

Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry

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Chemicals are a part of modern life. Products are the main emissions of the chemical and pharmaceutical industries. This makes it difficult to hold them back efficiently. Very often they do not become degraded or fully broken down to water, carbon dioxide and inorganic salts. Often, unknown transformation products are formed in the environment. Therefore, according to the principles of green chemistry, the functionality of a chemical should not only include the properties of a chemical necessary for its application, but also easy and fast degradability after its use. Taking into account the full life cycle of chemicals will lead to a different understanding of the functionality necessary for a chemical. In the present discussion, improvement of synthesis and renewable feedstock are very prominent, whereas the environmental properties of the molecules are somewhat underestimated. To stimulate the discussion about the future role of degradable chemicals several examples are presented to underline the feasibility and the economic potential of this approach, called benign by design.

The problem—persistent chemicals

Chemicals are a part of modern life and are present in all spheres of human life. They are used as pharmaceuticals, pesticides, detergents, fertilizers, dyes, paints, finish, preservatives, food additives among others. They contribute to our well being, high life expectancy and economic prosperity. If they are constituents and ingredients of consumer or household products and other open applications they are often emitted into the environment by non-point sources. Very often they do not become degraded, *i.e.* they are not, or are only incompletely, broken down to water, carbon dioxide and inorganic salts. Unknown transformation products can result from such biological and chemical processes such as hydrolysis, redox-reactions or photolysis. These unknown chemical entities can remain in the environment and can also be toxic for humans and environmental organisms. In this case, the situation may be worse as we usually have much less knowledge about the dead end transformation products with regards to their fate, and their effects on the environment than on the parent compounds. Even if there is some degree of degradation, the parent compounds will nevertheless be present at constant levels in the environment if the input rate is higher than their rate of degradation or mineralization. This can be called second order persistency or pseudo persistency. Persistency is one of the most important criteria in the environmental assessment of chemicals.^{1–4} A long half life of chemicals in the environment results in a wide range for the chemicals. That is,

they will be present in big compartments for a long time.² For chemicals and transformation products with such properties, it is not possible to carry out a risk assessment. The bigger the scales involved, the more uncertainty increases and the more possible effects cannot be tested in lab trials. Polychlorinated biphenyls (PCBs) is a classical example of persistent pollutants. PCBs were synthesized for the first time in 1877, and already in 1899 severe health problems (chloracne) associated with the handling of PCBs were reported. Throughout the years the poisoning of rice oil by these compounds and their neurotoxic effects as well as carcinogenicity has been described in detail. Despite this knowledge, it took until 1999 to ban PCBs fully within the EU—100 years after the first reports of its severe toxicity.³ This example demonstrates that it is not only the time scales of the chemicals themselves and the environmental processes impacted by them but also the time scales of economical and political systems which have important effects. In addition, the use of persistent chemicals is often associated with high costs in the long run—at least for the general public. In the Stockholm convention, a half life of more than 50 days in water is set as a criterion for POPs. Recent research showed chemicals that are less persistent and have higher polarity than PCBs are distributed globally too, and can also accumulate in humans.⁴ A statistical correlation between the persistency of chemicals and the prevalence of chemicals present in the environment which can initiate cancer has been only recently reported.⁵ It should be mentioned that chemicals which are of high interest for green chemistry are not necessarily themselves in line with the principles of green chemistry. An example is ionic liquids. Ionic liquids help chemists to contribute to sustainable chemistry because they offer an opportunity to reduce waste which is formed during the synthesis of chemicals. However, they are not biodegradable and they can be toxic for environmental organisms.⁶

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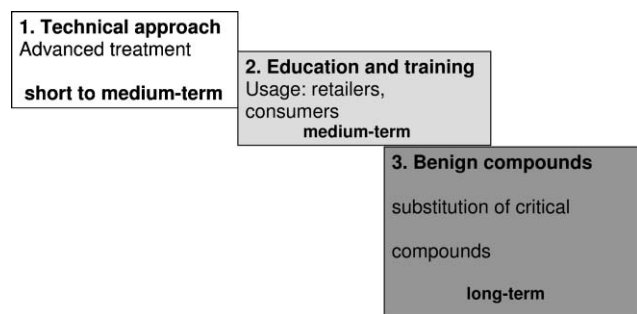


Fig. 1 Strategies to reduce the input of chemicals into the environment (www.start-project.de).

In general, three different approaches for preventing the input of chemicals into the environment are possible. These are depicted in Fig. 1. In the meantime, we have learned that the main emission of chemical and pharmaceutical industries is their products. If the chemicals themselves are the products, *e.g.* detergents, pesticides, dyes, paints, flame retardants, pharmaceuticals, personal care products, and others, these very often end up in the environment in the long term. Therefore, an important task is to focus not only on the optimization of the chemical synthesis of a molecule and its use but also to include the molecules themselves. Therefore, “chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous products”.¹ Product design as an important part of green chemistry was addressed more detailed in 2002.⁷

The conventional wisdom assumes that a chemical needs to be stable to be successful in the market and the idea described above is in itself a contradiction. The approach of designing chemicals according to both the requirements of application *and* the environment, *i.e.* along their whole life cycle, is quite ambitious. It is at the core of chemistry and pharmacy. In this article, examples of chemicals satisfying the benign-by-design approach are given to move forward the discussion about the feasibility and the range of this approach. For this purpose, historical examples are outlined. A focus is on pharmaceuticals. For them the barriers are much higher than for other chemicals. Beside the requirements to be fulfilled by other chemicals, they have to be of low or even no human toxicity. If it is possible to design benign pharmaceuticals it should be possible for other chemicals too.

General approaches for the prevention and reduction of the input of chemicals into the environment

The traditional short-to-medium term approach for the prevention and reduction of the input of chemicals into the environment within and after their use is containment. This is not possible for chemicals used in every day life. In such cases, treatment of emissions *e.g.* effluent treatment, air treatment, or waste treatment is applied (“end of the pipe technology”, strategy 1 in Fig. 1). The shortcomings of this approach are clear: it is difficult, if not impossible, to apply such an approach if the entry of the chemicals into the environment is by non-point sources. Furthermore, very often not all trace compounds are fully removed by such treatment.

More than a decade ago, it was learned that treatment of emissions is often not satisfying and is itself creating new problems. For example, stable transformation products are often formed by end of the pipe treatment. Sometimes, *e.g.* if oxidation techniques are applied, mutagenic transformation products result. Sorption onto powdered charcoal and other so called “advanced” treatment removes some additional compounds, but not all. In any case, such an advanced treatment results in further energy demand and may create new waste to be treated. Furthermore, end of the pipe treatment creates additional costs. End of the pipe treatment can be seen as an opportunity to gain time in order to develop more sustainable approaches, but again this approach creates its own problems. It is a non-sustainable approach. Furthermore, a certain type of technology tends to persist once installed on a large scale. That is, if a big investment has been directed to one type of problem solution (*e.g.* advanced waste water treatment) this technology has a tendency to persist for a long time even if the problems have changed, the technology has advanced or they are no longer adequate for a certain problem.

Containment at the source and responsible care as well as product stewardship (medium-term strategy 2 in Fig. 1) have been created and implemented within a number of industries. This approach contributes to the reduction of emissions there. In the case of chemicals used in open systems, this approach also has its limitations and is not always very efficient. Therefore, other approaches should be considered too. In the following section, the third approach depicted in Fig. 1 will be discussed in more detailed because it is the one which must become a part of green chemistry, not only by enabling chemistry to contribute to sustainability but to make chemistry itself more sustainable.

Structure and properties—at the core of chemistry

One of the principles of green chemistry is the design of environmentally friendly products. This includes the design of environmentally friendly chemicals and pharmaceuticals (long-term strategy 3 in Fig. 1). One possibility to implement such an approach is to design chemicals in such a way that they are readily degradable after their use. This means that the functionality of a chemical consists of more than simply the properties required for successful applications. Functionality in a broader and sustainable sense would also include the ready and complete degradability of a molecule after its use, for example in traditional sewage treatment. Starting from this assumption, it is necessary to include properties necessary for both successful applications on the one hand, as well as after application on the other hand, at the time when new chemical entities are created. A life cycle engineering of chemicals is needed. The conventional wisdom assumes that a chemical needs to be stable to be successful in the market and the idea described above is by itself a contradiction. A closer look reveals that this is not necessarily the case.

The approach of designing chemicals according to both the requirements of application *and* the environment, *i.e.* along their whole life cycle, looks like a totally new approach. Instead, it is at the core of chemistry and pharmacy. Chemistry and the chemist’s language are about the relation of the

structure of a chemical and its properties, *e.g.* its reactivity. Even a small change in the structure of a chemical may have tremendous effects on its properties. Benzene is (after metabolic activation) a carcinogen. It is only slowly biodegradable. Simply the insertion of an oxygen atom into a carbon hydrogen bond results in a new compound, phenol with very different properties which are significant for its use and its fate in the environment. In contrast to benzene, phenol is readily aerobically biodegradable, not carcinogenic and active against bacteria. Therefore, it has long been used as a disinfectant. This fundamental connection between structure and properties can be used for the approach of benign by design. It allows the theoretical design of molecules and the assessment of their properties before they are even synthesised.

In the case of molecules of a more complex structure than benzene and phenol, human expertise is limited. Therefore, within the last decades computer based systems have been developed. These so called expert systems assist human experts with the handling and application of this complex type of knowledge.⁸⁻¹⁰

This approach is currently widely in use within pharmaceutical industries and to some extent also in chemical industries.^{8,10} It will be of increasing importance within REACH for the assessment of chemicals and is already applied broadly for this latter purpose by the U.S. EPA.⁹ Modern pharmaceutical synthesis and drug discovery uses this understanding by applying general rules, such as Lipinsky's rule of five (log *P* from 1 to 5, molecular weight from 100 to 500, number of H-donors from 0 to 5, number of H-acceptors from 0 to 9, number of rotatable bonds less than 10) and computer-based structure activity relationships.¹⁰ Starting from a lead structure, the desirable activity of a molecule is improved by systematic variation of its chemical structure. At the same time, unwanted properties such as mutagenicity are reduced. The successful candidates are more active and at the same time exhibit less side effects than the original chemical. To have as little side effects as possible means that the inherent safety of the chemicals has been improved and the total functionality of the molecule has been improved as well. A new understanding would be to regard low biodegradability after use as an unwanted side effect also.

In the meantime, there is broad knowledge available as to how certain functionalities govern the properties of a given pharmaceutical lead structure.¹⁰ This is demonstrated in Fig. 2 for the lead structure of the quinolones which are used as antibiotics. The carboxyl function is indispensable for the binding to the target (gyrase) and can therefore not be modified. *R*₁ controls pharmacokinetics and efficacy. Whether "X" is nitrogen or oxygen impacts the activity, *R*₇ controls the activity spectrum and is also related to pharmacokinetics. The given example for *R*₇ enables activity against gram-negative bacteria. Introduction of the fluorine atom resulting in the modern group of fluoroquinolones increases activity. This also seems to be responsible for the increased photosensitivity of patients treated with fluoroquinolones.

This is understandable in terms of the change of the electronic properties of the benzene ring due to the high electronegativity of fluorine. The resulting increase in the energy gap between the highest occupied molecular orbital

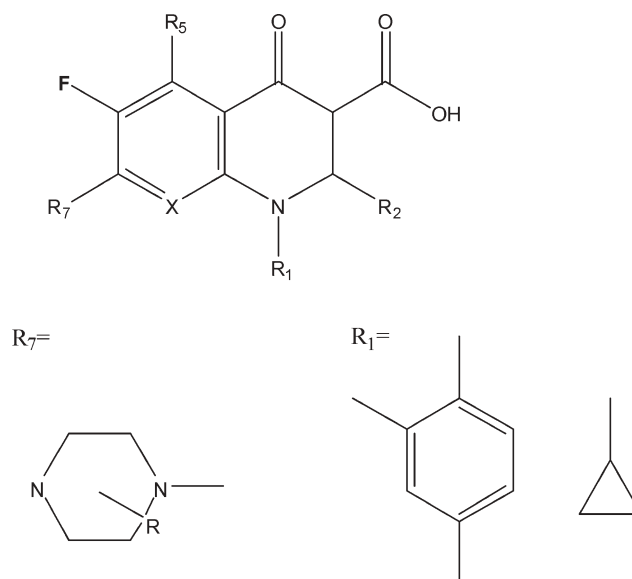


Fig. 2 Structure activity relationships of quinolones

(HOMO) and the lowest unoccupied molecular orbital (LUMO) leads to absorption of radiation with higher energy. A higher energy transfer into the skin of a treated patient is the consequence. At the same time the C–F-bond contributes to the low biodegradability of the fluoroquinolones for the same reason. The C–F-bond is very stable.¹¹ Due to the fluorine atom attached to the aromatic ring system it is poor in electrons and therefore can also not easily be oxidized by aerobic bacteria and/or radiation of lower energy. Furthermore, by the introduction of the fluorine atom, an important position for hydroxylation as a first step of the biodegradation of aromatics is blocked. As both vicinal positions are not aromatic hydrogen atoms, the formation of a dihydrol is not possible. Both electronic and steric factors contribute to the low biodegradability of fluoroquinolones such as ciprofloxacin.

To put such an approach into the context of green and sustainable chemistry, it is necessary to challenge the paradigm of the stability of chemicals as an indispensable property for their application. Normally, we speak of the stability of a chemical without mentioning the context of a certain environment. We assume that the stability of a chemical is an intrinsic property of a chemical. However, it is the result of the interaction of a molecule with its environment. Stereochemistry and electronic properties of a molecule on the one hand and the constraints set by its environment on the other hand govern the interaction. Therefore, the reactivity of a molecule, *i.e.* the kinetics and thermodynamics, depend on both the properties of the molecule *and* its environment. This is one of the basic principles of chemistry: change the conditions, *e.g.* temperature or moisture, and a molecule may then react in a different way or with a different velocity.

Within the life cycle of a chemical the conditions offered by its environment can often vary. Access of light, pH-value or redox-potential varies with the environment. Additionally, bacterial diversity and differing bacterial density are found in different compartments. Therefore, the metabolic diversity of

bacteria and the potential and pathways for the breakdown of molecules are different. For example, the conditions of a pharmaceutical on the shelf (*e.g.* pure and dry, exclusion of light, room temperature) are different from the ones in the human body (moisture, higher temperature, certain more or less specific enzymes, low pH in the stomach, anaerobic conditions and bacteria in the gut and the intestine) from those in sewage (often high pH, aerobic conditions and bacteria at a different density with enzymes of different type, substrate and activity) and again from those in surface water (neutral pH, low bacterial density, access of light) and sediments (oxygen rich and anoxic conditions, different pH, different matrix for sorption). If we are aware of those facets that are of significance for the “stability” of a chemical, this knowledge can then be used to design chemicals not only for optimised performance during their application but also within the further stages of their life cycle. The same holds for the degradation of molecules as a special type of reaction. From another point of view, stability and degradability are a question of velocity, *i.e.* the relation of the time scales of the different reaction pathways. The challenge is to design a molecule in such a way that its lifetime is sufficient for its use but short enough under environmental conditions.

It also has to be noted that some chemicals are used because of their low stability, such as monomers or pro-drugs such as the anti-neoplastic compounds ifosfamide or cyclophosphamide, which are activated in the human body in order to exert their desired effects.¹² A fully stable chemical would often not be of any use in most cases, because it would not undergo any interaction or reaction with its environment, which is often the prerequisite of its application. At the least, bioactive chemicals such as pesticides, disinfectants and pharmaceuticals have to have a certain amount of reactivity within their range of application. If they do not they would not be bioactive and therefore would be worthless for their intended use. They exert their reactivity within a special environment, *e.g.* within the human body, where they are activated in a specific manner. Other examples of reactive chemicals are coatings.

From the past to the future

The future basis of our designing and handling of chemicals has to abandon the control-oriented end of the pipe approach of the past. This attitude assumes complete knowledge and controllability. Because of the success of emission reduction, the products themselves are now the main emissions of the chemical and pharmaceutical industries. Therefore, an additional focus on the improvement of the chemicals themselves is necessary. Not only for environmental reasons, but also because of economical considerations, it will be necessary in the future to take sustainability into account when a chemical is first developed and designed. That means that, as a very first step, easy degradability after use or application is taken into account even before a chemical's synthesis. Such an approach is not completely new. For example, it is quite common during the development of pharmaceuticals with respect to unwanted side effects.

Compounds with few or no side effects or low toxicity can be called inherently safe.¹⁰ Such chemicals need only little or

no special safety measures or special knowledge by a user or applicant. A more holistic understanding of this concept means that chemicals should not only have the lowest possible impact on humans handling and ingesting such compounds but also on the environment. If there is no exposure of the environment to such compounds, no effects have to be considered. This means a different understanding of the functionality of a chemical. It includes its manufacturing and use, as well as its fate after use. Such chemicals are benign by design. For such chemicals a life cycle assessment and optimization is performed according to the specific conditions present at the different life stages before its synthesis and introduction into the market. These include:

- raw materials
- synthesis
- production
- use
- fate after use

Such an approach requires the chemist doing synthesis to have a different understanding. This is because the chemist has to think interdisciplinarily and take into consideration the world outside his laboratory. He is not only a craftsman who assembles molecules, but is also an architect who designs them. This includes accounting for not only the functionalities of a molecule that are necessary for its application but also those which are important throughout its entire life cycle. This is the part of sustainability which is specific for chemistry and is at the core of this new understanding of chemistry. It includes the sustainable use of resources as well as improved efficiency and efficacy. However, it is more than that. Through this approach the criteria of sustainability are applied to chemistry itself, and this requires interdisciplinary thinking.

At first glance, it does not seem very likely that the outlined approach (strategy 3 in Fig. 1) is feasible, nor that it can contribute much to the goals of green and sustainable chemistry. However, looking into chemical literature under the special focus of stability as described above shows that there are quite a lot of examples that demonstrate the feasibility of the approach. Pharmaceuticals are the molecules which present the biggest challenge because they should be very bioactive in terms of desired activity and at the same time inactive in terms of unwanted side effects. Therefore, examples from this area have been chosen to demonstrate the feasibility of the approach.

5-Fluorouracil is one of the important cytostatic agents which has been in medical use for long time. It acts as an anti-metabolite by replacing the natural compound uracil which is a basic constituent of RNA and DNA. A small change in the chemicals' structure, replacement of one hydrogen atom in uracil by a fluorine atom, makes it highly active as an anti-metabolite. The carbon–fluorine bond is well known for its chemical stability.¹¹ Therefore, 5-fluorouracil (Fig. 3) is not readily biodegradable.¹³ The negative effect of fluorine on the biodegradability of organic compounds is also found for the structurally similar compounds gemcitabine and cytarabine (Fig. 3), which also act as anti-metabolites and are used as cytostatic agents. Gemcitabine and cytarabine have been developed in order to improve pharmaceutical properties. They illustrate that improved pharmaceutical properties can

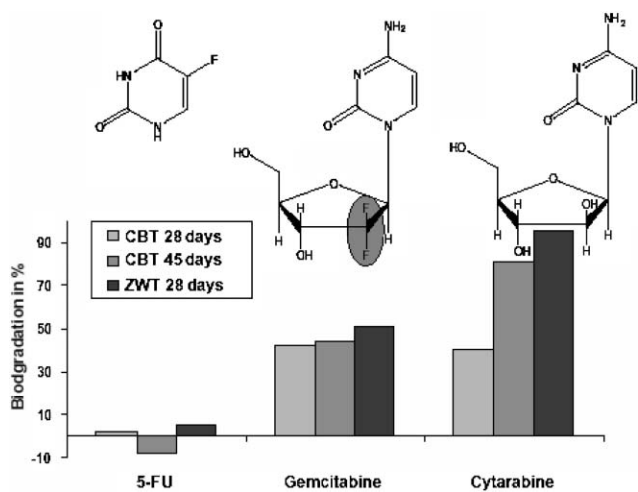


Fig. 3 Different biodegradability and elimination of structurally related anti-metabolites in the closed bottle test (CBT) and in the Zahn-Wellens test (ZWT)¹³

also result in improved environmental performance. A more detailed analysis of their biodegradability shows that the improved biodegradability of cytarabine as compared to gemcitabine is not only due to the sugar moiety without fluorine atoms but that the cytosine moiety has also been degraded.¹³

Another example is the cytostatic agent glufosfamid (β -D-glucosylisophosphoramidmustard: β -D-Glc-IPM; Fig. 4). In this case the stereochemistry is of importance, not only for the molecule's activity but also for its biodegradability. Glufosfamid was developed from ifosfamid, which is one of the classical alkylating cytostatic agents.

The goal of the structural change was to improve its pharmacological properties, such as uptake in the bowel, in order to reduce undesired side-effects. For this purpose, the active moiety (Fig. 5) was kept while the other part of the molecule was modified. β -D-Glc-IPM is now under clinical trial phase III. However, it has been found that the β -D-Glc-IPM not only has the desired pharmacological properties,¹⁴ but it is also much more biodegradable than ifosfamid, which is not biodegradable, as are most other cytostatic agents studied to date.

In contrast to β -D-Glc-IPM the β -L isomer is neither pharmacologically active nor biodegradable.^{14,15} The lack of biodegradability of the β -L isomer is quite understandable. In the human body, as in nature, the vast amount of enzymes catalyzing reactions of sugars is for β -D isomers, as most naturally occurring sugars and derivatives are based on β -D

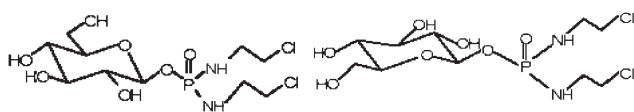


Fig. 4 Left: glucosylisophosphoramidmustard (β -D-Glc-IPM; INN = Glufosfamid). Right: β -L-glucosylisophosphoramidmustard (β -L-Glc-IPM).

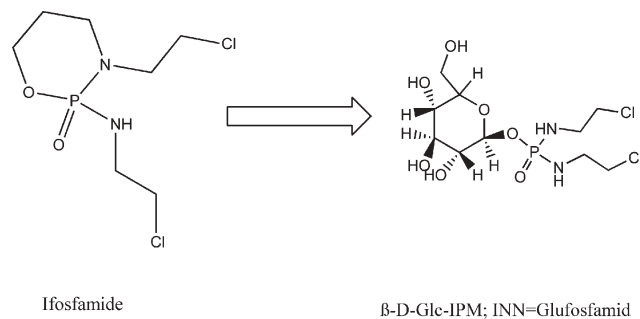


Fig. 5 Modification of the chemical structure of ifosfamid to improve sorption in the bowel by keeping the active principle (bold bonds) to β -D-Glc-IPM (INN = glufosfamid) also resulted in improved biodegradability under environmental conditions.^{14,15}

isomers. It should be emphasised that chemicals of natural origin are often better biodegradable than synthetic ones, but not in general. The uniqueness of a structure and its synthesis and metabolic pathways it fits in may also be of importance.

The different conditions along the life cycle of a chemical

β -D-Glc-IPM can serve as an illustrative example of which benefits can be gained if the whole life-cycle of a molecule is taken into account. One may ask why β -D-Glc-IPM is a promising pharmaceutical that is now under clinical trial phase III despite its good biodegradability, *i.e.* "instability" under environmental conditions. Enzymes modifying and degrading sugars are present in the human body too. A closer look shows that there are significant differences within the human body and the environment.

•Compound related:

◦The concentration of the compound is much lower in the environment than in the human body. This affects biodegradation and photodegradation.

•Environment/application related:

◦The presence of other organic material is higher in the gut than in most environmental compartments. This can affect the (bio)availability and solubility of the compound.

◦Parameters such as pH and redox conditions are of importance for non-biotic degradation by hydrolysis, oxidation and reduction.

◦Access of light is not possible in the human body and can be prevented by storage in brown glass on the shelf. In surface water and top soil the access of light (including high energy radiation such as UV light, which is of the utmost importance for photodegradation of organic compounds) is much more extensive than in rooms or in sewage treatment, in soil or sediments. Other organic material such as humic acids is present in environmental waters and may

serve as transmitters of light energy for indirect photolysis (type II photolysis).

◦Moisture is low when stored as a powder on the shelf. Therefore, hydrolysis is very slow.

•Microbiology related:

◦The diversity and prevalence of bacteria and enzymes is quite different between the bowel and the environment because of differing conditions. Furthermore, fungi are present in the environment and normally not in the human body.

◦In the bowel the ambient temperature is body temperature, which is preferred by thermophilic bacteria. The temperature is lower in sewage treatment and the aquatic environment where mesophilic bacteria are present.

◦In the bowel nutrient rich conditions are found by bacteria, whereas in the environment we have some food rich compartments such as sewage treatment and compartments with a shortage of nutrients (e.g. surface water).

◦In the bowels the conditions are anaerobic. In most environmental compartments aerobic conditions are found. This again selects different bacteria in differing densities with different metabolic capacities and activities.

◦Moisture is low when stored as a powder on the shelf preventing bacterial growth.

◦Redox conditions and pH are additional parameters that are different in the human body and the environment. pH is far below 7 in the stomach, whereas it is mostly above 7 in sewage.

Because of these different conditions, the potential for degradation of chemicals is different at different life stages of a chemical. If the different conditions and dependencies along the life cycle of a molecule are taken into account, stability during the application phase and degradability thereafter are not necessarily in opposition. This knowledge can be used to design chemicals according to the properties of a molecule within the different phases of its life cycle. That means a chemical's structure and its expected environment at each stage need to be looked at as a unit. In other words, the full functionality of a molecule includes the properties necessary for good performance within all life stages of a molecule—not only during the application. This holds not only for its fate after application but also all the other principles of green chemistry such as the preference for renewable resources, as well as aspects of synthesis such as waste minimization and atomic economy.

Examples demonstrating the feasibility

Linear alkylbenzenesulfonates (LAS) are among the most widely used chemicals. Several million metric tons are used as

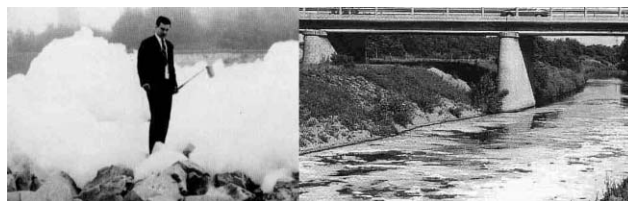


Fig. 6 Foaming in sewage treatment and on rivers in the 1950s caused by non-biodegradable TPS (with permission from the Archives of the Henkel Company, Düsseldorf).

laundry detergents per year worldwide. Its predecessor was tetrapropylene sulfonate (TPS) which was introduced into the market in the 1950s. Its biodegradability was low and resulted in strong foaming during sewage treatment and in rivers (Fig. 6).

As this effect was clearly visible for everyone the authorities took action and announced a special regulation which would soon come into effect. After this announcement the detergent industries started to work on a more biodegradable detergent. LAS were introduced into the market as a substitute for TPS before the new regulation came into force (Fig. 7). In Germany the so called *Detergentengesetz* came into force in 1961 and was the first environmental regulation in this country. The alkyl chain of LAS is not branched. It is derived from naturally occurring lipids. This is the reason for its biodegradability: the biodegradation pathway starts with a β -oxidation at its end. Then C_2 -units are removed stepwise. This is just the reversal of the natural pathway of its synthesis, the acetyl-CoA-mechanism. Because of the branching and C_3 -units this pathway is blocked in TPS. Another interesting detail is that LAS is more toxic to aquatic organisms than TPS but because of the good biodegradability of the latter during sewage treatment this has not prohibited its broad introduction into the market.¹⁶

EDDS (Fig. 8) is another example of a chemical that has been introduced into the market because of its good biodegradability compared with that of its predecessor ethylenediamine tetra acetate (EDTA).^{7,17} EDTA has long

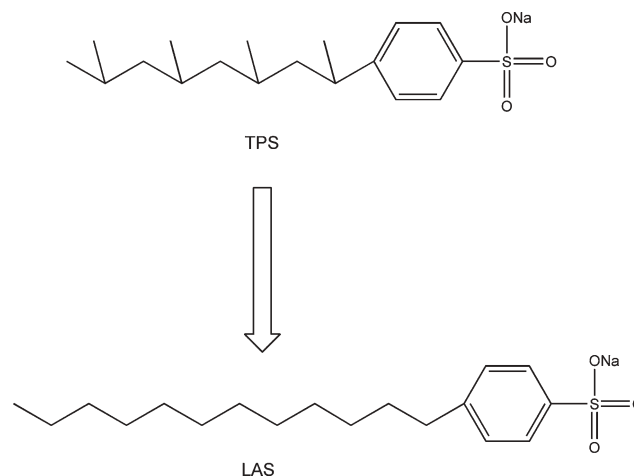


Fig. 7 Change of chemical structure of TPS aimed at improved biodegradability: LAS

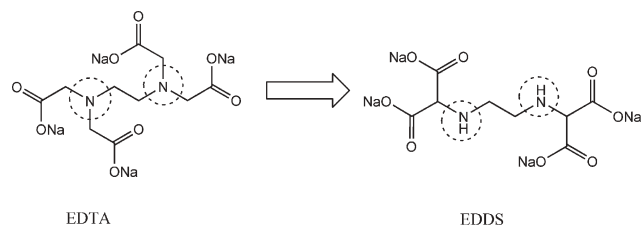


Fig. 8 Improvement of biodegradability and application range by structural change of complexing agents: [*S,S*]-EDDS is readily biodegradable whereas EDTA is not¹⁷

been in use as a complexing agent. Due to its heavy use and its low biodegradability it has been and still is frequently found in the environment, especially in sediments, where it remobilizes heavy metals. EDTA contains two tertiary nitrogen atoms. These are known to impede biodegradability. Moving the acetyl groups attached directly to the nitrogen atoms to carbon atoms results in secondary nitrogen atoms which are less constraining. The resulting new compound *N,N'*-ethylenediamine disuccinic acid (EDDS, IUPAC name: 2-[2-(1,2-dicarboxylethylamino)ethylamino]butanedioic acid)) differs by the type of the amino groups and the [*S,S*] isomer is much more biodegradable. [*S,S*]-EDDS is a derivative of aspartic acid, a naturally occurring amino acid. [*S,S*]-EDDS also works well as a complexing agent and for some applications is even an improved complexing agent. The secondary nitrogen atoms can function as additional binding sites. Interestingly, the stereo-isomeric [*R,R*]-EDDS is not biodegradable.

The targeted introduction of photochemical deactivation after use of an antibiologically active compound has been only recently described.¹⁸ An impressive example of the improvement of specificity, efficacy and environmental properties combined with economical success is the history of the pesticides. Dichlorodiphenyl trichlorethan (DDT) and other chlororganic chemicals such as γ -hexachlorocyclohexane and the bicyclic chlordiens such as aldrin and dieldrin are very persistent and are part of the dirty dozen mentioned in the Stockholm convention. After some time the more easily biodegradable organic phosphorous esters were developed (*e.g.* parathion). The more specific pyrethroids belong to the following generation of pesticides. Their lead structure is photo-sensitive and they are by far less toxic against humans. Carbamates are accessible to hydrolysis. The latest examples are the spinosoides (*e.g.* SpinosadTM) and the acyl ureas (*e.g.* HexaflumuronTM). Spinosad for example has been awarded with the Green Chemistry Award because of the combination of its activity to targeted pests and a better environmental and toxicological profile than most synthetic insect control agents.¹⁹

Rational design: life cycle engineering by molecular design

The correlation of structure and properties is at the core of chemistry and chemical language. This allows for a better design of chemicals. For photochemical degradation, important substructures are already known (chromophores), as well as for hydrolysis (*e.g.* ester groups) and biodegradation.⁷

Biodegradation of organic chemicals is impeded by fluorine atoms.¹¹ This is demonstrated by the examples of chloro-fluorohydrocarbons (CFCs), fluorinated hydrocarbons (FCs), and only recently the ubiquitous presence of perfluorinated octanesulfonates (PFOS) in the environment.⁴ For molecules that contain different functional groups, empirical knowledge about desired properties and degradability is necessary but often not sufficient to assess their properties. Chemical structure is not the only important criteria for a chemical's biodegradability. Size matters too. The bigger a molecule, the lower its biodegradability. If a molecule is too big it cannot be transported into the cell of a degrading bacterium and/or is not accessible for enzymes. In this respect, it will be of interest to have more biodegradability data of ionic liquids with long alkyl chains and the biodegradability of nano-particles. They offer advantageous new properties. However, their size may prevent their biodegradation in the environment.

For a more systematic approach (quantitative) structure activity relationships ((Q)SARs, here used in a broader sense: also including structure property relationships (SPRs) and other relationships) are an invaluable help for the directed design of new chemical entities.^{6–10,20} Recently, expert systems have become available to predict the properties of molecules using (Q)SARs. With some of these computer based systems it is even possible to enlarge the knowledge space. Their application allows at least an orientation in the right direction. For example, when a lead structure for a pharmaceutical has been found, variations of this structure are screened by such *in silico* systems in order to find the most promising candidates in terms of activity with the lowest amount of unwanted side effects. This results in the saving of costs, time and animal trials. In environmental science, such approaches have been used to date exclusively in a retrospective manner for the assessment of already existing chemicals. The design of pharmaceuticals by application of such computer methods has been only recently reported.¹⁰ These systems also allow including good biodegradability as a property of possibly successful candidates. Considering the functionalities of molecules over their entire life cycle brings into the foreground the application of such methods for the design of new chemicals and to include good degradability such as hydrolysis, photolysis, biodegradation and other elimination pathways such as sorption onto particulate matter and bioaccumulation in organisms under environmental conditions. They can be combined with systems that allow the prediction of metabolites. By doing this, the metabolites of biotransformation in the human body or the transformation products in the environment can be included before a molecule is even synthesized, *i.e.* a pre-production risk assessment and ranking would be possible.

The potential—politics and economics

The approach described here is not a new one. The examples presented, however, show that the approach is feasible. It is a sustainable one whose application is not limited to the so-called developed countries but can be used everywhere—in contrast to technique based treatment, *i.e.* end of the pipe technologies such as waste water treatment which in the long

run are not sustainable and which have their own limitations. In the declaration of Rio within agenda 21 adopted in Rio de Janeiro in 1992, it was stated that it is important to intensify the research for the development of safe substitutes for long living chemicals (Agenda 21, # 19.21).²¹

By 1994, a commission of the German parliament developed perspectives for the sustainable handling of chemicals.²² The principle of the environmentally benign design of chemicals for sustainable development was emphasized. The European Parliament and the European Commission expressed within the 6th Environmental Program that chemicals should be produced and used within one generation only in such a way that results in no negative impact on the environment.²³ This is underlined with the introduction of the new European legislation for chemicals. One of the main ideas of REACH⁸ is to minimize the impact of chemicals on humans and the environment along their whole life cycle. Chemicals and pharmaceuticals that are benign by design contribute to this goal. The German expert panel that advises the federal government on environmental issues expects that in the medium and long term the market for environmental friendly substitutes and new products will increase.²⁴ The activities of the U.S. EPA in green chemistry which have a focus on the synthesis processes are well known. The biggest potential within sustainable chemistry is expected to come from computer supported methods.²⁵

The ways in which how chemistry itself can be made more sustainable and how it can contribute to sustainable development in general are clear, we only have to apply them. Appropriate assessment methods are necessary and have been described already elsewhere in detail.

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