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Mechanistic investigation of an anomalous anchimeric assistance in the acid hydrolysis of the ether linkage. Part 4☆

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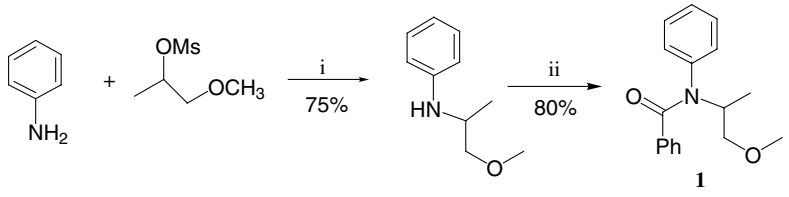
Abstract—Kinetic investigation of the acid hydrolysis of *N*-(methoxyprop-2-yl)benzanilide (**1**) was performed in 8.84 M HCl and/or DCl at 75.1°C. The formation of 2-(*N*-phenylamino)propanol (**4**) was explained and the mechanism, involving an initial ether cleavage anchimerically assisted by the amide group, was clarified. The overall process evolves through three steps involving two intermediates. The rate constants of the individual processes have been determined by UV and ^{1}H NMR spectroscopic techniques.

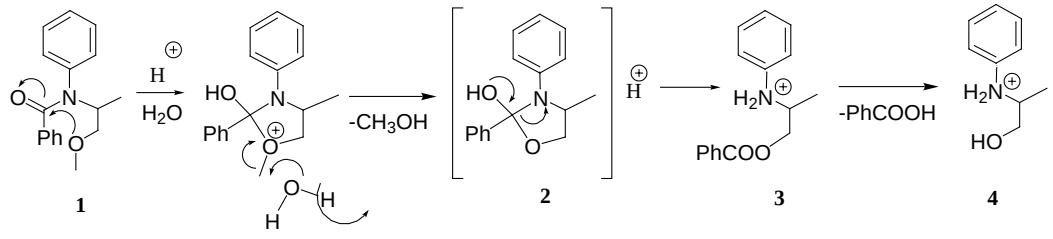
1. Introduction

Owing to our interest in the investigation of ether cleavage anchimerically assisted by an amide group,[1–3] we have focused our attention on the substrate **1**, synthesized as reported in Scheme 1 (see also Experimental section).

The substrate **1** differs from those previously studied[1,3] because it is lacking alkyl substituents in the 2,6 positions of the aniline ring, i.e. the chirality axis is absent. This feature causes an interesting different behaviour during the acid hydrolysis of the ether function whereby the vicinal amide group participates in the reaction. In fact, at the end of the reaction only the aminoalcohol **4** (in addition to the methanol and benzoic acid) was found instead of the cyclic oxazolidine derivative, as previously observed[1,3] for analogous substrates, i.e. the participating group was lost (Scheme 2). Since to the best our knowledge there has not been any example described in the literature in which the assisting group becomes detached from the reacting moiety,



Scheme 1. (i) Et_3N in benzene at reflux for 40 h; (ii) PhCOCl and Et_3N in $CHCl_3$ at reflux for 3 h.



Scheme 2.

☆ See Refs. 1–3.

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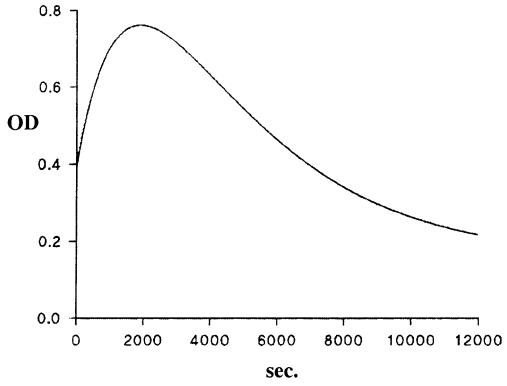


Figure 1. Plot of absorbance vs time for the hydrolysis of **1** followed at λ=260 nm in 8.84 M HCl at 75.1°C. Experimental points are hidden by the solid line calculated by using equation (1).

we found it interesting to investigate the reaction mechanism involved in this case.

2. Results and discussion

To examine the optical density (OD) vs time behaviour at various wavelengths, repetitive wavelength scans of UV absorbance recorded during the acid hydrolysis of **1** in 8.84 M HCl at 75.1°C were performed. Examination of the plot (not reported) showed that at all $\lambda \geq 238$ nm as the reaction progresses the OD initially increases rapidly, reaches a maximum value after about 2000 s and then decreases until it becomes asymptotic. Conversely, at $225 \leq \lambda \leq 238$ nm the OD continues to increase also after 2000 s reaching a constant value.

As shown in Fig. 1, the behaviour observed at λ=260 nm is generally typical of a process formed by two consecutive first-order reactions with kinetic constants k_1' and k_2', the variation of OD being expressed by the following equation:[4a,b]

$$OD_t = A_0\{\epsilon_3 + (\epsilon_1 - \epsilon_3)\exp(-k_1' t) + k_1'(\epsilon_2 - \epsilon_3) \times [\exp(-k_2' t) - \exp(-k_1' t)]/(k_1' - k_2')\} \quad (1)$$

where A_0 is the initial concentration of **1**, $A_0\epsilon_2$ the optical density of the intermediate, while $A_0\epsilon_1 = OD_0$ and $A_0\epsilon_3 = OD\infty$ are the optical densities measured at t=0 and t=∞, respectively. The experimental values of OD vs time, obtained by performing the hydrolysis of **1** in 8.84 M HCl at 75.1°C, were fitted well by the equation (1). The values of ϵ_2=8800 M^{-1} cm^{-1}, k_1'=6.69×10^{-4} s^{-1} and k_2'=3.39×10^{-4} s^{-1} (Table 1) have been computed by best fitting of kinetic data to equation (1) by a non-linear iterative least square procedure[5] and taking the experimental values of ϵ_1=2950 M^{-1} cm^{-1} and ϵ_3=1050 M^{-1} cm^{-1}. Although determination of the rate constants that govern the steps of consecutive first-order reactions becomes difficult when k_1' and k_2' have close values,[6] the experimental points in Fig. 1 practically coincide with the solid line calculated using equation (1) (r=0.9998) and the standard deviation is less than the estimated standard error in the measurements.

Since the reaction product is the aminoalcohol **4**, the hydrolytic process necessarily involves a step in which the cleavage of methyl ether is assisted by the vicinal amide group which, despite what generally occurs,[7] is lost (Scheme 2). Therefore, the first step must be the nucleophilic attack of the ether oxygen on the protonated amide group (neighbouring group participation), as already reported.[1,3] The successive water attack on the cyclic oxonium ion gives the intermediate **2** and methanol is released.

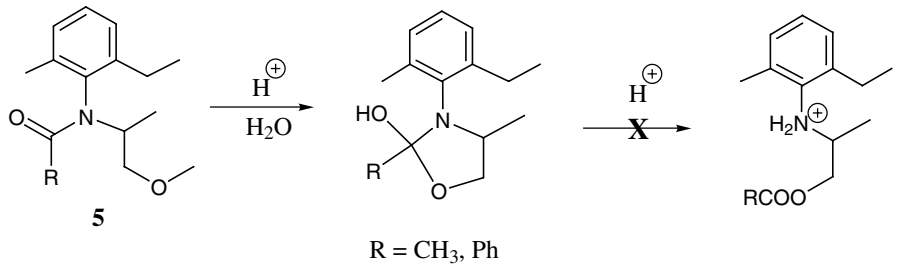
However, in contrast to previous observations for other substrates which gave a cyclic intermediate that was stable in acid medium[1,3] (Scheme 3), the hypothesized intermediate **2** evolves to the final product **4**.

Since it is not possible to assign the sequence of the rate constants in a consecutive-reactions process, the values of k_1' and k_2' in equation (1) being interchangeable, [4a,b] we attempted to isolate the reaction intermediate to submit it to kinetic investigations in order to attribute the rate constant to the single steps evidenced in the plot of Fig. 1. To this end, substrate **1** was hydrolysed in 8.84 M HCl at about 75°C and the reaction, monitored by TLC, was stopped after about 20 min by basification. The ^{1}H NMR and GMS analysis highlighted the presence of three products: the aminoester **3**, largely abundant, in addition to both the starting (**1**) and the final product (**4**). The aminoester **3** was then synthesized and submitted to acid hydrolysis in 8.84 M HCl at 75.1°C. The kinetics, monitored spectrophotometrically at λ=260 nm, gave a pseudo first-order rate constant k_3'=2.36×10^{-4} s^{-1} and highlighted two relevant features: (a) the molar extinction coefficient of **3** (ϵ = 1160 M^{-1} cm^{-1}) is considerably smaller than that of both intermediate and substrate **1**; (b) similar values of OD_0 and OD_∞, the latter being only 10% lower. Such a low difference in the OD value associated with the **3**→**4** process (in comparison to that associated with the **2**→**3** step) does

Table 1. Rate constants of acid hydrolysis of **1** and **3** at 75.1°C measured by UV and ^{1}H NMR

Acid hydrolysis of	UV[a]			^{1}H NMR		
	$10^4 \times k_1'$ (s^{-1})	$10^4 \times k_2'$ (s^{-1})	$10^4 \times k_3'$ (s^{-1})	$10^4 \times k_1$ (s^{-1})	$10^4 \times k_2$ (s^{-1})	$10^4 \times k_3$ (s^{-1})
1						
8.84 M HCl	6.69±0.07	3.39±0.08				
8.84 M DCl	10.9±0.09	1.7±0.01		8.9±0.2	3.5±0.1	3.8±0.2
3						
8.84 M HCl			2.36±0.03			

Estimated standard error with ±95% confidence interval is reported.
[a] Measured at λ=260 nm.



Scheme 3.

not allow detection by a UV method[6] of the third step (i.e. the conversion of **3** into **4**). From these findings, it appears evident that the second section of the plot in Fig. 1 is not consistent with the hydrolysis of **3** although its rate constant ($k_3'=2.36\times10^{-4}\ s^{-1}$) is comparable with $k_2'=3.39\times10^{-4}\ s^{-1}$, calculated for **1** on the basis of a biphasic process [equation (1)]. Thus, the molar coefficent $\epsilon_2=8800\ M^{-1}\ cm^{-1}$ can be reasonably ascribed to the cyclic intermediate **2** (not isolable from the reaction mixture) and the k_2' to the conversion of **2** into **3** (Scheme 2). In order to ascertain whether the aminoester **3** is an intermediate in the pathway of acid hydrolysis of **1**, or if it is originated from decomposition of **2** (owing to basification to stop the reaction), we turned to the ^1H NMR technique which, contrary to UV, can monitor the concentration of each species and then it is very useful in assigning the rate constant to individual steps. To this end the substrate **1** (dissolved in 8.84 M DCl/D_2O) was submitted to a kinetic investigation by ^1H NMR spectroscopy in tubes thermostated at 75.1°C and the spectra recorded at fixed times confirmed the presence of **3** in the reaction mixture. Fig. 2 shows the molar percentage concentration of each product vs. time (see Experimental section). The experimental concentration-time curves were fitted by the appropriate equations,[8] which describe a consecutive irreversible three-step process **1→2→3→4**, the respective rate constants being k_1, k_2 and k_3.

In Fig. 2, curve 1 describes the disappearance of the starting **1**, while curves 2 and 3 the formation and the successive disappearance of **2** and **3**, respectively. Finally, curve 4 represents the formation of the final product **4**. The curves were plotted by using an iterative non-linear least squares procedure[5] and the three pseudo first-order rate constants were calculated according to the following equations for a consecutive three-step reaction:[9]

$$[\mathbf{1}]_t = [A_0]\exp(-k_1 t) \tag{2a}$$

$$[\mathbf{2}]_t = [A_0]k_1[\exp(-k_1 t) - \exp(-k_2 t)]/(k_2 - k_1) \tag{2b}$$

$$[\mathbf{3}]_t = [A_0]k_1k_2[\exp(-k_1 t)/(k_2 - k_1)(k_3 - k_1) + \exp(-k_2 t)/(k_1 - k_2)(k_3 - k_2) + \exp(-k_3 t)/(k_1 - k_3)(k_2 - k_3)] \tag{2c}$$

$$[\mathbf{4}]_t = [A_0]k_1k_2k_3\{(1/k_1k_2k_3) - 1/k_1[\exp(-k_1 t)/(k_2 - k_1) \times (k_3 - k_1)] - 1/k_2[\exp(-k_2 t)/(k_1 - k_2)(k_3 - k_2)] - 1/k_3[\exp(-k_3 t)/(k_1 - k_3)(k_2 - k_3)]\} \tag{2d}$$

where A_0 is the initial molar percentage concentration of **1**, and $[\mathbf{1}]_t$, $[\mathbf{2}]_t$, $[\mathbf{3}]_t$, $[\mathbf{4}]_t$ are the molar percentage concentrations of the respective compounds at the time t. The value of k_1, obtained from equation (2a), was introduced in equation 2(b) to calculate k_2. Then, k_3 was evaluated introducing the values of k_1 and k_2 in equation (2c). The rate constant values thus obtained, $k_1=8.9\times10^{-4}\ s^{-1}$, $k_2=3.5\times10^{-4}\ s^{-1}$ and $k_3=3.8\times10^{-4}\ s^{-1}$ (Table 1) introduced in equation (2d) fit the experimental data fairly well.

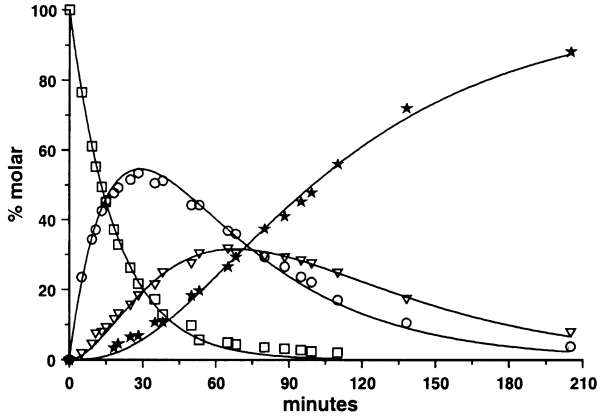
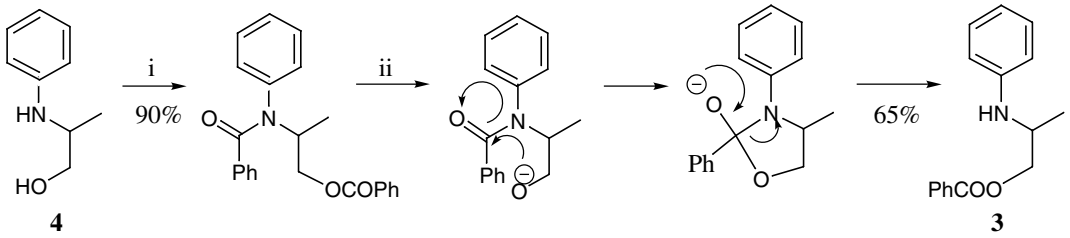


Figure 2. Plots of percentage molar concentrations (evaluated by ^1H NMR) vs time for: hydrolysis of **1** (open square), formation and decomposition of **2** (open circle) and **3** (open inverted triangle) and formation of **4** (star). Kinetics performed in 8.84 M DCl/D_2O at 75.1°C. The points are experimental and the curves are calculated from a least square fit to equations 2a, b, c, d (see text).

In order to realize the correspondence of k_1 and k_2 calculated by the ^1H NMR technique (relative to the first and second step, i.e. the cyclization of **1** and decomposition of **2**) with k_1' and k_2' obtained by the UV spectroscopy, we followed the kinetics of hydrolysis of **1** in 8.84 M DCl/D_2O at 75.1°C by the UV method. The rate constants $k_1'=10.9\times10^{-4}\ s^{-1}$ and $k_2'=1.7\times10^{-4}\ s^{-1}$ thus obtained (Table 1) are in reasonable agreement with k_1 and k_2, respectively, determined by the ^1H NMR spectroscopy. In actual fact, the differences in the values obtained can be ascribed both to the lower accuracy of ^1H NMR measurements (in comparison with the UV method) and to differences in the activity coefficients[9] due to the largely different concentration of the substrate **1** in the solutions employed for UV (1.3×10^{-4} M) and ^1H NMR (3.8×10^{-2} M).



Scheme 4. (i) PhCOCl and TEA in $CHCl_3$ 50 h at reflux; (ii) $Na_2CO_3.H_2O$ in H_2O/acetone 2 h at rt.

3. Conclusions

In this paper we have described the acid hydrolysis of substrate **1** and ascertained the unusual mechanism involving the loss of the assisting vicinal amide group. A reasonable explanation of the different behaviour towards the acid hydrolysis between the substrates **1** and **5**, previously investigated,[1,3] could be based on the different basicity of the leaving group during the opening of the cyclic intermediate. In fact, in substrate **1** the leaving group is better than in **5** owing to a lower basicity arising from the overlap of the phenyl ring and the lone pair on the nitrogen. The *o*-alkyl substituents in **5** strongly reduce the conjugation of the nitrogen lone pair with the phenyl ring and increase the basicity, as reported for *N*-alkyl substituted anilines.[10]

Kinetics followed by ^1H NMR demonstrated that the reaction follows a three-step mechanism (Scheme 2), while the kinetic experiments performed by the UV technique showed that the third step, i.e. the process **3→4**, cannot be detected, the OD decrease being very small. The cyclic intermediate **2** (not isolable) was indirectly highlighted as a consequence of the anchimeric assistance of the vicinal amide group, while the aminoester **3** has been ascertained as an intermediate by isolation.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded with a Varian Gemini 300 (300 MHz) instrument by using $CDCl_3$ as solvent and the coupling constants (*J*) are in Hz. IR spectra were obtained with a Nicolet 210 instrument. UV spectra and kinetic measurements were recorded on a Perkin–Elmer Lambda 6 spectrophotometer.

4.1.1. *N*-(Methoxyprop-2-yl)benzanilide (1) (see also the Appendix). 2.2 mL of aniline (24 mmol) and 4.5 g (24 mmol) of (±)-(methoxyprop-2-yl) methanesulphonate (prepared from (±)-methoxy-2-propanol and methanesulfonylchloride by the usual procedure) were refluxed for 40 h in benzene (20 mL) in the presence of triethylamine (TEA) (3.4 mL, 24 mmol). Pure *N*-(2-methoxymethylethyl)aniline was recovered as an oil in 75% yield after purification by silica gel chromatography eluting with hexane/ethyl acetate [δ_H 1.24 (3H, d, *J*=6.3, $CHCH_3$), 3.39 (3H, s, OCH_3), 3.43 (2H, m, OCH_2CH), 3.67 (1H, m, $CHCH_3$), 3.83 (1H, bs, NH), 6.67 (3H, m, Ph), 7.18 (2H, m, Ph)]. The intermediate product (1.65 g, 10 mmol) was dissolved in 15 mL of $CHCl_3$ and TEA (1.4 mL, 10 mmol) was added. Then, benzoyl chloride (1.5 mL, 13 mmol) dissolved in 5 mL of $CHCl_3$ was dropped into the stirring solution and the reaction mixture was refluxed for 3 h. After evaporation of the solvent, the residue was acidified with diluted HCl and extracted with ethyl acetate. Evaporation to dryness in vacuo gave the crude reaction product that, after silica gel chromatographic purification eluting with hexane/ethyl-acetate, was recovered pure as an oil in 80% yield. ν_{max}(neat)=1659, 1606, 1493, 1347, 1109, 698 cm^{-1}; δ_H 1.18 (3H, d, *J*=7, $CHCH_3$), 3.39 (3H, s, OCH_3), 3.41 (3H, m, OCH_2CH), 7.06–7.29 (10H, m, Ph); δ_C 15.6, 51.5, 58.5, 73.6, 127.2, 127.4, 128, 128.5, 128.8, 130.3, 137, 139.6, 171; [Found: C, 75.84; H, 7.1. $C_{17}H_{19}NO_2$ requires: C, 75.81; H, 7.11%].

4.1.2. 2-(*N*-phenylamino)propylbenzoate (3). It was synthesized by following the procedure summarized in Scheme 4. Benzoyl chloride (7 mL, 60 mmol) in $CHCl_3$ (10 mL) was dropped into a solution of 2-(*N*-phenylamino) propanol (**4**) (3 g, 20 mmol) and TEA (5.6 mL, 40 mmol) in $CHCl_3$ (20 mL). The reaction mixture was refluxed for about 50 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate and washed with diluted HCl. The organic solvent was evaporated and the pure dibenzoyl derivative was isolated in 90% yield after silica gel chromatography eluting with hexane/ethyl acetate [δ_H 1.32 (3H, d, *J*=7, $CHCH_3$), 4.42 (2H, m, CH_2O), 5.4 (1H, m, $CHCH_3$), 7.15 (10H, m, Ph), 7.5 (3H, m, Ph), 8.05 (2H, m, Ph)]. The intermediate product (3.6 g, 10 mmol) was dissolved in acetone (60 mL) and $Na_2CO_3.H_2O$ (1.24 g, 10 mmol) in water (30 mL) was added. The reaction mixture was stirred at rt and monitored by TLC. After about 2 h the acetone was evaporated in vacuo and the residue was extracted with ethyl acetate. The organic solvent was evaporated and the residue submitted to silica gel chromatographic purification eluting with hexane/ethyl acetate. The product was recovered as a wax in 65% yield. ν_{max}(neat)=3393, 1699, 1603, 1460, 1280, 1117, 751, 710; δ_H 1.37 (3H, d, *J*=6.5, $CHCH_3$), 3.94 (1H, m, $CHCH_3$), 4.24 (1H, dd, *J*=5.5, 11.1, CH_aCH_bO), 4.5 (1H, dd, *J*=5.2, 11.1, CH_aCH_bO), 6.74 (3H, m, Ph), 7.21 (2H, m, Ph), 7.5 (3H, m, Ph), 8.4 (2H, m, Ph); δ_C 18.1, 47.7, 67.8, 113.2, 117.6, 128.3, 129.3, 129.5, 133, 146.9, 166.5; [Found: C, 75.25; H, 6.73. $C_{16}H_{17}NO_2$ requires C, 75.27; H, 6.71%].

4.1.3. 2-(*N*-phenylamino)propanol (4). It was obtained by stirring **1** (1.35 g, 5 mmol) in 10 mL of 8.84 M HCl at about 70°C for 6 h. The reaction mixture was concentrated in vacuo, made alkaline and extracted with ethyl acetate. The product, after evaporation of the organic solvent, was recovered as an oil in practically quantitative yield. ν_{max}

(neat)=3376 (br), 1599, 1507, 1321, 1042, 751, 698; δ_H 1.22 (3H, d, J=6.3, CH_3CH), 3.55 (1H, dd, J=6, 10.7, CH_aCH$_b$O), 3.67 (1H, m, CHCH$_3$), 3.76 (1H, dd, J=4.2, 10.7, CH$_a$CH_bO), 6.75 (3H, m, Ph), 7.2 (2H, m, Ph); δ_C 17.4, 50.6, 65.9, 113.8, 117.9, 129.2, 147.2; [Found: C, 71.8; H, 8.7. $C_9H_{13}NO$ requires C, 71.49; H, 8.67%].

The product can be also synthesized starting from aniline and (±)-ethyl 2-bromopropionate followed by lithium borohydride reduction, as previously described[3] for an analogous derivative.

4.2. Kinetic Experiments

The kinetic measurements of acid hydrolysis of **1** were performed in 8.84 M both in HCl and DCl at 75.1°C by following the progress of the reaction by UV absorption spectroscopy at λ=260 nm. 20 μL of the stock solution of **1** (0.015 M in MeOH or MeOD) were added to 3 mL of HCl or DCl thermostated in 1 cm path cell of the spectrophotometer. The rate constants for the acid hydrolysis of **1** were obtained from the equation 1 by plotting 200–300 values of OD with an iterative non linear last square routine.[5] Initial estimate of adjustable parameters of equation 1 were obtained from the approximate evaluation of the single first order rate constants by employing the data where the reactions are predominantly occurring. OD_∞ values were taken after at least ten half lives. Very good plots were obtained with confidence limit 95% and correlation coefficients above 0.9998 (Fig. 1). Identical procedure was used for the acid hydrolysis of **3** in 8.84 M HCl at 75.1°C.

The kinetic monitoring by ^{1}H NMR was performed in tubes thermostated at 75.1°C by using a 0.038 M solution of **1** in 8.84 M DCl/D_2O (see text). At fixed times samples were taken and quickly cooled to room temperature, the ^{1}H NMR spectrum recorded and the molar percent concentrations of each reaction product versus the time were plotted (Fig. 2). The percentages were calculated from the integral values measured for the CH_3 doublets attributed, by comparison with the authentic samples, to the starting **1** (at 0.95 and 1.05 ppm), to the aminoester **3** (at 1.5 ppm) and to the aminoalcohol **4** (at 1.15 ppm). Consequently, the fourth doublet (at 1.3 ppm) has been ascribed to the intermediate **2**. The chemical shifts are determined by using 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (DSS) as reference. The rate constants for the single steps were obtained from the equations 2a, b, c, d reported in the text.

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Appendix A

The substrate **1** was not prepared by methylation of *N*-(hydroxy-2-propyl)aniline metalled with NaH, as done for **5**,[1,3] because in this case the alkylation occurs at the nitrogen atom predominantly. Also the acylation is not selective furnishing a mixture of *N*-(hydroxy-2-propyl)-benzanilide and 2-(*N*-phenylamino)propylbenzoate (**3**). Attempts addressed to the double acylation, followed by the selective removal of ester function by alkaline hydrolysis, were unsuccessful because, instead of the expected hydroxybenzanilide, the product **3** was prevalently obtained. This fact suggests that in alkaline medium the alkoxyanion induces a transacylation of the benzoyl group to the alcoholic oxygen giving an ester through a probable pentatomic cyclic intermediate, as depicted in Scheme 4.

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