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Fenton-RAFT polymerization: an “on-demand” chain growth method

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Abstract: Fine control over the architecture and/or microstructure of synthetic polymers is fast becoming a reality, thanks to the development of efficient and versatile polymerization techniques and conjugation reactions. However, the transition of these syntheses to automated, programmable, and high-throughput operating systems is a challenging step needed to translate the vast potential of precision polymers into machine-programmable polymers for biological and functional applications. Chain-growth polymerizations are particularly appealing for their ability to form structurally and chemically well-defined macromolecules through “living”/controlled polymerization techniques. Even using the latest polymerization technologies, the macromolecular engineering of complex functional materials often requires multi-step syntheses, purification of intermediates, and sub-optimal yields. To develop a proof of concept of a framework polymerization technique that is readily amenable to automation requires several key characteristics. In this study we describe a novel approach that we believe can meet these requirements, opening avenues toward automated polymer synthesis.

The use of automation in chemical synthesis is considered an enabling technology for the future development of synthetic drugs, materials, and biosynthetic conjugates.[1] Recent examples in the field of small molecule organic chemistry demonstrate both the extraordinary engineering feats required for system development, and also the remarkable benefits associated with such systems.[2] Advances in synthetic polymer chemistry have enabled the synthesis of a wide range of controlled macromolecular architectures (i.e. ‘secondary structures’),[3] as well as some aspects of monomer sequence control (i.e. ‘primary structure’) in attempts to mimic the precisely defined biopolymers found in nature.[4] These advanced polymer materials show high potential in a diverse range of applications, from excipients in therapeutic formulations[5] to single-molecule data storage devices.[6] However, if these applications are to be realized, cost-effective synthetic protocols to produce them need to be developed. We, and others[7], believe that automation – allowing a degree of programmability – will play a key role in new material discovery and polymer bio-mimicry.

We envisaged that for access to the most diverse range of polymer architectures and molecular structures, a chain-growth polymerization would be best suited. Particularly, “living” or controlled polymerizations that retain an active chain-end are appealing due to their ability to be easily “re-activated” when a multi-step reaction is required. For programmable viability and ease of system configuration, the polymerization should demonstrate some key characteristics: 1) fast polymerization kinetics (i.e., short reaction times); 2) a degree of oxygen-tolerance; 3) high chain-end fidelity; 4) quantitative monomer conversions; and 5) the use of environmentally benign reagents/solvents (e.g., water) at ambient temperatures. Reversible addition-fragmentation chain transfer (RAFT) polymerization[8] is a method of reversible deactivation radical polymerization (RDRP) that has demonstrated many of these features. For example, relatively fast reaction kinetics can be achieved by using photolytically labile photoinitiators,[9] or by employing flow[10] or microwave reactor conditions.[11] Oxygen-tolerant RAFT polymerizations have recently been reported by the Boyer group through the use of an active photocatalyst,[12] and the Stevens group via an enzyme employed to sequester dissolved oxygen.[13] Both methods were shown to be effective at oxygen removal, thereby allowing the RAFT polymerization to proceed; however, the kinetics of the reactions were typically on a timescale of hours. The seminal work of Perrier et al. showed that with high chain end retention, RAFT polymers could be used for the synthesis of complex multiblock structures via a sequential monomer addition approach.[14] Each polymerization step was taken to near-quantitative monomer conversions and the multi-step process performed without intermediate purification. The system was latter optimized to give rapid reaction times (< 3 min for each block) and demonstrated oxygen-tolerance (performed in open reaction vessels).[15] However, high reaction temperatures were required, limiting the scope for thermo-responsive or volatile monomers to be used. Below, we present a novel RAFT polymerization strategy that can furnish structurally well-defined polymers at room temperature on the timescale of minutes. Moreover, a simple method of *in situ* degassing is presented, allowing for the synthesis of linear polymers with near-quantitative monomer conversions in only a few minutes, requiring no laborious set up or expensive equipment. This technique therefore meets many of the requirements set out above, providing the foundation for its potential as a method for the automated/programmable synthesis of complex polymer structures.

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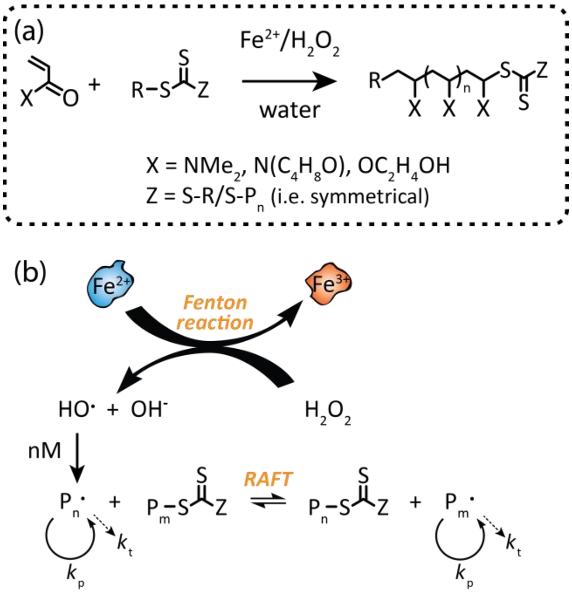

Scheme 1. (a) Fenton-RAFT reaction scheme, and (b) proposed mechanisms of initiation and degenerative chain transfer (i.e. RAFT process) allowing control of polymer chain growth.

Initially, we sought a rapid chemical reaction that could generate a high flux of active radicals to initiate the RAFT polymerization and provide short reaction times. The Fenton reaction,[16] i.e. the catalytic decomposition of hydrogen peroxide (H_2O_2) in the presence of ferrous ions (Fe^{2+}),[17] was identified due to its facile nature at ambient temperatures,[18] the low cost and ready availability of the required reagents (as well as their environmentally benign nature),[19] and the high activity of the generated hydroxyl radicals towards vinyl monomer addition.[20] Redox-initiation systems for RAFT polymerization employing an ascorbic acid (AA)/H_2O_2 redox pair have recently been reported,[21] however, although hydroxyl radicals are the initiating species in both cases this system differs from the Fenton system in several key aspects: 1) the reported timescales are comparatively slow (see Figure S3, ESI for direct kinetic comparison); and, 2) the AA/H_2O_2 system is non-catalytic[22], whereas only a catalytic amount of Fe^{2+} is required in the Fenton system due to its regeneration from Fe^{3+} (see equations in ESI).[23] This is important for subsequent re-activation steps and minimization of reagent loadings. Initially, a system containing a water-soluble acrylamide monomer (*N*,*N'*-dimethylacrylamide (DMA)) together with a trithiocarbonate (TTC) RAFT agent displayed relatively high monomer conversion (*ca.* 40 – 80%) within 1 minute (following sparging with inert gas) in the presence of the Fenton reagents, with monomer conversion generally increasing with H_2O_2 loading (Figure 1a). Despite the extremely fast reaction time, the polymer dispersities observed via gel permeation chromatography coupled with a laser light scattering detector (GPC-LS) were low ($Đ < 1.1$), and the number-averaged molecular weighs (M_n) were in close agreement with their theoretical values as calculated via ^1H NMR analysis (Figure 1b, Table S1, ESI). These results were highly encouraging; however, it was observed that for most of the experiments the polymerization had stopped after the first minute, with only minor increases in conversion with time observed for the highest H_2O_2 loadings (Figure S1, ESI). This indicates that the radical source was rapidly exhausted, and is thought to be due to the depletion of H_2O_2 (*vide infra*). At higher H_2O_2 loading concentrations the occurrence of non-propagative hydroxyl

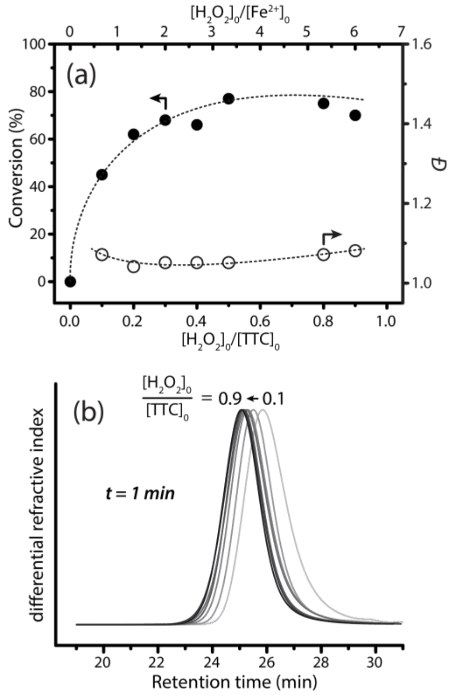

Figure 1. (a) Dependence of monomer conversion and *Đ* values vs. $[H_2O_2]_0/[Fe^{2+}]_0$ after 1 minute (with $[Fe^{2+}]_0$ = 0.15 eq.); (b) GPC chromatograms of resulting polymers (note: TTC refers to the trithiocarbonate RAFT agent).

Table 1. Characterization data for synthesized polymers after 1 minute of Fenton-RAFT polymerization (all with DP = 200).

Monomer	Conv. (%)[a]	$M_{n,th}$ (Da)[b]	$M_{n,GPC}$ (Da)[c]	$Đ$[c]
DMA[d]	61	12 380	12 100	1.04
DMA[e]	56	11 390	13 900	1.06
DMA‡[f]	85	17 140	17 500	1.04
NAM[g]	64	18 400	27 700	1.02
HEA[g]	61	14 500	19 000	1.04

[a]Determined via ^1H NMR analysis. [b]Calculated via the equation: $M_{n,th} = (\frac{conv.}{100} \times DP) \times MW_{monomer} + MW_{TTC}$. [c]From LS data processed using Astra software package. [d]$[H_2O_2]_0/[Fe^{2+}]_0/[TTC]_0$ = 0.2/0.15/1. [e]$[H_2O_2]_0/[Fe^{2+}]_0/[TTC]_0$ = 0.5/0.025/1. [f]$[H_2O_2]_0/[Fe^{2+}]_0/[TTC]_0$ = 0.5/0.15/1. [g]$[H_2O_2]_0/[Fe^{2+}]_0/[TTC]_0$ = 0.23/0.07/1. ‡Sample after 5 minutes.

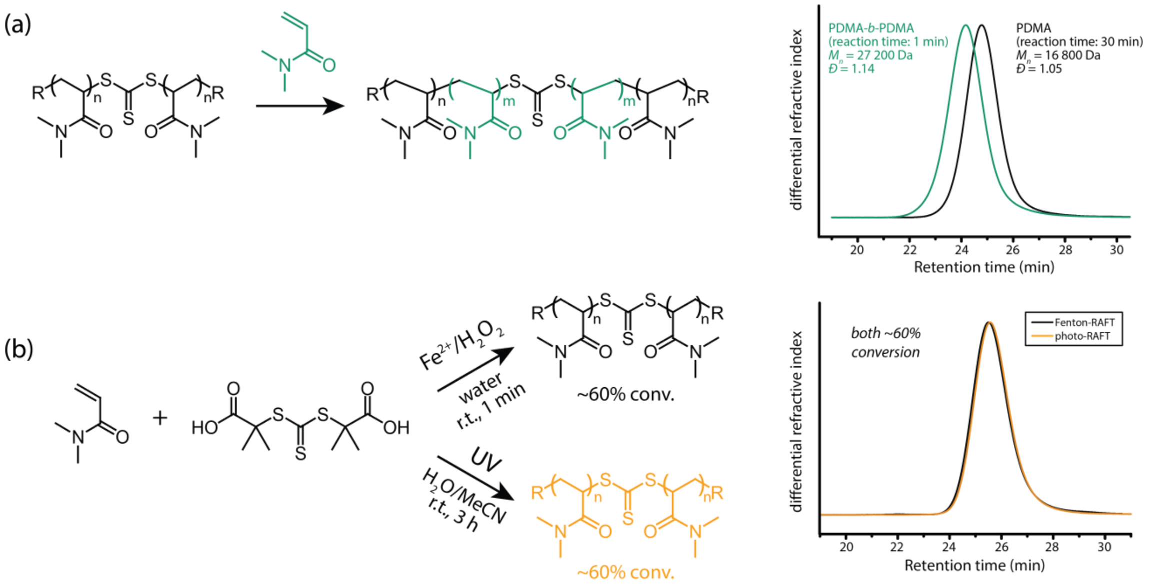

Figure 2. (a) Synthesis of (pseudo) block copolymer in 1 minute via Fenton-RAFT; and (b) Direct comparison to poly(DMA) synthesized via a photo-iniferter/RAFT polymerization to those synthesized using Fenton-RAFT at the same monomer conversion.

radical 'wasting' reactions can occur, lowering (or stopping completely) the observed rate of polymerization (see equations in ESI). These kinetic results indicate that the radical concentration is not constant, which differs from most RDRPs. Importantly, for the polymerizations that did show continued monomer conversion, linear growth of the molecular weights were observed (Figure S1c-d, ESI), indicative of the "living" character.[24] Regardless of the radical concentration profile, well-defined polymers were obtained in all cases, indicating the strength of the RAFT agent in controlling propagating radicals via a process of rapid degenerative chain transfer (Table 1).

Control experiments were performed in which Fe^{2+} or the RAFT agent were selectively omitted, resulting in no polymer formation after 60 minutes, and the formation of a physical gel (Figure S2, ESI), respectively. These control reactions verify that the Fenton reaction is responsible for initiation, while the RAFT agent allows for control over the polymer chain growth.

Further investigations into the loading level of Fe^{2+} (Table S2, ESI), and the ratio between H_2O_2 and Fe^{2+} (Table S3, ESI) demonstrate the importance of the catalytic system in both the activation and deactivation of active (initiating and propagating) radicals in the system, and are consistent with reports of free radical polymerization demonstrated by Dainton et al.[25] Careful analysis of the results revealed that for successful polymerization H_2O_2 must be employed in molar excess relative to Fe^{2+}, with an optimum molar ratio determined to be a three-fold excess of H_2O_2 (Entry 15, Table S3, ESI), achieving a conversion of 85% within 5 minutes. The requirement for an H_2O_2 excess becomes stricter at lower overall loadings (Entry 2, Table S3, ESI), and relaxed at higher loadings (Entry 18, Table S3, ESI). It should be pointed out that care was taken to avoid oxidation of the Fe^{2+} catalyst prior to the polymerization reaction (see Experimental section in ESI), as the oxidized Fe^{3+} is thought to contribute to inhibition of the polymerization. It is anticipated that this redox-state sensitivity may be leveraged for finer control over the activation/deactivation equilibrium in an analogous manner to Cu(I)-mediated atom transfer radical polymerization (ATRP).[26]

To assess the chemical fidelity of the synthesized polymers with regards to incorporation of the RAFT agent functionality, we conducted a chain extension experiment. The chain extension was performed under the same reaction conditions but with the isolated poly(DMA) acting as the 'macro-RAFT agent'. After 1 minute of reaction time the GPC chromatogram displayed a clear shift to a higher molecular weight species, with a symmetrical peak shape and minimal tailing towards lower molecular weight species (Figure 2a). Given the symmetrical nature of the RAFT agent, the trithiocarbonate should be embedded at the mid-chain position of the formed polymers. To test this, aminolysis was performed on a series of the synthesized polymers, with GPC chromatograms displaying clean shifts to a single polymer peak of approximately half the molecular weight, further confirming the uniformity of the polymers (Figure S4, ESI). It has been reported that H_2O_2 can directly transform thiocarbonyl RAFT end groups into hydroxyl groups,[27] however the trithiocarbonates used in this study show no evidence of this transformation occurring during Fenton-RAFT, as demonstrated by the aminolysis experiments as well as the relatively close match between theoretical and observed molecular weights. As a final test, we wished to compare the polymers formed via the Fenton-RAFT system to those synthesized via a photo-iniferter/RAFT ('photo-RAFT') technique, which has recently been demonstrated to be capable of forming polymers of extremely low dispersity and high chemical fidelity,[28] as well as ultrahigh molecular weights.[29] Using a mild UV light source, an analogous photo-RAFT reaction was conducted in the absence of the Fe^{2+}/H_2O_2 initiation system. The polymerization was stopped after 3 h of irradiation, giving a monomer conversion of 60%. As shown in Figure 2b, the overlays of the resulting GPC chromatograms are almost indistinguishable, despite the Fenton-RAFT reaction requiring only 1 minute of reaction time. It should be pointed out that the α-chain end fidelity of the polymers synthesized via photo-RAFT is expected to be significantly higher, due to the potential for direct initiation via hydroxyl radicals in the Fenton-RAFT system.[30] Nevertheless, control over both the molecular weight and the polymer dispersity appears excellent in the case of the Fenton-RAFT polymerization, while the timescale of the reaction is dramatically shorter.

To examine the versatility of this reaction, we conducted a series of experiments in which the targeted DP was changed to give polymers of different chain lengths, and also attempted the polymerization of a range of water-soluble monomers. Changing the targeted chain length is readily achieved by using different molar ratios of monomer to RAFT agent. As shown in Figure 3, well-defined poly(DMA) resulted in all cases, with monomer conversions of 65 – 77% observed within 1 minute, narrowly dispersed polymer peaks, and molecular weights close to their theoretical values (Tables S4 - S6, ESI). For these experiments, the catalyst system (i.e., Fe^{2+}/H_2O_2) can be kept constant relative to the monomer concentration, or relative to the RAFT agent. Both were attempted and worked for all DPs attempted; however, it was noticed that for low RAFT agent concentrations polymerization was low and/or inconsistent, thought to be due to the low concentration of H_2O_2 in these cases. Therefore, for targeted DPs > 200 the molar concentrations of Fe^{2+}/H_2O_2 were fixed at 3.3/11 mM, providing high monomer conversions in 1 minute. When a DP of 500 was attempted a bimodal peak distribution was observed (Figure S5, ESI), which may be due to the sterically-hindered mid-chain position of the symmetrical RAFT agent leading to increased termination when the chain length becomes long.[31] Nonetheless, these results are promising for the rapid synthesis of polymers of varying molecular weight.

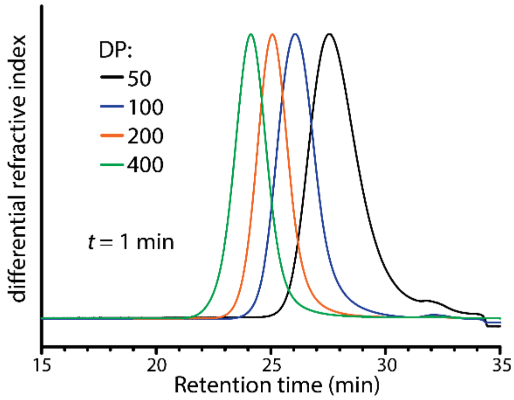

Figure 3. GPC chromatograms of poly(DMA) formed at various targeted degrees of polymerization (DP = $[DMA]_0/[TTC]_0$). $[DMA]_0/[TTC]_0/[H_2O_2]_0/[Fe^{2+}]_0$ = x/1/0.5/0.15 (except for DP400, which used a ratio of 400/1/1/0.3), and the monomer concentration was fixed at 4.4 M. All GPCs are from samples extracted after 1 minute..

Next, several monomers were attempted under the optimized conditions. Both acrylamides and acrylates were found to polymerize well, with the synthesis of well-defined poly(*N*-acryloylmorpholine) (PNAM) and poly(2-hydroxyethyl acrylate) (PHEA) formed with monomer conversions > 60% within 1 minute, low dispersities (*Đ* < 1.1) and molecular weight values in relatively good agreement with their theoretical values (Figure S6, ESI). Polymerization of the bulky acrylate monomer oligo(ethylene glycol) methyl ether acrylate (OEGA, MW = 480 g mol^{-1}) proceeded rapidly, however, a bimodal peak was observed via GPC. As for the case with long chain lengths, this is believed to be due to the steric hindrance of the brush-like segments surrounding the mid-chain trithiocarbonate group leading to cleavage of the polymer at high monomer conversions.[31] Polymerization of a slower propagating methacrylate-type monomer (2-hydroxyethyl methacrylate (HEMA)) occurred up to ca. 18% monomer conversion in 1 minute, however, despite the employed RAFT agent being able to exert good control over this monomer in a traditional RAFT reaction,[8b] the Fenton-RAFT case led to a broad polymer dispersity and an observed molecular weight significantly higher than the theoretical value, indicating a loss of control. Optimization of the reaction to allow polymerization of these monomers is ongoing. Regardless, the successful polymerization of both acrylate and acrylamide monomer types, as well as monomers with functional side groups (e.g., HEA) is highly encouraging for the synthesis of various water-soluble polymers via Fenton-RAFT.

Lastly, we were interested in the ability to perform this reaction without traditional degassing (i.e., inert gas sparging or freeze-pump-thaw cycling). An experiment was thus conducted in which the Fenton reagents were added continuously to an open flask without attempts to remove oxygen. Polymerization was observed once the molar concentration of Fe^{2+} and H_2O_2 reached 7 mM and 18 mM, respectively (Figure S7, ESI). Using this as a guide, we then performed the Fenton-RAFT reaction with varying amounts of (non-degassed) solutions of either H_2O_2 or Fe^{2+} added ('spiked') into the flask throughout the reaction. When no additional reagents were added to the initial mixture, no polymerization was observed. However, spiking the reaction

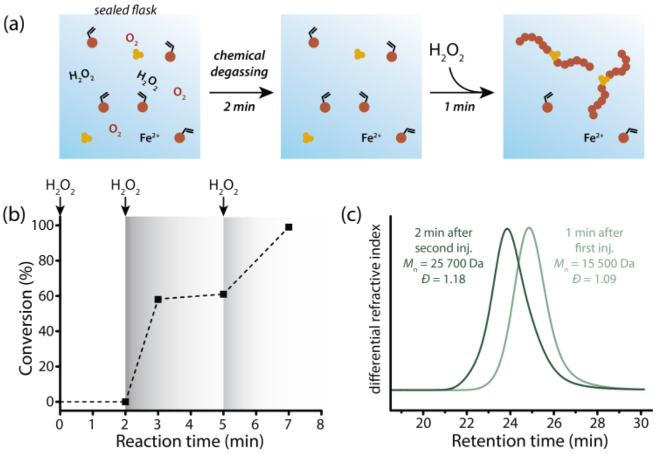

Figure 4. (a) Schematic of approach to perform Fenton-RAFT without inert gas sparging: contents of reaction mixture placed in sealed round bottom flask then 'spiked' with additional H_2O_2 after a prescribed time to initiate polymerization; (b) Monomer conversions measured during 'spiking' experiment; and (c) GPC chromatograms at total reaction times of 3 and 7 minutes (with ca. 60 and > 99% conversion, respectively).

mixture with H_2O_2 resulted in significant polymerization, with periods of dormancy between each addition, demonstrating the potential for "on-demand" chain growth (Figure 4, Figure S8, ESI). From these results, it appears that the initial H_2O_2 present is first consumed via a reaction dissolved oxygen,[32] providing a means of 'chemically degassing' the reaction mixture.[33] With sequential H_2O_2 addition, the monomer conversion reached > 99% (Figure 4b). The dispersity of the final polymer was slightly higher than those obtained in the physically degassed system, though still acceptable ($Đ$ = 1.18, Figure 4c). It was observed that the molecular weights for the polymers synthesized without prior degassing were slightly higher than their theoretical values, which may be due to partial oxidative degradation of the RAFT agent.[34]

In conclusion, a facile technique for the synthesis of controlled polymers has been realized using the Fenton reaction. The ability to degas the reaction mixture using the same catalyst system, then grow the polymer chain through sequential H_2O_2 addition is highly promising for the development of an automated/programmable polymerization system utilizing sequenced reagent injection. The benign reaction conditions (room temperature, aqueous solvent) are non-demanding and the system is demonstrated to be compatible with a range of functional monomers. It is anticipated that the source of ferrous ions and other key parameters including reaction pH will have a significant influence on the success of the reaction. We are currently investigating these effects, as well as the use of continuous addition techniques to further optimize the polymerization with regards to monomer conversion and polymer dispersity, the results of which will be the subject of a forthcoming paper. We believe that this simple and rapid technique represents a milestone step toward the development of machine-programmable synthetic polymers for biomedical applications.

Experimental Section

See Supporting Information for full experimental details, including a video demonstration the method of chemical degassing via sequential H_2O_2 addition.

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Keywords: RAFT • Fenton • radical polymerization • hydroxyl radicals • programmable polymer synthesis

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COMMUNICATION

The use of the Fenton reaction in controlled radical polymerization is reported for the first time. Together with a suitable thiocarbonylthio RAFT agent, the polymerization is demonstrated to furnish well-defined linear polymers within a few minutes at ambient temperature. These features meet several key criteria thought to make this technique particularly promising for transferal to automated polymer synthesis by design.

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Fenton-RAFT polymerization: an on-demand chain growth method

Electronic Supplementary Information

Fenton-RAFT polymerization: an "on-demand" chain growth method

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Experimental

Materials: Monomers *N*,*N*-dimethylacrylamide (DMA, Sigma Aldrich, 99%), *N*-acryloyl morpholine (NAM, Sigma-Aldrich, 97%), 2-hydroxyethyl methacrylate (HEMA, Sigma-Aldrich, 98%), and oligo(ethylene glycol) methyl ether acrylate (OEGA, Sigma-Aldrich, M_n 480) were deinhibited by passing over inhibitor removers and/or basic alumina prior to use. 2-Hydroxyethyl acrylate (HEA, Sigma-Aldrich, 96%) was purified as described previously.[1] Hydrogen peroxide (H_2O_2, 30 wt.%, Chem-supply Co.), ammonium ferrous sulphate hexahydrate ($(NH_4)_2Fe(SO_4)_2{\bullet}6H_2O$, abbreviated to Fe^{2+}, Uni Lab Co.), L-ascorbic acid (BDH Lab Supplies, >99%), and ethanolamine (≥98%, Sigma-Aldrich) were used as received. *S,S'*-Bis(α,α'-dimethyl-α''-acetic acid)-trithiocarbonate (*bis*-TTC) was synthesized according to a previously published procedure[2] and characterized via ^1H and ^{13}C NMR spectroscopy.

RAFT polymerization of DMA initiated by the Fenton reaction:

A typical procedure involved mixing all reagents except Fe^{2+} together in a 5 mL round-bottom flask, then sparging with inert gas (N_2/Ar) for 20 minutes. The solid Fe^{2+} salt was dissolved in pre-degassed water to avoid undesired oxidation. An aliquot of this stock Fe^{2+} solution was added via a degassed syringe to initiate the Fenton-RAFT polymerization and mark $t = 0$. In our experience, changing the order of Fe^{2+} and H_2O_2 addition resulted in no polymer formation after 30 min. We believe this to be due to oxidation of the dissolved Fe^{2+} to the inactive (or less active) Fe^{3+} form. Samples were extracted after various reaction times via degassed syringe for ^1H NMR and GPC analysis to monitor monomer conversion and polymer formation, respectively. These were diluted immediately with D_2O (or H_2O), which was found to be sufficient for quenching the reaction based on control experiments in which hydroquinone was also added to ensure radical quenching. No difference between these two cases was observed, and so for the rest of the experiments dilution and exposure to oxygen were the sole means of quenching the reaction.

Fenton-RAFT of differing targeted degrees of polymerization (DP)

To access different chain lengths, the initial molar ratio of monomer to RAFT agent was modified. The ratio of the Fenton reagents (i.e., Fe^{2+} and H_2O_2) was fixed relative to the RAFT agent. Polymer conversion in excess of 50% was observed for all cases within a few minutes, independent of the targeted DP. It should be noted that for targeted DPs <50, the RAFT agent was poorly soluble in the initial H_2O/monomer mixture and so these reactions were unsuccessful.

Fenton-RAFT of different monomers

The standard procedure described above was used for all polymerizations of different monomers, with the monomer concentration set at ca. 50wt% (except for OEGA, which due to its high viscosity was performed at 20wt%). For all cases the ratio of reagents was $[\text{monomer}]_0/[\text{TTC}]_0/[H_2O_2]_0/[Fe^{2+}]_0 = 200/1/0.23/0.07$.

Characterization

Nuclear Magnetic Resonance (NMR) Spectra. NMR spectroscopy was carried out on a Varian Unity 400 MHz spectrometer operating at 400 MHz. Deuterated solvent ($CDCl_3$ or D_2O) was employed as reference and sample concentrations were approximately 10 mg mL^{-1}.

Gel permeation chromatography (GPC): The polymerization mixtures were analyzed directly by aqueous GPC using an eluent of Milli-Q water with 0.1 vol% trifluoroacetic acid (TFA). The system was operated at a flow rate of 1 mL min^{-1} at 25 °C. A Shimadzu Liquid Chromatography system was utilized, equipped with a Shimadzu RID-10 refractometer (λ = 633 nm) and Wyatt 3-angle light scattering detector, with three Waters Ultrahydrogel columns in series ((i) 250 Å porosity, 6 μm diameter bead size; (ii) and (iii) linear, 10 μm diameter bead size) for separation. The dn/dc values of polydimethyl acrylamide (PDMA) in the above eluent was calculated to be 0.190 mL g^{-1} at 25 °C using a method of 100% mass recovery on a sample prepared from isolated PDMA to an accurate concentration. dn/dc values of PHEA (0.134 mL g^{-1}) and POEGA (0.140 mL g^{-1}) were determined via 100% mass recovery, while the value for PNAM (0.163 mL g^{-1}) was taken from the literature.[3] Molecular weight and dispersity values were then calculated using the

Wyatt ASTRA SEC/LS software package. For analysis of the PHEMA sample, a GPC system using DMF (with 0.05M LiBr) was utilized that consisted of three phenogel columns (Phenomenex, 5 µm) in series with a Shimadzu RID-10 refractometer. The flow rate was 1 mL min^{-1} and the column oven was set at 45°C. This system was calibrated via narrowly dispersed poly(styrene) standards and molecular weight data reported as poly(styrene) equivalents.

Chain extension experiment

Chain extension was performed to assess the "livingness" of the formed polymers. To avoid extraneous issues such as monomer compatibility or differing re-initiation efficiencies etc., the same monomer was employed for both 'blocks'. Therefore, the isolated polymer was employed as RAFT-macroinitiator for the synthesis of a *pseudo* diblock copolymer (PDMA-*b*-PDMA) at room temperature. The same condition as the Entry 3 in Table S1 was set for the copolymerization.

Aminolysis experiment

To determine the existence of the trithiocarbonate moitey in the polymer chains, 5 mL of ethanolamine was added to the reaction mixture of Entries 1 (repetition 3), 2 (repetition 1), and 3 (repetition 1) after a polymerization time of 30 minutes. The cleavage reaction was left for 3 hours before GPC analysis.

Fenton reaction chemistry

Fenton reaction describes the generation of hydroxyl radicals ($HO^\bullet$) through the activation (reduction) of hydrogen peroxide (H_2O_2) by ferrous (Fe^{2+}) ions *via* a complex reaction sequence as following:[4]

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + HO^\bullet + OH^- \quad (k= 63\text{-}76\ M^{-1}\ s^{-1}) \tag{S1}$$

$$Fe^{3+} + H_2O_2 \longrightarrow Fe^{2+} + HO_2^\bullet + H^+ \quad (k= 0.001\text{-}0.01\ M^{-1}\ s^{-1}) \tag{S2}$$

In the presence of an excess amount of H_2O_2 and Fe^{2+}, the non-specific reactivity of $HO^\bullet$ results in various competitive processes (see Equations (S3)-(S5)) which are undesirable for other organic oxidation process.[5] The presented rate constants are taken from the literature.[6] These are considered inhibitory reaction pathways in the current study.

$$Fe^{2+} + HO^\bullet \rightarrow Fe^{3+} + OH^- \quad (k = 3.2\times10^{8}\ M^{-1}\ s^{-1}) \tag{S3}$$

$$H_2O_2 + HO^\bullet \rightarrow HO_2^\bullet + H_2O \quad (k = 3.3\times10^{7}\ M^{-1}\ s^{-1}) \tag{S4}$$

$$HO^\bullet + HO^\bullet \rightarrow H_2O_2 \quad (k = 6\times10^{9}\ M^{-1}\ s^{-1}) \tag{S5}$$

Table S1. Characterisation data of the synthesised PDMA with varied H_2O_2 concentration when $[Fe^{2+}]_0$ = 0.15 eq. (3.3 mM).

Entry[a]	$[M]_0/[TTC]_0$	$[H_2O_2]_0/[TTC]_0$	$[H_2O_2]_0$ (mM)	Repetition	Time (min.)	Conversion (%)	$M_{n,GPC}$ (Da)	$M_{n,th}$ (Da)[b]	Đ
1	200	0.1	2.2	1	1	49	---	---	---
					5	49	---	---	---
					30	49	---	---	---
				2	1	42	7 400	8 610	1.07
					5	42	7 300	8 610	1.06
					30	42	7 900	8 610	1.05
				3	1	48	9 200	9 800	1.05
					5	48	9 000	9 800	1.05
					30	48	---	---	---
				4	1	40	6 700	8 410	1.09
					5	40	6 500	8 410	1.10
					30	40	6 700	8 410	1.09
2	200	0.2	4.4	1	1	62	11 500	12 580	1.03
					5	62	11 300	12 580	1.04
					30	62	11 200	12 580	1.04
				2	1	61	12 100	12 380	1.04
					5	61	---	---	---
					30	61	---	---	---
3	200	0.3	6.6	1	1	67	12 900	13 570	1.08
					5	75	16 900	15 150	1.04
					30	80	16 800	16 140	1.05
				2	1	71	13 900	14 360	1.04
					5	71	---	14 360	---
					30	71	14 100	14 360	1.05
					40	71	13 600	14 360	1.02
				3	1	66	14 100	13 370	1.04
					5	66	14 000	13 370	1.04
					30	66	14 100	13 370	1.04
4	200	0.4	8.8	1	1	65	12 400	13 170	1.06
					5	71	13 800	14 360	1.04
					30	85	16 400	17 140	1.04
				2	1	67	14 400	13 570	1.04
					5	74	16 100	14 950	1.04
					30	79	16 700	15 950	1.04
5	200	0.5	11	1	1	77	15 300	15 550	1.05
					5	85	17 500	17 140	1.04
					30	90	18 700	18 130	1.05
6	200	0.8	17	1	1	75	13 800	15 160	1.07
					5	90	---	---	---
					15	>99	18 300	19 910	1.12
7	200	0.9	20	1	1	70	11 800	14 160	1.08
					5	83	---	---	---
					15	>99	17 100	19 910	1.29
8	200	0	0	-	30	0	---	---	---

(a) In all experiments solvent is water (~600 µL). The molar concentration of monomer is fixed as 4.4 M. The ratio $[Fe^{2+}]_0/[TTC]_0$ is 0.15 for all experiments. Degree of polymerization was set as 200 in all experiments ($[DMA]_0/[TTC]_0$ = 200:1); (b) Theoretical molecular weights are calculated using the formula: $M_{n,th} = [Monomer]_0/[TTC]_0 \times conversion \times (M_n)_{monomer}/100+(M_n)_{TTC}$.

Table S2. Characterisation data of the synthesised PDMA with varied Fe^{2+} concentration when $[H_2O_2]_0$ = 0.5 eq. (11 mM).

Entry[a]	$[M]_0/[TTC]_0$	$[Fe^{2+}]_0/[TTC]_0$	$[Fe^{2+}]_0$ (mM)	Time (min.)	Conversion (%)	$M_{n,GPC}$ (Da)	$M_{n,th.}$ (Da)[b]	$Đ$
1	200	0.025	0.55	1	56	13 900	11 390	1.06
				5	66	15 900	13 370	1.05
				30	76	18 500	15 350	1.04
				60	83	---	---	---
2	200	0.05	1.10	1	50	14 200	10 200	1.07
				5	70	20 900	14 160	1.05
				30	85	27 400	17 140	1.04
				60	85	27 900	17 140	1.05
				90	85	---	---	---
3	200	0.1	2.20	1	65	9 900	13 170	1.05
				5	75	11 900	15 150	1.04
				30	92	15 000	18 240	1.04
				60	92	---	---	---
				90	92	---	---	---
4	200	0.15	3.30	1	77	15 300	15 550	1.05
				5	85	17 500	17 140	1.04
				30	90	18 700	18 130	1.05
5	200	0.25	5.50	1	58	9 900	11 780	1.07
				5	58	---	---	---
				30	58	---	---	---

(a) In all experiments solvent is water (~600 μL). The molar concentration of monomer is fixed as 4.4 M. Degree of polymerization was set as 200 in all experiments ($[DMA]_0/[TTC]_0$ = 200:1); (b) Theoretical molecular weights are calculated using the formula: $M_{n,th.} = [Monomer]_0/[TTC]_0 \times conversion \times (M_n)_{monomer}/100 + (M_n)_{TTC}$.

Table S3. DMA conversion values in Fenton-RAFT polymerization versus different molar concentration of Fenton reaction's reagents.

Entry	[Fe^{2+}] (mM)	[H_2O_2] (mM)	[H_2O_2]/[Fe^{2+}]	Time (min)	Conversion (%)
1	0.075	0.075	1	60	0
2	0.075	0.1	1.3	30	0
3	0.075	1	13.3	120 (left for 3 days)	30 (30)
4	0.075	1.5	20	30	60
5	0.375	0.5	1.3	120 (left for 3 days)	0 (0)
6	0.5	0.5	1	30	0
7	0.55	11	20	30	76
8	1.00	0.5	0.5	10	0
9	1	1	1	10	0
10	1	1	1	120 (left for 3 days)	0 (0)
11	1	1.5	1.5	5	25
12	1	2	2	5	38
13	1.1	11	10	5	70
14	2.2	11	5	5	75
15	3.3	11	3.3	5	85
16	3.3	17	5.2	5	75
17	3.3	20	6	5	70
18	3.3	2.2	0.7	5	45
19	3.3	4.4	1.3	5	62
20	3.3	6.6	2	5	71
21	3.3	8.8	2.7	5	73
22	5.5	11	2	5	58

In all experiments solvent is water (~600 µL). The molar concentration of monomer is fixed as 4.4 M. Degree of polymerization was set as 200 in all experiments ($[DMA]_0/[TTC]_0$ = 200:1.

1. Kinetic analysis and control reaction

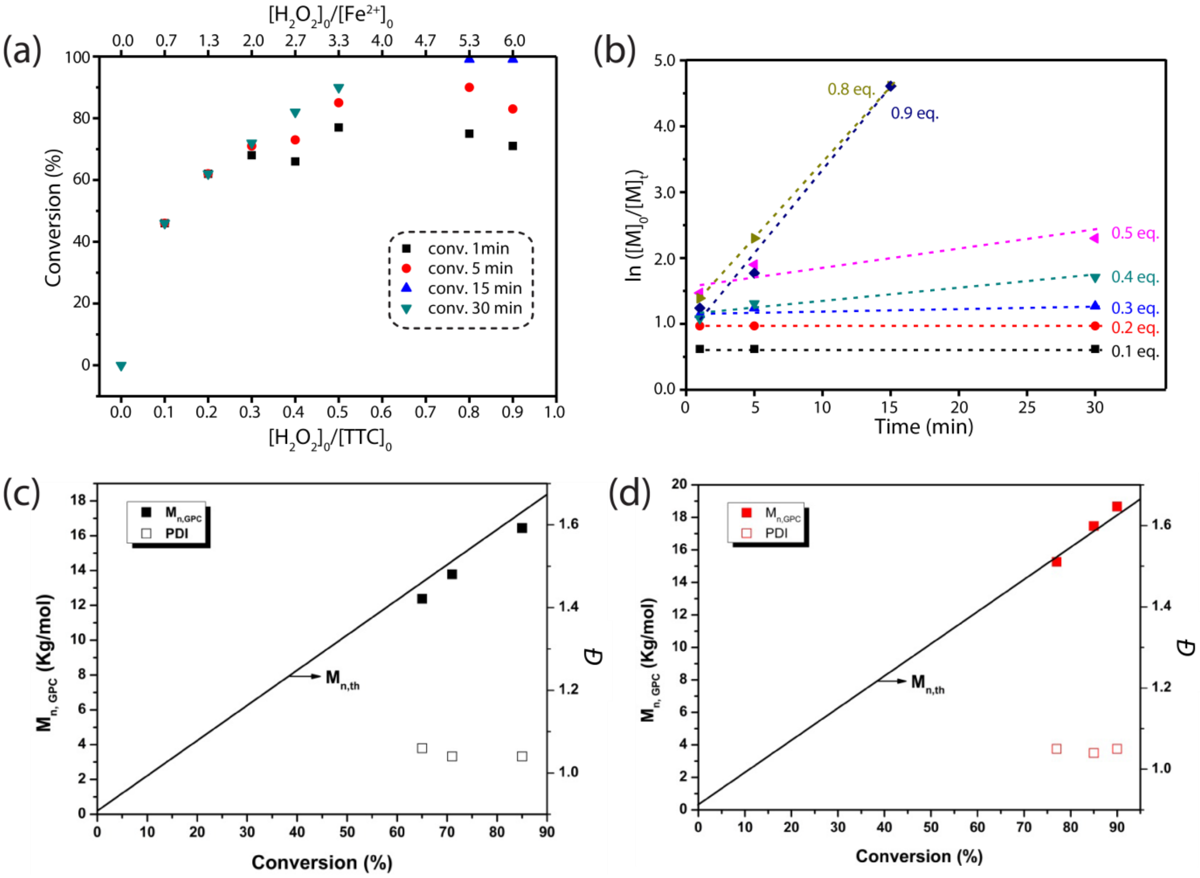

Figure S1. (a) and (b) depict conversion data for Fenton-RAFT polymerization at different polymerization times (note: the dotted lines in the *ln* plots are to guide the eye), while (c) and (d) show the growing polymer for the cases where $[DMA]_0/[TTC]_0/[H_2O_2]_0/[Fe^{2+}]_0$= 200/1/0.4/0.15 and 200/1/0.5/0.15, respectively.

Figure S2. Physical gel obtained from the Fenton reaction conducted in the absence of the *bis*-functional trithiocarbonate RAFT agent.

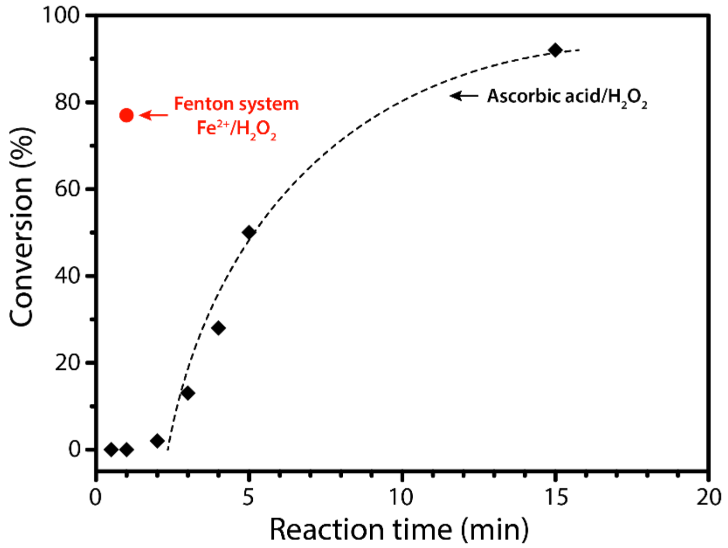

Figure S3. Kinetics of ascorbic acid/H_2O_2 redox pair. The Fe^{2+}-mediated Fenton system after 1 minute is shown as a comparison. For both reactions the molar ratios were: [DMA]/[TTC]/[H_2O_2]/([asc. acid] or [Fe^{2+}]) = 200/1/0.5/0.15, with a monomer concentration of 4.4 M.

2. Cleavage of formed polymers via aminolysis, different targeted DPs and different monomers

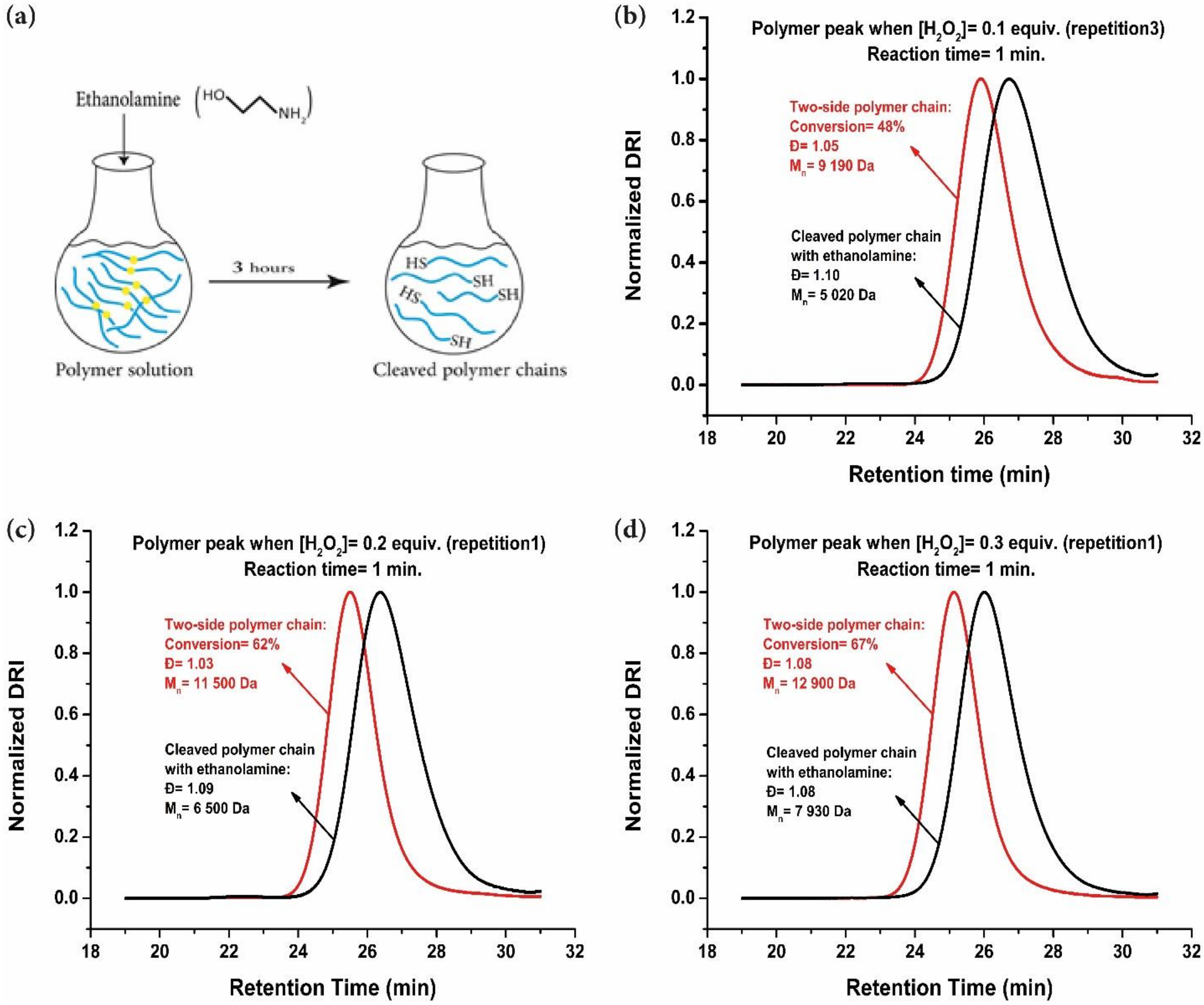

Figure S4. (a) Schematic illustration of ethanolamine addition to the polymer solutions in order to demonstrate existence of thiocarbonylthio groups in the polymer chain; a clear shift of polymer peaks for cleaved polymer chains obtained from entries (b) 1 (repetition 3), (b) 2 (repetition 1) and (c) 3 (repetition 1) after 3 hours of cleavage reaction.

Table S4: Different targeted DPs for polymerization of DMA via Fenton-RAFT with Fe^{2+}/H_2O_2 kept constant *relative to monomer*.[a]

DP	*t (min)*	*conv. (%)*	$M_{n,th}$ *(Da)*	$M_{n,GPC}$ *(Da)*	*Đ*
50	1	29	-	-	-
50	5	51	2 800	3 500	1.09
100	1	65	6 700	7 400	1.03
100	5	77	7 200	7 700	1.03
200	1	77	15 500	15 300	1.05
200	5	85	17 100	17 500	1.04
400	1	65	26 000	26 000	1.08
400	5	71	28 400	28 300	1.09

[a] Monomer concentration was fixed at 4.4 M, $[H_2O_2]_0$ = 11 mM, $[Fe^{2+}]_0$ = 3.3 mM.

Table S5: Different targeted DPs for polymerization of DMA via Fenton-RAFT with Fe^{2+}/H_2O_2 kept constant *relative to*

RAFT agent.[a]

DP	*t (min)*	*conv. (%)*	$M_{n,th}$ *(Da)*	$M_{n,GPC}$ *(Da)*	*Đ*
50	1	72	3 900	6 100	1.17
50	5	83	-	-	-
100	1	77	7 900	8 200	1.04
100	5	88	-	-	-
200	1	77	15 500	15 300	1.05
200	5	85	17 100	17 500	1.04
400	1	32	13 000	15 000	1.09
400	5	34	-	-	-
500	1	55	27 500	32 800	1.30
500	5	80	39 900	49 200	1.22

[a] $[DMA]_0/[TTC]_0/[H_2O_2]0/[Fe^{2+}]_0 = x/1/0.5/0.15$, monomer concentration was fixed at 4.4 M.

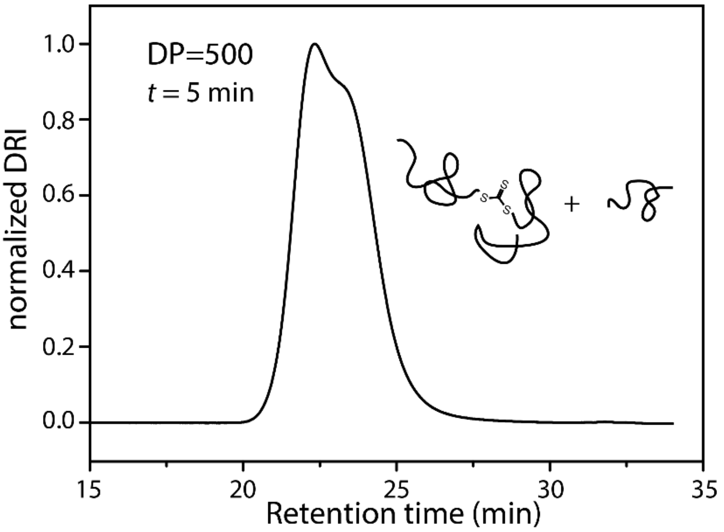

Figure S5. GPC chromatogram of poly(DMA) synthesized with a targeted DP of 500. The biomodal distribution is thought to be due to the steric hindrance surrounding the trithiocarbonyl RAFT agent when long chain lengths are reached, which leads to an increase in termination and chain breaking reactions.[7]

Table S6: DP100 reproducibility study.[a]

Experiment #	*DP*	*t (min)*	*conv. (%)*
1	100	1	80
	100	5	92
2	100	1	85
	100	5	88
3	100	1	70
	100	5	89

[a] $[DMA]_0/[TTC]_0/[H_2O_2]0/[Fe^{2+}]_0 = \mathit{100}/1/0.23/0.07$, monomer concentration fixed at 4.4 M.

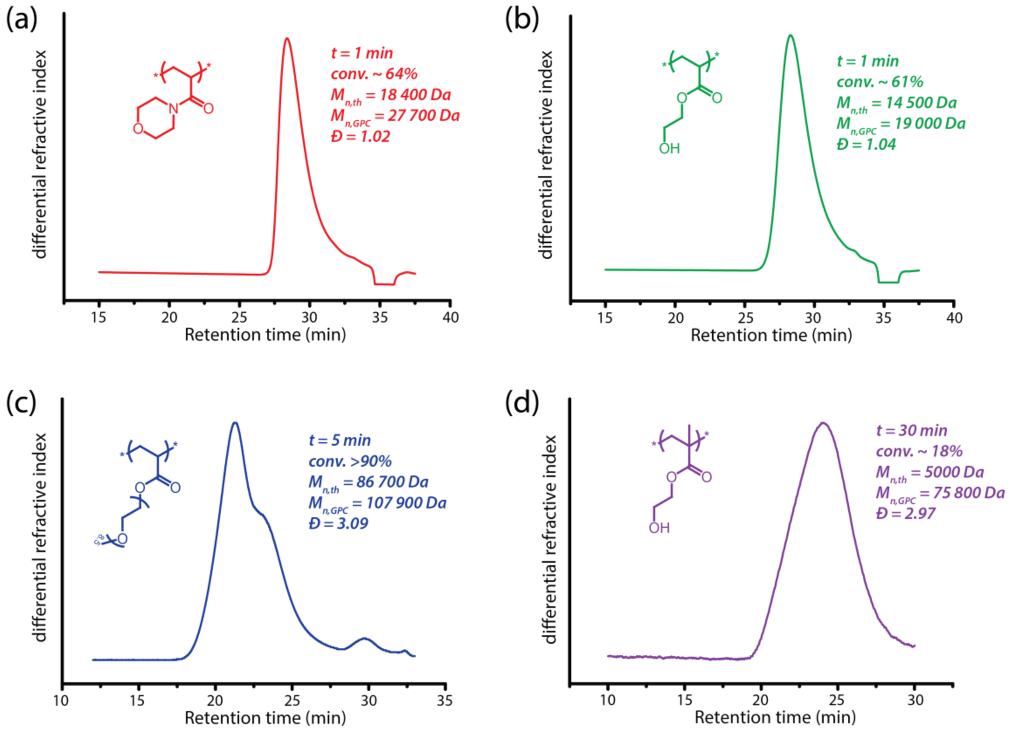

Figure S6. GPC chromatograms of polymers formed from different monomers using Fenton-RAFT, where [monomer]$_0$/[TTC]$_0$/[H$_2$O$_2$]$_0$/[Fe^{2+}]$_0$ = 200/1/0.23/0.07 for all cases, and the monomer concentration was ca. 50wt% (except for OEGA, which was performed at 20wt%). *N*-acryloyl morpholine (a) and 2-hydroxyethyl acrylate (b) appear to work well. The bulky oligo(ethylene glycol) methyl ether acrylate monomer (c) (MW = 480 g mol^{-1}) polymerized rapidly, however a bimodal distribution was observed and is thought to again be due to the steric hindrance of the mid-chain RAFT agent leading to cleavage at this position.[7] The broad dispersity value is thought to be due to the bimodality of the peak. Polymerization of methacrylate-type monomer (HEMA) displays lack of control (d). Note: PHEMA was run on a DMF-GPC system with no light scattering detector and so the molecular weight was determined via calibration with poly(styrene) standards.

3. Fenton-RAFT polymerization without prior degassing

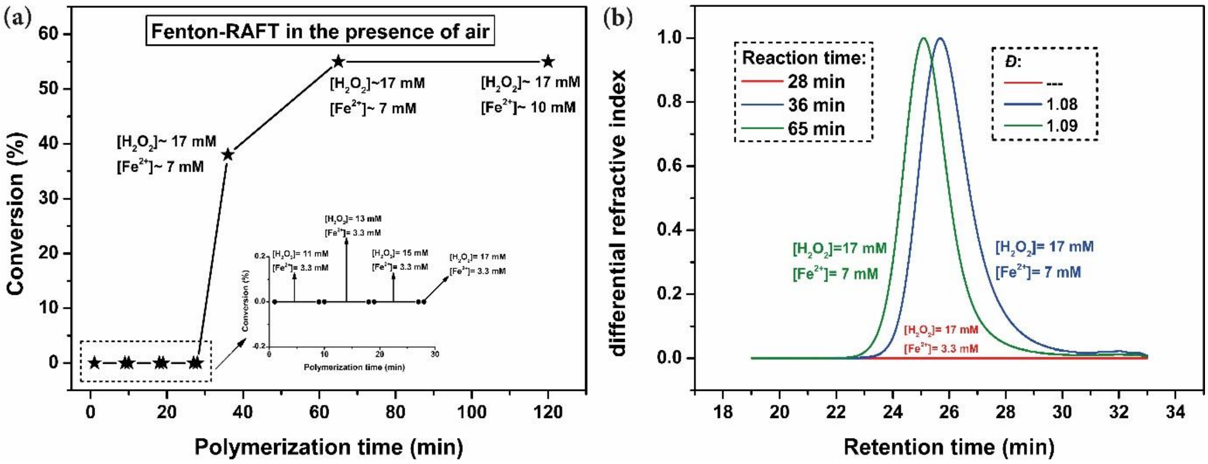

Figure S7. Experiment in which Fenton reagents (i.e., Fe^{2+} and H_2O_2) were added continuously to an open flask and the reaction monitored via (a) ^{1}H NMR to determine the monomer conversion, and (b) GPC to analyse the formed polymer products.

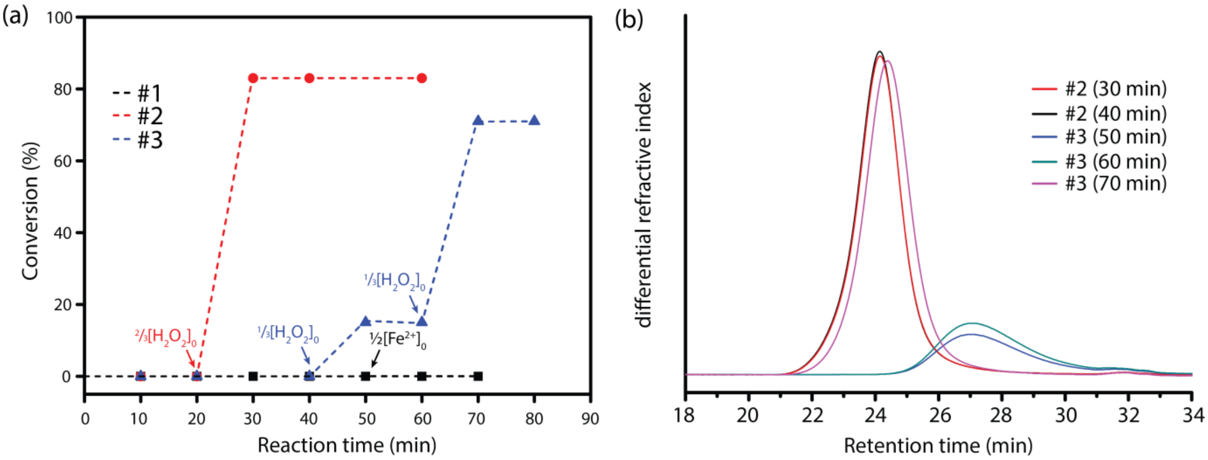

Figure S8. Experiment in which Fenton reagents (i.e., Fe^{2+} and H_2O_2) were 'spiked' into a sealed flask and the reaction monitored via (a) ^{1}H NMR to determine the monomer conversion, and (b) GPC to analyse the formed polymer products.

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