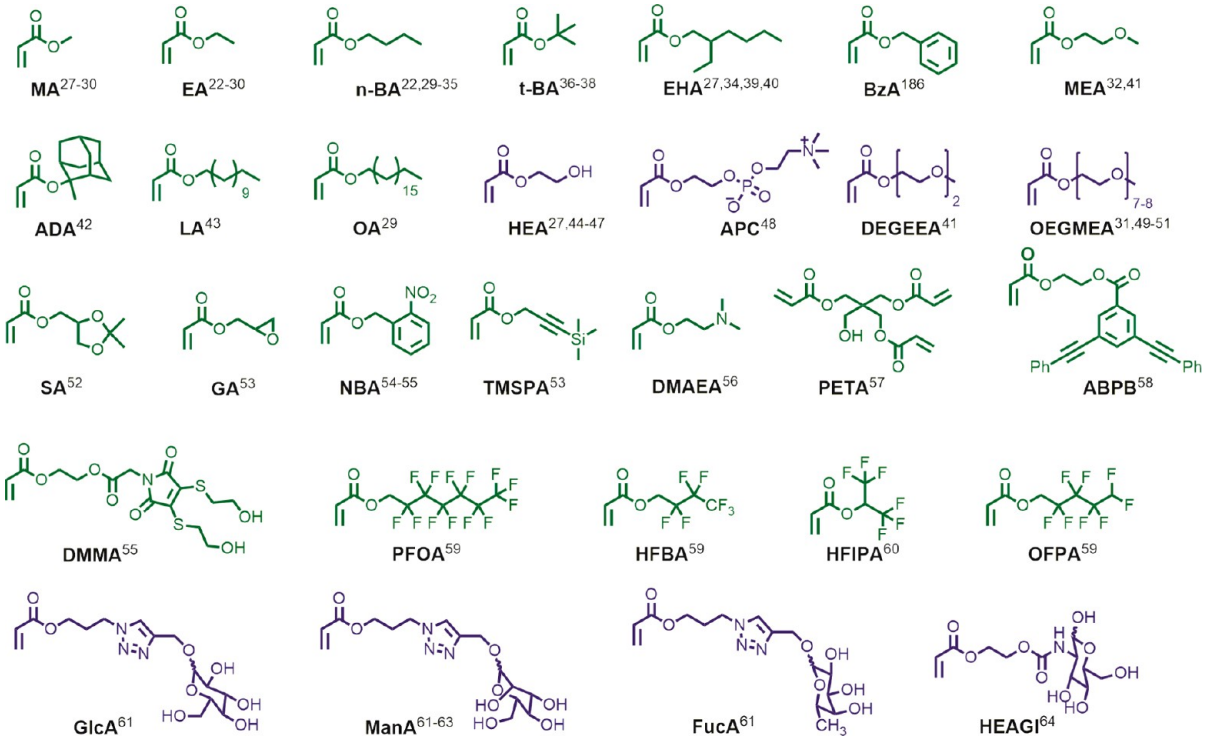
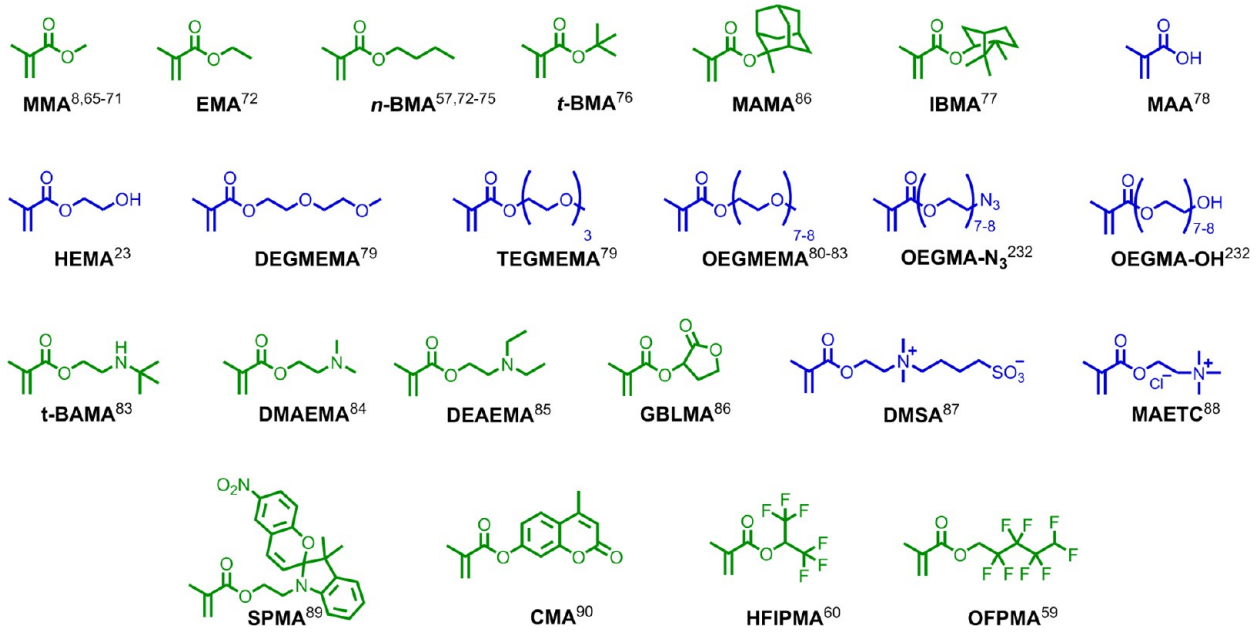
Scheme 1. Acrylates Used in SET-LRP (Blue, Hydrophilic and Water Soluble; Green, Hydrophobic and Water Insoluble)



Scheme 2. Methacrylates Used in SET-LRP (Blue, Hydrophilic and Water Soluble; Green, Hydrophobic and Water Insoluble)



by the Furukawa laboratory.[15,16] However, these experiments were not performed in the presence of disproportionating solvents. Cu(0)[17−19] and other metal(0) species such as Ni(0)[20] and Pd(0)[21] were later used to mediate living radical polymerization and radical step polycondensation.

Since its invention, SET-LRP has evolved in an efficient method for the ultrafast synthesis of a wide variety of vinylic polymers under mild conditions using incredibly low catalyst loadings.[8] SET-LRP shows quantitative initiator efficiency and as such allows the preparation of ultrahigh molar mass polymers. For example, the syntheses of near perfectly and perfectly monofunctional and bifunctional poly(methyl acrylate) (PMA) with M_n close to 1,600,000 g mol^{-1}[5,8,22] and poly(2-hydroxyethyl methacrylate) (PHEMA) with M_n up to 1,020,000 g mol^{-1}[23] have only been possible by using the SET-LRP methodology. This method has also been exploited for the preparation of well-defined polymers from a large diversity of acrylates, acrylamides, and methacrylates with different polarity profiles, block copolymers, and also high-order multiblock copolymers prepared even at complete monomer conversion.[8,9] In this Perspective, we aim to highlight recent developments on SET-LRP and discuss the current applications mostly in the

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synthesis of biomacromolecules and their conjugates. Mechanistic studies were discussed previously[6,7,9,24−26] and therefore will not be repeated here.

2. BRIEF OVERVIEW AND DEVELOPMENTS ON SET-LRP

2.1. Suitable Monomers for SET-LRP. SET-LRP represents the most efficient polymerization protocol for the accelerated synthesis of well-defined polymers from a great variety of monomers. Acrylates such as methyl acrylate (MA),[27−30] ethyl acrylate (EA),[22,30] butyl acrylate (*n*-BA),[22,27,29−35] and *tert*-butyl acrylate (t-BA) are by far the most investigated monomers (Scheme 1).[27−30,36−38]

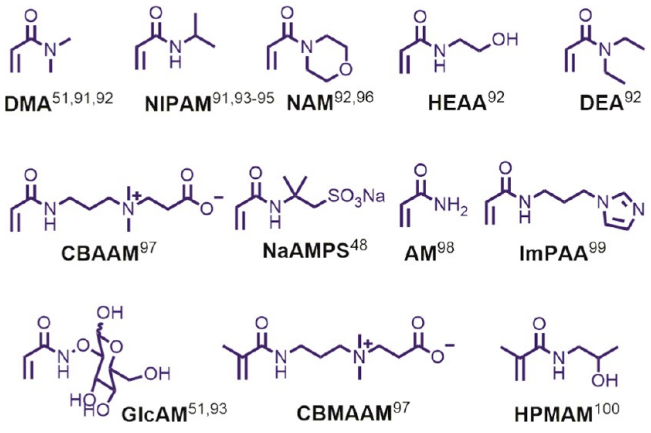
However, during the last few years, the palette of acrylates suitable for polymerization by SET-LRP has been greatly expanded. Monomers such as 2-ethylhexyl acrylate (EHA),[27,34,39,40] benzyl acrylate (BzA),[186] and 2-methoxyethyl acrylate (MEA)[32,41] have successfully produced the corresponding polyacrylate under SET-LRP conditions. The list is so broad that it ranges from hydrophobic such as adamantly acrylate (ADA),[42] lauryl acrylate (LA),[43] and octadecyl acrylate (OA)[29] to hydrophilic and water-soluble acrylates such as 2-hydroxyethyl acrylate (HEA),[27,44−47,49,51] 2-acryloyloxyethyl phosphorylchlorine (APC),[48] di(ethylene glycol) 2-ethylhexyl ether acrylate (DEGEEA),[41] and oligo(ethylene oxide) methyl ether acrylate (OEGMEA).[30,31,49−51] Monomers such as solketal acrylate ((2,2-dimethyl-1,3-dioxolan-4-yl)methyl acrylate) (SA),[52] glycidyl acrylate (GA),[53] *o*-nitrobenzyl acrylate (NBA),[54] dithiophenolmaleimide acrylate (DMMA),[55] acrylic acid 3-trimethylsilanyl-prop-2-ynyl ester (TMSPA),[53] *N*,*N*-dimethylaminoethyl acrylate (DMAEA),[56] pentaerythritol triacrylate (PETA),[57] and 2-(acryloyloxy)ethyl 3,4-bis(2-phenylethynyl)benzoate (ABPB)[58] have been polymerized by SET-LRP leading to functionalized polymers. Our laboratory also reported the polymerization of several semifluorinated acrylates such as 1*H*,1*H*,2*H*,2*H*-perfluorooctyl acrylate (PFOA),[59] 2,2,3,3,4,4,4-heptafluorobutyl acrylate (HFBA),[59] 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA),[60] and 1*H*,1*H*,5*H*-octafluoropentyl acrylate (OFPA),[59] whereas others reported that SET-LRP is also compatible with sugar-containing acrylates such as glucose acrylate (GlcA),[61] mannose acrylate (ManA),[61−63] fucose acrylate (FucA),[61] and 2-[(D-glycosamin-2-*N*-yl)carbonil]oxyethyl acrylate (HEAGI).[64]

To date, the list of methacrylates that have been polymerized under SET-LRP conditions is almost as extensive as that of acrylates (Scheme 2). These results allow for the conclusion that SET-LRP also produces well-defined polymethacrylates. In the initial report on SET-LRP,[8] polymerization of methyl methacrylate (MMA) was demonstrated in a series of nonoptimized kinetic experiments in dipolar aprotic solvents using 2,2-dichloroacetophenone (DCAP) and phenoxybenzene-4,4′-disulfonyl chloride (PDSC) as initiators and Cu(0)/PMDETA and bpy as catalytic systems. Later, our group and others reported that the SET-LRP of MMA can be performed under many other conditions[65−71] (e.g., fluorinated alcohols[72,73] or acetic acid[74] as solvent and in the presence or air).[66] SET-LRP of ethyl methacrylate (EMA),[72] butyl methacrylate (*n*-BMA),[57,72,75] *tert*-butyl methacrylate (*t*-BMA),[76] methyl adamantly methacrylate (MAMA),[86] and isobornyl methacrylate (IBMA)[77] also produced the corresponding polymethacrylates, whereas methacrylic acid (MAA) could be copolymerized with MMA.[78] Hydrophilic methacrylates such as 2-hydroxyethyl methacrylate (HEMA),[23] di(ethylene glycol) methyl ether methacrylate (DEGMEMA),[79] tri(ethylene glycol) methyl ether methacrylate (TEGMEMA),[79] oligo(ethylene glycol) methyl ether methacrylate (OEGMEMA),[80−83] and the corresponding azide (OEGMA-N_3) and hydroxyl (OEGMA−OH) derivatives, functional methacrylates such as 2-(*tert*-butyl-aminoethyl) methacrylate (t-BAMA),[83] 2-(dimethylamino) ethyl methacrylate (DMAEMA),[84] 2-(diethylamino)ethyl methacrylate (DEAEMA),[85] and γ-butyrolactone methacrylate (GBLMA),[86] as well as ionic *N*,*N*-compounds such as dimethyl-*N*-methacryloyloxyethyl-*N*-sulfobutyl ammonium (DMSA)[87] and [2-(methacryloxy)ethyl]-trimethylammonium chloride (MAETC)[88] have also been successfully polymerized under optimized SET-LRP conditions. Complex methacrylates such as 1′-(2-methacryloxyethyl)-3′,3′-dimethyl-6-nitrospiro(2*H*-1-benzopyran-2,2′-indoline) (SPMA)[89] and 7-(2-methacryloyloxy)-4-methylcoumarin (CMA)[90] also tolerated the mild reaction conditions of SET-LRP. In the same way as the corresponding acrylates, SET-LRP of 1,1,1,3,3,3,-hexafluoroisopropyl methacrylate (HFIPMA)[60] and 1*H*,1*H*,5*H*-octafluoropentyl methacrylate (OFPMA)[59] were also successful in 2,2,2-trifluoroethanol (TFE) but in this case at higher temperature (50 °C).

The polymerization of some acrylamides such as *N*,*N*-dimethyl acrylamide (DMA) and *N*-isopropylacrylamide (NIPAM) was also reported by our group to be feasible in some dipolar aprotic and polar protic solvents in the presence of externally added $CuCl_2$ to mediate deactivation in the early stages of the reaction.[91] Later, the development of aqueous SET-LRP methodologies allowed the polymerization of DMA,[51,92] NIPAM,[51,93−95] *N*-acryloylmorpholine (NAM),[92,96] 2-hydroxyethyl acrylamide (HEAA),[92] *N*,*N*-diethylacrylamide (DEA),[92] and (3-acryloylamino-propyl)-(2-carboxyethyl)-dimethylammonium (CBAAM)[97] demonstrating in all cases fast polymerization rates and narrow molecular weight distributions. 2-Acrylamido-2-methylpropanesulfonic acid sodium salt (NaAMPS),[48] acrylamide (AM),[98] *N*-(3-(1*H*-imidazole-1-yl)-propyl) acrylamide (ImPAA),[99] glucose acrylamide (GlcAM),[51,93] and the methacrylamides (3-methacryloylamino-propyl)-(2-carboxy-ethyl)dimethylammonium (CBMAAM)[97] and *N*-(2-hydroxypropyl) methacrylamide (HPMAM)[100] have also been studied (Scheme 3).

Finally, although having received less attention, it is important to mention that styrene (St) and acrylonitrile (AN)[101−106] could also be successfully polymerized with

Scheme 3. Acrylamides and Methacrylates Used in SET-LRP (Blue, Hydrophilic and Water Soluble)



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good control and reasonable dispersities under optimized conditions, demonstrating the versatility of this technique. In fact, Haddleton and co-workers recently reported one set of universal conditions for the efficacious polymerization of MA, MMA, and St (using an identical initiator, ligand, copper salt, and solvent) based on commercially available and inexpensive reagents.[107] The versatility of these conditions was demonstrated by the near quantitative polymerization of these monomers to yield well-defined polymers over a range of molecular weights and low dispersities (~1.1−1.2).

In the context of this Perspective, it is necessary to highlight that SET-LRP has also successfully polymerized VC.[8,108,109] PVC has been used for medical applications for more than a half-century and represents one of the most important commodities in the modern world.[110] To date, only SET-LRP and SET-DTLRP[111−116] are able to polymerize VC in a controlled fashion in terms of predictable molecular weight and high-level retention of the active chain ends. Moreover, PVC prepared using both polymerization procedures exhibits higher thermal stability and syndiotacticity than the homologous polymer resulting from a conventional free-radical polymerization. SET-LRP and SET-DTLRP not only provide a suitable pathway to PVC homopolymers but also to more complex architectures (i.e., block copolymers) with various applications in the medical field without the need for undesired plasticizers required to control the glass transition temperature of the flexible PVC.[8,108,109,111−116]

2.2. Tolerance to Air and Radical Scavengers of SET-LRP. From a technologic point of view, the tolerance of SET-LRP to the presence air and radical scavengers, classically used as stabilizers in commercially available vinyl monomers, is important. The rigorous oxygen-free environment required for most LRP techniques demands rigorous deoxygenation procedures because many transition metal catalysts, such as Cu(I)X, are easily oxidized. In the case of Cu(0) powder-catalyzed SET-LRP, any adventitious air introduced into the reaction mixture is consumed by oxidation of Cu(0) to Cu_2O. However, Cu_2O can still directly participate in the activation step in LRP but does it more slowly than Cu(0).[8,9,17,117] In addition, Cu_2O can also disproportionate to Cu(0), but this process is slower than the corresponding disproportionation of Cu(I)X. This is because Cu_2O is insoluble, and therefore, its disproportionation involves a heterogeneous process. Cu(I)X is soluble, and its disproportionation takes place through a homogeneous process. Interestingly, SET-LRP catalyzed by Cu(0) wire exhibits an intrinsically higher tolerance toward oxygen because a combination of heterogeneous and "nascent" Cu(0) is the activator. In fact, the SET-LRP of MA[118,119] and MMA[66] using Cu(0) wire could be simplified by eliminating tedious and time-consuming deoxygenation procedures such as freeze−pump−thaw cycles or inert gas purging.[124] Whereas the presence of oxygen immediately stopped the polymerization, using a blanket of nitrogen in the reaction mixture, the polymerization produced, after an induction period in the range of 10 min, polymers with predictable molecular weight and low dispersity (~1.1−1.2).[118] Additionally, the presence of hydrazine hydrate as reducing agent yielded a faster polymerization via the in situ reduction of the Cu_2O from the wire surface of Cu(0).[66,118,119] In fact, SET-LRP by Cu(0) wire is not just living but also has been demonstrated to be the first example of immortal LRP.[120] The immortality of the SET-LRP process catalyzed by Cu(0) wire was supported by unsuccessful interruption of the polymerization of MA via exposure to O_2 from air. As can be seen in Figure 1, although the polymerization stopped multiple times when the reaction

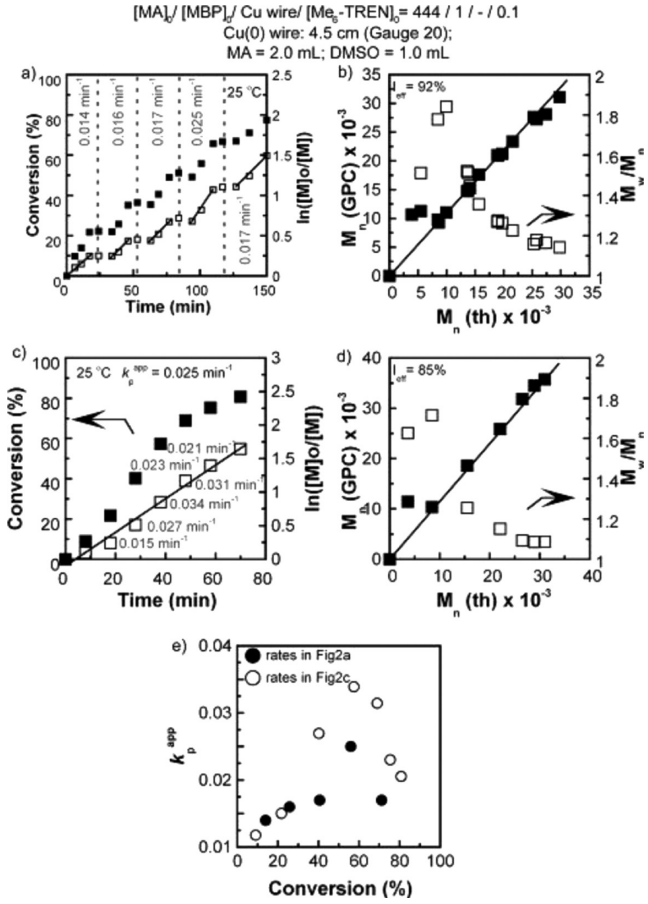

Figure 1. Kinetic plots of SET-LRP of MA initiated by methyl 2-bromopropionate (MBP) in DMSO at 25 °C using 4.5 cm of 20 gauge Cu(0) wire as catalyst (a and b) with four time exposures to air flow during the middle of reaction and (c and d) without air exposure; (e) plot of rate constants obtained from (a and c) versus conversion of monomers. Reaction conditions: $[MA]_0/[MBP]_0/[Me_6\text{-TREN}]_0$ = 444:1:0.1, $[MA]_0$ = 7.4 mol/L, MA = 1.0 mL, DMSO = 0.5 mL. Reproduced from ref 120, with permission from John Wiley and Sons. Copyright 2010 Wiley Periodicals, Inc.

mixture was exposed to air, the SET-LRP process restarted each time, showing the same conversion as in the control experiment with no interruptions after releasing the reaction vessel and reestablishing the catalytic cycle.

Because of their high reactivity, commercial vinyl monomers are stabilized with radical scavengers to prevent inadvertent polymerization during transport, storage, and handling. The robustness of SET-LRP to the stabilizer hydroquinone monomethyl ether (MEHQ) added as a solid to the polymerization mixture was investigated by our laboratory.[121] SET-LRP of MA initiated with methyl 2-bromopropionate (MBP) or bis(2-bromopropionyl)ethane (BPE) in DMSO or methanol proceeded to near quantitative conversion with excellent predictability of molecular weight and reasonable dispersity (~1.2) regardless of MEHQ loading level (1:0 initiator/MEHQ to 1:10 initiator/MEHQ).[121] Interestingly, only at the highest loading level was a small induction period attributable to the presence of trapped O_2 in the solid MEHQ observed. Although the addition of MEHQ did retard the

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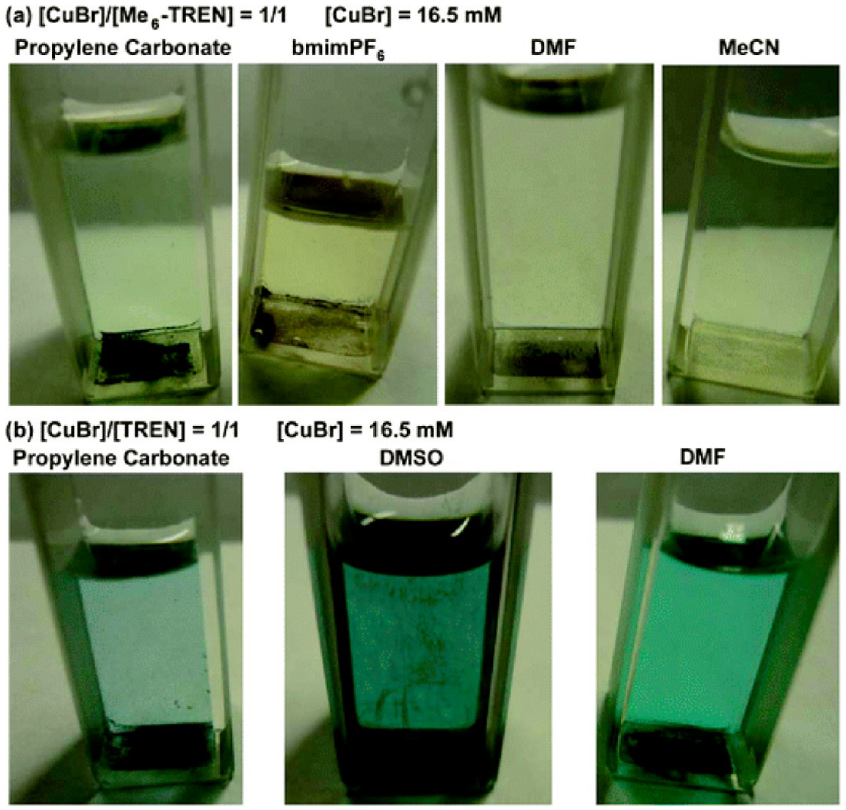

Figure 2. Visual observation of Cu(0) nanoparticles and $CuBr_2$ generated from the disproportionation of CuBr in polar aprotic solvents in the presence of Me_6-TREN (a) and TREN (b). Conditions: solvent = 1.8 mL; [CuBr]/[N-ligand] = 1:1. Pictures were taken 10 min after mixing the reagents. Reproduced from ref 14, with permission of The Royal Society of Chemistry. http://dx.doi.org/10.1039/C2PY21084C.

polymerization rate, the rate decrease was not significant (~10%). In a further publication, the kinetics of SET-LRP was investigated using both inhibited MA as supplied by Aldrich, containing ~100 ppm of MEHQ, and MA passed through a basic Al_2O_3 chromatographic column to remove the stabilizer.[122] In the same way as in the previous study, the presence of homogeneous radical MEHQ stabilizer in MA only slightly compromised the rate of polymerization. Therefore, from a technologic point of view, the fact that SET-LRP is compatible with commercial-grade inhibited monomers is noticeable.

2.3. Cu(0) Catalysts for SET-LRP: Recent Advances. Cu(0) in any available form, including powder,[8,123] wire,[124] tube,[125] and even coins,[126] can be used as catalyst in SET-LRP. As mentioned above, the disproportionation of Cu(I)X generated by activation with Cu(0) into nascent, extremely reactive Cu(0) nanoparticles and $Cu(II)X_2$ is extremely important for the success of the polymerization.[9] This phenomenon was confirmed by direct visualization combined with UV−vis spectroscopy of the disproportionation of CuBr in a survey of different polar solvents (e.g., water, DMSO, propylene carbonate, and DMF) and combinations of solvents in the presence of N-ligands such as Me_6-TREN and TREN.[8,14] On the other hand, in a polar solvent such as MeCN, which acts as a good stabilizing ligand for Cu(I)X, no insoluble Cu(0) nanoparticles were observed, suggesting that disproportionation does not occur (Figure 2).

Nascent Cu(0) colloidal nanoparticles activate the initiator and dormant chains via a heterogeneous SET mechanism, although most likely, atomic Cu(0) generated by disproportionation may be activated via a homogeneous process.[25] To assess how nascent Cu(0) mediates the SET-LRP, the interruption of SET-LRP of MA in DMSO using Cu(0) wire was investigated using two different procedures.[12] First, during the SET-LRP process, Cu(0) wire was lifted from the reaction mixture, leaving colloidal Cu(0) and soluble CuBr and $CuBr_2$ species in solution. After that, the polymerization continued although at a much slower rate. However, when the reaction mixture was decanted from one Schlenk flask containing the catalyst to another one without Cu(0) catalyst, the reaction was completely interrupted, confirming that the soluble CuBr generated during the polymerization cannot be the catalytic species at levels present in SET-LRP.[10] These interruption experiments demonstrated that colloidal Cu(0) particles generated via disproportionation all along the polymerization are able to sustain the reaction even in the absence of Cu(0) wire. In a further study, the nucleation and growth of nascent Cu(0) was also investigated by scanning electron microscopy (SEM).[11] It was observed that, after disproportionation and the SET-LRP process, the surface roughness of Cu(0) wire increased dramatically by the formation of Cu(0) clusters and high-density craters and large valleys, respectively. However, it was observed that not all Cu(0) generated by disproportionation nucleates and grows on the Cu(0) surface, and therefore, the polymerization mixture contains stabilized Cu(0) particles in solution. These observations correlate with the experiments mentioned above, where SET-LRP proceeds even after removing the Cu(0) wire from the reaction mixture.

It is well-known that the form and size of the Cu(0) powder used has an important effect on the polymerization kinetics of SET-LRP.[10,125] A decrease in particle size produces a significant increase in the apparent rate constant of propagation (k_p^{app}) while preserving good levels of control.[10] For example, it was

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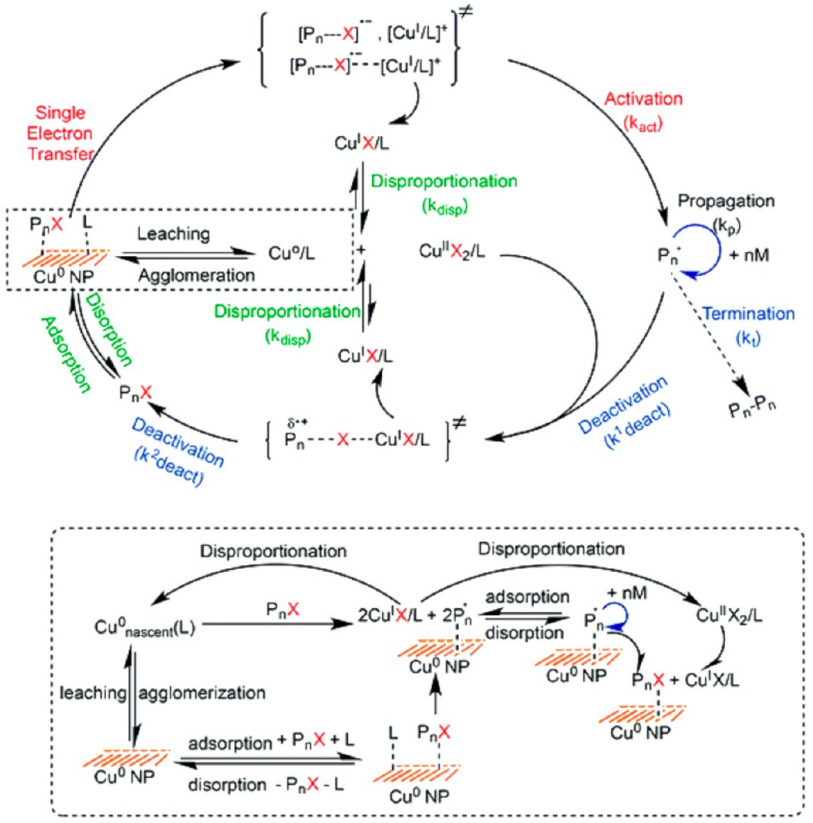
Scheme 4. Proposed Mechanism for Aqueous SET-LRP by in Situ-Generated Cu(0) Nanoparticles Obtained by Disproportionation of CuBr/Me_6-TREN; Reproduced from Ref 49 with Permission of The Royal Society of Chemistry[a]



[a]http://dx.doi.org/10.1039/c4py01748j.

reported that a decrease of the Cu(0) particle size from 425 to 0.05 μm (50 nm) increases the k_p^{app} for SET-LRP of MA by almost an order of magnitude.[10] However, regardless of the Cu(0) particle size used, first-order SET-LRP kinetics is observed up to 100% monomer conversion. The experiments performed using Cu(0) wire demonstrated a SET-LRP process with greater control of molecular weight distribution than that of Cu(0) powder.[124] Interestingly, a series of kinetic experiments were used to measure the external rate order (vis-à-vis surface area) for Cu(0) wire catalyst as well as to predict the k_p^{app} from predetermined wire dimensions. This combination of characteristics associated with Cu(0) wire-catalyzed SET-LRP including facile catalyst preparation, handling, and recovery (the wire is usually wrapped around the stir bar), the high level reproducibility, as well as good molecular weight control make this methodology amenable for the synthesis of tailored vinylic polymers.

As mentioned above, Cu(0) in any form is susceptible to be oxidized to Cu_2O at any time and therefore should be preserved under an anaerobic atmosphere. This is especially important in the case of "nascent" Cu(0) powder, usually prepared via disproportionation of Cu(I)X.[131] Cu_2O can act as a catalyst for SET-LRP but is known to be less active than Cu(0).[8,9,17,117] In this context, methods for the activation of the Cu(0) wire surface using hydrazine hydrate ($N_2H_4{\cdot}H_2O$) treatment[127] or acid dissolution[128] of Cu_2O were also elaborated. Interestingly, self-activation of the Cu(0) wire, following an unknown mechanism, was observed in certain fluorinated alcohols.[129] As a continuation of these experiments, our laboratory recently reported a multiple-stage activation of the catalytically inhomogeneous Cu(0) wire used in SET-LRP by a combination of acetone washing, razor blade scratching, and either reduction or acid dissolution of the Cu_2O from the surface.[130] A notorious increase in catalyst activity (82% higher k_p^{app} for the polymerization of MA in DMSO) was achieved following a simple protocol consisting of three sequential steps: (i) acetone washing, (ii) scratching, and (iii) immersion in a 96.1% H_2SO_4 solution.

Colloidal Cu(0) isolated after in situ disproportionation of Cu(I)X in the presence of Me_6-TREN in polar solvents and their binary mixtures with water was also used in SET-LRP.[131] The resulting nanopowder, prepared to mimick the nascent Cu(0) catalyst generated during SET-LRP, provided a faster polymerization than any commercial class of Cu(0) powder, Cu(0) wire, or CuBr. Using monomer/initiator ratio $[MA]_0/[MBP]_0$ = 222:1, this catalytic system afforded an ultrafast polymerization reaching 80% monomer conversion in only 5 min. Despite the high polymerization rate, a high-level retention of active chain ends was observed. Meanwhile, nascent Cu(0) generated by disproportionation of CuBr/Me_6-TREN in pure water and mixtures of water with other solvents has also been used. Hydrophilic acrylamides, such as DMA, NAM, and GAM, and other hydrophilic monomers have been successfully polymerized following this protocol.[51,49,91,92,96] In the preparation of multiblock polyacrylamides, the monomer addition sequence was crucial for obtaining polymers with highly functional halogen chain ends. It was demonstrated that the rate of disappearance of halogen chain ends is higher in tertiary acrylamides (DMA, DEA, NAM) in comparison with secondary monomers such as NIPAM and HEAA.[92] On the

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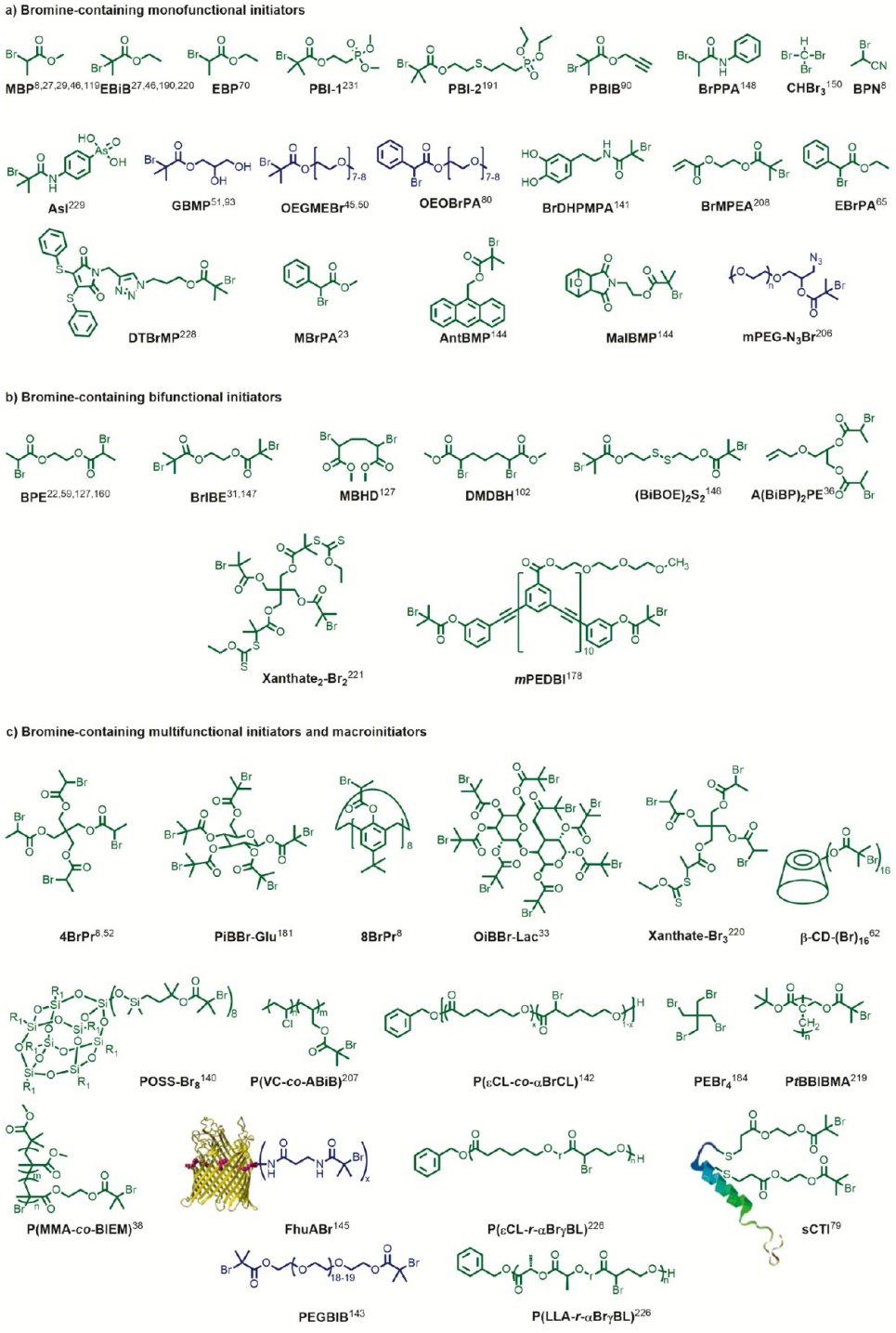
Scheme 5. Bromine-Containing Initiators Suitable for SET-LRP (Blue, Hydrophilic and Water Soluble; Green, Hydrophobic and Water Insoluble)[a]



[a]Note that polysaccharide-derived macroinitiators and those used in surface-initiated SET-LRP are not included.

other hand, the SET-LRP of HEA and OEGMEA was also investigated at temperatures from −22 to +25 °C using in situ-generated Cu(0) and OEGME-Br (see Scheme 5) as initiator.[49] Unexpectedly, both monomers showed higher k_p^{app} values at 0 °C than at 25 °C. Moreover, although the theoretical chain-end functionality at complete monomer conversion should be at around 0%, the amphiphilic POEGMEA prepared at 0 °C shows a remarkable 88% experimental chain-end functionality at 100% conversion.[49] This unexpected high chain-end fidelity was attributed to the slow desorption of the hydrophobic backbone containing the propagating radicals of these amphiphilic polymers from the Cu(0) surface due to their strong hydrophobic effect. Polymer radicals adsorbed on the surface of the catalyst undergo monomer addition and reversible deactivation but do not undergo bimolecular termination that requires desorption (Scheme 4).

As an alternative source of Cu(0) catalyst for SET-LRP, the direct reduction of $CuCl_2$/Me_6-TREN using the strong

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reducing agent $NaBH_4$ in water was recently reported by the Monteiro and Percec laboratories in a joint publication.[94] The advantage of using $NaBH_4$ is the stoichiometric production of Cu(0), allowing predefined ratios of Cu(0) activator to Cu(II) deactivator. With this aqueous phase system, NIPAM was polymerized within minutes and with controlled and narrow molecular weight distributions in agreement with an ideal living radical behavior.[94] In a further publication, the same authors elaborated a method to produce PNIPAM polymers with stable "click" functional end-groups in aqueous media via the in situ azidation at the bromine polymer chain ends.[95] Note that in 2011, Zhu and co-workers already envisioned the in situ generation of Cu(0) from Cu(II) ($CuSO_4 \cdot 5H_2O$) using hydrazine hydrate as a methodology to mediate SET-LRP.[132] The generation of Cu(0) from $Cu(II)X_2$ salts has also been successfully applied to SET-LRP in multiphasic systems (vide infra).[133−135]

2.4. Initiators for SET-LRP. SET-LRP requires, just as all the other metal-catalyzed LRP techniques, the correct selection of initiator. A variety of initiators including mono-, bi-, and multifunctional as well as macroinitiators have been used in SET-LRP.[9,123,136] Suitable initiators must provide rapid and quantitative initiation to produce well-defined polymers with narrow molecular weight distributions. Nevertheless, a too fast initiation would result in increased levels of bimolecular termination of primary radicals.[137] In this context, the reactivities of initiator and monomer should be matched. In SET-LRP, methyl 2-bromopropionate (MBP) and ethyl α-bromoisobutyrate (EBiB) are the most commonly used monofunctional initiators for acrylate-type monomers because of their structural resemblance to the polyacrylate growing species.[9] A combination of kinetic experiments and computational calculations for the heterolytic bond dissociation energies and electron affinities of both initiators in the dissociative electron transfer (DET) step of SET-LRP of MA suggested that EBiB is more effective in the Cu(0) wire-catalyzed SET-LRP of acrylates.[138] Inspired from both monofunctional initiators, a great variety of 2-bromopropioates has been employed in the SET-LRP of acrylates as well as methacrylayes, acylamides, and VC (Scheme 5).[9,123,139−148]

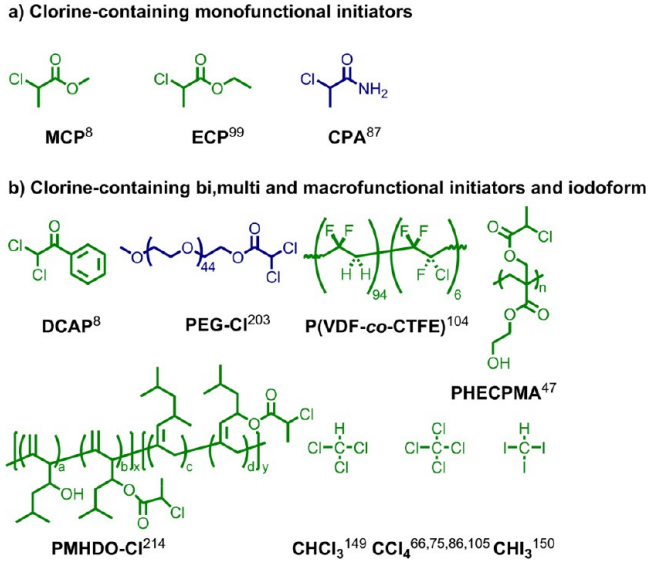
Chlorine-containing initiators and macroinitiators have also been used in SET-LRP (Scheme 6).

Some chlorine α-chloroesters such as methyl 2-chloropropionate (MCP),[91,100,149] 2,2-dichloroacetophenone (DCAP),[71] and ethyl 2-chloropropanoate (ECP)[99] were also used as initiators in the SET-LRP of acrylates, methacrylates, acrylamides, and styrenes. The haloforms $CHCl_3$,[8,149] $CHBr_3$,[8,150] and CHI_3[8,150] have also been employed for the SET-LRP of MA in DMSO at 25 °C. $CHCl_3$ and $CHBr_3$ are monofunctional initiators for MA, whereas CHI_3 performs as a monofunctional initiator at low conversion but transitions to a bifunctional one at high conversion. Note that SET-LRP initiated by $CHCl_3$ requires small levels of $CuCl_2$ to control the LRP. $CHBr_3$ has also been successfully used to initiate the SET-LRP of VC.[8,109] In conclusion, almost all the reported initiators used in other metal-catalyzed LRP techniques including sulfonyl chlorides, bromides, and iodides[17,67,72,151−158] as well as N-halide initiators[1,159] can be used in SET-LRP as such or modified to become soluble in various media, including water (Scheme 7).

2.5. Solvents for SET-LRP: Recent Advances. SET-LRP is traditionally performed in one phase. Although water[4,46,49−51,87,92,95,100,122] and DMSO[8,22,23,42,50,66,120,131,160,168] were the first solvents reported to be compatible with SET-LRP, to date, the list of suitable solvents includes but is not limited to alcohols,[91,119,160] dimethylformamide (DMF),[14,122] dimethylacetamide (DMAC),[14,122] ethylene carbonate,[14,122] propylene carbonate,[14,122] different mixtures of solvents with water,[14,91,122,164] and mixtures of two solvents.[14,164] Polyethylene glycol, polypropylene glycol, and their binary mixtures with DMSO and ethanol,[161] as well as ionic liquids,[8,162] fluorinated alcohols[29,59,72] such as TFE and 2,2,3,3-tetrafluoropropanol, and dimethyl lactamide (DML)[163] have also been demonstrated to be promising reaction media. Therefore, SET-LRP is the ideal method for the polymerization of polar monomers in polar solvents.[164] Several hydrophilic monomers have also been polymerized following SET-LRP conditions in blood serum,[165] phosphate buffer solution,[51] as well as different alcoholic beverages.[166] The crucial Cu(I)X disproportionation step taking place in polar solvents, water, and in their mixtures borders the diversity of polymers accessible by SET-LRP.[8,23,27,29,167] Attempts to perform SET-LRP in non-disproportionating solvents such as MeCN and toluene resulted in polymers with poor chain end functionality[168,169] due to the insolubility of $Cu(II)X_2$ in nondisproportionating and nonpolar solvents.[14] As can be seen in Figure 3, regardless of the size of the Cu(0) catalyst, the SET-LRP of MA in DMSO produces a PMA with a remarkable bromine chain-end functionality (~97%) up to high conversion. Conversely, in MeCN and in toluene, the functionality of the chain ends decreases continuously throughout the polymerization.[168,169]

In nonpolar solvents, the monomer mediates the disproportionation of Cu(I)X into Cu(0) and $Cu(II)X_2$ behaving as a ligand to Cu(I)X and $Cu(II)X_2$ species through interactions with its double bond as well as carbonyl groups in the case of acrylates and methacrylates and phenyl groups in styrene.[14] The PMA with ultrahigh M_n obtained by SET-LRP in DMSO resulted in a gel consisting of the soluble PMA that is not soluble in the reaction media beyond a certain degree of

Scheme 6. Chlorine and Iodine-Containing Initiators Suitable for SET-LRP (Blue, Hydrophilic and Water Soluble; Green, Hydrophobic and Water Insoluble)[a]



[a]Note that polysaccharide-derived macroinitiators and those used in surface-initiated SET-LRP are not included.

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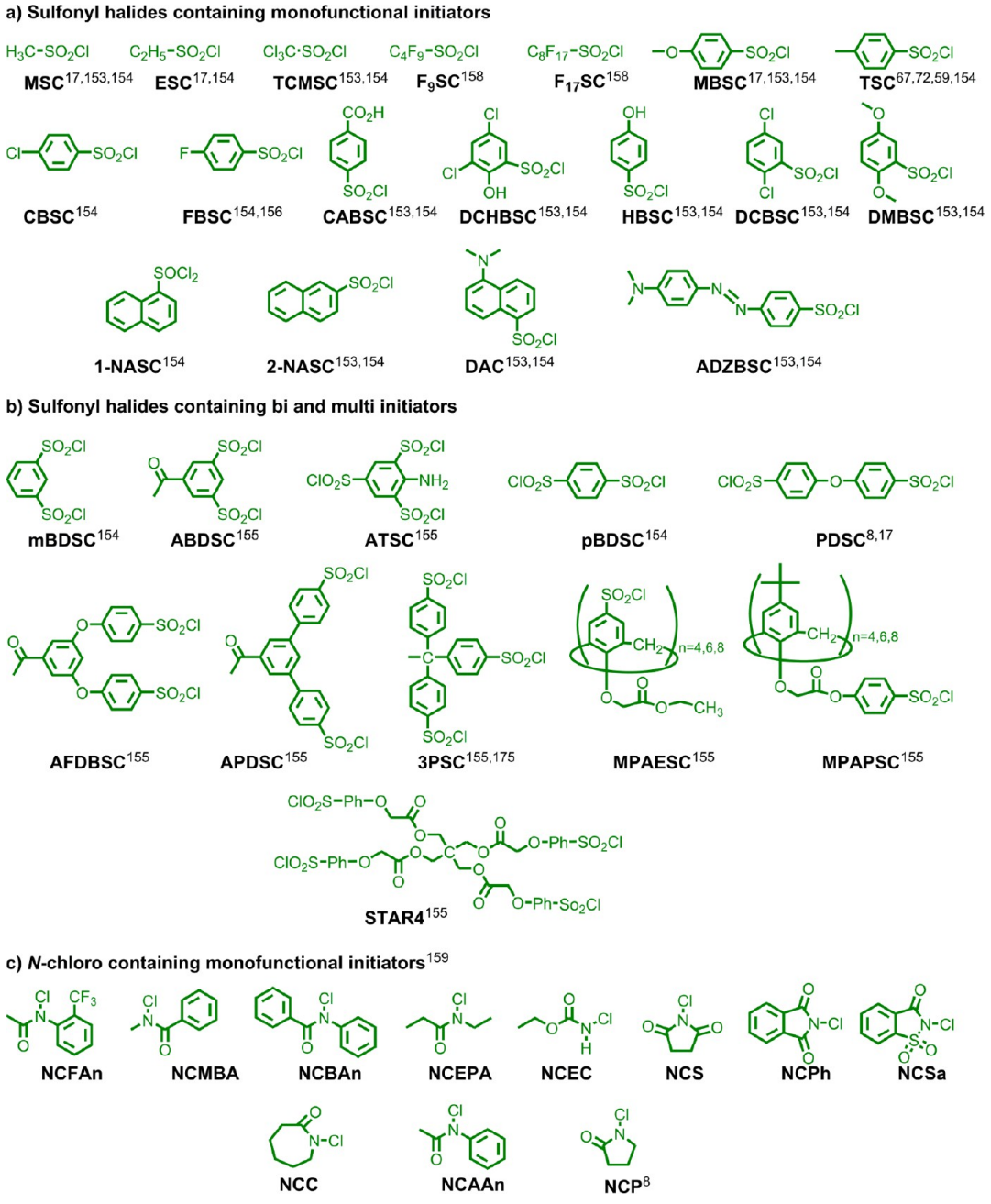
Scheme 7. Sulfonyl Halides and N-Halides Suitable for SET-LRP (Green, Hydrophobic and Water Insoluble)



polymerization.[22,60] Nevertheless, it was observed that even at the gel state, the SET-LRP process continues. These experiments and the self-generated biphasic regime, containing the polymer solution and an immiscible Cu(II)X_2 solution observed in our laboratory[5,22,60] and in the Haddleton laboratory,[33,43,170] during the polymerization of *n*-BA and other hydrophobic monomers, inspired the recently developed SET-LRP methodology in multiphase such as biphasic and triphasic systems.[133,134]

Biphasic SET-LRP involves a water-soluble solvent that disproportionates Cu(I)X into Cu(0) and Cu(II)X_2, such as an alcohol[133] or a water-soluble solvent that does not disproportionate Cu(I)X, such as MeCN.[134] In the presence of water, a nonpolar monomer such as BA, a ligand such as Me_6-TREN and Cu(II)X_2, a first phase consisting of BA monomer and solvent, and a second one containing water, Cu(II)X_2, and the ligand are generated.[133−135] These two phases are immiscible.[133−135] Reduction of Cu(II)X_2 to Cu(0) with $NaBH_4$ in the water phase initiates the SET-LRP process. Two options are available during this SET-LRP methodology. In the first one, the polymer remains soluble in the organic phase and the process consists of a biphasic system. In the second one at a certain conversion, which corresponds to a certain polymer molecular weight, the polymer becomes insoluble in the organic phase, but its glass transition temperature is below the polymerization temperature and therefore it forms a gel in the organic phase. In this case, SET-LRP proceeds in three phases consisting of the polymer gel swelled in the organic phase and the water phase. These recent advances will definitively broaden the monomers and solvents traditionally employed in SET-LRP to a new range of nonpolar hydrophobic compounds.

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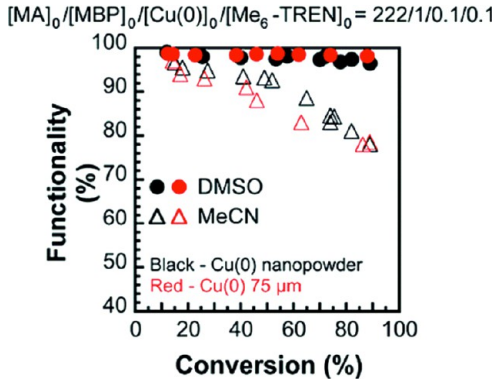

Figure 3. Evolution of bromine chain-end functionality with conversion in solvents mediating different degrees of disproportionation. Reaction conditions: MA = 1 mL, solvent = 0.5 mL, $[MA]_0/[MBP]_0/[Cu(0)]_0/[Me_6\text{-TREN}]_0$ = 222:1:0.1:0.1, 25 °C, Cu(0) 75 μm or Cu(0) nanopowder. Reproduced with permission from ref 168. Copyright 2012 American Chemical Society.

In addition, a synergistic effect occurring during the biphasic SET-LRP in ethanol−nonpolar solvent−water mixtures was recently described by our laboratory.[135] The addition of at least 10% of nonpolar solvents such as hexanes, toluene, anisole, ethyl acetate, diethyl carbonate, and cyclohexane to the ethanol−water reaction mixture transforms SET-LRP of *n*-BA from a triphasic to a biphasic system that is feasible for technological developments. This biphasic SET-LRP shows a maximum rate of polymerization at a certain volume fraction of hexanes, whereas when the hexane concentration is maintained constant, and a maximum rate is observed at a certain volume fraction of water.

2.6. SET-LRP: An LRP Technique Providing Perfect or Near Perfect Chain-End Fidelity. LRP techniques require high polymer chain-end fidelity when the target is the preparation of well-defined polymers with complex topologies and architectures. In this context, termination processes and other competing side reactions that compromise the functionality of the chain ends are undesirable.[171] To this day, nobody can question that SET-LRP provides perfect or near perfect chain-end fidelity at very high monomer conversion when performed under proper conditions. Quantitative and/or extremely high levels of active chain ends at >90% in most cases[10,22,128,168,172,173] and even at >99% or 100% conversion under certain conditions have been reported.[168,174] This has systematically been demonstrated by a series of in-depth structural analyses of polymers by NMR, matrix-assisted laser desorption ionization-time-of-flight (MALDI-TOF), and re-initiation experiments reported by our and other laboratories over the last 10 years.[10,22,128,168,172,173,175,176] As an example, Figure 4 shows the MALDI-TOF spectra of PMA isolated at 99% monomer[168] before and after nucleophilic displacement with thiophenolate via thio-bromo "click" methodology.[168,177] A shift in the MALDI-TOF peaks corresponding to the difference between thiophenolate and -Br groups must be observed after the thio-bromo "click" reaction (Figure 4).[168] When bimolecular termination occurs, it can be detected after the thio-bromo "click" reaction by MALDI-TOF analysis.[168]

Without a perfect or near-perfect preservation of the halogen chain ends, the preparation of macromolecular structures with the current level of complexity would not have been possible. Some outstanding examples are the successful preparation of (i) perfectly bifunctional polyacrylates,[22] (ii) ultrahigh molecular weight polymers[8,23,34,160] including foldamer-linked polymers,[178] (iii) high-order multiblock copolymers using iterative strategies,[30,92,167,175,179] (iv) gradient copolymers[180] and other complex polymer topologies and architectures,[181] such as macrocycles[182] and stars,[52,183,184] dendritic macromolecules prepared in combination with thio-bromo "click" chemistry,[185] and size-tunable polymeric nanoreactors,[186] as well as (v) the development of novel strategies for the synthesis of biomacromolecules and their conjugates (vide infra).

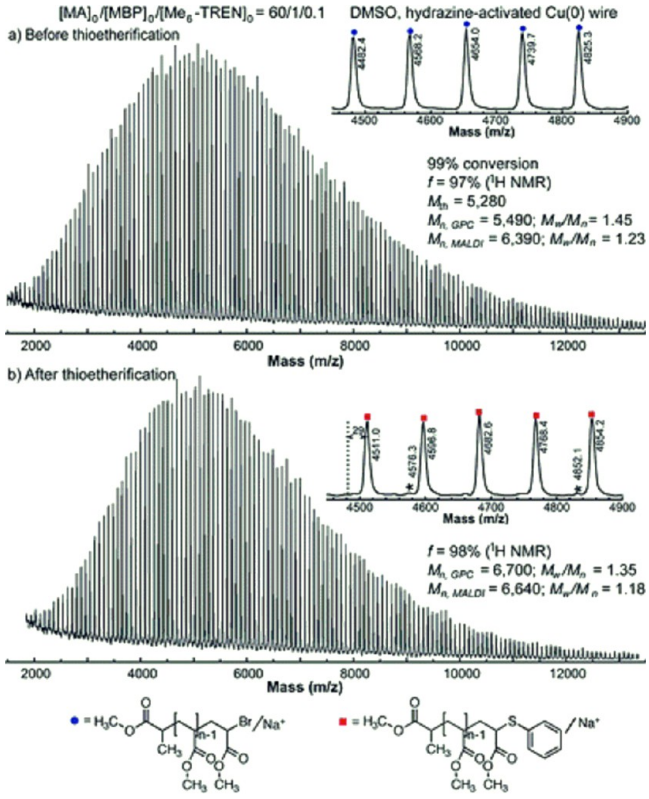

Figure 4. MALDI-TOF spectra of monofunctional PMA obtained at 99% conversion (M_n = 5490, M_w/M_n = 1.45) (a) before and (b) after nucleophilic displacement of the bromine chain end with thiophenol. Polymerization conditions at 25 °C: MA = 2 mL, DMSO = 1 mL, $[MA]_0/[MBP]_0/[Me_6\text{-TREN}]_0$ = 60:1:0.1, hydrazine-activated Cu(0) wire = 0.5 cm of 20 gauge wire. Reproduced with permission from ref 168. Copyright 2012 American Chemical Society.

2.7. SET-LRP in Continuous Flow. The Hutchinson laboratory was the first to develop a reactor setup for SET-LRP in continuous flow processes using the walls of readily available copper tubing as a catalyst source.[187,188] The polymerization time (residence time) could be easily tuned by adjusting the copper tubing length or changing the flow rates. MBP-initiated SET-LRP of MA in DMSO with Me_6-TREN as ligand showed a fast polymerization rate due to the huge volume-to-surface ratio, whereas the mass of copper consumed was found to be nearly negligible (0.01% of the total reactor weight). Monomer conversions of 43 and 67% were obtained at a mean residence time of 4 and 16 min, respectively. Although there was some broadening of the molecular weight distribution due to channeling inside the reactor, reinitiation experiments demonstrated that the polymer chains retained a high-level of functionality. The combination of living polymer produced at high polymerization rates and low volatile organic solvent content demonstrated the potential of this reactor for scale-up SET-LRP. Later, the same group improved the original setup

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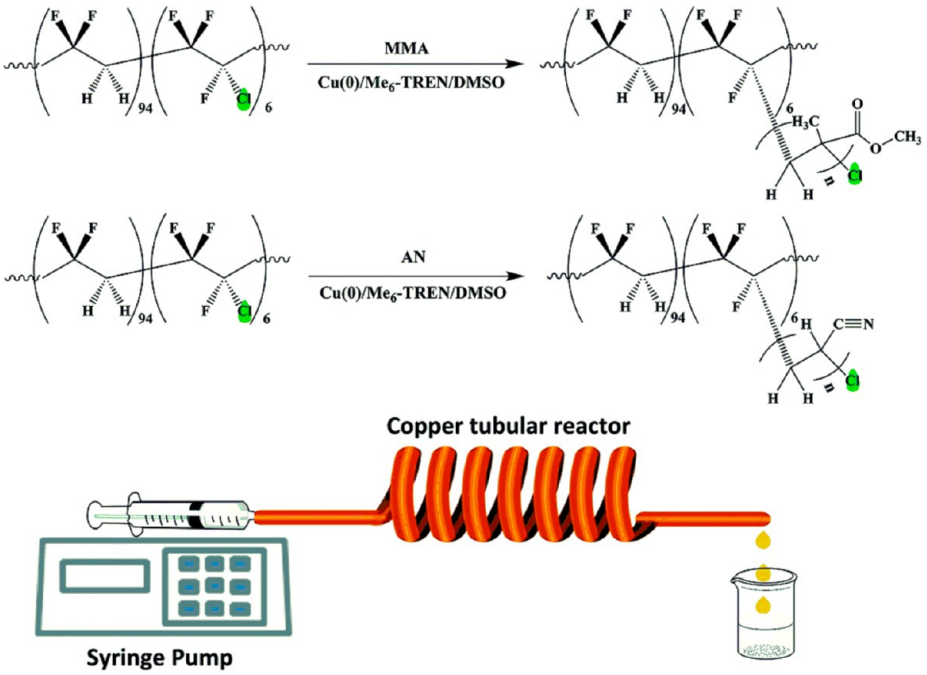

Figure 5. SET-LRP of MMA and AN initiated with P(VDF-*co*-CTFE) and a schematic diagram of the copper tubular reactor. Reproduced from ref 104, with permission of The Royal Society of Chemistry. http://dx.doi.org/10.1039/c5py01728a.

using a short copper coil to initiate the polymerization and generate soluble copper species instead of using copper tubing to construct the entire reactor, whereas the bulk of polymerization took place in inert stainless steel tubing.[189] For polymerization to be mediated in the absence of a copper surface, ascorbic acid was used as a reducing agent to regenerate activating copper species. Polymerizations of MA were conducted at ambient temperature with 30 wt % DMSO as solvent, producing a well-defined living polymer at 78% monomer conversion for a residence time of 62 min. The SET-LRP in continuous flow has also been proven as an efficient strategy for the preparation of copolymers via the "grafting from" approach. Guo and co-workers used a P(VDF-*co*-CTFE) macroinitiator to polymerize MMA and AN in the presence of a copper tubular reactor working in both continuous and batch mode (Figure 5).[104] Working with the continuous flow mode, the SET-LRP process showed diminished inconsistent induction times, accelerated rates, and lower reaction temperatures.

Meanwhile, Haddleton and co-workers developed a simple, easy to construct benchtop plug flow reactor consisting of polytetrafluoroethylene tubing with a Cu(0) threaded core (wire).[190] The SET-LRP of MA was optimized by changing the residence time within the flow reactor. By simply modifying both the length of the reactor and the flow rate, these authors were able to produce narrow dispersity PMA with a high level of active bromine chain ends.

3. RECENT APPLICATIONS

3.1. Synthesis of Glycopolymers. In the last several years, SET-LRP has been proven to be a very efficient polymerization methodology that allows facile access to well-defined glycopolymer architectures. Glycopolymers as synthetic materials bearing natural carbohydrate-based derivatives have long been known as vaccines and explored to deliver therapeutics in a targeted fashion. Protein−carbohydrate interactions play an important role in many biological processes including cell interactions with immune systems, tumor metastasis, adhesion of infectious agents to host cells, and many more. Bonilla and co-workers envisioned for the first time the possibilities of SET-LRP in this field.[64] Amphiphilic di- and triblock copolymers, containing HEAGI and *n*-BA or MMA, were prepared via SET-LRP using Cu(0) generated by disproportionation of CuCl in DMF solution in the presence of PMDETA. The self-organization of these water-soluble block glycopolmers was studied observing the formation of micelles with narrow dispersities and diameters between 10 and 20 nm. All the water-soluble glycopolymers showed selective interaction with Concanavalin A lectin, being stronger as the carbohydrate block length increased. Later, Haddleton and co-workers used Cu(0)-mediated SET-LRP to tailor mannose, glucose, and fucose functionalities in a controlled sequence for binding to the dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN; CD209) to inhibit the HIV envelope glycoprotein gp120 interaction.[61] Glycopolymers with higher mannose content showed higher-affinity binding although the effect of the glycomonomer sequence was inconclusive. The same group later reported the preparation of star-shaped glycopolymers containing a cyclodextrin (CD) core and oligosaccharide chains by direct Cu(0)-mediated SET-LRP of glycomonomers from a CD-based macroinitiator (β-CD-$(Br)_{16}$).[62] More recently, Becer and co-workers reported the preparation of several types of amphiphilic block coglycopolymers via SET-LRP by using MA and a ManoA and/or poly(ethylene glycol) as hydrophobic and hydrophilic blocks, respectively.[63] The synthesized well-defined amphiphilic glycopolymers self-assembled in water to generate glyconanoparticles with different morphologies such as spherical and worm-like micelles as well as spherical vesicles. Surface plasmon resonance (SPR) spectrometry measurements showed that the size and shape of nanoparticles containing the same number of mannose units have a significant effect on the binding level with

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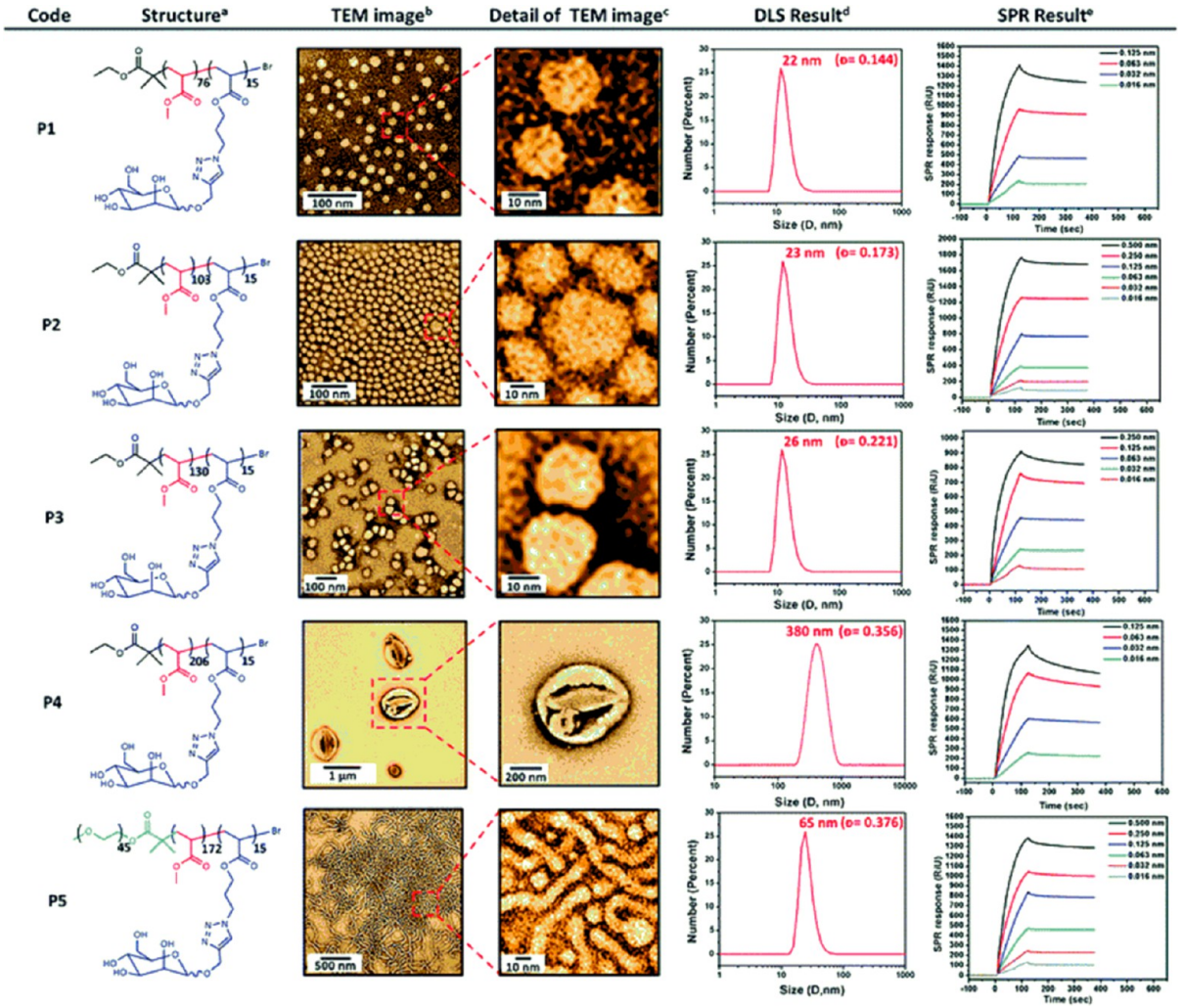

Figure 6. Characterization of glyconanoparticles and their respective binding with DC-SIGN. (a) Chemical structures of polymers, (b) TEM images of glyconanoparticles in selected solvent conditions, (c) zoomed in TEM images, (d) size of glyconanoparticles via DLS, and (e) DC-SIGN binding of glyconanoparticles measured by SPR. Reproduced with permission from ref 63 under a Creative Commons Attribution-NonCommercial 3.0 Unported License (https://creativecommons.org/licenses/by-nc/3.0/). Published by The Royal Society of Chemistry.

DC-SIGN (Figure 6). Although the direct polymerization of glycomonomers via SET-LRP has been traditionally performed in DMSO,[61−63] aqueous conditions have also been used successfully.[51,93]

As an alternative approach to the synthesis of sequence-controlled glycopolymers, Haddleton and co-workers combined SET-LRP with thiol-halogen, thiol-epoxy, and copper-catalyzed alkyne azide coupling click chemistry to give a new route to high-order multiblock glycopolymers.[53] A similar approach was used by the laboratories of Haddleton, Boyer, and Davis and co-workers to easily prepare diblock PEG glycopolymers using a phosphonic functional initiator (PBI-2).[191] The synthesized phosphonic ester terminal diblock glycopolymers were further hydrolyzed to phosphonic acid end groups prior to assembly on iron oxide nanoparticle (IONP) surfaces. Mannose-nanoparticle bimolecular recognition was extended to cell membrane receptors and confirmed by an increased uptake of nanoparticles into lung cancer cells, demonstrating that sugar-coated IONP may become an essential part of theranostic nanoparticle design, enhancing both targeting and diagnosis.

3.2. Modification of Polysaccharides by SET-LRP. As a water-tolerating polymerization protocol that can be performed under benign conditions, SET-LRP has been used to graft polymers from polysaccharides, previous functionalization of their backbones with alkyl halide initiators. SET-LRP is appealing for this purpose because polysaccharides are usually accompanied by wound water and typically do not lend themselves to classical vinylic copolymerization. SET-LRP strategy has been used to produce graft copolymers and brush-like structures from a variety of the biobased substrates such as cellulose,[68,192−195] various hemicelluloses,[97,98,196−198] chitosan,[199] dextran,[200] and alginate[88] in homogeneous conditions. Combining the polysaccharide structure with vinyl polymerization chemistry offers a whole new set of opportunities to derive hybrid glycomaterials with new innovative property combinations. For example, Jin and co-workers were able to regulate the thermal sensibility of hydroxypropyl cellulose by SET-LRP grafting of short PNIPAM chains in a water/THF mixture of solvents.[193] On the other hand, Albertsson and co-workers successfully grafted CBAAM and CBMAAM zwitterionic carboxybetaines in a controlled fashion via aqueous SET-LRP from a galactoclucomannan microinitiator without the use of any toxic catalyst at room temperature.[97] In this case, the prepared glycopolymers

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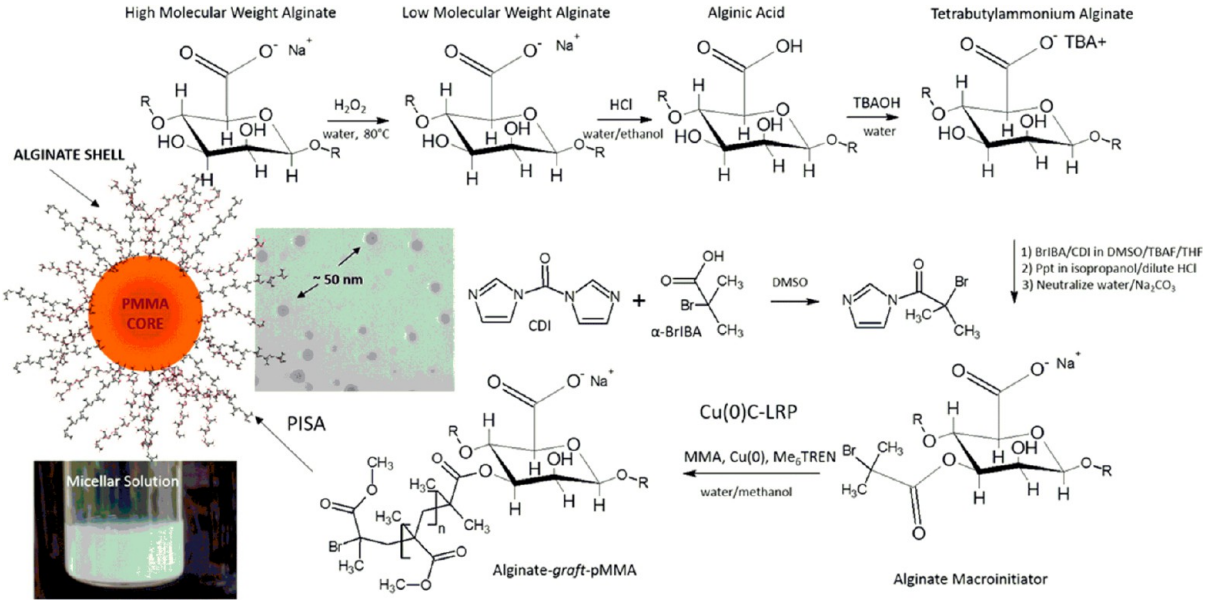

Figure 7. Summary of the synthetic route for the preparation of alginate-*g*-PMMA micelles via polymerization-induced self-assembly SET-LRP. Reproduced with permission from ref 88. Copyright 2015 American Chemical Society.

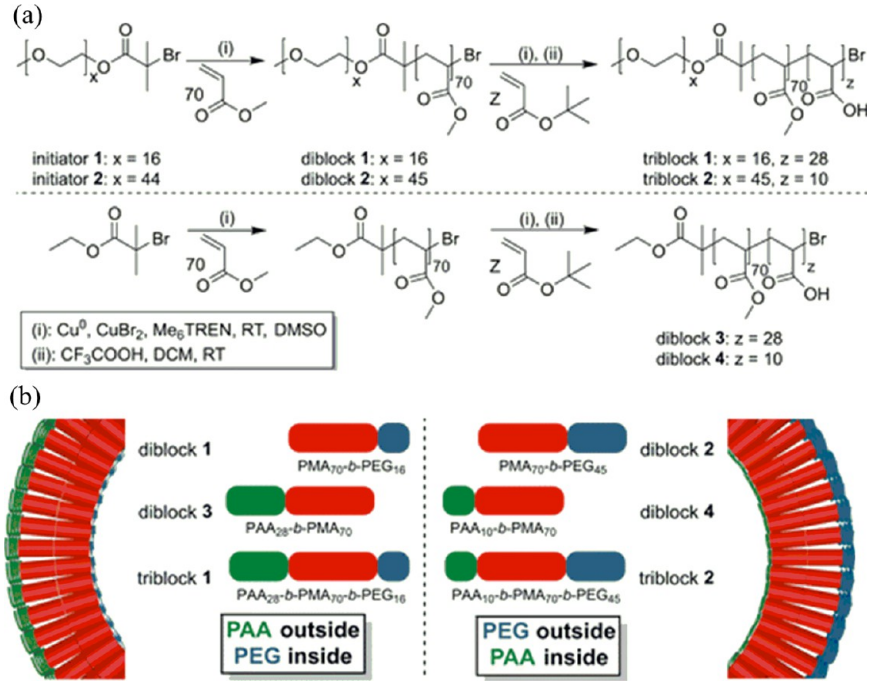

Figure 8. (a) Synthesis of di- and triblock copolymers via SET-LRP and (b) block copolymer design. Diblocks 1/3 and triblock 1 are designed so that the larger PAA block will orient to the outside of the vesicle whereas the inner leaflet will mostly be comprised of the smaller PEG block. This is in contrast to diblocks 2/4 and triblock 2 in which the sizes of the PEG and PAA blocks are reversed to present the PEG block externally. Reproduced with permission from ref 223. Copyright 2016 American Chemical Society.

self-assembled in aqueous solution into well-defined spherical nanoparticles with a nonfouling poly(carboxybetaine) corona. All nanoparticles presented hydrodynamic radii below 100 nm, which together with the unmatched resistance to fouling results in a very promising system for bioapplications. Neufeld and co-workers reported an original approach to graft vinylic polymers from alginate, a poorly modifiable polysaccharide due to its insolubility in any solvent except water (Figure 7).[88] SET-LRP polymerization induced self-assembly of the amphiphilic grafted alginate polymer that formed micelles with diameters measured by light scattering and electron microscopy in the range of 50–300 nm.

The synthesis of block-structured copolymers based on polysaccharides has also been proved successful. In this line, a monofunctional initiator was successfully synthesized from galactoglucomannan on its reducing end using an amino functional α-bromoisobutyric derivative.[201] The macroinitiator was used to initiate SET-LRP of MMA, MAETC, and NIPAM using Cu(0)/Me_6-TREN as a catalyst producing diblock copolymers with molar masses ranging from 5,200 to 50,000

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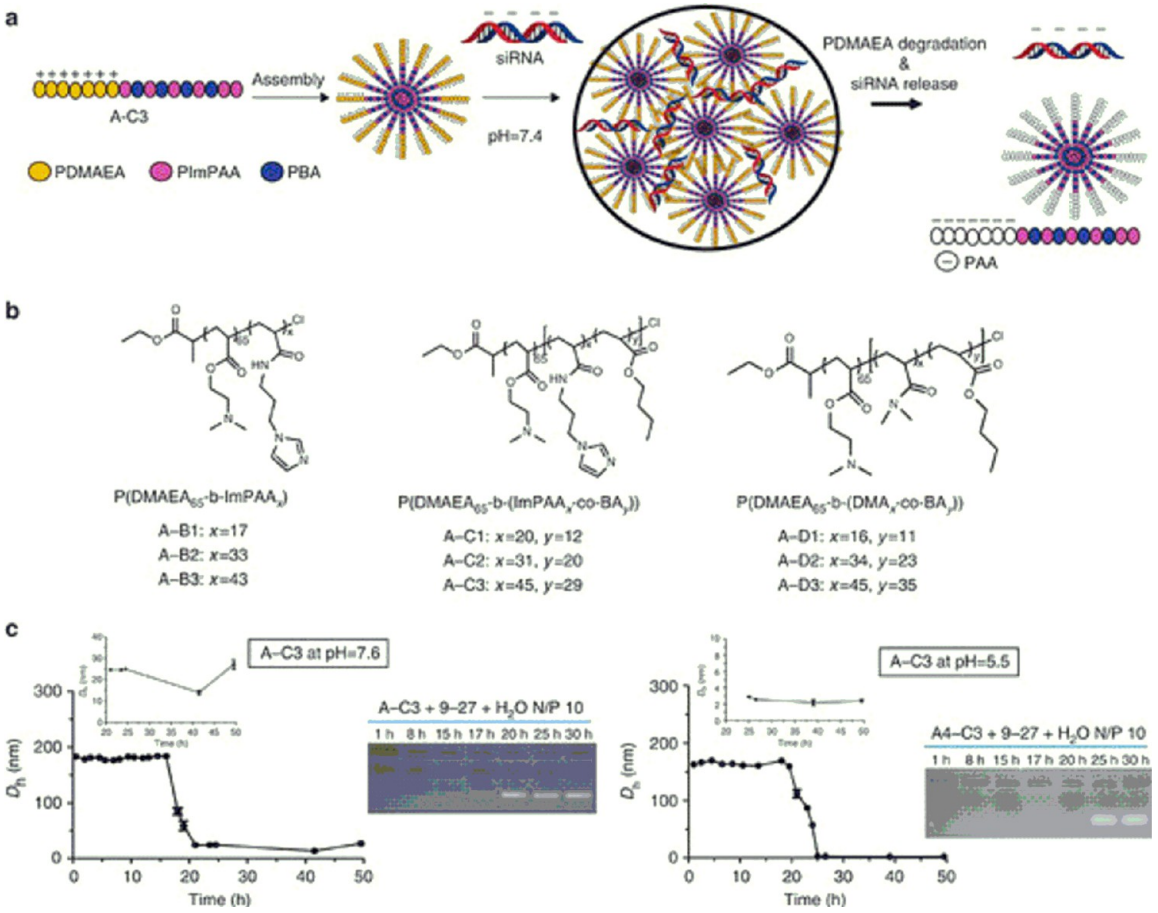

Figure 9. (a) Mechanism for polymer assembly, binding with siRNA, and release of siRNA through a self-catalyzed degradation of PDMAEA, (b) chemical structures of the nine block copolymers, and (c) degradation profile of polymer A−C3 at pH 7.6 and 5.5 when complexing with oligo DNA as measured by DLS and the time for release of the oligo DNA from the polymer carrier. Reprinted by permission from Macmillan Publishers Ltd.: Nature Communications, ref 224, copyright (2013). http://www.nature.com/ncomms/.

g mol^{-1}. The formed diblock copolymers could be used in food formulations as stabilization agents due to their easily tunable properties such as amphiphilicity or charge. More recently, SET-LRP was used to functionalize chitosan in a well-controlled manner.[88] First, a chitosan-based 2-bromoisobutyryl ester macroinitiator was synthesized and then used to initiate the SET-LRP of MAETC in an ionic liquid system using Cu(0) wire. A linear relationship between the $\ln([M]_0/[M]_t)$ and time, the linear increase of number-average molecular mass with conversion, as well as the low polydispersity index of the polymer confirmed the "living/controlled" features of the polymerization through SET-LRP. The presence of PMAETC segments improved the antimicrobial activity of chitosan, showing much better inhibitive capability against *Escherichia coli*.

3.3. Micellar and Vesicular Structures as Drug Delivery Vehicles. Since the pioneer work of Monteiro and co-workers,[52] SET-LRP has been proven to be an outstanding tool for the precise preparation of a variety of amphiphilic block copolymers with different architectures with, in some cases, promising applications.[31,36,41,45,84,85,89,202−222] Taking advantage of SET-LRP, Monteiro and co-workers reported the preparation of linear and 4-armed star copolymers composed of MA and SA.[52] The subsequent deprotection of the solketal side chains produced amphiphilic copolymers that self-assembled in water into micellar and vesicular structures. AB_2-type amphiphilic block copolymers based on PEG and PNIPAM were also accessible using SET-LRP.[203] More recently, Mason and Thordarson synthesized a family of amphiphilic di- and triblock copolymers based on PEG, PMA, and PMMA via Cu(0)-mediated SET-LRP with the aim of generating polymer vesicles, or polymersomes, with an asymmetric membrane (Figure 8).[223] The aqueous self-assembly of these polymeric amphiphiles was studied using asymmetric field-flow fractionation and cryoelectron microscopy. Utilizing mixtures of diblock copolymers with differing hydrophilic moieties resulted in the formation of vesicles with heterogeneity across the membrane reminiscent of the natural cell membrane.

The applications for this system are broad because could be used as drug delivery scaffolds, to control which surface is presented to the cell, or as synthetic cell mimics, mimicking the natural cell heterogeneity and controlling the orientation of membrane proteins. One of the most outstanding examples that illustrates the synthetic potential of SET-LRP is the sophisticated polymer delivery carrier reported by Monteiro and co-workers that mimics the influenza A virus escape mechanism from the endosome to the cytosol with excellent knockdown of protein production using small interfering RNA (siRNA) (Figure 9).[224] SET-LRP was used to prepare a unique polymer that could bind the negatively charged siRNA through positive electrostatic binding, change conformation in a low pH

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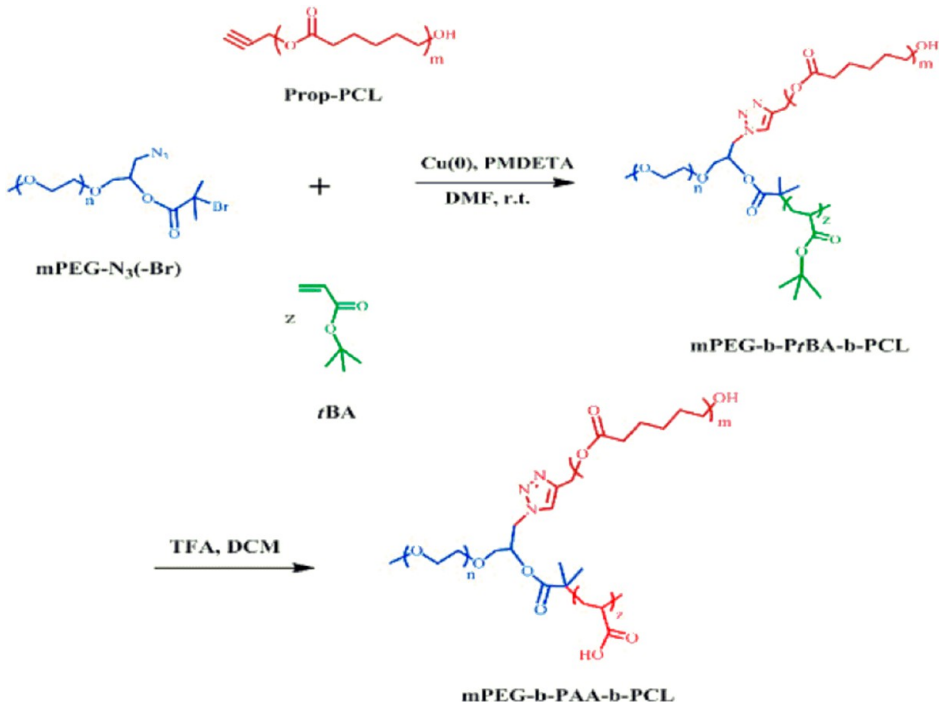

Figure 10. Synthesis of ABC miktoarm star terpolymers in one-pot combining click chemistry and SET-LRP. Reproduced from ref 206, Copyright (2015), with permission from Elsevier.

environment (e.g., pH ∼5.5), bind to the endosomal membrane, and escape to the cytosol.

This polymer component degrades from a cationic polymer (PDMAEA) to an anionic poly(acrylic acid) (PAA), a self-catalyzed hydrolysis mechanism independent of the pH or molecular weight of the polymer. Incorporation of this polymer component into a diblock copolymer consisting of a second block of PImPAA and Pn-BA produced a polymer system that could be taken up by cells in less than 4 h, escape the endosome mimicking the influenza virus mechanism, and release all siRNA in a time-dependent manner into the cytosol to downregulate specific proteins.[99,224] The same group subsequently complexed this polymer with plasmid DNA to determine both its cellular entry and nuclear pathways to HEK293 cells.[225] Also outstanding is the light and pH dual stimuli-responsive $PSPMA_{10}$-*b*-PAA_{40} block copolymer showing solvatochromic, isomerization, and "schizophrenic" behaviors synthesized via sequential SET-LRP at 30 °C in an oxygen-tolerant system and hydrolysis reaction.[89]

SET-LRP has also been combined with other synthetic methodologies to obtain the targeted amphiphilic structures. For example, He and co-workers reported the preparation of linear−dendritic-like amphiphilic P(D or L-lactide)-*b*-PAA copolymers that self-assembled into vesicles in an aqueous environment combining SET-LRP and thio-bromo "click" reaction with ring opening polymerization.[36] The size of the formed aggregates changed with variation of the pH value, indicating that these aggregates possess promising pH-dependent swelling and shrinking properties, which endow the formed aggregates with great potential for a controllable drug delivery system. As can be seen in Figure 10, a combination of copper-catalyzed alkyne azide coupling click reaction and SET-LRP was used to prepare pH-responsive ABC-type miktoarm star terpolymers PEG-*b*-PAA-*b*-PCL using mPEG-N_3Br as a functional hydrophilic initiator for SET-LRP (Figure 10).[206] The terpolymers, exhibiting an extremely low cytotoxicity against Hela cells, formed micelles that were used as carriers for naproxen. The in vitro release behavior of naproxen exhibited pH dependence due to swelling of the micelles at high pH values caused by the ionization of carboxylic acid groups of PAA.

On the other hand, well-defined amphiphilic graft copolymers were also accessible via a "grafting from" approach. For example, Huang and co-workers reported the $[(\eta^3\text{-allyl})\text{-NiOCOC-F}_3]_2$-initiated living coordination polymerization of 6-methyl-1,2-heptadiene-4-ol (MHDO) to produce double bond-containing PMHDO-containing pendant hydroxyl moieties.[85] Subsequently, the PMHDO-Cl macroinitiator, prepared by esterification with 2-chloropropionyl chloride, was used to graft hydrophilic PDEAEMA chains. The synthesized PMHDO-*g*-PDEAEMA graft copolymers aggregated to form diverse micelles in different salinities and pH water environments. Polyester macroinitiators prepared by ring-opening polymerization have also been used to initiate SET-LRP and provide a route to "near perfect graft copolymers" with a degradable backbone.[226]

3.4. Polymer−Protein Conjugates. In the past decade, the "grafting from" conjugation methodology of synthetic polymers to protein and peptides has emerged as a powerful and popular technology for bioconjugation mostly due to the development of LRP techniques. Haddleton and co-workers successfully employed SET-LRP for the synthesis of tunable thermoresponsive polymer−protein conjugates. DEGMEMA, TEGMEMA, and an equimolar mixture of both were polymerized directly from a salmon calcitonium (sCT) macroinitiator readily synthesized in a one-pot protocol utilizing thiol-ene chemistry to yield well-defined conjugates.[79] SET-LRP was conducted at room temperature using DMSO as a solvent and Cu(0) wire as the heterogeneous catalyst. SEC with UV detection confirmed the incorporation of the peptide

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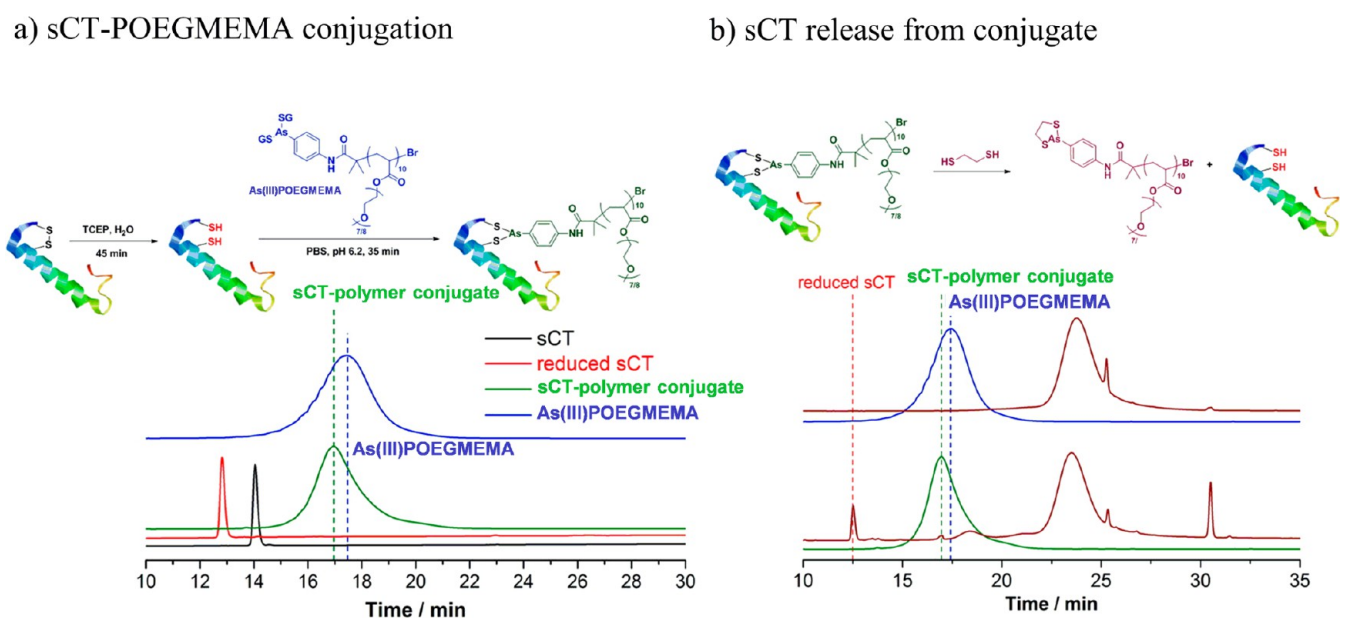

Figure 11. (a) Conjugation of sCT to As(III)POEGMEMA (2.5 equiv) via sequential reduction conjugation. (b) Release of sCT from the sCT-POEGMEMA conjugate using 1,2-ethanedithiol (bottom spectra) and control reaction of **4** and EDT (top spectra). Adapted with permission from ref 229. Copyright 2015 American Chemical Society.

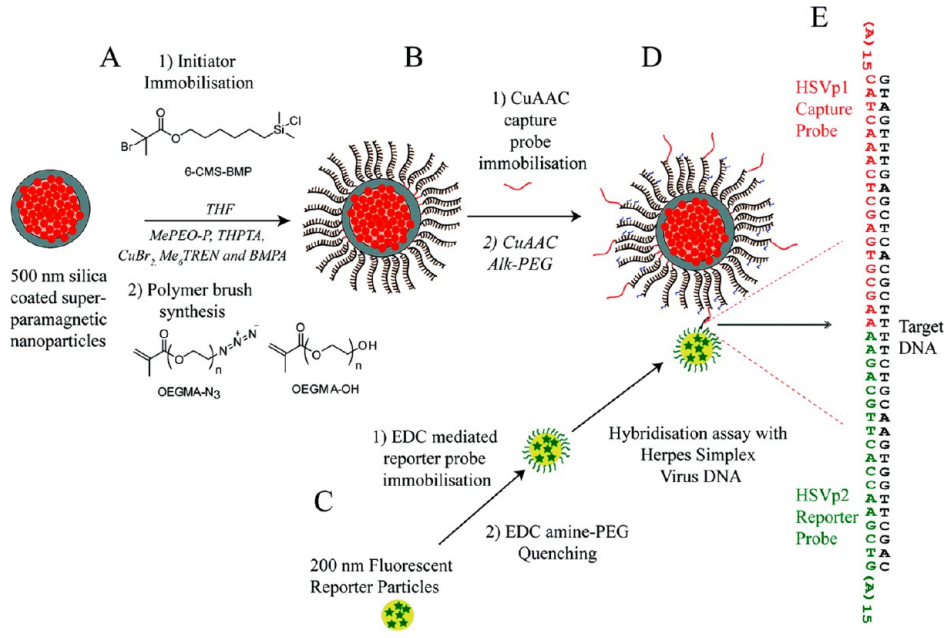

Figure 12. Scheme for magnetic particle polymer modification and subsequent coupling of DNA oligonucleotides. Reproduced with permission from ref 232. Copyright 2012 American Chemical Society.

in all of the polymers. Conjugates with tunable cloud points ranging from 24 to 51 °C were synthesized using only DEGMEMA and TEGMEMA. A recent publication from the same group reported that aqueous SET-LRP performed at ambient temperature or below (0 °C), as biologically mild reaction conditions for fragile proteins, provided better control.[227] In this study, the primary amine groups at the N-terminus of each peptide chain and side-chain lysine amino acid residues of five commercially available proteins and peptides, including bovine serum albumin and bovine insulin, were modified using NHS-ester activated initiators. The corresponding modified proteins were tested as macroinitiators to produce amphiphilic copolymers via direct polymerization of different vinylic monomers. Interestingly, the insulin−polymer conjugates formed spheres in water, and their self-assembly behavior could be controlled via thermal control, carbohydrate−polymer interactions, and protein denaturation.

Alternatively, the direct reactions of certain SET-LRP functional polymers with protein and peptides have also been reported as promising reversible conjugation strategies. Inspired by the oxytocin degradation pathway, Haddleton and co-workers described the SET-LRP synthesis of α-functional dithiophenol maleimide polymers as disulfide bridging agents for this therapeutic peptide.[228] This successful polymer−peptide conjugation resulted in bioconjugates with higher stability at high temperature than those of the native peptide.

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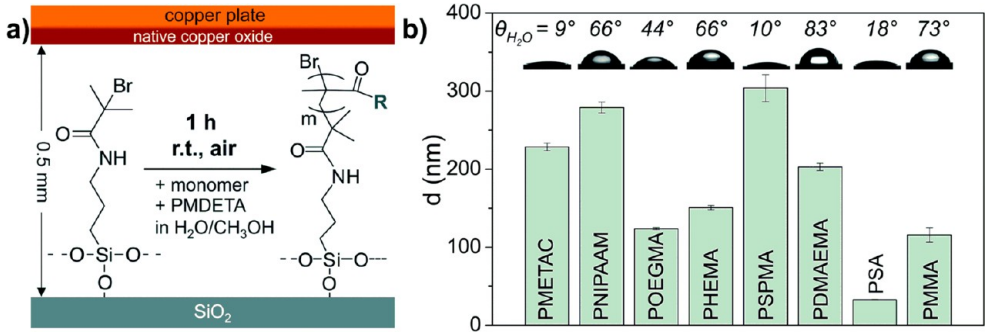

Figure 13. (a) Reaction scheme for the surface-initiated polymerization using a surface-modified silicon wafer piece bearing a standard initiator, a facing copper plate at a distance of 0.5 mm, and a solution of the monomer with the ligand (PMDETA) in water/methanol. (b) Polymer brush layer thickness, *d*, as determined by ellipsometry and water contact angles for the polymer brushes after SI-CuCRP for 1 h at ambient conditions (room temperature, handling in air). Reproduced with permission from ref 249 under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/). Published by The Royal Society of Chemistry.

Moreover, the reversible nature of this conjugation approach highlights the possibility of reformation of the native peptide, potentially preventing the loss of biological activity.

Finally, arsenic-containing polymers were recently readily prepared by aqueous SET-LRP to utilize the entropy-driven association between trivalent organic arsenicals and closely spaced dithiols as a novel bioconjugation approach (Figure 11).[229] For probing the viability of this approach, *p*-arsanilic acid was amidated using 2-bromoisobutyryl bromide furnishing an As(V)-functional initiator, which was used to polymerize hydrophilic monomers such as NIPAM, NAM, and OEGMEMA via aqueous SET-LRP. Polymerizations were completed within 30 min, as demonstrated by ^{1}H NMR, and showed good correlation between theoretical and experimental molecular weights and narrow dispersities attained from SEC. Arsenic end-functional POEGMEMA was conjugated to sCT, and it was demonstrated that the peptide could be chemically released from the polymer upon addition of strong chelating agents, such as 1,2-ethanedithiol. The thermodynamically driven release of sCT from its conjugates evokes the potential for targeted and controlled release of the peptide in the presence of biological chelating dithiols.

3.5. Surface-Initiated SET-LRP. Surface-initiated SET-LRP has been applied to different particles and nanoparticles. Charleux and co-workers reported for the first time robust conditions for grafting hydrophilic polymer chains using Cu(0)-mediated polymerization from concentrated bromine-functionalized latex particles used as synthesized via classic emulsion polymerization.[230] A successful surface-initiated SET-LRP of NAM was demonstrated to proceed at room temperature even from raw particles containing surfactant and initiator remaining from the emulsion polymerization. The "grafting from" approach could also be used to build up polymers from superparamagnetic iron oxide nanoparticles[231] and silica-coated superparamagnetic nanoparticles.[232] In the latter example, the rapid and highly efficient surface-initiated SET-LRP for the copolymerization of azide-modified and hydroxyl OEGMEMA monomers provided the nanoparticles with a low fouling and chemically functional (through the azide moiety for coupling and immobilization of oligonucleotides) brush coating (Figure 12). Consecutive click reactions enabled the tuning of both herpes simplex virus capture probe density and subsequent backfilling of the polymer brush to fill voids within the brush, thus providing the opportunity for further development of core−shell particles for improved amplification-free detection of DNA.[232,233]

Graphene oxide/polymer hybrid nanocomposites were also successfully prepared using surface-initiated SET-LRP after the covalent anchoring of bromine-containing initiating sites onto the surface of graphene oxide.[76,234,235] After functionalization with Pt-BMA chains (71.7 wt % grafting efficiency), the modified graphene nanosheets still maintained the separated single layers and showed better dispersity in various organic solvents.[76] The same approach was used to graft PNIPAM[234] and PHEA[235] chains, producing nanohybrid materials with good dispersibility in organic solvents and aqueous media. Interestingly, the aqueous dispersion of graphene oxide−PNIPAM nanocomposites showed reversible temperature switching self-assembly and disassembly behavior at approximately 40 °C. Recently, an attractive strategy for the functionalization of carbon nanotubes based on a combination of mussel-inspired chemistry and SET-LRP was reported.[236,237] In this procedure, CNTs were first coated with polydopamine through rather mild alkaline conditions. Then, polydopamine-functionalized CNTs bearing amino and hydroxyl groups were further reacted with bromo isobutyryl bromide to introduce the alkyl halide initiating groups for SET-LRP. Subsequently, POEGMEA and PNIPAM chains were grown on the surface of CNTs using CuBr/Me_6-TREN as a catalytic/ligand system in H_2O/toluene and H_2O/DMF mixtures while retaining their pristine structure but significantly improving their dispersibility in both polar and nonpolar solvents.[236] Thermoresponsive PNIPAM brushes were also grafted from cellulose nanocrystals and fibers via SET-LRP.[238−241] Cellulose produced from cotton fibers was also grafted with *n*-BMA and PETA via SET-LRP to prepare oil-absorbing materials.[57] A similar approach was also applied to hair keratin fibers[242] and peanut shells.[243] Other eco-friendly adsorbents were also prepared from wheat straw matrix by grafting PAN brushes.[244] This adsorbent, prepared by SET-LRP and a modification process that introduced amidoxime groups onto the surface of wheat straw, exhibited a superior adsorption capacity to Hg(II) and could probably be applied to separate Hg(II) from a multi-ionic aqueous solution.

The surface of silicon wafers could also be engineered with various polymer brushes by surface-initiated SET-LRP catalyzed by colloidal Cu(0) prepared by ligand and solvent-mediated disproportionation of Cu(I) to Cu(0) and Cu(II).[42,245,246] For example, certain surface properties of silicon surfaces were easily tuned by grafting PNIPAM-*co*-PADA

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brushes. A systematic variation of polymerization conditions such as time, catalyst, and monomer concentration allowed for controlling the wettability and thermosensibility of such surfaces.[42] A photoinduced approach was also employed to assemble nonfouling brushes of HPMAM from silicon surfaces using copper concentrations as low as 80 ppb.[247] Alternatively, Jordan and co-workers recently described a methodology for surface-initiated SET-LRP presenting the peculiarity of using a Cu(0) plate as a catalyst. This method allowed for building up a broad variety of defined polymeric brushes (i.e., PSt, PMMA, Pt-BMA, and PMAETC) under ambient conditions on the wafer scale (Figure 13).[248] This high oxygen tolerance technique homogeneously covers the entire silicon wafers with a high grafting density polymeric coating formed by high molecular weight polymers with narrow dispersities.[249] These simple and low-cost experimental conditions are expected to allow researchers from various technological fields to prepare the desired grafted surfaces required for their needs.

CONCLUSIONS AND FUTURE PERSPECTIVES

The field of single-electron transfer−living radical polymerization (SET-LRP) was comprehensively reviewed up to the year 2015 in three recent reviews from two different laboratories.[123,136,139] This Perspective brings to the broad biomacromolecules community the most recent advances accomplished in the past several years and also covers the literature from 2015 up to February 2017. This Perspective also discusses the impact and potential of SET-LRP in macromolecular design, synthesis, and characterization as well as its application to the synthesis of polymer materials of interest to the field of biomacromolecules and their conjugates. Developments since 2015 have continued to demonstrate that SET-LRP is the method of choice for LRP in water, "the solvent of biology". Because all biological systems are synthesized by Nature in water and are also stable in water, SET-LRP in water provides an important new synthetic tool for the preparation of biomacromolecules and of biological conjugates. Therefore, SET-LRP in water is expected to provide rapid developments in the area of biomacromolecules. A simple search through Web of Knowledge using "SET-LRP" as a keyword resulted in 478 hits, which clearly confirms its importance in different fields of science where the number of publications continues to increase and impact other areas of LRP since the concept was initially introduced in 2002[4] and first published in 2006.[8] The convenient use of Cu(0) powder or wire as catalyst under mild conditions reported by the diversity of methodologies discussed in this Perspective, combined with an excellent correlation between the theoretical and experimental molecular weight, narrow molar mass distribution, and perfect or near perfect retention of chain-end functionality, have made SET-LRP an attractive choice for the synthesis of tailored polymers including high-order multiblocks, graft copolymers, polymer brushes, and more complex architectures in polar solvent and in water. The results discussed in this contribution demonstrate that, leaving out discussions regarding the mechanism, these appealing characteristics of SET-LRP have attracted the attention of researchers working at the interface of polymer science with biomacromolecules, nanomedicine, bioconjugates and biology, which we envision will continue into the future. We also expect that SET-LRP will soon expand into the area of renewable resources and many other emerging fields. Finally, another Perspective on the methodology and mechanism of SET-LRP will represent the topic of a different publication. Last but not least, an elegant Photo-SET-RAFT combined living radical polymerization of activated and nonactivated monomers mediated by Ir that also tolerates oxygen has recently become available.[250] Various Photo-SET polymerizations are evolving from different laboratories, and although they were planned to be discussed in a methodology-mechanistic Perspective, this comprehensive publication is also recommended to the readers of Biomacromolecules interested in methods related to the classic SET-LRP.

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Notes

The authors declare no competing financial interest.

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