

## Chlorine-free synthesis: An overview\*

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**Abstract:** Since the Industrial Revolution, chlorine has featured as an iconic molecule in process chemistry even though its production by electrolysis of sodium chloride is very energy-intensive. Owing to its high energy and reactivity, chlorine allows the manufacture of chlorinated derivatives in a very easy way:  $\text{AlCl}_3$ ,  $\text{SnCl}_4$ ,  $\text{TiCl}_4$ ,  $\text{SiCl}_4$ ,  $\text{ZnCl}_2$ ,  $\text{PCl}_3$ ,  $\text{PCl}_5$ ,  $\text{POCl}_3$ ,  $\text{COCl}_2$ , etc. in turn are pillar intermediates in the production of numerous everyday goods. This kind of chloride chemistry is widely used because the energy is transferred to these intermediates, making further syntheses easy. The environmental and health constraints (toxicity and eco-toxicity, ozone layer depletion) and the growing need for energy (energy efficiency, climate change) force us to take advantage from available knowledge to develop new chemical strategies. Substitution of chlorine in end products in compounds where “chlorine is used in the making” means that we avoid electrolysis as primary energetic source; this makes chemistry “without chlorine” considerably more difficult and illustrates why it has not found favor in the past.

The rationale behind this Special Topic issue is to seek useful and industrially relevant examples for alternatives to chlorine in synthesis, so as to facilitate the development of industrially relevant and implementable breakthrough technologies.

**Keywords:** beyond-chlorine chemistry; chlorine; green chemistry; metrics; sustainable chemistry.

### INTRODUCTION

In the last 20 years, chemists have put enormous effort into designing chemicals with various applications ranging from medicines and cosmetics to materials and molecular machines. However, for the most part, 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 uses an analysis of the chemical structure of a molecule to identify which part of the molecule provides the characteristic or property that is desired from the products and which 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., metrics and computational studies), the choice of which is largely dependent on the amount of information that exists on the particular substance.

The greatest potential to designing 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.

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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 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 the alkyl chain length on toxicity is unknown, an empirical structure–activity relationship of this kind offers a good 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 suitable 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 that 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 necessary.

Finally, 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, owing 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, which often controls 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 (ODSs).

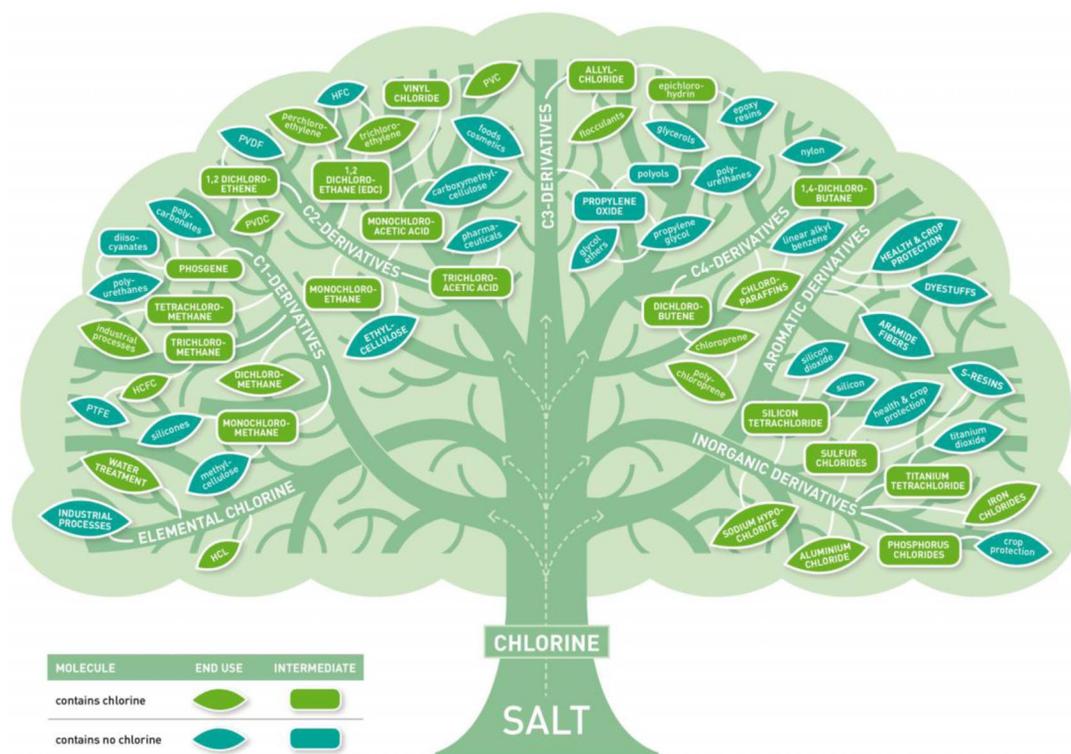
In the past, it was often the goal of the chemist to design substances that were robust and could last as long as possible. This philosophy has resulted in a legacy of wastes, persistent toxic and bioaccumulative substances, and lingering toxic waste sites. Nowadays, it is known that it is more desirable 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, utilization, 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.

## CHLORINE CHEMISTRY

Among halogens, chlorine is by far the most abundant chemical in nature and also the easiest to produce and use. This explains its predominant and seemingly irreplaceable role in the chemical industry (Fig. 1). Five hundred companies at 650 sites around the world have the capacity to produce over 58 million t of chlorine and 62 million t of its co-product, caustic soda, per year.

For example, the European chloro-alkali industry had a production in 2009 of 9.1 million t at about 80 plants, mostly (about 95 %) via electrolysis-based techniques (chlor-alkali industry); the sector directly employs about 40 000 people in 20 European Union (EU) countries. Germany is Europe's largest chlorine producer, accounting in 2009 for 43.5 % of European production [1].

Owing to their peculiar characteristics, halogens are widely used by all sectors of the chemical industry to produce solvents, catalysts, building blocks, additives, and drugs. Chlorine is a major building block in today's chemistry. More than 90 % of pharmaceuticals contain or are manufactured using chlorine, which is also used in the production of 86 % of crop protection chemicals. Furthermore, halogens are contained in several commodities that we all use daily as plastics (e.g., chlorine is contained in polyvinyl chloride, PVC, one of the most widely used plastic materials), solvents for dry cleaning and metal degreasing, textiles, agrochemicals and pharmaceuticals, insecticides, dyestuffs, household cleaning products, and disinfectants. Chlorine is used extensively in organic and inorganic chemistry as



**Fig. 1** Chlorine tree showing most of the derivatives and applications of chlorine chemistry.

an oxidizing agent (i.e., water disinfectant) and as a leaving group in substitution and elimination reactions. Chlorine compounds find use as intermediates in the production of a number of important commercial products that do not contain chlorine. Foremost examples are: polycarbonates, polyurethanes, silicones, polytetrafluoroethylene, carboxymethyl cellulose, and propylene oxide.

Through a chain of chemical derivatives and relatively easily made compounds and intermediates, such molecules have used the intrinsic energy available through the use of chlorine primarily produced via electrolysis.

### Environmental and health concerns

The widespread use of halocarbons was often driven by observations that most of them were more stable than other substances. Their stability tended to encourage beliefs that they were mostly harmless, but starting from the mid-1920s it was discovered that they can cause chloracne or fatal liver diseases in workers in the chemical industries. By the 1950s, toxicity and health hazards related to halocarbons were widely reported.

Concerns about the environmental and health impact of halocarbons were first raised early in the 1960s in studies about DDT and other halocarbon pesticides. Today, they are widely recognized as persistent pollutants and doubts were recently (2006) raised even about very stable molecules such as perfluorooctanoic acid (PFOA) and Teflon, just to mention a few.

Today, European and international legislation for environmental protection is becoming stricter and recognizes that there is a growing need for replacement of halogenated compounds at a productive and end-user level. Besides EU directives, which tackle global environmental concerns (e.g., sustainable development) through prescription about chemical production in the frame of a multi-sector

approach (political, scientific, economical, and social), some regulations are specific to ban or restrict the production of some chemical compounds or byproducts at an industrial level.

The EU has recently established REACH (Registration, Evaluation, Authorization and Restriction of Chemicals), a single integrated system for the registration, evaluation, and authorization of chemicals, together with the European Chemicals Agency (ECHA). REACH requires firms that manufacture and import chemicals to evaluate the risks resulting from the use of those chemicals and to take the necessary steps to manage any identified risk. Industry has the burden of proving that chemicals placed on the market are safe. By the end of 2008, ECHA received approximately 2.75 million requests for preliminary authorization concerning about 150 000 compounds collected in an ECHA online database. Among them, over 20 000 substances are chlorinated and more than 4000 are brominated (this excludes those where “chlorine is used in the making”, which would increase these numbers considerably). The process for authorization will be long (possibly ending in 2018), but a significant fraction of halogenated substances are at risk of rejection, thus forcing their replacement at a productive level.

Furthermore, some international conventions ban or restrict production of specific chemicals. At least two need to be mentioned. The Stockholm Convention on Persistent Organic Pollutants (most of which contain chlorine; byproducts of both domestic and industrial activities) and the Montreal Protocol on Substances That Deplete the Ozone Layer which control the phase-out of ODS production and use. The application of both is managed by the United Nations Environmental Program (UNEP), and all their prescriptions will come into force within 2020. Finally, we must cite the Kyoto Protocol about greenhouse gas (GHG) emissions, which was adopted almost worldwide and then mostly disregarded. International agreements about a follow-up to the Kyoto Protocol are currently in progress (UN Climate Change Conference COP-15, Copenhagen, Denmark, 7–18 December 2009 and preparatory agreements during the G8 summit in L'Aquila, Italy, July 2009).

Today the European and international legislation and EU directives for environmental protection are becoming stricter and recognize that there is a growing need for replacement of particular halogenated compounds at a productive and end-user level.

In 2007, the Intergovernmental Panel on Climate Change (IPCC) stated that some halocarbons were a direct cause of global warming, owing to their nature as GHGs. Some of them are ODSs. Halogen-based materials may show an indirect toxicity or eco-toxicity, releasing halogen atoms/molecules and/or harmful compounds, e.g., in case of accidental fires, a case of particular interest for the electric distribution industry.

## Energy

Since the Industrial Revolution, the halogen chlorine remains “an iconic molecule” for industrial chemical production. Even though its production by the electrolysis of sodium chloride is very energy-intensive, it is still used because it allows the manufacture of chlorinated derivatives in a very easy way, owing to its high energy and reactivity; for example, easily obtained from chlorine are  $\text{AlCl}_3$ ,  $\text{SnCl}_4$ ,  $\text{TiCl}_4$ ,  $\text{SiCl}_4$ ,  $\text{ZnCl}_2$ ,  $\text{PCl}_3$ ,  $\text{PCl}_5$ ,  $\text{POCl}_3$ ,  $\text{COCl}_2$ , etc., which in turn are pillar intermediates in the production of numerous everyday goods. This kind of chloride chemistry is widely utilized because the energy is transferred to these intermediates, making further syntheses easy; a good number of fundamental reactions of the industrial production are based on the synthesis of chloride compounds obtained by reaction with  $\text{SOCl}_2$ ,  $\text{COCl}_2$ , or  $\text{AlCl}_3$  as a catalyst.

From the comparison of energy consumption (expressed in terms of  $\text{kg CO}_2/\text{kg}$ ) in the chloro-alkali, cement, and iron/steel industries shown in Table 1, it can be pointed out that the chlorine industry is extremely energy-intensive, giving a contribution comparable to the iron and steel industry in terms of  $\text{CO}_2$  production/kg product. Actually, 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 have both a direct (as GHGs) and indirect ( $\text{CO}_2$  production) impact on climate change at a global level.

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

	Chloro-alkali manufacturing	Cement	Iron and steel
Kg CO <sub>2</sub> /Kg	1.5	0.95	1.7
World production (2008)	20 Mt (Europe); 21 Mt (China)	2.3 Bt	1.2 Bt

Estimates of the global warming potential (GWP) resulting from chlorine use and the primary energy consumed by the chlorine industry in Europe are 0.29 and 0.45 % of the total GWP and primary energy consumption, respectively. 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.

### Beyond chlorine chemistry

Chlorine-based chemistry very often does not obey the principles of atom economy (AE) and waste minimization introduced, respectively, by B. Trost and R. Sheldon; in fact, halogen anions are byproducts of many organic reactions and represent a waste to be disposed of.

Primary questions are: Can we pursue an intrinsically safer, cleaner, and more energy-efficient alternative to chlorine chemistry? Many of society's greatest challenges and fortune depend on the development of the chloro-alkali industry; but is chlorine-based chemistry sustainable?

The environmental and health constraints (toxicity and eco-toxicity, ozone layer depletion) and the growing need for energy (energy efficiency, climate change) force us to take advantage of available knowledge to develop a new chemical strategy. By the motivation given, it seems appropriate to refer to chlorine-free chemistry as "beyond-chlorine chemistry".

The beyond-chlorine strategy has two approaches, bottom-up and top-down, as follows:

- The bottom-up approach deals with new halogen-free reactions and processes being presently investigated on a lab scale in academies, that could be proposed for exploitation by industry through scaling up for future production (the most appropriate term would be *green chemistry*).
- The top-down approach moves from the industrial needs in basic and applied research; that can be fulfilled through the collaboration with academic partners, and is directed to design halogen-free alternatives for industrial products and processes (the most appropriate term would be *sustainable chemistry*).

Beyond-chloro does not mean, of course, that we should avoid chloride anion, for example in salads, pasta, and other foods; it is noteworthy that Laura Rossi's paper in this issue reports the higher greenness of Cl<sup>-</sup> anion in regard to other anions. Under this context, it is difficult to imagine a disinfectant for water better and less harmful than chlorine.

The substitution of chlorine compounds and of compounds where "chlorine is used in the making" means that we avoid electrolysis as primary energetic source; however, this makes chemistry "without chlorine" considerably more difficult and illustrates why it has not been adopted before.

Four of the above-mentioned seven topics supported by the Organisation for Economic Co-operation and Development (OECD) concern chlorine-free chemistry (specifically Nos. 1, 2, 5, 7).

## CONTENTS OF SPECIAL TOPIC ISSUE

The rationale behind this special topic issue is to seek useful and industrially relevant examples for alternatives to chlorine in synthesis, so as to facilitate the development of industrially relevant and implementable breakthrough technologies.

The 29 papers herein can be partitioned into the following parts:

1. Chlorine-free reagents and reaction selectivity
2. Chlorine-free catalysts
3. Carbonate chemistry
4. Chlorine-free solvents
5. Benign chloro-free methodologies
6. Metrics on chlorine-free syntheses

### Part 1: Chlorine-free reagents and reaction selectivity

Nowadays, it is particularly urgent and timely to investigate 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.

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). Both high selectivity and high conversion must be achieved in order for a synthetic transformation to generate little or no waste. 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.

In this context, electrophilic aromatic substitution by benzyl alcohol is reported in the paper by Prof. Parvulescu, "Replacing benzyl chloride with benzyl alcohol in heterogeneous catalytic benzylation of aromatic compounds".

Very recently, a few authors have published papers on sustainable phosphorous chemistry, dealing with Wittig reaction not involving halogen derivatives [2]. This idea of considering alternative pathways is also gaining interest for other chemical elements such as phosphorous. This aspect is illustrated by Prof. Trofimov's paper, "Novel general halogen-free methodology for the synthesis of organophosphorus compounds".

Establishing innovative solutions that allow substitution of processes consuming phosgene and thionyl chloride by economically competitive and eco-efficient alternatives is a huge challenge for chemists. Phosgene is currently valued as a versatile activating agent and, as such, is essential to the production of chemical intermediates, engineering plastics, agrochemicals, and pharmaceuticals. At 2.2 million t, phosgene is the second largest European outlet of chlorine (17 % at 1.8 million t), and globally it accounts for 5 million t of chlorine consumption per annum. In addition to its energy-intensive production process from chlorine and carbon monoxide, phosgene is highly toxic (currently classified as a viable chemical warfare agent), corrosive, and aggressive, and in most applications its use results in the stoichiometric formation of large amounts of solid waste (1.2 t of sodium chloride per t of phosgene or equivalent amount of salt). Carbamates and ureas are here synthesized by chlorine-free chemistry (Deng, "Environmentally benign and effective syntheses of N-substituted carbamates via alcoholysis of disubstituted ureas over  $\text{TiO}_2/\text{SiO}_2$  catalyst" and Vavasori, "Phosgene-free synthesis of 1,3-diphenylurea via catalyzed reductive carbonylation of nitrobenzene").

Globally, the market for the poly-iodinated imaging materials is between 4 to 5 kT, and much of the mass of these poly-iodinated compounds (>50 %) is from the iodine. With three iodine atoms per molecule and with an equivalent of chlorine being used for every atom, a move to oxygen-based oxidants would be clearly beneficial. Moreover, preferred ways of activating electrophiles for other uses may result from the work. Dr. Lattuada (“Green approaches to the production of iopamidol”) shows how to reduce the amount of thionyl chloride used in the synthesis of iopamidol.

## Part 2: Chlorine-free catalysts

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

It is important to develop halogen-free Lewis acid catalysts that will replace the highly wasteful chlorinated “catalysts” now used by the fine chemicals and pharmaceutical industry for the wide-ranging Friedel–Crafts reaction: a key aspect of all the catalysts developed should be their high selectivity. Highly active catalysts are needed and often are prepared by unconventional methods (Lokteva, “Laser electrodispersion as a new chlorine-free method for the production of highly effective metal-containing supported catalysts”).

A foremost example of chemistry that produces less waste is represented by zeolites [3]. They 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  $\text{AlO}_4$  and  $\text{SiO}_4$ ; each  $\text{AlO}_4$  tetrahedron in the framework bears a net negative charge, balanced by a cation. Some zeolites are found in nature as minerals, many others are synthesized by industry or in the laboratory. Zeolites have many applications. The first major use for zeolites was in the purification of water [4]. Water can be softened by passing it through a zeolite, with pores that incorporate calcium and magnesium ions, rendering the water softer. Zeolites are also used in agriculture, their pores can be filled with potassium, ammonium ions, fertilizer, or other micronutrients [5]. The use of zeolite catalysts in the production of organic (fine) chemicals has appeared as a major new direction [6]. The main advantage of these materials is that their pore size, shape, and properties can be modeled according to the needs of the reaction to be conducted, and to the substrate used (obviously this is not as straightforward as it seems) [7]. 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 an alternative to the cumene process) [8]. For instance, the hydrogen form of zeolites (prepared by ion exchange) are powerful solid-state acids [9] and can facilitate a host of acid-catalyzed reactions, such as isomerization, alkylation, and cracking, because, owing to the thermal stability of their structure, they can be used at high temperature. A comprehensive review on zeolite catalysts is reported here (Guisnet, “Molecular sieve catalysts as substitutes for metal chlorides in the chemical industry: Some selected examples”).

One way to significantly reduce the amount of waste is to substitute traditional acids and Lewis acids with recyclable solid acid catalysts (like heteropolyacids) [10]. Heteropolyacids are largely used for oxidation processes owing 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 [11]. 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 [12]. Examples in catalysis and esterification reactions are here reported (Romanelli, “Simple halogen-free synthesis of aryl cinnamates using Mo-Keggin heteropolyacids as catalyst” and Hou, “Polyoxometalate and copolymer-functionalized ionic liquid catalyst for esterification”).

Other examples of efficient organic synthesis by chlorine-free catalysts are also reported in this issue (Jiang, “Chlorine-free copper-catalyzed oxidative synthesis of 1,3,4-oxadiazoles with molecular oxygen as the sole oxidant” and Wu, “Selective epoxidation of propylene to propylene oxide with H<sub>2</sub> and O<sub>2</sub> over Au/Ti-MWW catalysts”).

### Part 3: Carbonate chemistry

Among the most promising molecules that could aid the substitution of several chlorine-based chemicals, there is CO<sub>2</sub> and, consequently, CO<sub>2</sub> organic compounds (Fig. 2). CO<sub>2</sub> is regarded as an extremely promising building block. However, there is one major problem in the utilization of CO<sub>2</sub>-derived organic chemicals because they are very stable, so they require an energy input to activate and consequently to react. In this regard, one of the objectives is to develop new synthetic pathways and methodologies for the activation of CO<sub>2</sub> organic compounds, i.e., dialkyl carbonates (DACs) and dimethyl carbonates (DMCs) in particular [13]. Once synthesized by phosgene, DACs and DMCs are, since the 1980s, produced by clean processes [14]. Remarkably, DACs are renowned for possessing properties of low toxicity and high biodegradability, which make them true green solvents and reagents and thus appropriate alternatives to chlorine-chemistry.

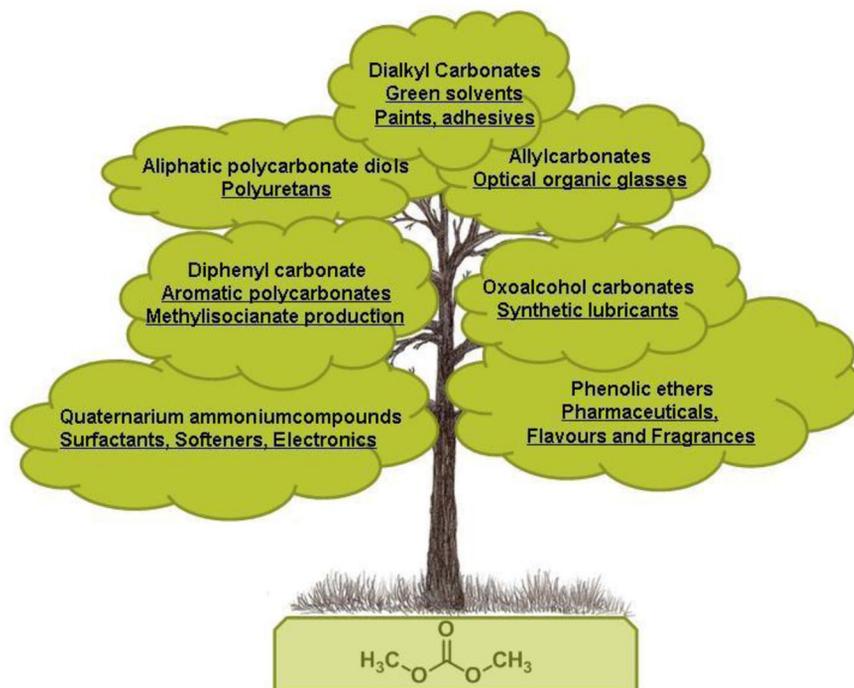


Fig. 2 Carbonate sapling showing most of the applications of dialkyl carbonate chemistry.

It is worth noting that DMCs have numerous similarities with chlorine chemistry: because its reactivity is tunable, DMCs can be used either as a methoxycarbonylation or methylation agent replacing:

1. SOCl<sub>2</sub>: DMC can be employed in place of SOCl<sub>2</sub> for the synthesis of methoxycarbonyl derivatives of alcohols to be used instead of alkyl chlorides in some SN<sub>2</sub> reactions.

2.  $\text{COCl}_2$ : DMC and organic carbonate can be used in place of the  $\text{COCl}_2$  for the synthesis of urethanes, ureas, and their derivatives.
3. Chlorinated solvents: Organic carbonates can be used in place of  $\text{CH}_2\text{Cl}_2$  and other chlorinated solvents.

Organic carbonates are an alternative to chloride chemistry: *ex-ante*:  $\text{CO}_2$  and  $\text{CO}_2$  derivate chemistry substitute the chlorine-based chemistry so as to reduce the world demand for chlorine and thus  $\text{CO}_2$  emissions owing to energy consumption; *ex-post*: organic carbonates are synthesized starting from the  $\text{CO}_2$  insertion into epoxides: this allows the re-use of  $\text{CO}_2$  emitted.

DMC is not toxic because it does not methylate at low temperature as the commonly used methylating agents; however, for the same reason, it is less reactive than dimethyl sulfate (DMS) or chloro methane (MeCl). Comparing the reactivity of esters with DMC, the latter is a better methylating agent as acetate anion is a worse leaving group than methylcarbonate one. However, esters react faster at the carbonyl center: this means that DACs are more stable, so they can be used as solvents.

DMC at the present is widely used for the synthesis of pharmaceutical intermediates, flavors and fragrances, surfactants, softeners, electronics, aromatic polycarbonates, methylisocyanate production, optical organic glasses, polyurethanes, synthetic lubricants, etc. Furthermore, DMC does not smell and is designated as an oxygenated fuel additive of gasoline or diesel oil to replace *tert*-butyl methyl ether [15], meanwhile ethyl-methyl carbonate is used as solvent in lithium batteries.

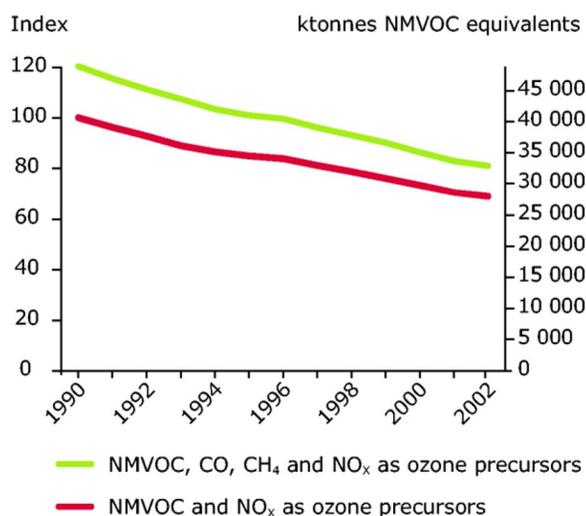
In the last 20 years, the reactivity of DMC in particular and DAC in general has been widely investigated as shown by the exponential increase in the number of publications (50 % increase in the last 10 years). Thus, information on DMC is nowadays good enough to extend its boundaries into innovative and exciting directions in both fundamental (pure) and applied research. From a scientific and technical point of view, the most important appealing feature is the possibility of finding new synthetic pathways to obtain absolutely new products for the synthesis of heterocyclic and cyclic carbamates, which opens up the way for DAC chemistry to new unexpected frontiers of research and applications.

Organic carbonate chemistry is here presented as:

- Reviews: He, "Organic synthesis using carbon dioxide as phosgene-free carbonyl reagent"; Sun, "Recent progress in phosgene-free methods for synthesis of dimethyl carbonate"; Hu, "Chlorine-free catalysts for green synthesis of cyclic carbonates from carbon dioxide"; and Pyo, "Cyclic carbonates as monomers for phosgene and isocyanate-free polyurethanes and polycarbonates".
- Dialkyl carbonate synthesis: Qin, "Direct synthesis of dimethyl carbonate from methanol and carbon dioxide over organotin functionalized mesoporous benzene-silica" and Han, "Synthesis of unsymmetrical organic carbonates catalyzed by a sulfonic acid-functionalized zirconium phosphate".
- Dialkyl carbonate utilization: Garcia, "Activity of ceria and ceria-supported gold nanoparticles for the carbamoylation of aliphatic amines by dimethyl carbonate"; Tundo, "Phosgene-free carbamoylation of aniline via dimethyl carbonate"; and Aricò, "Cyclization reaction of amines with dialkyl carbonates to yield 1,3-oxazinan-2-ones".

#### Part 4: Chlorine-free solvents

Solvents account for the vast majority of mass wasted in syntheses and processes. Besides, solvents often pose several serious issues for human health as they are toxic, flammable, and/or corrosive, as well as to the environment owing 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, direct toxicity to humans is only one aspect of the hazards that solvents possess. The use of certain volatile organic compounds (VOCs) as



**Fig. 3** An example of non-methane volatile organic compound (NMVOC) reduction during the last 20 years in Europe.

solvents and other uses has generated great concern about their ability to elevate atmospheric ozone levels (Fig. 3).

Some of the main areas of research on alternative solvents include solventless systems, aqueous applications, supercritical fluids, and ionic liquids (ILs).

Green solvents and, in particular, nonchlorinated solvents are widely discussed in the papers of this special issue; ILs without halogens are emphasized as a new field of research and application. ILs offer alternatives to conventional molecular solvents for many synthetic transformations. These solvents are often fluid at room temperature, and consist entirely of organic ionic species; they have no measurable vapor pressure, and hence can emit no VOCs. Their uses and applications have been pioneered by Prof. Seddon. An interesting application of ILs is their use in cellulose processing. Making cellulosic fibers by dissolving the so-called pulp involves the use, and subsequent disposal, of great volumes of various chemical auxiliaries. However, ILs can greatly simplify these processes, serving as solvents that are nearly entirely recyclable. BASF is currently investigating the properties of fibers spun from an IL solution of cellulose in a pilot plant.

Synthesis of chloride-free ILs either from other anions (Seddon, "A greener, halide-free approach to ionic liquid synthesis") or from natural feedstocks (Rogers, "Chlorine-free alternatives to the synthesis of ionic liquids for biomass processing") is reported.

Utilization of chlorine-free ILs as solvent is also discussed (Chiappe, "Synthesis of glycerol carbonate from glycerol and dimethylcarbonate in basic ionic liquids").

### Part 5: Benign chloro-free methodologies

Catalytic hydrogenation, oxidation, and carbonylation are good examples of highly atom-efficient and low-salt processes. Industrial sustainable chemistry is not an emerging trend, but is already a reality thanks to the application of "green" chemistry and engineering expertise [16]. The generation of copious amounts of inorganic salts can similarly be largely circumvented by replacing stoichiometric mineral acids, such as  $\text{H}_2\text{SO}_4$ , 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 mineral acids. While many of these processes are catalytic, some require stoichiometric amounts of Brønsted or Lewis acids [17].

Oxidation reactions are reported in this special issue (Liu, “Aerobic oxidation of 5-hydroxymethylfurfural to 2,5-diformylfuran on supported vanadium oxide catalysts: Structural effect and reaction mechanism”), hydrogenation reactions (Jiang, “Hydrogenation of methyl laurate to produce lauryl alcohol over Cu/ZnO/Al<sub>2</sub>O<sub>3</sub> with methanol as the solvent and hydrogen source”), hydrolysis (Zhang, “Effective catalysis of poly(ethylene terephthalate) (PET) degradation by metallic acetate ionic liquids”) and green solvent utilization (Rauter, “Environmentally friendly approaches towards new antibiotics from sugars”).

## Part 6: Metrics of chlorine-free syntheses

Metrics in green chemistry are indicators of environmental issues and pollution associated with chemicals manufacturing. Green metrics provide information already in the design phase of a chemical process and indicate 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.

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 as follows:

- The *effective mass yield* is defined as the percentage of the mass of desired product relative to the mass of all non-benign materials used in a synthesis [18].
- The *E factor* is defined as total waste per product, which is an output-oriented indicator, defined as waste per mass unit of the product ( $\sum \text{waste [kg]}/\text{product [kg]}$ ) [19].
- The *atom economy* (AE) describes 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, AE can be written as: % AE = (molecular weight of desired product/molecular weight of all reactants)  $\times$  100 [20].
- The *mass index* (MI), which is an input-oriented indicator, is defined as the mass of all raw materials used for the synthesis per mass unit of the purified product ( $\sum \text{raw materials [kg]}/\text{product [kg]}$ );
- A method enabling the comparison of different chemical reactions in terms of potential environmental impact and identification of 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*.
- The American Chemical Society Green Chemistry Institute’s Pharmaceutical Roundtable has chosen process mass intensity (PMI) [21].

Prof. Rossi (“Alternatives to free molecular halogens as chemoselective reactants: Catalysis of organic reactions with reusable complexes of halogen metal salts”) shows that metrics are not against the utilization of chloride anion: vice versa, it has a lower impact on chemical processes.

In 2005, J. Andraos, 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 [22]. In this context, in order to identify a sustainable threshold, he also proposed that reactions considered to be green are characterized by a minimum AE of 61.8 % coupled with high yield and high solvent recovery and run under stoichiometric conditions [23].

From these bases, Dr. Andraos built up meticulously the algebra of organic synthesis by employing green metrics [24]. Application of these concepts to chlorine-free chemistry is reported (Andraos, “A green metrics assessment of phosgene and phosgene-free syntheses of industrially important commodity chemicals”).

## CONCLUSIONS

A few impacts on our everyday life can be attained from beyond-chlorine green and sustainable chemistry. For example:

**Industrial safety:** Replacement of dangerous reagents such as phosgene, thionyl chloride, methyl halides, etc., will definitively improve workers' safety in chemical industries and surrounding communities. In fact, most of the research pursued in this project has a potential generic applicability to other industries besides the ones involved in this IUPAC project. Quite clearly, the need not to handle hazardous chloride derivatives would have industrial safety benefits, reducing risk to employees and corrosion risk to plants.

**Energy saving:** Reduced dependence on chlorine electrolysis will increase energy saving and will produce a smaller CO<sub>2</sub> footprint because of lower energy consumption. Halogen-free chemistry may be considered a highly efficient resource.

**Employment and new jobs:** A high training and dissemination backbone will lead to the training of new scientists who are fully aware of the needs of the industries as well as of the environmental problems connected with industrial chemical research. This might create a new class of scientific community—highly qualified and driven by the idea of improving chemical synthetic methodologies with a special focus on the sustainable aspects of processes.

Beyond-chlorine chemistry should provide numerous other opportunities for alternative applications and derivatives, resulting in new, competitive, and resource-efficient process knowledge, based on novel chlorine-free synthetic reactions, for the production of safe and eco-efficient chemical intermediates and materials relevant to many sectors. These technologies are expected to significantly enhance the long-term competitiveness of industry as a whole, especially if this generic philosophy will be adopted by other resource-intensive sectors of industry. The combination of innovative process technology and highly selective, multifunctional catalysts will serve as a model example and bring about a radical shift in the way chemical conversion processes will be designed, allowing the chemical industry to set future sustainable standards and to be closer to customers' needs and requests.

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