Ring size configuration effect and the transannular intrinsic rates in bislactam macrocycles

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We have synthesized compounds: *N*-(2-aminoacetyl)-2-pyrrolidone (**1**) and *N*-(2-aminoacetyl)-2-piperidone (**2**). When these compounds are dissolved in aprotic or protic solvents a fast equilibrium *ca.* 1:1 between the cyclol form (tetrahedral intermediate) and the bislactam macrocycle is established. The same result has been reported previously[3] for *N*-(2-aminoacetyl)-2-caprolactam (**3**). For compounds **2** and **3**, dynamic ^{1}H-NMR (using the methylene signals α to the carbonyl and to the amino group) through spectrum simulation has been used to evaluate the exchange between the two mentioned forms at different pH. However, for compound **1** the exchange was evaluated using magnetization transfer technique. The more stable bislactam configuration of the macrocycle form in compounds **2** and **3**, is the *trans–cis* (one lactam with the cyclic alkyl chains *trans* oriented and the other *cis* oriented). However, the same form for compound **1** has a more stable *cis–cis* bislactam configuration. This difference in configuration induces substantial changes in the appearance of the methylene ^{1}H-NMR signals that precludes the use of line-shape analysis to evaluate the rates. The rate law for the proposed mechanism of exchange between the cyclol form and the macrocycle is: $K = [\text{macrocycle}]/[\text{cyclol}] = k_{\text{obs.f}}/k_{\text{obs.r}} = K_a k_2[H_2O]/[H^+]/k_{-2}K_w/[H^+] = K_a k_2[H_2O]/k_{-2}K_w$; where K_a is the acidity equilibrium constant of the cyclol form, $K_w = 10^{-14}$ M^2 and k_2 and k_{-2} are the second order rate constants for the specific exchange catalysis. Therefore, both, the macrocycle formation ($k_{\text{obs.f}}$) and the cyclol formation ($k_{\text{obs.r}}$) are specific base catalyzed; however the equilibrium constant is independent of pH. Since K is *ca.* 1, the $\Delta G^{\neq}$ associated with the measured rate constants represent the intrinsic barrier for this non-identical thermoneutral transformation where a cleavage of a tetrahedral intermediate is involved. The activation energies associated with the reverse rate constants then correspond to the intrinsic barrier for transannular cyclolization.

Introduction

Continuing with our effort[1–3] in preparing stable tetrahedral intermediates and measuring their intrinsic rates, we have synthesized *N*-(2-aminoacetyl)-2-pyrrolidone (**1**) and *N*-(2-aminoacetyl)-2-piperidone (**2**) and followed their intramolecular interconversions in D_2O using dynamic ^{1}H-NMR. When compound **2** is dissolved in D_2O a fast 1:1 equilibrium is established between the corresponding tetrahedral intermediate **2a** and the diamide macrocycle **2b** ($n = 2$ in Fig. 1). The open form **2c** could not be detected by ^{1}H-NMR. This result is similar to the one previously found[3] for *N*-(2-aminoacetyl)-2-caprolactam (**3**) in which **3a** is identified in the ^{1}H-NMR spectrum by the typical AB system that form the non-equivalent geminal methylene protons vicinal to the carbonyl and to the amino group (see Fig. 1). The same protons in **3b** are also non-equivalent due to the fact that the more stable configuration of the bislactam macrocycle (orientation of the cyclic alkyl R on each lactam: RCONHR) is the *trans–cis* one and its transformation to the *cis–trans* form is slow in the ^{1}H-NMR time scale. The *trans–cis* $\rightleftharpoons$ *cis–trans* transformation is slow due to the fact that the two amide-nitrogen electron pairs have to be rotated from their ideal conjugated positions in order for the transformation to occur. A similar slow transformation has been reported[4] for the symmetric bislactam macrocycle: 1,6-diazacyclodecane-2,7-dione. In the *cis–trans* configuration of **3b** one of the methylene protons lies aligned with the carbonyl group and the other perpendicular to the carbonyl causing an important anisotropic effect that shifts its resonance frequency to high field. Therefore, an AX system instead of an AB one is observed for these methylene protons of **3b**. When the pH is increased, a specific base catalysis is experimentally observed by means of the

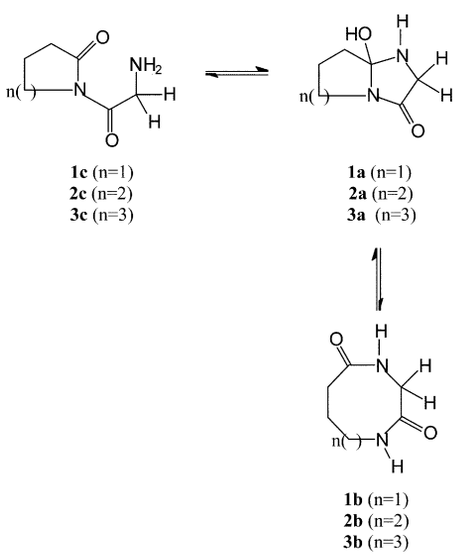

Fig. 1 Possible isomers present at equilibrium for compounds **1**, **2** and **3** (n = 1, 2 and 3). The isomers are assigned by the chemical shift and multiplicity (^{1}H-NMR) of the methylene protons shown in the figure. An AB system is typical for the form **a** (cyclol).

^{1}H-NMR signals broadening for both systems: AB and AX. Using line shape analysis, the broadening of both systems can be followed independently, and their pseudo-first order rate constants for their corresponding transformation obtained. Since the **3a** $\rightleftharpoons$ **3b** equilibrium constant remains unchanged in the pH interval of study[3] (4 < pH < 12), a mechanism in which

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3a is transformed to **3b** from its conjugated base $\mathbf{3a}^-$ (rate limiting) has been proposed. According to the mechanism, the equilibrium constant should be independent on pH since: $K = [\mathbf{3b}]/[\mathbf{3a}] = k_{obs.f}/k_{obs.r} = k_2[H_2O]/[H^+]/k_{-2}K_w/[H^+] = k_2[H_2O]/k_{-2}K_w$. As mentioned above, compound **2** behaves similar to **3**, and its specific catalyzed rate constants k_2 and k_{-2} and the corresponding uncatalyzed ones k_0 and k_{-0} are reported in this work. Since the equilibrium constant $K = [\mathbf{2b}]/[\mathbf{2a}]$ is *ca.* 1, these measured rates are the intrinsic rates for these non-identical thermoneutral reactions and their $\Delta G^{\neq}$ values can be regarded as the intrinsic barriers for these transformations that are valuable since quantitative extrapolation to the actual activation energy for the non-thermoneutral reaction can be achieved using different approaches.[5,6]

For compound **1**, one of the methylene signals α to the carbonyl and to the amino group corresponds to the cyclol **1a** (Fig. 1). However, the other observable ^{1}H-NMR signal appears quite different in the ^{1}H-NMR spectrum as compared to the ones assigned to **2b** or **3b** (AX system). In fact a singlet is observed instead for the AX system. The more stable *cis–cis* configuration of the eight-membered ring bislactam **1b** configuration in principle makes this signal indistinguishable from the open form **1c** (see Fig. 1). However, the final signal assignment is made using kinetic criteria. A final resumé for the intrinsic rates and barriers for the intramolecular interconversions of **1**, **2** and **3** at 25 °C are given.

Experimental and results

Synthesis and ^{1}H-NMR signal identification

***N*-(-2-aminoacetyl)-2-pyrrolidone (1).** Compound **1** was synthesized following the procedure previously reported.[7,2] However, the following modifications of the original methodology were implemented: In the preparation of the *N*-(-2-azidoacetyl)-2-pyrrolidone from *N*-(-2-chloroacetyl)-2-pyrrolidone, acetonitrile was used as a solvent instead of a 3:2 mixture of acetone–water. In the reduction of *N*-(-2-azidoacetyl)-2-pyrrolidone, ethylacetate was used as a solvent instead of methanol. Reduction was carried out at 20 psi H_2 instead of 40 psi. At 40 psi H_2 in methanol, a rupture of the reaction mixture to 2-pyrrolidone and glycine was observed. The reaction product *N*-(-2-aminoacetyl)-2-pyrrolidone was characterized by mass spectroscopy, UV, IR and ^{1}H-NMR:

Mass spectrum: *m*/*z* 142 (molecular peak), 114, 96, 86, 69 and 37; UV (H_2O)/nm: 202–204 and 217–220; IR/cm^{-1}: 3590, 3376, 1702 and 1742; ^{1}H-NMR ($CDCl_3$): 2.10(m, 4H), 2.30(t, 2H), 2.60(t, 2H), 3.40(t, 2H), 3.8(t, 2H), 4.00(s, 2H), 4.60(AB, 2H).

The ^{1}H-NMR is quite simple and different from what we have obtained[3] for compound **3** and compound **2** (this work). As pointed out in the Introduction, the possible isomers present in equilibrium are easily identified by the ^{1}H-NMR signals of the methylene group attached to the carbonyl and to the amino group (Fig. 1). In the case of the tetrahedral intermediate form (cyclol form), these signals appear as expected as an AB system (ν_a = 1843 Hz, ν_b = 1837 Hz, J = 9 Hz in a 400 MHz magnet) due to the molecule asymmetry that makes the two geminal protons non-equivalent. However, these signals become a singlet in D_2O due to high sensitivity of this AB system ($\Delta\nu_{ab}$ = 6 Hz and J = 9 Hz) to the exchange rate. This signal thus represents compound **1a**. However, there is only one other extra signal attributable to methylene protons that appears as a singlet at 4.00 ppm. In principle, this signal can not be assigned to the macrocycle diamide since the same protons for **2b** and **3b** appear as two different signals coupled between them and with a difference in chemical shift >1 ppm. This fact, led us[2] to assign this signal to the open form **1c**, in which a singlet should be expected due to the internal free rotation of the molecule . However, as we will discuss later, the last singlet signal could also be attributed to **1b** since the bislactam macrocycle configuration is the *cis–cis* (instead of *cis–trans* as in **2b** and **3c**) in which the methylene protons are rapidly interconverted on the NMR time scale. In the discussion we will argue this matter further.

***N*-(-2-aminoacetyl)-2-valerolactam (2).** Compound **2** was synthesized according to the procedure reported by Rapoport *et al*.[7] Since the ^{1}H-NMR is quite similar to that of **3**, previously[3] characterized, only ^{1}H-NMR data is reported: ^{1}H-NMR ($CDCl_3$): 1.75(m, 4H), 2.32(m, 2H), 2.72(AX, 1H), 3.28(m, 2H), 4.03(AX, 1H), 4.30(AB, 2H).

The ^{1}H-NMR spectrum is quite similar to the one reported[1] for **3**. In fact, the methylene protons α to the carbonyl and to the amino group of **2a** appear as an AB system centered at 4.30 ppm with the following characteristics: ν_a = 1278 Hz, ν_b = 1310 Hz, J = 13 Hz. These values (slow exchange conditions) were used to perform simulations in D_2O. The signals for the same protons in the structure **2b** (macrocycle diamide) appear at a different chemical shift forming an AX system. One of the diasterotopic protons appears at 4.03 ppm as a multiplet and the other at 2.72 ppm. Therefore, there is a difference of 1.3 ppm between the two geminal protons. We have attributed[3] this difference to an anisotropic effect induced by the carbonyl group. The most stable configuration[8] for the bislactam **2b** is the *cis–trans* one that forces one of the geminal protons (A) to be aligned to the carbonyl group and the other (X) perpendicular to it. These signals are coupled and each one is additionally coupled to the two amide hydrogens. The coupling constants obtained from the ^{1}H-NMR in $CDCl_3$ and double irradiation experiments are: J_{AX} = 10 Hz, J_{ANH} = 3 Hz, J_{ACONH} = 3 Hz, J_{XNH} = 7 Hz, J_{XCONH} = 3 Hz. These values (slow exchange conditions) were used to perform simulations in D_2O.

Dynamic NMR and rate constants

***N*-(-2-aminoacetyl)-2-valerolactam (2).** The k_{obs} values for the interconversion between forms **2a** and **2b** at 25.0 °C and at different pD (pD = pH + 0.4),[9] were obtained using simulations according to the equation of Fung and Olympia[10] (for **2a** transformation, the AB system coalescences) and the gamma program developed by Ernst *et al.*[11] (for **2b**, the A and X system coalescence). A 300 MHz BRUKER instrument was used to obtain the experimental spectra. As for the case[3] of compound **3**, a tendency of both AB and AX systems to coalescence was observed when increasing pD. Therefore, specific base catalysis is operating in $k_{obs.f}$ and also in $k_{obs.r}$, which makes the equilibrium constant $K = k_{obs.f}/k_{obs.r} = [\mathbf{2b}]/[\mathbf{2a}]$ independent on pD, as experimentally observed by the relative signal integrations for **2a** and **2b**, in the pD range of the study. The reaction mechanism, as we have proposed[3] for the transformation of **3a** and **3b** forms, is shown in Fig. 2, where $K = k_{obs.f}/k_{obs.r} = k_2[D_2O]K_a/k_{-2}K_w$, where $[D_2O]$ = 55.5 M, K_a is the acidity equilibrium constant for the conjugated acid of **2a** (pK_a[2] = 13.2) and $K_w = 1 \times 10^{-14}$ M[2]. The k_2 and k_{-2} values have been obtained through out best fitting of the experimental points in a $k_{obs.}$ *vs.* pD profile (not shown) to the equations: $k_{obs.f} = k_0 + k/[H^+]$ and $k_{obs.r} = k_{-0} + k'/[H^+]$, where k_0 and k_{-0} are the uncatalized rates, obtained directly at the level of low pD in the k_{obs} *vs.* pD profile, $k = k_2[D_2O]K_a$ and $k' = k_{-2}K_w$. The k_0 and k values are: 1.0 s^{-1} and 1×10^{-9} M s^{-1} and the k_{-0} and k' values are: 1.5 s^{-1} and 3×10^{-9} M s^{-1}. Therefore, $k_2 = 1.4 \times 10^2$ M^{-1} s^{-1} and $k_{-2} = 3 \times 10^5$ M^{-1} s^{-1}.

***N*-(-2-aminoacetyl)-2-pyrrolidone (1).** As described above in *Synthesis and ^{1}H-NMR signal identification*, when compound **1** is dissolved in $CDCl_3$ and in D_2O there are two conformers in a ratio *ca.* 1:1. One of these conformers is the cyclol **1a** and the other one is either the open form **1c** or the macrocycle **1b**. These conformers are recognized by means of the ^{1}H-NMR signals of the methylene protons attached to the carbonyl group and to

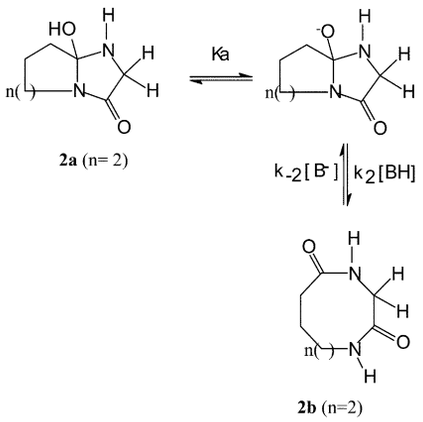


Fig. 2 Interconversion mechanism between forms **2a** and **2b**. According to the proposed mechanism, the rate law is given by: K = [**2b**]/[**2a**] = $k_{obs.f}/k_{obs.r}$ = k_2K_a[BH]/$k_{-2}K_w$. Therefore, the equilibrium constant K (B = OH) is independent on pH but $k_{obs.f}$ and $k_{obs.r}$ are specific base catalyzed, as it has been experimentally found.The same mechanism is proposed [3] for the interconversion of **3a** ⇌ **3b** (n = 3) and **1a** ⇌ **1b** (this work).

the amino group. The AB signal at 4.60 ppm corresponds to the cyclol form and the singlet at 4.00 ppm corresponds either to **1c** or to **1b**. The assignment of the singlet to the open form **1c** is more likely because a singlet should be expected for this form due to the intramolecular free rotation that makes these two protons equivalent on average. As we will see in the Discussion, the above argument proves to be naive based on the difference in the bislactam configuration stabilities in **1b** when compared to **2b** and **3b**. In fact the configuration of the bislactam macrocycle of **1b** is *cis–cis*. This means that the methylene protons rapidly interconvert appearing in the NMR as a singlet. The same interconversion for **2b** and **3b** is slow because slow rotation on each lactam system is required in order to accomplish the *cis–trans* ⇌ *trans–cis* transformation. Therefore the macrocycle structure **1b** can not be discarded and the observed singlet could be assigned to this form. Independent of which form is responsible for the observed singlet, the kinetics of the interconversion between the two observed conformers of **1**, can be followed by dynamic ^{1}H-NMR. However, line shape analysis can not be used since the two signal (4.00 ppm and 4.60 ppm in $CDCl_3$ and 4.18 and 4.58 in D_2O) at 400 MHz, will require rates >160 s^{-1} in order to observe coalescence. Since the pseudo first-order rates values under the condition of the study are quite lower than the above value, the line shape method has to be discarded as the kinetic technique. However, magnetization transfer [12,13] is suitable to follow the exchange between the two signals. A 400 MHz JEOL Eclipse instrument was used to obtain the T_1 values and to perform the magnetization transfer experiments. Rates constants were then obtained by means of saturation of one of the signals and observing the decrease in intensity (I^i) of the other signal relative to its intensity value (I^0) without saturating the first signal. The decreased intensity fraction is then equal to: $(I^0 - I^i)/I^0 = -k_{obs}/(k_{obs} + 1/T_1)$; where k_{obs} is the rate constant of formation of the form that is being irradiated and T_1 the observed signal longitudinal relaxation time at 25 °C and at each pD (maintained with phosphate buffer, general catalysis was not observed). Measured T_1 values are in the range: 1.5–1.7 s. Therefore, the obtained rate constants are meaningful in the range *ca.* 0.1–15 s^{-1}. Two k_{obs}: $k_{obs.f}$ and $k_{obs.r}$, were obtained at each pD. Plots of k_{obs} *vs.* pD are shown in Fig. 3. As shown, both $k_{obs.f}$ and $k_{obs.r}$, are uncatalyzed and specific base catalyzed. From best fitting of the experimental points to $k_{obs.f} = k_0 + k/[H^+]$, the k_0 (k_{-0} from $k_{obs.r}$)) values and the apparent k (k' from $k_{obs.r}$) values were obtained. In Fig. 4 the $k_{obs.f}$ *vs.* pD best fitting is shown. The k_0 were obtained directly from the k_{obs} *vs.* pD plots and the k_2 values (see proposed mechanism, Fig. 2) from the apparent rate

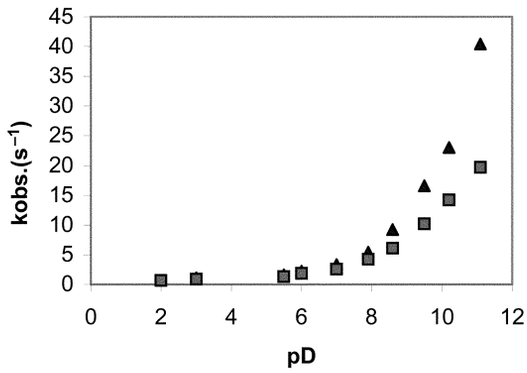


Fig. 3 k_{obs} (s^{-1}) values for the diamide formation ($k_{obs.f}$, triangles) and the cyclol formation ($k_{obs.r}$, squares) at 25.0 °C. Values obtained independently using magnetization transfer (see Experimental). Note that $1 < k_{obs.f}/k_{obs.r} = K < 2$. By means of the signal integrations at each pD, the same range for the equilibrium constant K is found.

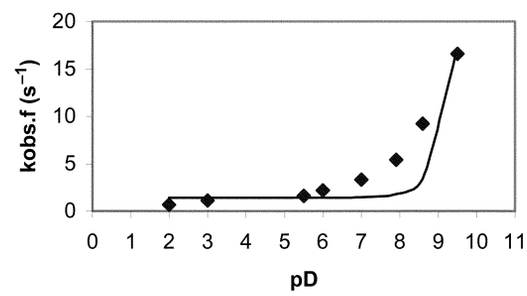


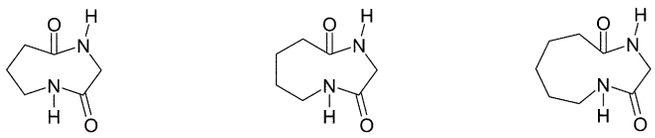
Fig. 4 $k_{obs.f}$ *vs.* pD plot at 25 °C for compound **1**. The experimental points and the best fit to the equation: $k_{obs.f} = k_0 + k/[H^+]$, with k_0 = 1.2 s^{-1} and $k = 5 \times 10^{-9}$ M s^{-1}. Best fitting of the experimental points at 7 < pH < 8.5 may be obtained using the equation: $k_{obs.f} = k_0 + k/[H^+] \times [H^+]/([H^+] + 10^{-7.5}) + k'/[H^+]$. The second term corresponds to the participation of the zwitterionic form of the cyclol form of pK_a = 7.5.[2]

constant (k) obtained in the best fitting. The obtained values for the formation of **1b** or **1c** are : $k_0 = 1.2\ s^{-1}$ and $k_2 = k/K_a[H_2O] = 5 \times 10^{-9}$ M $s^{-1}/10^{-12.9}$ M × 55.5 M = 7.1×10^2 M^{-1} s^{-1}. The obtained rates of formation for cyclol **1a** are: $k_{-0} = 1.2\ s^{-1}$ and $k_{-2} = k'/K_w = 4 \times 10^{-9}$ M $s^{-1}/1 \times 10^{-14}$ $M^2 = 4 \times 10^5$ M^{-1} s^{-1}

Discussion

A fundamental point for the discussion is the correct assignment of the singlet at *ca.* 4 ppm that appears in the ^{1}H-NMR spectrum of **1**. As mentioned above, two characteristic signals are found in the ^{1}H-NMR: the unassigned one (singlet) at 4 ppm and the one at *ca.* 4.6 ppm that has been properly assigned to the cyclol **1a**. An important factor for the assignment of the signal at *ca.* 4 ppm is the actual configuration of the bislactam **1b**. In Table 1 the energy [8] of the different configurations: *trans–cis*, *cis–cis* and *trans–trans* of the diamide groups for the bislactam macrocycles **1b**, **2b** and **3b** are shown. The energy values shown correspond to the molecular optimization *via* the total energy (steric energy) minimization of the force field of the MM+ method.[8] It is evident that the most stable configuration for the 9 and 10 membered macrocycles **2b** and **3c** is the *trans–cis* one. In fact, this has been corroborated by the experimental ^{1}H-NMR observation in which the methylene protons attached to the carbonyl amide and to the amino amide groups become non-equivalent due to the slow rotation that interconvert both protons through the *trans–cis cis–trans* transformation. This originates as an AX system with an important separation between the two signals due to an anisotropic effect induced by the vicinal carbonyl group, as it has been confirmed in this work for **2b** and as it has been previously reported [3] for **3b**. However, for **1b** the more stable configuration is the *cis–cis* one in which the methylene protons become equivalent since they rapidly exchange *via* pseudorotation. Therefore, for **1b** a singlet should

Table 1 Steric energies (total force field energy for the MM+ method[8]) for the three possible conformations of the two amide systems in the macrocycles **1b**, **2b** and **3b**. For the drawings the *trans–trans* configuration has been used. However, the more stable ones are: *cis–cis* for **1b**, and *trans–cis* for **2b** and **3b**. Energy ranges are the steric energy values obtained from optimization starting from different structure drawings of the same configuration



1b **2b** **3b**

cis–cis	*cis–cis*	*cis-cis*
1.93 kcal mol^{-1}	6.30 kcal mol^{-1}	7.87 kcal mol^{-1}
trans–cis	*trans–cis*	*trans–cis*
3.99–5.27 kcal mol^{-1}	2.94–6.30 kcal mol^{-1}	1.07–2.21 kcal mol^{-1}
trans–trans	*trans–trans*	*trans–trans*
13.56–14.13 kcal mol^{-1}	8.10–12.31 kcal mol^{-1}	8.28–10.57 kcal mol^{-1}

Table 2 Equilibrium rate constants at 25 °C and energy values calculated according to the Eyring equation for the (**a**) cyclol ⇌ (**b**) macrocycle transformation. k_0 and k_{-0} are the uncatalyzed rate constants for the forward and reverse reaction and k_2 and k_{-2} are the specific base catalyzed rate constants for the forward and reverse reaction. The reported rate constants were obtained by best fitting of the k_{obs} *vs.* pD experimental points to the general equations: $k_{obs.f} = k_0 + k/[H^+]$ and $k_{obs.r} = k_{-0} + k'/[H^+]$, where $k = k_2K_a[D_2O]$ and $k' = k_{-2}K_w$. $K_a = 10^{-12.9}$ (from ref. 2), $[D_2O] = 55.5$ M and $K_w = 1 \times 10^{-14}$ M^2. *n* values refer to the lactam size as in Fig. 1: $n = 1$, five membered, $n = 2$, six membered and $n = 3$, seven membered

System	K = [**1b**]/[**1a**]	k_0/s^{-1} ($\Delta G^{\neq}$/kJ mol^{-1})	k_2/M^{-1} s^{-1} ($\Delta G^{\neq}$/kJ mol^{-1})	k_{-0}/s^{-1} ($\Delta G^{\neq}$/kJ mol^{-1})	k_{-2}/M^{-1} s^{-1} ($\Delta G^{\neq}$/kJ mol^{-1})
1a ⇌ **1b** ($n = 1$)	1	1.2 (72.4)	7.1×10^2 (56.6)	1.2 (72.4)	4×10^5 (44.3)
2a ⇌ **2b** ($n = 2$)	0.6	1 (72.9)	1.4×10^2 (60.7)	1.5 (71.9)	3×10^5 (41.7)
3a ⇌ **3b** ($n = 3$) (ref. 3)	0.5	2 (71.1)	1.8×10^2 (59.8)	4 (69.4)	1×10^5 (44.3)

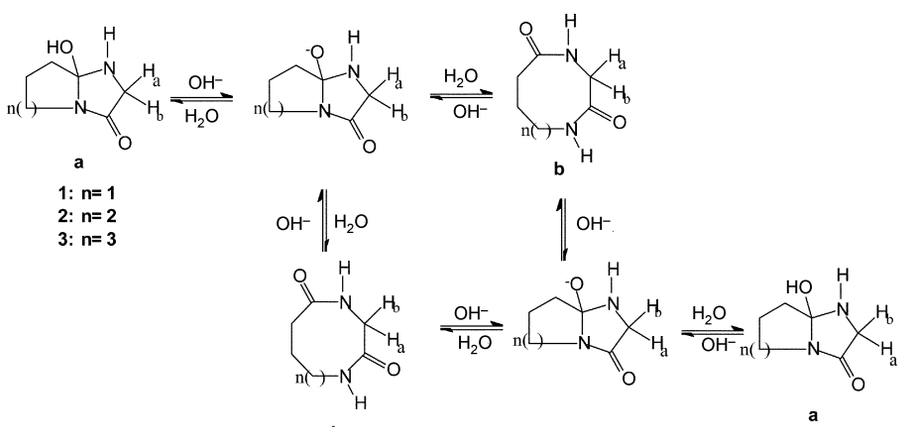


Fig. 5 Mechanistic scheme showing the specific base catalyzed interconversion of the methylene protons H_a and H_b of the two forms **a** (cyclol) and **b** (macrocycle). For configurational and stereochemistry details see ref. 3.

be expected for the macrocycle methylene protons attached to the carbonyl amide and the amino amide. Then, the signal at 4 ppm could be also assigned to **1b**. To distinguish between **1c** (open form) and **1b** (macrocycle) we must find another argument different from the ^{1}H-NMR multiplicity one. The argument that allows us to distinguish the right form is a kinetic one. If the observed exchange measured by magnetization transfer is between **1a** (cyclol) and **1b** (macrocycle), an unchanged equilibium constant K = [**1b**]/[**1a**] in the pD range of the study should be obtained, since according to the proposed mechanism of Fig. 2, $K = k_{obs.f}/k_{obs.r} = K_ak_2[H_2O]/[H^+]/k_{-2}K_w/[H^+] = K_ak_2[H_2O]/k_{-2}K_w$. However, if the exchange is between the cyclol **1a** and the open form **1c**, the K value will become pD dependent, since the pK_a of the amino group of this form is *ca.* 8.7.[2] For instance, if the mechanism is through the free amino base but specifically base catalyzed, $k_{obs.r}$ will become pD independent at pD < 8.7 and the $K = k_{obs.f}/k_{obs.r}$ pD dependent at these pD values. As observed in Fig. 3, the equilibrium constant K is pD independent in the pD interval of the study. Therefore, we conclude that what we have measured *via* magnetization transfer is the exchange between the cyclol **1a** and the macrocycle **1b** and that the signal at 4.0 ppm corresponds to the methylene protons of **1b** and not to **1c**. In Fig. 5 the general mechanism for the exchange **a** ⇌ **b** for compounds **1**, **2** and **3** is shown.

In Table 2 we have summarised the rate constants and energy barriers obtained in this work for the **1a** ⇌ **1b** and **2a** ⇌ **2b** exchange and the ones for **3a** ⇌ **3b**, previously reported.[3] As shown, the values are similar for the three systems. However, there is a tendency in the equilibrium rate constant towards the macrocycle when n (see Fig. 1) decreases and also in k_2 values that may be related to the cyclol ring strain.

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References

1 O. Núñez, J. Rodríguez and L. Angulo, *J. Phys. Org. Chem.*, 1993, **7**, 80.
2 (*a*) L. Angulo and O. Núñez, *J. Chem. Res. (S)*, 1996, 214–215; (*b*) L. Angulo and O. Núñez, *J. Chem. Res. (M)*, 1996, 1123.

3 E. Tineo, S. V. Pekerar and O. Núñez, *J. Chem. Soc., Perkin Trans. 2*, 2002, **2**, 244.
4 T. Winkler and T. Leutert, *Helv. Chim. Acta*, 1982, **65**, 1760.
5 J. P. Guthrie, *Acc. Chem. Res.*, 1983, **16**, 122.
6 S. S. Shaik, H. B. Schlegel and S. Wolfe, *Theoretical Aspects of Physical Organic Chemistry. The SN2 Mechanism*, John Wiley & Sons, Inc., New York, 1992.
7 G. I. Glover, R. B. Smith and H. Rapoport, *J. Am. Chem. Soc.*, 1965, **87**, 2003.
8 HyperChem for Windows, Molecular Mechanics, Method MM+.
9 P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, 1960, **64**, 188.
10 B. M Fung and P. M. Olympia, *Mol. Phys.*, 1970, **19**, 685.
11 S. A. Smith, T. O. Levante, B. H. Meier and R. R. Ernst, *J. Magn. Reson.*, 1994, **106a**, 75.
12 R. A. Hoffman and S. Forsen, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1966, **1**, 15.
13 D. Neuhaus, M. Williamson, *The Nuclear Overhauser Effect In Structural and Conformational Analysis*, VCH, UK, 1989, p. 143.