

# - THE CHEMICAL ELEMENT -

## Chapter 6. The Greening of Chemistry

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### 1. Introduction: Green Chemistry

#### 1.1. The history of Green Chemistry

Several Green Chemistry concepts and manufactures, as well as, green research fields were already investigated and utilised before the term Green Chemistry came into use. This is because chemists have always pursued the aim to be at the service of humanity with idea of improving the lifestyle of humankind. An emblematic example is the Solvay process for the production of  $\text{Na}_2\text{CO}_3$ .

Leblanc process came to dominate alkali production in the early 1800s and consisted of the reaction of salt, limestone, sulphuric acid, and coal to produce soda ash (sodium carbonate).

However, the expense of its reagents and its polluting by-products (HCl) called for the development of new processes. Thus, in 1860s Ernest and Albert Solvay developed a new process. The ingredients used for this process were readily available, inexpensive and *green*: salt brine (NaCl) and limestone ( $\text{CaCO}_3$  from mines) to produce soda ash and as by-product calcium chloride ( $\text{CaCl}_2$ ) in aqueous solution. An important key point to be mentioned is that the reaction between NaCl and  $\text{CaCO}_3$  does not occur directly as it needs a series of steps involving at least five reactions and six chemical intermediates:  $\text{NH}_3$ ,  $\text{NH}_4\text{Cl}$ ,  $\text{CaO}$ ,  $\text{Ca}(\text{OH})_2$ ,  $\text{CO}_2$ , and  $\text{NaHCO}_3$ . The Solvay process is very efficient mainly because the intermediates are all reclaimed and reused.

More recently, but still prior to the exploitation of Green Chemistry, there were other poignant examples of sustainability in chemistry:

- *Alkyl polyglycosides for the synthesis of fatty alcohols.* Fatty alcohols can be obtained either from petrochemical sources (synthetic fatty alcohols) or from natural renewable resources such as fats and oils. They have several applications as surfactants in hard surface cleaners and laundry detergents. Since the 1980s, the production of alkyl polyglycosides has relied completely on sugars: renewable raw materials. The research and development work in this field led to the solving of chemical, performance, and technical problems related to the use of renewable materials. As a result, alkyl polyglycosides became available in industrial quantities (Cognis industries) and a multitude of patents, scientific papers and articles appeared in specialist scientific journals.
- *Phase-transfer catalysis as a green approach to waste minimization in chemical industry (I).* This key synthetic methodology was developed in the 1970s and it makes use of heterogeneous two-phase systems i.e. water and organic solvent. Importantly it is applied and applicable to a great variety of reactions (for more details see the paragraph on use of alternative solvents – water) and it is a good example of the transfer of know-how from academia to industry.
- *Chlorofluorocarbon (CFC) substitution.* Paul J. Crutzen, Mario J. Molina and F. Sherwood Rowland, conducted investigations on the ozone layer depletion for which they were jointly award the Nobel Prize for Chemistry in 1995. Their work ultimately led to the substitution of chlorofluorocarbons. A CFC is an organic compound that contains only carbon, chlorine, and fluorine, commonly known by the DuPont trade name Freon. Many CFCs have been widely used as refrigerants, propellants (in aerosol applications), and solvents, the most common being dichlorodifluoromethane (Freon-12). However, since the late 1970s, the use of CFCs has been heavily regulated after Crutzen, Molina and Sherwood Rowland reported on their destructive effects on the ozone layer (due to the presence of chlorine in these molecules). The manufacture of such compounds has been phased out by the Montreal Protocol (1987). Work on alternatives for chlorofluorocarbons led to the use of hydrochlorofluorocarbons (HCFCs) which are less stable in the lower atmosphere, enabling them to break down before reaching the ozone layer. More recently alternatives lacking the chlorine, the hydrofluorocarbons (HFCs) have demonstrated an even shorter lifetimes in the lower atmosphere. Along with ammonia and carbon dioxide, hydrocarbons have negligible environmental impacts and are also used worldwide in domestic and commercial refrigeration applications, and are becoming available in new split system air conditioners.

The first seeds of Green Chemistry were sown in the early 1960s when environmental statutes and regulations began to proliferate at an exponential rate especially after the publication of the book *Silent Spring* published by Rachel Carson, which stimulated widespread public concerns with respect to pesticides and pollution of the environment (2). These regulations established restrictions on the use of chemicals, imposed toxicity tests of chemical substances and finally provided incentives for industry to eventually find replacements, substitutes, or alternatives for polluting reagents. So, the public's demand for more information about chemicals had grown rapidly (2). In the United States, this culminated with the establishment of the Emergency Planning and Community Right-to-Know Act (EPCRA), which made public relevant data on chemicals being released to the air, water, and land by industry (1980) (3). As a consequence, industry was confronted by tremendous pressure, not only to reduce the release of toxic chemicals into the environment, but also to reduce the use of hazardous chemicals overall. Each of these incentives has combined to make the 1990s the decade during which green chemistry was introduced and it has found implementation and commercialization on a wide industrial scale. In particular, since 1990 in the USA, sustainable chemistry has been a focus area by the Environmental Protection Agency (EPA) (4), involving a great deal of activity in research, symposia, and education. At same time, the scientific community was also strongly involved in exploiting sustainable chemistry. In 1993 P. T. Anastas and C.A. Farris published the first book of the ACS Symposium series: "Benign by Design, Alternative Synthetic Design for Pollution Prevention" (5). The book was based on the symposium "Physical Chemistry and the Environment" sponsored by the Division of Environmental Chemistry at the 206<sup>th</sup> National Meeting of the American Chemical Society in Chicago (22-27 August 1993, Illinois). The book provided a great opportunity for several chemists who were pioneers in the field of "benign by design" chemistry to present their basic research in addition to encouraging many scientists to become involved in environmentally responsible chemistry (6). In the same year in Italy (1993), the Consorzio Interuniversitario Nazionale "La Chimica per l'Ambiente", INCA was established, with the aim to unite the academic groups concerned with chemistry and the environment (7). One of its focus areas being pollution prevention through research for cleaner reactions, products and processes with both academia and industrial applications (Figure 1). Besides, INCA remains constantly involved in the dissemination of Green Chemistry as demonstrated by the numerous books published (Green Chemistry Series) (8), school awards for undergraduate students (9), publication of a magazine for young green chemists (10) and the organization of ten editions of the Summer School in Green Chemistry (Figure 2) (11).



**Figure 1.** Picture representing the chemistry at the service of the environment (picture taken from the cover of “Introduzione alla Chimica Verde (Green Chemistry) ”eds P. Tundo, S. Paganelli - Lara Clemenza. In Italian) (8).

Despite the continued involvement of the industrial and scientific community in the field of sustainable chemistry, it was only between 1996 and 1997 that the term green chemistry was first used. Other terms have been proposed, such as “chemistry for the environment” but this combination of words does not capture the economic and social implications of the concept of sustainability. Herein the term Green Chemistry will be used according to the IUPAC definition (International Union of Pure and Applied Chemistry) that states: “Green Chemistry includes the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances” (12). This definition well represents the importance of fundamental research as a base for Green Chemistry development.



**Figure 2.** Tenth Edition of the Summer school on Green chemistry Organized by INCA (Cà Dolfin, Cà Foscari University, Venezia, 2008)

In this context, Paul Anastas (EPA), and John C. Warner developed the twelve principles of Green Chemistry (13), which illustrate the definition of this new field in a practical and easy to understand sense. The principles cover the main concepts of the Green Chemistry that are still valid today: 1) *prevention*, 2) *atom economy*, 3) *hazard-free chemical syntheses*, 4) *safer chemicals* and 5) *solvents*, 6) *energy efficiency*, 7) *renewable feedstocks*, 8) *reduce derivatives*, 9) *catalysis*, 10) *degradation*, 11) *pollution prevention* and 12) *inherently safer chemistry* (14).

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#### Blue Box 1

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#### - An Outstanding Father Figure of the Green Chemistry -



Joseph Breen - born in Waterbury, Connecticut in 1942, dedicated his entire life to public service: he served in the Marine Corps during the Vietnam War, he then moved into the Peace Corps, and finally he spent 20 years at the U.S. Environmental Protection Agency.

Joe Breen played a major role in creating the “Design for the Environment” and “Green Chemistry” Programs. Both these programs were funded with the intent to reduce risk and protect human health and the environment. After 20 years at the EPA, he retired in 1997 and co-founded (and served as Executive Director of) the Green Chemistry Institute (GCI), a nonprofit organization in Rockville dedicated to research and education on environmentally friendly chemical synthesis and processing. The GCI promoted Green Chemistry through information and dissemination; research and fellowships; participation in conferences, workshops and symposia; international outreach; awards and recognition; and education. The Green Chemistry Institute now operates as an independent institute within the American Chemical Society. The GCI also provides national recognition for outstanding student contributions to furthering the goals of green chemistry. The most famous awards, in fact, are the ones established in memory of Kenneth G. Hancock and Joseph Breen (died in 1999) (15).

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In August 1996 International Union of Pure and Applied Chemistry (IUPAC) (16) began its involvement in the Green Chemistry field by the foundation of the Working Party on Synthetic Pathways and Processes in Green Chemistry (17). In September 1997 the First International Conference on “Challenging Perspectives on Green Chemistry” was held in Venice (Figure 3) (18). Since then IUPAC has been actively involved in several projects related to Green Chemistry (19).

In July 2001, IUPAC approved the establishment of the sub-Committee on Green Chemistry (Division III). The committee's primary focus is to establish and carry out educational Green Chemistry programs. Since its conception, the subcommittee has actively organized international workshops, symposia and conferences, in addition to the preparation and dissemination of numerous books on global topics related to green/sustainable chemistry specifically aimed at university students (20).

INTERNATIONAL CONFERENCE ON  
**GREEN CHEMISTRY**  
**CHALLENGING PERSPECTIVES**

Venezia (Italy), September 28 - October 1, 1997

Sponsored by the  
International Union of Pure and Applied Chemistry

Co-sponsored by ACS, EPA and UNESCO

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- CHEMICAL PROCESSES: STATE OF THE ART FOR THE ENVIRONMENT
- INHERENTLY SAFE PROCESSES
- INHERENTLY SAFE PRODUCTS
- CATALYSIS AND BIOCATALYSIS
- SOLVENTLESS PROCESSES AND ALTERNATIVE SOLVENTS
- RESEARCH POLICIES



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**Figure 3.** Poster of the First International Conference on “Challenging Perspectives on Green Chemistry” (Venezia 1997)

In 1997, after more than a year of planning by individuals from industry, government and academia, the Green Chemistry Institute (GCI) was incorporated as a not-for-profit corporation devoted to promoting and advancing green chemistry. In January 2001, GCI joined the American Chemical Society (ACS) in an increased effort to address global issues at the cross road of chemistry and the environment.

In the late nineties with the new millennium looming, interest in Green Chemistry became widespread. In 1998 upon an EPA proposal, the Organization for Economic Co-operation and Development (OECD), instituted a Directive Committee for the development of sustainable chemistry and finalised a programme called “Sustainable Chemistry” that included chemistry aimed at pollution prevention and better industrial performance. The activity commenced with a survey of the Steering Group [USA, Italy, Japan, Germany, Belgium, Canada, Mexico, Sweden, UK, and Business and Industry Advisory Committee to the OECD (BIAC)] on programs and initiatives on Green Chemistry launched worldwide by governments, industries and academia. The USA and Japan were nominated co-leaders in the field of research and development while Italy was appointed leader of the Educational Act. In consideration of the survey results, the policy and programmatic aspects of the sustainable chemistry activity were discussed at the Venice Workshop (October 1998) in the presence of representatives from government, industry and academia from 22 countries and subsequently approved at the OECD meeting in Paris (June 6, 1999).

As a result of this meeting the following seven research areas in green/sustainable chemistry were identified:

- *Use of Alternative Feedstocks*: the use of feedstocks, which are renewable rather than depleting and less toxic to human health and the environment.
- *Use of Innocuous Reagents*: the use of reagents that are inherently less hazardous and are catalytic whenever feasible.
- *Employing Natural Processes*: use of biosynthesis, biocatalysis, and biotech-based chemical transformations for efficiency and selectivity.
- *Use of Alternative Solvents*: the design and utilization of solvents, which have reduced potential for detriment to the environment and serve as alternatives to currently used volatile organic solvents, chlorinated solvents, and solvents which damage the natural environment.
- *Design of Safer Chemicals*: use of molecular structure design - and consideration of the principles of toxicity and mechanism of action - to minimize the intrinsic toxicity of the product while maintaining its efficiency of function.
- *Developing Alternative Reaction Conditions*: the design of reaction conditions that increase the selectivity of the product and allow for dematerialization of the product separation process.
- *Minimizing Energy Consumption*: the design of chemical transformations that reduce the required energy input in terms of both mechanical and thermal inputs and the associated environmental impacts of excessive energy usage.

Despite being issued in 1998, these areas of research are still current as they vividly represent the main lines of development of green chemistry.

In 1999, the Royal Society of Chemistry introduced a new journal entirely dedicated to sustainable chemistry: *Green Chemistry*. This journal, as it is stated on the RSC webpage, *provides a unique forum for the publication of original and significant cutting-edge research that reduces the environmental impact of the chemical enterprise by developing alternative sustainable technologies*. Since then several new journals dedicated to Green Chemistry have appeared, such as: *ChemSusChem* (21), *Energy and Environmental Science* (22), *Environmental Chemistry* (23), *Journal of Environmental Monitoring* (24) to mention but a few.

In 2006 following the launch of the IUPAC Green Chemistry Subcommittee within the III Division, the Consorzio INCA in collaboration with the German Chemical Society (GDCh) organized the first International IUPAC Conference dedicated to Green-Sustainable Chemistry (ICGC-1), currently in its 3<sup>rd</sup> edition (Figure 4) (25).



**Figure 4.** 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> International IUPAC conferences on Green Chemistry (13).

It is also important to mention the foundation of the Cost Action D29 (Sustainable/Green Chemistry and Chemical Technology), which is a network comprising of 26 COST (European Cooperation in Science and Technology) countries. This network aims to develop sustainable industrial chemicals and chemical based consumer products utilising sustainable and environmentally friendly processes and to establish a common understanding of the current status and the future research, development, and educational needs of Sustainable/Green Chemistry and Chemical Technology for Europe. The achievements of this Action have been disseminated through Action workshops and Working Group meetings, presentations in international conferences and the publication of many research articles in peer-reviewed journals.

Finally it should be mention that another important step in the history of green chemistry has been realised by the introduction of Registration, Evaluation and Authorisation of Chemicals Regulation (REACH), which was formally adopted on the 18<sup>th</sup> of December 2006 by the European Council of Environment Ministers. This new regulation aims to improve the protection of human health and the environment through improved assessment of chemical substances.

This Regulation gives greater responsibility to industry as manufacturers and importers and ultimately calls for progressive substitution of the most dangerous chemicals by greener alternatives (26).



### **NOP: a handbook for green reactions**

Chemists are well aware that beside the theoretical knowledge, it is of the utmost importance to be equipped with a sound manual ability in the laboratory. In Germany, for instance, the Organisches Prakticum (OP) – a handbook for laboratory experimentation - is a must-have for organic synthesis. Now, a group of researchers have published on the net a new version of this handbook called NOP (N for Nachhaltigkeit: Sustainability). Naturally, the content revolves naturally around the concepts of energy consumption, atom economy and (eco)toxicity of organic reactions. It contains an introduction to Green Chemistry, a number of “green” experiments and exhaustive toxicity data of the compound employed. The website is available in German, English, Arabic, Greek, Indonesian, Russian, Turkey and shortly also in Italian (27). NOP is a very innovative and powerful tool for the acquisition of eco-friendly laboratory techniques for students and teachers.

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### **1.2 Green Chemistry in the economy: the Chinese Circular Economy (CE)**

The rapid growth of China's material consumption poses profound challenges to sustainable development in the country and the rest of the world. China is now consuming about half of the world's cement, over 30 per cent of its steel and more than 20 per cent of its aluminium. It is also the leading consumer of fertilizers and the second largest importer of forest products in the world. Because of such rapid growth, the natural resources of China are depleting quickly. To solve this problem, China's leadership, inspired by Japanese and German Recycling Economy Laws, formed a Circular Economy (CE) initiative that started 10 years ago and that has major strategic importance worldwide (28). The Circular Economy approach to resource-use efficiency integrates cleaner production and industrial ecology in a broader system encompassing industrial firms, networks, eco-industrial parks, and regional infrastructure to support resource optimization (Figure 5).

The three basic levels of the Circular Economy action are:

- At the *individual firm level*, managers must seek much higher efficiency through the following three *Rs* of CE: *Reduce* consumption of resources and emission of pollutants and waste, *Reuse* resources, and *Recycle* by-products.
- The second level is to reuse and recycle resources within industrial parks and clustered or chained industries, so that resources will circulate fully in the local production system (the Chinese use the term “eco-chains” for by-product exchanges).
- The third level is to integrate different production and consumption systems in a region so the resources circulate among industries and urban systems.



**Figure 5.** A heart representing the concept of Circular Economy: a heart that recycle the waste into new useful green products. This image taken from the cover of Chemistry International (29) the newsmagazine of IUPAC.

According to the principles of CE, state owned and private enterprises, government and private infrastructure and even consumers all have a role to play in achieving CE. CE in many ways resembles the concept of industrial metabolism. It focuses on the input-output analysis of material flows transformed by production and consumption. In fact, the Circular Economy concept brings together cleaner production and industrial ecology, with its application as eco-industrial development.

The essence of the CE concept is the exchange of materials where one's waste, including energy, water, materials - as well as information - is another facility's input.

Comparable to the Chinese concept of CE, is the idea of Green Economy, pursued in Europe and America. Green Economy is a new economic development model born in contrast to the existing black economic model based on fossil fuels. The Green Economy is based on ecological economics, which consider the impact of human economic activities on climate change and global warming. In the midst of the global economic crisis, the UNEP United Nations Environment Program called for a global Green New Deal according to which governments were encouraged to support their economic transformation into a greener economy. The Green economy supports green and renewable energy as a replacement for fossil fuels and promotes energy conservation for efficient energy use. The green economy aims to create green jobs, ensure real, sustainable economic growth, while preventing environmental pollution, global warming, resource depletion, and environmental degradation (30).

### 1.3 Award for Green Chemistry Research

Green Chemistry research is supported by several awards that incentivises innovation and excellence in the Green Chemistry field. Some examples are (31):

*The Presidential Green Chemistry Challenge.* In the USA, The Presidential Green Chemistry Challenge was established by President Clinton in 1995 to recognise and promote fundamental and innovative chemical methods that accomplish pollution prevention through reduction at source and that have broad applicability in industry. The Presidential Green Chemistry Challenge Awards Program was established to recognise technologies that incorporate the principles of green chemistry into chemical design, manufacture and use. The evaluation of the new technology's impact include consideration of the health and environmental effects throughout the technology's lifecycle with recognition that incremental improvements are necessary (4).

*Award for Green Products and Processes* (32). This award was presented by INCA to Italian Companies that excelled in developing green processes and products. Examples of companies that have received the award are: Enichem, Polimeri Europa, Ausimont, Ilva Polimeri, Lamberti, Lonza Group, Mapei and Valagro.

*The European Sustainable Chemistry Award* (33). In 2010, EuCheMS (the European Association for Chemical and Molecular Sciences), with the backing of the European Environment Agency (EEA) and the support of SusChem (European Platform for Sustainable Chemistry) and CEFIC (European Chemical Industry Association), launched the European Sustainable Chemistry Award. This new award intends to raise the profile of sustainable chemistry and to stimulate innovation and competitiveness. The first Award, a prize of €10,000, was presented during the 3<sup>rd</sup> EuCheMS Chemistry Congress, on 29 August – 2 September 2010 in Nürnberg, Germany.

*The Institution of Chemical Engineers Award* (34). The IChemE awards is given for Innovation and Excellence in the Green chemical technology and sustainability area.

*Green and Sustainable Chemistry Network Award (Japan).* The Green & Sustainable Chemistry Network (35) as established in March, 2000 to promote research and development for the Environment and Human Health and Safety through the innovation of Chemistry. One of the activities, GSCN established in 2001 was the "GSC Awards". GSC Awards are to be granted to individuals, groups or companies who greatly contributed to promote GSC through their research,

development and their industrialization in the fields of development of industrial technologies, reduction of environmental burden (such as carbon dioxide, waste, landfill, harmful by-products etc.) and of establishing new philosophies/methodologies in research. The achievements are awarded either by the Minister of Economy, Trade and Industry, or by the Minister of the Environment, or by the Minister of Education, Sports, Culture, Science and technology, depending on their application.

*RACI Green Chemistry Challenge Award.* The Royal Australian Chemical Institute Green Chemistry Challenge awards recognise and promote fundamental and innovative chemical methods in Australia that accomplish pollution prevention through reduction at source and that have broad applicability in industry. They also recognise contributions to education in Green Chemistry. The Green Chemistry Challenge Awards are open to all individuals, groups and organisations, both non-profit and for profit, including academia, and industry.

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### Blue Box 3

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#### - Green Chemistry Research Institutions and Associations -

Since 1996 when the term Green Chemistry was coined, several research centres and associations supporting this new research area have formed. Some examples of national and international organization in Green Chemistry are:

#### National/International Organizations

IUPAC - Subcommittee on Green Chemistry  
Organic and Biomolecular Chemistry Division (III) (16)



Interuniversity National Consortium "Chemistry for the Environment" (Italy) (7)



Green Chemistry Network (UK) (36)



Green & Sustainable  
Chemistry Network (Japan) (35)



Environment Protection Agency (USA) (4)  
The US EPA's Green Chemistry Program



Green Chemistry Institute (USA) (37)



Canadian Green Chemistry Network (38)



### Some Research Institutes (40)

- Carnegie Mellon University Institute for Green Oxidation Chemistry (USA)
  - Centre for Green Chemistry University of Monash (Australia)
  - Centre for Green Manufacturing University of Alabama (USA)
  - Center for Sustainable and Green Chemistry (DK)
  - Chemical Process Engineering Research Institute Centre for Research & Technology (Greece)
  - Göteborg University's Centre for Environment and Sustainability (SE)
  - Green Chemistry Centre of Excellence at York (UK)
  - Green Chemistry Network Centre (Dehli Univ., India)
  - Greek network of Green Chemistry (Greece)
  - Institute of Applied Catalysis A research network for catalysis (UK)
  - Institute for a Sustainable Environment University of Oregon (USA)
  - NSF Science and Technology Center for Environmentally Responsible Solvents and Processes University of North Carolina; Chapel Hill (USA)
  - Queen's University Ionic Liquid Laboratories (QUILL) Queen's University of Belfast (UK)
  - The Clean Technology Research Group University of Nottingham (UK)
  - University of Leicester Leicester Green Chemistry Group (UK)
  - University of Leeds Leeds Cleaner Synthesis Group (UK)
  - University of Notre Dame Energy Centre (Indiana, USA)
  - Green Chemistry Network of Spain REDQS (ES)
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## 2. Areas of Green Chemistry

In order to achieve the best possible results, the G8 Countries aim to exploit Green Chemistry in relation to the need of each individual Country. Thus, each Country requires Green Chemistry to be involved in solving specific questions: Latin America to the exploitation of renewable resources, the Arab Regions to water quality and treatment, the Far East Countries to anti- and de-pollution issues. Adoption of the Green Chemistry principles is now possible because present European technology has the capacity to build new protocols for manufacturing molecular species.

Besides, despite the fact that more than ten years have passed since the seven research areas in green/sustainable chemistry were identified by the OECD, these thematic spheres remain the undisguised focus of Green Chemistry research (41).

A short report on each thematic area highlighting their advances and future research follows.

## 2.1 Alternative feedstocks

The synthesis and manufacture of any chemical substance begins with the choice of a starting material. In many cases, the selection of a starting material can be the most significant factor in determining the impact of the synthesis on the environment. Certainly, a first-level assessment of any starting material must be whether or not the substance itself poses a hazard in terms of toxicity, accident potential, possible ecosystem damage, or in another form. In this context, it is understandable that the feasibility and benefits of using bio-based, as opposed to petroleum-based, starting materials have been actively investigated in both academia and the chemical industry. To ensure a high degree of product safety for consumers and the environment, renewable resources have shown to have advantages when compared to petrochemical derived raw materials and can therefore be regarded as being the preferred source of raw material in Green Chemistry. Besides, the current high prices for petroleum and natural gas have spurred the chemical industry to examine alternative feedstock for the production of commodity chemicals. In this prospect, over the last 30 years, alternatives to conventional petroleum and natural gas feedstock have been developed, in particular by the exploitation of biomass.

Biomass is biological material derived from living, or recently living organisms, such as wood, carbohydrates, waste and gas (Figure 6). Biomass energy is derived from several distinct energy sources: refuse, wood, waste and landfill gases (42).

There are a number of technological options available to make use of a wide variety of biomass types as a renewable energy source. Conversion technologies may release the energy directly, in the form of heat or electricity, or may convert it to another form, such as liquid biofuel or combustible biogas (43). The most conventional application of biomass still relies on direct incineration. Currently, the New Hope Power Partnership is the largest biomass power plant in North America (44).



**Figure 6.** Biomass is biological material derived from living, or recently living organisms, such as wood, animal waste etc.

The 140 MW facility uses sugar cane fibre and recycled urban wood as fuel to generate enough power for its large milling and refining operations as well as to supply renewable electricity to nearly 60,000 homes.

The facility reduces dependence on oil by more than one million barrels per year, and by recycling sugar cane and wood waste, preserves landfill space in urban communities in Florida. A biomass power plant's size is often determined by biomass availability in its close proximity as transport costs of the (bulky) fuel plays a key factor in the plant's economics. However, biomass can be converted to other usable forms of energy by turning the raw materials, or feedstocks, into a usable form such as transportation fuels. These are produced by biomass through biochemical or thermochemical processes and they include ethanol, methanol, biodiesel, biocrude, and methane.

- Ethanol is the most widely used biofuel today (45). Brazil has the largest and most successful bio-fuel programs in the world, involving production of ethanol fuel from sugarcane, and it is considered to have the world's first sustainable biofuels economy. In the United States alone, more than 1.5 billion gallons are added yearly to gasoline as an oxygenate, to improve vehicle performance and reduce air pollution. Ethanol is produced from the fermentation of sugar by enzymes produced from specific varieties of yeast. Traditional fermentation processes rely on yeasts that convert six-carbon sugars to ethanol using a process similar to brewing beer. Ethanol made from cellulosic biomass materials or other agricultural feedstock is called second generation bioethanol. Ethanol can be used in its pure form (neat), as a blend with gasoline, or as a fuel for fuel cells.
- Methanol also can be used as a transportation fuel. Currently methanol is produced using natural gas, but it can also be produced from biomass through a two-step thermochemical process. First, the biomass is gasified to produce hydrogen and carbon monoxide. These gases are then reacted to produce methanol. Methanol can be used in its pure form (neat), as a feedstock for the gasoline additive methyl *tert*-butyl ether (MTBE), or as fuel for fuel cells.
- Biodiesel is a renewable diesel fuel substitute that can be made by chemically combining any natural oil or fat with an alcohol (usually methanol). Any vegetable oils, animal fats, and recycled cooking greases can be transformed into biodiesel and there are many different ways to do it. Biodiesel can be used neat or as a diesel additive and is typically used as a

fuel additive in 20% blends (B20) with petroleum diesel in compression ignition (diesel) engines. Other blend levels can be used depending on the cost of the fuel and the desired benefits.

- Methane is the major component of compressed natural gas. Methane, in a blend of other gases, can be produced from biomass by a biochemical process under anaerobic digestion conditions.

However, it should be also considered that there are several issues in the replacement of petroleum by biomass feedstocks that include impurities, variability of feedstock composition, distributed supply, scalability and pathways for breakdown of cellulose. Although some large-scale chemical production occurs as a by-product of fuel production, widespread use of biomass feedstocks for commodity chemical manufacture will require sustained research and development in a variety of fields such as plant science, microbiology, genomics, catalysis, and chemical separations technologies.

Another example of alternative feedstock is lignin. Lignin is a complex chemical compound most commonly derived from wood and it is one of the most abundant organic polymers. In 1998, a German company, Tecnar, developed a process for turning lignin into a substance, called Arboform (46). When lignin is combined with resins and flax, it forms a bio-plastic mass that looks and feels like wood and can be used to make several products such as furniture, toys, loudspeakers and even car interiors. Most significantly, Arboform is biodegradable and its raw material lignin is available in abundance, making it an environmentally friendly material that can potentially save significant natural resources. When the item is discarded, it can be burned just like wood. At the present time arboform costs €2.50 per kilogramme. The inventors Jürgen Pfitzer and Helmut Nägele have been awarded the European Inventor Awards 2010 for their studies.

Besides, currently there are several ongoing investigations for seeking high value application of lignin for Green Chemistry in particular in the fields of carbon fibres, aromatic chemicals, polymer resins and antioxidants.

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#### ----- Blue Box 4 -----

#### - Light as emerging feedstock -

Light is another emerging feedstock in a broad sense, a safe alternative to toxic catalysts in many synthetic transformations. In addition to utilising UV light, the most renewable and environmentally ideal energy source is sunlight. In this regard, the quote (given roughly a century ago during a conference in New York) by Giacomo Ciamician - the founder of photochemistry - is particular



pertinent (47): "On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plants and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry but mankind is".

Although it appeared (and still is) futuristic, we now know that many of these former fictions can be realized and applied. Noteworthy, it must be stated that photochemistry is already largely used in several laboratory and industrial applications (for example in the synthesis of benzyl halides). However, photocatalytic systems that are able to operate effectively and efficiently not only under UV light but also under the most environmentally ideal energy source, sunlight, are yet to be established.

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## 2.2 Use of Innocuous Reagents

As in the selection of a starting material, the selection of a reagent must include an evaluation to identify what the hazards associated with a particular reagent are. This evaluation should include an analysis of the reagent itself, as well as an analysis of the synthetic transformation associated with the use of that reagent (i.e., to determine product selectivity, reaction efficiency, separation needs, etc.).

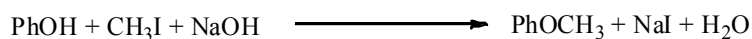
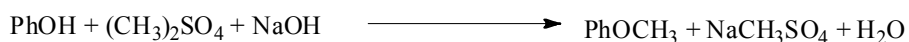
In order to evaluate the hazards inherent to the use of a certain reagent several issues have to be address:

### 2.2.1 *Less hazardous reagent*

Firstly, an investigation should be undertaken to determine if alternative reagents are available that are either more environmentally benign themselves or are able to carry out the necessary synthetic transformation in a more environmentally benign way. In order to answer this question alternative reagents must be identified and any hazardous properties that they possess must be compared with those associated with the reagent originally selected. One example of an innocuous reagent is dimethyl carbonate (DMC) (48).

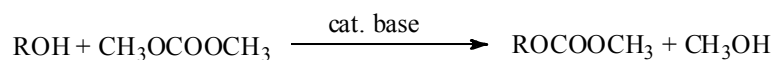
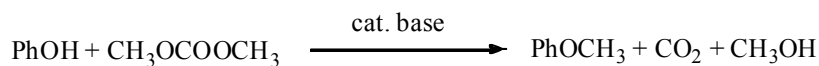
DMC is an environmentally benign substitute of phosgene (49) in carboxymethylation reactions and of dimethyl sulphate (DMS) (50) and methyl halides (51) in methylation reactions. Reported toxicity and ecotoxicity data classify DMC as both a non-toxic and environmentally benign chemical (52). DMC does not produce inorganic salts. In fact, the leaving group, methyl carbonate, decomposes giving only methanol and CO<sub>2</sub> as by products.

In this context, Scheme 1 shows the methylation of phenol by methyl halide (CH<sub>3</sub>X) and DMS to give anisole, and the alkoxycarbonylation of an alcohol by phosgene (COCl<sub>2</sub>).



**Scheme 1.** Methylation and alkoxy-carbonylation using DMS, CH<sub>3</sub>I and COCl<sub>2</sub> (under batch conditions)

DMC is able to perform the same reactions, using a catalytic amount of base and producing only methanol and CO<sub>2</sub> as by-products (Scheme 2). Besides, no inorganic salts have to be disposed of and therefore it can also be used in continuous-flow synthesis.



**Scheme 2.** Methylation and methoxycarbonylation using DMC

DMC is classified as a flammable liquid, does not smell (methanol-like odour) and does not have irritating or mutagenic effects by either contact or inhalation. Therefore, it can be handled safely without the special precautions required for the poisonous and mutagenic methyl halides and DMS, and extremely toxic phosgene. DMC is also widely used for its many applications. In fact, recent research indicates DMC as an oxygenated fuel (53) additive (due to the high percentage of oxygen in the molecule) of gasoline or diesel oil to replace the methyl-*tert*-butyl ether (MTBE). DMC can reduce the surface tension of diesel boiling range fuels leading to an improved (diesel) fuel with better injection delivery and spray. This and other applications led to an enormous effort in the investigation of low-cost synthesis of DMC.

Besides these applications, DMC is considered green because:

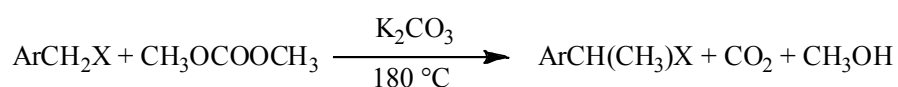
1. It is produced according to a green synthesis (see blue box 5)
2. It is non toxic
3. It produces no inorganic waste when utilized in synthesis
4. It led to unexpected and even surprising reaction pathways

Concerning point 4, DMC has a very selective behaviour reacting with different nucleophiles

(such as primary amines, CH<sub>2</sub> acidic compounds, phenols, etc.) acting as alkylating or carboxymethylating agent. In fact, DMC, as electrophile, has three reactive centres that can interact with nucleophiles: the carbonyl, and two methyl groups. Such centres can be classified according to the Hard- Soft Acid-Base (HSBA) theory (54): the carbonyl group is the harder electrophile, as a result of its polarized positive charge and sp<sup>2</sup> hybridization (thus it preferably reacts with harder nucleophiles); the two methyl groups represent softer electrophiles, thanks to their sp<sup>3</sup> orbital and their saturated carbon atom, which has a weaker positive charge (thus it preferably reacts with softer nucleophiles).

Numerous investigations have verified the compliance of reactivity of ambident nucleophiles and electrophiles with the HSAB theory (55). Many ambident nucleophiles are known, but few ambident electrophiles have been studied. As a result of its ambident electrophilic character DMC can be used either for carboxymethylation or methylation reactions both with high selectivity (up to 99.9%).

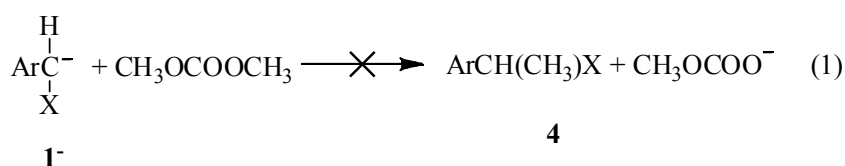
It can act as an efficient carboxymethylating agent (as phosgene substitute) for a wide string of nucleophiles. For example the carboxymethylation of amines to carbamates, which has great industrial importance in the synthesis of urethane (56), aromatic polycarbonates and isocyanate (57). Therefore, the areas in which DMC is used as an actual or potential phosgene substitute correspond to the main areas of phosgene industrial applications. Carbamates are very useful compounds widely used in the synthesis of pesticides, fungicides and herbicides, pharmaceuticals, cosmetics and polyurethanes, in addition to be employed as a protecting group. DMC has been successfully used for the methylation of arylacetonitriles and methyl aryl acetates at the α position. In fact, the reaction of CH<sub>2</sub> acidic compounds such as arylacetonitriles, aryl acetates, aryloxyacetic esters, sulfones, sulfoxides, and lactones with DMC is highly selective, as it yields the sole monomethyl derivative (Scheme 3) (58). Regardless of the high temperature and the great excess of alkylating agent (DMC is also the solvent of the reactions), at complete conversion of the substrate, selectivity for the monomethylated product is often >99%.



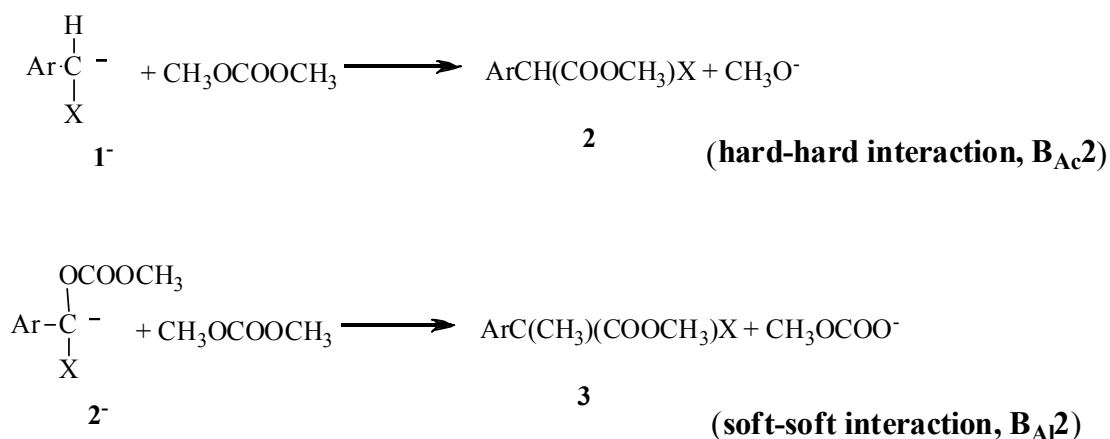
**Scheme 3.** Monoalkylation of nitriles, esters and sulfones, X= CN, COOCH<sub>3</sub>, SO<sub>2</sub>R, SO<sub>2</sub>Ar, etc.

Scheme 3 refers to monoalkylation of nitriles, esters, and sulfones. This reaction has an industrial relevance, since ArCH(CH<sub>3</sub>)COOH are well know anti-inflammatory agents.

The reason for the selectivity in monomethylation of these compounds is not immediately evident. Isolation of intermediates and a detailed kinetic study showed that the reaction mechanism does not imply a simple nucleophilic substitution (59) (eq 1).



Instead, monomethylation derives from an unusual reaction pathway that involves the reactivity of anion  $\mathbf{1}^-$  and anion  $\mathbf{2}^-$ , according to two consecutive nucleophilic displacements: the first one follows a  $\text{B}_{\text{Ac}2}$  mechanism, while the second occurs through a  $\text{B}_{\text{Al}2}$  mechanism, according to the Hard-Soft Acid-Base (HSAB) theory.



**Scheme 4.** Mechanism of the monoalkylation of nitriles, esters, and sulfones.

Thus,  $\mathbf{4}$  is produced through a series of consecutive pathways, all of them being very selective. Scheme 4 accounts for such a behaviour: the reaction proceeds through the carboxymethylation specie  $\mathbf{2}$ , which afterward reacts with the methyl of DMC.

In summary, while anion  $\text{ArCH}^-X$  does not give  $\text{ArC}(\text{CH}_3)_2X$ , also anion  $\text{ArC}^-(\text{COOCH}_3)X$  does not allow the formation of  $\text{ArC}(\text{COOCH}_3)_2X$ .

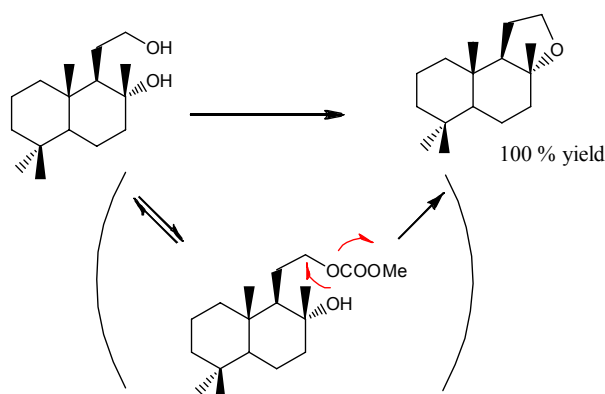
We can assert that anions  $\mathbf{1}^-$  and  $\mathbf{2}^-$  give different compounds since they have different soft/hard character. Their difference in hardness provides a reason for the discrimination observed between the two electrophilic centers of DMC. The hard nucleophile  $\mathbf{1}^-$  attacks only the carbonyl of DMC (eq. 2), while the anion of the product  $\mathbf{2}^-$  is a softer nucleophile thus it selectively produces the methyl derivative (eq. 3). The change in hardness/softness of the anion, due to the presence of the

carboxymethyl group, is enough to significantly alter the reactivity of the DMC molecule. Since hard-soft and soft-hard interactions are inhibited, neither double methylation nor double carboxymethylation take place.

DMC has also emerged as methylating agent in organic synthesis (60). Even though its reactivity is lower than widely used methyl halides and dimethyl sulfate it has the great advantage of being less toxic.

Finally, in recent year DMC has been also used for intramolecular cyclisation for the synthesis of heterocycles with applications in cosmetics and fragrances (61).

An emblematic example is (-)-norlabdane oxide that represents one of the preferred synthetic compounds with desirable ambergris-type odour and it is commercially available under various trade names (notably as amberlyn, ambroxan, ambrofix, ambrox or amberoxide). (-)-Norlabdane oxide is industrially synthesised by cyclisation of the related diol, amberlyn diol, in acidic conditions. This reaction leads to a mixture of ambroxan (ca 60%) and by-products deriving from the concurrent elimination reaction (62). Under acidic condition this reaction is not environmentally friendly and leads to a partial racemic mixture of products. Recently DMC was used for efficient cyclisation of the amberlyn diol in a short time spam and quantitative yield (Scheme 5). Noteworthy, the reaction maintains the chiral integrity of the starting material.



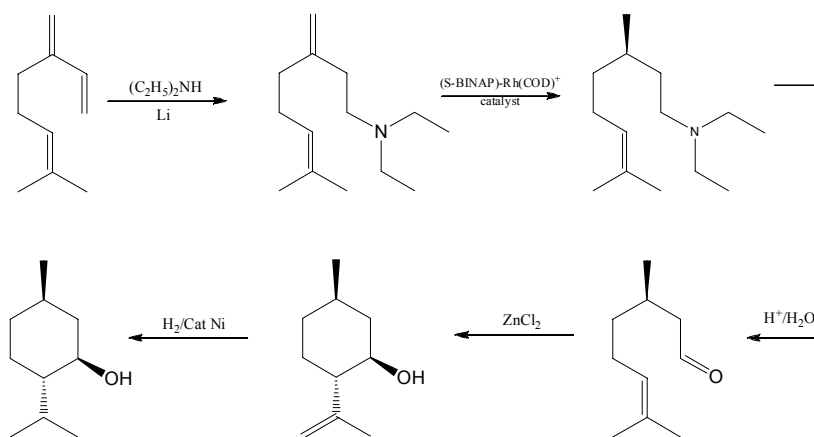
**Scheme 5.** Green synthesis of Ambroxan by DMC chemistry (base, DMC, 90 °C, 3h). The reaction mechanism is reported in brackets.

#### Blue Box 5

#### - Green Synthesis of Menthol -

An example of Green Chemistry applied to fragrances is the synthesis of menthol (Scheme 1). Menthol is an organic compound made synthetically or obtained from peppermint or other mint oils. Menthol has local anaesthetic and counterirritant qualities, and it is widely used to relieve minor throat irritation, but it also has applications in perfumery and in some beauty products such as

hair-conditioners. As with many widely-used natural products, the demand for menthol greatly exceeds the supply from natural sources, thus most of the menthol used in industry is made synthetically. In particular, menthol is manufactured as a single enantiomer (94% ee) on a scale of 3,000 tons per year by Takasago International. This process involves an asymmetric synthesis reaction developed by a team led by Ryoji Noyori and it is green and highly efficient (63).



**Scheme 1.** Green synthesis of menthol

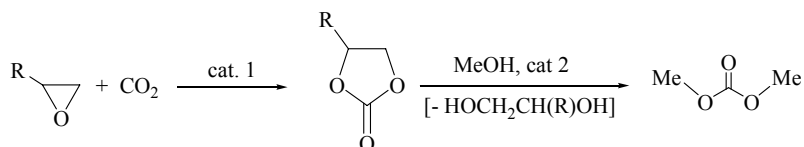
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**Blue Box 6**

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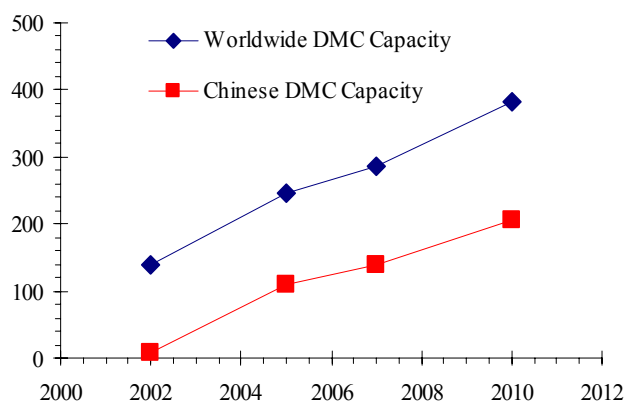
**Green production of dimethyl carbonate – A case study -**

DMC was, for long time, produced from phosgene and methanol. In this synthesis, HCl was an unwanted side product. However, since the mid eighties DMC is no longer produced from a phosgene pathway. Nowadays the industrial procedure to DMC - developed and recently industrialized principally in China (Figure 1) - does not use any chlorine, but consists of the cleavage of cyclic carbonates (Scheme 1). Currently several catalysts are under investigation for the synthesis of the cyclic carbonate which is an important green reagent and intermediate for the synthesis of DMC (64).



**Scheme 1.** Insertion of CO<sub>2</sub> into an epoxide and cleavage of the resultant cyclic carbonate. Step 1. Catalyst: MgO, CaO. Step 2. Catalyst: zeolites exchanged with alkali and/or earth metal ions. R = H and CH<sub>3</sub>

The current industrial application of DMC include: polycarbonates (53%), coating and paints (29%), agrochemicals (12%), electrolyte solvents (2%), pharmaceuticals and cosmetics (5%).



**Figure 1.** Production of DMC in China compared with DMC world production.

### 2.2.2 *Generate less waste*

An important consideration and benefit associated with the use of a particular reagent is whether it is responsible for the generation of more or less waste than other reagents. The amount of waste either generated or eliminated, however, cannot be the only consideration. The type of waste generated must also be assessed. Just as not all chemical products are equal in terms of their hazard, neither are chemical waste streams. Waste streams therefore must also be assessed for any hazard properties that they possess. The way the problem is approached obviously includes recycling and reuse, but focuses mostly on prevention, and therefore reduction, of waste production. The idea of high conversion efficiency in a chemical process is expressed in the concept of atom economy (see metrics) postulated by Trost (65).

These considerations explain why oxidation reactions involving oxygen and hydrogen peroxide have been an outstanding priority in the last twenty years. For green oxidation reactions we refer to oxidations that use atmospheric oxygen or molecular oxygen as oxidant. They are considered green because they produce water as a by-product, they require the use of nontoxic solvents (water or CO<sub>2</sub>) and mild reaction conditions. From these observations, it is clear that oxygen is the ideal oxidant (66) to be used due to the high active oxygen percentage content (theoretically 100%) (67). However, oxidations using air as a reagent are difficult to control and intrinsically nonselective when selectivity is very often a crucial parameter. Besides, very few reactions have been found where both atoms of oxygen can be transferred to the substrate; more often O<sub>2</sub> acts as an oxidant with 50% of active oxygen content leading to the formation of 1 equivalent of water. For these reasons, hydrogen peroxide is a more practical oxidant (active oxygen content 47%); it produces water as the only by-product, and a very high selectivity can be obtained. However, hydrogen peroxide used for fine chemical production, can undergo radical decomposition to water and oxygen

(68) (catalase reaction). Therefore, there is a great effort to develop systems able to selectively activate oxygen and hydrogen peroxide for oxidative transformations. In this context, both homogeneous and heterogeneous catalysis plays a key role. Oxidation reactions are critical to pharmaceutical, petrochemical, and agricultural industries. Several examples of how environmentally benign oxidants such as molecular oxygen, hydrogen peroxide or  $N_2O$  can be activated on heterogeneous catalysts have been reported (69). Direct oxidation of isoprenol,  $\beta$ -picoline and benzene are chosen as examples for continuous gas phase processes, and oxidation of cyclopentanone, limonene, pinene, and propylene as examples of semi continuous or batchwise processes in the liquid phase (70).

A foremost example of chemistry that produces less waste is represented by zeolites (71). Zeolites are crystalline aluminosilicates of group IA and group IIA elements, such as sodium, potassium, magnesium and calcium. They have a three-dimensional framework of tetrahedra  $AlO_4$  and  $SiO_4$ ; each  $AlO_4$  tetrahedron in the framework bears a net negative charge, balanced by a cation. Some zeolites are found in nature as minerals, many others are synthesised by industry or in the laboratory. Zeolites have many applications. The first major use for zeolites was in the purification of water (72). Water can be softened by passing it through a zeolite, with pores that incorporate calcium and magnesium ions rendering the water softer. This same type of zeolite is being increasingly used in place of polluting phosphate chemicals in laundry detergents (73). Zeolites are also used in agriculture (74), their pores can be filled with potassium, ammonium ions, fertilizer or other micronutrients. The use of zeolite catalysts in the production of organic (fine) chemicals has appeared as a major new direction (75). The main advantage of these materials is that their pore size, shape and properties can be modelled according to the needs of the reaction to be conducted, and to the substrate used (obviously this is not as straightforward as it seems) (76). This improves the energy-efficiency of many industrial processes, especially in the hydrocarbon industry. It also removes the need to use other potentially polluting catalytic alternatives. This has led to numerous applications and patents in the industry (i.e. production of phenol by alternative process to the cumene process) (77). For instance, the hydrogen form of zeolites (prepared by ion-exchange) are powerful solid-state acids (78), and can facilitate a host of acid-catalyzed reactions, such as isomerisation, alkylation, and cracking since due to the thermal stability of their structure, they can be used at high temperature.

### 2.2.3 *High conversion and selectivity*

Utilizing a reagent that is more selective means that more of the starting material is going to be converted into the desired product. On the other hand, high product selectivity does not always



translate into high product yield (and less waste generated). As reported by Sheldon, both high selectivity and high conversion must be achieved in order for a synthetic transformation to generate little or no waste (79). Utilizing highly selective reagents can mean that separation, isolation, and purification of the product will be significantly less difficult. Since a substantial portion of the burden to the environment that chemical manufacturing processes incur often results from separation and purification processes, highly selective reagents are very desirable in green chemistry.

#### 2.2.4 *Catalyst*

One of the most important aspects in the use of benign reagent is the substitution of antiquated stoichiometric methodologies with cleaner catalytic alternatives. Indeed, a major challenge in chemicals manufacturing in general is to develop processes based on H<sub>2</sub>, O<sub>2</sub>, H<sub>2</sub>O<sub>2</sub>, CO, CO<sub>2</sub> and NH<sub>3</sub> as the direct sources of H, O, C and N. Catalytic hydrogenation, oxidation and carbonylation are good examples of highly atom efficient, low-salt processes. The generation of copious amounts of inorganic salts can similarly be largely circumvented by replacing stoichiometric mineral acids, such as H<sub>2</sub>SO<sub>4</sub>, and Lewis acids and stoichiometric bases, such as NaOH, KOH, with recyclable solid acids and bases, preferably in catalytic amounts. A large number of industrial processes are based on the use of inorganic or minerals acids. While many of these processes are catalytic, some require stoichiometric amounts of Lewis acid (e.g., acylation using AlCl<sub>3</sub>). Isolation of the product necessitates neutralization steps to remove the acid, resulting in enormous quantities of hazardous waste, with the cost of disposal of this waste often outweighing the value of the product. In fact, Lewis-acid catalyzed reactions are of great interest because of their unique reactivities and selectivities and mild reaction conditions used (80). A wide variety of reactions using Lewis acids have been developed, and they have been applied to the synthesis of natural and unnatural compounds. However, in most of the reactions Lewis acids have to be used in stoichiometric amount. On the other hand, an interesting class of Lewis acids are lanthanide triflates Ln(OTf)<sub>3</sub> (81). They are stable and work as Lewis acids in water. Investigations conducted in this field indicated that not only Ln(OTf)<sub>3</sub> (Ln ) La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu) but also scandium (Sc) and yttrium (Y) triflates were shown to be water-compatible Lewis acids. Thus, these rare-earth metal triflates [RE(OTf)<sub>3</sub>] have been regarded as new types of Lewis acids. Many useful reactions are catalyzed by rare-earth metal triflates in aqueous media (82). In most cases only catalytic amounts of the triflates are required to complete the reactions in most cases. Furthermore, rare-earth metal triflates can be recovered easily after reactions and reused without loss of activity

(83). An example of their use is the catalytic acylation of phenols with acid anhydrides using  $\text{Sc}(\text{OTf})_3$  (84).

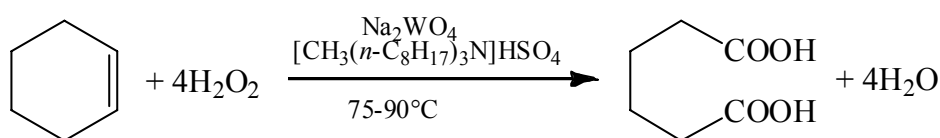
One way to significantly reduce the amount of waste is to substitute traditional acids and Lewis acids with recyclable solid acid catalysts (i.e. heteropolyacids) (85). Heteropolyacids are largely used for oxidation processes due to their low toxicity and high acidity. Heteropolyacids have been used in a variety of acid-catalyzed reactions such as esterification, etherification, hydration of olefins and dehydration of alcohols (86). Recently, Keggin-type heteropolyacids have been used in multiphase conditions in a range of processes i.e. preparation of heterocycles, protection/deprotection of organic functional groups, and oxidation processes, as well as, conversion of 2,6-dimethylphenol to 2,6-dimethyl-1,4-benzoquinone, and selective oxidation of sulfides to sulfoxides with hydrogen peroxide (87).

In any case, it must be mentioned that if a catalyst can be used, it should be used in “catalytic amount”. If a reagent can be utilized and yet not consumed in the process, it will require less material to continuously effect the transformation. This implies that catalysis has to be as efficient (not only effective) as possible, involving a high turnover.

#### 2.2.4.1 The practical elegance in synthesis in Green Chemistry catalysis

Professor Ryoji Noyori (born September 3, 1938) won the Nobel Prize in Chemistry in 2001 with William S. Knowles for the study of chirally catalyzed hydrogenations and with K. Barry Sharpless for their study on chirally catalyzed oxidation reactions (Sharpless epoxidation).

Noyori believes strongly in the power of catalysis and of green chemistry. In a recent article he argues for the pursuit of “practical elegance in synthesis: that is chemical synthesis must be intellectually logical and technically truly efficient” (88). According to Noyori every reaction in multi-step synthesis should proceed with a high atom economy, and the overall synthesis must be accomplished with a low E-factor. In fact he states that “chemists today are asked to develop perfect chemical reactions that proceed with 100% yield and 100% selectivity without forming any waste products. Molecular catalysis, together with traditional heterogeneous catalysis, significantly contributes to the realization of this goal.”



**Scheme 6.** Green oxidation of cyclohexene for the synthesis of adipic acid

A clear example of practical elegance in synthesis is the green oxidation of cyclohexene for the synthesis of adipic acid (Scheme 6). Noyori proved that if a mixture of cyclohexene and H<sub>2</sub>O<sub>2</sub> in the presence of small amounts of Na<sub>2</sub>WO<sub>4</sub> and methyl- (trioctyl)ammonium hydrogensulfate as phase-transfer catalyst is stirred at 75–90 °C, adipic acid is directly obtained as shiny, colorless, analytically pure crystals in a high yield. This procedure is much more environmentally benign than the commonly used oxidation of a cyclohexanol–cyclohexanone mixture with nitric acid (89).

### 2.3 Employing Natural Processes

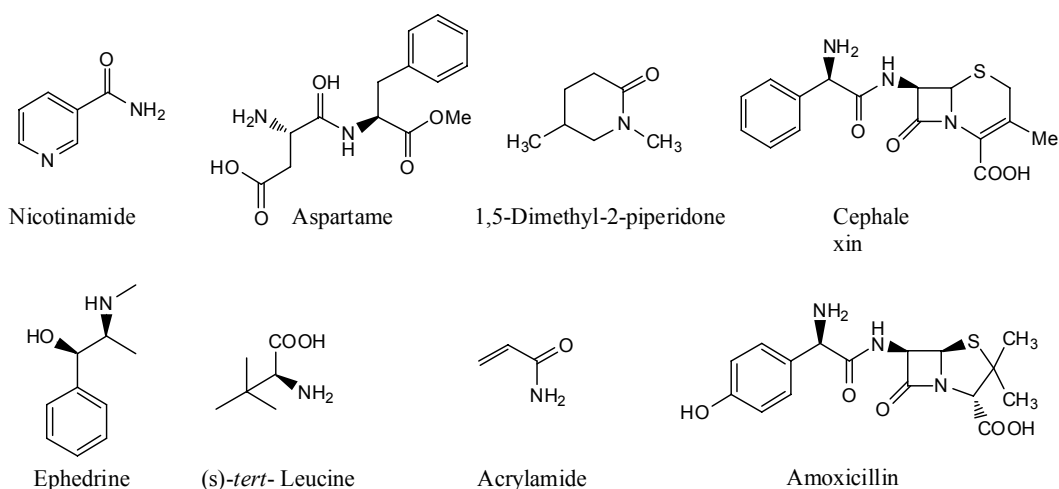
Biocatalysis has emerged as an important tool in the industrial synthesis of bulk chemicals (90), pharmaceutical and agrochemical intermediates, active pharmaceuticals, and food ingredients (91). The potential applications of biocatalysis for the synthesis of chemicals, is highlighted by several industrial processes that are operational in several manufacturers such as Merck (92), BASF (93), DSM (94), Lonza (95), Roquette (96) and Cognis (97). These industries employ enzymes for the synthesis of medium to high priced compounds that cannot be produced equally well using a chemical approach (Figure 7).

An example of biocatalysis employed for synthetic natural pathways is the bacterial fermentation to produce lactic acid from corn starch or cane sugar. The lactic acid so obtained is then used as starting material to achieve polylactic acid (PLA) (98). PLA has a wide range of applications, such as woven shirts, microwavable trays, hot-fill applications and engineering plastics. PLA is currently used in a number of biomedical applications, such as sutures, stents, dialysis media and drug delivery devices.

In this sense, the use of biosynthesis, biocatalysis and biotech-based chemical transformations can make an important contribution to green chemistry for both efficiency and selectivity. The range of reactions that can be carried out with microorganisms and the range of microorganisms that have been already isolated is enormous. Thus, much effort goes into the selection of new enzymatic activities. The use of biotech-based chemical transformations have high efficiency and selectivity; are carried out in water at ambient temperature and pressure; do not require tedious protection and deprotection of functional groups; shorten reaction sequences with fewer steps and remove the need for organic solvents. Besides, another great advantage of biocatalysis in industry is the reduction of waste.

Enzymes often represent almost zero waste for companies as they can be reused, and once they reach the end of their service life they can be discarded through conventional waste streams. Conversely, the chemical catalysts that enzymes often replace are heavy metals, which are tightly regulated and in many cases hazardous to the environment and human health. On the other hand, a

common problem in biocatalysis is that many of the desired substrates have very low solubility in water, and the catalytic activity for most enzymes is significantly reduced by the addition of even small quantities of organic solvents.



**Figure 7.** Examples of API manufactured using biocatalysts (by many steps) (99).

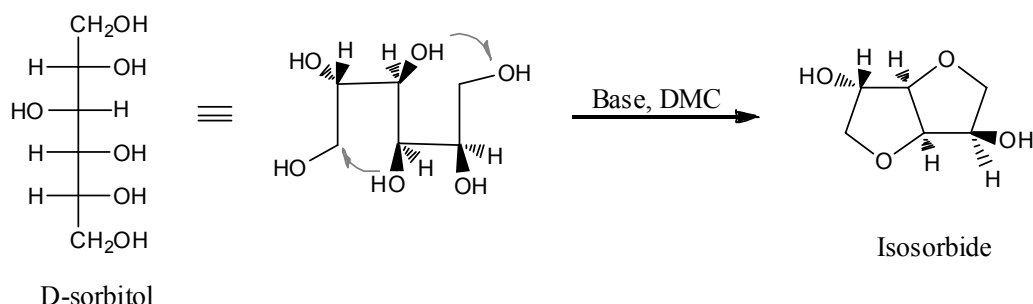
Traditionally this has limited the use of biocatalysts, but now several examples have shown that biocatalysts can be evolved to function in nonaqueous solvents, allowing for their use with water-insoluble substrates. In fact, for a biocatalyst to be effective in an industrial process, it must be subjected to improvement and optimization, and in this respect the directed evolution of enzymes has emerged as a powerful enabling technology. Currently, large-scale industrial applications of enzyme catalysis include the thermolysin-catalysed synthesis of the low-calorie sweetener aspartame, the synthesis of semi-synthetic  $\beta$ -lactam antibiotics with the use of acylases, acrylamide and nicotinamide (99). The enzymes most utilised include lipases and other esterases (for ester formation including transesterification; aminolysis and hydrolysis of esters); proteases (ester and amide hydrolysis, peptide synthesis); nitrilases and nitrile hydratases; hydrolases (hydrolysis of epoxides, halogenated compounds, and phosphates; glycosylation) and oxidoreductases (e.g. enantioselective reduction of ketones). However it is worth mentioning that another drawback of biocatalysis is that enzymes are very specific, thus they can be only used for one reaction at a time. In fact it is impossible at the moment to realize the synthesis of a natural product or of an Active Pharmaceutical Ingredients and Intermediates (API) in one step by biocatalysis.

----- **Blue Box 7** -----

**- Isosorbide: an example of Green Chemistry applied to renewables -**

Cyclic ethers in the form of anhydro sugar alcohols have many applications in industry, in particular in food industry and in the therapeutic field and are employed as monomers for polymers and

copolymers. Such anhydro sugar alcohols are derivatives of mannitol, iditol, and sorbitol. In particular isosorbide, an anhydro sugar alcohol derived from sorbitol, is useful as a monomer in the manufacture of polymers and copolymers, especially polyester polymers and copolymers. Isosorbide is obtained by dehydration of sorbitol by an acid-catalyzed reaction that leads to different anhydro-compounds, but also to polymer-like products. Due to the industrial relevance of this substrate, the one-pot cyclisation of D-sorbitol to isosorbide has been greatly investigated.



**Scheme 1.** One-step synthesis of isosorbide by DMC chemistry

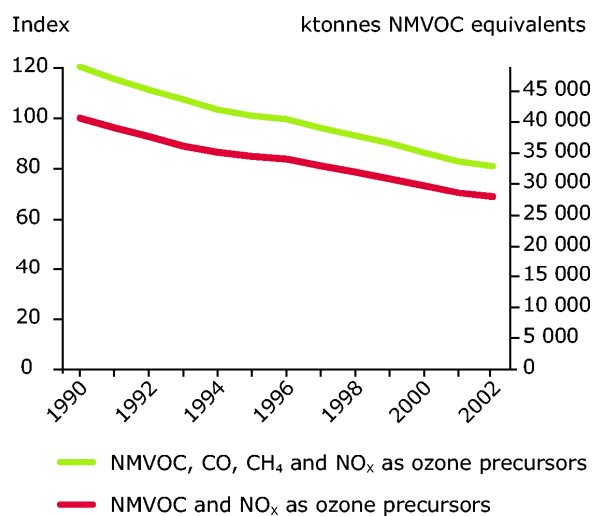
Recent studies demonstrated that DMC can be used as an efficient dehydrating agent in the cyclisation of D-sorbitol to isosorbide in up to quantitative yield (Scheme 1) (61). The main difference between this synthesis and the acid-catalyzed reaction normally used for the synthesis of isosorbide is that the DMC-mediated reaction incorporates two important concepts of the sustainable chemistry: it uses green reagents and a renewable as starting material. This renders this reaction extremely appealing for industrial exploitation.

Noteworthy, the synthesis of isosorbide represents a one-pot double cyclisation reaction. Additionally, the four chiral centres were not affected by the reaction, as it easily occurs in the present industrial processes that utilise the acidic promoted cyclisation.

## 2.4 Use of Alternative Solvents

The use of solvents in every day laboratory work and in the chemical industry is ubiquitous (100). Solvents are often supposed to disappear at the end of the reaction, nevertheless they are part of the process and consequently they must be treated and disposed of (or eventually recycled). Nowadays, with increasing regulatory pressure focusing on solvents, there is significant attention being paid to green alternatives to traditional solvents which is perhaps the most active area of Green Chemistry research (100). In fact, solvents account for the vast majority of mass wasted in syntheses and processes. Besides, traditional solvents pose several serious issue to human health being toxic, flammable, and/or corrosive, as well as to the environment due to their volatility and solubility, which has caused enormous air, water and soil pollution over the years. Halogenated solvents such as carbon tetrachloride, perchloroethylene, and chloroform have been implicated as potential and/or suspect carcinogens, while other classes of solvents have demonstrated neurotoxicological effects. However, the direct toxicity to humans is only one aspect of the hazards that solvents possess. The use of certain volatile organic compounds (VOCs) as solvents and other uses has generated great

concern about their ability to elevate atmospheric ozone levels (Figure 8).



**Figure 8.** An example of non-methane volatile organic compounds (NMVOC) reduction during the last 20 years in Europe (101)

Other substances used as solvents have also been found to possess significant global warming potential and are thought to contribute to the overall greenhouse gas loading in the environment. In an effort to address all these concerns for health and environment, chemists started to search for safer solutions.

As an example, DMC-derivate solvents have recently been demonstrated as efficient alternative solvents for varnishes. Noteworthy, the varnish containing the new DMC-based solvent no toxicity and an improved filming performance (specifically 2(2methoxy-2ethoxy)ethyl methyl carbonate) (102).

In this context, some of the main areas of research on alternative solvents include solventless systems, aqueous applications, supercritical fluids, ionic liquids and reduced hazard organic solvents.

- Solventless Reactions. Whenever feasible, the best solution would be to avoid the use of solvent since including a supplementary element in a chemical reaction always require an extra energy consumption to remove it at the end of the process (103).
- Water. The increased focus on water in synthetic organic chemistry during the past few decades has resulted in a large number of reactions that can now be performed successfully in an aqueous medium (104). Among these reactions are allylation reactions, the aldol condensation, the Michael addition, the Mannich reaction, indium-mediated allylation and Grignard-type additions, hydroformylation (105) and the benzoin condensation. In some

reactions the properties of water have even led to improved results thanks to the hydrophobic effect and easier separation, as a lot of organic substances are not water soluble. An example of the application of water in a chemical process as a green approach to waste minimization is that of Phase-Transfer Catalysis. (PTC).<sup>1</sup> This key synthetic methodology - developed before the concept of Green Chemistry have been formulated - utilises water as the solvent and is applied in, and applicable to, a great variety of reactions in which inorganic and organic anions or carbenes react with organic substrates. It makes use of a heterogeneous two-phase system—one phase (water) being a reservoir of reacting anions or base for generation of organic anions, whereas organic reactants and catalysts are located in the second, organic phase. The reacting anions are continuously introduced into the organic phase in the form of lipophilic ion-pairs with lipophilic cations supplied by the catalyst. PTC can be carried out in liquid-liquid, solid-liquid, and gas-liquid conditions. The latter (Gas-Liquid Phase-Transfer Catalysis, GL-PTC) is of importance in green chemistry because it is performed under continuous-flow conditions (106). Transforming batch reactions into continuous-flow processes is a challenge for chemical engineers, but results in harmful reactions being avoided, easier reaction control and the volume in which the reaction takes place being greatly reduced. Noteworthy, it must be mentioned that the use of water in an industrial processes can also lead to water contamination, which is energy intensive to clean.

- Supercritical fluids (SCF). SFCs can be obtained from water, carbon dioxide, methane, methanol, ethanol or acetone to mention but a few. They include substances which have been simultaneously heated and compressed above their critical points. In particular in the last twenty years, there has been incredible growth in research involving the use of carbon dioxide as an environmentally benign solvent for chemical reactions and polymerizations both in academia and in industry. CO<sub>2</sub> is a nontoxic, nonflammable, and inexpensive solvent (107). While CO<sub>2</sub> is a gas under ambient conditions, its liquid and supercritical states are easily attained by compression and heating. Both liquid and scCO<sub>2</sub> have a tuneable density (and dielectric constant) that increases with increasing pressure or decreasing temperature. Many small molecules are soluble in CO<sub>2</sub>, including high-vapor-pressure solvents such as methanol, acetone, and tetrahydrofuran, numerous vinyl monomers, and azo- and peroxy-initiators. Besides, scCO<sub>2</sub> is also widely used because it does solubilize H<sub>2</sub> and O<sub>2</sub>. Water and ionic compounds are insoluble, as are most polymers. The two methodologies described by Howdle for dissolving ionic/polar species in scCO<sub>2</sub> led to a broadening of the range of

applications for supercritical solvents.  $\text{ScCO}_2$  has found a wide range of industrial applications, the first and most cited being the decaffeination of coffee beans.

- **Ionic Liquids.** Another class of solvents investigated for possible green solvents are ionic liquids, which offer alternatives to conventional molecular solvents for many synthetic transformations (108). These solvents are often fluid at room temperature, and consist entirely of organic ionic species; they have no measurable vapour pressure, and hence can emit no VOCs. Their uses and applications having been pioneered only recently by Seddon. An interesting application of IL is in their use in cellulose processing (109). Making cellulosic fibres by dissolving the so-called pulp involves the use, and subsequent disposal, of great volumes of various chemical auxiliaries. However, IL can greatly simplify these processes, serving as solvents that are nearly entirely recyclable. BASF is currently investigating the properties of fibres spun from an IL solution of cellulose in a pilot plant (110).

In this sense green chemistry entails the use of alternative green solvents that are non-toxic while preserving (or eventually improving) the efficiency of the synthesis in comparison to classical organic solvents while maintaining the same reaction conditions.

## **2.5 Design of Safer Chemicals**

In the last twenty years, chemists have put enormous effort into designing chemicals with various applications ranging from medicines and cosmetics to materials and molecular machines. However, their work demonstrated a quite surprising lack of interest in taking hazards into consideration in the design process.

The design of safer chemicals is a process that utilises an analysis of the chemical structure to identify what part of a molecule is providing the characteristic or property that is desired and what part of the molecule is responsible for the toxicity or hazard. Once this information has been ascertained, it is possible to maintain efficiency of function while minimizing the hazard. The goal of designing safer chemicals can be achieved through several different strategies (i.e. computational studies), the choice of which is largely dependent on the amount of information that exists on the particular substance.

The greatest potential to design a safer chemical, in terms of toxicity or other hazards to human health and the environment, is in cases where a mechanism of action is known. Simply stated, if the pathway toward toxicity is known, and if any step within that pathway can be prevented from occurring, then the toxic endpoint will be avoided.



Although mechanisms of action may be unknown, there are often detailed correlations, by way of structure–activity relationships, that can be used to design a safer chemical. As an example, if the methyl-substituted analogue of a substance is known to have a high toxicity, and that the toxicity decreases as the substitution moves from ethyl to propyl, etc., it would be reasonable to increase the alkyl chain length to design a safer chemical. Even when the reason for the influence of alkyl chain length on toxicity is unknown, an empirical structure–activity relationship of this kind offers a powerful design tool.

Another important approach for the design of safer molecules is the elimination of toxic functional groups. If there is little information about the specific variations in a chemical's toxicity with structural modification or in the mechanism by which that toxicity is produced, the assumption that certain reactive functional groups will react similarly within the body or in the environment is often a good one. The assumption is especially good if there is data on other compounds in the chemical class that demonstrate a common toxic effect. Here, the design of a safer chemical could possibly proceed by removing the toxic functionality which defines the class. In some cases, this is not possible because the functionality is intrinsic for the desired properties of the molecule. In such a case, there are still options, such as masking the functional group as a nontoxic derivative form and only releasing the parent functionality when and where necessary.

Finally, if through the above methods, the structural feature of the molecule that needs to be modified in order to make it less hazardous cannot be identified, there is still the option of making the substance less bioavailable. If the substance is unable, due to structural design, to reach the target of toxicity, then it is in effect innocuous. This can be achieved through a manipulation of the water-solubility/lipophilicity relationship that often control the ability of a substance to pass through biological membranes such as skin, lungs, or the gastrointestinal tract. The same principle applies to designing safer chemicals for the environment, such as replacement for ozone-depleting substances. In the past, it was often the goal of the chemist to design substances which were robust and could last as long as possible. This philosophy has resulted in a legacy of wastes, persistent toxic and bio-accumulative substances, and lingering toxic waste sites. Nowadays it is known that it is more desirable to avoid substances that persist indefinitely in the environment or in landfill, and to replace them with those that are designed to degrade after use. Polymeric materials, for instance, should have no negative effect on the environment during their production, utilisation or disposal. Therefore, the design of safer chemicals cannot be limited to hazards associated with the manufacture and use of the chemical, but also to its disposal, *i.e.* its full life cycle.

## 2.6 Developing Alternative Reaction Conditions

The use of alternative reaction conditions has experienced great development in the last twenty years. Energy sources such as UV light, microwaves or ultrasound can be used in a controlled way to increase the efficiency of a chemical reaction, thus making it more eco-friendly.

Microwave chemistry, the science of applying microwave irradiation to chemical reactions, for instance, has been widely investigated since 1986. Microwaves will generally heat any material containing mobile electric charges, such as polar molecules in a solvent or conducting ions in a solid. As a result microwave heating has benefits over conventional ovens: *i.e.* reaction rate acceleration, milder reaction conditions, higher chemical yield, lower energy usage and different reaction selectivity. Microwave heating is very attractive for chemical applications and has become a widely accepted non-conventional energy source for performing organic synthesis. A large number of examples of reactions have been described in organic synthesis: solvent-free reactions, cycloaddition reactions, the synthesis of radioisotopes, fullerene chemistry, polymers, heterocyclic chemistry, carbohydrates, homogeneous and heterogeneous catalysis, medicinal and combinatorial chemistry and Green Chemistry (111).

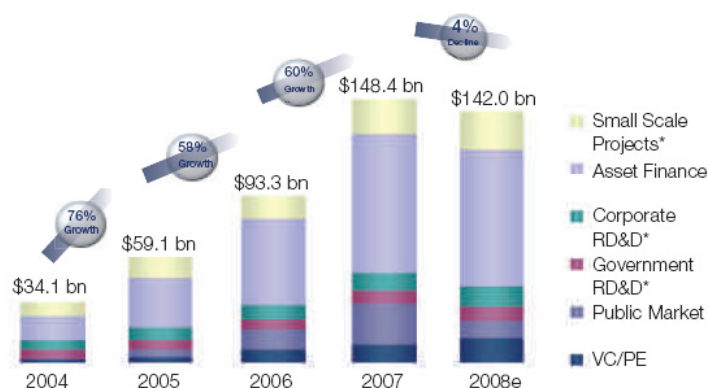
Acoustic waves are also considered as alternative reaction conditions to mechanical milling. In particular, acoustic milling is generated between 2 disks counter rotating at 30 000 rpm with a gap as small as 200  $\mu$ m. Materials are introduced in the centre of the disks, and transformed to nanometric powders with no crushing. This process is considered to be energetically greener and costs are claimed to be 10 times less (112).

## 2.7 Minimizing Energy Consumption

Chemistry and energy are two concepts that are strictly linked together. In particular in recent years a great deal of investment have been made both by the American and European governments in order to promote Clean Energies development at different level (Figure 9). The design of chemical transformations can reduce the required energy input in terms of mechanical, thermal, and other energy inputs, and the associated environmental impacts of excessive energy usage. In many aspects, design for energy minimization is inherently coupled with the design for material efficiency. For instance, when utilising new solvents such as scCO<sub>2</sub>, often the separation, a processes which requires significant energy inputs, is also greatly increased. Furthermore, if a synthetic transformation is developed using a catalytic system rather than a stoichiometric process, the activation energy required for the conversion to occur is significantly lowered.

Noteworthy, the chemical industry accounts for high energy consumption and CO<sub>2</sub> emissions. The industry typically consumes 25-30% of the total energy used annually by the entire manufacturing

sector. The two categories of plastic manufacturing and basic organic compounds represent more than one half of chemical industry energy use. This energy relates to energy of the molecular bonds and to some distinct manufacturing procedures, such as distillation, crystallization, separation, etc. The potential energy savings in the chemical industry are enormous. Improving atom economy, utilizing less hazard reagents, reducing waste, adopting intelligent energy activation and alternative separation procedures will allow the relationship between industry and energy to be reassessed.



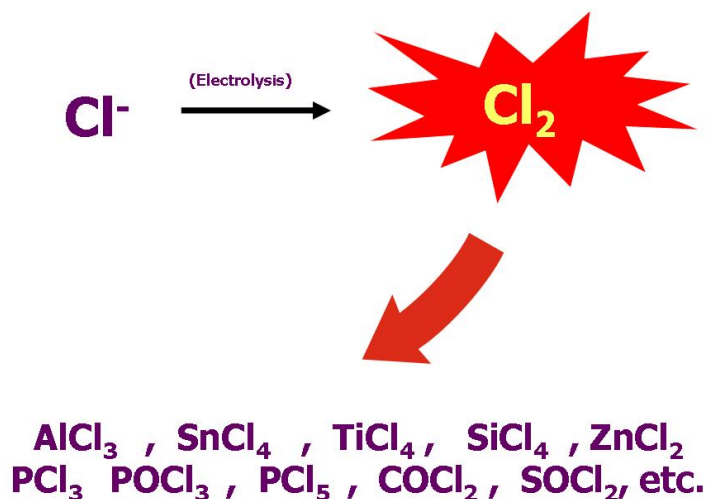
**Figure 9.** Total Global New Investment in Clean Energy, 2004-2008, US\$ billions (113)

A convincing example is represented by the chlorine-based industry. Chlorine stands as “an iconic molecule” for industrial production. Starting from a chlorine anion,  $\text{Cl}_2$  can be easily obtained by electrolysis. Following, many intermediates are produced starting from  $\text{Cl}_2$  ( $\text{AlCl}_3$ ,  $\text{SnCl}_4$ ,  $\text{SOCl}_2$ ,  $\text{COCl}_2$ ,  $\text{TiCl}_4$ ,  $\text{POCl}_3$ ,  $\text{ZnCl}_2$ ,  $\text{SiCl}_4$ ,  $\text{PCl}_3$ ,  $\text{PCl}_5$ , etc.), which in turn are starting reagents and catalysts for the production of numerous common everyday goods (Figure 10). Thus, each compound is the starting point of a chain leading to essential chemical derivatives.

Through a chain of chemical derivatives and relatively easily obtained compounds and intermediates, such molecules have utilised the intrinsic energy available through the use of chlorine primarily produced *via* electrolysis. More than 20 million tonnes of chlorine and co-products caustic soda and hydrogen are produced each year at about 80 plants across Europe, mostly (about 95%) *via* electrolysis-based techniques (chlor-alkali industry). Chlorine production is extremely energy intensive; recent data reported a decreasing consumption trend in Europe from 2001 to 2007. Estimates for the Global Warming Potential (GWP) resulting from chlorine use and the primary energy consumed by the chlorine industry in Europe are 0.29% of the total GWP and 0.45% primary energy consumption (Table 1) (114).

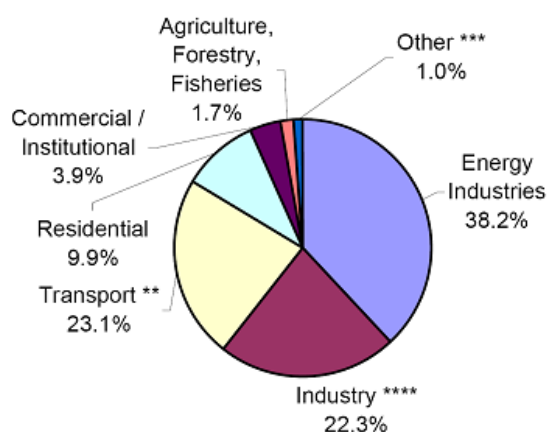
So, besides their (eco-)toxicity, a major concern with chlorine derivatives is the large amount of energy necessary for their production. This is why chlorinated molecules may have both a direct (as greenhouse gases) and indirect (energy production) impact on climate change at a global level.

The substitution of compounds where “chlorine is used in the making”, means that  $\text{Cl}_2$  can be avoided as a primary energetic source; this however makes chemistry “without chlorine” considerably more difficult and illustrates why it has never been taken on before.



**Figure 10.** Synthesis of chlorine derivatives by electrolysis

It must be stated that chemists have always worked with the intent to substitute  $\text{S}_{\text{N}}2$  with  $\text{B}_{\text{Ac}}2$  following a chlorine-free idea. However, the search for chlorine-free chemistry will not imply a drastic change in the industrial chemical processes, it is more an evolution of production pathways driven by industrial needs related to the modern market.



**Figure 11.** CO<sub>2</sub> Emissions by sector (Shares of total CO<sub>2</sub> Emissions: 2007)

Besides, reduced dependence on chlorine electrolysis will increase energy saving and will produce a smaller CO<sub>2</sub> footprint. Decreasing CO<sub>2</sub> emissions is a crucial step for containing industrial

environmental pollution. Figure 11 clearly shows the impact of the chemical industry on CO<sub>2</sub> production.

The whole of Europe produces 5.21 trillion t CO<sub>2</sub>eq per year and has a primary energy consumption of about 55 trillion GJ per year. In the following table the primary energy consumption and GWP of three different materials are shown.

**Table 1.** Comparing CO<sub>2</sub> emissions in cement, iron, steel and chloro alkali production

	<b>Chloro-Alkali manufacturing</b>	<b>Cement</b>	<b>Iron and Steel</b>
<b>Kg CO<sub>2</sub>/Kg</b>	1.5	0.95	1.7
<b>World Production (2008)</b>	Europe 20 Mtons China 21Mtons	2.3 Btons	1.2 Btons

An approximate estimate of the share of environmental impact caused by the use of chlorine in the State-of-the-Art production ranges between 20 – 55% of the whole production chain, beginning from the extraction of the raw materials down to the manufacturing of the chlorine-derived products. This environmental impact potential can be reduced by the development of chlorine-free production routes.

From a scientific and technical point of view, many scientists were and are devoted to a progressive substitution and prevention of the use of halogens (principally chlorine) according to Green Chemistry principles. A poignant example is in the field of Friedel-Crafts acylations and hydroxyalkylation. These reactions produce chemicals - such as aromatic ketones, alkenyl ketones and hydroxyalkyl derivatives – that are either valuable intermediates or end active ingredients in an extensive range of high value-added products within pharmaceuticals, flavours, fragrances, and fine chemicals<sup>1</sup>. However, Friedel-Crafts “catalysts” are frequently halogenated Lewis acid activating compounds, AlCl<sub>3</sub>, TiCl<sub>4</sub>, SnCl<sub>4</sub>, BF<sub>3</sub>, ZnCl<sub>2</sub>, which present significant health, safety and environmental challenges for batch processing typically used in smaller companies (115). The acylating processes also suffer from the production of copious amounts of aqueous effluent, generated when the products are released from activating agent/product complexes by hydration with water. The costs associated with overcoming these problems are increasing, and challenge the position of traditional acylation routes as economically viable processes for chemical companies. Some major chemical companies use liquid HF process systems, but the capital and running costs exceed the capabilities of small scale manufacturers.

To avoid the production of chlorine by-products during acylation reactions, three classes of alternative reagents can be utilized: carboxylic acids, carboxylic acids anhydrides and mixed

carboxylic acid anhydrides. In this regard, a great variety of solid acid catalysts can be studied to perform the acylation reaction with carboxylic acids and carboxylic acid anhydrides and with some mixed anhydrides (in particular acyl-carbonates). The different classes of catalysts to be studied range from clays, zeolites, metal oxides, acid-treated (mixed) metal oxides and heteropoly acids (116).

### 3. Metrics in Green Chemistry

Metrics in Green Chemistry are very important indicators of environmental issues and pollution associated with chemicals manufacturing. Metrics evaluation is often required for the assessment of the operations of a process plant, as they indicate human toxicity, toxicity pathway and ecotoxicity.

The most common green metrics for the evaluation of a chemical process are:

- the *effective mass yield* defined as the percentage of the mass of desired product relative to the mass of all non-benign materials used in a synthesis (117);
- the *E Factor* defined as total waste per product; which is an output oriented indicator, defined as waste per mass unit of the product ( $\sum \text{waste [kg]} / \text{product [kg]}$ ) (118);
- the *atom economy* (AE) describing the conversion efficiency of a chemical process in terms of atoms involved. In an ideal chemical process, the amount of starting materials or reactants equals the amount of all products generated and no atom is wasted. Thus atom economy can be written as: % atom economy = (molecular weight of desired product/molecular weight of all reactants) x 100 (119);
- the *mass index* (MI), which is an input oriented indicator, defined as the mass of all raw materials used for the synthesis per mass unit of the purified product ( $\sum \text{raw materials [kg]} / \text{product [kg]}$ )

Green metrics provide information already in the design phase of a chemical process and indicating consumptions measured as material and energy flows, and waste or toxic release emissions. Thus, by their application, chemists can improve their awareness of environmental issues related to new products as well as to existing ones. For example, utilizing these metrics, some comparative evaluations have been carried out to define the “greener” methylating agent among dimethyl carbonate, dimethyl sulphate and methyl iodide. The data collected demonstrates that DMC is the more eco-friendly reagent (120).

As evidence of the important role played by these green indicators, in 1998 an Ecometrics workshop was held in Switzerland with the participation of academia, industry and decisions

makers in order to discuss the need of metrics for the environment and to evaluate the best indices to address environmental issues (121). The key role of the metrics was confirmed during the First International Conference on Green & Sustainable Chemistry held in Japan in 2003. During this meeting life cycle approach (122) was also recognized as a method to be taken into account when conducting the environmental assessment of a material.

In 2005 J. Andraos, a professor at York University (Canada) investigating the application of reaction metrics in organic reactions and total syntheses, proposed a formalism to unify the metrics used for chemical reactions and introduced the *stoichiometric factor* (SF), making use of algorithms to calculate reaction metrics and to compare the green performances (123). In this context, in order to identify a sustainable threshold. Andraos also proposed that reactions considered to be green are characterized by a minimum atom economy of 61.8% coupled with high yield and high solvent recovery and run under stoichiometric conditions (124).

A method enabling the comparison of different chemical reactions in terms of potential environmental impact and to identify the critical phases of a synthesis process was developed by Metzger and Eissen. This method, called EATOS (Environmental Assessment Tool for Organic Synthesis), envisages two metrics as tools: the *mass index* and the *E factor*.

By the means of EATOS software, other environmental indices are calculated that also consider the weighting factors (125) such as input material prices, for risk of the R-phrases and for output materials toxicity and ecotoxicity. The same authors have also introduced in the EATOS tool the cost index. This tool has been utilized by various researchers to evaluate, the “greenness” of pyrazole derivatives (126), of photochemistry (127) and of functionalization of heterocyclics (128). This software, elaborating data relative to reagents, solvents, auxiliary materials, products and secondary products, provides an evaluation graph, useful for the understanding of which phase has more environmental impact and to compare different processes. Finally, it must be mentioned that despite all the work so far conducted in the field of green metrics, due to the complexity of a chemical process, the debate on the best metrics to be used and the threshold for deciding the “greenness” reactions still remains open.

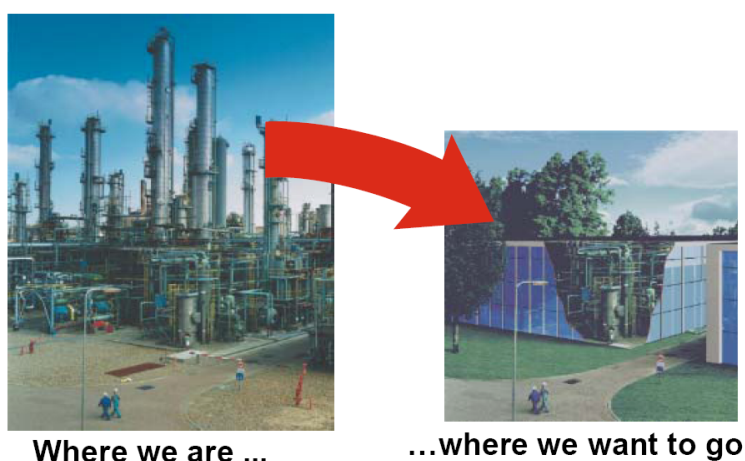
## 4. Conclusions and Future perspectives

Since 1990, Green Chemistry has gained ever increasing importance in organic synthesis, inspiring scientists in academia, industry, and research institutes around the world. The results so far achieved are encouraging: a new “generation” of reactions that avoid the use of toxic and dangerous chemicals and/or waste have been developed, new eco-compatible solvents have been discovered, compounds that perform comparably or better than those already in existence, but that are biodegradable have been produced and energy requirements have been reduced. However, the road is still open and big challenges for scientist remain around the corner.

In this prospect the future of Green Chemistry relies upon three open roads: new renewable feedstock, new synthetic pathways and new products.

Regarding the field of renewable feedstock, the recent BP oil drilling disaster in the gulf of Mexico which began on the night of April 20, 2010 with a tragic explosion that claimed 11 lives, and that now has become the largest environmental disaster in US history, teaches us a hard lesson: fossil fuel utilisation has several dangerous repercussions. Their constant depletion leads to a continuous prospecting for oil in ever more isolated and/or difficult to reach sites. Besides, their use results in large amount of CO<sub>2</sub> emissions and environmental damage. In this prospect, the use of renewable feedstocks is a necessity that chemists must work on to both ensure the energy needs of future generations and most importantly to preserve a green future for our children and grandchildren (Figure 12).

### Sustainability of Chemical Industry:



**Figure 12.** From the current industrial scenario to green industrial chemistry.<sup>41</sup>



New synthetic pathways is also a field with high competition that will employ the talents of many of the next generation of organic and inorganic chemists. It is important to emphasize the huge efforts needed in pursuing synthetic pathways that mimic natural processes in order to avoid emissions into the environment of products that nature is not able to take in and degrade. As chemistry is fast advancing, the sooner more chemists start working in this direction the better it will be for humankind.

Finally, new products should also be taken into account. In fact, the modification of existing products according to human needs should be achieved using Green Chemistry as focal reference point. The new products must be intrinsically secure since they are made for consumers *i.e.* for us. In this context solvents surely have great importance. Chemists must use solvents that not only are environmental friendly but that also aid the efficiency of the reaction being worked on.

Noteworthy chemists must also be aware that to develop green chemistry following the principles of Green Chemistry is not enough. In fact, they should be focused on exploiting new green synthetic routes that are as good or better than the ones currently used by the industry. This means that the economical aspects related to a reaction *i.e.* reagents employed, energy consumed, waste disposal should also and foremost be kept in mind.

In this sense, Green Chemistry has several essential targets to achieve in the near future, targets that can be achieved only by a strong connection between fundamental research and industry. Nowadays industry has the skills to work for the welfare of people and to ultimately demonstrate that chemistry is an essential support for the development and evolution of humankind.

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50. Dimethyl sulfate is extremely toxic compound, it is absorbed through the skin, mucous membranes, and gastrointestinal tract. There is no strong odour or immediate irritation (apart from eye irritation) to warn of lethal concentration in air. Delayed toxicity allows potentially fatal exposures to occur prior to development of any warning symptoms. Symptoms may be delayed 6-24 hours. Besides, its hydrolysis products, monomethyl sulfate and methanol, are environmentally hazardous. In water, the compound is ultimately hydrolyzed to sulfuric acid and methanol.
51. Methyl halides are generally toxic as well as possibly carcinogenic. Breathing methyl iodide fumes, for instance, can cause lung, liver, kidney and central nervous system damage. It causes nausea, dizziness, coughing and vomiting. Prolonged contact with skin causes burns. Massive inhalation causes pulmonary edema.
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