DE GRUYTER

GREEN CHEMISTRY AND TECHNOLOGY

Edited by Mark Anthony Benvenuto and George Ruger

GREEN CHEMICAL PROCESSING

Mark Anthony Benvenuto, George William Ruger, Jr. (Eds.)

Green Chemistry and Technology

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Volume 6

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About the series

Green Chemical Processing is a continuing series of volumes composed of refereed chapters, with upcoming volumes having submission dates of 15 June and 15 December each year. All areas of green chemistry, pending as well as established, are considered and welcome.

If you are interested in contributing a chapter, please contact series editor Mark Benvenuto, of the University of Detroit Mercy, at: benvenma@udmercy.edu concerning the appropriateness of your topic. We are interested in any and all new ideas that examine any of the twelve principles of green chemistry.

For more information on all previous and upcoming volumes of *Green Chemical Processing*, see

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Mark A. Benvenuto

1 Introduction

Abstract: This volume contains several chapters on different aspects of green chemical principles as applied to industrial production, education, and research opportunities. Included are chapters by one of the developers of the early improvements in ibuprofen production, as well as one by a former president of the American Chemical Society. Also, several educators and researchers who have incorporated green principles into their teaching or their research efforts have provided chapters, one of which does an excellent job of bridging the expanse from the teaching laboratory to the research lab and experience.

Keywords: industrial green chemistry, greening curriculum, undergraduate research, STEM

1.1 Introduction

This is the sixth volume in the continuing series Green Chemical Processing. We have collected some contributions in this volume that we believe showcase points of view not often seen elsewhere. They include the following:

A chapter by one of the first people to be involved with the greening of the production of ibuprofen – Dr. Murphy. As well, we are honored to have a former president of the American Chemical Society, Professor Ann Nalley, write a chapter on her experiences and the evolution of green chemistry in an academic environment. Both are authors who have points of view that many of us have not seen, and so are quite important in the greater discussion about what is green, both in industry and in academe. But each chapter in this volume is important, we believe.

1.2 The chapters

1.2.1 Exploring the vastness of design space for greener solution using a quality approach

Dr. Mark Murphy presents a somewhat different way of thinking about the greening process, and emphasizes an industrial setting for future improvements His chapter draws on decades of knowledge and experience related to improving the

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efficiency with which products are made. The chapter places emphasis on green solutions to existing problems being coupled to real world situations.

1.2.2 Technology supporting green chemistry in chemical education

Professor Ann Nalley has been kind enough to write a chapter for this volume discussing the evolution of green chemistry, and its incorporation into education over the course of the past decades. Her perspective spans from a beginning as an educator during a time when green chemistry was not even part of the equation for educating students, to a far more modern experience in which green principles are incorporated as part of student learning and are a part of how the instructor designs experiments.

1.2.3 Greening the curriculum broadly

Professor Mark Mason at the University of Toledo has written a chapter that approaches green chemistry in education from a wider point of view, what might be called the “30,000 foot view.” His discussion on the University of Toledo School of Green Chemistry and Engineering may engender numerous new ideas for other colleges and universities, as well as industrial units, where improvements in an understanding of green chemistry can be put into effect. He and his colleagues have developed a program that spans the undergraduate and graduate curriculum, and that includes teaching the future teachers.

1.2.4 Sustainability and green initiatives

Professor Narayan has provided a chapter rich in detail as to how experiments in the lab can be greener, and more aimed at sustainable models. Such efforts are definitely educational, and often resonate with students, their intended audience. If we are to move greener ways of doing business in the future, we will definitely have to impress on our students an awareness of the green chemical principles today.

1.2.5 Bringing green chemistry to undergraduate research

Undergraduate research has over the course of decades gone from being a luxury to be practiced only in limited circumstances to a well-established method of bringing some of the best learning to students almost immediately as they begin their college experience. Professor Welch has contributed an excellent chapter that illustrates how learning and undergraduate research can be dovetailed, and how green chemistry and its principles can be the center of such experiences. The examples she uses are excellent projects that have led to tangible results. She also makes the connection between such research projects and student retention in the STEM fields. The chapter should be useful to anyone considering the addition of research to their curriculum.

1.2.6 Chlorpyrifor reduction

The chemistry and remediation of chlorinated and phosphate pesticides is an area examined by the research of Professor and Dean Obare and her team, and a continuing problem created by the long-term use of a wide variety of pesticides. She and her researchers have explored a novel method of treating the residues of pesticide applications, one that is environmentally far friendlier than that which has been used previously. This subject is one that may mushroom in the future; and is one for which Professor Obare is definitely on the cutting edge.

1.2.7 Analytical techniques and green chemistry principles

Professor Gionfriddo has provided a very informative chapter about micro-extraction techniques and their connection to green chemical principles and greener processes. This area of analytical chemistry – the reduction of sample size – has often been driven by efficiency of a technique or some potential forensic application. In this chapter the connection is also made to the inherently greener aspects of such improved, modernized techniques. The examination of instrumental techniques in terms of all the principles of green chemistry, and the attention paid to waste and pollution reduction that she and her team provides are definitely laudable and at the forefront of the field.

1.3 Summary

We believe the chapters we have gathered in this volume represent a continued widening of the overall understanding of the principles of green chemistry and their application into new areas. As we have noted in the previous volumes of this series, what is presented here are chapters that do not all fall neatly into the categories people now consider the mainstream of green chemistry subjects – traditionally organic syntheses. But a continued expansion of topics is necessary if we intend to effect real change in the wide area of greening, be it in industry, in business, or in education.

If what you read in this volume is of interest, or whets your interest into different aspects of green chemistry, we encourage you to examine what has been published in previous volumes as well as to examine what has been presented. This series is open-ended, and we are eager to speak with potential authors about subjects that may fit into some upcoming volume.

Mark A. Murphy

2 Exploring the Vastness of design space for greener solutions using a quality approach

Abstract: Chemistry and biology constitute Vast and/or infinite design spaces which can be used by scientists and engineers to generate new and ever more complex chemical molecules and other structures having new emergent properties. A Vanishingly small proportion of those new molecules can generate even more complexity and new emergent properties by interacting with other molecules, bio-molecules, or complex collections of biomolecules. Large degrees of unpredictability reign throughout that Vastness, as well as in the Environment, and human society and behavior. Yet Life, the Earth's ecosystem, consciousness, and civilized human societies evolved from simpler systems, despite the Vastness and unpredictability. Green Chemistry and Engineering emerged over the last few decades from an evolutionary search for new processes and products for the benefit of humans and the planet that are both economically viable and do less harm to the Environment. The author, who originally conceived, in 1984, the BHC Ibuprofen Process that won one of the very first Presidential Green Chemistry Awards, was inspired and guided in significant part by the "Quality" philosophy, teachings and methods of W. Edwards Deming. Deming's Quality philosophy and methods adapt the empirical/reductionist perspectives and approaches of the Scientific Method, to readily integrate holistic, human, and ethical goals, ideas, and perspectives, in order to identify and solve Real-World problems. Deming's methods include his "PDCA" circles, which, when continuously iterated, can guide scientists, engineers, and their interdisciplinary team-mates as to what to do toward the development and evolution of Real-World processes and products that create little waste, and therefore are both economically and ecologically beneficial, via a process of human guided and human accelerated evolution.

Keywords: Green Chemistry, Green Engineering, pollution prevention, ethics, leadership, W. Edwards Deming, quality, evolution, unpredictability

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2.1 Green chemistry should focus on scientific solutions to real-world environmental situations

According to the US EPA's website in 2012,[1]

> Green chemistry consists of chemicals and chemical processes designed to reduce or eliminate negative environmental impacts. The *use and production* of these chemicals may involve reduced waste products, non-toxic components, and improved efficiency. Green chemistry is a highly effective approach to *pollution prevention* because it applies *innovative scientific solutions to real-world environmental situations*. (italics made for emphasis)

There is much justifiable emphasis in this EPA definition on "use and production," "Pollution Prevention," and on the application of "innovative scientific solutions to real world environmental situations." It seems obvious from this definition, and from common sense, that Green Chemistry (and Green Chemists and Green Engineers) should address themselves (though perhaps not exclusively) to "Real-World" situations and considerations.

This author has relevant "Real-World" experiences. Some readers will be familiar with the BHC Ibuprofen process that is well known as one of the earliest "Green Chemical" inventions. This author first conceived the BHC Ibuprofen process in 1984, then the process was developed and commercialized by an interdisciplinary team at Celanese Corporation (which later became Hoechst Celanese Corporation, which entered into a joint venture with Boots Pure Drug PLC, the original inventors of Ibuprofen, to form BHC). The BHC Ibuprofen process invention was first published as a European patent publication in 1988, and ultimately issued as a US patent in 1991 [1], as well as in many other countries. The BHC Ibuprofen Process was commercialized in 1992, then won Chemical Engineering Magazine's biannual Kirkpatrick Award in 1993 [2], and later won one of the very first Presidential Green Chemistry Awards, in 1997 [3].

However, a "narrative" grew over the subsequent decades, to the effect that Green Chemistry originated in the early 1990's, from legislation at the U.S. Congress and/or high-level decisions and actions taken at the US Environmental Protection Agency ("EPA") (see for example Linthorst [4], and Anastas and Beech [5]). There can be no doubt that the actions of the Congress and EPA during and after the 1990s tremendously sped the growth of "Green Chemistry", especially in Academia. But this author recently published an Open Access article, written from an

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[1] The quotation was accessed on the EPA website, https://www.epa.gov/greenchemistry in 2012, but that specific quotation is no longer easily available there. But very similar passages are still recited at multiple other locations, including https://nepis.epa.gov/Exe/tiff2png.cgi/P1004H5E.PNG?-r+75+-g+7+D%3A%5CZYFILES%5CINDEX%20DATA%5C00THRU05%5CTIFF%5C00001355%5CP1004H5E.TIF

inventor’s perspective (see Murphy [6]), that documented that many of the strategies techniques, elements, and aspects of Green Chemistry were in *actual commercial practice* in some major segments of the oil and commodity chemical industries for *decades* prior to the 1990s. That article argued that “Green Chemistry” (or at least many of its components) gradually evolved over many decades, mostly in industry, via the interactions of a very complex and intertwined set of international scientific, technical, human, social, environmental, and economic factors and events, including the traditions of science, and the “Quality” movement that swept America in the 1980s. This author is also currently completing work a separate manuscript that will document the history of *many* efforts, in industry and in various international government organizations, in the 1970s and 1980s, directed toward “Pollution Prevention” methods and goals that were the precursors of the currently popular “Green Chemistry” terminology.

In the intervening decades since the 1990s, Green Chemistry and Green Engineering have exploded into an international scientific phenomenon and “movement” (see Anastas and Beech [5], Figure 2.1). The concepts of Green Chemistry have obviously struck tremendous moral, ethical, and scientific chords among many scientists and engineers in both industry and academics. A good moral, ethical, and economic argument for pursuing Green Chemistry and Green Engineering is now obvious.

Figure 2.1: A single PDSA Cycle.

A complex set of intertwined historical events and factors is difficult enough to understand while looking backward toward the past. But the results to be anticipated *in the future* from the interactions of a similar but constantly changing set of complex and intertwined factors are Vastly more difficult to predict. As Niels Bohr purportedly once said, “prediction is very difficult, especially about the future.” This article will however argue, from an inventor’s perspective, that despite such Vastness and unpredictability, there are ethical, rational, systematic, and economically beneficial things that practicing Green Chemists and Engineers can *DO* to guide and accelerate their own and society’s evolution toward a cleaner, greener, and economically better future.

2.2 Chemistry and biology remain unpredictable sciences

Today a very great deal is objectively and scientifically known about chemistry and biology, and about the physical laws, principals, and “rules of thumb” that govern chemical structures and chemical and biological reactions. But chemistry and biology nevertheless remain as somewhat unpredictable sciences. There are multiple reasons for that unpredictability.

Chemistry lies near the interface of classical physics and the quantum realms. We believe (with ample reason) that quantum mechanics (and its often hugely complex and counter-intuitive phenomena) ultimately controls the interactions between the protons, neutrons, and electrons within an atom. Quantum mechanics also controls the formation and stability of chemical bonds, and therefore ultimately the structures and many of the properties of isolated molecules. But practical and accurate solutions to the equations of quantum mechanics remain mostly beyond our practical reach for all but relatively simple “gas phase” molecules, even using our fastest computers and best algorithms.[2] In this authors experience (while working with quantum chemists as members of multi-functional teams) quantum chemists still cannot make reliable quantitative (or in many cases even qualitative) predictions about many very important practical chemical questions, including the weak interactions between non-covalently bonded molecules. Quantum chemists also still have great difficulty making practically useful quantitative predictions about the reactions of and between molecules, as is unavoidably necessary to build larger and more complex molecules, molecular structures, biological organelles, etc.

The unpredictability of the chemical arts has long been recognized by the patent law courts, which have stated for example[3]; “[I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement.”

Another phenomenon adds to the unpredictability, namely the “emergence” of new and unexpected properties as molecular size, complexity, and intermolecular interactions grow. According to Luisi [7],

> The term emergence describes the onset of novel properties that arise when a certain level of structural complexity is formed from components of lower complexity. This is often summarized in the popular statement the ‘the whole is more than the sum of the parts’.

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[2] As the number of atoms per molecule grows, the number of resulting combinations and permutations of electrons and atoms rapidly approaches infinity, even for conventionally covalently bonded molecules, and rapidly surpasses the computational capacity of any known or knowable computer.

[3] See the Manual of Patent Examining Procedure § 2164.03, Relationship of Predictability of the Art and the Enablement Requirement, quoting In re Marzocchi, 439 F.2d 220, 223–24, 169 USPQ 367, 369–70 (CCPA 1971).

Luisi observed that

> Chemistry (and biochemistry and by inference biology) . . . . is based in large part, on reactions that proceed from atoms to molecules, from molecules to molecular complexes, or from monomers to polymers – namely it is characterized in large part by an increase of molecular complexity in order to achieve novel properties.

The formation of micelles or vesicles from surfactant molecules such as phospholipids was one example cited. The formation of a literally infinite variety of proteins from the very small set of 20 naturally occurring amino acids is another example.

Luisi illustrated such "Vast"[4] possibilities and the new properties that emerge with increasing molecular size and complexity via the example of hemoglobin, which is the oxygen-carrying protein in red blood cells. Hemoglobin is a "tetramer" composed of four myoglobin protein subunits, each of which subunits has some oxygen binding capability in the form of a normal hyperbolic saturation curve. But the interactions between the four myoglobin subunits of the hemoglobin tetramer modify the oxygen carrying properties of the subunits so that the new and biologically much superior oxygen carrying properties of hemoglobin emerge.

But how could any human possibly foresee or "invent" either myoglobin or hemoglobin? Each myoglobin subunit is composed of 153 of the 20 naturally occurring amino acids (and a metalloporphyrin ring). The myoglobin sequence of 153 amino acids is only one of 20^{153} (about 10^{200}) possible protein chains! Luisi remarks that "since the theoretical number of chains is so large (in first approximation infinite) we cannot pinpoint myoglobin in this haystack." The set of 153 amino acid proteins that contains myoglobin/hemoglobin is finite, but unimaginably "Vast". Compare the set of all proteins containing the 20 natural amino acids, which is far more Vast. The Vast set of 153 amino acid proteins is only a "Vanishingly small" subset of all the proteins!

Luisi then goes on to consider the emergence of "hierarchical systems", i. e. "a system composed of subsystems that in turn have their own subsystems." An example of such hierarchical systems[5] is life itself.

> The single components, such as DNA, proteins, sugars, vitamins, lipids, etc., or even the cellular organelles such as vesicles, mitochondria, Golgi islands etc., each *per se* are inanimate substances. From this multitude of non-living structures, life arises once a given space/time organisation of these non-living components is given. Life itself is indeed the most dramatic outcome of emergence.

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[4] This article adopts the "Vast" and "Vanishingly" small terminology explained in Dennet [8], for sets that are finite, but unimaginably small or large. "Vast" means "Very much more than astronomically".

[5] For an introduction to concepts related to such complex hierarchical systems, consider Holland [9].

Daniel C. Dennett, a scientific philosopher from Tufts University, also addressed formidable questions of “Vastness” in the context of biological and cultural evolution [8], and later in the context of the evolution of free will [10]. Dennett explored the incomprehensible “Vastness” of the “design space” he identified as the “Library of Mendel,” formed by combining the five naturally occurring nucleotides into DNA and/or RNA chains. Dennett then addressed the recognition that “it is certain that there are Vastly more ways of being dead, or rather not alive” in that infinite design space [8].[6] Dennett then goes on to describe and analyze in depth how nature explores such incomprehensibly Vast and unpredictable “Design Spaces” for viable ways of being alive (rather than not alive), via the processes of natural selection, i. e. evolution.

2.3 Social interactions also remain unpredictable

Both of Dennett’s books also addressed the extremely important role of human cultural evolution by means of “memes” (culturally transmitted “good ideas”) in the context of individual human consciousness, free will, and even broader human society. Serious discussion of those topics is certainly too Vast a topic to be addressed here, but Dennett certainly leaves a reader with a vivid impression of the incomprehensible size, importance, and unpredictability of both the resulting physical and cultural questions, but also about how both Nature and human beings cope with such challenges. The ultimate answer is, of course, evolution.

However, human beings (especially “experts”) often dramatically deceive themselves (and the rest of us) in terms of their ability to accurately predict the future outcomes of a wide variety of Vastly complex cultural, economic, and technical events and activities. In recent years Nassim Nicholas Taleb has written a series of critically and academically acclaimed best-selling books, the best known of which are “The Black Swan – The Impact of the Highly Improbable” [12], and “Antifragile – Things That Gain from Disorder” [13]. In his books, Taleb describes the huge effects and impact of highly improbable and unpredictable events (which he terms “Black Swans”) on the course of human psychological, social, and economic affairs.

Taleb is highly critical of alleged “experts” in the economic, business, and social sciences, who he argues are little better at predicting future events and outcomes than common people from the street. Taleb is also highly critical of the “fraudulent” mathematical analysis used by most economists and business leaders to justify their dubious predictions of final future outcomes and uncertainties in economic and business affairs. Taleb asserts that those predictions are typically based in part on “The Bell Curve, That Great Intellectual Fraud”. Taleb explains that many of the

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[6] Dennett [8], Chapter 5, quoting Dawkins [11].

unpredictable and highly unexpected “Black Swans” come from far outside normal “six sigma” statistical limits that get calculated via a traditional Gaussian bell curve analysis, and are instead found in the “long tail” of very low probability but very high impact events that relate to and can derive from the iterative and non-linear mathematics of the “fractal” based processes of nature (see for example Mandelbrot [14], “The Fractal Geometry of Nature”). Taleb also argues that most humans (including self-described “experts”) often use “narratives” to deceive themselves and us into ignoring the “Black Swans,” and ignoring the incomprehensible range of possible outcomes and the unpredictability and large impact of those outcomes.

But if we cannot predict outcomes very accurately, how can politicians and “policy makers” justify their repeated and continuing failing attempts to manipulate both people and the law to “equalize” the unpredictable outcomes? Some “equalization” may be possible with respect to past events and injustices, but how can it possibly be done accurately and effectively with respect to a Vastly unpredictable and unforeseeable future?

In view of all the complexity and unpredictability, what is a practicing scientist, including a Green Chemist, Biologist, or Engineer, supposed to *DO* in the face of such intimidatingly complex uncertainties, issues, probabilities, and problems? Should Green Chemists and Biologists and Engineers simply rely on and meekly obey and/or comply with the instructions of far-away “experts,” such as corporate managements, governments, or academia, to tell them what they need to *DO* on a daily and detailed basis? Surely not!

As documented in this author’s recent paper [6], this author was inspired and guided during the time of the invention of the BHC Ibuprofen Process by ideas and processes relating to “Quality”. This author still believes “Quality” principals can help lead and guide Green Chemists toward what identifying what they need to *DO*, out in the Vast and unpredictable Real-World, as individuals and/or in collaborating teams, to create new useful things and/or evolve toward a cleaner, greener future.

2.4 W. Edwards Deming, quality, and “continuous improvement”

William Edwards Deming was an American engineer, statistician, professor, author, lecturer, and consultant.[7] He was perhaps best known for his early work in post-

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[7] This section on Deming’s personal history and teachings borrows substantially from the history given in a Wikipedia article available at http://en.wikipedia.org/wiki/W._Edwards_Deming, and various materials available on the website of the non-profit Deming Institute, https://deming.org/, and supplemented by this author’s own training and experience in Deming-based methods and Quality philosophy, as well as quotes from Deming’s Book “Out of the Crisis,” originally published in 1982 and republished in 2000, and used herein with permission from the Deming Institute and MIT Press.

WWII Japan. After WWII, Deming taught top Japanese management how to rebuild their economy, by focusing the attention and efforts of both management and employees on improving design and execution of their production processes (and thus service), product quality, and sales through various problem identification and problem-solving methods, with emphasis on the applications of statistical methods. In 1960, the Prime Minister of Japan, acting on behalf of Emperor Hirohito, awarded Deming Japan's Order of the Sacred Treasure, Second Class.

In June 1980, Deming was featured prominently in an NBC "White Paper" documentary[8] titled "If Japan Can . . . Why Can't We?" (The original video can be viewed via the link in footnote 8.) The documentary described the increasing industrial competition the United States was then facing from Japan, and highlighted Deming's early corporate consulting activities in Japan and later in the US and described some of Deming's teachings and methods.

Ford Motor Company was one of the first major American corporations to seek help from Deming, in 1981. GM, Dow Chemical, and other major national corporations soon followed suit. In 1986, Ford came out with a profitable line of cars, the Taurus-Sable line. In a letter to Autoweek Magazine, Donald Petersen, then Ford Chairman, said, "We are moving toward building a Quality culture at Ford, and the many changes that have been taking place here have their roots directly in Deming's teachings." President Reagan awarded the National Medal of Technology to Deming in 1987, and in 1988 Deming received the Distinguished Career in Science award from the National Academy of Sciences. Deming passed in 1993, as he was finishing his second book, "The New Economics for Industry, Government, Education" [15]. Multiple books have since been written about his life and accomplishments, see for example, Gabor [16] and Gluckman [17].

Deming's teachings rejected many tenets of traditional American management theories and rejected traditional numerical financial and/or "management by objective" methods and goals. Deming instead emphasized teaching upper management to focus on "leadership", by enabling and training lower level managers and employees to focus on customer needs and the details of improving their own work and production processes, via use of statistical and non-statistical tools for problem identification and problem solving, and "Continuous Improvement" principals and methods.

In his book "Out of the Crisis" [18],[9] Deming said:

> To manage, one must lead. To lead, one must understand the work that he and his people are responsible for. Who is the customer (the next stage), and how can we better serve the customer? An incoming manager . . .. must learn from his people what they are doing and must

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[8] To view the original NBC documentary, see a YouTube video made available by the Deming Institute, https://www.youtube.com/watch?v=vcG_Pmt_Ny4&t=825s.

[9] This author certainly hopes readers will purchase and read Deming's original books.

> learn a lot of new subject matter .... *Focus on outcome is not an effective way to improve a process or an activity.* (italics made for emphasis)
>
> As we have already remarked, management by numerical goal is an attempt to manage without knowledge of what to do, and in fact is usually management by fear.

An introductory comment in “Out of the Crisis” [18] explained:

> *Failure of management to plan for the future and foresee problems has brought about waste of manpower, of materials, and of machine-time, all of which raise the manufacturer’s cost and price that the purchaser must pay. The consumer is not always willing to subsidize this waste* (italics made for emphasis). The inevitable result is loss of market. Loss of market begets unemployment. Performance of management should be measured by potential to stay in business, to protect investment, to ensure future dividends and jobs through improvement of product and service for the future, not by the quarterly dividend.
>
> It is no longer socially acceptable to dump employees onto the heap of unemployed. Loss of market, and resulting unemployment, are not foreordained. They are not inevitable. They are man-made.

Deming also asserted there is a strong connection between improvements in Quality and improvements in productivity and cost [18]. He reported meeting with union workers at the companies he consulted with, and asking the question; “Why is it that productivity increases as quality improves?” Deming reported that the answers he got were “Less Rework” and “Less Waste.” Deming commented that “There is no better answer.”

The teachings of W. Edwards Deming have been summarized as follows:[10]

> Dr. W. Edwards Deming taught that by adopting appropriate principles of management, *organizations can increase quality and simultaneously reduce costs by reducing waste, rework,* staff attrition and litigation while increasing customer loyalty. *The key is to practice continual improvement and to think of manufacturing as a system, not as bits and pieces.* (italics made for emphasis)

Regarding the question of “What is Quality?” Deming wrote [18];

> Quality can be defined only in terms of the agent ... In the mind of the production worker, he produces quality if he can take pride in his work. Poor quality, to him, means loss of business, and perhaps his job. Good quality, he thinks, will keep the company in business. All this is as true in the service industries as it is in manufacturing.
>
> Quality to a plant manager means to get the numbers out and to meet specifications. His job is also, whether he knows it or not, continual improvement of processes and continual improvement of leadership.
>
> The difficulty in defining quality is to translate future needs of the user into measurable characteristics, so that a product can be designed and turned out to give satisfaction at price that the user will pay. This is not easy, and as soon as one feels fairly successful in the endeavor, he finds that the needs of the consumer have changed, competitors have moved in ...

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[10] This passage was reported in the Wikipedia article in 2015 as an excerpt from Deming’s own training materials.

Deming obviously believed Real-World “Quality” to be a semi-subjective/semi-objective matter which can vary according to the details of job function, employee, product, customer, and time. Deming also recognized that Real-World production and sales of products and/or services to Real-World customers is inherently a multi-disciplinary activity, and strongly encouraged the formation of multi-disciplinary “Quality Circle” teams for most industrial projects.

Deming also advocated that all managers and employees should study and/or understand what he called a System of Profound Knowledge, consisting of four parts[11]:

1. *Appreciation for a system*: understanding the overall processes involving suppliers, producers, and customers (or recipients) of goods and services;
2. *Knowledge about variation*: the range and causes of variation in quality, and use of statistical sampling in measurements;
3. *Theory of knowledge*: the concepts explaining knowledge and the limits of what can be known.
4. *Psychology*: concepts of human nature and behavior.

Deming believed that the intimate details of what was going on the shop floor and in other lower level functions was very important to producing the good Quality that would lower costs and win customer loyalty. Therefore, the psychology, strategies, and ethics required to obtain active participation and contributions from lower level employees absolutely required that those employees be treated fairly and well. Similarly, Deming believed that while cost is very important to many customers, customers also value many other kinds of “Quality” as well, and that they want to be treated fairly and well in order for them to maintain their loyalty as customers.

Deming offered fourteen “key principles” to managers for transforming business effectiveness [18]. A few of the fourteen principals most relevant to this article are copied below.

1. Create constancy of purpose toward improvement of product and service, with the aim to become competitive, stay in business and to provide jobs.
2. Cease dependence on inspection to achieve quality. Eliminate the need for inspection on a mass basis by building quality into the product in the first place.
3. Improve constantly and forever the system of production and service, *to improve quality, productivity, and waste, and thus constantly decrease costs*. (italics made for emphasis)
4. Institute training on the job.

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[11] The italicized portions of these passages appeared in the Preface of “The New Economics” [15]. The non-italicized words were not part of Deming’s original text, but were found in the Wikipedia article in 2015, and are attributable to unknown authors.

5. Institute leadership (see Point 12 and Ch. 8 of "Out of the Crisis"). The aim of supervision should be to help people and machines and gadgets do a better job. Supervision of management is in need of overhaul, as well as supervision of production workers.
6. Drive out fear, so that everyone may work effectively for the company. (See Ch. 3 of "Out of the Crisis")
7. Break down barriers between departments. *People in research, design, sales, and production must work as a team*, in order to foresee problems of production and usage that may be encountered with the product or service. (italics made for emphasis)
8. (a) Eliminate work standards (quotas) on the factory floor. Substitute with leadership.
   (b) Eliminate management by objective. Eliminate management by numbers and numerical goals. Instead substitute with leadership.
9. Institute a vigorous program of education and self-improvement.

Notice that Deming put much emphasis on complex human factors, such as customer desires, and "[l]eadership, the aim of which is to help people and machines and gadgets do a better job." Similarly, Deming put much emphasis on education and training of the workforce, and teamwork, "in order to foresee problems of production and usage that may be encountered." *Much* in the way of ethical principles and treatment (a very complex and emergent set of human-interaction based phenomenon) is required from everyone, especially Managers, in a system that relies so heavily on voluntary human interactions and cooperation. Such a view is a *far* cry from the pseudo-mathematical assertions of far too many of our economists, lawyers, and business managers, namely that the primary goal of business managers should be "maximizing profit"!!

Deming also had a list of "Seven Deadly Diseases" of American managers and workers [18]. They included:

1. Lack of constancy of purpose to plan product and service that will have a market and keep the company in business, and provide jobs.
2. Emphasis on short-term profits
3. Mobility of management
4. Running a company on visible figures alone, with little or no consideration of figures that are unknown or unknowable.
5. Excessive medical costs

In the opinion of this author, Deming's approach started with the principals and techniques of science, engineering, mathematics, and economics, then considered the role of both the good and bad parts of human behavior and psychology, then combined it all into a holistic system, process, and theory of Management that has demonstrated its potential to make all the parts function better individually, and better together as a whole, out in the Real-World, all over the world.

Decades later many companies continue to educate their executives, managers and lower level employees in Deming's methods (though clearly some others do not). The non-profit W. Edwards Deming Institute, continues such education in Deming's methods, see https://deming.org/. The W. Edwards Deming Center for Quality, and Competitiveness, at the Columbia Business School (established in 1991, see https://www8.gsb.columbia.edu/deming/the_deming_cup) annually awards a "Deming Cup" to world recognized business leaders who have made outstanding contributions in the area of operational excellence and have fostered the culture of continuous improvement in the organization. The winners include executives from IBM (2010), Intermountain Health and Chrysler Group (2011), Macy's (2012), S.C. Johnson (2013), Dupont (2014), American Express and Cleveland Clinic (2015), and Honeywell and PepsiCo (2016), and General Electric and Marriot International (2017). Furthermore, the Deming Prize, a global quality award currently administered by Japanese Union of Scientists and Engineers, has been awarded since 1951 to individuals and businesses that have successfully implemented Total Quality Management (TQM) programs, see https://en.wikipedia.org/wiki/Deming_Prize.

Since 1995, Dow Chemical has devoted a section of its website to its "Quality Culture" which is "achieved through teamwork and continual improvement." See https://www.dow.com/en-us/about-dow/our-company/beliefs-and-culture/quality-culture. Dow is also "dedicated to sustainability," see https://www.dow.com/en-us/science-and-sustainability. It may not be mere coincidence that the very first Presidential Green Chemistry Award, in 1996 in the category of "Greener Reaction Conditions" was given to the Dow Chemical Company, for an invention entitled "100 Percent Carbon Dioxide as a Blowing Agent for the Polystyrene Foam Sheet Packaging Market."[12]

2.5 Holism, reductionism, MU, quality, and human guided evolution

An important personal influence on this author has been the "Quality" philosophy described in Robert Pirsig's [19] bestselling book, "Zen and the Art of Motorcycle Maintenance, an Inquiry into Values." "Zen and the Art" is a semi-autobiographical philosophical novel that describes, via a beautiful *and* terrifying personal story, Pirsig's early experiences in the Sciences, and later attempts to build a new academic Philosophy based on "Quality."

Pirsig loved riding motorcycles, and the holistic, liberating, emotional, "in the now" joy that many people (including this author!) experience while riding a

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[12] See the EPA's Presidential Green Chemistry Award Website at https://www.epa.gov/greenchemistry/presidential-green-chemistry-challenge-1996-greener-reaction-conditions-award.

motorcycle. But Pirsig also loved repairing and maintaining his own motorcycle, and the rational, reductionist thinking he needed to understand the structure and functions of each part of his motorcycle, in order to be able to properly diagnose, repair, and/or maintain the whole motorcycle.

Pirsig's friends who rode with him also shared the holistic joys of riding a motorcycle. But some of Pirsig's friends could not understand, and were often suspicious of, and even feared, motorcycle maintenance and the rationalist/reductionist thinking involved in motorcycle maintenance. So Pirsig's friends hired "experts" to maintain their motorcycles rather than do it themselves, with very mixed results, because too often those "experts" executed their jobs poorly. Pirsig explored that seemingly small conflict between the holistic joys of motorcycle riding and his friend's distaste for the rationalist/reductionist thinking required to maintain the motorcycles. "Zen and the Art" used that small conflict as a metaphor for much larger, deeper and more general emotional and philosophical conflicts between holistic and reductionist viewpoints of Reality. Pirsig tried to explore and resolve those larger conflicts in "Zen and the Art."

During his philosophical studies, Pirsig visited India for a time to study Eastern Philosophies and Religions, including Zen. Pirsig learned some valuable holistic attitudes and techniques for attaining "peace of mind", a mental state he found very useful and valuable, even while doing his rational/reductionist work. But Pirsig could not really accept Zen's typical total rejection of rational thought as a method for dealing with the uncertainties and unpredictability of life.

Pirsig returned to the US and attempted to build an academic philosophy based on "Quality", as a potential solution to the many more general holism versus reductionism conflicts. But despite his great efforts, Pirsig found he could not rationally define "Quality" in abstract reductionist terms, even though both he and his students "knew what it was!". The reactions of the academics of Pirsig's time (the 1950s) to his inability to rationally and generally define "Quality" in reductionist terms eventually resulted in some devastating personal setbacks for Pirsig. But Pirsig's eventual recovery and later writings about it all converted him into a world famous and best-selling author.

"Reductionism" can be rationally defined to be a mental viewpoint holding that "the whole is just the sum of the parts." Mathematicians, scientists, and engineers often hold and very often use such a view of Reality. In contrast, "Holism" can be rationally defined to be a viewpoint that "the whole can be more than sum of the parts." Pirsig argued that his motorcycle, viewed as a whole, is something completely new, with new (emergent!) properties, new (emergent!) functions, and other new (emergent!) "qualities" that are much more and much different than a mere random "sum" of the pistons, cylinders, wheels, and other motorcycle parts. These conflicting points of view regarding Reality can be and are of course debated.

In his 1979 Pulitzer Prize winning book, "Gödel, Escher, Bach; An Eternal Golden Braid, A Metaphorical Fugue on Minds and Machines in the Spirit of Lewis Carrol", Douglas R. Hoffstadter [20] took the "holism vs reductionism" debate to unexpected heights. A discussion of the wondrous variety of topics covered by Hoffstadter's book is impossible in this space but included number theory and Gödel's mathematical proofs that formal mathematical systems at sufficient levels of complexity so as to be capable of self-reference can and do contain "undecidable propositions". Hoffstadter also rationally discussed the origin of life on the planet via evolution, and the origin, emergence, and nature of intelligence and consciousness in the brain. Furthermore, Hoffstadter explored some of the ways in which artists like Escher assembled their drawings, and/or musicians like Bach assembled musical notes together, to produce holistically pleasing pieces of art.

Hoffstadter also discussed at some length the relevance of certain concepts from Zen, including the concept of "MU", which "unasks" reductionist questions.[13] Chapter 11 of Hoffstadter's book, entitled "Ant Fugue," deals extensively with "MU," as well as a dialog between holist *and* reductionist ideas about how thought and consciousness emerge in the brain from the firings of individual neurons.[14] One core message of Hoffstadter's Chapter 11 was that the holism-reductionism debate should be "unasked," because the workings of the human brain cannot be understood solely in terms of the parts (the neurons and their relationships to each other) or solely in terms of the whole (thought and consciousness). Elsewhere in his book, Hoffstadter applied similar reasoning to the origins of DNA, proteins, and life itself on the planet. Again, Hoffstadter argued that his readers should "unask" the holist-reductionist debate, in order to attain a higher level of understanding of many important facets of the Real-World.

Retroactively understanding Reality and the Laws of Nature, from both a reductionist scientific viewpoint and a holistic/ philosophical/emotional viewpoint, is quite a task. But looking forward to artificially create or improve a new material thing or process, and then successfully get it out into an uncertain and unforeseeable Real-World, is also quite a (somewhat different) task.

W. Edwards Deming, using his mostly systematic and reductionist communications style, nevertheless asked his followers to ask *both* reductionist and holistic questions, over, and over, and over again, using iterations of a systematic method known as a Plan-Do-Study-Act cycle. A diagram of a single PDSA cycle, and some explanatory comments (as reproduced from the Deming Institute website, https://deming.org/explore/p-d-s-a), is shown below in Figure 2.1.[15]

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[13] For a general discussion of "MU", consider Wikipedia at https://en.wikipedia.org/wiki/Mu_(negative).

[14] A copy of Hoffsteader's Chapter 11, as well as an explanatory commentary thereon, is available at http://www.jimpryor.net/teaching/courses/intro/notes/mindsi11.html.

[15] The PDSA Circle shown above in Figure 2.1 was initially copied from the Deming Institute website in 2015, but that version of the PDSA Circle graphic had substantive precursors. Figure 5, chapter 2 of "Out of the Crisis" [18] illustrated one such precursor, which Deming then termed a "Shewhart Cycle". A closer and more modern version, which Deming termed "The Shewhart Cycle for Learning and Improvement – The PDSA Cycle" was shown as Figure 13 of Chapter 6 in "The New Economics" [15]. The PDSA cycle graphic in Figure 2.1 is used with the permission of The W. Edwards Deming Institute® and MIT Press.

> The cycle begins with the Plan step. This involves identifying a goal or purpose, formulating a theory, defining success metrics and putting a plan into action. These activities are followed by the Do step, in which the components of the plan are implemented, such as making a product. Next comes the Study step, where outcomes are monitored to test the validity of the plan for signs of progress and success, or problems and areas for improvement. The Act step closes the cycle, integrating the learning generated by the entire process, which can be used to adjust the goal, change methods, reformulate a theory altogether, or broaden the learning – improvement cycle from a small-scale experiment to a larger implementation Plan. These four steps can be repeated over and over as part of a never-ending cycle of continual learning and improvement.[16]

Notice that only one PDSA step, the "DO" step, involves direct physical acts out in the Real-World. The other three steps, "PLAN", "STUDY", and "ACT" are predominantly mental activities.

The goal in "Quality"/PDSA strategies is not to re-discover or re-confirm the Laws of Nature. The goal in a PDSA approach is to find ways to apply the many Laws of Nature we already know, to provide higher Quality goods or services for the needs and desires of Real-World people, in an efficient low waste, and environmentally friendly manner. For a long time, many people typically thought (correctly) that cleaning up or reworking waste was expensive. But after leaders like Deming, and after decades of Green Chemistry, it has become obvious that waste prevention, or use of renewable materials, or providing better recycle potential can be both ethically *and* economically desirable, and often achievable. Such strategies can potentially provide wide-ranging benefits far into the future.

Identifying a goal or purpose in the *PLAN* step should involve both holistic and/or reductionist considerations. Improving "Quality" can be a holistic goal that considers both Society's, the Environment's and your particular customer's desires and needs. Choice of a goal or problem to be addressed should involve physical, scientific, and practical considerations, as well as human and ethical considerations, and the pre-existing knowledge you and/or your teammates hopefully already have or can find about the problem to be addressed and solved. New ideas and theories are often based in pre-existing knowledge about the problem you have chosen and technologies you already know. If you are working on a complex product having multiple components, or a product made by a complex multi-step process, you may need to narrow your focus toward and/or investigate one or more of the sub-parts or sub-processes. Any potential for simultaneous reductions in cost and/or waste should *always* be considered in the *PLANNING* stage. Whether or not to pursue a particular *PLAN* that satisfies some of your goals, but negatively affect other goals can be a difficult question with no easy answers, but the choices are probably yours at this early stage in many cases.

Ideas (hypotheses) will likely quickly almost suggest themselves, and hopefully quickly get elaborated into knowledge and/or theories about the Real-World

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[16] Used courtesy of The W. Edwards Deming Institute®and MIT Press.

problem you have selected. “Theory of knowledge” was one of the four components of Deming’s System of Profound Knowledge.[17] Deming commented as follows:

> Knowledge is built on theory. The theory of knowledge teaches us that a statement, if it conveys knowledge, predicts future outcome, with risk of being wrong, and that it fits without failure observations of the past.
>
> Rational prediction requires theory and builds knowledge through systemic revision and extension of theory based on comparison of prediction with observation.

While building/evolving your knowledge and theories, consult your current or potential team-mates at all levels, including the lower level team-mates. The theoretical process or sub-process you currently have in your mind may be very complex and/or different in subtle but important ways from the one that is happening out in the Real-World plant, or in the field with the customers. Lower level team members, including salesmen and field people, may have some very valuable information about such things. They will probably communicate with you better and/or help you more if they subjectively believe you are treating them fairly and well, i. e. in a “Quality” way. They may even want to join your team! After such communications, you may need to adjust your theories and other plans for subsequent actions.

Next comes the very practical and reductionist question of defining measurable success metrics. “Quality” may not be generally and abstractly definable, but a good scientist or engineer can often define one or more aspects of the “Qualities” of a particular product or process more narrowly and in more reductionist and measurable terms, hopefully measurable characteristics that your customers understand and agree with. Hopefully your *PLAN* is now complete.

In the “*DO*” step, the team should do its best to put the *PLAN* into action as applied to the Real-World process, or preferably a small-scale test.

In the *STUDY* step, measured outcomes and/or success metrics from the “*PLAN*” are empirically evaluated to test the validity of the *PLAN* and its theories and predictions, for signs of progress and success, or for problems and areas for improvement. Properly applied empirical analysis via statistical methods can be extremely valuable in the *STUDY* step. Pay special attention to results or data points that fall outside calculated statistical bounds (i. e. six sigma boundaries), they may well be hints about unexpected results from “out of control” sub-processes. Those “out of control” sub-processes and results, whether positive or negative from a Quality perspective, probably deserve more investigation and/or troubleshooting, or maybe even a new and different line of investigation and/or PDSA circles.

The *ACT* step closes the PDSA cycle, by integrating the learning, progress, and/or Quality improvements generated by the prior steps. The information learned can be used for the next PDSA cycle to adjust the goal, change methods, reformulate a theory altogether, or broaden the learning for the next cycle. If statistical analysis

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[17] See Deming [15], in the Preface and Chapter 4.

suggests that the measurable metrics have indeed been reliably improved, the team should consider standardizing the underlying changes in the *Real-World* processes, thereby "locking in" any resulting gains in Quality, with improved confidence that those gains can be maintained in the future in the Real-World process or product, without the need for costly inspection and rework of unacceptable quality product.

Hopefully your customers will notice and like the Quality improvements that have emerged from your "Quality" processes, but do not be surprised if some customers neither notice nor even like your improved Qualities. The improved Qualities that have emerged from your efforts may not matter to some customers, even though those improved Qualities can still have value to you and/or other customers.

Notice that the PDSA cycle is based on the Scientific Method, but unlike Scientific Method traditions, which are often said to urge scientists try to always maintain an "objective/reductionist" perspective while observing and understanding Nature and its laws, the PDSA cycle approach to solving complex Real-World problems readily incorporates *both* reductionist/objective perspectives and approaches, *and* holistic/subjective and/or "Quality" considerations.

The four steps of the PDSA cycle should be repeated over and over and over to produce continuous learning and improvement. A conceptual diagram[18] suggesting the results from a repetition of PDCA cycles (which is a slight variation on a PDSA cycle) is shown in Figure 2.2 below:

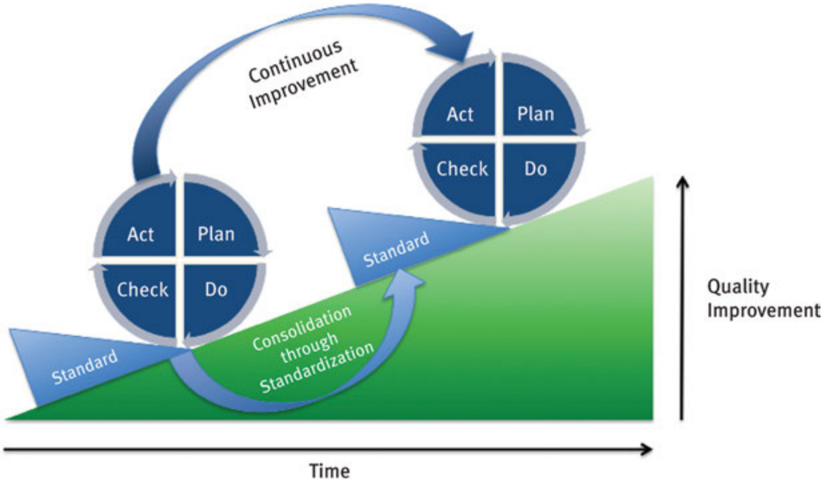

Figure 2.2: Conceptual Repetition of PDCA / PDSA Cycles.

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[18] This diagram was copied from An Open Access Wikipedia article on the PDCA cycle available at https://en.wikipedia.org/wiki/PDCA, wherein the diagram is attributed to Johannes Vietze, who authorized its copying and use.

As the PDSA/PDCA cycles are continuously repeated, the resulting Quality outcomes (physical and/or mental) improve and/or emerge.[19] The resulting Real-World process improvements and physical outcome improvements can optionally be consolidated and standardized. Externally observable improvements in Quality may not however always appear in the smooth linear manner Figure 2.2 suggests. The externally observable improvements in Quality may sometimes appear (at least to outsiders and customers) to emerge in unexpected jumps or leaps, as they did in the case of new products or processes such as the BHC ibuprofen process.

The repetition/iteration of PDSA cycles suggested by Figure 2.2 is, of course, really a general logical method for producing human guided and human accelerated evolution!!

The PDSA and "Continuous Improvement" methods are adaptable to an incredibly wide variety of Real-World processes. Such "Continuous Improvement" methods have already in fact, as seen above, been successfully implemented in the Real-World by large numbers of organizations, in many industries, all over the World.

2.6 What should an ethical green chemist or engineer choose to *DO* now?

The phenomenal growth of Green Chemistry and Engineering over the last few decades has clearly struck a tremendous moral and ethical chord among many technical people from many kinds of training, backgrounds, and positions. That growth seems easy to understand from a holistic/emotional perspective, a perspective most of us naturally use daily in much of our lives. Trying to "Save the Planet!" (or the Climate or the Ecology) is an obvious moral/ethical inspiration. But such a sentiment alone doesn't give anyone much of any guidance as what they can or should actually *DO*.

Furthermore, too many people at too many levels of knowledge and power continue to deceive themselves and others with "narratives" (see Taleb [12], chapter 6), in order to convince themselves and others of their "expertise", perhaps in order to maintain their personal money or power or position. Too often they dramatically overestimate their ability to predictably manipulate the future outcomes of extremely complex processes and holistic phenomena, including Economies, Climate, or Ecology. Too many "experts" routinely lecture others[20], or even try to legally coerce large numbers of others, into doing what the "experts" command that those multitudes should do. But if we all look closely and honestly at Reality, and ourselves in the mirror, we see that the outcomes from such complex holistic

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[19] The repetition of PDSA cycles illustrated in Figure 2.2 is a form of iteration of simpler and/or lower level steps. Such iterative processes have become increasingly well understood to be a source of the emergence of complex hierarchical systems and networks, see Chamberlin [21], Holland [9].

[20] See Taleb [12], chapter 13, on "Lecturing Birds How To Fly" and the "Harvard-Soviet Illusion."

phenomena are more than somewhat unpredictable, and the possibilities are Vast, for any of us, even if we are "experts."

But if we can't accurately predict the future, or future outcomes from such infinitely Vast and complex phenomena, what can we *DO*? An anecdote from this author's experiences seems relevant. This author has a friend, Ms Lynn Hill of Blowing Rock North Carolina, who obtained an Ivy League degree in Urban Planning several decades ago. After graduation Lynn went to India for several months to work with Mother Teresa, now a Nobel Peace Prize winner, and posthumous Catholic Saint. Lynn says that she asked Mother Teresa, "How is it that you've managed to accomplish such incredible things in your life?" Lynn says that Mother Teresa simply replied: "I focus on solving the problems that are before me every day."

The problems before chemists, biologists, engineers, and their teammates relate to chemistry, biology, engineering, and their derivative businesses and customers, areas where they can perhaps lay claim to at least some genuine expertise with respect to both the many parts, people, and the whole process and outcomes. But as we have seen, the possibilities even in those narrowed areas of exploration are still Vast and/or infinite, and the future outcomes remain unpredictable despite our best efforts and intentions.

Fortunately, Green Chemists and Engineers (considered as a group) may have higher than average inclinations and/or abilities to think (as individuals and in groups) from *both* holistic and reductionist points of view while pursuing their goals of improving the particular products or processes they are working on, while simultaneously reducing waste and cost.

This author believes that concepts of "Quality," whether from Deming, Pirsig, religions, or from deep within each of us as individuals, can help lead and guide scientists and engineers and people from other disciplines, both as individuals and in teams, through an infinite complexity of good, bad, and grey choices toward a better future, even if it often leads there via totally unforeseeable paths.

Quality as a goal can unite, rather than divide or coerce, people of widely varying backgrounds, training, and political persuasions. This author believes that Quality scientific, statistical and management techniques, as taught by genuine leaders such as W. Edwards Deming, can help guide scientists, engineers, academics, managers and even lower level employees as to what they need to *DO* to produce "better" Quality in the future.

Individuals and/or small teams should consider working together using a PDSA approach, as a way to focus on the particular products or processes or services they provide (or want to provide) to their customers every day, whoever the customers are. Why do the customers need or use the product or service, so that it has a Real-World use and/or market? What do the customers subjectively like and/or dislike about it? What is the process by which the product or service is made or provided? Can you think of areas within those processes wherein waste of materials, labor, or machine time occurs, or where rework of bad product or service is necessary? If so, you just identified potential areas for focus and improvement. Talk to customers and potential team-mates you respect and trust, especially people from other disciplines whose help you may need, they may have some valuable perspectives and/or ideas on such questions.

Formulate a theory about how and why the waste occurs, and how the waste might be prevented or minimized. If you can successfully prevent the generation and/or production of waste, there is at least a good chance that economic advantages will accompany the potential waste reductions.

Plan a test for your theory. Empirically evaluate the predicted and measured outcomes (using statistical methods if possible) to see if there were indications your theory was correct. If the results are not what you predicted, your theory may need revision, expansion, or re-evaluation. Were there any data points that fell outside the calculated statistical bounds, and what can you find out about what happened there? Could any sub-processes have caused the problems? If so, you may need to investigate the sub-process with a new PDSA cycle?

What time and external resources will you need to test your theory? This is likely a point at which you may need to begin to recruit the support more team-mates, or Management, in order to obtain the time and resources you will need. Interpersonal ethics are extremely important to the functions of a small team. It is astounding to witness the joyous teamwork and amazing results that can emerge when everybody in a small team continuously iterates the familiar “Golden Rule,” namely “Do unto others as you would have them do unto you.” It can be horrendous (as this author has also experienced) to suffer through the failures and misery that can occur when one or more people on a team (especially the Mangers) regularly fail to observe that “Golden Rule.”

When you start to ask for significant time and/or resources, new and complex issues begin to emerge. When it is time to approach Managers for more resources, keep in mind that Managers are often very busy people, with many potential issues and problems vying for their attention. You and/or your team will need very good human, communication, and ethics skills and approaches, to go along with your Plan. Hopefully you will already have gathered at least some data or information showing some clear potential for success.

If you are very fortunate, your Managers and/or evaluators may understand Quality concepts, the goals you are trying to achieve, the approach you are taking, and that their own real job is Leadership, rather than dictating top-down orders as to exactly what everyone below them should do. Bring along the potential team-mates you have recruited and talk to your Managers about how your Plan considers or addresses customer and/or market needs. Explain why your Plan has potential to reduce cost and waste and improve one or more Qualities you think the customers will approve of and pay for. Finally, many Real-World Managers (and many external people) are still motivated by ideas of profit. If there is anything you can say with reasonable supporting logic, say what you can about potential market sizes and/or potential for profit. Hopefully Management will approve your Plan for a test.

Unfortunately, in the Real-World of modern international corporations, there are still many Managers (or government officials, or academics) who either have not been trained in, or do not believe in Quality principals and approaches. Particularly in the economic and social sciences, there are still many people (especially lawyers and politicians) who do not understand much about complexity, unpredictability, and/or evolution. They tend to leap toward attempts to directly manipulate, dictate, or equalize future outcomes. Some of those self-styled “Leaders” may become corrupted by power, their egos, and/or focus on “profit,” and do some stupid and/or unethical things. Such things have certainly happened throughout human history, so be alert and Realistic. If current Management doesn’t understand such things, you may eventually have to move elsewhere where Managers and/or decision makers do understand, appreciate, and encourage such approaches.

Lastly, Robert Pirsig believed in a very personalized approach to identifying and producing “Quality”. “The real cycle you’re working on is a cycle called yourself.” Nobody else has to grant an individual permission to work on improving themselves, their values and attitudes, and their focus and attention on what they are actually doing. Strive to bring a “Zen-like” focus to improving yourself, your own processes, and the things you produce every day. If you really *DO* that, and you actually conceive or discover a new high Quality invention, you will have a *much* better chance of convincing your co-workers, corporate managers, customers, and/or the government and/or regulators to give you the support and permission you’ll need in order to get a new Greener invention out of the lab, and out into the Real-World.

Mark A. Murphy PhD, J.D. lives in North Carolina, and is continuing his career writing about and creating Quality, and leading by example, somewhere at the interfaces of science, business, and law.

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E. Ann Nalley

3 Technology supporting green chemistry in chemical education

Abstract: Changes in technology have affected the way we teach, the way students learn and the way chemical research is conducted. Rapid changes in technology have greatly improved laboratory instrumentation, data collection and treatment and have greatly enabled Green Chemistry. This chapter will trace the career of a 4-year college professor who began teaching as a high school teacher in the sixties and transcended to the collegiate level. She will describe how changes in technology changed the way we teach chemistry and how this has enabled us to introduce green chemistry at all levels to our students. This chapter will highlight changes in technology which have enabled educators both in teaching chemistry labs and conducting research to employ green chemistry.

Keywords: STEM green education, chemical education, chemical technology, green chemistry teaching

3.1 Introduction

When I took my first high school course in 1958, the concept of green chemistry was nonexistent. The basic concept of safety in the academic laboratory was essentially not addressed. For example, the laboratory manual, I used in high school gave the following directions; “go into the stockroom and taste some typical acids. Record your test result in the table.” Some of my fellow students and I did exactly that. The first acid I selected was picric acid. It was a large 5-pound bottle containing an orange solid. I dipped my finger into the large bottle and dipped up a small amount of the solid and touched it to my tongue. As soon as it touched my tongue, I felt an extreme burning sensation and ran out of the stockroom quickly to a water fountain in the hall. I washed out my mouth several times with water but the effects of the burn on my tongue are still there and I still speak with a lisp. I was extremely lucky that the effects were not greater. Our high school chemistry lab had a table in the back of a classroom and there were no safety features in the room. In spite of that, I still enjoyed my chemistry class and went on to major in chemistry and eventually earned a Ph.D. in chemistry. As I progressed through my chemistry career, not much changed in terms

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of safety. Few of the chemistry laboratory courses I had in college had adequate fume hoods if any. In reading the early history of chemistry, there are many instances where there was an appreciation of the fact that professors thought the presence of many vapors in the lab meant good chemistry.

I began my teaching career in 1965 as a high school chemistry teacher. By that time there was a little more emphasis on safety in the laboratory but again my high school laboratory had two tables in the back of the class room. We did very simple experiments once a week and they were very short. The concept of a fume hood did not exist.

I taught 1 year and went back to school to earn a M.S. Degree in Chemistry. The research project I selected for my master's research was Polarography using a DME (Dropping Mercury Electrode). Boy did I need green chemistry. The fume hood in our research lab did not work and my first assignment in the research lab was to clean up 500 pounds of Mercury which was pooled in all of the drawers in the lab and when you opened the bottom drawer of each bench, there were pools of Mercury as large as a toddler swimming pool. I vacuumed up all that Mercury and placed it in large containers and then began the process of purifying it. I washed it first by dropping in through a pin hole in a filter paper into carbon tetrachloride to remove the grease. I then washed it with nitric acid to remove the mercuric oxide. The last step in the purification was to distill the mercury in the fume hood. By the end of my first summer of the mercury reclamation, I realized that the fume hood was not working. I notified my research advisor and he notified the laboratory safety officer (I don't think they called him that at the time). They repaired the hood but by then I had distilled more than half the mercury. I must have good genes because if I developed mercury poisoning I never felt it's effects. Boy did I need green chemistry.

I finished my Master's degree and moved to Cameron University to begin my teaching career in 1969. Cameron had moved from a community college in 1967 to a 4-year college in 1969 and in the spring of 1970 we graduated our first. B.S. student with majors in chemistry. The facilities we used for chemistry laboratories were carry overs from the community college. We were in a very small building with three chemistry labs. Each lab contained one fume hood, no safety shower, no eye wash, and no visible safety devices. There was one fire extinguisher for the whole building and that was in the hall. I purchased an eye wash bottle and we required all students to wear safety glasses but it was up to each faculty member to set up their own labs. At that time our glass ware consisted of very large 250 and 500 ml flasks and everyone thought larger is better so we could have large yields. We started out with large amounts of starting materials so we could obtain large yields. We did not have ground glass joints so we used rubber stoppers and glass rods. Students learned to bend glass and design their own equipment. It was 15 years later before we ordered ground glass joints in glassware kits which were $24/40 joints. We continued to use very large amounts of starting materials in our reactions and we had large amounts of chemicals to dispose of. Of course that meant dumping them down the drain. The organic lab which also doubled as a bio-chemistry lab was also my research lab. Undergraduates who performed research had to find a time when the lab was not used for classes to perform their research. We had to choose short experiments which could be performed and cleaned up in a short time or leave a reaction in the only hood in the laboratory with a note attached. If a reaction required a long reaction time, then it often had to be left refluxing in the hood for extended periods of time sometimes 24 h to 48 h. Boy did we need green chemistry.

One of the most important factors in making it possible to introduce the principles of green chemistry in the academic laboratory was the technology incorporated into the manufacturing of chemical fume hoods [1]. Although chemical fume hoods have been around since 1900, the advent of technology has made them much more efficient. Thomas Edison seems to have been one of the first scientists to be concerned about laboratory ventilation. Edison used the fireplace chimney in his lab to exhaust noxious fumes and odors from his experiments with heated rubber compounds, using the natural draft of the chimney to expel the gases. In 1923, one of the first recognizable fume hoods in the modern sense of the word was in use at the University of Leeds. This unit consisted of a large cupboard standing at working height and incorporating vertical rising sashes arranged like parallel windows [1]. Considerable advances in fume hood technology were made during the second world war in response to the fear of exposure to highly toxic chemicals and radioactive materials. Against this catastrophic backdrop, significant progress in safety, ventilation and fume hood design were made. Also during the war years, the high-efficiency particulate air (HEPA) filter was developed by the body which later became the Atomic Energy Commission. The development of the HEPA filter had a dramatic effect on the effectiveness of fume hoods and biological safety cabinets, greatly increasing protection for users.

In the fall of 1996, Cameron University completed the construction of a new sciences complex which housed the new chemistry teaching facility, with five teaching laboratories and an actual research laboratory. All of the teaching labs had six fume hoods with the exception of the organic lab which had eight. Even the research lab had three hoods. We were forward looking with our lab design, and the hoods were designed to exchange air every 9 min. The tall towers protruding from the top of the building not only allowed for air exchange, but were also equipped with scrubbers. Every lab was equipped with a safety shower, an eye wash, a fire blanket and two fire extinguishers. We replaced the organic glassware kits with smaller glassware ($14/20) joints. We were ready to move into the twenty-first century, and we were ready for green chemistry.

The idea of green chemistry was initially developed as a response to the Pollution Prevention Act of 1990, which declared that U.S. national policy should eliminate pollution by improved design (including cost-effective changes in products, processes, use of raw materials, and recycling), instead of treatment and disposal. Although the U.S. Environmental Protection Agency (EPA) is known as a regulatory agency, it moved away from the “command and control” or “end of pipe” approach in implementing what would eventually be called its “green chemistry” program. By 1991, the EPA Office of Pollution Prevention and Toxics had launched a research grant program encouraging redesign of existing chemical products and processes to reduce impacts on human health and the environment. The EPA, in partnership with the U.S. National Science Foundation, then proceeded to fund basic research in green chemistry in the early 1990s. The 12 Principles of Green Chemistry were published in 1998, providing the new field with a clear set of guidelines for further development [2]. In 1999, the Royal Society of Chemistry launched its journal, Green Chemistry.

3.2 My first attempts at green chemistry

When I first began to teach chemistry in 1965 as a high school chemistry teacher, the term green chemistry had little meaning. At the high school level, we had very limited time for laboratory and the most sophisticated lab we did was the titration of an unknown acid with a base or the effect of acid–base indicator on solutions. We had limited equipment and the students worked as groups of three. I was always careful to use very dilute acids and bases, and we used a lot of vinegar and red cabbage.

Not much changed, when I moved to Cameron in 1969. Our labs were small; our equipment and chemical supplies were very limited. As long as we used dilute solutions and lots of vinegar and baking soda, we were complying with the principles of green chemistry as we know them today. The first 2 years I taught at the university level, I taught general chemistry, and it was easy to comply with principles of green chemistry (which had not been invented yet). Even at that stage in my career, I felt an obligation to try to make the chemistry lab both interesting and educational. My challenge came when I was assigned to teach two classes of organic chemistry. One of them was known as Aggie Organic. It was an organic class where we taught organic chemistry in one semester. The course was designed for agriculture majors and had not been taught at Cameron before. The other class was Organic Chemistry for Home Economics majors and, again, had not previously been taught at Cameron. I adopted the same basic organic textbook for both classes but the challenge was the laboratory portion of the class.

The Aggie Organic class met for one hour four days a week and one 3-h lab which met once a week. The objective of the lab was to teach some organic chemistry while at the same time incorporating principles of agriculture into the course. Students who completed the class would have a major in agriculture usually in agronomy or breeds of livestock. Many would continue their studies in graduate school to acquire a Ph.D. in agriculture. Since the course had not been taught at

Cameron before, I had the freedom to develop the course to try to meet the objectives of the agriculture program at Cameron. In the first part of the semester, I taught common techniques used in a traditional organic laboratory. These included: determination of melting points of organic compounds and how to identify an unknown organic compound using mixed melting points, recrystallization of benzoic acid, separation of an acid–base mixture using extraction, paper chromatography of food coloring, and separation of a mixture using fractional distilla-ion. In the second half of the lab, I designed labs which were more related to agriculture. We used the Kjeldahl determination of total nitrogen. We analyzed total nitrogen in wheat, total nitrogen in different brands of cereal, and total nitrogen in different brands of dog food. We synthesized azo dyes in the lab and then tested the compatibility of the dyes with treated cotton, raw cotton, treated wool and raw wool. I obtained raw cotton from the Faxon Cotton Gin and bought mercerized cotton and treated wool from fabric shops. I obtained raw wool from the sheep farm at Cameron. We synthesized gun cotton from raw cotton and made cellulose acetate from cotton balls. The students made home-made lye soap from lard and compared the properties of the lye soap with the properties of detergents. I used very few commercial organic compounds, and the greatest danger were the mixtures of nitric and sulfuric acid which we had to prepare for the cellulose acetate and gun cotton. I had begun to integrate green chemistry into my labs without realizing it because most of my materials were natural products. I am not sure who learned more those first few years, the students or me, but we certainly had fun, and the students could see the relationship between agriculture and chemistry.

I used a similar approach in teaching the organic for home economics students. Again the course was a one-semester course with three hours of lecture and one three hour lab each week. I taught organic techniques during the first half of the lab and the second half was designed to introduce students to organic chemistry of food and textiles. We used the Kjeldahl analysis to determine total nitrogen content of cereals and compared whole grain oats with cheerios. We synthesized dyes and tested them on different types of fabrics and examined the changes which occur in both cotton and wool when they are processed compared to raw cotton and wool.

Those courses led to a research project which I directed with agriculture students. We had a greenhouse and we tested different soil types and nutrients to develop optimum growing conditions for aloe vera plants. This project lasted over a 2-year period and was really green chemistry. We grew the plants under different conditions and harvested them at various stages in their growth cycle. We analyzed them by extraction and digestion methods to determine the total galactomannans at various stages in their growth cycle. It was an ambitious project but it resulted in the development of the optimum conditions for growing aloe vera plants in a greenhouse and led to our receipt of an SBIR grant to build a green-house aloe vera farm.

As the enrollment in our agriculture program declined, we were forced to drop the Aggie Organic and required the agriculture majors to take the same organic courses as the chemistry and biology majors. For me, it was a sad time, and the days of designing agriculture organic labs were gone. I was forced to teach using standardized organic lab manuals, which at that time were very abundant. There was little attention given to either the safety of chemicals used in the syntheses or to the by-products of the reactions in these lab manuals. Many reactions required at least two to three hour reflux time and many labs required two-three lab periods to complete. The time period for these organic labs ran from about 1976–1997. We were still using $24/40 lab kits and we usually started with as much as 25–40 g of starting materials in order to produce good yields after the purification process. That meant lots of solvents for purification, if we used extraction and there was certainly no economy in terms of the time required for synthesis and purification. We usually had fairly good yields but that also meant we had to do something with the student preps. We analyzed them if we had time using our IR which required at least 15 min to run each IR and the IR was housed in a different building than the organic lab. I would run back and forth between buildings trying to oversee the students running their IRs and those who were completing their purifications. Our waste disposal at that time was to pour all waste down the drain. Not only were our methods not green, but also not safe for the student or the instructor. Those were not good days for teaching organic chemistry. Early in my career, I became concerned about my choice of chemicals I selected to use in laboratory when one of my students who was pregnant gave birth to a still-born at the very end of the semester. After that, I researched every chemical I used in organic labs and made sure that they were not carcinogenic or teratogens. We began to make disposable gloves available to students in all of our labs. We had no safety officer or stock room manager at that time so each faculty had the responsibility for safety in their lab. This was a meager attempt at green chemistry, but it was the best I could offer at that time.

When we moved into our new building in 1997, we moved into the twenty-first century. We were equipped with a large chemical stockroom which included safety cabinets for acids and bases, a flame proof storage facility for organic solvents, including storage cabinets for different types of flammable organic chemicals. We had a stockroom manager and a safety officer. There was adequate storage for all types of glassware and appropriate storage capacity for chemicals in our stockrooms. The teaching and research labs were equipped with hoods, safety showers and other types of safety equipment. Cameron was now governed by the Board of Regents of the University of Oklahoma, and we were able to arrange with them for pick up for our hazardous and chemical waste disposal. All of our organic labs were equipped with $14/20 glassware kits and we revised our curriculum to reduce the quantities of reactants we used in every experiment. As we reduced the quantity of the starting materials, we also reduced our chemical waste, including solvents, by-products and products produced in each experiment. This was the real beginning of our conversion to green chemistry labs at Cameron University. We developed safety instruction videos and incorporated a vigorous safety training program for all students enrolled in chemistry courses including research. This safety training included protocols for waste disposal and appropriate methods of cleaning up chemical spills. Every lab included gloves and other safety equipment. We continued to monitor the chemicals we used in the labs assuring that we used neither carcinogens or teratogens in our organic laboratory experiments.

Our challenge came in organic chemistry II labs. We began teaching our organic II labs as a synthesis lab. The students were organized into small companies and were allowed to design the experiments they conducted in the laboratory. They used Organic Syntheses to look up a basic synthesis and modified the synthesis by replacing the chemicals and/or solvents and scaling down the size of the reaction to 0.1 mole. The goal of the lab was to design a synthesis which would produce a profit. Using Organic Syntheses as a model meant that the students had to read Organic Synthesis and became familiar with any safety precautions associated with the lab. The students had to "purchase" the chemicals they used for each lab from the instructor and then were allowed to "sell" their products to the instructor. They prepared profit/loss sheets which allowed them to calculate the profit they made in each experiment. This is a great way to teach atom economy. This meant they had to become familiar with grades of chemicals and differences in prices of the various grades. They also had to purify their products and then prove the quality of the product using IR, NMR and other physical properties. This was quite a learning experience for the students, and they became very familiar with MSDS sheets and attached them to their final lab reports. The challenge for the instructor was to assure the safety of the synthesis and the quality/safety of the products the students synthesized, so every synthesis had to be approved before the students could perform them. A limitation which continued to be a hurdle for organic faculty at Cameron was the time required for a synthesis and the time required to purify products. We were severely limited in the number of syntheses we could perform since our labs met only once a week for three hours.

3.3 Incorporation of Vernier lab quests

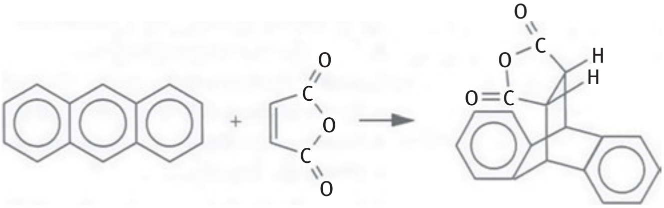
In the fall of 2011, our faculty made the commitment to introduce more technology into our undergraduate laboratories. We upgraded the organic lab by installing three new rotatory evaporation systems, installed high vacuum distillation systems on all of our lab benches, purchased an additional FTIR, and upgraded our NMR with Anasazi EFT-60 system. Our proposal for acquisition of a Rayonet Photochemical Reactor System was funded, and we now had the capability to run photochemical reactions in our organic labs. This provided us with another opportunity to introduce more green chemistry in our labs. Our students were coming to Cameron from high schools which had electronic data collection systems, and we felt that it was time to upgrade our labs not only in terms of data collection, but also in terms of technology. We examined a number of chemistry lab electronic data acquisition and data management systems. We selected to use the Vernier data acquisition system, because not only did it provide us with the acquisition systems we needed for chemistry, but would also assist us in upgrading our physics labs.

We wrote the proposal and received the funding to purchase sufficient Labquest II data acquisition equipment for both freshmen laboratories and our organic lab, as well. We also purchased Vernier equipment for our physics labs. Our challenge was to rewrite our general chemistry and organic lab manuals to incorporate the new technology into many of our labs. We were very excited because this would now require us to redesign our labs, not only to incorporate technology, but to allow our students to collect data much more rapidly and still have time in the lab to process the data and discuss it. Active student involvement in scientific practices and procedures represents both a key goal of science instruction and an important means to help students build their scientific understanding. The Vernier system provided us with a means to allow our students to use hands-on probes, sensors, and other technology tools connected to the stand-alone data-collection device, the Labquest II. This meant that our student did not have to bring a laptop computer to the lab. The Labquest II could also be used to not only visualize the data, but to analyze it as well. The next step was to install wireless printers in our labs and we were on a roll. The students could perform a lab experiment, analyze and treat the data and print out their lab reports in a single laboratory period. We saw an immediate change in the students' understanding of the science principals involved in the lab and an elevation of, not only their test scores, but also their satisfaction with the laboratories.

In the organic lab, we had to revise all of our procedures for all organic labs. We made a significant upgrade in green technology when we adopted the Vernier data collection system. Our oil bath melting point apparatus were replaced with Vernier Melt Temp digital melting point apparatus and each station in the lab had their own melting point apparatus. This enabled the students to perform melting points much faster. Mercury thermometers were eliminated from all labs and were replaced with both short range and wide range digital temperature probes. The wide range probes fit out $14/20 distillation adapters. Now we were able to monitor the temperature changes in a distillation or in a boiling point determination, and no longer did we have to worry about broken thermometer mercury spills. We equipped every lab bench with a Vernier Gas Chromatograph and could monitor either distillations or chemical reactions using gas chromatography. The students could perform a fractional distillation in the lab, collect the fractions, monitor the temperature for each fraction, determine the composition of the components in each fraction, integrate the peaks and print out both chromatograms and the percent of each component in the mixture using the wireless printer. The way we teach organic chemistry labs has definitely changed as we have incorporated more technology. My dream of having a polarimeter to measure optical activity in my organic labs came true. We were able to purchase a Vernier Polarimeter for every lab station in our organic lab, and now when we teach optical activity in lecture we incorporate appropriate labs in our schedule to illustrate optical activity. We continue to add more Vernier probes and instruments and continue to rewrite our laboratory procedures, becoming more and more green as we become more efficient and more effective in our teaching.

3.4 Microwave technology in organic labs

With the many changes we made in our laboratories, my impatience grew with the amount of time required to carry out many basic organic syntheses and I began to look for a more efficient way of performing organic syntheses. I wanted to follow the pattern we had set in our general chemistry labs which allowed the students to collect data, examine the data and discuss it in a single laboratory period. I read many articles in the literature where faculties were using microwave technology to carry out organic syntheses. I was able to get funding to purchase ten digital commercial microwave ovens for my organic lab. I along with my research students spent two semesters investigating organic syntheses which could be carried out in a commercial domestic microwave oven. This was a major project, because there were many factors to be considered, the most important one, of course, was safety. We had to find reactions which could be carried out using water as a solvent or high boiling nonflammable solvents or, in many cases, use reactions which were did not require solvents. I spent many hours researching the literature to find appropriate reactions, and, in many cases, I carried out the reactions before I asked my students to perform them. In spite of the many obstacles, we were able to develop a number of reactions which could be carried out in domestic microwaves. We carried out the reactions in our research, developed the appropriate conditions for obtaining maximum yields, followed through with purification techniques and analyzed the products using IR, NMR and physical properties to characterize the products. Our next step was to rewrite the procedures as an organic lab experiment and to incorporate these experiments into my organic curriculum. My research students were very patient and committed, and we were able to develop ten experiments which we could incorporate into our undergraduate organic labs using domestic microwave ovens to perform the syntheses. But there were still problems to overcome. Students did not always read the instructions and did not program their microwaves correctly. If they did not set up the appropriate power and times for the reactions, then we had boil overs, and in some cases dissolved the paint off the inside of the oven or, in some cases destroyed the oven. I do not teach all of the labs, and even though I tried to caution the other lab instructors, we still had accidents. I had to continuously try to find funding to add more microwave ovens. But when we were able to get the students to follow instructions we were able to carry out reactions like the Diels-Alder synthesis with Maleic Anhydride and Anthracene, Figure 3.1, in 15 minutes and recrystallize the product in the same laboratory period [3].



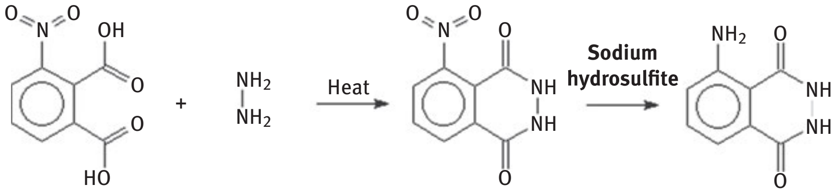
anthracene
(diene)

maleic anhydride
(dienophile)

(adduct)

Figure 3.1: Diels–Alder reaction of anthracene with maleic anhydride.

We were successful with other reactions which are difficult to perform because of the high temperatures required to make them work like the synthesis of luminol, Figure 3.2, which works well in a microwave oven [4].



6 **3-Nitrophthalic Acid**

7 **Hydrazine**

8

1 **Luminol**

Figure 3.2: Equation for the Synthesis of Luminol in a microwave reactor.

3.5 CEM explorer microwave reactor

I have to thank my research students who worked with me over the past 7 years who helped develop experiments using the Rayonet Photochemical Reactor, Vernier technology and with the domestic microwave ovens. We used the Rayonet Photochemical Reactor to carry out the classical synthesis of benzopinacol from benzophenone, Figure 3.3 and Figure 3.4. The energy obtained from light allows the benzophenone to abstract a proton from the 2-propanol (isopropyl alcohol); thus, benzophenone is reduced to benzopinacol [5]. The reaction works best when the long-wavelength (450 nm) lamps are used. This reaction, which for many years was carried out by

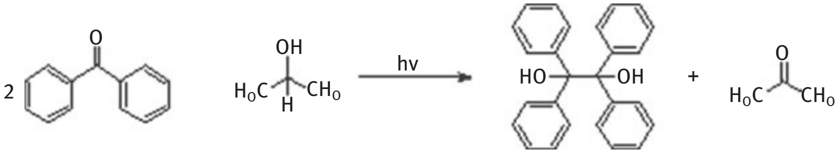


Figure 3.3: Synthesis of benzopinacol by a photochemical reaction.

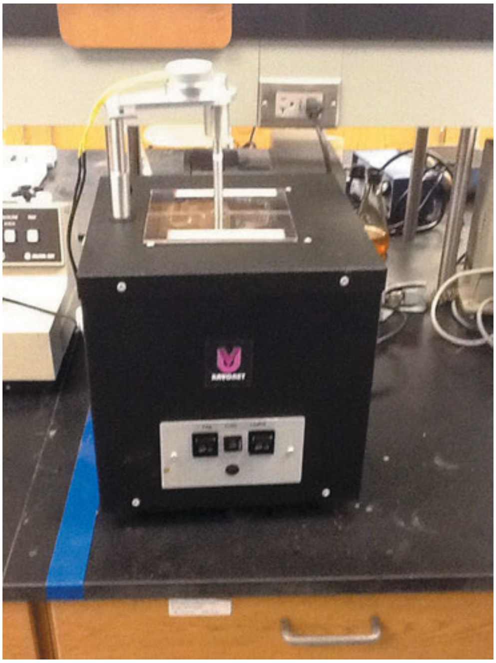


Figure 3.4: Rayonet photochemical reactor.

mixing the reactants in a flask and placing it on the roof for a week, could now be carried out in one afternoon with yields of 80% or better.

Now we were ready for a new dimension and that dimension was the acquisition of the CEM Explorer Microwave Reactor. I read about the capability of the CEM Explorer Microwave Reactor and was determined to acquire one. I wrote a proposal to purchase one and it was funded and we were able to purchase a robotic CEM Explorer Microwave Reactor, as seen in Figure 3.5. This allowed us the versatility of running a reaction at different temperatures, different pressures and different powers. The beauty of this reactor is that it allows us to prepare the reaction, place it in a reaction vessel equipped with stirring bars, place it in the reactor, seal it and program it with different sets of reaction conditions. The robotic arm places the reaction in the reactor, seals it and sets up the program we have preprogrammed to run the reaction. The reaction is then allowed to run and then automatically cooled down

Figure 3.5: CEM microwave reactor.

before the robotic arm replaces it in the carousel. Many of the anxieties over running microwave reactions were removed with the acquisition of the CEM reactor.

For the past two years, it has been housed in the research lab and has been used by the research students only. Our goal is to develop experiments which can be performed in the CEM reactor which can then be adapted as experiments for organic chemistry II labs. The CEM reactor is safer to use than traditional domestic microwave ovens, but it is limited by the fact that the reaction vessels have a maximum volume of 10 ml, which means we are limited in terms of the size of the reactions we can run. Our yields are typically low, but we have not had time to conduct as many reaction as we need to in order to maximize the yields in our reactions. Another limiting factor is the time required to complete a reaction because of the way the reactor operates. It takes at least 15–20 min to run any reaction even though the actual time required to carry out a reaction may be only 10 min. For example, when we run a microwave facilitated reaction in the CEM reactor. We prepare a reaction mixture and place it in a 10 ml reaction vessel and load the reaction parameters. This activates the robotic arm which places the sample in the reactor and starts the program which has been set up. The sample is sealed and then heated to the reaction temperature (about 5 min depending on the starting temperature). After the starting temperature is reached, the reaction begins and runs for the preset reaction time which is usually between 5 and 15 min. At the end of the reaction time, the system cools down to about 60 degrees Celsius. The robotic arm removes the sample and returns it to the carousel. This takes a total of about 25 to 30 min per sample. That means that in order to run 10 samples requires a total of 250 to 300 min (about 5 h).

We have to select labs which can be run in 5 min at low temperatures so we are still using domestic microwave ovens to carry out most of our organic syntheses but this is better than setting up a reflux and running a reaction for two hours. So microwave technology has enabled us to perform more syntheses and still have time to purify our products and characterize them by NMR., IR and physical properties. Our limitation for converting more of our synthesis to applications with Microwave Synthesizers is at this point is the cost of the microwave reactors. We need more than one reactor or a larger one in order to move from microwave synthesis using domestic microwave ovens to commercial Microwave Reactors.

3.6 Microwave and ultrasonic synthesis in undergraduate research

The addition of the CEM Microwave Reactor to our undergraduate research lab has really changed the way we do research, and it has really sparked an interest on the part of many of our students to participate in an undergraduate research project. The students are especially interested in using green chemistry in organic synthesis.

I have already discussed my first attempts at using microwave technology by using domestic microwave ovens to carry out organic syntheses. If one carefully considers all of the ramifications of using domestic microwave ovens, and if the students are carefully supervised, then you can have some success in carrying our organic synthesis both as a laboratory synthesis and in a research project, but there are challenges and certainly limitations.

Many of the challenges were removed when we moved to the CEM Microwave Reactor because of the safety issues, which are not a problem with it. For example; when you use a domestic microwave, you cannot seal a reaction mixture. Our reaction vessel is usually a 250 ml Erlenmeyer flask with a 50 ml beaker inverted over the top. There are problems with low boiling solvents and we have to keep adding solvents after each heating cycle. We have investigated using ethylene glycol as a solvent for many reactions but as we move to higher boiling solvents we encounter the problem of separating the product from our solvent. With reactions like the synthesis of luminol, triethylene glycol works great in the microwave oven and the product in very in soluble and can be removed by filtration. I have been blessed to have more than 25 students who have been willing to try different experimental conditions using both the domestic microwave oven and the CEM Microwave Reactor. The beauty of microwave facilitated reactions in that it enables us to carry out many reactions which are much greener and cannot be performed using conventional synthetic methods. One of my favorites is the synthesis of acyl amides using urea as a starting material. The classical synthetic method for the synthesis of acyl amides has always been to react an acid with thionyl chloride to prepare the acyl halide and then to react the acyl halide with ammonia. This reaction was never a favorite of mine. We had to set up the reaction in the hood and weigh out the thionyl chloride very quickly (in the hood) and transfer it to a reaction flask and if we refluxed the reaction we always added a drying tube or a vapor trap. Even the distillation and purification of the product was no fun because acyl halides are unstable. To prepare an amide using microwaves we simply mix the carboxylic acid with a stoichiometric amount of urea and react it in a microwave oven or microwave reactor for a designated amount of time, and then isolate the acyl amide as the product [6]. We use a really low–cost starting material, urea, which is readily available, and a carboxylic acid. We have performed this synthesis with a number of carboxylic acids and have obtained yields on the order of 75% to 80%. Another great synthesis is the synthesis of tetraphenyl porphyrins using microwaves [7].

Using another green approach to organic synthesis this past year, we investigated the use of ultrasonic devices in the promotion of organic synthesis. We began with a repeat of a synthesis which we performed using microwaves, the synthesis of Tetraphenyl Porphyrins. We began using ultrasonic baths and recently acquired an ultrasonic horn. Ultrasound energy has proven to minimize waste, decrease reaction times, and sometimes eliminate the use of solvents in or ganic chemistry synthesis. Since these are good properties for green chemistry. Ultrasound was be utilized to synthesis imidazoles by reacting aromatic aldehydes (**38**) and ethylenediamine (**39**), with NBS as oxidant and water as solvent to produce Imidazoles (**40**) (Figure 3.6) [8].

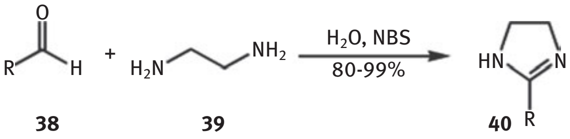


Figure 3.6: Synthesis of Imidazoles from aldehydes and ethylene diamine.

Imidazoles (**40**) are key groups inside heterocycles, and as they are not only a cornerstone of the synthesis pathway of these compounds, but also form part of potential and marketed drugs. Our yields on these reactions range from 29% to as high as 65% depending on the substituents on benzaldehyde. We still have much work to do on the use of ultrasonic waves in organic synthesis. We recently acquired an ultrasonic horn and we want to investigate the potential of using it in organic synthesis.

3.7 Green chemistry for high school students

The Department of Chemistry, Physics and Engineering at Cameron University has hosted summer science academies for high school students for more than 18 years. These academies were ten-day residential academy where students lived in the dorm at Cameron for the 2-week period. There were 24 high school students from Oklahoma who participated in the program each summer. These academies introduced students to those concepts necessary to understand why very small systems exhibit unique behavior. Activities were divided evenly between chemistry and physics activities and concepts. The academy featured activities designed to attract the students to careers in science, mathematics and engineering. One of the favorite activities was the construction of a robot which they then programmed. During the summer of 2018, our funding was reduced and the length of the academy was reduced to one week. We did not have time to construct a robot but we still wanted to include the concept of robotics in the academy. In physics we used robots which had been constructed in the past and had the students write programs to operate them. In chemistry, we wanted to demonstrate how robotics is used in both chemical analysis and chemical synthesis. Since our CEM Microwave Reactor is a robotic system, we designed a synthesis which enabled the high school students to carry out an organic synthesis.

For the last 5 years, we have required the students to prepare homemade lye soap in a domestic microwave oven. They were allowed to add food coloring, to make the soap pretty and to add a scent to make it smell good. We used scented oils which were supplied to us from a local cosmetic plant. In the summer of 2018, the students selected their favorite scent and synthesized esters using microwave energy to produce their favorite scent. Each student group of two were allowed to choose an alcohol and acetic acid from a table which would produce their favorite scent [9]. They mixed their alcohol and acid together in a microwave vial and added a drop of sulfuric acid as the catalyst. We explained to them that the reaction would produce a scented oil which can be used as an additive to perfumes, soaps, cosmetics, room deodorizers, etc. They mixed their reactants in the microwave vial, added a stirring bar and a cap. They placed it in the reactor and programmed each mixture. They pressed play to start the reaction. The robotics system ran each vial while the students went back to the lab to make their homemade lye soap. They used their scented esters to make novelty soaps. This activity introduced them to robotics and the application of microwave energy in green synthesis. In the picture below (Figure 3.7), one of the students, a high school sophomore, operates the microwave synthesizer. The students loved watching the synthesizer operate.

Not only did the soap smell good, but it was also beautiful and made great presents for their mothers. They used jello molds to make the pretty cakes of soap (Figure 3.8).

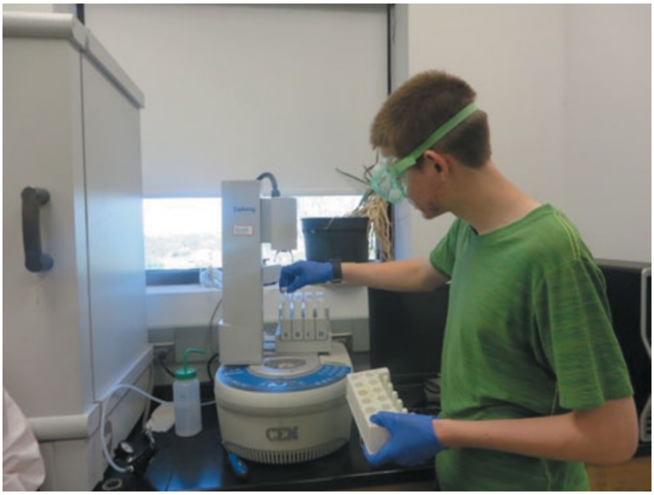


Figure 3.7: A high school student removes the finished esters from the microwave reactor.

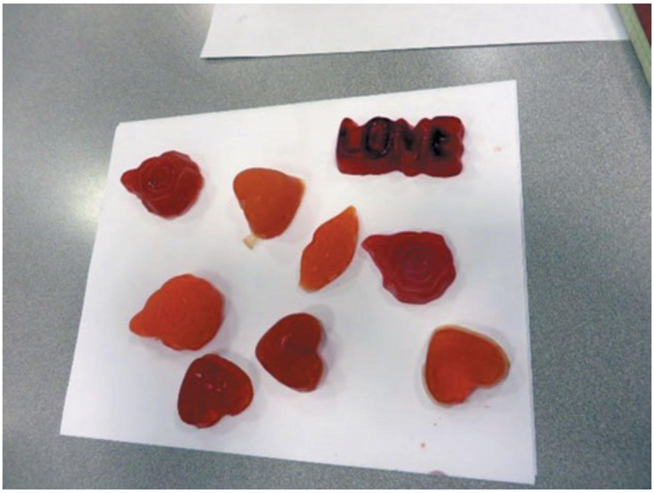


Figure 3.8: Home-made lye soap made in a microwave oven.

3.8 Conclusion

Technology has changed the way we teach and has enabled us to introduce green chemistry at all levels when we teach chemistry to our students. Allowing many chemical reactions to be completed in minutes, microwave heating has revolutionized preparative chemistry. As a result, this technology has been widely adopted in both academic and industrial laboratories. Integrating microwave-assisted chemistry into undergraduate laboratory courses enables students to perform a broader range of reactions in the alloted lab period. As a result, they can be introduced to chemistry that would otherwise have been inaccessible due to time constraints (for example, the need for an overnight reflux). A number of the chemical transformations use water as a solvent in lieu of classical organic solvents. This contributes to greener, more sustainable strategies for faculty and students, while maintaining high reaction yields. The advantages inherent in microwave use make it ideal for the undergraduate laboratory experiments. Although students are exposed to many different reactions in the classroom, many important organic reactions described in undergraduate textbooks are presently not included in the laboratory course owing to long reaction times, high temperatures, or sensitive reagents that present a potential danger to the students. This provides an excellent opportunity for undergraduates to adapt classical syntheses to microwave technology.

Technology has affected the way we teach, the way students learn and the way chemical research is conducted. It has also produced a safer greener environment for students to learn and practice chemistry. Rapid changes in technology have greatly improved laboratory instrumentation, data collection and treatment. Computer molecular modeling provides an avenue for predicting toxicity, biodegradability, and other properties of chemicals, which are directly related to industrial applications. It is difficult for a small university to afford the latest in technology but industries are generally well equipped. The future for green chemistry is bright as we adapt technology in both academic and industrial labs [10–13].

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Lindsey A Welch

4 Catalyzing learning with green chemistry undergraduate research

Abstract: Green chemistry and sustainability are important concepts to incorporate into the undergraduate chemistry curriculum. Through the development of innovative undergraduate chemistry research projects in these areas, retention of students in the physical sciences can be improved. This paper describes two projects in undergraduate catalysis research: hydrogenation of furfural and the esterification of biooil from pyrolyzed wood. Catalytic transfer hydrogenation (CTH) of furfural with Pd/C led to the production of furfuryl alcohol, furfuryl isopropyl ether, 2-methylfuran, and tetrahydrofurfuryl alcohol. The metal chloride additives improved selectivity for furfuryl alcohol and furfuryl isopropyl ether. Catalytic conversion of pyrolyzed wood biooil in ethanol with a solid acid catalyst yielded ethyl esters, including ethyl acetate and ethyl propionate, as characterized by GC/MS These projects are described in the context of engaging undergraduate students in hands-on research for the purpose of improving retention and persistence, as well as preparing young scientists to enter graduate programs and the STEM workforce.

Keywords: hydrogenation, biofuel, pyrolysis, green chemistry, furfural, esterification, catalysis

4.1 Green chemistry connections

The growing need to address climate change is a challenge which has been embraced by the scientific community, and educating the younger generation about sustainable lifestyles through the undergraduate curriculum is a rising trend. Additionally, institutions of higher education have taken significant strides in implementing sustainable practices not only to appeal to the environmentally-conscious young generation, but also to improve energy efficiency to have a positive impact on the financial bottom line. However, recent campus action plans have shown a lack of consistent sustainable initiatives beyond operational elements [1]. Furthermore, there is a need for educating college students to develop a new generation of leaders who embrace sustainability. Previous work has shown that the community which surrounds young people will influence their perceptions of sustainability, which suggests that a comprehensive model toward embracing green practices will have a more significant

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impact [2]. So, incorporating green chemistry into the academic curriculum via undergraduate research is one important method by which educators can illustrate the importance of sustainability to college students.

The 12 principles of green chemistry, as described by Anastas [3], include such initiatives as using safer solvents, improving energy efficiency, using renewable feedstocks, catalysis, and promoting safer chemistry in the laboratory. Each of these principles serves as a key component in the undergraduate research curriculum to be described in this paper. Furthermore, the implementation of catalysis for the conversion of renewable feedstocks in the laboratory provides students a means to be engaged through the application of concepts in lecture to the real-world goal of developing sustainable energy options.

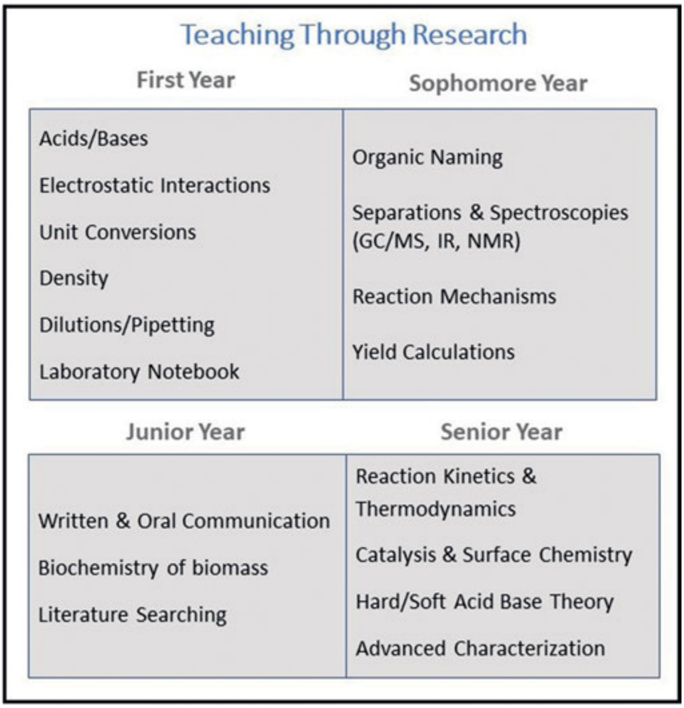
Wherever possible, safer solvents should be used to reduce the amount of waste from halogenated solvents and those which contribute to volatile organic compound (VOC) pollutants, which can form ozone in the atmosphere [4]. Light alcohol solvents (i. e. isopropyl alcohol and ethanol) have been chosen for projects in this research program to limit the impact of waste and environmental risk [5]. In addition to the low environmental impact of these solvents, they are also optimal for efficiency, cost, and safety for undergraduate students.

The booming field of renewable energy research has continued to grow despite recent developments in the collection and use of abundant natural gas stores [6] within the United States. Renewable energy feedstocks have been categorized within the four generations of biomass. The first generation biomass feedstock consists of edible crops such as corn, which most commonly can be converted to ethanol via fermentation. Second generation biomass includes non-edible feedstocks such as switchgrass and hemicellulosic biomass from crops which do not threaten the supply of food crops as the world population is expected to surpass 9 billion people by 2040. In an effort to decrease reliance on arable land to grow energy crops, the development of third generation feedstocks includes aquatic biomass feedstocks such as algae, microbial biomass and crops optimized through genetic modification [7]. The fourth generation biomass feedstocks encompass "carbon negative" sources of energy through technologies such as carbon capture and sequestration, and conversion of carbon dioxide into liquid fuels through catalytic reduction [8]. The research to be presented in this chapter has a focus on second generation feedstocks, specifically the hemicellulosic biomass conversion to liquid fuels using liquid phase catalysis.

Catalysis is a highly important principle of green chemistry, which can easily be incorporated into the undergraduate chemistry curriculum. Undoubtedly, most undergraduate organic chemistry laboratory courses include some sort of acid-catalyzed process such as dehydration or esterification. However, the use of the typical mineral acid (sulfuric acid or phosphoric acid) is neither sustainable nor particularly safe due to the corrosive properties of the acid. An alternative is the use of solid acid catalysts for these common processes because of the benefit of reusability and the elimination of the need for corrosive mineral acids in the laboratory. This substitution presents a prime opportunity to educate students about the benefits of renewable practices and incorporate interdisciplinary concepts in the laboratory. The examples of research projects presented here will demonstrate the incorporation of several green chemistry principles in a program designed to engage undergraduates and educate students about the importance of sustainability.

4.2 Applied learning from day one

The research projects described in this paper were designed to be approachable for students at all levels in the undergraduate curriculum. Because the concepts required to complete the projects include introductory chemistry content such as density, dimensional analysis and acid/base chemistry, students were successfully recruited as early as the first semester. Students were then retained through subsequent years because the projects gradually incorporated more complex concepts such as instrumental analysis of products, as well as provided a venue to develop oral and written communication skills. An organized display of how these catalysis projects were aligned with the undergraduate chemistry program is shown in Figure 4.1.



Teaching Through Research

First Year	Sophomore Year
Acids/Bases Electrostatic Interactions Unit Conversions Density Dilutions/Pipetting Laboratory Notebook	Organic Naming Separations & Spectroscopies (GC/MS, IR, NMR) Reaction Mechanisms Yield Calculations
Junior Year	**Senior Year**
Written & Oral Communication Biochemistry of biomass Literature Searching	Reaction Kinetics & Thermodynamics Catalysis & Surface Chemistry Hard/Soft Acid Base Theory Advanced Characterization

Figure 4.1: Teaching through research.

In the first year, students were encouraged to use their introductory chemistry lecture concepts of density, limiting reagents, and dimensional analysis to determine reaction concentrations and percent yields for their reactions. Additionally, students began to develop simple lab techniques like pipetting and preparation of serial dilutions to create calibration curves for product quantification. Students are taught how to maintain a proper laboratory notebook and a safe, efficient workspace in the laboratory. Lab safety is a crucial aspect of training new research students. Acid/base chemistry was a key concept in both projects described in this chapter. Students in the first year of college learn how acids and bases are defined and apply this knowledge to a real problem in the laboratory.

In the second year of study, topics in organic chemistry can be reinforced through these projects. Simple naming of organic molecules and the introduction of infrared spectroscopy and mass spectrometry in lecture allows students to understand the importance of the science in a research space. Specific reactions covered in organic chemistry such as addition/hydrogenation and esterification are given life in the research lab. While students may see the use of sodium borohydride as a reducing agent or a mineral acid to achieve esterification, the research lab provides an alternative approach to the science and instills the concepts of reaction mechanisms learned in the classroom. Furthermore, students continue to practice the concepts learned in the first year so that content retention is less of an issue for students. Analytical chemistry, which is offered in sophomore year for our institution, reinforces acid/base chemistry and the importance of accuracy, precision and statistical analysis of data.

In junior year, the development of more refined oral and written communication skills is a stronger focus. Additionally, upper-level courses such as biochemistry and instrumental analysis bolster the understanding of concepts which have been introduced in the research space. Renewable energy research relies on the students connecting an array of concepts from many of the fields in chemistry. Biochemistry introduces the biologically relevant molecules (e. g. carbohydrates and lipids) found in biomass feedstocks. Retaining knowledge of organic functional groups from sophomore year to relate to these biologically relevant molecules creates a more cohesive learning experience. Students in the junior year are also introduced to the importance of literature searching and critical review of work in the field. Upper level topics in chemistry include physical chemistry (kinetics and thermodynamics), inorganic chemistry (advanced acid/base theories and catalysis) and advanced characterization techniques.

4.3 High impact practices

Incorporation of high impact practices in the undergraduate curriculum range from mentorship, to undergraduate research, to capstone experiences have shown positive student outcomes in learning [9]. A focus on mentoring through undergraduate research in green chemistry creates an environment where students can learn in an engaged setting. Studies have shown that the role of mentoring undergraduate research is most effective when it involves both instrumental and socioemotional support. Robnett et al. reported that when a faculty mentor serves students by providing content-based support as well as by connecting with them on a personal level, the students are more inclined to develop STEM (science, technology, engineering and mathematics) efficacy and improve their self confidence in their abilities in science [10]. Furthermore, there is support that combining socioemotional, culturally relevant, and research content-based mentoring improves student learning and success, which is particularly important for students from underrepresented groups and first generation college students [11].

Mentorship can come in many forms. In the undergraduate curriculum, two dominant methods of mentorship are in faculty-student and peer mentoring. Examples of peer-mentoring include the Peer-Led Team Learning (PLTL) approach, which has been reported to be successful in the STEM field, particularly with minority students [12, 13]. Both of these approaches can work hand-in-hand to promote a sense of science identity in students who may struggle with the challenges associated with being a first generation college student and/or a student from an underrepresented group. Faculty mentors can provide a personal connection with students in a way that is often foreign to first generation students. In high school, course instructors are viewed as authoritative figures who may not engage with students on a personal level. Alternatively, in the college setting, faculty members forge long-standing professional relationships with their students by serving as a source of information and guidance. It is in these relationships where students can learn the benefits which networking can offer and how their strengths and weaknesses will determine how best they can fit into the STEM workforce. Both content and socioemotional mentoring play important roles in instilling the sense of science identity in students.

4.4 Retention, preparation for graduate studies, broadening participation

While not all students who begin an undergraduate research project will persist in the project until graduation, the importance of student engagement plays a role in the retention of these individuals at the institution. Students who have even limited experience in hands-on research in the undergraduate program benefit from close interactions with a faculty mentor as well as fellow students. Soft skills of interpersonal communication, leadership, and teamwork are valuable for any student, no matter what path may be taken after graduation. Students who participate in undergraduate research are more likely to pursue graduate degrees, and these students with laboratory experience will likely be more successful in graduate research [11].

Broadening participation in the STEM fields for individuals from underrepresented groups is an initiative which can be addressed by developing more substantial recruiting programs in undergraduate research. Specifically, women and students of color are still currently underrepresented in the physical sciences. According to the National Science Foundation (NSF), baccalaureate degrees in the physical sciences awarded to women in the United States has actually declined from 42.4% to 39.1% female from 2006–2016 [14]. The field of catalysis is dominated by members of the engineering field, which is historically non-diverse, both in gender and race. As of 2018, there are only six historically black colleges and universities (HBCUs) with undergraduate chemical engineering programs accredited by the Accrediting Board of Engineering and Technology (ABET), which represents less than 4% of all accredited programs. African Americans only represent about 3.5% of chemical engineers, although they represent about 13% of the US population [15]. A study at Spelman College, a historically black women's college, found that successful attainment of women in STEM fields was achieved through supportive peer environments and positive influences from faculty mentoring. They also note that undergraduate research opportunities are valued by the students not only for the intellectual impact, but also for financial benefits in the form of scholarships and fellowships [16]. Therefore, the implementation of undergraduate research programs in green chemistry have the potential to broaden participation of women and underrepresented groups in the physical sciences, while also educating the younger generation about the importance of sustainable practices. Cedar Crest College is a predominantly undergraduate institution (PUI) which has a traditional population of students being predominantly female. Additionally, as of 2019 the student population is 35% first generation college student, and 34% representing racial or ethnic minorities. Two examples of undergraduate research projects in green chemistry are described below.

4.5 Examples

4.5.1 Hydrogenation project

Catalytic hydrogenation in the undergraduate laboratory curriculum often utilizes common reducing agents such as sodium borohydride ($NaBH_4$) or uses elemental hydrogen (H_2), which poses a safety concern due to its flammability. In the presence of H_2 at modest pressures, readily available commercial catalysts such as supported palladium on a carbon support (Pd/C) can reduce unsaturated molecules in the time frame of an undergraduate laboratory. An alternative method to achieve hydrogenation is through catalytic transfer hydrogenation (CTH). CTH often uses a protic solvent as a hydrogen source. Several examples of CTH in undergraduate laboratory courses have been described in the Journal of Chemical Education. For instance, 4-vinylbenzoic acid can be reduced over Pd/C with cyclohexene as a hydrogen source to form 4-ethylbenzoic acid [17]; nitrobenzene, benzophenone, and fluorenone can be reduced to aniline, phenylmethane, and fluorene [18], respectively, over 10% Pd/C with ammonium formate as a hydrogen source; chalcones [19] can also be reduced over 10% Pd/C with ammonium formate as a hydrogen source; castor oil [20] can be reduced over Pd/C using limonene as a hydrogen source.

In this section, the use of light alcohol solvents as a hydrogen source will be described in the context of an undergraduate research project in chemistry. Specifically, students investigated reduction of furfural using isopropyl alcohol (IPA) as a CTH solvent. Furfural is considered a platform chemical in the conversion of hemicellulosic biomass to renewable fuels. Derived from the dehydration of xylose, a tree sugar, furfural can be reacted to form many products such as furfuryl alcohol (through catalytic reduction) and 2-methyl furan (through catalytic reduction and subsequent hydrogenolysis). Previous work has shown the utility of light alcohol solvents as hydrogen sources in the selective reduction of bio-derived compounds in the liquid phase. Panagiotopoulou et al. reported that of a variety of primary and secondary light alcohol solvents for CTH of furfural over a $Ru/RuO_2/C$ catalyst, IPA, 2-butanol and 2-pentanol yielded the most 2-methyl furan, which is a desirable chemical for its high energy density as a fuel [21].

One of the challenges in the upgrading of furfural in light alcohol solvents is in optimizing the selectivity for a desired product. A drawback to CTH with light alcohol solvents is that the solvent may react with furfuryl alcohol and result in etherification. Furanyl alcohols and 5-hydroxymethylfurfural were converted to ethers over Amberlyst-15, a commercial catalyst with Bronsted acidity, in ethanol and butanol [22, 23]. Furfuryl ethers have been reported as byproducts in the hydrogenation of furfural over supported transition metal catalysts [24, 25].

The goal of the research in CTH was to determine if metal salt additives may improve the selectivity toward the hydrogenation product furfuryl alcohol. Bimetallic catalysts have shown promise in the selective hydrogenation of aldehydes, for instance cinnamaldehyde was selectively converted to cinnamyl alcohol using a 4% Pt/C catalyst pretreated with $FeCl_2$ in the liquid phase under high pressure of hydrogen gas [26]. Other bimetallic catalysts were prepared for the reduction of cinnamaldehyde by loading Pd [27] or Pt [28] on metal oxide supports to yield cinnamyl alcohol with high selectivity. Galvagno et al. reported the success of converting cinnamaldehyde selectively to cinnamyl alcohol over Pt/nylon catalyst when $SnCl_4$, $GeCl_4$ and $FeCl_3$ were combined in the reaction mixture as additives in the solvent [29]. Selective hydrogenation of furfural to furfuryl alcohol and 2-methyl furan was achieved over a $Pd\text{-}Ru/TiO_2$ catalyst in octane at room temperature and low pressures of hydrogen [30]. We hypothesize that the combination of metal chloride additives in light alcohol solvents can be used to optimize the selective CTH of furfural to furfuryl alcohol.

CTH reactions were carried out in a 100 mL fixed-head stainless steel Parr microreactor. 5wt% Pd/C or 5wt% $Pd(OH)_2$ catalyst (10–20 mg) was combined with light alcohol solvent (40 mL), furfural (0.9 mL) and metal chloride (5mol% with respect to furfural) in the reaction vessel and flushed with dry nitrogen before sealing the reactor for two hours at 200 °C and approximately 60 bar pressure. Metal chlorides tested in this study included iron (III) chloride and nickel (II) chloride. Samples were collected before and after the batch reaction and analyzed with an Agilent 6890 GC/MS using 2-octanol as an internal standard. Product yields were calculated with calibration curves of the analytical standards.

Successful CTH of furfural to furfuryl alcohol was achieved by this process. Results shown in Figure 4.2 indicate that the presence of the metal chloride salts enhanced selectivity to furfuryl alcohol and limited the production of 2-methyl furan. However, furfuryl isopropyl ether was the dominant product in the presence of iron (III) chloride. It is hypothesized that the production of the ether could be limited by altering the reaction temperature. Panagiotopoulou et al. reported that the ether and 2-methyl furan product formation is dependent on temperature, and lower reaction temperatures may be more optimal for selective conversion to furfuryl alcohol [21]. Future work in our group will continue this research.

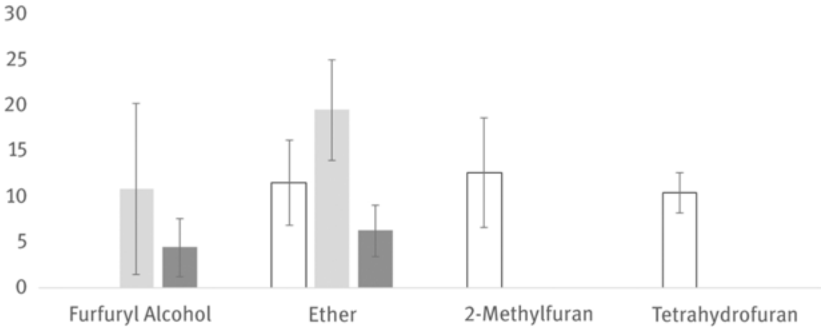


Figure 4.2: Hydrogenation results.

4.5.2 Pyrolysis oil upgrading

Another form of hemicellulosic biomass feedstock is the oil produced from pyrolyzed wood. This viscous oil offers a broad number of compounds which include complex aromatic structures as well as small molecular weight acids. Pyrolysis oil exhibits a low pH (typically between 2–4) due to the high content of weak acids such as acetic acid. In order to use this biomass feedstock to yield products of higher heat value (HHV), the use of ethanolysis over solid acid catalysts can be used. Presented here is an undergraduate research project where pyrolyzed wood biooil was upgraded via ethanolysis over sulfated silica catalysts.

Undergraduate organic chemistry laboratory courses typically include an experiment in esterification of a carboxylic acid to form an ester. These reactions often use a mineral acid catalyst such as sulfuric acid or phosphoric acid to achieve this conversion. The use of a heterogeneous catalyst which acts as a solid acid can improve this process by introducing a reusable solid material and eliminating the corrosive and hazardous mineral acid. In this project, biooil from pyrolyzed wood was upgraded to exhibit fewer corrosive properties (increased pH) and an HHV through the conversion of carboxylic acids to ethyl esters in the presence of ethanol and a solid mixed metal oxide catalyst. The catalyst was a Ni-W-promoted zirconia catalyst prepared via an incipient wetness impregnation technique to combine the transition metal precursors with a zirconium hydroxide support. The biooil was reacted in a 100 mL stainless steel Parr microreactor at 250 °C in ethanol with a solid acid catalyst. Students characterized the biooil pre- and post-reaction with an Agilent 6890 GC/MS.

The aroma of the biooil changed from a smoky, burned wood odor to that of a fruity odor post-reaction, which is indicative of the successful esterification of the component acids in the biooil. The resulting gas chromatograph data for the biooil before and after ethanolysis is shown in Figure 4.3. The lower chromatograph displays acetic acid as a major component, which is converted through ethanolysis to ethyl acetate, as shown in the upper chromatograph. Other ester products were observed, including ethyl propionate, ethyl butyrate and ethyl butenoate, which are identified with arrows in Figure 4.3. These low-boiling products could be distilled from the reacted biooil for collection. Additionally, the pH of the biooil was increased from 2.5 to 4.5, which indicates a decrease in corrosive properties of the oil. Students also classified the components of the biooil mixture to identify that common compounds were furanics, phenolics, and linear carboxylic acids.

4.6 Summary and conclusions/outcomes

These projects served as models to train students in green chemistry research which were accessible to students at any level of undergraduate education. Students involved in this work were majors in chemistry, genetic engineering, mathematics, and physics, and ranged from first-year to college juniors. The projects employed green chemistry ideas to engage these undergraduate students in original work which allowed them to apply their knowledge from chemistry courses to renewable energy research. The hydrogenation project employed CTH to reduce furfural to furfuryl alcohol with light alcohol solvents in the presence of metal chloride additives. This work will continue in the future to correlate the impact of these

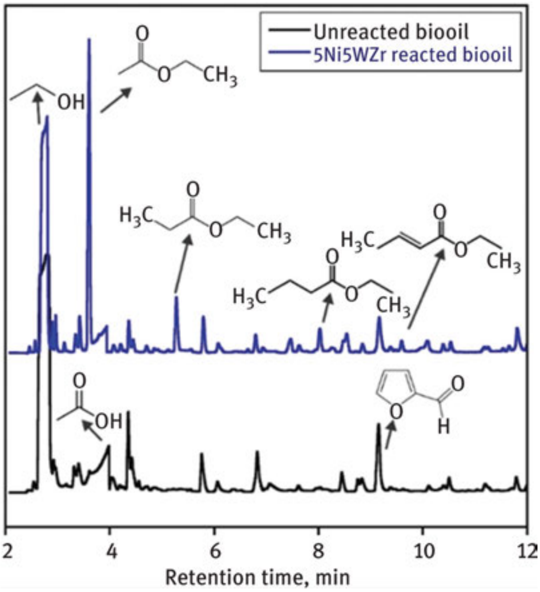


Figure 4.3: GC of pyrolysis oil.

additives on the catalytic conversion of furfural and other similar unsaturated aldehydes. The pyrolyzed wood biooil upgrading project investigated the ethanolysis of the biooil to esterify component acids such as acetic acid to the ethyl ester products. The upgrading of this biooil was able to reduce the acidity from pH 2.5 to 4.5.

The successful implementation of green chemistry principles such as using safer solvents, improving energy efficiency, using renewable feedstocks, catalysis, and promoting safer chemistry in the laboratory was achieved by designing catalysis research projects employing light alcohol solvents to convert renewable feedstocks to higher-energy content products. CTH eliminated the need for elemental hydrogen, a flammable gas which presents safety threats in the laboratory. Many related research projects can be developed using these principles to promote safer, greener chemical processes and to educate the next generation of chemists.

As a traditional women's college, our institution's mission statement is to educate the next generation of women leaders. In this role, we have the ability to reach young female science majors to build meaningful mentor-student connections and promote diversity in the STEM workforce. Particularly, in the field of physical sciences, which includes chemistry and physics, approximately 39% of baccalaureate degrees and 31% of doctoral degrees were awarded to women in 2016 [14]. The field of catalysis is dominated by chemical engineers, and engineering is one of the STEM fields with the lowest number of degrees awarded to women in 2016 (21% and 24% of baccalaureate and doctoral degrees, respectively). Furthermore, baccalaureate and doctoral degrees awarded to underrepresented minorities in all of STEM fields was 22% and 9%, respectively. Where these numbers shift is in the field of biological sciences, where women are the majority. These statistics from NSF support the argument that an increased effort in recruiting and retaining students in the physical sciences is important to promote diversity and inclusion in the STEM workforce. A model which incorporates green chemistry in undergraduate research can educate the younger generation about sustainability and engage them to persist in the science and engineering fields.

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Saraswathi Narayan

5 Sustainability and some green initiatives in undergraduate education

Abstract: Green Chemistry is also known as sustainable chemistry or benign chemistry. It is concerned with developing processes and products that reduce or eliminate the use of and generation of hazardous substances. In the 21st century today's students are particularly interested in matters that affect their health and well-being of the planet. To deal with such challenges of students the concept of Green and Sustainable Chemistry not only offers an excellent opportunity to address some of these concerns, but also provides us with a useful way to advance the way we do chemistry. Green chemistry is an ideal focus for undergraduate science education. A strong laboratory component is at the heart of many science courses. In this chapter some of the green chemistry principles and methodologies used to device certain undergraduate laboratory experiments and research are discussed.

Keywords: Green Chemistry principles, microwave synthesis, polymer supported p-toluene sulfonic acid polymer-[PS_PTSA], super critical fluid extraction of caffeine, Biotage phase separator, microscale chemistry

This chapter focuses on applying green chemistry principles to various laboratory experiments and sustainability issues in general across Science Education. They are based on the 12 Green Chemistry Principles [1]. Green Chemistry is currently the International chemical topic at the forefront of scientific research. Its fundamental objective is to conserve resources and prevent pollution and modify traditional chemistry. Green chemistry is an ideal focus for undergraduate science education because it:

- presents a modern version of the traditional chemistry curriculum
- uses less toxic or nontoxic chemicals,
- makes experiments safer for students
- reduced cost with less expensive solvents and equipment
- fewer toxic waste disposal fees and merges scientific concepts with sustainability
- gives undergraduate students opportunities to participate in meaningful laboratory experiments and research projects.

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Green Chemistry is also known as sustainable chemistry or benign chemistry. It is concerned with developing processes and products that reduce or eliminate the use of and generation of hazardous substances. In the twenty-first century today's students are particularly interested in matters that affect their health and well-being of the planet. To deal with such challenges of students the concept of Green and Sustainable Chemistry not only offers an excellent opportunity to address some of these concerns, but also provides us with a useful vehicle to advance the way we do chemistry. A strong laboratory component is at the heart of many science courses, we present. We should present experiments that highlight alternatives and bring out the philosophy behind them. Since the Pollution Prevention Act of 1990 [2] many industries and academia have devised novel technologies and processes to avoid the formation and /or use of hazardous substances. Many chemists have devised greener reaction conditions for old syntheses by either using water as a solvent or completely eliminating hazardous organic solvents. Many pesticides have been developed that are less toxic to the environment and less toxic to nontarget organisms and biodegrade to harmless substances. More recent publications cover the many aspects of this "greener" technique and its practical applications [3–7].

In recent years, more interest in green chemistry [8–10] has been developed. It is a major challenge for organic chemists to find an efficient, and nonpolluting synthetic procedures that reduce the use of toxic organic solvents and toxic reagents. Conventional methods of many organic compounds that are synthesized in the lab and are very time consuming. Prior to the development of Green chemistry in our laboratory we synthesized caffeine using an inexpensive uracil [11] in five simple steps as described by Figure 5.1 and Figure 5.2. Uracil 1 is first converted to I, 3-dimethyluracil 2, followed by nitration, reduction, and cyclization to theophylline and finally methylation of theophylline forms caffeine. Methylation using NaH/ DMSO/CH_3I gave the best yield as shown in Table 5.1.

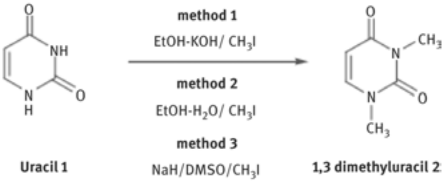


Figure 5.1: N-Methylation of Uracil **1** [11].

Most of the intermediates as well as caffeine were produced in good yield as can be seen from Table 5.1. This method makes use of the free available Uracil which is starting material in this method. Uracil is a common and naturally occurring pyrimi dine derivative. Even to date these methods have been used extensively since it was

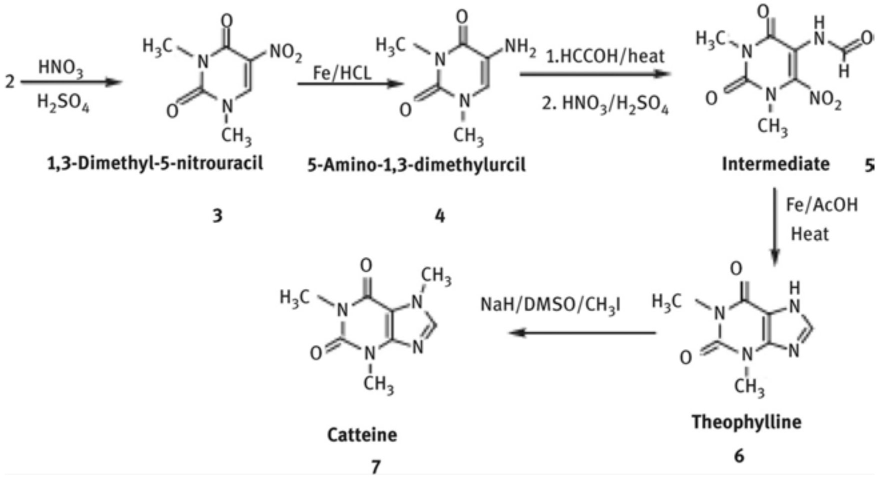


Figure 5.2: Matthew et al [**11**].

Table 5.1: Melting points and percent yields of Compounds **2–7**.

Compound	Method	M.p. (°C)[a]	Yield (%)
2	1	119.0–121.5	10
2	2		20
2	3		60
3	Nitration with HNO_3/H_2SO_4	121.0–122.0	64
4		294.0–295.5	70
5			In situ
6		273.0–274.5	75
7	3	234.0–236.5	95

[a] Purity of the samples was checked by mixed melting point methods.

published in 2003. There have been more than 804 reads and 14 citations as per Research Gate [12]. Through Research Gate there is access to 130 + million publications and also connections with 15 + million researchers.

Ho Xien from the University of Jinghua, China [13] developed a green technology method for caffeine synthesis following the 3R rule **R**educe, **R**euse, **R**ecycle. They recovered and recycled the production of chloroacetic acid and hydrochloric acid. Reciprocating plate extraction column was used to recover and increase the yield of caffeine in addition to reduce the addition of chloroform feed and energy consumption. The Sulfonated kerosene extract was used to recover the highly toxic chloroform. Further theophylline in the aqueous effluent was extracted with 2-

ethylhexanol extraction process. 2-Ethylhexanol (abbreviated 2-EH) is a branched, eight-carbon colorless chiral alcohol, poorly soluble in water but soluble in most organic solvents. Iron powder or hydrogen gas typically used as reductant was replaced by an electrocatalysis hydrogenation, a potential green technology method.

Several Laboratory experiments were designed in our laboratory using green chemistry principles based on 3 R rule: Reduce, Reuse and Recycle and other principles of Green chemistry. Some typical experiments are: Extraction of caffeine using Biotage phase separators [14] and super critical extraction techniques [15, 16], synthesis of aspirin and synthesis of fruit flavors using microwave techniques and a nontoxic and an eco-friendly catalyst: p-toluenesulfonic acid-polymer supported (30–60 mesh) pellets **[PS-PTSA**] [17, 18].

Extraction of caffeine from tea leaves, a typical nursing laboratory experiment is liked by most students. Benzene, chloroform, and trichloroethylene (TCE) that are now considered as toxic solvents were used in early decaffeination processes. In the early 1970's dichloromethane became the solvent of choice because of its lower toxicity and its ability to selectively dissolve caffeine without carrying off sugars, peptides, and flavor ingredients from caffeinated products. When evidence suggested that CH_2Cl_2 might be carcinogenic, its use was sharply curtailed. Ethyl acetate was used as a replacement for dichloromethane during the 80's and early 90's. Although it is moderately toxic, coffee makers considered ethyl acetate as "natural" because it has a pleasant fruity odor. However, ethyl acetate is a flammable liquid. It is harmful if swallowed or inhaled. It also affects the central nervous system and causes irritation to skin, eyes and respiratory tract. Extraction of caffeine from tea leaves where toxic solvent like dichloromethane CH_2Cl_2, is still used in traditional approach. In the greener approach to make the separation easier and faster a Biotage phase separator [14] was used based on minimal exposure and recovery of dichloromethane that was recycled.

The complex acidic tannins present in tea leaves are generally converted to their salts by adding either sodium carbonate or calcium carbonate (see the flow chart) Figure 5.3. Caffeine is then isolated from the basic solution using dichloromethane or chloroform. During this extraction students usually struggle to separate the organic layer from the dark basic aqueous solution due to emulsion formation even if they shake it gently using a separatory funnel. In the two-hour period the students rush to complete the lab and get poor yield of caffeine. In order to avoid the emulsion formation and to have a clean separation, this experiment describes an easy separation of organic layer by using a Biotage Phase Separator. The Biotage separators are fitted with a selectively permeable insert that separates organic phase from the aqueous phase under gravity unlike the conventional separatory funnels Figure 5.4. The separation is very clean, and caffeine is obtained in good yield after removing the solvent by distillation. Students can extract caffeine from different brands of tea to compare the percentage yield of caffeine- Table 5.2.

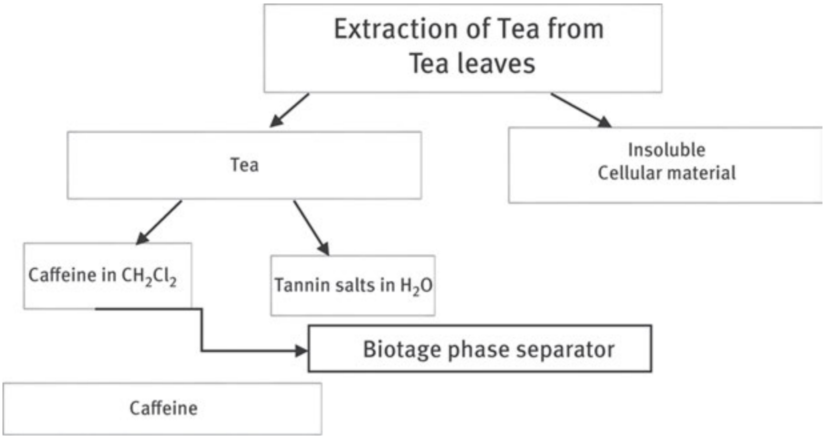


Figure 5.3: Extraction steps. Isolation of caffeine from Tea leaves-Flow Chart.

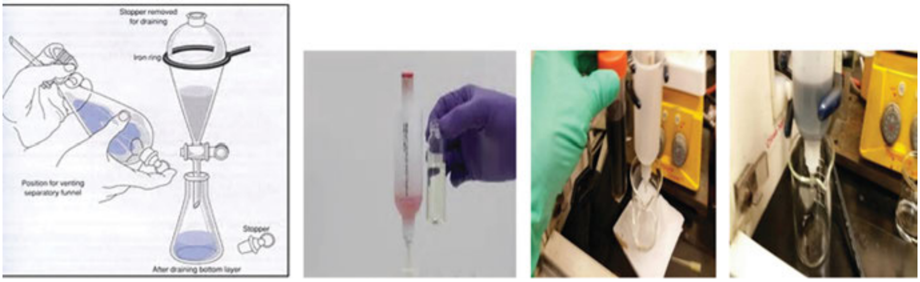


Figure 5.4: Comparison of Seperatory funnel (left) vs Biotage Phase separator [14].

Table 5.2: Typical results of caffeine from some brands of tea.

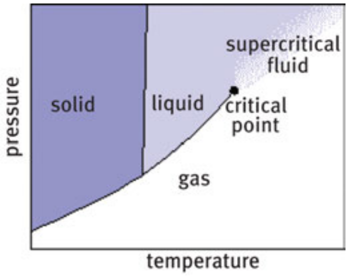
Results	**Milligrams of caffeine**	
Brand	**Solvent isopropanol**	**Dichloromethane**
English 100% pure black tea (1 tea bag)	29	40
Twinning English afternoon 100% pure black tea (2 tea bag)	19	80
Irish 100% pure black tea Decaffeinated (2 tea bags)		8
Tetley Tea (1 tea bag)		32
Tetley Ginger flavor (1 tea bag)		26
Weis market Decaf 1 tea bag		6
Tazo Awake Keurig brand – English Breakfast – 1 cup		35
Lipton Tea Decaf (2 tea bags)		9
Lipton tea Natural energy 2 tea bags		67

Extraction of caffeine using Biotage Phase separator
Stages of extraction of caffeine

The values of caffeine obtained were in most cases as claimed from different brands of tea indicating the efficiency of the extraction techniques. The solvent dichloromethane was recovered by simple distillation and recycled.

5.1 Super critical extraction of caffeine from tea leaves

In this method a nontoxic and more environmentally benign solvent like supercritical fluid carbon dioxide (CO_2) was used. Carbon dioxide supercritical fluid (temperature above 31.1 °C and pressure above 73 atm) exhibits both liquid and gas-like behavior [16, 19]. It behaves like gas, and permeates a porous substance, while also exhibiting liquid properties to dissolve substances.



Phase diagram for CO_2 [19].

The fluid-like carbon dioxide serves as a good solvent for many organic compounds [20]. Super critical fluid extraction shows numerous advantages compared to traditional organic solvent extraction. It is safer to handle and there is no residual solvent in the final product. This translates into lower operating costs. The extraction process is simple. Supercritical carbon dioxide can be forced through the tea leaves to extract caffeine efficiently. This experiment teaches the students not only about the properties of supercritical carbon dioxide, but also the extraction of natural products using green solvents. A simple device was developed to handle supercritical carbon dioxide. This experiment conforms to Green Chemistry principles of # 1, 3, 6, 10 and 12. Decaffeination is a fairly easy process since caffeine is polar and water-soluble.

5.2 How CO_2 decaffeination works

CO_2 is a nontoxic, nonflammable, colorless and odorless gas which is a naturally-occurring part of the air we breathe. Although elevated levels of CO_2 in our atmosphere contribute to global warming, it's generally a pretty inert substance. Under

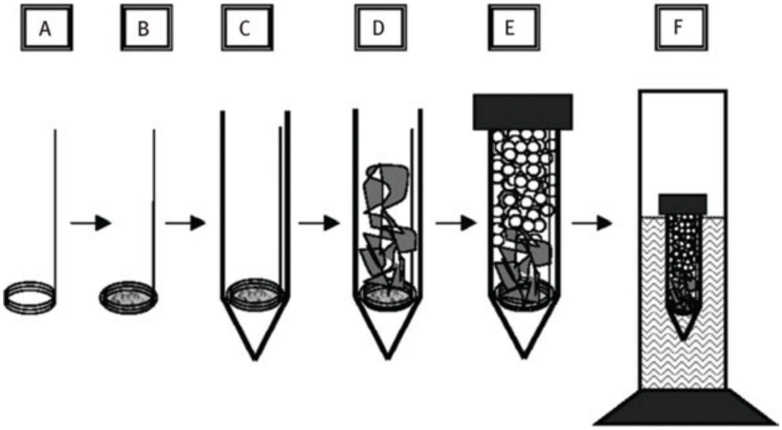


Figure 5.5: Illustration of the liquid CO_2 extraction procedure. A solid trap is constructed by (A) bending copper wire into coils and a handle, (B) placing filter paper or metal screen between the wire coils, and (C) placing the solid trap in a centrifuge tube. For extraction, (D) tea leaves are placed in the tube, and (E) the tube is filled with crushed dry ice and sealed with a cap. (F) The prepared centrifuge tube is placed in the water in the graduated cylinder, and the liquefaction and extraction occur over the following 3 min. This journal is © The Royal Socisety of Chemistry 2004 – Green Chem., 2004, **6**, 355–358 [16, 21].

pressure and temperature, however, CO_2 is able to flow freely through natural materials (like tea) and has strong solvent capabilities. This is called its “supercritical” state (which is why CO_2 decaffeination is also referred to as “supercritical CO_2 decaffeination” or “supercritical fluid extraction”).

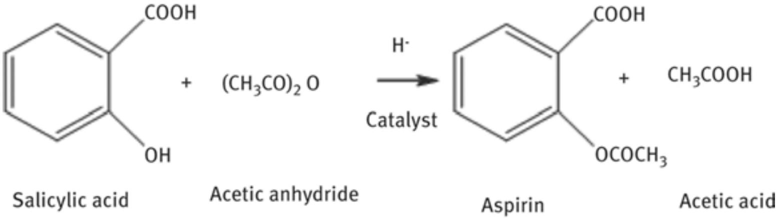
Dry ice sublimes at atmospheric pressure and temperatures above −78 °C. If the CO_2 is sealed in a vessel during sublimation, the internal pressure in the vessel increases. After the temperature and pressure have increased sufficiently, liquid carbon dioxide forms. Due to this accessible phase change, carbon dioxide can be used for bench top extraction processes. A setup similar to the one shown here [16, 21] was used.

Tea leaves, a wire and filter paper or metal screen solid trap are placed in a 15 mL polypropylene centrifuge tube with plug seal cap (Corning catalog #430,052). The centrifuge tube is completely filled with crushed dry ice, capped tightly, and dropped (tapered end down) into a plastic cylinder or polycarbonate bottle which is half-filled with warm (40–50 °C) tap water. As pressure builds in the tube, gas escapes slowly through the threading of the cap. After approximately fifteen seconds, the solid begins to melt, and liquid CO_2 appears in the tube. Solid, liquid, and gas phases are visible in the tube for a short period of time. The liquid boils, and gas escapes for almost 3 min. During this time, the liquid CO_2 moves through the solid, extracts the caffeine from the tea leaves, and collects in the bottom of the tube. The solid trap successfully prevents the tea leaves from moving into the tip of the tube during extraction because the wire coils are supported by the sides of the centrifuge tube at the point where it narrows. After the extraction solvent completely evaporates, isolated product remains in the bottom of the tube. Once the liquid has stopped bubbling and gas is no longer escaping, the centrifuge tube is removed from the cylinder with tweezers, and the extraction process is repeated by refilling the tube containing the tea leaves and solid trap with dry ice, recapping it and replacing it in the cylinder. Two or three extraction cycles result in isolation of approximately 50–75 mg of caffeine. Typical yields are comparable to organic solvent extraction or cold pressing (1–2% recovery, based upon initial mass of tea leaves used during extraction). The extracted product is predominantly caffeine and was characterized by its melting point.

Microwave application in organic synthesis is another initiative toward greening a laboratory method. In the past few years microwave assisted synthesis of organic compounds has received great attention [22] due to several advantages, such as dramatic reduction of reaction time and greater choice of solventless reactions. Microwave assisted synthesis known since 1986 has greatly accelerated and resulted in an improved yield. This technology has been introduced in several undergraduate laboratories and in research projects. Since the reaction times are considerably shorter, it widens the scope for the students to explore otherwise inaccessible reactions that require longer period of refluxing. This technique has unquestionably improved our lives. Many reactions can be carried out in a solvent free or in benign solvents like water. This allows us to introduce the concepts of green chemistry. The Principles of Green Chemistry [1] apply to most of the synthetic routes with microwave irradiation. Microwave assisted reactions are “cleaner”, and produce minimum waste.

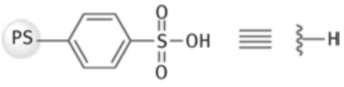
The preparation of aspirin and organic esters used as fruit flavors is a common experiment for a General, Organic and Biochemistry nursing chemistry students [23–25].

In a conventional method Aspirin (acetyl salicylic acid) is generally prepared [23] by reacting salicylic acid with excess acetic anhydride using H_2SO_4 or H_3PO_4 as a catalyst.



Synthesis of Aspirin from Salicylic acid. General method.

Instead, in the greener method, an ordinary simple kitchen microwave will be used in place of boiling water bath and a nontoxic and an eco-friendly catalyst: p-toluenesulfonic acid-polymer supported (30–60 mesh) pellets [PS-PTSA] [17, 18], to avoid handling corrosive acids The same reaction will be completed in a matter of minutes. The catalyst used comes in the form of pellets that can be handled easily. It can be recycled under careful conditions. Green chemistry makes use of the following ideas that apply to this experiment: These are some of the results obtained by students over two or three semesters using different catalysts. As you can see the % of aspirin recovery was much higher using the eco-friendly catalyst-Table 5.3.



Structure of PS-PTSA

Polymer supported Catalyst Aldrich Catlalog # 532312 **[18]**.

Table 5.3: Results for two semesters. (Percent yield of aspirin is the average result for all the groups)-Using [PS-PTSA].

Catalyst	Microwave power (%)	Reaction time (Secs.)	Average yield (%)
H_2SO_4	100	5 s	60
H_2SO_4	80	10 –15	60
H_3PO_4	100	10 s	58.2
H_3PO_4	80	10 s	58.2
PTSA	100	10 s–15 s	77
PTSA	80	30 s	77
PS-PTSA	100	20 s–35 s	70.6
PS-PTSA	80	60 s	70.6

Percent yield of aspirin

Similar methods using [PS-PTSA] was used for the synthesis of esters in place of the conventional toxic acids like sulfuric or phosphoric acids or p-toluenesulfonic acid [23–25].-Table 5.4.

$$\mathrm{RCOOH} + \mathrm{R'OH} \overset{\mathrm{H}^+}{\longleftrightarrow} \mathrm{RCOOR'} + \mathrm{H_2O}$$

Where H^+ is an acid such as phosphoric, sulfuric acid or p-toluenesulfonic acid used as a catalyst. These acids are corrosive and toxic. In terms of toxicity p-toluenesulfonic acid is hazardous, skin irritant, corrosive, lung irritant. It may cause damage to kidneys. Similarly, other acids also have several toxic effects.

Table 5.4: Reaction time for esterification using microwave technique.

Carboxylic acid	Alcohol	Ester	Fragrance	Average reaction time at 80% power of microwave
Acetic acid	Propyl	Propyl acetate	Pear 	30 s–2 min
Acetic acid	Isoamyl	Isoamyl acetate	Banana 	30 s–2 min
Butyric acid	Butyl	Butyl butyrate	Pineapple 	30 s–2 min
	Ethyl	Ethyl butyrate	Strawberry 	30 s–2 min

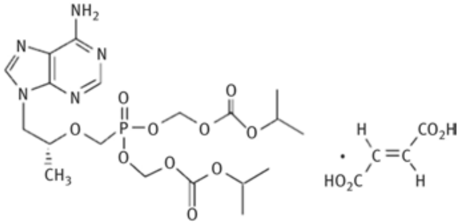
Extraction of different fruit flavors

The above table indicates the amount of time taken by this technique compared to regular methods that usually take a much longer period of time heating in a water bath.

5.3 Microwave assisted reactions in medicinal chemistry

TDF **1** serves as a prodrug of the molecule Tenofovir ((R)-9-[2-(phosphonomethoxy) propyl] adenine) or (PMPA) **2** a class of antiviral drug known as nucleotide analogue reverse transcriptase inhibitors (NtRTIs). They block reverse transcriptase, which is an enzyme crucial to viral production in HIV infected people. When

HIV infects a cell, reverse transcriptase copies the viral single stranded RNA genome into a double-stranded viral DNA. The viral DNA subsequently is integrated into the host chromosomal DNA which then allows host cellular processes, such as transcription and translation to reproduce the virus. (Reverse Transcriptase Inhibitors) RTIs block reverse transcriptase's enzymatic function and prevent completion of synthesis of the double stranded viral DNA thus preventing HIV from multiplying.

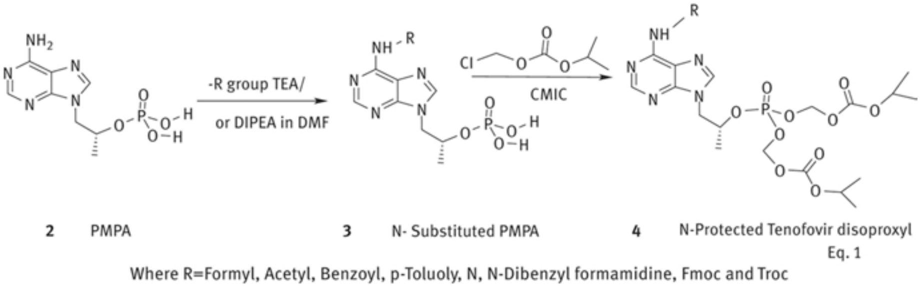


1 Tenofovir Disoproxil Fumarate

TDF structure **1**. NtRTI-Nucleotide Reverse Transcriptase Inhibitor-TDF **1**.

The method used to manufacture the drug Tenofovir disoproxylfumarate involves multiple steps, uses expensive reagents in the final stages and results in a poor yield [26]. During the final stages of synthesis several side products are formed that interferes in the overall yield of the salt Tenofovir disoproxil fumarate. One of the possible ways to avoid the side products is to protect the exocyclic amine group in the adenine moiety of TDF (sabbatical research) [27]. The research was focused on the protection of the primary amine group as a possible approach during the initial stages of Tenofovir synthesis to inhibit its participation in the chemical reactions due to its basic and nucleophilic nature. Primarily this is achieved by delocalization of the lone pair of electrons.

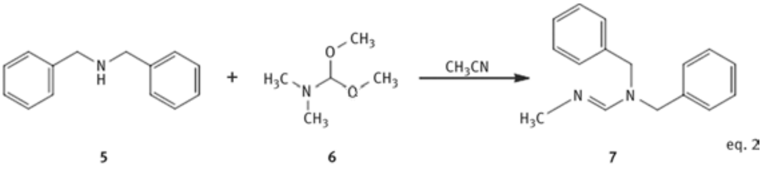
Steps used in conventional or traditional method was to protect the -NH_2 group and continue the synthesis of TDF and then deprotect the -NH_2 group. Part of the research was Sabbatical at Howard University and the rest of the work was continued with Stevenson University students (Susie Sun, Amber Wilson, Janine Ladzinski, Hira Munir and Jahnavi Patel) [28]. This was done by protecting the amine group on the adenine moiety of the PMPA using various groups like: formyl, acetyl, benzoyl, p-Toluoyl, *N*, *N*-dibenzyl formamidine, (Fmoc) 9-Fluorenylmethoxycarbonyl (Fmoc) and 2, 2, 2-Trichloroethyloxycarbonyl (Troc). Further coupling reaction of the N-protected PMPA **3** with Chloromethyl Isopropyl Carbonate (CMIC) formed N-protected – Tenofovir Disoproxil. In the final step of the reaction N-protected group were removed by catalytic hydrogenation followed by adding fumaric acid to form the salt TDF (not shown here). eqs. (1)–(3) shows the steps followed to make N-protected PMPA.



Sequence of steps for TDF starting from PMPA. N-protected PMPA research SU.

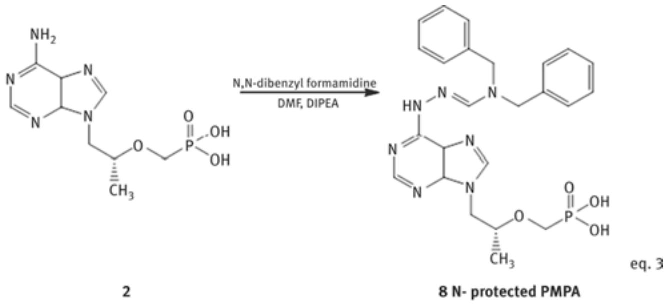
A typical reaction consisted of dissolving PMPA **2** the starting material in dimethyl formamide (DMF) or N-methyl pyrrolidine (NMP) along with either triethylamine (TEA) or diisopropylethylamine (DIPEA) as a co solvent. The protecting group also dissolved in the same solvent was added carefully to PMPA at ice temperature. The reaction was followed by either TLC/HPLC using pH 5.5 buffer. The reaction conditions were optimized for each protecting group by carrying out the reaction at various temperatures and using different ratios of PMPA and the protecting groups. The isolated products **4** formed were then identified using spectroscopic methods. The optimum temperature was 55 °C. Without isolating the products, coupling reaction with Chloromethyl Isopropyl Carbonate (CMIC) and fumaric acid were added to the same pot to form TDF. Ethyl acetate extraction of the product yield was not as expected and were all around 30%.

The *N, N*-dibenzyl formamidine group has been found to be effective as a protective group for primary amines as it is stable to a variety of conditions and can be removed by catalytic hydrogenation [29]. Dibenzylamine **5** was refluxed overnight in acetonitrile with N, N-dimethylformamide dimethyl acetal **6** to form N, N-dibenzyl formamidine **7**. The reaction progress was followed on TLC using ethyl acetate/hexane solvent mixture (see eq. (2)).



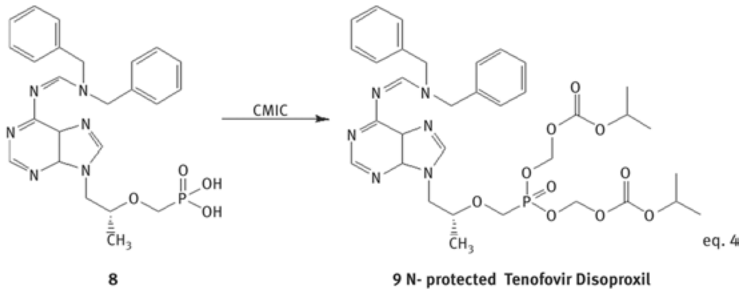
Formation of N,N-dibenzyl formamidine **7**. Stephanie Vincent et al- [29].

The protective group, N, N-dibenzyl formamidine **7**, was added to PMPA **2** in DMF along with either TEA or DIPEA as a co solvent. The N-protected PMPA **8** was then isolated (38%) after removing the solvents under vacuum. (See eq. (3))



N.N-dibenzyl formamidine protected PMPA **8**. Janine Ladzinski **[28]**.

The compound **8** the N- protected PMPA was further treated with Chloromethyl Isopropyl Carbonate (CMIC) to form the Tenofovir disoproxil. Results indicated that the optimized time for the reaction of protected PMPA with CMIC was one hour with a yield of 54.64% of the N-Protected Tenofovir Disoproxyl **9**.

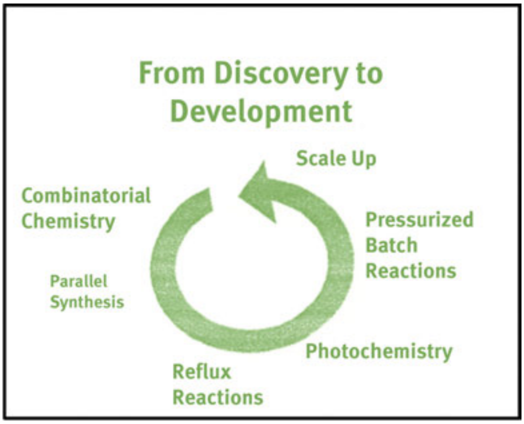


N-protected PMPA with CMIC. Janine Ladzinski **[28]**.

Houghton et al. [30]. Showed a rapid, mild method for Phosphonate Diester Hydrolysis: Development of a One-Pot Synthesis of Tenofovir Disoproxil Fumarate from Tenofovir Diethyl Ester.

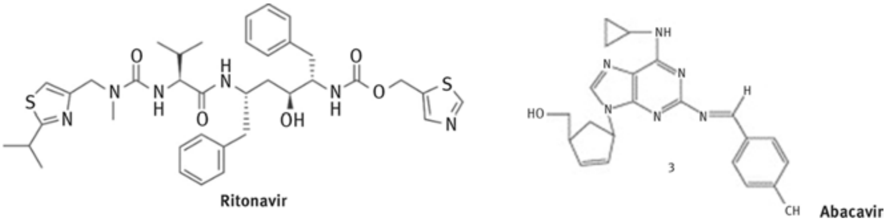
As can you see from the above reactions, they were very time consuming, even if they were relatively successful. These processes were not based on Green Chemistry principles [1].

Instead of continuing the conventional approach an attempt was made to use a greener method using microwave synthesizer in our lab to make TDF. The effectiveness of microwave chemistry in dramatically reducing reaction times (reduced from days to hours to minutes and seconds) has been proven in several different fields of organic chemistry [31]. The time saved is of great importance especially in medicinal chemistry and Pharmaceutical industries “where time is money.” In the last 2 decades, microwave assisted synthesis has taken organic chemists by storm [32]. It is a very useful tool in the laboratory due to its wide compatibility of solvents and their applicability to a variety of reactions. Microwave accelerated reactions include from Discovery to Development chemistry.



Microwave application. Small scale to Indutrial scale procesess.

Many of the reactions can be performed either solvent free or using water as solvent in microwave assisted techniques. It utilizes the ability of mobile electric charges present in liquid or conducting ions in solid to transform electromagnetic energy into heat. Synthesizing HIV drugs using microwave irradiation is not new. Several HIV-1 Protease Inhibitors and similar drugs [33, 34] have been synthesized using microwave irradiation techniques in very high yield in a matter of minutes.

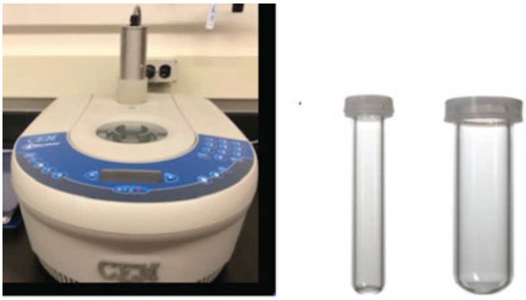


HIV drugs. Microwave irradiation methods for HIV drug synthesis **[34]**.

In our laboratory, as a preliminary study, Microwave assisted synthesis was used for some of our research projects in improving the synthesis of an HIV drug tenofovir disopropoxyl fumarate (TDF) to reduce the cost of the drug and to prevent the formation of several side products.

5.4 Microwave synthesis using CEM

One such microwave system used in our laboratory was developed by CEM Corporation- (Figure 5.6).



CEM Microwave **Synthesizer** Reaction vessels

Figure 5.6: CEM corporation Model.

Reactions are usually performed in a sealed (or closed) heavy duty pressure vessels or tubes with a specifically designed cap. Reaction mixtures are usually heated to temperatures well above the boiling point of the solvent. Power level, pressure, temperature and time can be varied to optimize the reaction conditions. Microwave-assisted reactions are known for its speeding the reactions. It is clean, more energy efficient, economic and eco-friendly that complies with Green Chemistry principles. This technique has frequently been proposed as the "technology of tomorrow" as early as 2006 [32].

A greener approach of microwave assisted synthesis (unpublished results) of the protective group N, N-dibenzyl formamidine dimethyl acetal **8** was used in our research as a preliminary run for comparison with the conventional method. Several runs of the reactions were carried out using different levels of power, pressure, temperature and hold time to optimize the reaction conditions. Only the optimized conditions are shown in Table 5.5. Microwave method gave exactly the same results as the conventional method for compound **8.** This was confirmed by the identical IR obtained by both methods (see the IR spectra below).

Table 5.5: Microwave settings.

Power	Pressure	Temperature	Time	Hold time
150W	250 psi	115 °C	5 min	10 min

Optimized Reaction conditions

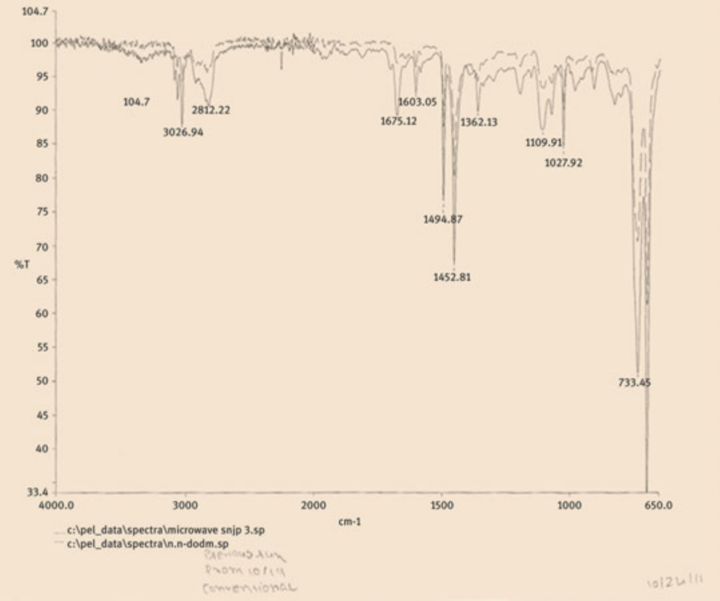


Figure 5.7: IR spectra comparison of Microwave assisted and conventional method protected N, N- Dibenylformamidine protected PMPA. JP, SS **[28].**

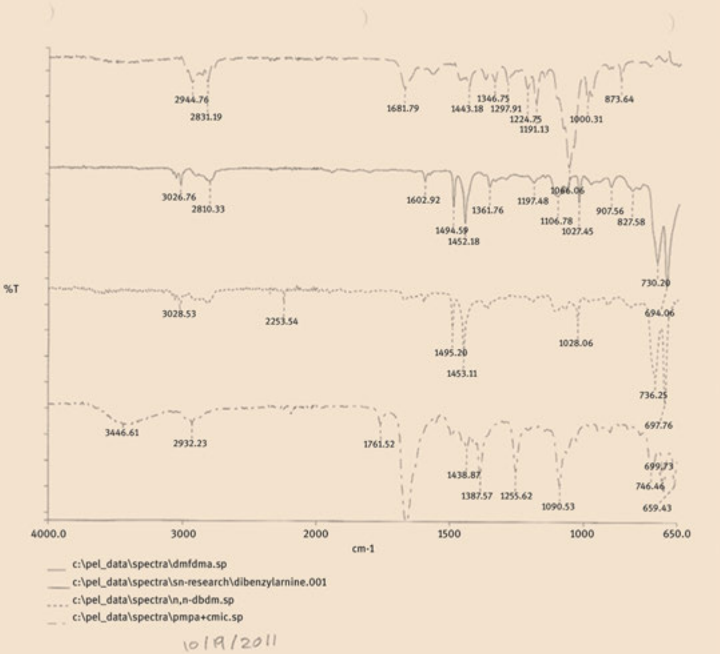
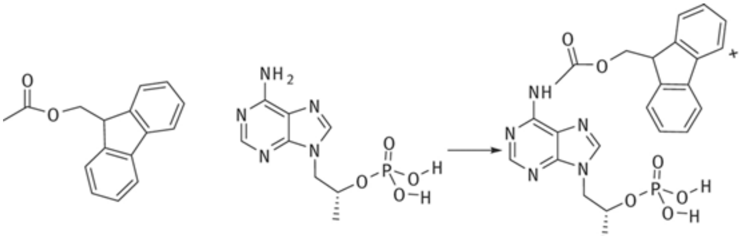
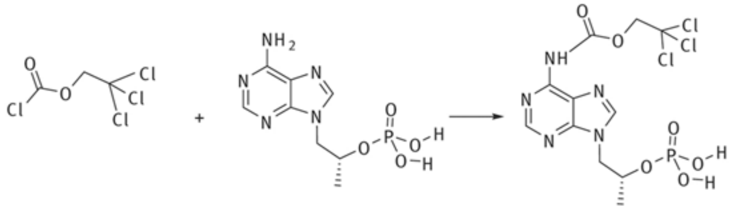


Figure 5.8: IR spectrum of N,N-dibenzyl formamidine, Dibenzyl amine, N,N- Dibenzylformamidine diacetal, N- protected PMPA in ordre from the top. Follow up of the reaction with IR JP **[28].**

Other protective groups like 9-Fluorenylmethoxycarbonyl (Fmoc) and 2, 2, 2-Trichloroethyloxycarbonyl (Troc) [35] were also used that were considered to be base sensitive amino protecting groups [36]. Same optimized reaction conditions as shown in Table 5.5, were used for the reactions shown in eqs. (5) and (6) to form the Fmoc and Troc protected PMPA.



10 Fmoc **2** PMPA **11** Fmoc protected PMPA Eq 5



12 Troc Chloride **2** PMPA **13** Troc protected PMPA Eq 6

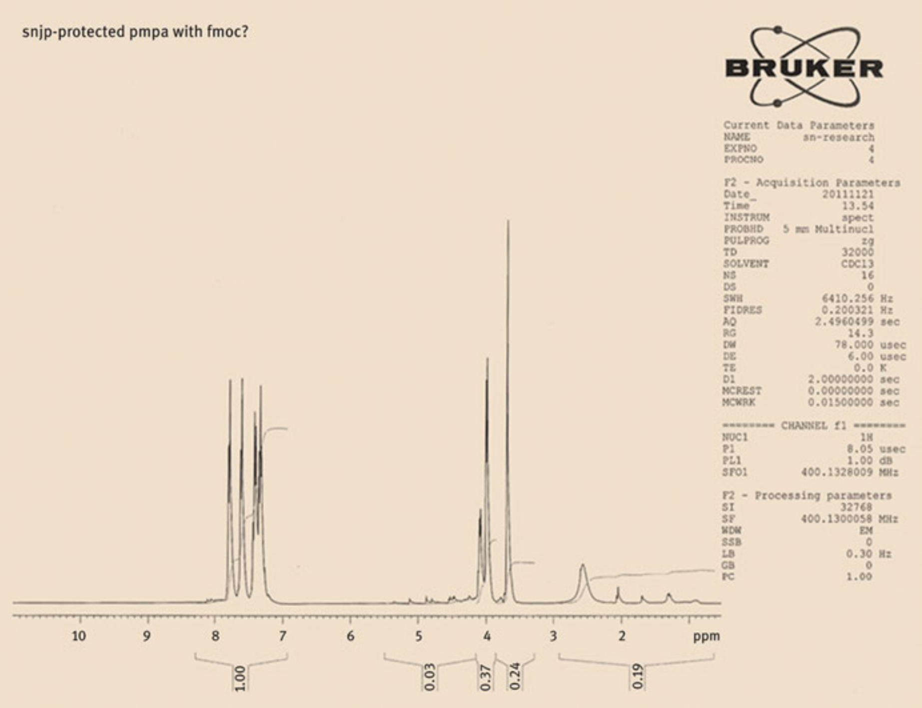
Formation of FMOC **10** and **TROC 12** protected PMPA **11**. Reaction sequences SN, JP **[28]**.

Reactions were followed by TLC. The products obtained were then characterized using IR and NMR (Figure 5.9 and Figure 5.10) and they matched with the compounds prepared by conventional methods.

No attempt was made to remove the protective from the product at this point. However, this work will be continued in future to remove the protective groups appropriately to isolate the pure TDF. Microwave synthesis in conclusion was much more effective than the conventional methods.

Microscale chemistry [37–42, 44] experiments uses small quantities of chemicals and simple equipments. These have the following advantages

- Reducing safety hazards-chances of accidents are much less.
- Uses milligrams /mmol quantities as opposed to macrogram scale
- Saves time for preparation
- Reduced waste disposal
- Lower costs for chemical substances and equipment
- Smaller storage area
- Reduced reliance on intensive ventilation system
- Pleasant working atmosphere



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RG                   14.3
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DE                   6.00 usec
TE                    0.0 K
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MCREST         0.00000000 sec
MCWRK          0.01500000 sec

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LB                   0.30 Hz
GB                      0
PC                   1.00
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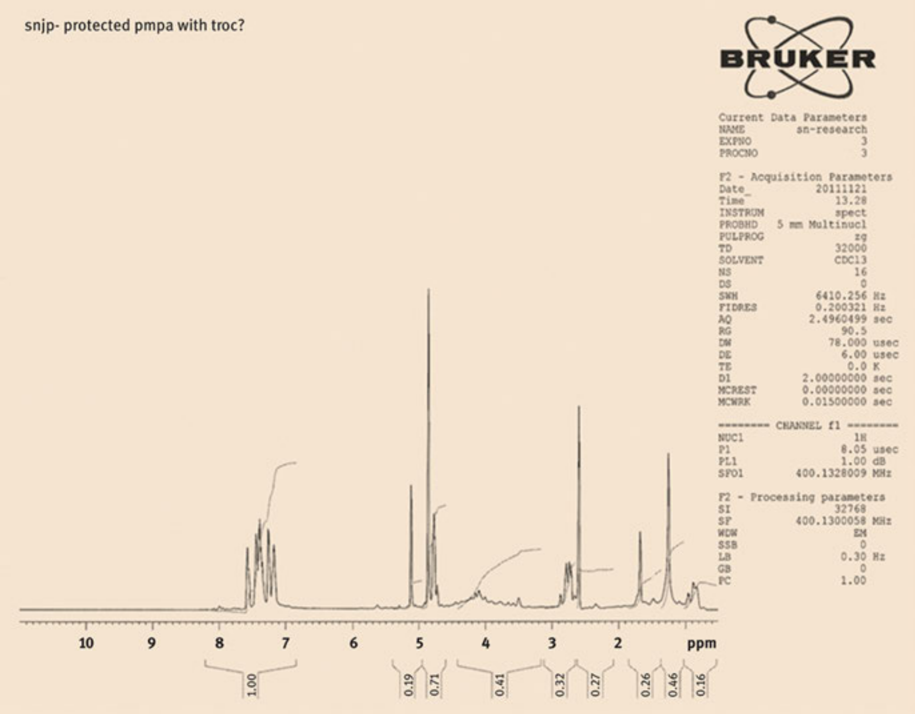
Figure 5.9: NMR of Fmoc and Troc protected PMPA.
Jahnavi Patel and S. Narayan.

- Shorter reaction times
- More time for evaluation and communication.

Many organic experiments are usually done using microscale or small scale, chemistry for the past several years in several, colleges and universities. Some typical experiments that are being done in our institution are, microscale boiling point (Figure 5.11), microscale distillation, fractional distillation using the Hickmann–Hinkle still (Figure 5.12), extractions and synthesis reactions using conical vials and several other microscale equipments.

Micro boiling points are determined using an oil bath, melting point tube and fine capillary [45]. The liquid is loaded into a melting point tube to a depth of 1–2 cm. A fine capillary tube sealed at one end is placed in the melting point tube with the open end of the capillary down. When the boiling point of the liquid is exceeded, bubbles will flow from the open end of the fine capillary and rise to the surface. The heat is then reduced so that the oil bath cools slowly. The boiling point will be the temperature at which bubbling ceases and the liquid starts to flow back into the fine capillary. With a little practice student can finish determining the boiling much faster than the macro boiling point setup and with few drops of the liquid.



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FIDRES           0.200321 Hz
AQ              2.4960499 sec
RG                   90.5
DW                 78.000 usec
DE                   6.00 usec
TE                    0.0 K
D1             2.00000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   8.05 usec
PL1                  1.00 dB
SFO1          400.1328009 MHz

F2 - Processing parameters
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SF            400.1300058 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
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Figure 5.10: PMPA protected with Troc. Jahnavi Patel and S. Narayan.

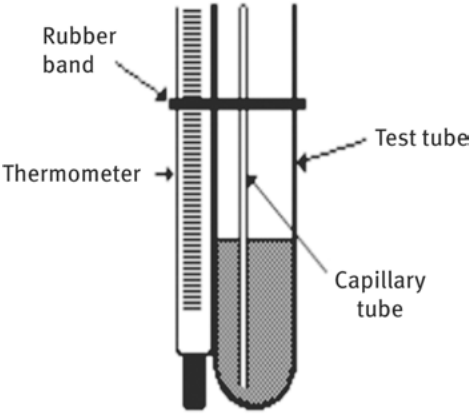

Figure 5.11: Micro boiling point apparatus. Organic Lab experiments.

Fractional distillations are done using Hickman still [46] and the fractions can be easily separated through the side port with a syringe. Figure 5.12 shows a typical setup using a mini hot plate and a sand bath. A conical vial with a spin vane (in place of boiling stone) to prevent bumping used.

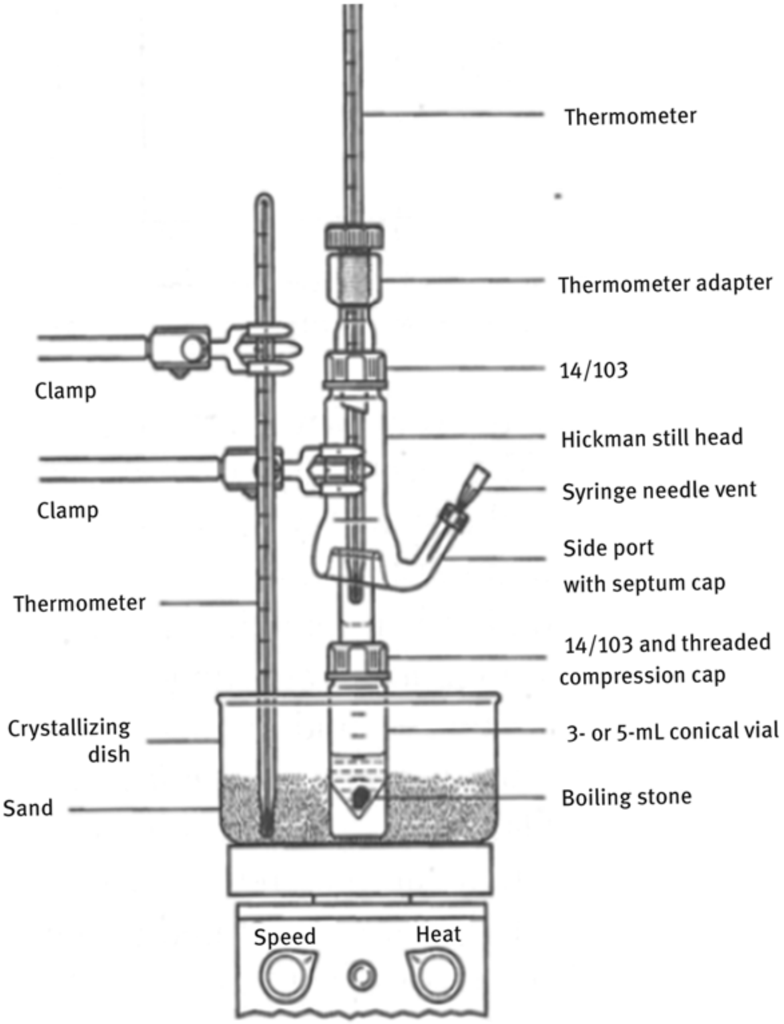

Figure 5.12: Hickmann–Hinkle Still for fractional distillation. Micro/Mini ACE Glass Set up.

Many of our organic chemistry experiments are also being done on a microscale level using the Micro/Mini Lab ACE Glass Incorporated shown below for the past 20 years, to prevent wastage and save money, besides several other advantages.

Several other experiments will be developed based on “Green Chemistry Principles”. The implementation of such techniques as a part of undergraduate research laboratory courses will help to raise a generation of chemists that is familiar with the concepts of green chemistry from an early stage, which in turn should be of great benefit for the whole society. We need to make our chemistry more efficient, less wasteful, more sustainable, and safer. Currently we are using Computer

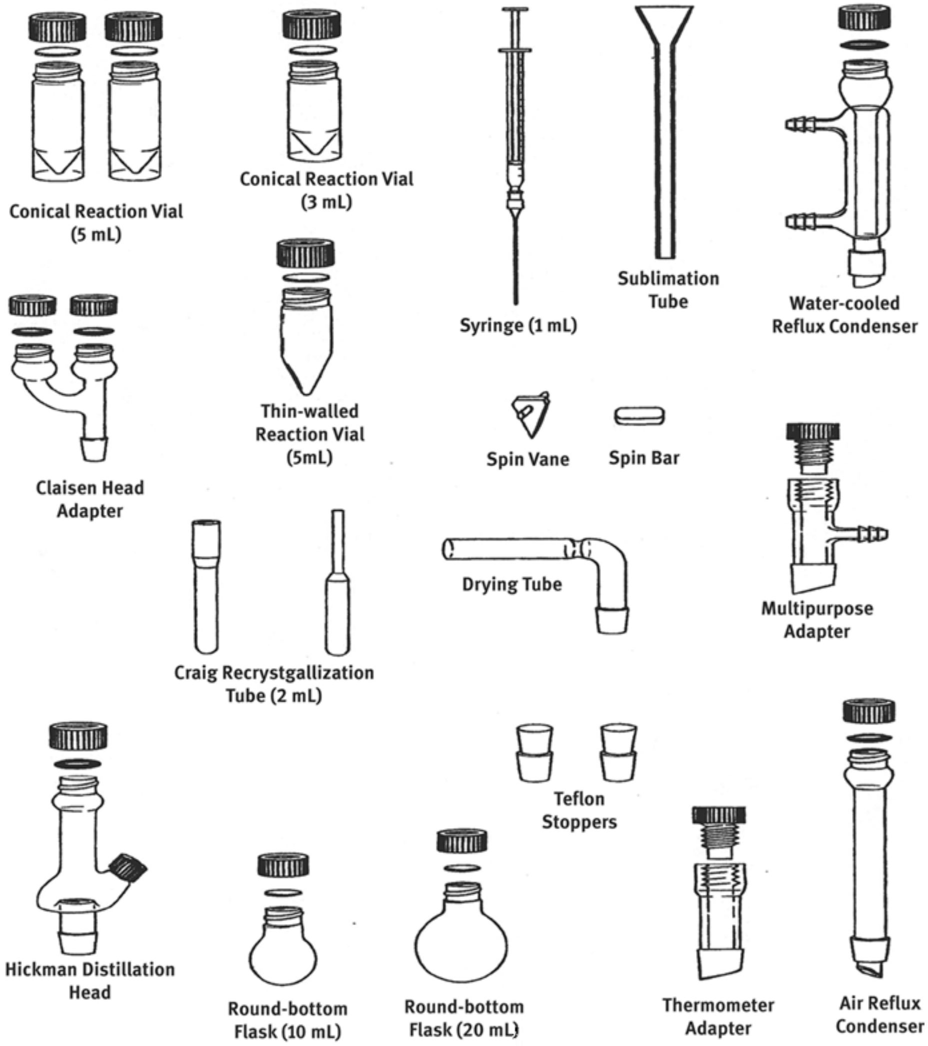

Figure 5.13: Components of a micro/mini Lab set. ACE Glass Kit.

Aided Drug Design (CADD) tools to improve the efficiency and efficacy of drug development and discovery that can save time and money before you venture synthesizing them in the lab. We are in the early stages of development.

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Mark R. Mason

6 Greening the curriculum at the University of Toledo School of green chemistry and engineering

Abstract: This paper provides a brief overview of the formation, organization, and mission of the School of Green Chemistry and Engineering (SGCE) at the University of Toledo, and a description of SGCE efforts to introduce principles of green chemistry and green engineering into the undergraduate and graduate curriculum. This includes development of selected new courses and new academic programs such as a Minor in Green Chemistry and Engineering, a Professional Science Master's Degree in Green Chemistry and Engineering, and an online Master in Education and Science in Chemistry degree aimed at College Credit Plus credentialing of high school chemistry teachers in Ohio.

Keywords: curriculum, green chemistry, green engineering, professional science master's degree

6.1 Introduction

There is continued interest in incorporating the principles of green chemistry and green engineering into the college [1], and even K-12 [2], curriculum in the United States. This implementation at colleges and universities has been slow, but steady, since the dissemination of green chemistry principles in the early 1990s [3] and subsequent formulation of complementary principles of green engineering [4, 5]. The Department of Chemistry and Biochemistry and the Department of Chemical Engineering at the University of Toledo (UT) had faculty with interests in green chemistry and engineering since the late 1990s, and these interests finally culminated in formation of the School of Green Chemistry and Engineering in 2011 and subsequent formation of associated new courses and academic programs. This paper describes our experiences at the UT. While all of the efforts of the SGCE and curricular details, such as learning objectives for each new course or program, are not provided, a description of our experiences and perspectives, our challenges and frustrations, as well as our successes on implementation of green chemistry into undergraduate and graduate curriculum will be of benefit to others contemplating ways to further incorporate green chemistry and green engineering into their programs.

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https://doi.org/10.1515/9783110669985-006

6.2 Overview of the University of Toledo

The UT is a metropolitan public research university with over 20,000 students. It was established in 1872 and joined the public university system of the State of Ohio in 1967. It is currently one of 14 public colleges and universities in Ohio. In 2006, the UT merged with the Medical University of Ohio to form the third largest public university in Ohio based on budget. The UT is comprised of 13 different colleges, and is one of only 27 public universities in the United States with colleges of business, education, engineering, law, medicine, and pharmacy. The university also operates a hospital on the health sciences campus. The UT offers more than 300 undergraduate, graduate, and professional programs, including undergraduate, masters, and doctoral degrees in biology, chemistry, engineering, environmental sciences, medicinal chemistry, pharmacy, physics and numerous other subjects.

The UT, like many other public colleges and universities in Ohio and across the country, is confronted with challenges related to enrollment, funding, relevance, public opinion, and long-term sustainability [6]. The UT has struggled with periods of stagnant or decreasing enrollment, and this is particularly challenging in a region of the country where the number of direct from high school students has been decreasing for several years. The UT operates in a political and economic environment where the State Share of Instruction has significantly decreased over the past three decades, shifting the financial burden to students, their families, and universities. Of course, students and their families simply cannot afford continual tuition and fee increases, and this has led to increased scrutiny of public universities from lawmakers, resulting in several state-imposed, as well as internal, tuition freezes over the past decade, further exacerbating budgetary constraints at the university. Furthermore, former UT President Dan Johnson has noted the growing gap between university curricula and the needs of the current U.S. workforce, and academia's apparent lack of understanding and/or slow response to the needs of employers [6]. These issues are briefly noted here because they underlie the need for new revenue-generating programs and curricular revisions that meet workplace needs as discussed in subsequent sections of this paper.

6.3 Formation, organization, and mission of the SGCE

In 1998, Professor Mark Mason moved his research group to the UT and quickly had the opportunity to collaborate with two of his new colleagues in chemistry and chemical engineering on some rhodium-catalyzed hydroformylation of alkenes in supercritical carbon dioxide. From that collaboration, and from strategic planning sessions in the Department of Chemistry in 1999, it was apparent that there were several faculty with interests in green chemistry and green engineering at the UT. Unfortunately, this was a period of deep budget cuts at UT and a severe shortage of faculty in the Department of Chemistry, further exacerbated by the loss of some supportive faculty and administrators to retirements and external advancement opportunities. Thus, it was difficult for green chemistry and green engineering initiatives to gain traction in the Department of Chemistry or the Department of Chemical Engineering during that period. It was not until almost a decade later that the departments were nearly fully staffed and the fiscal position of the university improved.

In 2010, then President Lloyd Jacobs solicited proposals for the formation of new interdisciplinary schools at the UT. With urging and strong support from alumna Nina McClelland, former Dean of the College of Arts and Sciences, as well as support and guidance from College of Natural Science and Mathematics Dean Karen Bjorkman, College of Engineering Dean Nagi Naganathan, College of Business and Innovation Dean Tom Gutteridge, Director of UT Innovation Enterprises Rick Stansley, and Department of Chemistry Chair Alan Pinkerton, Professors Mark Mason and Glenn Lipscomb proposed the formation of the UT School of Green Chemistry and Engineering (UT SGCE). This proposal was ultimately one of five selected for approval from 36 submissions, and the formal announcement by President Jacobs was made at a reception attended by green chemistry founder Paul Anastas, ACS Green Chemistry Institute Director Robert Peoples, and NSF Chemistry Division Director Matthew Platz in July of 2011 [7].

The SGCE is an interdisciplinary school led by the College of Natural Science and Mathematics and the College of Engineering, with additional participation of the College of Business and Innovation and faculty participation from the College of Pharmacy and Pharmaceutical Sciences. The SGCE is currently comprised of 24 tenured or tenure-track faculty from 5 departments in 3 different colleges, and its mission is to improve the human condition through research, education, and outreach activities that promote safe and sustainable use, production, and recycling of chemical materials. In formation of the SGCE, synergy was envisioned with several university entities, including the UT Lake Erie Center located on the shores of Maumee Bay, the UT School of Solar and Advanced Renewable Energy, and the Wright Center for Photovoltaics Innovation and Commercialization.

The value propositions the SGCE offered to the university and associated colleges and departments were to provide unique educational and research opportunities for UT students, to provide national visibility in a way not easily achieved in our otherwise traditional chemical engineering and chemistry departments of moderate size and resources, and to provide academic courses and programs that can attract new graduate and undergraduate students to participating departments and colleges. The value proposition to the administration was revenue-generation through new academic programs, increased enrollment, and research initiatives to help combat decreasing State Share of Instruction and flat enrollment.

The aim in developing the organizational structure of the school was to promote mutually beneficial academic programs and research projects across departmental and college boundaries, and to do so in a way as to avoid perception that the SGCE is competing with departments and colleges for limited resources, including faculty lines, staff support, laboratory and office space, and budget. The director and associate director of the SGCE work with deans and department chairs, for example, to make sure pertinent courses and academic programs are developed, supported, and staffed, working within existing organizational constraints of each department and college. There are no faculty appointed directly to the SGCE, although some faculty searches and a faculty line were provided to promote the SGCE. Faculty have generally been supportive and choose to participate in SGCE activities based on their interests in green chemistry and green engineering and perceived benefits to them and their respective departments. The level of participation varies from person to person and over time.

The SGCE established an external advisory board comprised of members with interests and expertise in green chemistry, green engineering, and/or related areas from regional industry, non-profit organizations, and governmental agencies. The SGCE Advisory Board meets biennially with feedback solicited from members more frequently by email, phone, and in person at conferences and other venues.

6.4 Green chemistry and green engineering curriculum and new academic programs

After decisions on basic organization, mission, and vision of the SGCE had been made and initial marketing strategies had been developed, the decision was made to focus initial efforts on developing new academic programs, required courses to support those programs, and to embed the principles of green chemistry and green engineering into the undergraduate and graduate curricula. Development of appropriate coursework and curriculum was crucial to having a viable and externally visible program, to help recruit undergraduate and graduate students interested green chemistry and engineering, and to retain the support of department chairs, deans, and other administrators. These efforts continue and what is described herein is a report on progress to date.

6.4.1 Challenges, limitations, and approaches to implementation

Challenges hindering the implementation of green chemistry in the undergraduate and graduate curricula have been documented by others [8–10]. These challenges often include a subcritical mass of faculty with interests and/or expertise in green chemistry and related topics, resistance of established faculty to change and no financial or other incentives for faculty to change, and lack of support of colleagues who may view green chemistry as a separate area of chemistry unrelated to their interests, rather than simply good or better chemistry with principles that should be incorporated into all areas of chemistry. And for science and engineering departments that have doctoral level graduate programs, faculty are driven, at least in part, by research priorities, the constant search for funding, and dissemination of research results by publication in scientific journals and presentations at conferences. This is particularly true for faculty early in their career. At the UT, for example, chemistry faculty are evaluated for tenure and promotion, as well as annually, based on research efforts that typically account for 40% or more on annual workload agreements. Thus, development of new courses and academic programs often requires a critical mass of committed senior, or at least tenured, faculty members.

Another challenge is that more content and/or course requirements cannot simply be added to an already dense curriculum in chemistry and chemical engineering. In fact, public colleges and universities in Ohio are already under pressure from the Ohio Department of Higher Education to reduce the number of credit hours required for undergraduate degrees, a difficult challenge for chemistry and biochemistry programs that want to be certified by the American Chemical Society [11].

There is also no commonly accepted green chemistry or green engineering curriculum, and questions still remain as to how much toxicology should be introduced in the chemistry curriculum, and when and where that material would be best introduced. Efforts are ongoing to address these issues. In 2018, the ACS Committee on Professional Training, with help from the ACS Green Chemistry Institute, released a supplement to the 2015 ACS Guidelines and Evaluation Procedures for Bachelor's Degree Programs [11] on incorporation of green chemistry into the curriculum [12]. Beyond Benign has developed student-learning objectives for green chemistry [13], and also established a Toxicology for Chemists Working Group [14] to address implementation of toxicology in the curriculum. Nonetheless, these issues still represent a challenge. There are also financial limitations to implementing new courses.

6.4.2 Guiding principles to curriculum revisions and new program development

The initial steps in revising the curriculum and formulating carefully selected new programs were to further educate UT faculty on the subject material, see what others had done previously at other colleges and universities, determine what industry needed in terms of green chemistry and green engineering knowledge and skills, try to assess market demand for any potential new programs, and solicit feedback from industry groups. Several UT faculty attended and participated in scientific conferences such as ACS Green Chemistry and Engineering Conferences, green chemistry sessions at regional meetings of the ACS, Michigan Green Chemistry Conferences, Green Chemistry and Commerce Council Innovator's Roundtables, and even a Global Green

Chemistry Centers [15] meeting held at the University of Massachusetts Boston. Green chemistry experts were invited to UT as seminar speakers and members of the SGCE consulted materials posted by the ACS Green Chemistry Institute [16] and the Green Chemistry and Commerce Council [17], as well as learning objectives and education materials posted by Beyond Benign [13]. The UT also made the Green Chemistry Commitment [18] in 2014.

The SGCE looked at what other colleges and universities had done or were doing at that time, particularly efforts at the Berkeley Center for Green Chemistry [19], the Center for Green Chemistry and Green Engineering at Yale University [20], the Center for Green Chemistry at the University of Massachusetts Boston [21], the University of Oregon [22], and more recently, the University of Minnesota [23] and the associated NSF Center for Sustainable Polymers [24]. The Green Chemistry Initiative [25] and curricular efforts at the University of Toronto [26] are also noteworthy.

The SGCE also monitored degree requirements for PhD programs in green chemistry at the University of Massachusetts Boston [27] and now the University of Massachusetts Lowell [28], the MS degree in environmental and green chemistry at George Washington University [29] and the MS degree in green chemistry at Chatham University [30]. There are green chemistry degrees outside of the United States, such as the MSc in green chemistry and sustainable industrial technology at the University of York [31] and the MSc in green and sustainable chemistry at University of Nottingham [32]. There is also a new BS degree in green chemistry at the University of Michigan Flint, developed in part by UT doctoral graduate, Associate Professor Nick Kingsley [33].

Hence, development of the curriculum was guided by all material accumulated and advice and guidance received from many people outside of the university. In addition, development of the curriculum was heavily guided by the Green Chemistry and Commerce Council (GC3) Policy Statement on Green Chemistry in Higher Education [34]. This policy statement gives the following list of skills desirable amongst current and future science and engineering employees of chemical and chemical-related industries:

- A working knowledge of the Twelve Principles of Green Chemistry.
- A working knowledge of the Principles of Green Engineering.
- A basic understanding of toxicology and public health, including addressing data gaps and tools for evaluation of toxicity, alternatives and trade-offs.
- The ability to recognize and assess the relative "greenness" (incorporating life-cycle impacts) of a chemical, product, material, or process. This includes familiarity with tools and strategies for evaluating alternative options.
- An understanding of how molecular and material design can affect the health, environmental, and performance attributes of a chemical or material.
- An awareness of environmental laws, policies, and market drivers that influence the use or generation of hazardous substances in industry.

- An appreciation of performance, economic, technical, and other considerations that are critical in moving from laboratory to commercial production of a new chemical, material, product, or process.

After consideration of all available information and advice, the SGCE chose the best approach for UT students and faculty and for the institution. Our choices were aided by the following principles. First, members felt strongly that the program should incorporate principles of green chemistry and green engineering. The two sets of principles are complementary, and implementation of green chemistry on an industrial scale requires the adoption of green engineering. There was also a desire to expose chemistry and other science majors to chemical engineering and green engineering fundamentals. Second, the number of new course offerings had to be kept to a minimum. The aim was to repurpose and update existing courses to meet the needs of new academic programs, and embed as much green chemistry and green engineering content in existing courses as possible, including large enrollment general chemistry and organic chemistry sequences. New courses would have to be utilized for more than one degree program to ensure economically viable enrollments each year. Third, new academic programs would require strong potential for new student enrollment and revenue-generation. Whenever appropriate, the aim was to implement courses in a distance learning format to reach a greater number of potential students.

6.4.3 New courses

At the beginning of this process, there were courses offered by several departments that could be adopted for use in new green chemistry and engineering programs, either as elective or required courses, at the undergraduate and/or graduate level. These included courses on Biofuels, Chemistry of Sustainable Energy Resources, Environmental Geochemistry, Environmental Economics, Environmental Policy, Hazardous Waste Management, and Life Cycle Assessment. However, no courses were offered in green chemistry or environmental chemistry, and there was no coverage of toxicology in the undergraduate chemistry curriculum. Two chemical engineering courses also needed to be repurposed and modified for use in the new green chemistry and engineering programs. Following is an overview of key new or revised courses.

6.4.3.1 Green chemistry

This new course was first offered to UT chemistry graduate students in the fall of 2013, and as course content was expanded in subsequent years, the course was offered to junior and senior undergraduate students in chemistry, chemical engineering, environmental science, and related fields as long as the student had successfully completed the sophomore-level organic chemistry sequence. Although this course is cross-listed at the graduate and senior undergraduate levels, there are additional learning objectives and a written paper and oral presentation required for graduate students.

The course introduces the principles and applications of green chemistry, including the prevention of waste and increased materials and energy efficiency in chemicals production, the importance of biodegradation and biodegradation pathways for chemicals released into the environment, safer solvent substitutions in industrial processes and consumer products, homogeneous and heterogeneous catalysis, abiotic depletion of the elements, and renewable feedstocks and conversion of biomass to chemicals and fuels and polymers. Basic concepts of chemical toxicology and the effects of anthropogenic chemicals on human health are discussed, as are concepts of risk and hazard and methods for chemical alternatives assessment [35] including basic GreenScreen [36] benchmarking. Green chemistry metrics such as atom economy, E-factor and process mass intensity are presented with many examples chosen from US EPA Green Chemistry Challenge Award winners [37]. Life cycle assessment and eco-efficiency models [38] are introduced to further justify the green chemistry metrics. The course also includes a review of historically important environmental and chemical-related laws and regulations that influence the use or generation of hazardous substances in industry in the United States and the European Union. Market drivers and business principles, such as the Triple Bottom Line, that influence the choice of chemical processes and chemicals used in industry and in production of consumer products are also reviewed. Since the SGCE emphasizes the importance of green chemistry and green engineering, and since very few science majors are introduced to concepts in engineering, this course also overviews fundamentals of conventional reactors (batch, plug-flow, continuous stirred tank reactor), heat and mass transfer limitations of these reactors, advantages and disadvantages of batch and continuous-flow processing, and approaches to inherently safer design, process intensification, and in-process monitoring. The brief overview of these chemical engineering topics is a nice introduction for science majors who go on to take additional courses in green engineering, but for most students, this may be their only introduction to these topics.

6.4.3.2 Environmental chemistry

The course on Environmental Chemistry was first offered at UT in the spring of 2014 in a traditional lecture format, but an online version of the course was subsequently developed and offered beginning in the spring of 2017. The course is offered as a graduate course, cross-listed at the undergraduate level for juniors and seniors that have successfully completed the organic chemistry sequence. Graduate students have additional learning objectives and must complete additional educational components.

The course focuses on the chemistry of air, water, and soil with specific emphasis on the effects of human-made chemical products and byproducts on the environment.

Reactions of anthropogenic chemicals with the terrestrial environment, transport and partitioning of these chemicals in the environment, and the ultimate fate of these chemicals and degradation products are emphasized. Course content builds on topics covered in the course on green chemistry, and connections with green chemistry are highlighted. Specific topics covered include volatile organic compounds and their impact on the ozone layer, smog, and ground-level air pollution. Energy use, fossil fuels, carbon dioxide emissions and sequestration, and the greenhouse effect are also covered, as are persistent organic pollutants such as PCBs, certain pesticides and herbicides, and heavy metal contamination.

6.4.3.3 Green engineering principles

This course covers the principles of chemical process analysis and design for the development of green engineering processes. Common components of chemical processes are reviewed and quantitative analyses of process performance and economics developed. The impact of design variables on materials and energy usage is demonstrated. The course begins with coverage of how to convert the Earth's resources into useful products, and then moves on to process flow variables, diagrams, and balances, mathematical analysis of material balance equations, the synthesis of reactor flow sheets, selection of separation technologies, and process energy calculations. Key learning objectives include how to identify different types and the components of chemical process diagrams, perform mass and energy balances for chemical processes, identify different types of fluid flow, heat transfer, separation, and reactor equipment and determine required size, and how to determine process economic analysis and profitability.

Undergraduate and graduate chemistry majors with at least two years of undergraduate calculus and one semester of physical chemistry are eligible to take this course, with permission, as part of the green chemistry and green engineering programs. The course thus acts as a "bridge course" that provides the necessary background for science students to take a select number of engineering courses, including Green Engineering Applications, without completing a large number of prerequisite courses.

6.4.3.4 Green engineering applications

This course has been offered at the UT for several years and was updated to emphasize the applications of green engineering principles in the chemical industry. Metrics for comparing process options are introduced along with common techniques for improving process performance. The course covers risk concepts, methods for evaluating fate and exposure, process safety, and environmental performance. Course coverage also includes flowsheet analysis, heat integration, and sustainability metrics. Students are required to complete four mini-projects, submit a short report, and give an oral presentation. The projects are broadly in the areas of chemical alternatives assessment and solvent selection, safety assessment, process (flowsheet) environmental and economic assessment, and heat integration. This course is cross-listed at the graduate and senior undergraduate levels. Graduate students must complete an additional literature review. Doctoral students must also complete a supplemental project.

6.4.4 New programs

6.4.4.1 Minor in green chemistry and engineering

The minor in chemistry is very popular among UT undergraduate students majoring in biology, biology/premed, chemical engineering, environmental sciences, medicinal chemistry and pharmacy. For students with interests in green chemistry, green engineering, and sustainable chemistry, we utilized some of the new courses discussed above to create the Minor in Green Chemistry and Engineering. Students must complete the undergraduate general chemistry and organic chemistry sequences and then complete the courses Green Chemistry and Green Engineering Principles. Additional electives must be selected from the options shown in Table 6.1 to get to the minimum 21 credit hours. The minor has been available for the past year and initial feedback shows considerable interest, particularly among chemical engineering majors.

Table 6.1: Requirements for the minor in green chemistry and engineering.

Course		Title	Credit hours
The following are required:			
CHEM	2410	Organic chemistry I	3
CHEM	2420	Organic chemistry II	3
CHEM	4200	Green chemistry	3
CHEE	4010*	Green engineering principles for chemical processes	3
Select at least one of the following courses:			
CHEM	4210	Environmental chemistry	3
CHEE	4110	Green engineering applications in chemical industries	3
Select at least one of the following courses:			
CHEM	3810	Chemistry of sustainable energy resources	3
CHEE	4120	Biofuels	3
EEES	4220	Environmental geochemistry	3
EEES	4450	Hazardous waste management	3
ECON	3240	Environmental economics	3
PSC	4340	Environmental policy	3
Total			**21**

*In lieu of taking CHEE 4010, chemical engineering majors must take one additional course from the two lists of optional courses.

6.4.4.2 Professional science master's degree in green chemistry and engineering

A Professional Science Master's (PSM) degree is a multidisciplinary degree that has the majority of the curriculum devoted to science and/or engineering skills, but also requires a professional skills component that may include aspects of business, communication, law, and/or management [39]. A PSM degree requires a team-oriented capstone project or industrial internship, and each PSM program must be overseen by an industrial advisory board. PSM programs require evaluation by, and affiliation with, the National Professional Science Master's Association [40]. There are currently more than 350 PSM degrees offered in the United States, 15 of which focus on some aspect of chemistry or biochemistry, and none of which include green chemistry or green engineering aside from the PSM degree in green chemistry and engineering at the UT, which was approved in the fall of 2015. As previously noted in Section 6.4.2, Chatham University offers an MS degree in green chemistry [30], and George Washington University offers an MS degree in environmental and green chemistry [29], but neither of these are currently designated as a PSM degree.

The PSM degree in green chemistry and engineering was designed for students who want to concentrate their MS studies on principles of green chemistry and green engineering and incorporate aspects of business and other professional skills components into their MS degree. It is designed as a terminal degree with immediate employment opportunities in industry, government, and non-governmental organizations. Although the PSM degree in green chemistry and engineering is not a traditional research-based MS degree, it does benefit from the coursework and research opportunities available through the long-standing MS and PhD programs in the Department of Chemistry and Biochemistry and the Department of Chemical Engineering. This PSM program is unique in terms of incorporating green chemistry, green engineering, business skills, an industrial internship and guidance of an industrial advisory board into a single master's program.

The PSM in green chemistry and engineering is comprised of four components; a green chemistry and green engineering core, a business core, chemistry and engineering foundation courses, and an industrial or government internship (Table 6.2). The chemistry and engineering foundation is strengthened by 12 credit hours of elective courses chosen from traditional courses in analytical chemistry, organic chemistry, inorganic chemistry, materials science, catalysis, chemical engineering, and environmental engineering, including optional courses in biofuels, life cycle assessment, and hazardous waste management.

The internship can be completed at any company, government, or non-governmental entity that provides direct, hands-on experience that combines green chemistry, green engineering, and business principles in a professional setting. The internship project must be approved by the SGCE and the student must be supervised and mentored by a qualified member of the company. The intern is paid and must complete a minimum of 400 h on the project. An employee of the company can pursue the PSM degree and fulfill internship requirements at work with prior

Table 6.2: Requirements for the PSM degree in green chemistry and engineering.

Course	Title	Credit hours
CHEM 6200	Green chemistry	3
CHEM 6210	Environmental chemistry	3
CHEE 6010	Green engineering principles for chemical processes	3
CHEE 6110	Green engineering applications in chemical industries	3
BUAD 6600*	Supply chain management	3
EFSB 6690	Technology commercialization	3
OR		
EFSB 6590	New venture creation	3
CHEM/CHEE 6970	Graduate industrial internship	6
	Elective courses in chemistry, chemical engineering, and materials science	12
Total		**36**

*For most non-business majors, BUAD 6600 has a prerequisite of OPMT 5520, Analysis of Manufacturing and Service Systems.

approval of the SGCE. The student must submit a written report summarizing the internship experience, and the supervisor provides the SGCE with a written evaluation of the student’s performance.

During the initial development of this PSM degree program, some faculty were concerned about negative effects on our traditional research-based MS and PhD programs. The main concerns were that the PSM degree program would compete with traditional research-based programs for students and for assistantship support of those students. These concerns were alleviated when it was made clear that PSM students do not receive assistantship or tuition support as is provided to research-based masters and doctoral students in chemistry and engineering, and that students that pursue a PSM degree are typically not interested in traditional research-based degrees. PSM degrees are often popular among employees of local or regional industry.

6.4.4.3 Master in education and science in chemistry

The Master in Education and Science in Chemistry degree program has existed at the UT for over two decades, and is aimed at students wishing to become high school chemistry teachers or current teachers. Unfortunately, enrollments had been very low and there were few graduates over the period of the program.

In 2014, the State of Ohio announced a new initiative called College Credit Plus [41] and this program was subsequently implemented in academic year 2015–16.

Ohio's College Credit Plus is a dual-enrollment program for college-ready students in grades 7–12 that enables students to earn college and high school credits at the same time. Courses can be in-person or online. In-person courses can be taught by high-school teachers with proper credentialing and in conjunction with a public college or university in Ohio. Tuition, books, and fees for College Credit Plus courses are free to Ohio residents that attend an Ohio public school.

In response to the new College Credit Plus initiative and the resulting interest in credentialing high school teachers, Rebecca Schneider of the College of Education, and Andy Jorgensen of the Department of Chemistry and Biochemistry, led an effort to revise the Master in Education and Science in Chemistry degree program to an online delivery. The SGCE assisted in this effort by developing some new chemistry courses and by converting the courses green chemistry and environmental chemistry to an online format as part of the chemistry component as seen in Table 6.3.

Table 6.3: Requirements for the master of education and science in chemistry.

Course	Title	Credit hours
CHEM 5100	Principles of organic and inorganic chemistry	4
CHEM 5160	Chemistry laboratory techniques development	2
CHEM 5170	Chemistry instrumentation techniques	2
CHEM 5230	Chemistry of sustainable materials	4
CHEM 6200	Green chemistry	3
CHEM 6210	Environmental chemistry	3
CI 6830	Curriculum issues and trends	3
CI 6690	Theory and research in science education	3
CI 6900	Master's research seminar	3
EDP 5310	Issues and innovations in learning and instruction	3
RESM 5520	Applied assessment for improved practice	3
TSOC 5300	Philosophy and education	3
Total		**36**

The revised online Master in Education and Science in Chemistry degree is designed for Ohio teachers licensed in AYA (Adolescence to Young Adults) chemistry or integrated science. Program completers earn a Master of Education and Science degree and become qualified to teach College Credit Plus courses in chemistry. There is a residency requirement on the UT's main campus of one week each during two summers. Students must have adequate undergraduate preparation in chemistry beyond the traditional organic chemistry sequence. Students who already have a master's degree in education can pursue the education specialist degree. The chemistry requirements for the education specialist degree are the same as for the Master in Education and Science in Chemistry Degree (Table 6.3), but there are six credit hours less of elective education courses.

All of the online courses in Table 6.3 were developed to meet Quality Matters (QM) standards, and thus far each course has received QM certification except for Chemistry Instrumentation Techniques. QM is a non-profit, quality assurance organization that uses certified peer reviewers to evaluate courses to meet QM rubric standards [42]. This leads to better course design, ease of navigation, and better student outcomes. Receipt of QM course certification is an accepted indicator of course rigor and quality.

6.4.5 Enrollments

It is too early to determine the success of these programs based on enrollments. For example, the first full-time student graduated with a PSM degree in green chemistry and engineering in December of 2017, and a few part-time students who are employed in local industry have taken courses toward completion of the PSM degree, but it will be a few years before we can provide reliable and useful information on enrollments, graduation rates, and demographics of PSM degree recipients. Similarly, the first cohort of students received the Minor in Green Chemistry and Engineering in May and August of this year. Aside from qualitative information that this minor is very appealing to undergraduates majoring in chemical engineering, it is too soon to evaluate the success of this program. For the MES in chemistry degree program, there was a large cohort of 17 high-school teachers who completed the program in 2017. Unfortunately, the State subsequently discontinued the tuition subsidy for teachers seeking College Credit Plus credentialing, and enrollment plummeted in the MES in Chemistry program. This was also true for the analogous MES programs in Biology and English. It is not clear what will happen with enrollments in the MES in Chemistry degree program in coming years, but enrollments are likely to be low without some form of tuition subsidy for the teachers.

Enrollment data can be shared for the courses on green chemistry and environmental chemistry since these were first offered in the fall of 2013 and spring of 2014, respectively. Both courses were initially offered as special topics courses to chemistry graduate students, and hence enrollments were modest. As the courses were offered to graduate students in chemical engineering and then undergraduate students in chemistry and chemical engineering, enrollments increased as seen in Figure 6.1 and Figure 6.2. There was fluctuation in enrollments due to some initial

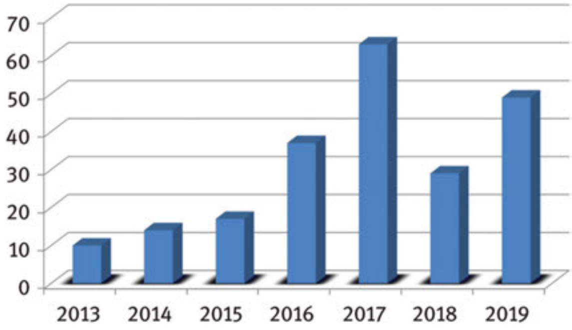

Figure 6.1: Enrollment in green chemistry. Enrollment is plotted as the number of students enrolled per calendar year. The course is offered only once per year.

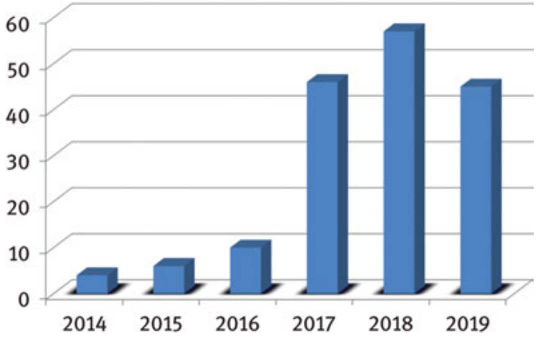

Figure 6.2: Enrollment in environmental chemistry. Enrollment is plotted as the number of students enrolled per calendar year. The course is offered only once per year.

scheduling conflicts and a large cohort of MES teachers in the fall of 2016 and spring of 2017, but it appears that enrollments will stabilize at greater than 40 students for each course per year.

Enrollment data is also available for Green Engineering Principles in Chemical Processes (Figure 6.3) and Green Engineering Applications in Chemical Industries (Figure 6.4). Enrollment has been low in the Green Engineering Principles course since engineering students do not take this course. The course is designed for chemistry students and allows them to subsequently take selected courses in engineering without numerous prerequisites. Enrollment has varied in Green Engineering Applications, but the spike in enrollment in 2019 is very encouraging. Enrollments are anticipated to increase and stabilize in both courses as more students learn about and pursue the Minor and the PSM degree in green chemistry and engineering.

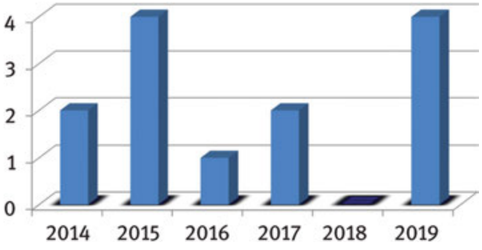

Figure 6.3: Enrollment in green engineering principles. Enrollment is plotted as the number of students enrolled per calendar year. The course is offered only once per year. It was not offered in 2018.

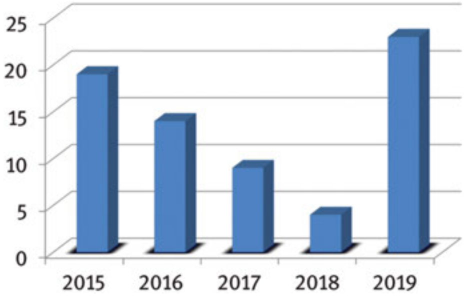

Figure 6.4: Enrollment in green engineering applications. Enrollment is plotted as the number of students enrolled per calendar year. The course is offered only once per year.

6.4.6 Current programmatic initiatives

Current curricular initiatives include development of an accelerated BS/MS degree program for chemistry and chemical engineering majors, offering the core courses for the PSM degree online, and offering the online versions of the green chemistry, environmental chemistry and green engineering courses to students at other universities for transfer credit. Incorporation of green chemistry and engineering principles into traditional courses such as general chemistry and organic chemistry sequences is also ongoing.

6.5 Conclusions

Significant progress has been made in defining the mission, vision, and organization of the SGCE [43], as well as in incorporating the principles of green chemistry and green engineering into the curriculum at the UT. Although there is excitement and optimism about the new courses, new degree programs, and ongoing programmatic initiatives described above, the long-term sustainability of these programs and the impacts on enrollment and revenue generation will not be evident for several more years.

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Dedication

The author and everyone associated with the UT School of Green Chemistry and Engineering dedicate this paper to the memory of Professor Dean Giolando. Professor Giolando was a strong supporter of green chemistry, sustainability, and the School of Green Chemistry and Engineering. He contributed to the curriculum development described above in many ways, including development of the online graduate course Chemistry of Sustainable Materials, and the undergraduate course on Chemistry of Sustainable Energy Resources. Professor Giolando’s research focused on improvements to photovoltaics and solar energy.

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Emanuela Gionfriddo

7 Green analytical solutions for sample preparation: solid phase microextraction and related techniques

Abstract: For at least three decades, the analytical chemistry community is striving to apply the principles of Green Chemistry to the development of analytical methods. Many efforts have been made to outline the concept of Green Analytical Chemistry, which helped to redefine analytical procedures and drastically changed the philosophy of analytical method development. This book chapter describes the 12 principles of Green Analytical Chemistry and various methodologies for the assessment of the greenness of analytical methods. The three main steps in the analytical method development – sample preparation, separation and detection- are described in a "green perspective". Special emphasis is given to the description of green sample preparation procedures, in particular to Solid Phase Microextraction, that, since its introduction in 1989 by Janusz Pawliszyn, has drastically revolutionized the methodology of sample preparation, providing a convenient and green alternative to already existing methods.

Keywords: green analytical chemistry, sample preparation, microextraction

7.1 Introduction

Chemistry related disciplines have always been perceived by the public as waste-producing and polluting sciences, which could potentially pose health hazards to the human population. In many instances, the irresponsible use of chemistry, non-compliance to safety advisories and negligent laboratory waste disposal procedures have led to dramatic cases of environmental pollution and consequents harm to the human and animal population of the regions affected. Moreover, developments of pharmaceuticals, phytosanitary products, and many other industrial commodities have become tied to our every-day life in spite of the environmental consequences that their production, use and disposal can create.

However, especially in the last three decades, the concept of "Green Chemistry" has inspired the scientific community toward the development of more sustainable and environmentally friendly chemical processes mainly aimed to minimize the

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production of toxic laboratory waste and maximize pollution prevention. The general concept of Green Chemistry, defined as the “use of chemistry techniques and methodologies that reduce or eliminate the use or generation of feedstocks, products, byproducts, solvents, reagents, etc. that are hazardous to human health or the environment” [1], can be applied to various chemistry subdisciplines, including Analytical Chemistry, setting the basis for the development of more specific concepts, such as “Green Analytical Chemistry”.

7.1.1 Principles of Green Analytical Chemistry (GAC)

The urgent act of applying the Green Chemistry principles to analytical chemistry methodologies has emerged to minimize chemical waste produced by analytical methods for the analysis of different matrices, including environmental samples. Often these methods may have a significant environmental and human impact, especially when the chemicals employed for analysis are even more toxic than the analytes of interest [2].

Green Analytical Chemistry (GAC) applies the philosophy and the general principles of GC to common methodologies used in analytical chemistry. Among the twelve principles of GC proposed by Anastas and Warner in 1998 [1], concepts such as elimination or minimum consumptions of organic solvents, optimization of energy consumption, reduction of real-time pollution, minimization of laboratory waste, and safer chemistry for accident prevention can be well applied and refined in the analytical chemistry laboratory. Considering that not all the principles of Green Chemistry can be directly implemented to analytical procedures – e. g. the maximization of atom economy – Gałuszka et al. [3] proposed in 2013, 12 principles of GAC and the mnemonic SIGNIFICANCE based on the Green Chemistry principles, with direct correlation to analytical chemistry practices (Figure 7.1). It is important to stress that analytical methods complying with the GAC principles still must comply with performance parameters such as accuracy, reproducibility, and sensitivity; this, in turn, results in the ultimate challenge for the analytical chemistry community. In general, for any analytical procedure, the greater the number of steps involved, the less green the analytical procedure is, mainly because of the increased amount of energy used and the larger volume of waste produced in each step of the procedure.

As a consequence, the first approach to improve the greenness of any analytical protocol would be reducing the overall number of steps from sampling to instrumental analysis. However, some of the steps cannot be skipped and are inevitable. The role of green analytical chemistry is to search for more environmentally friendly analytical methodologies without compromising the quality of the measurements.

To confirm the increased interest and concern of the analytical community toward the impact that analytical protocols may have on the environment and human health, Figure 7.2 shows that from 1992 to 2019 an exponential increase of publications per

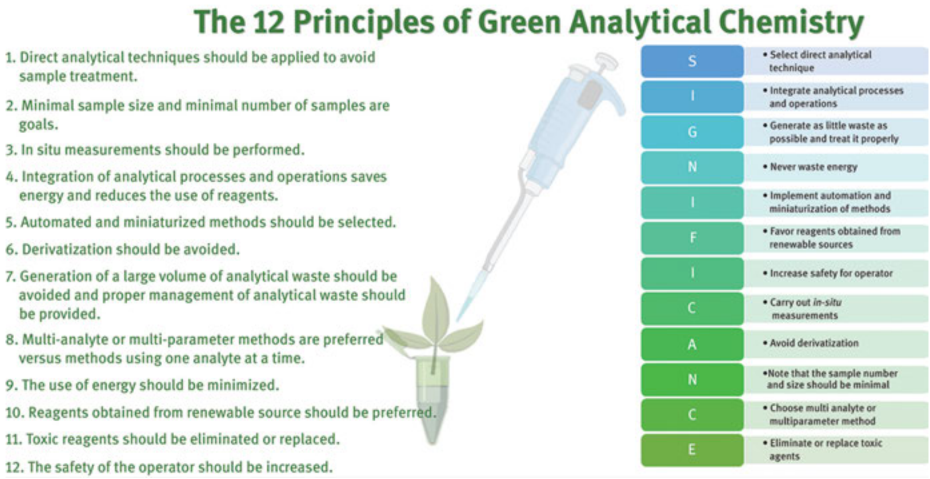

Figure 7.1: The 12 principles of analytical chemistry and the SIGNIFICANCE mnemonic.

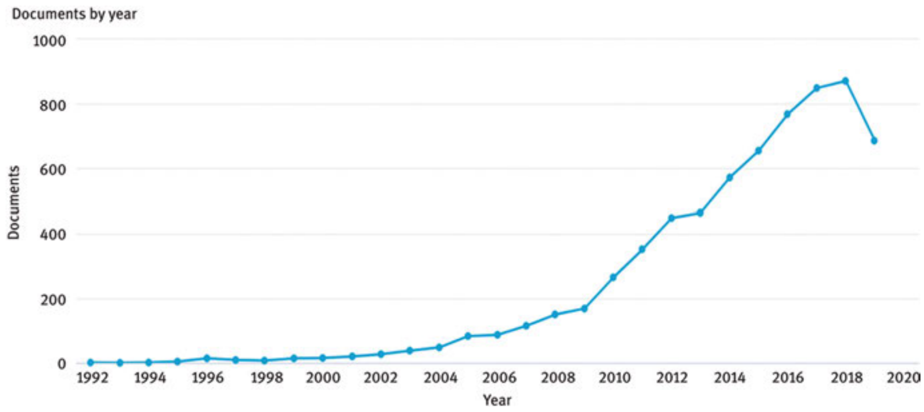

Figure 7.2: Number of documents containing the keywords “green analytical chemistry”, “green analytical method”, “environmentally friendly method”, “clean analytical chemistry” published from 1992 to 2019. Source: Scopus.

year were found with keywords such as “green analytical chemistry”, “green analytical method”, “environmentally friendly method”, and “clean analytical chemistry”.

As mentioned earlier, some traditional GC metrics introduced for synthetic procedures, such as Atom Economy, E-factor and Reaction Mass Efficiency do not well fit the purpose of GAC. Thus, new parameters that closely conform to analytical issues should be considered to evaluate the “greenness” of analytical protocols. The greenness assessment of analytical methods (mostly for environmental analysis) is based on four criteria related to the properties of reagents used in the method or the amount and type of waste produced [2]: (1) persistent, bioaccumulative, toxic; (2) hazardous; (3) corrosive ($pH < 2$ or >12); and, (4) volume (mass) of waste. Various on-line resources are available for the purpose of comparing the greenness of analytical methods, such as the National Environmental Methods Index (NEMI) – www.nemi.gov.

As an alternative strategy, Gałuszka et al. proposed an Analytical Eco-Scale assessment [4] as an analogous approach to the Eco-Scale used for evaluating the greenness of organic synthesis processes [5].

According to the analytical Eco-Scale, the ideal green analytical method scores 100 points. Penalty points are assigned to each analytical procedure, solvent, and instrumentation based on how much they diverge from the ideal green analysis (Table 7.1). The sum of the penalty points collected is then used for the Eco-Scale calculation according to the following formula:

$$Analytical\,Ecoscale = 100 - total\,penalty\,points$$

Table 7.1: Examples of penalty points (PPs) for hazards and energy of selected reagents and analytical techniques. Table reprinted from Ref. [4] copyright 2012, with permission from Elsevier.

Reagent	Number of pictograms	Signal word	Penalty points
Acetic acid (glacial)	2	Danger	4
Acetic acid (30%)	1	Danger	2
Acetylene	2	Danger, Warning	3
Ammonia solution (25%)	3	Danger	6
Benzoic acid	1	Warning	1
Dichloromethane	1	Warning	1
Hydrochloric acid (30%)	2	Danger	4
Hydrogen peroxide (30%)	2	Danger	4
n-Hexane	4	Danger	8
Nitric acid (65%)	2	Danger	4
Potassium dichromate	5	Danger	10
Sodium hydroxide (30%)	1	Danger	2
Sulfuric acid (25%)	1	Danger	2
Technique		**Energy used**	
FTIR		<0.1 kWh per sample	0
Immunoassay			
Spectrofluorometry			
Titration			
UPLC			

Table 7.1 (continued)

Reagent	Number of pictograms	Signal word	Penalty points
UV–Vis Spectrometry AAS		≤1.5 kWh per sample	1
GC ICP-MS LC NMR		1.5 kWh per sample	2
GC-MS LC-MS X-ray diffractometry			

FTIR, Fourier transform infrared spectroscopy; UPLC, Ultra-performance liquid chromatography; AAS, Atomic absorption spectrometry; GC, Gas chromatography; ICP-MS, Inductively coupled plasma mass spectrometry; LC, liquid chromatography; NMR, Nuclear magnetic resonance spectroscopy; GC-MS, Gas chromatography-mass spectrometry; LC-MS, liquid chromatography-mass spectrometry.

Analytical methods that collect >75 points are ranked as excellent, >50 points as acceptable, and <50 as inadequate in terms of green analysis. Penalty points for physical, environmental, and health hazards are assigned on the basis of the Globally Harmonized System of the Classification and Labeling of Chemicals (GHS). For reagents, two signal words are used in GHS: “danger” (more severe hazard, category 1 and/or 2) and “warning” (less hazard, other categories). Each hazard is assigned penalty points – based on the classification by GHS – as follows: none (no pictogram) = 0 penalty points; less severe hazard = 1 penalty point; more severe hazard = 2 penalty points.

To calculate the penalty points related to energy consumption, the guidelines proposed by Raynie and Driver [6] can be used: the greener laboratory practices and instruments that consume <0.1 kWh per sample are assigned 0 penalty points, e. g. immunoassays, titration, hot-plate solvent evaporation (<10 min), needle evaporators, sonicators, and UV–Vis spectrophotometers. The most energy-consuming techniques such as NMR, GC-MS, LC-MS, X-ray diffraction, and hot-plate solvent evaporation (>2.5 h) are assigned two penalty points. It is worth mentioning that many modern analytical measurements may not rank at the top of the Eco-Scale due to the energy consumption of the analytical instrumentation used (NMR or GC-MS) or the amount of solvent used as mobile phases in chromatography (LC, LC-MS). However, it must also be considered that some analytical methods (e. g. multiresidue analysis at trace levels) cannot avoid using certain types of analytical instrumentation due to performance requirements. In these cases, the use of the analytical Eco-Scale becomes important to identify other weak points in the analytical procedure and aid in the pursuit of new and green alternatives.

An additional tool to assess the greenness of analytical protocols was proposed in 2018 by Płotka-Wasylka [7]. The Green Analytical Procedure Index (GAPI) uses the principles provided by NEMI and analytical Eco-Scale and offers a visual representation that allows an "at a glance" comparison of the greenness of different methods. GAPI uses a pictogram and a color scale to assess the greenness of an analytical method. The pictogram is composed of five pentagrams, four representing the stages of an analytical method and the materials used, and one at the center to summarize the overall method greenness. If a circle is present in the central pentagram, the method is quantitative (Figure 7.3). The other four pentagrams are divided into three or four zones corresponding to various steps of each stage of the method; these zones are assigned a color based on their compliance to the GAC principles (Table 7.2). Figure 7.3 shows how intuitive this strategy is for the greenness assessment of multiple analytical methods.

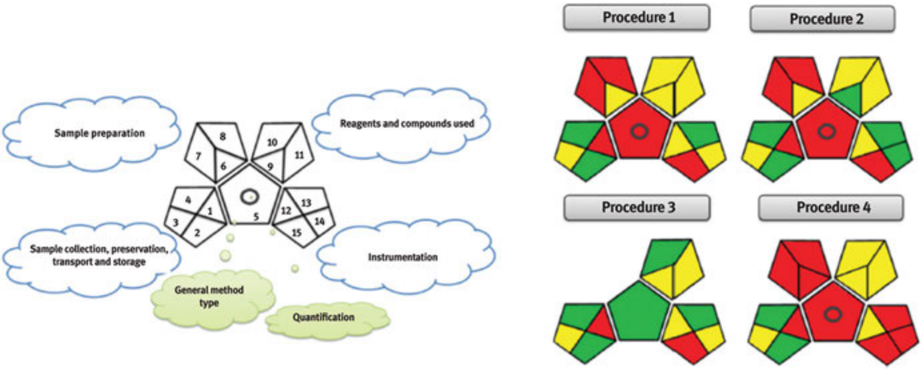

Figure 7.3: Description of the GAPI pictogram (left) and for four reported analytical procedures applied to biogenic amine determination in wine samples compared by the GAPI strategy (right). Reprinted from Ref. [7] copyright 2012, with permission from Elsevier.

GAC principles and greenness assessment strategies put scrutiny on all the stages of an analytical method, namely sampling, sample preparation, and instrumental analysis. Each of these steps contributes to energy consumption, waste production, and the use of organic solvents. If we consider the various steps of an analytical procedure, sampling always represents the very first challenge for the green analytical chemist. One of the main strategies for greening the sampling step is to minimize the amount of sample collected in accordance with the second principle of GAC. This directly translates to less energy consumption to transport the sample in the laboratory and less waste generation related to the containers used for

Table 7.2: Green analytical procedure index parameters description. Reprinted from Ref. [7] copyright 2012, with permission from Elsevier.

Category	Green	Yellow	Red
Sample preparation			
Collection (1)	In-line	On-line or at-line	Off-line
Preservation (2)	None	Chemical or physical	Physico-chemical
Transport (3)	None	Required	–
Storage (4)	None	Under normal conditions	Under special conditions
Type of method: direct or indirect (5)	No sample preparation	Simple procedures, e. g. filtration, decantation	Extraction required
Scale of extraction (6)	Nano-extraction	Micro-extraction	Macro-extraction
Solvents/reagents used (7)	Solvent-free methods	Green solvents/reagents used	Non-green solvents/reagents used
Additional treatments (8)	None	Simple treatments (Clean up, solvent removal, etc.)	Advanced treatments (derivatization, mineralization, etc.)
Reagent and solvents			
Amount (9)	<10 mL (<10 g)	10–100 mL (10–100 g)	>100 mL (>100 g)
Health hazard (10)	Slightly toxic, slight irritant; NFPA health hazard score = 0 or 1.	Moderately toxic; could cause temporary incapacitation; NFPA = 2 or 3.	Serious injury on short-term exposure; known or suspected small animal carcinogen; NFPA = 4.
Safety hazard (11)	Highest NFPA flammability or instability score of 0 or 1. No special hazards.	Highest NFPA flammability or instability score of 2 or 3, or a special hazard is used	Highest NFPA flammability or instability score of 4.
Instrumentation			
Energy (12)	≤0.1 kWh per sample	≤1.5 kWh per sample	>1.5 kWh per sample
Occupational hazard (13)	Hermetic sealing of analytical process	–	Emission of vapors to the atmosphere
Waste (14)	<1 mL (<1 g)	1–10 mL (1–10 g)	>10 mL (<10 g)
Waste treatments (15)	Recycling	Degradation, passivation	No treatment
ADDITIONAL MARK: QUANTIFICATION			
Circle in the middle of GAPI: *Procedure for qualification and quantification*		No circle in the middle of GAPI: *Procedure only for qualification*	

NFPA: National Fire Protection Association

sampling. Ideally, on-line sampling represents an acceptable green approach while off-line sample collection should be avoided. Sample preservation is another stage of sampling that plays a very important role in the overall quality of the analysis because it assures the representativeness of the sample. Sample preservation methods could be physical (refrigeration, freezing, filtration) and chemical (acidification, alkalization, addition of preservation agents). However, sample preservation cannot be considered a green step in an analytical procedure, because it requires energy and/ or the use of chemicals. The best option for a green analytical procedure is to avoid sample preservation, if possible.

As part of the sampling stage of an analytical method, sample transportation should also be considered when evaluating the greenness of the overall analytical procedure. In this case, too, the greener approach is to avoid sample transportation by using on-site sampling tools or portable analytical instrumentation.

The very last step of the analytical protocol that can influence its greenness is instrumental analysis. As mentioned earlier, assessing the greenness of an analytical method also must account for the required performance and the existence of any alternatives that are able to provide the same quality criteria. As an example, even if mass spectrometry (MS) does not fall among the greenest instrumental techniques, its ability to extract chemical fingerprints from trace levels of analyte is invaluable and not always achievable by other greener methods. More so, coupling mass spectrometry to separation platforms such as gas-chromatography (GC), liquid chromatography (LC), and capillary electrophoresis (CE) or inductively coupled plasma (ICP) enables the simultaneous detection and characterization of a wide range of analytes in very complex matrices. According to GAC principle 8, multianalyte and multiparameter methods can drastically lower the environmental impact of the chemical analysis since one analytical run is able to give information related to multiple target analytes. In light of this, the use of analytical instrumentation able to simultaneously detect multiple chemicals (e. g. mass spectrometry, ICP-AES) should always be preferred. Moreover, according to GAC principles 1, 3, and 5, the greenest option in terms of methods and instrumentation should involve direct, automated, and miniaturized analytical techniques. GAC principle 4 suggests that the integration of analytical processes also improves their greenness. An example could be microdevices that allow the coupling of multiple steps of chemical analysis [8].

Chemometric tools can also contribute to a reduction in the amount of energy needed, the reagents used, and the waste produced by analytical methods [9]. Initially used as a data processing strategy, chemometrics has now developed as an excellent green strategy to reduce the need for external calibrations and specific procedures to determine each of the properties or components of a sample [10]. Moreover, multivariate experimental design approaches such as Factorial Designs and Central Composite Designs enable the analyst to drastically reduce the number of experiments needed during the method development for optimization of various parameters, with the additional advantage of providing a more comprehensive view of the variables affecting the method performances and potential interactions between these factors [11].

7.1.2 Sample preparation in a “green” perspective

Among the various steps of the analytical method, sample preparation represents, without doubt, the bottleneck of the entire protocol. With the goal of extracting the analytes of interest from the matrix into a media compatible with injection into analytical instruments, significant amounts of organic solvents, energy, and laboratory consumables are usually employed, often affecting the greenness of the procedure. In light of this, many efforts have been made to improve the greenness of this critical step of any analytical method, promoting the development of numerous sample preparation techniques [12, 13].

According to GAC principle 1, sample preparation or sample pretreatment should be avoided in favor of direct analytical techniques. Although ideal, circumventing the sample preparation step is not always possible, especially when dealing with complex matrices that can cause interferences during instrumental analysis. From a green perspective, sample preparation should also adhere to GAC principle 2, by using a minimum amount of sample; principle 3, by allowing for portability and in situ measurements; principle 4, by integrating analytical procedures; principle 5, by allowing for on-line sampling and automation; principle 6, by being able to extract the analytes without need for derivatization (unless indispensable for instrumental analysis); principle 7, by minimizing, or better avoiding the production of laboratory waste at each extraction cycle; principle 9, by minimizing the amount of energy used for matrix treatment, purification, and extraction of the analytes; principle 10, by minimizing or avoiding the use of toxic solvents or materials; and principle 12, by ensuring the safety of the operator during sample preparation procedures.

Historically, the main disadvantages of conventional sample preparation procedures were related to the large use of organic solvents and the production of laboratory waste. However, since these factors also drastically affect the overall cost of the analysis and its throughput, many efforts have been made toward the development of alternative sample preparation technologies able to provide a more convenient workflow in many aspects, including compliance to GAC rules while still maintaining or improving the analytical performances for the method developed.

7.2 Evolution of sample preparation toward greener strategies

The most traditional methods for sample preparation and extraction, indicated by their use as reference or standards procedures for several decades – e. g. Soxhlet extraction, liquid–liquid extraction (LLE), and wet- and dry-ashing methods – are often time and energy-consuming, not automated, and require large amounts of solvents or strong acids. Thus, these methods are not in line with the basic principles of GAC. Considering that sample preparation/extraction has always been the most crucial step of analytical method development as well as the most polluting, many laboratories in the world are focusing their research efforts in greening sample preparation procedures according to the GAC principles [12, 14].

Initial attempts of greener sample preparation were ultrasound-assisted extraction (UAE), pressurized solvent extraction (PSE), microwave-assisted extraction (MAE), and supercritical fluid extraction (SFE). UAE uses the power of ultrasounds to provide a more efficient extraction in less time; however, it still requires high volumes of solvent to achieve exhaustive extraction and additional procedures to reduce the solvent injected into analytical instrumentation, in order to concentrate the analytes. MAE has the advantage of using microwaves and smaller solvent volumes for extraction. Due to the high temperatures (in the 50–200 °C range) and high pressures used for MAE, it is possible to use water as an extraction media instead of organic solvent, thus improving the greenness of the method. However, high consumption of energy is needed for the microwave reactor. PSE is the greener direct evolution of Soxhlet extraction, where the solvents are used near their supercritical region and at high temperatures to produce high diffusion rates of solutes in the solvent and the high pressure allows increased permeation of the solvent in the sample. PSE provides high extraction efficiency with relatively low solvent volumes (10–40 mL) and short extraction time (15–20 min). Similarly, SFE meets the requirements of GAC compared to traditional extraction methods since the extraction fluid is CO_2 in its supercritical state. Supercritical CO_2 can be considered as an ideal green solvent since it is non-flammable, non-toxic, abundant, renewable, easy to prepare, and does not produce waste. SFE still requires energy to maintain the temperature and pressure conditions to keep the CO_2 in supercritical conditions.

With the development of extraction procedures employing solid sorbents as extraction media, the amount of organic solvents employed has been drastically reduced, consequently providing greener sample preparation alternatives. Among others, Solid Phase Extraction (SPE) is certainly the most widely used sample preparation/extraction method for a broad range of applications that encompass food, environmental, and biological analayis [15]. Although the sorbent is a solid, the use of organic solvents is still needed to condition the SPE cartridge and for eluting the analytes of interest. However, the volumes needed are drastically minimized compared to other methods. SPE can also meet the requirements of GAC since it can be easily automated: on-line SPE constitutes a very convenient strategy that minimizes the sample volumes, the sample handling by the operator, and the overall analysis time. Although the consumption of solvents is drastically minimized, SPE cartridges have limited reusability, contributing to the production of laboratory waste.

Another sample preparation procedure quite widespread in environmental and food analysis is the Quick Easy Cheap Effective Rugged Safe (QuEChERS) [16], which is a dispersive approach especially suitable for complex samples. Although the method provides very clean extracts, high recovery, and is suitable for the simultaneous extraction of hundreds of analytes, the production of laboratory waste remains the main challenge in terms of its compliance with GAC principles. In a classical QuEChERS procedure, the first step involves the extraction of the sample with an organic solvent, typically acetonitrile, followed by the partitioning of two phases promoted by the addition of salt, with the supernatant being subsequently purified by Dispersive Solid Phase Extraction (DSPE). Usually, commercially available QuEChERS kits are extremely convenient for users since they provide a rapid solution for sample preparation needs, however, these kits are not reusable and the production of laboratory waste is noticeable. Nevertheless, many efforts are being made in the attempt to further miniaturize the QuEChERS strategy and enable its automation (even if partial).

Certainly, the miniaturization of the sample preparation/extraction strategies, such as miniaturized LLE and μ-SPE, is a convenient approach in reducing the amount of sample needed, the reagent consumption, and the production of laboratory waste [17, 18]. However, the development of microextraction techniques in the past two decades (fundamentally different from miniaturized exhaustive approaches) has played a critical role in the quest toward developing greener analytical methods [19]. The development of solid-phase microextraction (SPME) in 1989 by Pawliszyn [20], has drastically revolutionized the methodology of sample preparation and extraction, providing a convenient and green alternative to already existing methods. Moreover, SPME paved the way toward the development of various techniques able to fulfill several analytical needs while complying with most of the GAC principles. Microextraction methods are characterized by volumes of extractant substantially smaller (typically <100 μL or <100 mg) than the sample (>1 mL); this implies that at equilibrium, the extracted fraction of analyte is frequently negligible (or not exhaustive). Techniques such as dispersive liquid-liquid microextraction [21], single drop microextraction [22], hollow fiber liquid-phase microextraction [23], membrane-based microextraction [24], stir bar sorptive extraction [25], microextraction in packed syringes [26], and needle trap extraction [27] are only some of the microextraction techniques developed and successfully employed in past decades, all of which substantially reduce reagents consumption and laboratory waste. Similarly to microextraction approaches using micro volumes of extraction phase, another step toward ideal green sample preparation methods relies on the green and sustainable production/synthesis of solid or liquid sorbents. In this context, many research groups in the world have focused their efforts in developing and testing green extraction phases such as ionic liquids [28] and biopolymers [29], or refining synthetic procedures for the production of synthetic sorbents, such as metal-organic frameworks (MOFs) and nanoparticles [30].

7.3 Solid phase microextraction: a green and alternative tool for sample preparation

7.3.1 Principles, configurations, and compliance with the GAC principles

Solid Phase Microextraction is an equilibrium based, non-exhaustive extraction technique with the unique feature of merging sample preparation and extraction into a single and solventless step. Originally, SPME was mainly developed for the extraction of small organic molecules (<1000 Da generally); however, further developments of the technique and, in particular, of new extraction phase chemistries, enabled extraction of metal ions [31, 32] and small peptides [33] as well. In its original format, SPME is constituted of a layer of extraction phase coated on a fiber-like support with dimensions ranging from 5 to 150 mm length and 10 to 100 µm in diameter [34]. When the SPME fiber is exposed to the headspace (HS-SPME) or directly into the matrix of interest (direct immersion, DI-SPME) a partitioning equilibrium of the analyte between the matrix and extraction phase is established. This implies that the amount of analyte extracted by an SPME device from a matrix is time-dependent until equilibrium is reached [34]. When equilibrium is achieved between all the phases involved in the extraction process (e. g. sample matrix and extraction phase in the case of DI-SPME or sample matrix, headspace, and extraction phase in the case of HS-SPME), the amount of analyte extracted, n^{eq}, by the SPME device is directly correlated with the analyte's initial concentration in the sample C_s as shown in eq. (7.1):

$$n^{eq} = \frac{K_{es} V_e V_s}{K_{es} V_e + V_s} C_s \,, \tag{7.1}$$

where K_{es} is the distribution coefficient of the analyte between the matrix and extraction phase, V_e is the volume of the extraction phase, and V_s is the volume of the sample. Contrary to other extraction techniques defined as exhaustive (e. g. SPE), the absolute recovery $\mathrm{R_{abs}}$ for SPME (eq. (7.2)) does not reach values close to 100% due to the non-exhaustive nature of the microextraction process. A common misconception about SPME is that its non-exhaustive nature can prevent the achievement of quantitative analysis; however, as shown in eq. (7.1) and according to various calibration strategies developed and validated both for extraction under equilibrium and pre-equilibrium conditions [35], the technique is fully suitable for the quantitation of target molecules. More so, in cases when the volume of the sample is big enough that $V_s \gg K_{es} + V_s$, eq. (7.1) can be simplified to eq. (7.2)

$$n^{eq} = K_{es} V_e C_s \tag{7.2}$$

Equation (7.2) has important implications in the analytical point of view: the amount of analyte extracted at equilibrium by an SPME device becomes independent from the volume of the sample when the product of the extraction phase volume and the distribution coefficient of the analyte can be considered negligible compared to the sample volume. When this condition subsists, sampling by SPME becomes very convenient and enables quantitative on-site measurements (e. g. sampling lakes or air) or in-vivo determinations (e. g. in blood vessels) without the need of controlling or knowing the volume of the sampled matrix.

After extraction, the analytes extracted onto the SPME coating must be properly desorbed and transferred to the analytical instrument for analysis. Generally, the most common modes of desorption can be divided into two categories:

- Thermal Desorption (TD): The distribution coeffcient K_{es} that controls the partition equilibria of analytes between the sample matrix and the extraction phase coated on an SPME device, decreases in magnitude when the temperature of the coating increases. This phenomenon can be exploited to release the analytes from the SPME device to the analytical instrumentation. TD is the desorption mode of choice for the use of SPME with gas-chromatography (GC) [36]. After extraction, the fiber is exposed to the high temperatures of the GC injector and the analytes are consequently desorbed and transferred to the chromatographic column. An alternative method of performing TD on SPME devices is by exposure to the hot reactive plasma emitted by a DART (Direct Analysis in Real Time) ionization source prior to direct analysis by MS [37]. Generally, TD methods can be considered the greener option for SPME desorption since they are relatively quick (1 to 20 min), no use of solvent is involved, and no additional consumption of energy is needed compared to non-SPME methods using the same type of instrumentation.
- Solvent Desorption (SD): This desorption method consists of immersing the SPME device into a solution of organic solvents (and water when necessary) that have a stronger affinity for the analytes than the extraction phase. With the aid of vigorous agitation, the analytes will re-partition from the SPME device to the desorption solution, which can then be injected into analytical instrumentation (generally liquid-chromatography, LC). This method is less green than TD since small amounts of organic solvent are used, additional energy is required to provide the agitation, and desorption times are generally longer (15 to 90 min). However, with the development of new SPME-MS methods [38], SD has shifted toward greener strategies requiring only a few microliters of solvent (<20 µL) and a few seconds of desorption time.

The versatility of SPME also consists of the variety of geometries available to address many analytical needs not met by other sample preparation techniques (Figure 7.4). The first and most used SPME geometry to be developed to date is, without a doubt, the fiber SPME, which can be adapted for different assemblies suitable for gas-chromatography and LC. From the classical fiber geometry other devices were developed: Arrow SPME [39] to provide a more robust assembly for gas-chromatography with the ability to accommodate a higher amount of extraction phase, recessed SPME [40] for the convenient sampling of fish tissue, and many other miniaturized devices for analysis of small sample volumes [41] including

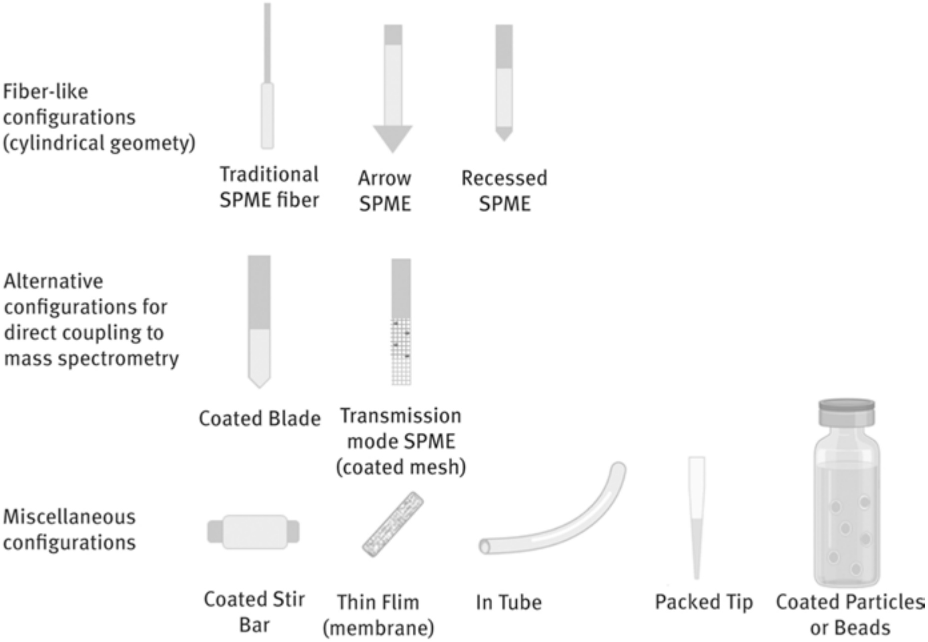

Figure 7.4: Most common configurations of SPME devices.

single cells [42]. SPME devices in fiber geometry can also be directly coupled to mass spectrometry for an even greener analytical approach that can provide both qualitative and quantitative results [38]. In recent years, two special configurations of SPME were designed *ad hoc* for convenient direct coupling to mass spectrometry: Coated Blade [43] for Coated Blade Spray-MS and Transmission-mode SPME [37] for DART-MS As an alternative configuration of SPME, TF-SPME has been widely used for residue analysis due to the high surface-to-volume ratio that is able to merge higher capacity and fast extraction kinetics [44, 45]. Other SPME configurations are summarized in Figure 7.4 and broadly described elsewhere [34].

Overall, SPME is a good example of a green sample preparation technique considering its features and mode of use. In Table 7.3, the 12 principles of GAC are listed together with the reasons why SPME fulfills them.

7.3.2 SPME applications in food, environmental and bio-clinical analysis, and greenness assessment

SPME has been widely used for food, environmental, and bio-clinical analysis, and several applications have been broadly reviewed [34, 38, 51, 54–56]. It is out of the scope of this report to describe the ever-growing number of SPME methods developed; however, an attentive comparison in terms of analytical performance,

Table 7.3: SPME compliance with the 12 GAC principles.

The 12 principles of Green Analytical Chemistry and SPME	
#1 Direct analytical techniques should be applied to avoid sample treatment.	SPME often does not require sample treatment of the matrices analyzed (e. g. centrifugation, filtration, etc.) especially after the development of matrix compatible coatings that are suitable for direct immersion in untreated complex matrices [46]. Direct coupling of SPME to mass spectrometry demonstrates ultrafast analysis throughput with the advantage of cleaner spectra provided by the capability of SPME to minimize extraction of matrix interferences [38].
#2 Minimal sample size and minimal number of samples are goals.	Due to the miniaturized geometry of SPME, small sample volumes down to 2 µL can be sampled and single-cell analysis is possible [47–49].
#3 In situ measurements should be performed.	SPME allows for on-site and in-vivo sampling with no need of transporting the sample to the laboratory [50, 51]. In addition, SPME is also compatible with portable analytical instrumentation [52, 53].
#4 Integration of analytical processes and operations saves energy and reduces the use of reagents.	SPME allows for simultaneous extraction and preconcentration of the analytes from a sample matrix by a single solventless step.
#5 Automated and miniaturized methods should be selected.	SPME can be easily automated by commercially available autosamplers both for gas- and liquid- chromatography. Moreover, automation of the entire extraction process is also possible offline by combining 96 SPME probes into a brush-like device compatible with 96 well plates.
#6 Derivatization should be avoided.	When necessary, on-fiber derivatization strategies can be developed to minimize the amount of derivatization agents used.
#7 Generation of a large volume of analytical waste should be avoided and proper management of analytical waste should be provided.	Minimal analytical waste is generated due to the minimized use of solvent and the reusability of the SPME devices.
#8 Multi-analyte or multi-parameter methods are preferred over methods using one analyte at a time.	SPME is suitable for selective analysis of a few target analytes, multiresidue analysis, and untargeted analysis. One SPME extraction can provide a chemical snapshot of the system investigated. Multivariate techniques can be used for simultaneous optimization of multiple parameters affecting the SPME extraction.
#9 The use of energy should be minimized.	SPME extraction requires minimum energy consumption for stirring and heating the samples and for the use of autosamplers.
#10 Reagents obtained from renewable sources should be preferred.	It is possible to obtain SPME sorbents from biopolymers or biomaterials available from renewable sources.

Table 7.3 (continued)

The 12 principles of Green Analytical Chemistry and SPME	
#11 Toxic reagents should be eliminated or replaced.	In general, SPME does not involve the use of toxic reagents.
#12 The safety of the operator should be increased.	SPME procedures are easy and safe for the operator.

workflow throughput, and greenness, is here provided for selected studies related to the three fields of investigation specified above.

The first case of study is an application of new matrix compatible SPME fibers for the determination of agrochemicals in untreated food samples by DI-SPME and its comparison with a QuEChERS method [57]. The SPME device used for this work was developed to overcome the challenges in DI-SPME related to using conventional SPME fibers with a rough coating surface. The roughness of the outer surface of conventional SPME devices can promote the occurrence of fouling when directly exposed to untreated complex matrices, resulting in a limited lifetime and instrumental contamination. The smooth outer morphology of the matrix compatible coating, namely PDMS/DVB/PDMS, drastically minimizes the occurrence of fouling and allows for a more effecting rinsing of the device when necessary [58, 59]. This feature also avoids the need for pre-treating the matrix prior to extraction (centrifugation, filtration, dilution, etc.), thus further greening the already convenient strategy for extraction and preconcentration of the analytes.

The method developed was suitable for multiresidue analysis of triazoles fungicides in strawberries and grape pulp by GC-ToF/MS. An attentive optimization has been performed on all the parameters that most influence the SPME procedure (pH, ionic strength, organic solvent content). A matrix-matched calibration protocol, using signal correction by isotopically labeled internal standards, was developed and validated for both the matrices tested. Afterward, the DI-SPME method performance was compared to the QuEChERS AOAC (Association of Official Analytical Chemists) Official Method 2007.01. Table 7.4 shows a general comparison between the two methods in terms of the number of analytical steps in the protocol, and the amount of sample and reagents used. Figure 7.5 shows the general workflow of the two methods.

This example shows how SPME represents a more convenient one-step extraction protocol compared to QuEChERS. As reported in Table 7.4, the QuEChERS method employs a larger amount of solvent and chemicals, includes multiple steps that require more analytical consumables to be used (centrifuge tubes, vials, salts, sorbents etc.), and cannot be easily automated, thus exposing the user to solvents and chemicals for a longer period of time.

In terms of method performances, SPME reached lower limits of quantitation (LODs) than the QuEChERS method for both grape analysis, ranging from 0.25 to

Table 7.4: Comparison of the analytical workflow and materials used in method QuEChERS AOAC official method 2007.01 and the DI-SPME method described in ref. [57].

	QuEChERS AOAC Official Method 2007.01	**DI-SPME Method**
Amount of sample per analysis	15 g	9 g
Amount of organic solvent used	15 ml of acetonitrile (1% formic acid)	5 µl of acetonitrile (for internal standards spiking)
Other chemicals used for extraction/purification	$MgSO_4$, sodium acetate, PSA	none
Other procedures	Shaking, vortexing (1 min × 2), centrifuging at 300 rpm (2 min × 2)	5 min incubation at 500 rpm and 50 °C, 15 min extraction at 500 rpm and 50 °C
Automation	no	yes
Injection into analytical instrumentation	1 µl of the final extract injected into the GC-MS at 260 °C	SPME fiber injected into the GC-MS injector for 5 min at 260 °C

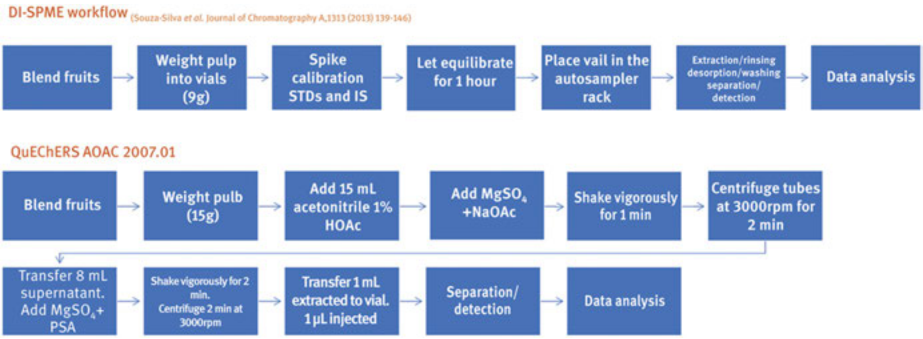

Figure 7.5: DI-SPME [57] and QuEChERS AOAC Official Method 2007.01 workflows.

5 µg/L for SPME and 50 µg/L for QuEChERS, and for strawberry analysis ranging from 0.5 to 5 µg/L for SPME and 50 µg/L for QuEChERS. Moreover, SPME provided cleaner chromatograms due to the removal of matrix interferences during the extraction process.

In terms of environmental analysis, Piri-Moghadam *et al.* developed and validated a multiresidue method for analysis of pesticides in environmental waters by TF-SPME-GC-MS [60]. The method was optimized and validated using two types of TF-SPME devices – DVB/PDMS self-supported and DVB-PDMS supported by a carbon fiber fabric – and its performances compared to the US EPA 8720 method based on LLE. The TF-

SPME did not involve the use of organic solvents except 60 µL of acetonitrile for spiking internal standards and only 30 mL of sample was used per analysis. The LLE method, on the other hand, employed 800 mL of sample per analysis that was sequentially extracted with aliquots of 50 mL of dichloromethane. After pH adjustments to acidic, basic, and neutral conditions, the extracts were combined and concentrated prior analysis into the GC-MS The greenness of the two methods was evaluated by the Eco-Scale assessment described earlier [4]. The LLE method collected over 40 penalty points mainly related to the use of a large amount of organic solvent and production of waste, while the TF-SPME method only collected 20 penalty points. In addition, superior analytical performances were obtained by the TF-SPME method as shown in Table 7.5.

Also, in the field of bioanalysis, the requirement for greener techniques has resulted in attempts to replace traditional LLE methods with alternatives that could guarantee minimum sampling handling, effective cleanup, and high-throughput. As an example, in whole blood analysis, LLE and SPE have been widely used even though

Table 7.5: Comparison of method detection limits for TF-SPME and LLE methods. Reproduced from ref [60], copyrights 2017, with permission from Elsevier.

Pesticides	**MDL (µg L^{-1})**		
	TFME (PDMS/ DVB membrane)	**TFME (PDMS-DVB-carbon mesh supported membrane)**	**LLE**
2,4-DCP	0.025	0.050	0.25
2,4,6-TCP	0.010	0.025	0.50
2,3,4,6-TeCP	0.010	0.01	0.50
Trifluralin	0.025	0.025	1.0
Bendiocarb	0.010	0.025	2.0
Phorate	0.10	0.10	0.50
Carbofurane	0.050	0.050	5.0
Simazine	0.075	0.075	1.0
Atrazine	0.075	0.025	0.50
PCP	0.050	0.025	0.50
Terbufos	0.10	0.10	0.50
Diazinon	0.025	0.025	1.0
Triallate	0.025	0.025	1.0
Metribuzine	0.050	0.075	5.0
Methyl parathion	0.25	0.25	1.0
Alachlor	0.025	0.025	0.50
Carbaryl	0.050	0.050	5.0
Prometryn	0.025	0.025	0.25
Malathion	0.25	0.25	5.0
Metalachlor	0.010	0.025	5.0
Chlorpyrifos	0.050	0.10	1.0
Cyanazine	0.050	0.050	1.0
Ethyl parathion	0.025	0.025	1.0

MDL: Method Detection Limit

both suffer from limitations that restrict their use for other applications, mainly due to the complexity of the whole blood matrix. SPME, on the other hand, was not widely used for analysis of blood until the advent of biocompatible coatings and convenient SPME device geometries [61, 62]. SPME also provides similar advantages for bio-clinical analysis in terms of the greenness of the sample preparation approach, as described above. In addition, SPME provides a significant advantage for the sampling of tissues as it allows for in-situ and in-vivo sampling due to the miniaturized geometry of the extraction probes. This translates into a significant advantage in terms of energy saving, especially related to transportation of biological fluids and tissue in refrigerated conditions prior to the analysis in order to preserve the integrity of the sample. Figure 7.6

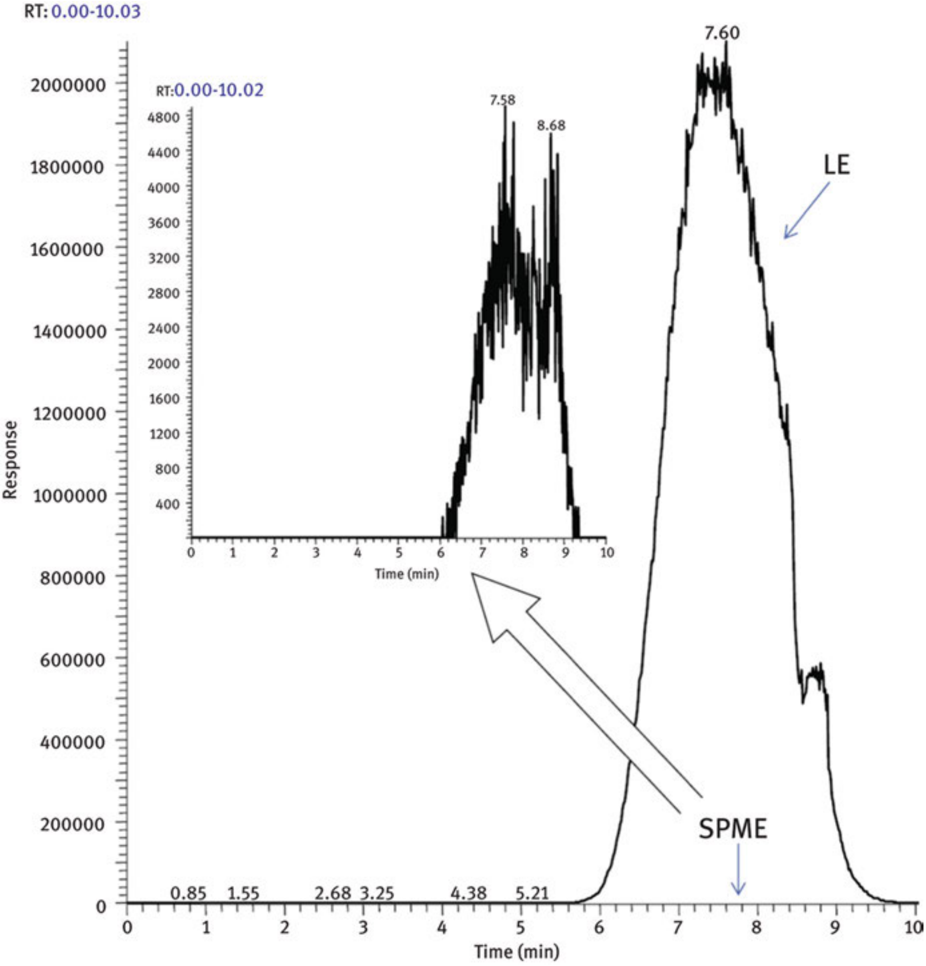

Figure 7.6: LC-MS (full scan) analyses of blank samples performed after extraction from lung using solvent extraction and fiber SPME (the background consists mainly of phospholipids). Reproduced from ref [19], copyrights 2015, with permission from Elsevier.

shows the advantage that SPME provides over LLE in terms of coextraction of interferences: biocompatible coatings ensure that no matrix components are carried with the SPME device, facilitating the elimination of matrix effects and drastically reducing the need for frequent instrument maintenance.

7.4 Conclusion and future perspectives

With the increasing concern for environmental pollution, analytical procedures must adapt and comply with standards aimed at the reduction of waste and toxic solvent use. Sample preparation and extraction procedures have often been classified as the least environmentally friendly stage of the entire analytical protocol, due to the large amount of solvents and the consumables needed to efficiently extract the analytes of interest and obtain clean extracts for injection into analytical instrumentation. Many efforts have been made with the purpose of greening sample preparation and certainly, the introduction of SPME had revolutionized sample preparation and extraction by compling with the principles of GAC. Since the introduction of the classical fiber geometry, SPME has evolved into various configurations able to satisfy different analytical needs and still drastically reduces the amount of waste produced compared to other techniques. Moreover, the use of biosorbents or materials synthesized by green protocols further reduces the impact of this technique on the environment. With the continuous development of new methods for laboratory analysis as well as in-vivo and on-site measurements, the use of SPME constitutes a convenient approach, as it is able to replace or complement most sample preparation techniques currently in use and provides a significant implementation of environmentally friendly practices into the analytical chemistry laboratory.

Dedication

This book chapter is dedicated to the bright memory of Prof. Giovanni Sindona, Professor of Chemistry at The University of Calabria (Italy), who inspired many to always look far, never give up, and get out of their comfort zones to achieve great things. He was a great scientist, a dedicated mentor, and a wonderful person that will be dearly missed.

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Stephanie Santos Díaz, Hazim Al-Zubaidi, Amir C. Ross-Obare
and Sherine O. Obare

8 Chemical reduction of chlorpyrifos driven by flavin mononucleotide functionalized titanium (IV) dioxide

Abstract: For many decades, organohalide and organophosphate compounds have shown significant detrimental impact on the environment. Consequently, strategies for their remediation continue to be an area of emerging need. The reduction of the chlorpyrifos pesticide, a molecule that bears both organohalide and organophosphate functional groups, is an important area of investigation due to it toxic nature. In this report, we demonstrate the effectiveness of the biological molecule, flavin mononucleotide (FMN) toward chemically reducing chlorpyrifos. The FMN was found to be highly active when anchored to nanocrystalline TiO_2 surfaces. The results show new directions toward the remediation of organic contaminants under mild reaction conditions.

Keywords: chlorpyrifos, pesticides, photoreduction, flavin mononucleotide, titanium dioxide nanoparticles

8.1 Introduction

Pesticides are chemicals widely used to maintain agricultural farms and can be classified by their function or purpose as herbicides, insecticides, rodenticides, bactericides, larvicides and fungicides. Pesticides can also be classified according to their chemical composition; examples include carbamates, organophosphates, pyrethroids, and nitrophenols [1]. Rapid population growth has led to the need to increase the production of agricultural products, which has consequently required the use of millions of tons of pesticides [2]. A large number of pesticides are considered to have harmful effects toward the ecosystem, especially the aquatic system (surface and ground water), as well human health by entering the food chain as a residue in agricultural products [3–5].

About 900 pesticides are commercially available [6]. Significant detrimental health impacts have occurred due to excessive human exposure to pestides. The most toxic pesticides are the organophosphates and the carbamates, which can cause severe poisoning [7]. Pesticides can be found in our houses, workplaces,

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schools, yards, and playgrounds. Lawn sprays and bug sprays are abundant sources for pesticides in our homes. Furthermore, inhalation and skin contact are the most common ways to be exposed to pesticides [8, 9].

Chlorpyrifos, Figure 8.1, can be classified as an organohalide and an organophosphate pesticide and can be hazardous to human health if exposed to it in significant amounts. This pesticide can enter the body by skin contact, inhalation or ingestion. Once it is inside the body, chlorpyrifos targets acetylcholinesterase, the enzyme responsible for acetylcholine breakdown [10]. The pesticide binds to the enzyme and inactivates it, resulting in acetylcholine accumulation at nerve ends. This causes an excessive transmission of nerve impulses that can eventually lead to death [11]. The effect that chlorpyrifos has on the nervous system of organisms makes it one of the the world's leading pesticides [12].

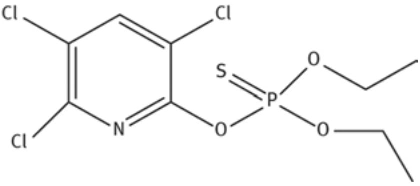


Figure 8.1: Chemical structure for chlorpyrifos.

Studies have shown that less than 5% of the sprayed pesticide reaches the target [13, 14], and the rest remains in the environment. Researchers around the world have detected chlorpyrifos in different ecosystems [15–18], which is why the pesticide's degradation pathway needs to be studied. Several techniques have been developed for chlorpyrifos breakdown, for example, the use of microorganisms [19–21], nanoparticles [22] and photocatalysis [23, 24]. These techniques have mutual disadvantages that its effectiveness depends on pesticide concentration, pH, and temperature – factors that cannot be controlled when the method is applied practically. Another potential concern is that after the degradation, the obtained products include 3,4,6-trichloro-2-pyridinol (TCP), which is more toxic than the parent compound.

Bootharaju et al. [22] found that gold (Au) and silver (Ag) nanoparticles (NPs) attached to alumina surfaces were effective in the degradation of chlorpyrifos. The attachment of the nanoparticles to the alumina surface allowed recyclability of the nanoparticles. The results showed that an optimal solution pH is needed for effective degradation; consequently it was found that a high pH caused NP instability, while low pH resulted in a decrease in the rate of chlorpyrifos degradation [22].

Lu et al. [25] reported a study of the degradation of chlorpyrifos by a bacterial strain [25]. The study showed that *strain DT-1* was able to degrade chlorpyrifos and its breakdown products was TCP and diethylthiophosphate. Even though TCP has antimicrobial characteristics, *Cupriavidus sp. DT-1* used the products as a carbon source, allowing it to grow. The concentration of every substance plays an important role in the outcome of this technique. The investigators reported that the increased concentration of TCP led to growth in the DT-1strain, which consequently resulted in the reduction in the rate of degradation of TCP. Thus, during a 16 hr timeframe, 43.4% of 80 mg/L TCP was degraded. Comparatively, at a TCP concentration of 100 mg/L, the growth was inhibited by 1.2% during the same timeframe. Briceño et al. [21] used actinobacteria to study the degradation of chlorpyrifos. In this study, *Streptomyces sp. AC5* and *Streptomyces sp. AC7* were used and it was found that chlorpyrifos degradation occurred and led to accumulation of organic acids, consequently decreasing the medium's pH [21].

The literature shows that there is a wide range of microorganisms and strains that can degrade chlorpyrifos [19] at different environments, and the degradation processes are influenced by various parameterts including concentration, temperature, and pH.

Other researchers have developed pesticide degradation techniques based redox processes, some of which involve the use of TiO_2 catalysts. [23–27]. For example, Ismail et al. [23] used TiO_2 NPs in the presence of gamma irradiation, yielding reactive oxygen species [23]. Furthermore, they studied the effect of H_2O_2 addition, and found that it enhanced the degradation of chlorpryrifos because it produced an increased amount of reactive oxygen species in the form of hydroxyl radicals. Affam et al. [24] also investigated the effect of H_2O_2, by adding it to TiO_2 during a photocatalytic reaction [24]. The authors reported that the addition of H_2O_2 resulted in increased efficiency toward the degradation process. A smilar process was used by Rao et al. [28] toward the degradation of the pesticide simazine [28].

Here, we aim to develop a green process to degrade chlorpyrifos using FMN and FMN functionalized on the surface of TiO_2. A previous project carried out in our labs showed how FMN, when functionalized on the surface of TiO_2, effectively led to the degradation of organohalides [29]. The rationale for using FMN in this study, is its biocompatability and that it is an environmental friendly molecule.

In this work, TiO_2 NPs were synthetized and characterized, followed by the attachment of FMN molecules to the NP surface. Photoirradiation of FMN, in the presence and absence of TiO_2, led to photoreduced products and their effect on chlorpyrifos reduction was investigated.

8.2 Experimental section

8.2.1 Materials and methods

The following chemicals were used for the experiments: riboflavin 5'-phosphate sodium salt (flavin mononucleotide or FMN; ~ 85%, HPLC grade), titanium (IV) isopropoxide [$Ti(iOPr)_4$; 97%], methanol (MeOH; ≥ 99.9%, HPLC grade), and chlorpyrifos (Pestanal, Analytical Standard). All were purchased from Sigma Aldrich Chemical Company and each was used as received. Quartz cuvettes with a 1 cm path length were used as the cell for all optical measurements.

8.2.2 Preparation of TiO_2 nanoparticles and functionalization with FMN

The TiO_2 nanocrystalline was synthesized by the hydrolysis of (2.49 mmol, 0.74 mL) titanium (IV) isopropoxide [$Ti(iOPr)_4$], (4.37 mmol, 0.25 mL) acetic acid in 49 mL of ethanol. The solutions were mixed and stirred for 2 h. A scanning electron microscope (SEM) was used to image the TiO_2 nanoparticles, showing that they are nanocrystalline. FMN was attached to the surface of TiO_2 nanoparticles by mixing TiO_2 solution with FMN in MeOH solution. Absorption spectra, measured with a Cary 50 UV–visible absorbance spectrophotometer, were obtained to ensure the functionalization.

8.2.3 Monitoring reactivity of $FMNH_2$ toward chlorpyrifos

The reaction took place in the absence of oxygen. To accomplish these conditions, the solution was purged with nitrogen gas. The solution of FMN@TiO_2 was irradiated using 1000-W Xe lamp with a KV 370 cut-off filter. The irradiation times were approximately 30 minutes for all samples. All absorption spectra were acquired on a Cary 50 UV–visible spectrophotometer. The diluted chlorpyrifos was added using a syringe.

8.3 Results and discussion

8.3.1 Photoreduction of FMN to $FMNH_2$ and its reactivity toward chlorpyrifos

The reduction of FMN was examined in both water and in methanol. The reduction process was mediated by photolysis. UV–visible absorbance spectroscopy was used to characterize FMN in solution before and after the irradiation process. The resulting spectrum will show characteristic peaks at different wavelengths for each substance. In aqueous solution, FMN peaks were observed at 375 and 445 nm. (Figure 8.2) The molar absorptivity for the peak at 375 nm is 12,188 ± 1000 and for the peak at 445 nm, 14,168 ± 800. The photolysis product is FMNH•, with absorbance at 400 nm and 345 nm.

In methanol (MeOH) solution, the FMN peaks were at 355 nm and 445 nm (Figure 8.3). The molar absorptivity for the 355 nm peak was 11,701 ± 4510 and for the one at 445 nm, 13,667 ± 4110. Once the solution undergoes photolysis, FMN peaks disappear and a new one belonging to $FMNH_2$ appears at 320 nm. All the characteristic peaks are consistent with literature reports [30].

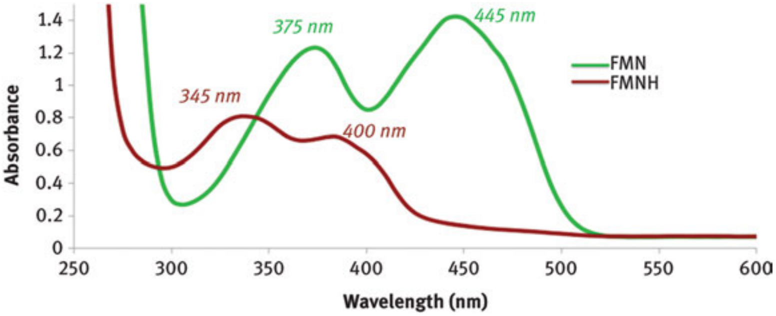


Figure 8.2: UV–visible absorbance spectrum: FMN and FMNH• in H_2O.

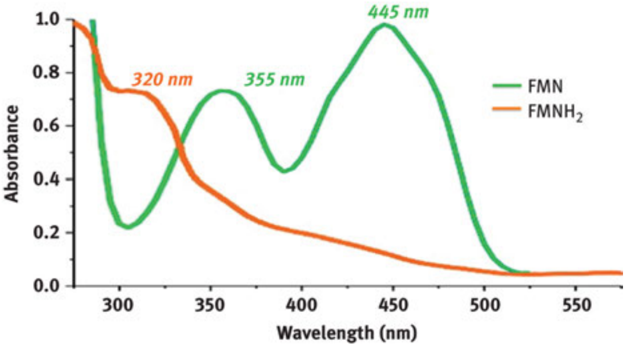


Figure 8.3: UV–visible absorbance spectrum: FMN and $FMNH_2$ in methanol.

FMN was reduced to FMNH• following a one-electron reduction process. Further reduction of FMNH• led to the production of $FMNH_2$, as shown in Figure 8.4.

The photolysis of FMN in solution resulted in the formation of FMNH•. Upon the addition of chlorpyrifos, no significant change in absorbance was observed (Figure 8.5). The results showed that FMNH• is not a strong enough of a reducing agent for chlorpyrifos. Further photolysis of FMN did not lead to formation of $FMNH_2$, thus it was decided to attached the molecule to the TiO_2 surface via the phosphonic acid functional group, to allow TiO_2 conduction band electrons to catalyze the reduction of FMN to $FMNH_2$ [31].

8.3.2 Photoreduction of FMN @ TiO_2 nanoparticles and its catalytic reactivity with chlorpyrifos

Once the FMN is bound to TiO_2 nanoparticles, a series of redox (reduction/oxidation) reactions are expected (Figure 8.6). The photoirradiation process resulted in electron-hole separation, leading to electrons accumulating in the conduction

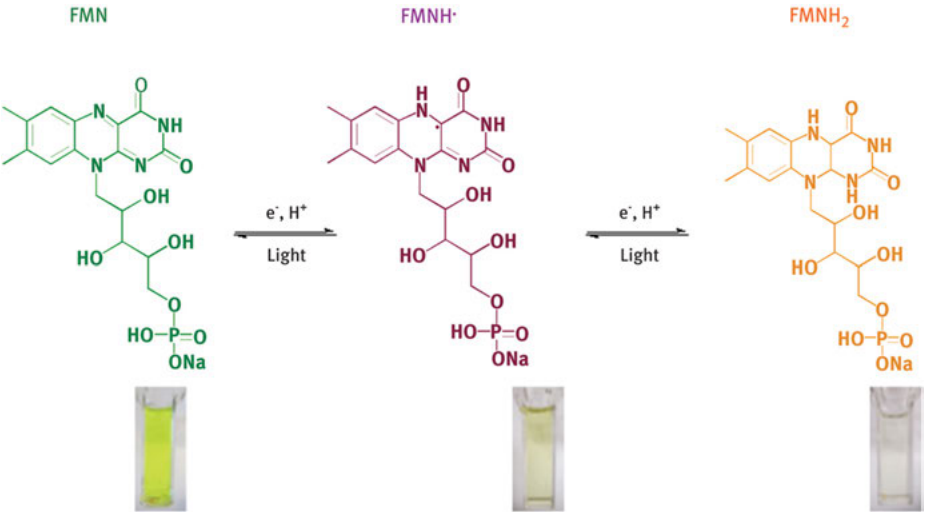


Figure 8.4: FMN redox states. The different products can be achieved by photolysis in different solvents.

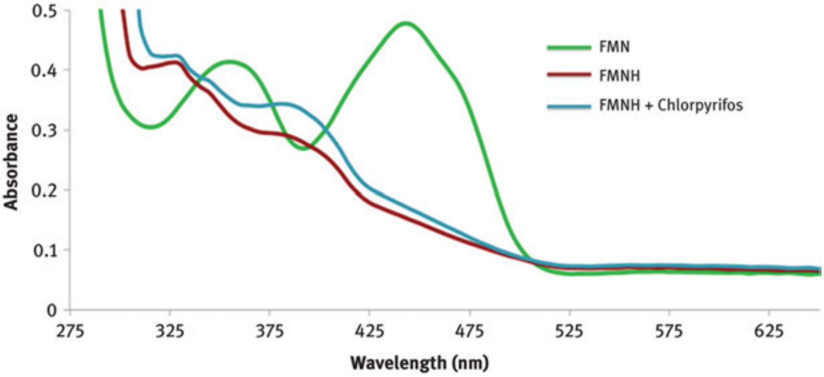
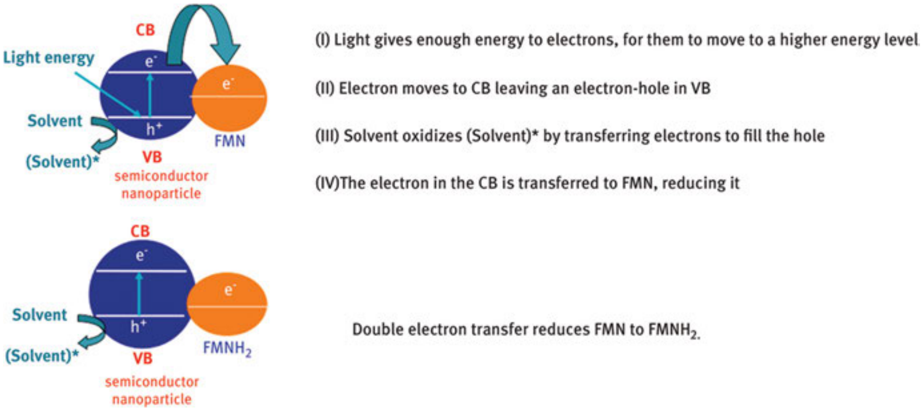


Figure 8.5: UV–visible absorbance spectrum: Addition of chlorpyrifos to reduced FMN methanol.

band (CB), while the holes remained in the valence band (VB) of TiO_2. The electron led to further reduction of FMN to $FMNH_2$.

A previous project [29] used FMN attached to TiO_2 thin films; however, in this work the TiO_2 NPs were used in colloidal for, resulting in an increased surface area of the NPs, and consequently the catalysts surface area. Figure 8.7 shows a scanning electron microscope (SEM) image of the TiO_2 nanoparticles

TiO_2 photolysis was performed to confirm electron-hole separation. Both absorbance at 650 nm and the blue color of the solution are signs that electrons are



(I) Light gives enough energy to electrons, for them to move to a higher energy level

(II) Electron moves to CB leaving an electron-hole in VB

(III) Solvent oxidizes (Solvent)* by transferring electrons to fill the hole

(IV)The electron in the CB is transferred to FMN, reducing it

Double electron transfer reduces FMN to $FMNH_2$.

Figure 8.6: Electron transfer mechanism between TiO_2 and FMN.

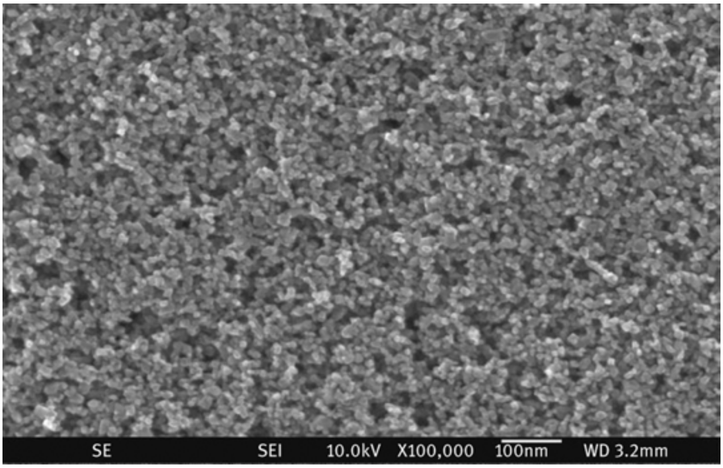


Figure 8.7: SEM image of TiO_2 nanoparticles.

accumulating at TiO_2 conduction band. (Figure 8.8) The color change is due to the absorbance at 650 nm [32].

Figure 8.9 shown the absorbance spectra of FMN functionalized on colloidal TiO_2 NPs. Upon photoreduction of the FMN/TiO_2 we observed the disappearance of the peak at 445 nm that is characteristic of FMN indicating the reduction to $FMNH_2$. Addition of an aliquot of chlorpyrifos to the $FMNH_2$/TiO_2 solution led to the appearance of the peak at 445 nm that is characteristic of FMN, thus indicating that chlorpyrifos oxidized $FMNH_2$ to FMN and in turn was reduced during this process.

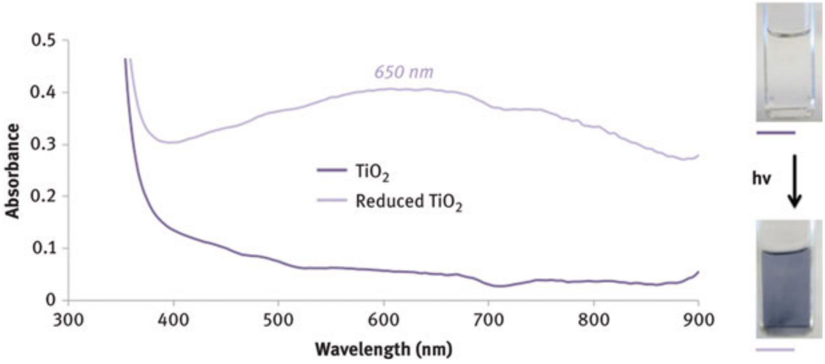


Figure 8.8: UV–visible absorbance spectrum of TiO_2 before and after reduction.

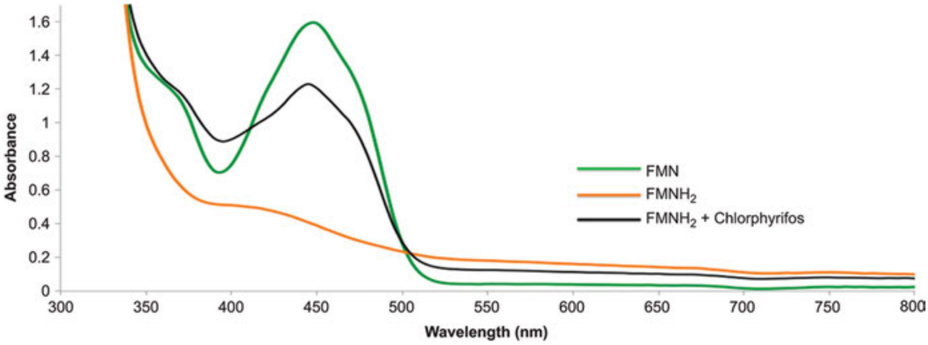
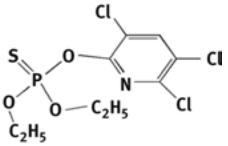
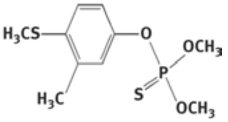
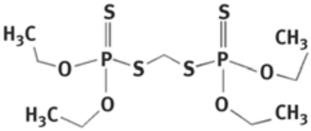
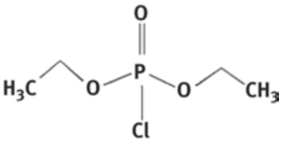


Figure 8.9: UV–visible absorbance spectrum: addition of chlorpyrifos to reduced FMN@TiO_2 in methanol.

8.3.3 Monitoring reactivity of $FMNH_2$ towards chlorpyrifos

In order to obtain a rate constant (k) for chlorpyrifos' reduction, kinetic measurements were investigated. For this reaction, absorbance versus time profiles were obtained and plotted using: ln (A/A_o) vs. time (s), to obtain k_{obs} (s^{-1}) and k_{obs} (s^{-1}) vs. chlorpyrifos concentration (M), to obtain k ($M^{-1}s^{-1}$). The rate constant for chlorpyrifos reduction is $0.427 \pm 0.007\ M^{-1}s^{-1}$. When compared to the rate constant for other organophosphate compounds [33], chlorpyrifos' is relatively low. Chlorpyrifos is both an organohalide and organophosphate (Table 8.1), both being sites apt for reduction to occur.

Table 8.1: The organophosphorus pesticides with their reduction rate constant.

OP compound	**$FMNH_2/TiO_2$ (e^-) $_{(MeOH)}$ ($M^{-1}\ s^{-1}$)**	**Molecular structure**
Chlorpyrifos	0.427 ± 0.007	
Fenthion	2.1 ± 0.1	
Ethion	4.5 ± 0.1	
DCP	12.6 ± 0.1	

DCP = diethylchlorophosphate

8.4 Conclusions

Developing materials that are reactive toward toxic pesticides is an important process for both chemistry as well as future agricultural applications. The increased use of chemicals being introduced into the environment necessitates scientists and engineers to adopt pathways that allow their elimination, although other researchers continue to find alternate strategies to avoid the use of pesticides all-together. In the work described herein, we showed that FMN and $FMNH^\bullet$ are not strong enough as reductants to react with chlorpyrifos. However, when reduced to their two-electron two-proton counterpart, $FMNH_2$, the reduction of chlorpyrifos was observed. The advantage of using $FMNH_2$ is that it is a natural compound that is environmentally friendly. We anticipate that as more is understood about the role of $FMNH_2$ in the environment, it will find new use toward the remediation of various contaminants.

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