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Explaining Unexpected Data via Competitive Equilibria and Processes in Radical Reactions with Reversible Deactivation

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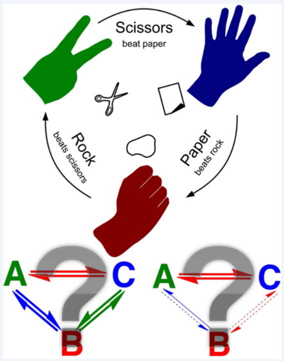


CONSPECTUS: In the game rock–paper–scissors, each of the three options, or pathways, has an equal chance of dominating, that is, rock beats scissors, scissors beats paper, and paper beats rock. In the classical form of the game, there is no one dominant pathway to follow, but they are all balanced in likelihood. However, in chemical reactions with several competing reagents, the question must be asked, are all competing reactions and pathways accessible? A related question is, if there are two, or more reversible processes that compete for the same reagent, will both processes equilibrate simultaneously, or will one process dominate system? Can these competing processes shed light on otherwise puzzling data?

Several unexpected and counterintuitive experiments have been reported in radical reactions with reversible deactivation. These unexpected observations can be illustrated by the near absence of the products of conventional bimolecular radical coupling in the radical transformation of methylcobaltamine to acetylcobaltamine. Another counterintuitive observation is a difference in the copolymer composition in some copolymerizations proceeding via reversible-deactivation radical polymerization (RDRP) vs conventional radical polymerization (RP), for example, nitroxide mediated polymerization of styrene and methyl methacrylate. A similarly puzzling phenomenon is the reduction in the branching fraction in poly(acrylates) polymerized by RDRP vs conventional RP. In the three previously mentioned cases, the radicals formed in reversible deactivation radical reactions are identical to those formed in the corresponding conventional radical process; therefore an explanation for the discrepancy in the outcomes of the reaction is needed.

Other unexpected observations include the presence of initial periods of slower monomer consumption in RDRP reactions initiated by a conventional radical initiator with certain chain transfer agents, while changing the nature of chain transfer agent can lead to an acceleration of the reaction during the initial period. Similarly, in Cu mediated atom transfer radical polymerization (ATRP) with initiators for continuous radical regeneration (ICAR) initiated by a conventional radical initiator, the rate of polymerization should not depend on either the alkyl halide concentration or the Cu concentration. However, experiments show that the rate could be 10 times faster with alkyl halide than without alkyl halide. Finally, in aqueous media, the presence of active alkyl halides can appear to stop the disproportionation of Cu^I complexes. These unusual data point to a more complex mechanism than originally envisioned, and in fact all these counterintuitive observations can be explained by the concept of competing equilibria and processes. In these cases, the presence of two or more reactions competing for the same reagent typically causes one pathway to dominate, while the rate of the other pathways are diminished. Alternatively, the competing pathways and processes can cause one or more reversible or pseudoreversible reactions to be imbalanced and lead to products distinct from the case where rates of forward and reverse reactions are balanced. In this Account, the concept of competitive processes and equilibria is developed and used to explain each of the unusual observations highlighted above.

■ INTRODUCTION

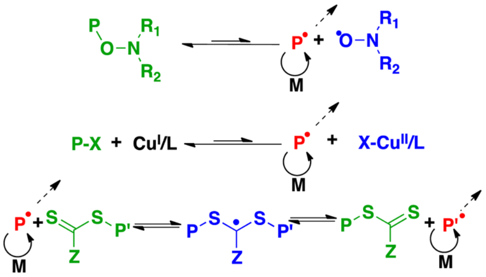
At chemical equilibrium, the rates of forward and reverse reactions are equal. However, sometimes several reactions concurrently exist and compete for a reagent. The question arises, will all processes equilibrate concurrently or will one process dominate and force other processes out of equilibrium? One example of competing processes is the Finkelstein reaction, where alkyl chlorides and potassium (or sodium) iodide, fully soluble in acetone, give alkyl iodides in high yields although C–Cl bonds are much stronger than C–I bonds. This occurs due to the low solubility of the byproduct, KCl (or NaCl), in acetone, which shifts the equilibrium toward alkyl iodides, according to Le Chatelier's principle.[1] In contrast, under fully homogeneous conditions, acetone with Li cations, the alkyl chloride forms almost quantitatively from the alkyl iodide, following C–halogen bond stability.[2]

Recently, reactions involving reversible deactivation have been used to control radical polymerizations (RP), providing macromolecules with predefined molecular weights (MW) and architectures.[3−7] Reversible-deactivation radical polymerization (RDRP) reactions rely on the equilibrium between growing radicals and dormant species. Scheme 1 shows the three most commonly used RDRP methods: nitroxide mediated polymerization (NMP),[4] atom transfer radical polymerization (ATRP),[5,6] and reversible addition–fragmentation chain transfer polymerization (RAFT).[7] An interesting question arises when additional processes compete for the reagents in Scheme 1.[8−11] Will all equilibria be established simultaneously, or will some processes be out of equilibrium for most of the reaction?

Received: May 22, 2014
Published: September 23, 2014

dx.doi.org/10.1021/ar500199u | *Acc. Chem. Res.* 2014, 47, 3028−3036

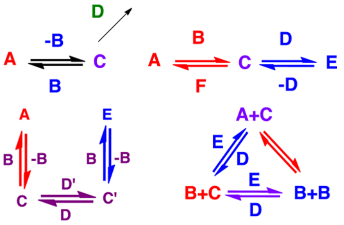
Scheme 1. Typical RDRP Methods: (top) NMP, (middle) ATRP, and (bottom) RAFT



In the literature, there are several unexpected experiments. These include organic radical reactions leading virtually to no homocoupled products,[12,13] radical copolymerization of two comonomers with significant deviations from the Mayo–Lewis predictions,[8,9,14] suppression of branching in the RDRP of acrylates in comparison with conventional RP,[15] RAFT reactions with either slower or faster monomer consumption during the initial phase compared with the steady state,[16,17] ATRP reactions that lead to significant retardation,[18,19] and essentially no disproportionation of Cu^I complexes in aqueous media if alkyl halides are present.[20]

These seemingly unrelated and unusual data are explained by the coexistence and competition among various processes. Competitive processes occur whenever one product or reagent can participate in several processes with at least one reversible reaction. This can be as simple as the reversible reaction competing with the irreversible reaction shown in Scheme 2 (top left), when the product of one equilibrium is the reagent for a second one, Scheme 2 (top right), as well as more complex cases as shown in Scheme 2 (bottom left and right). Scheme 2 relates to several examples used throughout this Account. The top left of Scheme 2 describes the persistent radical effect, if A is a stable covalent compound, B is a persistent radical, and C and D are two propagating radicals. The bottom left of Scheme 2 is relevant to copolymerization if A and E represent two different dormant species, C and C′ represent two distinct radicals, B is a radical deactivator, and D and D′ are two different monomers. The bottom left of Scheme 2 also describes branching in acrylates; if A and C are secondary dormant and active species, respectively, E and C′ are tertiary dormant and active species, respectively, with transfer and monomer (D) addition exchanging C and C′ (although if transfer is intramolecular, there is no reagent D′). The top right of Scheme 2 describes the retardation due to competition between ATRP and organometallic mediated radical polymerization (OMRP), if A represents the Cu^{II} deactivator in ATRP, C represents the active Cu^I complex, and E represents a Cu^{II} organometallic complex, with B and D representing propagating radicals and F representing an alkyl halide. Finally, the bottom left of Scheme 2 can represent the complex reactions involving the three common oxidation states of Cu, Cu^0, Cu^I, and Cu^{II}, represented by A, B, and C that can exchange either among themselves or in the presence of alkyl halides denoted D and radicals denoted E.

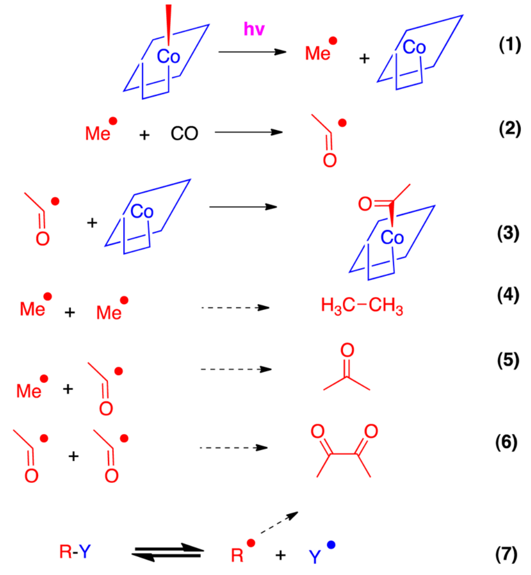
Scheme 2. Examples of Competitive Processes and Equilibria



THE PERSISTENT RADICAL EFFECT

The persistent radical effect (PRE) occurs whenever there are two radicals or radical like species, where one is a typical reactive radical, and the other one is a stable or persistent radical with a much lower self-termination rate but a fast and reversible cross-coupling rate. Examples of persistent radicals include the triphenylmethyl radical, (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) radical, cobalt porphyrin species, or other organometallic complexes.[13] The PRE dictates that when the conventional and persistent radical are generated at the same rate, a small amount of self-termination between two conventional radicals leads to a buildup of the persistent radical.[13] This statistically favors the cross-coupling between the persistent and conventional radical. Eventually, the process is dominated by reversible cross-coupling between the persistent and active radical with a very low pseudostationary concentration of reactive radicals, which implies that the rate of homocoupling is significantly lower than the rate of cross-coupling. PRE can explain why the reaction in Scheme 3 leads to almost quantitative formation of the cross-coupled acetylcobalt porphyrin complex and negligible formation of ethane, acetone, or biacetyl produced by conventional radical coupling.[12,13] PRE applies to other radical reactions and is the key to ATRP and NMP.[13]

Scheme 3. Formation of Acetylcobaltamine from Methylcobaltamine Essentially without Products of Reactions 4–6 with Equation 7 Summarizing the Concept of PRE



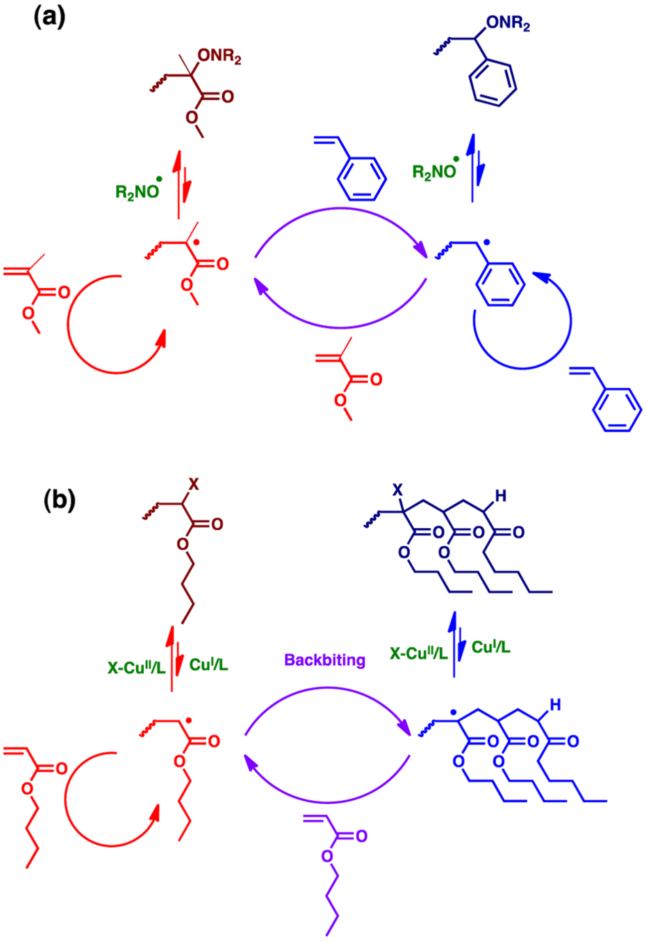
COPOLYMERIZATION OF TWO DIFFERENT MONOMERS AND BRANCHING IN ACRYLATES

The copolymerization of two monomers in RDRP and the branching in acrylates in RDRP are competitive processes.

Activation–deactivation between two distinct radicals and dormant species, as well as exchange between the two different radicals concurrently occur.

The copolymerization of methyl methacrylate (MMA) and styrene (S) via NMP is shown in Scheme 4a, although it can be extended to any comonomers copolymerized by RDRP.[14] There are three competing processes: activation and deactivation for MMA species and for S species and cross-propagation. In conventional RP, cross-propagation is the only process, the steady state concentrations of both radicals are established quickly, and composition follows the Mayo–Lewis equation. In RDRP, copolymer composition can be different.[9]

Scheme 4. (a) The Copolymerization of MMA and S by NMP with Three Distinct Processes and (b) Transfer and Branching in Acrylates by ATRP, also with Three Competing Processes



Transfer in acrylate RP generates tertiary radicals, which react with monomer, reforming the secondary radicals and creating a branch in the second step. In RDRP such as ATRP, in addition to these secondary and tertiary radical exchange reactions, the secondary and tertiary species are subject to activation/deactivation equilibria. This gives the competing processes shown in Scheme 4b, which can suppress branching by either patching the tertiary radical that is formed by backbiting or decreasing the likelihood of backbiting, as will be discussed subsequently.

Deviations of copolymer compositions formed via RDRP methods from those predicted by the Mayo–Lewis equations have been reported.[8,14] This was unexpected, since the propagating radicals are identical in RDRP and conventional RP. However, careful examination of Scheme 4a shows that with a preferred cross-propagation in one direction, for instance, from MMA to S, with dominant deactivation of the S radicals, there can be a significant deviation from the Mayo–Lewis composition, since the Mayo–Lewis equations assume that the rates of cross-propagations in both directions are equal.[14] These deviations have been noticed in reaction such as the copolymerization of MMA and *n*-butyl acrylate (BA) by ATRP and S and BA or MMA and S by NMP.[8,9,14]

Figure 1a shows a discrepancy between the copolymer composition for the NMP of MMA and S and conventional RP, predicted by the Mayo–Lewis model. Initially, S is consumed faster than predicted by the Mayo–Lewis equation. The instantaneous composition approaches the Mayo–Lewis prediction at ca. 3% conversion, but differences in the cumulative compositions remain until high conversion.

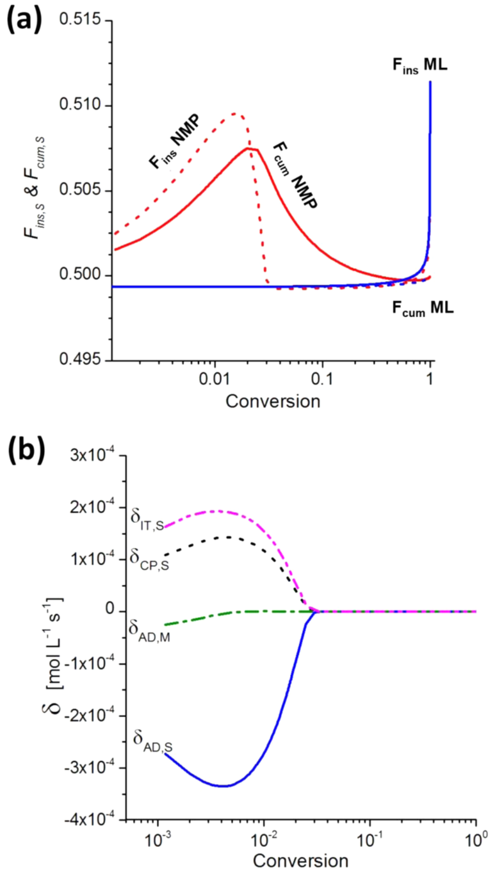


Figure 1. (a) Instantaneous (solid lines) and cumulative (broken lines) composition in the copolymerization of MMA (M, M1) and S (M2) and fraction of MMA units (M1) in NMP and in conventional RP (Mayo–Lewis prediction, ML). (b) Difference in rates of forward and reverse reactions in NMP copolymerization of MMA and S. Conditions: $[S]/[MMA]/[I\text{-}ONR_2]$ = 417:417:1; 90 °C. Adapted with permission from ref 14. Copyright 2014 WILEY-VCH Verlag.

Figure 1b illustrates the differences in the rates of initiation for S and termination ($\delta_{IT,S}$), the rates of activation and deactivation of polyMMA alkoxyamines and radicals ($\delta_{AD,M}$), the rates of activation and deactivation of polyS alkoxyamines and radicals ($\delta_{AD,S}$), and the rates of MMA and S cross-propagations ($\delta_{CP,S}$). Figure 1b indicates an imbalance of rates below 3% conversion, with the significantly larger rate of cross-propagation of MMA radical to S than of S to MMA. Also, the rate of polyS radical deactivation is much larger than the rate of activation of polyS alkoxyamine, although the activation and deactivation of MMA species is balanced above 1% conversion. The rate of initiation toward S exceeds the rate of termination for the first 3% conversion.[14] The pathway governed by competitive processes continues until the initiator is converted to polymer, and the rates of all coupled forward and reverse reactions balance. Another example of competitive processes is the copolymerization of BA with methacrylate based macromonomers.[21] In conventional RP, the incorporation of methacrylate macromonomer is slow due to diffusion effects, leading to its relatively slow incorporation.[21] In contrast, in ATRP due to the intermittent activation−deactivation cycles, the macromonomer concentration does not become depleted near the growing chain end, and the methacrylic macromonomer is incorporated at a rate similar to MMA.[21]

Scheme 4b shows these competitive processes, relevant to the ATRP of poly(BA). These competitive processes can explain the reduced fraction of branches in polyacrylates prepared by RDRP methods such as ATRP and RAFT, compared with polymers prepared by conventional RP.[15] The branching fractions in RAFT and ATRP reactions performed at 80 °C are compared with those in conventional RP in Figure 2, calculated using the formulas for the cumulative branching fraction outlined by Ahmad et al.,[15] determined by ^{13}C nuclear magnetic resonance (NMR) as a proportion of quaternary carbons.

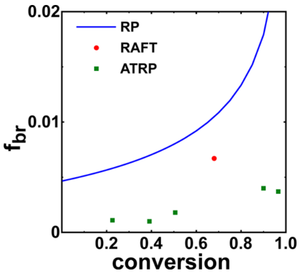


Figure 2. Cumulative branching fraction for conventional RP compared with the experimentally measured branching fraction obtained by RAFT and ATRP for the bulk polymerization of BA. The secondary propagation rate coefficient is 49600 M^{-1} s^{-1},[22] intramolecular transfer rate coefficient is 1600 s^{-1},[23] and intermolecular transfer coefficient is 200 M^{-1} s^{-1}.[15] Adapted with permission from ref 15. Copyright 2009 WILEY-VCH Verlag.

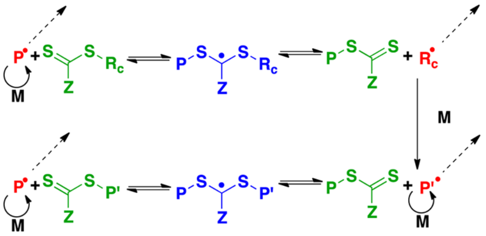
Lower branching fractions can be explained by competitive processes, since after backbiting, the tertiary radical has two possibilities.[10] One is to react with monomer and form a branch, and the second is to be deactivated and form a tertiary dormant species. In certain cases, the second fate is dominant, and the tertiary species lay dormant until they are reactivated at a later time, delaying the branching and decreasing the branching fraction.[10] These tertiary dormant species have been detected in nitroxide mediated polymerization.[24] NMR experiments have not shown significant concentrations of the tertiary bromides in ATRP systems,[25] although concentration is approximately 0.5−1% of repeat units, which is similar to the NMR error.

An alternative explanation is that the short transient radical lifetime in RDRP decreases the likelihood of transfer events, which are also competitive processes.[26] In most chemical systems, molecular motion and rearrangement occur on the nanosecond time scale; for instance, conformational rearrangement of PEO in water occurs within ca. 1 ns.[27] The nanosecond time scale of molecular rearrangement, compared with the microsecond to millisecond time scales of chemical reactions, imply that chemical reactions are independent. Although both models describe competitive processes, further research is needed to discriminate between them.

■ SELECTIVE INITIALIZATION IN RAFT

RAFT polymerization and initiators for continuous activator regeneration (ICAR) ATRP, initiated by azobis(isobutyronitrile) (AIBN), proceed with the rate controlled by AIBN decomposition, similar to conventional RP. However, long induction periods were reported in some RAFT polymerizations,[28] while other RAFT polymerizations showed faster monomer consumption in the initial period.[29] RAFT initialization data can be explained by competitive processes and equilibria.[16,30] The initialization in RAFT can be viewed as competitive processes between the addition and fragmentation involving the initial leaving group R and the polymer P, as shown in Scheme 5. Efficient initialization requires the initial chain transfer agent (CTA) to be fully converted to a macroCTA, before the macroCTA grows. Once the radical R_c is liberated, it must react with monomer before it enters the main RAFT equilibrium. This addition can be faster or slower than the polymer propagation.[28]

Scheme 5. Initialization Process in RAFT



The key questions here are which way the intermediate radical fragments, toward P or R_c, how quickly R_c reacts with monomer, and how quickly the pre-equilibrium (Scheme 5, top) converts only to the main equilibrium (Scheme 5, bottom).

The data in Figure 3a shows that in the RAFT of S initiated by AIBN with the cyano-2-isopropyl dithiobenzoate (AD), the pre-equilibrium strongly favors the formation of the small molecule radical, which reacts with S to become the unimeric species (ASD).[29] Higher MW species, such as AS_2D form only after the complete conversion of the small molecule, AD, to the unimer, ASD. In the case of the cyanoisopropyl radical and S, the cyanoisopropyl radical adds significantly faster to styrene than styrene adds to a polystyryl radical.[29]

Selective initialization also explains the induction period in the polymerization of methyl acrylate with cyano-2-isopropyl dithiobenzoate[16] or the induction periods of almost a day observed in the polymerization of vinyl acetate with cyano-2-isopropyl *O*-ethyl xanthate.[17] Here, the RAFT intermediate radical fragments almost exclusively toward the small molecule radical, but monomer addition to the small molecule radical is much slower than that to the polymeric radical.[28]

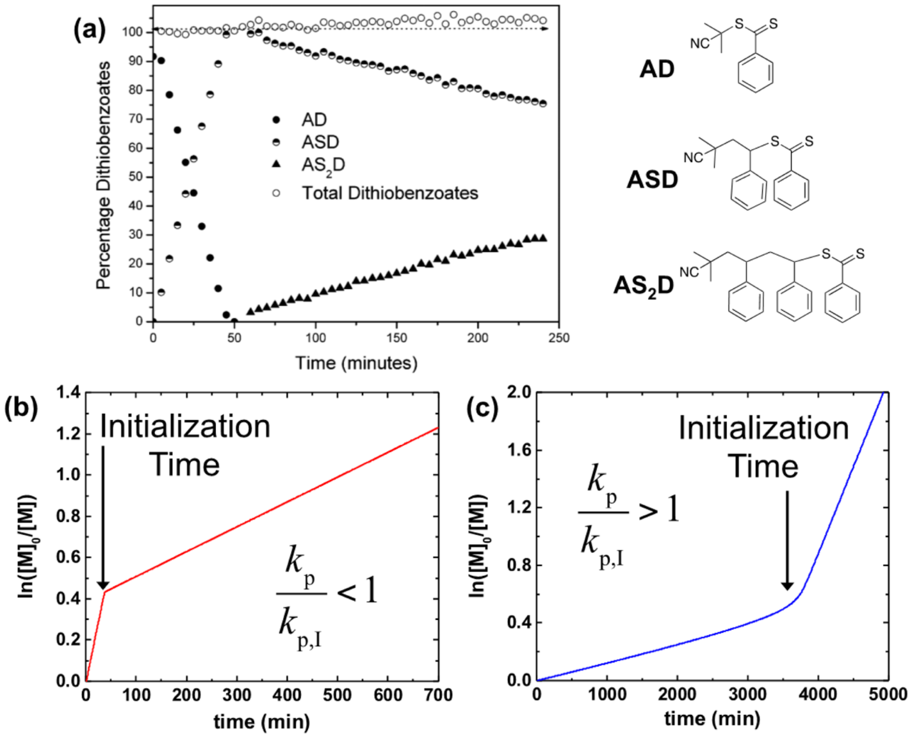


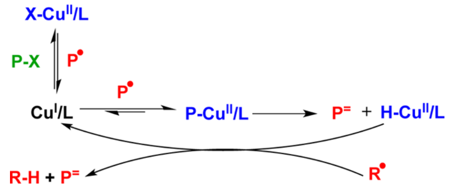
Figure 3. (a) Selective initialization data. [S]/[AD]/[AIBN] = 5:1:0.25, [S] = 3.6 M in C_6D_6, 70 °C. (b) Acceleration of monomer consumption during the initialization period. (c) Retardation of monomer consumption during the initialization period. Adapted with permission from ref 29. Copyright 2004 American Chemical Society.

For effective RAFT polymerization, the intermediate radical containing one P and one R_c group should fragment almost exclusively toward the small radical R_c. If the small molecule radical adds the first monomer faster than the polymer adds monomer, the polymerization during the initialization phase will be accelerated, like in Figure 3b,[29] whereas if the small molecule radical adds monomer slower than the polymer adds monomer, there will be an induction period, like in Figure 3c.[29]

ATRP COMPETING WITH OTHER METAL CATALYZED REACTIONS

There are numerous reports of catalytic and transition metal mediated radical polymerizations with a variety of competing mechanisms.[19,31−33] An interesting case is the plausible interplay of ATRP with OMRP and catalytic radical termination (CRT). Ideally, the rate of ICAR ATRP only depends on the AIBN decomposition rate and does not depend on the concentration of alkyl halide or catalyst.[34] However, some highly active Cu^I catalysts, such as Cu^I/TPMA*, (TPMA* is tris((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amine), may participate in OMRP deactivation reactions between Cu^I/L and radicals forming organometallic species R-Cu^{II}/L. R-Cu^{II}/L can be reactivated or participate in β-H elimination to form H-Cu^{II}/L species. The latter paramagnetic species can terminate rapidly with radicals and regenerate Cu^I/L that can again participate in CRT, as shown in the bottom part of Scheme 6.[19,35]

Scheme 6. Competition between ATRP (left, vertical pathway) and OMRP/CRT (bottom pathway)



CRT is responsible for the significant retardation observed in AIBN initiated polymerizations of acrylate. With just 100 ppm (ppm, as a molar ratio to monomer) of Cu^I/TPMA*, the reaction required 30 h to reach 75% conversion, whereas under the same conditions but without Cu^I/TPMA*, the reaction reached 75% conversion in 20 min.[19] This retardation was observed under ICAR ATRP conditions but without alkyl halide. However, when a similar reaction was performed in the presence of the alkyl halide, ethyl α-bromoisobutyrate (EBiB), the rate was 10 times higher.[18] The reason for the significantly faster reaction with the alkyl halide was the substantial decrease in the concentration of Cu^I/L species due to ATRP equilibrium favoring X-Cu^{II}/L species, as shown in Scheme 6. With the diminished Cu^I/L concentration, the catalytic radical termination occurs at a lower rate, and the polymerization rate is increased, as seen in Figure 4. In Scheme 6, with no alkyl halide, only the OMRP/CRT processes occur, while in the presence of alkyl halide, the ATRP equilibrium decreases the Cu^I concentration and the contribution of the OMRP/CRT pathways decreases significantly.[19]

DISPROPORTIONATION AND COMPETITIVE PROCESSES IN RDRP IN THE PRESENCE OF Cu^0

A fascinating example of competitive processes and equilibria is RDRP in the presence of Cu^0 in polar media, such as dimethyl sulfoxide (DMSO) or water. There are three oxidation states of Cu: Cu^0, Cu^I, and Cu^{II}, which can interchange directly through comproportionation or disproportionation or with the assistance of alkyl halides (activation) and radicals (deactiva-

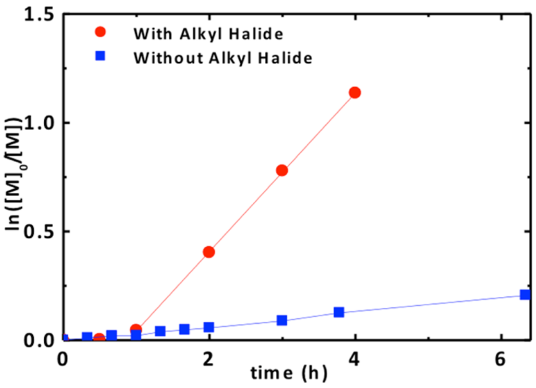
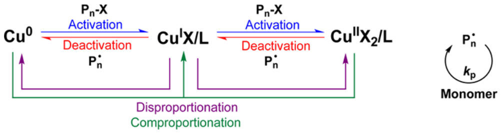


Figure 4. Kinetics of ATRP with 100 ppm of Cu, in the presence or absence of alkyl halide. Conditions with alkyl halide: [BA]/[EBiB]/[AIBN]/[TPMA*]/[$Cu^{II}Br_2$] = 160:1:0.2:0.06:0.016 Conditions without alkyl halide: [BA]/[AIBN]/[TPMA*]/[$Cu^I(CH_3CN)_4BF_4$] = 160:0.2:0.06:0.016. Both cases, [BA] = 5.6 M, 20% (v/v) anisole, T = 60 °C. Adapted with permission from refs 18 and 19. Copyright 2012 American Chemical Society.

tion).[36,37] These competing equilibria of comproportionation/disproportionation, activation of alkyl halides by Cu^0 or Cu^I, and deactivation by Cu^{II} or Cu^I are shown in Scheme 7. Unless otherwise specified, speciation is not explicitly considered, and the concentration of Cu in a given oxidation state is denoted by Cu^0, Cu^IX/L, $Cu^{II}X_2/L$.

Scheme 7. Competing Equilibria of Comproportionation/Disproportionation, Activation of Alkyl Halides by Cu^0 and Deactivation of Radicals by Cu^I, and Activation of Radials by Cu^I and Deactivation of Radicals by Cu^{II}



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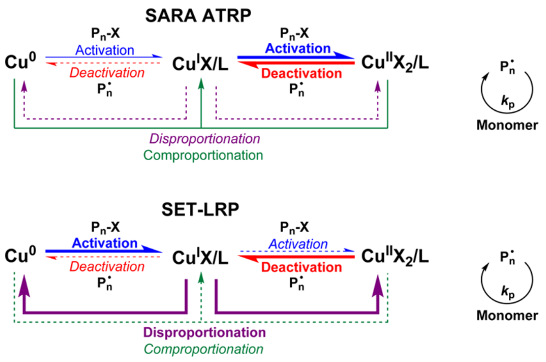
There are two models for RDRP in the presence of Cu^0.[38] Supplemental activator and reducing agent (SARA) ATRP relies on the ATRP reactions of alkyl halide activation by Cu^I and radical deactivation by Cu^{II} occurring with the highest rate. In SARA ATRP, Cu^0 is a supplemental activator of alkyl halides and a reducing agent of Cu^{II}, through comproportionation, with these reactions compensating for radical termination.[36,37,39−41] In SARA ATRP, the kinetic contributions of disproportionation and radical deactivation by Cu^I are negligible.[36,37,39−41] These reactions are shown in Scheme 8 (top).

The other model is single electron transfer living radical polymerization (SET-LRP).[42] In SET-LRP, the dominant reactions are activation of alkyl halides by Cu^0, deactivation of radicals by Cu^{II}, and disproportionation of Cu^I species to regenerate Cu^0 and Cu^{II}. In SET-LRP, there is minimal activation of alkyl halides by Cu^I, due to instantaneous disproportionation, and negligible deactivation of radicals by Cu^I or comproportionation, as shown in Scheme 8 (bottom).

Cu^I lies at the center of the competitive processes in Scheme 7. The key question is "what is the major reaction pathway for Cu^I?".[20] Does Cu^I primarily activate alkyl halides or disproportionate?[20] This can be answered by model experiments.

Scheme 8. SARA ATRP Mechanism (top) and SET-LRP Mechanism (bottom)[a]



[a] Line thicknesses denote the contribution of the reaction, with bold reactions being dominant, thin solid lines contributing, and thin dashed lines being negligible. For simplicity, the products of activation and deactivation, and stoichiometric balance in comproportionation and disproportionation reactions are omitted.

In model experiment 1, to Cu^IBr, a mixture of 18% oligo(ethylene oxide) acrylate (OEOA, M_n = 480) and 82% H_2O containing 10 mM of the ligand tris(2-(dimethylamino)-ethyl)amine (Me_6TREN, 5-fold excess to Cu^IBr) was added. This mixture was allowed to react for 20 min, after which point 50 mM of an active alkyl halide, 2-hydroxyethyl α-bromoisobutyrate (HEBiB), was added.[20] The reaction was monitored for an additional 40 min. In model reaction 2, to a solid Cu^IBr, a mixture of 18% OEOA and 82% H_2O containing 10 mM Me_6TREN (5-fold excess to Cu^IBr) *and* 50 mM HEBiB was added. The only difference between these two experiments was whether the HEBiB was added 20 min into the experiment (expt 1) or at the start of the reaction (expt 2).[20]

Figure 5a shows the evolution of the UV−vis−NIR spectrum for model experiment 1, while Figure 5b shows the evolution of the UV−vis−NIR spectrum for model experiment 2.[20,38] Figure 5a illustrates, before the addition of HEBiB, a relatively slow buildup of both Cu^I, which absorbs strongly below 450 nm, and Cu^{II}, which absorbs strongly below 380 nm and between 600 and 1100 nm. This evolution is due to the slow dissolution of Cu^I and partial disproportionation of dissolved Cu^I to Cu^0 and Cu^{II}. Figure 5a shows that within 30 s of adding HEBiB to this reaction mixture (time needed to record the spectrum), the Cu^I completely disappears and there is commensurate generation of Cu^{II}.[20] The subsequent slow increase of Cu^{II} is due to the slow reaction of alkyl halides with Cu^0, which occurs for 30 min after the addition of HEBiB.[20] This is consistent with the SARA ATRP and not the SET-LRP mechanism.

In contrast model experiment 2, where HEBiB was added at the start of the reaction, shows only a continuous increase in the Cu^{II} concentration over time, as seen in Figure 5b.[20] Furthermore, this reaction gave a clear blue solution, with negligible precipitate. This leads to the question, "how can alkyl halides effectively switch off disproportionation?"

The answer lies in the competitive equilibria shown in Scheme 7, which indicate that Cu^I is capable of both disproportionation and activation of alkyl halides. In the absence of alkyl halides, only disproportionation can occur. However, when Cu^I can activate an alkyl halide or disproportionate, the activation pathway is favored, as evidenced by the absence of Cu^I and the absence of Cu^0 precipitate. The large ATRP equilibrium constant decreases the Cu^I concentration to

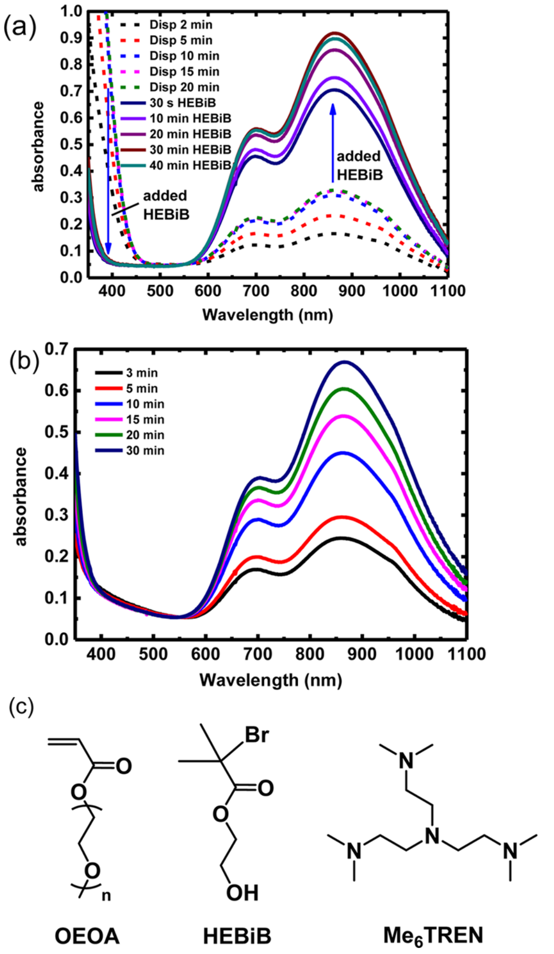


Figure 5. UV−vis−NIR spectra recorded (a) 20 min into the reaction $[Cu^IBr]_0$ = 2 mM and $[Me_6TREN]_0$ = 10 mM in OEOA (18 wt %) in water before and after the addition 50 mM HEBiB at 22 °C (injected after 20 min) and (b) 20 min into the reaction $[Cu^IBr]_0$ = 2 mM and $[Me_6TREN]_0$ = 10 mM in OEOA (18 wt %) in water with initially added $[HEBiB]_0$ = 50 mM at 22 °C. (c) Structures of OEOA, HEBiB, and Me_6TREN. Reproduced with permission from ref 20. Copyright 2014 American Chemical Society.

such a low level that disproportionation between two Cu^I species is very slow.

To analyze this system further, kinetic simulations were performed, using experimentally determined rate coefficients.[20] Figure 6a shows the simulated concentration of all species in solution for a typical polymerization of OEOA in 82% water, initiated by HEBiB, with Me_6TREN as the ligand and an excess of halide salt. In these simulations, the associations of halide with the Cu^I and Cu^{II} complexes were considered, since in aqueous media dissociation of the $Cu^{II}X/L$ deactivator to a free halide anion, X^- and a Cu^{II} complex cannot be neglected.[20] Figure 6a indicates that the majority of the Cu is in the form of Cu^{II}, with only 1% of the Cu being Cu^I.[20]

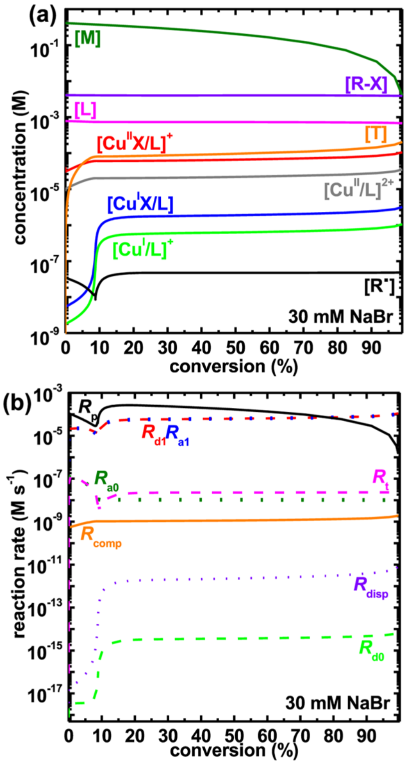


Figure 6. (a) Concentration of various species and (b) rates of reaction for RDRP in the presence of Cu^0 in water with 30 mM of NaBr under conditions $[OEOA]_0/[HEBiB]_0/[Cu^{II}Br_2]_0/[Me_6TREN]_0$ = 100:1:0.01:0.2, OEOA/H_2O = 18/82 (w/w), and 10 cm of Cu^0 wire (*d* = 1 mm) in 6 mL at 25 °C. Reproduced with permission from ref 38. Copyright 2014 Royal Society of Chemistry. In panel a, [R−X] represents the sum of [HEBiB] and poly(OEOA) with a halogen end group, [M] is the monomer concentration, [L] is the concentration of Me_6TREN, [T] is the concentration of terminated species, and $[R^\bullet]$ is the concentration of all radicals.

The simulated reaction rates are displayed in Figure 6b.[38] The fastest reaction is propagation, that is, monomer consumption (R_p). The next fastest reactions are the ATRP reactions of alkyl halide activation by Cu^I (R_{a1}), and radical deactivation by Cu^{II} (R_{d1}). The activation and deactivation reactions are balanced, with equal forward and reverse reaction rates. The two next fastest reactions, but occurring 2−3 orders of magnitude slower than ATRP reactions, are alkyl halide activation by Cu^0 (R_{a0}) and radical termination (R_t). These two reactions are almost balanced, meaning that Cu^0 acts as a supplemental activator and compensates for radicals lost to termination. The next most significant reaction, occurring 1 order of magnitude slower than activation of alkyl halide by Cu^0, is comproportionation of Cu^0 with Cu^{II} (R_{comp}). Disproportionation (R_{disp}) of Cu^I is 3 orders of magnitude slower than comproportionation, and radical deactivation by Cu^I (R_{d0}) is 7 orders of magnitude slower than comproportionation. Similar rate profiles were observed in DMSO based systems.[41]

In this system, comproportionation and disproportionation do not reach equilibrium within the time needed to reach 90% monomer conversion, and neither do alkyl halide activation by Cu^0 and radical deactivation by Cu^I. Although disproportionation can be thermodynamically favored over comproportionation[43] and relatively fast,[20,44] the Cu^I complexes are so ATRP active that they rapidly react with alkyl halides and generate Cu^{II} in the process, pushing the Cu^I concentration to a very low level (ca. 1 μM). This decreases the rate of disproportionation, which is proportional to $[Cu^I]^2$.

It has been stated that RDRP in the presence of Cu^0 is a complex reaction mechanism, and "complex reaction mechanisms, as all other complex systems, cannot be understood by studying their parts in isolation."[45] This statement is correct. Looking *only* at isolated reactions cannot reveal the mechanism.

However, isolated reactions should be studied to obtain kinetic parameters, which can be combined into a composite model. The analysis of all competing processes in RDRP in the presence of Cu^0 shows that the mechanism follows SARA ATRP.

CONCLUSIONS

Throughout this Account, we have outlined the concept of competitive processes and equilibria. These competitive processes occur whenever there are two or more distinct pathways for a compound. They are interesting from a fundamental perspective, but also practically, since RDRP reactions can lead to products with compositions and structures different from those synthesized under conventional RP.

These competitive processes can clarify a variety of otherwise unexpected data and explain why RP can proceed in the near absence of conventional radical termination products, why RDRP can form copolymers with different compositions and branching, why retardation and induction periods are observed in some systems, and why disproportionation of Cu^I species in aqueous media can be suppressed in the presence of alkyl halides.

The answer to these questions lies in the fact that among the competitive processes, one reaction occurs with a noticeably higher rate and is favored. When one reaction dominates, it often suppresses the other reactions involving that reagent, leading to a decrease in the rate of the nondominant reaction. With this framework of competitive processes established, the toolbox can be applied to other mechanisms and explain a variety of other counterintuitive experiments.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

This work was funded by the National Science Foundation (Grants CHE 14-00052 and DMR 09-69301) and the CRP Consortium at Carnegie Mellon University.

Notes

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ACKNOWLEDGMENTS

We thank Dr Mingjiang Zhong for discussions.

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