

Innovations and Green Chemistry



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As we look across the field of Green Chemistry since its emergence as a cohesive field of study beginning with the development of environmentally friendly processes in the early 1990s,¹ it is possible to identify certain trends where much research has focused and where significant advances have been made. Certainly the area of environmentally benign solvents has been one of the leading research areas of Green Chemistry with great advances seen in aqueous (biphase) catalysis^{2,3} and the use of supercritical fluids⁴ in chemical reactions. While the greenness of ionic liquids^{5,6} and fluorous media⁷ will ultimately depend on their individual properties with respect to health and the environment, the sustainability of new biobased solvents⁸ has to be proven as well. There has been a renewed focus on the age-old pursuit of the organic chemist to design and successfully apply the ideal synthesis in terms of efficiency, with atom^{9–11} and step economy¹¹ being a major goal. New catalytic processes continue to emerge to advance the goals of Green Chemistry, while techniques such as microwave^{12–14} and ultrasonic synthesis¹⁵ as well as in situ spectroscopic methods^{16–17} have been used extensively, leading to spectacular results. These research areas are a glimpse of some



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of the many topics directly relevant to Green Chemistry being pursued by researchers around the world.

With all of the research successes realized in Green Chemistry over the past 15 years, it is necessary to recognize and understand that the field is in a nascent stage and that some of the most important research questions within it are only now beginning to be identified and pursued. As a research community, it is important to accelerate the pursuit of these research areas by clearly enunciating the great research challenges, the great scientific unknowns within the field of Green Chemistry. Only through this exercise will the top institutions, the major funding agencies, and the primary industrial users of these innovations understand the power and potential of Green Chemistry research discoveries and be willing to provide the support and funding needed to see this field reach its potential.

The current portfolio of feedstocks that are used today as the basis of the chemical enterprise is likely to be shifting, perhaps dramatically over the coming decades, for reasons related to supply, performance, economics, public pressures, and government policies.^{8,18–27} The shift toward a more diverse feedstock base is an important future research area in Green Chemistry. While useful breakthroughs have been made in demonstrating how to use biobased materials such

as sugars and starches for basic chemical building blocks, it is an important realization that if the scientific innovations are going to be able to be translated to the realm of economic viability and societal benefit, these feedstocks will have to be accessed in a way that does not compete with land and agricultural resources for food and feed production. This likely means that important research challenge for Green Chemistry will be accessing the biobased building blocks through the utilization of agricultural waste products. This can only be met by systematically exploiting the vast biofeedstocks which Nature graciously provides us, through broad-scale basic research toward the development of efficient, environmentally benign, and economical process methodologies for the large-scale conversion of biomass (carbohydrates, proteins, fats, terpenoids) into industrially viable products, such as bulk and intermediate chemicals, pharmaceuticals, and polymeric organic materials. In this endeavor, national and supranational funding institutions will have to play an active role, not only by funding corresponding activities in a broad time frame (5–10 years) but also by elaborating a concise long-term strategy that takes root in academia and the chemical industry. The basic strategy should be directed not only at the generation of the very same basic chemicals that are well accessible from petrochemical sources but also toward the development of products with analogous industrial application profiles, with as little alteration of the structural framework of the components of the biomass as possible.

The largest material produced in the world every year by volume is ligno-cellulose (typically containing 40–50 wt % cellulose, 25 wt % hemi-cellulose, and 25 wt % lignin), which provides strength to trees and plants. There are research groups currently striving to take on the important challenge of how to convert ligno-cellulose into a form that can be exploited as a fundamental building block in a wide range of transformations. This is a necessary characteristic to be a genuine foundation for the broad scope of products in the chemical enterprise. In order for this challenge to be met, others in the chemistry, biochemistry, and molecular and materials science communities must engage along with the current leading Green Chemistry researchers in pursuing this central challenge. New catalysts, new enzymes, new processing systems, and new plant hybrids may all be part of the future solutions to the use of biobased building blocks that will be built on the Green Chemistry research starting to be engaged today. Only through this research can we achieve the benefits of the plentiful, renewable feedstocks available in ways that take advantage of their intrinsic value. This includes outstanding complexity, as witnessed by the high degree of chirality that could and should be exploited and the biodegradability that allows the materials to remain within the carbon cycle on a human time scale rather than a geologic time scale.

Alternative feedstocks will not be limited to plant-based sources; rather, they will necessarily include a diverse set of cheap, available, benign materials. One of the largely untapped sources for chemical building blocks is found as waste in our economy and society today. Another of the largest materials produced in the world is chitin, the substance making up (among other things) the exoskeleton of shellfish. The quantities of chitin unused and disposed of as waste are vast and need to be appropriately exploited.²⁸ While a small number of leaders in the Green Chemistry field have demonstrated the potential of using substances

such as chitin,²⁹ it is again the case that it represents only a fraction of what is possible and necessary to redesign our current portfolio of building blocks of the chemical enterprise. The utilization of perhaps the world's greatest waste product, carbon dioxide, is also a key research area for the future.³⁰ The excellent work on using carbon dioxide in such applications as the basis for new polymers or as a drilling aid by a number of groups thus far has provided a glimpse of what is possible. However, in order for the utilization of carbon dioxide to truly have an impact, it will need to be incorporated on a vastly larger scale in such applications as building materials, road surfaces, and synthetic soils. Basic insight into the development of thermodynamically uphill catalytic systems will likely be needed to deal with the energy balance of carbon in a high oxidation state to make it a useful starting material.

The synthetic methods that we use to transform our starting materials will need to be the focus of basic research in Green Chemistry, since those methods that are still widely used are lacking both in terms of material and energy efficiency as well as in terms of the consequences of the reagents being used for humans and the environment. As we as a chemistry community have sought to impart greater reactivity on our reagents and substrates in order to reduce reaction times and energy requirements, the correlation between reactivity and toxicity³¹ has often not been incorporated into the design of our synthetic methodologies. The insights by leading Green Chemistry researchers today take advantage of understanding biological transformations that impart reactivity both spatially and temporally through the use of geometric contortion of a reaction sight. The generation of catalysts able to carry out these type of transformations will mean being able to essentially use very unreactive substrates and reagents while achieving the selectivity, low energy, and rapid reaction times desired without the use of substances as hazardous to humans and the environment. Currently, the depth of understanding of being able to design these systems based on first principles does not exist and should be considered by top catalyst researchers as a challenge for future research.

With the successes that catalysts have brought to the chemical enterprise over the course of the past 40 to 50 years,³² we have yet to meet the challenge of designing multifunctional catalysts that are capable of carrying out transformations at more than one site with selectivity. Green catalysis particularly could have a key role in maximizing atom efficiency and process simplicity in the manufacture of fine, specialty, and pharmaceutical chemicals and materials. In the area of homogeneous catalysis, the integration of single site catalysis with facile catalyst separation and recycling should be the primary focus of future research activities.³³ The design of novel catalysts with preferential solubility in green solvents could result in commercially attractive catalytic systems. The effective utilization of enzymes in novel chemical transformations should be another important objective of green catalyst development.³⁴ The application of the fundamental understanding of the mechanisms of enzymatic reactions in the design of biomimetic analogues could lead to new and effective catalytic systems.³⁵ The development of single site heterogeneous catalysts (e.g., uniform site selectivity and activity)³⁶ could be another approach to secure sustainable/green industrial catalysts. The incorporation of molecular level shape selectivity in all classes of catalysts could open the way to substrate selective conversion of complex materials including oil-based and/or

renewable raw materials. Since most of the chemicals that contain chiral centers could interact with our environment, the application and/or design and synthesis of chiral catalysts should also be included. Finally, the development of novel catalytic materials, addressing the engineering and commercialization issues, should also be incorporated.

During the course of two centuries of synthetic chemistry, one of the great achievements, perhaps of human history, is the mastery of the covalent bond to the point where it can be said with considerable confidence that synthetic chemists are capable of making virtually any small molecule that can be drawn. This cannot be said of the mastery of weak bonds. There have been great advances in the understanding of weak bond interactions in explaining the performance of certain molecules and materials.³⁷ There has also been excellent science conducted that explains particular synthetic interactions through the understanding of weak bond interactions in the transition states of certain reactions as well as in the reactant–solvent system. For example, hydrogen bonds in aqueous systems could be a key designer tool to achieve high selectivity at economical reaction rates.² Tuning the attractive interactions between aromatic rings in substrate(s) and chiral catalyst(s) or reagent(s) could be a key part of a green process development. This foundation allows us to realize that we are at the beginnings of meeting the great research challenge of being able to use weak forces as a design tool for imparting new properties and performance in molecules and materials and creating new synthetic methods and pathways. Again, leading groups are providing a glimpse of the potential of this research challenge if successfully engaged.

On the other end of the spectrum, we recognize the challenge of being able to manipulate strong bonds in a relatively facile manner. The ability to directly derivatize carbon–fluorine bonds, as an example, is a great challenge.³⁸ An ongoing challenge that a number of researchers are undertaking includes the ability to eliminate substitution reactions through the application of direct derivatization of an otherwise unactivated carbon–hydrogen bond.³⁹ The consequences for successful research in this area for the goals of Green Chemistry are potentially dramatic from the point of view of minimizing waste, energy, and hazard.

The role of energy in the chemical enterprise is of course multifaceted. One aspect includes every step of a chemical process at the industrial level that requires an energy input either for intrinsic or operational performance. The other aspect includes the fact the chemistry creates the materials and systems needed to generate, store, and transport the energy required by our economy and our society. A central goal of Green Chemistry is not only to ensure that energy efficiency is ingrained from the molecular level and through our products, processes, and systems, but also to ensure that the nature of that energy is sustainable to both humans and the biosphere. In order to achieve these goals, fundamental research is needed on several important areas. The design of chemical transformations that minimize energy input has long been recognized as an important goal for primarily economic reasons and needs to continue, likewise with the tremendously energy intensive area of separations. The distillation operations alone in the U.S. consume more than twice the energy than is used by the entirety of the nation of Switzerland on an annual basis. Designing systems of separation that minimize energy consumption will be increasingly important as a Green Chemistry goal.

Alternative energy systems that meet the needs of the current generation while ensuring the ability of future generations to meet their needs is one of the great challenges of our time and a central Green Chemistry research challenge. If discussions of alternative energy futures are to be realized, whether based on solar energy, biofuels, sustainably produced hydrogen, or other alternatives and combinations of the above, the materials that will be required for these systems will be designed by chemists who need to ensure that the new materials do not introduce unacceptable problems of toxicity, persistence, bioaccumulation, and depletion of finite resources as they seek to solve our immediate energy issues. The understanding that we are immersed in a sea of renewable energy needs to be engrained. Our future energy approaches should be focused on the capture and conversion of these existing energy reservoirs rather than the so-called generation of energy from combustion-based depletion of finite sources and should be recognized as central to our Green Chemistry research challenges.

The solvents that currently remain the basis of our chemical operations are still largely organic, contain various health and environmental concerns, are derived from petroleum, and are driving much of our solution chemistry and separation issues. While there have been very notable Green Chemistry successes over the years beginning to address these issues, there is much fundamental research to be conducted. The development of solvents that not only accomplish heat and mass transfer but also simultaneously catalyze transformations and result in product separation so as to drive the chemical equilibrium is still largely a distant goal that requires fundamental research. Smart solvents that sense certain conditions, such as heat, and are designed to respond accordingly have been demonstrated and should be developed. So-called obedient solvents that change basic physical and chemical properties as a response to an imparted stimulus have also been demonstrated.^{40,41} Discovering the new applications for ancient solvent systems such as water⁴² will continue to be an important area of investigation for Green Chemistry researchers. There are major opportunities to extend the use of water as a solvent for organic reactions, both at ambient and elevated temperatures. It should be important to demonstrate the viability of both commercial and technical processes based on fluoruous and ionic liquids as well as supercritical fluids. Key questions include reaction modeling, scale-up rules, and reactor engineering. At the same time, there is a need for increased understanding on a molecular level of reactions in these media and how, if at all, the reaction mechanisms differ from those in more conventional media. The most challenging problem with supercritical CO₂ is to develop chemistries which will allow CO₂ to be used as both solvent and feedstock for the generation of higher value chemicals. There is also a need to develop “greener” organic solvents, which can be derived from renewable feedstocks or can be designed at the molecular level to have reduced environmental impact.

The potential environmental and health hazards of both industrial chemicals and chemical based consumer products should be treated as intrinsic properties and should be minimized during design. First of all, the molecular level understanding of the relationship between structure and toxicity of chemicals is the only approach to design less or ideally nontoxic products. While decreasing the intrinsic toxicity of chemical based consumer products should be the primary focus, understanding the toxicity of secondary

degradation products generated after their use should also be considered.

In the design of target molecules, materials, composites, and formulations, there is a tremendous amount of basic research yet to be done. With the tremendous advances that have been made in understanding the relationship between molecular structure and biological activity as it relates to drug discovery,^{43,44} there is a great deal to build on for Green Chemistry purposes. Currently, there is not a systematic way to design our molecules in a way so as to ensure that the molecular structure and the derived physical chemical properties do not facilitate adverse consequence in the body or the biosphere. Basic research on known mechanisms of toxic action (and the elucidation of as yet unknown mechanisms) is central to the ability of future synthetic chemists to design safer chemicals. The range of afflictions ranging from cancer to endocrine disruption⁴⁵ to coral bleaching can be minimized as we achieve the fundamental molecular level understanding of the basis of hazard. This complex challenge for Green Chemistry may only be possible with the collaboration of other disciplines such as toxicology and ecosystem biologists. As an example, the molecular-level understanding of hazard currently does not begin to address the impacts of synergistic chemicals that have a multiplicative biological consequence when in the presence of their complementary chemicals. Basic research in collaboration with other disciplines will be needed to develop the beginnings of heuristic design rules for safer chemicals to be used by chemical designers. Even the simplest of these challenges—to target molecular design to minimize the ability of a chemical to cross biological interfaces and manifest hazard—is something generally not incorporated into a design protocol, with the important exception of the pharmaceutical industry.

Another approach to increase the sustainability of both industrial chemicals and chemical based consumer products is the minimization of materials needed to achieve the same performance. Therefore, the fundamental understanding of achieving the same or better product performance with less material (e.g., thinner polymers, higher biological activity, better stability, etc.) should be developed.

The development of recyclable chemical based consumer products could significantly reduce the use of virgin raw materials in the chemical and allied industries and lower the amount waste generated. The key challenge in this area is to develop a molecular level understanding of the relationship between the structure and the recyclability of the product without compromising the performance of the product. For example, the introduction of molecular functionalities (or switches) that would be resting during the normal use of the product but could be turned on during the recycling processes is an attractive approach for consideration.

If the development of recyclable chemical based consumer products is limited by the intrinsic nature of the chemical used, the replacement of components of the products that are persistent with biodegradable chemicals should be preferred. While the intrinsic biodegradability of chemical based consumer products should be the primary focus, understanding the biodegradability of secondary degradation products generated after their use should also be considered.

During the use phase of a chemical, it should be recognized that certain substances are designed to be toxic and cause adverse consequence to a living thing, such as a pest being the target of a pesticide. While some advances are being made in this area, much fundamental research is needed to

ensure that the mechanism of action of the chemical is targeted to a specific biological pathway unique to the pest, thereby reducing the chance of putting other living systems at risk. In addition, it will be necessary to design molecules such that they exist and retain structural integrity only as long as is necessary to accomplish their purpose. For example, research is needed to ensure that after a pesticide, pharmaceutical, or antibiotic performs its desired function, it will be able to degrade into innocuous products rather than persist, bioaccumulate, and biomagnify after its useful time has passed.

The prevention of accidents involving chemicals has traditionally been considered as an engineering issue. The accidental potentials of chemicals can alternatively be approached using molecular engineering by selecting inherently safer chemicals and reaction types during the design of green processes.

One of the greatest challenges is the last one percent! Today's scientific and technological establishment (or professors and managers) gives high rewards to those that discover and develop new chemical reactions or processes with high yields, mostly between 95 and 99%. While achieving "100%" or an enzyme-like performance is remarkably difficult, no rewards are given to those who get the last 1%.

Finally, the success of Green Chemistry ultimately depends on the practicing chemists who will use the same brilliance and creativity that is the long tradition of chemistry and use it with the new perspective for transformative innovations for sustainability.

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