Highly reactive α-bromoacrylate monomers and Michael acceptors by Cu(II)Br₂-dibromination of acrylates and instantaneous E2 by ligand

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Depending on the order of addition to the reaction mixture, acrylates can undergo SET-LRP or dibromination by Cu(II)Br₂ and spontaneously dehydrohalogenate to provide the corresponding highly reactive α-bromoacrylate monomer and Michael acceptor.

Depending on the combination between solvent, ligand and initiator Cu(0)-catalyzed radical polymerization can proceed by a single-electron transfer living radical polymerization (SET-LRP) mechanism or by a combination of SET-LRP and atom transfer radical polymerization (ATRP) mechanisms.[1] Water,[2] hydrogenated and fluorinated protic, dipolar aprotic, other polar solvents[3] and monomer[4] as well as their homogeneous[5] and biphasic mixtures[6] that mediate the disproportionation of Cu(I)X into Cu(0) and Cu(II)X₂ and together with suitable ligands,[7] monomers and initiators[8] mediate SET-LRP. Solvents that do not mediate the disproportionation of Cu(I)X into Cu(0) and Cu(II)X₂ are usually nonpolar solvents such as toluene.[9] The classic polar

solvent that does not mediate this disproportionation is acetonitrile. [10] When these non-disproportionating solvents are employed in Cu(0)-catalyzed radical polymerization the early stages of the polymerization proceeds by a SET-LRP mechanism and subsequently, as the Cu(I)X accumulates, the mechanism of the reaction may change from SET-LRP to ATRP. [1a,b] When non-polar solvents or even polar non-disproportionating solvents are employed the resulting polymers have poor chain-end functionality. [9,10] Nonpolar solvents exhibit poor solubility for Cu(II)X$_2$ and the mechanism of ATRP requires bimolecular termination to create the equilibrium concentration of Cu(II)X$_2$ demanded to establish the persistent radical effect. [11] Therefore, it is not surprising that the resulting polymer chain-ends exhibit poor functionality. [9,10] Consequently, SET-LRP represents the method of choice when quantitative or near quantitative chain end functionality is demanded. [12] Homogeneous and biphasic mixtures of different solvents including with water have been employed in order to remediate the poor chain-end functionality attained in non-disproportionating solvents and to develop new SET-LRP methodologies. [1b] Mixtures of the non-disproportionating solvent acetonitrile with DMSO and with water in biphasic systems have been employed to access SET-LRP with acetonitrile as solvent. [6a,b,10] In all cases, the mixture is prepared by mixing ligand with monomer, initiator and eventually Cu(II)X$_2$ in this order before degassing the reaction mixture and placing it in contact with Cu(0) wire, [13] powder/nanopowder [14] or Cu(0) generated *in situ*. [15] Here we report that the inversion of the order of reagents from the one mentioned above to acrylate monomer, Cu(II)Br$_2$ in acetonitrile mediates an extremely efficient Cu(II)Br$_2$-promoted bromination of the vinylic monomer at room temperature. Scheme 1a,b depicts the reaction taking place with methyl acrylate an butyl acrylate (MA and BA, respectively).
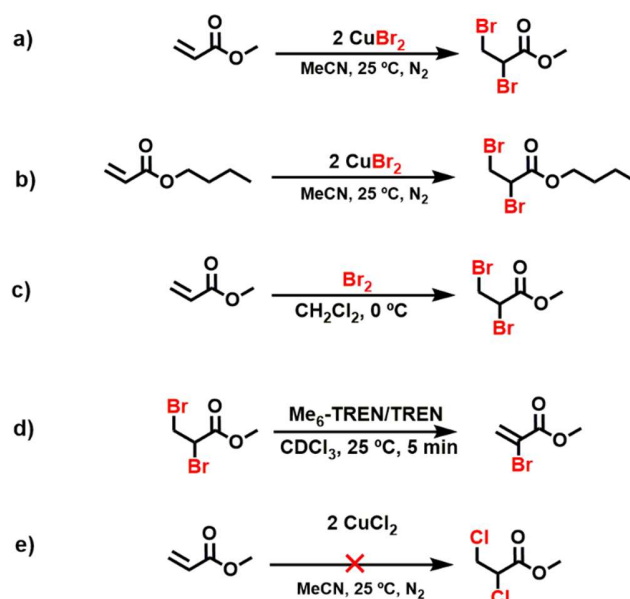
Scheme 1. Cu(II)Br$_2$-dibromination of MA and BA in acetonitrile at 25 ºC (a and b), dibromination of MA with Br$_2$ (c), dehydrobromination of methyl 2,3-dibromopropionate mediated by Me$_6$-TREN or TREN (d) and non-observed Cu(II)Cl$_2$-promoted dichlorination of MA in acetonitrile at 25 ºC (e).

The Cu(II)Br$_2$-mediated bromination process of MA and BA can be monitored by ^{1}H NMR directly in acetonitrile (Fig. 1a). The rate of bromination at 25 ºC is similar for both monomers during the first hours of reaction. Approximately 50% of the initial monomer was converted to the corresponding dibromoderivative in 2 h. Later, the rate of bromination is higher for MA than BA. Notice that no chlorination was observed under the same reaction conditions with Cu(II)Cl$_2$ at 25 ºC or higher temperatures (Scheme 1d). Fig. 1b shows ^{1}H NMR spectra for the Cu(II)Br$_2$-promoted bromination of MA recorded at different reaction times. Most obvious ^{1}H NMR marker that confirms the Cu(II)Br$_2$-promoted bromination is the disappearance of the characteristic vinylic signals of MA (H$_{1-3}$) and the emergence of new signals corresponding to the dibrominated derivative (H$_{1'-3'}$ and a'). Fig. 2a shows the ^{1}H NMR spectrum of the methyl 2,3-dibromopropionate isolated after the Cu(II)Br$_2$-dibromination of MA.
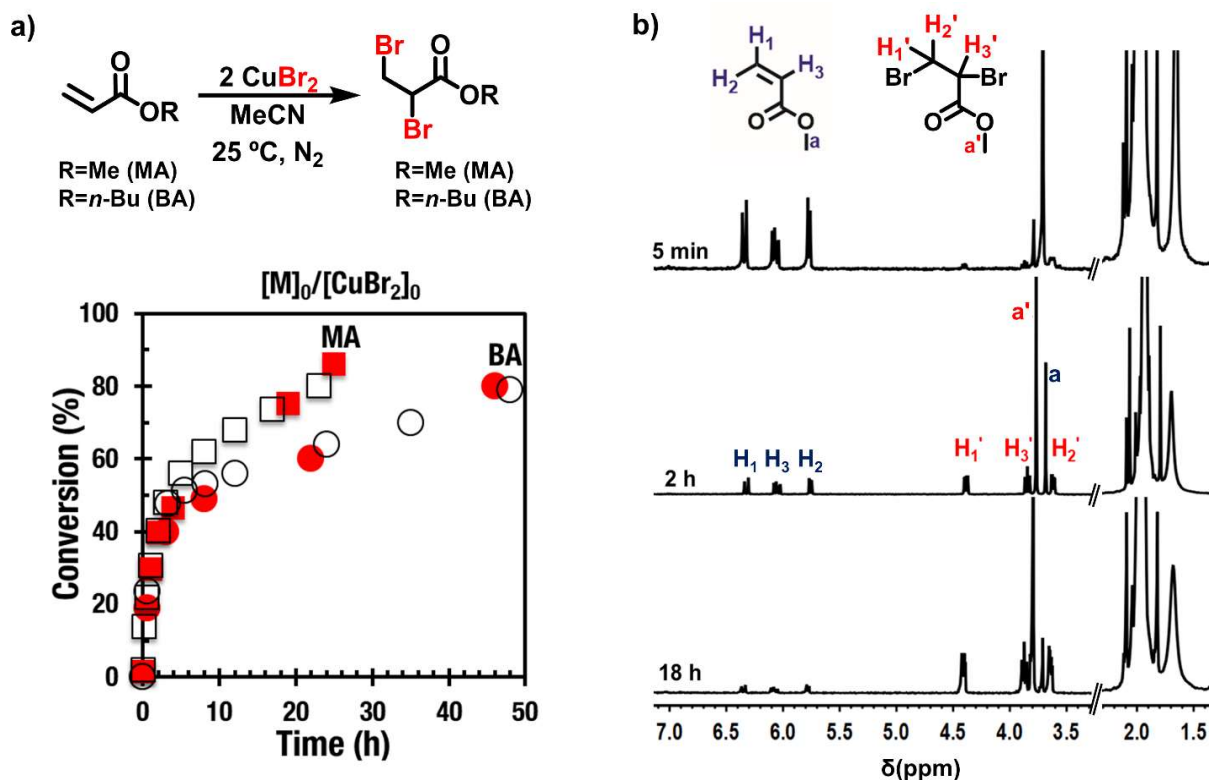
Fig. 1 Cu(II)Br$_2$-mediated dibromination of acrylates in acetonitrile at 25 °C. (a) Conversion vs. time plots in the bromination of MA and BA. Data in different colors are from duplicated experiments performed by different researchers. (b) 500 MHz ^{1}H-NMR spectra recorded over time for the bromination of MA.

Note that the bromination of acrylates with Cu(II)Br$_2$ gives the same product as the one generated by bromination with Br$_2$ (Scheme 1c).[16] It is important to point out also that no bromination occurred using DMSO as solvent under strictly similar conditions. However, the fact that the Cu(II)Br$_2$-promoted halogenations of various unsaturated compounds was reported to occur in other polar solvents such as alcohols and DMF,[17] suggests that may take place also in DMSO under other conditions.

Control experiments carried out in the presence of classic SET-LRP ligands such as tris(2-dimethylaminoethyl)amine (Me$_6$-TREN) and tris(2-aminoethyl)amine (TREN) pointed toward the importance of the reagents mixing order to avoid this undesired reaction during LRP protocols.
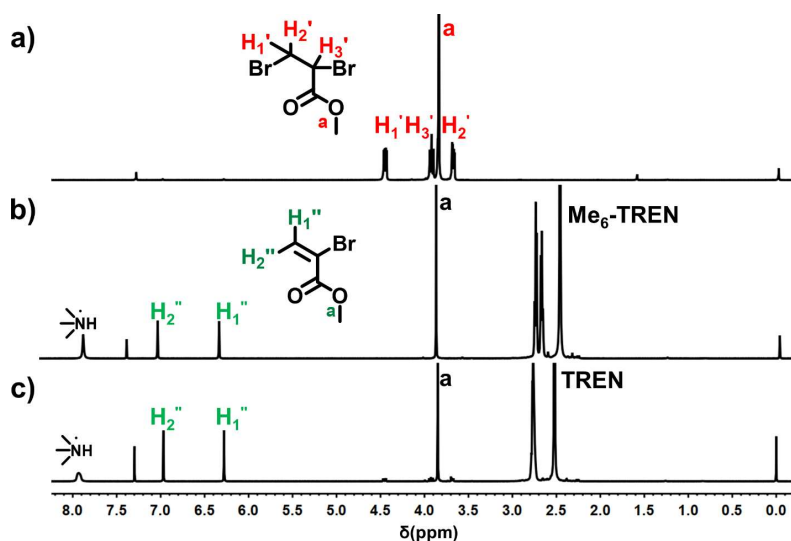
Fig. 2 E2 elimination of methyl 2,3-dibromopropionate promoted by ligand. 500 MHz ^{1}H-NMR spectra recorded in CDCl$_3$ of (a) methyl 2,3-dibromopropionate produced by dibromination of MA with Cu(II)Br$_2$, (b) methyl α-bromoacrylate produced from methyl 2,3-dibromopropionate in the presence of a stoichiometric amount of Me$_6$-TREN, and (c) methyl α-bromoacrylate produced from methyl 2,3-dibromopropionate in the presence of stoichiometric amount of TREN.

In fact, when the reaction was prepared by dissolving monomer, ligand and Cu(II)Br$_2$ in acetonitrile, No dibromination product was detected by ^{1}H NMR after 24 h when the rat room temperature. Most interesting was, however, that the addition of stoichiometric amounts of Me$_6$-TREN or TREN to methyl 2,3-dibomopropionate in CDCl$_3$ produced the complete disappearance of the signals associated to this product in few minutes at 25 ºC (Fig. 2b and c, respectively). Inspection of the ^{1}H NMR spectra clearly indicates the base-mediated spontaneous E$_2$ dehydrobromination process that generate the corresponding α-bromoacrylate derivative. The two characteristic germinal protons of methyl α-bromoacrylate appear at appear at 6.3 and 7.0 ppm (H$_{1''}$ and H$_{2''}$, respectively). The same reaction was observed using Me$_6$-TREN and TREN although the methylated ligand mediated a faster E2 elimination reaction. In this case the complete disappearance of the characteristic signals of the dibrominated acrylate was observed after 5 min. α-Haloacrylates are very reactive monomers[18] and Michael acceptors[19] that undergo radical

polymerization and Michael addition with a variety of Michael donors. The halogenation of olefins with both $Cu(II)Br_2$ and $Cu(II)Cl_2$ was known to organic chemists but was not extensively investigated from the mechanistic and preparative points of view.[17] However, these side reactions seem to have been unknown to the polymer chemistry community. Hence, when the role of addition of acrylate monomer, solvent, $Cu(II)Br_2$ and ligand is not maintained in the proper sequence, α-bromoacrylate derivatives can be generated in the reaction mixture and its copolymerization with its parent acrylate can generate hyperbranched/crosslinked rather than linear polymers.[20] In addition, α-bromoacrylates can provide Michael adducts with the ligand and generate new initators that can affect the functionality of the polymer chain-end(s).[21] A series of control experiments were performed to demonstrate that the presence of α-bromoacrylate derivatives is undesirable. The $Cu(0)$ wire/Me_6-TREN-catalyzed SET-LRP of MA was investigated in the presence of 3% of methyl α-bromoacrylate at 25ºC in a biphasic acetonitrile/water 8/2 v/v mixture.[6b] Under these conditions, the progressive formation of an insoluble gel on the $Cu(0)$ wire surface was observed. ^{1}H NMR analysis showed that no soluble polymer was present in the reaction mixture. This gel, generated by crosslinking of poly(methyl acrylate) (PMA) chains containing methyl α-bromoacrylate repeating units, was insoluble in common organic solvents. Gel formation was also observed in our laboratory and others in aqueous SET-LRP.[2b,22,23] Repeating the polymerization in a homogeneous reaction mixture using DMSO as solvent furnished near identical results. Attempts to avoid the formation of crosslinked material by reducing the amount of $Cu(0)$ wire or preforming the polymerization in the presence of externally added $Cu(II)Br_2$ deactivator (5 mol-% relative to initiator) resulted unsuccessful (Fig. 3). These results support the importance of avoiding traces of α-bromoacrylate derivatives in the polymerization mixture to practice clean and efficient polymerization processes.
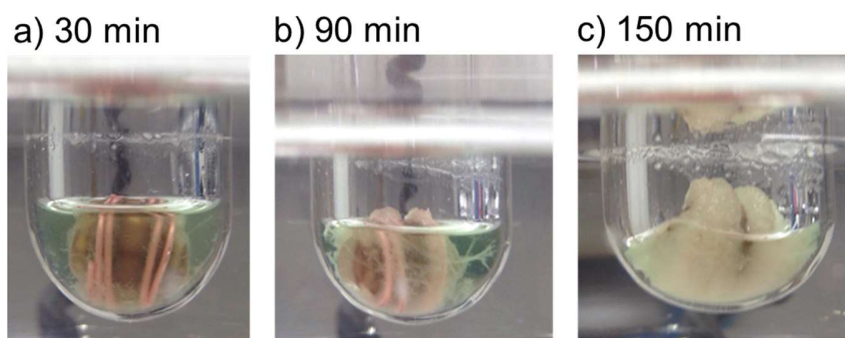
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Fig. 3 Gel formation during the Cu(0) wire-catalyzed SET-LRP of MA in the presence of 3 mol-% methyl α-bromoacrylate in DMSO. Reaction conditions: MA = 0.97 mL, methyl α-bromoacrylate = 54 mg, DMSO = 0.5 mL, [monomers]/[MBP]/[Me$_6$-TREN]/[Cu(II)Br$_2$] = 222/1/0.1/0.05, 12.5 cm Cu(0) wire 20 gauge, 25°C.

Conclusions

Cu(II)Br$_2$, but not Cu(II)Cl$_2$, dibrominates acrylate monomers such as MA and BA in acetonitrile at 25 °C to generate the corresponding dibrominated derivative. Subsequent addition of a stoichiometric amount of Me$_6$-TREN or TREN to this product spontaneously produces the α-bromoacrylate. This bromination reaction does not occur in the presence of ligand. α-Bromoacrylates are reactive monomers that are known to undergo radical polymerization. However, under SET-LRP and ATRP conditions α-bromoacrylates would produce hyperbranched polymers. The products are also very reactive Michael acceptors that undergo additional side reactions with excess ligand and other Michael donors including Me$_6$-TREN and TREN. These side reactions together with the electrophilic halogenation of acetone with Cu(II)Br$_2$ reported recently from our laboratory[6d] must be considered during the practice of current SET-LRP and ATRP methodologies as well as during the invention of new processes.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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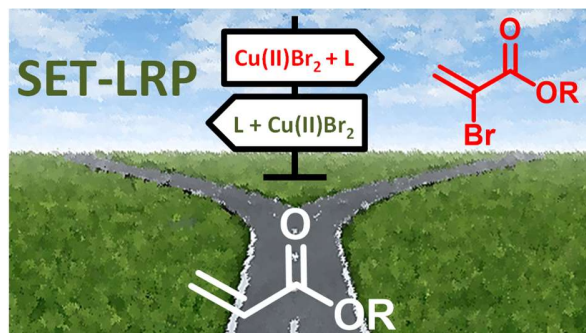
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