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Unusual Ammonolysis of a Secondary Amide Assisted by Unsubstituted Vicinal Amide Group

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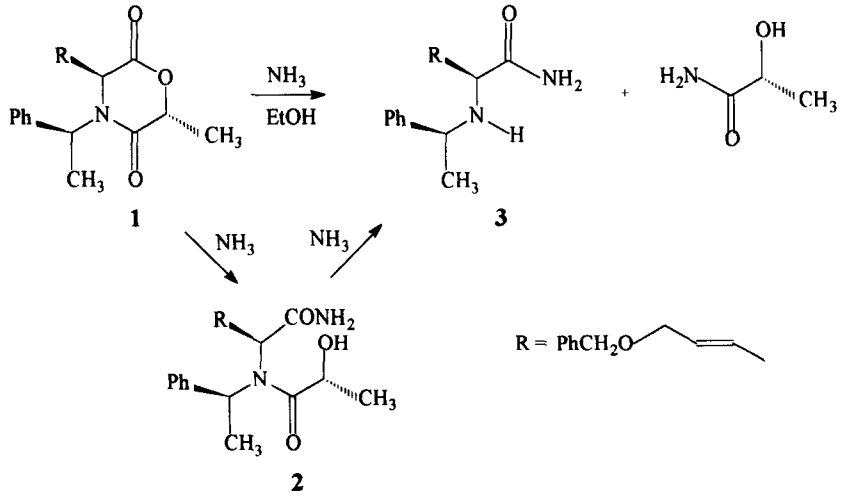
Abstract. Evidence for the participation of neighboring -$CONH_2$ group in the ammonolysis of disubstituted amide was obtained. The surprising conversion of **1** into **3** in very mild conditions is a process formed by two consecutive first order reactions. Kinetics were performed in ethanol at various temperatures and NH_3 concentrations. The ammonolysis of the isolated intermediate **2** allowed the unambiguous attribution of k_1 and k_2 to steps **1**→**2** and **2**→**3**, respectively (Scheme 1). The thermodynamic parameters of activation for both steps of the process were evaluated.

Recently we reported an interesting case of intramolecular participation of amide group which induces the acid hydrolysis of methyl ether linkage in very mild conditions[1]. During enantioselective synthesis of the natural and unnatural α-aminoacids we observed a further example of neighboring -$CONH_2$ group assistance. In fact, by subjecting lactone **1**[2] to ammonolysis (5 hours at r.t. in NH_3 saturated ethanol) in order to obtain the diamide **2**, to our great surprise we observed the formation of **3** (and (R)-lactamide) exclusively in practically quantitative yield (see Scheme 1).



1 **3** **2**

Scheme 1.

The monitoring of the reaction by TLC showed the rapid formation of an intermediate which was successively converted into the final product **3**. We therefore attempted to stop the reaction and isolate this product whose ^{1}H-NMR spectrum was consistent with the diamide **2** (see experimental).

We envisaged that the unexpected cleavage of secondary amide function in such mild conditions could arise from participation of neighboring -$CONH_2$ group obtained by ammonolysis of lactone **1**. Thus, we decided to investigate the conversion of **1** into **3** at various temperatures and concentrations of ammonia and to elucidate the reaction mechanism. In order to highlight and evaluate the assistance of the vicinal amide group, we subjected the derivative **4** to ammonolysis, as reference compound (Scheme 3). To our knowledge the intramolecular assistence of -$CONH_2$ group in the cleavage of a disubstituted amide in the presence of NH_3 has not previously been reported.

EXPERIMENTAL

GENERAL. ^{1}H- and ^{13}C-NMR spectra were recorded with Varian Gemini 300 (300 Mhz) spectrometer. Mass spectra were obtained on a GC-MS HP 5890 instrument with electronic ionization technique (at 70eV) by using a HPS cross-linked 5% phenyl methyl silicone column. UV spectra were recorded on a Perkin-Elmer Lambda 6 spectrophotometer. Chromatographic purification was performed 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 $KMNO_4$.

PREPARATION OF PRODUCTS

(3S,6R)-4-N-((S)-1-Phenylethyl)-3-(4-benzyloxy-2(E)-buten-1-yl)-6-methyl-1,4-morpholin-2,5-dione (1). The (6R)-4-N-((S)-1-phenethyl)-6-methyl-1,4-morpholin-2,5-dione was alkylated with mesylate of 4-benzyloxy 2(E)-butenol following the procedure previously described[2] for similar derivatives. After chromatographic purification the product was isolated as an oil; ^{1}H-NMR δ 1.62 (d,3H,J=6.8Hz), 1.66 (d,3H,J=7.2Hz), 2.65 (m,2H), 3.9 (dd,1H,J=6.6, 6.6Hz), 3.97 (m,2H), 4.5 (s,2H), 5.05 (q,1H,J=6.8Hz), 5.7 (q,1H,J=7.2Hz), 5.7-5.9 (m,2H), 7.3 (m,10ArH); ^{13}C-NMR δ 16.6, 17.5, 36.3, 52.4, 56.3, 69.5, 72.2, 73.6, 125.3, 127.1, 127.6, 127.7, 128.3, 129, 132.2, 138, 138.1, 166.5, 166.8.

(2S,4S)-2-(4-Benzyloxy-2(E)-buten-1-yl)-4-phenyl-3-((2R)-2-hydroxypropion-1-yl)-3-aza-pentanamide (2). Morpholindione derivative **1** (1.32 g, 3 mmol) was added to 20 ml of ethanol saturated with NH_3 at r.t. The solution was stirred at r.t. and after about 15 minutes the reaction was stopped by adding diluted HCl and extracted with ethyl acetate. The product, which resulted instable, was rapidly purified by silica gel chromatography and isolated as an oil; ^{1}H-NMR δ 1.52 (d,3H,J=6.6Hz), 1.62 (d,3H,J=6.9Hz), 2.87 (m,2H), 3.47 (dd,1H,J=7.6, 7.6Hz), 3.95 (m,2H), 4.5 (s,2H), 4.53 (q,1H,J=6.6Hz), 5.15 (q,1H,J=6.9Hz), 5.55-5.85 (m,2H), 7.3 (m,10ArH); ^{13}C-NMR δ 18.2, 21.8, 32.7, 55.3, 60.5, 65.9, 70.3, 72.4, 126.7, 127.2, 127.6, 127.8, 128.3, 128.4, 128.9, 130, 137.9, 173.2, 176.2. It is important to point out that, even at r.t., the product **2** suffers spontaneous cyclization to lactone **1** in few hours.

(2S,4S)-2-(4-Benzyloxy-2(E)-buten-1-yl)-4-phenyl-3-aza-pentanamide (3). A solution of **1** (1.32 g, 3 mmol) in 20 ml of ethanol was cooled at 0°C then insuffled with NH_3. After about 30 minutes the reaction flask was stopped and kept at r.t. overnight. After testing by TLC in 50% hexane/ethyl acetate, the reaction was evaporated in vacuo and extracted with ethyl acetate. After chromatographic purification, the product was obtained as an oil in 90% yield and from aqueous solution the (R)-lactamide was recovered; ^{1}H-NMR δ 1.4 (d,3H,J=7Hz), 2.2-2.6 (m,2H), 3 (dd,1H,J=5.6, 7.8Hz), 3.72 (q,1H,J=7Hz), 4 (m,2H), 4.5 (s,2H), 5.4-5.8 (m,

2H), 7.3 (m,10ArH); ^{13}C-NMR δ 24, 36.6, 57, 59.2, 70.2, 72, 126.4, 127.2, 127.5, 127.6, 128.3, 128.4, 129.4, 130.3, 138, 144.4, 177.5.

(3S,6R)-4-N-((S)-1-Phenylethyl)-3-(4-benzyloxy-2(E)-buten-1-yl)-2-hydroxy-6-methyl-1,4-morpholin-5-one (4). Obtained by the reduction of **1** with 2M $LiBH_4$ in THF at r.t. overnight, the product was isolated as an oil after chromatographic purification; ^{1}H-NMR δ 1.55 (d,3H,J=6.8Hz), 1.65 (d,3H,J=7.2Hz), 2.45 (m,2H), 3.15 (m,1H), 3.95 (m,2H), 4.37 (q,1H,J=6.8Hz), 4.5 (s,2H), 5.0 (d,1H,J=1Hz), 5.5-5.75 (m,2H), 5 97 (q,1H, J=7.2Hz), 7.25-7.45 (m,10ArH); ^{13}C-NMR δ 17.4, 21.2, 36.1, 51.9, 56.2, 69.6, 70.1, 72.2, 89.9, 127.6, 127.7, 127.8, 127.9, 128.3, 128.4, 130.6, 138, 139.4, 169.3.

KINETIC STUDIES

The ammonolysis of substrate **1** was performed in ethanol at seven temperatures, in the range 10.5-33.7°C, and in various concentrations of NH_3 (Table 1). The reaction was followed spectrophotometrically by measuring the optical density at λ=230 nm vs. time. The kinetics, performed in duplicate run, were carried out by adding 25 μl of a stock solution $5x10^{-2}$ mol l^{-1} of the substrate in ethanol to a thermostatted cell (1-cm length) of spectrophotometer containing 3 ml of an ethanolic solution of NH_3. After mixing, the concentration of **1** was $4.2x10^{-4}$ mol l^{-1}. Experiments performed at 21°C and [NH_3]=4.52 M showed that a two-three fold change in the lactone **1** concentration produced no variation in the calculated rate constant value (k_1 and k_2) within the experimental errors. The compound **3** and (R)-lactamide were the only products recovered from ammonolysis of **1**, as shown by comparison of ^{1}H-NMR of the reaction products with those of authentic sample in the same conditions. All kinetics were followed for at least five half lives taking 500 points and OD_∞ values were taken after at least ten half lives. The ammonolysis of substrate **2** was similarly performed at 21°C in 3.8 M NH_3 and the pseudo first order rate constant ($k_{obs}=2.42x10^{-4}s^{-1}$) was obtained from the slope of the $\ln(OD_\infty-OD_0)/(OD_\infty-OD_t)$ equation vs.time by using a least square routine. The concentrations of ammonia were determined by titration before and at the end of the kinetic runs (1-3% differences were observed specially at 30 and 33.7°C). The molar extinction coefficent of **2**, determined at 21°C, resulted 2590 (±2%) l $mol^{-1}cm^{-1}$.

RESULTS AND DISCUSSION

Figure 1 illustrates two typical runs showing that the process is formed by two consecutive first order reactions **1**→**2**→**3**. The formation and the disappearance of the intermediate in the course of the ammonolysis of **1** in ethanol was monitored by the variation of optical density (OD) expressed by the following equation (1)[3] being [**1**]=A_0 and [**2**]=[**3**]=0 when t=0 :

$$OD = A_0[(\varepsilon_1-\varepsilon_3)\, e^{(-k_1t)} + k_1(\varepsilon_2-\varepsilon_3)\,(e^{(-k_2t)} - e^{(-k_1t)}) / (k_1-k_2) + \varepsilon_3] \quad (1)$$

Thus, $A_0\varepsilon_1=OD_0$ (i.e., absorbance at t=0), $A_0\varepsilon_3=OD_\infty$ (i.e., absorbance at t=∞) and $A_0\varepsilon_2$ is the absorbance of **2** at A_0 concentration.

The k_2 and $A_0\varepsilon_2$ values have been previously determined from the first order rate constant equation by considering the right descending part of the absorbance-time curve (see Figure 1). Thus, k_1 and OD_∞ values have been computed by introducing k_2, OD_0 and $A_0\varepsilon_2$ values into the equation (1) and by performing the best fitting of experimental data (optical density) using a non linear least squares method[4]. Since the values of k_1 and k_2 in the equation (1) are interchangeable[3], the attribution of k_2 to the second step was possible by performing the ammonolysis of intermediate **2** at 21°C in 3.8 M NH_3 (Figure 2).

The value of k_2 ($2.42 \times 10^{-4} s^{-1}$) calculated from the experimental curve coincided with the one calculated by the equation (1) for the ammonolysis of **1** in the same conditions (Table 1).

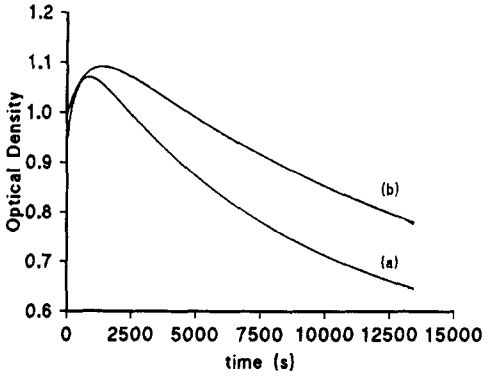


Figure 1. Variation of O. D. vs Time for the Ammonolysis of **1** at 13.5°C in (a)=3.72 M, (b)= 2.26 M NH_3.

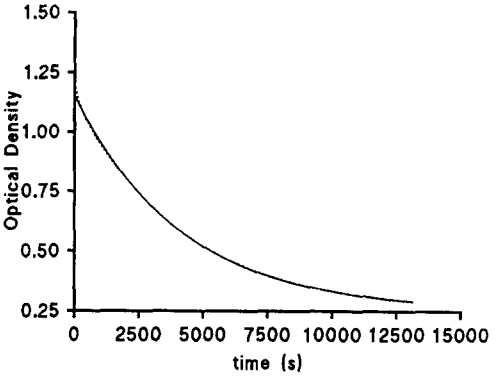


Figure 2. Variation of O. D. vs Time for the Ammonolysis of **2** at 21°C in 3.8 M NH_3.

In all cases investigated the experimental curves (dotted line) and the best computed ones (full line) are indistinguishable, as shown in Figure 1. The values of ε_2 and OD_∞, obtained by the fitting of equation (1), are also in good agreement with the experimental data, molar extinction of **2** and OD_∞ of reaction, respectively.

In the experimental conditions employed the spontaneous solvolyses were not detectable in any cases and the pseudo first order rate constants k_1 and k_2 (Table 1) showed a linear dependance on the NH_3 concentration according to the equation $k = k' [NH_3]$ (k'_1 and k'_2 being the second order rate constants for the steps **1**→**2** and **2**→**3**, respectively). One example is reported in Figure 3. The observed linearity in a large range of NH_3 concentration lead us to neglect term of second order in ammonia and to exclude general base catalysis which often occurs in the amminolysis of esters specially when performed in low dielectric constant aprotic solvents[5].

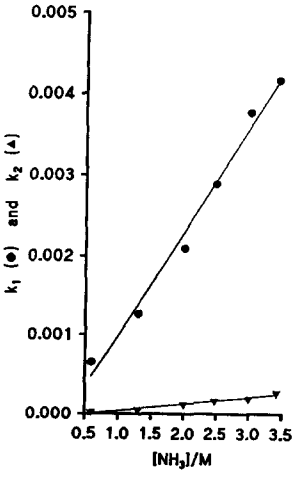


Figure 3. Dependence on NH_3 concentration of k_1 and k_2 for kinetics performed at 30°C.

Table 1. Experimental Conditions and Rate Constants of Ammonolysis of **1** in Absolute Ethanol.

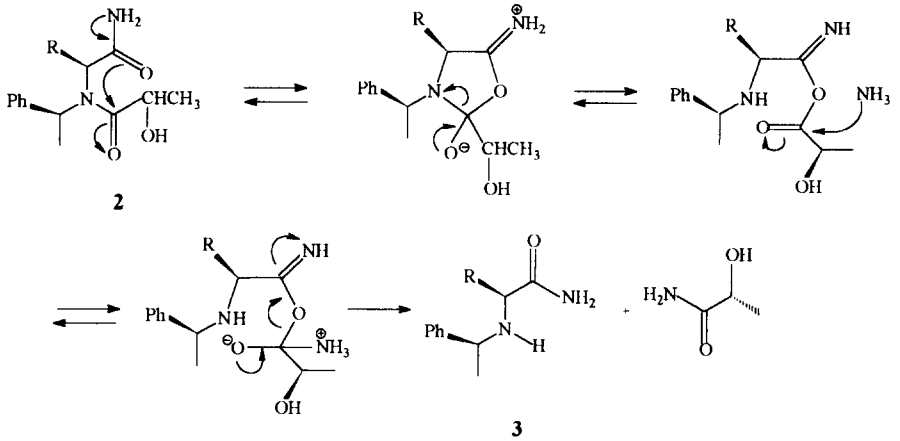
t(°C)±0.1	$[NH_3]$/mol^{-1}	k_1/ s^{-1} (a)	k'_1/ mol^{-1}ls^{-1}(b)	k_2/ s^{-1} (a)	k'_2/ mol^{-1}ls^{-1}(b)
10.5	1.77	7.80×10^{-4}	$(5.92\pm0.69)\times10^{-4}$	3.30×10^{-5}	$(2.21\pm0.14)\times10^{-5}$
	2.02	1.10×10^{-3}		3.77×10^{-5}	
	2.18	9.06×10^{-4}		4.10×10^{-5}	
	2.34	1.16×10^{-3}		5.00×10^{-5}	
	3.02	1.70×10^{-3}		5.68×10^{-5}	
	3.72	1.80×10^{-3}		7.52×10^{-5}	
	3.90	2.17×10^{-3}		8.22×10^{-5}	
13.5	1.92	1.01×10^{-3}	$(6.61\pm0.42)\times10^{-4}$	5.96×10^{-5}	$(3.66\pm0.67)\times10^{-5}$
	2.26	1.23×10^{-3}		7.39×10^{-5}	
	2.57	1.44×10^{-3}		1.02×10^{-4}	
	3.10	1.89×10^{-3}		1.13×10^{-4}	
	3.72	2.16×10^{-3}		1.25×10^{-4}	
15.4	1.30	8.31×10^{-4}	$(8.48\pm0.5)\times10^{-4}$	5.49×10^{-5}	$(3.21\pm0.05)\times10^{-5}$
	2.06	1.27×10^{-3}		8.10×10^{-5}	
	2.67	1.99×10^{-3}		1.01×10^{-4}	
	3.26	2.48×10^{-3}		1.19×10^{-4}	
	3.88	2.93×10^{-3}		1.38×10^{-4}	
21.0	1.56	1.37×10^{-3}	$(9.15\pm0.2)\times10^{-4}$	9.61×10^{-5}	$(6.38\pm0.25)\times10^{-5}$
	2.08	1.79×10^{-3}		1.16×10^{-4}	
	2.92	2.67×10^{-3}		1.82×10^{-4}	
	3.82	3.40×10^{-3}		2.38×10^{-4}	
	4.62	4.16×10^{-3}		2.85×10^{-4}	
25.3	1.30	1.34×10^{-3}	$(9.54\pm0.6)\times10^{-4}$	6.33×10^{-5}	$(7.3\pm0.36)\times10^{-5}$
	2.06	2.01×10^{-3}		1.22×10^{-4}	
	2.67	2.85×10^{-3}		1.55×10^{-4}	
	3.26	3.17×10^{-3}		2.15×10^{-4}	
	3.88	3.79×10^{-3}		2.49×10^{-4}	
30.0	0.595	6.50×10^{-4}	$(1.34\pm0.06)\times10^{-3}$	2.17×10^{-5}	$(8.81\pm0.74)\times10^{-5}$
	1.30	1.26×10^{-3}		4.98×10^{-5}	
	2.00	2.09×10^{-3}		1.18×10^{-4}	
	2.48	2.89×10^{-3}		1.65×10^{-4}	
	3.00	3.77×10^{-3}		1.91×10^{-4}	
	3.42	4.16×10^{-3}		2.69×10^{-4}	
33.7	0.715	1.18×10^{-3}	$(1.32\pm0.07)\times10^{-3}$	5.75×10^{-5}	$(1.31\pm0.05)\times10^{-4}$
	1.39	2.23×10^{-3}		1.30×10^{-4}	
	2.06	2.77×10^{-3}		2.39×10^{-4}	
	2.67	3.77×10^{-3}		2.98×10^{-4}	
	3.26	4.63×10^{-3}		3.90×10^{-4}	

(a) calculated from equation (1) from O.D. values recorded vs. time; (b) calculated from $k=k'[NH_3]$ equation

From the rate constant values reported in Table 1, it is possible to draw some conclusions. The values of k'_1 are very similar to that measured for the ammonolysis of an activated ester as ethyl chloroacetate in water at 25°C ($k_N=3\times10^{-3}$mol^{-1}ls^{-1})[6]. In other hand the k'_2 values seem too high to be attributed to the ammonolysis of an amide, particularly in the very mild conditions employed, in consideration of the amide exchange being normally a very difficult reaction[7]. Even the second order rate constants for the acqueous alkaline hydrolysis of aliphatic

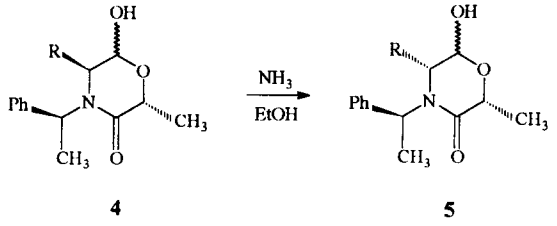
amides, which indeed occur at higher temperatures, are found to be noticeably smaller[8] (for example, k_{OH}= $7.3x10^{-7}mol^{-1}ls^{-1}$ for butyramide at 100°C in water). In addition, it is important to underline that the ammonolysis of reference compound **4**, which contains the amide function, did not occur (see before).

Therefore, we hypothesize that the second step of the process occurs because of the intramolecular participation of $-CONH_2$ involving the nucleophilic O-attack on the disubstituted amide group. So, a cyclic intermediate is formed whose opening yields a reactive imminoester intermediate (similar to that formed in ester[9a] or amide[9b] synthesis from carboxylic acids by DCC) which undergoes ammonolysis giving **3** and (R)-lactamide (Scheme 2).



Scheme 2.

In order to determine the rate enhancement caused by the assistance of neighboring group, we subjected lactol **4** to ammonolysis in which both the electronic and geometric features of amide group are similar to these of intermediate **2**. After 360 hours at r.t. in 3.8 M NH_3, the compound **4** did not undergo ammonolysis to any detectable extent, but underwent exclusively a partial isomerization at C-3 (Scheme 3), as evidenced by spectroscopic data [10].



Scheme 3.

However an approximate value of the observed assistance of $-CONH_2$ in the conversion of **2** into **3** can be evaluated as already reported[11]. Assuming that in the order of 1% of ammonolysis of **4** could have occurred,

but not detected, a pseudo first order rate constant of $\cong 3x10^{-9}s^{-1}$ can be estimated. Therefore, the rate acceleration could be evaluated at about $8x10^4$.

The thermodynamic parameters of activation (reported in Table 2) for both steps of the process were evaluated by plotting log k'_1 and log k'_2 vs. 1/T which give good straight lines, as shown in Figure 4.

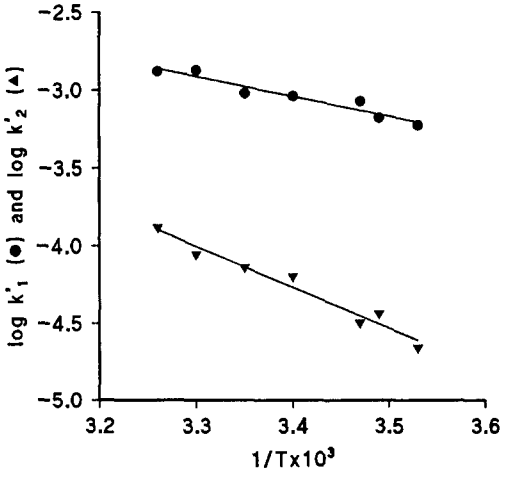


Figure 4. Plot of log k'_1 and k'_2 vs. 1/T for ammonolysis of **1** and **2**, respectively.

Table 2. Thermodynamic Activation Parameters for the Ammonolysis of **1** and **2**[a].

Activation parameters	Lactone **1**[b]	Intermediate **2**[b]
$\Delta F^{\neq}$/Kcal mol^{-1} c)	21.5±1	23.1±1.6
$\Delta H^{\neq}$/Kcal mol^{-1} d)	5.3±0.7	11.5±1.1
$\Delta S^{\neq}$/cal deg^{-1} mol^{-1} e)	-54.2±2.5	-38.7±3.8
$T\Delta S^{\neq}$/Kcal mol^{-1}	-16.2±0.7	-11.5±1.1

a) crrors shown arc standard dcviations; b) calculated from $k=k'[NH_3]$; c) calculated at 25°C from $\Delta F^{\neq} = RT\ln(kT/hk)$; d) calculated at 25°C from $\Delta H^{\neq}=E_a-RT$; e) calculated from $\Delta S^{\neq}=(\Delta H^{\neq}-\Delta F^{\neq})/T$.

The activation parameters values are consistent with the hypothesized mechanism reported in Scheme 2. Indeed, the 5.3 Kcal mol^{-1} value of $\Delta H_1^{\neq}$ for the ammonolysis of lactone **1** (which appears relatively small if compared with the ammminolysis of phenyl acetates[12] in water, generally above 10 Kcal mol^{-1}) could be ascribed to a favoured approach of the NH_3 to the carboxylic group, owing to an attractive dipole-dipole interaction between the ammonia and the polar amide group lying in the opposite side of the heterocyclic ring. The 11.5 Kcal mol^{-1} value of $\Delta H_2^{\neq}$ for the ammonolysis of the intermediate **2**, which indeed falls in the range for the amminolysis of phenyl acetates[12] in water as well, cannot be attributed to the unassisted transamidation of **2** for which a large value should be expected, considering that even the alkaline hydrolysis of amides[13] requires 16-23 Kcal mol^{-1}.

Concerning the activation entropy, the large negative values obtained can be explained on the basis of the following arguments. The $\Delta S_1^{\neq}$ (-54.2 cal $deg^{-1}mol^{-1}$) relative to the lactone ammonolysis reflects the loss of entropy associated both with the ring opening and with the good solvation of transition state owing to the large charge development on the attacking ammonia as accepted for the amminolysis of alkyl and phenyl acetate in acqueous[14] and in aprotic solvent[15]. In the other hand, the value of $\Delta S_2^{\neq}$ (-38.7 cal $deg^{-1}mol^{-1}$) less negative can be attributed only to the solvent effect on the zwitterionic tetrahedral intermediate (Scheme 2)
Lastly, work is in progress, on similar substrates, in order to better understand the mechanism involved in the second step and to attempt an interesting application of the reaction to the cleavage of peptides.

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10. About 70% of the trans (3S,6R)-**4** isomer was isomerized into the cis (3R,6R)-**5** one. This latter isomer was isolated by chromatographic purification (R_f value of TLC was greater for **4** than for **5**); ^{1}H-NMR δ 1.48 (d, 3H,J=7Hz), 1.54 (d,3H,J=7Hz), 1.98 (m,2H), 3.25 (ddd,1H,J=1, 3, 10.8Hz), 3.85 (m,2H), 4.4 (q,1H,J=7Hz), 4.45 (s,2H), 5.1 (d,1H,J=1Hz), 5.3 (m,2H), 5.95 (q,1H,J=7Hz), 7.25-7.45 (m,10ArH). By irrading the (C-6)-CH_3 of **5** a 3% nOe was observed on the (C-3)-CH_2. To GMS analysis the cis isomer **5** showed a smaller retention time than the trans **4** one and both the products gave the same fragmentation : MS m/z 216 (9), 200 (10), 186 (11), 110 (15), 105 (85), 96 (16), 91 (100), 79 (15), 77 (22).
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