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Catalytic Intramolecular Participation of Amide Group in the Acid Hydrolysis of Methyl Ether Linkage

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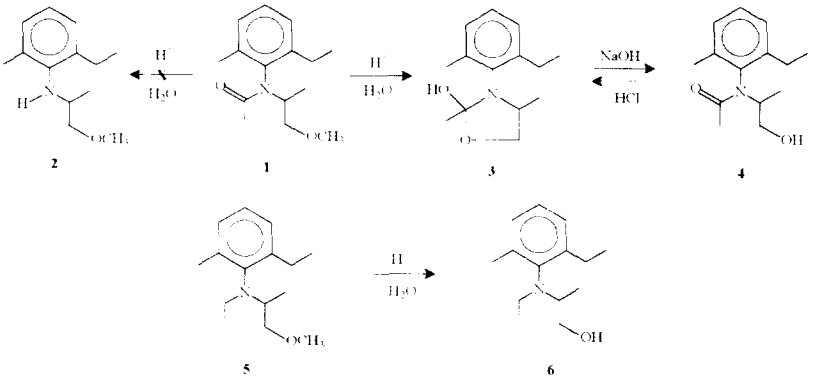
Abstract Evidence for the acid catalyzed hydrolysis of methyl ether linkage assisted by the neighboring amide function was obtained. The hydrolysis rate of **1** to **3** was measured at least 1.7×10^3 fold higher than that of the reference compound **5**. The values of thermodynamic parameters suggest that the participation of neighboring amide group in **1** is accompanied by a lower activation enthalpy with respect to the unassisted reaction in **5**. Experimental evidence, such as the kinetic isotope ratio, the positive ϕ value of Bunnett-Olsen equation and $\Delta S^{\ddagger}$ value suggests an A_2 mechanism.

In the course of the synthesis of some metabolites of Metolachlor (an herbicide used for the control of a wide variety of weeds), we submitted the product **1** to acid hydrolysis of amide group (at reflux temperature) in order to obtain the corresponding aniline derivative **2**. Unexpectedly, the compound **4** was the sole reaction product recovered after alkalinization and, what is more, this derivative did not suffer further acid hydrolysis of acetamide group under our experimental conditions. We envisaged that the observed methyl ether cleavage in such conditions could arise from participation by neighbouring amide group owing to the formation of a cyclic oxazolidine intermediate (Scheme 1).



Scheme 1.

Although in the last two decades the intermolecular participation of vicinal groups have been extensively studied, it is a topic of current interest[1]. However there are a few examples of neighbouring amide group participation[2]. In particular, the observed intramolecular assistance of amide function in the O-CH_3 cleavage

has not so far been reported in the literature. Indeed, the only example of an amide group participation in the acid catalyzed fission of an O-C bond was reported for a phenyl ether[3]. Thus, we found it interesting to study the acid hydrolysis of compound **1** at various acid concentrations and to investigate the reaction mechanism. In this paper we describe the first example in which an amide group catalyzes the acid hydrolysis of a vicinal methyl ether linkage in relatively mild conditions. In order to evaluate the rate enhancement caused by the assistance of the vicinal group, we performed kinetic study of acid hydrolysis of methyl ether **5**, a reference compound without the amide function.

EXPERIMENTAL

General. ^{1}H- and ^{13}C-NMR spectra were recorded with Varian Gemini 300 (300 Mhz) spectrometer. Mass spectra (MS) were obtained on a GC-MS HP 5890 (series II) instrument with electronic ionization technique (at 70eV) by using a HPS cross-linked 5% phenyl methyl silicone column. HPLC measuraments were run on Hewlett Packard HP 1090 Liquid chromatography apparatus by using the Hypersil 100 C-18 column (250x4.6 mm). UV spectra were recorded on a Perkin-Elmer Lambda 6 spectrophotometer. Chromatographic purification was performed by using silica gel 60 (230-400 mesh). All reagents were obtained from commercial sources and are of analytical grade. Water was deionized and redistilled from $KMnO_4$.

N-(2-ethyl-6-methylphenyl)-N-(methoxyprop-2-yl)acetamide (1). It was prepared by hydrogenolysis of Metolachlor [N-(2-ethyl-6-methylphenyl)-N-(methoxyprop-2-yl)chloracetamide] with 10% Pd/C in methanol and in the presence of $(C_2H_5)_3N$. The compound **1** was obtained pure after silica gel chromatographic elution with hexane/ethyl acetate. ^{1}H-NMR ($CDCl_3$) (as a mixture of diastereomers) δ 1.05-1.15 (2d,3H,J=6.8Hz), 1.25 (t,3H,J=7.5Hz), 1.68 (2s,3H), 2.2-2.3 (2s,3H), 2.55 (m,2H), 3.35-3.4 (2s,3H), 3.45 (m,1H), 3.55-3.7 (m,1H), 4.25 (m,1H), 7.2 (m,3ArH)

N-(2-ethyl-6-methylphenyl)-N-(hydroxyprop-2-yl)acetamide (4). It was obtained by submitting **1** to hydrolysis in 18%HCl at 80°C for 3 hr (Scheme 1). After cooling the reaction was made alkaline with NaOH, the product was then extracted with ethyl acetate and purified by silica gel chromatography eluting with hexane/ethyl acetate. ^{1}H-NMR ($CDCl_3$) (as a mixture of diastereomers) δ 1.1-1.15 (2d,3H,J=7Hz), 1.24-1.26 (2t,3H,J=7.5Hz), 1.72 (2s,3H), 2.2-2.3 (2s,3H), 2.5-2.7 (2q,2H,J=7.5Hz), 3.75-4.1 (m,3H), 4.65 (bs,OH), 7.1-7.3 (m,3ArH), ^{13}C-NMR (CDCl3) (as a mixture of diastereomers) δ 13.99, 14.42, 14.66, 14.76, 18.65, 18.78, 22.97, 23.0, 23.59, 23.81, 58.64, 59.41, 67.28, 67.5, 126.87, 126.97, 128.35, 128.83, 128.93, 135.95, 141.48, 141.79, 173.32, 173.56, MS m/z 235, 206 (5), 204 (30), 177 (4), 163 (12), 162 (100). The two peaks diagnostically useful can be reasonably attributed to the fragments 204 (M-CH_2OH) (typical of primary alcohols) and 162 (204-CH_2CO).

N-ethyl,N-(methoxyprop-2-yl),2-ethyl-6-methyl,aniline (5). It was easily prepared by reducing **1** with $LiAlH_4$ in dry THF. The product **5** was recovered pure after silica gel chromatography eluting with hexane/ethyl acetate. ^{1}H-NMR ($CDCl_3$) (as a mixture of diastereomers) δ 0.85-0.95 (2t,3H,J=7.1Hz), 0.95-1.05 (2d,3H,J=6.4Hz), 1.18-1.28 (2t,3H,J=7.5 Hz), 2.27-2.3 (2s,3H), 2.55-2.8 (m,2H), 3.05-3.25 (m,3H), 3.32-3.34 (2s,3H), 3.3-3.55 (m,2H), 6.95-7.1 (m,3ArH).

N-ethyl,N-(hydroxyprop-2-yl),2-ethyl-6-methyl,aniline (6). It was synthetized by alkylating 6-ethyl-o-toluidine with ethyl-2-bromopropionate, in refluxing toluene, followed by acylation with acetyl chloride and successive reduction by $LiAlH_4$. The desired product **6** was submitted to silica gel chromatographic purification

eluting with hexane/ethyl acetate ^{1}H-NMR ($CDCl_3$) (as a mixture of diastereomers) δ 0.95 (m,6H), 1.2-1.3 (2t,3H, J=7.5Hz), 2.28-2.36 (2s,3H), 2.55-2.7 (m,1H), 2.78 (q,1H,J=7.5Hz), 3-3.25 (m,2H), 3.38 (m,1H), 3.52 (m,1H), 3.8 (m,1H), 6.95-7.1 (m,3ArH)

The formation of intermediate **3** [**3-(2-ethyl-6-methylphenyl)-2-hydroxy-2,4-dimethyl-oxazolidine**], stable to further acid hydrolysis, was supported by the following experimental evidences.

By monitoring the change of ^{1}H-NMR spectrum of **4**, in 20% DCl/D_2O, vs. time (the sampling tube being in thermostated probe at 50°C) it was possible to observe the progressive disappearance of the signals at δ 4.6 (m,CH-N), 4.05 (m,CH-O), 3.85 (m,CH-O), 2.6 (m,CH_2-Ph), 2.3 (2s,CH_3-Ph), 2.2 (2s,CH_3C-N), 1.32 (t, $C\underline{H}_3CH_2$-Ph), 1.28 (2d,$C\underline{H}_3$CH-N) and the contemporary appearance of new absorbances at δ 5.6 (m,CH-O), 5.05 (m,CH-O and CH-N), 2.7 (q,CH_2-Ph), 2.47 (2s,CH_3-Ph), 2.43 (2s,CH_3C-O), 1.55 (2d,$C\underline{H}_3$CH-N), 1.35 (2t,$C\underline{H}_3CH_2$-Ph). In the formed compound all the protons, with exception of the methyl of C_2H_5-Ph group, are shifted at lower fields with respect to the starting product **4**. After 5 hr at 50°C, the ^{1}H-NMR spectrum was found to be the same as the product obtained from the acid hydrolysis of **1** (Scheme 1). The aqueous acid solution of **3** was then evaporated in vacuo to dryness and the residue submitted for spectroscopic analysis: ^{1}H-NMR ($CDCl_3$) (as a mixture of diastereomers) δ 1.1-1.2 (m,CH_3), 1.25 (t,$C\underline{H}_3CH_2$-Ph,J=7.5Hz), 1.65 (2s,CH_3), 2.18-2.22 (2s,CH_3-Ph), 2.45-2.70 (2q,$CH_3C\underline{H}_2$-Ph,J=7.5Hz), 3.6 (m,CH-O), 4-4.25 (m,CH-O and CH-N), 7.2 (m,3ArH), ^{13}C-NMR ($CDCl_3$) (as a mixture of diastereomers) δ 13.96, 14.34, 15.22, 15.41, 18.7, 19.02, 22.98, 23.06, 23.78, 23.87, 47.05, 47.21, 56.36, 56.9, 126.8, 126.84, 128.47, 128.82, 136.15, 136.6, 141.94, 142.17, 171.64; MS m/z 235, 218 (4), 217 (22), 216 (4), 203 (6), 202 (50), 188 (8), 175 (8), 174 (24), 170 (5), 161 (15), 160 (100). The following fragments can be reasonably attributed to the peaks diagnostically useful : 217 (M-H_2O), 202 (217-CH_3), 174 (202-CO), 160 (174-CH_2). As can be observed, the spectroscopic data of **3** are totally different to those registered for compound **4** (see above).

To GMS analysis the product **3** showed a smaller retention time than **4**, according to the smaller polar cyclic structure and, similarly, the R_f value of TLC (on silica gel sheet) was greater for **4** than for **3**.

By making alkaline the reaction mixture of acid hydrolysis of **1**, the compound **4** was isolated. The 2-hydroxy-oxazolidine derivative **3** was also recovered by acid treatment of **4**.

KINETIC STUDIES

The hydrolysis of **1** was performed at 50, 57.8, 69.9 and 79.9±0.1°C in various HCl concentrations and at 57.8 ±0.1°C in DCl (Table 1). The reaction was followed spectrophotometrically by measuring the increase of optical density (OD) at λ=266 nm. Stock solutions of the substrate were made in 2N HCl/CH_3OH or 2N DCl/CH_3OD 50% v/v. Runs were started by adding 30 μl of these solutions to a thermostatted cell of spectrophotometer containing 3 ml of acid solutions. After mixing, the concentration of **1** was in the range of 10^{-3} - 2.10^{-3} mol l^{-1}. All the kinetics were performed in duplicate run. The compound **3** is the only reaction product recovered from acid hydrolysis of **1**, as shown by comparison of ^{1}H-NMR and MS spectra of the reaction product with those of authentic sample in the same conditions.

The pseudo first order rate constants (k_{obs}) were obtained from the slopes of the $\ln(OD_\infty-OD_0)/(OD_\infty-OD_t)$ equation vs. time by using a least square routine (correlation coefficients were above 0.999). OD_∞ values were taken after at least then half lives. The second order rate constants (k_{H^+} or k_{D^+}) were calculated from the equation $k_{obs} = k_{H^+}[H^+]$. Concentrations of $[H^+]$ and $[D^+]$ at the suitable temperatures were corrected by means of the density values of HCl[4] and DCl[5], respectively (see Table 1).

The kinetic of acid catalysed cyclization of **4** to **3** were also followed spectrophotometrically (at λ=266 nm) at 57.8°C and different HCl concentrations[6]

Table 1 Experimental Conditions and Rate Constants for Acid Hydrolysis of **1**

t(°C) ±0.1	[HCl] mol l^{-1}	k_{obs} s^{-1}	k_{H+} $mol^{-1}l\ s^{-1}$	[DCl] mol l^{-1}	k_{obs} s^{-1}	k_{D+} $mol^{-1}l\ s^{-1}$
79.9	8.29	3.03×10^{-3}	3.66×10^{-4}			
	7.06	2.43×10^{-3}	3.44×10^{-4}			
	5.84	1.75×10^{-3}	3.00×10^{-4}			
69.9	8.33	1.33×10^{-3}	1.60×10^{-4}			
	7.09	1.04×10^{-3}	1.47×10^{-4}			
	5.87	6.31×10^{-4}	1.07×10^{-4}			
57.8	8.37	3.39×10^{-4}	4.05×10^{-5}	6.78	3.51×10^{-4}	5.18×10^{-5}
	7.84	2.95×10^{-4}	3.76×10^{-5}	6.35	3.18×10^{-4}	5.01×10^{-5}
	7.13	2.65×10^{-4}	3.72×10^{-5}	5.64	2.64×10^{-4}	4.68×10^{-5}
	6.36	2.29x10-4	3.60×10^{-5}	5.37	2.49×10^{-4}	4.64×10^{-5}
	5.90	1.79×10^{-4}	3.03×10^{-5}	4.74	1.94×10^{-4}	4.09×10^{-5}
	4.75	1.10×10^{-4}	2.32×10^{-5}	4.25	1.75×10^{-4}	4.12×10^{-5}
	+0.33MKCl	1.26×10^{-4}				
	+0.66MKCl	1.45×10^{-4}				
	+1.00MKCl	1.50×10^{-4}				
50.0	8.41	1.26×10^{-4}	1.50×10^{-5}			
	7.16	1.04×10^{-4}	1.45×10^{-5}			
	5.93	7.33×10^{-5}	1.24×10^{-5}			

The acid hydrolysis of the reference compound **5** was performed in the range 69.9 - 99.3±0.1°C, because the rate is slower than **1**. Compound **6** was the only product of acid hydrolysis of **5**, as shown by comparison of ^{1}H-NMR and MS spectra of the reaction product with those of authentic samples in the same conditions[7].

The kinetics were performed in sealed glass ampoules kept in a thermostatted bath under the conditions reported in Table 2 by using concentrations of **5** in the range 2.7×10^{-2} - 3.5×10^{-2} mol l^{-1}. At set times the ampoules were cooled, 4 ml of solution neutralized with 8.5N NaOH and adjusted till pH≅1.5. Since there are no differences in the UV spectra of compounds **5** and **6**, the disappearance of **5** was measured by HPLC (UV detector at λ=266 nm). The reaction mixtures were eluted with a solution of 0.02M ammonium phoshate buffer (pH=8.5) and 10% aqueous acetonitrile (the gradient ranging from 60:40 to 100%, respectively, in 10 min. at a flow rate of 1.5 ml/min).

The rate constants were determined from equation $\ln C = \ln C_0 - kt$; the effectiveness of the procedure was assured by the verified linearity (areas vs C) in the range of concentrations 1.66×10^{-3} - 8.52×10^{-3} mol l^{-1}.

Table 2 Experimental Conditions and Rate Constants for Acid Hydrolysis of **5**

t(°C) ±0.1	[HCl] mol l^{-1}	k_{obs} s^{-1}	k_{H+} $mol^{-1} l\ s^{-1}$
99.3	8.20	1.56×10^{-5}	1.9×10^{-6}
90.0	8.25	6.20×10^{-6}	7.5×10^{-7}
79.9	8.29	1.74×10^{-6}	2.1×10^{-7}
69.9	8.33	6.44×10^{-7}	7.7×10^{-8}

RESULTS and DISCUSSION

As results from the second order rate constants calculated at 79.9°C (Tables 1 and 2), the assistance of neighbouring amide group is shown by the strong enhancement of the hydrolysis rate of **1** with respect to that of **5**. In fact, we observed an increase at least of 1.7×10^3 fold which may undoubtedly be attributed to the formation of a cyclic intermediate owing to the presence of an amide group. The formation of 2-hydroxy-oxazolidine derivative **3**, rapidly converted to **4** in alkaline medium, has been deduced on the basis of the experimental results reported above. In addition, the acid catalyzed cyclization of **4** to **3** proceeded with a rate 2-4 times higher[6] with respect to the hydrolysis of **1**.

The second order rate constants of acid hydrolysis of **1** increase by increasing HCl concentrations (Table 1). These results can be attributed to the difference in ionic strength of the solutions, the reaction involving an ion and a neutral molecule. Indeed, at [HCl]=4.75 mol l^{-1} if KCl is added the observed first order rate constant increase as showed in Table 1.

We think the A_2 mechanism, involving the solvent attack on the cyclic cation intermediate, in respect to the alternative A_1 (see Scheme 2), is favoured by the following experimental evidences.

Firstly, the Hammett-Zucker correlation $\log k_{obs}$ vs $\log[H^+]$ (plot not reported) is linear with a slope of 2.2, while a downward curvature is obtained by plotting $\log k_{obs}$ vs. $-H_0$. Although the slope is found to be different to the predicted unitary value, the linearity of the correlation is generally associated with an A_2 mechanism[8]. A more rigorous treatment, based on the Bunnett-Olsen acidity function, concerns the correlation $\log k_{obs}+H_0 = \phi (H_0+\log[H^-]) + C$ (plotted in Figure 1) which is linear with a slope of 0.78 in agreement with the water involvement in the rate determining step[8].

Secondly, although unambiguous conclusions cannot be drawn from the kinetic isotope ratio for the acid hydrolysis of **1** at 57.8°C (the k_{H+}/k_{D+} value ranging from 0.55 to 0.72) (Table 1) lies in the range generally expected for an A_2 reaction in which this ratio is determined by the solvent isotope effect on the protonate substrate[9].

Lastly, $\Delta S^{\ddagger}$ value of -7.8 cal deg^{-1} (see later on) agrees with those expected for an A_2 mechanism: indeed, significative examples are the hydrolysis of diethyl ether (-9 cal deg^{-1}) and ethylene oxide (-6.1 cal deg^{-1}), while more positive values are generally found for an A_1 reaction[9].

Unfortunately, in the literature other kinetic data are not available on the acid hydrolysis of ethers to compare with our experimental values.

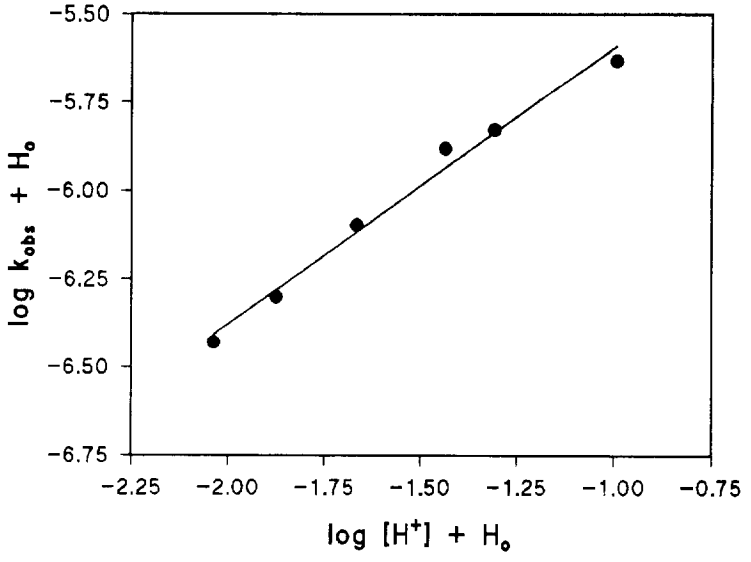


Figure 1 Plot of log k_{obs} + H_O vs log[H^+] + H_O for the Hydrolysis of **1** at 57.8°C.

The thermodynamic parameters of activation for the acid hydrolysis of **1** and **5** were evaluated by plotting log k_{H+} vs. 1/T (which gave a good straight line) and the values were reported in Table 3. Differences in the activation energy, between anchimerically assisted and unassisted reactions, would be generally expected to residue in a less negative entropy of activation (entropic advantage), accompanied in some cases by a lower enthalpy of activation. The thermodynamic activation parameters indicate that the lowering of the $\Delta F^{\ddagger}$ for **1** (assisted acid hydrolysis) with respect to **5** (unassisted acid hydrolysis) is due essentially to an appreciable decrease of $\Delta H^{\ddagger}$ (about 4 Kcal), while the values of $T\Delta S^{\ddagger}$ appear comparable (the difference of 1.0 Kcal being within the experimental error). Therefore, the intramolecular participation of the neighboring amide group appears to affect the enthalpic activation parameter almost exclusively.

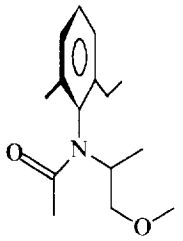


Figure 2

It is important to note here that the phenyl ring and the amide group in **1** are not coplanar on account of a strong steric strain, between the ortho alkyl substituents and the $CH_3C{=}O$ mojety, which causes a high energy barrier to the rotation along the Ph-N bond. Indeed, this results in an axis of chirality, the diastereomers being discernible both in ^{1}H-NMR and MS spectra. From the geometry of **1**, obtained by molecular mechanic calculations[11], it has been found that in the energetic minimum the angle between the aromatic ring and the plane of amide group is about 77° (Figure 2), the difference on energy between the diastereomers being 0.5 Kcal/mole

Therefore, the observed differences in the activation energy can be tentatively explained by unallowed free rotation around the Ph-N bond which probably gives to the substrate **1** a more rigid structure which might favour an intramolecular reaction, with a consequent decrease in the activation enthalpy.

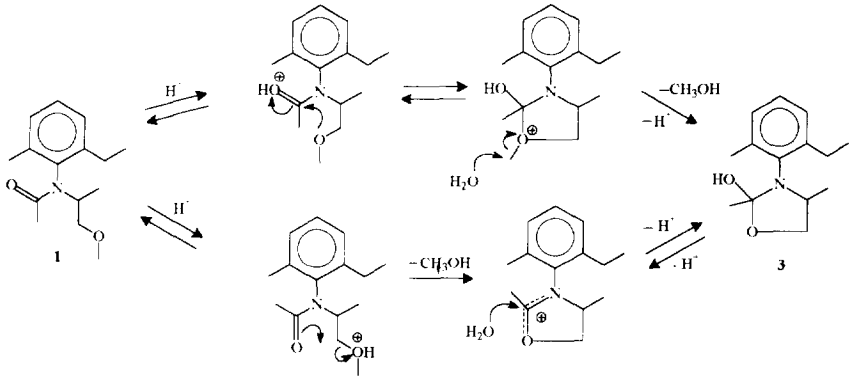
Table 3 Thermodynamic Activation Parameters for the Acid Hydrolysis of **1** and **5**[a)]

	compound **1**[b)]	compound **5**[c)]
$\Delta F^{\ddagger}$/Kcal mol^{-1} d)	26.1±0.9	31.2±1.3
$\Delta H^{\ddagger}$/Kcal mol^{-1} e)	23.6±0.6	27.7 0±1
$\Delta S^{\ddagger}$/cal deg^{-1}mol^{-1} f)	-7.8±1.9	-10.8±2.8
$T\Delta S^{\ddagger}$/Kcal mol^{-1}	-2.5±0.6	-3.5±0.9

a) errors shown are standard deviations, b) from k_{H^+} means values calculated in the range 5.93-8.41 of HCl concentrations (Table 1); c) from k_{H^+} values reported in Table 2; d) calculated at 50°C from $\Delta F^{\ddagger}=RT\ln(kT/hk)$ equation[10], e) calculated at 50°C from $\Delta H^{\ddagger}=E_a-RT$ equation; f) calculated from $\Delta S^{\ddagger}= (\Delta H^{\ddagger}-\Delta F^{\ddagger})/T$ equation.

Besides, it is interesting to note that both $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ values of unassisted hydrolysis of the reference compound **5** are in good agreement with those reported by Koskikallio[12] for the acid hydrolysis of diethyl ether, a substrate comparable to **5**. On the other hand, the second order rate constant evaluated for **5** at 120.1°C, by thermodynamic parameters, resulted 2.5 fold higher than the value reported by Koskikallio in HCl, but obtained in different conditions.

As would be expected, the effectiveness of neighbouring group assistance depends on the ease with which the molecular geometry required for participation can be achieved. The most rapid processes occur when a five membered ring formation is involved. Therefore, as shown in Scheme 2, two reaction paths are possible for the conversion of **1** to **3**. In the first route (top) the ethereal oxygen, participating as a nucleophile, attacks the protonated amide group while the second pathway (bottom) involves protonation of ethereal oxygen followed by nucleophilic attack of amide group. In both the cases the amide group participates to the formation of a cyclic pentatomic intermediate, postulated as cation, which successively undergoes the nucleophilic attack of water to give the oxazolidine derivative **3**. Most probably, the 2-hydroxy-oxazolidine **3** is stable in acid medium because the protonation of hydroxyl group furnishes a carbocation (resonance stabilized by the flanked N and O atoms) that undergoes the nucleophilic attack of water to return to the cyclic derivative **3**.



Scheme 2

The pK_a values reported in the literature for acetamide (-1.4[13]), dimethyl ether (-3.8[14]), diethyl ether (-3.6[14], -5.1[15]) and methyl isopropyl ether (-3.5[14]), indicate that the amidic oxygen is more basic than the ethereal one (at least about 2.5 pK_a units). Thus, considering the experimental evidence discussed above that support an A_2 mechanism, we suggest that the first route (top) hypothesized in Scheme 2 is a more reliable explanation of the results obtained.

Further investigations on the other substrates are in progress in order to attempt to better clarify the unusual observed enthalpic advantage, instead of the entropic one.

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5. The values of density at 57.8°C, determined experimentally, are reported in the order *% w* , *d* : 13.86, 1.150; 15.35, 1.156, 17.26, 1.165, 18.10, 1.168, 21.48, 1.183.

6. The [HCl]/mol l^{-1} and k_{obs}/s^{-1} values are reported in the order : 8.37, $7.23x10^{-4}$; 7.13, $6.86x10^{-4}$; 5.9, $4.88x10^{-4}$; 4.75, $3.84x10^{-4}$.

7. At 99.3°C, the presence of an impurity ascribable to the chloroderivative was revealed by GMS analysis.

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