SHORT PAPER

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Synthesis and reactivity of phenyl-*N*-methyl-*N*-thiobenzoylcarbamate in basic media

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Phenyl-*N*-methyl-*N*-thiobenzoylcarbamate was prepared from the reaction of thiobenzamide anion with phenylchloroformate in DMF and kinetic data obtained for the basic hydrolysis, have been interpreted in terms of a $B_{Ac}2$ mechanism involving general bases catalysis.

Bases can bring about the hydrolysis of esters by two mechanisms,[1, 2] the first is a general base catalysis, where attack of a water molecule on the carbonyl group of the ester is assisted by partial bond formation to the base, and the second is a nucleophilic catalysis where the base attacks the ester directly to give an intermediate which is rapidly hydrolysed. Gold and co-workers[3, 4] have demonstrated that, in certain instances, the two mechanisms may occur concurrently. In these cases, it would be difficult to detect general base catalysed reaction because nucleophilic catalysis becomes the predominant pathway, mainly due to the Brönsted β value, which is higher for nucleophilic catalysis than for general base catalysis.[5] However, Butler and Robertson[6] reported a method of demonstrating the persistence of a general base catalysed reaction, even when the reaction appears to be completely nucleophilic, which makes use of a base and its sterically hindered analogue

In the present work the synthesis and kinetic study of basic hydrolysis of phenyl-*N*-methyl-*N*-thiobenzoylcarbamate (PMTC) are reported.

Experimental

General procedure for the preparation of thiocarbamates: To a solution of *N*-methylthiobenzamide (3.9 mmol), prepared according Lawensson's procedure, in DMF was added dropwise sodium hydride (80% dispersion in oil, 4.2 mmol) in DMF and phenylchloroformate (4.2 mmol). The reaction was stirred for 24 h and worked up by adding water and dichloromethane. The organic layer was dried with magnesium sulphate, filtered and evaporated to dryness. Column chromatography with a proper eluent afforded the pure thionocarbamate.

Phenyl-N-methyl-N-thiobenzoylcarbamate: Yellow gum (0.075 g, 7.09%). IR (NaCl neat) ν_{max}/cm^{-1}: 1742 (C=O), 1104 (C=S). ^1H NMR ($CDCl_3$: δ 7.59 (2H, d, *J* = 7.2 Hz, H-2), 7.43 (1H, t, *J* = 7.2 Hz, H-4), 7.36 (2H, t, *J* = 7.2 Hz, H-3), 7.25 (2H, m, H-3'), 7.17 (1H, t, *J* 7.2 Hz, H-4'), 6.70 (2H, d, J= 7.5 Hz, H-2'), 3.89 (3H, s, N-$\underline{C}H_3$). ^{13}C NMR (100.4 MHz, $CDCl_3$): 210.8 (C=S), 152.8 (C=O), 150.2 (C-1'), 146.4 (C-1), 130.7 (C-4), 129.3 (C-3), 128.3 (C-3'), 126.6 (C-2), 126.2 (C-4'), 120.5 (C-2'), 41.1 (N–$\underline{C}H_3$). HRMS Ei (+): *m/e* 271.0675 (M^+), (calc.) 271.0662.

D_2O was supplied by CIEMAT (Spain). All others reagents and solvents were obtained from Merck or Aldrich and used without purification. Perkin Elmer Lambda 17 or Hewlett Packard 8453 spectrophotometers, both provided with thermostated cell holders, were used for the kinetic studies. Kinetic measurements were carried out at 25 °C and at a constant ionic strength of 0.5 mol/dm^3, by continuously monitoring the decrease in absorbency at 300 nm corresponding to the hydrolysis of thiobenzoyl carbamate. In all cases reactions were carried out with carbamate concentrations much lower than those of other reagents. Absorbance-time data always fitted the first order-integrated equation and values of the observed pseudo first-order rate constant, k_o, were reproducible to within 5%. In the cases when $k_o > 3 \times 10^{-2} S^{-1}$ an Applied Photophysics DX. 18MV stopped-flow was used.

Results and discussion

In the experimental conditions used, hydrolysis of PMTC gave rise to thioamide and phenol in either sodium hydroxide solution or in piperidine buffer. The influence of the concentration of OH^- on the reaction rate was studied ranging $[OH^-]$ between $2.9 \times 10^{-5} - 7 \times 10^{-2}$ M. In the cases of low concentrations of OH^-, buffer solutions of $NaHCO_3$/ NaOH were used, and in the cases of high concentration of OH^-, sodium hydroxide was added to the reaction mixture. The values obtained for the pseudo first-order constant $k_{o,}$ are shown in Fig.1, the plot being a good straight line that passes through the origin. These results are indicative of a first order dependence on the concentrations of OH^-. The data obtained in the study of the influence of $[OH^-]$ can be fitted to eqn (1).

$$k_o = k_{OH}\,[OH^-] \qquad (1)$$

From the slope of the plot, a value of 1.61 dm^3 mol/s for k_{OH}, the second order rate constant, was obtained for the hydrolysis of PMTC.

To study the mechanism of the process in more detail, the possibility of the existence of general base catalysis was investigated. To accomplish this, buffers of piperidine, tetramethylpiperidine, morpholine, piperazine, butylamine and trifluoroethanol were employed. The observed first-order rate constants k_o were found to increase linearly with increasing buffer concentration as found for piperidine, for

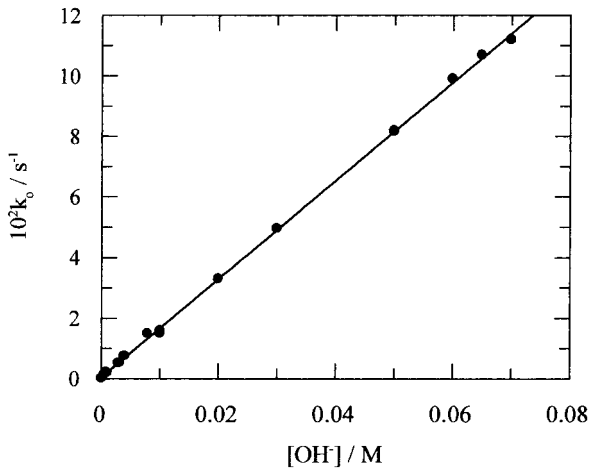

Fig. 1 Influence of OH^- concentration on the reaction time

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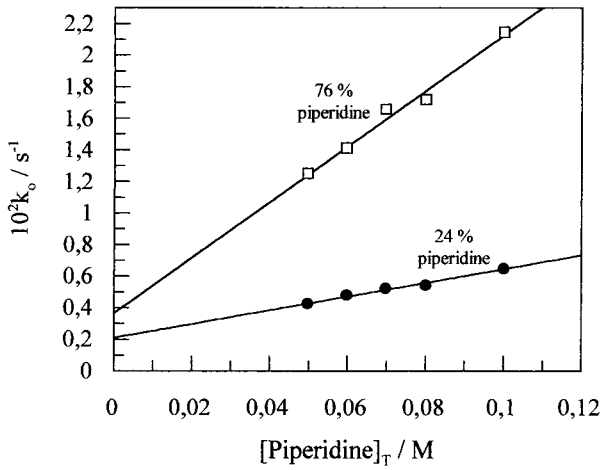


Fig. 2 Influence of piperidine buffer on the reaction rate. (●) pH = 10.5, (□) pH = 11.0

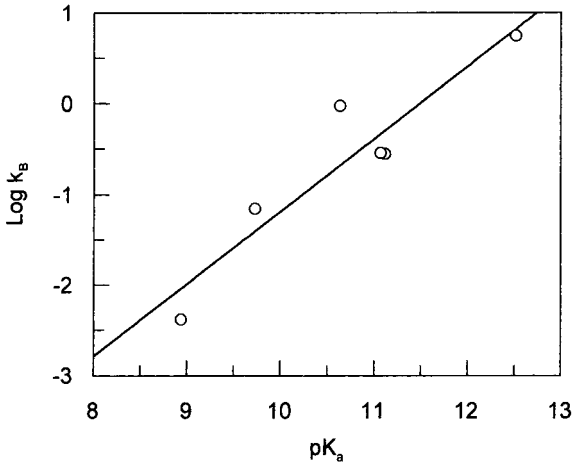


Fig. 3 Brönsted plot for the general base catalysis of the hydrolysis of thiobenzoyl carbamates

example (Figure 2). The increase in slope with increasing fraction of buffer base indicates general base catalysis.[7] This finding suggests that hydrolysis of PMTC is subject to a general base catalysis, according to eqn (2), where k_B is the second-order rate constant for the catalytic process in presence of buffers.

$$k_o = k_{OH}[HO^-] + k_B\,[\text{Buffer}] \qquad (2)$$

The buffer independent rates of hydrolysis, $k_o = k_{OH}\,[OH^-]$, obtained by extrapolation of the observed rate constant to zero buffer concentration, for all buffers studied, were found to correlate with the values of k_o obtained in the study of the influence of NaOH concentration.

From the slopes of the plots of k_o versus buffer concentration, it is possible to obtain the values for k_B, (eqn. (2)) for every buffer studied (Table1). Figure 3 shows the Brönsted plot relating catalytic efficiency (log k_B) with the pK_a of the catalyst. The slope obtained gave rise to the β value of 0.7. This value is in accordance with a general base catalysis. In aqueous solutions, the β values observed for general base catalysed hydrolysis of esters are usually *ca* 0.4–0.7,[8,9] while those ascertained for nucleophilic reactions of amines with esters are *ca* 0.8–0.9.[6,10]

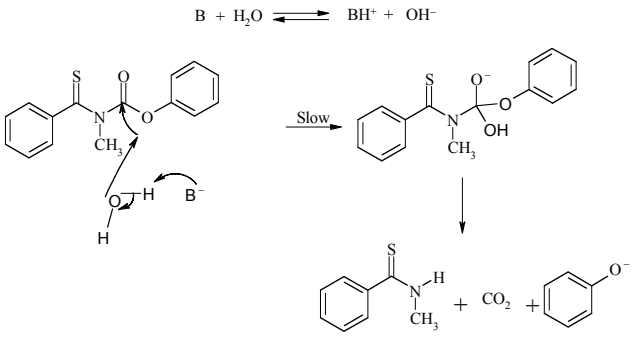
Another fact that suggests that the reaction is subject to a general base catalysis and rules out the possibility of a nucleophilic catalysis, is the similarity in values obtained for k_B, both in presence of piperidine and tetramethylpiperidine (its hindered analogue), 0.277 and 0.285 $dm^3/mol/s^{-1}$, respectively.

One last indication about the nature of the reaction was obtained when the reaction was carried out in D_2O and the corresponding solvent isotope effect was measured. For this purpose the influence of the concentration of piperidine on the reaction rate in D_2O was studied and the results were compared with a similar study in water. The values obtained for the solvent isotope effect were k_{H2O}/k_{D2O}= 1.3, which suggests that a water molecule may be involved in the rate-determining step of the reaction[6], as occurs in a typical general base catalysed reaction. The mechanism for the basic hydrolysis of PMTC is shown in Scheme 1.

The results obtained for the solvent isotope effect, the Brönsted plot, together with the comparison of the second-order rate coefficients for the sterically unhindered and hindered piperidine, all favour a general base catalysed hydrolysis of the substrate. A nucleophilic pathway would certainly involve a lower isotope effect, a different Brönsted coefficient and a strong steric effect for piperidine buffer

Table 1 Second order rate constants for the hydrolysis of PMTC catalysed by buffers

BUFFER	pK_a	Log k_B
Morpholine	8.94	–2.3872
Piperazine	9.73	–1.1579
Butylamine	10.64	–0.0256
Tetramethylpiperidine	11.07	–0.5452
Piperidine	11.12	–0.5581
Trifuorethanol	12.52	–0.7355



Scheme 1

catalysis. The absence of any nucleophilic intermediate formed in the course of the reaction in presence of the buffer piperidine also rules out completely the possibility of any nucleophilic catalysis.

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