Computer-assisted prediction of the degradation of chemicals: hydrolysis of amides and benzoylphenylureas

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Experimental kinetic data have been generalized to allow the quantitative prediction of the hydrolysis of amides and ureas under acid and base catalysis with the EROS 6 computer program. The two different reaction pathways have been compared revealing that base-catalysed hydrolysis at pH 7.0 is about 1000 times faster than acid-catalysed hydrolysis. The equations for calculating kinetic data have been applied to several benzoylphenylureas including important agrochemicals to predict half-lives and the amounts of products of the various hydrolysis pathways.

1. Introduction

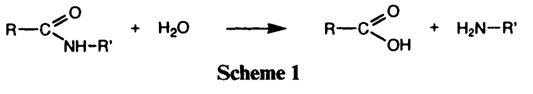
The prediction of the course and products of a chemical reaction is of paramount importance in organic chemistry. In particular, the degradation of chemicals in the environment is of great concern. Agrochemicals are intended to be exposed to the environment, therefore a knowledge of their degradation products is indispensable. Such knowledge is at present acquired by time-consuming and expensive laboratory and field experiments. It would be immensely helpful to be able to predict the degradation products of an agrochemical in advance.

The decomposition pathway of a compound is dependent on its chemical structure and on the reaction conditions. Degradation reactions proceed by metabolic processes in plants, animals and microorganisms as well as by chemical processes on the surface of plants and in the soil. All this adds up making the task of predicting the degradation of a chemical highly complicated.

For many compounds hydrolysis is one of the major degradation reactions in the environment. Even if we restrict ourselves to a consideration of hydrolysis reactions, the situation might still be quite complicated. A molecule may contain several sites susceptible to hydrolysis and one must therefore evaluate the various pathways of hydrolysis in order to make reasonable predictions. Even more complicating is the fact that the environmental conditions existing in soil or in the various species (plants, animals, microorganisms) may drastically influence hydrolysis reactions.

Conditions for hydrolysis fall into two categories, which are physical or chemical in nature. Some physical phenomena such as absorption may decrease the solubility of a compound in water and thus *decrease* the rate of hydrolysis. Any chemical influence can only contribute to an *increase* in the degradation of a compound, compared with hydrolysis in pure water, either by increasing the rate of hydrolysis through some kind of catalysis (*e.g.*, enzymes), or by favouring a pathway that competes with hydrolysis. However, such a pathway can compete with hydrolysis in pure water only if this process is faster than hydrolysis. Thus, a knowledge of the rate of hydrolysis gives the limiting situation for the degradation of a compound in the environment, provided it can be dissolved in water. Any other process can only contribute to a *faster* degradation of a compound.

Several reasons have led us to investigate the hydrolysis of substituted benzoylphenylureas. First, this class of compounds comprises several important agrochemicals. Secondly, the major site of hydrolysis in these compounds is the amide bond (Scheme 1) and a number of data are available for the rate of hydrolysis of amides, both under acid and base catalysis. Furthermore, benzoylphenylureas have three different amide bonds and thus can be taken as test cases for developing methods that allow one to make predictions when there are competing reactions. Fig. 1 shows the three sites for hydrolysis of amide bonds in substituted benzoylphenylureas.



Scheme 1

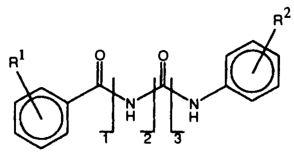


Fig. 1 The three sites for hydrolysis of substituted benzoylphenylureas

Finally, as amide bonds are contained in many compounds introduced into the environment both from natural and artificial sources, any modelling of the hydrolysis of amides and benzoylphenylureas can be extended to a wide range of other compounds (*e.g.*, peptides).

2. A basic approach to modelling chemical reactions

Any attempt at making predictions first needs a model of the system under investigation. This is also true when one wants to predict the course of a chemical reaction and, in fact, chemists have built models of reactions from early on. The desire to understand the underlying principles governing organic reactions has led to a series of models for electronic, energetic and steric effects such as charge distribution and inductive, resonance and polarizability effects acting in organic compounds. However, most of these models are only qualitative or semi-quantitative at best and are therefore inappropriate for making quantitative predictions. Limited success has been achieved by the development of quantitative values for substituent constants and their application to the prediction of equilibrium and rate constants by linear free energy relationships (LFER) such as the Hammett and Taft equations.

Our approach to the problem of model building for chemical reactions falls into two phases, the development of conceptual and of statistical models.

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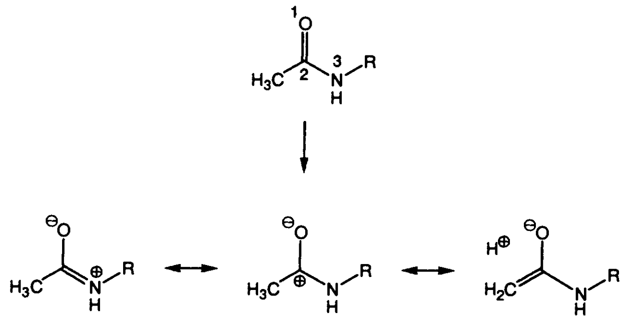


Fig. 2 Definition of the parameter $R^{+}_{(2-1)}$ for resonance and hyperconjugation stabilization of a positive charge at the carbonyl carbon atom of amides

2.1. Conceptual models

The attractiveness of the various chemical effects, inductive, resonance or polarizability, lies in their broad applicability to the entire range of organic chemistry. To make up for their deficiencies of either being only of a qualitative nature or, when quantified as a substituent constant, of being only applicable to a narrow range of chemical reactions, we have developed a series of empirical methods for calculating quantitative measures of such effects.[1-7] This is achieved by fast empirical methods. For atoms, the σ- and π-orbital electronegativities,[2] χ_σ and χ_π, partial σ, π and total atomic charges,[3,4] q_σ, q_π and q_{tot} and the polarizabilities[5] α_d are determined. The charges and electronegativities are calculated by the procedure for partial equalization of orbital electronegativities (PEOE).[3,4,6]

For bonds, differences in the charges of the atoms, Δq, the differences in the electronegativities of the atoms, $\Delta\chi$, the σ-bond polarity, Q_σ, the bond polarizabilities, α_b, the stabilization of charges by the resonance effect and hyperconjugation, R^+/R^-, as well as bond dissociation energies, E_{bd},[7] are calculated. The sum of σ charges, Q_σ, shifted across a bond during the PEOE procedure is a measure of bond polarity.

The effects contributing to the stabilization of a positive charge by the resonance effect $R^{+}_{(2-1)}$ in amides is given by Fig. 2. The notation of the variable for resonance stabilization is such that the indices give the bond that is formally broken and the first index shows the atom that obtains the positive charge. For molecules, the mean polarizability,[5] $\bar{\alpha}$, and the heat of formation,[7] $\Delta_f H^0$, are calculated. In the correlation equations derived in this study, charge values are given in units of an electron, electronegativities in eV, resonance parameters in 1/eV and polarizabilities in Å^3.

All these techniques are combined in the computer program package PETRA (Parameter Estimation for the Treatment of Reactivity Applications).

2.2. Statistical models

Chemical reactions are usually simultaneously influenced by several of these chemical effects. To unravel the importance of the individual contributions to the reactivity of a specific reaction, experimental data on the reaction of interest are correlated with the values calculated for the various physicochemical effects by statistical methods. Specifically, in the present study we have correlated rate constants or free energies of activation for the hydrolysis of amides under acid and base catalysis with the physicochemical variables by multilinear regression analysis (MLRA). Thus, a linear relationship between the physicochemical variables and the logarithms of the rate constants was assumed and equations of the form given in eqn. (1) were obtained. In this equation, $\Delta G^\ddagger$ is the free energy of activation, the physicochemical variables are indicated by x_i and the coefficients c_0, c_1, *etc.*, showing the importance of the individual effects are determined by MLRA.

$$\Delta G^\ddagger = c_0 + c_1x_1 + c_2x_2 + \cdots + c_nx_n \qquad (1)$$

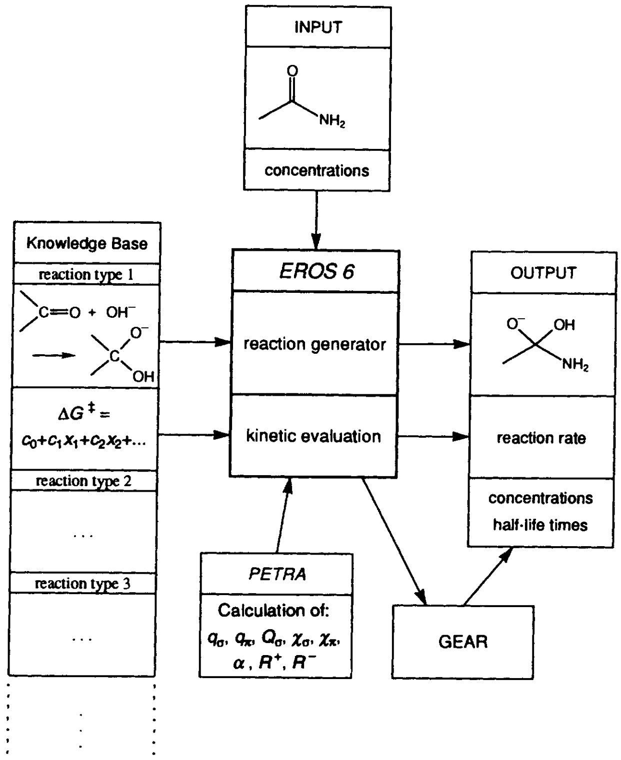


Fig. 3 Reaction prediction with the EROS 6 system. The knowledge base contains a description of the changes in bond and electron distribution of a reaction type. It can further comprise an equation for a quantitative estimation of kinetic parameters allowing one to estimate reaction rates. These can be used, together with data on the concentration of starting materials, to calculate half-lives and the concentration of products by the GEAR algorithm.[8] See section 2.1 for an explanation of the symbols.

Linear equations of the form of eqn. (1) were derived by using a variety of electronic and energy variables, x_i (see section 2.1). The selection of the appropriate variables, x_i, was performed both by statistical and physicochemical considerations. Both automatic stepwise multilinear regression analysis using the SPSS statistical package as well as by MLRA with manually selected variables deemed of importance on physicochemical grounds was performed.

An equation was considered acceptable only if the statistical model was significant and if the variables selected for equations of a sort similar to eqn. (1) were measures of effects that were concluded to be of importance on mechanistic grounds. Furthermore, a coefficient, c_i, required a sign that was consistent with the physicochemical interpretation.

2.3. EROS: a system for reaction prediction

The methods developed in this study have been integrated into the EROS (Elaboration of Reactions for Organic Synthesis) system, version 6, in order to make optimum use of these methods and to provide for a flexible user interface.[8] EROS is a computer program system for the prediction of organic reactions. It has a highly modular design, keeping its chemical knowledge in two separate parts (Fig. 3).

One part of the chemical knowledge is procedural in nature and comprises the methods for the calculation of electronic and

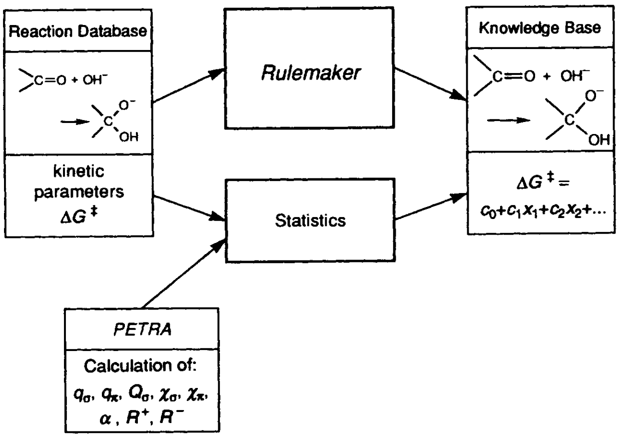


Fig. 4 Automatic knowledge acquisition by the RULEMAKER package. The symbols are explained in section 2.1.

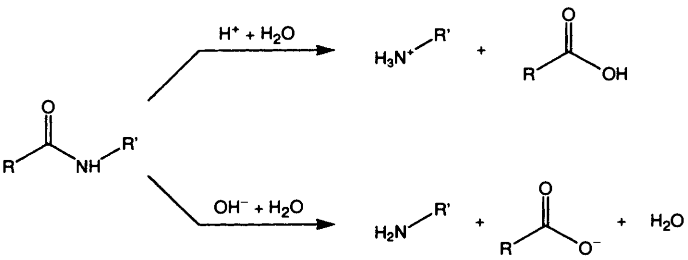


Fig. 5 The hydrolysis of amides in water; the two essential mechanisms

energy effects[1–7] that are included in the program package PETRA (see section 2.1). The other part of the knowledge base comprises rules on chemical reactions. Each rule on a certain reaction type contains information about the rearrangements of the bonds and electrons during a reaction. Additionally, restrictions on the application of a reaction are included. This information is derived from observations on chemical reactions. If experimental kinetic data on a series of individual reactions are available they can be used to derive, by statistical methods, a general equation that allows one to calculate reaction rates (see section 2.2).

During an EROS 6 run, reactions are performed on the starting materials according to the reaction generators coded in the reaction rules and describing how bonds and electrons are rearranged during a reaction.

The starting materials are graphically input. If the rule includes an equation for kinetic modelling, it is used to calculate the rate of the reaction under consideration. The reaction rates can be used, in conjunction with information on the concentration of starting materials to calculate half-life times and product concentrations using the GEAR algorithm[9] that performs a numerical integration of the differential kinetic equations.

2.4. Automatic knowledge acquisition

The procedure for deriving a reaction rule will be briefly described. Rules are extracted from a database of reactions. This reaction database can be downloaded from a large database or input by a system such as CHEMBASE.[10] It comprises a set of reactions of a single type (*e.g.*, addition of OH^- to an amide) and their corresponding rate or equilibrium constants from chemical literature. The RULEMAKER is a package of computer programs for the automatic derivation of the formal part of a reaction rule from the database (Fig. 4). It includes a check of the consistency of the reactions and kinetic parameters in the database. Electronic properties are calculated for every reactant and product molecule by the empirical methods mentioned in section 2.1.

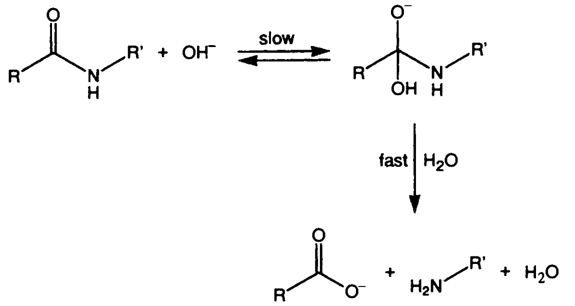


Fig. 6 Mechanism of the hydrolysis of amides under base catalysis

Another program extracts the formal part of the reaction rule from the reactions in the database. This section of the rule includes constraints on a reaction and the reaction generators for the atoms and bonds. A multilinear regression analysis (MLRA) procedure is used to arrive at the regression equation describing the relationship between rate or equilibrium constants and the corresponding electronic variables of the compounds. The MLRA procedure is performed in a separate program run.

A set of reaction rules for different reaction types can be combined into a rule file to make a set of reactions available to the reaction prediction system.

3. The hydrolysis of amides

The amide bond is of fundamental importance in organic chemistry and in biological systems. The transfer of an acyl unit from an amide is quite important in biological systems; acyl transfer to water, the hydrolysis of amides, being one such process.

The hydrolysis of amides under the influence of enzymes is a much studied process. Far fewer investigations, however, have been devoted to the hydrolysis of amides under non-enzymatic conditions. This is largely due to the inherent stability of the amide bond that causes amides to cleave only under rather drastic conditions, *e.g.*, high temperature and rather low or high pH.

The hydrolysis reaction of amides in water can be performed either under acid or under base catalysis (Fig. 5). The present knowledge on the mechanism of amide hydrolysis under H_3O^+ and OH^- catalysis has recently been summarized.[11]

4. Results and discussion

In order to make predictions on the amounts of the different products of complex hydrolysis reactions, the kinetics of the reactions need to be modelled. This kinetic modelling can be performed by predicting either the logarithms of the formal rate constants log k or the corresponding free energies of activation $\Delta G^\ddagger$. These quantities can be calculated from each other as given in eqns. (2) and (3).

$$k = \frac{k_b T}{h}\cdot\exp\left(\frac{-\Delta G^\ddagger}{RT}\right) \quad \begin{array}{l} k = \text{rate constant;}\\ k_b = \text{Boltzmann constant;}\\ h = \text{Planck constant}\end{array} \tag{2}$$

$$\Delta G^\ddagger = RT\left[\ln\left(\frac{k_b T}{h}\right) - \ln k\right] \tag{3}$$

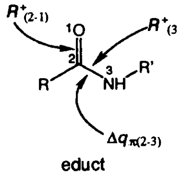


Fig. 7 Variables used in eqn. (5)

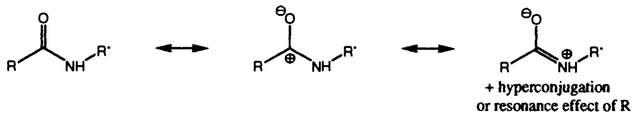


Fig. 8 $R^+_{(2-1)}$ measures the resonance and hyperconjugation effect of R on a formal positive charge on the carbon atom

4.1. The hydrolysis of amides under base catalysis

The hydrolysis of amides under base catalysis can be expressed as a two-step reaction (Fig. 6). The rate-determining step of this reaction is the addition of the hydroxide ion to the amide. Thus, the rate of hydrolysis depends on the concentrations of both the amide and the hydroxide ion. Once the tetrahedral intermediate is attained, the products are formed in a fast reaction. Therefore, only the kinetics of the addition of hydroxide ion to the amide need to be modelled explicitly.

The pseudo-first-order rate constant k_ψ is measured experimentally at a specific pH value. In order to obtain a standardized rate constant k_p, the pseudo-first-order constant k_ψ is divided by the concentration of OH$^-$ [eqn. (4)].

$$k_p = \frac{k_\psi}{[\mathrm{OH}^-]} \tag{4}$$

A database of rate constants for the base-catalysed hydrolysis of 38 benzamides, anilides and phenylureas was compiled from data published in the literature (Table 1). All rate constants were measured at a temperature of 25 °C. The rate constants k_p were converted into values of the free energy of activation, $\Delta G^\ddagger$, through eqn. (3). This dataset was subdivided into a training set of 32 reactions and a test set of five reactions.

The result of the multilinear regression analysis is given by eqn. (5). This equation has a correlation coefficient, r, of 0.958

$$\Delta G^\ddagger = 107.6\,(\pm 7.4) - 198.1\,(\pm 36.6)\cdot\Delta q_{\pi(2\text{-}3)} + 1.39\,(\pm 0.20)\cdot R^+_{(2\text{-}1)} + 1.10\,(\pm 0.19)\cdot R^+_{(3\text{-}2)} \tag{5}$$
$$(\text{in kJ mol}^{-1})$$

and a standard error, s, of 3.29 kJ mol^{-1} (0.58 log k units) in a range of 27 kJ mol^{-1} for the experimentally observed values. Application of eqn. (5) to the five test data shows a standard error of 1.82 kJ mol^{-1} (0.31 log k units).

The first variable, $\Delta q_{\pi(2\text{-}3)}$ gives the difference in the π-charge between the carbon atom (atom 2) and the nitrogen atom (atom 3) of the amide group (see Fig. 7). The coefficient of this variable has a negative sign in eqn. (5) and thus larger values of this charge difference lead to a decrease in $\Delta G^\ddagger$ and thus to an increase in the reaction rate. This is consistent with the physicochemical interpretation that a higher polarity of this bond should facilitate attack of the nucleophile at the carbonyl carbon atom (atom 2).

The other two variables are all measures of resonance stabilization. $R^+_{(2-1)}$ indicates the stabilization of a positive charge on the carbonyl carbon atom (atom 2) by the nitrogen atom and by the substituent R (see Fig. 8). $\mathrm{R}^+_{(3-2)}$ measures the stabilization of a formal positive charge on the nitrogen atom through resonance and hyperconjugation coming from the substituent R'.

Table 1 Experimental *vs.* predicted free energy of activation for the base-catalysed hydrolysis of amides (training set)

R^1	R^2	$\Delta G^\ddagger$/kJ mol^{-1} exp.	exp.–calc.	Ref.
Benzamides: R^1–Ph–CO–NH–R^2				
H	H	107.62	2.08	12
H	Me	109.29	0.36	13
2-H	H	113.60	0.01	12
2-Me	H	113.22	−0.22	14
2-Et	H	111.37	−1.82	15
2-Bu^t	H	105.06	0.93	14
3-Me	H	103.45	−0.58	14
3-Cl	H	115.90	2.28	12
4-Me	H	116.40	1.65	15
4-Pr^i	H	116.00	1.38	15
4-Bu^t	H	105.82	−2.98	12
4-Cl	H	102.79	−3.44	12
4-NO$_2$				
Anilides: R^1–CO–NH–Ph–R^2				
Me	H	98.36	1.18	16
CF$_3$	H	90.97	0.51	17
CCl$_3$	H	91.56	0.64	18
2-Me-1,4-oxathien-3-yl	H	111.80	−1.49	19
Me	2-NO$_2$	89.39	−0.83	20
H	3-NO$_2$	91.04	1.32	21
H	4-Me	99.67	−1.91	16
Me	4-CHO	94.64	−3.58	22
Me	4-OMe	100.10	−1.42	16
Me	4-NO$_2$	89.70	−0.78	23
Et	4-NO$_2$	89.93	0.15	23
COMe	4-NO$_2$	89.56	−0.11	23
Me	4-Cl	91.25	1.58	16
Et	3-Cl, 4-Cl	101.56	2.40	19
CH=CHMe	3-Cl, 4-Cl	103.18	1.83	19

Table 2 Experimental *vs.* predicted free energy of activation for the base-catalysed hydrolysis of amides (test set)

R^1	R^2	$\Delta G^\ddagger$/kJ mol^{-1} exp.	exp.–calc.	Ref.
Benzamides: R^1–Ph–CO–NH–R^2				
2-Pr^i	H	112.62	−0.69	14
4-Et	H	116.51	1.64	15
Anilides: R^1–CO–NH–Ph–R^2				
Me	3-NO$_2$	93.17	−2.03	21
H	4-NO$_2$	89.55	−2.42	23
Pr^n	4-NO$_2$	91.25	1.50	23

Both resonance variables have coefficients with a positive sign in eqn. (5). This is consistent with a physicochemical interpretation: increased stabilization of a positive charge on the carbon (atom 2) or nitrogen atom (atom 3) stabilizes the starting material, the neutral amide. Such stabilization makes attack of the hydroxide anion more difficult and thus decreases the reaction rate.

Tables 1 and 2 give the experimental *vs.* the predicted free energies of activation.

4.2. The hydrolysis of amides under acid catalysis

The hydrolysis of amides under acid catalysis consists of four reaction steps. These are the protonation equilibrium, the addition of water, the transfer of the proton from the oxygen to the nitrogen atom and the cleavage to the products (Fig. 9). Each step must be modelled independently. The protonation equilibrium has to be described in two steps. The protonation

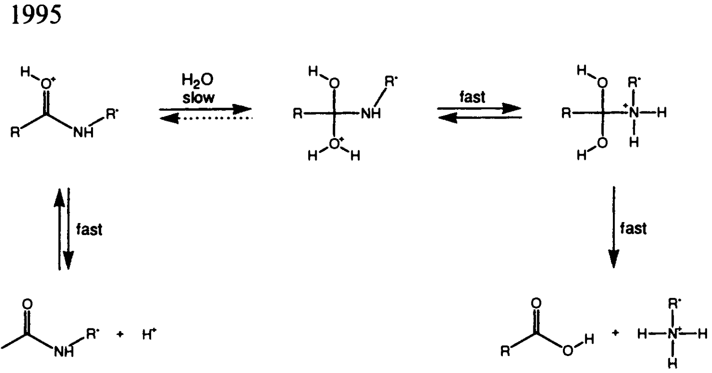


Fig. 9 Mechanism of the hydrolysis of amides under acid catalysis[8]

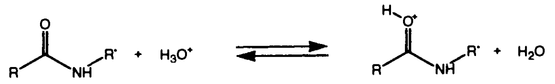


Fig. 10 Protonation equilibrium of amides

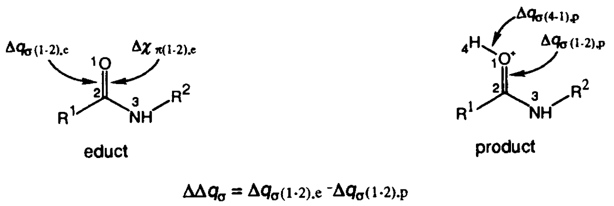


Fig. 11 Variables used in eqn. (6)

of the amide and the reverse reaction, the deprotonation of the protonated amide. Thus, altogether five reaction rules are necessary for the kinetic modelling of the entire reaction. The first two reaction steps have to be included in the kinetic modelling as the concentration of protonated amide is the basis for the further modelling and the addition of water is the rate-determining step. The last two steps are fast compared with the rate-determining step. Therefore, the specification of the exact quantitative values for these steps is neither necessary nor possible; rate constants are set to comparably high values that will not influence the overall reaction rate.

4.3. Modelling the protonation equilibrium

The first step of the hydrolysis under acid catalysis is the protonation equilibrium of the amide (Fig. 10). Two reaction rules are necessary for the modelling of the equilibrium, the first one performing the protonation of the amide, the second one modelling the deprotonation step. These two steps are combined in an equation modelling the pK_a value of the equilibrium. A data set with pK_a values of 71 protonated aliphatic amides, benzamides, naphthylamides, phenylureas and alkylcarboxamides has been derived from the literature[24–28] for the statistical analysis.

Multilinear regression analysis leads to eqn. (6) with three

$$\begin{aligned} \mathrm{p}K_a = {} & 46.7\,(\pm 6.2) - 36.2\,(\pm 5.7)\cdot\Delta q_{\sigma,\mathrm{p}(4-1)} - \\ & 2.33\,(\pm 0.48)\cdot\Delta\chi_{\pi,\mathrm{e}(2-3)} - 42.21\,(\pm 7.9)\cdot\Delta\Delta q_\sigma \qquad (6) \\ & \Delta\Delta q_\sigma = \Delta q_{\sigma,\mathrm{e}(1-2)} - \Delta q_{\sigma,\mathrm{p}(1-2)} \end{aligned}$$

parameters describing the pK_a value of the protonated amide. In this equation the index, e, denotes the variables for the unprotonated, (educt), p, the variables for the protonated amide.

The correlation coefficient, *r*, is 0.743, the standard error, s, 0.59 pK_a units over a range of 3.07 pK_a units.

The variable $\Delta q_{\sigma,p(4-1)}$ used in eqn. (6) is the difference in the σ-charge between the carbonyl oxygen atom 1 and the hydrogen atom 4 bonded to this oxygen atom (see Fig. 11). A protonated amide should be more acidic the higher this charge difference, *i.e.*, the more polar this bond is. This is reflected by the negative sign of the coefficient bound by MLRA.

The variable $\Delta\chi_{\pi,e(1-2)}$, the difference in the π-orbital electronegativity between the carbonyl oxygen atom 1 and the carbonyl carbon atom 2, is the extent of the contribution of the dipolar resonance structure of the carbonyl double bond in the uncharged amide (3 = educt). The higher this contribution, *i.e.*, the more important the resonance structure with a negatively charged oxygen atom, the easier should be a protonation at this site. This is borne out by the negative sign of the coefficient of this variable.

The variable $\Delta\Delta q_\sigma$ is the difference in the σ-charge difference between the carbonyl oxygen and carbon atom of the unprotonated (*e*) and protonated (*p*) amide, respectively. Thus, this variable is the difference in σ-bond polarity of the carbonyl bond induced by the protonation reaction. It can be interpreted as a measure of both the inductive and the resonance effect resulting from the substituents. The coefficient of this variable has a negative sign in eqn. (6) and thus larger values of this variable lead to a decrease in the pK_a value, to a less stable protonated form of the amide. This is consistent with the physicochemical interpretation that the higher donor and resonance capacity of R^1 and NHR^2 should lead to a more stable protonated amide.

The statistical quality of eqn. (6) is not very high. However, one must take into account that experimental pK_a values from different laboratories are compared in this study. Sometimes these values differ by as much as one pK_a unit for the same compound[24,27,28] and thus the error in the experimental values can be estimated to be at least 0.5 pK_a units. The standard deviation of 0.59 pK_a units obtained with eqn. (6) is thus in the range of the experimental error. Eqn. (6) is therefore of sufficient quality when compared with the experimental error. As the correlation coefficient of eqn. (6) is, at 0.743, rather poor, a model with more variables has been developed and tested. Multilinear regression analysis leads to an equation with seven variables. This model has been designed for higher quality predictions, and is of better statistical quality (r = 0.827, s = 0.53 pK_a units). As a set of rather complex variables is used we refrain from a detailed explanation of this model.

The conclusion that the moderate quality of the correlation is attributed to the rather large error range in the experimental data and to the implicit inclusion of solvent effects is supported by a study on proton affinities of amides.[29] With essentially the same physicochemical variables as used in the present study much better correlations are obtained as higher quality data and data uncorrupted by solvent effects are available.

Table 3 compares the experimental pK_a values with those calculated according to eqn. (6).

Table 3 Experimental *vs.* predicted pK_a values of protonated amides

		pK_a		
R^1	R^2	exp.	exp.–calc.	Ref.
Aliphatic amides: R^1–CO–NH–R^2				
H	Me	−1.55	−0.50	24
H	Et	−1.45	−0.38	24
H	Pr^i	−1.30	0.22	24
H	CH_2Ph	−1.93	−0.83	24
Me	H	−1.12	−0.12	24
Me	Bu^t	−0.41	0.70	25
Me	Ph	−1.03	0.33	26
Me	4-Me–C_6H_4	−0.49	0.87	25
Me	4-OMe–C_6H_4	−1.00	0.36	25
Me	4-Cl–C_6H_4	−1.31	0.06	25
Me	4-NO_2–C_6H_4	−1.35	0.15	25
Et	CH_2COOH	−1.93	−0.76	24
Pr^n	H	−1.08	0.05	24
Benzamides: R^1–Ph–CO–NH–R^2				
H	H	−1.84	0.36	24
4-Me	H	−1.67	0.52	24
4-Cl	H	−1.45	0.66	26
4-Br	H	−2.02	0.07	24
4-OMe	H	−1.44	0.57	24
4-NO_2	H	−2.03	1.10	26
3-NO_2	H	−2.42	0.46	24
3-NO_2, 4-Br	H	−2.63	0.05	24
3,5-NO_2	H	−3.04	0.37	24
3,5-NO_2, 4-Me	H	−2.69	0.60	24
2,3,6-Cl	H	−3.30	−1.30	24
3,4,5-OMe	H	−1.82	0.28	24
2,4,6-NO_2	H	−4.08	0.17	24
2,4-Cl, 3,5-NO_2	H	−3.73	−0.70	24
H	Me	−1.59	0.55	24
H	Et	−1.92	0.23	24
4-Me	Et	−1.77	0.38	24
4-OMe	Et	−1.60	0.36	24
4-Cl	Et	−2.21	−0.15	24
3-Me	Et	−1.88	0.28	24
3-Cl	Et	−2.28	−0.07	24
3-Br	Et	−2.40	−0.21	24
3-NO_2	Et	−2.54	0.29	24
H	CH_2CF_3	−3.33	−1.11	24
4-Me	CH_2CF_3	−3.00	−0.78	24
Benzamides: R^1–Ph–CO–NH–R^2 (*contd.*)				
4-OMe	CH_2CF_3	−2.70	−0.67	24
4-Cl	CH_2CF_3	−3.41	−1.28	24
3-Me	CH_2CF_3	−3.20	−0.97	24
3-Cl	CH_2CF_3	−3.62	−1.34	24
3-Br	CH_2CF_3	−3.64	−1.38	24
3-NO_2	CH_2CF_3	−3.83	−0.93	24
H	2-NH_2–C_6H_4	−2.25	0.12	27
2-Me	2-NH_2–C_6H_4	−1.98	0.38	27
2-OMe	2-NH_2–C_6H_4	−1.72	0.40	27
2-Cl	2-NH_2–C_6H_4	−2.36	−0.13	27
2-NO_2	2-NH_2–C_6H_4	−2.71	0.54	27
2-NH_2	2-NH_2–C_6H_4	−2.38	−0.51	27
H	OH	−1.93	0.25	24
4-Me	OH	−1.72	0.46	24
4-OMe	OH	−1.48	0.49	24
4-OH	OH	−1.54	0.43	24
4-Cl	OH	−2.05	0.01	24
2-Naphthylamides: R^1–Napht–CO–NH–R^2				
H	H	−1.95	0.18	24
Phenylureas: R^1–Ph–NH–CO–NH–R^2				
H	H	−1.30	0.13	24
4-Me	H	−1.22	0.21	24
4-Pr^i	H	−0.99	0.44	28
4-Bu^n	H	−0.99	0.44	28
4-OMe	H	−0.84	0.60	28
4-OEt	H	−0.80	0.64	28
4-F	H	−1.12	0.33	28
4-Cl	H	−1.48	−0.03	24
4-Br	H	−1.57	−0.13	24
4-NO_2	H	−1.83	−0.25	28
3-Me	H	−1.18	0.26	24
3-OH	H	−1.31	−0.14	24
3-NO_2	H	−1.64	−0.19	28
Alkylcarboxamides: R–O–CO–NH–R′				
Et	H	−3.03	−0.41	24
Et	CH_2COOH	−3.77	−1.14	24

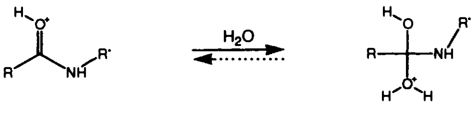


Fig. 12 The rate determining step in the acid-catalysed hydrolysis of amides

4.4. Modelling the addition of water to the conjugate acid of amides

The addition of water to the conjugate acid of an amide is the rate-determining step (Fig. 12). The rate of hydrolysis of amides depends on the concentration of the conjugate acid of the amide, the concentration of water and the temperature. As the addition of water is the second step of the hydrolysis, the true rate constant for the addition reaction cannot be measured directly. Instead, a pseudo-first-order rate constant, k_ψ, for the overall reaction can be determined. k_ψ has to be corrected according to eqn. (7), as only the protonated part of the amide undergoes the addition of water leading to the hydrolysis products.

$$k_p = k_\psi \cdot \frac{[A] + [AH^+]}{[AH^+]} \qquad (7)$$

In weak acids the protonation ratio can be calculated from the pH value, in strong acids it has to be estimated from acidity functions H_A, which have been tabulated for amides.[30]

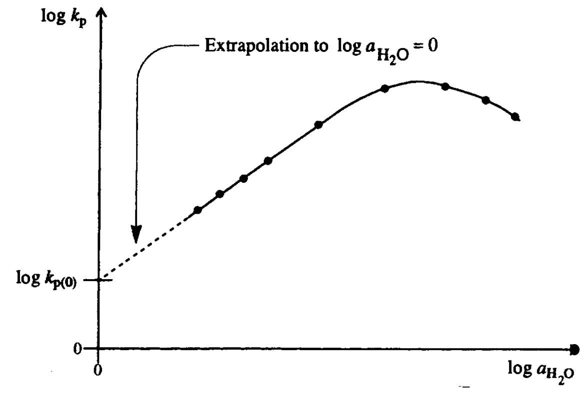


Fig. 13 Extrapolation to the standardized rate constant $k_{p(0)}$

This corrected rate constant k_p cannot be used directly, because hydrolysis was performed in concentrated acids. In order to obtain the standardized rate constant $k_{p(0)}$, an extrapolation of log k_p to an acid concentration of zero was made (Fig. 13). From these standardized rate constants, $k_{p(0)}$, values for $\Delta G^\ddagger$ were calculated with eqn. (3).

Rate constants of 76 hydrolysis reactions of alkylcarboxamides, benzamides, anilides, benzanilides and phenylureas at

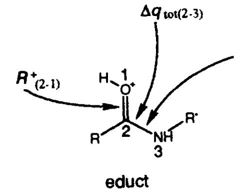


Fig. 14 Variables used in eqn. (8)

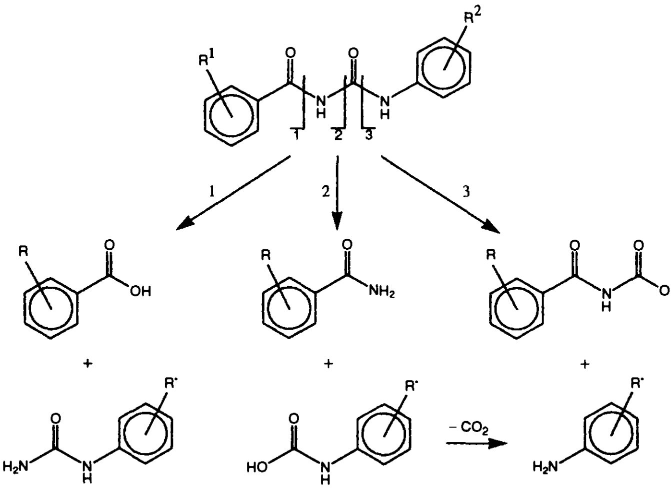


Fig. 15 Three pathways for the hydrolysis of substituted benzoylphenylureas

different temperatures and concentrations of acid have been taken from the literature. The largest set of data have been measured at a temperature of 100 °C. Acid-catalysed hydrolysis of 34 amides has been determined at this temperature. This set of data was split into 27 values for deriving an equation by MLRA and seven values for testing it. The training set led to eqn. (8).

$$\Delta G^{\ddagger} = 61.1\,(\pm 5.9) + 1.32\,(\pm 0.21)\cdot R^{+}_{(2-1)} + 0.33\,(\pm 0.04)\cdot R^{+}_{(3-2)} - 51.8\,(\pm 6.3)\cdot \Delta q_{\text{tot}(3-2)} \quad (8)$$

$$(\text{in kJ mol}^{-1})$$

The correlation coefficient, r, is 0.913; the standard error, s, is 3.13 kJ mol^{-1} in a range of 23 kJ mol^{-1}.

The two variables $R^{+}_{(2-1)}$ and $R^{+}_{(3-2)}$ used in eqn. (8) describe the stabilization of a formal positive charge by the resonance effect (Fig. 14). The higher the values of $R^{+}_{(2-1)}$ and $R^{+}_{(3-2)}$ the more is the protonated amide stabilized, the less prone it is to hydrolysis. This is reflected by the positive sign of the coefficients for these two variables in eqn. (8).

The variable $\Delta q_{\text{tot}(2-3)}$ used in eqn. (8) is the difference in the total charge between the carbonyl carbon atom 2 and the nitrogen atom 3. The coefficient of this variable has a negative sign in eqn. (8) and thus larger values of this variable lead to a decrease of the $\Delta G^{\ddagger}$ value and an increase in reaction rate. The more polar this bond, the easier will be an attack of water at the carbonyl carbon atom.

The seven test data not used in the derivation of eqn. (8) gave a standard deviation, s, of 3.13 kJ mol^{-1} when predicted by eqn. (8). The results obtained with eqn. (8) are contained in column 5 of Table 4.

In order also to make use of the kinetic data measured at temperatures other than 100 °C, temperature was included as an additional variable in an MLRA study. The justification for using temperature as a variable in a linear equation can be found in the Gibbs–Helmholtz equation $\Delta G = \Delta H - T\Delta S$, showing that ΔG is linearly dependent on temperature, T.

MLRA of the free energy of activation for acid-catalysed hydrolysis of all the 76 amides for which data were found in literature provided eqn. (9). The correlation coefficient, r, is 0.823, the standard error, s, 3.63 kJ mol^{-1} in a range of 30.8 kJ mol^{-1}.

$$\Delta G^{\ddagger} = 66.89\,(\pm 6.7) + 1.16\,(\pm 0.14)\cdot R^{+}_{(2-1)} + 0.06\,(\pm 0.01)\cdot T \quad (\text{kJ mol}^{-1}) \quad (9)$$

Only the amount of the resonance stabilization of a positive charge at the carbonyl carbon atom, $R^{+}_{(2-1)}$, was used as a variable describing an electronic effect (see Fig. 14). The coefficient of the variable $R^{+}_{(2-1)}$ bears a positive sign. This is consistent with the physicochemical interpretation that a better stabilization of the charge hinders the nucleophilic attack of the water and thus enlarges $\Delta G^{\ddagger}$ and decreases the reaction rate. Table 4 contains the experimental *vs.* predicted free energy of activation values ($\Delta G^{\ddagger}$).

4.5. Reaction to the products

The last two reaction steps, the addition of water and the reaction to the final products need no kinetic modelling. In the reaction rule the rate constants are fixed to a value that is high compared with that of the rate-determining step. These values are considered in the calculation of the overall rate.

4.6. Extrapolation to acylureas

One aim of the study was the prediction of rate constants for the hydrolysis of benzoylphenylureas. No experimental data are available for these compounds. Compounds closest to these systems for which experimental data have been determined are acylureas.

For the acid-catalysed hydrolysis of acylureas three experimental data are available.[45] The half-life times calculated with eqns. (9) and (2) show a high degree of correspondence with the experimental values (Table 5). Thus, it can be concluded that the extrapolation of the models developed for the hydrolysis of amides to the prediction of rate constants of benzoylphenylureas might be warranted.

4.7. Comparison of acid with base catalysis

The next investigation addressed the problem of the relative importance of acid- and base-catalysed hydrolysis of amides under neutral conditions. Reaction rates were calculated according to eqns. (5) and (2), as well as eqns. (9) and (2) at pH 7. The results are contained in Table 6. The rates at pH 7 have to be extrapolated by the Brønsted equation from the values at pH 1, 2 and 3 (13, 12 and 11, respectively) as a direct calculation would lead to very long computation times in the solution of the set of differential equations by the GEAR algorithm[9] during the calculation of the final concentrations with the low starting value of 10^{-7} mol dm^{-3} for the H_3O^+ or OH^- ion, respectively. The results indicate that in water the base-catalysed hydrolysis reaction is about 1000 times faster than acid-catalysed hydrolysis.

5. Applications

A major point of interest in this investigation was the prediction of the reaction rates for the chemical degradation of benzoylphenylureas *via* hydrolysis under acid or base catalysis. Benzoylphenylureas show three potential pathways for hydrolysis leading to two main groups of final products (Fig. 15). Cleavage at site 1 leads to substituted benzoic acids and

Table 4 Experimental *vs.* predicted free energy of activation $\Delta G^\ddagger$ for the addition of water to protonated amides

			$\Delta G^\ddagger$			
R^1	R^2	$T/^\circ C$	exp.	exp.–calc.[a]	exp.–calc.[b]	Ref.
Aliphatic amides: $R^1-C{=}OH^+-NH-R^2$						
H	H	25	85.06		−8.15	31
Me	H	25	98.56		1.13	31
Me	Et	25	111.29		10.06	32
Et	H	25	97.48		0.10	31
NH_2	H	100	115.53	4.69	7.98	33
NH_2	Et	100	113.24	−2.24	1.94	33
Benzamides: $R^1-Ph-C{=}OH^+-NH-R^2$						
H	H	25	101.04		−0.38	34
H	H	40	102.78		0.45	34
H	H	60	103.31		−0.34	34
H	H	75	104.42		0.25	34
H	H	85	104.54		−1.74	34
H	H	100	103.33	−0.36	−2.93	35
H	Me	50	110.48		3.69	34
H	Me	65	111.37		3.59	34
H	Me	85	111.98		−1.74	34
H	Me	100	112.23	3.75	2.17	36
4-Me	OH	50	98.81		−10.13	37
4-Cl	Me	100	111.70	−0.27	−1.84	38
4-Cl	Et	100	111.12	−0.62	−2.33	38
4-Cl	Pr^i	100	115.86	4.33	2.56	38
4-Cl	Bu^n	100	113.33	1.61	−0.11	38
4-Cl	Bu^t	100	107.18	−2.54[c]	−6.03	38
Anilides: $R-C{=}OH^+-NH-Ph-R'$						
Me	H	25	97.35		0.84	39
Me	H	80	100.29		0.25	39
Me	H	100	99.95	1.43	−1.39	35
Me	2-NO_2	50	97.44		−0.19	40
Me	2-NO_2	60	99.39		1.11	40
Me	2-NO_2	70	100.25		1.28	40
Me	2-NO_2	80	101.21		1.63	40
Me	2-NO_2	90	102.03		1.79	40
Me	4-Me	100	102.69	1.61	1.35	36
Me	4-OH	100	104.76	5.03[c]	3.47	36
Me	4-OMe	100	103.30	3.79	1.98	36
Me	4-OEt	100	103.63	4.14	2.28	36
Me	4-F	100	102.57	4.38	1.31	36
Me	4-Cl	100	97.82	−0.36	−3.48	36
Me	4-Br	100	97.02	−1.29	−4.29	36
Me	4-I	100	97.27	−1.13	−4.05	36
Me	4-COOH	100	93.49	−2.94	−7.54	36
Me	4-NH_2	100	93.75	−5.98[c]	−7.59	36
Me	4-NO_2	100	89.09	−5.58[c]	−1.78	36
Me	4-SO_3H	25	94.41		−1.49	41
Me	4-SO_3H	30	94.94		−1.28	41
Me	4-SO_3H	40	96.41		−0.45	41
Me	4-SO_3H	80	99.61		0.17	41
Me	4-SO_3H	90	101.01		0.92	41
Me	4-SO_3H	100	98.67	1.72	−2.05	41
Benzanilides: $R^1-Ph-C{=}OH^+-NH-Ph-R^2$						
H	H	80	101.87		−1.15	42
H	4-Me	80	100.92		−2.15	42
H	4-OMe	80	105.69		2.66	42
H	4-Cl	80	103.20		0.19	42
H	4-NO_2	80	97.21		−1.80	42
4-Me	H	80	101.53		−10.48	42
4-OMe	H	80	104.25		−6.43	42
4-Cl	H	80	102.57		−3.76	42
4-NO_2	H	80	103.74		−1.73	42
Phenylureas: $R^1-NH-C{=}OH^+-NH-Ph-R^2$						
H	H	70	108.50		4.66	43
H	H	80	108.44		3.92	43
H	H	90	107.91		2.77	43
H	H	100	108.16	0.18[c]	2.42	43
H	H	110	107.17		0.76	43
H	3-Me	100	108.85	0.91	3.03	43
H	3-NO_2	100	106.52	−0.74	0.88	44
H	4-Me	100	106.86	−3.69	1.05	44

Table 4 (*contd.*)

			$\Delta G^‡$			
R^1	R^2	T/°C	exp.	exp.–calc.[a]	exp.–calc.[b]	Ref.
H	4-Pr^i	100	110.31	−0.15	4.46	44
H	4-Bu^n	100	110.34	−0.16[c]	4.45	44
H	4-OMe	100	109.62	0.66	3.82	44
H	4-OEt	100	110.03	1.08	4.22	44
H	4-F	70	109.61		5.90	43
H	4-F	80	109.57		5.26	43
H	4-F	90	109.72		4.71	43
H	4-F	100	108.90	1.28	3.26	43
H	4-F	110	108.93		2.60	43
H	4-Cl	100	106.29	−1.54	0.56	44
H	4-Br	100	105.65	−2.10	−0.05	44
H	4-NO_2	100	104.51	−1.19[c]	−0.23	44

[a] Prediction by eqn. (8). [b] Prediction by eqn. (9). [c] Test data not used in the derivation of eqn. (8).

Table 5 Experimental *vs.* calculated [eqn. (9)] half-lives for acid-catalysed hydrolysis: initial concentrations: 1.0 × 10^{-3} mol dm^{-3}, pH 1.38

	$t_{\frac{1}{2}}/10^{-3}$ s		
R–CO–NH–CO–NH_2	exp.[a]	calc.	T/°C
R = methyl	3.35	3.41	80
R = ethyl	2.51	3.09	90
R = phenyl	114.6	58.7	90

[a] Ref. 45.

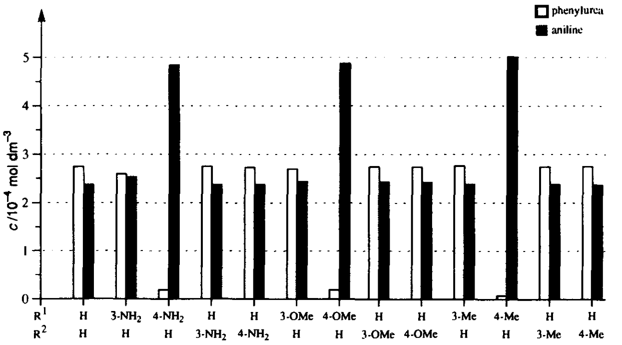


Fig. 16 Prediction of substituent effects on the hydrolysis of *N*′-benzoyl-*N*-phenylurea using the reaction rule for the mechanism under basic conditions: product ratios (pH = 7.0, initial concentration of the amide = 1 × 10^{-3} mol dm^{-3}, temperature = 25 °C, conversion = 50%)

phenylureas. The other two pathways through cleavage at sites 2 and 3 yield substituted anilines and benzamides. Therefore, in the following investigation the two pathways 2 and 3 are considered together.

To investigate the effect of substitutions on the half-life times and product distribution, the six substituents NH_2, OMe, Me, Cl, NO_2, COMe were introduced. All combinations of substitutions at either the 2-, 3- or the 4-position both in the benzoyl and aniline part of *N*′-benzoyl-*N*-phenylurea were used. As the calculations for the substituents at the 2- and 4-position lead to nearly the same result, only the results for substituents at the 3- and 4-position are included in the figures presented here. After conversion of 50% of the urea, numerical integration of the system of kinetic equations was stopped and the concentrations (c_1, $c_2 + c_3$) and half-life times ($t_{\frac{1}{2}}$) of the primary hydrolysis products were determined.

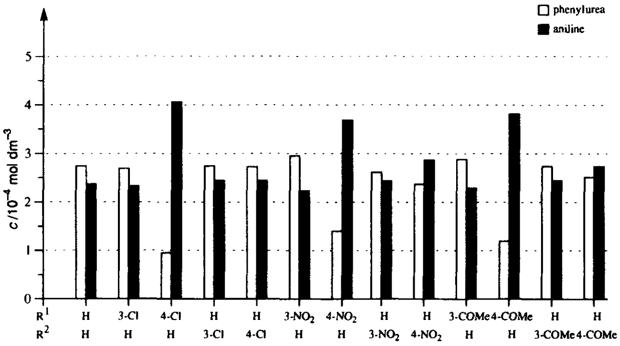


Fig. 17 Prediction of substituent effects on the hydrolysis of *N*′-benzoyl-*N*-phenylurea using the reaction rule for the mechanism under basic conditions: product ratios (pH = 7.0, initial concentration of the amide = 1 × 10^{-3} mol dm^{-3}, temperature = 25 °C, conversion = 50%)

5.1. Calculation of half-life times and concentrations

The half-life times and concentrations of the two groups of products (phenylurea from site 1 and anilines from sites 2 and 3) are given in Table 7 and Figs. 16–19. They were calculated at pH 7.0 and a temperature of 25 °C. The initial concentration of the urea was given at 1 × 10^{-3} mol dm^{-3}. The concentrations in Figs. 16 and 17 have been calculated using the model for the base-catalysed reaction mechanism [eqn. (5)], the concentrations in Figs. 18 and 19 result from the application of the model for the acid-catalysed reaction mechanism [eqn. (9)].

5.2. Discussion of the substituent effects on half-life times

Base-catalysed reactions: most substituents in the aniline part at position 3 are predicted to have no significant influence on the half-life of the compounds whereas substituents at the 4 position of the benzoyl part (R^1) decrease the rate of base-catalysed hydrolysis.

Acid-catalysed reactions: substituents at positions 3 and 4 both in the benzoyl and the aniline part have no large influence on the half-life times of the compounds.

In all cases, base-catalysed amide hydrolysis at pH 7 is faster by about a factor of 1000 than the acid-catalysed reaction at this pH value (*cf.*, Table 6).

5.3. Discussion of substituent effects on product ratios in base-catalysed hydrolysis

Unsubstituted aromatic rings (R^1 = R^2 = H) are predicted to give nearly equal amounts of phenylurea and aniline on base-catalysed hydrolysis.

Table 6 Prediction of half-lives of the hydrolysis of *N'*-benzoyl-*N*-phenylurea (initial concentration of the amide = 1×10^{-3} mol dm^{-3}, T = 25 °C, conversion = 50%)

Conditions	$t_{\frac{1}{2}}$/s			
Basic	pH 13 1.63×10^3	pH 12 1.62×10^4	pH 11 1.63×10^5	extrapolated to pH 7 1.63×10^9
Acidic	pH 1 1.16×10^6	pH 2 1.15×10^7	pH 3 1.15×10^8	extrapolated to pH 7 1.15×10^{12}

Table 7 Prediction of substituent effects on the hydrolysis of *N'*-benzoyl-*N*-phenylurea: half-lives (pH = 7.0, initial concentration of the amide = 1×10^{-3} mol dm^{-3}, T = 25 °C, conversion = 50%)

R^1	R^2	$t_{\frac{1}{2}}$ (base)/ 10^{-9} s	$t_{\frac{1}{2}}$ (acid)/ 10^{-12} s
H	H	1.63	1.15
3-NH_2	H	1.73	1.28
4-NH_2	H	5.43	1.78
H	3-NH_2	1.63	1.22
H	4-NH_2	1.62	0.89
3-OMe	H	1.62	1.25
4-OMe	H	4.53	1.78
H	3-OMe	1.63	1.18
H	4-OMe	1.63	0.94
3-Me	H	1.63	1.26
4-Me	H	3.43	1.90
H	3-Me	1.63	1.21
H	4-Me	1.63	1.18
3-Cl	H	1.53	1.30
4-Cl	H	3.53	1.58
H	3-Cl	1.63	1.21
H	4-Cl	1.62	0.95
3-NO_2	H	1.42	1.47
4-NO_2	H	2.02	1.75
H	3-NO_2	1.53	1.13
H	4-NO_2	1.21	0.80
3-COMe	H	1.52	1.29
4-COMe	H	2.43	1.63
H	3-COMe	1.63	1.22
H	4-COMe	1.31	0.83

Substitution in the benzoyl part (R^1): substitution at position 3 of the benzoyl system gives nearly equal amounts of phenyl urea and aniline. The influence of the various substituents on the product ratio is only small. Substitution at the position 4 always leads to aniline as the major product. Substituents with a $+M$ effect (NH_2, OMe, Me) at position 4 show a higher preference for aniline than substituents with a $-M$ effect.

Substitution in the aniline part (R^2): all substituents in the aniline part are predicted to yield nearly an equal amount of phenylurea to aniline. The variation of the substituents reveals only a small influence on the product ratio.

5.4. Discussion of substituent effects on product ratios in acid-catalysed hydrolysis

For unsubstituted aromatic rings ($R^1 = R^2$ = H) cleavage to aniline is predicted to be slightly preferred.

Substitution in the benzoyl part (R^1): substituents at position 3 leads to a product ratio of about 2:1 (phenylurea to aniline). On the other hand, substitution at position 4 yields aniline as the favoured product. In the case of substituents with a $+M$ effect (NH_2, OMe, Me) this preference is very distinct. Chlorine and substituents with a $-M$ effect (NO_2, COMe) reveal a preference of only about a factor of 3–4.

Substitution in the aniline part (R^2): for substituents at positions 3 and 4 cleavage to aniline is slightly preferred. The influence of the various substituents is small.

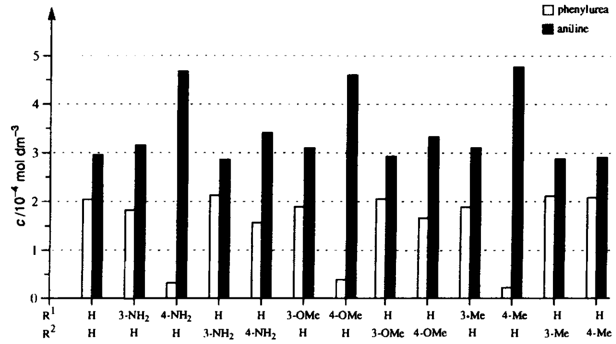


Fig. 18 Prediction of substituent effects on the hydrolysis of *N'*-benzoyl-*N*-phenylurea using the reaction rule for the mechanism under acidic conditions: product ratios (pH = 7.0, initial concentration of the amide = 1×10^{-3} mol dm^{-3}, temperature = 25 °C, conversion = 50%)

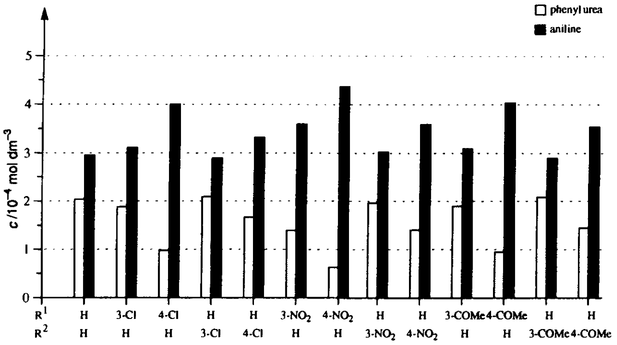
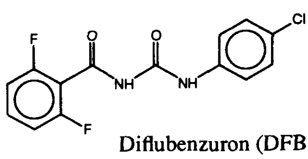


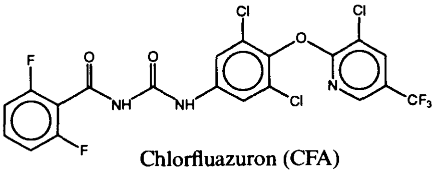
Fig. 19 Prediction of substituent effects on the hydrolysis of *N'*-benzoyl-*N*-phenylurea using the reaction rule for the mechanism under acidic conditions: product ratios (pH = 7.0, initial concentration of the amide = 1×10^{-3} mol dm^{-3}, temperature = 25 °C, conversion = 50%)

5.5. Comparison with LFER treatment

Further to distinguish our approach to the prediction of substituent effects on reaction rates it might be helpful to compare it with a linear free energy relationship (LFER) approach. In fact, substituent effects on reaction rate in aromatic compounds have been extensively treated by Hammett-type equations. Such a treatment might also be feasible for the hydrolysis of amides containing substituted phenyl rings; *e.g.*, as in benzamides or substituted anilides. Surprisingly, no extensive study on such compounds was found in the literature. Even if such a treatment might be



Diflubenzuron (DFB)



Chlorfluazuron (CFA)

Fig. 20 Commercial agrochemicals: Diflubenzuron (DFB) and Chlorfluazuron (CFA)

Table 8 Prediction of half-lives and product ratios for the hydrolysis of the two agrochemicals DFB and CFA (see Fig. 20) and a comparison with an experimental value for the half-life of DFB

	DFB	CFA
pH 7, initial concentration 10^{-3} mol dm^{-3}, T = 25 °C		
$t_{1/2}$/s	5.4×10^8	5.1×10^8
c_1 (phenylurea)	3.24×10^{-4}	3.79×10^{-4}
$c_2 + c_3$ (aniline)	1.76×10^{-4}	1.21×10^{-4}
pH 10, initial concentration 10^{-3} mol dm^{-3}, T = 36 °C		
$t_{1/2}$/s	2.7×10^6	2.5×10^6
$t_{1/2}$/s (ref. 46)	2.6×10^5	—

feasible for benzamides and anilides, separately, the combination of the two systems into one, *e.g.*, as in benzoylanilides would require a completely new treatment. Furthermore, the extension of LFER equations derived for benzamides, anilides and benzoylanilides to *N*′-benzoyl-*N*-phenylureas is not possible.

In our approach, however, such an extrapolation is possible, as the physicochemical variables are calculated by treating each molecule as an entity, not making an artificial separation into skeleton, reaction site and substituent as in the LFER approach. Furthermore, direct calculations on each molecule allow one also to treat multiply substituted compounds such as Diflubenzuron, DFB (Fig. 20).

In the LFER approach, a treatment of multiply substituted compounds such as DFB requires the additivity of substituent effects to be assumed, certainly a gross simplification for such a system with strong interactions between substituents. For a compound like CFA (Fig. 20), certainly no substituent constants are available for the substituted pyridinone system acting as a substituent on the aniline system. Again, by direct calculation of electronic effects as performed in our study, the treatment of such novel systems causes no problems.

5.6. Extension to agrochemicals

In order to stress the point made in the previous section, predictions on the half-lives and product ratios for the two agrochemicals DFB and CFA are given in Table 8. Little is known about the stability of *N*′-benzoyl-*N*-phenylureas towards hydrolysis. Only one value for a commercial agrochemical was found in literature.[46] Diflubenzuron is reported to have, at a temperature of 36 °C and a pH of 10, a half-life of 3 days (2.6×10^5 s). Application of eqns. (2) and (5) (which are valid for 25 °C) and allowing for an increase in the reaction rate by a factor of two for an increase in temperature of 10 °C leads to a predicted value at this temperature and pH-value of about 2.7×10^6 s.

The correspondence between the experimental and the calculated value must be considered satisfactory in view of the errors in the experimental data used for deriving the equations of this study, the empirical nature of the methods for calculating physicochemical effects and, particularly, the need to extrapolate to a class of compounds (*N*′-benzoyl-*N*-phenylureas) not contained in the datasets for deriving the equations. Furthermore, it may even be that the half-life reported in the experiment might include not only hydrolysis but also some other process. It has already been said in the introduction that any additional degradation process can only contribute to a decrease in the stability of a compound; values calculated by the equations derived in this study are *limiting* values and, in reality, the degradation of a compound might occur faster. Thus, it might as well be that the actual rate of the hydrolysis proper is even closer to our estimated value.

6. Conclusions

The studies reported here follow a well-established method for knowledge acquisition in organic chemistry: to derive from a series of experimental observations some general knowledge on a certain reaction type. By using methods for the quantification of fundamental electronic effects, experimental kinetic data for a given reaction type are generalized to equations that allow the calculation of free energies of activation and reaction rates of any instance of this reaction type.

In particular, methods are derived for acid- and base-catalysed amide hydrolysis. It is shown that the equations derived from aliphatic amides, benzamides, anilides and phenylureas can be extrapolated to acylureas. This provides justification for extrapolation to the hydrolysis of substituted *N*′-benzoyl-*N*-phenylureas. In this way, the influence of substituents on the two phenyl rings on half-lives and product ratios is estimated. This allows the prediction of the stabilities and products of hydrolysis of some important agrochemicals. Inclusion of these equations into the knowledge base of the expert system EROS allows the automatic prediction of the degradation of chemicals in the environment.

Clearly, the quality of the predictions relies heavily on the quality of the experimental data used to derive the models and equations of our study. It is our hope that our report will encourage more investigations aimed at high quality kinetic data of fundamental organic reaction types.

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