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Ammonolysis of morpholine-2,5-diones: participation of the primary amide group. Part 2

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The ammonolysis of three morpholine-2,5-dione derivatives was investigated and the mechanism ascertained by kinetic studies and theoretical calculations. The kinetics, followed by high-performance liquid chromatography analysis, evidenced the presence of two intermediates, which were isolated and characterized. The ammonolysis occurs with a complex mechanism involving two consecutive reactions followed by two parallel ones. The second step of the whole reaction involves an anchimeric assistance of the primary amide group. The pseudo-first-order rate constants were calculated by appropriate equations, which describe the single steps of the process. Computational density functional theory investigations of vicinal primary amide group participation were performed using a model compound, and the transition states were generated. The theoretical calculations evidenced the essential role exerted by ammonia, which acts as a proton transfer. Copyright © 2011 John Wiley & Sons, Ltd.
Supporting information may be found in the online version of this article.

Keywords: ammonolysis; anchimeric assistance; computational investigations; kinetic investigations; morpholine-2,5-diones; primary amide group participation

INTRODUCTION

In the last decades, the intramolecular participation of vicinal groups represents an interesting topic in organic chemistry because it could be involved in the catalytic process of enzymes.[1,2] However, the intramolecular participation of amide group was ignored in proposed mechanisms of many enzymatic reactions. This is mainly because the intramolecular involvement of amide function has not been enough investigated in simple model of organic reactions, and in any case, high effective intramolecular catalysis has not been observed. A significant example in biochemistry of the intramolecular amide group participation has been shown to involve anchimeric assistance from the acetamido group that promotes glycosidic bond breaking.[3–5]

Various works have been focused on the participation of amide group in the hydrolysis of esters,[6–8] but, to the best of our knowledge, only the example previously reported by us takes into account the tertiary amide ammonolysis assisted by a vicinal primary amide group.[9] In the present paper, our aim is to examine thoroughly the mechanism previously hypothesized by investigating other morpholine-2,5-dione derivatives.[9] Really, in recent experiments, we isolated a reaction intermediate not previously detected. Thus, we synthesized and submitted to kinetic studies the racemate of 3,6-*trans* morpholine-2,5-dione derivatives **1**, **2** and **3** in order to ascertain the structure of the intermediate and verify the possible influence of the alkyl substituent at N-4 (Scheme 1) on the efficiency of intramolecular catalysis, that is, the anchimerically assisted process. In fact, in previous kinetic studies concerning the acid hydrolysis of the ether linkage assisted by the vicinal secondary amide group, we observed a remarkable reaction rate change with the bulkiness of the alkyl substituent at the carbonyl group.[10]

RESULTS AND DISCUSSION

In the previous work,[9] the kinetics were spectrophotometrically monitored, and the dependence of optical density versus time evidenced two step consecutive reactions. In the present study, we followed the ammonolysis of morpholine-2,5-dione derivatives **1**, **2** and **3** by high-performance liquid chromatography (HPLC) analysis because by this technique, it was possible to evidence two consecutive reactions (first-order rate constants k_1 and k_2) and two parallel ones (first-order rate constants k_3 and k_4) (Scheme 1). The first step is the opening of the morpholine-2,5-dione derivative **A** by ammonia to give the first intermediate **B**. The second step, that is, the conversion of the first intermediate **B** into the second one **C**, is the process, which involves the intramolecular participation of the secondary amide group induced by ammonia. Subsequently, intermediate **C** suffers two parallel reactions by means of the nucleophilic attack of ammonia or ethanol giving the 2-hydroxy-propionamide and **D** or **E**, respectively (Scheme 1).

The rate constants of the three steps were evaluated monitoring the concentration changes of **A**, **B**, **C**, **D** and **E** versus time by HPLC analysis. Because the rate constant $k_1 >> k_2$ (Table 1), the

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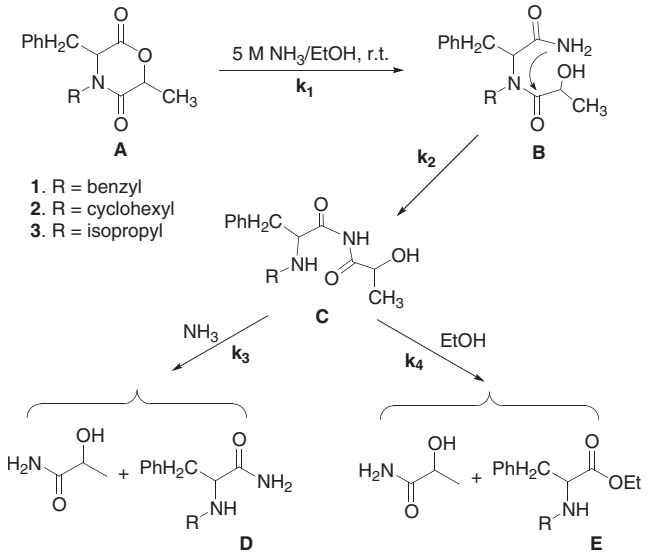
Journal of Physical Organic Chemistry



Scheme 1. Pathway of morpholine-2,5-diones ammonolysis

second step is not affected by the first one, and the overall kinetic process becomes less complex. Then, the process can be considered constituted by an independent first step, that is, the decomposition of **A**, followed by the decomposition of intermediate **B** and the conversion of **C** in **D** and **E** through two parallel reactions (Scheme 1).

Because $k_1 >> k_2$, we assumed the initial concentration $[B_0] = [A_0]$, that is, the starting concentration. The first-rate constants were calculated according to the following equations[11,12], which describe the dependence of the concentration of **A**, **B**, **C**, **D** and **E** versus time:

$$[A] = [A_0]e^{-k_1 t} \quad (1)$$

$$[B] = [B_0]e^{-k_2 t} \quad (2)$$

$$[C] = [B_0]\left[[k_2/(k_3 + k_4 - k_2)]e^{-k_2 t} - [k_2/(k_3 + k_4 - k_2)]e^{-(k_3+k_4)t}\right] \quad (3)$$

$$[D] = [B_0]\left[k_3/(k_3+k_4) - [k_3/(k_3 + k_4 - k_2)]e^{-k_2 t} - [k_2 k_3/(k_3 + k_4)(k_2 - k_3 - k_4)]e^{-(k_3+k_4)t}\right] \quad (4)$$

$$[E] = [B_0]\left[k_4/(k_3+k_4) - [k_4/(k_3 + k_4 - k_2)]e^{-k_2 t} - [k_2 k_4/(k_3 + k_4)(k_2 - k_3 - k_4)]e^{-(k_3+k_4)t}\right] \quad (5)$$

where k_1, k_2, k_3 and k_4 are the first-order rate constants of various reaction steps (Table 1).

Figures 1–6 show the concentration versus time dependence of the various compounds. The experimental curves are fitted by the appropriate Eqns 1–5, which describe the single steps of the overall process (Scheme 1). The curves in Figs 1, 3 and 5 describe the disappearance of the starting lactones investigated **1**, **2** and **3**. The curves in Figs 2, 4 and 6 show the disappearance of **B** (solid circle) and the formation and disappearance of **C** (open square), and finally the formations of **D** and **E** are displayed by solid triangle and star, respectively.

The k_2 value, obtained by Eqn 2, was introduced in Eqn 3 in order to calculate the rate constant of the disappearance of **C**, that is, $k_3 + k_4$ (Scheme 1). Then, the values of k_3 and k_4 were obtained by Eqns 4 and 5, respectively, taking into account that the decomposition of intermediate **C** occurs through two parallel reactions, and therefore the ratio $k_3/k_4 = [D]/[E]$ is constant within the experimental error (Table 1).

The curves (Figs 1–6) are plotted by using an iterative nonlinear least square procedure[13] and the pseudo-fist-order rate constants (k_1–k_4) were calculated according to Eqns 1–4. The best fit of the experimental points gives a correlation coefficient $R \geq 0.98$.

As it results from data reported in Table 1, the first step (k_1), that is, the lactone opening, is fast and is not significantly influenced by the substituent at N-4, in agreement with the Taft values σ_I, which are small and similar.[14] Also, the steric effect of the substituent at N-4, measured by v or Es constants,[15] does not exert a relevant effect on the reaction rate.

Conversely, the second step **B** → **C**, in which the anchimeric assistance is involved, appears sensible to both the steric and polar effect. Really, the k_2 increases 7–10-fold on going from substrate **1** to **3** according to the increase of both the steric and polar parameters of the substituents.[14,15]

In order to determine the rate enhancement induced by the neighbouring primary amide group, we take into account the reference substrate already used[9], which, subjected to ammonolysis, displayed an estimated rate constant $k = 3 \times 10^{-9}$/s. Therefore, the rate accelerations, k_2/k, measured for the substrates investigated are about 5×10^3 for **1**, 4×10^4 for **2** and 5×10^4 for **3**.

CHARACTERIZATION OF INTERMEDIATE C

The chemical structure of intermediate **C** was ascertained by examining the product obtained from the ammonolysis of the starting

Table 1. Pseudo-first-order rate constants measured at 25 °C ± 0.1[a]

Substrates	$10^{-3} \times k_1$/s[b]	$10^{-5} \times k_2$/s[c]	$10^{-5} \times k_3$/s[d]	$10^{-5} \times k_4$/s[e]	[D]/[E][f]
1	5.83 ± 0.5	1.56 ± 0.66	0.9 ± 0.66	0.53 ± 0.07	1.7
2	6.66 ± 0.5	12.0 ± 0.33	10 ± 1.0	1.33 ± 0.18	7.8
3	2.83 ± 0.33	16.0 ± 1.16	4.33 ± 0.5	1.55 ± 0.20	2.7

[a]Standard errors are reported.
[b]Decomposition rate constant of **A** calculated by the Eqn 1.
[c]Decomposition rate constant of **B** calculated by Eqn 2.
[d]Formation rate constant of **D** calculated by Eqn 4.
[e]Formation rate constant of **E** calculated by Eqn 5.
[f]Products ratio determined by HPLC analysis.

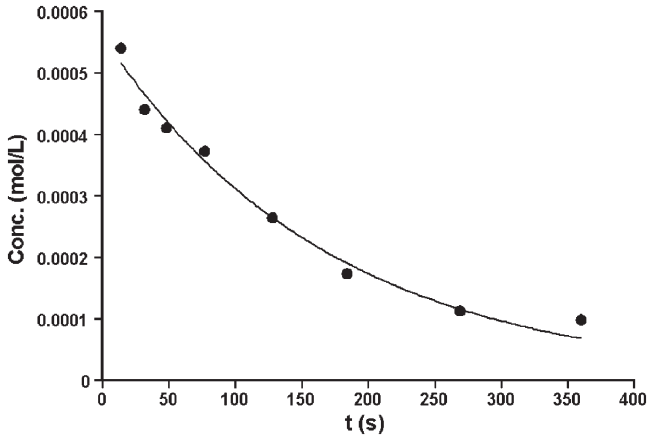


Figure 1. Dependence of the concentration of **1A** versus time. Points are experimental; the curve is calculated by Eqn 1

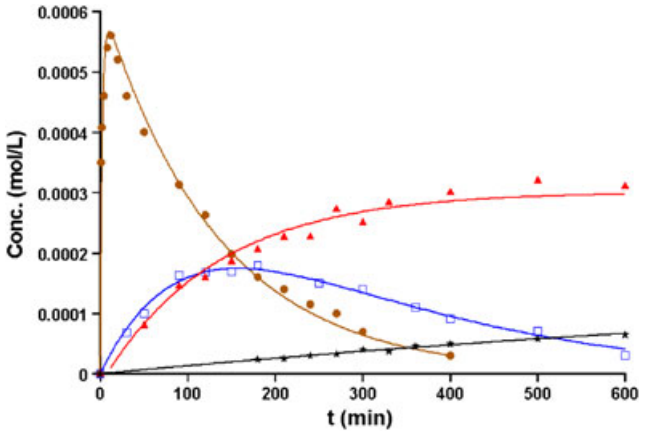


Figure 4. Dependence of the concentration of **2B** (●), **2C** (□), **2D** (▲) and **2E** (⋆) versus time. Points are experimental; the curves are calculated by Eqns 2–4 and 5, respectively

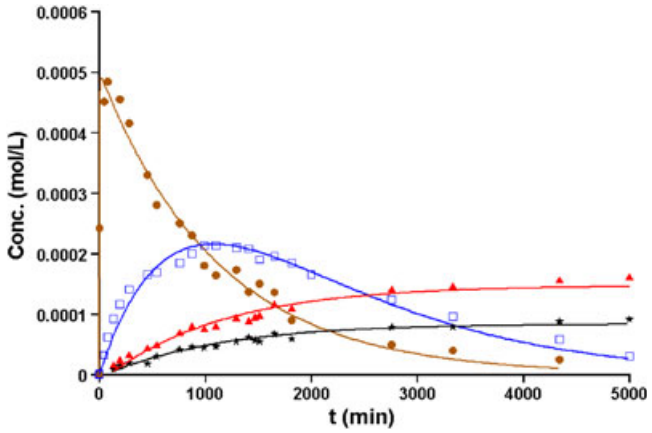


Figure 2. Dependence of the concentration of **1B** (●), **1C** (□), **1D** (▲) and **1E** (⋆) versus time. Points are experimental; curves are calculated by Eqns 2–4 and 5, respectively

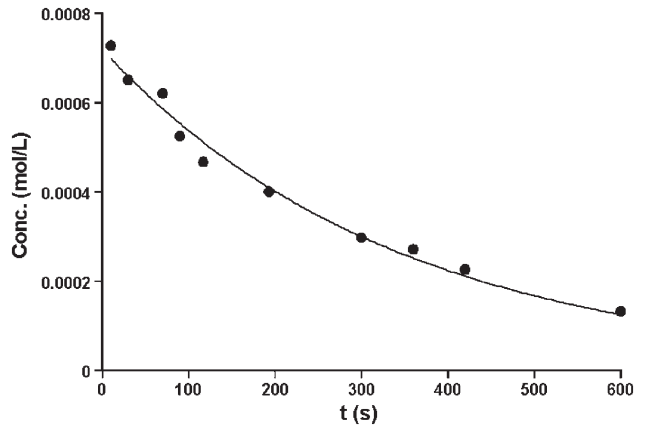


Figure 5. Dependence of the concentration of **3A** versus time. Points are experimental; the curve is calculated by Eqn 1

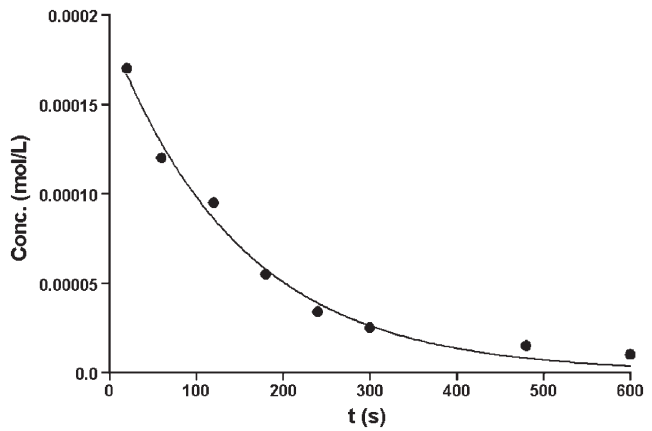


Figure 3. Dependence of the concentration of **2A** versus time. Points are experimental; the curve is calculated by Eqn 1

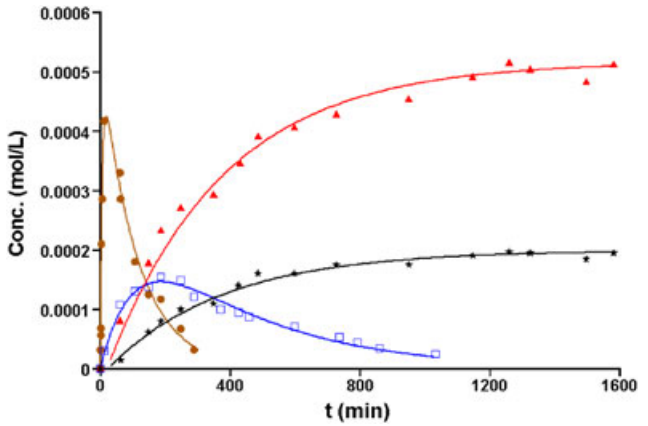


Figure 6. Dependence of the concentration of **3B** (●), **3C** (□), **3D** (▲) and **3E** (⋆) versus time. Points are experimental; curves are calculated by Eqns 2–4 and 5, respectively

lactone **2**. The investigation was performed on this substrate because the chromatographic separation of intermediate **2C** is easier than that of intermediates **1C** or **3C**. The ammonolysis was stopped after about 2 h, and the reaction mixture was worked up following the general procedure reported in the General section.

Journal of Physical Organic Chemistry

We wish to point out that, in addition to the intermediate described in Scheme 1, it is possible that the alternative intermediate isomer is **2Ciso** (Fig. 7), derived from the attack of the primary amide carbonyl oxygen (instead of nitrogen) on the tertiary amide carbonyl carbon. Nevertheless, **2Ciso** can be excluded because it is an imino ester, that is, the same very reactive intermediate hypothesized in the esters and amides synthesis from carboxylic acids in the presence of *N*,*N*′-dicyclohexylcarbodiimide.[16] On the contrary, the intermediate recovered is stable, being isolated by chromatographic elution. Besides, although the ^{1}H and ^{13}C spectra are consistent with both the structures **2C** and **2Ciso**, we observed a coupling between the imidic proton H_y and the carbon C_e by 2D experiments (refer to the EXPERIMENTAL section) and a very fast exchange in D_2O, which is consistent with the presence of an acid proton such as the imidic NH group. These findings, particularly the last two, substantiate the proposed structure of intermediate **2C**, which is strengthened by the theoretical calculations (refer to the THEORETICAL CALCULATIONS section).

THEORETICAL CALCULATIONS

In order to determine the pathway of the anchimerically assisted ammonolysis of intermediates **B** to **C**, density functional theory theoretical calculations were performed using a model compound **Bm** in which the *N*-alkyl and the benzyl groups in **B** were substituted with two methyl groups in order to simplify the calculations (refer to the Computational methods section for computational details). The reaction mechanism and the free energy profile for the formation of intermediate **Cm** are reported in Scheme 2 and Fig. 8, respectively.

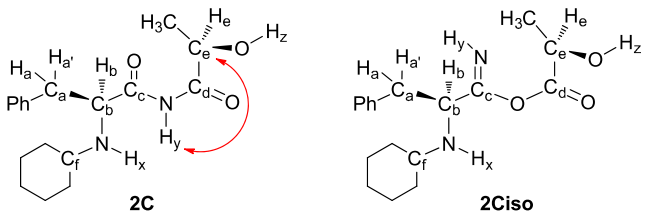


Figure 7. Structural isomers of intermediate **C**

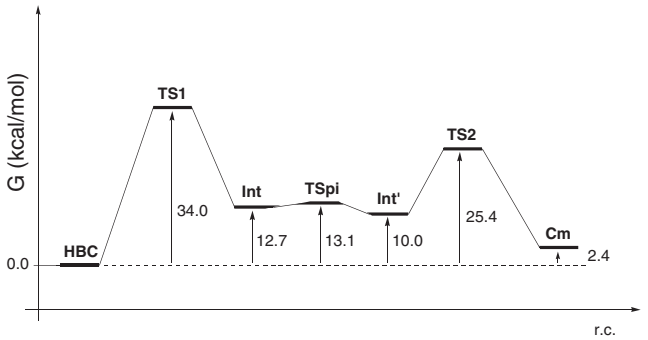
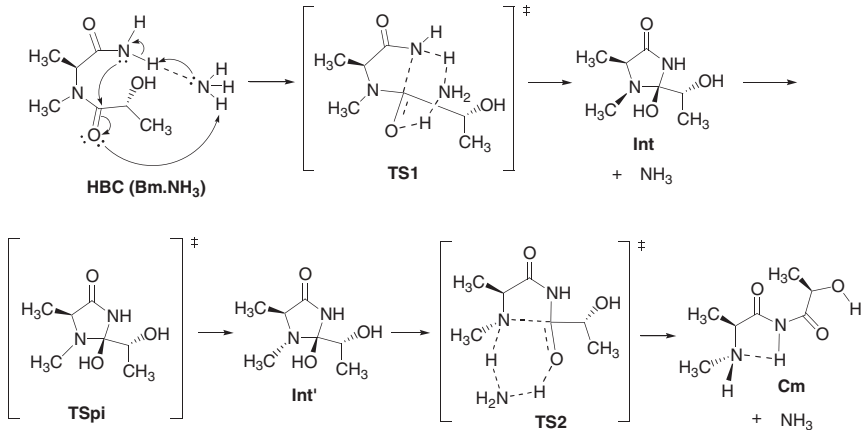


Figure 8. Free-energy profile for the formation of intermediate **Cm** assisted by ammonia. The barriers are referred to the hydrogen-bonded complex **HBC**

The calculations show the preliminary formation of a hydrogen-bonded complex **HBC** between **Bm** and NH_3, in which ammonia is placed at 0.1937 n/m from one of the hydrogen atoms of the primary amidic group. The free energy of this complex (−666.958216 hartrees) is taken as the zero point for the further steps. Then, a transition state (TS), **TS1**, is generated (Fig. 9A), in which we note the incipient formation of a N–C bond between the primary amide nitrogen and the tertiary amide carbonyl carbon (0.1977 n/m, 0.39 e^-). Ammonia acts as a proton transfer, taking a proton from the amidic group and giving a proton to the oxygen carbonyl group with the formation of an incipient O–H bond (0.1492 n/m, 0.17 e^-), which facilitates the contemporary nucleophilic attack of nitrogen on the carbonyl. The theoretical studies demonstrate the essential role of NH_3 in the neighbouring participation of the primary amide: in fact, in the absence of ammonia, we find a TS at very high energy, 65.3 kcal/mol in comparison with 34.0 kcal/mol (Supplementary material). Therefore, as observed in the experimental conditions employed, the reaction cannot occur in the absence of ammonia. The simultaneous formation of the C–N and O–H bonds leads to the cyclic intermediate **Int**, which, through the fast pyramidal inversion at the tertiary nitrogen in **TSpi** (0.4 kcal/mol above **Int**), gives the intermediate **Int′** that is the species really prone to the next step. The further breaking of the bond between the tertiary nitrogen and the ex-carbonyl carbon gives rise to the imide **Cm**. As we see in **TS2** (Fig. 9B), also this step is



Scheme 2. Reaction mechanism for the Cm intermediate

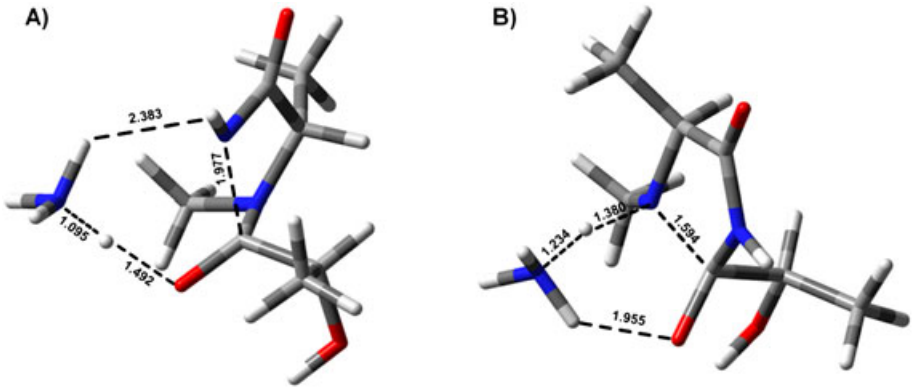
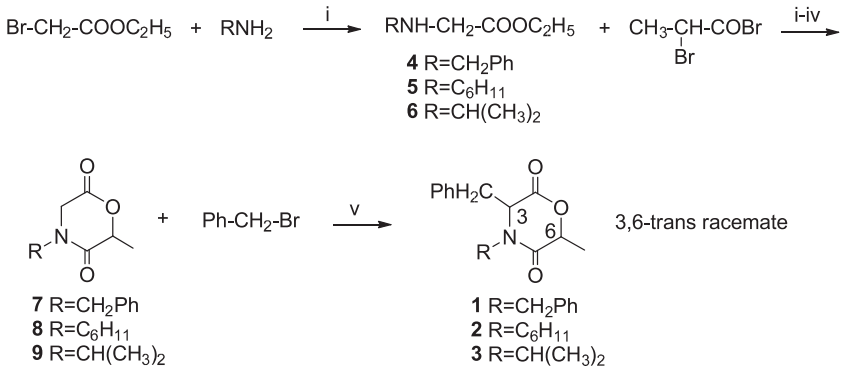


Figure 9. Transition states **TS1** (A) and **TS2** (B) with relevant interatomic distances (Å)



Scheme 3. (i) CH_2Cl_2/Et_3N/r.t.; (ii) NaOH/EtOH/H_2O; (iii) HCl; (iv) NaH (60% dispersion in mineral oil) in dry tetrahydrofuran (THF)/dimethylformamide at reflux; (v) 1 M lithium hexamethyldisilazide/THF at −78 °C

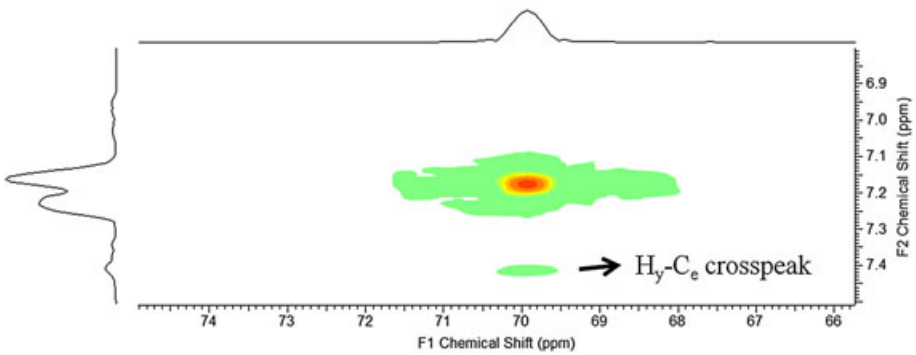


Figure 10. Expanded section of HMBC spectrum of intermediate **2C**

catalyzed by ammonia, which favours the contemporary transfer of the proton from oxygen to nitrogen. The low value of the activation energy of **TS2** (15.4 kcal/mol) makes the second step very fast and, consequently, this intermediate very unstable and not isolable in the course of the experimental work.

Two considerations deserve a brief comment. The first is that in **TS1**, we have the formation of a new chiral centre at C-5, giving rise to two diastereomeric intermediates. However, because the energies involved are very similar and the chiral centre is destroyed in the subsequent step, we consider only one path for simplicity. We have intensively investigated also the possible attack by the carbonyl oxygen of the primary amide on the tertiary amide carbonyl carbon (Fig. 9), but no corresponding TS was found.

SYNTHESIS OF THE SUBSTRATES 1–3

The substrates submitted to the kinetic investigations **1**, **2** and **3** were synthesized by following our procedure[17] outlined in Scheme 3, that is, based on the alkylation of the synthones 4-*N*-alkyl-1,4-morpholin-2,5-diones **7–9**. The products **1**, **2** and **3** were obtained with a total regioselection and with a practically total 1,4-*trans* induction, with respect to the methyl group at C-6, as previously observed for analogous morpholin-2,5-diones.[17–22] The *trans* isomers were isolated as racemates in good overall yield (after purification by silica gel chromatography), and the *trans* configuration was deter mined on the basis of ^{1}H NMR data and making use of our experience previously acquired on the morpholin-2,5-dione derivatives.[17–22]

Journal of Physical Organic Chemistry

CONCLUSIONS

In this paper, we describe the mechanism of the anchimerically assisted ammonolysis of three lactones (**1–3**). The kinetics, followed by HPLC analysis, evidenced a complex process involving two consecutive reactions and two parallel ones. We emphasize that all the compounds involved in the process have been isolated and characterized, and the first-order rate constants of the four steps have been calculated by the appropriate kinetic equations. The conversion of intermediate **B** into the **C** one is anchimerically assisted, and it appears sensible to both the steric and polar effect. Interestingly, the high rate enhancement caused by the assistance of the neighbouring primary amide group on the tertiary amide one is in the range 5×10^3–5×10^4.

Besides, on the basis of the theoretical calculations, we demonstrated that the highly effective intramolecular catalysis needs the presence of ammonia, which acts as proton transfer. In fact, on the basis of the theoretical calculations, the anchimerically assisted process cannot occur in the absence of ammonia (at least in the experimental conditions employed) because the corresponding TS is too high in energy to be competitive. In addition, the alternative pathway, involving the attack of oxygen of the primary amide group instead of nitrogen, can be excluded because the corresponding TS was not detected.

In this work, we have isolated intermediate **C** not previously noticed:[9] in fact, on the basis of the NMR analysis and the theoretical calculations, we ascertained the structure of the second intermediate **C**, which is different from that hypothesized in a previous study.[9]

Finally, we underline that examples of such a type of participation are not found in the literature.

EXPERIMENTAL

Kinetics

Kinetics of the ammonolysis of lactones **1–3** were followed by HPLC.

Preliminary experiments, performed by ^{1}H NMR and HPLC analysis, evidenced the complexity of the lactone ammonolysis, which give rise to two intermediates. Because the disappearance of the starting lactone **A** is meaningfully faster than the subsequent steps (Table 1), the kinetics were carried out in single tiny glass bottles (5 mL) sealed by a screw plug with Teflon septa. Kinetic runs were initiated by adding 100 µL of the stock solution of lactone (0.46 M for **1** and 0.31 M for **2** and **3**) in ethanol to each tiny bottle containing 3 mL of 5 M NH_3 solution in ethanol, prethermostatted at 25±0.1 °C. Then, the lactone concentrations employed for the kinetic measurements were 0.015 M for **1** and 0.01 M for **2** and **3**. The tiny bottles were kept in a thermostat, and the reaction was stopped by cooling each sample, removed at fixed times, in crushed ice and by adding 2 mL of cold 4.9 M HCl. The solution was then diluted with ethanol and water (enough to dissolve the NH_4Cl) to give a total volume of 25 mL in order to obtain an appropriate concentration to be analysed by using HPLC, according to the calibration straight line.

The steps subsequent to the decomposition of the starting lactone **A** were followed on one single suitable solution, and the concentrations versus time of **B**, **C**, **D** and **E** (Scheme 1) were monitored by using the HPLC analysis. Kinetic measurements were carried by using a solution of the starting lactone in 3 mL of ethanol, and 5 M NH_3 in ethanol (thermostatted at 25±0.1 °C) was added by a dropping funnel, in an inert atmosphere, to give a total volume of 100 mL in a volumetric flask. The final concentrations of the starting lactones **1–3** are the same as reported earlier. The glass flask was quickly stopped with a latex septum and kept at 25 °C. At fixed times, 2 mL of the solution were removed by means of 2.5 mL Hamilton TLL syringe (Bonaduz, GR, Switzerland), and the reaction was stopped by dissolving the sample in 2 mL of cold 4.9 M HCl and diluting to 25 mL, as previously described.

High-performance liquid chromatography analysis

The separation of the compounds **A**, **B**, **C**, **D** and **E** was performed by Hewlett Packard 1090 (Palo Alto, CA, USA) coupled with 5 µ C18 Luna column by using the mobile phase CH_3CN/phosphate buffer (0.03 M) at pH = 4.2 for the substrate **2** and at pH = 7 for **1** and **3**. The concentrations of **A**, **B**, **C**, **D** and **E** were calculated by the calibration line built with authentic samples at various concentrations (mol/L) and the area measured by HPLC. Retention times of various compounds and the elution conditions are reported in the Supplementary material.

Computational methods

All calculations were performed with the Gaussian 03W suite of programmes (Gaussian, Inc., Pittsburgh, PA, USA).[23] All the molecular geometries were optimized at the density functional theory level by using the Becke's three-parameter exchange functional in conjunction with the Lee-Yang-Carr correlation functional (B3LYP).[24] For all the atoms, the 6-311G (d, p) basis set was used. To take into account bulk solvent effects, full geometry optimizations within a continuum solvent model (with ethanol as solvent) were carried out via the self-consistent reaction field approach using the polarizable continuum model method.[25–27] Additional spheres were placed on hydrogen atoms that are transferred in the investigated TSs and were coherently used in all the calculations.

Calculations of the harmonic vibrational frequencies were carried out to determine the nature of each optimized critical point. For all the TSs, inspection of the negative frequency was sufficient to specify the corresponding reaction path. Gibbs free energies, taken as the sum of the electronic and thermal free energies at 298.15 K, are always used for discussing the energetics.

Geometries and energies of all calculated structures are reported in the Supplementary material.

Synthesis of the substrates (1–3)

General

^{1}H and ^{13}C NMR spectra were recorded on a Varian MR 400 spectrometer (Palo Alto, CA, USA) equipped with an indirect probe at 400 MHz and at 100 MHz, respectively, using $CDCl_3$ as the solvent at 25 °C, unless otherwise stated. Chemical shift was reported in ppm relative to tetramethylsilane, and the coupling constants (*J*) are in hertz. Melting points (m.p.) were measured on an Electrothermal IA 9000 apparatus (Thermo Fisher Scientific, Rochford, Essex, UK) and were uncorrected. Dry tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl and dry dimethylformamide (DMF) from calcium hydride. Chromatographic separations were performed with silica gel 60 (230–400 mesh).

General procedure to the N-alkyl-ethylglycinates (4–6)

To a stirred solution of the alkyl amine (100 mmol) and triethylamine (16.9 mL, 120 mmol) in CH_2Cl_2 (50 mL), cooled at 0 °C, ethylbromoacetate (13.2 mL, 120 mmol), diluted in 10 mL of CH_2Cl_2, was slowly added dropwise. The cooling bath was removed, allowing the reaction to warm up to room temperature (r.t.). The reaction mixture was then stirred at r.t. and followed by thin-layer chromatography (TLC) (extracting a basified aliquot with ethyl acetate and eluting with cyclohexane/ethyl acetate 40/60). After about 24 h, the organic solvent was evaporated under vacuum and the residue dissolved in diethyl ether (300 mL) and water (100 mL). After separation, the organic phase was washed with water and dried on $MgSO_4$, and the organic solvent was evaporated, being careful to the product **6**, which is volatile. The residue was submitted to silica gel chromatography, eluting with hexane/ethyl acetate, except the product **6**, which was eluted with petroleum ether/diethyl ether. The oily product was isolated pure in 72–83% yield.

N-Benzyl-ethylglycinate 4. The title product was obtained in 83% yield by using benzylamine. ^{1}H NMR δ: 1.27 (t, 3H, J = 7.2), 1.89 (bs, 1H), 3.41 (s, 2H), 3.81 (s, 2H), 4.19 (q, 2H, J = 7.2), 7.24–7.29 (m, 1ArH), 7.30–7.36 (m, 4ArH). ^{13}C NMR δ: 14.2, 50.1, 53.3, 60.7, 127.2, 128.3, 128.5, 139.6, 172.4. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.52; H, 7.82; N, 7.25.

N-Cyclohexyl-ethylglycinate 5. The title product was obtained in 80% yield by using the cyclohexylamine. ^{1}H NMR δ: 1.03–1.27 (m, 5H), 1.27 (t, 3H, J = 7.2), 1.57–1.65 (m, 1H), 1.63 (bs, 1H), 1.69–1.76 (m, 2H), 1.82–1.87 (m, 2H), 2.36–2.44 (m, 1H), 3.42 (s,2H), 4.18 (q, 2H, J = 7.2). ^{13}C NMR δ: 14.1, 24.7, 25.9, 33.2, 48.2, 56.3, 60.6, 172.7. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H,10.34; N, 7.56. Found: C, 64.92; H, 10.31; N, 7.55.

N-Isopropyl-ethylglycinate 6. The title product was obtained in 72% yield by using the isopropylamine. ^{1}H NMR δ: 1.06 (d, 6H, J = 6.4), 1.27 (t, 3H, J = 7.2), 1.67 (bs, 1H), 2.74–2.84 (m, 1H), 3.40 (s, 2H), 4.18 (q, 2H, J = 7.2). ^{13}C NMR δ: 14.2, 22.7, 48.3, 48.7, 60.7, 172.7. Anal. Calcd for $C_7H_{15}NO_2$: C, 57.9; H, 10.41; N, 9.65. Found: C, 57.91; H, 10.39; N, 9.68.

General procedure to 4-N-alkyl-6-methyl-1,4-morpholin-2,5-diones (7–9)

To a solution of **4**, **5** or **6** (50 mmol) and triethylamine (7.1 mL, 51 mmol) in CH_2Cl_2 (50 mL) stirred at 0 °C, (*R*,*S*)-bromopropionylbromide (5.4 mL, 51 mmol) in 10 mL of CH_2Cl_2 was slowly dropped. Then, the cooling bath was removed allowing the reaction to warm up to r.t., and the reaction mixture was stirred at r.t. monitored by TLC. After about 1 h, the organic solvent was evaporated under vacuum, the residue dissolved in ethyl acetate (200 mL) and the organic phase washed with diluted HCl, then with water. The organic extract, dried on $MgSO_4$, was evaporated *in vacuo*, and NaOH (4.0 g, 100 mmol) dissolved in 60 mL of 50% ethanol/water was added to the crude product. The reaction mixture was stirred at r.t. and monitored by TLC; after about 1 h, the starting material disappeared. The reaction mixture was then cooled at 0 °C and acidified with concentrated HCl (10 mL). After evaporation under vacuum of the most part of ethanol, the product was extracted with diethyl ether. The organic phase was dried on $MgSO_4$ and evaporated under vacuum, and the residue was dissolved in a mixture of anhydrous THF (50 mL) and anhydrous DMF (20 mL) under inert atmosphere. NaH (4.0 g of 60% dispersion in mineral oil, 100 mmol) was slowly added to the stirred solution, and when hydrogen evolution ceased, the reaction was refluxed and monitored by TLC (the sample was acidified and extracted with ethyl acetate). When the starting material disappeared (1–2 h), the reaction mixture was cooled at 0 °C and acidified with concentrated HCl. After evaporation under vacuum of the most part of solvent, the product was extracted with ethyl acetate and the organic phase washed with 0.1 M HCl, then with water. The organic phase was dried on $MgSO_4$ and evaporated under vacuum, and the residue was submitted to silica gel chromatography, eluting with hexane/ethyl acetate. The pure product was isolated in 55–74% yield.

4-N-Benzyl-6-methyl-1,4-morpholin-2,5-dione 7. The title pure product was obtained in 74% yield, as a colourless oil, by using intermediate **4**. ^{1}H NMR δ: 1.66 (d, 3H, J = 6.8), 3.97 (d, 1H, J = 18.0), 4.04 (d, 1H, J = 18.0), 4.58 (d, 1H, J = 14.8), 4.65 (d, 1H, J = 14.8), 4.95 (q, 1H, J = 6.8), 7.23–7.26 (m, 2ArH), 7.31–7.39 (m, 3ArH). ^{13}C NMR δ: 17.4, 47.4, 49.4, 75.0, 128.3, 128.4, 129.1, 134.7, 165.3, 166.2. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.12; H, 5.98; N, 6.38.

4-N-Cyclohexyl-6-methyl-1,4-morpholin-2,5-dione 8. The title pure product was obtained in 65% yield, as a white solid (m.p. 94–95 °C), by using intermediate **5**. ^{1}H NMR δ: 1.03–1.14 (m, 1H), 1.26–1.46 (m, 4H), 1.61 (d, 3H, J = 6.8), 1.66–1.73 (m, 3H), 1.81–1.87 (m, 2H), 4.03 (s, 2H), 4.32–4.39 (m, 1H), 4.86 (q, 1H, J = 6.8). ^{13}C NMR δ: 16.8, 25.0, 25.1, 25.2, 29.3, 29.4, 43.0, 52.2, 74.8, 165.6, 166.1. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.64; H, 8.13; N, 6.66.

4-N-Isopropyl-6-methyl-1,4-morpholin-2,5-dione 9. The title pure product was obtained in 55% yield, as colourless crystals (m.p. 74–76 °C), by using intermediate **6**. ^{1}H NMR δ: 1.15 (d, 3H, J = 6.8), 1.16 (d, 3H, J = 6.8), 1.61 (d, 3H, J = 6.8), 4.01 (s, 2H), 4.73–4.84 (m, 1H), 4.85 (q, 1H, J = 6.8). ^{13}C NMR δ: 17.0, 17.1, 19.2, 42.1, 44.4, 75.1, 165.7, 166.1. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.21; H, 7.64; N, 8.20.

General procedure of the alkylation of morpholin-2,5-diones (7–9)

Intermediates **7**, **8** or **9** (20 mmol) in dry THF (40 mL) were metalled with a 1 M solution of lithium hexamethyldisilazide (22 mL) at −78 °C under an inert atmosphere. After about 1h, benzylbromide (2.6 mL, 22 mmol) was added, and the reaction mixture, under stirring, was monitored by TLC. When the starting reagent practically disappeared, the cooling bath was removed, allowing the reaction to warm up to r.t. The reaction was then quenched with 1 M HCl (20 mL), and the organic solvent was evaporated under vacuum. After extraction with ethyl acetate (2 × 50 mL), the organic phase was washed with water (10 mL), dried ($MgSO_4$) and evaporated under vacuum. The residue was then submitted to silica gel chromatography, eluting with hexane/ethylacetate, and the product was isolated in 76–85% yield.

3-Benzyl-4-N-benzyl-6-methyl-1,4-morpholin-2,5-dione 1. The title pure product was obtained in 85% yield, as a colourless oil that solidifies on standing to white crystals (m.p. 100–102 °C), by using intermediate **7**. ^{1}H NMR δ: 1.41 (d, 3H, J = 6.8), 3.18

(dd, 1H, J = 4.8, 14.0), 3.22 (dd, 1H, J = 4.8, 14.0), 3.45 (q, 1H, J = 6.8), 3.85 (d, 1H, J = 14.8), 4.35 (t, 1H, J = 4.8), 5.39 (d, 1H, J = 14.8), 7.12–7.14 (m, 2ArH), 7.20–7.23 (m, 2ArH), 7.31–7.39 (m, 6ArH). ^{13}C NMR δ: 17.3, 36.8, 47.3, 59.8, 73.4, 128.2, 128.4, 129.1, 129.3, 129.7, 134.4, 134.9, 166.6, 167.3. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.57; H, 6.20; N, 4.54.

3-Benzyl-4-N-cyclohexyl-6-methyl-1,4-morpholin-2,5-dione 2. The title pure product was obtained in 79% yield, as a white amorphous solid (m.p. 109–111 °C), by using intermediate **8**.

^{1}H NMR δ: 1.09–1.22 (m, 1H), 1.31–1.46 (m, 2H), 1.33 (d, 3H, J = 6.8), 1.50–1.72 (m, 4H), 1.82–1.92 (m, 2H), 2.01–2.07 (m, 1H), 3.15 (dd, 1H, J = 6.0, 14.0), 3.29 (dd, 1H, J = 4.0, 14.0), 3.50 (q, 1H, J = 6.8), 4.11–4.19 (m, 1H), 4.50 (dd, 1H, J = 4.0, 6.0), 7.20–7.23 (m, 2ArH), 7.31–7.35 (m, 3ArH). ^{13}C NMR δ: 16.6, 25.1, 25.6, 25.9, 30.2, 31.4, 39.5, 55.7, 58.3, 73.3, 127.9, 129.0, 129.6, 134.5, 166.3, 167.7. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.47; H, 7.67; N, 4.66.

3-Benzyl-4-N-isopropyl-6-methyl-1,4-morpholin-2,5-dione 3. The title pure product was obtained in 76% yield, as a colourless oil, by using intermediate **9**. ^{1}H NMR δ: 1.29 (d, 3H, J = 6.8), 1.35 (d, 3H, J = 6.8), 1.36 (d, 3H, J = 6.8), 3.15 (dd, 1H, J = 6.0, 14.0), 3.30 (dd, 1H, J = 4.4, 14.0), 3.58 (q, 1H, J = 6.8), 4.40–4.50 (m, 1H), 4.47 (dd, 1H, J = 4.4, 6.0), 7.20–7.23 (m, 2ArH), 7.32–7.36 (m, 3ArH). ^{13}C NMR δ: 16.7, 20.2, 21.0, 39.5, 48.3, 58.5, 73.6, 128.1, 129.3, 129.7, 134.7, 166.5, 167.9. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.62; H, 7.35; N, 5.35.

Separation and characterization of the intermediates and reaction products

Five millimoles of lactone (**1**, **2** or **3**) was dissolved in dry ethanol (50 mL) at 0 °C; then, gaseous ammonia was bubbled for 30min. The flask was tightly capped and the cooling bath removed, allowing the reaction to warm up to r.t. At suitable times (Figs 1–6), ethanol and the excess of ammonia were evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (50 mL) and extracted with 1 M HCl. The organic phase, dried on $MgSO_4$, was concentrated under vacuum, and from the residue, submitted to silica gel chromatography, eluting with hexane/ethyl acetate, the pure intermediate **B** was isolated. The aqueous phase was neutralized with 1 M NaOH and extracted with ethyl acetate. The organic phase was dried on $MgSO_4$ and concentrated under vacuum, and the residue was submitted to silica gel chromatography, eluting with hexane/ethyl acetate to separate the pure compounds **C**, **D**, **E** and lactamide.

2-Benzyl-3-N-(benzyl)-4-oxa-5-hydroxyhexanamide 1B. The title pure product was isolated as a colourless oil from the ammonolysis of lactone **1**. ^{1}H NMR δ: 1.08 (d, 3H, J = 6.8), 3.21–3.32 (m, 2H), 3.38 (d, 1H, J = 8.4), 4.20 (d, 1H, J = 16.8), 4.34 (dq, 1H, J = 6.8, 8.4), 4.51 (d, 1H, J = 16.8), 5.21 (bs, 1H), 6.30 (bs, 1H), 7.12–7.17 (m, 4ArH), 7.23–7.32 (m, 6ArH). ^{13}C NMR δ: 21.1, 34.5, 49.0, 59.5, 65.5, 126.8, 127.0, 128.0, 128.8, 129.0, 129.1, 135.8, 136.8, 171.9, 177.7. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.22; H, 6.82; N, 8.55.

N-(2-Hydroxypropionyl)-3-phenyl-2-(benzylamino)propionamide 1C. The title pure product was isolated as a colourless wax from the ammonolysis of lactone **1**. ^{1}H NMR (40 °C) δ: 1.31 (d, 3H, J = 6.8), 2.05 (bs, 1H), 2.97 (dd, 1H, J = 7.6, 13.6), 3.08 (dd, 1H, J = 6.8, 13.6), 3.64 (dd, 1H, J = 6.8, 7.6), 3.73 (d, 1H, J = 13.2), 3.87 (d, 1H, J = 13.2), 5.14 (q, 1H, J = 6.8), 5.28 (bs, 1H), 5.85 (bs, 1H), 7.17–7.19 (m, 2ArH), 7.23–7.33 (m, 8ArH). ^{13}C NMR (40 °C) δ: 17.6, 39.2, 51.9, 61.7, 71.0, 127.3, 127.9, 128.5, 128.8, 128.9, 129.4, 136.4, 136.6, 172.3, 172. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.69; H, 6.77; N, 8.55.

2-(Benzylamino)-3-phenylpropanamide 1D. The title pure product was isolated as a white amorphous solid (m.p. 123–125 °C) from the ammonolysis of lactone **1**. ^{1}H NMR δ: 1.66 (bs, 1H), 2.77 (dd, 1H, J = 9.6, 13.6), 3.22 (dd, 1H, J = 4.4, 13.6), 3.38 (dd, 1H, J = 4.4, 9.6), 3.56 (d, 1H, J = 13.2), 3.75 (d, 1H, J = 13.2), 5.46 (bs, 2H), 7.05–7.07 (m, 2ArH), 7.16–7.19 (m, 3ArH), 7.21–7.32 (m, 5ArH). ^{13}C NMR δ: 39.3, 52.7, 63.2, 127.1, 127.3, 128.0, 128.6, 128.9, 129.2, 137.4, 139.2, 176.9. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.65; H, 7.15; N, 10.98.

Ethyl-2-(benzylamino)-3-phenylpropanoate 1E. The title pure product was isolated as a colourless oil from the ammonolysis of lactone **1**. ^{1}H NMR δ: 1.16 (t, 3H, J = 7.2), 1.68 (bs, 1H), 2.94 (dd, 1H, J = 7.2, 14.0), 2.98 (dd, 1H, J = 7.2, 14.0), 3.52 (t, 1H, J = 7.2), 3.64 (d, 1H, J = 13.2), 3.81 (d, 1H, J = 13.2), 4.10 (q, 2H, J = 7.2), 7.16–7.18 (m, 2ArH), 7.21–7.30 (m, 8ArH). ^{13}C NMR δ: 14.3, 39.9, 52.1, 60.8, 62.2, 126.8, 127.2, 128.3, 128.5, 129.4, 137.5, 139.7, 174.8. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.56; H, 7.44; N, 4.95.

2-Benzyl-3-N-(cyclohexyl)-4-oxa-5-hydroxyhexanamide 2B. The title pure product was isolated as a waxy solid from the ammonolysis of lactone **2**. ^{1}H NMR δ: 0.60–0.65 (m, 1H), 0.81–0.91 (m, 1H), 0.95–1.10 (m, 2H), 1.13–1.27 (m, 1H), 1.34 (d, 3H, J = 6.8), 1.52–1.62 (m, 3H), 1.65–1.70 (m, 1H), 1.77–1.83 (m, 1H), 3.16–3.24 (m, 1H), 3.30 (dd, 1H, J = 5.6, 13.6), 3.74 (dd, 1H, J = 10.0, 13.6), 3.87–3.92 (m, 2H), 4.31 (dq, 1H, J = 1.6, 6.8), 5.40 (bs, 1H), 7.15–7.31 (m, 5ArH), 7.44 (bs, 1H). ^{13}C NMR δ: 21.8, 24.8, 25.6, 25.8, 30.1, 30.8, 35.4, 57.9, 63.7, 65.4, 127.0, 128.7, 129.5, 137.7, 174.5, 176.6. Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 68.14; H, 8.21; N, 8.82.

N-(2-Hydroxypropionyl)-3-phenyl-2-(cyclohexylamino)propionamide 2C. The title pure product was isolated as white crystals (m.p. 105–107 °C) from the ammonolysis of lactone **2**. In this case, the sample was prepared by dissolving the compound in DMSO-d_6 under inert atmosphere, and about 30 mg of activated powdered 4 Å molecular sieves was then added. After stirring for 1 day, the solution was rapidly taken in an NMR tube and tightly capped. The tube was maintained vertical until the residual molecular sieves precipitated on the bottom. The complete signal assignment was then executed, except for those belonging to the aromatic ring and to the cyclohexyl ring, unnecessary to the purpose. The ^{1}H, ^{13}C and heteronuclear multiple-bond correlation (HMBC) spectra were acquired at various temperatures in order to determine the optimal condition for evidencing the H_y–C_e crosspeak (Fig. 10). Then, the decisive HMBC experiment was executed at 19 °C using 400 increments (^{13}C spectral window from −10 to 190 ppm) and 640 scans per increment, obtaining the expected crosspeak. Chemical shifts are reported in ppm relative to the solvent residual peak (2.50 ppm) and to the solvent peak (39.52 ppm) as the references for the ^{1}H and ^{13}C NMR experiments, respectively. The internally stored gHSQC and gHMBC sequences were used for the single and multiple

bond ^{1}H–^{13}C correlation experiments, respectively, using 400 increments (^{13}C spectral window from −10 to 190 ppm) and 640 scans per increment in the gHMBC experiment for evidencing the crosspeak between the imidic proton H_y and the oxydrilated carbon C_e (Fig. 10). The splitting of some signals in the ^{13}C NMR spectra is due to the presence of two rotamers. ^{1}H NMR δ: 0.84–0.93 (m, 1H), 0.98–1.16 (m, 4H), 1.14 (d, 3H, J = 6.8), 1.47–1.51 (m, 1H), 1.56–1.67 (m, 3H), 1.75–1.78 (m, 1H), 1.91 (bs, 1H), 2.32–2.37 (m, 1H), 2.80 (dd, 1H, J = 7.6, 13.2), 2.86 (dd, 1H, J = 6.8, 13.2), 3.65 (dd, 1H, J = 6.8, 7.6), 4.77 (q, 1H, J = 6.8), 7.19 (bs, 1H), 7.17–7.28 (m, 5ArH), 7.41 (bs, 1H). ^{13}C NMR δ: 17.4, 17.5, 24.0, 24.3, 25.7, 32.2, 33.6, 39.3, 54.1, 59.4, 59.5, 69.4, 69.5, 126.2, 126.3, 127.9, 128.0, 129.1, 129.2, 137.9, 171.8, 173.9. Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.9; H, 8.23; N, 8.80. Found: C, 67.85; H, 8.22; N, 8.81.

2-(Cyclohexylamino)-3-phenylpropanamide 2D. The title pure product was isolated as a white amorphous solid (m.p. 129–131 °C) from the ammonolysis of lactone **2**. ^{1}H NMR δ: 0.61–0.71 (m, 1H), 0.93–1.24 (m, 4H), 1.48–1.52 (m, 2H), 1.57–1.65 (m, 3H), 1.72–1.76 (m, 1H), 2.17–2.25 (m, 1H), 2.69 (dd, 1H, J = 9.6, 13.6), 3.23 (dd, 1H, J = 4.0, 13.6), 3.41 (dd, 1H, J = 4.0, 9.6), 5.40 (bs, 2H), 7.21–7.34 (m, 5ArH). ^{13}C NMR δ: 24.8, 25.0, 25.9, 32.9, 34.5, 39.6, 56.1, 61.5, 127.0, 128.8, 129.2, 137.7, 178.3. Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.0; N, 11.37. Found: C, 73.23; H, 9.02; N, 11.35.

Ethyl-2-(cyclohexylamino)-3-phenylpropanoate 2E. The title pure product was isolated as a colourless wax from the ammonolysis of lactone **2**. ^{1}H NMR δ: 0.94–1.03 (m, 1H), 1.11 (t, 3H, J = 7.2), 1.09–1.34 (m, 4H), 1.54–1.75 (m, 5H), 1.80–1.85 (m, 1H), 2.32–2.39 (m, 1H), 2.88 (dd, 1H, J = 7.6, 13.6), 2.96 (dd, 1H, J = 6.8, 13.6), 3.64 (dd, 1H, J = 6.8, 7.6), 4.06 (q, 2H, J = 7.2), 7.17–7.23 (m, 3ArH), 7.25–7.29 (m, 2ArH). ^{13}C NMR δ: 14.3, 24.8, 25.1, 26.1, 32.8, 34.2, 40.4, 55.3, 60.3, 60.6, 126.8, 128.5, 129.3, 137.6, 175.3. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.47; H, 9.11; N, 5.07.

2-Benzyl-3-N-(cyclohexyl)-4-oxa-5-hydroxyhexanamide 3B. The title pure product was isolated as a white amorphous solid (m.p. 164–165 °C) from the ammonolysis of lactone **3**. ^{1}H NMR δ: 0.48 (d, 3H, J = 6.4), 1.19 (d, 3H, J = 6.8), 1.35 (d, 3H, J = 6.4), 3.30 (dd, 1H, J = 5.2, 13.2), 3.71–3.77 (m, 2H), 3.81–3.85 (m, 2H), 3.74 (dq, 1H, J = 1.6, 6.4), 5.37 (bs, 1H), 7.16–7.31 (m, 5ArH), 7.40 (bs, 1H). ^{13}C NMR δ: 19.8, 20.4, 21.8, 35.3, 49.0, 62.7, 65.4, 127.1, 128.7, 129.6, 137.8, 174.4, 176.6. Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.84; H, 7.95; N, 10.04.

N-(2-Hydroxypropionyl)-3-phenyl-2-(isopropylamino)propionamide 3C. The title pure product was isolated as a colourless wax from the ammonolysis of lactone **3**. ^{1}H NMR (40 °C) δ: 1.02 (d, 3H, J = 6.4), 1.06 (d, 3H, J = 6.4), 1.24 (d, 3H, J = 6.8), 1.64 (bs, 1H), 2.73–2.83 (m, 1H), 2.90 (dd, 1H, J = 8.4, 13.2), 3.05 (dd, 1H, J = 6.0, 13.2), 3.68 (dd, 1H, J = 6.0, 8.4), 5.40 (bs, 1H), 6.00 (bs, 1H), 7.16–7.32 (m, 5ArH). ^{13}C NMR (40 °C) δ: 17.5, 22.3, 23.7, 40.0, 47.4, 60.7, 70.6, 127.1, 128.7, 129.4, 137.1, 172.8, 173.7. Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 65.11; H, 7.92; N, 10.10.

2-(Isopropylamino)-3-phenylpropanamide 3D. The title pure product was isolated as white crystals (m.p. 121–123 °C) from the ammonolysis of lactone **3**. ^{1}H NMR δ: 0.79 (d, 3H, J = 6.0), 0.95 (d, 3H, J = 6.4), 1.45 (bs, 1H), 2.48–2.57 (m, 1H), 2.64 (dd, 1H, J = 9.6, 14.0), 3.16 (dd, 1H, J = 4.4, 14.0), 3.28 (dd, 1H, J = 4.4, 9.6), 5.75 (bs, 2H), 7.20–7.33 (m, 5ArH). ^{13}C NMR δ: 22.5, 23.6, 39.5, 48.5, 61.9, 127.0, 128.8, 129.3, 137.7, 178.1. Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.98; H, 8.78; N, 13.54.

Ethyl-2-(isopropylamino)-3-phenylpropanoate 3E. The title pure product was isolated as a colourless wax from the ammonolysis of lactone **3**. ^{1}H NMR δ: 0.98 (d, 3H, J = 6.4), 1.04 (d, 3H, J = 6.4), 1.11 (t, 3H, J = 7.2), 1.60 (bs, 1H), 2.69–2.78 (m, 1H), 2.86 (dd, 1H, J = 7.6, 13.2), 2.97 (dd, 1H, J = 6.4, 13.2), 3.59 (dd, 1H, J = 6.4, 7.6), 4.06 (q, 2H, J = 7.2), 7.17–7.30 (m, 5ArH). ^{13}C NMR δ: 14.3, 22.2, 23.9, 40.4, 47.2, 60.6, 60.9, 126.8, 128.5, 129.3, 137.5, 175.3. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.72; H, 9.01; N, 5.93.

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