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The Use of Quantitative Structure-Activity Relationships for PREDICTING RATES OF ENVIRONMENTAL HYDROLYSIS PROCESSES

(Technical Report)

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Abstract - With the aim of setting up an evaluation on the use of QSARs for the prediction of various transformation processes, first of all a short introduction is given on the general principles that form the fundamentals of most QSARs developed so far. Thereupon a review, including the limitations of the relations presented, is given of the QSARs available at the moment for the calculation of rates of chemical hydrolysis of organic substances in the environment. On the basis of the results obtained general recommendations are given on the application of QSARs for the prediction of environmental process parameters. The review is restricted to the process of chemical hydrolysis, being a rather ubiquitous, environmentally relevant transformation route which is well described in literature and for which a relatively large number of QSARs have been developed so far.

INTRODUCTION

Under environmental conditions chemical compounds can be transformed or degraded by a number of different processes. These processes can roughly be divided into three separate categories:

1. Biodegradation; transformation by living organisms;
2. Photochemical transformation processes; abiotic degradation processes that are initiated by irradiation with sunlight;
3. Chemical transformation processes; degradation processes under the influence of chemical agents.

The importance of each of these three transformation pathways varies considerably and in particular depends on the medium in which a compound is present. For example, photochemical processes are important transformation pathways for compounds in the gas phase, whereas the contribution of these processes to the degradation of compounds present in the soil generally is negligible; for the compartments surface water, groundwater, soil and sediment, biodegradation often is the most important degradation process (ref. 1).

Biological conversions of organic compounds often proceed by way of rather specific processes. However, there is sufficient nonspecificity in various organisms to enable them to play an important part in the removal or degradation of a number of synthetic chemicals that are released in the environment. Many factors influence the microbial activity and consequently the biodegradability in a certain ecosystem. These factors may vary from experiment to experiment and from laboratory experimental conditions to field conditions. In this respect the most important variables are:

- the population, numbers and species of microorganisms;
- the concentration of the compound tested;
- the concentrations of organic and inorganic nutrients;
- the oxygen concentration;
- the temperature;
- the pH.

Photochemical degradation is an important process for atmospheric contaminants and for compounds that are located on certain surfaces, such as pesticides on the soil surface, on vegetation, or in surface water. A compound can be photochemically excited by direct absorption of light (sunlight with wavelengths above 290 nm) or by transfer of energy from an excited donor molecule (sensitizer). The ultraviolet absorption spectrum of a compound is generally an indication of its ability to absorb light; it depends on the matrix of the molecule (gas phase, absorbed on a solid, dissolved in a liquid). Once a molecule is in an excited state, it can loose its excess excitation energy not only by photochemical reactions but also in many other ways. The efficiency of these various processes again is dependent on the matrix in which the molecule is located. In addition, compounds can be converted by reactions with photochemically produced reactive intermediates, such as hydroxyl radicals.

As far as chemical transformation processes are concerned, the most important environmental processes again can roughly be subdivided into three distinct categories:

1. Oxidation reactions, a chemical process in which an electron-deficient particle (the oxidant) accepts electrons from the compound to be oxidized.
2. Reduction reactions, a chemical process in which electrons are transferred from an electron donor (the reductant) to the compound to be reduced.
3. Chemical hydrolysis reactions.

It will be clear that the different processes mentioned above do not make it easy to predict the persistence or degradability of a certain compound in the environment. It is even true that because of the large number of factors that influence the degradation rate, extrapolation of reaction rates and reaction products observed under laboratory conditions to environmental conditions appears to be only possible to a limited extent. Nevertheless, in order to be able to make predictions regarding the fate of chemicals in different environmental compartments it is necessary to have various models available, enabling both the calculation of the rates of each of the distinct processes mentioned above under realistic environmental circumstances and the prediction of the products formed. To this end at the moment an increasing number of Quantitative Structure Activity Relationships (QSARs) are being formulated that can be used by scientists, regulatory agencies and industry to make rapid, reliable and cost-effective predictions about the effects and environmental behaviour of chemicals; with respect to this it is estimated that up till now parameters needed for estimating environmental fate and transport properties have been measured for only 1 % of the compounds assumed to be manufactured (ref. 2). Also, in order to enable the prediction of realistic environmental concentrations of so-called new chemical substances (compounds of which usually insufficient data are available to enable the prediction of their environmental fate), models need to be used that are based on QSARs.

With the aim of setting up a critical evaluation on the use and the development of QSARs for the prediction of various transformation processes, in this contribution first of all a short introduction is given on the general principles that form the fundamentals of most QSARs developed so far. Thereupon a review is given of all QSARs available at the moment for the calculation of rates of chemical hydrolysis of organic substances in the environment. On the basis of the QSARs presented, a comparison is made between calculated rates of hydrolysis and rate constants measured under realistic environmental circumstances. On the basis of the results obtained general recommendations are given on the application of QSARs for the prediction of environmental process parameters. The review is restricted to the process of chemical hydrolysis. The reasons for selecting this process are threefold:

1- Chemical hydrolysis is a rather ubiquitous, environmentally relevant transformation route; most chemicals may be transformed by this process, with rates depending both on the compound itself and the prevailing environmental circumstances (temperature, pH for instance).
2- The process of chemical hydrolysis is relatively well described in literature; various rates of hydrolysis under various environmental circumstances are available from a large number of independent sources.
3- A relatively large number of QSARs for the calculation of rates of hydrolysis of divergent compounds have been developed so far.

In addition to QSAR-formulations, data bases for compound-specific properties and structural parameters are indicated. Thereupon also the limitations of the various relationships are discussed.

QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIPS

The origin of QSARs

The basis of QSARs is the connection that exists between compound-specific properties and environmental conditions on the one hand and structural parameters of the compounds to be investigated on the other (ref. 3-5). It is known from the chemical process technology that physico-chemical properties of a compound can be predicted from the molecular structure of the compound and the constants of its fragments. In their turn, these physico-chemical properties can be decisive for the properties of the compound in the environment. In the sixties Hansch and Fujita (ref. 6) developed a method to correlate quantitatively biological effects (toxicity, mutagenicity, carcinogenicity) and fate (accumulation, degradation) with various categories of chemical parameters. This was the beginning of the development and use of QSARs. Initially they were mainly applied to the development of medicines and pesticides, but from the mid seventies they have also been used and developed in the environmental sciences. By now a large number of relationships has been formulated in the latter field, both for different classes of compounds and for various biological phenomena in particular.

QSARs are composed of a triad of components: a characteristic biological or physico-chemical property, one or more chemical parameters, and a mathematical relation between them. The basis of the method as developed by Hansch is the postulated relationship between a certain property ($\underline{CP}$) and chemical parameters that influence it (for example, P, Q and R), as pictured in the following equation, in which both k and the upper-case letters a, b and c are constants:

$$[\underline{CP}] = \underline{k} \times [P]^{\underline{a}} \times [Q]^{\underline{b}} \times [R]^{\underline{c}} \tag{1}$$

This equation can be transformed to:

$$\log[\underline{CP}] = \underline{a} \times \log[P] + \underline{b} \times \log[Q] + \underline{c} \times \log[R] + \log[\underline{k}] \tag{2}$$

How does a QSAR formulator proceed?
First, a group related compounds is selected, typically a group of between five and fifty compounds is used. Then, the property of these compounds that has to be described, is measured (or these data are taken from the literature) and one or more chemical parameters of which it is assumed that they might play an important role are either calculated or measured. Finally the (logarithms of the) values obtained are subjected to linear regression, which is a simple statistical operation with which the best-fitting values of the constants are calculated.

It is also possible to formulate relationships between the structure of a compound and its properties under environmental conditions, which do not yield a numerical value but a classification. With the aid of such a relationship a compound, on the basis of its properties, is assigned to the groups of active (for example, degradable or carcinogenic) or inactive compounds. The relationships, which generally are of a complicated nature, are preferably mentioned structure-activity relationships (SARs). The statistical technique used in formulating them is pattern recognition.

The use of QSARs

QSARs can be employed in:

- the development of products, in particular fine chemicals;
- establishing priorities for further investigation of potentially dangerous compounds;
- choosing the kind of further study that is advantageous or necessary for a certain compound (toxicity, biodegradability);
- making a rapid risk assessment in case of a calamity.

QSARs can also play a part in the study of reaction mechanisms. This is particularly important in the field of toxicity. It is assumed that a (in a statistical sense) good QSAR for a certain class of compounds means that it is probable that these compounds are active in a corresponding way. Conversely, this often means that by formulating a QSAR for a property to be described, the understanding of the mechanisms of action is increased.

However, QSARs also have a number of important limitations. The major mistake that may be made originates from the fact that a group of similar compounds may be active as a result of different mechanisms of action. Moreover, the methodology of formulating QSARs is not yet completely developed and also (and more important) the methods are not always applied correctly. Regularly made mistakes relate to the correlation coefficient, which is a statistical parameter indicating how well a certain relationship corresponds with the starting values. For example, in order to obtain a value that is as favourable as possible, sometimes "extremes" are not taken into consideration or an irresponsibly large number of chemical parameters is incorporated into the QSAR. Inaccuracies may also arise when the data from which is started, for example, measured values taken from the literature, are not fully comparable (ref. 7). In addition, often insufficient attention is paid to the independence of the parameters used, and various other, often statistical-technical, considerations are overlooked.

Even QSARs that are thorough in a methodological sense can have their limitations. Predictions made with relationships obtained by means of linear regression generally have an inaccuracy of a factor of 2 to 5. Thus, these values are not more than an indication of the order of magnitude. Statements made on the basis of these QSARs will seldom be correct with a probability of more than 70%.

Another problem can be the validity range of a QSAR. Often it is not known with certainty whether a compound to be assessed belongs to the group of compounds for which a QSAR has been formulated.

Which QSARs are suitable to be used?

Some progress has been made in the use of physico-chemical properties for predicting the behaviour of chemical contaminants in the environment. The best results are obtained by correlating the rates of transport and exchange of compounds with various physical properties of these compounds (for example, vapour pressure, octanol-water partition coefficient and solubility in water). Up till now a number of divergent QSARs have been developed and were incorporated by the U.S. EPA into the QSAR-SYSTEM (QSAR/DATABASE) that may be used for the estimation of a number of mainly environmental transport properties of various uncharged organic chemicals (ref. 8).

The prediction of the overall rate of degradation of a contaminant (or, in other words, the persistence of chemicals in the distinct environmental compartments) on the basis of its physico-chemical properties has turned out to be less successful so far. This is, as shown above, particularly caused by both the large number of processes that may be involved and the complexity of several of the distinct transformation processes. Nevertheless, at the moment a large number of QSARs is available for the description of various transformation processes, based on a number of divergent molecular descriptors (ref. 9). Thus Atkinson (ref. 10) developed QSARs for the estimation of rate constants for the estimation of rate constants for the oxidation of organic compounds by hydroxyl radicals, whereas QSARs for the reduction of halogenated hydrocarbons were recently developed by Peijnenburg et al. (ref. 11). Additionally, several methods for the calculation of rates of hydrolysis will be described below.
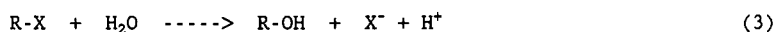
HYDROLYSIS

Hydrolysis of organic compounds in groundwater and surface water contributes considerably to the removal of these compounds from both these environmental compartments. In particular acid chlorides, esters, amides, carbamates, epoxides, imines and silanols are sensitive to hydrolysis (ref. 12,13). A large number of experimental investigations into the course of hydrolysis reactions of many organic compounds have been carried out. Mabey and Mill (ref. 12,14), Drossmann et al. (ref. 13), Jeffers (ref. 15) and Harris (ref. 16) have written extensive surveys of hydrolysis rates under environmental conditions.

In the sections that follow a summary of the process formulations will be given. However, it should be noted that QSARs set up for use in water-organic solvent systems are not included since it has been demonstrated that the polarity of the solvent has a large impact on the course of the hydrolysis so that translation of these QSARs to systems containing merely water is not possible (ref. 14).

Background

Hydrolysis is a chemical transformation process in which an organic molecule, RX, reacts with water, forming a new carbon-oxygen bond and cleaving a carbon-X bond in the original molecule (ref. 17). The net reaction is most commonly a direct displacement of X by OH:

$$R\text{-}X \ + \ H_2O \ \text{-----} > \ R\text{-}OH \ + \ X^- \ + \ H^+ \tag{3}$$

The importance of hydrolysis from an environmental point of view stems from the fact that upon introduction of a hydroxyl group into the parent molecule, chemicals are formed which are usually more susceptible to further attack through the processes of biodegradation and photolysis. Furthermore, the hydroxyl group makes the chemical more water soluble and hence reduces potential bioconcentration.

The process of hydrolysis can be distinguished from several other possible reactions between organic chemicals and water such as hydration reactions, additions to carbon-carbon bonds and elimination reactions. Since hydration reactions generally are reversible and therefore do not lead to a permanent chemical transformation of the organic species, whereas addition and elimination reactions generally require reaction conditions that are unlikely to occur in the environment, these reactions are not considered further.
Hydrolysis is a significant environmental fate process for many organic chemicals; it is actually not one reaction but a family of reactions involving compound types as diverse as alkyl halides, carboxylic acid esters, organophosphonates, carbamates, epoxides and nitriles. Many organic functional groups are relatively or completely inert with respect to hydrolysis, these include alkanes, alkenes, benzenes, biphenyls, PAHs, halogenated aromatics (PCBs), alcohols, phenols, ethers, ketones etc.

When an organic compound undergoes hydrolysis, a nucleophile (water or hydroxide ion) attacks an electrophile (carbon atom, phosphorus atom, etc.) and displaces a leaving group, some of which are depicted above. Nucleophilic displacement reactions usually proceed either by an S_N1 (unimolecular nucleophilic substitution) or an S_N2 (bimolecular nucleophilic substitution) reaction mechanism in which the rate determining steps are either the ionization of R-X to give a carbo cation or a nucleophilic attack on the central carbon atom at the

side opposite to the leaving group. S_N1 reactions are favoured by R-groups that form stable
carbonium ions, by X-systems that are good leaving groups and by high-dielectric-constant
solvents such as water. Conversely, S_N2 reactions are favoured by R-groups with low steric
hindrance and low carbocation stability and by X-groups that are poor leaving groups. In
nature there probably exists a continuum of mechanisms between the two extremes; in esti-
mating rates of hydrolysis it is important to consider whether the reaction of interest and
the available 'model reactions' (QSARs) involve similar mechanisms, evidence of which usual-
ly is available only from measured kinetic data such as thermodynamic activation parameters,
isotope effects etc.; normally these data are unavailable for the compounds for which hydro-
lysis data must be estimated. Thus it is recommended to select model reactions in which both
the R- and X-groups are as similar as possible to those of the compound whose hydrolysis
rate is unknown.

Despite the continuum of possible reaction mechanisms depicted above, it is generally ob-
served that hydrolysis reactions in surface water usually proceed by a pseudo-first-order
reaction:

$$d[\underline{C}]/d\underline{t} = \underline{k}_h \times [\underline{C}] \tag{4}$$

In this equation $\underline{k}_h$ is the pseudo-first-order rate constant for hydrolysis at constant pH.
$\underline{k}_h$ Contains contributions of the following processes:

    1.   Acid-catalysed hydrolysis;
    2.   Base-catalysed hydrolysis;
    3.   Hydrolysis by nucleophilic attack of water.

Consequently:

$$\underline{k}_h = \underline{k}_a \times [H^+] + \underline{k}_b \times [OH^-] + \underline{k}_n \tag{5}$$

In this equation $\underline{k}_a$, $\underline{k}_b$ and $\underline{k}_n$ are the second-order reaction rate constants for the acid-
catalysed, the base-catalysed and the neutral hydrolysis processes, respectively (all the
rate constants are of the dimensions s^{-1} or $l.mol^{-1}.s^{-1}$). Each separate rate constant indi-
cates a stoichiometric relationship between the compound to be hydrolysed and the reactants
acid, base or water, but it does not give an indication of the mechanism of the hydrolysis;
as stated above this mechanism can vary from class to class of compounds and it is even pos-
sible that compounds within a specific class of chemicals react by different mechanisms. We
also have to bear in mind that measured rates of reaction often are the sum of various pro-
cesses, which is illustrated by the following example (base-catalysed ester hydrolysis):

$$RC(O)OR' + OH \xrightarrow[k_2]{k_1} RC(O^-)OR'(OH) \xrightarrow{k_3} RC(O)O^- + R'OH \tag{6}$$
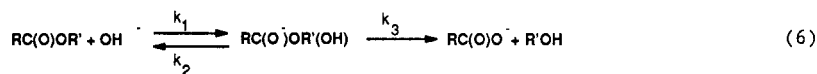
The second-order rate constant $\underline{k}_b$ for this reaction is:

$$\underline{k}_b = (\underline{k}_1/\underline{k}_2) \times \underline{k}_3 \times [OH^-] \tag{7}$$

This equation implies that in order to enable the correlation of $\underline{k}_b$ with structural
parameters, the correlations for $\underline{k}_1$, $\underline{k}_2$ and $\underline{k}_3$ need to be known. However, often this is not
the case (ref. 13).

Structure–activity relationships

Quantitative structure-activity relationships for the hydrolysis of diverse groups of
organic compounds have been developed. Several relationships have been derived in the form
of the Hammett equation (ref. 17-19):

$$\log \underline{k}_x = \log \underline{k}_0 + \rho \times \sigma \tag{8}$$

In this equation $\underline{k}_x$ and $\underline{k}_0$ are the reaction rate constants for the substituted and unsubsti-
tuted aromatic compounds, respectively, σ is the substituent constant and ρ is a constant
that is characteristic of the reaction under investigation. The Hammett relation relates
only to m- and p-substituted aromatic systems in which mainly electronic effects are
involved. In order to describe the reaction rate of aliphatic compounds, use can be made of
Taft's equation:

$$\log \underline{k}_x = \log \underline{k}_0 + \rho \times \sigma^* + \delta \times \underline{E}_s \tag{9}$$

In addition to the modified Hammett constant σ^*, in this equation $\underline{E}_s$ gives the contribution
of the steric influence of the substituents, whereas δ is a measure of the sensitivity to
steric influences of the reaction.

QSARs for hydrolysis can also be expressed by means of a relationship between the pK_a of the

leaving group and the reaction rate constant (Brönsted equation (ref. 20)):

$$\log \underline{k}_x = \rho \times pK_a + \log \underline{k}_0 \qquad (10)$$

Esters of carboxylic acids

Recently, Drossmann and Mill (ref. 21) have arranged an evaluation of published data on hydrolysis rates of aliphatic carboxylates. From this evaluation it becomes clear that for most of the esters studied the base-catalysed hydrolysis is the dominant transformation process under environmental conditions. Table 1 pictures both the available Hammett and Taft correlations. Mill et al. (ref. 22) have shown that the Taft equation mentioned in Table 1 may also be applied to more complex acyl groups. To this end the Taft constants of the various groups need to be added up. For fully aromatic carboxylates it appears that insufficient data are available to construct reliable correlations (ref. 14). Moreover, solvent effects play a major part for this kind of compounds. This already becomes evident from the fact that, for example, $\underline{k}_b$ of ethyl benzoate is 200 times as small in 50% acetonitrile than in water (ref. 22,23).

TABLE 1. QSARs for the calculation of rates of base-catalysed hydrolysis of esters, RC(O)OR′, in water: $\log \underline{k}_b = \rho \times \sigma^* + \delta \times \underline{E}_s + C$

R	R′	ρ	δ	C	References/notes
Alkyl	Ethyl	2.49	1.05	-0.96	12,24,25
Methyl	Alkyl	2.18	0.221	-0.96	21,23,24,26,27
Alkyl	Alkyl	2.32(R)	0.98	-0.74	--
		2.10(R′)			--
Alkyl	PhX	1.21	0.618	+0.0792	σ instead of σ^*
XPh	Alkyl	2.58	1.92	-1.10	σ instead of σ^*

Aromatic carbamates

Wolfe et al. (ref. 28) have studied the hydrolysis of this type of compounds thoroughly. They have formulated QSARs for the base-catalysed hydrolysis of the four carbamates listed in Table 2. The relationships all use the correlation between the $\underline{k}_b$ and the pK_a of the leaving phenol group.

TABLE 2. QSARs for the base-catalysed hydrolysis of carbamates, ZYNC(O)OPhX: $\log \underline{k}_b = \rho \times pK_a + C$

Z	Y	ρ	C
Ph	H	-1.15	13.6
Ph	Me	-0.26	-0.26
Me	H	-0.91	9.3
Me	Me	-0.17	-2.6

Phosphates

Wolfe et al. (ref. 29) have worked out QSARs for the hydrolysis of various phosphates and thiophosphates. These QSARs correlate $\underline{k}_b$, and in some cases $\underline{k}_n$, with the pK_a values of the leaving hydroxyl compound. Consequently, the QSARs have the form of those used for the carbamates: $\log \underline{k}_b = \rho \times pK_a + C$, in which $\rho = -0.24 \pm 0.03$ for compounds of the types $(RO)_2P(S)X$ and $(RO)_2P(O)X$, X being either a substituted phenoxy, or a methoxy or ethoxy group.

Acetals and ketals

Cordes (ref. 30) has reviewed the hydrolysis of acetals, ketals and orthoesters. It was possible to correlate $\log \underline{k}_a$ with σ^* ($\rho^* = -3.6$) for the acid-catalysed hydrolysis of aliphatic acetals and ketals. Relative rates of hydrolysis for acetals and ketals increase by a factor of 10^4 on changing from CH_2 to CHMe and another 10^4 for the second Me in $CME_2(OEt)_2$. The rate factor becomes 10^5 for substitution of Ph for H in this series (ref. 31).

Phthalic acid esters

With the intention of assessing the fate of a series of phthalic acid esters in aquatic

ecosystems, a linear free energy relationship was established for estimating alkaline hydrolysis rate constants of these compounds by Wolfe and co-workers (ref. 32). Linear regression gave the following equation for the second-order alkaline hydrolysis rate constant k_b (regression coefficient $R^2 = 0.975$):

$$\text{Log } k_b = 4.59 \times \sigma^* + 1.52 \times E_s - 1.02 \tag{11}$$

The authors also pointed that, although the values for σ^* and E_s are not generally listed in the tables of reference for longer alkyl chains, these values will probably not be significantly influenced by the length of the alkyl chain (ref. 17); thus it is proposed that for longer alkyl chains, the values given for a pentane-chain are to be used as a reference.
The same authors also observed that the rate ratio for the second-order-alkaline hydrolysis rate constants of the diester to the monoester is 12.

Other compounds

Generally applicable QSARs have not been formulated for compounds not described above. But for a small number of classes of compounds there are QSARs that correlate hydrolysis rates with structural parameters for a limited number of compounds with a minor variation in reactivity (ref. 30,33). However, because of the large number of hydrolysis rates that have become known by now, it is of not less importance that a large number of qualitative structure-activity relationships for a number of important classes of compounds are known. As examples may be mentioned:

- alkyl halides;
- amides;
- epoxides;
- anhydrides;
- isocyanates.

For example, it can be said of the last mentioned two classes of compounds and acid halides, $RC(O)X$, that they generally are so sensitive to hydrolysis that the half-life for this reaction will never exceed a few hours. It is known of other compounds, such as alkyl and aromatic amides and fluorine compounds, that they are generally insensitive to hydrolysis, so they can be considered to be resistant to this reaction. As an example of SARs available at the moment, a number of general rules for the hydrolysis of alkyl halides (ref. 14) are summarized in Table 3. As can be seen from this table, qualitative SARs generally are rather complex.

TABLE 3. Qualitative structure-activity relationships for the hydrolysis of alkyl halides (ref. 14).

Type	k_h (s^{-1})	Reactivity factors
R-F	$10^{-1} - 10^{-10}$	Only tertiary fluorides reactive.
R-Cl	$10^{-2} - 10^{-8}$	Chlorides and bromides the most reactive;
R-Br	$10^{-1} - 10^{-7}$	bromides 5 - 10 times as reactive as the
R-I	$10^{-5} - 10^{-8}$	corresponding chlorides.
R-CH$_2$-X	$10^{-3} - 10^{-6}$	Sensitive to steric influences.
R$_2$CH-X	$10^{-2} - 10^{-5}$	Sensitive to steric and electronic
Ar-CR$_2$-X	$10^{-1} - 10^{-7}$	influences.
R$_3$C-X	$10^{-1} - 10^{-7}$	Only steric effects on cyclic halides. Sensitive to electronic effects.
R$_2$C=CR-CH$_2$-X	$10^{-4} - 10^{-7}$	
R-CH$_{3-n}$X$_n$	$10^{-1} - 10^{-12}$	R-H very stable; aryl substitution increases reactivity.
R$_2$C=CRX	$<10^{-10}$	Very stable.
Ar-X	$<10^{-10}$	Very stable, unless there are strong electron donating substituents at the ring.
ArCH$_n$X$_{3-n}$	$10^{-2} - 10^{-5}$	Reactive.
R- or ArC(O)X	$>10^{-2}$	Reactive.

TRANSLATION OF PREDICTED RATES OF HYDROLYSIS TO RATE CONSTANTS FOUND IN THE FIELD

Despite the relatively large number of laboratory studies performed on assessing the factors that influence rates of hydrolysis, there is relatively little field data currently available. Partly this is caused by the observation that under natural circumstances, other processes like biodegradation, oxidation and photolysis make it difficult to unambiguously separate chemical hydrolysis. Also various other factors like for instance pH, temperature, reaction medium, adsorption of hydrophobic substances by humic acids or surface deposits, the presence of trace amounts of reactive nucleophiles such as bromide, catalysis by chemical adsorption on mineral surfaces and metal ion catalysis may significantly influence rates of hydrolysis of organic compounds (ref. 34).

In the main results under realistic experimental conditions tend to show somewhat reduced rates of hydrolysis, mainly as a result of surface adsorption (ref. 35). However, as recently reported by Haag and Mill (36), no significant differences in either the kinetics or the products formed were observed upon comparing neutral- and base-catalysed hydrolysis of a number of halogenated aliphatics in both pure water and in barely saturated subsurface sediment pores at 25-60 °C.

Results of Metwally and Wolfe on the hydrolysis of chlorostilbene oxide in homogeneous systems, aquifer samples and in sediment-water systems (ref. 37,38) are also relevant. In these studies chlorostilbene oxide was shown to undergo both acid catalysed as well as neutral hydrolysis. Differences from sterile buffer solutions could be well explained by sorption to the humic materials in case of natural waters and by biotic effects in sediment-associated water. Buffer catalysis was observed, but on the other hand a negative ionic strength effect was demonstrated. In case of aquifer samples, in which less than 29 % of the chlorostilbene oxide present was adsorbed, no significant heterolytic effects of the aquifer material on the kinetics of hydrolysis were observed. In sediment-water systems both dissolved and sorbed chlorostilbene oxide hydrolysed at either neutral or acidic pH values. It was shown that the neutral hydrolysis pathway (above pH 5) is neither retarded not promoted by sorption to the sediment. At pH values below 5, where acidic hydrolysis dominates, the rate constants were lower for the sorbed fraction than the rate constant in distilled water at the same pH.

Summarizing it will be clear that under realistic environmental circumstances various factors may greatly influence rates of hydrolysis. In general these factors may both retard and accelerate rates of hydrolysis; at the present state of art clearly a better understanding of the fundamentals of the hydrolytical transformation pathways is required. For those chemicals that undergo hydrolysis, the ability to estimate the rate constant in general depends on how much previous work has been done in that particular family. Once a constant is obtained it should be examined in light of the ecosystem where it will be used. This is necessary as the value derived from either a qualitative or quantitative structure-activity relationship derived under laboratory conditions may only have a limited relation to the real world.

CONCLUSIONS AND RECOMMENDATIONS

1. Various methods are available for the calculation of rates of hydrolysis of a wide range of organic compounds under laboratory conditions: relationships for the calculation of conversion rates of carboxylates, aromatic carbamates, phosphates, acetals, phthalic acid esters and ketals are known. However, these relationships mainly relate to the most important process under environmental conditions, viz. base-catalysed hydrolysis. Because other hydrolysis processes also contribute to the overall reaction rate, calculated rates of hydrolysis are generally an underestimation of the actual rates. The QSARs developed appear to be well suited for use in models describing the fate of chemicals in the environment.

2. In addition to the quantitative formulations mentioned above, a large number of qualitative structure-activity relationships is known. Because of the general nature of the rate predictions, such relationships usually are difficult to use in fate models.

3. Given the various factors that have the potential for impacting rates of hydrolysis under realistic environmental circumstances, a better understanding of the fundamentals of the hydrolytical transformation pathways is required. At the moment, for those chemicals that undergo hydrolysis, the ability to estimate the rate constant in the field in general depends on how much previous work has been done in that particular family. Once a constant is obtained it should be thoroughly examined in light of the ecosystem where it will be used.

4. The use of QSARs could increase considerably if limitations in some current QSAR techniques can be overcome. With respect to this it is clearly shown in this contribution

that the data needed to set up QSAR equations often are not readily available, whereas it has become evident that QSARs are frequently applicable only within narrow compound families in which the chemical structures are fairly similar. This necessitates the use of an increasing number of molecular descriptors whilst their definitions and similarities often are obscure. In general the understanding of the fundamentals of the current QSAR techniques is insufficient to accommodate chemicals sufficiently different in structure from those upon which the methods are based; in practice 'similarity' of structure can only be generated post hoc by reference to agreement with a given QSAR.

5.   In general it may be concluded that in principle QSARs provide important tools for assessing the fate of chemicals in the environment. At the moment, however, clearly far more research is needed in order to get a better insight in the fundamentals of QSARs. More attention should be paid to deriving QSARs at a basic molecular level, applicable to a wide range of compounds and to a wide range of transformation processes under realistic environmental conditions; apart from merely performing laboratory studies, more attention needs to be paid to assessing the impact of additional factors influencing the fate of chemicals in the real environment.

REFERENCES

1. P.J. Howard, J. Saxena and H. Sikka, Environ. Sci. Techn. 12, 398-407 (1978).
2. S. Borman, Chemical & Engineering News, 20-23 (1990).
3. B.T. Walton and T. Mill, Environ. Toxicol. Chem. 7, 403-404 (1988).
4. N. Nirmalakhandan and R.E. Speece, Environ. Sci. Techn. 22, 606-615 (1988).
5. J.L.M. Hermens, The handbook of environmental chemistry, vol. 2 part E. Reactions and processes, O. Hutzinger (ed.), pp. 111-162, Springer-Verlag, Berlin (1989).
6. C. Hansch and T. Fujita, J. Am. Chem. Soc. 86, 1616 (1964).
7. Y.C. Martin, J. Med. Chem. 24, 229-237 (1981).
8. U.S. Environmental Protection Agency, Environmental Research Laboratory, Duluth, Minnesota. The QSAR SYSTEM, a structure-activity based chemical modelling and information system.
9. W.J.G.M. Peijnenburg, RIVM report no. 718708002 (1989).
10. R. Atkinson, Int. J. Chem. Kin. 19, 799-828 (1987).
11. W.J.G.M. Peijnenburg, M.J. 't Hart, H.A. den Hollander, D. van de Meent, H.H. Verboom and N.L. Wolfe, Environ. Toxicol. Chem., submitted for publication (1991).
12. W. Mabey and T. Mill, J. Phys. Ref. Data 7, 383-415 (1978).
13. H. Drossman, H. Johnson and T. Mill, Chemosphere 17, 1509-1530 (1988).
14. T. Mill and W. Mabey, The handbook of environmental chemistry, vol. 2 part D. Reactions and processes, O. Hutzinger (ed.), pp. 71-111, Springer-Verlag, Berlin (1988).
15. P.M. Jeffers, Abstract 02-359, Internat. Chem. Congress of Pacific Basin Societies, Honolulu, Hawaii, December 17-22 (1989).
16. J.C. Harris, Handbook of Chemical Property Estimation Methods. Environmental behaviour of organic compounds, W.J. Lyman, W.F. Reehl and D.H. Rosenblatt (eds.), p.p. 7-1 - 7-48, McGraw-Hill, New York (1981).
17 N.B. Chapman and J. Shorter, Correlation analysis in organic chemistry, Plenum Press, New York (1978).
18. J. Shorter, Advances in linear free energy relationships, N.B. Chapman and J. Shorter (Eds.), chapter 2, Plenum Press, New York (1972).
19. J.O. Exner, Coll. Czech. Chem. Commun. 40, 2781 (1975).
20. N.B. Chapman and J. Shorter (Eds.), Advances in linear free energy relationships, Plenum Press, New York (1972).
21. H. Drossman and T. Mill, SRI, unpublished results.
22. T. Mill et al., Data generation in process and property constants used in fate assessment, EPA final report, EPA contract No. 68-03-2981 (1984).
23. R.J. Washkun, V.K. Patel and J.R. Robinson, J. Pharm. Sci. 60, 736 (1971).
24. E.J. Salmi and R. Leimu, Suomen Kemist. 20B, 43 (1964).
25. C.H. DePuy and L.R. Mahoney, J. Am. Chem. Soc. 86, 2653 (1964).
26. E.K. Euranto and A. Moisio, Suomen Kemist. 37B, 92 (1964).
27. S. Bogatov and E. Cherkasova, Org. React. (Tartu) 14, 165 (1965).
28. N.L. Wolfe, R.G. Zepp and D.F. Paris, Water Res. 12, 561 (1978).
29. N.L. Wolfe, Chemosphere 9, 571 (1980).
30. E.H. Cordes, Prog. Phys. Org. Chem. 4, 1 (1967).
31. M. Kreevoy and R.W. Taft, J. Am. Chem. Soc. 77, 5590 (1955).
32. N.L. Wolfe, W.C. Steen and L.A.Burns, Chemosphere 9, 403-408 (1980).
33. W.R. Mabey, H. Drossman, A.M. Liu and T. Mill, Toxic substances process data generation, EPA final report, EPA contract 68-03-2921, Task 18 (1984).
34. W. Brock Neely, Environmental exposure from chemicals, Volume I, W. Brock Neely and G.E. Blau (Eds.), pp. 157-173, CRC, Boca Raton, Florida (1985).
35. W. Walker, C. Cripe, P. Pritchard and A. Bourquin, Chemosphere 17, 2255-2270 (1988).
36. W.R. Haag and T. Mill, Environ. Sci. Techn. 22, 658-663 (1988).
37. M.E.-S. Metwally and N.L. Wolfe, Environ. Toxicol. Chem. 8, 553-562 (1989).
38. M.E.-S. Metwally and N.L. Wolfe, Environ. Toxicol. Chem. 9, 963-967 (1990).