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“Click” and Olefin Metathesis Chemistry in Water at Room Temperature Enabled by Biodegradable Micelles

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Abstract

The two laboratory reactions focus on teaching several concepts associated with green chemistry. Each uses a commercial, nontoxic, and biodegradable surfactant, TPGS-750-M, to promote organic reactions within the lipophilic cores of nanoscale micelles in water. These experiments are based on work by K. Barry Sharpless (an azide–alkyne “click” reaction) and Robert Grubbs (an olefin cross-metathesis reaction); both are suitable for an undergraduate organic laboratory. The copper-catalyzed azide–alkyne [3+2] cycloaddition of benzyl azide and 4-tolylacetylene is very rapid: the triazole product is readily isolated by filtration and is characterized by thin-layer chromatography and melting point analysis. The ruthenium-catalyzed olefin cross-metathesis reaction of benzyl acrylate with 1-hexene is readily monitored by thin-layer chromatography and gas chromatography. The metathesis experiment comparatively evaluates the efficacy of a TPGS-750-M/water medium relative to a traditional reaction performed in dichloromethane (a common solvent used for olefin metathesis).

Keywords

second-year undergraduate; upper-division undergraduate; laboratory instruction; organic chemistry; catalysis; green chemistry; micelles; microscale lab; solutions/solvents; aqueous solution chemistry

Green chemistry emphasizes the development of processes leading to products that minimize waste, as well as the use of hazardous substances.¹ For sustainable commercial processes, the proper selection of a reaction solvent is crucial. Water is the cheapest, safest, and most environmentally benign solvent. However, the poor solubility of neutral organic compounds in water has generally limited its use in synthetic organic chemistry. One method to circumvent this problem is to add small amounts of an amphiphilic molecule (a molecule that contains both hydrophilic and hydrophobic components) that spontaneously self-aggregates to form nanomicelles.² The hydrophobic core of each nanoparticle provides an environment for effecting homogeneous reactions between organic molecules.

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Supporting Information. Student lab experiments (including pre-lab and post-lab activities), instructor preparation notes and information, and photos of representative student data. This material is available via the Internet at <http://pubs.acs.org>.

The two experiments described here were developed for, and implemented in, an undergraduate organic laboratory course. Both utilize the biodegradable and commercially available amphiphile TPGS-750-M^{3,4} (Figure 1) in aqueous media. Although laboratory experiments that demonstrate the kinetic effects of micelles on simple substitution or complexation reactions have previously been reported,⁵ these are the first examples of synthetic organic laboratory experiments for undergraduates using an aqueous micellar reaction medium at ambient temperatures.

The two reactions featured in these experiments are shown in Schemes 1 and 2: a copper-catalyzed azide–alkyne [3+2] cycloaddition (CuAAC) reaction,^{6,7} often referred to as a “click” reaction,⁸ and an olefin cross-metathesis (CM) reaction.^{9,10} These are among the most versatile, powerful, and popular reaction types currently used by chemists, biologists, and materials scientists. CuAAC reactions have previously been featured in undergraduate laboratory experiments,¹¹ though the reactions in these cases required heating to 60–80 °C in organic solvents and longer reaction times. Olefin metathesis reactions, the topic of the 2005 Nobel Prizes in Chemistry¹² have also been featured in this *Journal*.^{13,14} Of these, only one has specifically dealt with olefin cross metathesis;¹³ lengthy reaction times (12 h) and anhydrous, inert conditions were needed. By contrast, the experiments presented herein were completed within a single, 3-hour laboratory period, employing conditions tailored to give highly chemoselective outcomes using commercial reagents. Moreover, the presence of TPGS-750-M enabled optimal reactant conversions to the desired products under ambient and safe, aqueous conditions.

Experimental Overview

Two experiments are described and have been tested with undergraduate organic laboratory students, both simultaneously (3 classes) and singly (1 class).

“Click” Experiment

Each student individually reacts benzyl azide (0.5 mmol) and 4-tolylacetylene (0.5 mmol) for 20 min at room temperature in water containing TPGS-750-M (2 wt %) and a copper catalyst. The triazole product¹⁵ is isolated by vacuum filtration and analyzed by thin-layer chromatography (TLC) and melting point.

Olefin Cross-Metathesis Experiment

Two olefin cross-metathesis reactions are performed by student pairs. The same reactants, but different solvents and additives, are used for each: one reaction is conducted in dichloromethane, the second in aqueous TPGS-750-M (2 wt %) with potassium hydrosulfate (0.08 equiv). Both experiments are carried out at ambient temperature on a 0.5-mmol scale, using benzyl acrylate (2 equiv), 1-hexene (1 equiv), and the Grubbs 2nd-generation catalyst (2.5 mol%). These reactions are monitored quantitatively by gas chromatography (GC) and qualitatively by TLC to assess reactant conversion to cross product. The products of these metathesis reactions are not isolated.

If desired, characterization of the cross product can be accomplished using gas chromatography-mass spectrometry (GC-MS) analysis. Flash chromatographic purification of the product is also an option if the metathesis reaction is allowed to run for 12 h; an additional laboratory period is required for characterization. Details on characterization (GC-MS; NMR) are provided in the Supporting Information.

Hazards

TPGS-750-M is generally regarded as benign. However, it may cause irritation or harm: avoid contact, inhalation, and ingestion. Hexanes are flammable and a skin irritant; *n*-hexane is also a neurotoxin. 4-Tolylacetylene is flammable, a skin and lung irritant, and harmful if swallowed. Copper sulfate is a skin and eye irritant and harmful if swallowed. Benzyl azide is flammable and should be kept away from heat to prevent explosions; for greater protection, it may be dispensed behind a blast shield. The product of the “click” reaction, 1-benzyl-4-*p*-tolyl-1*H*-1,2,3-triazole, should be viewed as a toxic irritant. Dichloromethane is a volatile, non-flammable liquid; chronic exposure can lead to an increased risk of developing cancer, in addition to adverse effects on the heart, central nervous system, and liver. Dichloromethane can also cause skin and eye irritation. Potassium hydrosulfate can cause severe skin burns and eye damage; inhalation may cause respiratory irritation. 1-Hexene and ethyl acetate are highly flammable; avoid exposure to ignition sources. Benzyl acrylate, dodecane, and 1-hexene are irritants. The cross product of the metathesis reaction [(*2E*)-2-heptenoic acid phenylmethyl ester] should also be viewed as an irritant; avoid inhalation and skin contact. The Grubbs 2nd-generation catalyst is a flammable solid: heat, sparks, open flames, and hot surfaces should be avoided with this solid; it is also an irritant. Silica gel is an inhalation hazard. Although the ethylene produced in the metathesis reactions is a flammable gas, it is not produced in sufficient quantities in the metathesis reactions to merit special handling protocols beyond that recommended for the flammable solvents used (e.g., ethyl acetate and hexanes). Ethyl vinyl ether (if used) is a flammable liquid, irritant, and toxic to the liver; ethyl vinyl ether can also form explosive peroxides. Gloves and protective eyewear should be worn for all of these experiments; all organic liquids should be handled in a well-ventilated fume hood.

Discussion

These experiments provided an excellent opportunity for students to develop an appreciation for the principles of green chemistry.^{16,17,18} The organic reactants were inexpensive, and the metals were used in catalytic amounts. Purification of the triazole product from the click reaction required only a simple filtration. When performed by three sections of a first-semester, organic chemistry laboratory class (15 students total), students obtained isolated yields ranging from 70 to 90%. Qualitative analysis of this reaction by TLC worked well for all of the students. Despite the extremely simple purification procedure to isolate the triazole product, student melting points (average student melting range: 151.5–153.6 °C) were found to strongly correlate with the reported literature value¹⁹ (151–153 °C).

The metathesis reactions did not involve product isolation when performed as described. This experiment was performed in four sections of an undergraduate organic chemistry class (19 students total). GC conversions to cross product at the 60-minute point were found to be comparable (46–51% conversion for the reactions run in dichloromethane and 43–47% conversion for the reactions run in TPGS-750-M), thereby illustrating a viable alternative to the use of a toxic solvent. In fact, if one were to gauge the “greenness” of these metathesis reactions by calculating the effective mass yield of each, it would be found that the reaction conducted in the aqueous solution of TPGS-750-M was far superior (4% vs 49%).²⁰

By TLC, students also observed that the aqueous metathesis reaction containing TPGS-750-M had a conversion to cross product comparable to that observed for the reaction run in dichloromethane. In some instances, a student acquired a poorly resolved TLC plate (due to merging or slanting lanes, different concentrations of sample between lanes, or TLC standards of insufficient concentration). This was readily remedied by repeating the TLC analysis at an alternative time point.

These appear to be the first experiments describing the use of a biodegradable amphiphile in teaching laboratories. TPGS-750-M, with its commercial accessibility and its ease of use, has provided an ideal platform to demonstrate the application of micellar catalysis to organic and organometallic reactions. Topically within the undergraduate curriculum, these experiments build off of initial discussions on solubility; the topic of micelles also provided a natural pedagogical transition to the topic of the lipid bilayers found in biological systems.

Although most organic chemistry textbooks currently do not include azide–alkyne cycloadditions or olefin metathesis reactions, these reactions play an important role in both academic and industrial laboratories. For discussion-based inquiry regarding the click reaction, the role of copper in accelerating the cycloaddition reaction was addressed.⁶ A rough analogy between azide–alkyne cycloadditions and the first step of alkene ozonolysis also provided a connection to topics covered in the lecture portion of the course. Lastly, to place this experiment within a broader context, the applications of CuAAC reactions to biological systems²¹ and a brief overview of the history of CuAAC reaction development were introduced, with particular attention given to the groundbreaking work of Huisgen⁷ and Sharpless.⁸

The olefin metathesis experiment enabled additional topics within green chemistry to be addressed, particularly with regard to the use of sustainable starting materials and the minimization of reaction byproducts.¹⁸ The olefin metathesis experiment also provided the opportunity to discuss the 2005 Nobel Prizes in Chemistry;¹² particular emphasis was given to reaction mechanism and scope. For example, the 1971 mechanism proposed by Hérisson and Chauvin²² was used to rationalize the formation of the cross product. Organic students readily comprehended the “molecular square dance” analogy provided by the Nobel press release,¹² which provided an excellent starting point to begin discussion. Elaborating off of this, examples of ring-closing and ring-opening metathesis were introduced in relation to the CM reaction, highlighting the diversity of transformations obtainable via a common mechanism. With an understanding of the mechanism, students were able to comprehend the purpose of adding potassium hydrosulfate to the aqueous phase of the CM reactions.³ A brief discussion on the commercialization of the olefin metathesis reaction²³ also resonated well with students, as it highlighted the “real world” applications associated with their laboratory experiment.

Conclusion

The two experiments described here proved to be rapid and reliable. They illustrated the principles of green chemistry, most notably focusing on catalysis and the use of an innocuous reaction medium. Both the click reaction, as well as the olefin cross-metathesis reaction, served as good introductions to concepts from organic, inorganic, organometallic, and biological chemistry. In their pre-lab and post-lab exercises, first-semester organic students demonstrated that they were able to effectively evaluate and appreciate both the conceptual and practical aspects of each experiment. From this, the successful execution of these organic laboratory experiments emphasized their applicability to the undergraduate curriculum.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Anastas, P.T.; Warner, J.C. *Green Chemistry Theory and Practice*. Oxford University Press; New York: 1998.
2. (a) Dwars T, Paetzold E, Oehme G. Reactions in Micellar Systems. *Angew Chem, Int Ed*. 2005; 44:7174–7199.(b) Khan, M.N. *Micellar Catalysis*. CRC Press; Boca Raton, FL: 2006.
3. (a) Lipshutz BH, Ghorai S, Abela AR, Moser R, Nishikata T, Duplais C, Krasovskiy A, Gaston RD, Gadwood RC. TPGS-750-M: A Second-Generation Amphiphile for Metal-Catalyzed Cross-Couplings in Water at Room Temperature. *J Org Chem*. 2011; 76:4379–4391. [PubMed: 21548658] (b) Lipshutz BH, Ghorai S. “Designer”-Surfactant-Enabled Cross-Couplings in Water at Room Temperature. *Aldrichimica Acta*. 2012; 45:3–16. [PubMed: 23807816]
4. [accessed Sep, 2013] Commercially available from Sigma-Aldrich. (#733857; www.sigmaaldrich.com)
5. (a) Corsaro G, Smith JK. Micelle Catalysis of an Aromatic Substitution Reaction. *J Chem Educ*. 1976; 53:589–590.(b) Corsaro G. Micelle Catalysis of an Ionic Substitution Reaction. *J Chem Educ*. 1980; 57:225–226.(c) García-Mateos I, Herráez MA, Rodrigo M, Rodríguez LJ, Velázquez MM. Catalysis by Micelles and by Cycloamyloses: A Comparative Set of Kinetic Experiments. *J Chem Educ*. 1981; 58:584–585.(d) Reinsborough VC, Robinson BH. A Convenient Stopped-Flow Experiment: Demonstrating the Influence of Micelles on Reaction Kinetics. *J Chem Educ*. 1981; 58:586–588.(e) Rodenas E, Vera S. Effect of Cationic Micelles on the Hydrolysis of 4-Nitrophenyl Acetate. *J Chem Educ*. 1985; 62:1120–1121.(f) Crujeiras J, Leis JR, Rios A. Micellar Effects on the Spontaneous Hydrolysis of Phenyl Chloroformate. A Kinetic Experiment for the Physical Chemistry Laboratory. *J Chem Educ*. 2001; 78:1538–1540.
6. For a review, see: Hein JE, Fokin VV. Copper-catalyzed Azide–Alkyne Cycloaddition (CuAAC) and Beyond: New Reactivity of Copper(I) Acetylides. *Chem Soc Rev*. 2010; 39:1302–1315. [PubMed: 20309487]
7. Huisgen, R. Historical Note, General Principle and Mechanistic Criteria. In: Padwa, A., editor. *1,3-Dipolar Cycloaddition Chemistry*. Vol. I. Wiley-Interscience; New York: 1984. p. 1-176.
8. (a) Kolb HC, Finn MG, Sharpless KB. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew Chem Int Ed*. 2001; 40:2004–2021.(b) Rostovtsev VV, Green LC, Fokin VV, Sharpless KB. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective “Ligation” of Azides and Terminal Alkynes. *Angew Chem Int Ed*. 2002; 41:2596–2599.
9. For reviews on cross-metathesis, see: Wenzel AG, Chatterjee AK, Grubbs RH, Ojima I, Hiyama T. Olefin Cross-Metathesis. *Comprehensive Organometallic Chemistry III: Review of the Literature 1993–2005*. Elsevier LtdOxford112006; :179–205.Chatterjee AK, Choi TL, Sanders DP, Grubbs RH. A General Model for Selectivity in Olefin Cross Metathesis. *J Am Chem Soc*. 2003; 125:11360–11370. [PubMed: 16220959]
10. Chatterjee AK, Morgan JP, Scholl M, Grubbs RH. Synthesis of Functionalized Olefins by Cross and Ring-Closing Metatheses. *J Am Chem Soc*. 2000; 122:3783–3784.
11. (a) Sharpless WD, Wu P, Hansen TV, Lindberg JG. Just Click It: Undergraduate Procedures for the Copper(I)-Catalyzed Formation of 1,2,3-Triazoles from Azides and Terminal Acetylenes. *J Chem Educ*. 2005; 82:1833–1836.(b) Mendes DE, Schoffstall AM. Citrus Peel Additives for One-Pot Triazole Formation by Decarboxylation, Nucleophilic Substitution, and Azide–Alkyne Cycloaddition Reactions. *J Chem Educ*. 2011; 88:1582–1585.
12. (a) Casey CP. Nobel Prize in Chemistry. Development of the Olefin Metathesis Method in Organic Synthesis. *J Chem Educ*. 2006; 83:192–195. 2005. (b) [accessed Sep 2013] Advanced Information on the 2005 Nobel Prize. http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2005/advanced-chemistryprize2005.pdf

13. Olefin CM experiment: Taber DF, Frankowski KJ. Grubbs's Cross Metathesis of Eugenol with cis-2-Butene-1,4-diol To Make a Natural Product. An Organometallic Experiment for the Undergraduate Lab. *J Chem Educ.* 2006; 83:283–284.
14. Metathesis polymerization and ring-closing metathesis experiments: Moorhead EJ, Wenzel AG. Two Undergraduate Experiments in Organic Polymers: The Preparation of Polyacetylene and Telechelic Polyacetylene via Ring-Opening Metathesis Polymerization. *J Chem Educ.* 2009; 86:973–975. Greco GE. Nobel Chemistry in the Laboratory: Synthesis of a Ruthenium Catalyst for Ring-Closing Olefin Metathesis. *J Chem Educ.* 2007; 84:1995–1997. Pappenfus TM, Hermanson DL, Ekerholm DP, Lilliquist SL, Mekoli ML. Synthesis and Catalytic Activity of Ruthenium–Indenylidene Complexes for Olefin Metathesis. *J Chem Educ.* 2007; 84:1998–2000. France MB, Uffelman ES. Ring-Opening Metathesis Polymerization with a Well-Defined Ruthenium Carbene Complex: An Experiment for the Undergraduate Inorganic or Polymer Laboratory. *J Chem Educ.* 1999; 76:661–665. Viswanathan T, Jethmalani J. The Aqueous Ring-Opening Metathesis Polymerization of Furan-Maleic Anhydride Adduct: Increased Catalytic Activity Using a Recyclable Transition Metal Catalyst. *J Chem Educ.* 1993; 70:165–167.
15. Iwasaki M. Microwave-Assisted Palladium-Catalyzed Direct Arylation of 1,4-Disubstituted 1,2,3-Triazoles with Aryl Chlorides. *Chem-Asian J.* 2007; 2:1430–1435. [PubMed: 17910013]
16. For overviews of green chemistry, see: Linthorst JA. An Overview: Origins and Development of Green Chemistry. *Found Chem.* 2010; 12:55–68. Hjerresen DL, Boese JM, Schutt DL. Green Chemistry and Education. *J Chem Educ.* 2000; 77:1543–1544. 1546–1547.
17. Click reactions and green chemistry: Gil MV, Arevalo MJ, Lopez O. Click Chemistry - What's in a Name? Triazole Synthesis and Beyond. *Synthesis.* 2007:1589–1620.
18. Dragutan, V.; Démonceau, A.; Dragutan, I.; Finkelshtein, ES. Olefin metathesis reactions and green chemistry: Green Metathesis Chemistry: Great Challenges in Synthesis, Catalysis and Nanotechnology (NATO Science for Peace and Security Series A: Chemistry and Biology). Springer; Dordrecht, The Netherlands: 2009.
19. Suarez JR, Trastoy B, Perez-Ojeda ME, Marin-Barrios R, Chiara JL. Nonafluorobutanesulfonyl Azide: A Shelf-Stable Diazo Transfer Reagent for the Synthesis of Azides from Primary Amines. *Adv Synth Catal.* 2010; 352:2515–2520.
20. See Supporting Information, p 4.
21. Best MD. Click Chemistry and Bioorthogonal Reactions: Unprecedented Selectivity in the Labeling of Biological Molecules. *Biochemistry.* 2009; 48:6571–6584. [PubMed: 19485420]
22. Hérisson JL, Chauvin Y. Catalysis of Olefin Transformations by Tungsten Complexes. II. Telomerization of Cyclic Olefins in the Presence of Acyclic Olefins. *Makromol Chem.* 1971; 141:161–176.
23. Rouhi AM. Olefin Metathesis: Big Deal Reaction. *Chem Eng News.* 2002; 80(51):29–33.

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Scheme 1.
Azide-Alkyne "Click" Reaction Using Nanomicelles in Water

Scheme 2.
Olefin Cross-Metathesis Reaction Using Nanomicelles in Water