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Kinetics of the hydrolysis of cyclic *N*-substituted sulfamides: 4-amino-2-cyclohexyl- and 4-amino-2-phenethyl-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxides

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ABSTRACT: The hydrolysis reactions of 4-amino-2-phenethyl- and 4-amino-2-cyclohexyl-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxide (**Ia** and **Ib**) were investigated in the range 24–73 °C in buffered aqueous solutions. The observed rate constants (k_{obs}) are independent of pH in the range *ca* 1–4 pH, but increase with increase in pH above *ca* 4. A linear log k_{obs} vs pH profile with unit slope is observed from pH *ca* 4 up to the highest experimental pH (*ca* 10). The products are the corresponding new compounds: 2-amino-2-[(*N*-substituted-sulfamoyl)imino]acetic acid salts. The C═N bond of these compounds hydrolyses further, in a slow reaction, to the sulfamide and oxalic acid derivatives. The substrates decompose to the final products without accumulation of the acetic acid derivatives under these experimental conditions. A mechanism is proposed. Rate constants and activation parameters are given for the first reaction step. Owing to steric effects, the reaction rate is higher for the *N*-phenethyl-substituted derivative than for the 2-cyclohexyl-substituted derivative. © 1998 John Wiley & Sons, Ltd.

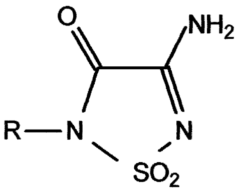
KEYWORDS: Cyclic *N*-substituted sulfonamides; 1,2,5-thiadiazole 1,1-dioxide derivatives; hydrolysis; kinetics

INTRODUCTION

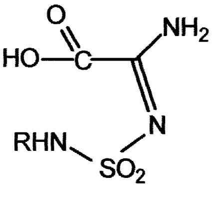
Thiadiazoles are molecules of interest owing to their actual or potential value as intermediates in fine chemistry and to their pharmacological properties.[1] Recent examples of 1,1-dioxide derivatives of thiadiazoles are related to their use β-lactam synthesis[2] or as potassium channel openers.[3] 4-Amino-3-oxo-1,2,5-thiadiazole 1,1-dioxides have been proposed as urea-equivalent fragments in the development of new antagonists of histamine H2 receptors.[1]

Compound **Ic** was synthesized in connection with a search for gastric acid antisecretory drugs by Alkorta *et al.*[4] The same group also reported that **Ic** hydrolyzes to form the salt of 2- amino-2-[(*N*-benzylsulfamoyl)imino]acetic acid (**IIcH**) in basic ([OH$^-$] = 2 M) solution.[5]

In relation to our interest in homogeneous reactions of thiadiazole derivatives,[6–9] in this work we studied the kinetics and mechanism of the hydrolysis of **Ia** and **Ib** over a wide pH range (*ca* 1–10) in buffered aqueous solutions at 24.0, 50.0 and 73.0 °C.



Ia: R = phenethyl
Ib: R = cyclohexyl
Ic: R = benzyl



IIaH: R = phenethyl
IIbH: R = cyclohexyl
IIcH: R = benzyl

Since the activity of gastric antisecretory drugs, including 1,2,5-thiadiazole 1,1-dioxide derivatives, have been related to the excellent electron-withdrawing properties of the heterocycle,[10] the stability of these compounds in aqueous media and the nature of their hydrolysis products are relevant for the understanding of the behaviour of the drugs in biological systems.

Kinetic rate constants and activation energies are

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given, together with spectroscopic and physical data for the new compounds (alkaline salts of **IIaH** and **IIbH**) and unreported ^{13}C NMR and UV spectroscopic data for the substrates **Ia** and **Ib.**

EXPERIMENTAL

Reactants, solvents and products. Reagent-grade acetonitrile (ACN), absolute ethanol (EtOH) and other solvents were purified by standard methods. Water obtained using a Milli-Q purification system (Millipore) was used.

*4-Amino-2-phenethyl-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxide (**Ia**).* This was synthesized[4] from a sample of 3,4-diamino-1,2,5-thiadiazole 1,1-dioxide kindly supplied by Professor V. J. Arán (Instituto de Química Médica, CSIC, Madrid, Spain). Its purity was checked by TLC and m.p. determination. Its IR spectrum (KBr disk) and ^{1}H NMR spectrum (DMSO-d_6) were coincident with those reported.[4] The ^{13}C NMR spectrum in acetone-d_6 shows weak signals at δ (TMS) 158.4 (s, C-4) and 155.2 (s, C-3) and stronger signals at 138.6 (s), 129.6 (s) 129.3 (s) and 127.5 (s) (phenyl) and 43.2 (s) and 34.3 (s) (aliphatic carbon atoms).

The UV spectrum in EtOH, ACN or aqueous solution presents two moderately intense absorption bands at λ_{max} = 208 nm [$\varepsilon = (11.9 \pm 0.6) \times 10^3$ l mol^{-1} cm^{-1}] and λ_{max} 230 nm [$\varepsilon = (9.1 \pm 0.4) \times 10^3$ l mol^{-1} cm^{-1}]. The spectra in EtOH or ACN solution do not change with time. The initial spectrum in aqueous solution does not depend on the pH of the solution.

*4-Amino-2-cyclohexyl-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxide (**Ib**).* The pure reagent (TLC, m.p., IR, ^{1}H NMR) was provided by professor VJ Arán. Its synthesis has been described.[4,11] The ^{13}C NMR spectrum in DMSO-d_6 presents weak signals at δ (TMS) 157.1 (s, C-4) and 154.4 (s, C-3) and stronger signals at 55.1 (s), 29.6(s), 25.2(s) and 24.8 (s) (C-1, C-2 and C-6, C-3 and C-5 and C-4 from the cyclohexyl substituent). The fast atom bombardment (FAB) mass spectrum of **Ib** in a thioglycerol matrix presents intense signals for positive ions at *m/z* 149 (**Ib** − cyclohexyl + H$^+$) and 232 (**IbH**$^+$). When KCl is added to the thioglycerol matrix a new intense signal at *m/z* 270 (**IbK**$^+$) is observed. The UV spectrum in aqueous, EtOH or ACN solution presents a moderately intense absorption bands at λ_{max} 230 nm [$\varepsilon = (9.9 \pm 0.5) \times 10^3$ l mol^{-1} cm^{-1}]. The spectra in EtOH or ACN solution do not change with time. The initial spectrum in aqueous solution does not depend on the pH of the solution.

*2-Amino-2-[(N-phenethylsulfamoyl)imino]acetic acid (**IIaH**) and 2-amino-2-[(N-cyclohexylsulfamoyl)imino] acetic acid (**IIbH**).* The alkaline salts (Na or K) of **IIaH** or **IIbH** were obtained by a different procedure to that reported for **IIc**$^-$ Ref. 5 owing to the fast decomposition reaction of **IIa**$^-$ observed in strongly alkaline solutions (see Results). Equimolar quantities of **Ia** or **Ib** and NaOH or KOH (0.02 M aqueous solution) were stirred at 25 °C (**Ia** or **Ib** do not dissolve completely) for 2.5 h. A homogeneous solution was obtained. The reaction mixture was vacuum evaporated and the solid residue was washed with acetone and dried to constant mass. The products were pure (TLC) and the yield was nearly quantitative. **IIaNa**: white solid, m.p. 209–210 °C (decomp.). The pK_a of the corresponding acid was measured in aqueous solution by potentiometric titration as *ca* 2. **IIbK**: white solid, m.p. 226–228 °C (decomp.). The compositions of the two new compounds by quantitative elemental analysis and atomic emission spectrometry are as follows. **IIaNa**: C 40.00, H 4.28, N 13.20, O 22.31, S 7.67, Na 7.85; calculated C 40.96, H 4.12, N 14.33, O 21.82, S 10.93, Na 7.84%. **IIbK**: C 33.85, H 4.96, N 14.21, O 23.52, S 8.59, K: 12.7; calculated, C 33.44, H 4.91, N 14.62, O 22.27, S 11.16, K 13.61%. Ash formation was observed in both cases in combustion analysis. This can account for the lower than expected sulfur content. **IIaNa**: IR spectrum [KBr disks, ν (cm^{-1})]: 3450, 3340 and 3300 (H—N); 3020 (H—C$_{ar}$); 2950 and 2860 (H—C$_{aliph}$); 1670 (C=N); 1630 and 1425 (CO_2^-); 1600 (phenyl, superimposed with 1630); 1320 and 1120 (SO_2). **IIbK**: 3410, 3300, 3080 (H—N); 2910 and 2850 (H—C of cyclohexyl); 1620 and 1430 (CO_2^-); 1310 and 1130 (SO_2). The most important differences from the respective reactants are the disappearance of the carbonyl band and the presence of carboxylate absorption.

The ^{1}H NMR spectrum of **IIaNa** (D_2O and DMSO-d_6) presents only the signals corresponding to the phenethyl substituent: two signals of similar intensity at δ (TMS) 7.31 and 7.26 (5H, d, phenyl); 2.80 (2H, s, methylenes) and 3.28 (2H, s, methylenes).

Its ^{13}C NMR spectrum (D_2O) shows δ (TMS) 129.8 (s), 129.6 (s) and 127.5 (s) corresponding to phenyl carbon atoms, and 45.0 (s) and 35.7 (s), due to methylenic carbon atoms.

The **IIbK** ^{13}C NMR spectrum (DMSO-d_6) presents four δ (TMS) signals between 24.61 and 52.07 (C of cyclohexyl) (see ^{13}C NMR of **Ib**), and only one weak signal at δ 162.2, assigned to the carboxylate C atom. The *N*-bonded carbon atom signal is not observed in either compound. The absence of the carboxylate carbon signal in **IIaNa** is probably due to the limited solubility of the compound in water and DMSO.

The UV spectrum of aqueous solutions of **IIaNa** [pH 3.62–8.01; ionic strength (μ) 0.05–0.8] shows an intense band at λ_{max} 208 nm [$\varepsilon = (15.2 \pm 0.7) \times 10^3$ l mol^{-1} cm^{-1}]. The extinction coefficient at 230 nm is $(6.4 \pm 0.3) \times 10^3$ l mol^{-1} cm^{-1}. The UV–visible spectra of **IIbK** (pH 4.00–9.64; μ = 0.0–0.4) present a wide, broad band with an ill-defined maximum at *ca* 210 nm.

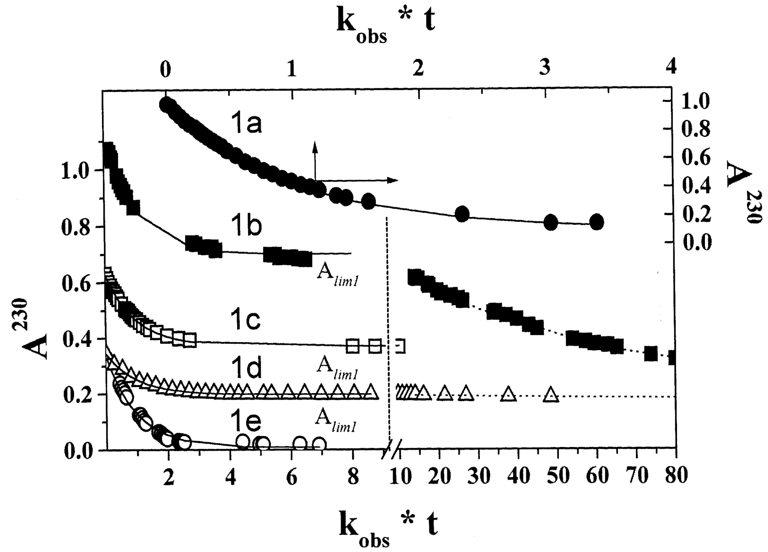

Figure 1. Time decay of the solution absorbance at 230 nm for **Ia** and **Ib** for several representative experimental conditions. A dimensionless ($k_{obs} \times t$) abscissa is used to facilitate comparisons. Filled symbols correspond to **Ia** and open symbols to **Ib.** Curve 1a: (●) $T = 73.0$°C; $k_{obs} = 6.06 \times 10^{-4}$ min^{-1}, pH = 2.02, $\mu = 0.05$; $[\mathbf{Ia}]_0 = 11.7 \times 10^{-5}$ M. Curve 1b: (■) $T = 50.0$°C; $k_{obs} = 1.97 \times 10^{-3}$ min^{-1}, pH = 5.34, $\mu = 0.01$; $[\mathbf{Ia}]_0 = 13.4 \times 10^{-5}$ M. Curve 1c: (□) $T = 24.0$°C; $k_{obs} = 5.05 \times 10^{-3}$ min^{-1}, pH = 7.66, $\mu = 0.1$; $[\mathbf{Ib}]_0 = 6.32 \times 10^{-5}$ M. Curve 1d: (△) $T = 73.0$°C; $k_{obs} = 1.09$ min^{-1}, pH = 7.90, $\mu = 0.4$; $[\mathbf{Ib}]_0 = 3.54 \times 10^{-5}$ M. Curve 1e: (○) $T = 73.0$°C; $k_{obs} = 4.15 \times 10^{-4}$ min^{-1}, pH = 0.59, $\mu = 0.45$; $[\mathbf{Ib}]_0 = 3.55 \times 10^{-5}$ M. Full and broken lines are least-squares fits to the exponential decays. The A^{230}_{lim1} absorbance (see text) is indicated

The extinction coefficient at 230 nm is $(6.4 \pm 0.3) \times 10^3$ l mol^{-1} cm^{-1}. A slight tendency for ε (230 nm) to decrease with decrease in pH is observed for both compounds, but it is within the limits of the reported error for the range of these parameters used.

Experimental measurements and procedures. UV spectral measurements were made with a Zeiss-PMQ3 or a Varian Cary 3 spectrophotometer equipped with thermostated cell holders.

^{1}H and ^{13}C NMR spectra were measured with a Bruker 200 MHz instrument and IR spectra with a Shimadzu IR-435 IR spectrophotometer. A ZAB-SEQ instrument was used for FAB mass spectrometry. Atomic emission spectrometric measurements were carried out with a Metrolab 4200 instrument.

pH was measured with a Parsec Vega VI apparatus. The pH cell was standardized immediately before each measurement using certified buffers at the same temperature as the unknown.

Kinetic measurements. The hydrolysis reactions of **Ia** and **b** were studied at three temperatures (24.0, 50.0 and 73.0 °C) by following the time decay of the absorbance at 230 nm (parallel measurements at 208 nm for **Ia** and 240 nm for **Ib** gave the same kinetic results). The pH was changed from *ca* 1 to *ca* 10. The buffers used were Na_2HPO_4–KH_2PO_4, NaOAc–HOAc and Na_2CO_3–$NaHCO_3$. HCl was used in the highly acid range. The total buffer concentration was changed by one order of magnitude to investigate specific catalysis. The ionic strength was changed from 0.05 to 0.8 (obtained with different concentrations of the standard solutions used for the preparation of the buffers or by addition of $NaClO_4$).

The reaction was carried in quartz cells of 1 cm optical path, provided with Teflon stoppers. Two cells containing measured equal volumes (*ca* 3 ml) of aqueous buffer of known concentration, pH and ionic strength were placed in a thermostated cell holder (± 0.1 °C). The reaction was initiated by adding (by means of a microsyringe) a measured volume of the stock solutions of **Ia** or **Ib** in ACN to the sample cell and shaking to homogenize. These initial mixing procedures typically took 5–10 s. The reaction was considered to initiate when half of the initial mixing time had elapsed.

The initial concentration of the reactants was varied experimentally in the range $(2.66–15.0) \times 10^{-5}$ M for **Ia** and $(1.00–10.0) \times 10^{-5}$ M for **Ib**.

Some kinetic runs were conducted in a thermostated stoppered flask from which samples of the reaction mixtures were taken at measured times and analyzed by TLC.

RESULTS AND DISCUSSION

We will represent the substrates or the products as **I** or **II** when describing common properties and behaviors. Detailed symbols (**Ia, IIbK, IIa**$^-$ or **IIbH**, for example) will be used when reference to a specific molecular or ionic species is required.

The absorbance of buffered aqueous solutions of **I** at

230 nm (A^{230}) decreased with time following a first-order rate law. The initial extrapolated absorbance value (A_0^{230}) agreed with the calculated absorbance for the initial concentration of **I** (**I**$_0$).

Typical absorbance–time curves are shown in Fig. 1(a)–(e). An adimensional time scale ($k_{obs} \times t$) is used to facilitate the comparison, k_{obs} values are reported in the figure captions for each curve.

The curves presented different characteristics that depended mainly on the experimental pH. In the lower pH range (*ca* < 4), the absorbance decayed following a single exponential law to a nearly zero value [Fig. 1(a), **Ia**, ●; Fig. 1(e), **Ib**, ○]. Complete spectra recorded during these runs showed that the absorbance decayed homogeneously in the range 200–300 nm. The solution did not absorb at longer wavelengths. No isosbestic point was observed.

At higher experimental pHs, the absorbance decayed to a practically constant value (A_{lim1}^{230}) in the kinetic runs at the lower temperatures [Fig. 1(b), **Ia**, ■; Fig. 1c, **Ib**, □; Fig. 1d, **Ib**, Δ). A_{lim1}^{230} agreed with the absorbance expected for complete conversion of **I** to **II,** as calculated from their (independently measured) extinction coefficients. A well defined isosbestic point was observed (*ca* 216 nm) when complete spectra were recorded at selected times during the kinetic run.

A subsequent and slower decay of the absorbance below $A_{\mathrm{lim1}}^{230}$was observed [Fig. 1(b), **Ia**, ■; Fig. 1(d), **Ib**, Δ) when absorbance–time data were recorded for more than *ca* 10 half-lives of the first exponential decay.

The practical absorbance plateau $A_{\mathrm{lim1}}^{230}$was prolonged and very clearly defined for **Ia** at all experimental temperatures and for **Ib** in all runs at 24.0 °C and most runs at 50.0 °C in the above-indicated pH range. The slow subsequent decay was, in fact, difficult to observe under these conditions owing to the long time required.

The transition from the first to the second absorbance decay was less clear in very fast runs (at high pH) at 50 and 73 °C with the substrate **Ib**. However, the absorbance–time data could be accurately fitted with a nonlinear least-squares routine to a double exponential decay law. The fitted limiting value for the first exponential decay matched the expected A_{lim1}^{230}.

Compound **I** was almost instantly converted into **II** when pHs higher than those shown in Fig. 1 were used (**Ia**: $T = 50$ °C, pH ≥ 9.5, for example). The initial extrapolated absorbance agreed with that expected for **II**, at a concentration equal to **I**$_0$, and the absorbance decreased thereafter to a limit of nearly zero.

To minimize the extent of this decomposition reaction, we modified the procedure for the synthesis of **II** from **I**, as indicated in the Experimental section. This second decomposition reaction is slower than the hydrolysis reaction of **I**, as mentioned above. For example, at pH 11.06 and 50.0 °C, **Ia** was converted into **IIa**$^-$ in a few seconds, whereas under in the same experimental conditions, **IIaNa** required more than 20 h to decompose.

The decomposition reaction of **II** was not investigated further. It must involve the hydrolysis of the remaining C=N bond to give oxalamide and *N*-substituted sulfamides and their further reactions to form oxalic acid salts and sulfamates.[12] Bands assignable to —SO_3^- and —C(O)N$<$ were observed in the IR spectrum of the reaction mixture after prolonged reaction times at alkaline pH. Oxalate salts were isolated and identified (IR) from the same reaction mixture.

TLC analyses of the reacting mixture were carried out for some slow kinetic runs. A gradual and steady replacement of **I** by **II** was observed during the first process and only **II** was present at the plateau. Beyond the end of the plateau, the concentration of **II** decreased slowly.

When the hydrolysis of **I** was attempted in unbuffered aqueous solution, the pH of an initially neutral 3.6×10^{-3} M unbuffered aqueous solution of **I** decreased to *ca* 4 in approximately 24 h, probably owing to the formation of a small amount of the acids **IIH**. Thereafter, the reaction continued as described above for the low pH limit (*ca* < 4.5) in buffered solutions.

Hydrolysis experiments with the alkaline salts of **II** as reactants did not produce **I**, but decomposed as mentioned above. However, **II** reverted to **I** in nominally anhydrous solvents. Thus, when a *ca.* 3×10^{-3} M solution of **II** in propanone (0.1% H_2O, Karl Fisher) was maintained at room temperature, TLC analysis showed the presence of **I** (**IIaNa** reverted nearly quantitatively in 2 days whereas **IIbK** reverted partially in a week). The attack of the amide nitrogen on the carboxylic carbon atom has been observed in similar systems.[13,14]

The observed pseudo-first-order rate constants (k_{obs}) for the hydrolysis of **Ia** and **Ib,** obtained from linear plots of $\ln(A_t^{230} - A_{\mathrm{lim1}}^{230})$ vs t, as a function of pH and temperature are shown in Fig. 2(a) (**Ia**) and (b) (**Ib**). The rate constant did not depend, within the experimental error, on the ionic strength of the solution or on the type or concentration of the buffers.

At all temperatures and for the higher experimental pHs, the log(k_{obs})–pH profiles are linear with a slope of practically unity (Fig. 2). A pH-independent rate constant limit was reached experimentally at the lower pHs. This limit was observed at all temperatures for **Ia** and at 73 °C for **Ib**.

The results were interpreted as a nucleophilic attack on the acylic carbon atom by water or OH$^-$ ions:

$$\mathbf{I} + H_2O \rightleftharpoons \mathbf{II} \qquad k_1^0; k_{-1}^0 \qquad (1)$$

$$\mathbf{I} + OH^- \longrightarrow \mathbf{II}^- \qquad k_2^{OH} \qquad (2)$$

$$\mathbf{II} \qquad \longrightarrow \text{Decomposition products} \quad k_3 \qquad (3)$$

The high pH zone of the log k_{obs} vs pH profile corresponds to the preponderance of OH$^-$ nucleophilic attack, which is practically irreversible in aqueous media.

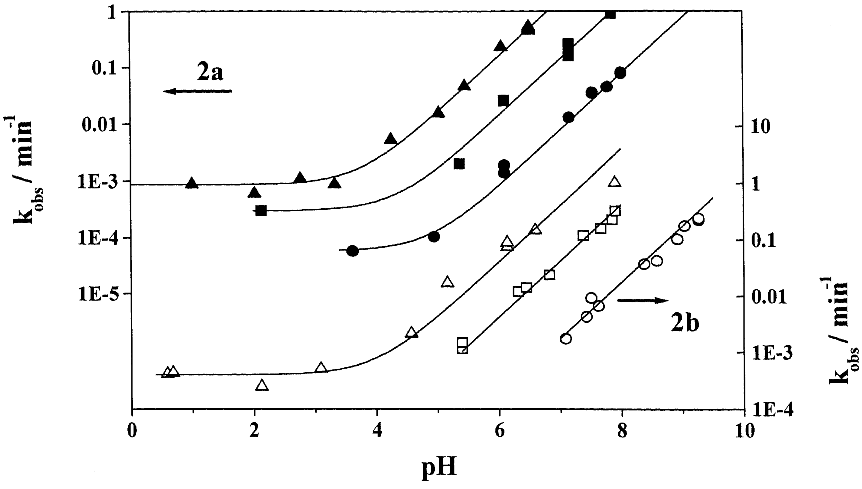

Figure 2. k_{obs} as a function of pH and temperature. Curves 2a: **Ia** (filled symbols); curves 2b: **Ib** (open symbols). Temperature: ●, ○, 24.0; ■, □, 50.0; ▲, △, 73.0 °C. Each point is the average of at least two experiments. Individual values differ by less than 5% from the average. pHs were measured at the experimental temperatures. Solid lines were calculated using the rate constants in Table 1. The slopes and regression coefficients (*r*) of the log(k_{obs}) vs pH profiles in the pH-dependent regions are as follows: **Ia**: (●) slope = 0.93, *r* = 0.99; (■) slope = 1.01, *r* = 0.99; (▲) slope = 1.01, *r* = 0.99; **Ib**: (○) slope = 0.93, *r* = 0.99; (□) slope = 0.93, *r* = 0.99; (△) slope = 0.92, *r* = 0.98.

Table 1. Calculated rate constants for the hydrolysis reaction of **Ia** and **Ib**

Compound	*T* (°C)	k_1^0 (l mol^{-1} min^{-1}) × 10^6	k_2^{OH} (l mol^{-1} min^{-1}) × 10^{-4}
Ia	24.0	1.05	7.3 ± 0.3
	50.0	5.48	24.0 ± 0.1
	73.0	16.1	86.0 ± 0.3
Ib	24.0	—	1.7
	50.0	—	7.5
	73.0	7.4	22.6

In the pH-independent region, the slow (equilibrium) water addition reaction forms the amino acid, which reacts further as mentioned. Hence

$$k_{obs} = \frac{k_1^0\, k_3}{k_{-1}^0 + k_3}[H_2O] + k_2^{OH}[OH\text{-}]$$

Since **II** was not observed either spectroscopically or by TLC in the kinetic runs at low pH and, as was noted, the absorbance decreased at all recorded wavelengths under these experimental conditions, it must be concluded that $k_3 \gg k^0_{-1}$ and, consequently $k_1^0 k_3/(k^0_{-1} + k_3) = k_1^0.k_1^0$ can be obtained from the rate at low pH values and k_2^{OH} from the data at high pH values. The calculated rate constants are given in Table 1. These values were used to draw the solid lines in the log k_{obs} vs pH profiles in Fig. 2(a) and (b). The dependence of the rate constants with temperature is ln[k_1^0 (**Ia**) (l mol^{-1} min^{-1})] = 5.6 ± 0.7 − (48 ± 2 kJ mol^{-1})/*RT*, *r* = 0.999; ln[k_2^{OH}(**Ia**) (l mol^{-1} min^{-1})] = 28 ± 1 − (43 ± 4 kJ mol^{-1})/*RT*, *r* = 0.995; ln[k_2^{OH}(**Ib**) (l mol^{-1} min^{-1})] = 28 ± 0.6 − (46 ± 3 kJ mol^{-1})/*RT*, *r* = 0.996.

The rate constant differences between **Ia** and **Ib** must be caused by differences in steric effects of the *N*-substituent. The steric hindrance is smaller for **Ia** than for **Ib** owing to the longer average distance from the bulky phenyl group to the acylic carbon and to the larger rotational freedom provided by the ethyl linkage between the phenyl group and the heterocycle.

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REFERENCES

1. V. J. Arán, P. Goya and C. Ochoa. *Adv Heterocycl. Chem.* **44,** 81 (1988).
2. Y. H. Lee, C. H. Lee and W. S. Choi. *Bull. Kor. Chem. Soc.* **17,** 290 (1996).
3. L. Dupont, B. Pirotte, P. Detullio and J. Delarge. *Acta Crystallogr. Sect. C* **52,** 1741 (1996).
4. I. Alkorta, V. J. Arán, E. Dávila, J. R. Ruiz and M. Stud. *Liebigs Ann. Chem.* 1135 (1989).
5. V. J. Arán, J. R. Ruiz and M. Stud. *J. Chem. Soc., Perkin Trans. 1* 955 (1987).
6. M. V. Mirifico, E. J. Vasini and J. E. Sicre. *Int. J. Chem. Kinet.* **23,** 197 (1991).
7. M. V. Mirífico, J. A. Caram, E. J. Vasini and J. E. Sicre. *J. Phys. Org. Chem.* **6,** 341 (1993).
8. M. V. Mirífico and E. J. Vasini. *An. Quim.* **91,** 557 (1995).
9. J. A. Caram, M. V. Mirífico, S. L. Aimone and E. J. Vasini. *Can. J. Chem.* **74,** 1564 (1996).
10. W. C. Lumma, Jr, P. S. Anderson, J. J. Baldwin, W. A. Bolhofer, C. H. Habecker, J. M. Hirsfield, A. M. Pietruszkiewicz, W. C. Randall, M. L. Torchiana, S. F. Britcer, B. V. Clineschmidt, G. H. Denny, R. Hirschmann, J. M. Hoffman, B. T. Phillips and K. B. Streeter. *J. Med. Chem.* **25,** 207 (1982).
11. V. J. Arán, A. G. Bielsa, J. R. Ruiz and M. Stud. *J. Chem. Soc. Perkin Trans. 1* **643** (1986).
12. A. Yamaguchi and K. Nakano. *Hiroshima Daigaku Kenkyu Hokoku* **21,** 23 (1972); *Chem. Abstr.* **79,** 65420 (1973).
13. M. K. Hargreaves, J. G. Pritchard and H. R. Dave. *Chem. Rev.* **70,** 439 (1970).
14. J. T. Eaton, W. D. Rounds, J. H. Urbanowicz and G. W. Gribble. *Tetrahedron Lett.* **29,** 6553 (1988).