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Amide and lactam hydrolysis of *N*-(2-hydroxyacetyl)-2-pyrrolidone: effective catalysis†

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ABSTRACT: When *N*-(2-hydroxyacetyl)-2-pyrrolidone (open form) is dissolved in water at pH > 8, irreversible cleavage of the exocyclic and endocyclic amide C—N bond occurs. The latter rupture corresponds to the lactam opening yielding *N*-(4-hydroxyacetyl)butanoic acid (NBA). NBA is produced from the ester hydrolysis of the ester-amide macrocycle that is in equilibrium with the cyclol form of the open form. We have previously reported this latter equilibrium for *N*-(2-aminoacetyl)-2-lactams. 2-pyrrolidone (lactam) and glycolic acid are produced from direct hydrolysis of the open form by means of the amide exocyclic cleavage. The [NBA]/[lactam] ratio increases at higher pH since the NBA production is second order with respect to [OH^-] while the corresponding lactam formation is only first order. The obtained kobs is hence the sum of the rate constants that yield lactam and NBA, respectively. This kobs is uncatalyzed and specific base catalyzed with unusually high rate constants of $2.1 \times 10^{-6}\,s^{-1}$ and $0.025\,M^{-1}\,s^{-1}$, respectively. The stability of the corresponding tetrahedral intermediate formed and the intramolecular alkoxy nucleophilic attack on the lactam carbonyl group combined with an effective protonation of the lactam nitrogen that promotes the C—N cleavage, contribute to increase the reaction rates and lactam opening. Rate constants for the two parallel reactions are obtained from kobs and [NBA]/[lactam] *versus* pH plots. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: hydrolysis; catalysis; lactam; amide; stable tetrahedral intermediate; cyclol; macrocycle; open form

INTRODUCTION

We have been interested in measuring intrinsic rates of intramolecular transformations in stable tetrahedral intermediates for some time. For example, we have reported[1,2] results on transannular intrinsic rates in bislactam macrocycles formed from *N*-(2-aminoacetyl)-2-lactams. We have used 2-pyrrolidone, 2-piperidone, and 2-caprolactam as the corresponding five-, six-, and seven-membered lactams. We have also reported[3] the rate of formation of the corresponding stable tetrahedral intermediates of *N*-heteroethylphtalimide (hetero: hydroxy, amino, and thioxy) and their rates of rupture to diacylimides. Subsequently, we synthesized *N*-(2-hydroxyacetyl)-2-pyrrolidone (**3**) expecting to observe similar chemical behavior to that observed in the *N*-(2-aminoacetyl)-2-lactams. However, somewhat unexpectedly, we found at pD > 7.5 an irreversible cleavage of the exocyclic and endocyclic C—N bond of **3** to yield, in the latter case, *N*-(4-hydroxyacetyl)butanoic acid (NBA) (**4**). This product corresponds to a lactam ring opening, a process of wide interest in bioorganic chemistry. NBA is a derivative of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter in the brain. GABA induces relaxation, analgesia, and sleep. It is produced in the brain from glutamate but is also available as a supplement pill. However, as a supplement it is not always an effective way to raise brain levels since it cannot easily cross the blood-brain barrier. Therefore, the use of a derivative such as γ-aminobutyric lactam (**1**) or even NBA (**4**) becomes of medical interest. On the other hand, lactam hydrolysis reactivity is an important topic in the design of antibiotics since it is well known that β-lactam antibiotics act by acylating a serine hydroxyl group in the catalytic center of bacterial protease. In fact, it has been found[4], that 2-pyrrolidone hydrolyzes with a specific base second-order rate constant of $5.59 \times 10^{-6}\,M^{-1}\,s^{-1}$ similar to *N*-methyl acetamide ($3.32 \times 10^{-6}\,M^{-1}\,s^{-1}$), two orders of magnitude slower than β-propiolactam ($2.37 \times 10^{-4}\,M^{-1}\,s^{-1}$). This stability of 2-pyrrolidone towards ring opening eliminated it as a potential antibiotic.

Peptide bonds hydrolyze with life-times of *ca*. 7 years under mild conditions[5] at 25 °C. Therefore, considerable effort has been focused on the design of a catalyst that hydrolyzes the amide bond under mild conditions using metal-promoted[6] artificial proteases. As non-metal

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catalysts, 4-heterocyclohexanones have been used[5] to promote intramolecular alkoxy attack in the hemithioacetal adduct formed by α-thiolacetamides nuclophilic attack, a reaction that mimics the hydrolysis of peptides by serine proteases. When tetrahydropyranose is used as catalyst and *p*-trifluoromethyl α-thiolacetanilide as substrate with [NaOH] = 0.2–2 M, a third-order rate constant of *ca*. $2 \times 10^{-3}\,M^{-2}\,s^{-1}$ is found. Therefore, second order rate constants of *ca*. $10^{-3}\,M^{-1}\,s^{-1}$ have been reported as an important catalytic reaction acceleration.

HIV-1 protease[7] hydrolyzes viral polyproteins into functional protein products that are essential for viral assembly and further activity, therefore, the effort to find HIV-1 protease is an important medical target. In fact, it has recently been pointed out[8] that in the dimer aspartyl protease active site there is formation of a tetrahedral-transition state intermediate in the hydrolysis of the peptides used as inhibitor. Therefore, the use of a reversible macrocycle peptide, such as the one produced in this work, may be of interest as an HIV-1 inhibitor.

In this work, we report the efficient *exocyclic* carbonyl hydrolysis of *N*-(2-hydroxyacetyl)-2-pyrrolidone (**3**) to produce the two products 2-pyrrolidone (lactam) (**1**) and glycolic acid (**2**). NBA (**4**) results from the *endocyclic* hydrolysis of the carbonyl group of **3**. (Scheme 1). The rates and equilibrium constants involved in this scheme have been measured and/or estimated. Furthermore, we attempt to explain the importance of the processes involved and of some of the products obtained.

EXPERIMENTAL

N-(2-hydroxyacetyl)-2-pyrrolidone (**3**) was synthesized from α-chloroacetic acid, benzylic alcohol, and 2-pyrrolidone (**1**) in four steps[9].

α-Benzylacetic acid

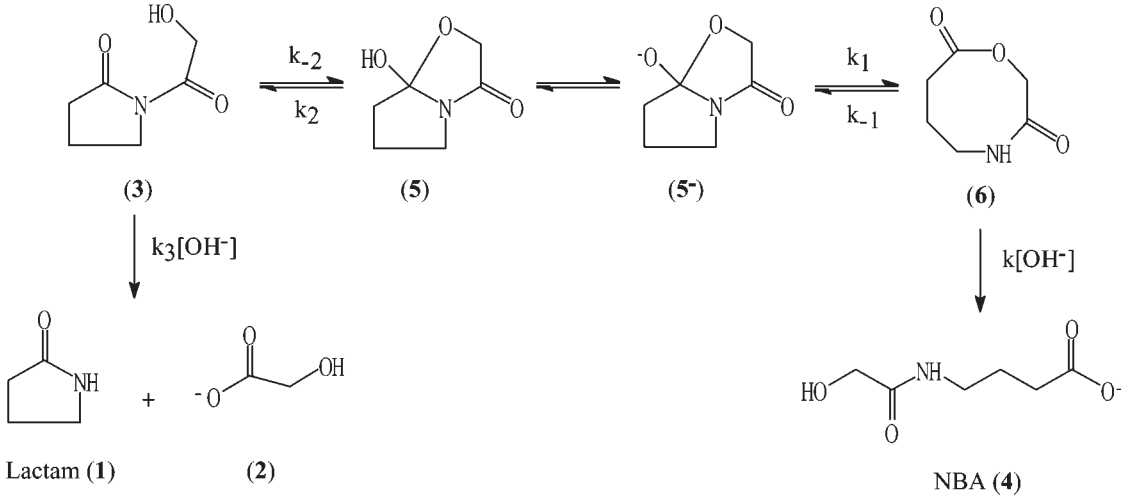
Six grams (0.15 mol) of potassium was added to a solution of 17 mL (0.16 mol) of benzylic alcohol in 200 mL of toluene. The final solution was refluxed for 4 h. To this solution, 0.8 g (0.07 mol) of α-chloroacetic acid in 50 mL of benzene was added gradually while stirring. The final mixture was refluxed for 16 h. After the reaction workup, a yellow liquid was obtained. Yield: 6.1 g (51%). NMR (^{1}H, $CDCl_3$): δ: 4.10 (s,2H); 4.6 (s,2H); 7.30 (s,5H); 9.5 (s,1H).

α-Benzylacetic acid chloride

Four grams (0.024 mol) of *α-benzylacetic acid* was dissolved in 25 mL of dry toluene. To this solution 3.5 mL (0.048 mol) of thionyl chloride was added. After addition, the solution was heated at 70–75 °C for 2 h. The thionyl chloride was removed by distillation to finally obtain a toluene solution of the target chloride. NMR (^{1}H,$CDCl_3$): δ: 4.49 (s,2H); 4.74 (s,2H); 7.30 (s,5H).

N-Benzylacetil-2-pyrrolidone

A solution of 4.1 g (0.048 mol) of 2-pyrrolidone and 3.8 g (0.0048 mol) of pyridine in 10 mL of dry toluene was kept at 0 °C in an ice bath. To this solution, was added 4.4 g (0.024 mol) of α-benzylacetic acid chloride while retaining the temperature at 0 °C. The reaction was kept at this temperature for 2 h. After that time, the reaction mixture was refluxed for another 2.5 h. A $CaCl_2$ trap was used during the whole reaction. After refluxing, the reaction mixture was cooled to 0 °C and mixed with 150 mL of water-ice at 0 °C. The organic phase was



Scheme 1. Competitive hydrolysis pathways for production of the pair 2-pyrolidone (**1**) and glycolic acid (**2**) from *exocyclic* carbonyl hydrolysis of *N*-(2-hydroxyacetyl)-2-pyrrolidone (**3**) and NBA (**4**) from its *endocyclic* hydrolysis

separated and washed with a saturated solution of $NaHCO_3$. The organic phase was then dried with anhydrous Na_2SO_4. The solution was filtered and excess toluene evaporated under reduced pressure at 60 °C. A solid was obtained. mp: 94–96 °C; yield: 3.4 g (61%). NMR(^{1}H,$CDCl_3$): δ: 2.10 (m,2H); 2.50 (t,2H); 3.80 (t,2H); 4.60 (s,4H); 7.30 (m,5H). Mass spectrum: *m/z*: 233 (M^+), 91 (M-142); 127 (M-106).

N-(2-Hydroxyacetyl)-2-pyrrolidone (3)

0.23 g (0.98 mmol) of *N*-benzylacetil-2-pyrrolidone was dissolved in 30 mL of ethyl acetate (HPLC grade). To this solution 0.43 g of Pd on Alumina (5%) catalyst in 35 mL of ethyl acetate was added. The mixture was reduced under a hydrogen atmosphere at 35 psi during 3 h. After the reduction, the mixture was filtered and the resultant liquid concentrated under reduced pressure. A white solid was obtained. mp: 62–63 °C (lit[10]: 64–65 °C); yield: 0.12 g (80%). NMR (^{1}H,$CDCl_3$): δ:2.10 (m,2H); 2.60 (t,2H); 3.30 (s,1H); 3.85 (t,2H); 4.70 (s,2H). NMR(^{1}H,D_2O): δ: 2.14 (m,2H); 2.65 (t,2H); 3.82 (t,2H); 4.70 (s,2H). Mass spectrum: *m/z*: 143 (M^+); 86 (M-57); 113 (M-30). IR (KBr): 3528 cm^{-1} (OH), 1732 cm^{-1} (C═O lactam), 1699 cm^{-1} (C═O amide). UV (H_2O): 226 nm.

Methyl ester of NBA

0.22 g (0.94 mol) of *N*-benzylacetyl-2-pirrolidone was dissolved in 30 mL of methanol (HPLC grade). To this solution 0.46 g of Pd-Alumina (5%) catalyst dissolved in 30 mL of methanol was added. The mixture was reduced under a H_2 atmosphere at 30 psi. After 3 h, the reaction was stopped and the mixture filtered. The resultant liquid was concentrated under reduced pressure at 40 °C. The CGMS spectrum of the liquid showed three peaks corresponding to toluene, *N*-(2-hydroxyacetyl)-2-pyrrolidone (**3**) and the methyl ester of *N*-(α-hydroxyacetyl)-γ-aminobutyric acid. Mass spectrum: 175 (M^+); 146 (M-29); 104 (M-71); 91 (M-84); 65 (M-110). NMR(^{1}H,$CDCl_3$): δ: 2.00 (m,2H); 2.45 (t,2H); 3.25 (t,2H); 3.80 (s,3H); 4.16 (s,2H). This compound was used to identify one of the hydrolysis products of **3**, the NBA (**4**).

Sample preparation

^{1}H NMR, was used to follow the hydrolysis of compound **3** at different pH values. The samples for each experiment were prepared by dissolving 25 mg of compound **3** in 0.7 mL of D_2O or in a solution of phosphate buffer in D_2O. NMR tubes of 5 mm were used to record the NMR spectra. According to the required pH, the following buffer solutions were used: $0 < pD < 2$, H_3PO_4; $2 < pD < 6$, KH_2PO_4; $6 < pD < 10$, K_2HPO_4; and $10 < pD < 13$, K_3PO_4. Buffer concentrations of 0.3, 0.5, 0.7, and 1.0 M and a [KCl] = 1 M were used. pD values were obtained directly from pH measurements by using the relation[10]: $pD = pH + 0.40$. The following values of pD were used to evaluate the equilibrium and hydrolysis rate: 0.4, 1.7, 4.9, 6.9, 7.4, 8.3, 10.5, 11.2, 11.8, 12.4, and 13.0. Equilibrium constants were evaluated in triplicate; a standard deviation <10% was obtained.

Rate constant measurements

Kinetics were measured by following the disappearance of the exocyclic methylene NMR (^{1}H) signal of compound **3** at *ca*. 4.6 ppm. Buffer phosphate (0.7 mL) in D_2O was used to dissolve compound **3** to yield a final concentration of 0.25 M in the NMR tube. Two kinds of experiments were conducted. One, keeping the buffer concentration constant at 0.5 M at pD: 7.3, 8.7, 10.8, 11.3, 12.7, and 13 and the second keeping pD constant at 8.7 and 12.7 and changing the buffer concentration to 0.3, 0.7, and 1.0 M. In all cases, a 400 MHz NMR, JEOL Eclipse Plus instrument, was used. Rate constants were obtained from the slope of a plot of ln ($I_t - I_{inf}$) *versus t*, where *I* is the NMR integral of the signal. Rate constants were measured in triplicate. The errors between measurements did not exceed 5%.

Identification of hydrolysis products

The lactam 2-pyrrolidone (**1**) and glycolic acid produced during the reaction were identified by adding these commercially available compounds to the reaction mixture and identifying the signals whose intensity increased. Signals of NBA (**4**) were identified by comparison with the NMR signals of the methyl ester of NBA that was synthesized in this work. Cyclol **5** and macrocycle **6** NMR signals were identified by changing the equilibrium toward the *N*-(2-hydroxyacetyl)-2-pyrrolidone (**3**) by decreasing the pH at *ca*. 2 of the reaction at pH *ca*. 12 and observing the disappearance of these signals. The cyclol and macrocycle signals were then assigned by analogy with similar systems previously identified[1,2] in our laboratory. Magnetization transfer experiments were also used to identify the corresponding methylene signals. In Table 1, the NMR signals for the reactants and products are shown. In Fig. 1, NMR spectra at pD = 3.0 and pD = 12.7 are shown.

DISCUSSION

The product pair 2-pyrrolidone (lactam) (**1**) and glycolic acid (**2**) is formed in the hydrolysis of *N*-(2-hydroxyacetyl)-2-pyrrolidone (**3**) via reaction of its exocyclic

Table 1. ^{1}H NMR chemical shift of reactants and products

Compounds	^{1}HNMR δ (ppm) in D_2O, pD = 12			
	N–**CH$_2$**–O	–C**H$_2$**N	–**CH$_2$**CO–	–CH$_2$–**CH$_2$**–CH$_2$–
(**1**)	—	3.45 (t)	2.36 (t)	2.12 (m)
(**2**)	3.96 (s)	—	—	—
(**3**)	4.70 (s)	3.82 (t)	2.65 (t)	2.14 (m)
(**4**)	4.08 (s)	3.26 (t)	2.21 (t)	1.78 (m)
(**5**)	4.55 (s)	3.44 (t)	2.85 (t)	2.13 (m)
(**6**)	4.35 (s)	3.33 (t)	2.53 (t)	1.90 (m)

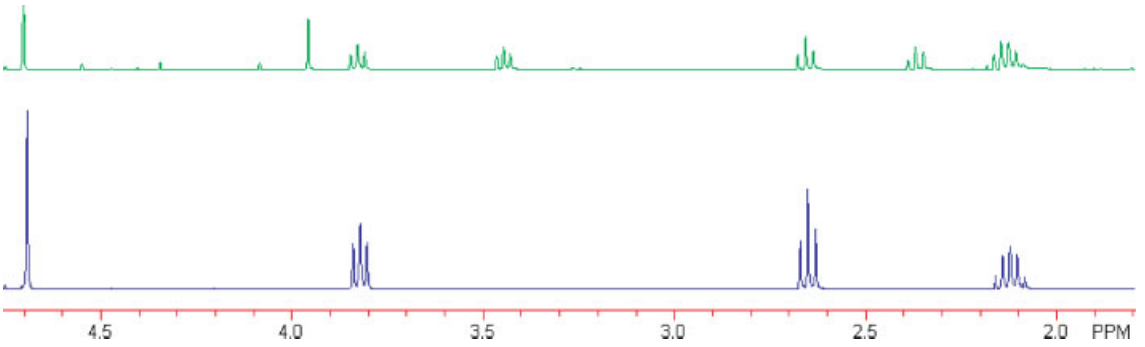


Figure 1. ^{1}NMR (400 MHz) spectra at pD = 3.0 (bottom) and pD = 12.7 (top). Bottom signals: 4.70 ppm –CO–C**H$_2$**–O compound **3**, 3.82 ppm, –C**H$_2$**N– compound **3**, 2.65,–C**H$_2$**–CO compound **3**, 2.14 ppm, –CH$_2$–C**H$_2$**–CH$_2$– compound **3**. Top signals: 4.70 ppm –CO–C**H$_2$**–O compound **3**, 4.55 ppm, –CO–C**H$_2$**–O Cyclol 4.35 –CO–C**H$_2$**–O, Macrocycle, 4.08 –CO–C**H$_2$**–O, NBA, 3.96 ppm –C**H$_2$**– glycolic acid (conjugate base), 3.82 ppm, –C**H$_2$**N– compound **3**, 3.45 –C**H$_2$**N– 2-pyrrolidone, 2.65, –C**H$_2$**–CO compound **3, 2.36, ppm** –C**H$_2$**–CO 2-pyrrolidone and 2.14 ppm, –CH$_2$–C**H$_2$**–CH$_2$– compound **3** and 2-pyrrolidone

carbonyl group. At the same time, NBA (**4**) is also produced in the reaction but via hydrolysis of the macrocycle (**6**) which is in equilibrium with the cyclol (**5**) (Scheme 1). Production of compound **4** is promoted at higher pD as depicted in Fig. 2 where a plot of log ([**4**]/[**1**]) *versus* pD is shown. The reaction rate is also catalyzed by OH^- as can be seen in a plot of log kobs *versus* pD (Fig. 3). The kobs at any pD is given by the sum of the rates of **1** and **2** formation plus the rate of formation of **4**. According to Scheme 1, the rate of formation of the pair **1** and **2**, is $r_L = k_3\,[OD^-]\,[\mathbf{1}]$. Assuming a steady state of [**1**] yields $r_L = (k_1k_3[OD^-]/(k_3[OD^-] + k_{-2}))$ [**5**]. The

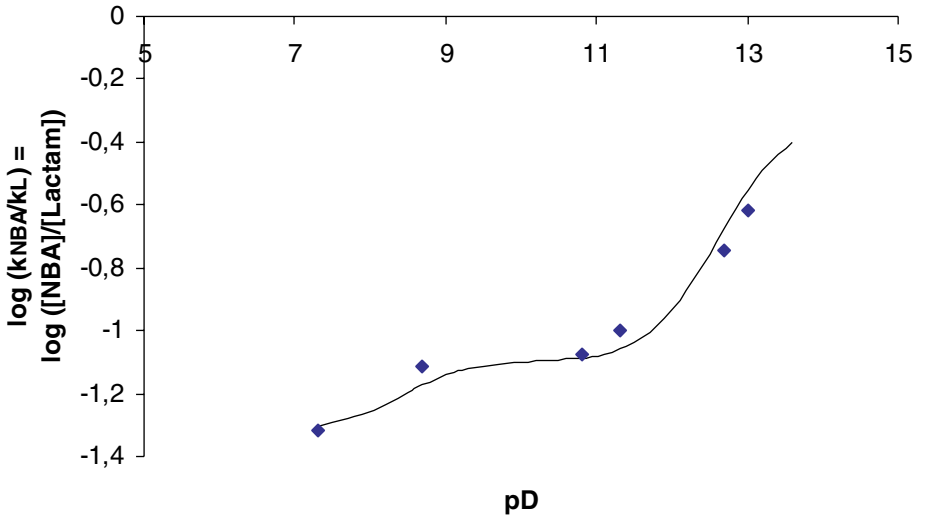


Figure 2. Plot of log ([**4**]/[**1**]) *versus* pD. Points: experimental measurements. Solid line: Best fit according to equation in text

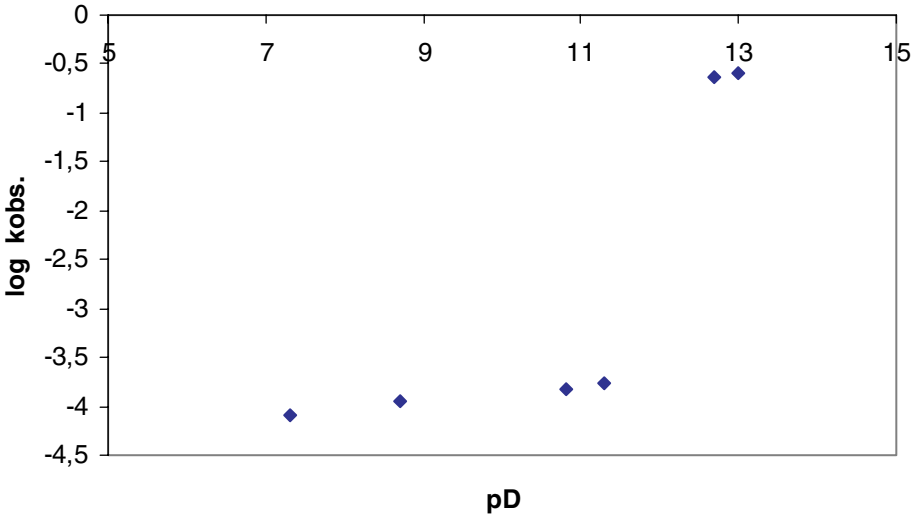


Figure 3. Plot of log kobs *versus* pD. Points: experimental measurements. Experimental p$K_a = 11.9$, from log $k_{max}-0.30$

rate of formation of **6** is then given by $r_{NBA} = k_1[OD^-]$ [**6**], which can be transformed into $r_{NBA} = (k[OH^-]k_{-1}/(k[OD^-] + k_{-1}))$ [$\mathbf{5}^-$], on assuming steady state for **6**. However, the two rates can be expressed in terms of the total amount of **5**, that is, $[\mathbf{5}]_T = [\mathbf{5}] + [\mathbf{5}^-]$, and, since $\mathbf{5}^-$ is the conjugate base of **5**, $[\mathbf{5}] = [D^+]/(Ka + [D^+])$ and $[\mathbf{5}^-] = Ka/(Ka + [D^+])$ where Ka is the acidity equilibrium constant of **5**. Therefore, the rate constants for lactam (k_L) and NBA (k_{NBA}) production are then given, respectively by:

$$k_L = (k_2k_3\,[OD^-]/(k_3[OD^-] + k_{-2})) \times [D^+]/(Ka + [D^+]) \quad (1)$$

$$k_{NBA} = (k[OD^-]k_1/(k[OD^-] + k_{-1}))Ka/(Ka + [D^+]) \quad (2)$$

The Ka value of **5** can be readily estimated from linear free energy relationships. For instance, using the pK_a value of Ethanol (15.9), a ρi value[11] for substitution at the α carbon and the following σi values[12]:

$$pK_a(5) = 15.9 - 8.4\,(\sigma i\,(OH) + \sigma i\,(NHCOEt)) = 15.9 - 8.4\,(0.25 + 0.25) = 11.7 \quad (3)$$

Two scenarios may then be used to simplify Eqns (1) and (2) at $pD < 11.7$ and at $pD > 11.7$. In the first case, $k_L = (k_1k_3[OD^-]/(k_3[OD^-] + k_{-2}))$ and $k_{NBA} = (k[OD^-]k_1/(k[OD^-] + k_{-1}))$ Ka/$[D^+]$. Assuming now that the equilibrium between the species **3**, **5**, and **6** is achieved rapidly as previously reported[1,2] for analogous compounds, k_{-2} and $k_{-1} > k_3[OD^-]$ and $k[OD^-]$, respectively. Therefore Eqns (1) and (2) can be transformed to:

$$k_L = k_2k_3[OD^-]/(k_{-2}) \quad (4)$$

$$k_{NBA} = (k[OD^-]\,k_1/k_{-1})\,(Ka/[D^+]) \quad (5)$$

This means that the rate of lactam formation is first order in $[OD^-]$ and that the rate of NBA formation is second order in $[OD^-]$. This conclusion is in agreement with the experimental result of Fig. 2 in which an increase in the ratio [**4**]/[**1**] = k_{NBA}/k_L is obtained when increasing the pD. Figure 3 also shows the essentially correctness of equations deduced above since kobs = $k_L + k_{NBA}$ in which k_L dominates when $pD < pK_a$.

When $pD > pK_a$, Eqns (1) and (2) may be transformed into the following expressions:

$$k_L = (k_2k_3[OD^-]/k_{-2})\,[D^+]/(Ka) \quad (6)$$

$$k_{NBA} = k[OD^-]k_1/(k_{-1}) \quad (7)$$

According to the last two equations, the rate of lactam formation becomes pD independent but the rate of NBA formation is now first order in $[OD^-]$. This means that even at high pD, the ratio [**4**]/[**1**] = k_{NBA}/k_L still depends on $[OD^-]$ but kobs should reach a constant value since the k_L term still dominates in the kobs expression. These conclusions are indeed in agreement with the experimental results of Figs 2 and 3.

It is important to remark that the last equations have been deduced in terms of the total concentration of compound **5**. In order to transform these equations as a function of the total concentration of reactants, the following considerations must be taken into account: $[1]_{Total} = [1] + [5]_{Total} + [6]$, $[5]_{Total}/[1] = K_C$ and $[6]/[5]_{Total} = K_M$, the total concentration of **5** in terms of the total amount of reactants becomes:

$$[5]_{Total} = [1]_{Total}/(1 + K_M + 1/K_C) \quad (8)$$

Therefore, if K_M and $K_C < 1$, then $[5]_{Total} = [1]_{Total}$. In any case, the correction of Eqns (1) and (2) and the equations derived from them, involves dividing or multiplying these equations by a constant that does not change the conclusions pointed out above.

Table 2. Rate and equilibrium constants experimentally measured and estimated

kobs (s^{-1})[1] ($k_3 + k$) ± 5%	K_B ($M^{-1} s^{-1}$)	pK_a (cyclol)	K_M ± 5%	K_C ± 10%
2.1×10^{-6}	($k_3 + k$) 2.5×10^{-2} ($B = OH^-$)[1] 5×10^{-7} ($B = HPO_4^{2-}$)[1] 6×10^{-4} ($B = PO_4^{3-}$)[1] k_3 4 ($B = OH^-$)[2] k 0.6 ($B = OH^-$)[2]	11.9[3] (11.7)[4]	1[5]	0.1 (pD = 12)[5]

[1] From kobs *versus* [B] plots.
[2] Estimated (see text).
[3] Experimental value from Fig. 3.
[4] Estimated value from Eqn (3).
[5] From ^{1}HNMR signal integration.

Estimates of the K_M and K_C values can be deduced from the NMR spectra at different pH. For instance, at high pH where the cyclol (**5**) and macrocycle (**6**) forms are detected (Fig. 1) with a low and almost equal signal intensity. Therefore, K_M is *ca*. 1. However, the K_C value is lower than 1 (*ca*. 0.1) as can be deduced from the relative intensity of the open form **3** and the cyclol **5** signals at pH *ca*. 12.

From Fig. 3, where a leveling in the plot is observed in accord with Eqn (6), the pK_a of the cyclol **5** can be experimentally evaluated. According to the plot in Fig. 3 this pK_a value is 11.7. This value is in good agreement with the one estimated, from linear free energy relationships, of 11.9. From Fig. 3 and according to Eqn (6) the leveling is equal to $k_2k_3 10^{-14}/k_{-2}$Ka, that is, $k_2k_3 10^{-2}/k_{-2}$. But $k_2/k_{-2} = 1/K_C = 0.1$ and the rate constant value at the leveling, according to Fig. 3, is 0.24 min^{-1} (4×10^{-3} s^{-1}). Therefore, 0.24 $min^{-1} = k_3 \times 0.1 \times 10^{-2}$ M and $k_3 = 240$ M^{-1} min^{-1} (4 $M^{-1} s^{-1}$).

Dividing Eqn (5) by (4), the [NBA]/[lactam] = [4]/[1] ratio is obtained: $[4]/[1] = (k \times 10\,M^{-1}/k_3)[OD^-]$. From a plot of [4]/[1] *versus* $[OD^-]$ (not shown), a slope (taking the last four points) of 1.52 ($R^2 = 0.98$) is obtained. Therefore, slope = 1.52 $M^{-1} = k \times 10^3$ M^{-1}/k_3 M^{-1}; from where a $k = 1.52 \times k_3/10 = 36$ M^{-1} min^{-1} (0.6 $M^{-1} s^{-1}$).

Under conditions in which lactam and NBA production is not catalyzed by base (Eqns (4) and (5), with the terms $k_3[OD^-]$ and $k[OD^-]$, respectively, equal to kw) still the NBA production is inversely dependent on $[D^+]$ as shown in Eqn (9) that represents Eqn (5) under non-catalyzed conditions.

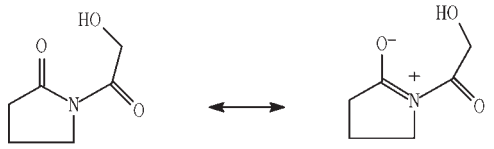
$$k_{NBA} = (kwk_{-1}/k_{-1})\ (Ka/[D^+]) \qquad (9)$$

This inverse dependency on $[D^+]$ is manifested in the ratio [NBA]/[lactam] at low pH as shown in Fig. 2. After this dependency a leveling is observed in Fig. 2. This means that in that range the NBA production is still non-catalyzed by base while lactam production is. This delay in NBA catalysis is a consequence of the one order of magnitude difference between the second-order rate constants k_3 and k. Therefore, the net effect (according to Eqn (9)) is the independence of the product ratio on $[OD^-]$. In Table 2, the experimentally obtained equilibrium and rate constants, estimated and derived in this work are shown.

Using the three first k_B values in the second column of Table 2 and the corresponding pK_a values for KH_2PO_4 (7.21), K_2HPO_4 (12.32), and H_2O (15.74), a $\beta = 0.55$ ($R^2 = 0.995$) is obtained. Since k_3 is the main path contributing to the base catalysis, the $\beta = 0.55$ value means that the proton transferred from water to the conjugate base of the catalyst has been transferred *ca*. 50% at the transition state of the k_3 step. Bi-functional catalysis with participation of the base-conjugated acid is also a possibility due to the need for protonation of the amino amide-leaving group. In fact, protonation of the leaving lactam (k_3 step) or amide group (k_1 step) is rate determining for the reaction product formation. At high pH water or the buffer-conjugated acid form may be acting as general acid catalyst. The planar five-membered ring of 2-pyrrolidone may also facilitate this protonation. In fact, protonation of the electron pair on nitrogen that is needed to promote the departure of the lactam occurs while maintaining the electron pair coming from the cleavage synperiplanar with the p orbital of the lactam carbonyl group. This induced stabilization at the transition state probably makes the difference in the observed chemistry of *N*-(2-hydroxyacetyl)-2-piperidone in which we have not detected lactam formation as compared with the one of compound **3**.

CONCLUSIONS

The second-order rate constant for hydrolysis of compound **3** to yield 2-pyrrolidone (**1**) and glycolic acid (**2**) is quite fast (4 $M^{-1} s^{-1}$) and comparable[13] to the hydrolysis rate of reactive *p*-nitrophenyl acetate



Scheme 2. Resonance form of compound **3** which favor nucleophilic hydroxyl attack on the exocyclic carbonyl carbon and retards the endocyclic carbonyl attack

($15\,M^{-1}\,s^{-1}$) at 25 °C and two orders of magnitude slower than the hydrolysis of *N*-acetylimidazole ($316\,M^{-1}\,s^{-1}$). This unusual reactivity is due to the restricted resonance between the nitrogen electron pair and the exocyclic carbonyl group that makes this carbonyl group reactive. The restriction is due to an efficient delocalization of the electron pair with the five-membered lactam carbonyl group (Scheme 2). In fact, this kind of delocalization has also been indicated[13] as that responsible for the high reactivity of *N*-acetyl-imidazole. In both cases, the delocalization of the electron pair on nitrogen is promoted by the planar structure of the five-membered ring that favors the maximum n-p orbital overlapping.

The formation of the GABA derivative NBA (**4**) is also fast ($0.6\,M^{-1}\,s^{-1}$) and its formation, relative to formation of **1**, is enhanced at higher pH. This tendency has been attributed to the formation of the derivative not directly from OH^- attack on the lactam carbonyl group but rather from the macrocycle **6** in equilibrium with the cyclol **5** and the *N*-(2-hydroxyacetyl)-2-pyrrolidone (**3**). The kinetic behavior shown in this work and the equilibrium established between the three forms mentioned above are strong arguments to support the proposal. The alternative, direct hydroxyl attack on the endocyclic carbonyl group is ruled out due to the kinetic argument and to the decrease in reactivity of this carbonyl group induced by the resonance form shown in Scheme 2. In fact, this low reactivity also influences the intramolecular alkoxyl attack. For instance, we have found[14] that in the case of the *N*-(2-hydroxyacetyl)-2-piperidone, the cyclol derivative is the more stable form at any pH. However, in the case of compound **3**, the cyclol form becomes relatively important only at high pD.

These results are then quite important to promote the hydrolysis of the unreactive five-membered 2-pyrrolidone lactam and may also be of relevance in the *in situ* production, at brain level, of a derivative of GABA that may act as inhibitory neurotransmitter. The reversible equilibrium established between cyclol **5** and macrocycle **6** present an interesting system that may attach reversibly to the active site of HIV-1 protease and act as its inhibitor.

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