SHORT PAPER

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Hydrolysis of benzothiazolylcarbamates in basic media†

Fátima Norberto*[b,c] , Mª Eduarda M. Araújo[a,c], Pablo Herves[d] and Lara Ribeiro[c]

[a]CECUL, [b]CECF: [c]Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande 1749-016 Lisboa Portugal

[d]Departamento de Química Física, Facultad de Ciencias, Universidad de Vigo, Spain

Secondary benzothiazolylcarbamates hydrolyse in basic media by an E1cB mechanism, while the corresponding tertiary carbamate hydrolyse by a general base $B_{Ac}2$ mechanism

Keywords: benzothiazolyl carbamates, hydrolitic mechanism, basic media

The hydrolytic conversion of aryl carbamates into amines and phenols is a base catalysed process, which may occur *via* an Elcb elimination or a $B_{Ac}2$ mechanism. Secondary carbamates with an α acidic hydrogen generally decompose by an E1cb unimolecular decomposition of the substrate anion,[1] while tertiary aryl carbamates with the proton blocked, hydrolyse by a bimolecular pathway of hydrolysis- $B_{Ac}2$ mechanism. Examples of $B_{Ac}2$ type reacting carbamates are the difunctional thiobenzoylcarbamates[2] and arenesulphonylcarbamates,[3] both of them undergoing general base catalysed reactions. An example of a nucleophilic catalysed $B_{Ac}2$ reaction is the one occurring with aryl acetates in the presence of imidazole.[4] Our study of the alkaline hydrolytic decomposition of both secondary and tertiary benzothiazolyl carbamates was intended to elucidate the mechanisms involved in this case.

Experimental

General- ^{1}H NMR spectra were recorded at 300 MHz (TMS internal standard; *J* in Hz) on a Bruker WP-300 apparatus, IR spectra on a Hitachi 270-50 apparatus and mass spectra on a Trio 1000 GC 8000 spectrometer. Melting points are uncorrected. Hydrolysis of carbamates was followed spectrometrically in a Shimadzu UV 1601-Visible spectrometer, in a 25° thermostated cell.

General procedures: 2-methylaminobenzothiazol was obtained by methylation of 2-aminobenzothiazol with formaldheyde.[4] All carbamates were prepared according to the following procedure: the parent amine was dissolved in anhydrous ethyl ether and 1 equiv. of triethylamine and 1 equiv. of the corresponding chloroformate were added. The reaction procceded overnight. After completion the reaction mixture was poured into water and extracted with ethyl acetate. The solvent was evaporated under vacuum and the carbamate purified by PTLC, or by crystallisation.

Reactions of hydrolysis of the substrates in NaOH solutions were followed spectrophotometrically at an appropriate wavelength, λ = 300 nm. Changes in absorbance corresponded either to the disappearance of substrate or appearance of phenol, and an isosbestic point at 274nm was observed for all reactions in sodium hydroxide solutions.

Repetitive scans in the UV region established that the reaction has tight isosbestic points indicating the absence of intermediates. Absorbance versus time plots were analysed in all cases to fit first-order rate plots.

4-Chlorophenyl N-(2-benzothiazolyl)carbamate **(1a)**: (336 mg; yield = 8.1%), crystals from ethyl acetate, m.p. = 272–274°C. ^{1}H NMR (300 MHZ, $CDCl_3$) 7.92 (1H, d, *J* = 7.96 Hz, H-7); 7.41 (1H, d; *J* = 8.12 Hz, H-4); 7.48 (2H, dd, *J*(3′, 2′) = 8Hz, *J*(5′,6′) = 2.2 Hz, H = 3',5'); 7.42 (1H, t, *J* = 8.04 Hz, H-5); 7.35 (2H, dd, *J* = 6.72 HZ, *J* = 2.2 Hz, H-2′,6′); 7.3 (1H, t, *J* = 8.28 Hz, H-6); IR(KBr) 1736 (C = O;)*m/z* 176 $[C_8H_4SN_2O]^+$ (95%); 148 $[C_7N_2SH_4]^+$ (34%); 128, 130 $[Cl\text{-}Ph\text{-}OH]^+$(97%, 31%), FAB (nitrobenzyline) 305$[M+H]^+$, HRMS $C_{14}H_9N_2O_2SCl$: calc 304.0073 and 306.0044, found 304.0083 and 306.0053.

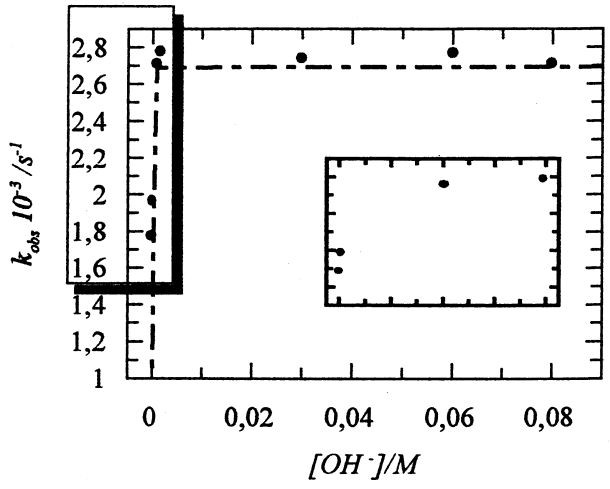


Fig. 1 Effect of hydroxide concentration on the rate of hydrolysis of **1a**.

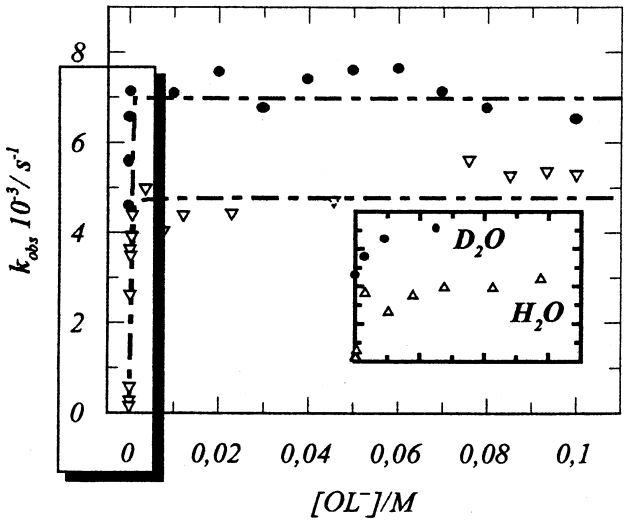


Fig. 2 Effect of lyoxide concentration on the rate of hydrolysis of **1b**.

* To receive any correspondence. E-mail: fatinor@fc.ul.pt

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Influence of piperidine concentration on the rate of hydrolysis of compound **1a**

$10^3 \times$ Piperidine/M pH 11.2	$10^3\ k_{obs}/s^{-1}$	$10^3 \times$ Piperazine/M pH 9	$10^3\ k_{obs}/s^{-1}$
4	2.74	4	2.07
6	3.05	6	1.93
8	2.83	8	2.04
10	2.77	10	1.96

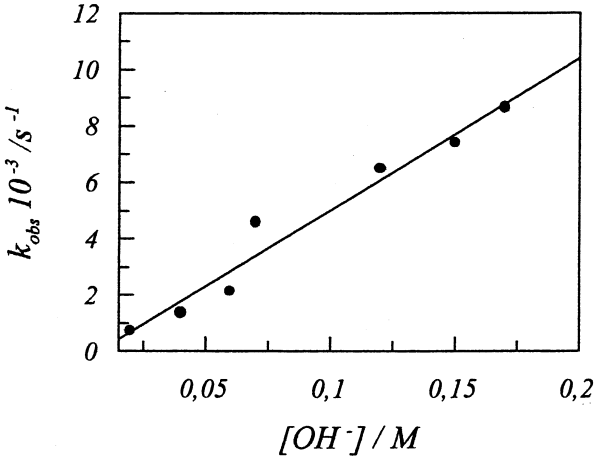


Fig. 3 Effect of hydroxide concentration on the rate of hydrolysis of **2**.

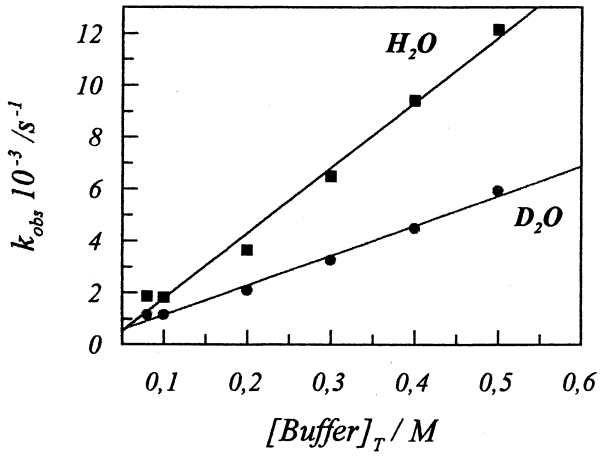
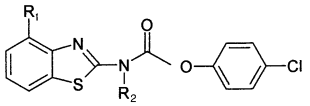
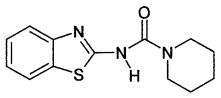


Fig. 4 Effect of pyrrolidine concentration both in water and deuterated water on the rate of hydrolysis of **2**.



1a R_1=H R_2=H
1b R_1=CH_3 R_2=H
2 R_1=H R_2=CH_3



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4-Chlorophenyl N-(2-(4-methyl)benzothiazolyl)carbamate **(1b)**: (863 mg; yield = 20.8%), crystals from ethyl acetate, m.p. = 176–178°C. ^{1}H NMR (300 MHZ, $CDCl_3$) 7.64 (1H, d, *J*(6,7) = 7.82 Hz, H-7); 7.38 (2H, d, *J*(2′,3′) = 8.88 Hz, H = 3′,5′); 7.22 (2H, m, H = 5,6); 7.17 (2H, d, *J*(3′,2′) = 8.88 Hz, H = 2′,6′); IR(KBr) 1746 (C = O); *m/z* 318, 320 [M^+] (8%, 3%); 190 [M^+- Cl-Ph-OH] (100%); 128, 130 [Cl-Ph-OH] (41%, 13%); HRMS $C_{15}H_{11}N_2O_2SCl$: calc 318.0186 and 320.0200, found 318.0235 and 320.0209.

4-Chlorophenyl N-(2-benzothiazolyl)-N-methylcarbamate **(2)**: (127 mg; yield = 8.2%), purification by ptlc (*n*-hexane/ethylacetate 8:2), m.p. = 143–144°C. ^{1}H NMR (300 MHZ, $CDCl_3$) 7.55 (1H, d, *J* = 7.24 Hz, H-7); 7.44 (1H, d; *J* = 8.04 Hz, H-4); 7.30 (2H, d, *J* = 8.08 Hz, H = 3′,5′); 7.25 (1H, t, *J* = 8.40 Hz, H-5); 7.06 (1H, t, *J* = 7.60 Hz, H-6); 7.02 (2H, t, *J* = 7.92 Hz, H-2′-6′); IR (KBr) 1748 (C = O); *m/z* 163 $[C_8N_2SH_7]^+$ (6%); 150 $[C_7H_6N_2S]^+$ (12%); 149 $[C_7H_5N_2S]^+$ (47%); 135 $[C_7H_5NS]^+$ (19%); 128,130[Cl-Ph-OH]$^+$ (14%, 5%); 111,113 [Cl-Ph]$^+$ (24%, 8%). HRMS $C_{15}H_{11}N_2O_2SCl$: calc 318.0186 and 320.0200, found 318.0237 and 320.0208.

Results and discussion

The rates of hydrolysis of benzothiazolylcarbamates were investigated in THF/water (2:8; v:v) because of the low solubility of the substrates in water.

Secondary benzothiazolylcarbamates: Figures 1 and 2 show a plot of first-order rate constants k_{obs} *vs* [OH^-] concentration for the hydrolysis of **1** and **2**. The data are consistent with an Elcb mechanism according to equation (1), with $K = K_a/K_w$.

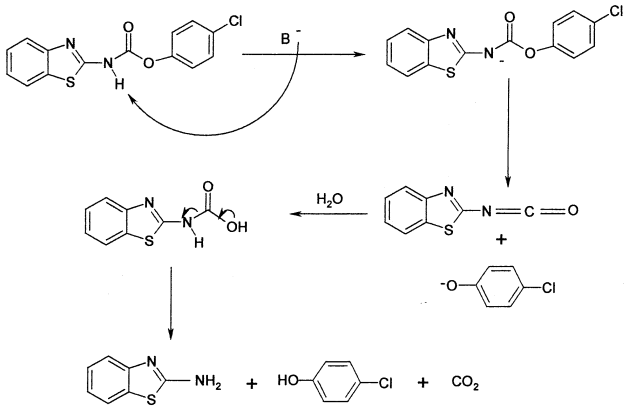
$$k_{obs} = \frac{k_1 K [OH^-]}{1 + K [OH^-]} \quad (1)$$

Adjustment of data to this equation gave rise to k_l and K_a which are respectively 2.69 $10^{-3}s^{-1}$ and 7.310^{-9}M for compound **la** and $4.810^{-3}s^{-1}$ and 2.510^{-9}M for compound **1b**. A plot of pH-rate was also done in D_2O for compound **1b**, and k_l and K_a were respectively 7.08 10^{-3} s^{-1} and 2.310^{-8} M and the value obtained for the solvent isotope effect for k_l is 0.68. This value of the kinetic solvent isotope effect is similar to 0.65, the one found for the alkaline hydrolysis of 5-nitrocoumarone, a lactone which hydrolyses by a $B_{Ac}2$ mechanism.[6] However, Pratt and Bruice[7] discussed the solvent isotope effect for a series of esters and concluded that this parameter is not a generally applicable criterion for distinguishing between the E1cB and the $B_{Ac}2$ mechanisms.

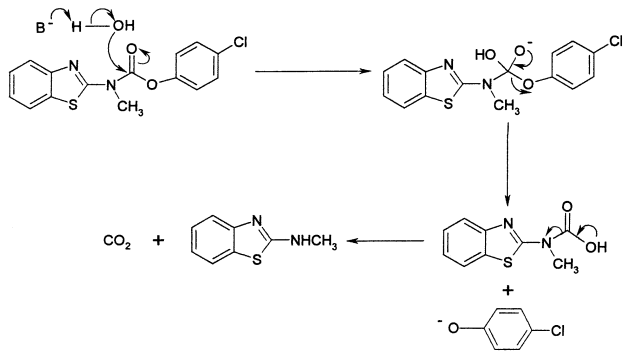
Effect of bases on hydrolysis of compound **la** was studied using piperidine and piperazine as buffers and no influence of base concentration was observed (Table 1). Pratt and Bruice[7] have used the study of influence of base catalysis to propose a change of rate determining step of hydrolysis of methyl nitrophenylmalonate depending on the pH.[7] At lower pH, the absence of general catalysis observed was related to a rate determining unimolecular process involving the release of phenol.

The absence of base catalysis observed in this case may be interpreted in favour of a pre-equilibrium formation of the carbamate anion with the subsequent release of phenol.

A rate-determining step of release of phenol is generally related to a very high sensitivity of rate to the electronic effects of the substituents on the phenol leaving groups.[1] Very large Hammett coefficients related to an E1cB mechanism have been found for the hydrolysis of thiocarbamates.[8] Attempts to study any substituent effect were not successful in this case since all other substituted arylbenzothiazolylcarbamates synthesised were insoluble in the reaction media used. Good evidence of the existence of an isocyanate intermediate was the formation of the urea (**3**) isolated after reaction of compound **1a** with piperidine (10 equiv.). The isocyanate comes after the rate determining release of phenol from the



Scheme 1
Mechanism of hydrolysis for secondary benzothiazolylcarbamates **1**.



Scheme 2
Mechanism of hydrolysis in basic media for benzothiazolyl-*N*-methylcarbamate **2**.

carbamate anion. Trapping of the isocyanate intermediate formed was an important evidence used by certain authors to discuss the E1cB mechanism of hydrolysis of phenyl *N*-phenylcarbamates,[9] and aryl *N*-methylaminosulfonates.[10]

The data obtained, the pH-rate profile, with a levelling off, absence of base catalysis, and the solvent isotope effect obtained are in favour of an E1cB mechanism of hydrolysis for compounds **1a** and **lb**. This involves prior dissociation of the substrate to form phenol and isocyanate, which then decomposes to aminobenzothiazol (Scheme 1). Further evidence of the E1cB mechanism consisted of the isolation of the product, which resulted from the trapping of isocyanate with the base piperidine.

Chloro phenyl N-methyl benzothiazolylcarbamate: First order rate constants for the hydrolysis of **2** as a function of OH^- are represented in Fig. 3, ($k_{OH^-} = 5.3810^{-2} \pm 4.910^{-3}$ $M^{-1}s^{-1}$), where we see a ratio of Ca 10^4 when we compare with the corresponding k_1K_a/K_w for **1b** ($12.10^2 \pm 3.4.10^2$ $M^{-1}s^{-1}$). One of the common chemical approaches to confirm an E1cB mechanism is comparison of the hydrolytic behaviour of both a secondary and a tertiary *N*-substituted compound. Study of the behaviour of compound **2** in more detail revealed a significant buffer catalysis when hydrolysis was followed in piperidine and pyrrolidine media, this last one, both in water and deuterated water (Fig. 4). The solvent isotope effect turned out to be $k_B(pyrr)(H_2O) / k_B(pyrr)(D_2O) = 2.510^{-2} \pm 1.310^{-3} / 1.1410^{-2} \pm 5.610^{-4} = 2.2$, a value which clearly indicates the participation of water in the transition state. The general base catalysis and the solvent isotope effect observed implicate a general base $B_{Ac}2$ mechanism for compound **2**. The second order rate constant in OH^- for compound **2** is six orders of magnitude lower than the value of k_1K obtained for compound **1a**, and this observation itself is a good confirmation of the proposed E1cB mechanism of hydrolysis for the secondary carbamate in opposition to the bimolecular pathway proposed for the tertiary carbamate where any formation of the substrate anion is blocked by the *N*,*N*-disubstitution.

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