DOI: 10.1002/marc.201900220

Article type: Feature Article

Fenton-Chemistry-Mediated Radical Polymerization

*Amin Reyhani, Thomas G. McKenzie, Qiang Fu, and Greg G. Qiao**

Polymer Science Group, Department of Chemical Engineering, The University of Melbourne
Parkville, VIC 3010, Australia

*E-mail: gregghq@unimelb.edu.au

In this review, the power of a classical chemical reaction, the Fenton reaction for initiating radical polymerizations, is demonstrated. The reaction between the Fenton reagents (i.e., Fe^{2+} and H_2O_2) generates highly reactive hydroxyl radicals, which can act as radical initiators for the polymerization of vinyl monomers. Since the Fenton reaction is fast, easy to set up, cheap, and biocompatible, this unique chemistry is widely employed in various polymer synthesis studies via free radical polymerization (FRP) or reversible addition–fragmentation chain transfer (RAFT) polymerization, and is utilized in a wide range of applications, such as the fabrication of biomaterials, hydrogels, and core-shell particles. Biologically-activated Fenton–mediated radical polymerization, which can be performed in aerobic environments, are particularly useful for applications in biomedical systems.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/marc.201900220](#).

This article is protected by copyright. All rights reserved.

1. Redox reaction in initiating polymerizations

Free radical polymerization (FRP) has been widely used to synthesize different types of hydrophilic and hydrophobic synthetic polymers in aqueous and organic media.^[1-5] The mechanism of consists of three fundamental steps: (i) *Initiation*, i.e. the formation of an active radical followed by its addition to a vinyl monomer; (ii) *Propagation*, i.e. the rapid and progressive subsequent addition of monomer molecules to the growing polymer chain; and (iii) *Termination*, i.e. the destruction of the active radical species, usually via bimolecular *combination* or *disproportionation*.^[6] In addition to these three reactions, chain transfer may occur. This is the transfer of the active radical from the active chain to a previously inactive one.^[7] The development of ‘living’ radical polymerization has been revolutionary for polymer chemists as radical-based techniques are more tolerant of functional groups and impurities than ionic mechanisms, and are currently the leading industrial method to manufacture commodity polymers.^[8] Since traditional FRP methods are generally "dead-end" polymerizations,^[9] the ‘living’ radical polymerization methodologies have played a crucial role in the development of modern polymer chemistry. Since the advent of reversible deactivation radical polymerization (RDRP) in 1982,^[10] a lot of powerful and robust techniques have been developed for the synthesis of polymers with diverse structures (linear, star, cyclic, etc.), compositions (block copolymer, gradient, alternating, block, etc.), and functionalities (thiol, amine, etc.).^[11] The main mechanism of RDRP which results in controllable polymerization is the establishment of a dynamic equilibrium between the propagating radicals (active polymers) and the dormant species *via* a reversible activation-deactivation process with rate constants k_{act} and k_{deact} , respectively.^[7, 12]

With the emergence of RDRP methods such as atom transfer radical polymerization (ATRP),^[13-15] nitroxide-mediated polymerization (NMP),^[16] and reversible addition-fragmentation transfer (RAFT)^[11, 17, 18] there has been significant effort to control these techniques *via* different physical and chemical stimuli.^[19-27] Of these, RAFT holds particular promise due to its compatibility with a diverse range of solvents, monomers, and operating conditions^[11, 24, 28-35]. Among RDRP methods, one might argue that RAFT is the most similar to traditional FRP, with the simple addition of a thiocarbonylthio-

containing compound chain transfer agent (CTA, termed as RAFT agent)^[36] that can mediate the polymerization, allowing the synthesis of well-defined polymers (**Scheme 1**). In fact, RAFT CTAs aid in achieving control of the radical polymerization *via* reversible addition of the thiocarbonylthio group and rapid fragmentation reactions.^[37, 38] Therefore, relatively analogous activation/initiation systems such as thermal,^[4, 11, 28-31, 39-41] photo,^[2, 24, 32-34, 42-49] enzyme,^[5, 23, 50-54] and redox^[3, 55-59] based radical formation can be employed to initiate both FRP and RAFT processes. Despite the huge advances made in this field, new techniques that can overcome some of the drawbacks of these systems are continuously sought. For example, using a thermal initiator requires a high operating temperature, limiting the possibility for *in situ* FRP/RAFT methods in biological systems, where temperature control is limited. The rate of visible light-activated RAFT polymerization without using photocatalysts is relatively slow,^[34, 60] while photocatalysts, e.g. iridium and ruthenium-based ones,^[24, 61] employed in photo-activated processes are expensive. Moreover, photo-mediated polymerization faces difficulties in terms of the equipment requisite to perform photo-initiation at scale.^[29]

Scheme 1. Schematic illustration of free radical polymerization and RAFT polymerization techniques. The CTA is used as a "RAFT agent" to mediate/control the polymerization, resulting in polymers with pre-determined and well-controlled molecular weight, architecture, composition, etc., via RAFT polymerization.

Redox-responsive polymerization systems have many advantages, including a low activation energy (40-85 kJ mol⁻¹), easy and facile control over the polymerization at ambient temperatures, very short induction periods, etc.^[56, 62] Polymerizations initiated by a redox reaction between an oxidizing

and a reducing agent are referred to as "redox polymerizations".^[63] Use of a redox pair for initiation of RAFT polymerization is easy to implement, as easy-to-handle, cheap, and metal-free redox pairs can be chosen.^[29, 59, 64-66] In industry, redox initiation systems are widely used in aqueous media.^[29, 66] Redox initiation for the RAFT polymerization of temperature-sensitive monomers such as NIPAM and *N*-vinyl pyrrolidone (VP) at ambient temperature has been demonstrated.^[59, 64] For instance, Bai et al.^[59] reported an inexpensive and effective redox pair consisting of potassium persulfate (KPS, $K_2S_2O_8$) and sodium thiosulfate (STS, $Na_2S_2O_3$) for the aqueous RAFT polymerization of NIPAM and acrylamide (AM) (both water-soluble) in the presence of 2-(1-carboxy-1-methyl-ethylsulfanylthiocarbonylsulfanyl)-2-methyl-propionic acid (CMP) as RAFT agent at room temperature. High molecular weight linear PNIPAM and PAM with low dispersity ($\bar{D} = 1.05$ for NIPAM after 6 h and 1.28 for PAM after 5 h) were achieved.

Peroxide initiators including tert-butyl hydroperoxide (TBHP),^[29, 65] benzoyl peroxide (BPO),^[55] and hydrogen peroxide (H_2O_2)^[53] have also been widely used to initiate radical polymerization. The TBHP/ascorbic acid (AsAc) pair has been used to initiate the aqueous RAFT polymerization of VP at ambient conditions in the presence of a xanthate RAFT agent without any observable side reactions.^[64] After 24 h monomer conversion was above 90%, and high molecular weights with narrow $\bar{D}$ values (<1.2) were obtained. Good chain-end fidelity of the RAFT agent in polymer chains was successfully shown through the synthesis of polyacrylamide (PAM)-PVP diblock copolymers with high blocking efficiency.^[64]

Using the TBHP/AsAc pair, Kempe and his group reported the synthesis of novel, thermos-responsive and functional comb polymers from poly(aminoester)s.^[67-70] Preparation of pyrrolidone-based homo- or block- polymers via RAFT aqueous polymerization using KPS/AsAc redox pair at 30 °C has been also reported.^[71]

Junkers and co-workers introduced a mild redox initiation system, i.e. cyclohexanone (CH)/TBHP mediated by an acid, to RAFT polymerization of *n*-butyl acrylate at room temperature.^[65] Destarac et al. reported TBHP/ Na_2SO_3 as a redox couple for initiation of RAFT polymerization of VP with a

xanthate-type CTA.^[72] Redox-initiated RAFT polymerization of the hydrophobic monomers methyl methacrylate (MMA), methyl acrylate (MA) and styrene (St) in bulk (or THF solution) were demonstrated at room temperature by using a traditional redox system: BPO and *N,N*-dimethylaniline.^[55] An and co-workers have reported a RAFT polymerization based on a H₂O₂/AsAc redox pair^[5, 73] for the generation of hydroxyl radicals. H₂O₂ was generated via an enzymatic process, consisting of glucose oxidase (GOx), β-D-glucose (DG), and dissolved oxygen. Well-defined linear polymers were obtained in both open and sealed vessels without prior deoxygenation. The initiation pathway reported in this work is different from those reported by Stevens and co-workers,^[74, 75] and our group,^[76-78] but provides a novel method for metal-free redox initiation utilizing enzymatic-degassing.

In this review, we highlight the capability of the Fenton reaction^[79, 80] for initiation FRP and RAFT systems, including potential uses in various applications.

2. Fenton Chemistry

The Fenton reaction was first described by H. J. H. Fenton, who in 1894 reported on the oxidation of malic acid by hydrogen peroxide in the presence of ferrous ions.^[81] It was later shown that hydroxyl radicals are the oxidants in this reaction,^[82, 83] forming the basis of a chemical process that is now widely used in applications ranging from industrial wastewater treatment to cancer therapeutics and biosensors.^[84-87] The Fenton reaction describes the generation of hydroxyl radicals (HO•) through the reduction process of hydrogen peroxide (H₂O₂) by ferrous (Fe²⁺) ions *via* the key reactions as following.^[88-92]

The main reaction which generates hydroxyl radical (HO•) is the spontaneous redox reaction resulting from the differing redox potentials of Fe²⁺ (E⁰(Fe³⁺/Fe²⁺) = +0.77 V vs. SHE) and H₂O₂ (E⁰(H₂O₂/HO•) = +0.80 V vs. SHE); this difference provides a thermodynamic driving force for the

electron transfer from Fe^{2+} species to H_2O_2 .^[93] Nevertheless, the lifetime of the generated $\text{HO}^\bullet$ is very short.^[94] In the presence of an organic substrate, $\text{HO}^\bullet$ may abstract a hydrogen atom from the substrate, generating an organic radical ($\text{R}^\bullet$).^[95, 96] This organic radical can subsequently go through a variety of chemical transformations to form diverse oxidation products.^[97] Excess H_2O_2 and Fe^{2+} could convert all organic compounds into carbon dioxide (CO_2) and water when there are no competitive scavengers of either $\text{R}^\bullet$ or $\text{HO}^\bullet$.^[93] Nevertheless, the non-specific increased reactivity of $\text{HO}^\bullet$ towards organic/inorganic substrates ($k > 10^8 \text{ M}^{-1} \text{ s}^{-1}$)^[98] results in a range of competitive processes (see Equations (3)-(5)) which are undesirable for the organic oxidation process.^[82, 97, 99, 100]

In practice, equation (4) takes place to an appreciable extent when a large excess of H_2O_2 compared to Fe^{2+} is present.^[101] Likewise, Fe^{3+} ions generated from reactions (1) and (3) react with hydroxide anions (OH^-) to form insoluble ferric hydroxide, which precipitates at neutral pH. This further leads to the reduction of overall oxidation efficiency and requires the addition of more Fe^{2+} .^[93] In an industrial context, hydroxyl radicals have long been employed as oxidising agents for the degradation of organic contaminants in wastewater streams.^[90, 97] It was also shown that at lower pH values (acidic water) an evolution of O_2 could be obtained as follows: ^[82, 102, 103]

The huge popularity and prevalent applicability of Fenton chemistry are due to the following reasons:^[84, 93] (1) the employment of easy-to-handle, cheap, abundant, and reactive reagents makes the process practically cost-effective; (2) oxidizing $\text{HO}^\bullet$ radicals are generated under ambient conditions,

avoiding the requirement of any complex reactor facilities; and (3) with regard to the highly rapid reaction between Fe^{2+} and H_2O_2 , the generation of $\text{HO}^\bullet$ happens in the shortest reaction time among all other advanced oxidation processes. The rate of the Fenton reaction increases with increasing temperature^[104] and pH (in the acidic range).^[105] Detailed studies of the kinetics have been reported by Meyerstein and co-workers.^[106] Due to the potential of the Fenton reaction in generating highly reactive hydroxyl radicals, it has also been employed extensively as an initiation system for FRP and RAFT processes,^[48, 76, 77, 107-111] and for the synthesis of hydrogels and ultra-high molecular weight (UHMW) polymers.^[78, 112-114] In the presence of sufficient amounts of monomer, all of the generated radicals go towards initiating the polymerization (i.e. no wasting reactions)^[115] and no evolution of oxygen occurs.^[116]

3. Fenton reaction-initiated FRP

Studies have been performed on the initiation of FRP by using Fenton chemistry.^[48, 107, 108, 117-119] One such example appeared as early as 1946 by Baxendale and co-workers.^[107, 117, 118] A wide variety of vinyl monomers (i.e., methacrylic acid (MAA), acrylonitrile (AN), St, MA, and MMA) were employed in a FRP conducted in aqueous solution and emulsion.^[107, 117] It was found out that the polymerization rate when initiated by the Fenton reaction is faster than that of a $\text{H}_2\text{O}_2/\text{AsAc}$ -mediated polymerization.^[76] The proposed mechanism for the Fenton FRP reaction is shown in **Scheme 2**, and includes the Fenton reaction (I & II), initiation step (III), propagation (IV) and termination reactions (V & VI).^[107] Baxendale and co-workers proposed a chain-breaking reaction in FRP^[107] regarding the evolution of oxygen during the reaction between H_2O_2 and Fe^{2+} in acid solution.^[82] Likewise, they observed that in the presence of excess H_2O_2 and monomer, not only was the rate of polymerization ultra-fast, but the oxygen evolution from H_2O_2 was suppressed. Moreover, it was demonstrated that reaction (II) could be suppressed if high concentrations of the monomer are used compared to the concentrations of H_2O_2 and Fe^{2+} .^[107] In their subsequent work, they studied the kinetics of MMA polymerization in aqueous emulsion and reported that higher concentrations of initiating agent (or MMA or *N*-cetyl trimethylammonium bromide as emulsifying agent) gave higher monomer conversions.^[117] Afterwards, by exploring the obtained distributions of molecular weights of

Poly(MMA) (PMMA) during polymerization they showed that experimental molecular weights matched well with the theoretical values.^[118] Baxendale and co-workers also reported aqueous emulsion polymerization of MMA, highlighting the independence of the initial rate of polymerization on the amount of discontinuous monomer phase and occurrence of initiation in the aqueous phase (i.e. outside of the monomer droplets).^[120]

Scheme 2. The proposed mechanism which includes initiation, propagation, and termination reactions for the Fenton-chemistry-mediated FRP of vinyl monomers in aqueous solution and emulsion as reported by Baxendale and co-workers.^[107]

AN was polymerized in an acidified solution by using a Fenton system, with no induction period observed.^[108] It was shown that the form of the contraction-time curves (first-order or second-order) depend on the monomer and catalyst concentrations (i.e., Fe²⁺/H₂O₂). A lower concentration of Fe²⁺ (2.5×10⁻⁵ M vs. 1×10⁻⁴ M) led to lower polymerization rates and first-order kinetics. Ferric ions (Fe³⁺) were suggested to be inhibiting the polymerization at high Fe²⁺ loadings, as the polymerization rate started plateauing after 30 min.^[108] This was similar to the previous work in which polyacrylamide radicals were subject to oxidative termination by Fe³⁺.^[47] Moreover, the [Fe²⁺]/[H₂O₂] ratio played an important role on the polymerization rate as an increase in the ratio (while initiation rate was kept constant) decreased the polymerization rate at low concentrations of monomer.^[108, 121] Later in 1962, the existence of hydroxyl end groups in polymer chains was detected by using a dye assay.^[122]

Formation of linear PMMA and poly(AN) (PAN) in textile fibres using Fenton chemistry was first reported by Lipson and Speakman.^[123]

A cascade approach consisting of GOx deoxygenation and Fenton chemistry initiation has been employed for the FRP of 2-hydroxyethyl methacrylate (HEMA).^[124] GOx can be found in various commercial applications such as: (1) glucose removal from dried egg, (2) enhancement of materials shelf life used in the food industry, (3) oxygen removal from fruit juices or canned beverages, and (4) biosensors for the detection/estimation of glucose level in industrial solutions and in blood.^[125] The high stability, robustness and activity of GOx have recently attracted the attention of polymer chemists for radical polymerization.^[124, 126-128] GOx oxidizes DG to D-gluconic acid (DGA) in the presence of molecular oxygen, generating H₂O₂ (**Scheme 3**).^[124, 125]

Scheme 3. a) Representation of H₂O₂ production from GOx/DG/oxygen redox system, and b) Oxidation process of DG and production of DGA in the solution.^[125]

The produced H₂O₂ is then reduced (decomposed) to hydroxyl radicals by Fe²⁺, initiating the polymerization.^[99, 124] Iwata and co-workers reported for the first time the FRP of HEMA using this cascade methodology at 37 °C, claiming that polymerization did not proceed in the absence of dissolved oxygen and Fe²⁺ ions. When the reaction solution was exposed to oxygen (air) or Fe²⁺, the polymerization began spontaneously (**Figure 1**).^[124]

Figure 1. Influence of a) oxygen and b) Fe^{2+} ions on the polymerization of HEMA in the presence and absence of each. The arrows indicate the introduction of air (in part a) and Fe^{2+} (in part b) into the reaction mixture. In the first 60 minutes in the absence of oxygen (part a, solid circles), and 90 minutes in the absence of Fe^{2+} (part b, hollow circles), polymerization did not start.^[124]

4. Applications of Fenton reaction–initiated FRP

Fenton–mediated FRP has been used in a wide range of applications such as template polymerization, bioelectrocatalysis, and graft copolymerization.^[101, 129-132] Fenton chemistry has been extensively employed as a redox initiation system in the graft copolymerization of vinyl monomers (e.g. MMA, acrylamide, vinyl acetate, etc.) onto natural substrates such as chitosan, starch, cellulose, lignosulfonates, viscose, wool, and cotton. It was observed that the graft yield increased with increasing H_2O_2 concentration up to an optimal concentration.^[133-142] It has been suggested that hydroxyl radicals formed via the Fenton reaction abstract hydrogen atoms from cellulose, which is a key point for grafting to occur in the presence of vinyl monomers.^[101] A failure in obtaining grafting polymerization onto starch with an azo initiator (i.e., azobisisobutyronitrile (AIBN)) was reported by Brockway and Moser,^[143] further verifying that grafting happens chiefly as the result of an attack on the starch by hydroxyl radicals formed via the Fenton reaction. The effect of temperature (from 25 °C to 45 °C) on a graft copolymerization system of poly(vinyl acetate) onto wool was investigated in detail by Misra and co-workers, showing that high temperatures leads to a maximum degree of

grafting.^[144] The Fenton reaction was reported to be more effective than FAS/KPS in the graft copolymerization of ethyl acrylate onto cellulose.^[145] In an aqueous graft copolymerization of MMA onto lignosulphonate, it was observed that polymerization for 100 minutes at a temperature of 30 °C was sufficient to achieve 80% monomer conversion and 60% grafting efficiency.^[141] A study on template polymerization of acrylic acid (AA) by means of Fenton chemistry showed an initiator complexation, where the presence of the template (either poly(vinyl pyrrolidone) or *N*-methyl pyrrolidone) dramatically decreased the polymerization rate.^[130] Polymerized methylacryloyl surfactant vesicles with different sizes ranging from 120 to 260 nm, which can potentially be used as carriers of therapeutic agents,^[146] were synthesized in aqueous solution at room temperature using the Fenton reaction.^[147]

FRP initiated by the GOx/DG/Fe²⁺ system via the Fenton reaction has been extensively employed to design and fabricate hydrogels and micro/nanogels.^[148] In a study from Bowman and co-workers in 2009^[99] polymerization of hydrogels using GOx/DG/Fe²⁺ (a cascade of GOx deoxygenation and the Fenton reaction) for cellular encapsulation was reported. The cascade initiation system was used for the encapsulation of NIH-3T3 fibroblasts into a 15 wt% poly(ethylene glycol) tetra-acrylate ($M_n \sim 20$ kDa) hydrogel scaffold. This work was a notable shift away from light-mediated hydrogel synthesis, which potentially has limitations in clinical applications in terms of light penetration, to a biocompatible, enzymatic chain initiation reaction.^[99] In their extensive studies on the GOx/DG/Fe²⁺ cascade, Bowman also demonstrated the use of Fenton-mediated FRP for bio-detection applications.^[149, 150] The GOx/DG/Fe²⁺-mediated FRP was employed to detect proteins in an enzyme-linked immunorbent assay (ELISA) substrate-style immunoassay, where immobilized GOx was coupled with antigen recognition through a biotin-avidin linkage as a dual-mode amplification strategy. The formation of the polymer was qualitatively observed visually and quantitatively measured by a plate reader. It was also demonstrated that at the lowest GOx concentration, the substrate formulations are highly sensitive to the concentration of both DG and Fe²⁺ (**Figure 2a**). Dependency of GOx and H₂O₂ decomposition on the pH of the reaction solution was also shown.^[149]

A similar GOx/DG/Fe²⁺ system was used to fabricate capillary-flow microfluidic valves that responded to a target antigen by blocking a microfluidic channel via rapid hydrogelation (**Figure 2b**).^[150] This stimuli-responsive channel blockage changed the fluid flow in the device leading to a binary signal that was detected through an instrument-free detection process (i.e., little or no supplemental diagnostic equipment), a feature promising for potential deployment in low-infrastructure diagnostic sites.^[150]

Pedrosa and co-workers applied the capability of the Fenton-FRP with a combination of a sensor platform in the fabrication of plasmonic nanobiosensors to detect DG levels in solution. Chain reaction amplification mechanisms for transducing chemical signals, which were released in biocatalytic reactions, were explored in detail. With a simple design, such sensors consisted of gold nanoparticles (AuNPs) covered on the surface of a grafted poly(2-vinylpyridine) (P2VP) film.^[151] The biosensor was prepared by grafting carboxyl-terminated P2VP onto the surface of glass slides functionalized with 3-glycidyloxypropyl-trimethoxysilane. The thickness of the formed polymer layer was estimated as 7±1 nm. Afterwards, citrate-stabilized AuNPs were absorbed by the surface of the brush.^[152] The DG sensing was carried out in the presence of monomer (MAA), Fe²⁺ ions, and GOx. The DG detection mechanism is based on the FRP of MAA. By blending PMAA and P2VP, a swollen grafted polymeric thin film led to a displacement of AuNPs in relation to their initial positions, therefore altering their plasmonic coupling. Simultaneously, the P2VP-PMAA polyelectrolyte complex formation led to a change of dielectric constant of the medium. Both factors together contributed to affect the AuNPs' plasmon resonance spectrum, observable as a redshift in the absorbance band (**Figure 2c**).^[151]

The GOx/DG/Fe²⁺-generated hydroxyl radicals have also been used to initiate radical-mediated thiol-ene reactions or synthesis of hydrogels. Such hydrogels were synthesized by exposing aqueous solutions of multi-functional thiol and allyl ether PEG monomers, along with the GOx/DG/Fe²⁺ combination, to oxygen (air). Although this system could effectively initiate the reaction after exposure to O₂, the polymerization rate did not increase with increasing Fe²⁺ concentrations owing to

inhibitory reactions. On the other hand, when Fe^{2+} was replaced with horseradish peroxidase the reaction was not subject to iron-mediated inhibitory reactions.^[153]

Figure 2. GOx/DG/ Fe^{2+} -mediated FRP systems for signal amplification and biosensors: a) Schematic approach to dual-mode signal amplification and biodetection;^[149] b) Molecular schematic depicting a competitive GOx-linked immunoassay with FRP-based detection. A simple visual readout of polymerized hydrogel in a microchannel provides an equipment-free readout for a protein biosensor;^[150] c) The optical resonance of AuNPs in response to polymeric layer formation provides an additional non-linear signal amplification mechanism to further boost sensitivity in the biosensors.^[151]

Fluorescent hydrogels with entrapped *Escherichia coli* cells were synthesized using the GOx/DG/ Fe^{2+} reaction cascade for the FRP of poly(ethyleneglycol) diacrylate (PEGDA) together with a fluorescent monomer (i.e., Polyfluor 570) via a fluorescent polymer shell (fur-shell) technology for

high-throughput screening of hydrolytic enzymes (**Figure 3**). Active cell population with five-time enrichment analyzed through flow cytometry analysis was reported. The performance of the fur-shell technology was validated by directed *Yersinia mollaretii* phytase (YmPh) evolution, which attained enhanced variants starting from a library containing 10^7 phytase variants and improved active population up to 89%. Such fur-shell technology represented a simple and rapid approach of identifying the most active variants from vast populations, as well as a platform for fabrication of polymer-hybrid cells for interactive biomaterials.^[154] Introduced by Nash and co-workers,^[155, 156] fluorescent hydrogels synthesized through the Fenton chemistry-mediated FRP process, were also employed for detecting and imaging the degradation (or hydrolysis) of cellulosic substrates.

Figure 3. Fur-shell technology using a GOx/DG/Fe²⁺ system, leading to formation of a fluorescent hydrogel shell: a) Glucose-6-phosphate is hydrolyzed by YmPh, releasing DG and inorganic phosphate; b) Generated DG is converted by GOx to DGA, producing H₂O₂, and accordingly in the presence of Fe²⁺, hydroxyl radicals; c) In the presence of these highly reactive radicals, PEGDA, 1-vinyl-2-pyrrolidone, and Polyfluor 570 (responsible for the fluorescence feature) polymerize and generate fluorescent hydrogels around *Escherichia coli* cells that express active YmPh variants.^[154]

Temperature-responsive poly(*N*-vinylcaprolactam) (PVCL) microgels have been recently synthesized with the GOx/DG/Fe²⁺ system in the presence of air (**Figure 4a**). A comparison between these microgels with ones made by a conventional azo initiator (i.e., 2,2'-azobis(*N*-(2-carboxyethyl)-2-methylpropionamidine) tetrahydrate (ACMA)) through reaction calorimetry illustrated that the rate of polymerization in the thermally-initiated reaction was higher compared to the enzymatically-initiated system, leading to lower polymer yields within the GOx/DG/Fe²⁺-mediated process (**Figure 4b**). Higher crosslinker concentrations led to higher polymer yields.^[157] The GOx/DG/Fe²⁺ system has also been used for the synthesis of poly(*N*-isopropylacrylamide) (PNIPAM)-DNA polymer films, which show pH-, SO₄²⁻-, and temperature-sensitive cyclic voltammetry (CV) and electrochemiluminescence (ELC) behavior toward tris(2,2'-bipyridine)ruthenium(II) (Ru(bpy)₃²⁺) in solution. This has been exploited to fabricate biomolecular logic devices.^[158]

Figure 4. a) Schematic illustration of enzymatic Fenton-reaction-initiated PVCL microgel synthesis; b) AFM images of PVCL microgels with different mole fractions of crosslinker (i.e., *N,N'*-methylenebisacrylamide (BIS)).^[157]

The kinetics of interfacial polymerization initiated by the GOx/DG/Fe²⁺ system were initially reported by Bowman and his group.^[113, 159] They explored the formation of 3D hydrogel multilayers at ambient conditions,^[159] where micrometer-scale, conformal, and uniform PEG-based hydrogel layers were polymerized within a few seconds. Introduction and incorporation of small molecules including fluorescein acrylate and fluorescent nanoparticles into crosslinked hydrogel layers during the FRP

reaction was investigated. The encapsulation of 0.2 μm -diameter nanoparticles into hydrogels during the Fenton-mediated FRP of 2-hydroxyethyl acrylate (HEA)/PEG(575) diacrylate (PEGDA₅₇₅) formulation caused minimum effects on reaction kinetics, with final acrylate conversions of $\sim 95\%$ attained within minutes. Combining photoinitiation with the GOx-mediated dip coating led to the temporal and spatial control, resulting in the polymerization of uniform secondary layers. Moreover, an increase in the PEGDA₅₇₅ fraction within the initial hydrogel substrate decreased the subsequent layer thicknesses because of lowered DG concentrations at the interface.^[159] In their subsequent work,^[113] they coated PEGDA₅₇₅ on hydrogel cores (made of PEGDA₅₇₅ synthesized in a cylindrical mold) immersed in an aqueous solution comprising of 15 wt% PEGDA₅₇₅, 0.005 wt% rhodamine-B acrylate, 3.1 μM GOx, and various concentrations of DG and Fe^{2+} (**Figure 5a**). The hydrogel core acted as a template, spatially confining DG prior to the FRP initiated via the Fenton reaction. Therefore, the location of DG was initially at the hydrogel boundary but is subsequently delocalized due to the rapid diffusion of DG into the bulk media. The rapid mass transport of the $\text{HO}^\bullet$ radicals resulted in the polymerization zone extending well into the bulk, thereby leading to conformal coatings that are several hundreds of micrometers thick, as also proved by previous studies.^[159] On the contrary, to accomplish such thickness is quite difficult by using conventional or other interfacial radical polymerizations that confine the initiator to the surface/interface primarily due to the very short lifetime of radicals, and thus, have considerably smaller diffusion length scales.^[160-162] The thickness of the formed film on the hydrogel core increased with polymerization time and an increase in hydroxyl radical concentration. Moreover, it was demonstrated that there are concentration thresholds for DG and Fe^{2+} above which no change in the film thickness was observed (**Figure 5b & c**). While the interfacial polymerization was allowed to continue for longer times, higher Fe^{2+} concentrations resulted in lower film thickness because the distance of H_2O_2 diffusion within the coating was significantly limited to the interface.^[113] The strict control of layer thicknesses combined with the Fenton-mediated FRP will benefit applications demanding the formation of 3D stratified and complex polymer-based structures.

Figure 5. Schematic illustration of the formation of a coating on hydrogel cores via interfacial polymerization initiated via Fenton chemistry. The polymerization initially occurs in the vicinity of the hydrogel core boundary, although it becomes delocalized due to the rapid diffusion of DG; b) Film thickness variation with the square root of DG concentration, and c) Fe^{2+} concentration after 1 min of immersion to form the coating layer.^[113]

Bowman and co-workers pushed the limits of GOx/DG/Fe²⁺-mediated interfacial polymerization by designing and forming core-shell particles which differs from previous studies^[113, 159] as self-supporting shell in the absence of a core was introduced.^[114] This study was concentrated on engineering the FRP reaction behavior and mass transport processes to promote an interfacially limited FRP process, controlling the shell formation rate and the structure of the core-shell particle. Shell formation on prefabricated polymeric hydrogel cores (i.e., formed of poly(PEGDA₅₇₅)) was

obtained by localizing the initiation reaction to the interface of the core and a surrounding aqueous monomer formulation into which it is immersed. The interfacially confined initiation reaction is accomplished by incorporating one or more of the initiating species in the particle core and the remainder of the complementary initiating components in the surrounding media such that interactions and the resulting initiation reaction occur at the interface. Likewise, the polymeric shell coated on the core by this technique was illustrated to be self-supporting following core degradation. Such phenomenon was achieved by fabricating the hydrogel core from degradable group-containing monomers (poly(ethylene glycol) diphotodegradable-acrylate (PEGdiPDA) and poly(ethylene glycol) tetrathiol (PEG4SH)), which could be irreversibly cleaved by light exposure following shell formation.^[114]

5. RAFT polymerization initiated by the Fenton reaction

In the last two years, the power of Fenton chemistry has utilised to initiate chemically- and biologically-activated RAFT polymerizations by Qiao and co-workers.^[76-78, 109, 163] The first example reported on the initiation of a RAFT process by using ammonium ferrous sulphate (i.e., source of Fe^{2+}) and H_2O_2 (**Figure 6a**), and was termed as Fenton-RAFT polymerization.^[76] The resultant aqueous Fenton-RAFT process at ambient temperature was easy to set up and ultrafast so that high monomer conversions (~ 70%) were achieved within just 1 minute. Prior to this, several approaches to increase the rate of RAFT polymerization had been taken, including the use of high reaction temperatures,^[164] fast photoinitiators,^[165] and the use of microwave reactor technology.^[166] The use of flow chemistry is also particularly beneficial in this regard,^[167] and some early studies appear promising for increasing the reaction kinetics of RAFT polymerizations.^[168] However, these do not represent a step-change in the choice of initiation pathway, but rather an enhancement of traditional techniques. As the chain transfer coefficients of the RAFT agents commonly employed have been demonstrated to be extremely high - indicating a rapid degenerative chain transfer – Qiao and co-workers were interested in testing whether the system was robust enough to handle an extremely rapid flux of radicals.^[76] Using a symmetrical RAFT agent (**Figure 6b**), different water-soluble monomers (i.e., *N,N*-dimethylacrylamide (DMA), *N*-acryloylmorpholine (NAM), and HEA) were polymerized

successfully with low dispersity ($D < 1.1$) and experimental number-averaged molecular weights (M_n) matching with theoretical values (**Figure 6c–e**). Full monomer conversion values were also achieved within 15 minutes when higher concentrations of H_2O_2 (i.e., 17 and 19 mM) were employed. The optimum concentrations of the Fenton reagents were found to be $[H_2O_2]_0 \sim 11$ mM and $[Fe^{2+}]_0 \sim 3.3$ mM within DMA polymerization, i.e., an H_2O_2 to Fe^{2+} ratio of ~ 3.3 , as reported by previous studies.^[111] This ratio agrees well with previously reported observations in the literature.^[169] It is generally accepted that both the ratio $[H_2O_2]_0/[Fe^{2+}]_0$, and $[Fe^{3+}]_0/[Fe^{2+}]_0$ play a crucial role to ensure the efficient production of $HO^\bullet$ radicals while minimizing “wasting” reactions (i.e., Equations 3-5).^[76, 90, 97, 111, 170] To determine the living character of the synthesized polymers, chain extension and aminolysis experiments, along with the synthesis of polymers with different chain lengths were executed. The Fenton-RAFT process was also demonstrated to be relatively tolerant towards air or dissolved oxygen, however, the resulting SEC chromatograms were broadened compared with the degassed case.^[76] Fenton-RAFT represented an interesting new approach for the rapid synthesis of controlled, “living” polymers using cheap and relatively benign reagents. The aqueous conditions and rapid reaction times make this technique of particular and great interest in the development of high-throughput or machine-programmable synthesis of polymers required for biomedical applications.^[171-173]

Figure 6. a) Fenton chemistry initiation system for RAFT polymerization; b) Structures of water-soluble monomers (M) and CTA (RAFT agents) employed in this study; SEC chromatograms of the synthesized polymers obtained from different monomers, i.e., c) DMA, d) NAM and e) HEA, using Fenton-RAFT process, where $[M]/[CTA]/[H_2O_2]/[Fe^{2+}] = 200:1:0.5:0.15$ for DMA case, and $200:1:0.23:0.07$ for NAM and HEA.^[76]

Following our investigations into Fenton redox chemistry for RAFT polymerization, we were motivated to explore alternative, biological Fenton reagents which may enable polymerization in more biologically-friendly environments. GOx is a well-known enzyme for the removal of dissolved oxygen in RDRPs,^[74, 174] and generates H_2O_2 as a by-product. We therefore demonstrated that a Fenton-RAFT polymerization can be activated by the GOx-generated H_2O_2 , and the iron-containing protein haemoglobin (Hb).^[77, 175] This biological cascade reaction was termed Bio-Fenton-RAFT (**Figure 7a**). **Figure 7b** illustrates the structures of employed water-soluble CTAs and monomers in this work. This Bio-Fenton-RAFT polymerization followed pseudo-first order kinetics with regards to monomer conversion up to near-quantitative values in non-degassed reaction mixtures (**Figure 7c**).

The resultant linear polymers showed very narrow dispersities ($\bar{D} < 1.1$) and molecular weights in agreement with their theoretical values (Figures 7d & e).

Figure 7. a) Proposed mechanism of an “enzyme-assisted” initiation system to generate a reactive hydroxyl radical requisite for initiating a RAFT polymerization. GOx is employed for the in situ conversion of dissolved oxygen to H_2O_2 in the presence of DG. H_2O_2 can then be coupled with Hb (either commercial or native) to generate hydroxyl radicals; b) chemical structures of acrylamide, acrylate, and methacrylate-type monomers and CTAs found to be effective in the Bio-Fenton RAFT system;^[77] c) kinetic study of DMA polymerization via Bio-Fenton RAFT process within 8 h; d) M_n and $\bar{D}$ values of the PDMA synthesized within 8 h of polymerization; e) SEC chromatogram of the PDMA formed after 8 h in such a system.

When the solvent (water) was replaced with various biological fluids (e.g., bovine and human serums), the reaction maintained its efficiency, demonstrating the high tolerance of this polymerization system towards dissolved species.^[77] The Bio-Fenton-RAFT system, therefore, offers

intriguing opportunities for *in situ* radical generation and subsequent “blood-catalyzed” polymerization reactions. Replacing the isolated Hb with *native* red blood cells (contained within an unprocessed sample of bovine blood, which was used as the solvent), we observed that the red blood cells could act directly as catalysts for this polymerization system. It was noticed that polymerization in water was successful, while no monomer conversion was observed in phosphate buffered saline (PBS). This was ascribed to the lysis of the blood cells in RO water (unbuffered water) because of an osmotic pressure which led to the release of hemoglobin into the reaction solution, increasing its availability for subsequent reaction with H_2O_2 . Optical microscopy (**Figure 8**) further demonstrated and confirmed the cell lysis under these conditions. Taken together, the results indicated that the content of red blood cells could be exploited as precursors for Fenton reaction-mediated radical polymerization.

Figure 8. Microscopic images of erythrocytes (red blood cells) obtained from a sheep blood sample: a) original; b) diluted in PBS buffer solution before BioRAFT polymerization; c) diluted in RO water before Bio-Fenton-RAFT polymerization; and d) after Bio-Fenton-RAFT polymerization of DMA in RO water.^[77]

Inspired by the dual catalyst system (GOx/Hb) employed in the Bio-Fenton-RAFT process, which provided controlled generation of hydroxyl radicals throughout the polymerization, we attempted dosing H₂O₂ gradually and continuously into the reaction solution using a syringe pump to *in situ* produce hydroxyl radicals. This methodology allowed for the synthesis of well-defined polymers with low dispersity values and quantitative monomer conversions using a standard Fenton-RAFT system.^[109] This demonstrates that by restricting the immediate flux of initiating radicals and ensuring sustained radical generation via a semi-batch Fenton-RAFT process over tunable time periods, metered H₂O₂ addition decreases the unwanted radical “wasting” reactions (i.e., Equations 3-5) and provides access to consistent full conversions with high chain-end fidelity.^[109] The concept of slow production of hydroxyl radicals led us to successfully synthesize extremely large polymers with unprecedented ultra-high molecular weight (UHMW) values up to 20×10^6 Da within a few hours (~6 h) via a Semi Bio-Fenton-RAFT process (i.e., Hb was replaced by ammonium ferrous sulphate to expedite the reaction).^[78] Under optimized catalyst concentrations ($[\text{GOx}]_0 = 250$ nM, $[\text{DG}]_0 = 100$ mM, and $[\text{Fe}^{2+}]_0 = 1$ mM), chain extension experiment furnished UHMW pseudo-triblock copolymers with $M_w \sim 2 \times 10^6$ Da and showed a monomodal polymer peak and narrow molecular weight distribution *via* SEC/LS analysis. This effect highlights the benefit of a catalytic system compared with a pure redox system due to the ability to continuously regenerate initiating components. By mimicking the GOx/DG system, a fixed amount of H₂O₂ (14.5 μ M) was injected into the reaction mixture within 1 hour using a syringe pump to make controlled UHMW polymers with $M_w \sim 1 \times 10^6$ Da. It was shown that the controlled addition of initiating radicals could lead to the synthesis of predefined UHMW polymeric materials via other RAFT processes.

The residual of employed catalysts (i.e., ammonium ferrous sulphate and Hb) is the main challenge in all above-mentioned Fenton-RAFT processes. To overcome this issue, our group aimed to

heterogeneously catalyze Fenton-RAFT polymerization using Fe^{2+} metal-organic framework (MOF) particles (**Figure 9a**).^[110] **Figure 9b** shows the structures of employed water-soluble CTAs and monomers in this work. Under optimum conditions ($[\text{Fe}^{2+}\text{-MOF}] = 0.4 \text{ mg mL}^{-1}$ and $[\text{H}_2\text{O}_2] = 35 \text{ mM}$), we demonstrated the stability and the recyclability of the MOF particles within the MOF-Fenton-RAFT polymerization by characterization of used particles and recycling experiments. The chemical valence of iron in our MOF particles before and after polymerization examined by X-ray photoelectron spectroscopy (XPS) were almost identical (**Figure 9c**), manifesting that the structure of Fe(II)-MOF was hardly altered during the RAFT polymerization. The $\text{Fe } 2p_{1/2}$ and $\text{Fe } 2p_{3/2}$ peaks of Fe(II)-MOF particles before and after polymerization are centered at 724.6 (722.4) eV and 710.8 (709.9) eV, respectively, which are consistent with Fe(II) species. In the recycling experiments, the MOF particles were readily removed and recovered by centrifugation after 30 min, followed by removal of the solvent, and reused under the same conditions as the first run (i.e., $[\text{DMA}] = 5 \text{ M}$, $[\text{H}_2\text{O}_2] = 35 \text{ mM}$, and $[\text{Fe}^{2+}\text{-MOF}] = 0.4 \text{ mg mL}^{-1}$). The MOF particles' catalytic activity was maintained after 5 consecutive runs of polymerization (**Figure 9d**), indicating good reusability. After half an hour monomer conversion and molecular weight values were almost constant in each cycle.

Figure 9. a) Proposed mechanism for MOF-Fenton RAFT polymerization; b) Chemical structures of monomers and CTAs employed in the MOF-Fenton RAFT system;^[110] c) XPS spectra of Fe(II)-MOF particles before and after polymerization; d) Monomer conversion after 30 min via the recycling runs of MOF particles via the MOF-Fenton-RAFT polymerization.

6. Conclusions and Future Outlook

Highly reactive hydroxyl radicals generated via chemically- and biologically-activated Fenton chemistry have been utilised to initiate FRP and RAFT processes. However, only the Fenton-mediated FRP system has been used in a wide variety of applications such as graft copolymerization, interfacial polymerization for the synthesis of hydrogels, and biodetection. Most recently, the Fenton reaction was employed to initiate RAFT polymerization either chemically (i.e., Fenton-RAFT activated by H_2O_2 and inorganic Fe^{2+} salts) or biologically (i.e. Bio-Fenton-RAFT activated by GOx and Hb or native red blood cells) in the presence

of oxygen (air). Future outlook for this research field could be focused on the following aspects:

1. Due to fast Fenton-mediated RAFT processes, compared to other rapid RAFT processes which need elevated temperatures or elaborate reaction conditions, programmable and automation-driven synthesis of libraries of well-controlled polymers with high chain-end fidelity become possible. This can include *in situ* polymerization in bio-related medium. Although the rate of the chemically activated Fenton-RAFT polymerization is faster than the conventional RAFT methods, highly exothermic nature of the Fenton reaction in high concentration of Fenton reagents can result in the evaporation and loss of volatile monomers like *N,N*-dimethylacrylamide. This will lead to the experimental molecular weights much lower than theoretical values at eliminate full monomer conversion values.
2. Conducting Fenton-RAFT in organic solvent with common monomers. The Fenton-RAFT process catalyzed by the heterogeneous catalysts (i.e., Fe(II)-MOF particles) can lead to the simple removal of the catalyst residuals at the end of reaction, and the polymerization of water-insoluble monomers (e.g., methyl acrylate, methyl methacrylate, styrene etc.) in organic solvents become possible.
3. With careful control of level of radical formation, high chain end fidelity can be achieved. Example of ultra high molecular weight polymer by Fenton RAFT is due to the high chain end fidelity. This will also make full conversion of monomers achievable. Due to such good control varied polymeric architecture will be expected by the Fenton-RAFT technique, either chemically or biologically activated, allow for a wide range of tailored structures and compositions for prospective applications, especially biomedical systems.

Overall, depending on the type of application and its required reaction conditions and outputs, a suitable Fenton-RAFT method can be selectively chosen.

Acknowledgements

A. R. is supported by the Melbourne International Research Scholarship (MIRS) and the Melbourne International Fee Remission Scholarship (MIFRS).

Conflict of Interest

The authors declare no conflict of interest.

Received: Month XX, XXXX; Revised: Month XX, XXXX; Published online:

Keywords

Fenton chemistry, free radical polymerization, hydroxyl radicals, RAFT polymerization

References

- [1] D. Colombani, *Progress in Polymer Science* **1997**, 22, 1649.
- [2] H. Gruber, *Progress in polymer Science* **1992**, 17, 953.
- [3] J. Shukla, D. Misra, *Journal of Polymer Science Part A: Polymer Chemistry* **1973**, 11, 751.
- [4] Y.-X. Liu, H.-M. Ma, Y. Liu, J.-J. Qiu, C.-M. Liu, *Polymer* **2016**, 82, 32.
- [5] L. Brocken, P. D. Price, J. Whittaker, I. R. Baxendale, *Reaction Chemistry & Engineering* **2017**, 2, 662.
- [6] D. Braun, *International Journal of Polymer Science* **2009**, 2009, 1.
- [7] A. Ravve, "Free-Radical Chain-Growth Polymerization", in *Principles of Polymer Chemistry*, Springer, 2012, p. 69.
- [8] K. Matyjaszewski, "Fundamentals of Controlled/Living Radical Polymerization", in *Encyclopedia of Radicals in Chemistry, Biology and Materials*, John Wiley & Sons, Ltd, 2012.
- [9] A. V. Tobolsky, *Journal of the American Chemical Society* **1958**, 80, 5927.
- [10] T. Otsu, M. Yoshida, T. Tazaki, *Die Makromolekulare Chemie, Rapid Communications* **1982**, 3, 133.
- [11] G. Moad, E. Rizzardo, S. H. Thang, *Australian Journal of Chemistry* **2012**, 65, 985.
- [12] Q. Zhang, Z. Zhang, W. Wang, J. Zhu, Z. Cheng, N. Zhou, W. Zhang, X. Zhu, *Journal of Polymer Science Part A: Polymer Chemistry* **2012**, 50, 1424.
- [13] J.-S. Wang, K. Matyjaszewski, *Macromolecules* **1995**, 28, 7901.
- [14] P. Krys, K. Matyjaszewski, *European Polymer Journal* **2017**, 89, 482.
- [15] K. Matyjaszewski, J. Xia, *Chemical reviews* **2001**, 101, 2921.
- [16] C. J. Hawker, A. W. Bosman, E. Harth, *Chemical Reviews* **2001**, 101, 3661.
- [17] J. Chiefari, Y. Chong, F. Ercole, J. Krstina, J. Jeffery, T. P. Le, R. T. Mayadunne, G. F. Meijs, C. L. Moad, G. Moad, E. Rizzardo, S. H. Thang, *Macromolecules* **1998**, 31, 5559.
- [18] G. Moad, E. Rizzardo, S. H. Thang, *Australian Journal of Chemistry* **2012**, 65, 985.
- [19] V. Nikolaou, A. Anastasaki, F. Alsubaie, A. Simula, D. J. Fox, D. M. Haddleton, *Polymer Chemistry* **2015**, 6, 3581.
- [20] A. Anastasaki, V. Nikolaou, Q. Zhang, J. Burns, S. R. Samanta, C. Waldron, A. J. Haddleton, R. McHale, D. Fox, V. Percec, *Journal of the American Chemical Society* **2014**, 136, 1141.

- [21] E. P. Magennis, F. Fernandez-Trillo, C. Sui, S. G. Spain, D. Bradshaw, D. Churchley, G. Mantovani, K. Winzer, C. Alexander, *Nature materials* **2014**, *13*, 748.
- [22] T. B. Silva, M. Spulber, M. K. Kocik, F. Seidi, H. Charan, M. Rother, S. J. Sigg, K. Renggli, G. Kali, N. Bruns, *Biomacromolecules* **2013**, *14*, 2703.
- [23] B. Zhang, X. Wang, A. Zhu, K. Ma, Y. Lv, X. Wang, Z. An, *Macromolecules* **2015**, *48*, 7792.
- [24] J. Xu, K. Jung, A. Atme, S. Shanmugam, C. Boyer, *Journal of the American Chemical Society* **2014**, *136*, 5508.
- [25] P. Maximiano, P. V. Mendonça, J. o. R. Costa, N. L. Haworth, A. n. C. Serra, T. Guliashvili, M. L. Coote, J. F. Coelho, *Macromolecules* **2016**, *49*, 1597.
- [26] N. Haridharan, R. Dhamodharan, *Journal of Polymer Science Part A: Polymer Chemistry* **2011**, *49*, 1021.
- [27] Y. Gu, J. Zhao, Q. Liu, X. Pan, W. Zhang, Z. Zhang, X. Zhu, *Polymer Chemistry* **2015**, *6*, 359.
- [28] M. Kopeć, P. Kryś, R. Yuan, K. Matyjaszewski, *Macromolecules* **2016**, *49*, 5877.
- [29] L. Martin, G. Gody, S. Perrier, *Polymer Chemistry* **2015**, *6*, 4875.
- [30] M. R. Hill, R. N. Carmean, B. S. Sumerlin, *Macromolecules* **2015**, *48*, 5459.
- [31] M. Roa-Luna, G. Jaramillo-Soto, P. V. Castañeda-Flores, E. Vivaldo-Lima, *Chemical Engineering & Technology* **2010**, *33*, 1893.
- [32] T. G. McKenzie, Q. Fu, M. Uchiyama, K. Satoh, J. Xu, C. Boyer, M. Kamigaito, G. G. Qiao, *Advanced Science* **2016**, *3*.
- [33] S. Shanmugam, J. Xu, C. Boyer, *J Am Chem Soc* **2015**, *137*, 9174.
- [34] T. G. McKenzie, Q. Fu, E. H. Wong, D. E. Dunstan, G. G. Qiao, *Macromolecules* **2015**, *48*, 3864.
- [35] R. Nicolaÿ, Y. Kwak, *Israel Journal of Chemistry* **2012**, *52*, 288.
- [36] D. J. Keddie, G. Moad, E. Rizzardo, S. H. Thang, *Macromolecules* **2012**, *45*, 5321.
- [37] N. V. Tsarevsky, B. S. Sumerlin, "Fundamentals of controlled/living radical polymerization", Royal Society of Chemistry, 2012.
- [38] B. D. Fairbanks, P. A. Gunatillake, L. Meagher, *Advanced drug delivery reviews* **2015**, *91*, 141.
- [39] M. R. Wood, D. J. Duncalf, P. Findlay, S. P. Rannard, S. Perrier, *Australian Journal of Chemistry* **2007**, *60*, 772.
- [40] L. Brocken, P. D. Price, J. Whittaker, I. R. Baxendale, *Reaction Chemistry & Engineering* **2017**, *2*, 662.
- [41] P. Garra, A. Caron, A. Al Mousawi, B. Graff, F. Morlet-Savary, C. I. Dietlin, Y. Yagci, J.-P. Fouassier, J. Lalevée, *Macromolecules* **2018**, *51*, 7872.

- [42] J. Xu, S. Shanmugam, H. Duong, C. Boyer, *Polym. Chem.* **2015**, 6, 5615.
- [43] S. Shanmugam, J. Xu, C. Boyer, *J. Am. Chem. Soc.* **2015**, 137, 9174.
- [44] S. Shanmugam, C. Boyer, *Journal of the American Chemical Society* **2015**, 137, 9988.
- [45] J. Xu, S. Shanmugam, C. Fu, K.-F. Aguey-Zinsou, C. Boyer, *Journal of the American Chemical Society* **2016**, 138, 3094.
- [46] F. S. Dainton, *The Journal of Physical Chemistry* **1948**, 52, 490.
- [47] F. S. Dainton, M. Tordoff, *Transactions of the Faraday Society* **1957**, 53, 666.
- [48] F. S. Dainton, M. Tordoff, *Transactions of the Faraday Society* **1957**, 53, 499.
- [49] M. Evans, M. Santappa, N. Uri, *Journal of Polymer Science* **1951**, 7, 243.
- [50] S. Kobayashi, H. Uyama, S. Kimura, *Chemical Reviews* **2001**, 101, 3793.
- [51] S. R. Zavada, T. Battsengel, T. F. Scott, *International journal of molecular sciences* **2016**, 17, 195.
- [52] N. Mita, S. i. Tawaki, H. Uyama, S. Kobayashi, *Macromolecular Bioscience* **2002**, 2, 127.
- [53] A. P. Danielson, D. B. Van Kuren, M. E. Lucius, K. Makaroff, C. Williams, R. C. Page, J. A. Berberich, D. Konkolewicz, *Macromolecular rapid communications* **2016**, 37, 362.
- [54] R. A. Derango, L.-c. Chiang, R. Dowbenko, J. G. Lasch, *Biotechnology techniques* **1992**, 6, 523.
- [55] H. Zheng, W. Bai, K. Hu, R. Bai, C. Pan, *Journal of Polymer Science Part A: Polymer Chemistry* **2008**, 46, 2575.
- [56] J. Luo, M. Li, M. Xin, W. Sun, *Macromolecular Chemistry and Physics* **2015**, 216, 1646.
- [57] M. Uhniat, R. Sikorski, L. Woroszilo, *Polymer Science USSR* **1981**, 23, 2622.
- [58] M. T. Taghizadeh, M. T. Salehi, *Iranian Journal of Polymer Science and Technology* **1995**, 4, 262.
- [59] W. Bai, L. Zhang, R. Bai, G. Zhang, *Macromolecular Rapid Communications* **2008**, 29, 562.
- [60] C. Ding, C. Fan, G. Jiang, X. Pan, Z. Zhang, J. Zhu, X. Zhu, *Macromol Rapid Commun* **2015**, 36, 2181.
- [61] M. Chen, M. Zhong, J. A. Johnson, *Chemical reviews* **2016**, 116, 10167.
- [62] S. ŞENEL, I.-Y. Belma, O. GÜVEN, *TURKISH JOURNAL OF CHEMISTRY* **1996**, 20, 62.
- [63] P. L. Nayak, S. Lenka, *Journal of Macromolecular Science-Reviews in Macromolecular Chemistry* **1980**, 19, 83.
- [64] A. Guinaudeau, S. Mazières, D. J. Wilson, M. Destarac, *Polymer Chemistry* **2012**, 3, 81.
- [65] J. Vandenbergh, B. Schweitzer-Chaput, M. Klussmann, T. Junkers, *Macromolecules* **2016**, 49, 4124.

- [66] G. Li, H. Zheng, R. Bai, *Macromolecular rapid communications* **2009**, *30*, 442.
- [67] K. Kempe, P. A. De Jongh, A. Anastasaki, P. Wilson, D. M. Haddleton, *Chemical Communications* **2015**, *51*, 16213.
- [68] P. A. De Jongh, A. Mortiboy, G. S. Sulley, M. R. Bennett, A. Anastasaki, P. Wilson, D. M. Haddleton, K. Kempe, *ACS Macro Letters* **2016**, *5*, 321.
- [69] A. M. Mahmoud, A. Rajakanthan, K. Kempe, *Polymer Chemistry* **2018**, *9*, 1562.
- [70] P. A. de Jongh, M. R. Bennett, G. S. Sulley, P. Wilson, T. P. Davis, D. M. Haddleton, K. Kempe, *Polymer Chemistry* **2016**, *7*, 6703.
- [71] O. Deane, J. Lovett, O. Musa, A. Fernyhough, S. Armes, *Macromolecules* **2018**, *51*, 7756.
- [72] A. Guinaudeau, O. Coutelier, A. I. Sandeau, S. p. Mazières, H. D. Nguyen Thi, V. Le Drogo, D. J. Wilson, M. Destarac, *Macromolecules* **2013**, *47*, 41.
- [73] Y. Lv, Z. Liu, A. Zhu, Z. An, *Journal of Polymer Science Part A: Polymer Chemistry* **2017**, *55*, 164.
- [74] R. Chapman, A. J. Gormley, K.-L. Herpoldt, M. M. Stevens, *Macromolecules* **2014**, *47*, 8541.
- [75] R. Chapman, A. J. Gormley, M. H. Stenzel, M. M. Stevens, *Angewandte Chemie* **2016**, *128*, 4576.
- [76] A. Reyhani, T. G. McKenzie, H. Ranji-Burachaloo, Q. Fu, G. G. Qiao, *Chemistry-A European Journal* **2017**, *23*, 7221.
- [77] A. Reyhani, M. N. Nothling, H. Ranji-Burachaloo, T. G. McKenzie, Q. Fu, S. Tan, G. Bryant, G. G. Qiao, *Angewandte Chemie International Edition* **2018**, *57*, 10288.
- [78] A. Reyhani, S. Allison-Logan, H. Ranji-Burachaloo, T. G. McKenzie, G. Bryant, G. G. Qiao, *Journal of Polymer Science Part A: Polymer Chemistry* **2019**.
- [79] K. Chemizmu, R. Fentona, *Ecological chemistry and engineering* **2009**, *16*, 347.
- [80] P. Wardman, L. P. Candeias, *Radiation research* **1996**, *145*, 523.
- [81] H. J. H. Fenton, *Journal of the Chemical Society, Transactions* **1894**, *65*, 899.
- [82] F. Haber, J. Weiss, *Proceedings of the Royal Society of London A: Mathematical, Physical and Engineering Sciences* **1934**, *147*, 332.
- [83] F. Haber, R. Willstätter, *Berichte der deutschen chemischen Gesellschaft (A and B Series)* **1931**, *64*, 2844.
- [84] P. V. Nidheesh, R. Gandhimathi, S. T. Ramesh, *Environmental Science and Pollution Research* **2013**, *20*, 2099.
- [85] C. Zhang, W. Bu, D. Ni, S. Zhang, Q. Li, Z. Yao, J. Zhang, H. Yao, Z. Wang, J. Shi, *Angewandte Chemie International Edition* **2016**, *55*, 2101.
- [86] L. Li, C. Zeng, L. Ai, J. Jiang, *Journal of Alloys and Compounds* **2015**, *639*, 470.

- [87] M. Barbeni, C. Minero, E. Pelizzetti, E. Borgarello, N. Serpone, *Chemosphere* **1987**, 16, 2225.
- [88] F. H.J.H., *Journal of the Chemical Society, Transactions* **1894**, 65, 899.
- [89] T. Rigg, W. Taylor, J. Weiss, *Journal of Chemical Physics* **1954**, 22, 575.
- [90] J. J. Pignatello, E. Oliveros, A. MacKay, *Critical reviews in environmental science and technology* **2006**, 36, 1.
- [91] G. Misra, U. Bajpai, *Progress in Polymer Science* **1982**, 8, 61.
- [92] W. Koppenol, *Free Radical Biology and Medicine* **1993**, 15, 645.
- [93] A. D. Bokare, W. Choi, *Journal of hazardous materials* **2014**, 275, 121.
- [94] J. C. Arthur Jr, O. Hinojosa, M. Bains, *Journal of Applied Polymer Science* **1968**, 12, 1411.
- [95] A. Y. Sychev, V. Isak, *Russian Chemical Reviews* **1995**, 64, 1105.
- [96] E. Karakhanov, S. Y. Narin, A. Dedov, *Applied organometallic chemistry* **1991**, 5, 445.
- [97] E. Neyens, J. Baeyens, *Journal of Hazardous materials* **2003**, 98, 33.
- [98] G. V. Buxton, C. L. Greenstock, W. P. Helman, A. B. Ross, *Journal of physical and chemical reference data* **1988**, 17, 513.
- [99] L. M. Johnson, B. D. Fairbanks, K. S. Anseth, C. N. Bowman, *Biomacromolecules* **2009**, 10, 3114.
- [100] P. Bautista, A. Mohedano, J. Casas, J. Zazo, J. Rodriguez, *Journal of Chemical Technology and Biotechnology* **2008**, 83, 1323.
- [101] A. Hebeish, J. T. Guthrie, "Grafting by Chemical Activation of Cellulose", in *The Chemistry and Technology of Cellulosic Copolymers*, Springer Berlin Heidelberg, Berlin, Heidelberg, 1981, p. 146.
- [102] M. L. Kremer, *Journal of Physical Chemistry A* **2003**, 107, 1734.
- [103] M. Kremer, *Physical Chemistry Chemical Physics* **1999**, 1, 3595.
- [104] H. Christensen, K. Sehested, T. Løgager, *Radiation Physics and Chemistry* **1993**, 41, 575.
- [105] K. M. Mostofa, C.-q. Liu, H. Sakugawa, D. Vione, D. Minakata, M. Saquib, M. A. Mottaleb, "Photoinduced generation of hydroxyl radical in natural waters", in *Photobiogeochemistry of Organic Matter*, Springer, 2013, p. 209.
- [106] S. Rachmilovich-Calis, A. Masarwa, N. Meyerstein, D. Meyerstein, R. van Eldik, *Chemistry – A European Journal* **2009**, 15, 8303.
- [107] J. Baxendale, M. Evans, C. Park, *Transactions of the Faraday Society* **1946**, 42, 155.
- [108] F. Dainton, P. Seaman, *Journal of Polymer Science* **1959**, 39, 279.
- [109] M. D. Nothling, T. G. McKenzie, A. Reyhani, G. G. Qiao, *Macromolecular rapid communications* **2018**, 39.

- [110] A. Reyhani, H. Ranji-Burachaloo, T. G. McKenzie, Q. Fu, G. G. Qiao, *Macromolecules* **2018**, *Accepted*.
- [111] A. Medalia, I. Kolthoff, *Journal of Polymer Science* **1949**, *4*, 377.
- [112] L. M. Johnson, B. D. Fairbanks, K. S. Anseth, C. N. Bowman, *Biomacromolecules* **2009**, *10*, 3114.
- [113] R. Shenoy, C. N. Bowman, *Biomaterials* **2012**, *33*, 6909.
- [114] R. Shenoy, M. W. Tibbitt, K. S. Anseth, C. N. Bowman, *Chemistry of Materials* **2013**, *25*, 761.
- [115] A. S. Sarac, *Progress in Polymer Science* **1999**, *24*, 1149.
- [116] M. K. Mishra, *Journal of Macromolecular Science-Reviews in Macromolecular Chemistry* **1981**, *20*, 149.
- [117] J. Baxendale, M. Evans, J. Kilham, *Transactions of the Faraday Society* **1946**, *42*, 668.
- [118] J. H. Baxendale, S. Bywater, M. G. Evans, *Transactions of the Faraday Society* **1946**, *42*, 675.
- [119] N. De, S. C. Mitra, S. Guchhait, R. S. Konar, *Indian Journal of Chemistry* **1995**, *34A*, 705.
- [120] J. Baxendale, M. Evans, J. Kilham, *Journal of Polymer Science* **1946**, *1*, 466.
- [121] W. Barb, J. Baxendale, P. George, K. Hargrave, *Transactions of the Faraday Society* **1951**, *47*, 462.
- [122] S. R. Palit, A. R. Mukherjee, *Journal of Polymer Science* **1962**, *58*, 1243.
- [123] M. Lipson, J. B. Speakman, *Nature* **1946**, *157*, 590.
- [124] H. Iwata, Y. Hata, T. Matsuda, Y. Ikada, *Journal of Polymer Science Part A: Polymer Chemistry* **1991**, *29*, 1217.
- [125] S. B. Bankar, M. V. Bule, R. S. Singhal, L. Ananthanarayan, *Biotechnology advances* **2009**, *27*, 489.
- [126] Y. Wang, L. Fu, K. Matyjaszewski, *ACS Macro Letters* **2018**, *7*, 1317.
- [127] D. K. Schneiderman, J. M. Ting, A. A. Purchel, R. Miranda Jr, M. V. Tirrell, T. M. Reineke, S. J. Rowan, *ACS Macro Letters* **2018**, *7*, 406.
- [128] J. Yeow, R. Chapman, A. J. Gormley, C. Boyer, *Chemical Society Reviews* **2018**, *47*, 4357.
- [129] B. Misra, R. Dogra, I. Kaur, J. Jassal, *Journal of Polymer Science Part A: Polymer Chemistry* **1979**, *17*, 1861.
- [130] J. Ferguson, A. Eboatu, *European Polymer Journal* **1989**, *25*, 731.
- [131] B. Misra, R. Dogra, I. Mehta, *Journal of Polymer Science Part A: Polymer Chemistry* **1980**, *18*, 749.
- [132] K. Zhang, W. Lian, S. Liu, H. Liu, *Journal of The Electrochemical Society* **2014**, *161*, H493.

- [133] M. M. El Awady, N. I. El-Awady, M. M. El-Din, *International Journal of Polymeric Materials* **2002**, 51, 1.
- [134] R. K. Samal, G. S. Giri, *Journal of Macromolecular Science, Part C: Polymer Reviews* **1992**, 32, 55.
- [135] S. Lenka, *Journal of Macromolecular Science, Part C: Polymer Reviews* **1982**, 22, 303.
- [136] M. K. Mishra, *Journal of Macromolecular Science, Part C: Polymer Reviews* **1982**, 22, 471.
- [137] A. Lagos, J. Reyes, *Journal of Polymer Science Part A: Polymer Chemistry* **1988**, 26, 985.
- [138] A. Hebeish, M. El-Rafie, E. Abdel Bari, A. El-Hussini, *Die Angewandte Makromolekulare Chemie: Applied Macromolecular Chemistry and Physics* **1980**, 88, 89.
- [139] C. E. Brockway, *Journal of Polymer Science Part A: Polymer Chemistry* **1964**, 2, 3721.
- [140] G. Richards, *Journal of Applied Polymer Science* **1961**, 5, 539.
- [141] C. Nam, T. Koshijima, E. Muraki, T. Maku, *Journal of Polymer Science Part A: Polymer Chemistry* **1971**, 9, 855.
- [142] M. S. Bains, "Inorganic redox systems in graft polymerization onto cellulosic materials", in *Journal of Polymer Science Part C: Polymer Symposia*, Wiley Online Library, 1972, p. 37/125.
- [143] C. Brockway, K. Moser, *Journal of Polymer Science Part A: Polymer Chemistry* **1963**, 1, 1025.
- [144] B. Misra, P. Chandel, R. Dogra, *Journal of Polymer Science Part A: Polymer Chemistry* **1978**, 16, 1801.
- [145] B. Misra, I. Mehta, R. Khetarpal, *Journal of Polymer Science Part A: Polymer Chemistry* **1984**, 22, 2767.
- [146] M. Reboiras, M. Jones, *Colloids and surfaces* **1991**, 57, 197.
- [147] M. Reboiras, G. Morris, M. Jones, *Colloids and Surfaces* **1990**, 49, 385.
- [148] X. Wang, S. Chen, D. Wu, Q. Wu, Q. Wei, B. He, Q. Lu, Q. Wang, *Advanced Materials* **2018**, 30, 1705668.
- [149] B. J. Berron, L. M. Johnson, X. Ba, J. D. McCall, N. J. Alvey, K. S. Anseth, C. N. Bowman, *Biotechnology and bioengineering* **2011**, 108, 1521.
- [150] B. J. Berron, A. M. May, Z. Zheng, V. Balasubramaniam, C. N. Bowman, *Lab on a Chip* **2012**, 12, 708.
- [151] L. C. Recco, I. Tokarev, S. Minko, V. A. Pedrosa, *Chemistry – A European Journal* **2014**, 20, 1226.
- [152] T. R. Antonio, M. F. Cabral, I. Cesarino, S. A. Machado, V. A. Pedrosa, *Electrochemistry Communications* **2013**, 29, 41.
- [153] S. Zavada, N. McHardy, T. Scott, *Journal of Materials Chemistry B* **2014**, 2, 2598.

- [154] C. Pitzler, G. Wirtz, L. Vojcic, S. Hiltl, A. Böker, R. Martinez, U. Schwaneberg, *Chemistry & biology* **2014**, *21*, 1733.
- [155] K. H. Malinowska, T. Verdorfer, A. Meinhold, L. F. Milles, V. Funk, H. E. Gaub, M. A. Nash, *ChemSusChem* **2014**, *7*, 2825.
- [156] K. H. Malinowska, T. Rind, T. Verdorfer, H. E. Gaub, M. A. Nash, *Analytical chemistry* **2015**, *87*, 7133.
- [157] E. Gau, F. Flecken, A. N. Ksiazkiewicz, A. Pich, *Green Chemistry* **2018**, *20*, 431.
- [158] T. Yang, J. Fu, S. Zheng, H. Yao, Y. Jin, Y. Lu, H. Liu, *Biosensors and Bioelectronics* **2018**, *108*, 62.
- [159] L. M. Johnson, C. A. DeForest, A. Pendurti, K. S. Anseth, C. N. Bowman, *ACS applied materials & interfaces* **2010**, *2*, 1963.
- [160] H. D. Sikes, R. R. Hansen, L. M. Johnson, R. Jenison, J. W. Birks, K. L. Rowlen, C. N. Bowman, *Nature materials* **2008**, *7*, 52.
- [161] D. Jiang, X. Huang, F. Qiu, C. Luo, L. L. Huang, *Macromolecules* **2009**, *43*, 71.
- [162] Y. Luo, H. Gu, *Macromolecular rapid communications* **2006**, *27*, 21.
- [163] T. G. McKenzie, A. Reyhani, M. D. Nothling, G. G. Qiao, "Hydroxyl Radical Activated RAFT Polymerization", in *Reversible Deactivation Radical Polymerization: Mechanisms and Synthetic Methodologies*, American Chemical Society, 2018, p. 307.
- [164] G. Gody, R. Barbey, M. Danial, S. Perrier, *Polymer Chemistry* **2015**, *6*, 1502.
- [165] Y. Shi, H. Gao, L. Lu, Y. Cai, *Chem. Commun.* **2009**, *11*, 1368.
- [166] D. Roy, A. Ullah, B. S. Sumerlin, *Macromolecules* **2009**, *42*, 7701.
- [167] T. Junkers, B. Wenn, *Reaction Chemistry & Engineering* **2016**, *1*, 60.
- [168] B. Wenn, T. Junkers, *Macromolecules* **2016**, *49*, 6888.
- [169] E. Brillas, I. Sirés, M. A. Oturan, *Chem. Rev.* **2009**, *109*, 6570.
- [170] A. Georgi, M. Velasco Polo, K. Crincoli, K. Mackenzie, F.-D. Kopinke, *Environmental Science & Technology* **2016**, *50*, 5882.
- [171] J. M. Ting, S. Tale, A. A. Purchel, S. D. Jones, L. Widanapathirana, Z. P. Tolstyka, L. Guo, S. J. Guillaudeu, F. S. Bates, T. M. Reineke, *ACS Central Science* **2016**, *2*, 748.
- [172] A. J. Gormley, J. Yeow, G. Ng, Ó. Conway, C. Boyer, R. Chapman, *Angewandte Chemie International Edition* **2018**, *57*, 1557.
- [173] S. Cosson, M. Danial, J. R. Saint-Amans, J. J. Cooper-White, *Macromolecular Rapid Communications* **2017**, *38*.

[174] F. Oytun, M. U. Kahveci, Y. Yagci, *Journal of Polymer Science Part A: Polymer Chemistry* **2013**, 51, 1685.

[175] S. Sadrzadeh, E. Graf, S. S. Panter, P. Hallaway, J. Eaton, *Journal of Biological Chemistry* **1984**, 259, 14354.

Amin Reyhani earned his B.Sc. in chemical engineering from Sahand University of Technology, Iran, in 2010. He completed his chemical engineering master's courses at Sharif University of Technology, Iran in 2012. He went on to complete his Ph.D. studies under the supervision of Prof. Greg Qiao and Dr. Qiang Fu at The University of Melbourne, Australia, class of 2019. His Ph.D. research focused on harnessing the power of a classical chemical reaction (i.e., Fenton reaction) in RAFT polymerization.

Qiang Fu received his B.E. in chemical engineering from the Shanghai Jiao Tong University in 2004. He completed his Ph.D. in polymer chemistry at Fudan University in 2009 before working as a postdoctoral fellow with Prof. Greg Qiao at the University of Melbourne. His research interests span from fundamental studies to applied sciences and encompass the fields of two-dimensional polymers, macromolecular engineering and self-assembly, and membrane materials for separations.

Greg Qiao received his Ph.D. at the University of Queensland in 1996. He joined the University of Melbourne in 1996 and became a full professor in 2009. He was an Australian Research Council's professorial Future Fellow (2012-2015) and the Chair of Polymer Division of the Royal Australia Chemical Institute (RACI) (2015–2016). His key research interests are in polymeric architectures, new activation methods for RAFT, peptide polymers, tissue scaffolds, and gas membranes.

The use of Fenton chemistry for traditional free radical and reversible addition–fragmentation chain transfer (RAFT) polymerizations have shown great promise in the synthesis of different types of polymers, and the fabrication of hydrogels and biomaterials. Herein, the power of the Fenton reaction for the initiation of various radical polymerization systems are discussed, and potential applications of the resulting materials highlighted.

RAFT Polymerization

Fenton-Chemistry-Mediated Radical Polymerization

A. Reyhani, T. G. McKenzie, Qiang Fu, G. G. Qiao*

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Reyhani, A;McKenzie, TG;Fu, Q;Qiao, GG

Title:

Fenton-Chemistry-Mediated Radical Polymerization

Date:

2019-09-01

Citation:

Reyhani, A., McKenzie, T. G., Fu, Q. & Qiao, G. G. (2019). Fenton-Chemistry-Mediated Radical Polymerization. *Macromolecular Rapid Communications*, 40 (18), <https://doi.org/10.1002/marc.201900220>.

Persistent Link:

<http://hdl.handle.net/11343/285981>