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Highly reactive α-bromoacrylate monomers and Michael acceptors by Cu(II)Br_2-dibromination of acrylates and instantaneous E2 by ligand

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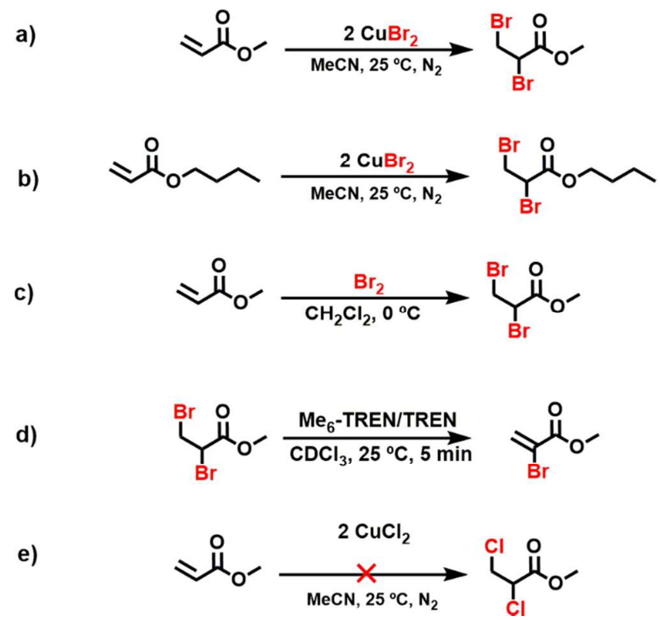
Depending on the order of addition to the reaction mixture, acrylates can undergo SET-LRP or dibromination by Cu(II)Br_2 and spontaneously dehydrohalogenate to provide the corresponding highly reactive α-bromoacrylate monomer and Michael acceptor.

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)X_2 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)X_2 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 ^{o}C 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.

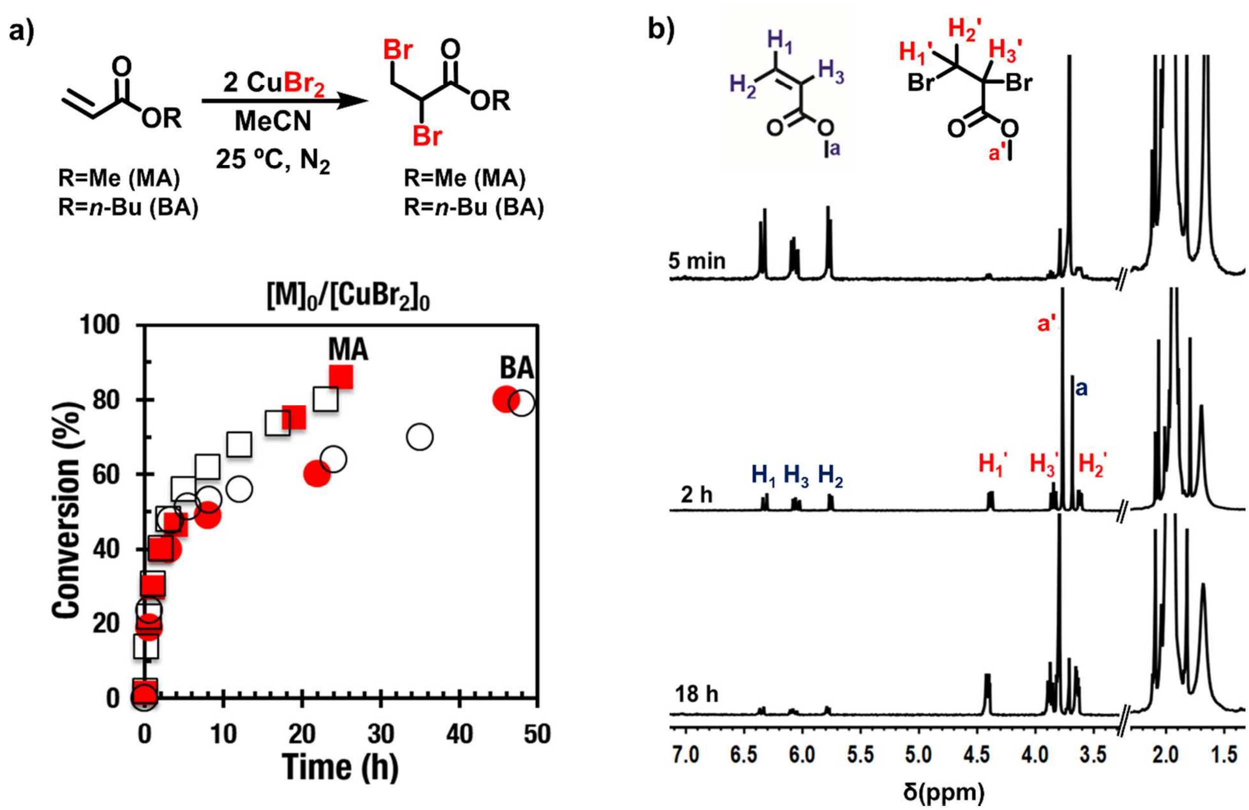


Fig. 1 Cu(II)Br_2-mediated dibromination of acrylates in acetonitrile at 25 ºC. (a) Conversion vs. time plots in the bromination of MA and BA. Data in different colors are from duplicated experiments performed by different researchers. (b) 500 MHz ^{1}H-NMR spectra recorded over time for the bromination 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.

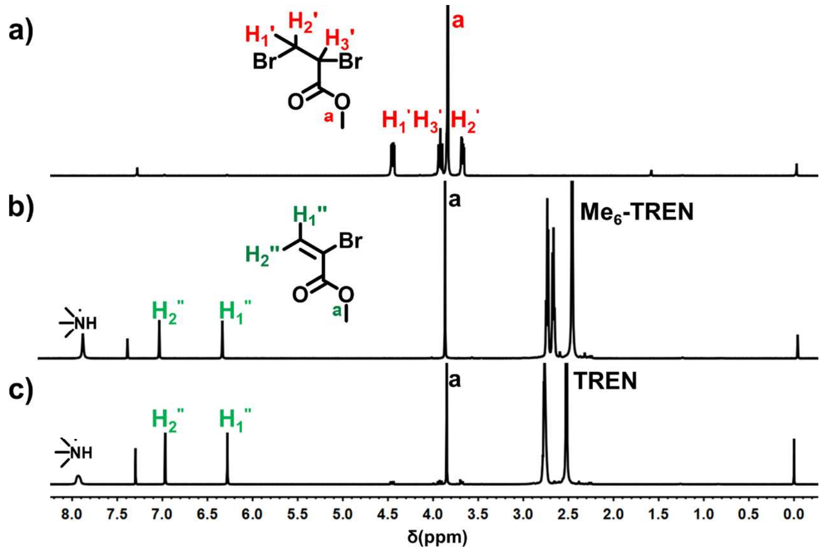


Fig. 2 E2 elimination of methyl 2,3-dibromopropionate promoted by ligand. 500 MHz ^{1}H-NMR spectra recorded in $CDCl_3$ of (a) methyl 2,3-dibromopropionate produced by dibromination of MA with Cu(II)Br_2, (b) methyl α-bromoacrylate produced from methyl 2,3-dibromopropionate in the presence of a stoichiometric 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 reaction was carried out at 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 generates 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) were 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.

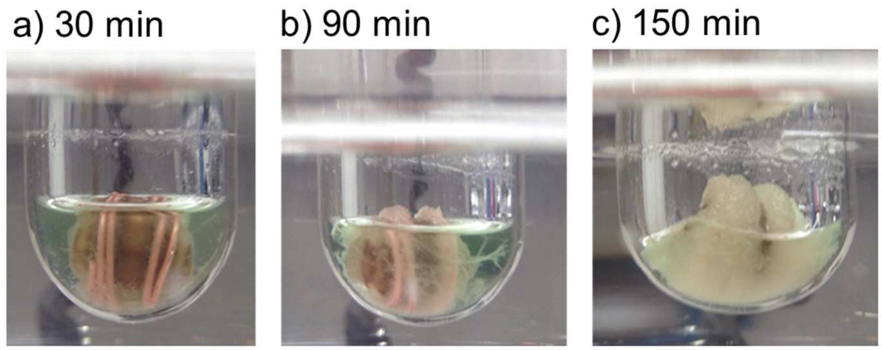


Fig. 3 Gel formation during the Cu(0) wire-catalyzed SET-LRP of MA in the presence of 3 mole% methyl α-bromoacrylate in DMSO. Reaction conditions: MA = 0.97 mL, methyl α-bromoacrylate = 54 mg, DMSO = 0.5 mL, [monomers]/[MBP]/[Me_6-TREN]/[Cu(II)Br_2] = 222/1/0.1/0.05, 12.5 cm Cu(0) wire 20 gauge, 25ºC.

Conclusions

Cu(II)Br_2, but not Cu(II)Cl_2, dibrominates acrylate monomers such as MA and BA in acetonitrile at 25 ºC 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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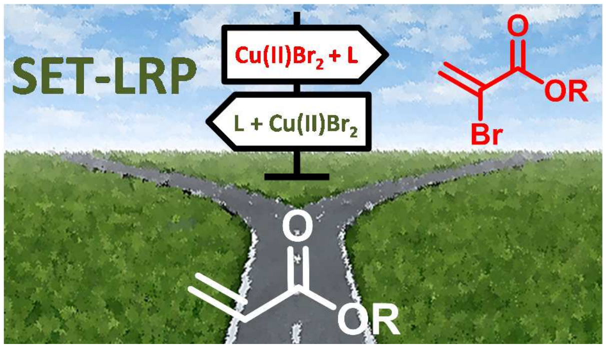

The importance of reagents order addition in SET-LRP.