PERKIN 2

Phenylureas. Part 2.[1] Mechanism of the acid hydrolysis of phenylureas

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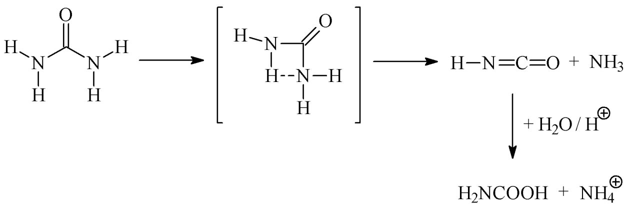
Received (in Cambridge, UK) 23rd October 2000, Accepted 27th July 2001

The mechanism of the hydrolytic decomposition of phenylureas in acid media is investigated. It includes, in part, knowledge already present in the literature. Over the investigated pH range the occurrence of a rate maximum in the pH curves due to the strongly reduced water activity at higher acid strengths is observed. An addition–elimination mechanism with rate-determining attack of water at the *N*-protonated substrate is proposed. The reversion of the substituent influence on the reaction rate with increasing acidity of the reaction medium points to a change of the hydrolytic decomposition mechanism in strongly acidic media.

Introduction

The hydrolysis of carboxylic acid esters and amides in acid media mainly proceeds according to an addition–elimination mechanism.[2–8] The carbonyl oxygen of the substrate is protonated in a preequilibrium, by which the electrophilicity of the carbonyl carbon is increased and, consequently, the nucleophilic attack of water is facilitated thereby forming a short-lived tetrahedral intermediate. In the case of carboxylic acid amides, protonation of the nitrogen is considered already to proceed in moderately acid solutions along with the protonation of the carbonyl oxygen. This can be deduced from theoretical considerations of the difference in the pK_a values of *O*- and *N*-protonated amides.[9,10]

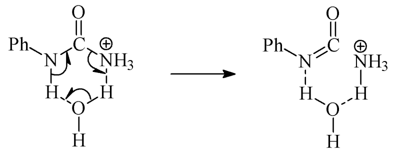
For the acid hydrolysis of alkylureas in solutions of low and medium acidity an elimination–addition mechanism *via* isocyanate is postulated. The decomposition of urea in weakly acid media proceeds without acid catalysis *via* a rate-determining intramolecular proton transfer and subsequent dissociation of the transition state[11,12] (Scheme 1). The reaction is decelerated with increasing acid content in media of low acidity due to a reduction in the concentration of the more reactive unprotonated urea species.[13] In high acidity ranges of the acid (*ca.* 70% w/w H_2SO_4), however, a maximum in the rate constant occurs, which is attributed to a changed reaction course—bimolecular attack of water at the diprotonated urea species.[14] The existence of such a species could be established for urea[15,16] and several substituted methylureas[17] in strongly acid solutions by ^{1}H- and ^{15}N-NMR spectroscopic investigations.



Scheme 1

Kallies and Mitzner[18] deduce from quantum-mechanical calculations that the protonation of the carbonyl oxygen of acyl compounds leads to an increase of resonance at the reaction centre in addition to the catalytically acting rise of electrophilicity of the carbonyl carbon. The increase of the resonance is due to the stronger involvement of the non-bonding electrons of the alcoholic oxygen with the aminic nitrogen, which has to be cancelled in the case of addition of a nucleophile. This negative catalytic effect towards a nucleophilic attack at the carbonyl group increases in the order ester, amide, urea because of the increasing resonance stabilization of the *O*-protonated substrate and can account for the change to an elimination–addition mechanism for the acid hydrolytic decomposition of ureas in contrast to esters and amides.

According to Giffney and O'Connor,[19,20] for phenylureas the elimination of the amine from the unprotonated or *N*-protonated urea is promoted by an intermolecular proton transfer *via* water (Scheme 2). An *N*-protonation besides the *O*-protonation is already considered to be possible in relatively weakly acid solutions. The existence of a six-membered cyclic complex between the *N*-protonated urea and water, however, could not be confirmed through quantum-mechanical calculations by Lee and co-workers.[21]



Scheme 2

The aim of the present investigations was to reexamine the mechanism of the acid hydrolysis of phenylureas. Mainly kinetic investigations were carried out with respect to structure–reactivity relations, specific acid catalysis and deuterium solvent isotope effects, the experimental results of Giffney and O'Connor[19,20] being in part included in the discussion.

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 acidic water–methanol solutions (9 : 1) at

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DOI: 10.1039/b008535i

Table 1 Rate constants (in s^{-1}) for the hydrolysis of phenylureas in 0.1 M H_2SO_4 at 80 and 90 °C

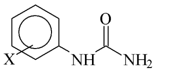
Structure **1**				Structure **2**				Structure **3**			
No.	X	$10^5 k_1$	$10^5 k_2$	No.	X	$10^5 k_1$	$10^5 k_2$	No.	R, R′	$10^5 k_1$	$10^5 k_2$
1a	*m*-NO_2	0.490	1.745	**2a**	3,4-Cl	2.732	9.555	**3a**	C_4H_9, H	0.272	1.077
1b	*m*-CF_3	0.659	2.025	**2b**	*p*-Cl	3.362	12.27	**3b**	C_2H_5, H	0.296	1.191
1c	*m*-Cl	0.653	2.178	**2c**	3-Cl, 4-OCH_3	3.556	11.91	**3c**	$CH(CH_3)_2$, H	0.478	1.862
1d	*p*-Cl	0.689	2.358	**2d**	3-Cl, 4-CH_3	3.615	13.20	**3d**	$CH(CH_3)_2$	7.212	24.84
1e	*m*-OH	0.821	2.524	**2e**	*p*-OC_6H_4Cl	3.391	13.47	**2f**	H	4.149	15.66
1f	H	0.881	2.854	**2f**	H	4.149	15.66	**3e**	$-C_5H_{10}-$[b]	6.397	22.92
1g	3,4-OCH_3	0.988	3.256	**2g**	*p*-$CH(CH_3)_2$	4.758	17.04	**3f**	C_3H_7	11.30	38.24
1h	$-OCH_2O-$[a]	0.960	3.136					**3g**	C_4H_9	15.30	56.08
1i	*p*-CH_3	0.970	3.191					**3h**	C_2H_5	15.76	58.00
1k	*p*-OCH_3	1.009	3.051					**3i**	$CH(CH_3)C_2H_5$	52.64	173.6
1l	2,5-OCH_3	1.192	3.728					**3k**	$CH(CH_3)_2$	207.9	63.09[c]
1m	*o*-OCH_3	1.381	4.341								

[a] 3,4-Methylenedioxy. [b] Piperidino. [c] Rate constant at 70 °C.

Table 2 Rate constants (in s^{-1}) for the hydrolysis of phenylureas at various H_2SO_4 concentrations

$[H_2SO_4]$/mol l^{-1}	**1f**, 90 °C, $10^5 k$	**2f**, 90 °C, $10^4 k$	**3k**, 80 °C, $10^3 k$
0.001	1.716	0.746	0.678
0.002			0.912
0.005	1.998	1.292	1.356
0.01	2.211	1.519	1.650
0.02	2.431	1.627	1.869
0.05	2.772	1.720	2.023
0.1	3.234	1.747	2.053
0.2	3.934	1.730	1.996
0.3	4.405	1.690	
0.5	5.028	1.632	1.730
0.9	5.651	1.440	

80 and 90 °C. The investigated phenylureas have the following basic structures.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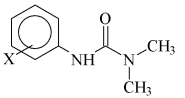
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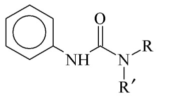
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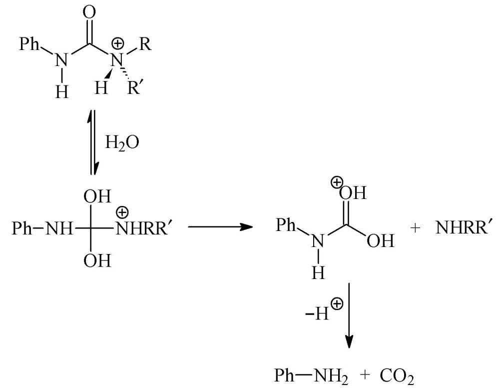
Table 1 contains pseudo first-order rate constants for the hydrolysis of the phenylureas in 0.1 M H_2SO_4 at 80 °C (k_1) and 90 °C (k_2). In Table 2 rate constants for the hydrolysis of three phenylureas at various hydronium ion concentrations are listed. All pseudo first-order rate constants are given in the unit s^{-1}.

The rate of hydrolysis of phenylureas is not directly proportional to the hydronium ion concentration, but rises with the acid strength only in solutions of low acidity, whereas it passes through a maximum and decreases again in stronger acid solutions in accordance with the results of Giffney and O'Connor.[19,20] This result clearly indicates the importance for the reaction course of water activity, which is appreciably reduced at relatively high concentrations of sulfuric acid.

A possible reaction mechanism is shown in Scheme 3. In the course of the hydrolytic decomposition the substrate is first protonated followed by a rate-determining attack by water. The tetrahedral intermediate then decomposes to an amine and a phenylcarbamic acid which again is decarboxylated very quickly under acidic conditions to form the corresponding aniline.

A Hammett plot for the hydrolysis of substituted *N*-phenylureas in 0.1 M H_2SO_4 at 90 °C (Fig. 1) results in a small negative reaction constant ρ of −0.33 ($R^2 = 0.952$). A similar reaction constant of −0.38 ($R^2 = 0.972$) 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 −0.36 ($R^2 = 0.962$) and −0.34 ($R^2 = 0.961$), 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 H_2SO_4 is increased by electron-donating substituents and decreased by electron-attracting substituents on the aryl group. Electron-donating substituents increase the electron density in the molecule and thus facilitate the protonation of the nitrogen of the alkylamine group which greatly supports the nucleophilic attack of water at the carbonyl carbon.



Scheme 3

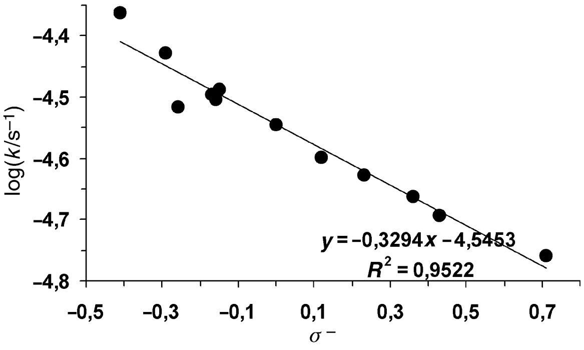


Fig. 1 Hammett plot for the hydrolysis of substituted *N*-phenylureas in 0.1 M H_2SO_4 at 90 °C.

In a similar manner the dependence of the hydrolysis rate on the basicity of the aminic leaving group can be interpreted. The hydrolysis rate basically increases with rising basicity of the amine leaving group. Stronger basic alkylamine groups facilitate the protonation of the alkyl–NH group.

According to the data of Giffney and O'Connor,[19,20] the influence of the substituents at the phenyl ring on the hydrolysis rate changes with increasing acidity of the reaction medium.

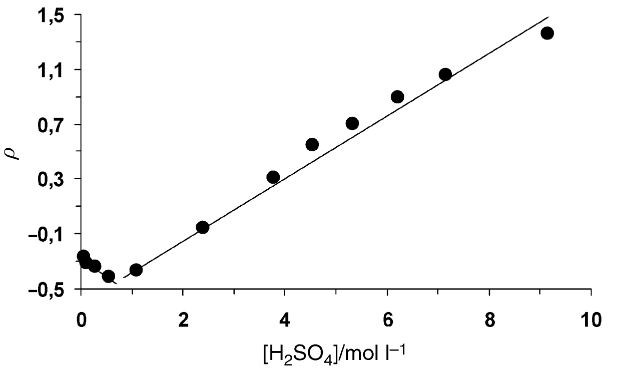
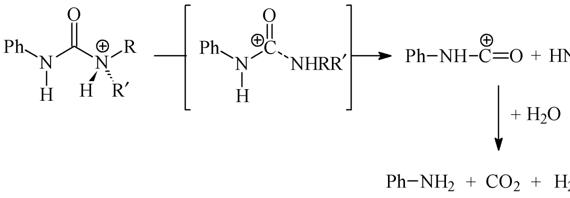


Fig. 2 Plot of reaction constants ρ *versus* H_2SO_4 concentration for the hydrolysis of substituted *N*-phenylureas at 101 °C (data from ref. 19 and 20).

Giffney and O'Connor measured the hydrolysis rates of *N*-phenylureas, variably substituted at the phenyl ring, at various sulfuric acid concentrations in the range 0.058 to 9.15 mol l^{-1} at 101 °C. Hammett plots of these data show that the substituent influence, as above, is found only up to a concentration of around 1 mol l^{-1}, while it is reversed in increasingly acidic solutions. From a concentration of around 4 mol l^{-1} the reaction constant remains positive over the whole substituent range. The changing dependence of the reaction constant ρ on the sulfuric acid concentration for the hydrolysis of substituted *N*-phenylureas is shown in Fig. 2.

This change of the substituent influence on the hydrolysis rate with increasing acid strength points to a changed reaction mechanism which is clearly due to the reduced water activity in high acidity ranges. This new mechanism is very likely to be an A1 mechanism as shown in Scheme 4 in which the aminic leaving group is eliminated without prior formation of a tetrahedral addition complex with water.



Scheme 4

For the hydrolysis of **1f** and **2f**, deuterium solvent isotope effects have been determined. For **1f** k_H/k_D is 1.15, for **2f** 0.98. 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.

Experimental

For experimental details see Part 1 of this series.[1]

Acknowledgements

This work was supported by the Innovationskolleg INK 16/A1-1 of the Deutsche Forschungsgemeinschaft.

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