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The E Factor: 15 years on

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The E Factor: fifteen years on

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The purpose of this perspective is to review the effect that the E Factor concept has had over the last fifteen years on developments in the (fine) chemical industry and pharmaceutical industry with regard to waste minimisation and to assess its current status in the broader context of green chemistry and sustainability. We conclude that the E Factor concept has played a major role in focusing the attention of the chemical industry world-wide, and particularly the pharmaceutical industry, on the problem of waste generation in chemicals manufacture. It provided, and continues to provide, the impetus for developing cleaner, more sustainable processes.

1. Introduction: origins of the E Factor concept

The fifteenth anniversary of the publication of the E Factor concept¹ seemed like a good moment in time to reflect on the effect it has had on process chemistry and process chemists and the role it may have played in promoting change. In the early 1980s our attention was drawn to the problem of waste in the (fine) chemicals industry by the closure of a phloroglucinol plant at Océ Andeno (later to become part of DSM Fine Chemicals). The plant was shut down because the cost of disposing of the waste was rapidly approaching the selling price of the product. As is shown in Fig. 1, the process involved vintage 19th century organic chemistry: oxidation of 2,4,6-trinitrotoluene (TNT) with potassium dichromate in fuming sulfuric acid (oleum), followed by Béchamp reduction with iron and hydrochloric acid to give, after *in situ* decarboxylation, 1,3,5-triaminobenzene.² Subsequent heating of the acidic solution of the latter afforded phloroglucinol.

This process generated *ca.* 40 kg of solid waste containing $\text{Cr}_2(\text{SO}_4)_3$, NH_4Cl , FeCl_2 and KHSO_4 for every kg of phloroglucinol. Based on this edifying experience we began

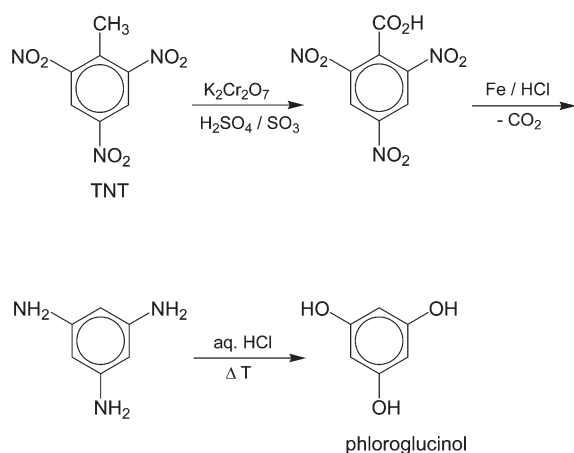


Fig. 1 Phloroglucinol manufacture from TNT.

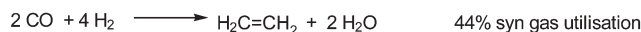
an inventory of the amount of waste formed in processes for the manufacture of other fine chemicals and pharmaceutical intermediates and some bulk chemicals. It soon became clear that tens of kg of waste per kg product was no exception in the fine chemicals industry. This led us, in the late 1980s, to propose what we called the E(nvironmental) Factor (kg waste/kg product) for assessing the environmental impact of manufacturing processes and the now well-known Table of E Factors was used to illustrate the problem of waste in different segments of the chemical industry (see later).

At about the same time we also began using what we called the *atom utilisation* concept for quickly assessing the environmental acceptability of processes at an early stage, by analogy with the use of '*syn gas utilisation*'. We developed the latter in the late 1970s to roughly assess the commercial viability of various processes for the production of commodity chemicals from syn gas.³ The idea was simple: the more atoms of the syn gas that ended up in the product the better. Methanol synthesis, for example, involves 100% syn gas utilisation, while ethylene utilises only 44%. Extension of this concept afforded the idea of using *atom utilisation* to assess the (potential) environmental acceptability of processes. An example, which we used to illustrate this concept, was a comparison of the traditional chlorohydrin route to ethylene oxide with the commercial process *via* oxidation of ethylene with molecular oxygen (see Fig. 2). The concept was reported in an interview published in 1991.⁴ At about the same time Trost published his elegant paper⁵ on the *atom economy* which became the widely accepted terminology, although it is also referred to as *atom efficiency*. We presented our concepts at the International Symposium on Catalytic Chemistry for Global Environment in Sapporo, Japan, in July, 1991, and they were subsequently published in 1992.¹

2. Enter green chemistry and sustainability

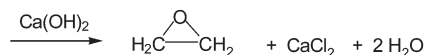
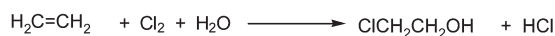
Interestingly, at about the same time the concept of green chemistry was being formulated, by Anastas^{6–10} at the US Environmental Protection Agency (EPA), to address the environmental issues of both chemical products and the processes by which they are produced. The guiding principle is the *design* of environmentally benign products and processes

Syn gas utilisation:

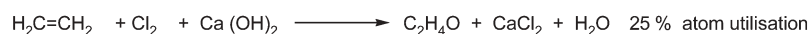


Atom utilisation:

1. Chlorohydrin process



Overall:



2. Direct oxidation



Fig. 2 Syn gas utilisation and atom utilisation.

(benign by design) which is embodied in the 12 Principles of Green Chemistry,⁶ the essence of which can be reduced to the following working definition.

Green chemistry efficiently utilises (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.

According to this definition 'raw materials' includes the source of energy. Green chemistry eliminates waste at source, *i.e.*, it is primary pollution prevention rather than waste remediation (end-of-pipe solutions). Prevention is better than cure (the first of the twelve principles of green chemistry). In the last fifteen years the concept of green chemistry has become firmly entrenched in both industrial and academic circles and several books have been devoted to the subject.^{6,7,9-14} Subsequently, Anastas and Zimmerman¹⁵ proposed the twelve principles of green engineering which embody the same underlying features—conserve energy and resources and avoid waste and hazardous materials—as those of green chemistry, but from an engineering viewpoint. More recently, a mnemonic, PRODUCTIVELY, has been proposed by Poliakov *et al.*¹⁶ which captures the spirit of the twelve principles of green chemistry and can be presented as a single slide.

An alternative term, often more favoured by the chemical industry, is sustainable development, a concept which dates back to the late 1980s and can be defined as:¹⁷ *Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs.* One could say that sustainability is our ultimate common goal and green chemistry is the means of achieving it.

3. E Factors and atom efficiency as green metrics

It is now generally accepted that two useful measures of the (potential) environmental acceptability of chemical processes

are the E factor,^{1,18-21} defined as the mass ratio of waste to desired product, and the atom efficiency, calculated by dividing the molecular weight of the desired product by the sum of the molecular weights of all substances produced in the stoichiometric equation. The enormity of the waste problem in chemicals manufacture is readily apparent from a consideration of typical E factors in various segments of the chemical industry (Table 1).

The E factor is the actual amount of waste produced in the process, defined as everything but the desired product. It takes the chemical yield into account and includes reagents, solvent losses, all process aids and, in principle, even fuel (although this is often difficult to quantify). There is one exception: we generally excluded water from the calculation of the E factor. For example, when considering an aqueous waste stream only the inorganic salts and organic compounds contained in the water are counted, the water itself is excluded. Inclusion of water used in the process can lead to exceptionally high E factors in many cases and can make meaningful comparisons of processes difficult.¹³

A higher E factor means more waste and, consequently, greater negative environmental impact. The ideal E factor is zero. Put quite simply, it is kilograms (of raw materials) in, minus kilograms of desired product, divided by kilograms of product out. It can be easily calculated from a knowledge of the number of tons of raw materials purchased and the number

Table 1 E factors in the chemical industry

| Industry segment | Product tonnage | E Factor (kg waste/kg product) |
|------------------|----------------------------------|--------------------------------|
| Oil refining | 10 ⁶ –10 ⁸ | <0.1 |
| Bulk chemicals | 10 ⁴ –10 ⁶ | <1–5 |
| Fine chemicals | 10 ² –10 ⁴ | 5–50 |
| Pharmaceuticals | 10–10 ³ | 25–100 |

of tons of product sold, for a particular product or a production site or even a whole company. It is perhaps surprising, therefore, that many companies are not aware of the E factors of their processes. We hasten to point out, however, that this situation is rapidly changing and the E factor is being widely adopted by the fine chemicals, pharmaceutical and even the bulk chemical industries. We also note that this method of calculation will automatically exclude water used in the process but not water formed.

Other metrics have been proposed for measuring the environmental acceptability of processes. Hudlicky and co-workers,²² for example, proposed the effective mass yield (EMY), which is defined as the percentage of product of all the materials used in its preparation. As proposed, it does not include so-called environmentally benign compounds, such as sodium chloride, acetic acid, *etc.* This is questionable as the environmental impact of such substances is very volume-dependent. Constable and co-workers of GlaxoSmithKline²³ proposed the use of mass intensity (MI), defined as the total mass used in a process divided by the mass of product, *i.e.*, $MI = E \text{ factor} + 1$, and the ideal MI is 1 compared with zero for the E factor. These authors also suggest the use of so-called mass productivity, which is the reciprocal of the MI and, hence, is effectively the same as EMY. Attempts have also been made to unify the different green metrics.²⁴ More recently, the Green Chemistry Institute Pharmaceutical Round Table has used the Process Mass Intensity (PMI), which is the same as Mass Intensity, to benchmark the environmental acceptability of processes used by its members (see the Green Chemistry Institute website). The latter include several leading pharmaceutical companies (Eli Lilly, GlaxoSmithKline, Pfizer, Merck, AstraZeneca, Schering-Plough and Johnson & Johnson). The aim was to use this data to drive the greening of the pharmaceutical industry.

In our opinion none of these alternative metrics offers any particular advantage over the E factor for giving a mental picture of how wasteful a process is. As noted above, the ideal (P)MI is 1 whereas the ideal E Factor is 0, which more clearly reflects the ultimate goal of zero waste.

As is clear from Table 1, enormous amounts of waste, comprising primarily inorganic salts, such as sodium chloride, sodium sulfate and ammonium sulfate, are formed in the reaction or in subsequent neutralisation and other work-up steps. One of the reasons that the E factor increases dramatically on going downstream from bulk to fine chemicals and pharmaceuticals is that the latter involve multi-step syntheses and pharmaceutical companies have emphasised that the *absolute* amount of waste is lower than in bulk chemicals because of the much lower production volumes involved. However, the larger E Factors in the fine chemical and pharmaceutical industries are also due to the widespread use of classical stoichiometric reagents rather than catalysts (see later). Hence, we felt that the lower absolute amounts, compared with bulk chemicals, should not be used as an excuse for not doing anything to reduce the E Factor of processes in the fine chemicals and pharmaceuticals segments. It was abundantly clear, 15 years ago, that a paradigm shift was necessary to change from the traditional concepts of process efficiency and optimisation that exclusively focus on chemical

yield of the desired product to one that assigns economic value to eliminating waste and avoiding the use of toxic and/or hazardous chemicals. It was necessary that enviro-economics become a major driving force in technological innovation.

4. Atom for atom

The atom utilisation, atom efficiency or atom economy concept, elegantly promulgated by Trost,²⁵ is an extremely useful tool for rapid evaluation of the amounts of waste that will be generated by alternative processes. It is calculated by dividing the molecular weight of the product by the sum total of the molecular weights of all substances formed in the stoichiometric equation for the reaction involved. For example, the atom efficiencies of stoichiometric (CrO_3) *versus* catalytic (O_2) oxidation of a secondary alcohol to the corresponding ketone are compared in Fig. 3.

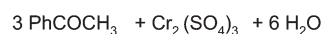
In contrast to the E factor, it is a theoretical number, *i.e.*, it assumes a chemical yield of 100% and exactly stoichiometric amounts and disregards substances which do not appear in the stoichiometric equation. A theoretical E factor can be derived from the atom efficiency, *e.g.*, an atom efficiency of 40% corresponds to an E factor of 1.5 (60/40). In practice, however, the E factor will generally be much higher since the yield is not 100%, an excess of reagent(s) is used and solvent losses and salt generation during work-up have to be taken into account.

It is interesting to calculate the atom efficiency of the phloroglucinol process discussed above. The stoichiometric equation for that process is shown in Fig. 4. This affords an atom efficiency of *ca.* 5% which translates to a theoretical E Factor of *ca.* 20, whereas in reality it is 40.

5. The nature of the waste

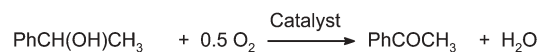
All of the metrics discussed above take only the mass of waste generated into account. However, what is important is the environmental impact of this waste, not just its amount, *i.e.*, the nature of the waste must be considered. One kg of sodium chloride is obviously not equivalent to one kg of a chromium salt. Hence, we introduced¹⁸ the term 'environmental quotient', EQ, obtained by multiplying the E factor with an arbitrarily assigned unfriendliness quotient, Q. For example,

Stoichiometric:



$$\text{Atom efficiency} = 360 / 860 = 42\% \quad E_{\text{theor}} = \text{ca. } 1.5$$

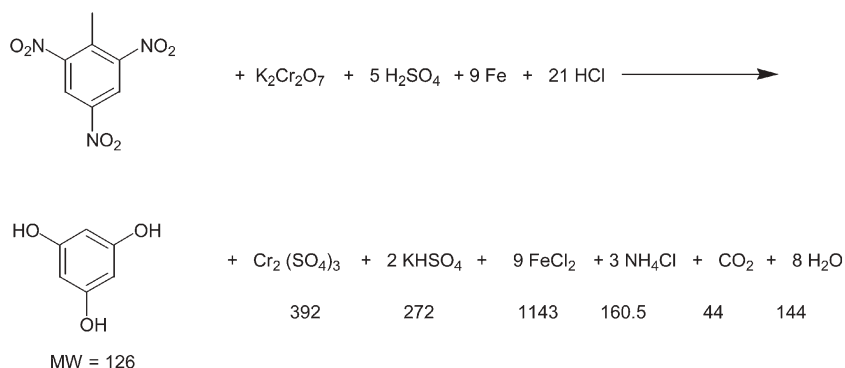
Catalytic:



$$\text{Atom efficiency} = 120/138 = 87\% \quad E_{\text{theor}} = \text{ca. } 0.1(0)$$

Byproduct: H_2O

Fig. 3 Atom efficiency of stoichiometric *versus* catalytic oxidation of an alcohol.



$$\text{Atom Efficiency} = 126 / (126 + 392 + 272 + 1143 + 160.5 + 44 + 144) = 126 / 2282 = \text{ca. } 5\%$$

Fig. 4 Stoichiometric equation of the TNT to phloroglucinol process.

one could arbitrarily assign a Q value of 1 to NaCl and, say, 100–1000 to a heavy metal salt, such as chromium, depending on its toxicity, ease of recycling, *etc.* The magnitude of Q is obviously debatable and difficult to quantify but, importantly, ‘quantitative assessment’ of the environmental impact of chemical processes is, in principle, possible. It is also worth noting that Q for a particular substance can be both volume-dependent and influenced by the location of the production facilities. For example, the generation of 100–1000 tons per annum of sodium chloride is unlikely to present a waste problem, and could be given a Q of zero. The generation of 10 000 tons per annum, on the other hand, may already present a disposal problem and would warrant assignation of a Q value greater than zero. Ironically, when very large quantities of sodium chloride are generated the Q value could decrease again as recycling by electrolysis becomes a viable proposition, *e.g.*, in propylene oxide manufacture *via* the chlorohydrin route. Thus, generally speaking the Q value of a particular waste will be determined by its ease of disposal or recycling. We also mention that, in our experience, organic waste is, generally speaking, more easy to dispose of than inorganic waste. This is important when considering biocatalytic processes (see later).

6. The role of catalysis

As noted above, the waste generated in the manufacture of organic compounds consists primarily of inorganic salts. This is a direct consequence of the use of stoichiometric inorganic reagents in organic synthesis, particularly in fine chemicals and pharmaceuticals manufacture. Examples which readily come to mind are stoichiometric reductions with metals (Na, Mg, Zn, Fe) and metal hydride reagents (LiAlH₄, NaBH₄), oxidations with permanganate, manganese dioxide and chromium(VI) reagents. A classic example is the phloroglucinol process discussed above, which combines an oxidation with stoichiometric amounts of chromium(VI) with a stoichiometric reduction with Fe/HCl. Similarly, a multitude of reactions, *e.g.*, sulfonations, nitrations, halogenations, diazotisations and Friedel–Crafts acylations, employing stoichiometric amounts of mineral acids (H₂SO₄, HF, H₃PO₄) and Lewis acids (AlCl₃, ZnCl₂, BF₃) are major sources of waste. The solution is

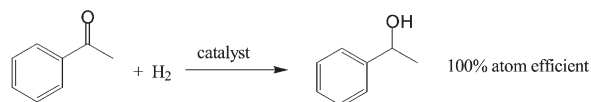
evident: substitution of antiquated stoichiometric methodologies with cleaner catalytic alternatives. Indeed, a major challenge in chemicals manufacture in general is to develop processes based on H₂, O₂, H₂O₂, CO, CO₂ and NH₃ as the direct sources of H, O, C and N. Catalytic hydrogenation, oxidation and carbonylation (Fig. 5) 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 H₂SO₄, and Lewis acids and stoichiometric bases, such as NaOH, KOH, with recyclable solid acids and bases, preferably in catalytic amounts.²⁶

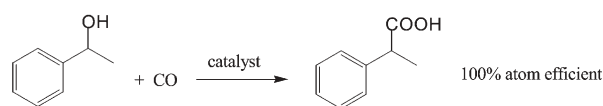
7. Bulk chemicals: propylene oxide and caprolactam

The waste problem is not limited to fine chemicals. Although catalytic processes have, for economic reasons, been widely applied in the manufacture of bulk chemicals, there are still some processes which use stoichiometric inorganic reagents

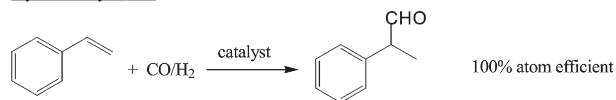
Hydrogenation:



Carbonylation:



Hydroformylation:



Oxidation:

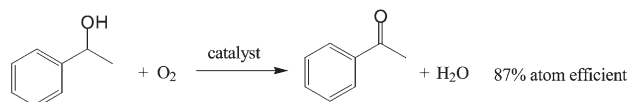
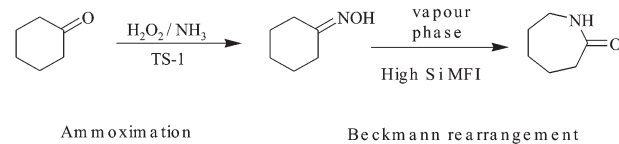


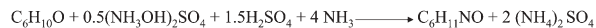
Fig. 5 Atom efficient catalytic processes.

and generate several kg of waste per kg of product (hence the range of <1–5 in Table 1). Although catalytic oxidation is widely applied in the bulk chemicals industry²⁷ there are still a few processes which use stoichiometric inorganic oxidants. A case in point is propylene oxide manufacture. The chlorohydrin route, which generates *ca.* 2 kg of CaCl₂, accounts for more than half of the *ca.* 4 million tons of propylene oxide produced annually. The rest is produced by so-called co-product processes which use oxygen as the primary oxidant but generate *tert*-butanol or styrene as the co-product. It has been known since the mid-eighties that titanium silicalite, developed by Enichem,²⁸ is able to catalyse the epoxidation of propylene with the green oxidant hydrogen peroxide, but the latter was too expensive for this application. However, Headwaters Technology Innovation (HTI) received a 2007 Presidential Green Chemistry Challenge Award for the development of a palladium–platinum nanocatalyst, which enables the direct synthesis of hydrogen peroxide from hydrogen and oxygen in high selectivity below the flammability limit of hydrogen.²⁹ Combination of this with the Enichem technology enables the direct synthesis of propylene oxide from propylene, hydrogen and oxygen, with water as the sole by-product (Fig. 6). This process is now being commercialised in partnership with Degussa (now Evonik). BASF, in partnership with Dow Chemical, have similarly commercialized the Enichem epoxidation technology but without the added benefit of direct formation of hydrogen peroxide from hydrogen and oxygen.³⁰

Similarly, Sumitomo has commercialised a process for caprolactam, the raw material for nylon 6, which involves combining the Enichem technology³¹ for ammoxidation of cyclohexanone with NH₃–H₂O₂ over the titanium silicalite catalyst (TS-1) with a novel vapour phase Beckmann rearrangement over a high-silica MFI zeolite,³² affording caprolactam in >98% yield based on cyclohexanone and 93%



Current process:



Atom efficiency = 29% ; E = 4.5

New process



Atom efficiency = 75% ; E = 0.32 (<0.1)

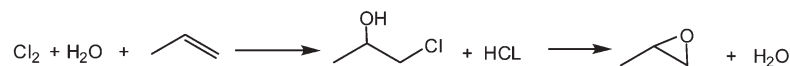
Fig. 7 Sumitomo caprolactam process.

based on H₂O₂ (Fig. 7). The conventional process involves the reaction of cyclohexanone with hydroxylamine sulfate (or another salt), producing cyclohexanone oxime, which is subjected to the Beckmann rearrangement in the presence of stoichiometric amounts of sulfuric acid or oleum. The overall process generates *ca.* 4.5 kg of ammonium sulfate per kg of caprolactam (Fig. 7). In contrast, the Sumitomo process generates two molecules of water as the sole co-product, *i.e.*, it is essentially salt-free. It was gratifying, therefore, that the Sumitomo scientist, Ichihashi, used the E Factor to illustrate the difference between the classical and the new, catalytic process (see Fig. 7).

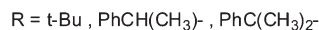
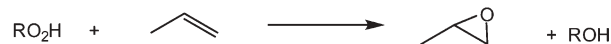
8. Catalytic C–C bond formation

C–C bond formation is a key transformation in organic synthesis and an important catalytic methodology for generating C–C bonds is carbonylation. In the bulk chemicals arena it is used, for example, for the production of acetic acid by rhodium-catalysed carbonylation of methanol. Since such

1. Chlorohydrin route



2. Hydroperoxide (coproduct) processes



3. Direct hydrogen peroxide process

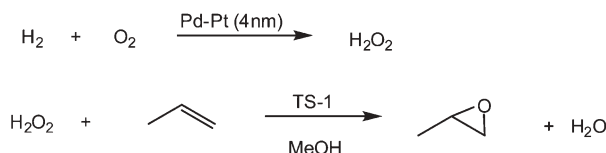


Fig. 6 Different processes to propylene oxide.

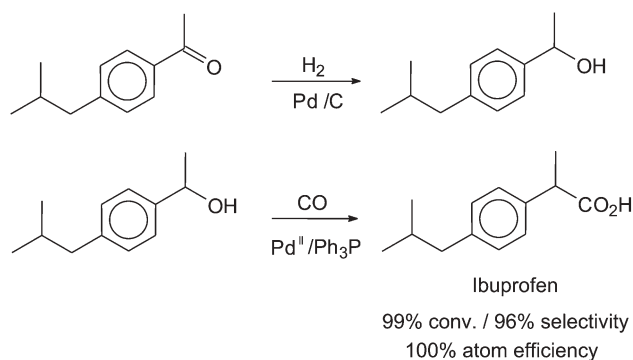


Fig. 8 Hoechst–Celanese process for ibuprofen.

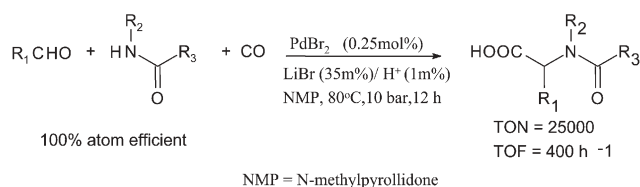


Fig. 9 Palladium-catalysed amidocarbonylation.

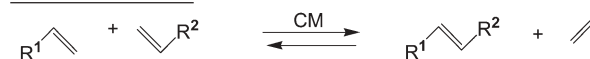
reactions are 100% atom efficient they are increasingly being applied to fine chemicals manufacture. An elegant example of this is the Hoechst–Celanese process for the manufacture of the analgesic, ibuprofen, with an annual production of several thousands tons. In this process ibuprofen is produced in two catalytic steps (hydrogenation and carbonylation) from *p*-isobutyrylacetophenone (Fig. 8) with 100% atom efficiency.³³ This process replaced a more classical route which involved more steps and a much higher E factor.

Another elegant example is the palladium-catalysed, one-step, 100% atom efficient synthesis of α -amino acid derivatives from an aldehyde, CO and an amide (Fig. 9).³⁴

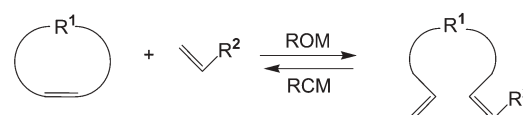
No discussion of catalytic C–C bond formation would be complete without a mention of olefin metathesis in its many forms: cross metathesis (CM), ring closing metathesis (RCM), ring opening metathesis (ROM), ring opening metathesis polymerization (ROMP) and acyclic diene metathesis (ADMET) (Fig. 10).³⁵ It should be noted, however, that olefin metatheses, in contrast to carbonylations, are often not 100% atom efficient in that they produce an olefin co-product.

Following its discovery in the 1960s olefin metathesis was applied to bulk chemicals manufacture, a prominent example being the Shell Higher Olefins Process (SHOP).³⁶ In the succeeding decades the development of catalysts, in particular the ruthenium-based ones developed by Grubbs, that function in the presence of most functional groups, paved the way for widespread application of olefin metathesis in the synthesis of complex organic molecules. The importance of olefin metathesis as a pre-eminent, green methodology for the formation of C–C bonds under mild conditions was underpinned by the award of the 2005 Nobel Prize in Chemistry to Chauvin, Grubbs and Schrock for the development of the olefin metathesis reaction. According to the Swedish academy olefin metathesis is “a great step forward for green chemistry”.

Cross metathesis



Ring opening / ring closing metathesis



Ring opening metathesis polymerization



Acyclic diene metathesis



Catalysts : Mo, W, Re and Ru complexes

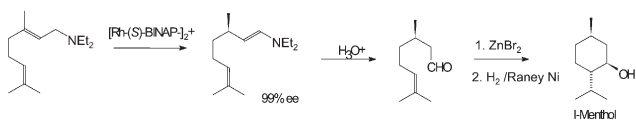
Fig. 10 Olefin metathesis reactions.

9. Chirotechnology and asymmetric catalysis

At roughly the same time that waste minimization was becoming an important issue enantiomeric purity of biologically active agents, *e.g.*, pharmaceuticals and pesticides, was becoming the focus of regulatory attention. We noted in 1993 that “the current climate of ‘environmentality’ is precipitating a dramatic move towards enantiomeric purity in bioactive agents”.³⁷ When a chiral molecule exhibits biological activity the desired activity almost always resides in one of the enantiomers and the other enantiomer is at best isomeric ballast that does not contribute to the desired effect. In the worst case scenario it may exhibit toxic side-effects, the most well-known example being the thalidomide tragedy in the 1960s. Pregnant women who received this drug in racemic form gave birth to deformed babies as a result of the mutagenicity of the “wrong” enantiomer. However, although this effect of chirality on biological activity was already known in the 1960s, it took about thirty years before sufficient regulatory pressure stimulated the shift towards marketing drugs in enantiomerically pure form. Consequently, in the last two decades there has been a marked trend towards marketing chiral pharmaceuticals and pesticides as pure enantiomers. This, in turn, generated a need for economically viable methods for their synthesis.

Here again, for economic and environmental viability, processes need to be atom efficient and have low E factors, *i.e.*, they should employ catalytic methodologies. This has manifested itself in the last 15 years in increasing attention for enantioselective catalysis, using enzymes (see later), chiral metal complexes or, more recently, chiral organocatalysts.³⁸ Its importance was underpinned by the award of the 2001 Nobel Prize in Chemistry to Knowles, Noyori and Sharpless for their contributions to enantioselective catalysis. Indeed, as Noyori has recently noted,³⁹ asymmetric hydrogenation is ideal green chemistry.

1. Takasago l-menthol process



2. Novartis (S)-metolachlor process

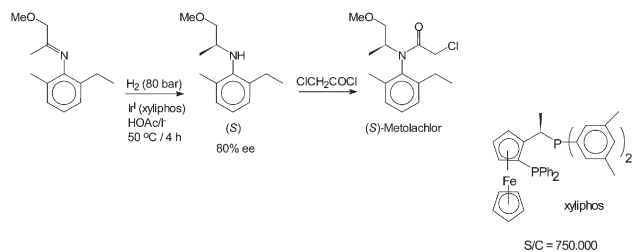


Fig. 11 Enantioselective catalysis in (*S*)-metolachlor and l-menthol manufacture.

Two elegant examples of highly efficient asymmetric catalysis on a multi-thousand tons per annum scale, which we have discussed in detail elsewhere,¹⁴ are the Takasago l-menthol process and the Syngenta (*S*)-metolachlor process, in which an enantioselective isomerisation and an enantioselective hydrogenation are the key steps, respectively (Fig. 11).

10. The question of solvents: non-conventional reaction media

Another important issue in green chemistry is the use of organic solvents. So many of the solvents that are favoured by organic chemists, such as chlorinated hydrocarbons, have been blacklisted that the whole question of solvent use requires rethinking and has become a primary focus, especially in the fine chemicals industry.^{40,41} In our original studies of E factors of various processes we assumed, if details were not known, that solvents would be recycled by distillation and that this would involve a 10% loss. However, the organic chemist's penchant for using different solvents for the various steps in multi-step syntheses makes recycling difficult owing to cross contamination. The benchmarking exercise performed by the GCI Pharmaceutical Round Table (see above) revealed that solvents were a major contributor to the E Factors of pharmaceutical manufacturing processes. Indeed, it has been estimated by GSK workers⁴² that *ca.* 85% of the total mass of chemicals involved in pharmaceutical manufacture comprises solvents. It is also worth noting that in the redesign of the sertraline manufacturing process,⁴³ for which Pfizer received a Presidential Green Chemistry Challenge Award in 2002, among other improvements a three-step sequence was streamlined by employing ethanol as the sole solvent. This eliminated the need to use, distil and recover four solvents (methylene chloride, tetrahydrofuran, toluene and hexane). Similarly, Pfizer workers also reported⁴⁴ impressive improvements in solvent usage in the process for sildenafil (Viagra) manufacture reducing the solvent usage from 1700 l kg⁻¹ of product used in the medicinal chemistry route to 7 l kg⁻¹ in the current commercial process, with a target for the future of 4 l kg⁻¹. The E Factor for the current process is 6, placing it more in

the lower end of fine chemicals rather than with typical pharmaceutical manufacturing processes.

These issues surrounding a wide range of volatile and non-volatile, polar aprotic solvents have stimulated the fine chemical and pharmaceutical industries to seek more benign alternatives. There is a marked trend away from hydrocarbons and chlorinated hydrocarbons towards lower alcohols, esters and, in some cases, ethers. Inexpensive natural products such as ethanol have the added advantage of being readily biodegradable and ethyl lactate, produced by combining two innocuous natural products, is currently being touted as an environmentally attractive solvent for chemical reactions.

The problem with solvents is not so much their use but the seemingly inherent inefficiencies associated with their containment, recovery and re-use. Alternative solvents should, therefore, provide for their efficient removal from the product and re-use. The subject of alternative reaction media also touches on another issue that is important from both an environmental and an economic viewpoint: recovery and re-use of the catalyst. An insoluble solid, *i.e.*, a heterogeneous catalyst, is easily separated by centrifugation or filtration. A homogeneous catalyst, in contrast, presents more of a problem and a serious shortcoming of homogeneous catalysis is the cumbersome separation of the catalyst from reaction products and the quantitative recovery of the catalyst in an active form. In pharmaceuticals manufacture quantitative separation of the catalyst is also important in order to avoid contamination of the product. Attempts to heterogenise homogeneous catalysts by attachment to organic or inorganic supports have, generally speaking, not resulted in commercially viable processes, for a number of reasons, such as leaching of the metal, poor catalyst productivities, irreproducible activities and selectivities and degradation of the support.

The conclusion is evident: we need to maintain the advantages of homogeneous catalysts while providing for facile separation of product and catalyst. This can be achieved by employing liquid–liquid biphasic catalysis, whereby the catalyst is dissolved in one phase and the reactants and product(s) in the second liquid phase. The catalyst is recovered and recycled by simple phase separation. Preferably, the catalyst solution remains in the reactor and is re-used with a fresh batch of reactants without further treatment or, ideally, it is adapted to continuous operation. Obviously, both solvents are subject to the same restrictions as discussed above for monophasic systems. Several different combinations have been intensely studied in recent years, including *water (aqueous biphasic)*, *supercritical CO₂*, *fluorous biphasic*, and *ionic liquids* and *multiphase homogeneous catalysis* has become an important area of research.⁴⁵ We also note that the use of water and supercritical carbon dioxide as reaction media is consistent with the current trend towards the use of renewable, biomass-based raw materials, which are ultimately derived from carbon dioxide and water.

The best solvent is no solvent and if a solvent (diluent) is needed then water has much to offer: it is non-toxic, non-inflammable, abundantly available and inexpensive. Furthermore, performing the reaction in an aqueous biphasic system,⁴⁶ whereby the catalyst resides in the water phase and the product is dissolved in the organic phase, allows for

recovery and recycling of the catalyst by simple phase separation. An example of a large scale application of this concept is the Ruhrchemie/Rhône Poulenc process for the hydroformylation of propylene to n-butanal, which employs a water-soluble rhodium(I) complex of trisulfonated triphenylphosphine (tppts) as the catalyst and has an E Factor of 0.1 compared with 0.6–0.9 for conventional monophasic hydroformylation processes.⁴⁷ Similarly, we have reported examples of aqueous biphasic carbonylations and oxidations.⁴⁸

An aqueous biphasic system is not the answer in all cases, however, and other alternative reaction media, such as fluorinated biphasic systems,⁴⁹ supercritical carbon dioxide,⁵⁰ and ionic liquids,^{51,52} have also been extensively studied, as well as biphasic mixtures of these alternative media,⁴² e.g., an ionic liquid with scCO₂. In a recent variation on this theme,⁵³ the so-called ‘miscibility switch’ was used to perform a catalytic reaction smoothly in a monophasic ionic liquid–scCO₂ mixture. Subsequent lowering of the pressure afforded a biphasic system whereby the catalyst was contained in the ionic liquid phase and the product in the scCO₂ phase, enabling their facile separation. Another approach worthy of mention is the use of amidine/alcohol or guanidine/alcohol mixtures as ‘switchable solvents’, whereby a switch from a low-polarity form to a high-polarity form is achieved upon treatment with carbon dioxide at atmospheric pressure.⁵⁴

11. Biocatalysis

Biocatalysis has many attractive features in the context of green chemistry: mild reaction conditions (physiological pH and temperature), an environmentally compatible, biodegradable catalyst (an enzyme) and solvent (water) combined with high activities and chemo-, regio- and stereoselectivities in reactions of multifunctional molecules. Furthermore, the use of enzymes generally circumvents the need for functional group activation and avoids the protection and deprotection steps required in traditional organic syntheses. This affords processes which are shorter, generate less waste and are, therefore, both environmentally and economically more attractive than conventional routes.

Biocatalytic processes can be performed with isolated enzymes or as whole cell biotransformations. Isolated enzymes have the advantage of not being contaminated with other enzymes present in the cell while the use of whole cells is less expensive as it avoids separation and purification of the enzyme. In the case of dead cells, the E Factors of the two methods are essentially the same: the waste cell debris is separated before or after the biotransformation. In contrast, when growing microbial cells are used, *i.e.*, in fermentation processes, substantial amounts of biomass can be generated as waste but little attention has been paid to this aspect. To our knowledge there are no reported E Factors for fermentation processes. This would seem to be a hiatus which needs to be filled. We note, however, that the waste biomass is generally easy to dispose of, *e.g.*, as animal feed, or can, in principle, be used as a source of energy for the process.

The time is ripe for the widespread application of biocatalysis in industrial organic synthesis. Advances in recombinant DNA techniques have made it, in principle,

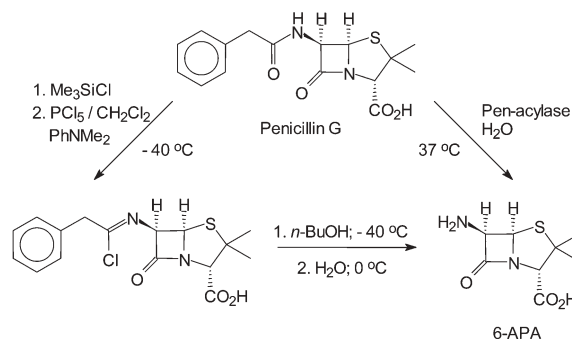


Fig. 12 Enzymatic *versus* chemical deacylation of penicillin G.

possible to produce virtually any enzyme for a commercially acceptable price and protein engineering has made it possible, using techniques such as site directed mutagenesis and *in vitro* evolution, to manipulate enzymes such that they exhibit the desired substrate specificity, activity, stability, pH profile, *etc.*⁵⁵ Furthermore, the development of effective immobilisation techniques has paved the way for optimising the performance and recovery and recycling of enzymes.⁵⁶

An illustrative example of the benefits to be gained by replacing conventional organic chemistry by biocatalysis is provided by the manufacture of 6-aminopenicillanic acid (6-APA), a key raw material for semi-synthetic penicillin and cephalosporin antibiotics, by hydrolysis of penicillin G.⁵⁷ Up until the mid-1980s a chemical procedure was used for this hydrolysis (Fig. 12). It involved the use of environmentally unattractive reagents, a chlorinated hydrocarbon solvent (CH₂Cl₂) and a reaction temperature of -40 °C. Thus, 0.6 kg Me₂SiCl, 1.2 kg PCl₅, 1.6 kg PhNMe₂, 0.2 kg NH₃, 8.4 l of n-BuOH and 8.4 l of CH₂Cl₂ were required to produce 1 kg of 6-APA.⁵⁸

In contrast, enzymatic cleavage of penicillin G (Fig. 12) is performed in water at 37 °C and the only reagent used is NH₃ (0.09 kg per kg of 6-APA), to adjust the pH. The enzymatic process currently accounts for the majority of the several thousand tons of 6-APA produced annually on a world-wide basis.

Similarly, subsequent enzymatic coupling of the side-chain to the 6-APA nucleus or the related 7-amino desacetoxycephalosporanic acid (7-ADCA) has replaced chemical coupling in the synthesis of certain semi-synthetic penicillins and cephalosporins.⁵⁷ An example of what can be achieved by applying modern biotechnology to biocatalysis is provided by the process developed by Codexis for the production of an intermediate for Pfizer’s blockbuster drug Atorvastatin (Lipitor). The process, for which Codexis received a 2006 Presidential Green Chemistry Challenge Award, involved three enzymatic steps (Fig. 13), all of which were optimised by *in vitro* evolution of the individual enzymes using gene shuffling.⁵⁹

12. Chemicals from renewable raw materials: biomass utilisation

Another important goal of green chemistry is the utilisation of renewable raw materials, *i.e.*, production of chemicals

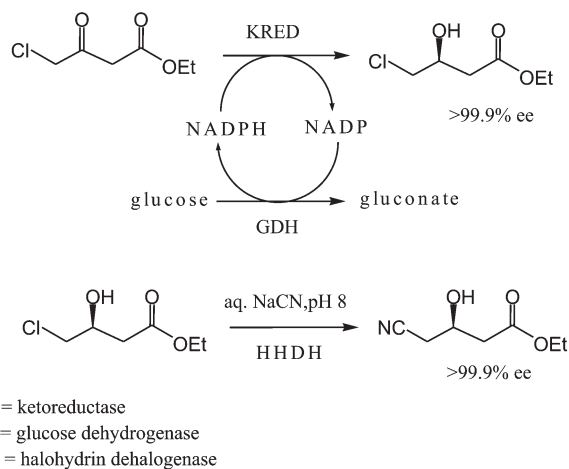


Fig. 13 Codexis process for atorvastatin intermediate.

from biomass rather than fossil resources such as oil, coal and natural gas. Here again, the processes used for the conversion of renewable feedstocks—mainly carbohydrates but also triglycerides and terpenes—should produce minimal waste, *i.e.*, they should be preferably catalytic in order to be sustainable.

In the short term maize is being used as a renewable raw material to produce bioethanol and chemicals such as lactic acid and 1,3-propanediol but it is clear that lignocellulosic materials, available as agricultural waste, *e.g.*, corn stover, or dedicated energy crops will be the feedstocks for second generation biofuels and biobased commodity chemicals. This will be necessary to avoid the food *versus* fuel dilemma. A so-called biobased economy is envisaged in which commodity chemicals (including biofuels), specialty chemicals such as vitamins, flavours and fragrances and industrial monomers will be produced in biorefineries.

Conversion of lignocellulosic biomass in biorefineries could involve thermochemical and/or biotechnological processes.^{60,61} In the former, pyrolysis or gasification of lignocellulose affords pyrolysis oil or syn gas, respectively. In the case of syn gas, the technologies developed in the 1970s, based on coal gasification, can be used to convert the syn gas to liquid fuels or chemicals.³ In the biotechnological approach, the lignocellulose is hydrolysed to liberate the lignin, which can be used as an energy source, and polysaccharides, which are depolymerised to fermentable sugars. This is currently the focus of considerable attention and is perceived as the key to developing a sustainable source of liquid fuels and chemicals.⁶² Metabolic pathway engineering⁶³ is used to optimise the production of the required product based on the amount of substrate (glucose) consumed, *i.e.*, the atom efficiency. Alternatively, the monosaccharides can be converted to valuable chemicals by chemical catalysis, *e.g.*, dehydration and/or hydrogenation.⁶⁴ Whichever approach is used, here again optimum biomass utilisation and minimisation/elimination of waste, that is low E Factors, is the key to sustainability. There is a clear need for a meaningful metric for comparing different methodologies for biomass conversion.

The (partial) shift from oil to biomass as a raw material will have far reaching consequences for the structure of the

chemical and allied industries. Different value chains will be formed. For example, a direct consequence of the recent enormous increase in biodiesel production is that the co-product, glycerol, has become a low-priced commodity chemical which could, in turn, form the raw material for other bulk chemicals such as 1,2- and 1,3-propane diol and acrylic acid.⁶⁵ These processes will also have to be efficient in raw material utilisation and generate minimum waste.

13. Conclusions and future outlook

As Lord Kelvin said: “To measure is to know”. Fine chemical and pharmaceutical companies always knew that their manufacturing processes were generating substantial quantities of waste but putting a number to it *via* the conception of the E factor really brought the message home. By publishing the table of E Factors we challenged the fine chemical and pharmaceutical industries to make the paradigm shift from a concept of process efficiency which was exclusively focused on chemical yield to one that is motivated by elimination of waste and maximisation of raw materials utilisation. The fact that the absolute amounts of waste generated in these sectors are lower than those in the bulk chemicals industry should not be used as an excuse not to address this issue. The E Factor provided a very simple means of measuring one’s performance and has been adopted by the chemical industry world-wide for this purpose. The pharmaceutical industry in particular has made substantial progress in the last few years and has adopted the E Factor, or its direct equivalent, as its measuring staff. This was underscored by the recent statement: “Another aspect of process development mentioned by all pharmaceutical company process chemists who spoke with C&EN is the need for determining an E Factor”.⁶⁶ Similarly, a recent publication from members of the ACS GCI Pharmaceutical Round Table identified a list of key areas where further improvement is most needed.⁶⁷

The impact of the E Factor has not been restricted to the fine chemicals industry but has also played a broader role as a “measure of the efficiency of the chemical industry”⁶⁸ and, hopefully, will continue to do so as the chemical industry progresses towards being a sustainable enterprise. Looking to the future, the displacement of archaic “stoichiometric” technologies by greener catalytic alternatives and the replacement of toxic and/or hazardous solvents and reagents with cleaner alternatives will continue to be important drivers. In addition, two other more recent trends will gain in importance. First, the change from fossil fuels to renewable resources as feedstocks for existing products, and second the development of new products that are biocompatible and biodegradable and are also produced from renewable resources by green catalytic processes with low E Factors.

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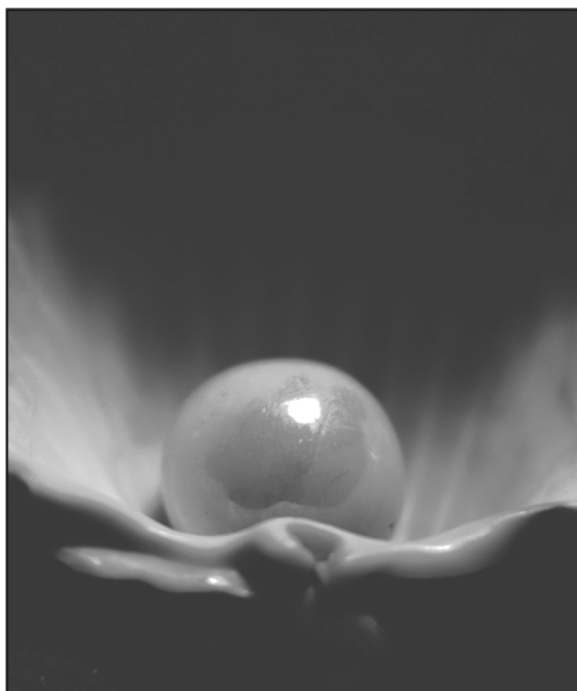
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