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Green Chemistry in the Fine Chemicals and Pharmaceutical Industries

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ABSTRACT: Biocatalysis is the main green chemistry technology adopted by the fine chemicals and pharmaceutical industries to manufacture chemicals with higher yield. Heterogeneously catalyzed processes using supported metal or molecular catalysts are still an exception. Reviewing the actual development of green chemistry in these important segments of the chemical enterprise, we investigate the reasons behind such a delay in innovation. Finally, we consider whether green metrics developed by chemists is actually purposeful to management, and find that this concept needs to be streamlined to include simple financial metrics quantifying the impact of prevention on the company's bottom line.

1. INTRODUCTION

Looking back to the practical achievements of green chemistry in the chemical industry, about 25 years after the introduction of the concept,[1] one is faced by a complex reality.[2] The global chemical industry was called to redesign chemical production to make it more sustainable. Action was undertaken to persuade industrial corporations to change through voluntary action such as, for example, the Responsible Care (RC) program to reduce pollution by industry self-regulation. However, it is enough to review achievements of RC in the chemical industry to find that plants owned by firms participating in the RC program actually raised their toxicity-weighted pollution by 15.9% relative to statistically equivalent plants owned by non-RC participating firms (an increase that is not simply due to increased output and sales).[3]

The fine chemicals and pharmaceutical industries are no exception. The latter industry is generally found weak in introducing catalytic (particularly heterogeneous catalytic) processes and in design of synthetic routes to incorporate such processes.

Following Anastas and Warner,[1] in 2011 Winterton published a book[4] in which green chemistry was put into wider historical and societal context. Similarly, Iles recently provided arguments[5] for which stagnation of green chemistry in the United States (most chemists not practicing green chemistry principles; most chemical companies still having not incorporated green chemistry into their products; law-makers having been largely oblivious; and even environmental organizations only beginning to become aware of green chemistry) has been due to the absence of societal input and public scrutiny of chemistry choices. Chemists advocating green chemistry, furthermore, have generally paid scarce attention to the limits imposed on synthetic processes by thermodynamics.[6]

In academia, green chemistry is flourishing. For example, more than 15 international Conferences and symposia devoted to green and sustainable chemistry were organized in 2013,[7] including the FineCat symposium focusing on the topic of this account.[8] New scientific journals, scholarship programs, and even research institutes have been founded, and a constant flow of review articles appears in the literature since two decades. Focusing on the topic of this account, one should also notice that China and India are each amongst the main countries contributing to advance green chemistry science for the production of fine chemicals. As representative recent examples we will briefly mention here metal nanoparticles deposited by halloysite studied by Zhang and co-workers[9] and the silica-encapsulated Pd sinter-resistant catalysts developed by Nandini Nevi's team.[10]

This journal, *Organic Process Research & Development*, publishes Green Chemistry Highlights twice a year. Thus, in the following, instead of reviewing achievements, we use selected examples of green chemistry methods actually practiced in the fine chemicals and pharmaceutical industries to show the potential and the current limitations of green chemistry manufacturing of fine chemicals. Finally, we consider whether green metrics developed by chemists is actually useful to managers as a decision-making tool and find that this concept needs to be simplified to include simple financial metrics for increasing efficacy of industry adoption of sustainable chemistry.

2. TRENDS IN THE FINE CHEMICALS INDUSTRY

Fine chemicals are pure substances produced in batch reactors in limited volumes (<5000 tons/year; more often <1000 tons/year), and sold at high price (>$10/kg) as starting materials for specialty chemicals, particularly pharmaceuticals and agro-chemicals. Despite rapid progress in flow chemistry,[11] the multipurpose continuously stirred tank reactor (CSTR) remains the core of a typical fine chemical plant. Synthetic processes carried out within the CSTR are catalytic, but generally utilize an homogeneous catalyst (very often an enantioselective metal catalyst), requiring numerous product isolation and purification steps. As a result the (*E*-factor) range of 25−100 kg of waste per kilogram of active pharmaceutical ingredient (API) manufactured proposed by Sheldon[12] in 1992 at the end of the "racemic era" is probably now more realistically 25−200 in the "chiral era".[13]

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A typical industrial CSTR has unit costs ranging from $1 milllion/m^3 for a Western plant, to $0.1 milllion/m^3 for a plant based in China or India.[14] This fact, coupled with low labor cost in Asian countries, simply explains why, in the last two decades, fine chemical production was outsourced to China and to India. The industry, in general, is fragmented with 2000−3000 fine chemical companies whose top 20 enterprises (17 of which are divisions of large chemical or pharmaceutical companies) account for only 20% of the total fine chemical sales.

The customer pharmaceutical industry, in its turn, is a product-oriented industry focusing on product innovation, and thus on time to market, with the aim of preventing obsolescence of the patent protecting a drug's exclusivity. The cost of drugs manufacturing, indeed, is not significant when the drugs go on the market. For comparison, in 2010 the market for pharmaceutical fine chemicals was valued at $23 billion, while the world pharmaceutical market generated a $835 billion turnover.[15]

Most generics, too, are currently being manufactured in low labor cost countries, where weak or absent environmental regulation has allowed for years polluting processes to be carried out with waste disposal as simple as its free discharge into the biosphere.

One might then reasonably argue about the manufacturing quality standards followed in contract manufacturing companies (CMOs) managed according to similar approaches. Indeed, the 2007 case of contaminated heparin from China, that killed more than 80 people in the United States;[16] or the 2010 case of ethylene glycol dispatched from China in place of glycerol, that killed several hundred people in China, Panama, Haiti, Bangladesh, Argentina, Nigeria, and India,[17] are just two examples of problems that led local authorities to increase regulatory safety oversight. Consequently many western pharmaceutical companies are either moving back their production capacity or adopting stringent audit procedures at suppliers' manufacturing sites.[18] The overall aim is to regain control on product quality, putting an end to what Grayson has perhaps aptly called the "madness"[19] of fine chemistry during the last two decades of economic globalization.

This change, coupled with new and stricter environmental regulation, requires that fine chemical companies switch to more efficient, cleaner processes to reduce the waste disposal costs and improve product quality. Remarkably, a number of Asian companies, for example Dr. Reddy's of India,[20] are actively adopting green chemistry practices also in countries that are, as mentioned above, among the main contributors to the progress of green chemistry.

The ultimate goal is to replace multistep homogeneous processes in batch with heterogeneously catalyzed processes in which the enzyme or the organo- or the metal catalyst rapidly and selectively mediates the desired reaction, avoiding waste generation while attaining higher conversion and yield than reaction under batch.

Thus, seen from this perspective catalysis becomes the "enabling technology"[21] identified by Alsters, a European industry's practitioner, as the key chemical technique allowing commercial production of APIs and fine chemicals at low cost in place of expensive chemical routes based on cumbersome processes and infrastructure economically not viable on large scale.

3. BIOCATALYSIS

Enzymes are highly enantioselective catalysts, often yielding enantiomeric excesses of over 99%. With the advent of molecular biology techniques, especially after the Mullis discovery of polymerase chain reaction,[22] and the heterologous expression in genetically optimized hosts,[23] production of enzymes from microbes in the amount required by industry became possible, opening the route to the long awaited application of enzyme catalysis in synthetic industrial processes.[24]

Using enzymes, no protection/deprotection steps (and groups) are required, while the mild reaction conditions of the biotransformation, often but not always in water, result in a longer life span of multipurpose CST reactors. Enantiomeric reduction, hydroxylation, oxidation, hydrolysis, and many other reactions are carried out over enzymes such as oxidoreductases, transferases, hydrolases, lipases, lyases, isomerases, and ligases, delivered by companies specializing in making enzymes.

Enzymes are already used in the synthesis of about 2/3 of chiral products produced on large industrial scale, as they allow doubling the yield from 50% to 100% by eliminating the need of formation of a salt with a chiral compound, crystallization, salt breaking and recycling of the chiral auxiliary.[25] Several valued chiral drugs, too, are manufactured through biocatalysis, including *sitagliptin* (Januvia), *rosuvastatin* (Crestor), *atorvastatin* (Lipitor) and *montelukast* (Singulair).

Enzymes, however, can be expensive and biocatalysis is still the exception, rather than the rule, for the organic synthesis of pharmaceuticals, flavour and fragrance, vitamin and fine chemicals.[26]

Biotechnology companies routinely explore promising new classes of enzymes, aiming to identify enzymes with broader substrate acceptance and higher selectivity, for example using directed evolution of enzymes for selecting thermostable enzyme mutants[27] or other biotechnology techniques to evolve customized enzymes capable of better industrial performance. Contract manufacturing companies, in their turn, work to further reduce process cost, increase productivity, and improve product quality, for example by developing disposable bioreactors amenable for fast downstream purification.

Heterogeneous biocatalysis with immobilized enzymes would benefit from the distinct advantages of heterogeneously catalyzed processes, such as process simplification (fast and easy product isolation, catalyst recovered by simple filtration after reaction), enhanced product quality and reduced environmental footprint. The world market of industrial enzymes, however, is dominated by nonimmobilized (mainly hydrolytic) enzymes, with only a small fraction of immobilized enzymes,[28] and this despite the fact that many different methods are available, such as CLEA (cross-linked enzyme aggregates),[29] CSDS (cross-linked spray dried enzymes), and the sol−gel encapsulated enzymes discovered by Avnir an co-workers in 1990.[30] Perhaps the single most important exception is the series of ORMOSIL-encapsulated lipases discovered by Reetz in 1994, and readily commercialized by Fluka.[31]

Bristol-Myers Squibb produces (*S*)-amino acids from a racemic amino acid by selective oxidation with amino oxidases immobilized on Celite.[32] India's Fermenta Biotech sells immobilized *Penicillin G Acylase* (Fermase PA850) for the synthesis of cephalasporins.[33] The company uses a platform technology (*Dilbeads*) to immobilize enzymes in macro porous polymer beads with epoxy or hydroxyl groups for enzyme

binding, which includes *Candida antarctica* lipase B or *CALB lipase* in immobilized form (Fermase CALB 10000) for various applications. Lonza has an immobilized whole cell industrial process for vitamin B3, namely nicotinamide used as a vitamin supplement for food and animal feed. A continuous biotransformation process on a scale of 6000 t/y is operated at low temperature and atmospheric pressure over cells of wild-type *Rhodococcus rhodochrous* J1 immobilized over alginate beads, an effective technology pioneered by Nagasawa and Yamada in Japan.[34]

In most of these cases, the immobilized enzymes and cells retain high activity when subjected to a constant and prolonged flux of substrates, while the technology continues to evolve rapidly. The sol−gel bioencapsulation within SiO_2,[35] in particular, offers unprecedented stability and good mechanical strength. Sol−gel encapsulated lipases, for example, are currently used for the industrial production of various specialty esters, aroma compounds, and cosmetic agents at Evonik.[36] The reaction for producing several hundreds of tons per year of cosmetic esters is carried out in flow over ORMOSIL xerogels doped with encapsulated enzymes and further inserted into advanced packed bed reactors. Degradation of the heterogeneous catalyst is significantly reduced, while enhanced product quality and lack of purification requirements support the economic viability of the new process replacing analogous reaction in the CSTR.

4. HETEROGENEOUS CATALYSIS

The potential relevance of heterogeneous catalysis to the fine chemicals industry cannot be underestimated. Stable and selective solid catalysts, when available, would be ideally suited for easily scaled-up continuous processes to produce the desired quantities of pharmaceutical or fine chemicals demanded by the customer. Annual conferences are organized, and themed journal issues on the topic are published. However, with the exception of heterogeneously catalyzed hydrogenation, when one compares the practical achievements with the scope and extent of research efforts, perhaps no other field in chemical research may record such poor practical achievements.

For instance, researchers at Solvias described in 2010 prolonged attempts to replace the corresponding Ir catalyst with $[Ir(COD)Cl]_2$ supported on chiral ligand *Josiphos* (a proprietary ligand from Solvias) immobilized on functionalized silica on polystyrene supports for the manufacture of the enantiopure herbicide, (*S*)-*metolachlor* at that time produced at >20,000 tonnes per year via asymmetric hydrogenation.[37] The conclusion was that the homogeneous catalyst was preferred over the supported analogue.

From asymmetric hydrogenation to carbon−carbon and carbon−nitrogen cross-coupling reactions, homogeneous organometallic catalysis is indeed widely employed both in the fine chemicals and in the pharmaceutical industries in synthesizing chiral and nonchiral compounds, with new developments relevant to the industry being introduced on a routine basis.[38] The reaction is carried out in the stirred reactor in solution, often using a volatile (and toxic) organic solvent. Upon reaction completion, the thermally sensitive catalyst must be separated from the product, whose low volatility excludes fractional distillation that would take place above the decomposition temperature of the catalyst. This separation problem has led to the introduction of metal-scavenging products and processes to remove metal impurities and meet the ever more stringent regulatory restrictions on the level of metals allowed in pharmaceutical products (few parts-per-million).[39]

Hence, instead of leach-proof solid catalysts, a number of metal-specific solid products such as polyolefin fibers, resins, and silicas functionalized with different organic groups (thiol, amino, carboxylic acid, phosphonic acid, acetate, and other groups) entered the market and are today widely employed to selectively bind and remove metal species, leaving the desired product in solution. The catalyst becomes an impurity, and the cost of its loss is added to the overall process cost, thus translating into higher product price.

Heterogenized Homogeneous Catalysts. As emphasized by Cole-Hamilton, the fine chemicals industry needs supported catalysts.[40] Consequently, large research efforts have been devoted in the last two decades to heterogenize and immobilize homogeneous catalysts over solid supports with the aim of obtaining leach-proof catalysts that combine the advantages of homogeneous catalysis (reactivity and selectivity) and of heterogeneous catalysis (recovery and recyclability).

Yet, most of the catalysts developed thus far suffer from severe leaching which compromises catalyst lifetime and contaminates reaction products. One of the few large-scale processes which uses supported catalysts is from a Japanese company (Chiyoda) that uses supported rhodium for methanol carbonylation.[41] Leaching of rhodium occurs, and the metal is trapped on a guard bed. The flows are thus reversed so that the guard bed becomes the catalyst bed. Another exception is heteropolyacids attached to alumina supports developed by Augustine and co-workers during the 1990s and later licensed to Johnson Matthey and Engelhard (the technology attaches the metal atom to an alumina support through a heteropolyacid).[42]

Usually, heterogeneous catalysts are differentiated on the basis of the three different methodologies for immobilisation: adsorption, encapsulation, and tethering (using covalent bonds or electrostatic interaction). We emphasize, instead, that the main difference among heterogeneous catalysts is between two-dimensional (2-D) surface-derivatized and 3-D encapsulated materials. In the first broad class of functional materials, the active species are left unprotected at the material's pore surface, whereas in encapsulated materials the entrapped species is protected within the materials inner porosity.

As a consequence, encapsulated materials are generally safer to handle as they are not pyrophoric. In general, however, the poor stability of many heterogenized systems explains why few catalytst have found industrial application. Only recently, a number of newly developed molecular and metal solid catalysts were commercialized, and industry is slowly starting to adopt some of them for replacing homogeneous catalysts. Examples include former Reaxa (now India's S. Amit & Co.) *EnCat* line of transition metal catalysts microencapsulated in polyurea,[43] Johnson-Matthey's *FibreCat* polyethylene and polypropylene fibers functionalized with ligands to bind and support the catalyst metal precursor complex,[44] PhosphoniX's functionalized silicas,[45] and SiliCycle's organosilica-entrapped Silia*Cat* series, whose oxidation organocatalyst, TEMPO, was first commercialized in 2007.[46]

Heterogenized Metal Nanoparticles. Catalytic hydrogenation over supported metal nanoparticles (MNPs) is the only widely used heterogeneously catalyzed reaction in the fine chemicals and pharmaceutical industry. Highly efficient and ecological heterogeneous hydrogenation processes are widely employed for the production of vitamins nutraceuticals,

pharmaceuticals, flavours and fragrances, agrochemicals and fine chemicals. In state of the art processes taught in 2012 by Roessler, a leading catalysis expert formerly with Roche and DSM,[47] metal loss varies from 2 to 5% for supported Pd and Pt catalysts through 5 times higher values for supported Ru (Table 1). After use, the catalyst is sent back to the manufacturer for refining and remanufacturing, with most valued metal value being recovered and made available for reuse.

Table 1. Typical losses at refining for platinum group metals used as hydrogenation catalysts [reproduced from ref 47, with kind permission]

metal	metal losses, %
Pd	2−5
Pt	2−5
Rh	5−10
Ru	10−15

Research in the field continues. *NanoSelect*, for example, is the trademark of the heterogeneous catalysts made by BASF through reduction−deposition of MNPs over supports such as activated carbon or titanium silicate with good control over metal crystallite size. The *NanoSelect* Pd catalyst, for example, is marketed as a lead-free alternative to the Lindlar catalyst for the hydrogenation of alkynes to alkenes (without further reduction into alkanes).[48] Interestingly, even if high metal concentration is possible, filtration experiments indicate that little metal leaching takes place during hydrogenation mediated by *NanoSelect* Pd at low Pd loadings, whereas this is not the case that at higher Pd-loadings when significant leaching of the valued metal takes place.

The first multipotent series of encapsulated MNPs was recently made available from SiliCycle. Its Silia*Cat* organosilica-entrapped palladium and platinum nanoparticles catalyze with excellent performance the stereoselective hydrogenation of vegetable oils,[49] formation of new carbon−carbon bonds,[50] as well as the ultraselective hydrosilylation[51] and hydrogenation[52] of alkenes, and many other reactions including debenzylation. The reasons for such enhanced performance of MNPs entrapped in organosilica xerogel matrices are due to better steric control over the substrate's interaction with the encapsulated MNPs, as well as to other subtle structural effects that were recently elucidated.[53]

Contrary to organic polymers, silica-based materials do not swell in organic solvent, whereas the catalytic species entrapped within the inner huge porosity of the amorphous silica matrix are physically and chemically stabilized and accessible to external reactants.[54] The sol−gel encapsulation indeed greatly improves the selective activity of many entrapped species including immobilized metal species, affording higher enantio-selection than nonimmobilized counterparts,[55] or 10-fold increase in enzymatic activity as shown by Reetz for ORMOSIL-entrapped lipases.[31]

Towards an Effective Greenness Metrics of Chemical Syntheses. Measurement of chemical synthesis "greenness" is important, and many authors have made important advances in synthetic route analysis for sustainability. Andraos, for example, has introduced a new benign index (BI) parameter, as a fraction between 0 and 1, that can be applied to assess the overall "greenness" of chemical reactions and synthesis plans.[56] Along with material efficiency, the index takes into account numerous environmental and health harm aspects (acidification−basification, ozone depletion, global warming, smog formation, inhalation and ingestion toxicity and carcinogenicity, bio-concentration, abiotic resource depletion, cancer potency, persistence, and endocrine disruption). The BI is then added (as another radial axis) to other material efficiency metrics to produce an overall radial hexagon diagram that can be used to evaluate the green merits of a chemical reaction.

Similarly, with the aim to move towards metrics based on life cycle assessment (LCA) methodologies, industry's researchers at different companies recently introduced process mass intensity and LCA tools to evaluate and benchmark progress towards more sustainable manufacturing of APIs and fine chemicals.[57]

These tools are important and useful, especially during the route development stages when life cycle inventory data are not readily available. Yet, management ladders need simpler metrics to help them in adopting decisions. In the 1960s Crosby, a medical doctor turned into manager at a large U.S. corporation, proposed the idea to use the price of nonconformity (PONC) as a simple financial measure to assess quality at work at both manufacturing and service companies.[58] Quality, according to this simple and yet fruitful approach, is obtained through prevention, rather than by control.

Crosby insisted that quality was free, because removing errors, omissions, and superfluous work from manufacturing processes did not add cost, but rather reduced it. Seen from this perspective, the large materials waste testified by the 25−200 *E*-factor of the fine chemicals and pharmaceutical companies stands as the hallmark of poor process quality, adding unwanted cost that a company would rather eliminate from its overall PONC, if only economically viable alternative technologies were available.

Industry's managers will then be presented with the overall cost of the process (C), including the intrinsic process cost (C_i) plus the PONC cost of producing unwanted byproducts (eq 1):

$$C = C_i + \text{PONC} \quad (1)$$

To reduce cost, a company will rightly undertake action to eliminate waste from the PONC voice in the above equation. Clearly, if the intrinsic cost of the new process proposed is higher than the reduction in PONC obtainable, the new process will either not be adopted, or it will be abandoned as happened recently with the production of fine chemicals in $scCO_2$ (supercritical carbon dioxide) at a fine chemicals company in the United Kingdom (Thomas Swan & Co) that recently ceased production of fine chemicals through heterogeneous catalysis in $scCO_2$.

On the other hand, when and where the economic advantages are significant and clearly communicated, such as in the case of the enzymatic biocatalytic processes for the manufacture of APIs mentioned above, such effective communication relying on clear financial figures will overcome any resistance to change.

In brief, the new catalysts and catalytic processes developed by research chemists and chemical engineers need to offer clear economic advantages that justify their adoption in replacement of older technology. Thanks to scientific and technical progress in catalysis and catalytic processes, this shift is becoming increasingly possible. Research chemists will thus consider these simple, but important, arguments throughout the research planning and execution to avoid disappointment when new technology, despite its technical advantages, remains confined to the laboratory.

5. OUTLOOK

Faced by rapidly increasing cost and by numerous safety and quality problems, the fine chemicals and pharmaceutical industries are clearly shifting to biocatalysis and, more slowly, to heterogeneous catalysis to replace traditional homogeneous synthetic processes in batch CSTR with green alternative methods, provided that they are economically viable.

The *E*-factor = 200 value of this industry, dwarfed by the typical *E* = 0.1 value of the petrochemicals industry,[10] stands as a mark to the industries' process obsolescence that, in its turn, stands against the sophisticated chemical structures synthesized by this industry. This conflict between product and process innovation can now be solved. A number of important industrial procedures are being revisited using heterogeneous catalysis in flow,[59] such as in the scaling up of artemisinin production currently attempted by McQuade and co-workers. Many companies (DSM, Lonza, Lilly, Novartis, GSK)[60] carry out large-scale processes in continuous process, even if they are generally not published.

Enzymatic processes in organic fine chemical synthesis are growing at fast rate especially for the manufacture of chiral fine chemicals. Heterogeneous catalysts, too, finally progressed up to a stage where the second-generation commercial functionalized materials lately became commercially available with pioneering companies offering solid catalysts suitable for selective hydrogenation, carbon−carbon coupling, debenzylation, hydrosilylation, and many other industrially relevant reactions, including conversion of natural terpenoids into valuable fragrances, perfumes, flavours, pharmaceuticals, and synthetic intermediates.[61]

In both cases (bio- and heterogeneous catalysis) production processes become similar to the zero-waste "lean" continuous processes today used by the most advanced manufacturing companies, in which products are obtained in seamlessly integrated zero-waste processes carried out in flow. This evolution will slowly but inevitably lead to realization of the ultimate goal of green chemistry in this strategic industry: chemical manufacturing with no waste generation and with minimal energy use. This progress, we argue in conclusion, will continue until visible light is used as an environmentally benign reagent for selective syntheses under ambient conditions over new solid photocatalysts.[62] Researchers capable of using simple financial metrics to assess the convenience of newly developed green processes, such as the one proposed herein, will only increase the rate of management uptake of clean chemical technology in this strategic industry.

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Notes

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