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Article

Kinetics and Mechanism of Hydrolysis of Benzimidazolylcarbamates

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Através da carbamoilação do 2-aminobenzimidazole com diferentes cloroformatos substituídos, sintetizaram-se novos *N*-[1-(2-amino)benzimidazolil]carbamatos. Estudou-se a hidrólise em meio aquoso destes carbamatos numa gama de pH compreendida entre 1 e 13, a uma temperatura de 25 ºC. Os parâmetros cinéticos avaliados levaram a concluir que até pH 4 a reação se processa por mecanismo que envolve o ataque bimolecular da água ao substrato *N*-protonado. Esta é a primeira vez que este comportamento é observado em carbamatos, sendo muito provavelmente devido à diferença de basicidade entre um dos azotos do anel de benzimidazolilo e o oxigênio da função carbamato. Para valores mais elevados de pH, os resultados são consistentes com um mecanismo $B_{Ac}2$, atuando a água como nucleófilo entre pH 4 e 7 enquanto que em pH superior o íon hidróxido é o nucleófilo.

Synthesis of new 2-aminobenzimidazole-1-carbamates was accomplished by carbamoylation of 2-aminobenzimidazole using different substituted phenyl chloroformates. The aqueous hydrolysis of the new compounds was examined in the pH range 1-13 at 25 ºC. The evaluated kinetic parameters led to the conclusion that up to pH 4 reaction proceeds by a bimolecular attack of water to the *N*-protonated substrate. This is the first time this behavior is described for carbamates, and can be ascribed to the higher basicity of the benzimidazolyl moiety when compared with the carbonyl oxygen. For higher values of pH, the results are consistent with a $B_{Ac}2$ mechanism with nucleophilic catalysis, but while between pH 4 and pH 7 water acts as the nucleophile, for pH> 7 the hydroxide ion is the acting species.

Keywords: reaction mechanisms, kinetics, heterocycles, carbamates, benzimidazole

Introduction

The 2-aminobenzimidazole ring system represents the core structure of a number of biologically significant molecules and its derivatives have been found to possess a wide spectrum of biological activity. Particularly, alkyl benzimidazole-2-carbamates show potent fungicide[1] and anti-helmintic activity,[2,3] being Carbendazim® a good example of a successful market fungicide. Nevertheless, there are, to our knowledge, no studies on aryl benzimidazole-1-carbamates, either in terms of synthesis, bioactivity or chemical reactivity. So, in the sequence of our on-going work about aryl carbamates we decided to synthesize new 2-aminobenzimidazole-1-carbamates. Kinetics and mechanisms of basic hydrolysis of carbamates are well documented in literature, leading to the conclusion that tertiary carbamates hydrolyze always via a $B_{Ac}2$ mechanism while secondary ones decompose by a unimolecular elimination, if they have a good leaving group, or via $B_{Ac}2$ mechanism if they do not have it.[4-6]

This paper, which presents unreported kinetic studies on tertiary carbamates, where the nitrogen atom is part of a cycle, involves the synthesis of new carbamates with potential bioactivity and the evaluation of the mechanism of hydrolysis of aryl benzimidazole-1-carbamates (**1a-d**, **2**) over the pH range 1-13.

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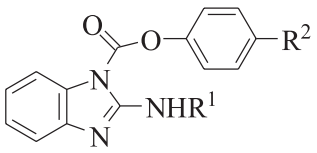


1a: $R^1 = R^2 = H$
1b: $R^1 = H$, $R^2 = CH_3$
1c: $R^1 = H$, $R^2 = OCH_3$
1d: $R^1 = H$, $R^2 = Cl$
1e: $R^1 = H$, $R^2 = NO_2$
2: $R^1 = CH_3$, $R^2 = H$

Results and Discussion

Synthesis

A number of methods for the synthesis of alkyl benzimidazole carbamates have been reported,[7] *N*- acylation of 2-aminobenzimidazole with alkyl chloroformates in aprotic solvents, or reaction with alkylcarbonates being the most common. The acylation of 2-aminobenzimidazole with alkyl chloroformates gives rise to benzimidazole-2-carbamates, via the formation of the *N* or *N, N'*-disubstituted benzimidazoles, which rearrange to the corresponding 1-carbamates with a base or by heat. There are, however, no reports of extending these methods to the synthesis of aryl benzimidazole carbamates. We found that aryl benzimidazole-1-carbamates can be obtained with moderate yields reacting 2-aminobenzimidazole with aryl chloroformates, even in presence of excess of base. We think that the hindrance of the exocyclic amine does not affect the stability of the endocyclic arylcarbamates, which are too stable and do not rearrange to the exocyclic ones.

Structure of compounds, including the site of carbamoylation, was elucidated both by spectroscopic and analytical data, including a single crystal X-ray diffraction, of which we show an example in Figure 1.

Reactivity

The pseudo first-order rate constants, k_{obs}, for the hydrolysis of compounds **1a**-**e** and **2** were measured at 25 ± 0.1 °C, either in aqueous HCl and NaOH or in buffer solutions (Table 1) and were found to be reproducible to within 5%. The pH rate profile obtained from the plot of log k_{obs} *vs.* pH is shown in Figure 2. Under these experimental conditions, the hydrolysis was found to

Table 1. Values of pH and k_{obs} for the hydrolysis of compounds **1a**-**e** and **2** at 25 °C

Catalyst (acid, basic or buffer)	pH	k_{obs} / (10^{-5} s^{-1}) **1a**	k_{obs} / (10^{-5} s^{-1}) **1b**	k_{obs} / (10^{-5} s^{-1}) **1c**	k_{obs} / (10^{-5} s^{-1}) **1d**	k_{obs} / (10^{-5} s^{-1}) **1e**	k_{obs} / (10^{-5} s^{-1}) **2**
HCl	1.0	3.16	2.23	2.57	8.22	45	2.27
HCl	2.0	3.42	1.92	1.58	7.64	42.7	2.00
Glycine	2.4	—	—	—	6.52	42.3	—
Formiate	3.0	—	2.01	2.27	6.13	42.1	—
Acetate	3.8	—	—	—	5.37	—	1.31
Acetate	4.0	—	—	—	—	25.5	—
Acetate	4.4	2.07	1.48	1.52	—	—	—
Acetate	5.0	1.02	—	—	1.20	6.38	0.197
Carbonate	5.6	0.46	0.19	0.19	—	—	—
Carbonate	6.3	—	—	—	0.197	6.90	—
Carbonate	6.4	0.21	—	—	—	—	—
Carbonate	6.7	—	—	—	0.21	8.46	0.033
Phosphate	7.2	0.16	0.074	0.074	—	—	—
Phosphate	7.4	—	—	—	—	5.20	0.066
Phosphate	8.3	—	0.97	1.00	3.97	16.6	—
Borate	8.8	2.50	—	—	14.5	61.7	—
Borate	9.3	7.37	—	—	—	96.1	4.06
Borate	10.0	40.1	17.9	21.4	119	400	35.2
Carbonate	10.6	—	24.5	35.5	304	1320	103
Carbonate	10.8	80.7	—	—	—	—	—
Carbonate	11.0	285	28.5	139	—	2250	—
Carbonate	11.3		—	—	—	5660	—
Carbonate	11.6	1030	—	—	—	7810	—
Carbonate	11.8	1550	—	—	—	—	—
Carbonate	11.9	2080	—	—	—	—	—
NaOH	12.0	2390	—	2340	5470	—	1880
NaOH	12.3	6000	—	4640	11000	—	3690
NaOH	12.5	9980	3390	6920	15700	—	5230
NaOH	12.6	11500	—	9320	—	—	7.760
NaOH	12.7	12800	7720	11400	—	—	10300
NaOH	12.8	—	14900	13800	—	—	—
NaOH	13.0	26300	19100	—	—	—	—

Total buffer concentration= 0.04 mol dm^{-3}, μ = 0.5 mol dm^3 $NaClO_4$.

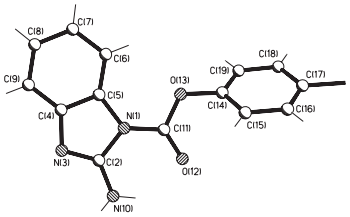


Figure 1. ORTEP drawing of **1d**, and selected structure parameters: N(1)–C(2) 1.411(6), N(1)–C(11) 1.354(6), C(2)–N(10) 1.320(6), C(4)–C(5) 1.383(6), C(6)–C(7), C(7)–C(8), N(10)–H(10A) 0.91(5), N(10)–H(10B) 0.81(5) C(11)–O(12) 1.207(6), C(2)–N(1)–C(5) 105.6(3), C(2)–N(1)–C(11) 124.5(4), C(5)–N(1)–C(11) 129.5(4), N(1)–C(2)–N(10) 121.1(4), C(2)–N(3)–C(4) 105.8(4), N(3)–C(4)–C(9) 128.1(4), N(1)–C(5)–C(4) 104.7(4), C(2)–N(10)–H(10B)121(4), C(2)–N(10)–H(10A) 118(3), N(1)–C(11)–O(12) 125.1(4, O(12)–C(11)–O(13) 123.4(4), H(10A)–N(10)–H(10B) 119(5).

follow a first order kinetics with respect to the substrate up to at least 90% completion of the reaction, being 2-aminobenzimidazole and phenol, or a substituted phenol, always the reaction products.

The pH rate profile indicates the existence of three different regions, according to different reactions of the substrate. The first region, up to pH 4 is a pH independent region with no buffer catalysis (equation 1); the second region is characterized by a decrease of k_{obs} with pH up to pH 7 (equation 2 or 2'); and, finally, for pH> 7 a highly dependent pH region is observed with buffer catalysis (equation 3). All studied compounds demonstrated a similar behavior and the data for all of them fitted well to the global equation obtained from the association of equations 1 (explained by water attack to the protonated substrate), 2 or 2' (explained either by the attack of water to the neutral species or the attack of hydroxide to the protonated substrate) and 3 (related to the attack of hydroxide to the neutral substrate). K_a is the acid dissociation constant for the protonated substrate obtained from kinetic parameters, K_w is the ionic product of water, and k_1, k_2 or $k_{2'}$ and k_3 are the second-order rate constants for reaction in solution up to pH 4, the intermediate region and the basic medium (Table 2), respectively.

$$k_{obs} = k_1 \frac{K_w[H_2O]}{K_a[OH^-]+K_w} \quad (1)$$

$$k_{obs} = k_2 \frac{K_a[H_2O][OH^-]}{K_a[OH^-]+K_w} \quad (2) \qquad k_{obs} = k_{2'} \frac{K_w[OH^-]}{K_a[OH^-]+K_w} \quad (2')$$

$$k_{obs.} = k_3 [OH^-] \quad (3)$$

Hydrolysis in acidic media

The compounds under study are quite basic and in the pH range studied they can be protonated, being thus possible the co-existence of both species, the neutral (S) and the protonated form (SH^+) of the substrate. Therefore, the pH independent region found in the pH rate profile up to pH 4, can be explained by the existence of these two species, and can be analysed as an attack of water on the protonated substrate. No buffer catalysis was observed in this region (Table 3).

Comparison of k_1 values obtained for compounds **1a-e** (Table 2) gives rise to a Hammett plot (Figure 3) indicative of a mechanism compatible with a bimolecular attack of water as the rate determining step.[8] This substituent effect is indicative of a pre-equilibrium

Table 2. Acid dissociation and rate constants for hydrolysis of carbamates **1a-e** and **2**

Compound	k_1 / (10^{-7} dm^3 mol^{-1} s^{-1})	k_2/ (10^{-8} dm^3 mol^{-1} s^{-1})	k_2/ (10^{-3} dm^3 mol^{-1} s^{-1})	k_3/ (dm^3 mol^{-1} s^{-1})	pK_a
1a	7.40	4.44	30.0	2.67	4.52
1b	4.67	1.35	1.00	1.96	4.70
1c	4.85	1.86	5.37	2.24	4.54
1d	16.5	3.25	9.82	5.08	3.26
1e	99.7	139	0.92	20.70	3.26
2	5.94	0.91	5.37	1.96	3.52

Table 3. Influence of buffer concentration on k_{obs} values for the decomposition of **1a** in acidic medium

[formate]/ (10^{-3} mol dm^{-3}) pH 3.3	k_{obs}/ (10^{-6} s^{-1})	[2,2'-iminodiacetonitrile]/ (10^{-3} mol dm^{-3}) pH 4.4	k_{obs}/ (10^{-6} s^{-1})	[2,2,2-trifluoroethylamine]/ (10^{-3} mol dm^{-3}) pH 4.9	k_{obs}/ (10^{-6} s^{-1})
4.52	28.7	2.0	18.7	1.9	29.5
5.44	29.2	2.1	20.0	2.3	28.5
6.44	28.8	2.5	19.5	2.8	29.5
7.52	29.5	2.9	19.5	3.2	28.8
10.46	29.5	4.1	19.2	4.6	29.8

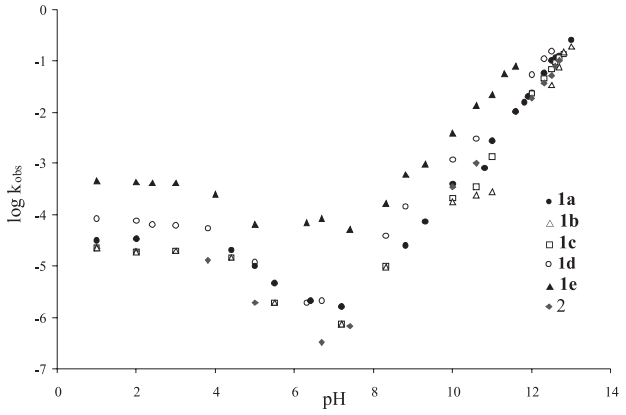


Figure 2. pH rate profile for the hydrolysis of **1a-e** and **2**.

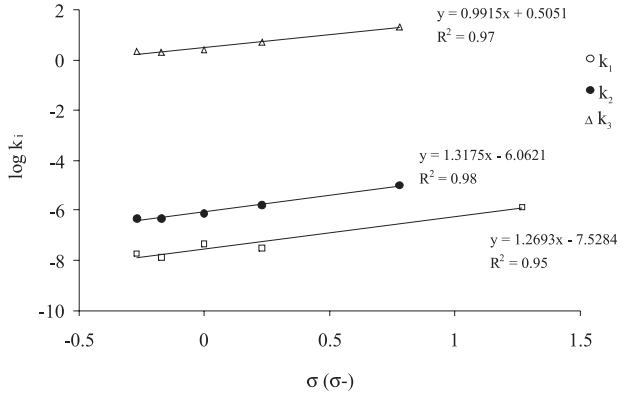


Figure 3. Hammett plots for the hydrolysis of compounds **1a-e**, in the three distinct pH regions, with k_i indicating rate constants in all three media.

protonation of the substrate followed by the rate determining formation of the tetrahedral intermediate, with decomposition occurring by benzimidazole acting as a leaving group. Indeed, there are three basic sites in the carbamate molecule, the exocyclic and endocyclic nitrogens and the acyl oxygen, and so any of the three tautomers can be the starting species in the hydrolysis. Based on pK_a calculations,[9] we predict the site of protonation to be the endocyclic nitrogen (pK_a exocyclic NH_2= -6.704; pK_a endocyclic NH= 4.100; pK_a oxygen= -2.541), generating a much more stable intermediate and a much better leaving group. Moreover, this pK_a value is in accordance with the one obtained by experimental adjustment to equation 1.

Hydrolysis of compound **2** was also done in deuterated media (Table 4) and comparison of the reaction performed in both media gave rise to the ratio of the slopes of both linear correlations in the two media, $k_1(H_2O)/ k_1(D_2O)$= 0.73. Again, this isotope effect is the one expected based upon the contribution of two processes: pre-equilibrium protonation of the substrate followed by the rate limiting step of attack at the carbamate function.[10] Therefore, in light of the overall evidence, we propose that acid hydrolysis of compounds **1a-e** and **2** proceeds *via* a bimolecular mechanism with acyl-nitrogen fission. This conclusion is supported by theoretical studies published for the acid hydrolysis of methyl carbamates.[11]

Table 4. Isotope effect for the hydrolysis of compound **2**

Hydrolysis in H_2O		Hydrolysis in D_2O	
[HCl]/ (10^{-2} mol dm^{-3})	k_{obs}/ (10^{-5} s^{-1})	[DCl]/ (10^{-2} mol dm^{-3})	k_{obs}/ (10^{-6} s^{-1})
1.0	1.63	1.0	8.17
3.0	1.79	3.0	9.54
5.0	1.76	5.0	12.0
10.0	2.27	—	—

Hydrolysis in basic media

The first order rate constants for the hydrolysis of compounds **1a-e** and **2** were measured in the presence of different NaOH concentrations and were observed to obey equation 3. For compound **1a** rate constants were also measured in a number of aqueous buffer solutions (Table 5).

From the linear correlation of k_{obs} *versus* free base concentration, second-order rate constants k_i were obtained and it was assumed that the basic form of the buffer was the only active species (Table 2); an example of base catalysis is shown in Figure 4.

Table 5. Influence of [buffer] on k_{obs} values for decomposition of **1a** in basic medium

[TFE]/ (10^{-3} mol dm^{-3}) pH 11.	k_{obs}/ (10^{-3} s^{-1})	[Pip]/ (10^{-3} mol dm^3) pH 10.8	k_{obs}/ ($10^{-3}s^{-1}$)	[TEA]/ (10^{-3} mol dm^{-3}) pH 10.3	k_{obs}/ ($10^{-4}s^{-1}$)	[PIPE]/ (10^{-3} mol dm^{-3}) pH 10.3	k_{obs}/ (10^{-4} s^{-1})	[MOR]/ (10^{-3}mol dm^{-3}) pH 9.4	k_{obs}/ ($10^{-5}s^{-1}$)
1.4	9.86	1.6	1.01	1.8	1.12	6.8	3.94	8.8	3.17
2.3	12.60	2.5	1.20	2.4	1.20	8.8	4.22	11.0	3.40
2.9	17.30	3.0	1.29	2.9	1.23	9.9	4.18	13.2	3.42
3.7	21.40	3.6	1.38	4.0	1.32	12.1	4.78	17.5	3.71
6.1	35.00	8.5	2.10	5.0	1.43	18.0	5.27	22.0	4.03

TFE-2,2,2-trifluorethanol, Pip-piperidine, TEA-triethylamine, PIPE-piperazine, MOR- morpholine

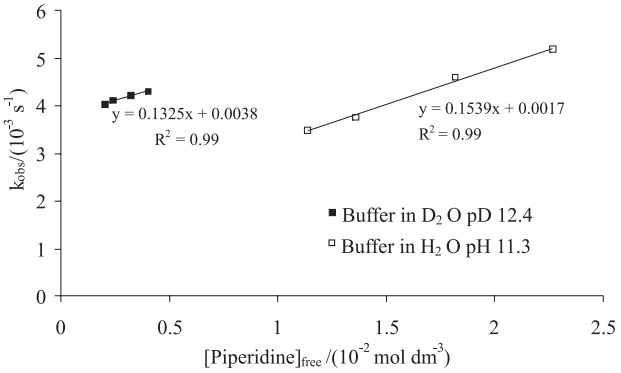


Figure 4. Isotope effect for the hydrolysis of compound **2** in piperidine media.

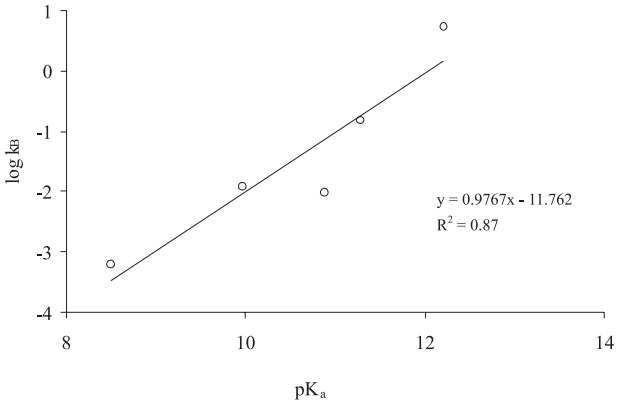


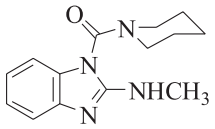
Figure 5. Brönsted plot for the hydrolysis of compound **1a**.

Buffer catalysis was observed in the region of pH> 7 and the second order rate constants obtained from the slopes of the plots of k_{obs} *versus* [buffer] were plotted against pK_a (literature values, calculated according to Davies equation for each experimental ionic strength) giving rise to a Brönsted correlation with a β value of 0.98 (Figure 5). The poor correlation obtained, due to the points for triethylamine and trifluorethanol, is explained by the first buffer being a tertiary nitrogen nucleophile and the last one an oxygen nucleophile, which is frequently described as an outlier in Brönsted plots. This value may indicate a nucleophilic catalysis, since Brönsted β values higher than 0.8 are characteristic of nucleophilic catalysed reactions. In fact, these processes have β values usually higher than the ones obtained for general base catalysed reactions, for which β between 0.4 and 0.7 are to be expected.[12]

As already said, the Brönsted parameter seems to point to a nucleophilic catalysed reaction in this case and so does the solvent isotope effect which is also an effective parameter to distinguish between a general base and a nucleophilic catalysed reaction. Comparison of catalysis in piperidine buffer, both in water and deuterated water for compound **2** gives, a value of 1.16 which is consistent with a rate determining step of attack of hydroxide on the neutral substrate[13] (Figure 4).

Comparison of k_3 for compounds **1a**-**e** give rise to a Hammett plot with a ρ value of 0.99 ($r^2 = 0.97$) which is also consistent with a $B_{Ac}2$ mechanism with nucleophilic catalysis,[8] where the rate determining step is the hydroxide attack on the neutral substrate.

Finally, another important evidence in favor of the mechanism of hydrolysis via a nucleophilic catalysis, where the base directly attacks the substrate in the rate determining step, is the formation of *N*-methyl-1-(piperidin-1-ylcarbonyl)-1*H*-benzimidazol-2-amine (**3**) which must be the result of the trapping of the reactive intermediate.



3

Hydrolysis in intermediate media

Reaction occurring in the intermediate pH region can be explained by one of two possibilities, related to the co- existence of both the neutral and the protonated species in this pH range. The two possibilities are the bimolecular attack of water to the neutral species (k_2) or of hydroxide to the protonated species ($k_{2'}$). Data adjustment to equations 1 and 2 or 2' in the Hammett plot gives rise to correlations which are better using a σ^- (1.27, R^2=0.95 for k_2 and 1.20, R^2=0.61 for k_2') than a σ value (1.82, R^2=0.88 for k_2 and 1.72, R^2=0.57 for k_2'). The results obtained point to a rational use of equations 1 and 2 for the data adjustment in this pH range. Correlation with σ seems surprising in this case since it is commonly used when there is substantial bond cleavage and significant increase in negative charge in carbamate O atom (*e.g.* E1cB mechanism). One explanation may be the presence of the rather electron-withdrawing benzimidazole group which increases the electron-delocalization in the substrate. With the formation of the tetrahedral intermediate the delocalization is modified, resulting in a great change in the electron density residing in the phenol oxygen.[4] A similar correlation with σ^-, this time of k_3, gave rise to a low ρ value (0.67, R^2=0.98) which is not easily explained by a rate limiting bimolecular process.

Thus in the intermediate region, reaction seems to occur by a much similar mechanism to the one acting in basic media, but with water acting as nucleophile. The higher ρ value, when compared with the one obtained in basic media can be explained by the much higher sensitivity of the

reaction to the substituent when water, which is a weaker nucleophile than hydroxide, is the attacking agent. The same sort of effect was observed for the hydrolysis of phenyl acetates by imidazole.[14] As to the leaving group ability, as pH increases the amount of protonation on the benzimidazole moiety decreases significantly and this moiety is no longer a good leaving group.

The above considerations led us to propose the mechanism depicted in Scheme 1 for the hydrolysis of benzimidazolylcarbamates.

Experimental

Melting points are uncorrected. All solvents and reagents were obtained from commercial suppliers and were used without further purification except THF and pyridine, which were freshly distilled from sodium benzophenone ketyl and potassium hydroxide, respectively. IR spectra were obtained using a Hitachi 270-50 spectrophotometer on KBr pastille and only diagnostic bands are reported on a cm^{-1} scale. ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100.4 MHz, respectively, in chloroform-*d* or d_6 DMSO as solvents, and chemical shifts are reported in parts per million (ppm, δ), using as reference the appropriate signal for residual solvent protons. Coupling constants are reported to the nearest 0.1 Hz. HMQC and HMBC correlations enabled the correct peak assignment.

HR-MS were performed by EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea, UK and elemental analysis was performed in Medac.Ltd, Brunel Science Centre, UK. Crystal X-ray diffraction was performed by EPSRC National Mass Crystalography Service, University of Southampton. Column chromatographies were carried out using 230-400 mesh silica gel. Thin-layer chromatography were performed on pre- coated silica- gel plates and spots were visualized by UV light (254 nm)

Benzimidazolyl carbamates were prepared by one of the following methods

Method A

2-aminobenzimidazole (1.0 g; 7.5 mmol) was dissolved in anhydrous pyridine and the corresponding chloroformate (7.5 mmol) added drop wise. The reaction was carried in an ice bath for approximately 30 minutes. The reactional crude was washed with cold water (*ca*. 30 cm^3); the white solid which precipitated was filtered off, washed with ethanol and diethyl ether and purified by column chromatography.

Method B

2-methylaminobenzimidazole (1.0 g; 7.5 mmol) was dissolved in anhydrous acetonitrile and K_2CO_3 (7.5 mmol) added, followed by addition drop wise of phenyl chloroformate (7.5 mmol). The reaction was allowed to proceed at r.t. for 3 hours. The residue was poured in cold water (*ca*. 30 cm^3); the white solid was filtered off, washed with ethanol and diethyl ether and purified by column chromatography.

*Phenyl 2-amino-1H-benzimidazole-1-carboxylate (**1a**)*

Method A

White crystals mp > 320 dec. (methanol); η = 7%; IR(KBr) ν_{max}/cm^{-1}: 3429, 1735; δ_H (400 MHz, $CDCl_3$) 7.79 (1H, d, *J* 8.0 Hz, H-7 *Benzim*), 7.51 (2H, t, *J* 8.0 Hz, *Ph*), 7.39 (1H, m 4-H, H-4 *Benzim*), 7.32 (1H, d, *J* 8.0 Hz, H-6 *Benzim*), 7.26 (3H, m, *Ph*), 7.12 (1 H, t, *J* 7.6 Hz, H-5 *Benzim*), 6.35 (2H, s_b N$\underline{H}_2$); δ_C (100.4 MHz, $CDCl_3$) 153.5 (C-2 *Benzim*), 149.7(C=O), 149.6 (C-1 *Ph*), 142.9 (C-8 *Benzim*), 129.9 (C-9 *Benzim*), 129.7 (C-3/ C-5 *Ph*), 126.8 (C-4 *Ph*), 124.5 (C-6 *Benzim*), 121.9 (C-2/ C-6 *Ph*), 120.1 (C-5 *Benzim.*), 115.6 (C-4 *Benzim.*), 114.0 (C-7 *Benzim.*); EI- MS 253 $[M]^+$, 160, 159, 132, 105, 94, 90, 77; HR-MS (ESI) 254.0920 (254.0924 $[M+H]^+$ for $C_{14}H_{12}N_3O_2$).

*4-Methylphenyl 2-amino-1H-benzimidazole-1-carboxylate (**1b**)*

Method A

White yellowish crystals mp > 320 dec. (ether/ acetonitrile); η = 31%; IR ν_{max}/cm^{-1}: 3440, 1739; δ_H (400 MHz, $CDCl_3$) 7.78 (1H, d, *J* 8.0 Hz, H-7 *Benzim.*), 7.38 (1H, d, *J* 7.4 Hz, H-4 *Benzim.*), 7.28 (2H, m, H-3 *Ph/* H-5 *Ph.*), 7.26 (1H, m, H-6 *Benzim.*), 7.19 (2H, d, *J* 8.4 Hz, H-2/ H-6 *Ph.*), 7.11 (1H, ddd, *J* 1.2; 7.4; 7.6 Hz, H-5 *Benzim.*), 6.62 (2H, s_b, N$\underline{H}_2$) 2.35 (3H, s, C$\underline{H}_3$); δ_C (100.4 MHz, $CDCl_3$) 153.6 (C-2 *Benzim.*), 150.9 (C=O), 147.4 (C-1 *Ph*), 142.4 (C-8 *Benzim.*), 136.9 (C-4 *Ph*), 130.4 (C-3/ C-5 *Ph*), 129.9 (C-9 *Benzim.*), 125.1 (C-6 *Benzim.*), 121.2 (C-2/ C-6 *Ph*), 121.2 (C-5 *Benzim.*), 116.7 (C-4 *Benzim.*), 114.3 (C-7 *Benzim.*), 21.0 ($\underline{C}H_3$); EI- MS $[M]^+$ 267, 160, 159, 132, 90, 77, 65, 51; $C_{15}H_{13}N_3O_2$ calcd. C 67.41, H 4.90, N 15.72; found C 67.22, H 4.85, N 15.76.

*4-Methoxyphenyl 2-amino-1H-benzimidazole-1-carboxylate (**1c**)*

Method A

Column chromatography hexane/ ethyl acetate 45: 55. White crystals mp > 320 dec. (ethanol); η = 52%;

IR (KBr) ν_{max} /cm^{-1}: 3462, 1735; δ_H (400 MHz, $CDCl_3$) 7.78 (1 H, d, *J* 8.0 Hz, H-7 *Benzim.*), 7.38 (1 H, d, *J* 7.6 Hz, H-4 *Benzim.*), 7.26 (1H, ddd, *J* 1.2, 7.4, 8.0 Hz, H-6 *Benzim.*), 7.23 (2 H, d, *J* 9.0 Hz, H-3/H-5 *Ph*), 7.13 (1H, ddd, *J* 1,2; 7.4; 7.6 Hz, H-5 *Benzim.*); 6.99 (2 H, d, *J* 9.0 Hz, H-2/H-6 *Ph*), 6.50 (2 H, s_b, N$\underline{H}_2$), 3.85 (3 H, s, OC$\underline{H}_3$); δ_C (100.4 MHz, d_6 - DMSO) 153.5(C-2 *Benzim.*), 151.1 (C=O), 143.1 (C-1 *Ph*), 142.1 (C-8 *Benzim.*), 158.2 (C-4 *Ph*), 129.9 (C-9 *Benzim.*), 125.1 (C-6 *Benzim.*), 122.3 (C-2/ C-4 *Ph*), 121.2 (C-5 *Benzim.*), 116.7 (C-4 *Benzim.*), 114.8 (C-3/ C-5 *Ph*), 114.3 (C-7 *Benzim.*), 55.7 (O$\underline{C}$H$_3$). EI- MS 287 [M]$^+$, 160, 159, 132, 128, 105, 90, 63; HR-MS (ESI) 288.0530 (288.0534 [M+H]$^+$ for $C_{15}H_{14}N_3O_3$).

*4-Chlorophenyl 2-amino-1H-benzimidazole-1-carboxylate (**1d**)*

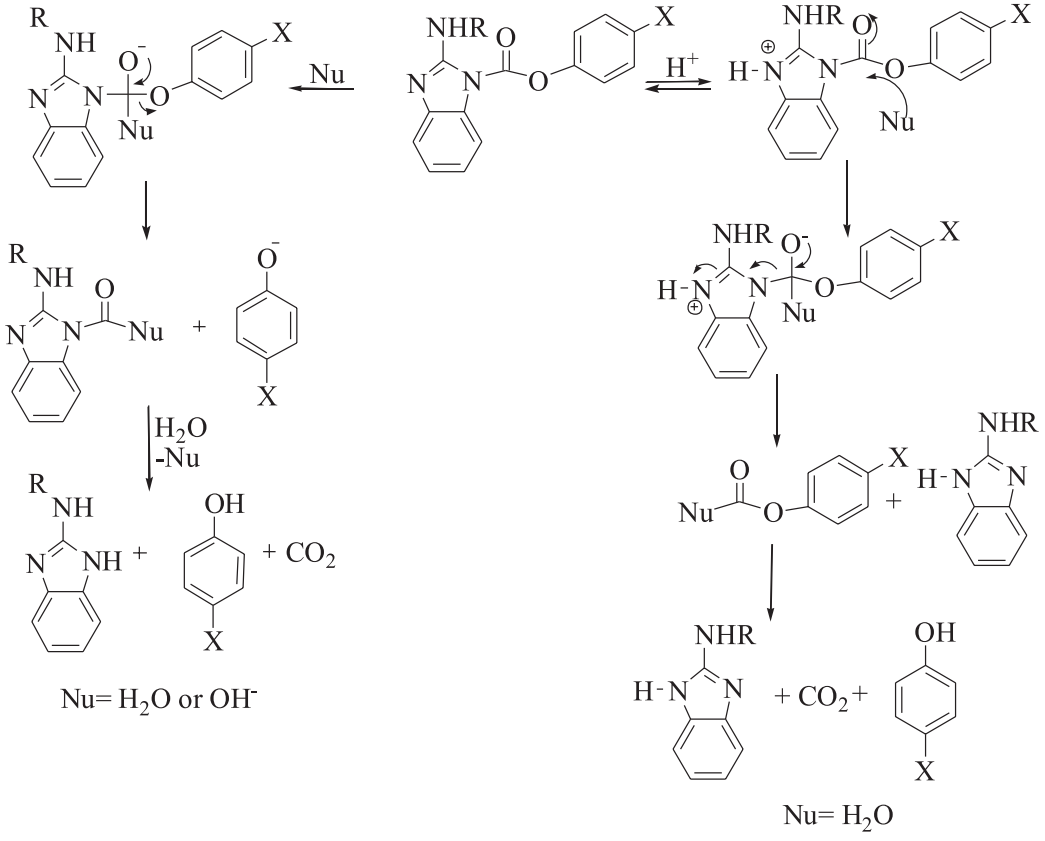
Method A

Column chromatography dicloromethane/ ethyl acetate 25: 75. White crystals mp > 320 dec. (ethanol/ THF); η = 10%; IR(KBr) ν_{max} /cm^{-1}: 3462, 1735; δ_H (400 MHz, $CDCl_3$) 7.75 (1 H, d, *J* 8.0 Hz, H-7 *Benzim.*), 7.47 (2H, d, *J* 8.8 Hz, H-3/ H-5 *Ph*), 7.39 (1 H, d, *J* 7.6 Hz, H-4 *Benzim.*), 7.28 (3H, m, H-6 *Benzim.*, H-2/ H-6 *Ph*), 7.12 (1H, ddd, *J* 1.2; 7.4; 7.6 Hz, H-5 *Benzim.*); δ_C (100.4 MHz, $CDCl_3$): 153.3 (C-2 *Benzim.*), 150.4(C=O), 148.0 (C-1 *Ph*), 142.4 (C-8 *Benzim.*), 132.7 (C-4 *Ph*), 130.0 (C-3, C-5 *Ph*), 129.8 (C-9 *Benzim.*), 125.3 (C-6 *Benzim.*), 122.8 (C-2/ C-6 *Ph*), 121.4 (C-5 *Benzim.*), 116.9 (C-4 *Benzim.*), 114.2 (C-7 *Benzim.*).; EI- MS 287 [M]$^+$, 160, 159, 132, 128, 105, 90, 63; HR-MS (ESI) 288.0530 (288.0534 [M+H]$^+$ for $C_{14}H_{11}N_3O_2Cl$.

*4-Nitrophenyl 2-amino-1H-benzimidazole-1-carboxylate (**1e**)*

Method A

Yellow crystals mp > 320 dec. (ether/acetonitrile); η = 10%; IR(KBr) ν_{max} /cm^{-1}: 3453, 1752; δ_H (400 MHz, d_6- DMSO) 8.41 (2 H, d, *J* 9.2 Hz, H-3/ H-5 *Ph*), 7.80 (2H, d, *J* 9.2 Hz, H-2/ H-6 *Ph*), 7.72 (1 H, d, *J* 8.0 Hz, H-7 *Benzim.*), 7.32 (2H, s_b, N$\underline{H}_2$), 7.25 (1H, d, *J* 7.6 Hz, H-4 *Benzim.*); 7.19 (1H, ddd, *J* 0.8; 7.2; 7.4 Hz, H-6 *Benzim.*), 7.04 (1H, ddd, *J* 1.2; 7.2; 7.2 Hz, H-5 *Benzim.*); δ_C (100.4 MHz, d_6- DMSO) 154.2 (C-1 *Ph*), 153.5 (C-2 *Benzim.*), 148.4 (C=O), 145.7 (C-4 *Ph*), 143.1 (C-8 *Benzim.*), 129.9 (C-9 *Benzim.*), 125.3 (C-3/ C-5 *Ph*), 124.5 (C-6 *Benzim.*), 123.6 (C-2/ C-6 *Ph*), 120.1 (C-5 *Benzim.*), 115.6 (C-4 *Benzim.*), 114.1 (C-7 *Benzim.*).; EI- MS 298 [M]$^+$, 160,



Scheme 1. Pathways for the hydrolysis of compounds **1a-d** and **2** both in acidic and basic media.

159, 139, 133, 105, 90, 63; HR- MS (EI) 298.06925 (298.06957 $[M]^+$ for $C_{14}H_{10}N_4O_4$).

*4-Phenyl 2-(methylamino)-1H-benzimidazole-1-carboxylate, (**2**)*

Method B

Column chromatography hexane/ ethyl acetate 3:7. White crystals mp 165.5-166.6 dec. (ethanol/dichloromethane), η = 41%; IR(KBr) ν_{max} /cm^{-1}: 3390, 1732, 1635; δ_H (400 MHz, d_6-DMSO) 7.72 (1 H, d, *J* 7.6, H-7 *Benzim.*), 7.53 (2H, AA'XX', H-3/H-5 *Ph*), 7.49 (2H, AA'XX', H-2/ H-6 Ph), 7.39 (1 H, m, H-4 *Ph*), 7.32 (1H, d, *J* 7.6 Hz, H-4 *Benzim.*), 7.19 (1H, ddd, *J* 1.2; 7.6, 7.6, H-6 *Benzim.*), 7.04 (1H, ddd, *J* 1.2; 7.6, 7.6 Hz, H-5 *Benzim.*), 3.02 (3H, d, *J* 4.8 Hz, $NC\underline{H}_3$); δ_C (100.4 MHz, d_6-DMSO) 153.9 (C-2 *Benzim.*), 149.6 (C-1 *Ph*/ C=O), 143.0 (C-8 *Benzim.*), 130.5 (C-9 *Benzim.*), 129.7 (C-3/ C-5 *Ph*), 127.0 (C-4 *Ph*), 124.4 (C-6 *Benzim.*), 121.9 (C-2/ C-6 *Ph*), 120.1 (C-5 *Benzim.*), 115.8 (C-4 *Benzim.*), 114.0 (C-7 *Benzim.*), 29.5 ($N\text{-}\underline{C}H_3$); EI- MS 268 $[M]^+$, 173, 146, 118, 90, 77; HR- MS (EI) 268.1083 (268.1081 $[M]^+$ for $C_{15}H_{13}N_3O_2$).

Kinetics

Kinetic runs were carried out in thermostated quartz cells, and were triggered by injecting a small aliquot of an acetonitrile solution of substrate into the reaction mixture, making the final concentration 1.10^{-5} mol dm^{-3} in an acetonitrile-water 20% (v/v) solution. Reactions were monitored with an UV spectrophotometer Shimadzu 1603 at 25 ± 0.1 °C , following either the decomposition of the substrate or the formation of the corresponding phenol and exhibited clear isosbestic points. For all compounds, pseudofirst-order rate constants were obtained from plots of ln $(A_t\text{-}A_\infty)$ for the decomposition of the substrate or ln $(A_\infty\text{-}A_t)$ for the formation of the product. The ionic strength of the reactions was kept constant at 0.5 mol dm^{-3} by addition of $NaClO_4$. pH measurement was made with an Orion Research Digital ionanalyser with a KCl/ AgCl electrode. Under the experimental conditions used, the reactions were found to follow first-order kinetics with respect to the substrate up to at least 90% completion of the reaction. In the study of acidic and neutral hydrolysis of substrates **1d** and **2**, whenever k_{obs} was lower than $2\ 10^{-5}$ s^{-1}, the initial rate method was used.

*N-Methyl-1-(piperidin-1-ylcarbonyl)-1H-benzimidazol-2-amine (**3**)*

Compound 2 (0.110 g; 0.4 mmol) was hydrolised in piperidine buffer pH 11.3 ($[Buffer]_{total}$= 1.0 mol dm^{-3}) in the same conditions of the kinetic assays (20% acetonitrile/ water, 25 ºC, μ= 0.5 mol dm^3 $NaClO_4$). The reaction was carried out for 24 hours. The pH of the reaction mixture was neutralized with HCl 1 mol dm^{-3}. The solvent was evaporated to dryness and the solid residue was extracted with acetonitrile. A solid-liquid extraction was performed and the organic phase was dried with Na_2SO_4, filtered off and evaporated to dryness. The presence of compound **3** was detected by TLC (AcOEt) and identified by HR-MS (ESI) 258.14732 (258.147512 M^+ for $C_{14}H_{18}N_4O$).

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