Mechanism of hydrolysis of substituted *N*-thiazolylcarbamate esters in OH^- solutions

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Substituted secondary *N*-thiazolylcarbamate esters and some tertiary *N*-methyl, *N*-thiazolyl carbamate esters have been synthesised and the mechanism of the OH^- catalysed hydrolyses investigated. These proved to be E1cB and BAc2 respectively, and this behaviour was compared with that of other carbamates.

Keywords: *N*-thiazolyl carbamate esters, heterocycles, hydrolytic mechanism, basic media, Hammett correlation

Thiazoles contain a small heterocyclic ring that plays an important role in living organisms, since it is present in biological molecules such as thiamine. Association of the thiazole ring with other azole derivatives showed an increased activity against resistant strains of *Candida* spp.[1] The new thiazolyl carbamates under study, containing the thiazol group directly linked to a carbamate function, revealed moderate antifungal activity against *C. albicans, C. tropicalis, C. glabrata, C. crusei* and *C. guilliermondii*.[2] Recently, a new class of inhibitors of bacterial cell-wall biosynthesis which contain an *N*-(2-thiazolyl) carbamate moiety, has been described.[3] Carbamates are already well established as antifungals and are not only used in medicine but also in crop protection.

Carbamates are rather labile in both acidic and basic media. Basic secondary carbamates containing acidic hydrogen on nitrogen are generally more reactive than the corresponding tertiary carbamates, which have no acidic hydrogen. During our ongoing studies on the reactivity of carbamates we investigated the reactivity of other secondary and tertiary *N*-heterocyclic carbamates, such as *N*-benzothiazolylcarbamates.[4,5] Both these carbamates give rise to the corresponding aminobenzothiazol and phenol. However, the secondary carbamates were found to react by an E1cB mechanism involving the rate-limiting unimolecular decomposition of the substrate anion (with formation of an isocyanate intermediate), while the tertiary analogues hydrolyse through a carbamic acid intermediate ($B_{Ac}2$ mechanism) which loses CO_2 giving rise also to the corresponding aminobenzothiazol.

Now we extend our investigation to the study of the reactivity of *N*-thiazolylcarbamates **1**–**9**, in order to investigate further the influence of similar heterocyclic species, and to complete the studies on the E1cB mechanism of hydrolysis of these compounds.

Experimental

^{1}H NMR spectra were recorded at 300 MHz (TMS internal standard) on a Bruker WP-300 apparatus, IR spectra on a Hitachi 270–50 apparatus and mass spectra on a Trio 1000GC 8000 spectrometer. Melting points are uncorrected. Hydrolysis of carbamates **1**–**8** was followed spectrophotometrically in a Shimadzu UV 1601-Visible Spectrometer, in a thermostated cell at 25°C.

General procedures

The synthesis of carbamates **1**–**6** and **9** was achieved by reaction of the corresponding 2-aminothiazol with the appropriate chloroformate by a previously described procedure.[5] Syntheses of phenyl *N*-(5-bromothiazolyl)carbamate **8**[6] and phenyl *N*-2-(5-methylthiazolyl) carbamate **7**[2] are described elsewhere.

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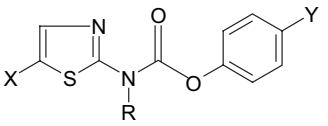


	1	2	3	4	5	6	7	8	9
R	H	H	H	CH_3	CH_3	CH_3	H	H	H
X	H	H	H	CH_3	CH_3	CH_3	CH_3	Br	NO_2
Y	H	Cl	OCH_3	H	Cl	OCH_3	H	H	H

Fig. 1

Hydrolyses of the substrates in NaOH solutions were followed spectrophotometrically at an appropriate wavelength. Changes in absorbance corresponded either to the disappearance of the substrate or appearance of phenol. Repetitive scans in the UV region showed tight isosbestic points, indicating the absence of intermediates. Isosbestic points were observed for all reactions in sodium hydroxide solutions. All absorbance versus time plots fitted pseudo first-order rate plots.

Synthesis: 2-methylamino-5 methylthiazol was obtained by methylation of 2-amino-5-methylthiazol with formaldehyde.[7] All carbamates were prepared according to the following procedure: the parent amine was dissolved in anhydrous ethyl ether and one equivalent of triethylamine and one equivalent of the corresponding chloroformate were added. The reaction proceeded 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 column chromatography or by crystallisation.

Kinetic method. The kinetics of hydrolysis of carbamates esters were studied in dioxane/water 10% (v/v) at 25.0 ± 0.2ºC and the ionic strength was kept constant at 0.5 M with $NaClO_4$. The decomposition of substrate for the secondary carbamates or formation of the corresponding phenol for the tertiary ones, was continuously monitored, λ = 280 (**1**–**3**), 290 (**7**–**9**), 236 (**4**, **5**), 243 (**6**) nm. All reactions were carried out under pseudo first-order conditions, the substrate concentration being much lower than the concentration (*ca* $1 \cdot 10^{-4}$ M) of other reagents.

The physical and spectroscopic data of compounds **1**–**6** and **9** are as follows (for AA'XX' systems in ^{1}H NMR $J^* = J_{23} + J_{25}$).

Phenyl N-2-thiazolylcarbamate **1**, yield = 10%, m.p. = 179–180°C (EtOH) (*lit.*[8] 178–180ºC, *n*-hexane). IR (cm^{-1}): 1739 (C=O). ^{1}H NMR: δ 7.51 (d, 1H, H_4, J = 3 Hz), 7.43 (d, 2H, $H_{2'}$, $H_{6'}$, O–Ph, J = 6 Hz), 7.29 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$,O–Ph), 6.98 (d, 1H, H_5, J = 3 Hz). MS: (*m/z*) 176 (5%, M^+-CO_2), 126 (100%, $C_4H_2N_2OS$), 94 (75%, PhOH). HRMS ($C_{10}H_8O_2N_2S$) exp. 220.03026, calc. 220.03010.

4-Chlorophenyl N-2-thiazolylcarbamate **2**, yield = 22%, m.p. = 213–215ºC (CH_2Cl_2/MeOH). IR (cm^{-1}): 1738 (C=O). ^{1}H NMR: δ 7.51 (d, 1H, H_4, J = 3.6 Hz), 7.43 (m, 2H, $H_{3'}$, $H_{5'}$, O–Ar, J^* = 9 Hz), 7.24 (d, 2H, $H_{2'}$, $H_{6'}$, O–Ar, J^* = 9 Hz), 7.01 (d, 1H, H_5, J = 3.6 Hz). MS: (*m/z*) 128 (50%, 4Cl–Ph–OH), 126 (10%, $C_4H_2N_2OS$). HRMS ($C_{10}H_7O_2N_2SCl$) exp. 253.99098, calc. 253.99113.

4-Methoxyphenyl N-2-thiazolylcarbamate **3**, yield = 21%, m.p. = 206–207ºC (EtOH). IR (cm^{-1}): 1727 (C=O). ^{1}H NMR: δ 7.49 (d, 1H, H_4, J = 3 Hz), 7.16 (m, 2H, $H_{3'}$, $H_{5'}$, O–Ar, J^* = 9 Hz), 6.97 (d, 1H, H_5,

J = 3 Hz), 6.94 (m, 2H, $H_{2'}$, $H_{6'}$, O–Ar, J* = 9 Hz), 3.82 (s, 3H, CH_3–Ph–OH). MS: (*m/z*) 206 (5%, M^+–CO_2), 126 (98%, $C_4H_2N_2OS$), 124 (100%, 4Me–Ph–OH). HRMS ($C_{11}H_{10}O_3N_2S$) exp. 250.04092, calc. 250.04066.

Phenyl N-methyl-N-2-(5-methylthiazolyl)carbamate **4**, yield = 25%, m.p. = 101–102ºC (EtOH). IR (cm^{-1}): 1724 (C=O). ^{1}H NMR: δ 7.41 (d, 2H, H_2, H_6, O-Ph, J = 6 Hz), 7.24 (m, 3H, $H_{3'}$, $H_{4'}$, H_5, O–Ph), 7.12 (1H, s, H_4), 3.75 (s, 3H, CH_3–N), 2.37 (s, 3H, CH_3–thiazolyl). MS: (*m/z*) 248 (20%, M^+), 204 (M^+–CO_2) 155 (60%, M^+–O–Ph), 127 (38%, $C_5H_7N_2S$), 114 (100%, $C_4H_4N_2S$ + 2H), HRMS ($C_{12}H_{12}O_2N_2S$) exp. 248.06225, calc. 248.06140.

4-Chlorophenyl-N-methyl-N-2-(5-methylthiazolyl)carbamate **5,** yield = 17%, m.p. = 98–99ºC (EtOH). IR (cm^{-1}): 1767, 1731 (C=O). ^{1}H NMR: δ 7.27 (s, 1H, H_4), 7.39 (m, 2H, $H_{3'}$, $H_{5'}$, O-Ar, J* = 9 Hz), 7.16 (m, 2H, $H_{2'}$, $H_{6'}$, O–Ar, J* = 9 Hz), 3.74 (3H, s, CH_3–N), 2.38 (3H, s, CH_3-thiazolyl). MS: (*m/z*) 282 (20%, M^+), 238 (50%, M^+–CO_2), 155(85%, M^+–4Cl–Ph–O), 127 (38%, $C_5H_7N_2S$), 114 (100%, $C_4H_4N_2S$ + 2H). HRMS ($C_{12}H_{11}O_2N_2SCl$) exp. 282.02221, calc. 282.02243.

4-Methoxyphenyl N-methyl-N-2-(5-methylthiazolyl)carbamate **6**, yield = 2%, m.p. = 83–84ºC (EtOH). IR (cm^{-1}): 1713 (C=O). ^{1}H NMR: δ 7.12 (m, 2H, $H_{3'}$, $H_{5'}$, O–Ar, J* = 9 Hz), 7.11 (1H, s, H_4), 6.92 (m, 2H, $H_{2'}$, $H_{6'}$, O–Ar, J* = 9 Hz), 3.82 (s, 3H, CH_3–OPh) 3.73 (s, 3H, CH_3–N), 2.37 (s, 3H, CH_3–thiazolyl). HRMS ($C_{13}H_{14}O_3N_2S$) exp. 278.07203, calc. 278.07196.

Phenyl N-2-(5-nitrothiazolyl)carbamate **9** yield = 3%, m.p. = 251–254°C (dec.) (*lit.*[9] 245–255°C, C_6H_6–DMF). IR (cm^{-1}): 1740 (C=O). ^{1}H NMR: δ 8.41 (s, 1H, H_4), 7.49 (d, 2H, $H_{2'}$, $H_{6'}$, O–Ph, J = 6 Hz), 7.34 (3H, m, $H_{3'}$, $H_{4'}$, $H_{5'}$). MS: (*m/z*) 171 (30%, M^+–HO–Ph), 125 (50%, 171–NO_2), 94 (100%, HO–Ph).

Results and discussion

The rates of hydrolysis of *N*-thiazolylcarbamates **1–9** (Fig. 1) were investigated in dioxane/water (1:9, v/v) due to the low solubility of the substrates in water.

Secondary carbamates

Under the conditions used, hydrolysis of compounds **1–3, 7** and **8** in sodium hydroxide solution gave the corresponding 2-aminothiazol and the corresponding phenol. The influence of OH^- concentration on the reaction rate was studied, and a plot of first-order rate constants k_{obs} *vs* [OH^-] for the hydrolysis of compound **1** is shown in Fig. 2.

The rate of hydrolysis is proportional to [OH^-] until it reaches a *plateau* region. This *plateau,* due to the pre-equilibrium ionisation of the substrate (K_a), is followed by a rate-determining decomposition to products (k_1), as shown in Equation 1:

$$\mathrm{SH + B \underset{\downarrow K_a}{\rightleftarrows} S^- + BH^+ \xrightarrow[\downarrow k_1]{} Products} \quad (1)$$

These data are consistent with an E1cB mechanism, Equation 2:

$$k_{obs} = k_1[OH^-]/K + [OH^-] \quad (2)$$

The anion formed was not distantly observed in the UV spectra. Compounds **2**, **3**, **7** and **8** exhibited a similar behaviour, and adjustment of their data to equation 2 gives the corresponding k_1 and $K = K_W/K_a$. Values of k_1 and K for the five secondary thiazolylcarbamates studied are listed in Table 1.

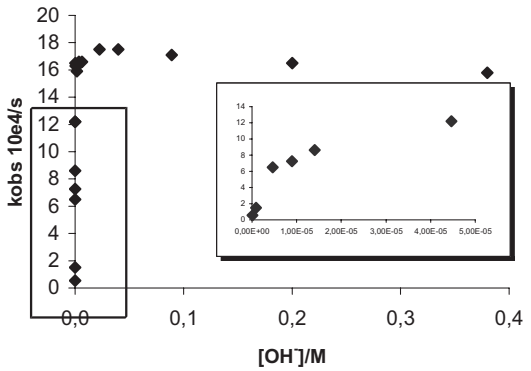


Fig. 2 Effect of hydroxide concentration on the rate of hydrolysis of compound **1.**

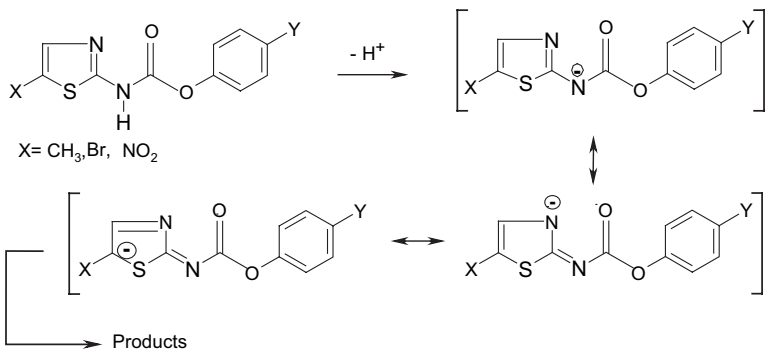
Table 1 Values of $k_1$and K for [OH^-]-catalysed hydrolysis of secondary thiazolylcarbamates (R = H), compounds **1–3, 7** and **8**

Compound	**1**	**2**	**3**	**7**	**8**
10^4 k_1/s^{-1}	16.6±0.3	81.6±2.9	4.3±0.1	20.2±0.9	3.2±0.2
10^5 K/M	1.18±0.1	0.09±0.02	2.25±0.6	6.5±2	1.1±0.3

Correlation of log k_1 *vs* σ_p^- values[10] for compounds **1–3** gave rise to a Hammett coefficient (ρ) of 3.43 (r^2 = 0.98). This is an expected result on the basis of a rate-determining departure of the phenoxide group from the anion intermediate formed in a pre-equilibrium step. Similarly high values were obtained for substituted phenyl *N*-phenyl carbamates (ρ = 3.17)[11] and substituted phenyl *N*-phenylsulfonyl carbamates (ρ = 2.93).[12] A similar high value (ρ = 2.45) was obtained for the basic hydrolysis of *N*-(2-pyridyl)carbamate esters,[4] another group of secondary *N*-heterocyclic carbamates. Evaluation of the substituent effect on the heterocyclic thiazole ring (compounds **1**, **7** and **8)** used log k_1 *vs* σ_p^- values[13] and gave a Hammett coefficient of –2.09 (r^2 = 0.94). Both the high and negative sign of ρ value, suggest a reaction which is very sensitive to substituents on the heterocyclic ring. In the alkaline media used, there is a high concentration of the carbamate anion and, consequently, the substituent effects greatly affect the anion reactivity, *i.e.* the rate of formation of N=C bond present in the isocyanate intermediate. The studied electron-attracting substituents on the heterocyclic ring are expected to change K_a and k_1 in opposite directions: the acidity of the nitrogen acidic hydrogen is increased by stabilisation of the anion due to the electron-withdrawing effect of the substituted thiazole ring, but the rate of decomposition of the stabilised anion, with formation of the isocyanate intermediate, is decreased (Scheme 1).

A similar negative ρ value, although with a smaller value due to the screening effect of the sulfonyl group, was observed for the *N*-(substituted arylsulfonyl) secondary carbamates (ρ = –0.66).[12] A ρ value of 0.64 was reported for *N*-(substituted phenyl)carbamates[11] a result which may be explained as the combination of the two opposite effects on k_1 and K_a.

An attempt to use σ_m values in Hammett plot of **1**, **7** and **8** gave a similar value of ρ (–1.88) and a slightly better correlation (r^2 = 0.99). However, the ρ value obtained from σ_p^- correlation agrees



Scheme 1 Delocalisation of the negative charge in the thiazole ring of the anionic intermediate of secondary carbamates.

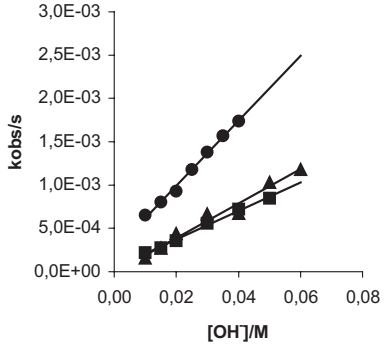


Fig. 3 Effect of hydroxide concentration on the rate of hydrolysis of tertiary compounds **4** (▲), **5** (●) and **6** (■).

with the experimental evidence concerning the low reactivity of the nitro derivative **9**, which, under the conditions used, showed no signs of decomposition after 24 h.[14]

The kinetic parameters obtained for the hydrolysis of these compounds suggest an E1cB decomposition mechanism. Additional support comes from comparison of the reaction of secondary carbamates with that of their *N*-methyl analogues.

Tertiary carbamates

Hydrolysis of the three tertiary compounds (**4**–**6**) also gave the corresponding phenol and 5-methyl-2-methylaminothiazol and showed a first-order dependence on [OH^-] (Fig. 3).

The second order rate constants obtained for these three compounds are listed in Table 2, with no significant water effect observed.

The Hammett coefficient obtained for correlation with σ_p^- ($\rho = 0.98$; $r^2 = 0.99$), points to a classical bimolecular mechanism of hydrolysis, with a rate-determining step of nucleophilic attack on the carbamate carbonyl electrophilic centre, the carbonyl carbon atom. The magnitude of ρ and the good correlation obtained is similar to the one for *N*-arylsulfonylcarbamates, $\rho = 1.2$ and $r^2 = 0.98$.[15] Like the sulfonyl group, the thiazol ring must have a strong electron-withdrawing effect on the nitrogen atom of the carbamate function, increasing the electronic delocalisation from the carbamate oxygen. Once the tetrahedral intermediate is formed, this delocalisation is removed resulting in a greater change in the electronic density of the phenol oxygen.

Comparison of the reactivity of thiazolylcarbamates with literature data

Comparison of the relative magnitude of the rate constant k_1 and K_a for the hydrolysis of the secondary *N*-heteroaromatic carbamates under study, *i.e.* phenyl *N*-2-thiazolylcarbamate **1,** ($k_1 = 1.67 \times 10^{-3}$ s^{-1}, $K_a = 0.07 \times 10^{-8}$ M), and 4-chlorophenyl *N*-2-thiazolylcarbamate **2** ($k_1 = 8.16\ 10^{-3}$ s^{-1}, $K_a = 1.04 \times 10^{-8}$ M), Table 1, with the related aryl and heteroaryl substrates known, *i.e.*, 4-chlorophenyl-*N*-4-nitrophenylcarbamate[11] **10** ($k_1 = 8.30$ s^{-1}, $K_a = 5.0 \times 10^{-13}$ M), phenyl-*N*-4-nitrophenylcarbamate[11] **11** ($k_1 = 1.54$ s^{-1}, $K_a = 3.2 \times 10^{-13}$ M), 4-chlorophenyl *N*-2-pyridylcarbamate[4] **12** ($k_1 = 35.6$ s^{-1}, $K_a = 2.1 \times 10^{-13}$ M), phenyl *N*-2-pyridylcarbamate[4] **13** ($k_1 = 8.3$ s^{-1}, $K_a = 1.4 \times 10^{-13}$ M), 4-chlorophenyl *N*-2-benzothiazolylcarbamate[5] **14** ($k_1 = 2.69 \times 10^{-3}$ s^{-1}, $K_a = 7.3 \times 10^{-9}$ M), all reactions done in $\mu = 1$ M, at 25 ºC, Table 3, shows that the thiazol ring is determinant in decreasing the magnitude of the rate constant (ratio 10^3) and increasing the value of K_a (ratio 10^4–10^5).

These results confirm the importance of the stability of the carbamate anion intermediate formed in an E1cB process. The thiazole ring, being an electron-withdrawing group, greatly increases the anion stabilisation, increasing the acidity of the carbamate but decreasing k_1. The presence of a phenyl linked to a thiazole group as in benzothiazolyl moiety does not change the general behaviour of these compounds.

Comparison of the relative magnitude of the rate constant for the hydrolysis of the tertiary heteroaromatic carbamates reported, Table 4, *i.e.*, *N*-2-(5-methylthiazolyl)carbamate **4** ($k_{OH^-} = 19.9 \times 10^{-3}$ $M^{-1}s^{-1}$) and 4-chlorophenyl *N*-methyl, *N*-2-(5-methylthiazolyl)carbamate **5** ($k_{OH^-} = 36.7 \times 10^{-3}$ $M^{-1}s^{-1}$), Table 2, with related aryl and heteroaryl substrates known, *i.e.* phenyl *N*-methyl-*N*-phenyl carbamate[11] **15** ($k_{OH^-} = 0.017 \times 10^{-3}$ $M^{-1}s^{-1}$), phenyl *N*-methyl-*N*-(2-pyridyl)carbamate[4] **16** ($k_{OH^-} = 0.6 \times 10^{-3}$ $M^{-1}s^{-1}$), 4-chlorophenyl *N*-(2-benzothiazoyl)-*N*-methylcarbamate[5] **17** ($k_{OH^-} = 53.8 \times 10^{-3}$ $M^{-1}s^{-1}$), leads us to consider that in this case, the strong electron-withdrawing effect of the thiazolyl ring makes the bimolecular $B_{Ac}2$ attack easier.

Comparison of the second-order rate constant obtained for the tertiary carbamate **4** with the value of k_1/K obtained for the analogous secondary carbamate **7**, gives a rate difference of *ca* 10^3 higher for compound **7**. This difference is not as high as the 10^6 that is observed for the secondary N-benzothiazolylcarbonates[5] and *N*-pyridylcarbamates[4] but closer to the 10^4 increase obtained for the *N*-phenyl carbamates.[11] If one compares the reactivity of the aryl/pyridyl and benzothiazolyl/thiazolyl pairs, one observes a somewhat inverse tendency, the tertiary thiazolyl-containing carbamates being more reactive, since the anion stability no longer exists as for the secondary compounds and the $B_{Ac}2$ mechanism, previously proposed for the benzothiazolylcarbamates,[5] is now favoured by the more electron-withdrawing thiazolyl group contained both in thiazolyl and benzothiazolyl derivatives.

Table 2 Values of second order rate constants, k_{OH^-}, for the hydroxide ion catalysed hydrolysis of tertiary (R =CH_3) carbamates **4**–**6**

Compound	**4**	**5**	**6**
$10^3\ k_{OH^-}/M^{-1}s^{-1}$	19.9± 0.07	36.7± 0.03	16.5± 0.02

Table 3 Literature k_1 and K_a values for the hydroxide ion catalysed hydrolysis of secondary carbamates related to reported compounds

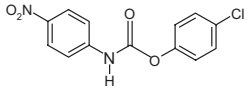
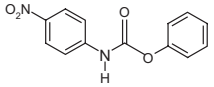
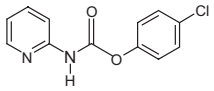
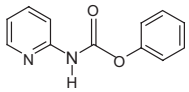
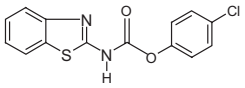
	Compound	k_1/s^{-1}	K_a/M
10[11]		8.3	5×10^{-13}
11[11]		1.54	3.2×10^{-13}
12[4]		35.6	2.1×10^{-13}
13[4]		8.3	1.4×10^{-13}
14[5]		2.69×10^{-3}	7.3×10^{-9}

Table 4 Literature k_{OH^-} values for the hydroxide ion catalysed hydrolysis of tertiary carbamates related to reported compounds

Compound	$k_{OH^-}/M^{-1}\ s^{-1}$
15[11]	0.17×10^{-4}
16[4]	6.0×10^{-4}
17[5]	5.38×10^{-2}

Conclusion

The results obtained confirm the existence of an E1cB mechanism for the hydrolysis of the secondary aryl *N*-thiazolylcarbamates esters, in contrast to a typical bimolecular process for the *N*-methyl analogues. Reaction rates for the secondary carbamates are higher than reaction rates for the tertiary analogue carbamates by a factor of *ca* 1500.

Comparison of the reactivity of thiazolyl containing carbamates with literature data indicates the strong electron-withdrawing ability of the thiazole ring as observed in their lower reactivity reaction proceeding by the in E1cB mechanism and a higher reactivity in the $B_{Ac}2$ process.

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References

1 A. Tsuruoka, Y. Karu, H. Karinuma, I. Tsukada, M. Yanagisava and T. Naito, *Chem. Pharm. Bull.*, 1997, **45**, 1169; A. Tsuruoka, Y. Karu, H. Karinuma, I. Tsukada, M. Yanagisava, K. Nara and T. Naito, *Chem. Pharm. Bull*., 1998, **46**, 623.
2 Patricia D. M. Rijo, Master Thesis, Faculty of Pharmacy, University of Lisbon, Portugal, 2003, pp. 74-76.
3 G.D. Francisco, Z. Li, J.D. Albright, N.H. Eudy, A.H. Katz, P.J. Petersen, P. Labthavikul, G. Singh, Y. Yang, B.A. Rasmussen, Y.I. Lin and T.S. Mansour, *Bioorg. Med. Lett.,* 2004, **14**, 235.
4 F. Norberto, S. Santos, D. Silva, P. Hervés, A.S. Miguel, F. Vilela, *J. Chem. Soc., Perkin Trans.,* 2002, **2**, 1162.
5 F. Norberto, M.E.M. Araújo, P. Hervés and L. Ribeiro, *J. Chem. Res. (S),* 2002, 598.
6 F.P. Norberto, J.N. Iley, M.E. Araújo and L.M. Morais, *Inform. Tecnol.*, 1999, **10**, 169.
7 Ö. Kemal and C.B. Reese, *J. Chem. Soc., Perkin Trans.*, 1569, 1981.
8 M. Nagano, J. Tobitsuka, M. Takashi and K. Oyamada, *Chem. Pharm. Bull*., 1972, **20**, 2618.
9 P. Islip, M.D. Closier and M.C. Neville, *J. Med. Chem*., 1972, **15**, 951.
10 J.C.R. Reis, M.A.P. Segurado and J.D.G. Oliveira, *J. Phys. Org. Chem.*, 1995, **8**, 671.
11 A.F. Hegarty and L.N. Frost, *J. Chem. Soc. Perkin Trans 2*, 1973, 1719.
12 A. Vigroux, M. Bergon, C. Bergonzi and P. Tisnès, *J. Am. Chem. Soc.*, 1994, **116**, 11787.
13 The use of σ_p values has been described previously: D.A. Forsyth and D.S. Noyce, *Tetrahedron Lett.,* 1972, **37**, 3893.
14 M.E.M. Araújo, L. Chambel, M. Machado, F. Norberto, T. Pamplona and R. Tenreiro, *XII Congresso Nacional de la Sociedad Española de Química Terapeutica,* Sevilha, 2001, Book of Abstracts, p 83.
15 M.E.M. Araújo, M. Campelo, J. Iley and F. Norberto, *J. Chem. Soc., Perkin Trans., 2,* 2001, 494.