

Phenylureas. Part 1. Mechanism of the basic hydrolysis of phenylureas

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The mechanism of the hydrolytic decomposition of phenylureas in basic media in the pH range 12 to 14 is investigated. In this pH range a levelling of the rate–pH curve is observed as well as a change of the substituent influence on the hydrolysis rate. These experimental findings suggest the formation of an unreactive side product of the phenylurea in a parasitic side equilibrium at sufficiently high pH. The urea dissociates at the aryl–NH group to give its conjugate base. For the hydrolytic decomposition of phenylureas an addition–elimination mechanism is proposed as has been established for the alkaline hydrolysis of carboxylic acid esters and amides.

Introduction

The hydrolysis of carboxylic acid esters and amides is generally accepted to proceed according to an addition–elimination mechanism in both basic and acid media.^{1–7} In the first reaction step, the addition step, the strongly nucleophilic hydroxide ions attack the electrophilic carbon of the carbonyl group, thus forming a tetrahedral intermediate. In the second reaction step the so-called leaving group, an alcoholate and amine respectively, is eliminated. Depending on the nature of R and R', the formation of a tetrahedral intermediate is in most cases the rate-determining step of the reaction. The existence of such intermediates is believed to be the case for many reactions of carbonyl compounds proceeding by an addition–elimination mechanism.

For some carboxylic acid amides in basic media a quadratic dependence of the decomposition rate on the hydroxide ion concentration is found over a large pH range, which can be explained by the occurrence, in equilibrium, of a dinegative intermediate formed by the deprotonation of the mononegative one.⁸ The occurrence of a dianionic intermediate is observed for the hydrolysis of activated amides such as formamides,⁹ acetanilides, trifluoroacetanilides^{10–14} and acetylpyrroles as well as benzoylpyrroles,^{15,16} whereas the hydrolytic decomposition of benzamides,^{17,18} toluamides^{19,20} and simple aliphatic amides^{21–23} proceeds mainly *via* a singly charged intermediate. In the latter case especially, the strongly basic leaving group is protonated at the nitrogen before its elimination with water acting as a general acid catalyst.

The basic hydrolysis of ureas has been documented only relatively rarely in the literature up to now. Due to a quadratic dependence of decomposition rate on hydroxide ion concentration, an addition–elimination mechanism as for the activated carboxylic acid amides is postulated for the decomposition of urea²⁴ and tetramethylurea,²⁵ in the course of which a carbamic acid is formed as the primary product. The acid hydrolytic decomposition of ureas has already been discussed in detail²⁶ and will be the subject of another publication.

The centre of interest of our investigations has been the mechanism of the hydrolytic decomposition of phenylureas in basic medium (pH range around 12 to 14), which has not been

discussed until now. Mainly kinetic investigations were carried out with respect to structure–reactivity relations, specific base catalysis and deuterium solvent isotope effects.

Results and discussion

The hydrolysis of phenylureas, variably substituted both at the phenyl ring and at the nitrogen of the leaving group, was studied kinetically in basic water–methanol solutions (9 : 1) at 80 and 90 °C. The phenylureas investigated have the following basic structures.

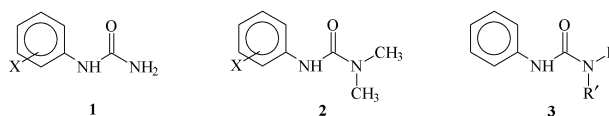


Table 1 contains pseudo first-order rate constants for the hydrolysis of these phenylureas in 0.1 M NaOH at 80 °C (k_1) and 90 °C (k_2). Furthermore, for some phenylureas rate constants for the hydrolysis in 0.01 M NaOH were determined (Table 2). In Table 3 rate constants for the hydrolysis of three phenylureas at various hydroxide ion concentrations are listed. All pseudo first-order rate constants are given in the unit s^{-1} .

The rate of hydrolysis of phenylureas is not directly proportional to the hydroxide ion concentration, but tends towards a limiting value at high hydroxide ion concentrations, as shown in the rate–pH profile for the hydrolysis of *N*-phenyl-*N*',*N*'-dimethylurea in Fig. 1. This behaviour differs from the alkaline hydrolysis of carboxylic acid esters and most carboxylic acid amides, but has been observed for the hydrolytic decomposition of some activated anilides, as for instance trifluoroacetanilide.¹⁴ The levelling of the rate–pH profile in these cases is explained by the dissociation of the anilides to unreactive conjugate bases in a parasitic side equilibrium at sufficiently high pH. The anilides are ionised at the NH proton.

Such an ionisation of the aryl–NH proton can be expected to occur in the case of phenylureas in basic solutions as well and is illustrated in Scheme 1. This shows a reaction mechanism which is in accordance with our experimental results.

In weakly basic media the hydrolysis of phenylureas presumably occurs *via* an addition–elimination mechanism in which an intermediate hydroxide ion addition complex is formed: following this mechanism water may act as a general acid and

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Table 1 Rate constants (in s⁻¹) for the hydrolysis of phenylureas in 0.1 M NaOH at 80 and 90 °C

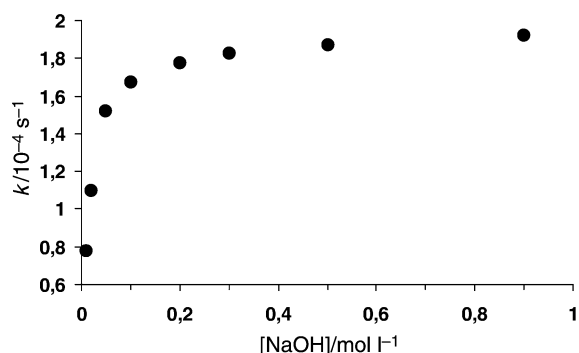
Structure 1				Structure 2				Structure 3			
No.	X	10 ⁵ k ₁	10 ⁵ k ₂	No.	X	10 ⁵ k ₁	10 ⁵ k ₂	No.	R, R'	10 ⁵ k ₁	10 ⁵ k ₂
1a	<i>m</i> -NO ₂	0.416	1.416	2a	3,4-Cl	2.858	11.00	3a	C ₄ H ₉ , H	0.326	1.075
1b	<i>m</i> -CF ₃	0.561	1.860	2b	<i>p</i> -Cl	3.308	12.57	3b	C ₂ H ₅ , H	0.362	1.338
1c	<i>m</i> -Cl	0.648	2.166	2c	3-Cl,4-OCH ₃	3.346	12.54	3c	CH(CH ₃) ₂ , H	0.509	1.728
1d	<i>p</i> -Cl	0.666	2.190	2d	3-Cl,4-CH ₃	3.634	13.09	3d	CH ₂ CH(CH ₃) ₂	1.279	3.500
1e	H	0.746	2.508	2e	<i>p</i> -OC ₆ H ₄ Cl	3.642	12.90	2f	H	4.227	15.16
1f	<i>m</i> -C ₂ H ₅	0.834	2.656	2f	H	4.227	15.16	3e	-C ₅ H ₁₀ ^a	6.437	21.12
1g	<i>p</i> -N(CH ₃) ₂	0.906	2.737	2g	<i>p</i> -CH(CH ₃) ₂	4.757	16.34	3f	C ₃ H ₇	10.56	32.26
1h	<i>p</i> -C ₂ H ₅	0.855	2.905					3g	C ₄ H ₉	13.68	41.84
1i	3,4-OCH ₃	1.010	3.217					3h	C ₂ H ₅	14.76	49.15
1k	<i>p</i> -CH ₃	0.895	2.871					3i	CH(CH ₃)C ₂ H ₅	22.92	57.98
1l	<i>p</i> -OCH ₃	0.913	2.990					3k	CH(CH ₃) ₂	129.9	46.60 ^b
1m	2,5-OCH ₃	0.983	3.200								
1n	<i>o</i> -OCH ₃	1.118	3.482								

^a Piperidino. ^b Rate constant at 70 °C.**Table 2** Rate constants (in s⁻¹) for the hydrolysis of phenylureas in 0.01 M NaOH at 90 °C

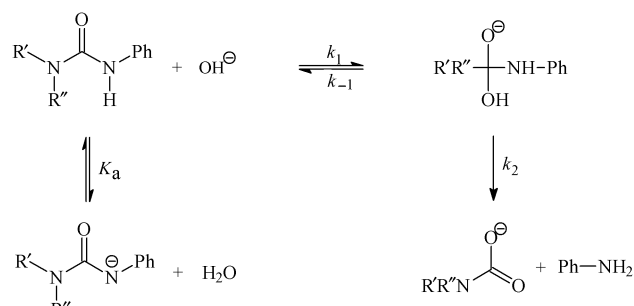
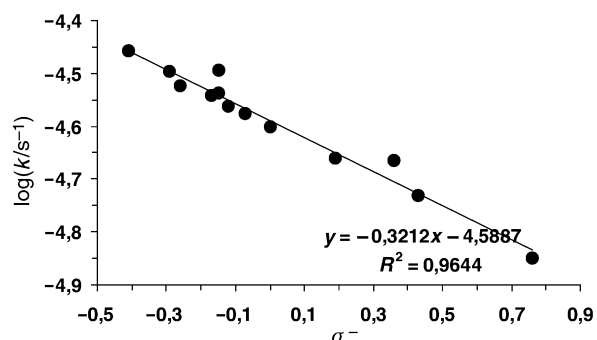
Structure 1			Structure 2		
No.	X	10 ⁵ k	No.	X	10 ⁵ k
1a	<i>m</i> -NO ₂	1.893	2a	3,4-Cl	5.315
1b	<i>m</i> -CF ₃	1.878	2b	<i>p</i> -Cl	6.173
1c	<i>m</i> -Cl	1.916	2c	3-Cl,4-OCH ₃	6.037
1d	<i>p</i> -Cl	1.855	2d	3-Cl, 4-CH ₃	6.320
1e	H	1.820	2e	<i>p</i> -OC ₆ H ₄ Cl	5.578
1f	<i>m</i> -C ₂ H ₅	1.812	2f	H	7.195
1g	<i>p</i> -N(CH ₃) ₂	1.787	2g	<i>p</i> -CH(CH ₃) ₂	7.257
1h	<i>p</i> -C ₂ H ₅	1.836			
1k	<i>p</i> -CH ₃	1.786			
1l	<i>p</i> -OCH ₃	1.630			

Table 3 Rate constants (in s⁻¹) for the hydrolysis of phenylureas at various NaOH concentrations

[NaOH]/mol l ⁻¹	1e, 90 °C, 10 ⁵ k	2f, 90 °C, 10 ⁴ k	3k, 70 °C, 10 ⁴ k
0.005	1.621		
0.01	1.841	0.780	1.927
0.02	2.005	1.101	2.993
0.05	2.224	1.518	4.362
0.1	2.431	1.672	5.202
0.2	2.662	1.775	5.722
0.3	2.827	1.827	5.882
0.5	3.023	1.875	5.945
0.9		1.922	5.978

**Fig. 1** Plot of experimental rate constant *versus* pH for the hydrolysis of *N*-phenyl-*N'*,*N'*-dimethylurea at 90 °C.

protonate the leaving group to facilitate its elimination. In stronger alkaline media the formation of the conjugate base of phenylurea caused by a deprotonation of the aryl-NH group through hydroxide ions gains in significance. This conjugate

**Scheme 1****Fig. 2** Hammett plot for the hydrolysis of substituted *N*-phenylureas in 0.1 M NaOH at 90 °C.

base is inactive towards hydrolysis, as the resonance in the anion increases the double bond character of the C–N bond compared to that in the urea and thereby stabilizes it against cleavage. Besides, the increased electron density impedes the attack of the hydroxide ions at the carbonyl carbon to form the intermediate tetrahedral complex.

In the case of phenylureas both the alkylamine and the arylamine can be considered to be the leaving group. However, it seems very likely that under basic conditions the less basic arylamine is a much better leaving group. The detection of anilines as reaction products by HPLC is important evidence for that assumption. Several authors^{24,25,27} reported that the carbamic acid formed after expulsion of the amine leaving group is a stable compound in basic and neutral solutions, whereas in acidic solutions immediate decomposition to the corresponding amine and carbon dioxide occurs. Consequently, were the alkylamine to be eliminated from the intermediate tetrahedral complex a stable phenylcarbamic acid should be formed and no aniline detected. This is clearly not the case; instead, the arylamine is subject to expulsion under formation of the corresponding alkylcarbamic acid.

A Hammett plot for the hydrolysis of substituted *N*-phenylureas in 0.1 M NaOH at 90 °C (Fig. 2) results in a small negative reaction constant ρ of -0.32 ($R^2 = 0.964$). A similar reaction constant of -0.26 ($R^2 = 0.988$) is obtained for the hydrolysis of substituted *N*-phenyl-*N',N'*-dimethylureas at 90 °C. The values for the rate data at 80 °C are -0.35 ($R^2 = 0.960$) and -0.34 ($R^2 = 0.987$), respectively. In the Hammett plots the Hammett constant σ^- was applied because of the direct resonance interaction between the $-M$ substituents and the $+M$ reaction center leading to an increased stabilisation of the negative charge at the reaction centre.

That is, the rate of the hydrolysis of phenylureas in 0.1 M NaOH is increased by electron-donating substituents and decreased by electron-attracting substituents on the aryl group. The dependence of the experimental hydrolysis rate on the hydroxide ion concentration according to Fig. 1 suggests that in 0.1 M NaOH the hydrolytically inactive conjugate base of the urea has already formed in appreciable amounts. The ionisation of the aryl-NH proton to form the base is facilitated by electron-attracting substituents, thus the side equilibrium between the urea and its conjugated base is shifted to the latter inactive species by such substituents. Consequently, less of the reactive substrate is available for the nucleophilic attack of hydroxide ions at the carbonyl carbon leading to a deceleration of hydrolysis. Electron-donating substituents, however, impede the deprotonation of the aryl-NH group and thus the formation of the unreactive conjugate base and lead to an acceleration of the hydrolytic decomposition.

In a similar manner the hydrolysis rate is influenced by the substituents at the alkylamine group. For the hydrolysis of phenylureas with the basic structure **3** in 0.1 M NaOH at 90 °C a plot of the reaction rate *versus* the basicity of the amine leaving group results in the following rough linear relation [eqn. (1)].

$$\log k = 3.68 \text{ p}K_a(\text{amine}) + 44.0 \quad R^2 = 0.851 \quad (1)$$

The high positive slope indicates that the hydrolysis of the investigated phenylureas is appreciably accelerated with increasing basicity of the alkylamine. As with electron-donating groups on the phenyl ring, stronger basic alkylamine groups impede the deprotonation of the aryl-NH group.

In 0.01 M NaOH the substituents on the aryl group are found to hardly influence the hydrolysis rate of the phenylureas. In the case of *N*-phenylureas a reaction constant ρ of 0.03 is found. That indicates a changeover of the substituent influence on the rate of the alkaline hydrolytic urea decomposition with decreasing concentration of the base. In weakly basic media the side equilibrium between the phenylurea and its conjugated base does not play a decisive role in determining the reaction course, the unionised substrate is nearly completely available for hydrolytic attack.

It is reasonable to assume that the hydrolysis occurs *via* an addition-elimination mechanism through an intermediate tetrahedral addition complex, eventually *via* a dinegatively charged complex too, as proposed for the alkaline hydrolytic decomposition of many carboxylic amides and of urea and tetramethylurea. In the case of rate-determining attack by hydroxide ions at the carbonyl carbon, electron-withdrawing substituents on the phenyl ring would accelerate the hydrolytic decomposition since they reduce the electron density in the molecule. Our investigations suggest a change to such a substituent influence in weaker alkaline media. However, the experimental data do not clearly exclude other possible reaction mechanisms. Extended kinetic investigations in buffered solutions of lower basicity are necessary to be certain about the hydrolytic decomposition mechanism of phenylureas in the low basic pH range.

For the hydrolysis of **1e** and **2f**, deuterium solvent isotope effects have been determined in 0.1 M NaOD at 90 °C. For **1e**

k_H/k_D is 1.21, for **2f** 0.99. As the rate constants are affected by an error rate of *ca.* 3%, an uncertainty of 6% maximum results for the isotope effects. Because of these low isotope effects, a proton transfer from or to water in a rate-determining step in the reaction course can be excluded. This is evidence for considering the addition step of the hydrolysis reaction to be the rate-determining step, and not the elimination step probably supported by a proton transfer from water to the aniline leaving group. However, it is not possible to draw any more detailed conclusions from k_H/k_D values of around 1, because isotope effects are generally influenced by more, partly compensating factors.⁸

Experimental

Preparations

(a) **Basic structure 1.** Potassium cyanate, dissolved in 10% acetic acid, was added to an equimolar amount of aniline, kept in water as a concentrated solution or suspension, at room temperature. A gas was formed (CO₂ in a side reaction) and the urea precipitated as a solid. It was recrystallised from water. Yield around 90%.

(b) **Basic structures 2 and 3.** Phenyl isocyanate was added to an equimolar amount of amine at 70 to 80 °C, both substances dissolved in toluene. The precipitating urea was recrystallised from a chloroform-hexane mixture (3 : 1). Yield around 70%.

All starting materials, which could be purchased from Aldrich, were applied without further purification. Identity and purity of the prepared compounds were established by ¹H-NMR and mass spectroscopic measurements.

Kinetics

Rate constants were measured by means of UV spectroscopy in a water-methanol mixture (9 : 1) on a UV-VIS Lambda 2 spectrophotometer from Perkin Elmer, using 1 cm pathlength quartz cuvettes. The concentration of the phenylureas was *ca.* 10⁻⁴ mol l⁻¹. The reaction mixture was thermostated for 5 to 10 minutes prior to recording the reaction course. The occurrence of isosbestic points in the UV spectra indicated the absence of long-lived intermediates. The hydrolysis reactions were observed for 2 to 3 half-change values, depending on the reaction time. The rate constants of the pseudo first-order reactions were determined from the slope of a plot of $\ln(E - E_\infty)$ against time, where E is the extinction of the urea in solution at λ_{max} of urea.

Product analysis

After definite time intervals the reaction mixtures were separated by high performance liquid chromatography (HPLC) for detection of reaction products and stable intermediates. An HPLC device with an RP column Eurospher C-18 and a UV detector from Knauer was used. The reaction mixture was detected at the λ_{max} of the respective phenyl urea; some mixtures were analysed at additional wavelengths. The respective substituted anilines were detected as reaction products, but stable intermediates were not found.

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