Optimization of a Metal Catalyzed Process – A Case Study of Metal-Mediated Radical Polymerizations

Overview

The focus of this experiment is catalyst research. Over a 5-week long project (plus time for discussion in the last lab period of the semester), you will use metal-mediated **a**tom **t**ransfer **r**adical **p**olymerizations (ATRP) as a case study to learn about discovering and improving catalysts. Over the first two weeks you will repeat known work to gain familiarity with the laboratory skills involved and to demonstrate that you can reproduce the expected results. In the third week you will present your results as a 5 minute Powerpoint presentation. We will then discuss ways of further exploring the known catalyst system and formulating hypotheses for improving catalyst performance. What were you curious about as you repeated the existing work? How would you make the process or the catalyst system more efficient? In the final three weeks of labs, you will set out to answer some of the questions raised in the discussion and conduct research to better our understanding of this catalyst system.

Introduction

Controlled radical polymerizations provide the power to dictate the composition, molecular weight and molecular weight distribution of macromolecules, and to precisely control their architecture. Atom transfer radical polymerization (ATRP) is one such technique, and its applications to the synthesis of new designer macromolecules have led to an unprecedented exploration of applications,[1-5] including the preparation of hybrid materials[6] and bioconjugates.[7,8] To get a glimpse of the importance and possible impact, please read an article by one of the pioneers of this work, Prof. Kris Matyjaszewski (Matyjaszewski, K., Spanswick, J. *Materials Today*, **2005**, *3*, 26).

Our society relies heavily on the production and use of synthetic polymers, and billions of pounds of these materials are produced annually in the United States alone. Many polymers are generated from vinyl monomers.

These monomers consist of an alkene functionality CH_2=CHR, where R can be H (ethylene), methyl (propylene), phenyl (styrene) or an ester (e.g. acetate for ethylacrylate), for example (Figure 1).

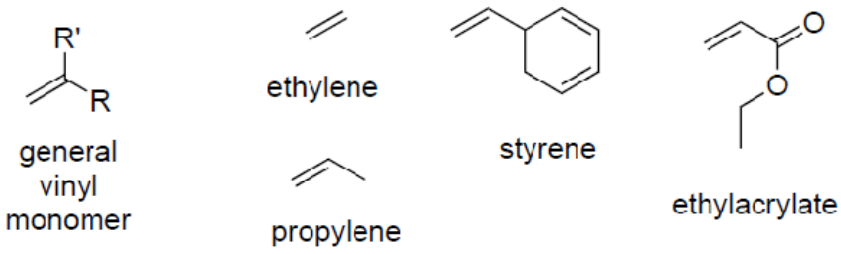

Figure 1: General structure of a vinyl monomer and four examples of these important polymer building blocks.

The most commonly used method to make these polymers is radical chain growth polymerization, a process that uses some of the radical chemistry that you might be familiar with from your first semester of organic chemistry. In free radical polymerizations of vinyl monomers the polymerization is initiated by the formation of a radical from an initiating species. This process is illustrated for the monomer styrene in Figure 2a. The initial radical can now react with a monomer molecule to start the polymerization process (Figure 2b). This process continues to form a long chain of a polymer until the radical chain end reacts with another radical to terminate the growth process (Figure 2c).

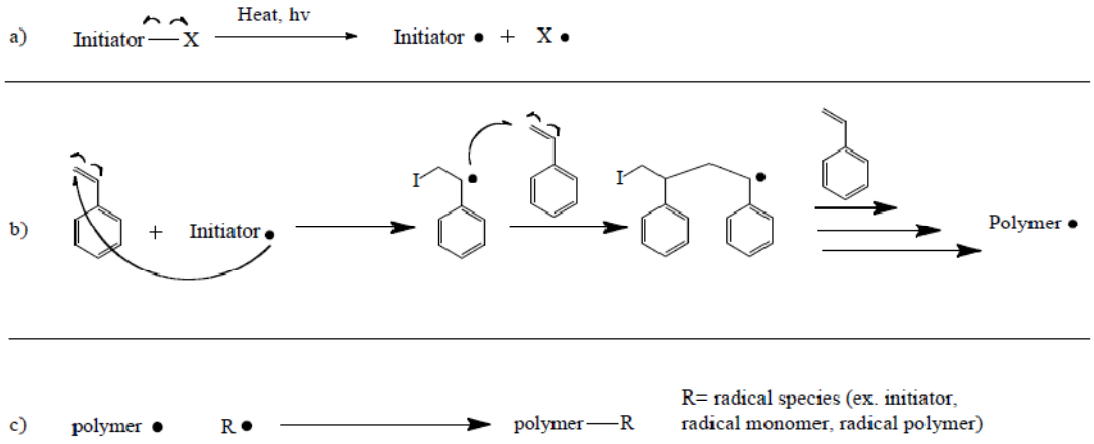

Figure 2: The Free Radical Polymerization of Styrene. An initiator radical is formed (a) and initiates the free radical polymerization (b). Polymerization ceases upon radical recombination (c).

A way to observe the polymer growth is to monitor the consumption of monomer and to determine the molecular weights of the polymers at these points of consumption or conversion. Using this data, we can plot the molecular weight of the polymers generated as a function of conversion of the monomer into polymer (Figure 3). For a conventional free radical polymerization high molecular weights of polymers are obtained even at low conversion. Although consumption of the monomer continues as the reaction progresses, new polymer molecules of similar high molecular weights form. Thus the average molecular weight of the products remains approximately the same throughout the reaction. More accurately, this process leads to a statistical distribution of molecular weights since the conditions change to favor longer or shorter chains. A number called the polydispersity (M_w/M_n) describes this distribution of chain lengths or molecular weights. M_w refers to the weight average molecular weight of the polymer population, M_n to the number average molecular weight. Both these numbers are generated in the measurement of the polymer molecular weights using size

Insert Figure 1 from supplemental materials of ref. 16.

Figure 3. Molecular weight as a function of percent monomer conversion for conventional and radical polymerizations.

exclusion chromatography. You will thus be able to calculate the polydispersity of your polymer products.

For our purposes of studying catalysts, we can use the polydispersity as a measure of the effectiveness of the catalyst. A value of M_w/M_n = 1.00 results from a product sample that contains only one size of molecules. For example, proteins and nucleic acids have a polydispersity of 1.00 because in nature, polymers can be made in a highly specialized and well-defined way. In contrast, the polydispersity in a conventional radical polymerization is typically 2.0 or higher. This number represents a product sample with molecular weights ranging from a few thousand to several hundred thousand grams per mole. Another characteristic of radical polymerizations is that radical chain ends react with each other to terminate chains with either saturated alkane or sterically hindered alkene chain ends, which makes further transformation of the chain ends into other types of chemical groups for modification of the polymer product difficult.

In air, carbon-centered radicals and catalysts are easily oxidized by oxygen. Therefore these polymerizations are carried out under inert atmosphere.

In this experiment you will be introduced to one of the most exciting recent advances in the field of radical polymerizations called Atom transfer radical polymerization (ATRP) pioneered at Carnegie Mellon University by Professor Krzysztof Matyjaszewski.[1] With ATRP, polymer scientists have the ability to control the radical process to prepare polymers with *well-defined* molecular weights (and therefore sizes and shapes) and with *functional groups* thus permitting further modification of the polymer product. In a way, ATRP and other like-techniques have enabled chemists to become macromolecular architects.

In ATRP, polymerization is mediated by a metal complex (Figure 4). After the initiation step described above, the rate of chain growth is now regulated by exchange of a halogen atom between a transition metal catalyst and the propagating radical. As a results of this capping of the growing polymer chains with halide, the number of radicals present at any one time is small, and the classical mode of termination of radicals is almost eliminated. The halide cap comes on and off in a periodic fashion, and for the entire population of growing polymer chains the halide capping occurs in a statistical manner. Nearly all the polymer chains grow at the same rate.

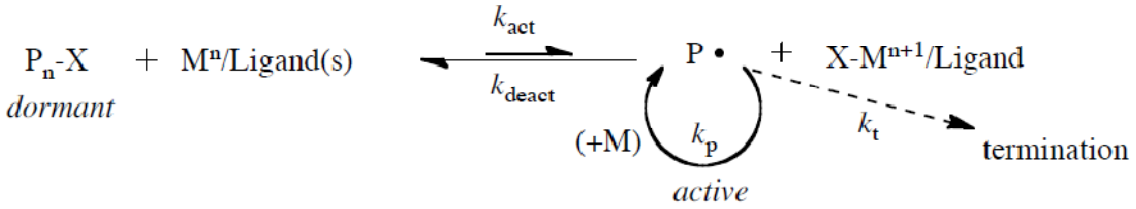

Figure 4: General Scheme of atom transfer radical polymerization. A transition metal catalyst [Mn/Ligand(s) mediates the equilibrium between the dormant and active polymer chains by facilitating the transfer of a halogen (X) between them. Propagation occurs by monomer (M) addition when the polymer is in its active state.

Consequences of regulating the growth of chains are:

- The molecular weight increases steadily with conversion. This increase is demonstrated in the plot of molecular weight vs. conversion shown in Figure 3 for controlled polymerization.

The result is a *well-defined* polymer sample with low polydispersity – meaning all the molecules in the sample have nearly the same molecular weight.

- Polymer chains have a halogen atom on the end when the reaction is finished. This end group gives the polymer *functionality* that can then be manipulated in a number of ways:
  - these polymers can then be extended with another monomer to form block copolymers,
  - the end group (i.e. halogen) can be transformed to another functional group such as an azido, amino, or hydroxyl group using standard organic synthesis techniques. With such diverse chemistry, the polymer can now be tethered to surfaces or incorporated into other polymers.

Since the original publications,[9-11] catalysts based on a number of metals have been reported, including systems with Ti, Fe, Ru, Rh, Ni, Pd, and Cu.[4,5] For copper, a variety of ligands have been investigated, including bipyridines, multidentate amines and pyridyl imines.[4,5,12-14] From these examples, we can gleam requirements for a potential ATRP catalyst:

1. The metal possesses an accessible one electron redox couple.
2. Reversible halogen atom transfer is a facile process. For that to be the case, the metal center must be sterically unencumbered in its reduced form to accommodate the halogen atom.
3. The ligand structure supports the changes to the metal coordination sphere during the redox process.

The goal of this experiment is to

a) Demonstrate controlled radical polymerization catalyzed by a copper pyridine-imine complex first developed by the Haddleton group at the University of Warwick, UK.[15]
b) Examine the effect of changing the catalyst system on its performance. One such change will be the introduction of a third pendant ligand arm to the pyridine imine ligand structure.

In the final week of the semester, you will present your results in a 10 minute presentation. A final report will be due by 6 PM, Sunday, December X. No late submissions will be accepted.

References

(1) Matyjaszewski, *et al*., Science **1996**, *272*, 866.
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(3) Davis, K.; Paik, K. H.-J.; Matyjaszewski, K. *Macromolecules* **1999**, *32*, 1767.
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(8) Vazquez-Dorbatt, V.; Maynard, H. D. *Biomacromol.* **2006**, *7*, 2297-2302.
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(10) Patten, T. E.; Xia, J.; Abernathy, T.; Matyjaszewski, K. *Science* **1996**, *272*, 866.
(11) Matyjaszewski, K. *Chem. Eur. J.* **1999**, *5*, 3095-3102.
(12) Haddleton, D. M.; Jasieczek, C. B.; Hannon, M. J.; Shooter, A. J. *Macromol.* **1997**, *30*, 2190-2193.
(13) Matyjaszewski, K.; Goebelt, B.; Paik, H.-j.; Horwitz, C. P. *Macromol.* **2001**, *34*, 430-440.
(14) O'Reilly, R. K.; Gibson, V. C.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **2003**, *125*, 8450-8451.
(15) Perrier, S.; Berthier, D.; Willoughby, I.; Batt-Coutrot, D.; Haddleton, D. M. *Macromol.* **2002**, *35*, 2941-2948.
(16) This lab was adapted from Beers, K.L.; Woodworth, B.; Matyjaszewski, K. *J. Chem. Ed.* **2001**, *78*, 544.

Hazards

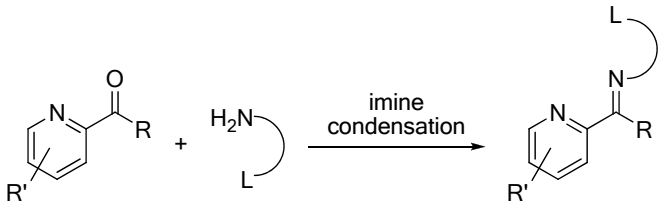
The experiments should be performed in a well-ventilated fume hood using your inert gas lines or in the glove box.
The monomer styrene is a suspected carcinogen, flammable, and a toxic irritant. Wear protective gloves particularly when handling the monomer.
Polymers can be disposed of as solid waste.

Experimental

Day 1 - Polymerization of Styrene and Ligand Synthesis

Working in pairs, the goals for today are to set up a polymerization of styrene using a copper(I)-*N*-alkyl-2-pyridylmethanimine complex as an ATRP catalyst (from Perrier, S.; Berthier, D.; Willoughby, I.; Batt-Coutrot, D.; Haddleton, D. M. *Macromol*. **2002**, *35*, 2941-2948) and to set up a ligand synthesis.

The synthesis of the pyridyl-imine ligands involves an imine condensation from aldehyde and amine starting materials. For the polymerization, you are supplied with all materials including the ligand. To prepare for the work in the second part of the project, you will also set up the synthesis of a new pyridyl-imine ligand with a third donor atom affording ligands of the general structure shown above.



Formation of pyridyl-imine ligands

See Prelab worksheet for details.

Polymerization of Styrene

Some prep work is carried out in a glove box, so all ligands and reagents were introduced into the glove box oxygen-free and dry. Styrene is used as received without removal of radical stabilizers.

Set-up an oil bath for 110°C. Weigh 0.44 mmol of solid CuBr into a 25mL Schlenk tube equipped with a stir bar. To this solid, add 2.5mL of toluene using a pipetor, followed by 1 mol equivalent of ligand using a syringe. With a syringe add 21.8 mmol of anisole (methoxybenzene, CAS Number, 100-66-3) to the reaction vial, remove the tube from the glovebox and allow the reaction mixture to stir for 10 minutes to allow ligation to occur.

Connect your tube to an Ar outlet of the Schlenk line and purge gently. Using a syringe, carefully add 44 mmol of styrene to the tube using a syringe, followed by 0.45 mmol of 1-ethyl-bromo-benzene initiator. Immediately following this addition, remove a 0.25mL aliquot for

analysis (t=0 sample) and store it in a vial in the freezer. Label this vial as your initial or standard sample.

Place the flask in a stirring, 110°C oil bath and note the time (to the minute) either with your watch or a timer. Collect aliquots at regular intervals to monitor the reaction: *every 30 minutes* remove another 0.4mL of the solution by syringe. Be sure to draw some gases from the headspace of the flask after you draw up the liquid to prevent spraying the contents of the syringe on the bench top once it is removed from the flask. Label the vials in consecutive order, swirl them in air for about 30 seconds to saturate the solution with air, then seal them with a cap and parafilm and place in the freezer. Note in your notebook the exact time that the samples are taken and any changes in color that you observe in a table with room for four more data columns (conversion, $M_{n,th}$, $M_{n,\mathrm{GPC}}$ and M_w/M_n). After your final sample during the lab period, return 4-6 hours after the polymerization has started to remove the Schlenk tube from the oil bath. Label it and place the reaction flask in the freezer until the next lab period.

Day 2 – Characterize ligands and polymer products

Goals

Obtain GC chromatograms and Gel Permeation Chromatography (GPC) traces for each polymer sample, and characterize your ligand thoroughly.

Characterization of Ligand

Characterize your ligand product by GC-MS, ^{1}H-NMR (in an appropriate solvent) and IR spectroscopy (salt plates, thin film).

Analysis of polymerization samples

You should have about 4-6 aliquot samples and one final polymerization sample to analyze for monomer conversion using GC and product molecular weights using GPC.

For the aliquots, dilute each of the samples with approximately the same volume of toluene. To remove catalyst residue filter the resulting mixture through a column of about 1/2 inch of basic alumina packed into a Pasteur pipette (with a small piece of cotton in the bottom). Collect the filtrate in a vial filled with about 4mL MeOH. Precipitation of a white substance is indicative of PS formation. If precipitation of PS has occurred, centrifuge the sample for 5-10 minutes. Collect the supernatant with a plastic syringe. Attach a 0.45μm PTFE syringe filter to the syringe and filter about 0.5mL of the supernatant into a clean vial containing 1.0mL of dichloromethane for GC analysis. For the samples with a white PS residue, wash with MeOH and air dry. Analyze these solid polymers by GPC.

For the final reaction mix, dilute with toluene and filter the solution through a column of about 1 inch of basic alumina packed into a pipette (with a small piece of cotton in the bottom) to remove catalyst residue. Collect the filtrate in a 50mL beaker filled with 35mL stirred MeOH. Aspirate a sample of about 1mL of the supernatant with a plastic syringe, attach a 0.45μm PTFE syringe filter to the syringe and filter into a clean vial containing 1.0mL of dichloromethane for GC analysis. Collect the white precipitate by filtration, dry it in a vac oven and weigh the product in the next lab period.

For all samples, run GC (FID detector) of the filtered supernatant to determine conversion using anisole as the internal standard.

For all polymer samples collected, obtain a GPC trace (THF) to determine M_n, M_w and PDI. To prepare samples for GPC, dissolve approximately 10 mg of each the isolated polymer samples in 1.0-2.0mL THF. Filter these samples through syringe filters before injecting into the GPC.

Experiment D: Metal-Mediated Atom Transfer Radical Polymerizations
Pre Lab Questions

Due at the beginning of lab - Monday, Oct. XX

Name: _____ Score /15

1. Write an experimental procedure for the synthesis of a pyridyl imine ligand using 2-(dimethylamino)ethylamine (CAS Number 108-00-9, $(CH_3)_2NCH_2CH_2NH_2$)) as the amine and pyridine-2-carboxaldehyde. The following excerpt is taken from a paper by Haddleton's grou detailing the synthesis of the pyridyl-imine ligands. This procedure should be used as a template for your process. (7 points)

***"N*-(*n*-Pentyl)-2-pyridylmethanimine.** An excess of *n*-pentylamine (29.0 mL, 0.25 mol) was added dropwise to a stirred solution of pyridine-2-carboxaldehyde (20.0 mL, 0.21 mol) in diethyl ether (20 mL) cooled in an ice bath. After complete addition of the amine, anhydrous magnesium sulfate (5 g) was added and the slurry stirred for 2 h at 25°C. The solution was filtered, solvent removed, and the product purified by distillation under reduced pressure to give a golden yellow oil. Yield: 35.8 g (96.7%). Bp 80 °C/0.4 Torr. ^{1}H-NMR ($CDCl_3$): δ 8.61 (m, 1H), 8.36 (s, 1H), 7.95 (m, 1H), 7.72 (m, 1H), 7.29 (m, 1H), 3.66 (t, 2H), 1.71 (sextet, 2H), 1.33 (overlapping quintets, 2H each), 0.89 (t, 3H). ^{13}C-NMR ($CDCl_3$): δ 161.6, 154.6, 149.3, 136.4, 124.5, 121.1, 61.6, 30.3, 29.4, 22.4, 14.0. IR: 1648 cm^{-1} (ν_{C-N}). MS (EI): *m*/*z* + 1 177 Da. Anal. Calcd for C11H16N2: C, 74.9; H, 9.2; N, 15.9. Found: C, 74.37; H, 9.16; N, 15.90."

2. In your **lab notebook**, create a reagent table for the ligand synthesis. (4 points)

3. In your **lab notebook**, write a flow chart of the experimental steps for the polymerization of styrene that would allow you to proceed without further reference to this lab manual. Create a reagent table for the experiment you will perform. (8 points)

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Experiment D: Metal-Mediated Atom Transfer Radical Polymerizations
In-Between Assignment 1

Due at the beginning of lab - Monday, Nov. 3

Name: _____ Score /10

Partner: _____

1. Submit a title page (no abstract needed yet) and an introduction for Lab D. To write the introduction, you are encouraged to complete a SciFinder or Web of Science search for references. Pick three to five articles to read to get a feel for the importance of this type of work. (10 points)

   You will be able to use this introduction and the feedback to write your final report.

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Experiment D: Metal-Mediated Atom Transfer Radical Polymerizations
In-Between Assignment 2

Due for class - Friday, Nov. 7

Name: _____ Score /15

Partner: _____

1. Construct four plots from the data that you've obtained:
    a. M_n versus monomer conversion (label the graph as either fractional or % conversion)
    b. M_w/M_n (polydispersity) versus monomer conversion
    c. % conversion versus time and
    d. ln(1-fractional conversion) versus time. (10 points)

2. Submit carefully annotated NMR spectra of the ligand you made, showing the assignments of peaks. To confirm the assignment of the peaks, you may want to do a literature search of the compounds. (5 points)

3. Using your work from assignments 1. and 2., as well as your reading, prepare a 5-10 minute presentation of your results. Also include a set of 3 suggestions or changes to the polymerization systems that you might consider exploring over the next three weeks.

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Experiment D: Metal-Mediated Atom Transfer Radical Polymerizations
In-Between Assignment 3

Due at the beginning of lab - Monday, Nov. 17

Name: _____ Score /10

Partner: _____

1. Submit experimental and up-to-date results sections for Lab D. Include any figures / schemes / tables necessary to clearly present your data. (10 points)

   You will be able to use these sections and the feedback to write your final report.

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Experiment D: Metal-Mediated Atom Transfer Radical Polymerizations
In-Between Assignment 4

Due at the beginning of lab - Monday, Nov. 24

Name: _____ Score /10

Partner: _____

2. Submit partial abstract and discussion sections for Lab D. Include any projected findings and suggestions for further work. (10 points)

   You will be able to use these sections and the feedback to write your final report.

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Experiment D: Metal-Mediated Atom Transfer Radical Polymerizations
Post Lab Questions

Due 6 PM - Sunday, December 7, 2008 – No Late Days

Name: _____ Score /100

Partner: _____

1. Your assignment is to produce a complete publication-like lab report, detailing the results of your work. This report is due by 6 PM, Sunday, December 7, 2008. Use your experiences with writing report sections from the previous labs as well as the following pages as guidelines for this style of report.

   Include figures and schemes to illustrate your results and support your conclusions, and be sure to have your references in proper ACS style format.