A facile route to end-functionalised polymers synthesised by SET-LRP *via* a one-pot reduction/thiol-ene Michael-type addition†

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We report the facile synthesis of well defined, disulfide containing polymers *via* SET-LRP. A one-pot reduction/conjugation reaction enables post polymerisation modification with functional (meth)acrylates and acrylamides.

Advances in controlled radical polymerisation (CRP) allow for the synthesis of functional polymers with excellent control over molecular weight, molecular weight distribution, architecture and the incorporation of various functionalities. CRP methods such as transition metal mediated living radical polymerisation or atom transfer radical polymerisation (ATRP),[1–4] Single Electron Transfer Living Radical Polymerisation (SET-LRP),[5] RAFT[6–10] and NMRP,[11] all posses relative disadvantages, for example, functional monomers that can promote side reactions or a loss of control,[12] whilst others can prove difficult to polymerise. Thus the majority of post polymerisation modification procedures are focused on the polymerisation of inert monomers that are subsequently modified into functional polymers.[12] The development of click chemistry has introduced a new class of reactions that enables the chemist to synthesise macromolecules in high yield with short reaction times, mild conditions and high selectivity.[13–15] In particular, thiol-ene click has caught the attention of numerous research groups.[14,16–18] The Michael-type addition of thiols to (meth)acrylates is an efficient, high yielding reaction that can proceed in minutes under mild conditions with catalytic amounts of amines or phosphines.[19,20] This chemistry has been utilised by conjugating small thiols to vinyl terminated macromolecules, and there are many examples of this in the literature.[14] Jones *et al.* have shown the versatility of the approach, by cleaving the disulfide bridge in the peptide Salmon Calcitonin and conjugating both sites to PEG-acrylate, in a reaction that is 100% efficient.[18] Polymers prepared by RAFT can also undergo a one pot modification, due to the unstable nature of the thiocarbonylthio end group. This can be readily cleaved with primary or secondary amines[21–23] that can also catalyse the Michael addition of an acrylate to the thiol terminated polymer.[24–28] We report a one-pot post-polymerisation modification of disulfide containing polymers, prepared using SET-LRP.

Disulfide containing small-molecules capable of initiating ATRP have been reported in the literature, and are commercially available from Aldrich.[29] This cleavable functionality is also commonly employed in the synthesis of cross-linkers to make biodegradable star polymers.[30,31] The precise mechanism of Cu(0) catalysed SET-LRP is a subject of debate and current investigation.[5,32,33] However, reports have shown that near-monodisperse polymers can be synthesised at ambient temperature at low reaction times when compared to conventional ATRP.[5,32] We have used Cu(0) as the catalyst, initiating SET-LTP of methyl acrylate to poly(methyl acrylate), poly[MA], (M_n = 6400 g mol^{-1}), to a targeted molecular weight and narrow polydispersity (M_w/M_n = 1.10) in 40 minutes at 25 °C. The first order kinetic plots and M_n *vs.* conversion graphs show characteristics typical for that of a living polymerisation (see ESI†). This allows for a thiol-ene click reaction, yielding macro-thiols *in situ*, as opposed to the conjugation of thiol-functional small molecules. The poly[MA] was reduced and conjugated in one pot to a variety of functional acrylates and methacrylates, allowing for further modification if required (Fig. 1). This reaction is applicable to most (meth)acrylates as well as most monomers that can be polymerised by living radical polymerisation.

The reaction conditions for the modification are mild, and result in high conversion to products. A 1 : 1 ratio of [phosphine] : [disulfide] is required for the reduction of the disulfide bond as the reduction results in the formation of a stable phosphine oxide. An excess of phosphine is used to facilitate both the reduction and to subsequently catalyse the Michael-type addition of the thiol to the (meth)acrylate. As it is difficult to calculate the exact M_n of the polymer an excess of the (meth)acrylate is used, and any remaining is removed following precipitation.

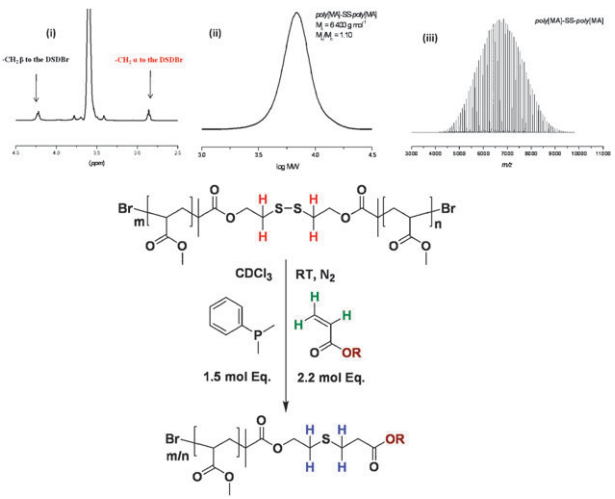

Fig. 1 General scheme showing the one pot redox/conjugation procedure. Also shown (i) ^{1}H NMR (δ = 2.5 ppm–4.5 ppm), (ii) GPC (chloroform eluent, PMMA as calibrants) and (iii) MALDI-ToF of the poly[MA] used in the conjugations reported.

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Progress of the reaction was monitored, and conjugation confirmed, by ^{1}H NMR. The shift of the CH_2 alpha to the S atom was monitored, which becomes a chiral multiplet at *ca.* δ = 2.7 ppm following conjugation, full analysis is presented in the ESI.† One of the most striking features of the ^{1}H NMR is the disappearance of the (meth)acrylic vinyl peaks in the conjugate, whilst the other protons remain. Analysis of the rates of conjugation can be difficult when monitoring the disappearance of vinylic protons as the initiation step of the reaction involves nucleophilic attack of the phosphine at the β-carbon of the vinyl group which can give a false indication of conversion to final product. The phosphonium-enolate intermediate is strongly basic which deprotonates the thiol to the thiolate anion required for the Michael-type addition.[20,34,35] Thus, MALDI-ToF MS was used to confirm that all free thiols have been functionalised. Any unreacted reduced polymer is readily detected, as shown for the initial reaction with hydroxyethyl acrylate, see ESI.†

Two different functional acrylates were chosen to exemplify the versatility of the reaction; hydroxyethyl acrylate and a hostasol functional acrylate to give a hydroxyl-functional and a UV/fluorescently tagged polymer respectively. The ^{1}H NMR indicates complete conjugation, Fig. 2. There is a disappearance of the vinyl peaks post purification, whist the CH_2 α and β to the ester in the HEA end group remain at δ = 4.4 ppm. The CH_2 alpha to the sulfur in the original polymer shifts from δ = 2.9 ppm to become a multiplet downfield at δ = 2.7 ppm, arising from the chiral coupling of the CH_2's either side of the sulfur.

Fluorescently tagging polymers is of interest for a number of applications, and there have been reports of using such monomers (*e.g.* hostasol acrylate)[36] in the literature. Hostasol acrylate was used in our study, to be conjugated to the reduced polymer. All of the characteristic peaks in the ^{1}H NMR indicate that complete conjugation is observed (see ESI†). MALDI-ToF of the original poly[MA] and the hostasol acrylate conjugate using 2-(4-hydroxyphenylazo)benzoic acid (20 mg mL^{-1}) as the matrix and NaI salt (2 mg mL^{-1}) with the analyte (5 mg mL^{-1}) are shown in Fig. 3. Complete conjugation, with no starting material remaining, is observed. The spacing between peaks = 86.02 which corresponds to M_r for methyl acrylate. The study was then expanded to propargyl acrylate, a

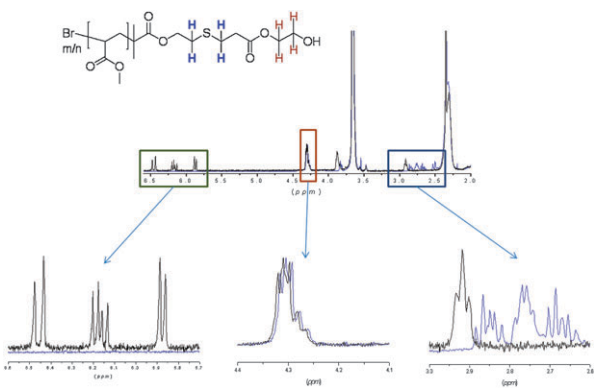


Fig. 2 ^{1}H NMR showing the reaction mixture in the absence of the DMPP catalyst (black) and the conjugate post-modification (blue).

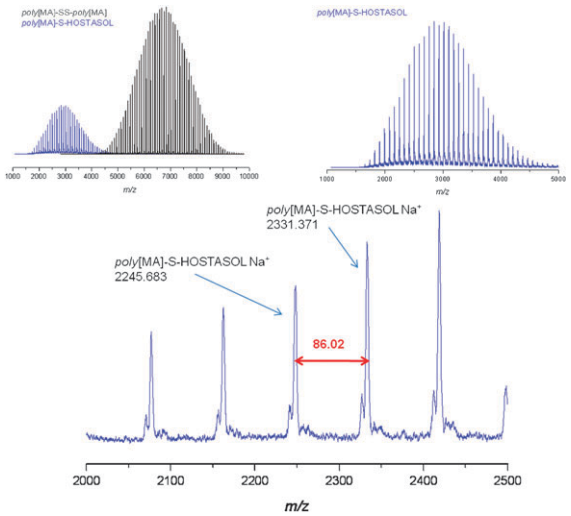
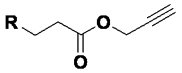
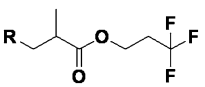
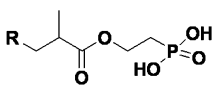
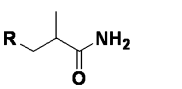


Fig. 3 MALDI-TOF of the poly[MA] (black) and the poly[MA]-S-hostasol conjugate (blue).

range of other functional methacrylates, an acrylamide and styrene, Fig. 4.

The propargyl functionalised polymer, **A**, has the ability to undergo further click reactions, with copper mediated azide–alkyne click (CuAAC).[13–15] This reaction requires an azide terminated molecule to be clicked onto the alkyne terminated polymer. Thus a functional azide that cannot be incorporated into polymers directly *via* SET-LRP could be introduced in a similar fashion, Fig. 4 and ESI.† Methacrylates conjugate to thiols at a slower rate than acrylates due to the electron donating methyl group and associated steric hindrance reducing the rate of the nucleophilic thiol-ene reaction.[19,20] Fluorinated

Monomer	Conjugate product	Final M_n g mol^{-1}	Final M_w/M_n
A		3 300	1.16
B		3 400	1.13
C		3 300	1.16
D		3 300	1.16

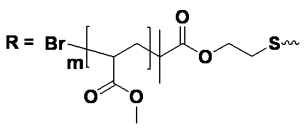


Fig. 4 Further conjugates made *via* the one pot red/con technique, using the conditions outlined in Fig. 1; polymer : acrylate : DMPP = 0.5 : 1.2 : 0.75, reaction carried out in $CDCl_3$, N_2 atmosphere. A = propargyl acrylate. B = trifluoroethyl methacrylate (TFEMA). C = ethylene glycol methacrylate phosphate (EGMAP). D = methacrylamide. See ESI† for full MALDI and ^{1}H NMR analysis.

polymers are of interest and thus trifluoroethyl methacrylate (TFEMA) was successfully conjugated to the cleaved poly[MA] to exemplify this. In addition to the conventional NMR analysis, ^{19}F spectra were also obtained, showing that different species to the starting materials were present in the conjugate, providing further evidence for the conjugate species. Phosphate functional polymers are of importance as dispersants and as surfactants and thus EGMAP was conjugated to yield phosphate terminated polymers with narrow M_w/M_n distributions.

Styrene is much less prone to this type of Michael addition due to lower electron withdrawing from the aryl group and an attempt to conjugate styrene by the same method was unsuccessful as expected and is reported for completeness. This result is in line with previous mechanistic studies that report that the Michael acceptor must be suitably activated for nucleophilic attack to occur.[37] Thus, a sufficiently good electron withdrawing group on the vinyl group is required for the Michael type addition to proceed. It is also possible to re-oxidise the thiol polymers back to a disulfide containing polymer in near quantitative yield using $FeCl_3$ as an oxidant as seen by both ^{1}H NMR and GPC, see ESI.†

Click chemistry has enabled a simple route to novel post-polymerisation modification techniques. This allows for facile introduction of functionality into polymers for further modification (HEA and propargyl acrylate) or to introduce a specific functionality *e.g.* TFEMA and EGMAP. This can be applied to any disulfide-containing polymer, followed by subsequent modification with any (meth)acrylate or acrylamide allowing for a new type of post-polymerisation modification.

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