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Cu(0)-Mediated Living Radical Polymerization : Recent Highlights and Applications; a Perspective

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ABSTRACT

Cu(0)-mediated living radical polymerization or single electron transfer living radical polymerization (Cu(0)-mediated LRP or SET-LRP) is a versatile polymerization technique that has attracted considerable interest during the past few years for the facile preparation of advanced materials. Importantly, the scope of Cu(0)-mediated LRP has been significantly expanded to include the polymerization of a large variety of functional monomers (*e.g.* acrylates, methacrylates, acrylamides, methacrylamides, styrene *etc.*) in several solvents *e.g.* with the resulting polymers possessing narrow molecular weight distributions (MWDs), fast polymerization rates and very high end-group fidelity (even at quantitative conversions) as exemplified by sequential chain extensions and block copolymerizations. These characteristics render Cu(0)-mediated LRP an ideal candidate for the facile synthesis of complex architectures that have found use in a large diversity of applications including glycopolymers, gene delivery, foldamers, polymer-protein conjugates and many others.

INTRODUCTION

Over the past 25 years remarkable advances have been made in the controlled polymerization of vinyl monomers. Initially, these were polymerized using enolates *via* an anionic polymerization methodology. Perhaps the most influential polymerisation protocol was Group Transfer Polymerization using Si-enolates,[1-3] developed by Owen Webster in the DuPont laboratories. Subsequently, related studies employing aluminium porphyrin enolates were also reported by Inoue[4, 5]. This work emerged from the use of mixed main group (Li and Al) metal alkyls and the addition of stabilisers including alkoxides and salts[6-12]. However, all of these methods had to use highly purified reagents and solvents in order to avoid polymer termination and often low temperatures were required to minimise nucleophilic attack at the polymer and monomer carbonyl groups. Only using these stringent conditions were dispersities < 1.2 achievable and this was usually the case only for methacrylates with acrylates providing a more difficult challenge. It was in order to provide more robust chemistry that could cope with less stringent reagent purity, to be able to utilize the vast array of functional methacrylates and to extend to acrylic monomers that radical based chemistry became very desirable. The development of living radical polymerization methods (LRP) (also often referred to as reversible deactivation radical polymerization (RDRP) by IUPAC) has changed the field of academic polymer science, providing access to facile synthesis of well-defined materials with both structural and functional diversity. Nitroxide mediated radical polymerization (NMP),[13] reversible addition-fragmentation chain transfer polymerization (RAFT),[14] atom transfer radical polymerization (ATRP)[15, 16, 17]and Cu(0)-mediated LRP (aka SET-LRP or SARA ATRP)[18, 19] have significantly contributed towards this field demonstrating remarkable regulation of molecular weight, end-group functionality, dispersity and architecture. It is now possible to polymerize highly functional acrylic and acrylamide monomers even in water in the presence of most common impurities at ambient temperature over the time period of minutes to give dispersities < 1.10 with almost perfect end-group fidelity.

The use of zero valent metals (both Cu(0) and Fe(0)) as an adjunct to ATRP was initially reported by Matyjaszewski and co-workers in 1997 (and subsequently in 2000) for the synthesis of well-defined poly(acrylates), poly(methacrylates) and poly(styrene) presenting relatively narrow MWDs ($Đ$ ~ 1.10 - 1.45) at high reaction temperatures (60 - 110 °C).[20] However, higher molecular weight polymers (M_n > 60000 g.mol^{-1}) and assessment of the end-group fidelity *via in situ* block copolymerizations were not performed. Interestingly,

the "non-disproportionating ligand" 4,4′-bis(5-nonyl)-2,2′-bipyridine (dNbpy) (that stabilises copper(I) *via* electron acceptance into a low lying π* orbital) was utilized for all the polymerizations and "disproportionating ligands" (those that stabilise copper(II)) were not employed[21] (the term "disproportionating ligand" is used to describe a ligand that facilitates the disproportionation of CuBr stabilizing Cu(II) relative to Cu(I)), the term "non-disproportionating ligand" is used to describe a ligand that does not facilitate the disproportionation of CuBr or stabilizes Cu(I) in preference of Cu(II)). It is noted that Percec and co-workers also used Cu(0) in 1998 with similar findings.[22, 23]

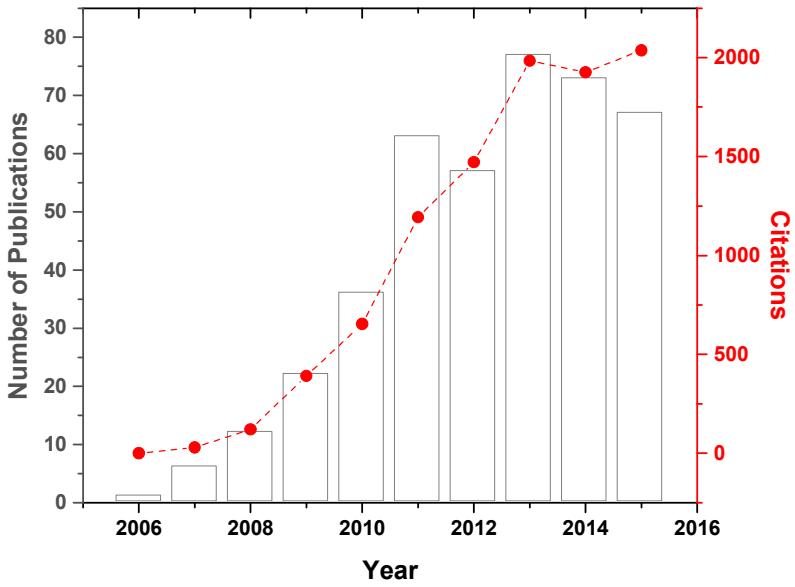

Figure 1: Published items and publications per year by Web of Knowledge, searching the term "Cu(0)-mediated LRP", November 2015.

The concept of Cu(0)-mediated LRP was initially introduced by Percec and co-workers in 2002[24] and attracted more attention in 2006, when the "*ultrafast synthesis of ultrahigh molecular weight polymers*" at ambient temperature or below from functional monomers containing electron withdrawing groups such as acrylates and methacrylates was reported.[18] Polar solvents, such as H_2O, dimethyl sulfoxide (DMSO), alcohols and ionic liquids were reported to encourage the disproportionation of $Cu^{I}Br$ into Cu^{0} and $Cu^{II}Br_2$ species in the presence of certain disproportionating ligands (*e.g.* tris[2-(dimethylamino)ethyl]amine (Me_6-Tren), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) *etc.*). The initial activation step was proposed to occur *via* Cu^{0}, either in the form of copper wire or copper powder, *via* SET to the electron acceptor alkyl halide. Without any

purification step the synthesis of high molecular weight polymers (M_n ~ 1400000 g.mol^{-1}) was reported in less than 3 h.

Since 2006, over 400 papers have been published in the literature around this topic (until November 2015), according to Web of Knowledge with the total number of citations exceeding 9500 (Figure 1). This perspective will initially discuss the potential and limitations of Cu(0)-mediated LRP, followed by the monomer, solvent, initiator, metal, deactivator and ligand compatibility of the technique. The main focus of this article is to highlight the recent developments in this area and the use of Cu(0)-mediated LRP as a versatile and robust polymerization method for the preparation of functional materials that can find use in a large diversity of applications.

ADVANTAGES AND LIMITATIONS OF Cu(0)-MEDIATED LRP

Cu(0)-mediated LRP is an attractive polymerization technique as it provides access to the fast polymerization of acrylates (usually < 2 h to reach full conversion), methacrylates and acrylamides (often < 10 min to reach full conversion) often with narrow MWDs ($Đ$ ~ 1.10) and very high end-group fidelity maintained even at full or near-full conversions. A large diversity of solvents have been so far been utilized for the Cu(0)-mediated LRP such as H_2O, DMSO, DMF, alcohols, including fluorinated alcohols, ionic liquids, alcoholic beverages, blood serum and many others. Many functional monomers have also been successfully polymerized, including unprotected monomers and monomers with sugar moieties (see monomer compatibility for more details). The polymerizations are often performed at ambient temperature or below, thus suppressing side reactions such as chain transfer events that can be more pronounced at higher temperatures.[25] A typical polymerization set up requires no more than 15 min whilst there is no need for strict deoxygenating procedures (bubbling with nitrogen is usually sufficient) and in many cases Cu(0)-mediated LRP has presented significant tolerance even in the presence of air.[26-28] Moreover, the heterogeneous nature of the copper(0) catalyst (can be removed by a simple filtration of the copper wire or particles) leaves the products with relatively low levels of copper residues and thus enabling the direct use of the material in applications where copper contamination is undesired.

Perhaps the most significant limitation of Cu(0)-mediated LRP, relative to RAFT, is that it cannot, to date, mediate the polymerization of less activated monomers such as vinyl pyrrolidone (VP) and vinyl acetate (VA) (although vinyl chloride has been successfully

reported).[18] Polymerization of styrene and methacrylamides has also not been well studied. Moreover, Cu(0)-mediated LRP cannot be conducted in the presence of significant amounts of acids (*e.g.* acetic acid) as the catalyst would be contaminated/complexed, although small amounts of acid (approx. 10%) can be tolerated.[29] In addition, efficient stirring is required for an effective polymerization, especially for the case of the copper wire systems as a consequence of a surface catalysed polymerization. Although a diversity of solvents have been utilized for Cu(0)-mediated LRP, DMSO and H_2O represent by far the most studied solvents. Finally, the gradual accumulation of $CuBr_2$, either by disproportionation or radical-radical coupling, can result in longer reaction times, while radical-radical coupling or loss of the Br end group can lead to irreversible cessation of the reaction. This is in contrast with RAFT, where the rate can be easier tuned by the addition of a suitable amount of free radical initiator.[30]

MONOMERS

By far the most studied class of monomers is acrylates (Figure 2) with methyl acrylate (MA) being widely employed for the optimization of the reaction conditions.[31-40] Ethyl acrylate (EA),[41] *n*-butyl acrylate (*n*BA),[41-48] t*ert*-butyl acrylate (*t*BA),[42, 43, 49, 50] hydroxy ethyl acrylate (HEA),[42, 43, 51, 52] 2-ethylhexyl acrylate (EHA),[42, 53, 54] 2-methoxyethyl acrylate (MEA),[44, 53] di(ethylene-glycol) 2-ethylhexyl ether acrylate (DEGEEA),[53] *o*-nitrobenzyl acrylate (NBA)[55] and oligo(ethylene oxide) methyl ether acrylate (OEOMEA)[56-58] have also been successfully polymerized *via* Cu(0)-mediated LRP. Monomers with long alkyl side chains, including lauryl acrylate (LA) and octadecyl acrylate (OA),[59] as well as semifluorinated acrylates[60, 61] (*e.g.* 1*H*, 1*H*, 2*H*, 2*H*-perfluorooctyl acrylate (PFOA), 2,2,3,3,4,4,4-heptafluorobutyl-acrylate (HFBA), 1*H*, 1*H*, 5*H*-octafluoropentyl acrylate (OFPA), 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA)) have also been reported to be compatible with the technique. Finally, several functional and pH-responsive acrylates, including several sugar acrylates[62] (*e.g.* mannose, glucose, fucose, galactose), glycidyl acrylate (GA),[63] trimethylsilyl propargyl acrylate (TMSPA),[63] 2-dimethylaminoethyl acrylate (DMAEA),[64] 2-[(*D*-glycosamin-2-*N*-yl)carbonyl]oxyethyl acrylate (HEAGI)[65] and solketal acrylate (SA)[66] have also been successfully polymerized.

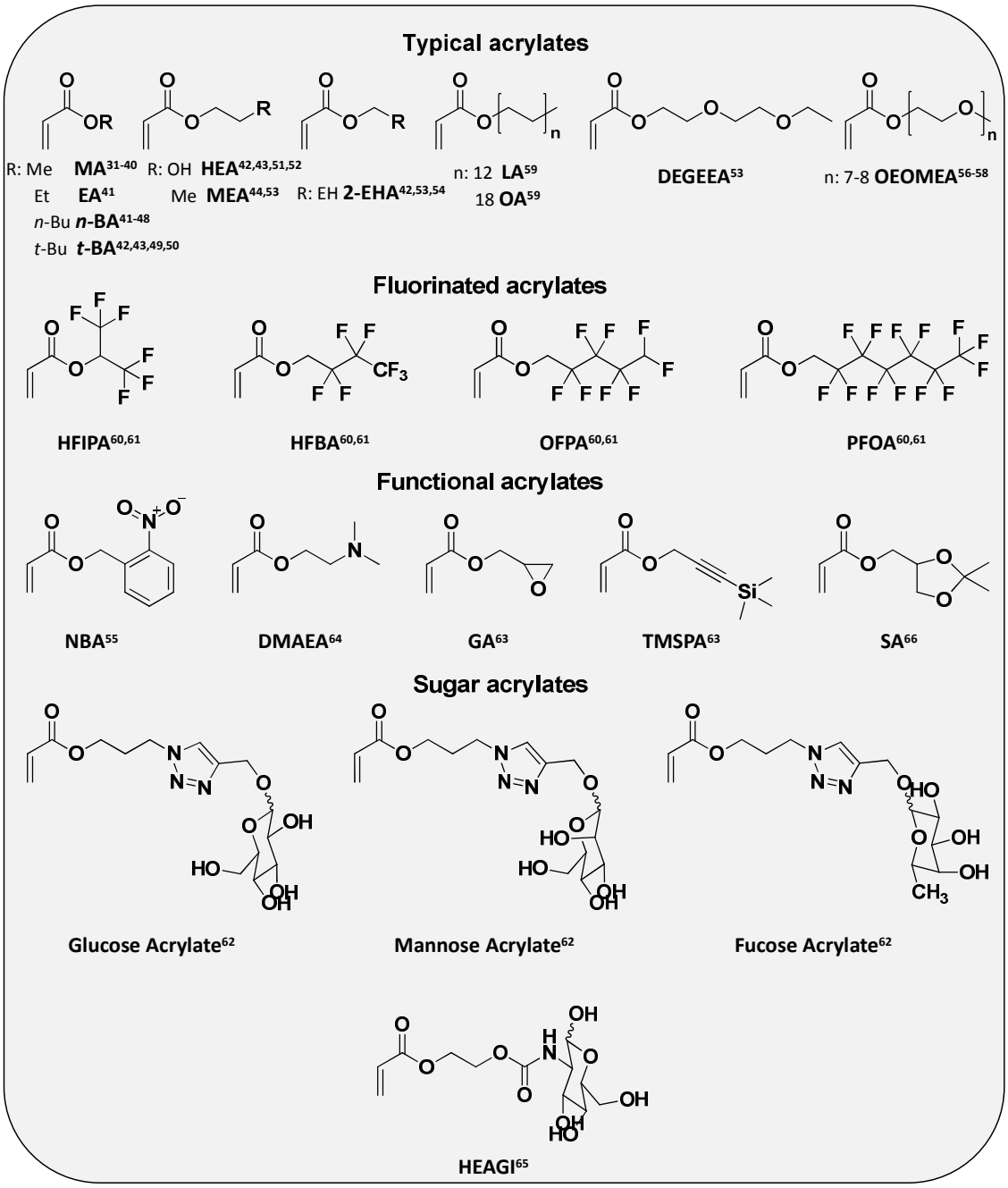

Figure 2: Acrylates polymerized *via* Cu(0)-mediated LRP.

Acrylamides have also been successfully polymerized by Cu(0)-mediated LRP demonstrating fast polymerization rates (reaching often full conversion in < 1 min), narrow MWDs and controlled chain length (Figure 3).[19] *N*-Isopropylacrylamide (NIPAM), dimethylacrylamide (DMA), 2-hydroxyethyl acrylamide (HEAA), *N*,*N*-diethyl acrylamide (DEA) and sugar-based acrylamide monomers have been reported with a good degree of control ($Đ < 1.18$)[19, 67] while an incremental increase in the [$Cu^{I}Br$]:[Me_6-Tren] ratio allowed for the polymerization of 4-acryloyl morpholine (NAM) at various degrees of polymerization (DP_n = 10-640).[68] It was shown that tertiary acrylamides (*e.g.* DMA, NAM, DEA) are more susceptible towards hydrolysis of the bromine chain end in comparison with secondary acrylamides (*e.g.* NIPAM, HEAA) as evidenced by chain extension studies.[48, 69] Copper wire has also been employed for the polymerization of acrylamides such as NIPAM,[70] DMA,[70] acrylamide (AM),[71] *N*-(3-(1*H*-imidazole-1-*yl*)propyl) acrylamide (ImPAA),[72] 3-acryloylamino-propyl)-(2-carboxy-ethyl)-dimethyl-ammonium (CBAAM).[73]

A few methacrylamides have also been studied by Cu(0)-mediated LRP (Figure 4), including *N*-(2-hydroxypropyl)methacrylamide (HPMAM),[74] methacrylamide[75] and carboxybetaine (3-methacryloylamino-propyl)-(2-carboxy-ethyl)-dimethyl-ammonium (CBMAAM).[76, 77]

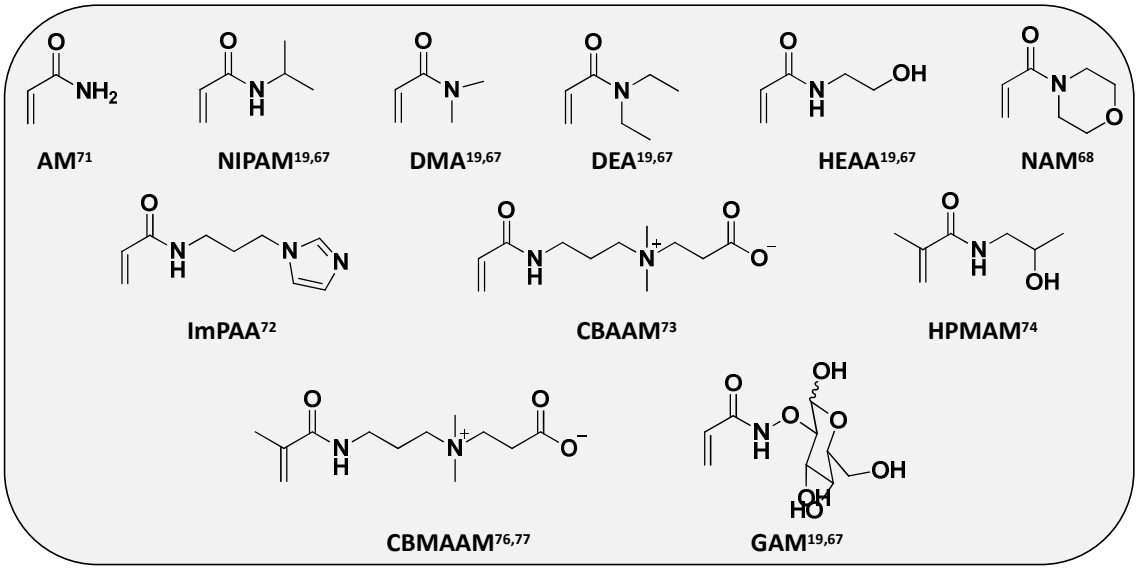

Figure 3: Acrylamides polymerized *via* Cu(0)-mediated LRP.

The combatibility of methacrylates with Cu(0)-mediated LRP has also been tested (although less studied than acrylates and acrylamides) (Figure 4). The polymerization of

methyl methacrylate (MMA) has been investigated in many solvents, both in the presence and absence of air presenting narrow MWDs and quantitative conversions.[29, 78-83] Oligo(ethylene oxide) methyl ether methacrylate (OEGMA),[28, 84-86] di(ethyleneglycol)methyl ether methacrylate (DEGMEMA),[87] tri-(ethyleneglycol)methyl ether methacrylate (TEGMEMA),[87] 2-hydroxyethyl methacrylate (HEMA),[88] butyl methacrylate (BMA),[89-91] tertiary butyl methacrylate (*t*BMA),[92, 93] ethyl methacrylate (EMA),[91] isobornyl methacrylate (IBMA),[94] *N*,*N*-dimethyl-*N*-methacryloyloxyethyl-N-sulfobutyl ammonium (DMBS),[95] 2-(*tert*-butyl-aminoethyl) methacrylate (TBAEMA),[85] γ-butyrolactone methacrylate (GBLMA),[96] methyl adamantyl methacrylate (MAMA),[96] 1,1,1,3,3,3-hexafluoroisopropyl methacrylate (HFIPMA)[61] and 1*H*, 1*H*, 5*H*-octafluoropentyl methacrylate (OFPMA)[60] also demonstrated good control over the MWDs. Perrier and co-workers also reported the Cu(0)-mediated LRP of styrene, although higher temperatures were utilized (~ 90 ºC).[97] Finally, poly(vinyl chloride) (PVC)[18, 24, 98, 99] and poly(acrylonitrile) (PAN)[100-106] have also been prepared by Cu(0)-mediated LRP with good control over the MWDs, highlighting the versatility of the technique (Figure 4).

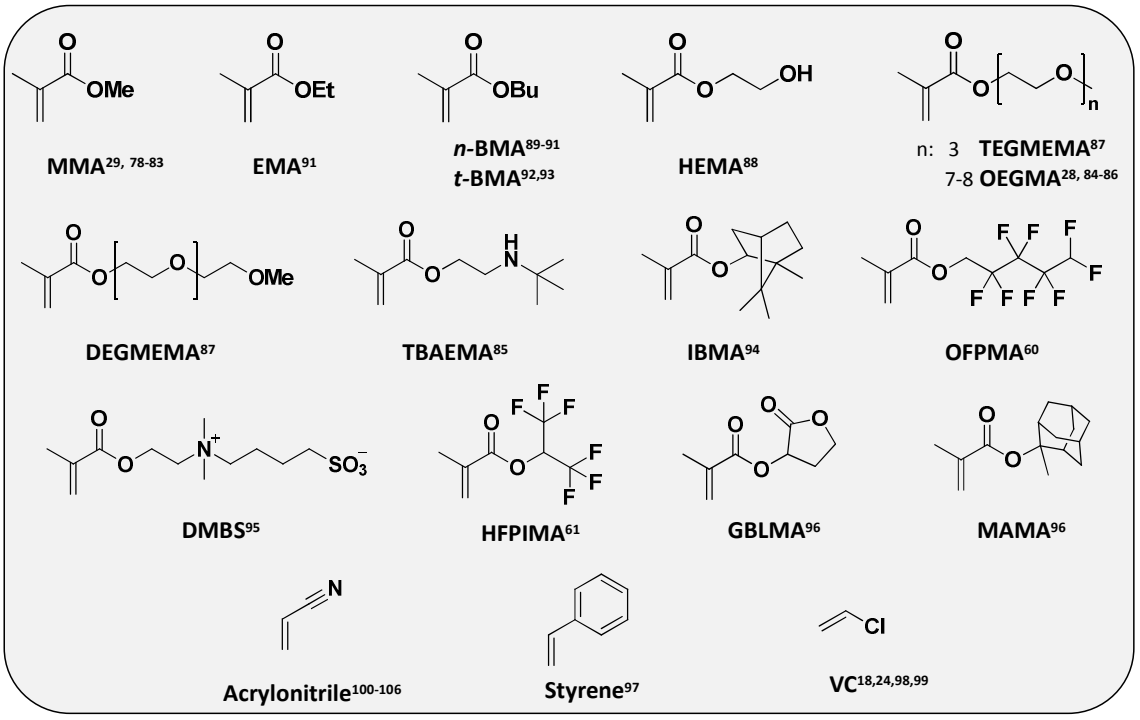

Figure 4: Methacrylates and other monomers polymerized *via* Cu(0)-mediated LRP.

SOLVENTS

The choice of solvent is of importance for Cu(0)-mediated LRP as it can either promote or disfavour the disproportionation of $Cu^{I}Br$ into Cu^{0} and $Cu^{II}Br_2$.[107] Polar solvents, such as H_2O and DMSO have been shown to facilitate disproportionation (to different extents) resulting in first order kinetics and very high end-group functionality, even at quantitative conversions. Although H_2O[19, 28, 51, 68, 69, 74, 80, 95] and DMSO[28, 32, 33, 41, 49, 51, 52, 55, 56, 63, 79, 81, 82, 88, 98, 101, 108] are by far the most studied solvents, alcohols have also been used, including methanol (MeOH),[27, 34, 70, 72, 80] ethanol (EtOH),[34] methoxyethanol,[109] phenol,[110] isopropanol (IPA),[59] *tert*-butanol (*t*BuOH),[34] 2,2,2-trifluoroethanol (TFE),[42, 53, 60, 91, 111, 112] 2,2,3,3-tetrafluoropropanol (TFP),[43, 91, 111] and 1,1,1,3,3,3-hexa-fluoro-2-propanol (HFIP).[81] Other polar solvents can also encourage the disproportionation of $Cu^{I}Br$ such as dimethyl formamide (DMF),[41, 65, 82, 90, 103, 113-115] dimethyl acetamide (DMAc),[116] ethylene carbonate (EC),[116] *N*-methyl-2-pyrrolidone (NMP)[109] and propylene carbonate (PC).[109] On the contrary, solvents such as toluene and acetonitrile (MeCN), produce two linear first-order kinetics and present a decrease in the chain-end functionality as they both discourage the disproportionation of $Cu^{I}Br$.[117, 118] However, binary mixtures of these solvents with disproportionating solvents will still result in an efficient Cu(0)-mediated LRP.[29, 36, 59, 78, 96, 97, 100, 109, 116-123] Cu(0)-mediated LRP has also been reported in non-polar solvents such as toluene, although poorer end-group fidelity was highlighted.[78, 97,117, 122] Hence, the scope of the technique can be expanded to include a large diversity of solvents and solvent mixtures.

INITIATORS

The selection of an appropriate initiator that matches the activity of the monomer is important in order to achieve a controlled polymerization with good agreement between theoretical and experimental molecular weights. As in ATRP, it is essential to have a rate of initiation faster than the rate of propagation and thus it is desirable to correlate the structure of the initiator centered radical with the propagating chain end radical. Thus, methyl 2-bromoproprionate (MBP)[27, 42, 43, 49, 52, 53, 65, 109, 116, 121] and ethyl *a*-bromoisobutyrate (EBiB)[42, 44, 52, 55, 63, 78, 81, 101, 124] are two of the most commonly used mono-functional initiators and have been reported to mediate the efficient polymerization of acrylates and methacrylates/acrylonitrile/acrylates respectively. Ethyl 2-bromoproprionate (EBP)[78, 97] (styrene and acrylates), poly(ethylene oxide) macroinitiator (PEO-Br)[51, 56] (acrylates), 1,2-

dihydroxy-propane-3-oxy(2-bromo-2-methylpropionyl (DHPOMBP)[19, 56, 58, 69] (acrylates), methyl α-bromophenylacetate (MBrPA)[88] (acrylates and methacrylates), oligo(ethylene oxide)-2-bromo-2-phenylacetate (OEOBrPA)[28] (acrylates and methacrylates) and ethyl-2-bromo-2-phenylacetate (EBrPA)[82] (acrylates and methacrylates) have also shown excellent compatibility with Cu(0)-mediated LRP. Chlorine α-haloester initiators have also been employed, including methyl-2-chloropropionate (MCP),[33, 70, 74] 2,2-dichloroacetophenone (DCAP)[113] and ethyl 2-chloropropanoate (ECP)[72] which effective mediated the polymerization of acrylamides methacrylates, acrylates and styrene. The controlled polymerization of acrylates and vinyl chloride has also been studied utilizing a variety of haloform initiators such as chloroform ($CHCl_3$),[33] bromoform ($CHBr_3$)[32] (both behave as mono-functional initiators throughout the polymerization) and iodoform (CHI_3)[32] (mono-functional at low conversion and bi-functional at higher conversions). Finally, sulfonyl halide initiators (*p*-toluene sulfonyl chloride (TsCl)[29, 60, 80, 83, 91] (methacrylates and acrylates), alkyl halide initiators (*e.g.* carbon tetrachloride (CCl_4)[79, 90, 96, 103, 114] (methacrylates and acrylonitrile), amide initiators (2-chloropropionamide (CPA)[95] and 2-bromo-2-*N*-phenyl-propionamide (BrPPA)[36] for acrylates, methacrylates and acrylamides), nitrile initiators (*e.g.* 2-bromoproprionitrile (BPN),[100] suitable for acrylates) and functional initiators (phosphonate bearing initiator (PBI),[125, 126] arsenic initiator (AsI),[127] dithiophenol maleimide initiator (DtMI),[128] and propargyl 2-bromoisobutyrate initiator (PBIB))[92] have also demonstrated to be effective Cu(0)-mediated LRP initiators (Figure 5).

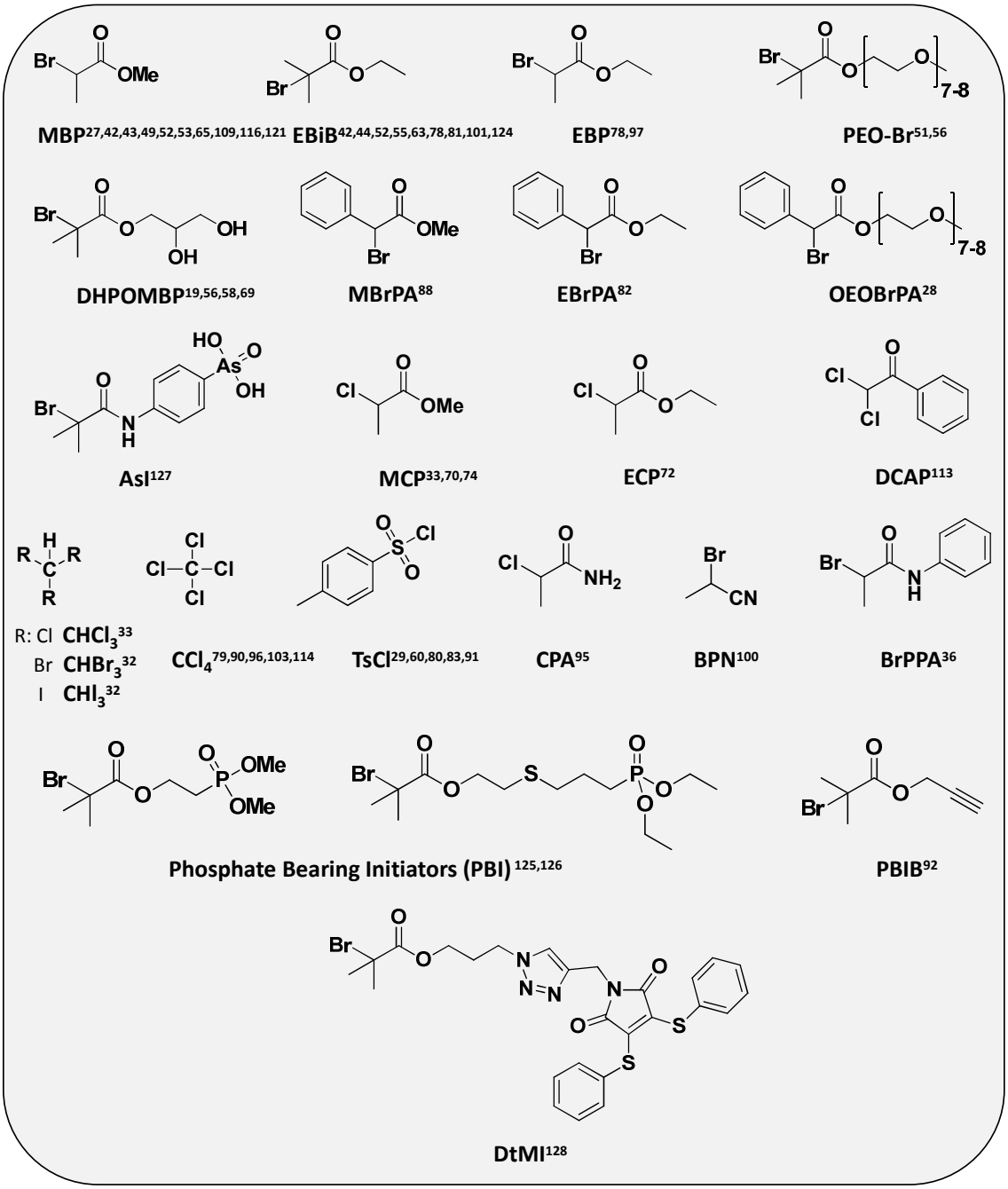

Figure 5: Monofunctional initiators employed in Cu(0)-mediated LRP.

Due to the low levels of termination, Cu(0)-mediated LRP is useful for the synthesis of telechelic polymers which due to the potential to functionalize both α and ω chain end post polymerization can further alter the properties of the materials.[129] A wide range of bi-functional initiators have been found to be compatible with Cu(0)-mediated LRP (Figure 6) including ethylene bis(2-bromoisobutyrate) (BrIBE),[48] bis(2-bromoproprionyl)ethane (BPE),[34, 41, 60, 130] dimethyl 2,5-dibromohexanedionate (MBHD),[130] dimethyl-2,6-

dibromoheptanedioate (DMDBH)[100] (acrylates and acrylonitrile), poly(ethylene glycol) bis(2-bromoisobuturate) (PEG-BEBiB),[58] *meta*-phenylene ethynylene dodecamer bi-functional initiator (*m*PEDBI)[131] and bis(2-(2′-bromoisobutyryloxy)ethyl)disulphide $(BiBOE)_2S_2$[75] (acrylates, methacrylates and acrylamides). Multi-functional initiators have also been employed by Cu(0)-mediated LRP (Figure 6) allowing the preparation of star polymers Among them, 4-arm initiators (*e.g.* pentaerythritol tertrakis(2-bromopropionate) (4BrPr)[66] and 2,2-dibromomethyl-1,3-dibromopropane ($PEBr_4$)),[132] 5-arm initiators (*e.g.* 1,2,3,4,6-penta-*O*-isobutyryl bromide-α-*D*-glucose) (PiBBr-Glu)[133] and 8-arm initiators (*e.g.* octa-*O*-isobutyrylbromide lactose) (OiBBr-Lac)[134] presented narrow MWDs and living characteristics.

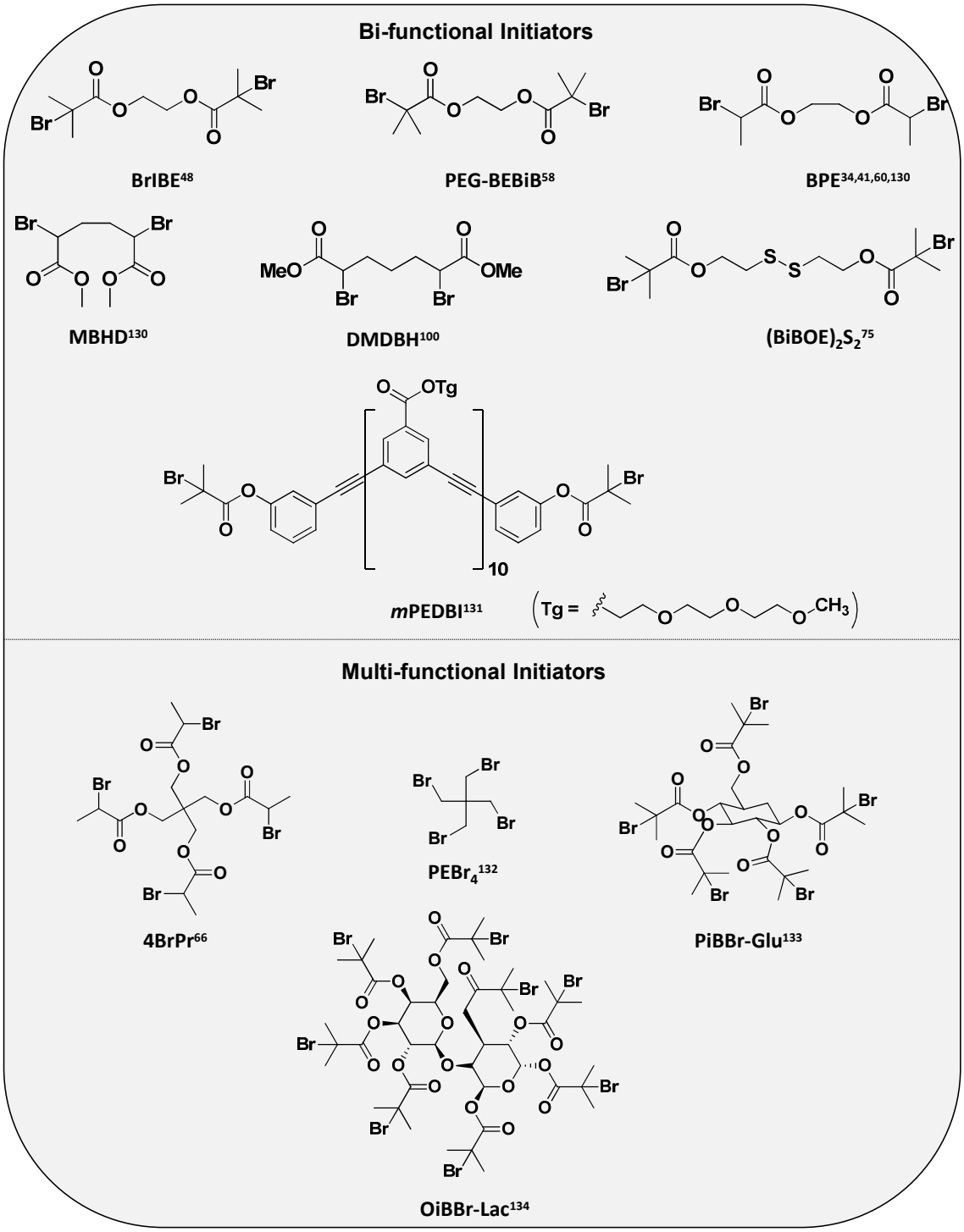

Figure 6: Bifunctional and multifunctional initiators employed in Cu(0)-mediated LRP.

Cu(0) AND OTHER METALS

The catalyst in Cu(0)-mediated LRP is a combination of metal and ligand. Although many zerovalent metals have been utilized for Cu(0)-mediated LRP, including iron (Fe),[135-

[142] nickel (Ni),[143] ytterbium (Yb),[144] lanthanum (La),[145, 146] gadolinium (Gd),[147] magnesium (Mg),[148] tin (Sn)[149] and samarium (Sm),[150] copper has been by far the most widely employed catalyst. When Cu(0) powder is employed, perfect or near perfect end group-fidelity can be maintained throughout the polymerization[32, 34, 41, 151] while decreasing the particle size results in an increase in the rate of the propagation.[120] Cu(0) wire is perhaps the most popular form of catalyst and is possibly a better alternative in comparison with Cu^0 particles as it provides better control over the MWDs, enhanced predictability, facile tuning of the reaction rate and recyclability.[152, 153] Finally, Cu^0 particles obtained *in situ via* the disproportionation of Cu^IBr in the presence of *N*-containing ligands (*e.g.* Me_6-Tren) in H_2O, DMSO and other polar solvents can also be used as the catalyst resulting in fast polymerization rates, narrow MWDs and high end-group fidelity as evident by *in situ* chain extensions and block copolymerizations. [19, 154-157] It should be highlighted that copper wire is proposed as the copper source in order to produce polyacrylates and methacrylates in organic media while the disproportionation protocol should be used for the production of polyacrylamides, polyacrylates and polymethacrylates in aqueous media.

Catalyst activation is very important for the outcome of the polymerization (in the case of copper wire).[130] Percec and co-workers typically utilize hydrazine to remove the layer of Cu_2O from the surface of the commercially available copper wire. Cu_2O has also been reported to efficiently activate Cu(0)-mediated LRP, however, it is slower than Cu(0).[24, 158-161] Switching from non-activated to activated copper wire results in acceleration of the polymerization rate (~ 2 fold)[130] as well as removal of the induction period typically observed when non-activated wire is used.[109, 116, 153, 162] A further method to remove the oxide layer from the surface of the copper wire is *via* dissolution in concentrated acid (typically HCl).[163] This method is often preferred due to its simplicity and speed. Finally, two fluorinated alcohols (TFE and TFP) have been found to self-activate the copper wire, resulting in similar polymerization rates to the previous methods as well as complete removal of the induction period.[42, 43, 60, 91, 112]

LIGANDS

Suitable ligands are typically *N*-containing ligands which can favour the disproportionation of Cu^IBr into Cu^0 and $Cu^{II}Br_2$.[156, 164] In addition, small changes in the ligand concentration may have a detrimental effect on the end-group fidelity of the polymer chains, thus careful optimization of the reaction conditions is required.[31, 156, 165] Me_6-Tren[19, 27, 32-34, 68, 78] is one of the most widely employed ligands and is highly recommended for the

polymerization of acrylates and acrylamides while PMDETA[44, 51, 65, 81, 97] (acrylates and methacrylates) and tris(2-aminoethyl)amine (TREN)[51, 98] (acrylates) are both good commercially available alternatives. 1,1,4,7,10,10-Hexamethyltriethylenetetramine (HMTETA),[90, 103, 114] 2,2′-bipyridine (Bipy)[100, 101] and diNbpy[97] have also been investigated. However, it should be noted that for - Bipy and substituted bpy disproportionation is reduced due to stabilization of $Cu^{I}Br$ and thus activation of the alkyl halide by both Cu^{0} and $Cu^{I}Br$ must occur during the polymerization. Ligands that have low lying π^* orbitals that can accept electron density stabilise copper(I) and are less attractive (*e.g.* pyridine imines and Bipy derivatives).

DEACTIVATOR

Cu(0)-mediated LRP has been initially reported to proceed in both the presence and absence of deactivating species, $CuBr_2$ (or $CuCl_2$ when a chlorine initiator has been employed). For instance, Whittaker and co-workers have utilized mass spectroscopy to compare two identical polymerizations in the presence and absence of $CuBr_2$. Despite reaching full conversion within 2 h for both cases, the polymerizations were allowed to continue for a further 3 days. Although SEC analysis revealed the absence of any significant coupling/termination peaks, MS detected the presence of terminated polymer chains when no $CuBr_2$ was used.[166, 167] Thus, the importance of the deactivator in Cu(0)-mediated LRP was highlighted, especially when high end group fidelity is required for subsequent post polymerization modifications or block copolymerizations. As expected, the presence of $CuBr_2$ at the beginning of the polymerization leads to further control over the molecular weight distributions, higher end-group fidelity and slower polymerization rates.[40] Therefore, it is crucial to optimize the concentration of $CuBr_2$, in order to achieve both good control and acceptable polymerization rates. In the literature different concentrations of $CuBr_2$ have been employed (0.01-0.40 equiv. relative to initiator).[133] A typical concentration of $CuBr_2$ is 0.05 or 0.10 equiv., although further optimization is required depending on the targeted DP_n, solvent and monomer structure.

RECOMMENED CONDITIONS FOR THE POLYMERIZATION OF (METH)ACRYLATES AND ACRYLAMIDES

As shown in the previous sections, a wide range of initiators have been utilized for the Cu(0)-mediated LRP of acrylates, methacrylates and acrylamides. Moreover, different

ligands and copper sources (*e.g.* copper wire, copper powder or Cu(0) particles obtained *via* the in situ disproportionation in pure H_2O) have been employed to facilitate the controlled polymerization of various monomers, further adding on the complexity of this multicomponent system. In order to provide some useful guidelines to afford the synthesis of well-defined polymers with high end group fidelity, the recommended conditions are summarized in Figure 7. EbiB is one of the most efficient and commonly employed initiators for the polymerization of acrylates in organic media (*e.g.* DMSO) and copper wire is the suggested copper source while for methacrylates TsCl should be preferred instead. Finally, for acrylamides, the pre-disproportionation protocol with DHPOMBP as the initiator gives rise to narrow MWDs and quantitative conversions within 15 min while block copolymers can also be obtained *via* in situ chain extensions (Figure 7). It is noted that further details and guidelines can be found in the literature.[168]

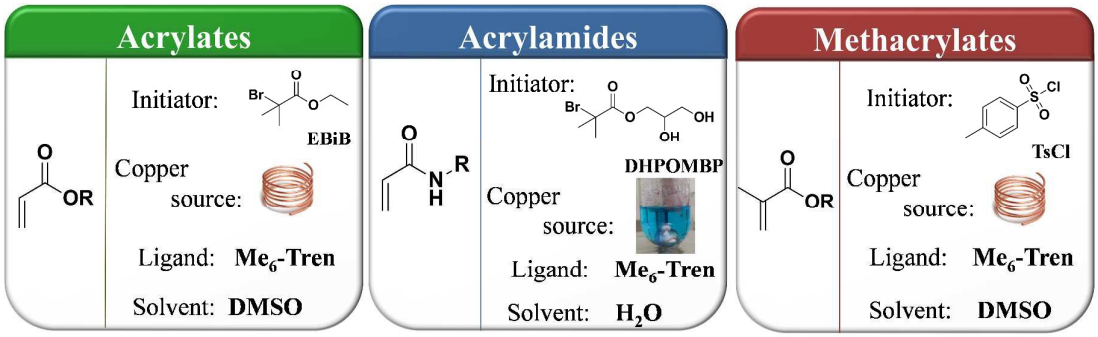

Figure 7: Recommended conditions for the controlled polymerization of acrylates, acrylamides and methacrylates.[19, 29, 124]

MECHANISM

Two models have been proposed to explain the mechanism of Cu(0)-mediated LRP; the Cu(0)-mediated LRP model as initially suggested by Percec and co-workers and the SARA-ATRP model was subsequently proposed by Matyjaszewski and co-workers as an attempt to reconcile the Cu(0)-mediated LRP experiments with the well-documented ATRP mechanism. Although both models involve the same components, the contribution of every reaction (*e.g.* disproportionation, comproportionation, activation by Cu^0, activation by Cu^IBr *etc.*) is proposed to be vastly different.[107, 169-175] As the focus of this perspective is not to discuss or clarify the mechanism, the reader is referred to the recent reviews for an in depth understanding.

RECENT HIGHTLIGHTS OF Cu(0)-MEDIATED LRP

AQUEOUS Cu(0)-MEDIATED LRP

An interesting contribution from our group using Cu(0)-mediated LRP over the past few years is the development of a polymerization protocol to perform Cu(0)-mediated LRP in water.[19] The key and necessary step in the process is to allow full disproportionation of $Cu^{I}Br/Me_6$-Tren into Cu^0 and $Cu^{II}Br_2$ in water prior to addition of both monomer and initiator where the relative concentrations of $[Cu^{I}Br]/[Me_6\text{-Tren}]$ is usually <1 and often close to 0.5 (for a demonstration of this protocol please watch the following video: http://goo.gl/zTG4ge). The synergistic effect of the disproportionation products is crucial and was identified by using the Cu^0 precipitate (after isolation) directly to catalyse (with additional Me_6-Tren) the same polymerization. However, broad molecular weight distributions were observed despite the fast polymerization rate. Furthermore, addition of initiator/monomer to the bright blue (d^9) $Cu^{II}Br_2/Me_6$-Tren solution (in the absence of Cu^0 precipitate) showed no detectable polymerization after 24 h *via* both SEC and NMR analysis. Thus, both Cu^0 and $Cu^{II}Br_2$ are required for a successful controlled polymerization. On the contrary, utilizing the disproportionation conditions (both Cu^0 and $Cu^{II}Br_2$) allow access to the synthesis of a large variety of water soluble polymers with controlled chain length and narrow MWDs ($Đ \sim 1.10$). Careful optimization of the reaction conditions allows for the variation of the polymerization degree (DP_n = 8 - 320). All polymerizations can be performed at ambient temperature or below reaching quantitative conversions in a few minutes. Typically it is difficult to maintain high end-group fidelity in aqueous copper-mediated living radical polymerizations due to the facile hydrolysis of the terminal halogen group *via* a cyclic onium intermediate.[176] However, in all the Cu(0)-mediated LRP polymerizations low dispersity was maintained from low to quantitative conversion without any detectable coupling peaks, even when the reactions were left to proceed overnight. Initially, chain extension was attempted at ambient temperature in order to qualitatively assess the terminal bromide. However, bimodal peaks were obtained *via* SEC, suggesting significant loss of the terminal bromide due to hydrolysis. As such, the chain extension was subsequently performed at lower temperatures (utilizing an ice bath). A clear shift from lower to higher molecular weight demonstrated that chain extension was efficient under these conditions and high end-group fidelity could be maintained. The versatility of the technique was further demonstrated by the polymerization of a plethora of acrylate and acrylamide monomers including PEGA, HEA, DMA and even an acrylamide-based

glycomonomer (Figure 8). Good agreement between the theoretical and the experimental values, low dispersities and fast polymerization rates were observed in all cases. Thus, this robust polymerization technique can be applied for a wide range of hydrophilic and non-hydrophilic monomers in aqueous and mixed solvents.

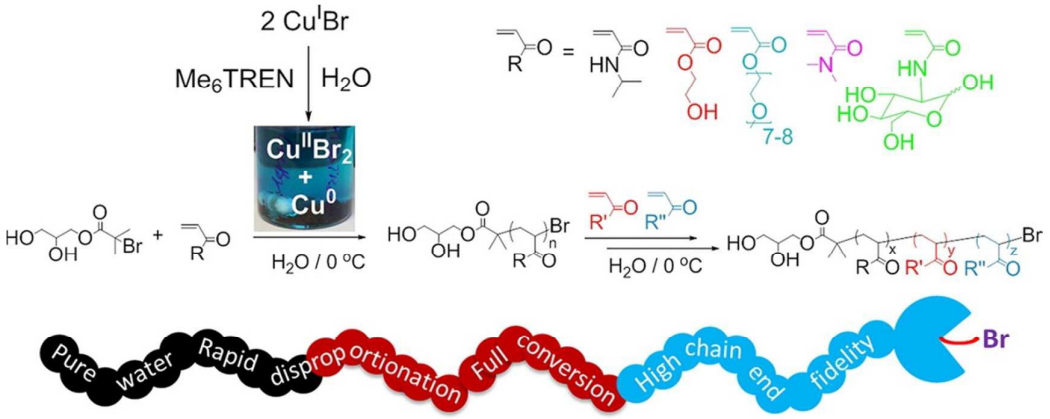

Figure 8: Schematic representation for the synthesis of a large variety of water soluble polymers by iterative Cu(0)-mediated LRP in H_2O. Reproduced from Ref. 19 with permission from the American Chemical Society.

"SPECIAL" SOLVENTS

SOLVENTS INDUCING PHASE SEPARATION

One particularly interesting and quite surprising highlight of Cu(0)-mediated LRP is the ability of some solvents to support the *in situ* separation of the catalyst from the polymer/monomer layer.[177] For instance, during the polymerization of *n*BA in DMSO the poly(*n*BA) undergoes phase separation after a certain molecular weight (~ 2500 g mol^{-1}) yielding a biphasic system that consists of a polymer-rich layer and a DMSO/monomer-rich layer (Figure 9a). Interestingly, the majority of the catalyst is accumulated in the solvent phase with only traces of catalyst (ICP-MS analysis: 0.016 wt% or 160 ppm) remaining in the polymer phase. Importantly and despite the phase separation, the polymerization proceeds with a high degree of control with narrow MWDs even at quantitative conversions and high end-group fidelity as exemplified *via* MALDI-ToF-MS analysis and *in situ* chain extensions. Thus, this convenient polymerization methodology allows for the generation of polymers with controlled chain length as well as efficient removal of the copper residues from the

polymer product without further purification. However, when a range of other alkyl acrylates were investigated the control over the polymerization was lost as the hydrophobicity of the monomer increases due to the increase in the alkyl chain length indicating that it is important for the monomer to be soluble in the polar solvent.

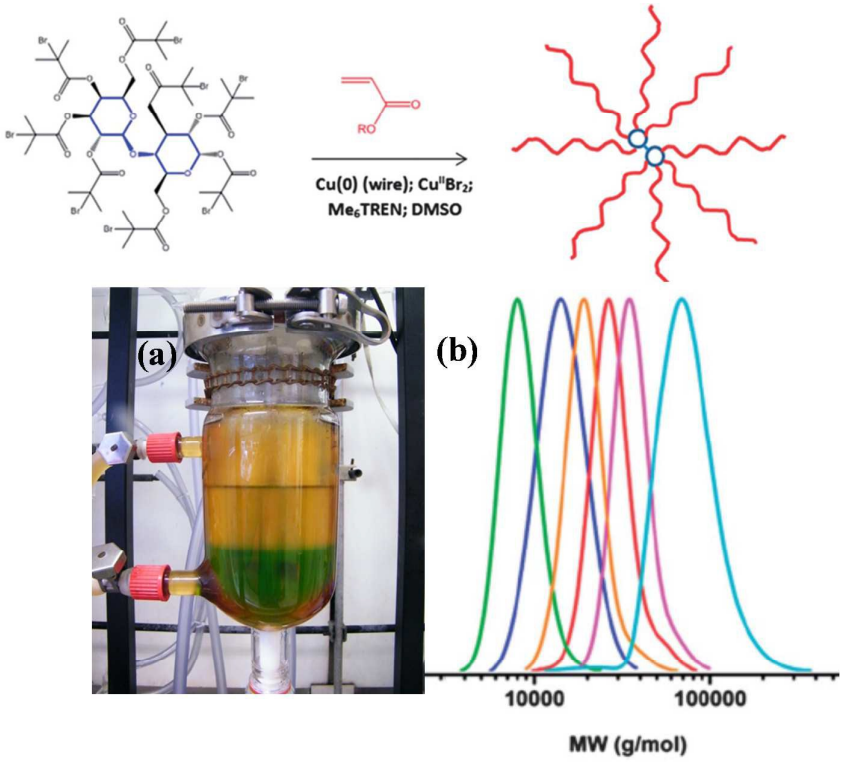

Figure 9: (a) Poly(*n*BA) self-generated biphasic system in DMSO and (b) SEC analysis for the poly(*n*BA) star polymers synthesis from an octa-functional lactose initiator *via* Cu(0)-mediated LRP in DMSO. Reproduced from Ref. 134 with permission from the Royal Society of Chemistry.

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In order to circumvent this and facilitate the polymerization of higher order acrylates to proceed through a self-generated biphasic system without loss of control it was postulated that a solvent which solubilizes the new hydrophobic monomer (*e.g.* LA) is required.[59] IPA was found to fully solubilize the LA monomer and thus it was anticipated that the Cu(0)-mediated LRP of LA could be realized with success depending on either retention of polymer solubility throughout the reaction or the capacity of IPA to support a self-generating biphasic system. Pleasingly, upon completion of the polymerization and cessation of the stirring two distinct layers could be observed. The upper phase was green whereas the lower phase was transparent and with higher viscosity than the upper phase. Careful sampling of the lower

phase revealed a low dispersity polymer ($Đ$ ~ 1.10) with high end-group fidelity (verified with post polymerization modification) and very low levels of copper (ICP-MS analysis: 160 ppm). As a comparison with the biphasic LA-IPA system, the polymerization of LA was also carried out in a binary solvent system (toluene/MeOH) in order to maintain homogeneous conditions throughout the polymerization. The absence of phase separation was inconsequential to overall polymerization control, as M_n increased linearly with conversion and dispersity values were as low as 1.10. Thus, both solvent systems can support the controlled polymerization of hydrophobic monomers with the IPA having the additional advantage of *in situ* separation of the catalyst from the polymer.

In a further contribution, the phase separation of lipophilic star polymers was explored during the Cu(0)-mediated LRP from multifunctional initiators.[134] An octa-functional lactose-based initiator was employed to target poly *n*BA star polymers over a range of molecular weights. The polymerizations were conducted in DMSO, a solvent that has been previously shown to support the self-generating biphasic system (Figure 9b). High molecular weight poly(*n*BA) star polymers with low dispersities ($Đ$ ~ 1.10) could be obtained even at high monomer conversions (> 90%) with mono-modal SEC chromatograms traces suggesting a low degree of star-star coupling. It was postulated that the observed degree of control may, at least in part, be a direct consequence of the star polymers phase separating from the reaction medium, thus rendering them less likely to undergo star-star coupling reactions due to a reduced concentration of active termini. Since the polymer exists in a high viscous phase it is conceivable that interactions between neighbouring star polymers may be reduced due to the high viscosity.

In order to verify this hypothesis and elucidate any role of the phase separation in limiting star-star coupling, the synthesis of poly(*n*BA) was attempted in IPA (Figure 10a), a solvent that would not induce phase separation of this monomer. In addition, poly(MA) was synthesized in DMSO as this particular solvent retains a homogeneous reaction mixture throughout the polymerization (Figure 10b). In both cases, obvious high molecular weight shoulders were observed *via* SEC thus highlighting the beneficial nature of the phase separation in suppressing radical-radical coupling between star polymers.

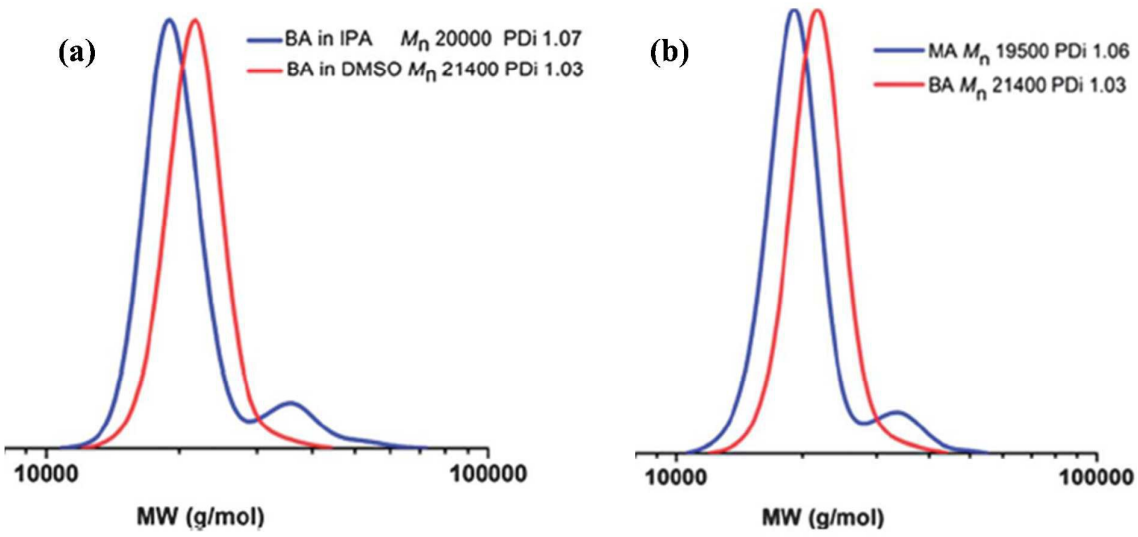

Figure 10: SEC comparison of (a) poly(*n*BA) stars prepared in IPA and DMSO and (b) similar MW poly(MA) and poly(*n*BA) stars prepared *via* Cu(0)-mediated LRP in DMSO. Reproduced from Ref. 134 with permission from the Royal Society of Chemistry.

Cu(0)-MEDIATED LRP IN BLOOD SERUM, ALCOHOLIC BEVERAGES AND PBS BUFFER

Although the development of robust CRLP techniques and their application in bio-polymer hybrid materials is a thriving area of both academic and industrial interest, reports on Cu-mediated LRP in true biological media are limited. Hence, the use of undiluted blood serum to promote the disproportionation of $Cu^{I}Br$ into Cu^{0} and $Cu^{II}Br_2$ was investigated resulting in quantitative degrees of disproportionation, similar to the pure aqueous system. Both NIPAM and DMA were homopolymerized with good degree of control giving polymers with low dispersities while the high end-group fidelity of the macroinitiators was identified through sequential block copolymerizations that showed a complete shift in the SEC chromatograms while maintaining low dispersities.[178] Thus, blood serum proved to be a compatible solvent for the polymerization of a plethora of hydrophilic monomers.

Haddleton and co-workers also performed the Cu(0)-mediated LRP of NIPAM in a range of commercial water-ethanol mixtures (Figure 11).[179] Reflecting the multi-national spread of researchers in the laboratory, a wide range of alcoholic beverages were employed in order to determine whether the different alcohol contents and the residual chemicals and sugars present from complex brewing and distillation processes would be detrimental for the

polymerization. Pleasingly, despite the various chemical functionalities and impurities present, all the alcoholic mixtures (*e.g.* Romanian brandy, English ale, Greek ouzo, Irish stout, Swiss liquor *etc.*) were found to support the controlled polymerization of NIPAM attaining very low dispersity polymers and quantitative conversions in a matter of minutes, highlighting the robustness of this polymerization protocol.

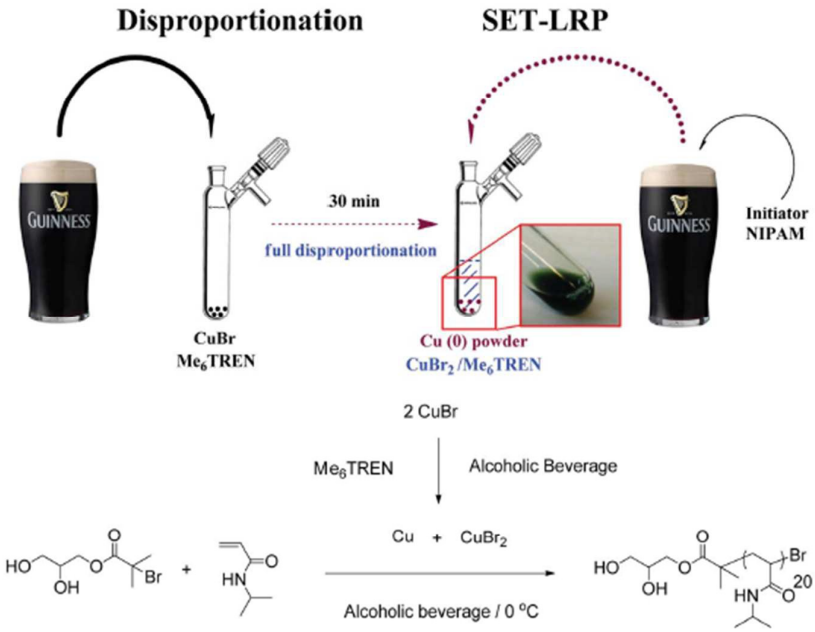

Figure 11: Typical polymerization procedure. Disproportionation of [Cu^{I} (Me_6-Tren)Br] into Cu(0) and Cu^{II} is first conducted in deoxygenated commercial beer/wine/cider/spirit followed by addition of a separate deoxygenated monomer/initiator solution. Note the patriotic green colour of the Guinness solution in this example. Reproduced from Ref. 179 with permission from the Royal Society of Chemistry.

Cu(0)-mediated LRP has also been conducted in PBS buffer, a medium used to mimic biological conditions.[19] Quantitative disproportionation of $Cu^{I}Br$ in Cu^{0} and $Cu^{II}Br_2$ was observed, although with a slower reaction rate in comparison with pure water. Well-defined polymers at quantitative conversions could be obtained with slightly higher dispersities ($Đ$ ~ 1.21-1.29) suggesting that the buffer was affecting the catalyst and the polymerization. Nevertheless, the robustness of the approach was once again highlighted.

COMPLEX ARCHITECTURES

SEQUENCE CONTROLLED-MULTIBLOCK COPOLYMERS

Natural polymers (*e.g.* nucleic acids, peptides, proteins *etc.*) are often capable of storing an abundance of information and are precisely constructed by cellular organelles. The ability to mimic these sophisticated structures by polymer chemists is highly desirable for applications where precision confers the potential for molecular targeting and recognition and is of increasing interest.[180] The addition of a single monomer unit *via* radical chain-growth polymerization techniques is challenging due to the reactive nature of the radical. However, the sequence of discrete regions within the overall macromolecular structure can be achieved by synthetic chemistry, although until recently isolation and purification of the growing polymer following each monomer addition was required in order to maintain high end-group fidelity for the subsequent chain extension. Many polymerization methods (including RAFT and ATRP) have been used to address this issue with ultimate goal to maintain high end-group fidelity, quantitative conversion and low dispersity for every block formation.[25, 30, 181-185]

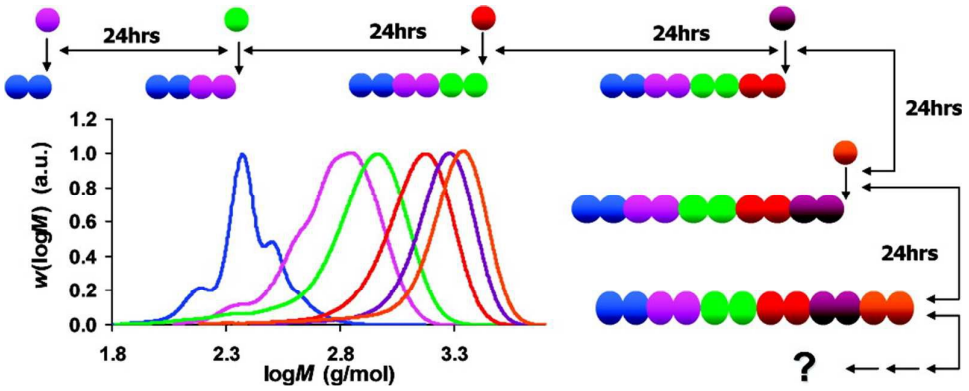

Figure 12: Schematic representation and SEC analysis of the synthesis of multiblock copolymers by sequential addition of monomers without intermediate purification *via* Cu(0)-mediated LRP in DMSO. Reproduced from Ref. 166 with permission from the American Chemical Society.

Whittaker and co-workers were the first to introduce a facile approach for the synthesis of high-order multiblock copolymers in organic media. Cu(0)-mediated LRP was employed for the sequence control polymerization of acrylates (DP_n ~ 2 per block) with very good control attained over the MWDs and minimal loss of end-group functionality by ESI-MS. Importantly, quantitative conversion can be achieved in every cycle (> 99%) and thus no purification methods are required between the intermediate monomer additions (Figure 12).

A well-defined hexablock copolymer was obtained demonstrating for the first time the possibility to obtain such highly complicated structures.[166] The same technique was also applied for the synthesis of star multiblock copolymers with similar degrees of control attained when an optimum amount of $Cu^{II}Br_2$ deactivator was chosen.[133] However, when higher molecular weights were targeted broader MWDs were obtained, indicating significant loss of control ($Đ \sim 1.7$). [180] Careful optimization of the reaction conditions (with respect to ligand and $Cu^{II}Br_2$), allowed for the synthesis of higher molecular weight block copolymers (~ 70000 g mol^{-1}) with low dispersity ($Đ \sim 1.10$). [40] Subsequently, this polymerization methodology was applied from Haddleton and co-workers for the synthesis of multiblock glycopolymers in various compositions containing mannose, glucose and fucose moieties in the presence and in the absence of monomer spacer.[62, 63]

For the synthesis of multiblock copolymers in aqueous media, the aqueous Cu(0)-mediated LRP protocol was employed, exploiting the rapid disproportionation of $Cu^{I}Br$ into Cu^0 and $Cu^{II}Br_2$. Thorough kinetic studies allowed for the synthesis of acrylamide multiblock copolymers with unprecedented rates of reaction and excellent control over chain lengths and MWDs. A series of control experiments were conducted to identify the limiting effects on the polymerization highlighting that the rate of bromine chain loss is enhanced for tertiary acrylamides (*e.g.* DMA, NAM) relative to secondary acrylamides (*e.g.* NIPAM, HEAM).[69] The same technique was subsequently applied for the synthesis of telechelic multiblock copolymers comprised of both acrylates and acrylamides (DMA, DEA, NIPAM, PEGA). The thermoresponsive nature of these materials was demonstrated *via* cloud points measurements while the typically unwanted hydrolysis of the α and ω end-group was exploited *via* isocyanate post-polymerization modification allowing for further altering of the material's properties (Figure 13).[58]

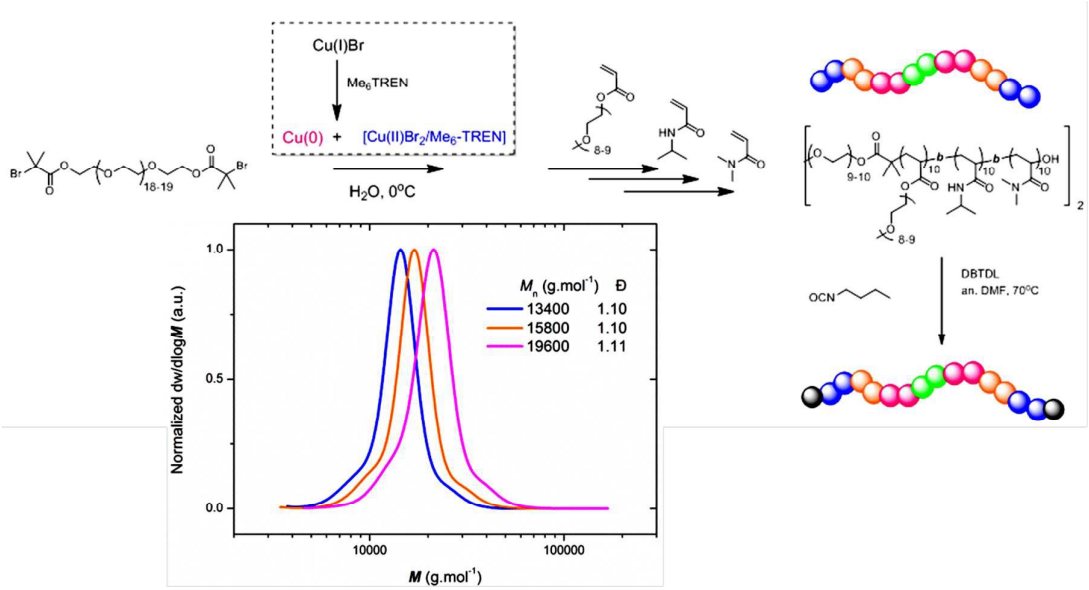

Figure 13: Schematic representation and SEC analysis of the synthesis of multiblock copolymers by sequential addition of monomers *via* aqueous Cu(0)-mediated LRP. Reproduced from Ref. 58 with permission from the Royal Society of Chemistry.

STARS AND HYPERBRANCHED STRUCTURES

Monteiro and co-workers were the first to employ Cu(0)-mediated LRP for the synthesis of star homo- and block copolymers. A 4-arm initiator was employed for the polymerization of MA which was subsequently chain extended with SA to yield, upon deprotection, a well-defined amphiphilic block copolymer (poly(MA)-*b*-(GA)) (Figure 14). The assembling of the latter one in water was also evaluated leading to the formation of vesicles.[66] A 5-arm glucose initiator was also employed by Whittaker and co-workers yielding low dispersity star polymers, even at quantitative conversions. In order to achieve this, careful optimization of the copper to ligand ratio was studied in order to minimize star-star coupling.[133] Haddleton and co-workers utilized a lactose based 8-arm initiator for the Cu(0)-mediated LRP of lipophilic monomers (*e.g.* BA, LA) resulting in low dispersities and minimal star-star coupling.[134] Core cross-linked star polymers have also been synthesized by Qiao and co-workers, exploiting the high end-group fidelity of Cu(0)-mediated LRP. Remarkably, quantitative star formation could be achieved in very high yields (> 99%) without the need to isolate the initial macroinitiators.[186] In a similar vein, Kond and co-workers utilized 2-(2-bromoisobutyryloxy) ethyl acrylate (BIBEA) as the inimer for the facile preparation of branched poly(MA) at ambient temperature.[187] Finally, Matyjaszewski and co-

workers reported the synthesis of hyperbranched polyacrylates in the presence of Cu(0)[188] while Percec and co-workers combined thio-bromo "click" chemistry with Cu(0)-mediated LRP to synthesize a new class of of poly(thioglycerol-2-propionate) (PTP) dendrimers.[35, 189] Recently Becer and cow-workers also reported pentablock star polymers obtained *via* aqueous Cu(0)-mediated LRP in less than 90 min with narrow MWDs.[190]

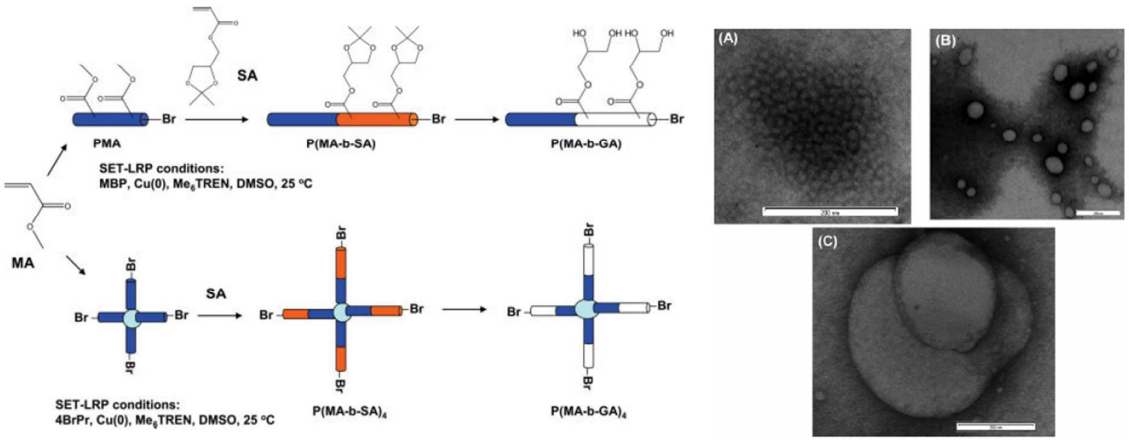

Figure 14: Cu(0)-mediated LRP methodology to prepare biocompatible amphiphilic linear/star block copolymers and TEM images of micellized amphiphilic block polymers : (A) P(MA_{50}-*b*-SA_{53}), (B) ($P(MA_{22}$-*b*-$GA_{29})_4$, and (C) $P(MA_{22}$-*b*-$GA_{29})_4$. Scale bar in all TEMs is 200 nm. Reproduced from Ref. 66 with permission from John Wiley & Sons, Inc.

CYCLIC POLYMERS

For the successful synthesis of cyclic polymers, very high end-group fidelity is required. Thus, Monteiro and co-workers exploited the high end-group fidelity of Cu(0)-mediated LRP to synthesize a large diversity of linear polymers, including polystyrene, poly(*n*BA) and PMA, with narrow MWDs, which were cyclisized post polymerization to form the desired cyclic polymers. The combination of three different cyclic polymers using two orthogonal coupling reactions in one pot at ambient temperature gave rise to the synthesis of an μ-ABC tricyclic miktoarm star polymer.[191]

APPLICATIONS

SURFACE-INITIATED Cu(0)-MEDIATED LRP

Cu(0)-mediated LRP has been utilized by Charleux and co-workers to grow NAM from the surface of latex particles (made by emulsion polymerization and functionalized with a Cu(0)-mediated LRP initiator) forming hydrophobic core/hydrophilic shell particles (Figure 15).[192] Carbon nanotubes have also been functionalized *via* Cu(0)-mediated LRP using OEOMEA. The functionalized nanotubes presented enhanced dispersibility in polar and non-polar solutions.[193] Improved dispersibility was also demonstrated when functionalized graphene nanosheets (with a bromine containing initiator) were tested. *t*BMA or NIPAM were utilized for the surface initiated Cu(0)-mediated LRP.[93, 194, 195] MMA, *t*BMA, NIPAM, DMAEMA, methacryloxyethyltrimethylammoniumchloride (METAC) and 3-sulfopropyl methacrylate potassium salt (SPMA) were also grafted *via* Cu(0)-mediated LRP from a copper plate. It was shown that the copper plate could be reused multiple times and only a minimal amount of chemicals were required in order to fabricate a variety of homo-, block, gradient and patterned polymer brushes as well as polymer brush arrays.[196] Silica surfaces[197] and cellulose nanocrystals[198-201] have also been employed with success for the surface Cu(0)-mediated LRP of NIPAM. Silicon wafers have also been functionalized by amino (meth)acrylate[202] and NIPAM.[203] In the latter case, the calculation of grafting parameters (*e.g.* surface coverage, grafting density and average distance between grafting sites) were also determined. Zhu and co-workers copolymerized MMA with 7-(2-methacryloloxy)-4-methylcoumarin (CMA) *via* surface Cu(0)-mediated LRP utilizing a propargyl initiator which was subsequently used to graft to silica particles.[92]In another contribution, PAN was grafted from wheat straw matrix, resulting in a novel agricultural residue adsorbent which was demonstrated to effectively adsorb Hg(II) from binary ion systems in the presence of other heavy metals.[204] Remarkably, the surface of sweet potato starch residue has also been used as a macroinitiator as a way of controlling heavy metal pollution.[205]

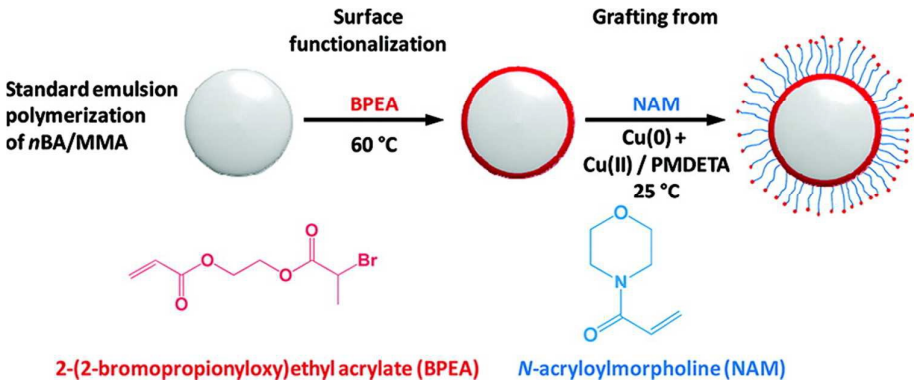

Figure 15: General scheme of the Cu-Mediated surface-initiated radical polymerization. Reproduced from Ref. 191 with permission from the American Chemical Society.

GLYCOPOLYMERS

Haddleton and co-workers have examined the binding ability of multiblock glycopolymers in various compositions (including mannose, fucose and glucose moieties).[62] The binding behaviour was tested towards dendritic cell-specific intercellular adhesion molecule- 3-grabbing non-integrin (DC-SIGN; CD209), which is a C-type lectin, present on both macrophages and dendritic cell subpopulations and plays a critical role in many cell interactions.[206-208] Polymers with a higher mannose content were shown to have a higher binding affinity although the effect of the sequence of each sugar was inconclusive. In a further report from the Haddleton group, the synthesis of star-based glycopolymers containing CD core and oligosaccharide chains was conducted *via* Cu(0)-mediated LRP utilizing a cyclodextrin (CD)-based initiator (Figure 16a). These glycoconjugates were demonstrated to bind with high affinity to DC-SIGN and could therefore be employed as inhibitors to prevent the binding of HIV envelope protein gp120 to DC-SIGN at nanomolar concentrations.[209] The same group has also reported the combination of Cu(0)-mediated LRP with thiol-halogen, thiol-epoxy and copper catalyzed alkyne azide coupling (CuAAC) "click" chemistry as an alternative route to the synthesis of sequence-controlled glycopolymers.[63, 67]

Moreover, the synthesis of diblock glycopolymers was demonstrated by Davis and co-workers utilizing organic Cu(0)-mediated LRP and "click" chemistry to attach three different carbohydrates *α-D*-mannose, *α-D*-glucose and *β-D*-glucose to iron oxide nanoparticle (IONP) surfaces. Mannose-nanoparticle biomolecular recognition has been extended to cell membrane receptors and demonstrated by an increased uptake of IONP@P(OEGA)-b-P(N3Man) into lung cancer cells, indicating that sugar functional coatings on IONP have the potential to improve targeting and be beneficial for therapeutic and diagnostic applications (Figure 16b).[125] Glycopolymers that interact with Concanavalin A (ConA)[65] as well as modified gold nanorods (GNRs) with glycopolymeric coatings[210] have also been synthesized *via* Cu(0)-mediated LRP. Cu(0)-mediated LRP of MA can be utilized as a powerful technique for the design of hybrid graft glycopolymers. Albertsson and co-workers designed a macroinitiator based on the heteropolysaccharide acetylated galactoglucomannan to enable the Cu(0)-mediated LRP of MA.[71, 211-214] Different types of cellulose macroinitiators,

including cellulose esters, cellulose di-acetate (CDA) and cellulose acetate butyrate (CAB), have also been employed.[215-217]

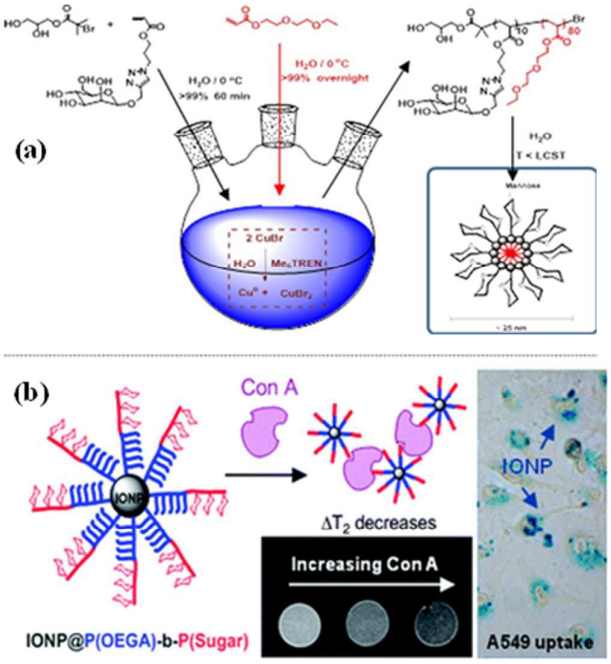

Figure 16: (a) Synthesis of a star diblock glycopolymer *via* Cu(0)-mediated LRP utilizing a (CD)-based initiator and (b) IONP@P(OEGA)-*b*-P(sugar) nanoparticles synthesized by combination of Cu(0)-mediated LRP and "click" chemistry. Reproduced from Ref. 209 and Ref.125 respectively with permission from the Royal Society of Chemistry.

POLYMER/PROTEIN CONJUGATES

Haddleton and co-workers utilized the "grafting from" approach to grow DEGMEMA and TEGMEMA from salmon calcitonin (sCT), a 32 amino acid calcitropic hormone used for the treatment of a number of hypercalcemia-related diseases. Thiolene chemistry and Cu(0)-mediated LRP were combined in this protocol to yield the one-pot synthesis of well-defined thermoresponsive conjugates which were analysed by SEC, lower critical solution temperature (LCST) and DLS.[87] Wilson, Davis and co-workers also used sCT to exploit the entropy-driven affinity of trivalent organic arsenicals for closely spaced dithiols as a novel route for polymer/protein conjugation. The conjugation of the trivalent arsenous acid (As(III)) derivative obtained from *p*-arsalinic acid (As(V)) was rapid (< 2 min) and was verified *via* HPLC and MALDI-ToF-MS. In addition, the trivalent organic arsenical was found to demonstrate enhanced specificity for disulphide bond bridging in the presence of

free cysteine residues relative to established maleimide functional reagents when bovine serum albumin was used as a model protein. Importantly, *p*-arsanilic acid was transformed into an initiator for the aqueous Cu(0)-mediated LRP resulting in hydrophilic arsenical-functional polymers which exhibited minimal cytotoxicity (Figure 17).[127] Finally, in a further contribution, α-funcional maleimide polymers were synthesized by Cu(0)-mediated LRP and their *in situ* reversible conjugation to oxytocin (a neurohypophyseal uterotonic non-apeptide) was demonstrated. The conjugation was shown to enhance the stability and thus the potential storage capacity/shelf life of the peptide prior to administrator.[128]

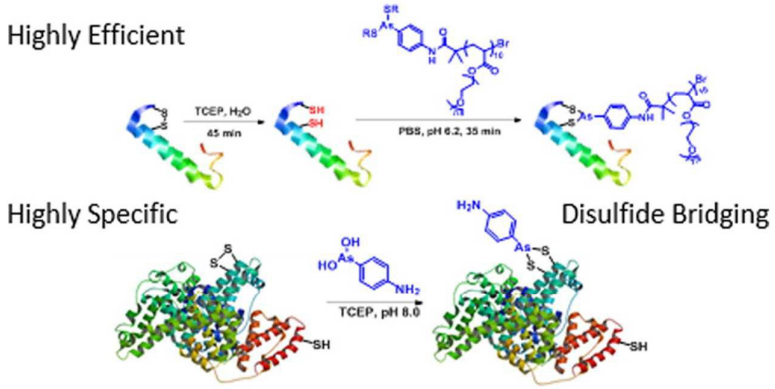

Figure 17: Arsenic functional polymers by aqueous Cu(0)-mediated LRP. Reproduced from Ref. 127 with permission from the American Chemical Society.

DRUG DELIVERY

Monteiro and co-workers reported the timed release of siRNA, mimicking the influenza virus escape mechanism. The novel diblock polymer carrier was synthesized by Cu(0)-mediated LRP and consists of PDMAEA (can bind to siRNA and release it at a defined rate) and PImPAA or poly(*n*BA) (to induce fusion with the endosome membrane) (Figure 18a,b). Optimum results showed > 80% of cell death when targeting the PKL1 pathway, which suggests that these effective and safe siRNA delivery carriers hold great promise for applications that are associated with the cure of several diseases.[64, 72] In addition, the same group employed Cu(0)-mediated LRP for the synthesis of diblock copolymers that would bind and protect pDNA, release it at specific time, and rapidly escape the endosome.[218] Finally, Cooper and co-workers copolymerized an azide monomer with OEGMA on magnetic nanoparticles *via* Cu(0)-mediated LRP in order to allow the immobilization of virus-specific capture oligonucleotides to the dense polymer brushes. These novel polymer

probe architectures can be a useful tool to enhance the sensitivity as well as contribute to clinically viable amplification-free DNA detection.[219, 220]

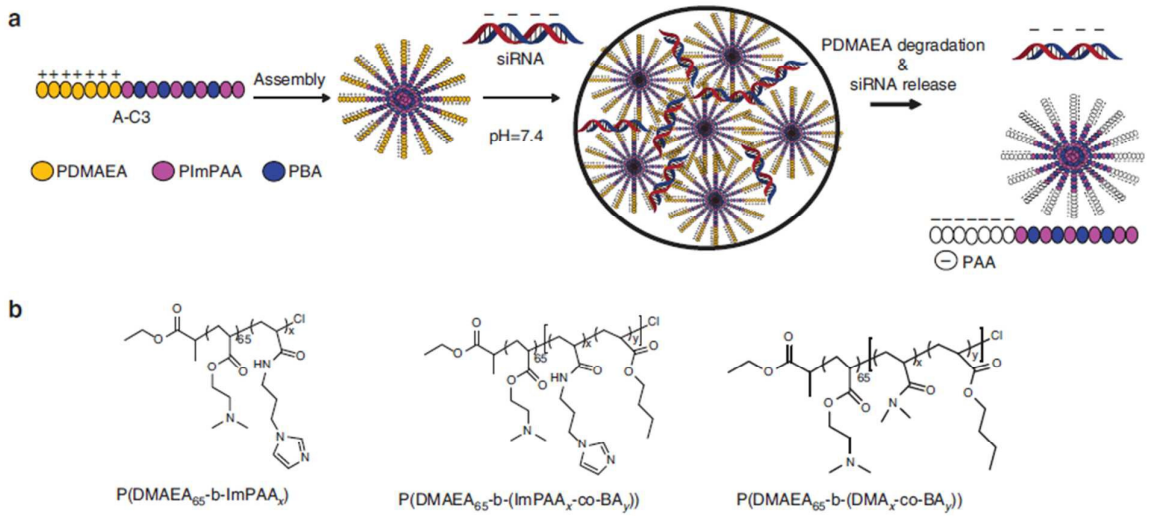

Figure 18: a) Mechanism for polymer assembly, binding with siRNA and release of siRNA through a self-catalyzed degradation of PDMAEA b) chemical structures of the block copolymers synthesized by Cu(0)-mediated LRP. Reproduced from Ref. 64 with permission from the Nature Publishing Group.

MECHANOPHORES AND FOLDAMERS

Moore and co-workers utilized Cu(0)-mediated LRP to polymerize MA and incorporate a chain-centered dicyano-substituted cyclobutane mechanophore *via* two types of *a*-bromoester initiators.[221, 222] The selective cleavage of the chain-centred mechanophore was achieved upon sonication of the polymers, forming reactive cyanoacrylates. These experimental findings were further supported by computational studies. The synthesis of mechanophore-linked polymers to produce a series of benzocyclobutenelinked PMAs polymers *via* Cu(0)-mediated LRP was also reported by the same group. In the latter approach, a mechanophore was placed near the center of the polymer where the ultrasound-generated forces are larger.[223] Subsequently, Osswald and co-workers exploited further Moore's approach presenting a systematic study of the effects of laser-based imaging on the activation and fluorescence behaviour of mechanochromic spiropyran integrated into PMA and PMMA matrices utilizing a confocal Raman microspectrometer.[224] High mechanophore content polyester-acrylate ABA block copolymers have also been reported by Craig and co-workers,[225, 226] while Stoddard's group utilized Cu(0)-mediated LRP of MA allowing access to well-defined polymers with exactly one mechanically interlocked molecule per polymer

chain (Figure 19).[227] Cu(0)-mediated LRP has also been employed for the synthesis of foldamer-linked polymers that consist of MA growing from a *meta* phenylene ethynelene (*m*PE) dodecamer bi-functional initiator, which was selected as it contains the minimal oligomer length to form a stable helix in solution. Altering the solvent environment in the vicinity of the foldamer was shown to promote the folded state and that when the entropic chain segment was larger than 50 kDa the structuring of the *m*PE oligomer was enhanced, even in a solvent that is otherwise denaturing the foldamer. Thus, Cu(0)-mediated LRP allowed access to a better understanding on the folding mechanism of these structures.[131]

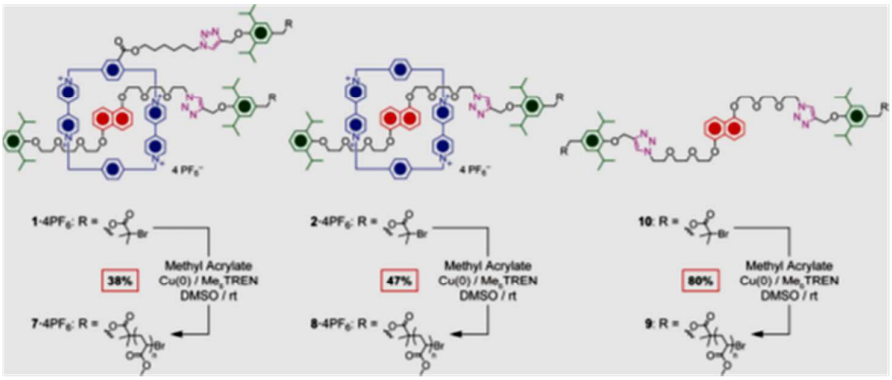

Figure 19: A foldamer, with polymer chains attached at each end, equilibrating between unstructured and helical conformations. Reproduced from Ref. 227 with permission from the American Chemical Society.

OIL ABSORBING AND PHOTORESIST MATERIALS

Cu(0)-mediated LRP allowed access to the synthesis of novel homogeneous polymer structures preserving functional ends and resulting in materials with enhanced oil absorbency. Fan and co-workers utilized a cellulose (produced from cotton fibers) macroinitiator and then grafted BMA and pentaerythritol acrylate (PETA) to render three-dimensional architecture (Figure 20).[89] In addition, the same monomers have been used to synthesize a novel high oil-absorbing crosslinked gel.[114] Finally, Fu and co-workers produced a highly oil-absorbing gel by crosslinking BMA with a small amount of divinylbenzene (DVB) *via* Cu(0)-mediated LRP.[90] Photoresist materials have also been synthesized by Cu(0)-mediated LRP. Percec and co-workers utilized Cu(0)-mediated LRP to polymerize GBLMA and MAMA in organic mixtures (both homopolymers and copolymers). First order kinetics and narrow

MWDs confirmed the living character of this system while due to the heterogeneous nature of the catalyst the polymers were colorless, providing access to low copper photoresist materials.[96]

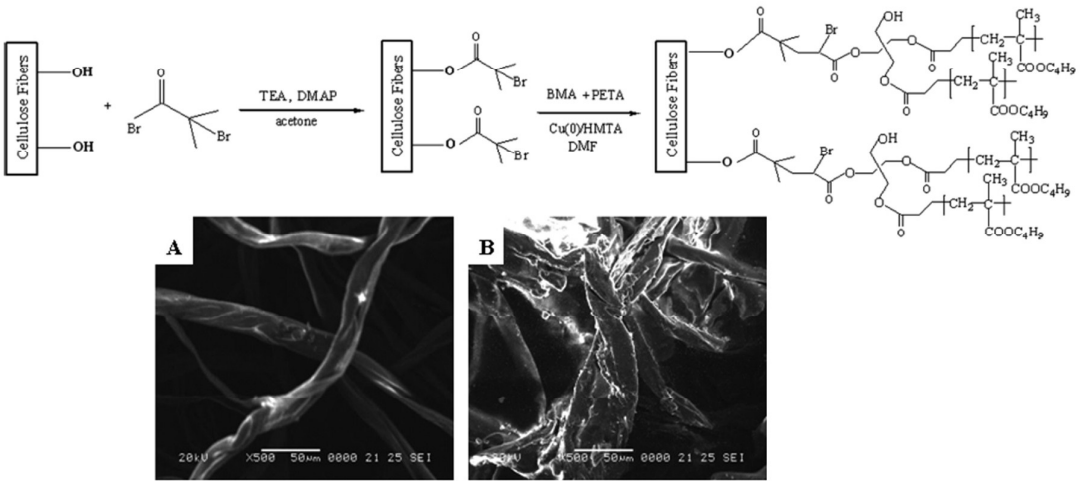

Figure 20: Synthetic route for the grafting of poly(BMA-co-PETA) from the surface of cotton fibers by Cu(0)-mediated LRP and SEM microscopy of (A) unmodified cotton fiber and (B) cellulose-based poly(BMA-co-PETA). Reproduced from Ref. 89 with permission from John Wiley & Sons, Inc.

OTHER APPLICATIONS

Other applications of Cu(0)-mediated LRP (Figure 21) include the development of novel nanoreactors,[73, 228, 229] the use of IONPs as MRI contrast agents[126] and the photo-patterning of non-fouling polymers and biomolecules on paper and on silicon surfaces.[77, 230] In addition, antibacterial agents[85] and novel skeleton weak anion-exchange monolith for high performance liquid chromatography have also been prepared by Cu(0)-mediated LRP.[231] Finally, Cu(0)-mediated LRP has also been translated into a continuous flow process.[232, 233]

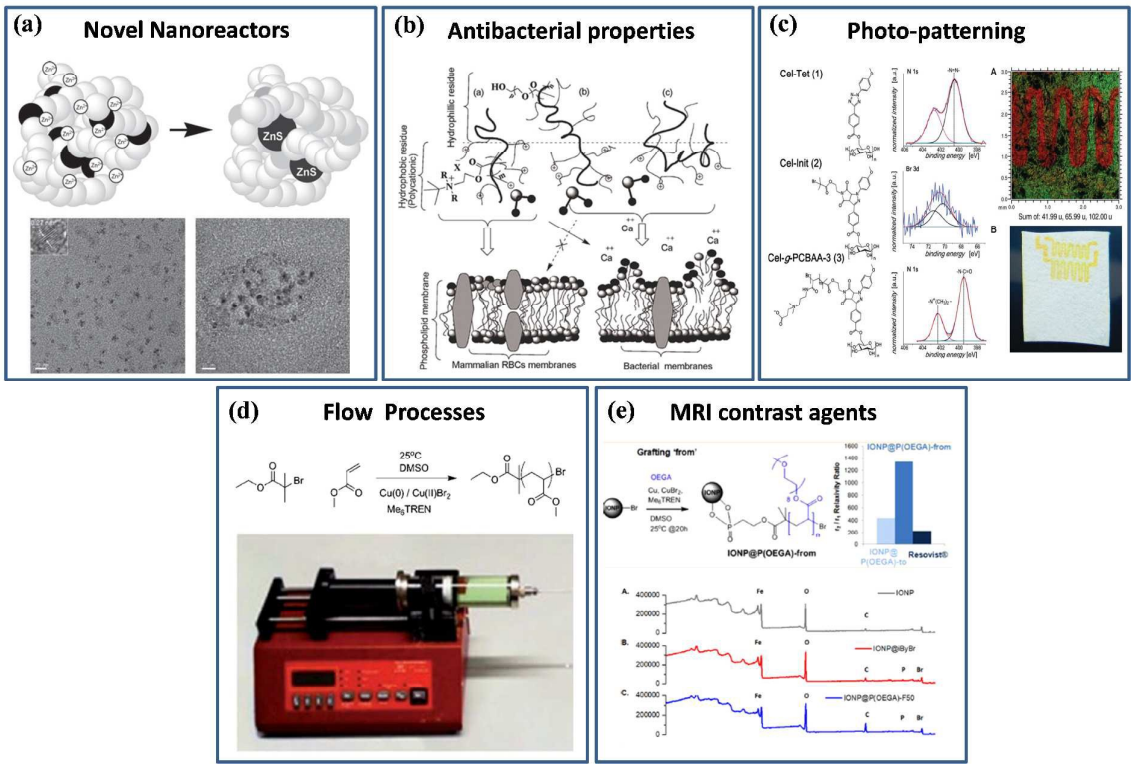

Figure 21: (a) Fabrication of ZnS nanocrystals in polymeric nanoreactors and TEM images. Reproduced from Ref. 228 with permission from John Wiley & Sons, Inc. (b) Biomimetic illustration showing the mode of action of different amphiphilic polycations in aqueous broth media on bacterial cell (E. coli) and mammalian RBC membranes. Reproduced from Ref. 85 with permission from John Wiley & Sons, Inc. (c) Characterization of the photo-patterned cellulose. Reproduced from Ref. 77 with permission from John Wiley & Sons, Inc. (d) Reaction setup: syringe pump holding a syringe fitted with copper wire threaded through 20 cm PTFE tubing. Reproduced from Ref. 232 with permission from the Royal Society of Chemistry. (e) Synthesis of functionalized IONPs *via* Cu(0)-mediated LRP utilizing a grafting "from" approach along with XPS analysis. Reproduced from Ref. 126 with permission from the American Chemical Society.

PERSPECTIVE

The scope of Cu(0)-mediated LRP has significantly expanded the last few years to include a variety of monomers, including acrylates, acrylamides, methacrylates and other monomers. The aqueous Cu(0)-mediated LRP protocol (exploiting the predisproportionation of CuBr) allowed access for the first time to the rapid polymerization of acrylamides and acrylates without compromising the control over the MWDs. Low dispersed poly(acrylates) and poly(acrylamides) (typically with $Đ \sim 1.10$) can now be obtained in a quantitative way

(>99% conversion) within a few minutes while high end group fidelity has also been demonstrated *via* sequential chain extensions and block copolymerizations. This very high end group fidelity for polymers synthesized in both aqueous and organic media has led to the development of complex and sophisticated architectures (*e.g.* multiblocks, stars, cyclic polymers *etc.*) paving the way for the synthesis of advanced materials. Already Cu(0)-mediated LRP has found use in a large diversity of applications such as glycochemistry and targeting, drug delivery, polymer/protein conjugates, surface-initiated Cu(0)-mediated LRP, mechanophores, foldamers, oil absorbing and photoresist materials, nanoreactors, antibacterial agents and many others. It is thus expected that the applicability of Cu(0)-mediated LRP will be further expanded as it is limited only by our own imagination. On the downside, the controlled polymerization of styrene and low activated monomers such as vinyl pyrrolidone still requires further elucidation and should be the focus of future studies as this will significantly broaden the scope and applications of the technique.

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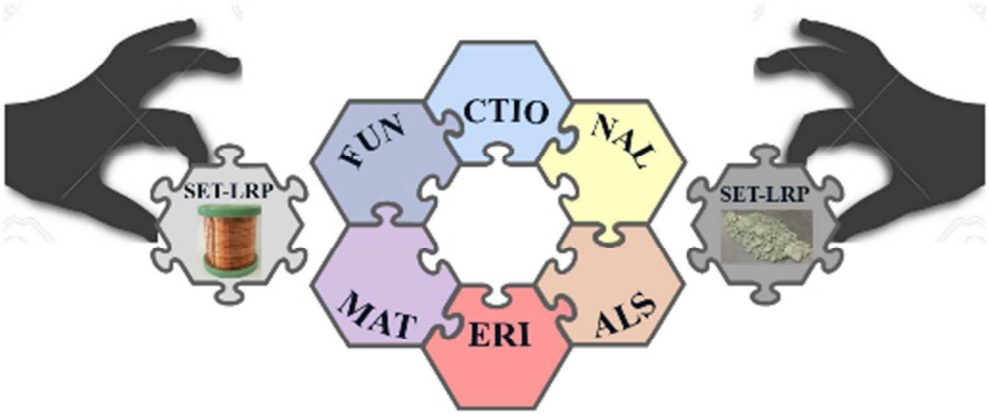

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