Kinetics and mechanism of hydrolysis of phenylureas

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The hydrolysis of phenylureas has been found to be affected by temperature, pH and buffer concentration. Kinetic evidence suggests that the formation of phenylisocyanate, the initial product in the title reaction, occurs *via* an intermediate zwitterion. Depending on pH and buffer concentrations, the zwitterion can be produced through three parallel routes: at low pH, specific acid–general base catalysis, followed by slow deprotonation of a nitrogen atom by a general base; at high pH, specific basic–general acid catalysis, followed by slow protonation of a N atom by a general acid; at intermediate pH the reaction proceeds through a proton switch promoted by buffers. Bifunctional acid–base buffers such as HCO_3^-/CO_3^{2-}, $H_2PO_4^-/HPO_4^{2-}$ and CH_3COOH/CH_3COO^- are very efficient catalysts. At high buffer concentration, as well as at pH < 3 or > 12, the breakdown of the zwitterion is rate-determining. The results are discussed in relation to recently published papers reporting different pathways.

Introduction

The hydrolysis of phenylureas is a topic of increasing interest [1–4] not only because of distinctive aspects of its reaction mechanism, but also for the importance of these molecules as the active principles of efficient herbicides widely used in agriculture.[5] It has been postulated that abiotic hydrolysis, at least in some cases, is a multi-stage reaction involving first the formation of isocyanate and ammonia derivatives (i), followed by hydrolysis to the carbamic acid derivative (ii) and then scission to carbon dioxide and the aniline derivative (iii).[2–4,6,7]

$$R–NH–CO–N< \longrightarrow R–NHCO + N< \quad \text{(i)}$$

$$R–NHCO + H_2O \longrightarrow RNHCO_2H \quad \text{(ii)}$$

$$RNHCO_2^- + H^+ \longrightarrow R–NH_2 + CO_2 \quad \text{(iii)}$$

The reaction (i) is rate-limiting for the overall process; therefore, the isocyanate and carbamic acid derivatives form a small proportion of the reacting mixtures.

Soil microorganisms mainly promote the demethylation reaction of *N′*-methyl derivatives of *N*-phenylureas.[8] As regards the mechanism of the first stage of hydrolysis, despite the extensive work done, no pathway has been proposed that fully satisfies the kinetic behavior. Recently, it has been proposed[2] that in acidic media the reaction proceeds through the protonation of the substrate followed by a rate-determining attack by water, giving a tetrahedral intermediate. This intermediate then decomposes to an amine and a phenylcarbamic acid which quickly decarboxylates under acidic conditions to form the corresponding aniline. In basic media it has been proposed[3] that the hydrolysis of phenylureas occurs *via* an intermediate hydroxide ion complex whose breakdown gives the final products. On the other hand, earlier works have produced evidence of the formation of zwitterionic intermediates in the conversion of ureas into isocyanates in aqueous solutions.[7] In the formation of these intermediates water molecules act as proton transfer agents to either the unprotonated or the *N*-protonated substrate.

The aim of this work was to get a better understanding of the kinetic behavior of the hydrolysis of phenylureas in aqueous solution in order to work out a kinetic mechanism more consistent with the body of information available. The study was carried out on 3-(3,4-dichlorophenyl)-1,1-dimethylurea (**I**, diuron), 3-(4-isopropylphenyl)-1,1-dimethylurea (**II**, isoproturon), 1-butyl-3-(3,4-dichlorophenyl)-1-methylurea (**III**, neburon) and 3-(3-chloro-*p*-tolyl)-1,1-dimethylurea (**IV**, chlorotoluron), representatives of the substituted phenylurea herbicide class. Preliminary results have been reported.[9]

Experimental

Materials

The phenylureas 3-(3,4-dichlorophenyl)-1,1-dimethylurea (**I**, diuron), 3-(isopropylphenyl)-1,1-dimethylurea (**II**, isoproturon), 1-butyl-3-(3,4-dichlorophenyl)-1-methylurea (**III**, neburon), 3-(3-chloro-*p*-tolyl)-1,1-dimethylurea (**IV**, chlorotoluron) and 3,4-dichloroaniline, were supplied by Dr. Ehrenstorfer GmbH, 3-isopropylaniline and 3-chloro-*p*-tolylaniline were obtained from Riedel-Dehaën. 3,4-Dichlorophenyl isocyanate was from Fluka. All the other chemicals were from Carlo Erba.

Kinetic measurements

Water solutions of the selected phenylurea (0.10 mM) at the desidered pH and buffer concentrations were filtered through a 0.45 μm membrane filter and then stored in a thermostated bath kept, unless otherwise stated, at 60.1 ± 0.1 °C. At preselected times, an aliquot was removed and analyzed by HPLC on a Waters system, consisting of a 515 HPLC Pump and a 2487 dual λ Absorbance Detector, equipped with a C_{18} reversed-phase column (3.9 × 150 mm). Phenylureas and their degradation products were eluted by a linear gradient of acetonitrile in water in 15 min, flow rate 1 mL min^{-1}, λ = 248 nm. The buffers were used in the concentration range of 10–500 mM and at a fraction (a) of the free base in the buffer of 0.2, 0.4, 0.6 and 0.8 for CH_3COOH/CH_3COO^-, pH 4.0–5.2 and $TrisH^+$/Tris, pH 6.9–8.1; at a = 0.2, 0.6 and 0.8 for HCO_3^-/CO_3^{2-}, pH 8.9–10.1 and $H_2PO_4^-/HPO_4^{2-}$ pH 6.0–7.2 The buffer 4-methylmorpholineH^+/4-methylmorpholine was used only at a = 0.6, pH 7.4. Dilute KOH and HCl were used in the pH ranges 1.0–3.0 and 11.0–13.0, respectively. In all samples, a constant ionic strength of 1 M was maintained by the addition of an appropriate volume of a concentrated solution of KCl.

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The pH values were measured by using a glass electrode at the same temperature and ionic strength as those of the rate measurements. The rate constants were calculated by least-squares analysis, assuming the reaction to be first-order in the starting phenylurea. The fitting of the experimental data was satisfactory for all samples.

The temperature effect on the reaction rate was analyzed by performing kinetic runs in the ranges 30–70 °C, 0.01–0.5 M phosphate buffer, fraction of the free base in the buffer = 0.6, and calculating the pre-exponential factor and activation energy from the linear regression of ln(k) *versus* 1/T by least-squares methods. No correction was made for the temperature dependence of the buffer pH value because in phosphate buffer the rate constant depends very little on pH. The entropy and enthalpy of activation were calculated by the standard formulae derived from the absolute theory of reaction rates.[10]

Characterization of the reaction products

The compounds of the degradation reactions of **I**, **II**, **III** and **IV** in aqueous solutions were identified by comparison with HPLC traces and UV spectra of pure samples. The compound obtained from **I** by spontaneous degradation in water–methanol mixtures and by the reaction of 3,4-dichlorophenylisocyanate with pure ethanol was identified by ^{1}H- and ^{13}C-NMR and mass spectra.

pK_a values

The equilibrium constants for the acid–base reactions of the Aryl-NH–CO–N< group to Aryl-N$^{(-)}$–CO–N< and Aryl-NH–CO–NH^{+}< of **I**, **II**, **III** and **IV** were calculated by the computer program SPARC developed by Carreira.[11] This program, based on structure activity relationships and perturbed molecular orbital theory, enables the calculation of the ionization pK_as for a large number of organic compounds from the molecular structures.

Results

Under all the experimental conditions, phenylureas underwent spontaneous irreversible hydrolysis at an appreciable rate giving detectable amounts of a single aromatic product, which was identified as the corresponding aniline derivative by HPLC co-injection of pure compounds and mass spectrometry techniques. The sum of the area of the phenylurea peak plus that of the aniline derivative, corrected by the different absorbances at the wavelength of the spectrometer detector, was constant during the kinetic runs, indicating the absence of reaction intermediates in an appreciable amount. Moodie and co-workers[12] reported a half-life value of 20 s for the non-catalyzed hydrolysis of phenylisocyanate in aqueous solution at 25 °C and, moreover, showed that the reaction is buffer-catalysed. Fast degradation to aniline derivatives may explain why we could detect no phenylisocyanate derivatives in water solution by HPLC. However, an indication that the reaction proceeds through phenylisocyanates was given by the analysis of the reaction products of **I** obtained in a water–ethanol mixture (50% ethanol). In this medium HPLC analysis revealed, besides the aniline derivative, another product, in 60% relative yield after 15 days, which was identified by ^{1}H- and ^{13}C-NMR, and by mass spectra, as ethyl 3,4-dichlorophenylcarbamate: ^{1}H-NMR δ 1.30 (3 H, t, CH_3), 4.22 (2 H, q, CH_2), 7.19 (1 H, dd, 6-H), 7.46 (1 H, d, 6-H), 7.59 (1 H, d, 6-H), 7.93 (s, 1 H, NH); ^{13}C-NMR δ 14 (CH_3), 61 (CH_2), 119 (*ortho* CH), 120 (*ortho* CH), 124.5 (*para* CCl), 130 (*meta* CH), 132 (*meta* CCl), 138.5 (CN); 153 (CO). An electron ionization mass spectrum, recorded on the quadrupole instrument Trio 2000, Fisons, gave *m*/*z* 233 (M+, 100%).

This compound was the exclusive product of the reaction of 3,4-dichlorophenylisocyanate with pure ethanol.

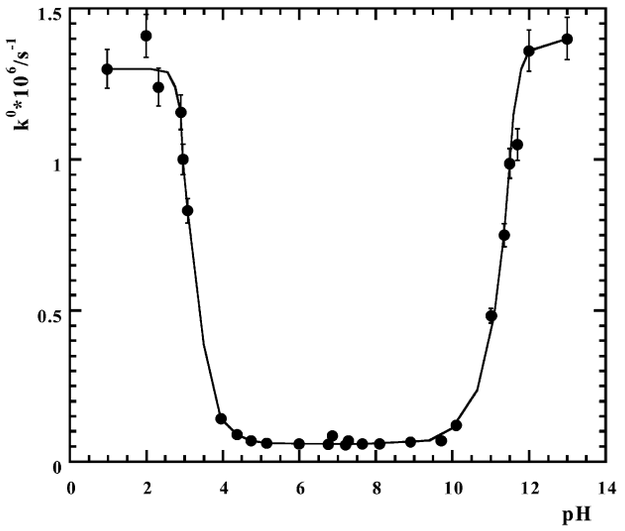

Fig. 1 pH rate profile for the degradation reaction of 3-(3,4-dichlorophenyl)-1,1-dimethylurea (diuron), at T = 60 °C and μ = 1 M (KCl). k_0 is the first-order rate constant at zero buffer concentration.

pH dependence of the reaction rate

Fig. 1 shows a plot of k_o *versus* pH for the phenylurea diuron, 3-(3,4-dichlorophenyl)-1,1-dimethylurea, where k_o is the observed first-order rate constant extrapolated to zero buffer concentration. In the pH range 5–9, the rate constant is substantially pH-independent, while at lower and higher pH values the slope of the curve markedly increases, suggesting an efficient catalysis by hydronium ion at low pH and by hydroxide ion at high pH. At extreme pH values (<2 or >12), the k_o value is again constant. The value of the pH at the inflection point ($d^2k/dpH^2 = 0$) observed at basic pH (pH = 11.5 ± 0.3) was close to, although not coincident with, the pK_a value computed for the deprotonation equilibrium of **I** at the same temperature as for the kinetic experiments and zero ionic strength (pK_a = 10.3). Similar pH–rate constant plots were observed for the other phenylureas studied in this work.

Temperature dependence of reaction rate

The Arrhenius plot for the limiting rate constants reached at high buffer concentrations is linear in the temperature range studied. The pre-exponential factor and the apparent activation parameters for **I** are respectively: ln A = 38 ± 1 s^{-1}; E_a = 127 ± 2 kJ mol^{-1}; $\Delta H^{\ddagger}$ =124 ± 2 kJ mol^{-1}; $\Delta S^{\ddagger}$ = 14 ± 8 J K^{-1} mol^{-1}.

Buffer catalysis

The observed pseudo-first-order rate constant (k_{obs}) determined at constant pH reveals a marked dependence on the buffer concentrations. For all the buffers tested the kinetic constant first increases rapidly at low buffer tested concentrations and then gradually levels off at higher concentrations, reaching a limit value that is independent of the type of buffer and its fraction of free base. The k_{obs}–buffer concentration plots for **I** at the fraction 0.6 of free base in the buffers are shown in Fig. 2. Fig. 3 shows the dependence of k_{obs} on the phosphate concentration for the hydrolysis of **I**, **II**, **III** and **IV**. The shape of the curves is the same for all the phenylureas tested. The dependence of the slopes of the k_{obs}–buffer concentration curves for **I** at zero buffer concentrations (k^{o}_{cat}), which measure the catalytic efficiency of the buffers, is shown in Fig. 4. Despite the large errors, due to the hyperbolic shape of the k_{cat}–buffer concentration curves, it is evident that, at least for some buffers, the curves do not pass through the origin of the axes at $\alpha = 0$ and at $\alpha = 1$, suggesting that both the acidic and basic forms of the buffers are catalysts of the reaction. It is interesting to note that

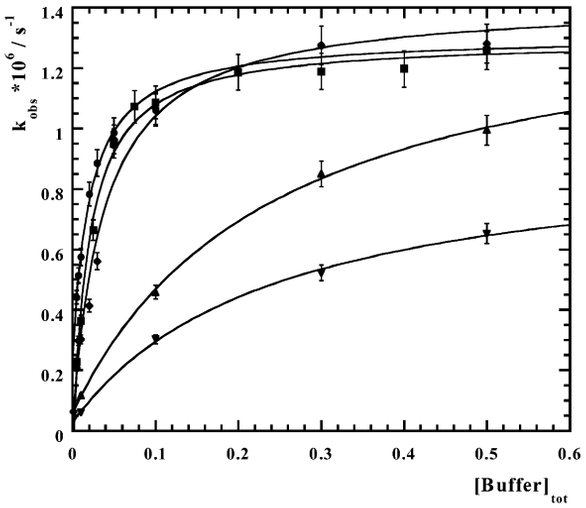

Fig. 2 Dependence of the observed first-order rate constant (k_{obs}) for the degradation reaction of 3-(3,4-dichlorophenyl)-1,1-dimethylurea on the total buffer concentration at the fraction 0.6 of free base, T = 60 °C and μ = 1 M: (●) = HCO_3^-/CO_3^{2-}, (▲) = TrisH$^+$/Tris, (▼) = 4-methylmorpholineH$^+$/4-methylmorpholine; (■) = $H_2PO_4^-/HPO_4^{2-}$, (◆) = CH_3COOH/CH_3COO^-.

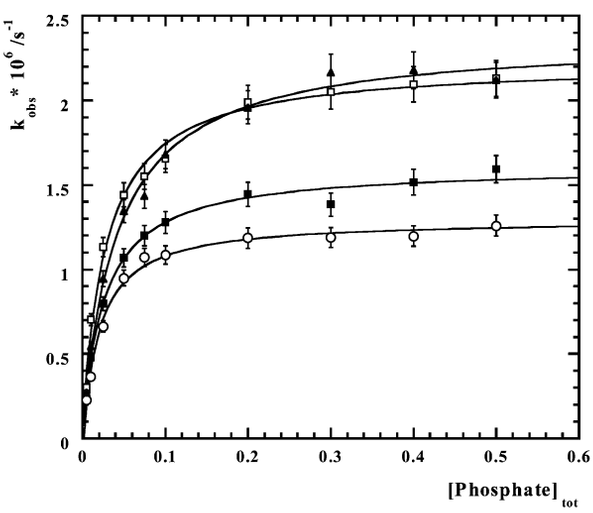

Fig. 3 Dependence of the observed first-order rate constant (k_{obs}) for the degradation reaction of 3-(3,4-dichlorophenyl)-1,1-dimethylurea (○), 3-(4-isopropylphenyl)-1,1-dimethylurea (▲), 1-butyl-3-(3,4-dichlorophenyl)-1-methylurea (□) and 3-(3-chloro-*p*-tolyl)-1,1-dimethylurea (■) on the total phosphate buffer concentration at the fraction 0.6 of free base, at T = 60 °C and μ = 1 M.

k^o_{cat} attains higher values with the buffers HCO_3^-/CO_3^{2-}, $H_2PO_4^-/HPO_4^{2-}$ and CH_3COOH/CH_3COO^- than for TrisH$^+$/Tris, suggesting that bifunctional acid–base buffers are particularly efficient catalysts. In line with this conclusion are the k_{obs}–buffer concentration plots reported in Fig. 2. Also worthy of note is the marked difference in the slope at zero buffer concentration between the bifunctional acid–base buffers CH_3COOH/CH_3COO^- and HCO_3^-/CO_3^{2-} and the monofunctional TrisH$^+$/Tris and 4-methylmorpholineH$^+$/4-methylmorpholine (the two lower curves in Fig. 2), although the pK_a values of the last two buffers are intermediate between those of the two bifunctional acid–base buffers. A more quantitative correlation of the catalytic rate constant with the pK_a of the buffers is shown in Fig. 5, the Brønsted plot. A linear relationship is usually expected in this kind of plot, which describes the relationship between the logarithm of the acid and basic ionization constants and of the second-order rate constant for the reactions subject to general acid or general base catalysis.[13]

We computed the values of k_{HA} for H_3O^+ and H_2O, pK_a = −1.7 and 15.7 respectively, by fitting the equation $k_0 = k_W[H_2O]$ + $k_{H_3O^+}[H_3O^+]$ to the k_0–pH data obtained in the pH range 3.0–6.0. The logarithm of the rate constants for the general acid catalysis, seen as a whole, does not fit a linear correlation. The data appear to fit two straight lines, one for the polyfunctional acid–base catalysts, HCO_3^-/CO_3^{2-}, $H_2PO_4^-/HPO_4^{2-}$ and CH_3COOH/CH_3COO^-, and the other for others.

Table 1 reports the k_{obs} limiting values obtained at high phosphate concentration and, for comparison, the values obtained in 0.1 M HCl and 0.1 M NaOH. For every compound the rate constant in these media had the same value within the experimental error.

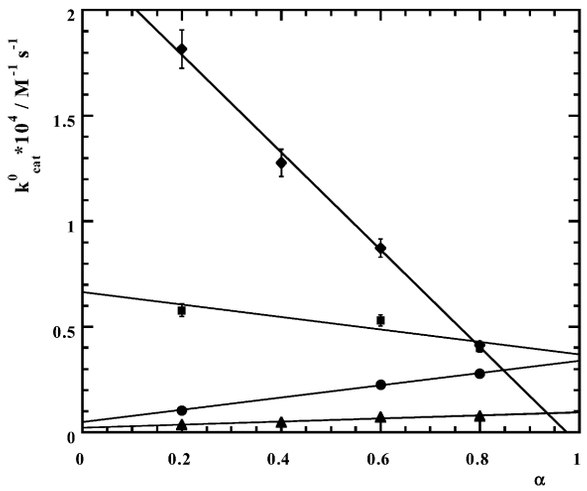

Fig. 4 Plot of the catalytic constant of the buffers at zero buffer concentration (k^0_{cat}) against the fraction (α) of the free base in the buffers for the degradation reaction of 3-(3,4-dichlorophenyl)-1,1-dimethylurea, T = 60 °C and μ = 1 M.

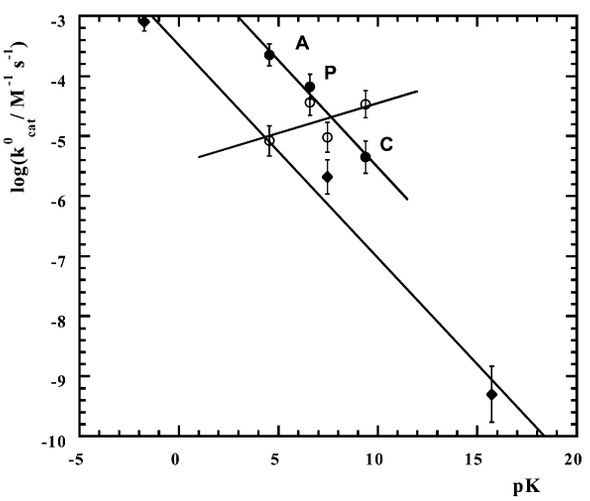

Fig. 5 Brønsted plot for the degradation reaction of 3-phenyl-1,1-dimethylureas to phenylisocyanates and dimethylamine: closed and open symbols show the second-order rate constants for the acidic and basic catalysis, respectively. The letters A, P and C mark the points for the acid catalysis of CH_3COOH/CH_3COO^-, $H_2PO_4^-/HPO_4^{2-}$ and HCO_3^-/CO_3^{2-}.

Discussion

The salient features of the kinetic behavior of phenylureas hydrolysis that are informative for the reaction mechanism can be summarized as follows:

a) hydronium and hydroxide ions and buffers are catalysts of the reaction;

b) both the acidic and basic forms of the buffers are catalysts of the reaction;

c) the nonlinear dependence of the rate constant on buffer concentrations suggests the existence of an intermediate, the

Table 1 Rate constants ($k \times 10^6/s^{-1}$) for the hydrolysis of 3-(3,4-dichlorophenyl)-1,1-dimethylurea (**I**), 3-(4-isopropylphenyl)-1,1-dimethylurea (**II**), 1-butyl-3-(3,4-dichlorophenyl)-1-methylurea (**III**), and 3-(3-chloro-*p*-tolyl)-1,1-dimethylurea (**IV**) in acidic, basic and high phosphate buffer concentration media: $T = 60$ °C, $\mu = 1$ M (KCl)

Phenylurea	HCl 0.1 M	NaOH 0.1 M	High phosphate concentration
I	1.3 ± 0.1	1.4 ± 0.1	1.3 ± 0.1
II	1.8 ± 0.1	2.0 ± 0.1	2.3 ± 0.1
III	1.9 ± 0.1	1.7 ± 0.1	2.2 ± 0.1
IV	1.8 ± 0.1	1.7 ± 0.1	1.6 ± 0.1

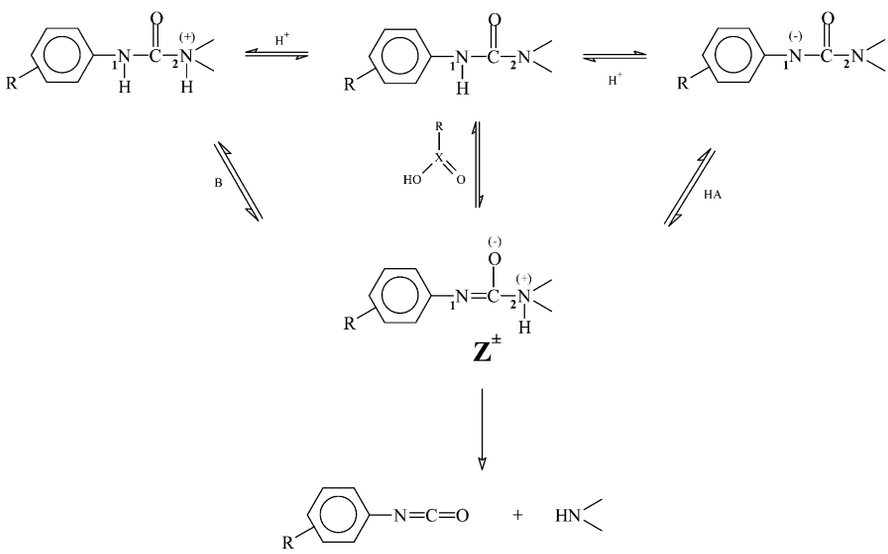

Fig. 6 Proposed mechanism for the degradation reaction of 3-phenyl-1,1-dialkylureas to phenylisocyanates and dialkylamine.

formation of which is rate determining at some catalyst concentrations, while, at others, the rate-limiting step is the conversion of the intermediate to products.[14] Moreover, the enhanced reactivity observed with the polyfunctional acid–base catalysts (HCO_3^-/CO_3^{2-}, $H_2PO_4^-/HPO_4^{2-}$ and CH_3COOH/CH_3COO^-) suggests that they take part in a proton switch step, as it is often observed in cases where such processes are involved;[15]

d) for each of the phenylureas studied we observed that the rate constant in the pH extreme regions and at high polyfunctional buffer concentration has, within the experimental errors, the same value. This is a clear indication that the hydronium and hydroxide ions, and the buffers lead to the same intermediate, whose decomposition at high catalyst concentrations is rate-limiting. Laudien and Mitzner reported[2,3] the values of the kinetic constants for about thirty phenylureas (including compounds **I** and **II**), recorded in 0.1 M H_2SO_4 and 0.1 M NaOH. Coherently with our results, the rate constant for every compound had an identical value, within the experimental errors, both in acidic and basic media;

e) the pH value at the inflection point observed at basic pH is not markedly different from the pK_a value computed for the deprotonation equilibrium of the substrate;

f) Finally, the low $|\Delta S^{\ddagger}|$ value observed for the reaction in high polyfunctional buffer concentrations ($\Delta S^{\ddagger} = 14 \pm 8$ J K^{-1} mol^{-1} for **I** in phosphate buffer) suggests that, from the starting substrate to the transition state of the rate-limiting step, there is no major change in the disorder or motional modes. It is worth noting that, for a multistep reaction in which the rate-limiting step is preceded by pre-equilibrium steps, the $\Delta S^{\ddagger}$ observed value is the sum of the activation entropy of the rate-limiting step and the entropy changes of the equilibrium steps.[16]

Reaction mechanism

A pathway for the formation of isocyanate and ammonia derivatives from phenylureas that fits the experimental data is shown in Fig. 6. Depending on pH and buffer concentrations the reaction starts by three parallel routes, each leading to the zwitterion $\mathbf{Z}^{\pm}$. At low pH and low buffer concentration the reaction proceeds through the pathway shown on the left: protonation of the dialkyl nitrogen atom $_2$N (fast equilibrium between the substrate and hydrogen ion, for **I** p$K_a = -2.5$), followed by slow deprotonation of the nitrogen atom $_1$N by the general base B. This is specific acid–general base catalysis, kinetically equivalent to general acid catalysis. At high pH the reaction proceeds (pathway on the right) prevalently through specific basic–general acid catalysis, kinetically equivalent to general base catalysis: fast reversible deprotonation of $_1$N (for **I** p$K_a = 10.3$), followed by slow protonation of $_2$N by the general acid HA. At high concentration of bifunctional acid–base buffers the reaction proceeds through a proton switch promoted by the buffers. At low catalyst concentrations (pH range 3–11 and low buffer concentrations) the formation of $\mathbf{Z}^{\pm}$ is rate-limiting, whereas at high catalyst concentrations, its degradation to the final product becomes rate-limiting, consequently the reaction rate no longer depends on pH and buffer concentration. Coherently with this mechanism, the $|\Delta S^{\ddagger}|$ value recorded at high bifunctional buffer concentrations is very low. Fig. 7 reports the proposed role for the bifunctional acetate catalysts. The acidic and basic sites act as concerted catalysts promoting the proton switch.

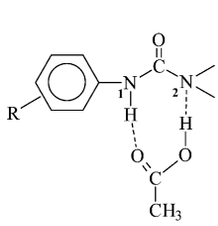

Fig. 7 Proton switch assisted by acetic acid.

In contrast to the mechanism reported here, Laudien and Mitzner ascribed the rate limiting value at high hydroxide ion

concentrations to the formation of an unreactive side product.[3] At low pH, according to these authors, the limiting value is due to the rate determining attack of a water molecule.[2] On the other hand, Sabaliûnas *et al*. hypothesized the formation of a dianion intermediate as the cause for the limiting value of the rate constant at high pH.[4]

Conclusion

The study of pH, buffer, and temperature effects on the formation of isocyanate and ammonia derivatives from phenylureas in aqueous solution has produced a detailed description of the reaction pathway. Depending on pH and buffers, the reaction starts along parallel routes, each leading to the same intermediate zwitterion. Bifunctional acid–base buffers, HCO_3^-/CO_3^{2-}, $H_2PO_4^-/HPO_4^{2-}$ and CH_3COOH/CH_3COO^-, are particularly efficient catalysts. At high buffer concentrations, as well as at pH < 3 or > 12, the breakdown of the zwitterion is rate determining. As the phenylureas are the active principles of herbicides widely used in agriculture, our results should be taken into account for the prediction of the fate of these xenobiotic compounds after their dispersal in the environment.

Acknowledgements

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References

1 (*a*) B. M. Berger, M. Müller and A. Aing, *Pest. Manag. Sci.*, 2001, **57**, 1043–1054; (*b*) B. M. Berger, *J. Agric. Food Chem.*, 1999, **47**, 3389–3396.
2 R. Laudien and R. Mitzner, *J. Chem. Soc., Perkin Trans. 2*, 2001, 2230–2232.
3 R. Laudien and R. Mitzner, *J. Chem. Soc., Perkin Trans. 2*, 2001, 2226–2229.
4 D. Sabaliûnas, J. Ellington and R. Lekevicius, *Int. J. Environ. Anal. Chem.*, 1996, **64**, 123–134.
5 C.D.S. Tomlin (ed.), *The Pesticide Manual, Eleventh Edition*, British Crop Protection Council, Farnham, 1997, pp. 443–445.
6 (*a*) C. J. Giffney and C. J. O'Connoe, *J. Chem. Soc., Perkin Trans. 2*, 1974, 362–368; (*b*) C. J. O'Connoe and J. W. Barnett, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1457–1461.
7 (*a*) A. Williams and W. P. Jencks, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1753–1749; (*b*) A. F. Hegarty and L. N Frost, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1719–1728.
8 (*a*) P. A. Ellis and N. D. Camper, *J. Environ. Sci. Health*, 1982, **B17**, 277–289; (*b*) E. Esposito, S. M. Paulillo and G. P. Manfio, *Chemosphere*, 1998, **37**, 541–548.
9 S. Salvestrini, P. Di Cerbo and S. Capasso, *Chemosphere*, 2002, **48**(1), 69–73.
10 K. A. Connors, *Chemical Kinetics: The Study of Reaction Rates in Solution*, VCH Publishers, New York, USA, 1990, pp. 187–243.
11 (*a*) L. A. Carreira, M. Rizk, Y. El-Shabrawy, N. A. Zakhari and S. Hilal, *Talanta*, 1996, **43**, 607–619; (*b*) S. Hilal, S. W. Karickhoff and L. A. Carreira, *Quant. Struct. Act. Relat.*, 1995, **14**, 348–355.
12 E. A. Castro, R. B. Moodie and P. J. Sansom, *J. Chem. Soc., Perkin Trans. 2*, 1985, 737–742.
13 A. A Frost and R. G. Pearson, *Kinetics and Mechanism*, John Wiley & Sons, Inc., New York, 1953, pp. 191–223.
14 (*a*) S. A. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, 1975, **97**, 6221–6230; (*b*) R. W. Nagorski, T. Mizerski and J. P. Richard, *J. Am. Chem. Soc.*, 1995, **120**, 4718–4719; (*c*) S. Capasso, A. Vergara and L. Mazzarella, *J. Am. Chem. Soc.*, 1998, **117**, 1990–1995.
15 (*a*) F. Hibbert, *Adv. Phys. Org: Chem.*, 1986, **22**, 113–212; (*b*) A. J. Kirby, *Adv. Phys. Org. Chem.*, 1990, **28**, 820–823.
16 N. S. Isaac, *Physical Organic Chemistry*, Longman Scientific & Technical, New York, 1992, pp. 77–113.