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Acidity effect on the cleavage of ether function intramolecularly assisted by the amide group. Part 5[☆]

Antonio Arcelli,* Romina Cecchi, Gianni Porzi,* Samuele Rinaldi and Sergio Sandri

Dipartimento di Chimica 'G. Ciamician' Via Selmi 2, Università di Bologna, Bologna, Italy

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Abstract—The rate dependence on both the acidity and the temperature of the hydrolysis of *N*-(methoxyprop-2-yl)benzanilide (**1**), assisted by vicinal amide function, was investigated and the thermodynamic activation parameters were calculated. The rate constant of the first step of the overall process increases when the acidity is raised, while the second step is slowed down. The negative value of $\Delta S^{\neq}$ ($-100.9\ \mathrm{J\ mol^{-1}\ K^{-1}}$) measured for the second step suggests the participation of water in the transition state. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

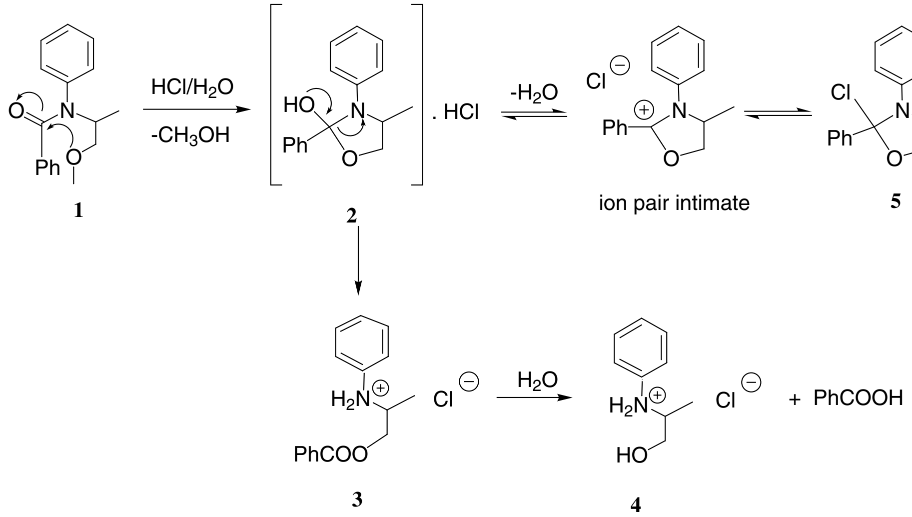
In continuation of our program aimed at the investigation of the acid ether cleavage anchimerically assisted by an amide function,[1–3] we recently focused our attention on substrate **1** in which the participating amide group is lost at the end of the reaction.[4] We demonstrated that the overall process evolves through three consecutive reactions involving two intermediates (**2**, **3**), as shown in the following Scheme 1.

In this report we wish to present further results of kinetic studies directed at the investigation of the influence of acidity on the hydrolysis of substrate **1** and the estimation of thermodynamic activation parameters aimed at improving the understanding of the complex reaction mechanism.

2. Results and discussion

2.1. Kinetic studies

Previously, we described[4] the hydrolysis of substrate **1** only



Scheme 1.

[☆] See Refs. 1–4.

Keywords: amides; cleavage reactions; ethers; kinetics; neighbouring group effect.

* Corresponding authors. Tel.: +39-051-20-99-512; fax: +39-051-20-99-574; e-mail: porzi@ciam.unibo.it

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Table 1. Rate constants measured by UV at 75.1°C at various HCl concentrations

Rate constants[a,b]	[HCl]/M					
	4.88	6.3	7.44	8.1	8.84	10.05
$k_{obs}\times10^4$ (s^{-1})	0.7±0.02 31.3±0.1	2.1±0.01 19.6±0.2	3.68±0.02 9.6±0.03	4.71±0.02 5.41±0.04	6.69±0.07 3.39±0.08	9.59±0.03 0.88±0.02

[a] Calculated by means of Eq. (1) (see Ref. 4).

[b] Estimated standard errors with ±95% confidence interval are reported.

at 8.84 M HCl and we observed that the reaction involves the opening of the intermediate 2-hydroxyoxazolidine derivative (**2**) giving the final amino alcohol (**4**), contrary to that previously observed for similar substrates.[1–3] Thus, in order to shed more light on this complex process, we have extended the kinetic investigation in a wide range of acidity (4.88–10.05 M HCl) and at various temperatures (Tables 1 and 2).

The kinetic measurements were performed by monitoring the change of the absorbance (O.D.) spectrophotometrically at $\lambda=260$ nm. The absorbance initially increases then decreases, showing the typical behaviour of a process formed by two consecutive first order reactions.[4] Since by UV techniques the overall hydrolytic process appears as a two-step system, the third step being undetectable,[4] for each HCl concentration investigated, a pair of first order rate constants have been found, but, as we are aware, in a consecutive reaction process it is difficult to assign the sequence of the rate constants.[5,6] An inspection of the rate constants obtained at 75.1°C (Table 1) and computed by the best fitting of the kinetic data to the appropriate equation[4] highlights that, at 8.1 M HCl the two rate constants are very similar, while at both lower and higher HCl concentrations they are different.

By the ^{1}H NMR method we showed[4] that in 8.84 M DCl the first step of the hydrolytic process (i.e. the cyclization of **1**) is faster ($k_1=8.9\times10^{-4}$ s^{-1}) than the decomposition step of the cyclic intermediate ($k_2=3.5\times10^{-4}$ s^{-1}). Therefore, in order to assign the kinetic constants to the individual steps at acidity below 8.1 M HCl, kinetic measurements in 6.3 M DCl at 75.1°C were followed both by UV and ^{1}H NMR methods.[4] The percent molar concentration–time curves (Fig. 1) were fitted well by the appropriate equations[4] which describe a consecutive irreversible three-step process **1**→**2**→**3**→**4**, the rate constants being $k_1=(4.9\pm0.1)\times10^{-4}$ s^{-1}, $k_2=(8.8\pm0.3)\times10^{-4}$ s^{-1} and $k_3=(3.1\pm0.05)\times10^{-4}$ s^{-1}, respectively.

Table 2. Rate constants measured by UV at 6.3 and 8.84 M HCl at various temperatures

T (°C)	$k_{obs}\times10^4$ (s^{-1})[a,b]			
	6.3 M HCl		8.84 M HCl	
	k_1 of **1**→**2**	k_2 of **2**→**3**	k_1 of **1**→**2**	k_2 of **2**→**3**
71.8	1.3±0.02	17.8±0.3	4.19±0.04	2.56±0.03
75.1	2.1±0.01 5.1±0.01[c]	19.6±0.2 8.85±0.08[c]	6.69±0.07 10.9±0.09[c,d]	3.39±0.08 1.7±0.01[c,d]
79.5	3.23±0.02	28.9±0.3	9.21±0.1	4.89±0.07
85.0	5.69±0.02	45.5±0.45	17.1±0.2	7.47±0.03
91.6	12.4±0.06	81±0.75	34±0.2	12.3±0.06

[a] Calculated by means of Eq. (1) (see Ref. 4).

[b] Estimated standard error with ±95% confidence interval is reported.

[c] Measured in DCl.

[d] Taken from Ref. 4.

Both the rate constants determined spectrophotometrically (Table 2) are in good agreement with k_1 and k_2 calculated by ^{1}H NMR data but, conversely to that previously observed in 8.84 M DCl,[4] the cyclization step of **1** occurs more slowly than the decomposition of intermediate **2**.

These results allow us to deduce that at HCl<8.1 M the second step (i.e. **2**→**3**) is faster than the first one (i.e. **1**→**2**), while at HCl>8.1 M, the rate constants are reversed. The assignment of the individual rate constants to the two reaction steps is consistent with the measured kinetic deuterium isotope effects, which show very close values at different acidities. In fact, for the first step (i.e. the cyclization of **1**) at 6.3 M HCl k_1(H)/k_1(D) is 0.4 and 0.6 at 8.84 M HCl, while for the second step (i.e. the decomposition of intermediate **2**) the ratio k_2(H)/k_2(D) is 2.2 and 2, respectively. Since the first step is a hydrogen ion catalysed reaction involving a rapid pre-equilibrium protonation of substrate **1** and the proton remains unaltered during the reaction, the kinetic deuterium isotope effect k_1(H)/k_1(D) will be prevalently determined by the ratio K_{SD+}/K_{SH+} which generally ranges between 0.3 and 0.5.[7a,8] Then, the magnitude of the isotope effect values found for the step **1**→**2** is in good agreement with a secondary isotope effect, typical for specific hydrogen ion catalysed reactions.[7a,8] A similar value (0.72 in 6.35 M HCl at 57.8°C) was previously obtained for the cyclization of *N*-(2-ethyl-6-methyl)-*N*-(methoxyprop-2-yl)acetamide which represents the rate

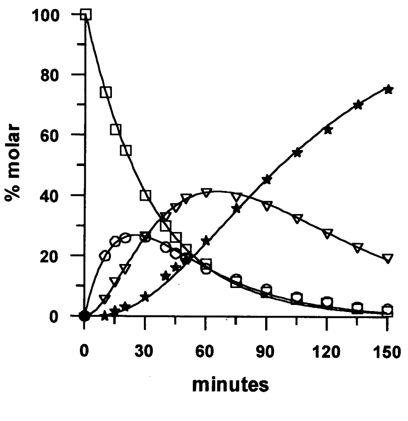

Figure 1. Plots of %molar concentrations (evaluated by ^{1}H NMR vs time for: hydrolysis of **1** (□), formation and deposition of **2** (○) and **3** (▽) and formation of **4** (★). Kinetics have been performed in 6.3 M DCl/D$_2$O at 75.1°C. The points are experimental and the curves are calculated from a least square fit to equations reported in Ref. 4.

Table 3. Thermodynamic activation parameters for **1**→**2** and **2**→**3** steps at both 6.3 and 8.84 M HCl

Calculated at 50°C	At 6.3 M HCl		At 8.84 M HCl	
	For step **1**→**2**	For step **2**→**3**	For step **1**→**2**	For step **2**→**3**
$\Delta G^{\neq a}$ (kJ mol^{-1})	115.4±4.6	106.6±6.3	112.9±5.7	112.7±2.5
$\Delta H^{\neq b}$ (kJ mol^{-1})	113.3±3.3	79.9±5	105.6±4.2	80.1±1.2
$\Delta S^{\neq}$ (J mol^{-1} K^{-1})	−6.3±8.4	−82.8±14.6	−22.7±11.9	−100.9±1.2
$T\Delta S^{\neq}$ (kJ mol^{-1})	−2.1±2.9	−26.7±4.6	−7.3±3.8	−32.6±0.4

Obtained from $k_{H+}=k_{obs}/[H^+]$; calculated at 50°C from the equation $\ln k_{H+} = \Delta S^{\neq}/R + \ln (kT/h) - E_a/RT$ plotting $\ln k_{H+}$ vs $1/T$ by means of a linear least square; standard errors are calculated according to Ref. 12.

[a] Calculated at 50°C from $\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$.

[b] Calculated at 50°C from the equation $\Delta H^{\neq} = E_a - RT$.

determining step of the hydrolytic process.[1] The magnitude of the isotope effect values found for the second step, the decomposition of **2** into **3**, could be consistent with a primary isotope effect, the breaking of the O–H bond being involved. The unfavourable activation entropy of −82.8 and −100.9 J mol^{-1} K^{-1} at 6.3 and 8.84 M HCl, respectively (Table 3), may be consistent with the participation of the water that should act by proton transfer from the –OH group to the nitrogen atom giving rise to a cyclic six member transition state (Fig. 2).

The plots in Fig. 3 show that the rate constant (k_2) for the opening of intermediate **2** is more sensitive to the acidity than that (k_1) of the cyclization of **1**. While the non linear increase of the rate constant measured for the first step with the acidity agrees with the Eq. (1) previously reported,[3] the reason for the rate decrease observed for the second step appears less easy to explain. Tentatively, a reasonable interpretation could be based on the existence of a rapid equilibrium between **2** and **5** that is shifted to the right when the acidity increases and therefore the formation of the aminoester **3** will be much slowed down (Scheme 1). ^{1}H NMR spectra performed at different acidities have not provided evidence for the zwitter-ionic species: in fact, in 8.84 M DCl all the signals suffer the same up-field shift (about 0.56 ppm), as compared to those recorded in 6.3 M DCl, and this effect is ascribable to the variation of the magnetic permeability of medium. However, it cannot be excluded that by increasing the acidity of the reaction medium, the formation of **5** across the intimate ion pair (probably present in very low concentration) might become important. Then, across the 'internal return'[9,10] the chloroderivative **5** should be in rapid equilibrium with the intimate ion-pair and the reactive species (i.e. the cyclic intermediate **2**) would be removed from the reaction.

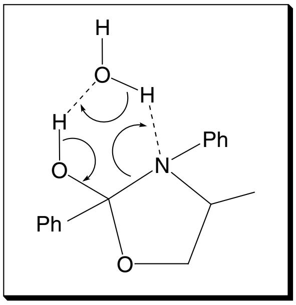

Figure 2.

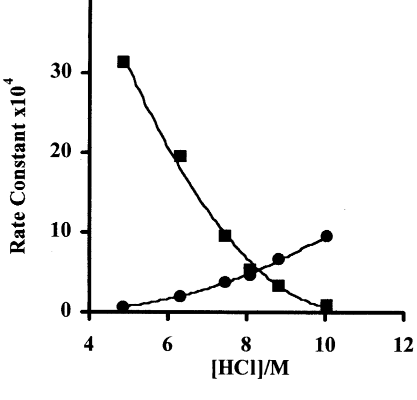

Figure 3. Dependence of k_1 (●) and k_2 (■) vs [HCl] at 75.1°C (see Table 1).

2.2. Thermodynamic activation parameters

The thermodynamic activation parameters, calculated from the linear relationship $\ln (k_{obs}/[H^+])$ versus $1/T$, at 6.3 and 8.84 M HCl, are reported in Table 3. The values found at 8.84 M HCl indicate that, although the two consecutive reactions show very similar $\Delta G^{\neq}$, the first step occurs with an appreciable entropic advantage ($\Delta\Delta S^{\neq}=$ 78.2 J mol^{-1} K^{-1}) which is counterbalanced by an unfavourable change in enthalpy. This result agrees with the entropy activation values generally observed in the cyclization reactions in comparison to the ring openings, for instance lactones,[7b] or reactions involving a water molecule in the transition state.[7c] Conversely, at 6.3 M HCl the second step is energetically favoured with respect to the first one by 8.8 kJ mol^{-1}, the lowering of $\Delta G^{\neq}$ being essentially due to an appreciable decrease of $\Delta H^{\neq}$ (33.4 kJ mol^{-1}) which exceeds the entropic disadvantage ($\Delta\Delta S^{\neq}=-76.5$ J mol^{-1} K^{-1}).

Thus, by increasing the acidity, the cyclization step is accompanied by an increasing enthalpic advantage, according to that previously observed,[3] while the opening of intermediate **2** is not favoured by a more negative entropy, the enthalpy remaining constant.

From the comparison of the $\Delta G^{\neq}$ value (112.9 kJ mol^{-1}) measured in 8.84 M HCl relative to the step **1**→**2** with that previously obtained (105 kJ mol^{-1}) for the hydrolysis of *N*-(2-ethyl-6-methylphenyl)-*N*-(methoxyprop-2-yl)benzamide[3] (**6**) in 8.7 M HCl it appears evident that substrate **1** cyclizes more slowly. A reasonable explanation for this result could be based on the lesser energy of rotation barrier along the Ph–N bond in substrate **1** than in **6**. Then, the mole fraction of the conformations favouring the intramolecular reaction (i.e. the near attack conformations[11]) will be minor because in the ground state the substrate **1** consists of more conformers in comparison to **6**. This fact is reflected by the greater value of $\Delta H^{\neq}$ (105.6 kJ mol^{-1}) at 8.84 M HCl with respect to 91 kJ mol^{-1} calculated for **6** at 8.7 M HCl.[3]

3. Conclusion

In this paper we have assigned the rate constants to the individual steps involved in the overall hydrolytic process investigated in the acidity range 4.88–10.05 M HCl.

Furthermore, an interesting result has also been found, namely, that the rate of the unusual decomposition of the intermediate **2** decreases by increasing the acidity medium. In our opinion such behaviour may be due to the formation of a rapid equilibrium between **2** and **5** (across an unreactive intimate ion-pair) which would cause a decrease of the reactive species (**2**) when the acidity medium increases.

Lastly, the unfavourable activation entropy measured for this step suggests the participation of water that should act by proton transfer from the –OH group of **2** to the nitrogen atom across a six member transition state.

The cyclization step of **1**, with respect to the previously[3] investigated acid hydrolysis of **6**, occurs with an enthalpic loss ($\Delta\Delta H^{\neq}$=14.6 kJ mol^{-1}) which is not balanced by the entropic gain ($\Delta T\Delta S^{\neq}$=6.7 kJ mol^{-1} K^{-1}).

4. Experimental

4.1. Preparation of the products

The products have been synthesized as previously reported.[4]

4.2. Kinetic experiments

The kinetics of the acid hydrolysis of **1** were monitored by UV on a Perkin–Elmer Lambda 6 spectrophotometer at λ=260 nm and by ^{1}H NMR on a Varian Gemini 300 (300 MHz) following the procedures already described.[4] Rate constants have been calculated as previously reported.[4]

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