Chem. Rev. **2007,** *107,* 2207–2227

Designing Small Molecules for Biodegradability

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Received September 14, 2006

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1. Introduction

Under Section 6602(b) of the Pollution Prevention Act (PPA) of 1990, Congress made it clear that prevention was the top priority in a hierarchy of pollution management options. The PPA established a national policy that pollution should be prevented or reduced at the source whenever feasible, pollution that cannot be prevented should be recycled in an environmentally safe manner whenever feasible, pollution that cannot be prevented or recycled should be treated in an environmentally safe manner whenever feasible, and disposal or other release into the environment should be employed only as a last resort and should be conducted in an environmentally safe manner.

The Act defines source reduction as any practice that "(i) reduces the amount of any hazardous substance...prior to recycling, treatment or disposal; and (ii) reduces the hazards to public health and the environment associated with the release of such substances, pollutants, or contaminants."

The Act contains no language to suggest that molecular design of a target substance was ever considered, but the notion of chemical design lurks in several places. For example, "reformulation or redesign of products" is specifically mentioned as an approach to source reduction. For the agricultural sector, pollution prevention approaches are described, and one is "adoption of less environmentally harmful pesticides", in addition to more traditional actions such as reduction in water or chemical input to sensitive areas.

It is not, or should not be, a great leap forward to incorporate the principles of safe design at the molecular level. Alternative synthetic design is now well established as a critical facet of green chemistry. EPA has supported a variety of extramural projects aimed at the development of safer technology for the synthesis of industrial chemicals, has organized symposia, and published the proceedings.[1] The "benign by design" concept has also been extended to the design of the molecule itself.[2] This makes sense because it is the design of the molecule, not the design of the synthetic sequence or industrial process, that is the earliest phase in the long process of commercializing a new chemical.

Industrial research and development increasingly incorporates the principles of green chemistry and the development of safer substitutes, but until now safer has usually meant less toxic. However, biodegradability should similarly be viewed as integral to product design. Chemicals that resist biodegradation remain available to biota to exert toxic effects, not all of which may be known or predictable at the outset. Persistent chemicals that are bioaccumulative are of even greater concern because levels may be achieved in organisms that appear safe on the basis of acute toxicity criteria, but which ultimately result in chronic or other unforeseen toxic effects. Biodegradation is also important because, as the PPA acknowledged in its hierarchy of options, pollution cannot always be prevented at the source and so must be treated. Microbial degradation is fundamental to many waste treatment methods and is the cornerstone of modern wastewater treatment. Thus, both treatability of generated wastes and

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10.1021/cr050952t CCC: $65.00

Dr. Boethling is a microbiologist in the U.S. Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT), Exposure Assessment Branch. He earned his PhD at UCLA in 1976 and came to EPA in 1980 after a postdoctoral fellowship under Prof. Martin Alexander at Cornell University. His expertise is in biodegradation and the design and development of environmental fate data resources and estimation methods. In the latter field, he has helped develop several widely used methods for estimating chemical properties and environmental fate and is the EPA's contact for the Estimation Programs Interface (EPI) Suite. Dr. Boethling is OPPT's lead for development of test guidelines in the areas of chemical properties and environmental fate. He has also been active in OPPT's work on persistent organic pollutants (POPs) and persistent, bioaccumulative, and toxic substances (PBTs); high production volume chemicals (HPVC) testing and assessment; and review of new chemicals under section 5 of the U.S. Toxic Substances Control Act. He has been a promoter of green chemistry principles since publication of the seminal American Chemical Society (ACS) symposia volumes 577 and 640 in the mid-1990s and was an editor (with Prof. Donald Mackay) of the *Handbook of Property Estimation Methods for Chemicals: Environmental Health Sciences* (2000 CRC Press).

safety of materials that ultimately enter the environment can be enhanced by responsible molecular design.

2. Scope of this Work

The present work focuses on small molecules and does not treat the large and growing literature on design, testing, and use of biodegradable polymers. For this, readers are directed to other reviews, for example, Platt[3] and Howard.[4] The first section briefly discusses the effects of chemical structure and environmental variables on biodegradability, with emphasis on generalizations that can be applied in chemical design. This is followed by the core of the work which is a review of examples from high-volume existing chemicals that illustrate biodegradability design principles. Following this is a brief discussion of several screening-level models, databases, and other tools that may be useful in chemical design. The last section further highlights ambiguities of designing for biodegradability in the real world.

3. Environment, Structure, and Biodegradability

By now hundreds of research papers, reviews, and books have been written on this topic. Biodegradability is affected not only by a compound's structure but also by exposure conditions, which broadly can mean the environment, waste treatment, standard laboratory tests, or research studies. List 1, adapted from Fewson,[5] summarizes possible reasons for recalcitrance (resistance to microbial attack). It can be seen that there are many variables that impact resistance to biodegradation and that these cover a spectrum from environmental to structural factors.

David DiFiore (top) is a senior project manager and **Elizabeth (Libby) Sommer** (bottom) is an environmental scientist with the Environmental Protection Agency's Design for the Environment (DfE) Program, part of EPA's Office of Pollution Prevention and Toxics. Under DfE's Formulator Program, David and Libby team with science and policy professionals who, in partnership with manufacturers, work to improve the environmental and human health profile of chemical-intensive products for industrial, institutional, and consumer applications. They are a bridge between the Agency's science experts and the chemical products community and help to build innovative government–industry partnerships that benefit both business and the environment. The DfE program works directly with EPA's Green Chemistry specialists to identify and recommend safer chemicals to its formulator partners. Since 1997, DfE has offered recognition to those companies who design for the environment and human health by using safer chemicals. To date, more than 160 chemical products have been recognized by the program. Among the projects Libby and David have contributed to are the CleanGredients database, detailed in this article, and the related DfE Screen for Surfactants, which represents aquatic toxicity and biodegradability criteria that a surfactant must meet to achieve DfE approval. DfE and Green Chemistry specialists evaluate biodegradability for all formulation components in conjunction with a chemical's other attributes. For ingredients like surfactants, where rate of biodegradation is key to safer chemistry, a DfE-recognizable chemical must be readily biodegradable, and very importantly, its degradation products must be of low concern.

List 1 leads to several generalizations about the effects of environmental variables on biodegradability. Some are quite obvious but also have limited value in chemical design. For example, biodegradation is more likely in nutrient-rich environments because such environments tend to support a larger and more varied (thus catabolically more versatile) microbial population; moreover, nutrients are less likely to limit outgrowth of degrading microorganisms should there be any such microorganisms in that particular place. Also, biodegradation rate more or less correlates with temperature; thus biodegradation is likely to be faster at higher temper-

List 1
Possible reasons for resistance of a substance to microbial degradation

Environment
- ► Appropriate microorganisms do not exist or are not present in the environment
- ► There are inadequate nutrients for the microbial population
- ► The temperature, pH or pO_2 is too low or too high; ionic conditions are unsuitable
- ► Concentration of substrate is too high (toxic) or too low
- ► The substrate is adsorbed or covalently attached to clays, humus, etc., or is physically inaccessible
- ► The substrate is not accessible to attack because it is too large and/or insoluble

Molecule
- ► The substrate
  - — is not transported into the cell
  - — is not a substrate for the available enzymes
  - — is not an inducer for appropriate enzymes or transport systems
  - — does not give rise to products that can integrate into normal metabolism
  - — is converted into products that are toxic or interfere with normal metabolism

atures, within the range considered normal for environmental conditions. Less obviously, biodegradation in aquatic environments usually is faster at the lower substrate concentrations typical of the environment, as compared to laboratory screening tests. It is hard to see much direct value for chemical design in the last item, but it may add perspective to comparative analysis of data from tests such as the Organization for Economic Cooperation and Development (OECD) ready biodegradability tests.[6]

Ready biodegradation tests are aerobic screening tests designed so that positive results are unequivocal and lead to an assumption that the test substance will undergo rapid and complete degradation in the environment.[7] By definition, ready tests are not simulation tests, and for practical reasons, they use unrealistically high levels of test substance. Because the tests are inexpensive, most biodegradation data for commercial chemicals have been derived using one or more of these methods. Laboratory simulation tests use more relevant test substance concentrations and are gaining currency, but the development of more practical (i.e., less expensive) methods continues to challenge microbiologists.

One generalization that does have potential importance in chemical design relates to water solubility and the tendency to adsorb to environmental solid phases, which tend to be opposite sides of the same coin. Water-soluble substances usually biodegrade faster than insoluble ones. The latter tend to adsorb strongly to solid phases, and for small molecules, sorption/sequestration is commonly associated with lower rates of biodegradation. Note however that low solubility does not necessarily imply recalcitrance or lack of bioavailability. Natural products such as fats and most alkanes from petroleum are quite hydrophobic, yet generally well degraded if other conditions are right. Many microorganisms secrete biosurfactants (e.g., rhamnolipids; see section 5.10) that enhance the rate of solubilization.

Once inside the cell, the reactions that a compound may undergo are determined by its molecular structure. Hundreds of transformations have been described in the literature, but almost all can be classified as oxidative, reductive, hydrolytic, or conjugative. The catabolic pathways employed by microbial populations are also diverse, but despite the immense structural variety of naturally occurring, as well as anthropogenic compounds, their utilization by microorganisms always involves the same basic strategy. That strategy is stepwise degradation to yield one or more intermediate products capable of entering the central pathways of metabolism. The overall objective is always to produce carbon and energy for growth. Detailed knowledge of how microorganisms accomplish this derives largely from studies of pure cultures (single strains or species) able to grow at the expense of the selected compound. Through such studies, biodegradation pathways have been defined by characterization of intermediate products and the enzymes that catalyze successive steps. In toto, the characterization of degradation pathways and enzymes developed over more than 50 years of research constitutes an immense and elegant contribution to biochemical knowledge.

4. Rules of Thumb

Generalizations about the effects of chemical structure on biodegradability certainly can be derived from such studies, but for a variety of good reasons, this is not the best approach if the ultimate objective is to just to get a general idea about relative biodegradability, in the context of chemical design. Alexander[8] articulated this concept as follows:

> Generalizations derived from studies of individual microorganisms suffer from the fact that they may not apply to an environment where the tested species is not present and where a population with an entirely different range of substrates assumes dominance in a particular biodegradation. Individual organisms have their physiological and catabolic idiosyncrasies, and the idiosyncrasies may not be related to the intrinsic resistance of chemicals to biodegradation. Because microbial strains, species and genera have enzymes with dissimilar substrate specificities, and probably different cell permeabilities, it is more difficult to establish generalizations than in chemistry.

Fortunately, over the last 50 years a kind of parallel universe has existed in which biodegradability studies have been conducted using a wide variety of mixed culture test systems. Much of the initial work was done in industry decades ago and concentrated on detergent chemicals and pesticides. About the same time, Alexander and others began research that over the years has extended knowledge to a much wider range of chemical structures. Starting in the late 1970s, standardized biodegradation tests for commercial chemicals were developed and gradually refined, and since then, they have gained broad acceptance. Ready biodegradability tests, especially, have a long history of successful application. They are used not only in regulatory testing but also as a kind of default method wherever screening-level information on biodegradability is needed.

A large number of generalizations about the effects of chemical structure on biodegradability have emerged from this work. These concern the effects of various substituent groups or substructures, the number of times a given substituent appears in a molecule, and substituent position. Also included are more ambiguous features, namely, size and, especially, branching. In 1980, Scow[9] called the generalizations “rules of thumb” and the name stuck, imparting a kind of immortality to the originator as well as the rules. However, it is important to understand that only a small number of generalizations are acceptable even for qualitative use, that is, at the screening level, and for every generalization there are many exceptions. Both will be illustrated in the examples that follow in later sections.

The following molecular features generally increase resistance to aerobic biodegradation: halogens, especially chlorine and fluorine and especially if there are more than three in a small molecule (iodine and (probably) bromine contribute to a lesser extent); chain branching if extensive (quaternary C is especially problematic); tertiary amine, nitro, nitroso, azo, and arylamino groups; polycyclic residues (such as in polycyclic aromatic hydrocarbons), especially with more

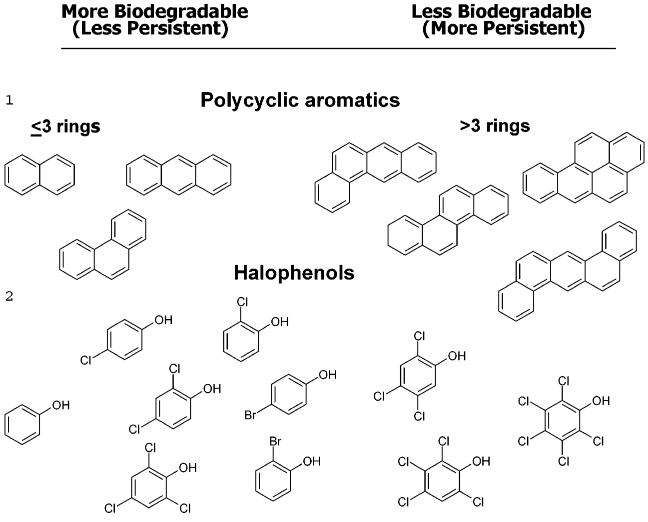


Figure 1. Biodegradability of halophenols and polycyclic aromatic hydrocarbons[109]

than three fused rings; heterocyclic residues, for example, imidazole; and aliphatic ether bonds (except in ethoxylates).

The addition of a chlorine atom to a phenyl ring makes the ring less susceptible to attack by oxygenase enzymes, which use an electrophilic form of oxygen as the oxidant. As a general rule, strongly electron-withdrawing substituents such as chlorine are therefore to be avoided if possible. On the other hand, it is sometimes assumed that even a single chlorine renders a compound recalcitrant. This is not so. In the case of halogenation and probably the other alleged negative influences as well, structural details are important. For example, for 2,4,5- and 2,4,6-trichlorophenol, the latter is readily degradable in OECD tests, but the former is not.[10] Figure 1 illustrates the "halogenation rule" graphically for some selected aromatic structures. The effect of polycyclicity on biodegradability of aromatics is also depicted.

Similarly there is a commonly held view that any branching, for example, even a single methyl group on an otherwise linear alkyl group, is to be avoided. This is a gross oversimplification. All that can be said with any confidence is that quaternary carbon is usually to be avoided, as is *extensive* methyl chain branching, which has no strict definition. Examples to illustrate the "chain branching rule" include polypropxylate (in contrast to polyethoxylate) functionality, tetrapropylenebenzenesulfonate (TPBS), and commercial nonylphenol ethoxylates (NPE), more on these later in this paper. Even for quaternary carbon, possibly the most coveted example of a negative structural influence, there are exceptions. There are few naturally occurring compounds with quaternary carbon,[11] but they do exist: for example, vitamin A, cholesterol, and pantothenic acid. The commercially important substance pentaerythritol also has quaternary C and is relatively biodegradable.

The following molecular features generally increase aerobic biodegradability: groups susceptible to enzymatic hydrolysis, chiefly esters (including phosphate esters) and also amides, but this is more equivocal; oxygen atoms in the form of hydroxyl, aldehyde, or carboxylic acid groups and probably also ketone but not ether, except in ethoxylate groups; and unsubstituted linear alkyl chains (especially ≥4 carbons) and phenyl rings.

Enzymatic hydrolysis of esters is probably the most familiar of these. It is a ubiquitous and critical step in the degradation of many so-called xenobiotic chemicals in part because esterase enzymes tend to have broad substrate specificity. The second rule is more subtle. In aerobic environments the first step in the biodegradation of many compounds is the enzymatic insertion of oxygen derived from molecular oxygen into the structure. This activity is performed solely by bacteria, and for small molecules, it is almost always the rate-limiting step in the degradation pathway. It is frequently observed that small molecules that already have oxygen in them biodegrade more readily than do the same molecules without the oxygen. For example, phenol degrades more readily in mixed culture than benzene; cyclohexanol and cyclohexanone degrade more readily than cyclohexane,[12] and alcohols and carboxylic acids degrade more readily than the corresponding aliphatic hydrocarbons.[13] The last of the three rules is relatively straightforward and was stated in a more general way above. It is that unsubstituted linear alkyl chains (especially with ≥4 carbons) and phenyl rings represent especially suitable sites for attack by oxygenase (oxygen-inserting) enzymes. In a sense, it is the next best thing if the molecule does not already have an "oxygen handle".

The number and positions of substituent groups appended to a base structure (such as a phenyl ring) also seem to have some bearing on biodegradability, but there are no rules of thumb that have much value in chemical design. For some polymers, such as modified cellulosics (e.g., methyl cellulose), the degree of substitution is a relatively precise concept and has predictive value. But there is not an analogous rule for small, nonpolymeric molecules. At present all that can be stated is that highly substituted structures are likely to be less easily biodegraded than much simpler compounds. Alexander's group did the original research that showed meta-substituted halophenols to be more slowly degraded in soil than ortho- and para-halophenols,[8] and for many years, this inspired unwarranted extrapolation to other classes of benzenoid compounds.[5,11] However, it is now clear that there are no broadly applicable generalizations about substituent position. Substituent position certainly does matter, but each class of compounds needs to be examined individually. Chapman expressed this succinctly.[14] He was talking about quaternary carbon in small molecules, but the concept applies generally. "Care must be exercised...to avoid drawing generalized, untenable conclusions about the resistance to biodegradation of a particular structure without reference to the entire molecule in which it is present and to the biodegradation mechanisms available for that class of compounds."

5. Designing Biodegradable Chemicals: Ten Examples

5.1. Alkylbenzene Sulfonates

The development of laundry detergents based on linear alkylbenzene sulfonate (LAS) is a brilliant success story, and a case can be made that this is still the best illustration to date of molecular engineering to enhance biodegradability and thus environmental acceptability. The replacement of soap as the workhorse surfactant in household laundry products occurred as early as the 1940s,[15] with the development of manmade alkylbenzene sulfonate (ABS) surfactants. At first, the alkyl chains were derived from a kerosene fraction, but these products were soon replaced by ABS produced from propylene tetramer. Tetrapropylene alkylbenzene sulfonate (TPBS) (Figure 2) was a more efficacious

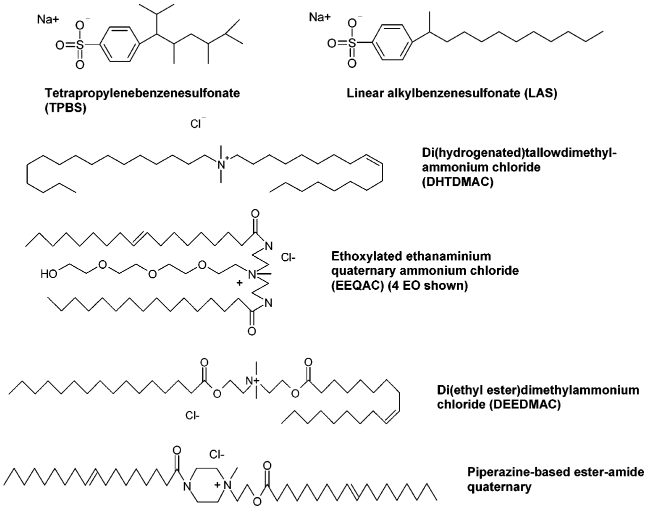


Figure 2. Chemical structures of several anionic surfactants and cationic fabric softeners.

and economical product, obtained via a one-step Friedel−Crafts process involving the addition of benzene at the double bond of the olefin feedstock to yield the branched alkylbenzene, followed by sulfonation of the benzene ring. As manufactured, TPBS is actually a complex mixture.

Environmental problems with these highly branched products appeared almost immediately because they were found to be incompletely biodegraded in municipal sewage treatment systems. Painter[16] offers a colorful description of what this meant in real terms:

> [TPBS] was degraded by only about 50% in sewage treatment units and as a result excessive foaming occurred in activated sludge aeration tanks, as well as in receiving rivers. The foaming was far worse than that caused by proteinaceous material in sewage prior to the introduction of synthetic surfactants and in extreme cases sewage-works operators were killed by asphyxiation after falling into foaming tanks from walkways made slippery by the foam...because of its incomplete biodegradation, the concentration of TPBS in river waters [was] as high as 2 mg L^{-1}, and water tended to foam when coming out of the tap.

Other results of the foaming were impaired efficiency of the treatment plants and increased dispersal of potentially pathogenic bacteria.[16] Public pressure and the threat of government regulation prompted industry to seek answers, and rather quickly, it was found that extensive methyl branching in the alkyl chain accounted for the resistance to biodegradation. Economical methods for manufacture of a more acceptable product were also quickly found. That product is LAS (Figure 2). This technology involved use of molecular sieves to obtain predominantly linear alkanes from petroleum, followed by any of several methods for producing the olefin. Voluntary changeover from TPBS to LAS was complete by the early 1960s in the U.S.[15]

LAS surfactants are almost completely biodegradable (>98%) in sewage treatment, and this has been amply demonstrated in hundreds of studies, including numerous monitoring studies conducted at full-scale treatment plants.[17] The history of TPBS and LAS illustrates the principle that extensive alkyl chain branching is to be avoided in chemical design. Another lesson of at least equal importance concerns the role of consumers in effecting change. TPBS was cheaper to make than LAS, but public pressure changed the economics.

Table 1. Biodegradability of Three Types of Dialkyl Quaternaries

QAC	hydrolyzable group	biodegradability	
		ready biodegradation (test method)	river die-away test
DHTDMAC[a]	none	0−5%[b]	10−20% in 63 days[c] 70% in 40 days
EEQAC[d]	amide	31%[e]	24−33% in 138 days
DEEDMAC[f]	ester	76% (OECD 301B)	$T_{1/2}$ = 1.1 days[g]

[a] Representative data for DHTDMAC, DSDMAC, and DTDMAC. *DTDMAC: Aquatic and Terrestrial Hazard Assessment. CAS No. 61789-80-8*; Technical Report No. 53; European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC): Brussels, Belgium, 1993. [b] In 26−30 days by unidentified CO_2 and BOD methods, probably similar to OECD 301B and 301D. [c] $^{14}CO_2$ from uniformly labeled alkyl-^{14}C. [d] Data for EO_1. *Information Review. Ethoxylated Quaternary Ammonium Compounds*; Draft final report IR-488; EPA Contract No. 68-02-4251 for the TSCA Interagency Testing Committee; Dynamac Corp.: Rockville, MD, 1988. [e] In 30 days by unidentified BOD method, probably similar to OECD 301D. [f] Giolando, S. T.; Rapaport, R. A.; Larson, R. J.; Federle, T.W.; Stalmans, M.; Masscheleyn, P. *Chemosphere* **1995**, *30*, 1067. [g] Acclimated activated sludge inoculum; $^{14}CO_2$ from methyl-^{14}C.

5.2. Dialkyl Quaternaries

Surface-active quaternary ammonium compounds (QACs) first gained prominence more than 50 years ago, with Domagk's discovery that the biocidal properties of simple quaternary ammonium compounds were greatly enhanced by the presence of a long alkyl group.[18] There are still many QAC-type biocides in use (see section 5.7), but household fabric softeners presently constitute the largest market by far for QACs. Other applications are mainly industrial and include multiple uses in textile processing, road paving, oil well drilling, mineral flotation, etc. Most uses of QACs, and especially the high-volume fabric softeners, lead to their release to municipal wastewater treatment systems. The fabric softener market is dominated by dialkyl quaternaries, in which hydrophobicity is imparted to the molecule by two linear alkyl chains in the C_{10-18} range. The hydrophobe is generally derived from purified animal fat (tallow) and consists of a mixture chiefly in the C_{16}−C_{18} (tallow fatty acids) range. Commercial products are of course mixtures.

Typical structures are shown in Figure 2 for three major classes of dialkyl QACs. Historically, the fabric softener market has been dominated by a QAC of the first type, di(hydrogenated or "hardened")tallow dimethylammonium chloride (DHTDMAC). The true aqueous solubility of DHTDMAC is exceedingly low, and the chemical sorbs strongly to solids in wastewater treatment and the environment. Removal in treatment is therefore high (>95%), but this does not necessarily correspond to ultimate biodegradation.[19] The heavy use of DHTDMAC in Europe before 1990, relatively low rate of biodegradation in aquatic sediments, and high intrinsic ecotoxicity has led to voluntary substitution with more biodegradable alternatives in several countries.[20] DHTDMAC is being replaced by dialkyl QACs with hydrolyzable amide or ester linkages between the hydrophobe (alkyl chain) and the two ethyl groups that are linked directly to the quaternary nitrogen center. Ester-amide quaternaries based on hydroxyethylpiperazine have been synthesized (Figure 2) and are stated to be biodegradable,[21] but not much information is available on their performance and properties.

Table 1 contains representative ready biodegradation and river die-away test data for the three major classes. Fewer

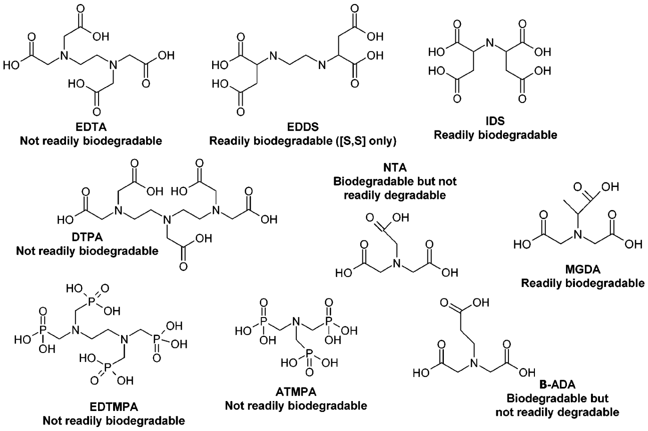


Figure 3. Chemical structures of some aminopolycarboxylate and polyphosphonate chelants. EDTA = ethylenediamine tetraacetic acid; EDDS = ethylenediamine disuccinic acid; IDS = iminodisuccinic acid; DTPA = diethylenetriamine pentaacetic acid; NTA = nitrilotriacetic acid; MGDA = methylglycinediacetic acid; EDTMPA = ethylenediamine tetra(methylenephosphonic acid); ATMPA = amino tris(methylenephosphonic acid); β-ADA = β-alaninediacetic acid. See text for sources of biodegradation data.

data are available for the DHTDMAC substitutes than for DHTDMAC and related compounds. From the data in Table 1, it appears that incorporation of amide groups in ethoxylated ethanaminium quaternary ammonium compounds (EEQAC) does not substantially improve biodegradability; however, several premanufacture notification (PMN) chemicals of similar structure passed RB tests. The weak ester linkages in di(ethyl ester)dimethylammonium chloride (DEEDMAC) allow this compound to be rapidly and completely biodegraded under the test conditions. This new, more biodegradable fabric softening agent represents another illustration of how safer surfactants can be developed byapplication of a known design principle: incorporation of ester linkages.

5.3. Chelants/Sequestrants

Chelating agents are high-volume chemicals used in a wide variety of consumer and industrial applications. These include not only the detergent industry, where they are used in laundry detergents, as well as household and industrial cleaners, but also the pulp and paper, textile, metals, photographic, leather, and cosmetic industries. The two principal classes of strong chelators are the aminopolycarboxylates and aminopolyphosphonates. Structures are shown in Figure 3 for the polycarboxylates ethylenediamine tetraacetic acid (EDTA), nitrilotriacetic acid (NTA), β-alaninediacetic acid (β-ADA), and diethylenetriamine pentaacetic acid (DTPA) and the polyphosphonates amino tris(methylenephosphonic acid) (ATMPA) and ethylenediamine tetra(methylenephosphonic acid) (EDTMPA). The environmental behavior of these compounds has been the subject of several reviews, for example for EDTA, Wolf and Gilbert;[22] for polycarboxylates, Bucheli-Witschel and Egli;[23] and for polyphosphonates, Gledhill and Feijtel.[24]

Except for NTA, the most commonly used chelators are poorly biodegradable, and some are quite persistent. Two potential substitutes with much more favorable environmental profiles are [*S*,*S*]-ethylenediamine disuccinate ([*S*,*S*]-EDDS) and sodium iminodisuccinate (IDS; chemical name D,L-aspartic-*N*-(1,2-dicarboxyethyl) tetrasodium salt) (Figure 3). Williams[25] summarized the history and use of aminopolycarboxylate chelants and highlighted the superior biodegradability of these and other potential replacements. Ethylenediamine disuccinate (EDDS) has two chiral carbons, and of the three stereoisomers, only one [*S*,*S*] is readily biodegradable; the others biodegrade to more persistent metabolites.[26] Accordingly, industrial applications of EDDS use trisodium [*S*,*S*]-EDDS.[27] The [S,S] stereoisomer of EDDS has been shown to be a superior chelant for remediation of metal pollution by ex situ soil washing.[28] In contrast, all stereoisomers of IDS are readily biodegradable.[29] IDS is two times "green" in the sense that not only is it readily biodegradable but also, unlike other aminocarboxylates, no hydrogen cyanide is used in its production, and the only waste product is ammonia which is recycled (refer to Baypure CX, Bayer Corp., product literature).

EDTA and EDDS are close analogs, but the biodegradable EDDS differs from EDTA in that it lacks tertiary amine nitrogens. This observation and the poor biodegradability of all aminopolyphosphonates that possess tertiary amine nitrogens are consistent with a view that this group is something to be avoided in chemical design. Of course rules are made to be broken, and it is noted that NTA and analogs like β-alaninediacetic acid (β-ADA) and methylglycinediacetic acid (MGDA) (Figure 3), which are tertiary amines, are biodegradable although not necessarily readily biodegradable.[23,30] Metal speciation is another factor that could account for differences in biodegradability between chelants of different types. Chelating agents generally are complexed with metal ions in biodegradation tests, as well as the environment, and the metal ion can have a substantial influence on biodegradability. Unfortunately no general pattern with respect to the influence of metal speciation on degradation can be deduced yet.[23] In the case of the phosphonates, also, resistance of the C$-$P bond is well-known[24] and may be sufficient to account for their poor biodegradability.

5.4. Drilling Base Fluids

Drilling fluid or "mud" is critical to oil and gas extraction and is required to cool and lubricate the drill bit, remove drill cuttings and transport them to the surface, prevent oil and gas from entering the well prematurely, and prevent the uncased wellbore from caving in (http://www.osha.gov/SLTC/etools/oilandgas/drilling/drillingfluid.html). Drilling mud consists of a base fluid and a variety of additives including weighting materials used to increase density, corrosion inhibitors, dispersants, biocides, etc. Water-based muds (WBMs) have a long history of use and are relatively inexpensive, but their performance is inadequate in many situations. Oil-based muds (OBMs) were developed to address WBM shortcomings and use diesel, mineral oil, or paraffins as the base fluid. Unfortunately, environmental problems can occur when OBMs are used in offshore drilling because the resulting cuttings piles create impaired zones beneath and adjacent to drilling platforms (http://web.ead.anl.gov/dwm/techdesc/discharge/index.cfm). Cuttings piles can contain 10% drilling fluid and may remain undisturbed on the sea floor for years.[31] Synthetic base fluids (SBFs) have been developed since the early 1990s for the purpose of providing OBM performance with the lower environmental impact of WBMs.

Commercially available SBFs include Fischer$-$Tropsch paraffins, linear alpha olefins (LAO), internal olefins (IO), and esters. Representative SBFs (Figure 4) have been tested,

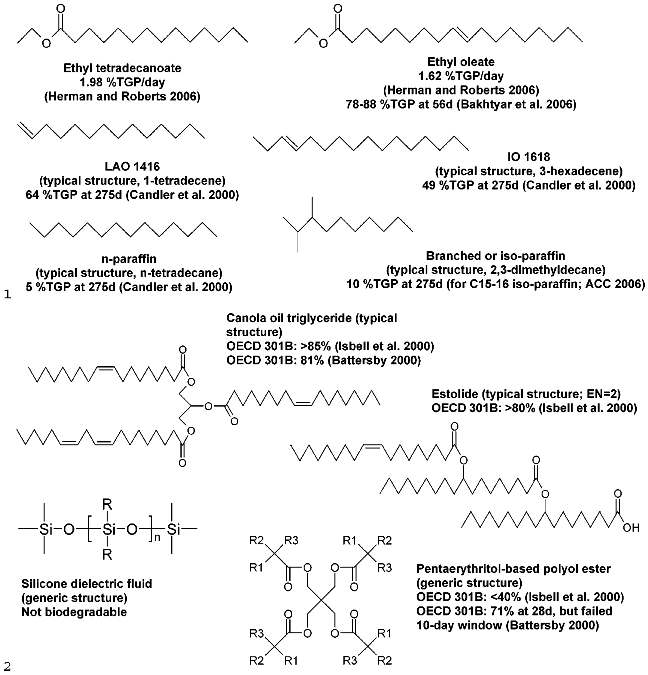


Figure 4. Chemical structures of some drilling base fluids, vegetable oil-based functional fluids, and other functional fluids. %TGP = percent of theoretical gas production in modified ISO 11734;[34] EN = estolide number.

and extensive data exist for both aerobic and anaerobic biodegradation. Recent work has focused on anaerobic biodegradation because anoxic conditions are expected to prevail in the centers of cuttings piles in the field.[32,33] Effluent guideline limitations established in 2001 require that SBFs to be used in offshore drilling be tested for sediment toxicity using the amphipod *Leptocheirus plumulosus* and for anaerobic biodegradability using a modification of ISO 11734[34] (http://web.ead.anl.gov/dwm/techdesc/discharge/index.cfm). Data obtained by this screening method and sediment simulation tests[32,33,35] have produced consistent rankings, with biodegradability ranked in the order from highest to lowest as ester $>$ LAO $>$ IO $>$ paraffins $>$ mineral oil and diesel. The esters, LAO, and IO degrade 2−3 times faster than mineral oil and diesel. Detailed study of a series of esters yielded a set of rules for selecting a specific structure or structures with maximum anaerobic biodegradability.[36]

Norman et al.[37] studied aerobic biodegradation of SBFs in soil and found that the ester and linear C_{12-17} paraffins degraded at much higher rates than branched paraffins and diesel. Available biodegradation data for SBFs thus yield a picture of SBF biodegradability that is consistent with rules of thumb: esters and linear hydrocarbons degrade appreciably faster than branched compounds and diesel (which is a mixture containing branched and unbranched, aliphatic and cyclic hydrocarbons varying in biodegradability). Moreover, unsaturated (olefinic) hydrocarbon SBFs biodegrade much faster than their saturated counterparts, consistent with $>$50 years' research on anaerobic microbial metabolism.[13] Aquatic sediment toxicity (*L. plumulosus* test) increased in about the same order as biodegradability decreased, ranked in order from lowest to highest as ester $<$ IO $<$ LAO $<$ paraffins $<$ diesel, indicating that high biodegradability and low toxicity are not necessarily mutually exclusive[32] (see section 8.1).

An encouraging feature of work in this field is the explicit attention given pollution prevention, in particular, the application of molecular design in the search for an optimum combination of toxicity and fate properties.[38,39,40] Unfortunately there are also complicating factors, as the ester SBFs that seem to have favorable aquatic environmental profiles also suppress root elongation in plants such as barley and alfalfa and are lethal (or their metabolites are lethal) to soil organisms such as earthworms.[37] This would appear to make them unsuitable for onshore drilling, where disposal of drill cuttings is a major issue and treatment methods such as landfarming and composting may be used. It is also important that even in offshore operations rapid biodegradation is not necessarily desirable, since although rapid biodegradation reduces the likelihood of direct aquatic toxicity, it may also hasten development of anoxic conditions.[32] This illustrates why safe chemical design in the real world is seldom a simple exercise.

5.5. Vegetable Oil-Based Functional Fluids

The 1976 U.S. Toxic Substances Control Act placed severe regulatory limits on polychlorinated biphenyl (PCB) manufacture and use in the United States. PCBs were widely used as *non*flammable dielectric and hydraulic fluids because of their excellent fire safety and functional properties. Various nonhalogenated fluids, designated "*less* flammable fluids" under the National Electrical Code, have taken their place as dielectric coolants for liquid-filled transformers. These include polydimethylsiloxanes (silicones), high molecular weight hydrocarbons based on mineral oils, synthetic polyol esters usually based on trimethylolpropane or pentaerythritol, and poly(alpha)olefins.[41,42] Typical structures are given in Figure 4. Silicones are essentially nonbiodegradable and mineral oils, being complex mixtures of cyclic and noncyclic hydrocarbons some of which are readily degradable and some not, have limited biodegradability in standard tests.[42,43] Polyol esters are more degradable but generally do not meet the formal pass criteria for ready biodegradability[43,44] (Figure 4).

The idea of using vegetable oils (seed oils) as dielectric coolants is not new, but until recently, they were considered unsuitable because they oxidize too easily, a consequence of unsaturation. Natural seed oils are mainly triglycerides, as shown for canola (rapeseed) oil in Figure 4, and are easily biodegraded under all conditions. According to McShane,[42] modern transformer design and suitable additives (e.g., antioxidants) largely compensate for the undesirable properties. Envirotemp FR3 is an example of a commercially available soy-based fluid and is used by a small but significant number of U.S. utilities (http://www.cooperpower.com/News/). Vegetable oils have also emerged as alternatives to petroleum-based lubricants,[45,46] hydraulic fluids,[47] metalworking fluids[48] (http://www.ars.usda.gov/AR/archive/may06/lube0506.htm), solvents for bitumen in road construction (http://www.baltic-network.de/index.php?page = 24), and base oil for printing inks (http://www.baltic-network.de/index.php?page = 9). A second problem with vegetable oils, especially in lubricant and hydraulic fluid applications, is their performance at low temperatures, a consequence of the oil's high pour point.[46] Here also chemical additives (called pour point depressants) can help mitigate the problem.

Hydrogenation improves oxidation stability. Reduction of unsaturation can be pursued through chemical modification or other means such as genetic engineering.[45,46,49] Soybean and canola oils have typical oleic acid contents of 26 and 54%, respectively,[50] but seed oils with high (75%) or ultrahigh (~85%) oleic acid content and reduced levels of polyunsaturated acids, such as linolenic acid, have been developed.[46]

Estolides constitute an entirely different approach to biodegradable but oxidation-stable lubricants. Estolides are esters formed when the carboxylic acid group of one fatty acid links to the site of unsaturation of another fatty acid molecule; Figure 4 has a typical structure (http://www.cyberlipid.org/fa/acid0005.htm). Estolides have good low-temperature properties, as well as oxidation stability, and are readily biodegradable.[44,51,52,53,54] The fatty acids can be derived from animal sources (e.g., tallow), as well as seed oils (http://www.ars.usda.gov/research/publications/ publications.htm?seq_no_115 = 185451). Fatty acids cost more than seed oils, but products formulated from estolides may require fewer additives than seed oil-based fluids.

Functional fluids clearly illustrate several biodegradability rules of thumb. Most importantly, the incorporation of hydrolyzable ester linkages greatly enhances biodegradability relative to mineral oils, which are the base fluids most commonly used at present. Vegetable oils are essentially hydrocarbons with built-in biodegradability. Synthetic esters (polyols) also benefit from this advantage, but squander it with steric hindrance and branching; according to one source, they also do not offer significant performance advantages (http://www.manufacturingcenter.com/ man/articles/m0901-soy.htm). Oxidation stability is a shortcoming of natural oils, but from the biodegradation perspective, it is better to reduce unsaturation than to add antioxidants. Fatty acids are readily degraded whether or not they have double bonds. In contrast antioxidants in transformer oils are almost always hindered amines or phenols, for example, 2,6-di-*tert*-butylphenol.[55] Such antioxidants have low ultimate biodegradability because of the *t*-butyl groups (0% degradation in ready biodegradation tests; http://esc.syrres.com/efdb.htm; see section 7.3), yet they offer stability only for a limited time.[55] Base fluids in the estolide class may be best of all from the triple perspectives of performance, biodegradability, and reduction of dependence on petroleum.

5.6. Ionic Liquids

Room-temperature ionic liquids (ILs) have generated considerable interest in the last 10 years, much of it based on their possible use as alternatives to conventional organic solvents in reaction and separation processes. Recent reviews have focused on catalysis,[56,57] asymmetric synthesis and chiral solvents,[58] nonaqueous biocatalysis,[59] carbohydrate chemistry,[60] and chemical analysis.[61] Uses as performance additives (e.g., plasticizers, antistats, and dispersants in paint) have received less attention but may be numerous. The full potential of ILs has not been explored, and practical applications in industrial processes are just beginning to appear.[62]

Despite the attention, there has been little study of their environmental behavior. The biodegradability of common ILs of the 1-butyl-3-methylimidazolium class has only recently been investigated.[63−65] The 1-butyl-3-methylimidazolium cation (Figure 5) was poorly degraded in the OECD 301D (closed bottle) ready biodegradation test. Significant ultimate degradation was observed for the 1-butyl-3-methylimidazolium octylsulfate salt (25% of theoretical oxygen demand or ThOD), but this could be attributed to degradation of the anion only because alkylsulfates are easily degraded.[15]

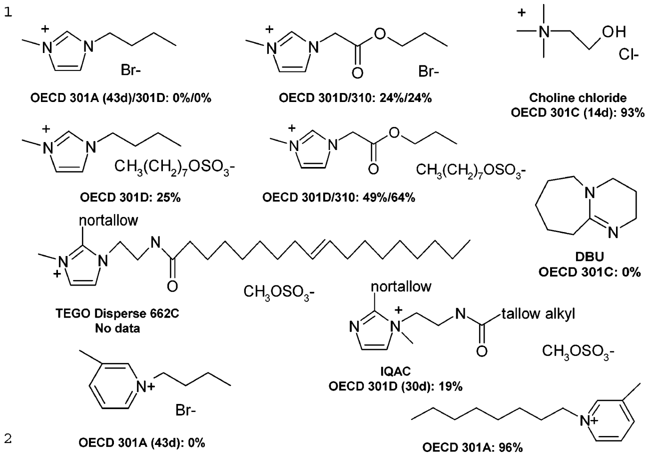


Figure 5. Chemical structures of some ionic liquids and related compounds. DBU = 1,8-diazabicyclo-[5.4.0]-undec-7-ene; IQAC = imidazolium quaternary ammonium compounds. See text for sources of biodegradation data.

Subsequent work focused on the effect of the incorporation of an ester linkage into the substituent on the first ring nitrogen.[65] This improved biodegradability, as measured in both closed bottle and sealed vessel CO_2 (OECD 310) tests (Figure 5), and the modified ILs met pass criteria for ready biodegradability if the counterion was octylsulfate.

Molecular engineering like this should be encouraged but caution is needed because it is easy to show that the observed percentage of degradation is consistent with attack on only the alcohol portion of the ester plus the octylsulfate ion, that is, no degradation of the imidazole ring. Similarly for the synthesized ILs with bromide ion, the observed percentage of degradation was lower and consistent with attack on only the alcohol. Few data are available, but the imidazole ring does appear to be rather resistant to microbial degradation. In one case, imidazolium quaternary ammonium compounds (IQAC) (Figure 5) used as fabric softeners, only 19% ThOD was observed at 30 days in a test presumably similar to OECD 301D.[66a] Also, IQAC is almost identical in structure to one of the unconventional ionic liquids (TEGO Disperse 662C; Figure 5) advocated for general use as plasticizers and additives for coatings.[62]

Work published by Rorije et al.[66b] suggests that the imidazole ring is not necessarily resistant to biodegradation but that N-substitution apparently blocks attack by enzymes in the urocanase pathway of histidine metabolism. Imidazolium ILs have substituents on both ring nitrogens, which would account for their limited biodegradability if this pathway predominates.

Murugesan and Linhardt[60] list several heterocyclic cations, in addition to imidazolium, that are currently used in ILs, for example, thiazolium, pyrazolium and oxazolium, but with the exception of pyridinium, few data are available on their biodegradation. Eckert and Liotta (http://www.che.gatech.edu/ssc/projects/smart%20surfactants.pdf) describe a reversible IL based on 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU, Figure 5), but this substance has been tested in the OECD 301C test and is not readily biodegradable,[67] which is typical although not universally true of N-heterocyclic structures. Recently Docherty et al.[68] studied the biodegradability of pyridinium and imidazolium ILs and reported that the former were in general more biodegradable than the latter, consistent with expectation based on a substantial body of data for pyridine, quinoline, and related compounds.[69] On the other hand, of several pyridinium ILs varying in alkyl chain length,

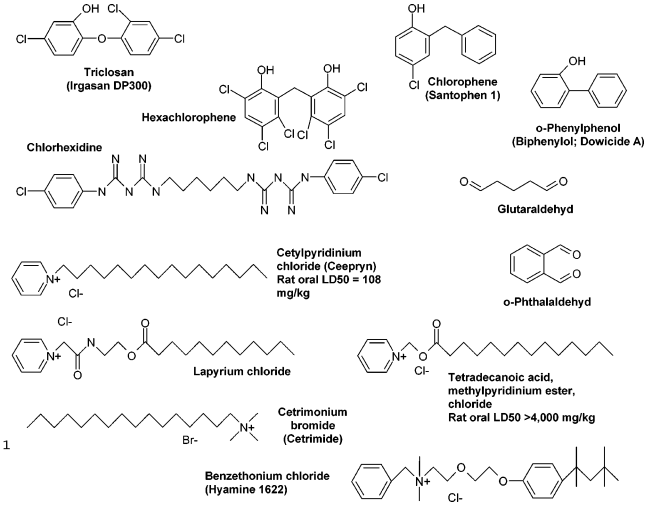


Figure 6. Chemical structures of some antiseptic and disinfectant substances.

only 1-octyl-3-methylpyridinium bromide (Figure 5) passed a ready biodegradation test. The 1-hexyl derivative was fully degraded but only with extended incubation (OECD 301A test), and the butyl derivative (Figure 5) showed no ultimate degradation.

Choline chloride has been used to develop ILs (called "deep eutectic solvents") for a variety of applications, and in contrast to the heterocyclics, is easily biodegraded[67] (Figure 5). Thus it seems worthwhile to invest more attention in choline-based or other biodegradable ILs, especially for applications expected to result in environmental emissions. Also, the recent biodegradation studies on imidazolium and pyridinium ILs suggest that pyridinium ILs should be synthesized that have alkyl groups linked via esters, analogous to the imidazolium esters synthesized by Gathergood et al.[65] Finally, there needs to be a systematic study of the biodegradability of heterocyclic cations used or contemplated for use in ILs. This should occur before widespread use and possible release to the environment.

5.7. Antiseptics/Disinfectants

Antiseptics and disinfectants are non-antibiotic biocides used to kill microorganisms or inhibit their growth. According to common terminology, antiseptics are applied to living tissue such as skin, whereas disinfectants are applied to inanimate objects like hard surfaces and surgical instruments. Many widely used antiseptics are membrane-active agents, but the precise mechanisms of action, though not known in detail in most cases, probably vary considerably.[70] Structures are given in Figure 6, and biodegradation data are summarized in Table 2 for selected antiseptics/disinfectants. With some exceptions, there has been relatively little study of their environmental behavior. Since these substances are intended to kill bacteria or inhibit their growth, published biodegradation data must be interpreted cautiously and with particular attention to test substance concentration. This means that data from ready biodegradation tests should be regarded with suspicion because these tests use initial concentrations that are in the same range (2−100 mg/L) as concentrations reported to be inhibitory in pure culture for target microorganisms.[70]

Chlorhexidine, a biguanide, is used in a large number of skin care and oral hygiene products. It is poorly degraded in screening tests and not readily degradable,[71] although biodegradation can be extensive in activated sludge with acclimation (http://esc.syrres.com/efdb.htm; see section 7.3). Among the phenolics, triclosan and hexachlorophene (Figure 6) are the most widely used.[70] Triclosan can be found in a huge and growing number of consumer products, although its biodegradability is somewhat controversial. Loss from the water column in rivers is rapid,[72] but 50% of the material entering conventional activated sludge treatment was found undegraded in the anaerobically digested, dewatered sludge in one study.[73] This suggests that the reported overall (influent vs effluent) removal of ∼95% (several studies, for example, McAvoy et al.)[74] may be misleading. Hexachlorophene was essentially undegraded in river water in one study[75] (Table 2). In contrast, there is little doubt that the phenolics chlorophene (2-benzyl-4-chlorophenol) and *o*-phenylphenol (Figure 6) are easily biodegraded in a variety of media (Table 2). Both are extensively removed in wastewater treatment, chlorophene somewhat less so than o-phenylphenol.[76]

Surface-active quaternary ammonium compounds (QACs) constitute another important class of antiseptics and disinfectants. Cetyltrimethylammonium bromide (Cetrimide), cetylpyridinium chloride (Ceepryn), and benzethonium chloride (Hyamine 1622) (Figure 6) are widely used, broad-spectrum microbicides. Benzethonium chloride did not degrade in river water[77] or respirometric tests.[78] In contrast, Larson showed that Cetrimide and similar alkyltrimethylammonium compounds are biodegraded in river water at realistic concentrations and in screening tests if their high toxicity is neutralized by stoichiometric levels of anionic surfactant.[79,80,81] Ceepryn is not readily biodegradable,[82] but by analogy with alkyltrimethyl QACs, microbial toxicity may account for this. Analogs of Ceepryn in which the alkyl group is linked to the rest of the structure via an ester include the antiseptic lapyrium chloride and tetradecanoic acid, methylpyridinium ester (Figure 6). Both should be more easily degraded than structures without hydrolyzable groups. The latter has lower mammalian toxicity than Ceepryn as well.

Aldehydes, especially glutaraldehyde (Figure 6) and formaldehyde, are widely used disinfectants with potential releases to the environment. Leung's review[83] on glutaraldehyde summarizes its environmental fate and effects. This simple compound is easily biodegraded under all conditions. Glutaraldehyde is the active in Dow's biocide G-Cide, which is used in their Glutex product line. It is being marketed as a broad-spectrum biocide effective against avian influenza H5N1, that is, the bird-flu virus (http://www.rsc.org/chemistryworld/News/2005/ December/01120501.asp). G-Cide is a complex of glutaraldehyde and ethoxylated C_{11-15} secondary alcohols with an average ethylene oxide (EO) chain length of nine. The nonionic surfactant's alkyl chain is linear and this substance also is easily biodegraded.[15] *ortho*-Phthalaldehyde[84] (Figure 6) has been suggested as a possible replacement for glutaraldehyde and, based on analogy with the easily degraded *o*-phthalic acid,[85,86] should behave similarly.

G-Cide is claimed to be active against a range of viral, bacterial, and fungal pathogens, yet is expected to be rapidly biodegradable at lower concentrations. Simple QAC antiseptics like cetyltrimethylammonium bromide (Cetrimide) are also very effective at typical usage levels, yet easily biodegraded when that property is desired. Thus it is not counterintuitive to state that biocides also can be designed for enhanced biodegradability. Antiseptics, disinfectants, and

Table 2. Biodegradability of Selected Antiseptics and Disinfectants

chemical	CAS no.	ready biodegradability	Biowin3[a]	other data
			biguanide	
chlorhexidine	55-56-1	NRB unspecified method[71]	1.40 (recalcitrant)	BS-1 (screening tests); BFA-2 (biological treatment simulation tests)[b]
			aromatic	
o-phenylphenol	90−43-7	RB sapromat method[c]	2.90 (weeks)	BF-1 (screening tests); BF-1 (biological treatment simulation tests); BF-3 (water grab sample die-away tests)[b]
chlorophene	120−32-1	RB sapromat method[c]	2.51 (weeks−months)	BF-1 (screening tests); BFA-2 (biological treatment simulation tests); BF-3 (water grab sample die-away tests)[b]
triclosan	3380−34-5	NRB 0% in OECD 301C[67]	1.94 (months)	rapid loss from surface water ($t_{1/2}$ on the order of hours), but probably due to photolysis[72,d]; high removal in activated sludge treatment (∼95% overall based on several studies)[73,74,e], but 50% present in dewatered sludge in one study[73], so biodegradative removal may be less than the overall removal, that is, subsequent exposure possible via waste sludge
hexachlorophene	70−30-4	(no data)	1.10 (recalcitrant)	BS-2 (water grab sample die-away tests)[b]
			cationic	
cetyltrimethylammonium bromide (Cetrimide)	57-09-0	NRB 0−7% in OECD 301A,B,C,D,E[f]	2.87 (weeks)	degraded in natural waters with $t_{1/2} = 2-3$ days or less; high removal (>95%) resulting from biodegradation, in activated sludge tests; well degraded in screening tests if toxicity is mitigated[19]
cetylpyridinium chloride (Ceepryn)	123−03-5	NRB 25% in OECD 301D[82]	2.82 (weeks)	with acclimation, >90% biodegradation of Ceepryn and close analogs in several activated sludge tests[19]
tetradecanoic acid, methylpyridinium ester, chloride		(no data)	2.93 (weeks)	(no data)
lapyrium chloride	6272−74-8	(no data)	2.78 (weeks)	(no data)
benzethonium chloride	121−54-0	(no data)	1.82 (months)	no significant degradation in river water[77] or respirometric (screening) tests[78]
			aldehyde	
glutaraldehyde	111−30-8	RB 64% in OECD 301D and 83% in OECD 301A[83]	3.02 (weeks)	biodegradable in seawater (52 and 73% in OECD 306 tests); 68% TCO_2 in aerobic river water-sediment test[83]
o-phthalaldehyde	643−79-8	(no data)	2.95 (weeks)	(no data)

[a] Biowin3, in Biowin (version 4.10), is one of six group contribution models for predicting aerobic biodegradation and is available as part of the Estimation Programs Interface suite of models (EPI Suite, version 3.20; free download at http://www.epa.gov/opptintr/exposure/pubs/episuite.htm). See text section 6.2. The numbers are direct output of Biowin3 and relate to aquatic biodegradation rate. They are interpreted via the indicated terms ("weeks"; "weeks−months"; etc.), which reflect predicted approximate time for complete ultimate biodegradation. [b] Environmental Fate Data Base (http://esc.syrres.com/efdb.htm); see text section 7.3. Each letter−number combination is a summary evaluation of all available experimental data for the study type, followed by an integer (1, 2 or 3) reflecting a judgment as to reliability of the evaluation. BF = biodegrades fast; BS = biodegrades slowly; BFA = biodegrades fast with acclimation; reliability 1 = chemical tested in 3 or more tests, consistent results; 2 = two tests, or results in >2 tests but with some conflicting data; 3 = only one test or uninterpretable, conflicting data. [c] Pauli, O.; Franke, G. *Gesundwes Desinfekt* **1971**, *63*, 150. [d] Singer, H.; Muller, S.; Tixier, C.; Pillonel, L. *Environ. Sci. Technol.* **2002**, *36*, 4998; Sabaliunas, D.; Webb S. F.; Hauk, A.; Jacob, M.; Eckhoff, W. S. *Water Res.* **2003**, *37*, 3145. [e] Thomas, P. M.; Foster, G.D. *Environ. Toxicol. Chem.* **2005**, *24*, 25; Thompson, A.; Griffin, P.; Steutz, R.; Cartmell, E. *Water Environ. Res.* **2005**, *77*, 63; Bester, K. *Arch. Environ. Contam. Toxicol.* **2005**, *49*, 9; Singer, H.; Muller, S.; Tixier, C.; Pillonel, L. *Environ. Sci. Technol.* **2002**, *36*, 4998; Sabaliunas, D.; Webb S. F.; Hauk, A.; Jacob, M.; Eckhoff, W. S. *Water Res.* **2003**, *37*, 3145. [f] Gerike, P.; Fischer, W. K. *Ecotoxicol. Environ. Saf.* **1979**, *3*, 159.

the like only need to be active in use, not after use. Further, the examples discussed in this section support biodegradability rules of thumb because, in all cases, the simplest compounds and those with linear alkyl chains or ester groups degrade well, whereas those with multiple halogens or highly branched alkyl chains do not (or degrade appreciably less quickly). Table 2 not only summarizes biodegradation data but also includes chemical structure-based biodegradability predictions from one of the Biowin models (see section 6.2), which track the data fairly well and can be used to make inferences about compounds lacking data. Maillard[87] listed six properties of an "ideal" biocide, as follows: It has a wide spectrum of activity. It is microbicidal at a low concentration and acts rapidly, notably on surfaces. It should not be neutralized or quenched easily (e.g., by hard water or organic load). It is nontoxic and degradable. It causes minimal damage to products or surfaces. Costs should be acceptable and supplies assured.

It seems from the above that products meeting many if not all of these requirements already exist.

5.8. Musk Fragrances

Synthetic musks are important ingredients for the fragrance industry. They are heavily used in laundry detergents, fabric softeners, cleaning products, air fresheners, etc., and in cosmetic and personal hygiene products such as hand soap, shampoo, and perfume. The three major classes of musks are the nitro musks, polycyclic musks, and macrocyclic musks. The OSPAR Commission (under the Convention for the Protection of the Marine Environment of the North-East Atlantic or "OSPAR Convention") summarized information on the environmental behavior of synthetic musks relevant to its charge, which is protection of the northeast Atlantic marine environment.[88] Most of the identified uses of synthetic musks are expected to lead to their release to municipal wastewater treatment and subsequently to the aquatic environment. The nitro and polycyclic musks are very poorly degradable and do not pass ready biodegradation tests.[88,89] Musk xylene, a nitro musk (Figure 7), is one of the most widely used. It is a candidate persistent, bioaccumulative, and toxic (PBT) substance under the OSPAR Convention and is on the OSPAR List of Chemicals for Priority Action. It also has been shown to have estrogenic activity in the E-screen assay, although estrogenic potency was low compared to 17β-estradiol.[90]

Macrocyclic musks are cyclic lactones or ketones with 15 or 16 ring carbons, and include natural products such as muscone (Figure 7). Ethylene brassylate (Figure 7) is a

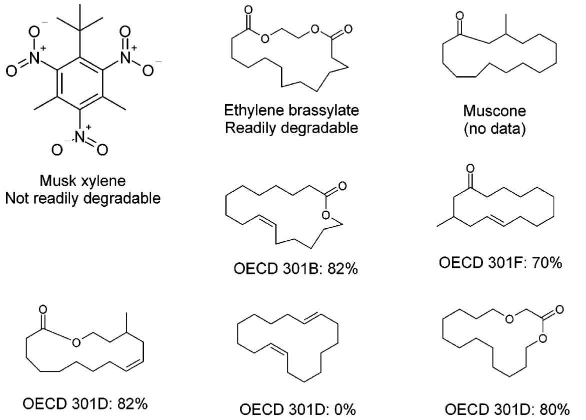


Figure 7. Chemical structures of nitro and macrocyclic musks and related compounds. See text for sources of biodegradation data.

macrocyclic musk in current use, described as readily biodegradable by OSPAR.[88] Fragrance producers have worked with EPA's Design for the Environment (DfE) Formulator Program (http://www.epa.gov/opptintr/dfe/pubs/projects/formulat/index.htm) to replace musk xylene with ethylene brassylate. Unfortunately, the macrocyclic musks are much more expensive than the other types and may have different odor and stability profiles.[88] These properties limit their ability to substitute in existing applications.

Musk xylene appears to be designed for maximum resistance to aerobic biodegradation with its *tert*-butyl group, multiple nitro groups, and high degree of ring substitution: every position on the ring has a substituent (one could still add halogens to the molecule!). In contrast, macrocyclic musks like ethylene brassylate are simple esters and are expected to be readily biodegradable. Although actual data were not found for this review, data for several analogs support this expectation (Figure 7). From the standpoint of design for biodegradability, the analog data are instructive because they illustrate two generalizations about positive influences. Of the five analogs, three have ester linkages, and all are readily biodegradable. Another analog is a ketone, which is also readily biodegradable, whereas the only macrocyclic hydrocarbon did not degrade. The message is that hydrolyzable groups (e.g., ester) are desirable but not required. It may be sufficient to have oxygen (aliphatic ether excepted) in or on a base structure.

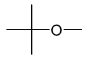
5.9. Gasoline Oxygenates: Methyl-*tert*-butyl Ether

The phaseout of lead-based octane enhancers in gasoline began in 1973 as a result of growing environmental and health concerns. Oxygenates, chiefly methyl tertiary butyl ether (MTBE) (structure 1), were added to replace the lead. The Clean Air Act Amendments of 1990 also led to a major increase in use of oxygenates because oxygenated gasoline (called "reformulated gasoline" or RFG) was required for the reduction of carbon monoxide and ozone in areas that did not meet ambient air quality standards. Initially oxygenates were added seasonally to reduce wintertime generation of carbon monoxide, but later, nonattainment areas were required to use RFG year round. In addition to MTBE, oxygenates in current use include ethanol, ethyl-*tert*-butyl ether (ETBE) (structure 2), and *tert*-amyl methyl ether (TAME) (structure 3). Production of MTBE was reported to be $\sim$9 billion kg in the U.S. in 1999 (http://water.usgs.gov/nawqa/vocs/national_assessment/report/chapter5.html) and 3 billion kg in the European Union in 2000.[91]

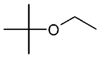
Table 3. Anaerobic Biodegradation of Gasoline Oxygenates in Aquifer Slurries[94]

chemical	octane rating	acclimation period	methane (%) theoretical
ethanol	29	25−30	91
isopropanol	118	15−20	112
t-butanol	103	>252	0
methyl ethyl ketone (MEK)	116	15−20	90
acetone	115	25	89
ethyl acetate	117	0−7	94
methyl *t*-butyl ether (MTBE)	118	>249	0
t-amyl methyl ether (TAME)	111	>182	0
diisopropyl ether	110	>252	0
di-*n*-butyl ether		>182	0
methyl *n*-butyl ether		84	99

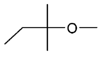
Research has shown MTBE to be quite persistent for such a small molecule. The environmental behavior of MTBE has been reviewed by Squillace et al.,[92] and more recently, MTBE biodegradation was reviewed by Fiorenza and Rifai.[93] Table 3 summarizes data from Suflita and Mormile[94] for anaerobic aquifer slurries for MTBE, as well as several other oxygenates. These data show that with the exception of methyl-*n*-butyl ether, compounds that contain a *tert*-butyl group, an aliphatic ether group, or both resisted biodegradation under these conditions. Given MTBE's low biodegradability, high water solubility (approximately 50 g/L at 25 C), and high concentration in oxygenated gasoline (10−15% by volume is common) and the huge infrastructure required to store, deliver and use gasoline, it should not be surprising that it is detected with high frequency in shallow groundwater.[95] Other monitoring studies are summarized in Fiorenza and Rifai.[93]



Methyl tert-butyl ether (MTBE) structure #1



Ethyl tert-butyl ether (ETBE) structure #2



Tert-amyl methyl ether (TAME) structure #3

MTBE has sometimes been described as recalcitrant, but recent work has shown it to be ultimately biodegradable, and biodegradation pathways have been established, though not in full detail. Nevertheless, much environmentally relevant research has been done, and it is clear that MTBE resists biodegradation under aerobic and anaerobic conditions. Beyond this, it seems doubtful that MTBE's persistence could have been seriously considered in any risk assessments conducted prior to its widespread use in RFG, because if it had been, it would have been obvious to any expert that the compound's quaternary carbon and aliphatic ether would render it difficult to degrade. Quaternary carbon is to be avoided in chemical design. The situation for aliphatic ether is less clear, but most data suggest it is negative for biodegradability in small molecules (ethoxylates are an exception).

5.10. Alkylphenol Ethoxylates

Alkylphenol ethoxylates (APE) are one of two major classes of nonionic surfactants, the other is linear alcohol ethoxylates (LAE). APE uses are mainly commercial. A little more than half the market is in pulp and paper, textile processing, coatings, agricultural pesticides, lube oils, metals, and plastics. Cleaning products make up about 45% of the market, most of which is industrial and institutional (30%). Household cleaning products account for 15% according to

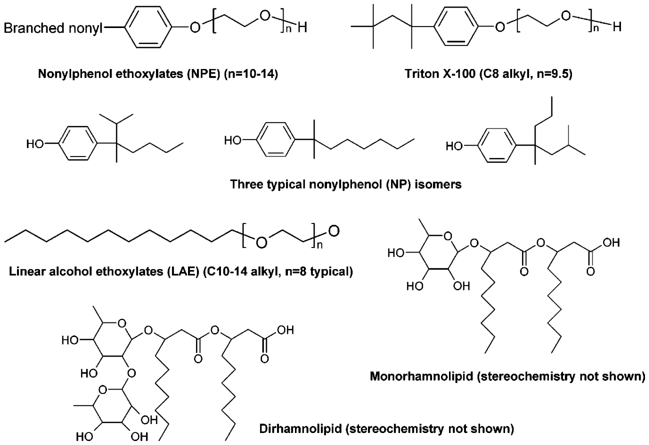


Figure 8. Chemical structures of alkylphenol ethoxylates, linear alcohol ethoxylates, rhamnolipid nonionic surfactants, and commercial nonylphenol.

the APE Research Council (APERC) (http://www.aperc.org/index.html). Nonylphenol ethoxylates (NPE) represent the largest class of APE and account for 75% of U.S. APE production; octylphenol ethoxylates (OPE) rank second. According to estimates from SRI Consulting,[96] consumption of NPE and OPE in North America in 2003 was 1.78×10^8 kg and 3.5×10^7 kg, respectively. A good example of NPE use is in printing. In screen reclamation, NPE are used in ink, emulsion and haze removal formulations, according to EPA's *Cleaner Technologies Substitutes Assessment* for the screen reclamation use cluster.[97]

Unlike LAE, most commercial APE are branched[98] (Figure 8). The synthesis of APE and the evolution of the manufacturing process are somewhat parallel to those of ABS surfactants.[99] As with ABS, the alkylphenol portion of the molecule is made by addition of an aromatic feedstock (phenol in this case) to the double bond of an olefin. At first the olefins were formed from polymerization of butene and isobutene, which resulted in alkyl groups with an abundance of quaternary carbons. These products were replaced by APE derived from "propylene trimer", which yields structures with less severe branching. However, GC-MS analysis of technical *p*-nonylphenol (NP) shows that commercial mixtures contain about 20 para-substituted isomers with differently branched alkyl chains and that isomers with quaternary carbon still predominate[100] (typical structures in Figure 8). Most of the isomers have linear (or monomethyl-branched) terminal alkyl groups with four to six carbons next to the quaternary carbon, which is connected to the phenol ring. Such structures can undergo at least one cycle of microbial β-oxidation, shortening the alkyl group by two carbons per cycle, before the quaternary carbon stops the process. This accounts for observations by Di Corcia et al. ,[101] who found that products of NPE having *both* partially degraded polyethoxylate and alkyl chains predominated in their biodegradation studies. It also accounts for their observation that these metabolites were essentially dead end products, characterized as extremely resistant to further degradation. It is all easily predicted from well-established knowledge of biodegradation pathways and biodegradability rules of thumb.

The amount of environmental risk posed by APE and especially NPE is a complex and contentious issue. Most attention has focused on NP itself and the mono- and diethoxylated NP adducts (NP1EO and NP2EO, respectively), which have been reported to be relatively stable intermediates in NPE biodegradation.[99] NP, NP1EO, and NP2EO are highly toxic to aquatic organisms, and the EPA has published ambient water quality criteria for NP (freshwater chronic = 6.6 μg/L)[102] (http://www.epa.gov/waterscience/criteria/nonylphenol/). In addition to their unfavorable aquatic toxicity profile, NP, NP1EO, and related compounds are weakly estrogenic in fish.[103] The actual margins of safety under environmental conditions for these effects are a subject of intense debate, but the current situation might not have arisen in the first place if APE were manufactured mainly from linear olefins. Substitution of a linear alkyl group would provide a major pathway for biodegradation, by analogy with LAS. This should lead to faster biodegradation and make transient accumulation of toxic intermediates very unlikely. Experimental data support this contention (Table 4). Studies[15] suggest that the principal route of breakdown becomes β-oxidation of the alkyl group rather than attack on the polyethoxylate chain.

Table 4. Biodegradability of Linear and Branched Alkylphenol Ethoxylates[15]

	% biodegradation			
APE[a]	linear[b]	branched	method[c]	analysis[c]
C_8APE_9	71	46	In, 28 days	Wt
	51	49	In, 20 days	Wt
C_9APE_9	65	25	RW, 15 days	CT
	65	30	SF, 5 days	CT
	88	55	CAS, 4 h	CT
	57	33	In, 9 days	CT
	66	32	In, 9 days	ST
	75	0	In, 9 days	F
	62	10	SF, 7 days	CT
	60	18	SF, 7 days	ST
	0−50	0	SF, 7 days	F
	89	75	RW, 10 days	CT

[a] APE = alkylphenol ethoxylate. C_8APE_9 = octylphenol with 9 ethoxy groups. C_9APE_9 = nonylphenol with 9 ethoxy groups. [b] Linear secondary. [c] Abbreviations: In = natural or synthetic medium inoculated with acclimated or unacclimated microorganisms; RW = river water die-away; SF = shake-flask culture; CAS = continuous flow activated sludge; Wt = weight of soluble organics in cell-free medium; CT = cobalt thiocyanate; ST = surface tension; F = foaming properties.

The substitution of linear for branched olefins never occurred on a large scale. Linear alpha olefins are commercially available and industrial processes exist to make them on a large scale (e.g., the Ziegler process for polymerization of ethylene), but for a variety of reasons, they are more expensive[15] and are described by APERC as "not likely to be commercially relevant" (http://www.aperc.org/nonyl-phenol0204.htm). However, this is not an impressive argument because the detergent industry faced and resolved similar issues with ABS. The difference is that environmental problems such as foaming in rivers were highly visible then, and the resulting public outcry, together with the threat of regulation, quickly led to action. It is also significant that the stringent biodegradability criteria adopted by the U.S. Soap and Detergent Association apply only to consumer products,[104] which make up only a small fraction of the APE market.

Other potential substitutes exist. Many companies recognized by EPA's DfE Formulator Program have substituted LAE for NPE. DfE is also developing the Safer Detergents Stewardship Initiative (SDSI) to encourage companies to switch from less degradable surfactants such as APE to more degradable substitutes like LAE. LAE (Figure 8) biodegrade rapidly and completely[15] and are competitive in cost. Rhamnolipid biosurfactants (Figure 8) represent another class of potential substitutes that is getting increased attention. Their favorable environmental profile results from superior biodegradability and low toxicity and is the reason that the most promising applications (at least in the short term) are in areas where environmental emissions are a major concern, for example, bioremediation and enhanced oil recovery.[105,106] Mohan et al.[107] compared the biodegradation kinetics of Triton X-100 (an APE, Figure 8) and a rhamnolipid and found the latter to be biodegradable under all conditions, whereas Triton X-100 was only "partially biodegradable" under aerobic conditions and persistent under anaerobic, nitrate-reducing, and sulfate-reducing conditions. Rhamnolipids are natural products that in addition to the sugar rhamnose, incorporate several familiar features that are positive for biodegradability, for example, ester linkage, carboxylic acid group, and linear alkyl groups. Rhamnolipid biosurfactants were the subject of an EPA Presidential Green Chemistry Challenge Award (http://www.epa.gov/opptintr/greenchemistry/).

6. Using Models in Chemical Design

6.1. Approaches to Modeling

Reliable computer models for prediction of biodegradability of organic chemicals from molecular structure would be very useful in chemical design. Some have fair accuracy but accuracy remains a major issue for all models. Most modeling work has been aimed at the development of qualitative structure/biodegradability relationships (SBR) that are broadly applicable to small organic molecules. Examples of qualitative endpoints are the prediction of pass/no pass in a ready biodegradability test and the assignment of qualitative descriptors such as fast/slow degradation based on a weight-of-evidence assessment of data. Quantitative measures of biodegradability (half-lives or rate constants) would probably be more useful in risk assessment and are essential for multimedia fate/transport modeling, but no broadly applicable models exist at present. A new model specific to petroleum hydrocarbons predicts half-life for this broad class of chemicals,[108] but users have not had much time to test it. However, the dearth of quantitative models matters little because an expression of relative biodegradability usually is sufficient in chemical design. No attempt is made to review models in detail here, and the reader is referred to Howard[109] for work published up to the mid-1990s, and Jaworska et al.[110] for more recent work.

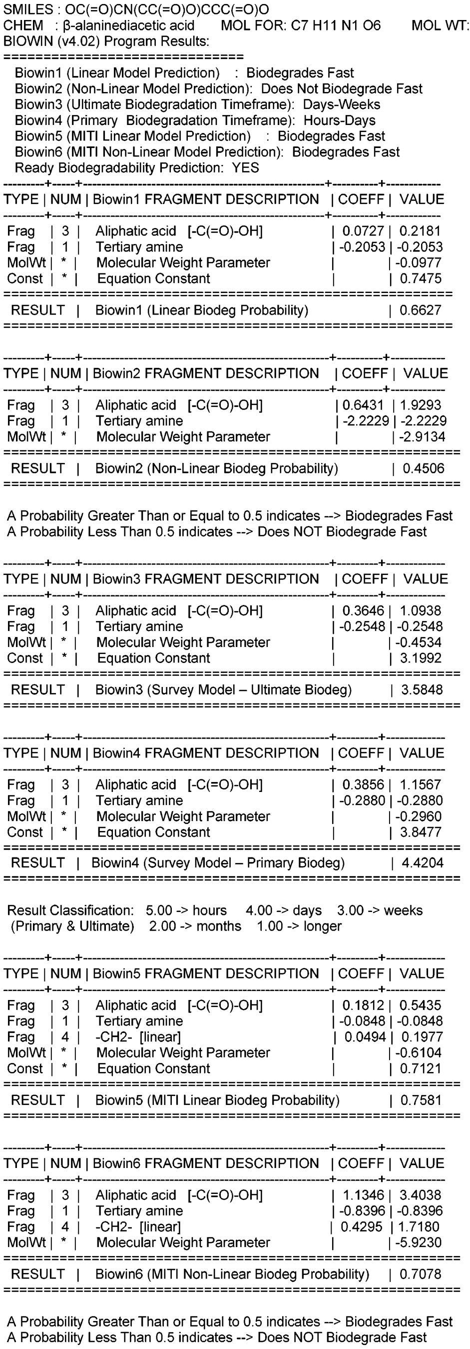
The history of structure/biodegradability relationships reveals an evolution from chemical class-specific to broadly applicable models and a concomitant evolution in statistical methodology from common regression methods to techniques used in chemometric analysis and artificial intelligence.[110] Group contribution models have been available since the mid-1980s. In this approach, the biodegradation endpoint is expressed as a linear or nonlinear function of the contribution of fragments (substructures) present in the molecule. Generally fragments are defined in advance of modeling by experts who are aware of biodegradation mechanisms and to be consistent with rules of thumb. Statistical manipulation is then performed on the training set of interest, after the chemicals have been parsed for the presence and numbers of the selected fragments. Statistical methods that have been used to determine the fragment contribution weights include multiple linear regression,[111−113] nonlinear regression,[111,113,114] and partial least-squares (PLS) regression.[115] It is evident from this description that such models have both statistical and mechanistic elements, despite being wrongly characterized by some as "non-mechanistic".

Chemometric and artificial intelligence methods have become popular in the last several years.[60] Chemometric analysis represents a modeling approach that includes a variety of statistical methods, in which both regression and classification models can be developed.[116] Chemometric analysis emphasizes statistical selection of relevant molecular descriptors, and attention is devoted mainly to the prediction power of the models. Often there is no obvious relationship between the descriptors selected and known biodegradation pathways or even generalizations about chemical structure and biodegradability. Artificial intelligence is also broad and includes biodegradability models based on inductive machine learning, as well as expert systems that attempt to predict pathways and products of biodegradation. Expert systems contain a set of transformation rules, and the library of rules is organized in a hierarchy that orders them according to their likelihood of being executed. Since they attempt to predict biodegradation pathways, such models are mechanistic in objective.

6.2. Group Contribution Models: Biowin

In the most recent version, Biowin (version 4.10) is a system of seven group contribution models for the prediction of aerobic and anaerobic biodegradation. It is available only as part of the Estimation Programs Interface suite (EPI Suite, version 3.20; free download at http://www.epa.gov/opptintr/exposure/pubs/episuite.htm) of models for chemical properties and environmental fate of discrete organic compounds. Like all models in EPI Suite, Biowin is intended for screening-level application. The six aerobic biodegradation models are best described as qualitative, although two models (Biowin3 and Biowin4) make semiquantitative predictions of degradation rate. Biowin1 and Biowin2 were developed using a database of weight-of-evidence (qualitative) biodegradability evaluations for 264 chemicals in the BIODEG database[117] (http://syrres.com/esc/efdb.htm). In contrast, semiquantitative estimates of rates of primary and ultimate biodegradation, gathered from a survey of experts who analyzed 200 carefully selected substances, were used to develop Biowin3 and Biowin4. Biowin5 and Biowin6 are analogous to Biowin1 and Biowin2 in that they estimate the likelihood of rapid biodegradation,[10] but they are based on a set of Japanese Ministry of International Trade and Industry (MITI) ready biodegradation data for 884 compounds[67] rather than weight-of-evidence evaluations. Biowin1, Biowin2, Biowin3, and Biowin4 use the same set of 36 substructures and MWt as variables, but they have different coefficients. Biowin5 and Biowin6 use a slightly different set of 42 substructures and MWt. A screening-level model for the prediction of anaerobic ultimate degradation in sludge digesters was developed recently (Biowin7; *Environ. Toxicol. Chem.*, in press) and installed in EPI Suite 3.20.

Figure 9 shows a sample Biowin output, in this case for β-alaninediacetic acid (structure in Figure 3). In full output mode, the identities of molecular fragments, their signs, and the number of instances in the molecule are given. Analysis of the signs of the Biowin coefficients yields interesting results that generally confirm generalizations about structure and biodegradability given earlier. Regression coefficients for the new anaerobic biodegradation model (Biowin7) were



```
SMILES : OC(=O)CN(CC(=O)O)CCC(=O)O
CHEM   : β-alaninediacetic acid      MOL FOR: C7 H11 N1 O6       MOL WT: 205.17
BIOWIN (v4.02) Program Results:
==============================
   Biowin1 (Linear Model Prediction)    :  Biodegrades Fast
   Biowin2 (Non-Linear Model Prediction):  Does Not Biodegrade Fast
   Biowin3 (Ultimate Biodegradation Timeframe):  Days-Weeks
   Biowin4 (Primary  Biodegradation Timeframe):  Hours-Days
   Biowin5 (MITI Linear Model Prediction)    :  Biodegrades Fast
   Biowin6 (MITI Non-Linear Model Prediction):  Biodegrades Fast
   Ready Biodegradability Prediction:  YES
---------+-----+--------------------------------------------------+----------+------------
TYPE | NUM | Biowin1 FRAGMENT DESCRIPTION   | COEFF |  VALUE
---------+-----+--------------------------------------------------+----------+------------
 Frag    | 3 |   Aliphatic acid   [-C(=O)-OH]               |  0.0727 |  0.2181
 Frag    | 1 |   Tertiary amine                             | -0.2053 | -0.2053
 MolWt |  * |   Molecular Weight Parameter                 |         | -0.0977
 Const |  * |   Equation Constant                          |         |  0.7475
==========================================================
  RESULT   |   Biowin1 (Linear Biodeg Probability)                  |  0.6627
==========================================================

---------+-----+--------------------------------------------------+----------+------------
TYPE | NUM | Biowin2 FRAGMENT DESCRIPTION    | COEFF |  VALUE
---------+-----+--------------------------------------------------+----------+------------
 Frag    | 3 |   Aliphatic acid   [-C(=O)-OH]               | 0.6431  | 1.9293
 Frag    | 1 |   Tertiary amine                             | -2.2229 | -2.2229
 MolWt |  * |   Molecular Weight Parameter                 |         | -2.9134
===========================================================
  RESULT   |   Biowin2 (Non-Linear Biodeg Probability)             |  0.4506
===========================================================

 A Probability Greater Than or Equal to 0.5 indicates --> Biodegrades Fast
 A Probability Less Than 0.5 indicates --> Does NOT Biodegrade Fast

---------+-----+--------------------------------------------------+---------+------------
TYPE | NUM | Biowin3 FRAGMENT DESCRIPTION    | COEFF |  VALUE
---------+-----+--------------------------------------------------+---------+------------
 Frag    | 3 |   Aliphatic acid   [-C(=O)-OH]               |  0.3646 |  1.0938
 Frag    | 1 |   Tertiary amine                             | -0.2548 | -0.2548
 MolWt |  * |   Molecular Weight Parameter                 |         | -0.4534
 Const |  * |   Equation Constant                          |         |  3.1992
===========================================================
  RESULT   |   Biowin3 (Survey Model – Ultimate Biodeg)            |  3.5848
===========================================================

---------+-----+--------------------------------------------------+---------+------------
TYPE | NUM | Biowin4 FRAGMENT DESCRIPTION   | COEFF |  VALUE
---------+-----+--------------------------------------------------+---------+------------
 Frag    | 3 |   Aliphatic acid   [-C(=O)-OH]               |  0.3856 |  1.1567
 Frag    | 1 |   Tertiary amine                             | -0.2880 | -0.2880
 MolWt |  * |   Molecular Weight Parameter                 |         | -0.2960
 Const |  * |   Equation Constant                          |         |  3.8477
===========================================================
  RESULT   |  Biowin4 (Survey Model – Primary Biodeg)             |  4.4204
===========================================================

 Result Classification:   5.00 -> hours     4.00 -> days    3.00 -> weeks
  (Primary & Ultimate)    2.00 -> months    1.00 -> longer

---------+-----+--------------------------------------------------+---------+------------
TYPE | NUM | Biowin5 FRAGMENT DESCRIPTION   | COEFF |  VALUE
---------+-----+--------------------------------------------------+---------+------------
 Frag    | 3 |   Aliphatic acid   [-C(=O)-OH]               |  0.1812 |  0.5435
 Frag    | 1 |   Tertiary amine                             | -0.0848 | -0.0848
 Frag    | 4 |   -CH2-  [linear]                            |  0.0494 |  0.1977
 MolWt |  * |   Molecular Weight Parameter                 |         | -0.6104
 Const |  * |   Equation Constant                          |         |  0.7121
===========================================================
  RESULT   |   Biowin5 (MITI Linear Biodeg Probability)            |  0.7581
===========================================================

---------+-----+--------------------------------------------------+---------+------------
TYPE | NUM | Biowin6 FRAGMENT DESCRIPTION   | COEFF |  VALUE
---------+-----+--------------------------------------------------+---------+------------
 Frag    | 3 |   Aliphatic acid   [-C(=O)-OH]               |  1.1346 |  3.4038
 Frag    | 1 |   Tertiary amine                             | -0.8396 | -0.8396
 Frag    | 4 |   -CH2-  [linear]                            | 0.4295  | 1.7180
 MolWt |  * |   Molecular Weight Parameter                 |         | -5.9230
===========================================================
  RESULT   |   Biowin6 (MITI Non-Linear Biodeg Probability)    |  0.7078
===========================================================

 A Probability Greater Than or Equal to 0.5 indicates --> Biodegrades Fast
 A Probability Less Than 0.5 indicates --> Does NOT Biodegrade Fast
```

Figure 9. Example of full output for the six current Biowin aerobic biodegradation models (EPI Suite 3.20): β-alaninediacetic acid (structure in Figure 3).

included in this analysis. As shown in Figure 10, all seven coefficients for the tertiary amine, aromatic NH/NH_2, and aromatic nitro fragments are negative. At the other end of the spectrum, all seven coefficients are positive for ester, phosphate ester, aldehyde, aliphatic and aromatic acid, aliphatic and aromatic alcohol, and unsubstituted phenyl groups. For several other fragments, that is, quaternary carbon, aliphatic and aromatic Cl, and pyridine, six of seven coefficients had the same sign (negative in this case). The molecular weight term was uniformly negative (six of six coefficients; only six because Biowin7 does not use this variable), consistent with the generalization that smaller is usually better for biodegradability.

The seven Biowin models represent four very different training sets. This is most obvious for Biowin7, which was

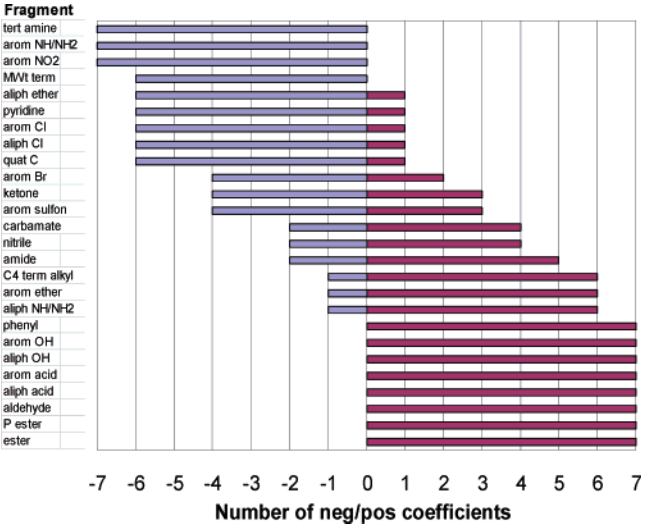


Figure 10. Distribution of signs (positive or negative) for the coefficients in the seven current Biowin models (EPI Suite 3.20). Abbreviations: arom (or aliph) NH/NH_2 = aromatic (or aliphatic) primary or secondary amine; arom sulfon = aromatic sulfonate; C_4 term alkyl = linear, unsubstituted terminal alkyl group with ≥ 4 C; phenyl = unsubstituted phenyl group (C_6H_5-); arom (or aliph) acid = aromatic (or aliphatic) $-COOH$ or salt. There are only six coefficients for carbamate, aromatic Br, nitrile, and the molecular weight term because these variables are not used in Biowin7. Fragments with inadequate representation in the model training sets (defined as <5 chemicals in at least two of the four model training sets) were not included in this analysis; therefore F, azo, *N*-nitroso, triazine, aliphatic Br, and aromatic I do not appear in the figure.

developed from a data set of 169 chemicals tested for methanogenic anaerobic biodegradation using the serum bottle method[118] (similar to ISO 11734). Alexander[8] stated that generalizations about structure−biodegradability relationships applicable to aerobic environments did not seem applicable to anaerobic environments, but Figure 10 suggests otherwise. That is, the major positive and negative influences, at least among those represented by Biowin fragments, are the same for both aerobic and anaerobic ultimate degradation. The drilling base fluids example in section 5.4 supports this conclusion because in several studies of anaerobic sediment biodegradation, esters and linear hydrocarbons invariably degraded faster than other tested structures. An additional rule for anaerobic conditions might be that unsaturated (olefinic) hydrocarbons degrade much faster than saturated hydrocarbons. The accuracy of a particular model for a particular compound or compound class will vary, but consistency of signs across so many different types of data argues for the validity of the rules of thumb they reflect.

6.3. Other Models based on Rules of Thumb

Gamberger et al.[119,120] applied artificial intelligence techniques (inductive machine learning method) to model biodegradability, first using a file of 293 substances from the BIODEG database in combination with a set of experts' judgments for 48 chemicals[121,122] and later MITI data from the same database[67] used to develop Biowin5 and 6. The final model consisted of a set of seven rules based on 11 structural descriptors, and it correctly classified 84% of the chemicals in the database with a well-balanced classification of easily and poorly biodegradable substances.[123] The structural descriptors included many of the same substructures used by the Biowin models, that is, ester, amide, and nitro groups. Rules of thumb were also used to develop the seven structural rules. The "presence of C−O bonds" is similar to the generalization given earlier wherein oxygen in the form of hydroxyl, aldehyde, or carboxylic acid (but not ether, except for ethoxylate) is considered a positive influence. However, the Gamberger et al. C−O feature includes not only substructures like OH and COOH but also noncyclic ether O, which leads to the misclassification of compounds such as diisopropyl ether and MTBE (note: Biowin also gets MTBE wrong). It is well-known that with the exception of ethoxylates, the ether linkage is associated with resistance to aerobic biodegradation in aliphatic compounds.[124]

This work shows that a very simple system can achieve reasonable accuracy overall, on par with that of models such as Biowin that contain many more variables. However, interpreting and applying the rules is not necessarily as straightforward as for Biowin output (Figure 9), which makes clear why the model produces a given result. Also, the inductive machine learning method should be extended to other training sets, since the MITI test represents only one measure of biodegradability and has many detractors. The Gamberger method can be applied now in chemical design, manually, but encoding the rules in a user-friendly computer program would greatly enhance its utility. We do not know if such a program exists.

In his review of screening-level estimation methods for biodegradability, Howard[109] analyzed and recommended the qualitative substructure model of Niemi et al.[125] and several models developed by Degner et al.,[112] in addition to Biowin. In both cases, many of the structural descriptors are similar or identical to fragments in Biowin and are consistent with generalizations about positive or negative effects given earlier. These models could also be useful in chemical design, but they suffer from significant shortcomings. The Niemi model[125] seems not to be available in Windows format, although a DOS-compatible program still exists and is part of the Micro QSAR 2.0 system. The Degner models[112] have relatively narrow applicability; for example, model 78, recommended by Howard,[109] applies to monocyclic aromatic compounds only. We do not know if they are available as computer programs.

6.4. CATABOL

CATABOL[126] is a hybrid consisting of a knowledge-based expert system for predicting biotransformation pathways, in tandem with a probabilistic model that calculates probabilities of the individual transformations and overall biochemical oxygen demand (BOD), extent of CO_2 production, or both. A novelty of the model is that the biodegradation extent is calculated on the basis of the individual steps in the entire pathway and not, as with all other models, from the parent structure per se. A second novelty is that CATABOL explicitly considers the effect of adjacent fragments before executing each transformation step. Currently, CATABOL contains over 550 principle transformations.[127] They often encompass more than one real biodegradation step to improve the speed of predictions. Before the transformation of a target fragment is executed, adjacent fragments are checked for inhibiting fragments. These inhibiting fragments may completely prevent the execution of the transformation or sometimes assign a lower probability for the reaction to occur. There are three or four inhibiting fragments per transformation and therefore over 2000 combinations of principal transformations and inhibiting fragments in the system. Spontaneous abiotic transformations (e.g., spontaneous hydrolysis) are included in pathway predictions.

The probabilities of individual transformations were deduced statistically from the 800+ compounds in the MITI database.[67] Similar principal catabolic reactions (those yielding similar BOD and having similar targets) are grouped and assumed to have the same probability. Since analysis of the MITI data yielded many transformations with equal probability, a hierarchy was needed, and this was established on the basis of expert knowledge. The hierarchy within each subset of transformations with equal probability can in principle capture effects of neighboring substituents. Moreover, through the analysis of the pathway and its critical steps based on individual transformation probabilities, CATABOL enables identification of potentially persistent catabolic intermediates and their molar amounts. CATABOL is still under development, but the approach shows considerable promise and may be quite useful in chemical design, especially in the identification of degradation products that may be persistent, bioaccumulative, or both. Potential disadvantages are the complexity of the system and reliance on data from the MITI test, which as stated above represents only one measure of biodegradability and is of limited utility. Information on the system can be found at http://www.oasis-lmc.org/.

6.5. Shortcomings of Group Contribution Models

Models like Biowin generally lack the sophistication required to consider the effects of neighboring substituents and substituent position. Examples are not difficult to find. Two examples from the extensive MITI data[38] are chlorinated phenols and naphthoic acids. The 2-, 3-, and 4-chloro; 2,4-, 2,6-, 2,3-, 2,5-, 3,5-, and 3,4-dichloro; and 2,4,5-trichloro phenols are all correctly predicted to not degrade in the MITI test. On the other hand both phenol and 2,4,6-trichlorophenol degraded in the MITI-I test, but only phenol is predicted to be degradable. For naphthoic acids, as indicated in Figure 10, all seven Biowin coefficients for the aromatic acid fragment are positive, and indeed Biowin5 and Biowin6 predict that 2-naphthoic acid should pass the MITI test, as it did. However, the models treat 1-naphthoic acid (which failed the MITI test) the same.

Test results can be at fault, but it seems best to assume that most of the time the model is the problem. An explanation in this case could be that the two naphthoic acids degrade by different pathways. More generally, it is common knowledge among biodegradation experts that isomers or otherwise similar chemicals are not necessarily degraded by identical pathways or at the same rate, even if they do share common intermediates. Decades of study of aromatic catabolism by bacteria and fungi have amply demonstrated that seemingly minor differences in chemical structure can lead to major differences in pathways of degradation and, therefore, equally large differences in rates of degradation and composition of the degrading populations:[8,14] we return to Chapman's admonition to avoid overgeneralizing.[14] It will be necessary to significantly improve our understanding of biodegradation mechanisms and pathways if we expect to make progress.

Group contribution models also assume linear additivity of fragments no matter what their type and number, a simplifying assumption necessary to make the approach practical. This yields reasonable results most of the time, when small molecules contain only commonly found fragments that are present in small numbers. However, wrong predictions become more likely even for positive fragments if their frequency is high. An example is *cis*-cyclopentane tetracarboxylic acid, a structure that is not easily degraded[111] despite Biowin's prediction to the contrary based on multiple occurrence of the carboxylic acid group. Additivity also works against the program in the case of EDTA (Figure 3), which is predicted to be readily biodegradable despite an abundance of data to the contrary. It should be noted, however, that Biowin1, Biowin2, and Biowin6 all give the correct answer; and the correct answer can be obtained from all six models if the structure is entered as the tetrasodium salt rather than the free acid.

Finally, not all fragments of significance for biodegradation are likely to be included or adequately represented in a given training set. This is the reason Biowin lacks coefficients for phosphonate (C−P bond), imidazole ring, pyrimidine ring, ethoxylate ether, alicyclic rings, quaternary nitrogen (although Biowin7 does have this fragment), etc. But a model can still have value in chemical design even if there is a "missing fragment", for example, if that feature is constant across a series of alternative structures. Ionic liquids are an example; there is no imidazole fragment in Biowin, yet the models give the correct answers. Obviously users need to be aware of any model's shortcomings.

6.6. Final Thoughts on Using Existing Models in Chemical Design

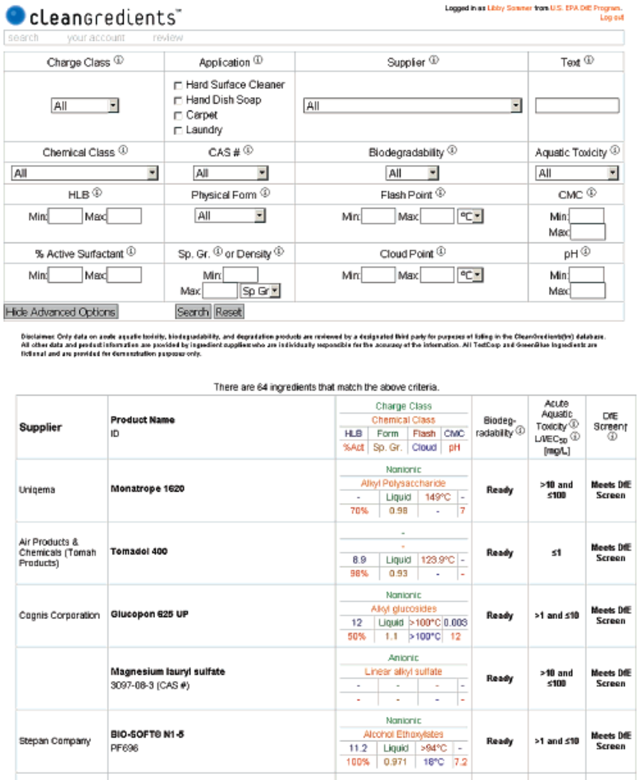
In principle, knowledge-based expert systems like CATABOL have the capability to correctly account for substituent position and number and can identify potentially persistent products, features that are beyond the capability of current group contribution models. But CATABOL is mostly untested. Despite their shortcomings, the Biowin models have reasonable accuracy and, given their transparency and convenience, should be useful in chemical design. On the other hand, it is worth considering that a program can be *too* convenient, to the extent that convenience fosters uninformed users and, potentially, uninformed molecular design. As noted above, the model coefficients also reinforce existing generalizations for the most part. Regardless of which model or models (if any) are used, it must always be kept in mind that rules of thumb and models are only a starting point in design for biodegradability. To paraphrase a favorite aphorism of environmental modelers, "All rules of thumb are half-truths...some are useful."

7. Database Resources for Chemical Design

There are many sources of data on environmental fate of chemicals including biodegradation. It is not possible to describe all of them here. Instead we list and briefly describe several resources that present biodegradation data in formats that seem particularly amenable to chemical design and product formulation.

7.1. CleanGredients

This new database presents reliable technical information on the environmental and human health attributes (e.g., aquatic toxicity and biodegradability) of chemicals used in cleaning products, thus helping product developers and users to improve the human and ecological health profiles of the products they design and use. The first CleanGredients module focuses on surfactants used in industrial, institutional, and household cleaning. The ingredients in this module can be queried by a wide variety of criteria, including surfactant class, chemical and physical properties, and surfactant properties such as critical micelle concentration (CMC, Figure 11 top). Typical initial search results are shown in Figure 11, bottom. Clicking on a product name brings more detailed information on the product and its health and environmental attributes, including biodegradation data (Figure 12).



Logged in as Libby Sommer from U.S. EPA DfE Program.
Log out

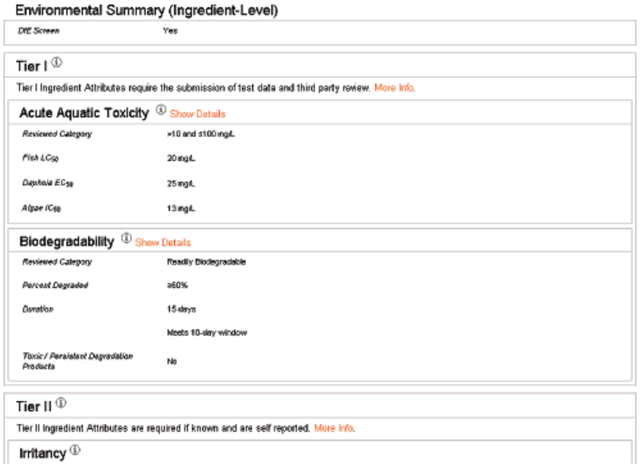
Charge Class: All
Application: ☐ Hard Surface Cleaner ☐ Hand Dish Soap ☐ Carpet ☐ Laundry
Supplier: All
Chemical Class: All
CAS #: All
Biodegradability: All
Aquatic Toxicity: All
Physical Form: All

Disclaimer: Only data on acute aquatic toxicity, biodegradability, and degradation products are reviewed by a designated third party for purposes of listing in the CleanGredients(tm) database. All other data and product information are provided by ingredient suppliers who are individually responsible for the accuracy of the information. All TestCorp and GreenBlue ingredients are fictional and are provided for demonstration purposes only.

There are 64 ingredients that match the above criteria.

Supplier	Product Name ID	Charge Class	Chemical Class	HLB	Form	Flash	CMC	%Act	Sp. Gr.	Cloud	pH	Biodegradability ⓘ	Acute Aquatic Toxicity ⓘ L/EC_{50} ⓘ [mg/L]	DfE Screen ⓘ
Uniqema	**Monatrope 1620**	Nonionic	Alkyl Polysaccharide	-	Liquid	149°C	-	70%	0.98	-	7	**Ready**	**>10 and ≤100**	**Meets DfE Screen**
Air Products & Chemicals (Tomah Products)	**Tomadol 400**	-	-	8.9	Liquid	123.9°C	-	98%	0.93	-	-	**Ready**	**≤1**	**Meets DfE Screen**
Cognis Corporation	**Glucopon 625 UP**	Nonionic	Alkyl glucosides	12	Liquid	>100°C	0.003	50%	1.1	>100°C	12	**Ready**	**>1 and ≤10**	**Meets DfE Screen**
	Magnesium lauryl sulfate 3097-08-3 (CAS #)	Anionic	Linear alkyl sulfate	-	-	-	-	-	-	-	-	**Ready**	**>10 and ≤100**	**Meets DfE Screen**
Stepan Company	**BIO-SOFT® N1-5** PF696	Nonionic	Alcohol Ethoxylates	11.2	Liquid	>94°C	-	100%	0.971	16°C	7.2	**Ready**	**>1 and ≤10**	**Meets DfE Screen**

Figure 11. CleanGredients database search page (top) and specimen initial search results (bottom). Reprinted with permission from the Green Blue Institute.



Environmental Summary (Ingredient-Level)

DfE Screen	Yes

Tier I ⓘ

Tier I Ingredient Attributes require the submission of test data and third party review. More Info.

Acute Aquatic Toxicity ⓘ Show Details

Reviewed Category	>10 and ≤100 mg/L
Fish LC_{50}	20 mg/L
Daphnia EC_{50}	25 mg/L
Algae IC_{50}	13 mg/L

Biodegradability ⓘ Show Details

Reviewed Category	Readily Biodegradable
Percent Degraded	≥60%
Duration	15 days
	Meets 10-day window
Toxic / Persistent Degradation Products	No

Tier II ⓘ

Tier II Ingredient Attributes are required if known and are self reported. More Info.

Irritancy ⓘ

Figure 12. Specimen ingredient-specific search results from the CleanGredients database. Reprinted with permission from the Green Blue Institute.

In the CleanGredients database, safer surfactants are defined by rate of biodegradation, the absence of degradates of concern, and aquatic toxicity. The database's objective is to communicate the distinguishing human and environmental

Table 5. Effects on Biodegradability of Chemical Structure Modifications Recommended for Reducing Toxicity

advice[129,130]	toxicity endpoint/ objective	effect on biodegradability
increase MW to >1000	lower aquatic toxicity	decrease
reduce water solubility to <1 μg/L	lower aquatic toxicity	decreases availability to biodegradation enzymes
increase steric hindrance at active site	lower aquatic toxicity	decreases availability to biodegradation enzymes
add bulky groups to or ortho to amines	reduce oncogenicity concern for aromatic amines	decreases accessibility to biodegradation enzymes
add hydrophilic groups, for example, sulfonate or COOH	reduce oncogenicity concern (enhance excretion)	may increase or decrease depending on group

health and safety attributes of surfactants and other cleaning chemicals, so that this information can be incorporated into product design and development, help organizations meet regulatory obligations, and assist sustainability initiatives, eco-labeling, etc. Although the focus is on product design (formulation) rather than chemical design, this resource is relatively unique in that provides a practical means for identification of environmentally preferable chemicals that still meet defined performance characteristics. Astute readers will have noticed that the latter information is in short supply in the preceding discussion of chemical design examples. CleanGredients is the result of a collaboration between the U.S. EPA and the GreenBlue Institute, with stakeholder involvement from cleaning product formulators and chemical manufacturers. The database is now available at http://www.cleangredients.org.

7.2. UMBBD

The University of Minnesota Biocatalysis/Biodegradation Database (UMBBD) (http://umbbd.msi.umn.edu/) is a rich source of information on microbial biocatalytic reactions and biodegradation pathways.[128] This information is derived from pure culture studies, which are useful for suggesting how a given substance might be degraded in the environment. From the perspective of chemical design, as noted earlier this approach is not the best if the objective is just to get a general idea of relative environmental biodegradability. However, the information in UMBBD (especially the biotransformation rules) can still be useful in chemical design because it may help identify when a given structural modification changes a molecule into one that is no longer a substrate for enzymes in an established pathway. Pathway information can also help identify potential degradates of concern.

UMBBD lists presently contain 154 pathways, 1021 reactions, 964 compounds, 638 enzymes, 375 microorganism entries, 239 biotransformation rules, 50 organic functional groups, 76 reactions of naphthalene 1,2-dioxygenase, and 109 reactions of toluene dioxygenase. Other useful features are the new Pathway Prediction System and Biochemical Periodic Table. The former predicts microbial catabolic reaction pathways using substructure searching, a rule database, and atom-to-atom mapping. The latter provides an overview of microbial interactions with essential and nonessential chemical elements, in the format of the periodic table. Information is accessed by clicking on the element symbol.

7.3. Other Databases

Under the Japanese Chemical Substances Control Law (CSCL), the Japanese National Institute of Technology and Evaluation (NITE) has developed the NITE database (http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html), which allows free access to biodegradation and other data on over 1000 discrete organics. Reference 67 is an older, hard copy version of this database. This represents the largest available collection of measured biodegradability data obtained using a single defined test protocol (the MITI-I test, OECD 301C). The NITE database is an excellent and frequently cited resource for chemical design, see section 8.1 for example. The BIODEG file of the Environmental Fate Data Base (EFDB) is another large database of biodegradation information,[117] available free at http://esc.syrres.com/efdb.htm. This database comprehensively covers biodegradation information from screening studies (various protocols), biological treatment simulations, grab sample tests, and field studies on over 800 chemicals. The BIOLOG file at the same website is more comprehensive (>8000 chemicals) but only provides references to biodegradation data. The Hazardous Substances Data Bank (HSDB), associated with the National Library of Medicine, has chemical properties, environmental fate, and biodegradation summaries for many chemicals and is free (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB). The data summaries are well written and usually comprehensive. See structure 6, in section 8.2.2, for an example of biodegradation data not found in the other common sources.

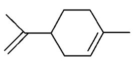
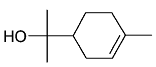
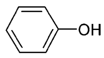
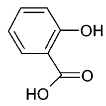
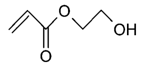
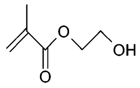
8. Real World Considerations

Biodegradability is never the only variable in chemical design, and it may not even be a principle one outside of the detergent industry. It is beyond the scope of this article to weigh all the factors that might contravene molecular design aimed at enhancing biodegradability. The objective here is to use toxicity and biodegradability to illustrate how inconsistency can arise and then look at examples to show that biodegradability may not be on anyone's mind when a chemical is described as green.

8.1. Toxicity versus Biodegradability

Lai et al.[129] and Newsome et al.[130] discussed the design of safer chemicals from the perspectives of chemical carcinogenesis and aquatic toxicology, respectively. As indicated in Lai et al. ,[129] the structural and molecular basis of carcinogenicity is quite well understood for aromatic amine dyes (e.g., benzidine-based dyes), and this enables a series of recommendations designed to reduce carcinogenicity potential, some rather specific. Two are given in Table 5. In the area of ecotoxicology, decades of research and testing on thousands of organic substances have yielded a series of generalizations on how aquatic toxicity can be reduced, through generic modifications that focus on properties such

Table 6. Lower Aquatic Toxicity Is Possible without Compromising Biodegradability: Examples

Chemical		Substitute chemical		
Structure	Biodegradability[a]	Structure	Toxicity[130]	Biodegradability[a]
d-limonene 	MITI: 41-98% (2 wk)	α-terpineol 	41 X ↓	MITI: 85% (2 wk) EFDB: BF-3
phenol 	MITI: 85% (2 wk) EFDB: BF-1	salicylic acid 	21 X ↓	MITI: 88% (2 wk) EFDB: BF-1
2-hydroxyethyl-acrylate 	MITI 76-80% (4 wk) EFDB: BFA-3	2-hydroxyethyl-methacrylate 	47 X ↓	MITI: 92-100% (2 wk)

[a] MITI = OECD 301C ready biodegradability test; either 2 weeks or 4 weeks duration;[67] EFDB = Environmental Fate Database, BIODEG file (http://syrres.com/esc/efdb.htm); BF-1 means biodegrades fast, highest reliability (1); BF-3 means biodegrades fast, lowest assigned reliability (3); BFA-3 means biodegrades fast but acclimation required, lowest assigned reliability (3). See reference 117 for details.

as water solubility, as well as specific changes in molecular structure aimed at reducing excess toxicity.[130] Several recommendations are given in Table 5, together with the effect the recommended action would most likely have on biodegradability. The postulated effects on biodegradability are based on generalizations discussed earlier in this paper.

In many cases, changes in chemical structure or properties that reduce toxicity also reduce biodegradability. For example, compounds with MWt > 1000 are in general not easily biodegraded. Thus, recommending that molecules be designed to be as large as possible could be viewed as promoting the replacement of biodegradable chemicals with more persistent ones. Obviously this was not the intended message. In cationic dyes with localized charge, the order of preference relative to aquatic toxicity (most to least preferred) is quaternary ammonium > tertiary amine > secondary amine > primary amine.[130] However, the order of preference for biodegradability, based on rules of thumb, is roughly the opposite: primary and secondary amine > tertiary amine and quaternary ammonium. Primary amines may be ecotoxic, but they are often quickly degraded in soil and water. Similarly a common recommendation is to increase steric hindrance to inhibit bioactivation, for example, by the addition of bulky groups (Table 5); yet this action will probably decrease biodegradability. The reason for this has a fundamental basis in biochemistry. Whether the process is bioactivation (higher organisms) or biodegradation (microorganisms), enzyme activity is at the core.

It is possible to reduce toxicity by molecular engineering without concomitantly increasing environmental persistence. We saw an example in section 5.7 with rat oral LD_{50} and the antiseptics cetylpyridinium chloride (Ceepryn) and tetradecanoic acid, methylpyridinium ester (Figure 6). Other examples are discussed in Newsome et al.[130] and summarized in Table 6. In all three examples, the proposed substitutes have similar uses and are at least as easily biodegraded, yet have more favorable aquatic toxicity profiles. The acrylates are interesting because ostensibly the methyl group's effect is to decrease or eliminate excess toxicity by increasing steric hindrance, but the methyl group apparently has little or no effect on microbial degradation. This suggests that compromise is possible and also shows that monomethyl branching is not an impediment.

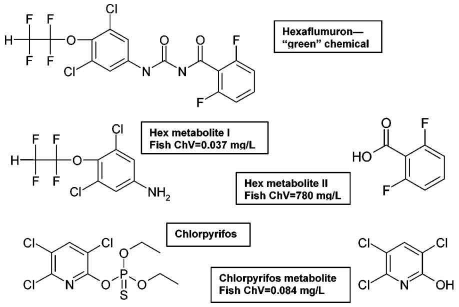


Figure 13. Chemical structures of hexaflumuron, hexaflumuron metabolites I and II, and chlorpyrifos and its principal metabolite. Fish ChV = fish chronic toxicity value.

8.2. Does Green Mean Biodegradable?

8.2.1. Hexaflumuron

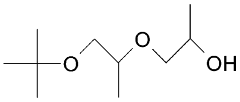
Hexaflumuron is the highly successful termite control agent in Dow's Sentricon system and a recipient of an EPA Green Chemistry Award (http://www.epa.gov/opptintr/greenchemistry/). Hexaflumuron replaces chlorpyrifos (Dursban) and has significant advantages in that it does not require widespread application and is used only when termite activity is detected and then only in monitoring stations. Henry[131] characterized toxicity to daphnia (an aquatic invertebrate) as "the only potential concern" and an unlikely problem because of the nature of the intended use.

Chemical structures for chlorpyrifos, hexaflumuron, and their principal known metabolites are shown in Figure 13. The identities of the metabolites are easily predicted from chemical structure by applying biodegradability rules of thumb and have been confirmed experimentally. Like musk xylene (Figure 7), hexaflumuron metabolite I seems optimized for persistence; viz., the presence of multiple Cl and F and aromatic amine N (Figure 10). Significantly, hexaflumuron metabolite I is more aquatically toxic than the principal metabolite of the ungreen chemical it replaces (Figure 13), based on ECOSAR prediction from EPI Suite (http://www.epa.gov/opptintr/exposure/pubs/episuite.htm). Thus, hexaflumuron may not be so green if in the future a new use leads to aquatic environmental exposure.

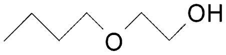
8.2.2. Premanufacture Notification (PMN) Case Study

Dipropylene glycol tertiary butyl ether (DGTBE, structure 4) was the subject of a nonconfidential PMN and proposed for use as a solvent for coatings and cleaners. Since DGBTE was intended to replace ethylene glycol monobutyl ether (MGBE, structure 5) and diethylene glycol monobutyl ether (DGBE, structure #6), other possible uses are numerous. The submitter filed a claim for pollution prevention (P2) recognition on the basis of DGTBE's lower acute toxicity. However, on the basis of experimental data, it is clear that DGBTE is substantially less biodegradable than are MGBE and DGBE. ECOSAR predictions also indicate that DGTBE is more aquatically toxic than DGBE and comparable to MGBE.

DGBTE's lower biodegradability is easily predicted from rules of thumb, avoid extensive branching and quaternary carbon, and real-world experience (oxygenates, especially MTBE; section 5.9). In addition, the *tert*-butyl analog of MGBE, 2-(*t*-butoxy)ethanol (structure 7), did not degrade in 16 days in a BOD-type screening test (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB, see section 7.3).

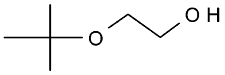


Structure #4
Dipropylene glycol tertiary butyl ether (DGTBE)
Biodeg data: *some* deg in 28d in OECD 301D, but only with acclimated inoculum



Structure #5
Ethylene glycol monobutyl ether (MGBE)
Biodeg data: 96% in 14d in OECD 301C test

Structure #6
Diethylene glycol monobutyl ether (DGBE)
Biodeg data: 89-93% in 28d in OECD 301C test



Structure #7
2-(t-Butoxy)ethanol
Biodeg data: 0% in 16d in BOD-type test

Therefore, because the nature of proposed and possible uses could lead to substantial emissions to landfill, as well as water, the possibility that DGBTE could behave like MTBE in the subsurface environment also must be acknowledged.

8.3. Beyond Biodegradability: Self-Regenerating Materials

Ultimately, designing for biodegradability seems less than ideal as an approach to source prevention. As long as there are emissions, there are treatment/remediation costs. This idea is embodied as the first principle of green chemistry:[132] *1. Prevention. It is better to prevent waste than to treat or clean up waste after it has been created.*

It is even better if the starting material regenerates itself or can be regenerated easily after performing its job. This is not as farfetched as it sounds. Switchable surfactants and reversible ionic liquids are a focus of current research. For example, Liu et al.[133] describe a switch based on alkylamidines that is triggered by bubbling CO_2 through the solution, and Eckert and Liotta (http://www.che.gatech.edu/ssc/projects/smart%20surfactants.pdf) describe several strategies including reversible surfactants based on thiirane oxide and piperylene sulfone "switches", for which mild heating regenerates the starting hydrophobe and pro-hydrophile. Commercial viability for these switches is unexplored territory, but other self-regenerating materials already exist and have niche applications.

9. Concluding Remarks

Absent specific knowledge of a chemical's environmental behavior, the way to design more biodegradable chemicals is to incorporate positive features like ester linkages and hydroxyl groups and exclude halogens, quaternary carbons, nitro groups, and the like. The more prominent positive and negative features are highlighted above and in Figure 10. However, chemists should be aware that generalizations are only a starting point in design. "All rules of thumb are half-truths...some are useful".

Because all computer models only represent approximations of imperfect underlying data, screening-level models like Biowin are even cruder than generalizations, a sobering thought. Still, predictive models based on rules of thumb provide a convenient way for chemists in research and development to quickly compare alternatives. They are not perfect, but do not need to be to have value in screening-level applications. CATABOL and UMBBD appear to be useful and perhaps underrated resources for identifying possible degradation products, another aspect of chemical design that could be important in many applications.

Product performance and economics obviously are as closely linked as biodegradability is to molecular structure. This makes the task of modifying molecular structure to enhance biodegradability potentially very difficult. Further, so many factors are involved in bringing a product to market that no one person could possibly possess all the knowledge required to make it happen. How many manufacturing chemists understand that by using tetrapropylene (hopefully described as "obsolescent" by Swisher[15] in 1987) or commercial nonylphenol as a feedstock, or by capping polyethoxylate nonionics with polypropylene oxide to maximize functional properties, they may be rendering an otherwise easily degraded molecule into one that is not? Equally, even idealistic microbiologists must appreciate that one needs to design an efficacious product and manufacture it economically to practice safe design in the first place. It is obvious that chemical design is just one facet of a multidisciplinary process and that biodegradation is only one factor in design, conclusions highlighted by Rieger.[134,135]

Safe chemical design, especially biodegradability, has long been prominent for high-volume, down-the-drain surfactants used in consumer products. However, decades of experience and the examples given in this review suggest that all industrial chemicals should reflect principles of safe design to the extent practicable. For example, transformer fluids (such as PCBs) and flame retardants (such as the brominated flame retardants) are not down-the-drain chemicals. Yet nobody would still argue that because they are not intended to be released to the environment, their biodegradability is irrelevant. We should not design, manufacture, and release to the environment new substances that are persistent and result in aesthetic or toxicity problems down the road. The desirability of integrating environmental considerations into business decisions and designing products to minimize their impact are nothing new and have long been acknowledged in the American Chemistry Council's Responsible Care program. What appears to be needed is more concerted implementation.

Safe chemical design is essential because of the following: Source prevention is cheaper than recycling, treatment, or disposal. Production, emissions, and exposure may increase if a chemical succeeds in the marketplace. If problems arise, they could be impossible to fix. We cannot know in advance all possible toxic effects of a new chemical. New uses often develop, and because they do, emissions and exposure may change. The global environment is interconnected

10. Acknowledgment

The senior author (R.S.B.) wishes to express his gratitude to Prof. Martin Alexander of Cornell University (emeritus). By extending environmental biodegradation studies broadly from a sound but limited basis in the surfactants and pesticides industries, he created an entire field and fostered the careers of numerous students and postdoctoral fellows including this one.

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CR050952T