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Laboratory Experiment

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An Undergraduate Chemistry Laboratory: Synthesis of Well-Defined Polymers by Low-Catalyst-Concentration ATRP and Postpolymerization Modification to Fluorescent Materials

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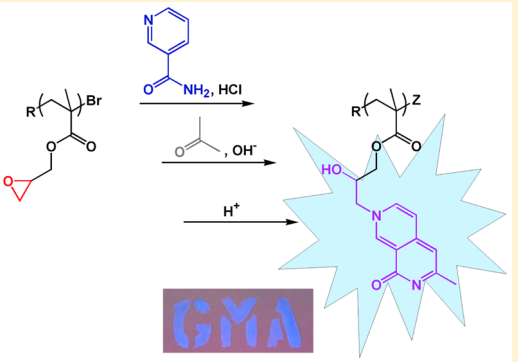
Supporting Information

ABSTRACT: A two-session experiment is designed to introduce undergraduate students to concepts in catalysis, transition metal complexes, polymer synthesis, and postpolymerization modifications. In the first session, students synthesize poly(glycidyl methacrylate) via low-catalyst-concentration atom transfer radical polymerization (ATRP). The low-catalyst-concentration technique simplifies the experimental setup, reduces the cost of the synthesis, eliminates the need for catalyst removal from the product, and thus ultimately makes ATRP an environmentally benign process. In the second session, students modify the well-defined epoxide-containing polymers with nicotinamide in the presence of acetone, to afford fluorescent polymers.



KEYWORDS: *Upper-Division Undergraduate, Inorganic Chemistry, Organic Chemistry, Laboratory Instruction, Polymer Chemistry, Catalysis, NMR Spectroscopy, Transition Elements, Hands-On Learning/Manipulatives*

INTRODUCTION

Macromolecules with well-defined architecture and functional groups situated at specified, desired locations (chain end(s), part of or pendant from the backbone, etc.) have numerous applications, which has fueled the search for novel synthetic procedures. Figure 1 presents several examples of functional macromolecules.

Controlled/"living" radical polymerization (CRP) techniques have been developed that allow for the precise synthesis of polymers with predetermined and desired molecular characteristics, such as size (molecular weight), topology, architecture, and placement of functionalities.[1,2] CRP experiments have been suggested for use in the undergraduate teaching laboratory, because they efficiently illustrate important concepts introduced as part of the core curriculum, including inorganic and physical chemistry (reaction kinetics and thermodynamics, catalysis, complex formation), organic chemistry (synthesis and reaction mechanisms), analytical chemistry (spectroscopy, chromatography, and other characterization techniques), etc.[3−6] One of the most popular and robust CRP methods is atom transfer radical polymerization (ATRP),[7−9] which relies on establishing an equilibrium between an alkyl halide type low-molecular-weight or polymeric dormant (i.e., unable to react with monomer) species and propagating radicals. The process is mediated (catalyzed) by a redox-active transition metal (e.g., copper) complex.[10] The lower oxidation state complex ($Cu^{I}L_n$, where L represents a ligand and n is a stoichiometric coefficient determined by the structure of L), referred to as the *activator*, reacts with the alkyl halide initiator (RX; X = Br or Cl), generating the primary propagating radical ($R^{\bullet}$) and the corresponding higher oxidation state complex containing a coordinated halide anion ($X\text{-}Cu^{II}L_n$), named *deactivator*. The radicals can propagate in the presence of a monomer and terminate, just as in conventional radical polymerizations, but can also be deactivated by a halogen transfer from the deactivator, a process yielding the dormant polymeric alkyl halide and the activator $Cu^{I}L_n$ (top part of Scheme 1; an example is shown, in which L = tris(2-pyridylmethyl)amine (TPMA)).

"Classical" ATRP reactions employed large amounts of catalyst, often comparable to that of the initiator. The development of very active ATRP catalysts made it possible to conduct the polymerizations using very low catalyst amounts. However, due to inevitable radical termination (radical combination and/or disproportionation), deactivator accumulates in the system (a process known as the *persistent radical effect*).[11] At the moment when the amount of terminated or "dead" (i.e., unable to be activated and subsequently grow) chains reaches the amount of catalyst present in the system, all the catalyst is present in the form of the high oxidation state complex, further activation of the dormant species cannot occur, and the polymerization stops.

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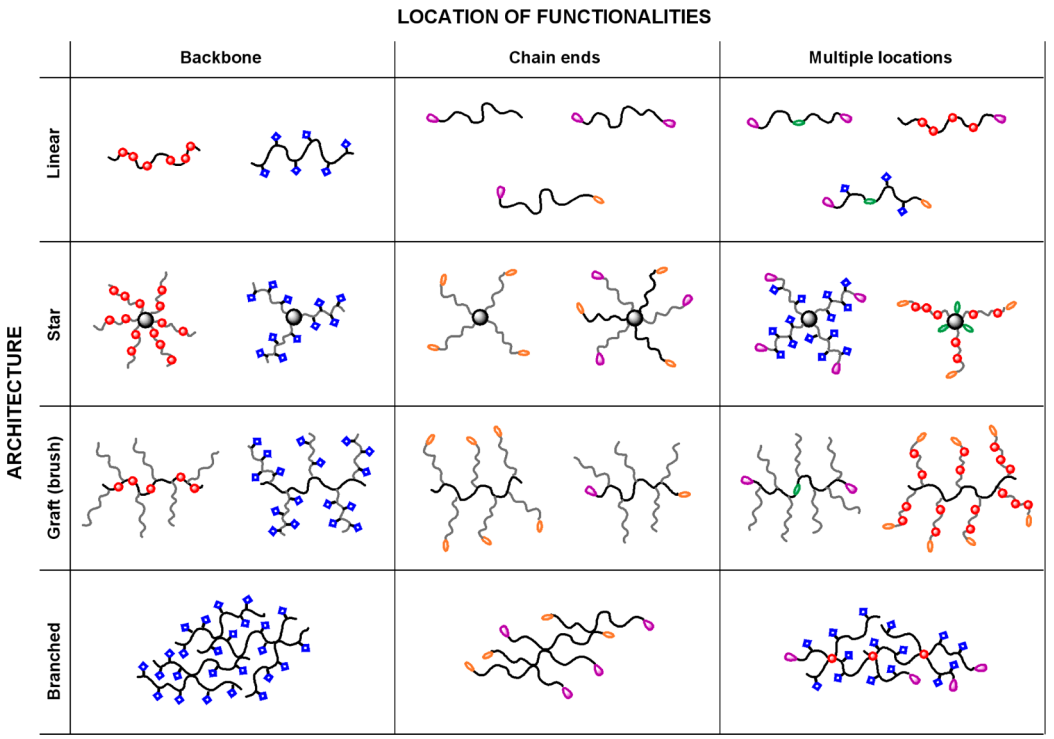
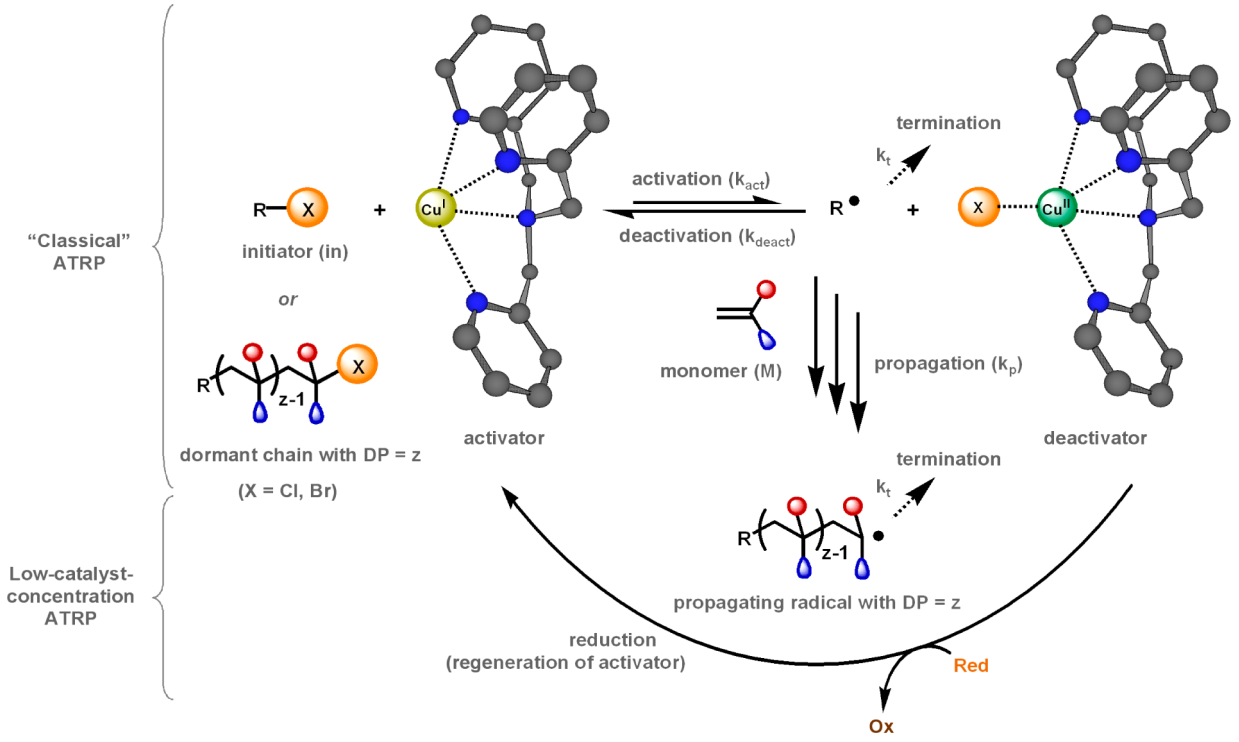


Figure 1. Examples of functional polymers made possible by controlled/"living" radical polymerization methods.

Scheme 1. Mechanism of "Classical" Cu-Mediated ATRP and Low-Catalyst-Concentration Methods



This may happen relatively early in the polymerization, i.e., at low monomer conversions. This is why "classical" ATRP cannot be carried out to high monomer conversions using extremely low catalyst amounts, even if the catalysts are very active. However, a remarkable degree of control over macromolecular characteristics can be attained. For instance, if all chains are formed within a narrow time interval, i.e., the initiation is fast compared to propagation, and the growing radicals are quickly deactivated to the dormant species before they can add to too many monomer molecules, all chains in the system grow slowly, and most of them are in the dormant state ("capped" with a halogen atom at the ω-end). As a result, at any given time, all macromolecules in the system have very similar sizes, and the size (or the number-average degree of polymerization, DP_n) of the macromolecules at that moment is determined by the initial molar ratio of monomer (M) to

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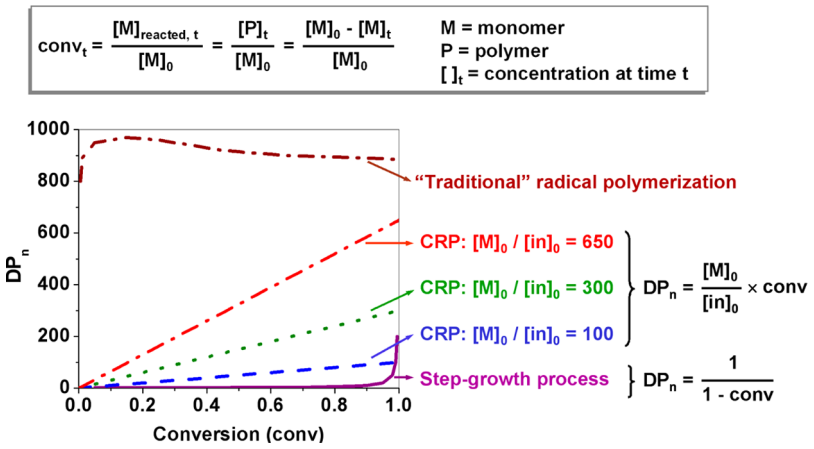

Figure 2. Evolution of number-average degree of polymerization (DP_n) with monomer conversion (conv) in step-growth, "traditional" radical polymerization, and controlled/living radical polymerization (CRP, including ATRP) using different molar ratios of monomer (M) to initiator (in). In "traditional" radical polymerization, radicals are generated throughout the reaction, propagate within milliseconds to high-molecular-weight polymer, and terminate. As a result, as soon as the polymerization commences, only high-molecular-weight macromolecules are present in the reaction mixture, the vast majority of which are in the form of "dead" chains, and only a very small fraction are in the form of growing radicals.

initiator (RX), and the monomer conversion (conv), as shown in Figure 2. An important factor to consider is the uniformity of chain size throughout the polymerization, which is related to the molecular weight distribution (MWD) dispersity ($\bar{D}$), defined as the ratio of the weight-average to the number-average molecular weight or degree of polymerization ($\bar{D} = M_w/M_n = DP_w/DP_n$). For perfectly uniform macromolecules, this ratio equals unity. In well-controlled ATRP, polymers with values of $\bar{D}$ below 1.2−1.3 are common.[8,9,12]

A major development in making ATRP a truly environmentally benign method was the realization that well-controlled reactions could still be carried out to high conversion using very low concentrations of catalyst if reducing agents are added to the reaction mixture[13] to transform part of the deactivator X-$Cu^{II}L_n$ (e.g., X-Cu^{II}/TPMA), which would normally accumulate in the system, back to the activator $Cu^{I}L_n$ (Cu^{I}/TPMA). When the reducing agent employed is not a radical able by itself to initiate polymerization (e.g., it is ascorbic acid, glucose, etc.), the process is named ARGET (*activators regenerated by electron transfer*) ATRP.[14] Alternatively, radicals formed by the decomposition of a radical source (e.g., azobis(isobutyronitrile) (AIBN)) can be used to reduce the deactivator, in which case the process is termed ICAR (*initiators for continuous activator regeneration*) ATRP.[15] One drawback of the latter method is the inevitable generation of some polymer chains initiated by the radical source (rather than only by RX). Low-catalyst-concentration ATRP methods are presented in the bottom part of Scheme 1. These systems allow for an overall decrease in the amount of catalyst needed to mediate a well-controlled polymerization, from 2,000−10,000 ppm used in "classical" ATRP to 10−100 ppm or less. This significantly reduces the cost of the syntheses, eliminates or minimizes the need of purification of the produced polymers, enables the synthesis of high-molecular-weight polymers, and even allows control over the width of the MWDs.[16]

In the experimental part of this work, which was developed for advanced undergraduate laboratories, the synthesis of well-defined polymers containing reactive epoxide functional groups by low-catalyst-concentration ATRP is demonstrated. The experiment has become an integral component of an upper-level undergraduate inorganic chemistry course in the Department of Chemistry at Southern Methodist University. The relatively complex mechanistic details of CRP combined with the complexities of NMR characterization and kinetics stimulate the students to assimilate information from all prior coursework and laboratory study while applying it to and learning about polymeric materials. In our department, this experiment follows the preparation of silicone-based putty by condensation polymerization, and so it illustrates polymerization by another basic polymerization method, i.e., chain-growth polymerization. The key points are to (i) contrast free radical polymerizations (where equilibrium between dormant and active chains does not exist) with the mechanistic differences and vast advantages of CRP; (ii) introduce key features of polymerization including monomer conversion, DP_n (M_n) and DP_w (M_w), and MWD dispersity; (iii) demonstrate the utility of NMR spectroscopy for monitoring a reaction process; (iv) show the relationship between kinetic data and mechanism; (v) demonstrate the role of transition metals in catalysis; and (vi) show efficient synthetically useful post-polymerization modification reactions. It is generally considered the most challenging experiment in the advanced course. The students not only answer a set of questions related to the experiments but also generate a journal style report with literature references, kinetic plots, and logical discussions.

EXPERIMENTAL OVERVIEW

The documented experiment takes the time of two 5-hour lab sessions if executed efficiently and with proper prelab preparation (particularly during the first day, when the polymerization is conducted). This experiment has been performed by about 40 students over the course of 5 terms of the advanced inorganic chemistry laboratory at SMU. Students can work in groups of two or more, but for the group members to take full advantage of what the experiment teaches, it is advisible that every individual carries out each analysis (syringe purging followed by sample collection, NMR analysis, and size exclusion chromatography (SEC) analysis) for at least one of the reaction mixture samples.

In the first day, students prepare a catalyst stock solution consisting of $CuBr_2$ and TPMA in DMF, purify the monomer, glycidyl methacrylate (GMA), prepare the reaction mixture,

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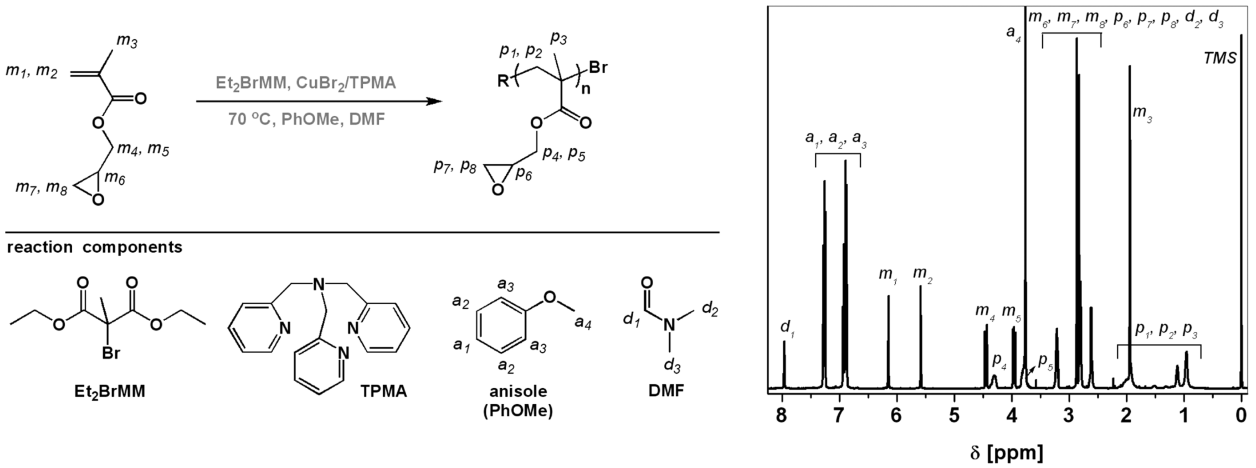

Figure 3. NMR spectrum of the reaction mixture with peak assignments.

remove oxygen/air, and carry out the polymerization using an active ATRP initiator, diethyl 2-bromo-2-methylmalonate (Et_2BrMM). Samples (ca. 0.3 mL) are taken at about 45 min, 1.5 h, and 2.5 h, and finally at 3.5 or 4 h, depending on the available time, with special care being taken to exclude oxygen as noted in the complete procedure (laboratory handout, Supporting Information). Each kinetic sample is analyzed by ^{1}H NMR spectroscopy (after dilution of part of it with $CDCl_3$) to determine the monomer conversion and by SEC to determine the molar mass and the shape and dispersity of the MWD. The conversion is determined as explained below, and then the function $\ln([M]_0/[M]_t)$ is calculated. With 3 or 4 kinetic samples, a plot is constructed of $\ln([M]_0/[M]_t)$, i.e., $\ln([GMA]_0/[GMA]_t)$, versus time (t). Similarly, plots of M_n and dispersity versus conversion are made to evaluate the "livingness" of the reaction. Ideally, M_n (or DP_n) should increase linearly with conversion with a slope determined by the targeted DP_n at complete conversion ($[M]_0/[RX]_0$, i.e., $[GMA]_0/[Et_2BrMM]_0$). After 4 to 5 h, the reaction mixture is cooled and exposed to air (which stops the polymerization), and the polymer is collected by precipitation in excess of diethyl ether. Initially, the experiment was conducted under ICAR conditions (i.e., in the presence of AIBN), due to the disadvantages of typical ARGET ATRP for the polymerization of GMA.[17] The discovery that the polymerization of epoxide-containing monomers can be undertaken without the addition of any external reducing agent[18,19] led to a small change, which made the synthesis both easier to carry out and more environmentally benign, as smaller amounts of chemicals are needed.

The second day is more relaxed as the procedure for polymer modification is less demanding (i.e., does not require anaerobic conditions) and the students get to see an application of their hard-earned product. The epoxide pendant groups on the polyGMA are converted to highly fluorescent groups by a ring-opening reaction, in which the pyridine nitrogen atom of nicotinamide (3-pyridinecarboxylic acid amide) serves as the nucleophile. The polymer is added to a solution of HCl and nicotinamide (slight excess to HCl) in DMSO-d_6, and then the solution is stirred at 60 °C for a total of 2.5 h. Treatment with acetone and NaOH and then acidification with HCl produces the fluorescent material, which students use to draw an "invisible" design on paper that appears under UV light.

Suggestions to enhance the success of the experiment and efficiency of time management are given in the instructor notes in the Supporting Information.

HAZARDS

Safety glasses and a lab coat or lab apron should be worn at all times, and the experiments should be carried out in a fume hood. All reagents and solvents should be considered hazardous or irritating upon contact or inhalation, and the organic solvents employed are potential fire hazards. MSDSs should be readily available in the lab. Polymeric materials are generally considered nontoxic, but since their biological effects have not been investigated, they should be handled as potentially hazardous, similar to any other chemicals with unknown toxicities.

RESULTS AND DISCUSSION

All experimental details are presented in the Supporting Information. The following section provides a description of the important concepts involved in the calculations used in monitoring the progress of the polymerization and post-polymerization modification reactions, along with a summary of student learning outcomes and experiences.

Day 1. Low-Catalyst-Concentration ATRP of GMA

The reaction scheme and the structures of all reagents and solvents are presented in Figure 3, along with an example of an NMR spectrum of the reaction mixture taken during the polymerization.

In order to confirm the livingness of the polymerization, the monomer conversion must be determined, in this case using ^{1}H NMR spectroscopy. The resulting spectrum is somewhat complex (Figure 3), but all of the peaks can be easily assigned to the protons of the reaction mixture components: solvents, monomer, and polymer. The peaks marked with an "a" in Figure 3 belong to protons of anisole, those marked with a "d" belong to DMF, "m" designates protons from the monomer, and "p" indicates protons from the polymer. As the reaction proceeds, the intensity of the peaks marked with "p" increases at the expense of those marked with "m." There are several ways to determine the monomer conversion by analyzing the NMR spectra of the reaction mixture, which are described below.

Comparing Integrals of Peaks Belonging to the Unreacted Monomer with Those of Peaks Belonging

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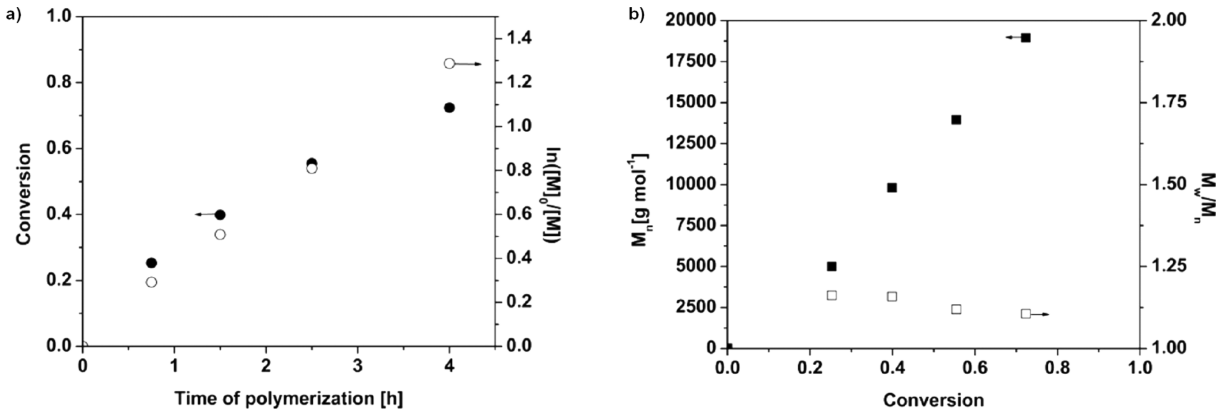

Figure 4. Kinetics (a) and evolution (b) of molecular weight and dispersity ($\bar{D} = M_w/M_n$) with conversion in the low-catalyst-concentration ATRP of GMA using no external reducing agent at 70 °C.

to the Polymer. When integrating, it is convenient to set the integral of the vinyl protons of the monomer (m_1 and m_2) to 1.00. The integral of m_4 (one of the two $-CO_2CH_2-$ protons of GMA) should also be equal to 1.00, but this signal may partially overlap with the signal of p_4 (one of the two $-CO_2CH_2-$ protons of the produced polyGMA). It is thus more convenient to integrate the two peaks (m_4 and p_4) together. Once the reaction has started, the total integral of protons m_4 and p_4 should exceed 1.00, since both monomer and polymer are present. The monomer conversion can be calculated from eq 1:

$$\text{conv} = \frac{I(m_4 + p_4) - 1}{I(m_4 + p_4)} \quad (1)$$

In eq 1, $I(m_4 + p_4)$ is the value of the total integral of the signals of protons m_4 and p_4, which are situated in the area between 4.6 and 4.2 ppm.

There are alternative peaks that can be conveniently analyzed. For instance, the entire area from 2.5 to 0.5 ppm can be integrated. In this region, there are peaks belonging to protons from the polymer (p_1, p_2, and p_3) but also to the methyl group protons from the methacrylate monomer (m_3). If the integrals of m_1 and m_2 are set to 1.00, then the integral of m_3 should equal 3.00. If this value is subtracted from the total integral for the area 2.5−0.5 ppm, the residue is the integral of the five protons from the polymer (two from the backbone methylene group (p_1 and p_2) and another three from the methyl group (p_3) pendant from the backbone). The monomer conversion can then be calculated using eq 2:

$$\text{conv} = \frac{\frac{I(m_3 + p_1 + p_2 + p_3) - 3}{5}}{\frac{I(m_3 + p_1 + p_2 + p_3) - 3}{5} + 1} \quad (2)$$

Obviously, using eq 1 may be practically more convenient, but eq 2 is presented for completeness and is beneficial to use for comparison.

Using Internal Standard.[20] If a compound is added to the system, which is unreactive and nonvolatile, i.e., its concentration remains constant throughout the reaction, it can be used to determine the monomer conversion, and is referred to as *internal standard*. It is important that it has NMR signal(s) that do not overlap with those of the monomer and polymer. At the beginning, before the reaction mixture is placed in the heating bath, a small sample is taken and analyzed by NMR spectroscopy. The spectrum of this sample obtained at "time zero" contains signals of the monomer and solvents. The peaks of the protons from the initiator (Et_2BrMM) and the ligand (TPMA) may not be visible due to the low concentration of these reagents. The ratio of the signals of the vinyl protons to those of the standard will decrease over time due to monomer consumption. If the initial ratio of the integral of one of the vinyl protons, say m_2, to that of the standard, say d_1 from DMF, is designated as R_0, and the ratio of the same integrals at time t is R_t, then the monomer conversion is calculated as shown in eq 3:

$$\text{conv} = 1 - \frac{R_t}{R_0} \quad (3)$$

It is preferable to select as internal standard a compound with proton peaks that are not too intense as compared to those of the monomer because the error in the calculated conversion may become significant, particularly as the monomer peaks decrease even further during the reaction. Consequently, DMF, present in a smaller amount than anisole and having a less intense peak (there is only one proton d_1 as opposed to the three anisole protons a_4), is a more suitable internal standard. If the exact amount of internal standard is known, R_0 can be estimated based on the amounts of reagents used in the reaction mixture, and the NMR analysis of a sample at "time zero" is not necessary. However, this is less accurate because, during the purging with nitrogen, small parts of the reaction mixture components may be "lost" due to partial evaporation.

It is a valuable exercise to try to determine the monomer conversion using all of the above approaches and compare them, for this will give the students a good idea about sources of error as well as reliability of experimental data.

If the polymerization is controlled/"living" (i.e., the number of propagating active centers is constant), the monomer consumption should follow a first-order kinetic dependence, although this is not a sufficient criterion for "livingness". Polymerization control can be ascertained by inspecting the evolution of M_n during the reaction, and the plot of M_n vs monomer conversion (not reaction time!) should be linear. In addition, the MWD should be narrow ($\bar{D} \leq 1.4$). A typical kinetic plot and evolution of M_n and $\bar{D}$ with conversion in the polymerization of GMA at 70 °C are shown in Figure 4.

Day 2. Alkylation of Nicotinamide with PolyGMA

Epoxides can react with a large variety of nucleophiles, and the reactions have found numerous applications in organic

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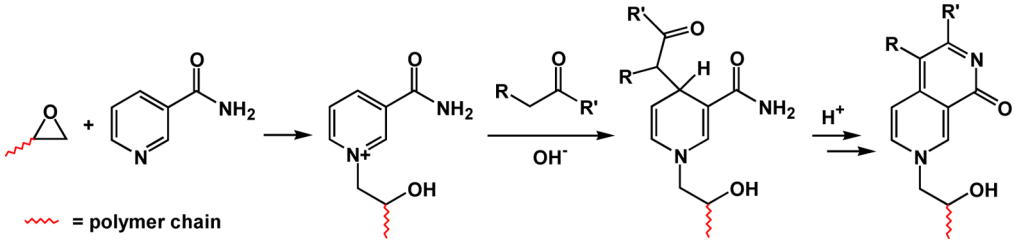
Scheme 2. Reaction of Epoxides with Nicotinamide Followed by a Reaction with a Ketone with α-Protons (with Respect to the Carbonyl Group) in an Alkaline Medium[a]



[a]Upon acidification, a highly fluorescent compound is formed.

synthesis.[21−25] In this experiment, the pyridine nitrogen atom of nicotinamide (3-pyridinecarboxylic acid amide) serves as the nucleophile, which is alkylated by the electrophilic epoxide to form an *N*-alkylpyridinium salt. The epoxide ring-opening requires a proton source to convert the alkoxide anion formed in the first step to a hydroxyl group. For a successful reaction, protonated nicotinamide (1:1 to epoxide groups) is used containing a slight excess of nonprotonated nicotinamide, which starts the reaction. It is essential to protonate the pyridine derivative prior to exposure to the epoxide-containing polymer and make sure that some unprotonated nucleophile is still present, because the direct reaction of free acid with the multiepoxide-containing polymer can lead to cross-linking. The polymer with pendant *N*-alkylpyridinium groups can be reacted with acetone in the presence of bases (Scheme 2)[26] to yield a highly fluorescent compound, which can be used as an "ink" (Figure 5). Even if some mild crosslinking takes place during the modification, the reaction mixture can still be used as an "ink" to draw on paper. If the crosslinking is very substantial, the fluorescence of the bulk material can be demonstrated by exposing the reaction mixture in the vessel to UV light.

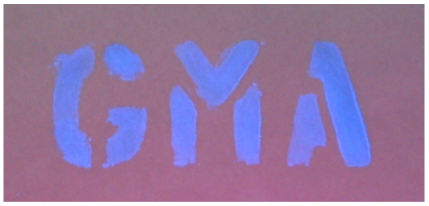


Figure 5. A stenciled drawing of the abbreviation, "GMA", made on paper with a solution of the fluorescent polymer as the "invisible ink" is shown under UV light.

As with the polymerization procedure, NMR spectroscopy is an excellent way to track the kinetics of the alkylation reaction (the first step shown in Scheme 2). The three proton peaks (p_6, p_7, p_8 (Figure 3)) of the epoxide groups are monitored over the progress of the reaction (Figure 6). As the ring-opening progresses, the intensity of these peaks decreases. The reaction is complete when the epoxide peaks have completely disappeared (ca. 2.5 h).

Students in this course have all completed first-year general chemistry, one year of organic chemistry, and one semester of quantitative analysis. All are concurrently enrolled in physical chemistry, and some are also enrolled in either biochemistry or advanced inorganic chemistry. Those with undergraduate research experience are far more prepared, produce better laboratory reports, and more successfully answer the questions. When possible, a more experienced and less experienced student are assigned to work together since both benefit by the teacher−student relationship. In a prior experiment offered in the class, the students prepare silicone-based putty, which is designed as a "warm-up" lab since it introduces many terms used in polymer chemistry. Most students successfully generated and at least partially controlled the GMA polymerization. Major sources of error have included inconsistent temperature of the oil bath (failure to read the hot plate−stirrer operation directions), failure to add initiator because the microsyringe had an undiscovered hairline crack or clogged needle, and, of course, inadvertent introduction of oxygen, which either stopped or slowed down the reaction. Regardless of the results they obtained, the students gained valuable technique experience since most had never worked with

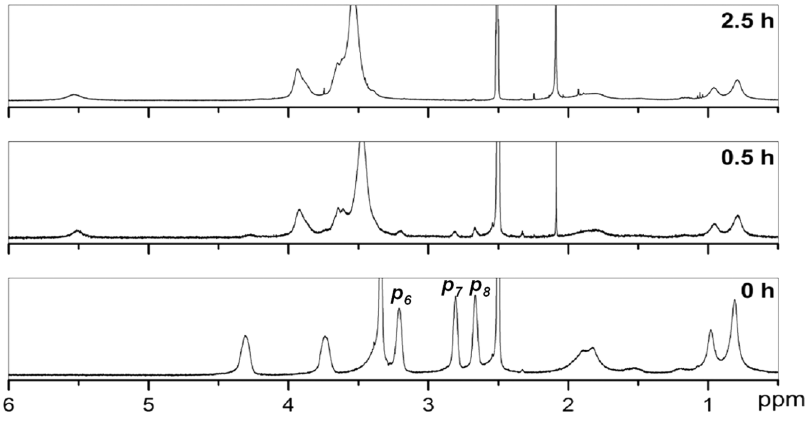


Figure 6. Kinetics of epoxide ring opening by nicotinamide.

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rigorous exclusion of oxygen. Generally, in the 4−5 h, students reached 40 to 80% conversion. All successfully generated the plots (conversion and $\ln([M]_0/[M]_t)$ vs time and M_n vs conversion). One student even calculated the apparent rate constant of propagation ($k_{p,app} = k_p \times [R^\bullet]$) from the slope of the first-order kinetic plot, even though this was not specifically requested. Students all seemed to understand the significance of the relatively narrow MWD dispersities, with some even discussing the mathematical derivations of the number- and weight-average molecular weights in the laboratory reports. All students seemed to fully grasp the significance of postpolymerization modification reactions for altering polymer properties, i.e., structure−property concepts. One of the most significant outcomes is that students demonstrated a far better understanding of the scope of NMR spectroscopy. The more mathematically inclined students were excited by the clever use of integration to follow reaction progress.

SUMMARY

An experiment was developed to introduce controlled/"living" polymerization techniques and postpolymerization modifications to undergraduate students. In the first session of the experiment, students synthesize poly(glycidyl methacrylate) (polyGMA) via low-catalyst-concentration ATRP and follow the reaction progress. The use of such techniques allows for a low maintenance experiment that simultaneously exemplifies a variety of important concepts and techniques commonly used in synthetic chemistry. In the second session, students modify the previously obtained polyGMA with nicotinamide in the presence of acetone, affording a fluorescent polymer.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00738.

CAS numbers for reagents, student laboratory handout, instructor notes, and sample student data (PDF, DOC)

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Notes

The authors declare no competing financial interest.

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