

III. GREEN CHEMISTRY LITERATURE REVIEW

A. Introduction

Green Chemistry is a term that describes the incorporation of P2 principles into scientific and engineering methodology utilized to design and synthesize chemicals. It is concerned with minimizing or eliminating the potential adverse impacts on health and the environment posed by the production or processing of industrial and consumer chemical products. The goal of green chemistry is to integrate the traditional industrial concerns of feedstock costs, optimization of yield, and energy burden with P2 theory and practice (1, 23).

Although the term “green chemistry” is used significantly in the literature, it is fairly non-descriptive and can impart a wide range of connotations¹. A more appropriate descriptor of P2 efforts in chemistry is *inherently safer chemistry* (ISC) because it implies a comparison between two chemicals or aspects of two chemical processes. An inherent attribute of a chemical or reaction is one which is a permanent and inseparable quality. It follows that inherently safer chemicals or reaction pathways are “safer” because of essential characteristics which are a part of their basic nature (24, 25).

The principles of ISC, which evolved from safety applications in the manufacturing sector, have been an underlying aspect of on-going chemistry research projects (1, 24, 25). Past examples include work in chiral catalysis pertaining to the development of stereo-selective reaction schemes. For many years chemists have been actively researching reactions that produce desired enantiomers from otherwise racemic mixtures, eliminating production of unwanted reaction co-products. Additional work in general catalysis and solid state chemistry has resulted in the development of alternatives which reduced the environmental burden posed by their traditional counterparts (1).

Modifications in the design, synthesis, transportation, and use of chemicals result in safer production and use conditions, as well as reduced environmental and health impacts (26, 27). The most effective modifications occur early in the design process and result in the greatest P2 value for the overall chemical life

¹The term *benign by design* (BBD) is also utilized in the literature to describe efforts to design chemicals or chemically-based manufacturing processes that are more environmentally favorable than those in current use (1, 23). BBD can, however, be interpreted to imply that a chemical or chemical reaction is harmless; that is, does not have potential environmental or human health impacts. In most instances this would be an incorrect assumption. This term is recognized, but is not used in this document.

cycle. Between 50% and 85% of the final cost of the product or process is committed during chemical design stages (24, 25). An equal amount of the environmental and human health impacts may also be defined during design and development stages (24, 25). In the spirit of P2, ISC principles provide chemists with strategic design options for modifying aspects of chemicals and reaction pathways to achieve specified environmental, health, economic, regulatory, and performance criteria. These options, which include the use of alternative chemical feedstocks, alternative chemical design, and alternative reaction conditions, mimic desired reaction characteristics and chemical functions (27). The following section summarizes innovative chemical science research related to ISC.

B. Alternative Chemical Synthesis

Alternative chemical synthesis refers to reactions that are selected, as an alternative to a current pathway, because they reduce potential negative environmental and health impacts (26). The utilization of reaction inputs which minimize or eliminate the use of hazardous substances will reduce the overall health and environmental risks associated with chemical synthetic pathways (1). One such strategy is to use fewer or no hazardous substances in a chemical reaction (24, 25). It is more desirable to avoid use of all hazardous chemicals where possible in synthetic pathway. This option will minimize and/or eliminate environmental and health impacts associated with a particular chemical reaction altogether.

The development of biological feedstocks to replace petroleum-based chemicals is an important part of alternative chemical synthesis research. The application of biotechnology to produce commodity chemicals has its roots in the pharmaceutical industry (28). It is estimated that approximately 540 million pounds of organic chemicals can be produced by bioconversion (28). Currently at least 95% of all organic chemicals are derived from raw or refined petroleum feedstocks in the United States (28). Crude petroleum is extracted from the earth in a reduced state. It therefore must undergo a high degree of oxidation, or refining, in order to distill it into functional chemical components (1, 28). These extraction and processing activities are plagued by pronounced ecological impacts (1, 10, 28). In addition, many of the feedstock chemicals derived from petroleum, such as benzene, are quite harmful to environment and health when utilized in chemical production processes (10, 28). Benzene itself is a integral

part of many manufacturing processes, with over 12 billion pounds produced in 1993 (1). Thus, finding alternatives to many petrol-chemical feedstocks is an important aspect of ISC research.

Biological chemical feedstocks are desirable alternative to petroleum-based chemicals because they constitute use of renewable resources and do not necessarily require significant processing (1, 28). Potentially viable feedstock alternatives for commodity and specialty chemicals are D-glucose and other lower sugars. Biomass feedstocks for glucose and other lower sugar polymers include starches (corn, wheat, sorghum, potatoes) and ligno-cellulosics (agricultural and forestry wastes, dedicated woody and herbaceous plants) (29). Since most of earth's biomass is in the form of ligno-cellulosics, current research focuses on using conversion of cellulose into glucose using microbes and other biological systems (28, 29).

The U.S. Department of Energy's Alternative Feedstocks Program is a consortium of five DOE laboratories which promote cost-effective industrial utilization of renewable biomass feedstocks in the manufacture of high-volume chemicals (28). This program is making progress in the development of alternatives for succinic acid production through fermentation of glucose feedstocks (28).

Frost and Draths are working with microbial biocatalysts (*Esecherichia coli*) to foster the production of adipic acid, a chemical intermediate of Nylon-6, 6, from D-glucose feedstocks (30). Their production methodology eliminates the need for benzene feedstocks for phenol production, extreme reaction conditions (250°C; 800 psi), and production of NO_x by-products. Over two million tons of adipic acid is currently produced from benzene feedstocks (30). This massive-scale of production is estimated to account for 10% of the annual increase in atmospheric nitrous oxide levels in the United States (28, 30).

Glasser and others are researching the viability of using cellulose fiber as a feedstock for reinforced plastics. The superior solubility and thermoplasticity of lignin makes it an appropriate use for engineering various plastics. In addition, cellulose fiber is a useful precursor for engineering plastics by cross linking (29).

The already highly oxidized state of many proposed biological feedstocks and the utilization of biological enzymes for catalyzed conversions allows many such reactions to occur under relatively mild temperatures and pressures (30). In addition to research in alternative biological feedstocks, many chemists are focusing on designing pathways using traditional methods in alternative ways to avoid particularly hazardous chemicals. Stern has developed a process that

avoids the use of chlorinated aromatics in the production of aromatic amines. This process entails the direct amination of nitro-benzene via nucleophilic aromatic substitution of hydrogen (31). Chapman reports successful replacement of benzene with mixed xylenes in the production of styrene in a single, high-temperature step (32).

A number of academic and commercial research projects are pursuing the development of an alternative to the use of toxic phosgene gas with carbon dioxide (1, 33). Currently over 2 billion pounds of phosgene is produced and utilized by chemical manufacturers each year (33). Gargulak and Gladfelter have developed a catalytic process for carbonylation of nitroaromatic compounds which avoids the traditional use of phosgene. This process can be utilized potentially in the manufacture of isocyanates (polyurethane feedstocks) and polycarbonates (33). In addition, Monsanto Chemical Company has developed a “dehydrating” agent (*O*-sulfobenzoic acid anhydride) for the highly selective conversion of amines and carbon dioxide into their corresponding amines. This dehydrating agent allows the company to avoid a previously utilized phosgenation reaction (27).

A second area of research in alternative reaction conditions is the use of innovative biological and non-biological catalysts. Improved catalytic efficiency results in decreased energy consumption, increased feedstock conversion, greater selectivity and yield, and reduced production of reaction residuals (47). Applicable reaction catalysts are simultaneously precise, efficacious, and environmentally safe (48). This allows use of less reactive (hazardous) feedstocks and milder processing conditions, reduces product purification steps, and produces fewer non-desirable reaction co-products (49). The expense associated with these complex catalysts is offset by the cost avoidance associated with their beneficial properties (49).

Simmons reports application of transition metal, metal oxide, and chiral metal complexes as potential alternative catalysis (47). Kraus is researching the application of photochemical catalysis in production of Friedel-Crafts acylation products. This reaction avoids traditional use of corrosive and air-sensitive acid chlorides, Lewis acids (i.e., aluminum chloride, stannic chloride, titanium tetrachloride), and solvents (i.e., nitrobenzene, carbon disulfide, carbon tetrachloride, methylene chloride) (50). Hendershot reports the use of clay-supported metal ions to replace Lewis acid catalysts, such as aluminum chloride, for Friedel-Crafts reactions (24, 25). Epling and Wang are combining the use of organic dye catalysts and visible

light to thermodynamically drive the oxidation of dithianes, benzyl ethers, and oxathianes. The underlying electron transfer mechanism of this reaction is analogous to one utilized by green plants to selectively oxidize water and reduce carbon dioxide during photosynthesis (51). Other catalysts are being developed to reduce the vapor pressure of volatile materials. For example, polystyrene sulfonic acid is a replacement for sulfuric acid catalysts in the production of methyl t-butyl ether (MTBE) from methanol and isobutene (24, 25).

Research in the use of zeolite catalysts focuses on their role as a host matrix in chemical reactions. These catalysts increase the efficiency of reactions by immobilizing reactants in their matrix structure (39, 47). Frei is experimenting with the use of an aluminosilicate zeolite in conjunction with red light to oxidize hydrocarbons at room temperature (48). Titanium silicalite-1 is another zeolite-based catalyst which activates hydrocarbons with aqueous peroxide. It has the advantage of shape selectivity, ease of recovery, separation of products, and catalyst regeneration. This catalyst system is being considered for commercial processes, such as epoxidation of olefins and production of catechol and hydroquinone and possibly Nylon-6 (48). Zeolite catalysts are also a potential replacement for highly caustic super-acids (hydrofluoric and sulfuric acids), super-bases, gasoline alkylation and olefin oxidation technology, and combustion technology (48, 49).

A growing area of catalysis research is the utilization of biological hosts to catalyze the production of specialty and commodity chemicals. Entire living organisms, such as microbes, and single gene-producing enzymes derived from microbial organisms are utilized in this capacity (28). Researchers use recombinant DNA techniques to clone and manipulate gene encoding enzymes in organism (28). Table 3 contains a number of examples of microbial biocatalysts and their resulting chemical products (28). Of note is the previously mentioned research of Draths and Frost who are using *E. coli* biocatalysts and glucose feedstocks for the synthesis of adipic acid (30).

TABLE 3: Microbial Catalytic Agents Utilized in Biochemical Manufacturing of Chemicals (28)

<u>MICROBE</u>	<u>UTILIZATION</u>
<i>Trichoderma reesei</i>	produce ethanol from cellulose through fermentation
<i>E. coli</i>	biocatalyst to convert glucose into chemicals
<i>Klebsiella pneumoniae</i>	enzymes to convert DHS to catechol used to produce vanillin, L-dopa, epinephrine, norepinephrine, and adipic acid (production nylon-6, 6).
<i>E. coli</i>	utilize DNA fragments isolated from <i>Klebsiella pneumoniae</i> to produce propanediol, acrolein, quinic acid
<i>E. coli</i> <i>Klebsiella oxytoca</i> <i>Erwinia sp.</i>	Use both glucose and hemicellulose 5-C sugars derived from ligno-cellulose for ethanol production
<i>Anaerobiospirillum succiniproducens</i>	synthesize succinic acid from glucose fermentation for industrial-scale production of commodity chemicals (succinate esters and derivatives—green solvents, 1,4 butanediol, tetrahydrofuran, biodegradable polyesters, maleic anhydride, gamma-butyrolactone)
<i>Lactobacillus</i>	Produce high yield of lactic acid used in food, chemical, and pharmaceutical engineering; intermediate for oxygenate chemicals, “green” solvents, and polyacetic acid (used in medical devices and biodegradable plastic)

Biomimetic catalysts mimic the action of biological systems to transfer or insert atoms into organic molecules under mild reactions conditions. Current research includes development of metalloporphyrin oxidation catalysts to mimic cytochrome P-450 system. Future applications include insertion of metal and metal complexes in organic syntheses to prevent leaching of reaction residuals (47). Phase transfer catalysts (PTC) promote chemical reactions between compounds which are mutually immiscible. They are being applied to polymer reactions, aromatic substitutions, dehydrohalogenations, oxidations, and alkylations of sugars and carbohydrates. PTCs provide industrial processes with increased rates of reaction, higher reaction specificity, lower energy requirements, and lower costs (47).

Enzyme catalysts are desirable for the synthesis of bioactive molecules as a result of their regio-selectivity, chemo-selectivity, and stereo-selectivity (47).

Similarly, antibody catalysts are desirable for their specificity and selectivity, derived from the structure of antigens in biological immune systems (47). The drawbacks associated with utilizing enzyme catalysts for manufacturing process are their high cost, instability at higher reaction temperatures ($>250^{\circ}\text{C}$), and problems with regeneration (47).

Another area of research in alternative reaction conditions category is the use of laser light in regulating chemical reactions. Intricately choreographed laser light pulses, tuned to specific frequencies, are being used to control the vibration of molecular bonds. Researchers hope to gain the ability to selectively weaken specific molecular bonds, thereby encouraging them to break more readily than intrinsically weaker ones. In this capacity, laser light may be used to micro-manage chemical reactions, chaperoning reactants along unnatural pathways through alteration of normal wave patterns and molecular motion (52).

C. Alternative Chemical Design

Alternative chemical design is the manipulation of molecular structure, functional groups, and stereochemistry to maintain desired chemical properties and use efficacy, while eliminating undesirable properties (26, 27). Isosteric replacement is the concept of modifying chemicals through the replacement of single atoms or entire functional groups with alternatives that have similar size, shape and electro-magnetic properties (1). The concept behind isosteric replacement is to eliminate one or more undesirable feature found in a material while retaining the desirable properties (34). Sieburth and others are researching isosteric replacement of carbon with silicon to enhance the degradation potential and other safety features of chemical pesticides (34).

Another application of isosteric replacement is the use of masked synthons to facilitate chemical transformations given unfavorable reactions conditions. Chemical equivalents are used to replace dangerous or toxic parent functional groups in chemical intermediates, promoting safer storage and use. DuPont's just-in-time (JIT) production process for methyl isocyanate (MIC) utilizes both masked synthons and improved catalytic oxidative-dehydrogenation to produce this agrochemical feedstock. This process allows production and conversion of MIC to the final agricultural chemical product in situ, eliminating the need for storage of large inventories of this highly toxic chemical (1, 24, 25).

Retrometabolic analysis is the utilization of known metabolic pathways to design chemicals which are more easily metabolized to excretable products (23).

Chemists in the pharmaceutical industry first applied this concept to redesigning of drugs whose metabolites caused adverse side-effects. Much of the current research focuses on determining the degradation potential and non-target effects of chemical pesticides (23). Similarly, retro-toxicological analyses are utilized to understand the metabolic transformations which give chemicals their hazardous chemical and physical characteristics. Information on the biochemical toxicity of a parent compound and its metabolites is used to redesign compounds in ways that eliminate toxicity and preserve desired functional characteristics (23). There is the potential for widespread use of these and other alternative chemical design techniques throughout the chemical industry.

The EPA and a number of researchers are currently focusing on the development of computer-aided chemical design software which incorporates environmental considerations into their design logic (15). Past efforts to develop computer software that facilitates the design of synthetic transformations did not include environmental and health criteria (35). Software under current development incorporates existing chemical and functional group properties, toxicity data, structure/activity relationships, and molecular composition to generate retroactive and proactive analyses. Milne, Wang, and Fung provide an evaluation of several predictive software packages for reagent and product toxicity, including TOPCAT, ADAPT, SIMCA, CASE, COMPACT, DEREK, HAZARDALERT, and ONCOLOGIC (35). Pharmaceutical and producers of consumer chemical products look at this technology as a potential replacement for expensive acute and chronic animal toxicity testing. However, toxicologists find the accuracy of many of software programs to be inconsistent and limited to simple molecular structures (36).

The SYNGEN program, unlike those previously mentioned, is a synthesis design program which generates the shortest synthetic pathway for a given target molecule from a catalogue of commercially available organic feedstocks (37). The inherent benefit of this software is its ability to prioritize alternative chemical pathways in terms of both cost and environmental impacts. ASPEN PLUS is a recently developed software program that estimates the molecular composition of reaction outputs (residuals, co-products, products) given the composition of process inputs and approximate knowledge of reaction conditions (temperature, pressure) and use of catalysts (38). Programs similar to SYNGEN and ASPEN PLUS may be applied by commercial, regulatory, and

educational purposes, to sensitize practitioners to the potential environmental impacts of alternative synthetic pathways of target molecules (39).

Scientists at the University of York in England are using computer virtual reality technology to assist in protein modeling research. Future applications of this work include predicting interactions between pharmaceutical molecules and molecular protein targets (40). This technology may also be applied to molecular manufacturing systems, or nanotechnology, for industrial scale production of chemicals and manufactured products. Nanotechnology relies on direct mechanical control of the trajectory of individual reactive molecules, allowing “construction” of chemicals one molecule at a time. Theoretically, such control enables precision in chemical processes, leading to greater synthetic efficiency and productivity, high product quality, low resource consumption, and avoidance of occupational and environmental emissions (40, 41, 42, 43).

D. Alternative Reaction Conditions

Alternative reaction conditions refer to changes in chemical production processes that reduce adverse environmental and health impacts and optimize reaction efficiency (24, 25, 26). This category of ISC includes use of replacements for volatile organic solvents, laser chemistry, and cascade chemistry.

Super critical fluids (SCF) are emerging as a replacement reaction media for volatile organic solvents. Fluids (gases and liquids) reach their critical level when they are heated and pressurized past the point where the gas and liquid phases merge into an indistinguishable phase (44). SCFs, such as super critical carbon dioxide (SC-CO₂), mimic the inherent properties of solvents in terms of their dielectric constant, polarity, solubility parameter, viscosity, and density (44). Adjustments in these properties are potentially achieved by “tuning” the fluids temperatures and pressure over its supercritical range. Researchers hope to utilize SCFs to control phase behavior, separation processes, reaction kinetics, and reaction selectivity (44).

Past applications of SCF technology include extraction processes (hops, oils, vitamins), decaffination of coffee beans, cleaning solvents, and analytical methodologies (1, 24, 25). Super critical carbon dioxide is utilized as a solvent in polymerization reactions (45) and catalytic transformations (46). Tanko and others are utilizing SC-CO₂ as a solvent for free radical brominations, resulting in reaction yield, time, and selectivities analogous to those observed with conventional organic solvents (i.e., CCl₄, CFCs, and benzene) (44). Hendershot notes that the

dangerously high reaction temperatures and pressure of supercritical technology present a trade-off when considering the replacement of volatile organic solvents (24, 25).

Aqueous-based, solid state, and neat reactions (solvent-less) are also favorable alternatives because they decrease worker inhalation exposures and potential ambient emissions (1). Aqueous-based reaction systems utilize water for conducting synthetic transformations. Neat reactions do not use solvents, thereby eliminating the need for post-reaction solvent recycling and management of reaction residuals. In addition to not producing spent solvents, the component chemicals of solid state reactions are characterized by low vapor pressures, decreasing worker inhalation exposure during production and use (1).

A final area of research in alternative reaction conditions is the use of cascade chemistry. Each reaction step of these multi-stage reactions creates the necessary conditions to trigger subsequent steps in the desired reaction pathway. Once the first reaction is initiated subsequent ones flow into one another like a series of waterfalls (53). All reactants are heated together in the same reaction vessel until the process is complete. Cascade chemical syntheses can be attained using relatively mild reaction conditions (25° C, atmospheric pressure) and relatively harmless solvents (i.e., water, alcohols, and acetone). However, heavy metal catalysts are still required for most cascade reactions under these conditions (53).