Pergamon

Tetrahedron, Vol. 53, No. 30, pp. 10513-10516, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00662-5

Participation of Neighbouring Amide Group in the Competitive Acid Catalysed Hydrolysis of Ether Linkage and an Intramolecular S_N2 Reactions. 2*

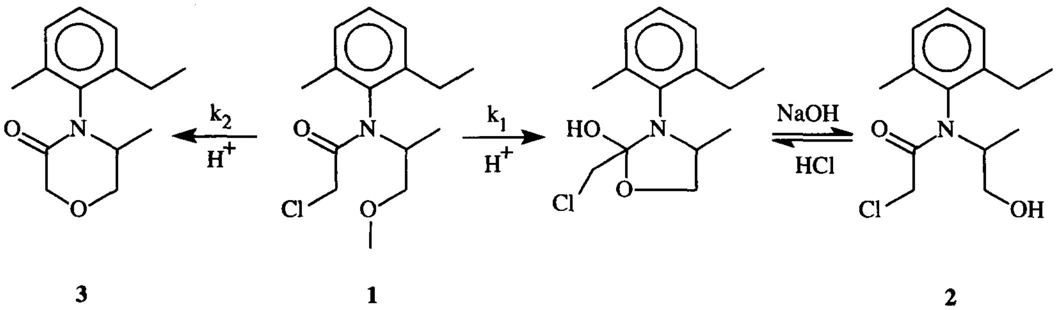
Antonio Arcelli, Matteo Papa, Gianni Porzi*, Sergio Sandri

Dipartimento di Chimica "G. Ciamician", Via Selmi 2, 40126 Bologna (Italy)
E-mail : Porzi@ciam.unibo.it

Abstract. The substrate **1** was submitted to acid hydrolysis and two reaction products (**2**,**3**) were obtained in competitive reactions (a parallel pathway). The experimental data, elaborated by using the expressions for the parallel first-order reactions, showed the formation of **3** (an intramolecular cyclization) about three-fold slower than **2** (the previously observed hydrolytic cleavage of ether linkage). Both the reactions appear to be assisted by the protonated neighbouring amide group.
© 1997 Elsevier Science Ltd.

Recently we observed the surprising ability of the amide group to assist the acid hydrolysis in mild conditions of the methyl ether linkage,[1] but still little is known about this topic. In order to extend our knowledge about such unusual neighbouring amidic group participation, we submitted the acid hydrolysis of N-(2-ethyl-6-methylphenyl)-N-(methoxyprop-2-yl)chloroacetamide **1** (Metolachlor) a herbicide used for the control of a wide variety of weeds, to kinetic investigations. The substrate **1** was chosen in an attempt to observe the influence of an electron-withdrawing substituent, such as the chlorine atom, on the rate of acid hydrolysis of the methyl ether linkage, with respect to the substrate previously investigated.[1]

In this report we wish to describe the first example of the neighbouring amide group contemporary participation in competitive acid hydrolysis of ether linkage and intramolecular S_N2 reaction (Scheme 1).



3 1 2

Scheme 1.

RESULTS AND DISCUSSION

Reported in Figure 1 are the concentration curves vs. time for the reactant **1** and for products **2**, **3**. The kinetic results were elaborated by using the expression for the parallel first-order reactions[2] because the ratio of products concentrations is substantially constant independent of time ([2]/[3] = 3±0.5). Besides, the compound **2**[3] submitted to heating at 60°C in 8.65 M HCl did not convert into **3** and likewise the last one did not give **2**. Thus, the overall coefficient $k=k_1+k_2$ was determined from the substrate **1** concentration dependence on time $C_1=C_0e^{-kt}$, while the rate constants for the formation of **2** (k_1) and **3** (k_2) were calculated by the equation $C_2=C_0k_1(1-e^{-kt})/k$ and $C_3=C_0k_2(1-e^{-kt})/k$, respectively (C_0 is the concentration of Metolachlor (**1**) at t=0). The values reported in Table 1 show that a considerable change of concentration of **1** does not modify the rate within the experimental error, confirming that the reaction is first order in substrate.

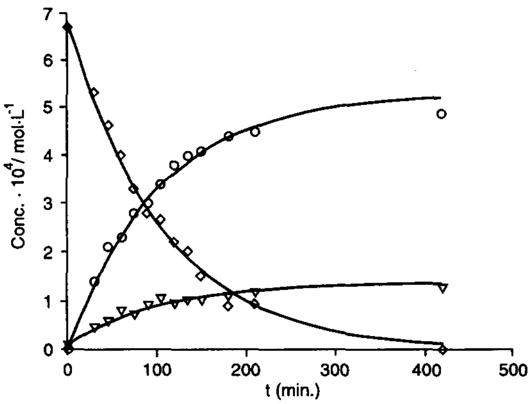


Figure 1. Hydrolysis of Metolachlor (**1**) at 57.8°C in 8.3 M HCl ([◊] **1**, [O] **2**, [∇] **3**).

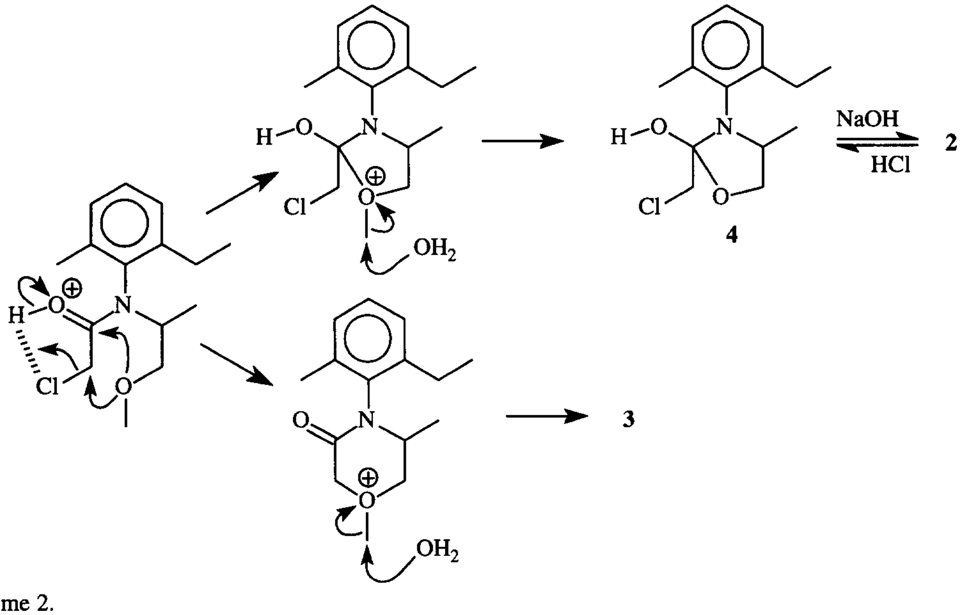
Table 1. Experimental data and rate constants (a) at 57.8°C in 8.65 M HCl

[Metolachlor (1)] / $M^{-1}L^{-1}$	$10^4 \cdot k$ / s^{-1}	$10^4 \cdot k_1$ / s^{-1}	$10^5 \cdot k_2$ / s^{-1}
$6.6 \cdot 10^{-3}$ (b)	2.2 ± 0.04	1.6 ± 0.02	5 ± 0.6
$3.2 \cdot 10^{-3}$ (b), (c)	1.9 ± 0.07	1.4 ± 0.03	4 ± 0.3
$1.65 \cdot 10^{-3}$ (b)	2.8 ± 0.13	2.0 ± 0.05	8 ± 0.2
$9.2 \cdot 10^{-4}$ (d)	2.52 ± 0.06		
$6.12 \cdot 10^{-4}$ (d)	2.27 ± 0.07		
$4.6 \cdot 10^{-4}$ (d)	2.3 ± 0.03		
$3.06 \cdot 10^{-4}$ (d)	2.2 ± 0.07		

(a) Standard errors are reported. Kinetics followed by : (b) HPLC, (c) In 8.3 M HCl, (d) The kinetics followed by UV give only the overall rate constants because the spectra of the products **2** and **3** are very similar.

The comparison of the pseudo-first order rate constant for the formation of **2**, $k_1=1.4 \cdot 10^{-4}$ s^{-1} (Table 1), with that measured for the corresponding non chlorinated compound previously investigated[1] ($k_{obs}=3.39 \cdot 10^{-4} s^{-1}$, at 57.8°C in 8.37 M HCl) shows that the acid hydrolysis of ether linkage on the Metolachlor (**1**) is slightly slower. Thus, the reaction is assisted and the participation of the neighbouring amide group can be estimated about $7 \cdot 10^2$-fold[1]. As generally occurs, the effectiveness of neighbouring-group participation depends on the ease with which the molecular geometry required for participation can be achieved. In this case, the lower rate observed could probably be ascribed to a minor electrophilicity of the carbonyl carbon owing to a smaller protonation of amide group in **1**. The measured $H_0^{1/2}$ (value at half neutralization)[4] was actually -4.6 for **1**, while that of the corresponding non-chlorinated substrate[1] was -3.2, as ascertained by plotting the optical density, D_0, at λ=265 and 257nm respectively, against H_0 function[5].

In the absence of a reference unassisted S_N2 reaction by the ether oxygen on the C-Cl bond, the rate enhancement, caused by the anchimeric assistance of amide group on the intramolecular nucleophilic cyclization, was tentatively evaluated by performing the solvolysis of **1** in 50% aqueous methanol at 57.8°C, since the nucleophilicities of hydroxy and alkoxy groups are comparable[6]. However, after about 500 hours, no appreciable amount of 3 nor of the product resulting from the substitution of the chlorine atom by -OCH_3 group was observed. Thus, it is reasonable to estimate the rate constant $<10^{-9}s^{-1}$, considering that 0.2% of solvolysis product could not have been detected by the usual analytical techniques. Therefore, the rate enhancement induced by the vicinal protonated amide group can be estimated $>4 \cdot 10^4$. This value is much too large to be exclusively attributed to the inductive effect of the protonated carbonyl group, therefore we suppose that the result can again be ascribed to the participation of the neighbouring protonated amide group which in one case allows cyclization to a six membered product 3 and in the other induces the formation of a stable cyclic intermediate 4, which is converted into 2 by making the reaction solution basic. We hypothesize that the high efficency of intramolecular S_N2 displacement could be ascribed to a strong hydrogen bond between the hydroxonium cation and the neighbouring chlorine atom (see Scheme 2).



Scheme 2.

In conclusion, as far we know, this is the first example in which dual assistance has been found: indeed, the protonated amide group assists both the nucleophilic acyl addition of oxygen ether to give a five membered ring intermediate 4 and the intramolecular S_N2 cyclization to the morpholinon derivative 3.

EXPERIMENTAL

General. ^1H- and ^{13}C-NMR spectra were recorded with a Varian Gemini 300 (300 MHz) spectrometer. HPLC measurements were run on a Hewlett Packard HP 1090 Liquid chromatography apparatus by using the Hypersil ODS 5μ column (250 x 4.6 mm). UV spectra were recorded on a Perkin-Elmer Lambda 6 spectrophotometer.

Products. The substrate 1, in 98% analytical grade, was provided by Ciba Geigy of Saronno (Varese). ^1H-NMR ($CDCl_3$) (mixture of diastereomers) δ 1.15 (2d,3H,J=7Hz), 1.26 (t,3H,J=7.5Hz), 2.24 (2s,3H), 2.58

(2q, 2H,J=7.5Hz), 3.27 (2s,3H), 3.45-3.55 (m,1H), 3.61 (2s,2H), 3.65-3.8 (m,1H), 4.23 (m,1H), 7.2 (m,3ArH).

N-(2-ethyl-6-methylphenyl)-N-(hydroxyprop-2-yl)chloroacetamide (2). This was prepared, as previously reported[7], starting from 6-ethyl-o-toluidine and purified by silica gel chromatography. ^{1}H-NMR ($CDCl_3$) (mixture of diastereomers) δ 1.18 (2d,3H,J=7Hz), 1.28 (2t,3H,J=7.6Hz), 2.25 (s,3H), 2.35 (s,3H), 2.6 (2q,2H, J=7.6Hz), 3.45 (bs,OH), 3.67 (2q_{AB},2H,J=13.9Hz), 3.9 (m,2H), 4 (m,1H), 7.2 (m,3ArH).

4-(2-ethyl-6-methylphenyl)-5-methyl-3-morpholinone (3). In an inert atmosphere, NaH (gr 0.2 of 80% dispersion in mineral oil, 6.66 mmol) was added to a stirred solution of **2** (gr 1.35, 5 mmol) in 30 ml of dry THF and the reaction mixture was refluxed for 6 hours. The solvent was removed in vacuo and 1M HCl was then slowly added to the residue. After extraction with ethyl acetate, the product was purified by silica gel chromatography and isolated in 90% yield. ^{1}H-NMR ($CDCl_3$) (mixture of diastereomers) δ 1.13 (2d,3H,J=6.5Hz), 1.23 (2t,3H,J=7.5Hz), 2.24 (2s,3H), 2.55 (2q,2H,J=7.5Hz), 3.75 (m,2H), 4.05 (m,1H), 4.37 (q_{AB},2H,J=16.7Hz), 7.2 (m,3ArH). Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; found: C, 72.25; 8.23.

Kinetic measurements. The acid hydrolysis of **1** was performed in HCl at 57.8°C and monitored by HPLC equipped with a UV detector at λ=215nm. The kinetics were performed in sealed glass ampoules kept in a thermostatted bath at various concentrations of **1** (see Table 1). At set times the ampoules were cooled, 5 ml of solution was diluted to 25 ml with 2M NaOH, in order to obtain a pH≅0, and the solution was submitted to HPLC analysis. The samples were eluted with 10% aqueous acetonitrile at a flow rate of 1.5 ml/min. The reaction was followed by recording both the disappearance of **1** and the formation of **2** and **3** during the time.The concentrations of **1**, **2** and **3** were determined by the calibration curves of the standard solutions in 1M HCl. The hydrolysis products **2** and **3** were identified by comparison of NMR, HPLC and MS spectra of the solution after completion of the reaction with the authentic samples (above described).

The kinetics were also followed by UV spectrophotometry by monitoring the increase of optical density at λ=265 nm. The experimental curves well fit the first order rate constant equation $\ln(OD_\infty\text{-}OD_0)/(OD_\infty\text{-}OD_t)$ vs. the time. Table 1 shows the experimental conditions and rate constants elaborated using a non linear least square routine (Fig.P 6.0 programme by Biosoft).

Acknowledgement. We are grateful to Miss S. Tomesani for her helpful assistance in the HPLC measurements and in determining mass spectra. Financial supports from the Italian C.N.R. and M.U.R.S.T. (quota 60%).

REFERENCES AND NOTES (* The reference 1 is considered to be part 1)

1. Arcelli, A., Porzi, G., Sandri, S.; *Tetrahedron* **1995,** *51*, 9729.
2. Moore, J.W. and Pearson, R.G.; In *Kinetics and Mechanism*, 3^ Edit., John Wiley & Sons 1981, page 284.
3. At 57.8°C in 8.65 M HCl, the product **2** gives the cyclic isomer **4** (Scheme 2) with a $k_{obs} = 7.1 \cdot 10^{-4}$ s^{-1}, about four-fold higher than the k_1 (Table 1). The intermediate **4** was isolated from the acid solution, after evaporation in vacuo to dryness: ^{1}H-NMR ($CDCl_3$) (mixture of diastereomers) δ 1.2 (2d,3H,J=6.4Hz), 1.26 (2t,3H,J=7.6Hz), 2.22 (s,3H), 2.28 (s,3H), 2.57 (2q,2H, J=7.6Hz), 3.6 (q_{AB},2H), 3.7 (m,1H), 4.1 (m,2H), 7.2 (m,3ArH).
4. Cookson, R.F., *Chem. Rev.* **1974,** *74*, 5.
5. Johnson, C.D.,Katritzky, A.R., Ridgewell, B.J., Shakir, N.,White, A.M., *Tetrahedron* **1965,** *21*, 1055.
6. Ritchie, C. D., In *Physical Organic Chemistry. The Fundamental Concepts*, Marcel Dekker, 1975, page 80.
7. Marucchini, C., Vischetti, C., Porzi, G.; *Fresenius Envir. Bull.* **1996,** *5*, 482.

(*Received in UK* 11 *April* 1997; *revised* 2 *June* 1997; *accepted* 5 *June* 1997)