Reactivity of *N*-pyridylcarbamates in basic media

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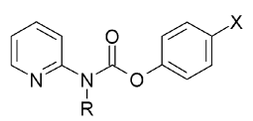
New secondary aryl *N*-pyridylcarbamates were prepared by reaction of the aminopyridine anion with aryl chloroformates and their hydrolysis was studied over the pH range from 12 to 13.7. The pH–rate profile points to an E1cB mechanism, involving pre-equilibrium deprotonation of the nitrogen atom to form an anion that undergoes rate-limiting decomposition into pyridyl isocyanate and a phenoxide ion. Further reaction of the highly reactive isocyanate with water affords *N*-pyridylcarbamic acid, which spontaneously decomposes to aminopyridine and carbon dioxide. The absence of significant base catalysis and the isolation of a new product resulting from trapping of the intermediate with the base piperidine are also consistent with an elimination–addition mechanism. Finally the observed substituent effect (σ^-) gives ρ 2.45 which is in accordance with a rate-determining departure of the phenoxide group from the anion intermediate formed in a pre-equilibrium step. Blocking the E1cb mechanism of the secondary carbamates by introduction of *N*,*N*-disubstitution in the substrate led to a rate-limiting decrease of *ca.* 10^6.

Introduction

For several years, research in our laboratories has been directed towards the search for new carbamates, compounds which are well known for their insecticidal and fungicidal activity.[1] The lability of these compounds in acid or basic aqueous media is an essential characteristic for evaluating their possible applications as biological agents.

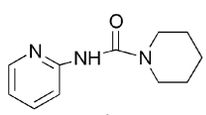
Carbamates can undergo hydrolysis reactions by a $B_{AC}2$ or an E1cB mechanistic pathway depending on their own structural properties.[2–5] Secondary aromatic carbamates, which have acidic protons in the α-position, are known to react by the E1cB mechanism, characterized by the pre-equilibrium formation of an unstable isocyanate This isocyanate intermediate, which is too labile to be detected directly, may be trapped through reaction with an amine such as piperidine. High values of ρ are expected,[6,7] and are clearly related to a rate-determining step that releases phenol following the pre-equilibrium of anion formation with isocyanate generation. An important criterion used for mechanistic clarification is blocking of the E1cB mechanism of secondary carbamates by introduction of *N*,*N*-disubstitution in the substrate. By comparing the pH–rate profiles of both substrates, one of which is incapable of forming the conjugated anion and is a model for the $B_{AC}2$ mechanism (which is easy to distinguish from nucleophilic catalysis using a base and its sterically hindered analogue),[8] one can get a good idea of the E1cB and $B_{AC}2$ mechanistic behaviour[9]

We have studied the chemistry of new phenyl *N*-benzoyl-, *N*-thiobenzoyl-[10] and *N*-arylsulfonyl-carbamates.[11] Based on literature data,[12] which indicate further biological interest in carbamates possessing a pyridine moiety in their structure, we extended our studies to several new *N*-pyridylcarbamates, **1a**–**e** and **2**.



1 R= H, X= H, Cl, F, CH_3, OCH_3

2 R=CH_3 X= H



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Experimental

Melting points are uncorrected. IR spectra were obtained using a Hitachi 270-50 spectrophotometer. ^{1}H NMR spectra were recorded using a Bruker 400, in $CDCl_3$ with TMS as internal standard. *J* values are given in Hz. HRMS were recorded on a Finnigan FT/MS 2001-DT mass spectrometer. Column chromatography was carried out with silica gel 60, 0.040–0.063 μm (Merck 9385). Thin layer chromatography (TLC) and preparative thin layer chromatography (PTLC) were performed on pre-coated silica gel 60 F_{254} (respectively Merck 5554 and Merck 5717). All solvents and reagents were obtained from Merck or Aldrich and used without further purification.

General procedure for the preparation of pyridylcarbamates

To a solution of 2-aminopyridine or 2-(*N*-methylamino)-pyridine (21 mmol) in DMF were added dropwise sodium hydride (80% dispersion in oil, 21 mmol) in DMF and the corresponding phenyl chloroformate (21 mmol). The reaction was stirred for 3 to 12 hours and worked up by adding water and dichloromethane; the organic layer was dried with magnesium sulfate and evaporated to dryness. Compounds **1a** and **1e** crystallized from the reaction mixture and were further purified by recrystallization. Column chromatography with *n*-hexane–ether (2 : 8), followed by recrystallization with dichloromethane afforded **1b**. Column chromatography with hexane–ether (4 : 6) and recrystallization with ether

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afforded compound **1c**. Compound **1d** was obtained after column chromatography with petroleum ether–ethyl acetate (8 : 2) and petroleum ether–ether (6 : 4) and recrystallization with methanol. Compound **2** was obtained in pure form after column chromatography with petroleum ether–ether (1 : 1) and recrystallization with ethanol.

Phenyl *N*-(2-pyridyl)carbamate 1a. 0.449 g, 13%, mp 155–156 °C (EtOH); ν_{max}/cm^{-1} (KBr) 1746 (C=O), 1590–1446 (C=C, C=N); δ_H (300 MHz, $CDCl_3$) 11.01 (1 H, s, N-*H*), 8.48 (1 H, dd, *J* = 0.9; 5.0, 6-H *py*), 8.13 (1 H, d, *J* = 8.4, 3-H *py*), 7.74 (1 H, ddd, *J* = 2.1; 7.4; 8.4, 4-H *py*), 7.44 (3 H, m, CH aromatic), 7.27 (2 H, m, CH aromatic), 7.03 (1H, dddd, *J* = 0.9; 5.0; 7.4, 5-H *py*); δ_C (100.4 MHz, $CDCl_3$) 152.2 (C=O), 152.0 (C-2 *py*), 150.5 (C-1 *Ph*), 147.6 (C-6 *py*), 138.8 (C-4 *py*), 129.5 (C-3, C-5 *Ph*), 125.9 (C-4 *Ph*), 121.8 (C-2, C-6 *Ph*), 119.0 (C-5 *py*), 112.9 (C-3 *py*). *m*/*z* (HRMS) 214.075083 (calc. for $C_{12}H_{10}N_2O_2$ 214.074228).

4-Chlorophenyl *N*-(2-pyridyl)carbamate 1b. 0.042 g, 1%, mp 189–190 °C (DCM); ν_{max}/cm^{-1}(KBr) 1749 (C=O), 1598–1449 (C=C, C=N); δ_H (300 MHz, $CDCl_3$) 8.33 (1 H, dt, *J* = 0.9; 4.8, 6-H *py*), 7.99 (1 H, d, *J* = 8.4, 3-H, *py*), 7.73 (1 H, ddd, *J* = 0.9; 7.2; 8.4, 4-H *py*), 7.36 (2 H, d, *J* = 8.1, 3-H, 5-H *Ph*), 7.16 (2 H, d, *J* = 8.1, 2-H, 4-H *Ph*), 7.05 (1 H, dd, *J* = 4.8; 7.2, H-5 *py*); δ_C (100.4 MHz, $CDCl_3$) 147.9 (C-6 *py*), 138.6 (C-4 *py*), 129.5 (C-3, C-5 *Ph*), 119.5 (C-5 *py*), 123.0 (C-2, C-6 *Ph*), 112.6 (C-3 *py*). *m*/*z* (HRMS) 248.035376 (calc. for $C_{12}H_9N_2O_2Cl$ 248.035255).

4-Fluorophenyl *N*-(2-pyridyl)carbamate 1c. 0.585 g, 18%, mp 176–177 °C (MeOH); ν_{max}/cm^{-1}(KBr) 1745 (C=O), 1591–1443 (C=C, C=N); EIMS (probe), 22 eV *m*/*z* 120 $[C_6H_4N_2O]^+$, 112 $[C_6H_5OF]^+$, 78 $[C_5H_4N]^+$; δ_H (300 MHz, $CDCl_3$) 8.37 (1 H, dd, *J* = 4.5; 1.2, 6-H *py*), 8.03 (1 H, d, *J* = 8.4, 3-H *py*), 7.74 (1 H, ddd, *J* = 1.2; 7.2; 8.4, 4-H *py*), 7.09 (2 H, dd, *J* = 9.1; 8.1, 2-H, 4-H *Ph*), 7.19 (2 H, dd, *J* = 4.5; 9.1, 3-H, 5-H *Ph*), 7.05 (1 H, m 5-H *py*); δ_C (100.4 MHz, $CDCl_3$) 161.5 (C-4 *Ph*), 151.1 (C-2 *py*), 147.9 (C-6 *py*), 138.6 (C-4 *py*), 123.1 (C-2, C-6 *Ph*), 119.5 (C-5 *py*), 116.3, 116.0 (C-3, C-5 *Ph*), 112.5 (C-3 *py*). *m*/*z* (HRMS) found 232.06398 (calc. for $C_{12}H_9N_2O_2F$ 232.06426).

4-Methylphenyl *N*-(2-pyridyl)carbamate 1d. 0.126 g, 4%, mp 174 °C (decomp.) (MeOH); ν_{max}/cm^{-1} (KBr) 1745 (C=O), 1589–1441 (C=C, C=N); EIMS (probe), 22 eV *m*/*z* 121 $[C_7H_8O_2]^+$, 120 $[C_6H_4N_2O]^+$, 108 $[C_7H_8O]^+$, 78 $[C_5H_4N]^+$; δ_H (300 MHz, $CDCl_3$) 8.41 (1 H, d, *J* = 4.8, 6-H *py*), 8.04 (1 H, d, *J* = 8.4, 3-H *py*), 7.72 (1 H, ddd, *J* = 1.8; 7.5; 8.4, 4-H *py*), 7.23 (2 H, d, *J* = 8.4, 2-H, 4-H *Ph*), 7.04 (1 H, dd, *J* = 4.8; 7.5, 5-H *py*), 7.11 (2 H, d, *J* = 8.4, 3-H, 5-H *Ph*), 2.38 (3 H, s, *CH*$_3$); δ_C (100.4 MHz, $CDCl_3$) 151.9 (C=O), 151.7 (C-2 *py*), 148.1 (C-4 *Ph*), 147.8 (C-6 *py*), 138.6 (C-4 *py*), 135.6 (C-1 *Ph*), 129.9 (C-3, C-5 *Ph*), 121.4 (C-2, C-6 *Ph*), 119.1 (C-5 *py*), 112.6 (C-3 *py*), 20.8 (*CH*$_3$). *m*/*z* (HRMS) 228.090749 (calc. for $C_{13}H_{12}N_2O_2$ 228.089878).

4-Methoxyphenyl *N*-(2-pyridyl)carbamate 1e. 0.873 g, 21%, mp 173–175 °C (MeOH); ν_{max}/cm^{-1}(KBr) 1742 (C=O), 1594–1445 (C=C, C=N); EIMS (probe), 22 eC *m*/*z* 124 $[C_7H_8O_2]^+$, 120 $[C_6H_4N_2O]^+$, 109 $[C_6H_5O_2]^+$, 78 $[C_5H_4N]^+$; δ_H (300 MHz, $CDCl_3$) 8.30 (1 H, d, *J* = 4.3, 6-H *py*), 7.97 (1 H, d, *J* = 8.4, 3-H *py*), 7.69 (1 H, ddd, *J* = 1.8; 7.8; 8.4, 4-H *py*), 7.10 (2 H, d, *J* = 9.0, 2-H, 4-H *Ph*), 7.01 (1 H, dd, *J* = 4.3; 7.8, 5-H *py*), 6.90 (2 H, d, *J* = 9.0, 3-H, 5-H *Ph*), 3.81 (3 H, s, *OCH*$_3$); δ_C (100.4 MHz, $CDCl_3$) 156.7 (C-4 *Ph*), 152.2 (C=O), 151.8 (C-2 *py*), 147.7 (C-6 *py*), 143.2 (C-1 *Ph*), 138.7 (C-4 *py*), 122.6 (C-2, C-6 *Ph*), 119.1 (C-5 *py*), 114.5 (C-3, C-5 *Ph*), 112.7 (C-3 *py*), 55.6 (O*C*H$_3$). *m*/*z* (HRMS) 244.083785 (calc. for $C_{13}H_{12}N_2O_3$ 244.084792).

Phenyl *N*-methyl-*N*-(2-pyridyl)carbamate 2. 1.4 g, 35%, mp 59–61 °C; ν_{max}/cm^{-1}(KBr) 1722 (C=O), 1590–1443 (C=C, C=N); EIMS (probe) 22 eV *m*/*z* 183, 135 $[C_7H_7N_2O]^+$, 107 $[C_7H_5O_2]^+$, $[C_5H_4N]^+$, 77 $[C_6H_5]^+$; δ_H (300 MHz, $CDCl_3$) 8.45 (1 H, d, *J* = 4.5, 6-H *py*), 7.79 (1 H, d, *J* = 8.4, 3-H *py*), 7.68 (1 H, ddd, *J* = 1.8; 7.5; 8.4, 4-H *py*), 7.37 (2 H, m, CH aromatic), 7.19 (3 H, m, CH aromatic), 7.07 (1 H, ddd, *J* = 7.5; 1.8; 4.5, 5-H *py*), 3.69 (3H, s, N-*Me*); δ_C (100.4 MHz, $CDCl_3$) 150.9 (C=O), 154.5 (C-2 *py*), 150.9 (C-1 *Ph*), 147.6 (C-6 *py*), 137.4 (C-4 *py*), 129.4 (C-3, C-5 *Ph*), 125.6 (C-4 *Ph*), 121.7 (C-2, C-6 *Ph*), 119.3 (C-5 *py*), 112.9 (C-3 *py*). *m*/*z* (HRMS) 228.089889 (calc. for $C_{13}H_{12}N_2O_2$ 228.089878).

Kinetic methods

***N*-(2-Pyridyl)carbamates.** The measurements were carried out with an SX.18MV Stopped Flow apparatus equipped with thermostated cell holders, which were used for the kinetic studies; the cells were kept at 27.0 ± 0.1 °C in the cell compartment of the apparatus. The kinetics of hydrolysis of *N*-(2-pyridyl)carbamates was studied in 1,4-dioxane–water 15% (v/v), with the ionic strength kept constant at 0.5 M with $NaClO_4$ (3 M), by continuously monitoring the increase in absorbance at 290 nm (compound **1a**), 300 nm (compounds **1b**, **1c** and **1d**) and 305 nm (compound **1e**) corresponding to the decomposition of substrate. In all cases, reactions were carried out under pseudo-first-order conditions, the carbamate concentration being much lower than those of the other reagents (*ca.* 7 × 10^{-5} M, except for **1b** which was about half of this value). The absorbance–time data for all of the kinetic experiments were fitted by first-order integrated equations, and the values of the pseudo-first-order rate constants (k_o) were reproducible to within 5%.

Hydrolysis of **1a** and **2** was accomplished in the presence of piperidine as buffer, at a concentration of 0.1 M.

Isolation of intermediate

Hydrolysis of **1a** was carried out in the presence of piperidine buffer (0.1 M) and compound **3** was isolated. *m*/*z* (HRMS) 205.122253 (calc. for $C_{11}H_{15}N_3O$ 205.1215).

Results and discussion

N-(2-Pyridyl)carbamates

Under the conditions used, the hydrolysis of phenyl *N*-pyridylcarbamate (**1a**) gave rise to 2-aminopyridine and phenol in sodium hydroxide solution and to piperidine-derived *N*-pyridylurea in the presence of piperidine buffer. The influence of OH^- concentration on the reaction rate was studied by varying the concentration from 0.01 to 0.5 M, using sodium hydroxide solutions. The rate of hydrolysis is proportional to the OH^- concentration until it reaches a plateau region (see Fig. 1). This plateau comes about because of the possible pre-equilibrium ionisation of the substrate (*K*), followed by its rate-determining decomposition to products (k_1), as shown in Scheme 1, which leads to eqn. (1).

$$k_o = \frac{k_1 K[OH^-]}{1 + K[OH^-]} \quad (1)$$

The best fit to the experimental data gives k_1 and $K = K_a/K_w$ for phenyl *N*-(2-pyridyl)carbamate (**1a**). Several other aryl pyridylcarbamates (**1b**–**e**) were also examined over a wide pH range in order to determine k_1 and the acidity constants of the carbamates, K_a, the results of which are summarised in Table 1.

Substituents on the aryl carbamate ring give rise to a Hammett correlation that is somewhat better using a σ^- value (ρ = 2.45, r^2 = 0.9884), rather than a σ value (ρ = 1.98, r^2 = 0.9274) for the substituent (Fig. 2). This result is expected on

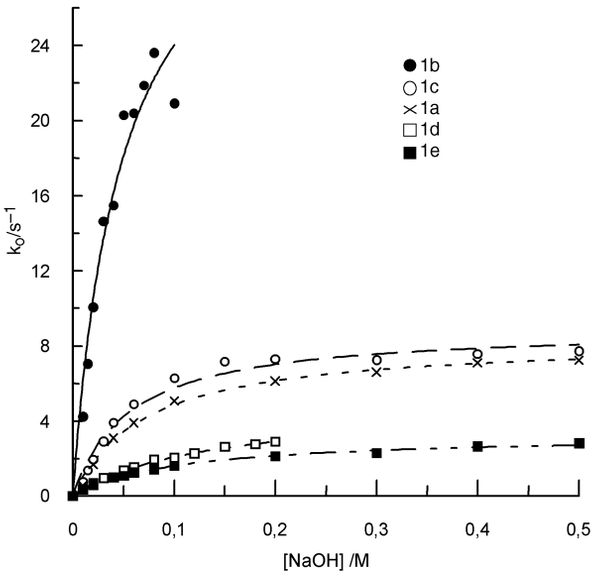
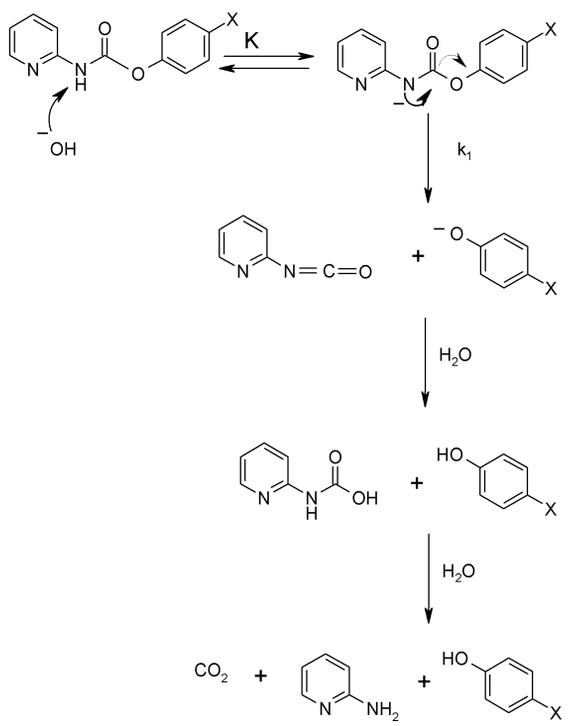


Fig. 1 Influence of [NaOH] on k_o for **1a**–**e**.



Scheme 1 Mechanism of hydrolysis of aryl *N*-pyridylcarbamates.

Table 1 Values of k_1 and K_a for *N*-(2-pyridyl)carbamates

X	k_1/s^{-1}	10^{13} K_a/M
H	8.30	1.4
CH_3O	3.26	1.0
CH_3	4.71	0.8
F	8.96	1.8
Cl	35.6	2.1

the basis of a rate-determining departure of the phenoxide group from the anion intermediate formed in a pre-equilibrium step. Another high value, $\rho = 2.86$, was observed for a typical E1cB process.[7] In fact, this mechanism is very sensitive to the nature of the leaving group, since the transition state is reached with almost complete acyl–oxygen bond cleavage. On the other hand, a $B_{Ac}2$ mechanism would certainly involve little acyl–oxygen bond cleavage in the transition state as judged from the low value (*e.g.* $\rho = 1.1$) for aryl acetates.[13]

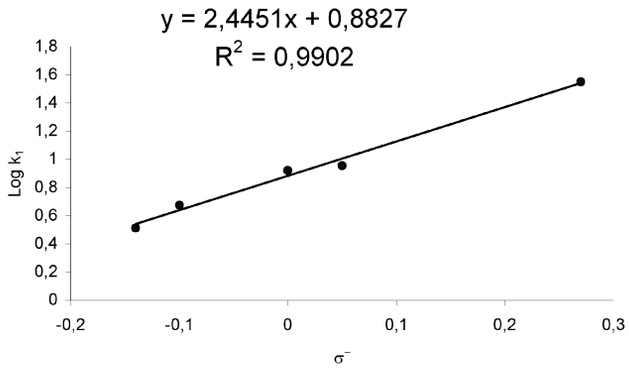


Fig. 2 Hammett plot for hydrolysis of *N*-aryl pyridylcarbamates showing the effect of the substituent on the leaving group.

To study the mechanism of the process in more detail, the effect of the buffer concentration on the reaction rate was evaluated, and so the reaction was studied in several bases using piperidine, piperazine and butylamine. No buffer effect was observed (Table 2), a result which is also in accordance with a rate-determining breakdown of the carbanion intermediate formed in the pre-equilibrium step. According to the literature,[14] decomposition of such a species is not dependent upon concentration of any buffer and the rate-limiting step only exhibits specific base catalysis.

Additional support for the proposed mechanism comes from comparison of the reaction of compound **1a** with that of its *N*-methyl analogue, **2**.

N-Methyl(pyridyl)carbamate

Hydrolysis of **2** in NaOH also gave rise to the corresponding phenol and *N*-methylaminopyridine and showed a first-order dependence on the concentration of OH^- (see Fig. 3). A second-

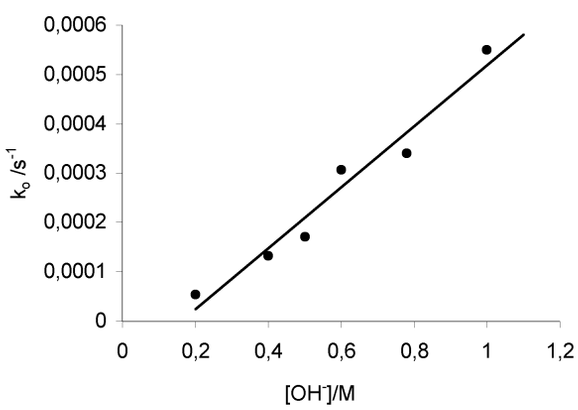


Fig. 3 pH–Rate profile for phenyl *N*-methyl(2-pyridyl)carbamate **2**.

order rate constant of 6×10^{-4} M^{-1} s was obtained, which, when compared with the value obtained for the analogous secondary carbamate, gives a rate difference of *ca.* 10^6. In this case, ionisation is blocked, and turns the substrate into a good model for the $B_{Ac}2$ mechanism (Scheme 2), which is known to occur with much smaller reaction rates.

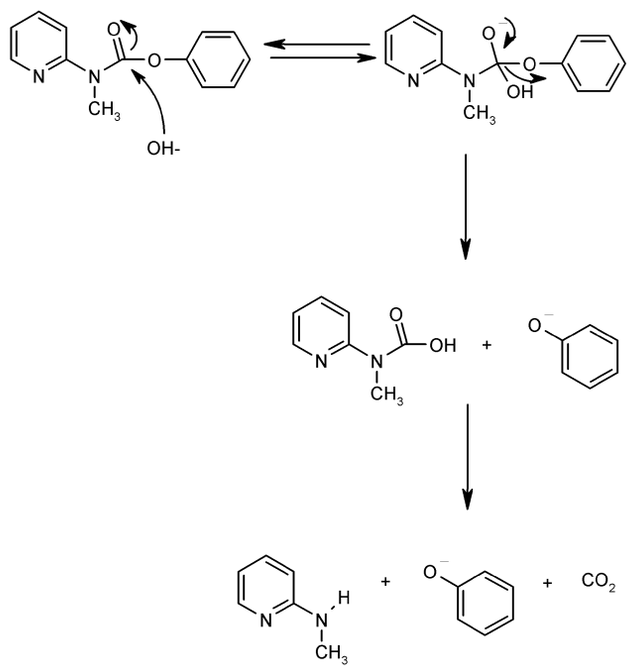
The possibility of catalysis by general bases was investigated and piperidine in H_2O was used as a buffer. The observed first-order rate constants k_o were found to increase linearly with increasing buffer concentration (Fig. 4), which suggests the involvement of the general base according to eqn. (2), where k_B is the second-order rate constant for the catalytic process in the presence of buffers.

$$k_o = k_{OH}[OH^-] + k_B[B] \quad (2)$$

The buffer-independent rate of hydrolysis for piperidine, k_{OH}[OH], obtained by extrapolation of the observed rate

Table 2 Base catalysis for 4-methoxyphenyl *N*-(2-pyridyl)carbamate (**1e**)

10^3 [Piperidine]/M	10^2 k_o/s^{-1}	10^3 [Piperazine]/M	10^3 k_o/s^{-1}	10^3 [Butylamine]/M	10^3 k_o/s^{-1}
2.50	2.61	4.30	4.0	2.28	4.2
2.00	2.58	3.44	4.1	1.82	3.5
1.50	2.51	2.58	3.5	1.37	3.9
—	—	2.15	3.6	1.14	4.1



Scheme 2 Mechanism of hydrolysis of phenyl *N*-methylpyridylcarbamate.

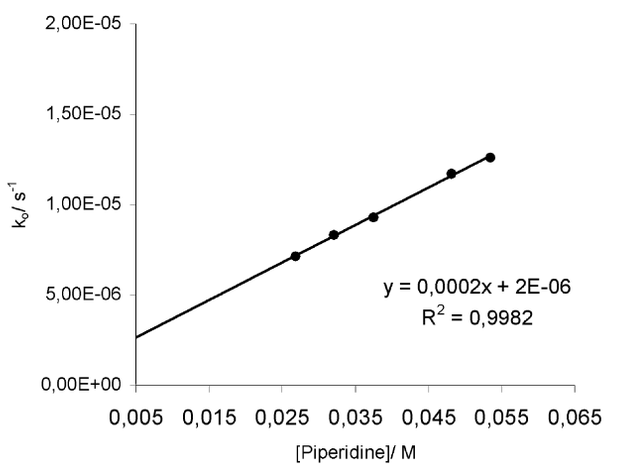


Fig. 4 Influence of piperidine concentration in H_2O upon hydrolysis of **2**.

constant to zero buffer concentration, was found to correlate with the value of k_o obtained in the study of the influence of the NaOH concentration.

Conclusion

The results show the existence of an E1cb mechanism for the hydrolysis of **1a**. The evidence includes the levelling off of the pH–rate profile, together with the absence of general base catalysis and the high substituent effect. All these favour a mechanism involving a rate-determining step for the departure of phenoxide, with formation of an isocyanate that subsequently decomposes to the products (Scheme 1). Identification of the presence of isocyanate was accomplished by its trapping with the buffer piperidine, as the corresponding urea was isolated at the end of the reaction. Further support that an elimination–addition mechanism, rather than a normal addition–elimination, is operating in this case, comes from the relative magnitude of the rate constants of the secondary carbamate when compared to those of the tertiary one (**2**), where substrate ionisation is no longer possible. The kinetic parameters obtained for hydrolysis of **2** suggest a bimolecular type of hydrolysis for *N*-methyl(pyridyl)carbamate.

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