Synthesis and morpholinolysis of *N,N*-diethyl carbamate derivatives of 4- HOAt, 7-HOAt and HOBt

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N,N-Diethyl carbamates of 1-hydroxy-7-azabenzotriazole (7-HOAt), 1-hydroxy-4-azabenzotriazole (4-HOAt), 1-hydroxybenzotriazole (HOBt), and 1-hydroxypyrrolidine-2,5-dione have been synthesised. The reactivities of these active esters have been determined by studying the kinetics and mechanism of their morpholinolysis in acetonitrile at different temperatures.

Keywords: 1-hydroxy-7-azabenzotriazole (7-HOAt), 1-hydroxy-4-azabenzotriazole (4-HOAt), 1-hydroxybenzotriazole (HOBt), morpholinolysis, morpholin-1-yl carbamate derivatives, four-membered transition state

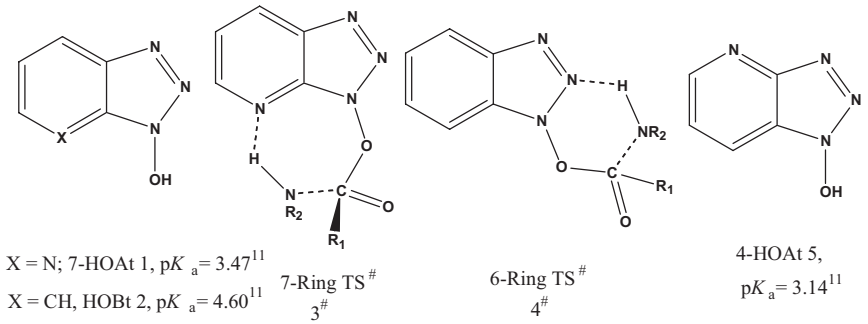

Fig. 1

Recently, 1-hydroxy-7-azabenzotriazole (7-HOAt) **1** and its derived phosphonium and uranium/guanidinium salts[1-3] have been described as more favourable coupling additives or reagents for both solution-[4] and solid-phase syntheses.[5]

Previous study has reported that 7-HOAt **1** is more efficient than HOBt **2** as a peptide coupling additive.[1,6] This is explained by the internal-base catalysed process implied by the 7-membered ring transition state[7] **3**# which was suggested to be more favourable than the 6-membered ring-one **4**#.[8,9] Alternatively, the special properties of the aza atom of the pyridine moiety, with its electron-withdrawing properties could provide a better leaving group and thus increased reactivity for the derived *O*-acyl ester towards nucleophilic reaction.[10] Although the latter effect can explain the increase in reactivity observed for 7-HOAt over HOBt, it cannot explain the smaller loss of configuration observed for 7-HOAt relative to both HOBt and 4-HOAt *O*-acyl esters. The reactivity of the three coupling additives **1, 2, 5** was compared for a system in which neighbouring group effects cannot be involved.[7] The S_N2 demethylation of the methyl ethers of the three isomers, in which the order of reactivity should be determined only by the leaving group ability, followed the order of acidity of the isomers. As expected the speed of S_N2 demethylation is correlated to the acidity of the HOXt system, with the most acidic derivative providing for the highest reactivity.[7] This is consistent with the pK_a values for 7-HOAt **1**, HOBt **2**, and 4-HOAt **5** as being 3.47, 4.6, and 3.14 respectively.[11]

On the other hand, the aminolysis reactions of aryl carbamate have been less studied kinetically.[12,13] The aminolysis mechanism of aryl carbamate **6** is quite similar to that of aryl carbonate **7** and aryl esters **8**. A change in the mechanism of aminolysis from stepwise through a zwitterionic tetrahedral intermediate or a concerted one has been reported and depends on the nature of amine, solvent and the reactivity of the substrate.

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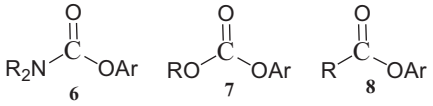


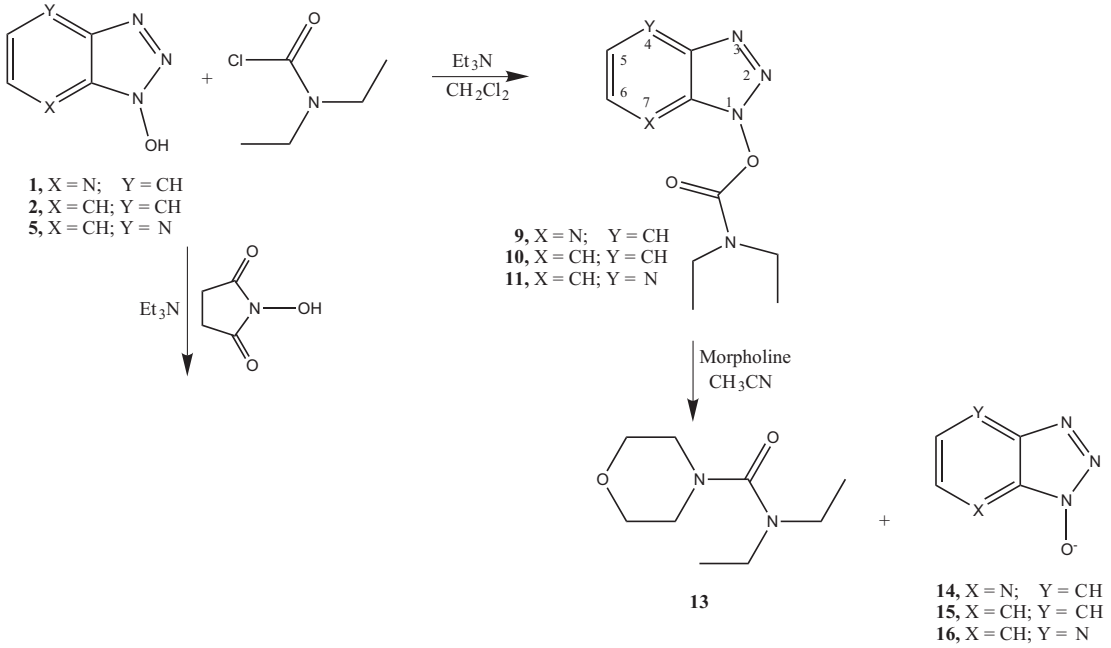
Fig. 2

The present work reports the synthesis of *N,N*-diethyl carbamate derivatives **9-12** of 1-hydroxy-7-azabenzotriazole (7-HOAt) **9,** 1-hydroxybenzotriazole (HOBt) **10**, 1-hydroxy-4-azabenzotriazole (4-HOAt) **11**, and 1-hydroxy-pyrrolidine-2,5-dione **12** and their reactions with morpholine chosen because it posses a comparable pK_a value to those reported for many amino acids and peptides[14] (Scheme 1). Further purposes of this study are to postulate the morpholinolysis mechanism and to examine the effect of the nature of the leaving group on the reactivity of the active esters **9–11,** Scheme 1.

Results and discussion

The active esters **9–11** can be readily prepared by the reaction of *N,N*-diethyl carbamoyl chloride with 1-hydroxy-7-azabenzotriazole (7-HOAt) **1**, 1-hydroxybenzotriazole (HOBt) **2** and 1-hydroxy-4-azabenzotriazole (4-HOAt**) 5** in methylene chloride, in the presence of two equivalents of triethylamine (TEA) at 0°C, with stirring for 3 h at room temperature (Scheme 1). The structures of compounds **9–11** were confirmed by elemental analysis and IR and NMR spectroscopy (Tables 1 and 2).

The IR spectra of **9**, **10** and **11** show sharp peaks at wave numbers 1781, 1770, and 1775 cm^{-1} respectively, corresponding to the C=O group. The ^1H NMR spectra of **9**, **10** and **11** in $CDCl_3$ show two triplet peaks in the range δ 1.20–1.26 and 1.36–1.45 ppm, and two quartet peaks in the range δ 3.39–3.45 and 3.56–3.64 ppm. The protons of one *N*-ethyl group are relatively shielded presumably because they are located in the cone field (anisotropic effect) of the carbonyl group (Fig. 3). The energy minimisation of compound **9** was processed utilising PM3/MOPAC[15]. Compounds **9** and **11**



Scheme 1

Table 1 Yields, colour, m.p.s., and elemental analyses of compounds **9–13**

Cpd	Yields/%	Colour	m.p./°C	Elemental analysis, Calc. (found)		
				C(%)	H(%)	*N*(%)
9	88	Colourless	65–66	51.06 (51.2)	5.57 (5.6)	29.77 (29.6)
10	84	Colourless	60–61	56.40 (56.6)	6.02 (5.9)	23.92 (23.8)
11	93	Colourless	61–62	51.06 (50.9)	5.57 (5.45)	29.77 (29.9)
12	94	Colourless	109–110	50.46 (50.6)	6.59 (6.7)	13.08 (12.95)
13	85	Colourless	oily	58.04 (58.2)	9.74 (9.9)	15.04 (14.8)

Table 2 ^{1}H and ^{13}C NMR data of compounds 9-13

Cpd	IR (KBr)/cm^{-1}	^{1}H NMR ($CDCl_3$) (δ)/ppm	^{13}C NMR ($CDCl_3$) (δ)/ppm
9	1781 (C=O)	1.26, 1.45 (2t, 6H, 2 CH_3, *J* = 7.2 Hz), 3.45, 3.64 (2 quart, 4H, 2 CH_2, *J* = 7.2 Hz), 7.40–7.44 (m, 1H, ArH), 8.40 (dd, 1H, ArH, *J* = 8.4 Hz, *J* = 1.6 Hz), 8.74 (dd, 1H, ArH, *J* = 4.8 Hz, *J* = 1.6 Hz)	13.2, 14.3, 42.6, 44.2, 120.9, 129.6, 135.2, 141.1, 151.7, 151.8
10	1770 (C=O)	1.23, 1.38 (2t, 6H, 2 CH_3, *J* = 7.7 Hz), 3.41, 3.57 (2 quart, 4H, 2 CH_2, *J* = 7.7 Hz), 7.37 (t, 1H, ArH, *J* = 7.7 Hz), 7.45-7.52 (m, 2H, ArH), 8.01 (d, 1H, ArH, *J* = 8.4 Hz)	13.2, 14.4, 42.5, 44.1, 108.75, 120.5, 124.8, 128.7, 129.2, 143.6, 151.8
11	1775 (C=O)	1.20, 1.36 (2t, 6H, 2 CH_3, *J* = 7.6 Hz), 3.39, 3.56 (2 quart, 4H, 2 CH_2, *J* = 6.9 Hz), 7.48 (dd, 1H, ArH, *J* = 9.2, 4.6 Hz), 7.90 (d, 1H, ArH, *J* = 9.2 Hz), 8.74 (d, 1H, ArH, *J* = 4.6 Hz)	(HMQC): 13.1 (CH_3), 14.3 (CH_3), 42.4 (CH_2), 44.1 (CH_2), 118.2 (CH, ArH at 7.90), 121.85 (C, ArH), 123.4 (CH, ArH) at 7.48), 149.1 (CH, ArH at 8.74), 151.4 (C, ArH), 154.2 (C=O)
12	1759 (C=O), 1742 (C=O)	1.20, 1.29 (2t, 6H, 2 CH_3, *J* = 6.8 Hz), 2.81 (s, 4H, 2 CH_2), 3.39 (m, 4H, 2 CH_2)	13.25, 14.0, 25.7, 42.3, 43.8, 151.2, 170.1
13	1638 (C=O)	1.10 (t, 6H, 2 CH_3, *J* = 6.9 Hz), 3.19 (m, 8H, 4 N-CH_2), 3.67 (t, 4H, 2 O-CH_2, *J* = 4.6 Hz)	

show three peaks corresponding to their three aromatic protons: The more deshielded protons of the pyridine nucleus resonated at 8.74 ppm corresponding to H-6 and H-5 for compounds **9** and **11** respectively because they are adjacent to the pyridine *N*-atom. Also unusually low *ortho*-coupling constants, $J_{5,6}$ = 4.8 and 4.6 Hz for compounds **9** and **11** respectively are observed; this is probably due to bond localisation in the pyridine ring.[16] The multiplet peak at 7.40–7.44 and the doublet peak at 7.48 ppm are analogous to H-5 and H-6 for compounds **9** and **11** respectively. While the remaining protons of the pyridine moiety resonate at δ 8.40 and 7.90 ppm corresponding to H-4 and H-7 for compounds **9** and **11** respectively. The ^{13}C NMR spectra of **9** and **11** each show ten resolved carbon signals: Four in the sp^3-carbon region, five in the aromatic carbon region and the carbonyl signals at δ 151.8 ppm and δ 154.2 ppm respectively. The HMQC of **11** confirms that the carbon signal at δ 118.2 ppm corresponds to the doublet CH signal at δ 7.90 ppm, whereas the carbon signal at δ 123.4 ppm corresponds to the doublet of doublet CH signal at δ 7.48 ppm and the carbon signal at

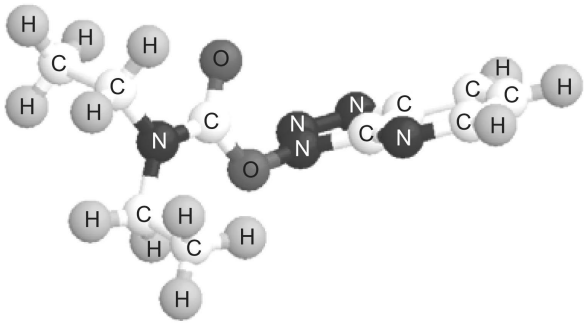


Fig. 3

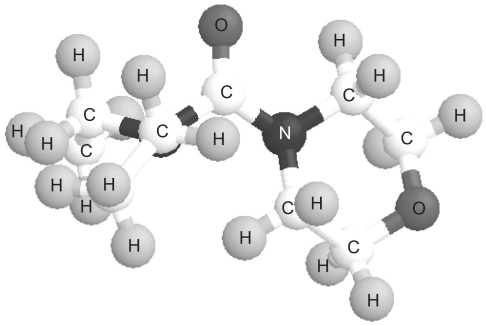


Fig. 4

δ 149.1 ppm corresponds to the doublet CH signal at δ 8.74 ppm. Compound **10** shows three peaks corresponding to the four aromatic protons and its ^{13}C NMR spectrum shows 11 resolved carbon signals: Four in the sp^3-carbon region, six in the aromatic carbon region and the carbonyl signal at δ 151.8 ppm.

The reaction of *N,N*-diethyl carbamoyl chloride with 1-hydroxy pyrrolidin-2,5-dione in the presence of triethylamine under the previous conditions gave diethylcarbamic acid 2,5-dioxopyrrolidin-1-yl ester **12** as indicated from its elemental analysis and IR and NMR spectrum (Tables 1 and 2). The ^1H NMR spectrum of compound **12** shows two triplet peaks at δ 1.20 and 1.29 ppm corresponding to the two CH_3 groups. It also shows a singlet peak at δ 2.81 and a multiplet peak at 3.39 ppm corresponding to the four CH_2 groups. Similarly, the chemical shift of both *N,N*-diethyl groups is affected by the anisotropic effect of the carbonyl group. The IR spectrum of **12** shows 2 peaks at 1759 and 1742 cm^{-1} corresponding to N–CO–O and the NC=O respectively. The ^{13}C NMR spectrum of **12** shows five resolved carbon signals in the sp^3-carbon region, and two carbonyl signal at δ 151.2 and 170.1 ppm corresponding to the N–CO–O and N–C=O respectively, indicating the only expected form, which is the *O*-acyl form. Compounds **9–11** are presumably in the *O*-acyl form rather than the *N*-acyl one[17,18] because their carbonyl absorptions occur at wave numbers near to that of compound **12**. This comes also from the coincidence of their ^{13}C nmr carbonyl group values in the range δ 151.8–154.2 ppm with that of **12** at δ 151.2 ppm confirming the *O*-acyl form.

The reaction of the aryl carbamate derivatives of 1-hydroxy-7-azabenzotriazole (7-HOAt) **9**, 1-hydroxybenzotriazole (HOBt) **10**, or 1-hydroxy-4-azabenzotriazole (4-HOAt) **11** with morpholine in acetonitrile afforded *N,N*-diethylmorpholine-4-carboxamide **13** (Scheme 1). The same product was also directly synthesised by the reaction of *N,N*-diethyl carbamoyl chloride with morpholine in methylene chloride. The elemental analysis of compound **13** indicates the replacement of the ester groups of compounds **9**, **10,** and **11** by the morpholin-1-yl group *via* a nucleophilic acyl substitution reaction. The IR spectrum of **13** shows a sharp peak at 1638 cm^{-1}, corresponding to the C=O group. The ^1H NMR spectrum of **13** shows one triplet at δ 1.10 ppm corresponding to the two CH_3 groups, one multiplet centred at δ 3.19 ppm corresponding to the four N–CH_2 groups (two CH_2–N of morpholinyl moiety and two CH_2 of *N,N*-diethyl moiety), and one triplet peak at δ 3.67 ppm corresponding to the two O–CH_2 groups. Interestingly, no difference is detected in the chemical shifts of both *N,N*-diethyl group protons which is in correspondence with the energy minimised calculation of compound **13** utilising PM3/MOPAC,[15] where the two ethyl groups are far from the cone field of the carbonyl group, Fig. 4.

The reactions of *N,N*-diethyl carbamates **9–11** with morpholine in acetonitrile at different temperatures (30–45°C) are measured spectrophotometically by monitoring the formation of 7-HOAt, HOBt, and 4-HOAt anions **14–16** at λ = 286, 317 and 275 nm respectively. The product **13** shows that compounds **9**, **10** and **11** undergo morpholinolysis of the ester group rather than the amide moiety indicating that $^-$OAt or $^-$OBt is the leaving group while –NEt_2 is the non leaving-one. The reaction obeys a clean second-order rate law, Eqn (2) and Eqn (3), where [Subs] and [Morph] are the concentrations of *N,N*-diethyl carbamate ester (**9**, **10** or **11**) and morpholine, respectively.

$$\text{Rate} = k_\Psi\,[\text{Sub}] \qquad (2)$$

$$k_\Psi = k_2\,[\text{Morph}] \qquad (3)$$

The second-order rate constant, k_2, summarised in Table 3 are obtained from a straight line plot of k_Ψ vs five to six [Morph], where k_Ψ is the pseudo-first-order rate constant. This indicates that the titled reactions are not amine catalysed. Thus, the morpholinolysis reaction is presumably proceeding concertedly which is in agreement with the typical mechanism of an ester and an amide. Table 3 reveals that the rate enhancement found of **11** (4-HOAt carbamate) relative to **9** (7-HOAt carbamate) and HOBt analogs **10** (HOBt carbamate) is in harmony with the order of p*K*a values of the liberated leaving groups.[7] Accordingly, this is consistent with increasing the stability of the leaving group anion liberated from **11** than **9** than **10** and is thus reflected in the faster morpholinolysis rate for **11** than for the corresponding **9** and **10**. Furthermore, the ratios $k_{4\text{-HOAt},\ \mathbf{11}}/k_{7\text{-HOAt},\ \mathbf{9}}$, $k_{7\text{-HOAt},\ \mathbf{9}}/k_{\text{HOBt},\ \mathbf{10}}$, $k_{4\text{-HOAt},\ \mathbf{11}}/k_{\text{HOBt},\ \mathbf{10}}$ at all temperatures are in the ranges (3.15–3.93), (1.37–1.70) and (4.6–6.10) respectively, Table 4. This indicates that the absence, the presence and the position of pyridine-N-atom as well as the pK_a of the leaving group have important effects on rates. Although, $k_{\mathbf{11}}/k_{\mathbf{9}}$ ratio is comparatively large, the pK_a difference of the leaving groups is quite small. Conversely, $k_{\mathbf{9}}/k_{\mathbf{10}}$ is lower, yet the pK_a difference is quite large. However, the $k_{\mathbf{11}}/k_{\mathbf{10}}$ ratio is higher than the other ratios while the difference of pK_a is relatively large. These data are presumably explained by the following concepts: the presence of the pyridine N-atom increases the rates of **11** and **9** more than **10** that contains no such atom, although the difference in pK_a values is quite high. The position of the pyridine N-atom is responsible for the increase in the rate of **11** more than for **9**, *i.e.* proximity effect of pyridine N-atom to the reaction centre, although the difference in pK_a is small, Table 4.

Further support for the concerted mechanism is provided by the high negative entropy of activation (Table 3), which is similar to that reported for the reaction of substituted benzylamines with *N*-ethyl thiocarbamates in acetonitrile.[12] This predicts a proton transfer in the transition state and suggests a hydrogen bond by internal base catalysed process to form a four cyclic transition state (structure **17**$^{\#}$). The relatively small $\Delta H^{\#}$ values with large negative $\Delta S^{\#}$ values in

Table 3 Second-order rate constants[a] and activation parameters[b] for the reactions of 9, 10 and 11 with morpholine in acetonitrile

Cpd.	10^4 k_2 (dm^3 mol^{-1} s^{-1})				$\Delta H^{\#}$/kcal mol^{-1}	$-\Delta S^{\#}$[b]/e.u.
		30°C	35°C	40°C	45°C	
9	3.74 ± 0.04	4.95 ± 0.05	5.36 ± 0.05	6.74 ± 0.06	6.41 ± 0.90	53.06 ± 2.90
10	2.26 ± 0.02	2.92 ± 0.03	3.41 ± 0.06	4.92 ± 0.06	8.40 ± 1.10	47.58 ± 3.40
11	13.79 ± 0.07	15.58 ± 0.01	18.44 ± 0.01	22.52 ± 0.02	5.57 ± 0.60	38.06 ± 3.30

[a]Correlation coefficient was 0.99 in most cases.
[b]Calculated by the Erying equation.

Table 4 Ratios between the second order constants of **9**, **10** and **11** and ΔpK_a of **1**, **2**, and **5**

Compounds	Ratio	ΔpK_a
11/9	3.15–3.93	0.13
9/10	1.37–1.70	0.33
11/10	4.60–6.10	0.53

Table 3 are in agreement with the proposed four-membered transition state[12] (structure **17**$^{\#}$). The $\Delta H^{\#}$ values are small due to a larger energy gain in C–N bond formation relative to the energy loss in C–O bond cleavage by the hydrogen bonding and the $\Delta S^{\#}$ values are largely negative due to the strained hydrogen bonded four-membered transition state **17**$^{\#}$.

Inspection of Table 3 shows that the reaction of morpholine with **9** gave a large negative $\Delta S^{\#}$ compared with those obtained from the reactions with **10** and the most reactive compound **11**. This is presumably attributed to the involvement of amine hydrogen in hydrogen bonding with the ester oxygen and the more electronegative pyridine N-atom[17] giving a more ordered transition state (structure **17a**$^{\#}$). The charges on the N-atoms are estimated utilising PM3/MOPAC.[15] While such hydrogen is probably bonded to the less electron density N-2 atom[15] in case of compound **10** and **11,** reflecting less negative $\Delta S^{\#}$ values (structures **17b**$^{\#}$ and **17c**$^{\#}$). The higher $\Delta S^{\#}$ value for **11** (*i.e.* contains pyridine N-4 atom) than **9** (*i.e*. contains pyridine N-7 atom) is presumably due to the lower electron density of the N-2 than that of N-7 which weakens the hydrogen bond between the amine hydrogen and N-2 in structure **17c**$^{\#}$.

In summary, we propose a concerted mechanism with a hydrogen bond cyclic transition state **17**$^{\#}$**a–c** for the morpholinolysis of **9–11** in acetonitrile on the basis of an uncatalysed reaction with relatively low $\Delta H^{\#}$ values with large negative $\Delta S^{\#}$ values. Also, (a) a strong push provided to expel the 7-OAt$^-$, 4-OAt$^-$ or OBt$^-$ by the nonleaving group –N(Et)$_2$, Scheme 1, (b) a destabilisation of the intermediate **17**$^{\#}$**a–c** by a powerful expulsion of the amine group,[19] and (c) the pyridine-N-atoms as well as the ability of the leaving group to depart play an important role in rate determination.

Experimental

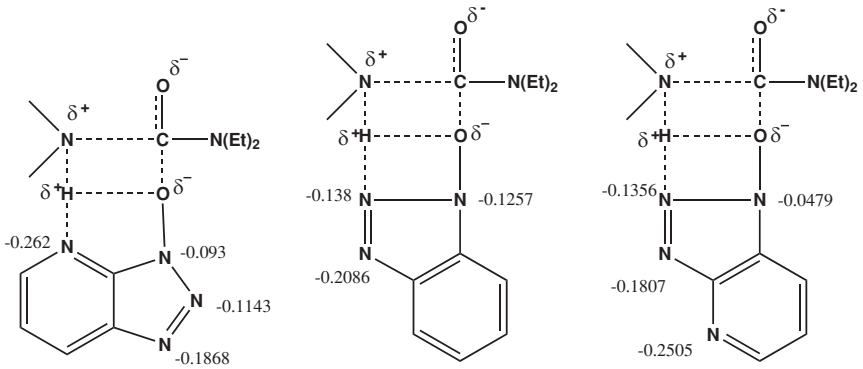
Materials

The solvents used for kinetic runs were reagent grade (BDH) and further purifications were carried out. Acetonitrile was used after distillation from K_2CO_3 anhydrous. Morpholine (99%) was used after distillation. Melting points were determined with a Mel-Temp apparatus and are uncorrected. Magnetic resonance spectra (^{1}H NMR and ^{13}C NMR spectra) were recorded on a Joel 500 MHz spectrometer with chemical shift values reported in δ units (part per million) relative to an internal standard. IR data were obtained on a Perkin–Elmer 1600 series Fourier transform instrument as KBr pellets. UV data were recorded on a Shimadzu (UV-160A) UV-Visible recording spectrophotometer. Elemental analyses were carried out at the Microanalytical Laboratories of the Beirut Arab University, Lebanon. The found values were within ± 0.3% of the theoretical values. The reactions were followed and the purity of the compounds checked by TLC on silica gel-protected aluminium sheets (Type 60 GF254, Merck) and the spots were detected by exposure to UV-lamp at λ 254 nm for few seconds. The compounds were named using Chem. Draw Ultra version 9, Cambridgesoft Corporation.

CAUTION: Acetonitrile is toxic to humans. Inhalation of acetonitrile may cause irritation of mucous membranes and higher concentrations can produce flushing of the face, chest tightness, weakness, nausea, vomiting, convulsions, shortness of breath and death. Acetonitrile vapour can cause redness of the eyes. *N,N*-Diethyl carbamoyl chloride can cause eyes, skin, nose, throat, respiratory system irritation; eye, skin burns; cough, wheezing, larnygitis, dyspnea; headache, nausea, vomiting; liver injury (potential occupational carcinogen). Morpholine can affect breathing and is an irritant, a skin allergen and a corrosive chemical.

General procedure for the preparation of N,N-diethyl-carbamate derivatives **9-12**

N,N-Diethylcarbamoyl chloride (10 mmol) was added to a mixture of (10 mmol) of 1-hydroxy-7-azabenzotriazole (7-HOAt) **1,** 1-hydroxybenzotriazole (HOBt) **2**, 1-hydroxy-4-azabenzotriazole (4-HOAt) **5**, or 1-hydroxy-pyrrolidine-2,5-dione and of triethylamine (Et_3N) (2.8 ml (20 mmol)) at 0°C in 5 ml methylene chloride. The reaction mixture was then stirred for 3 h at room temperature. The reaction mixture was diluted with 80 ml methylene chloride, and the mixture was washed with saturated sodium bicarbonate solution (2 × 10 ml), saturated sodium chloride solution (2 × 10 ml) and water (2 × 10 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure.



17a$^{\#}$**, 9,** $\Delta S^{\#}$**= –53.06** **17b**$^{\#}$**, 10,** $\Delta S^{\#}$**= –47.58** **17c**$^{\#}$**, 11,** $\Delta S^{\#}$**= –38.06**

Fig. 5

The crude product was purified by column (ethyl acetate/hexane, 1 : 2) or recrystallised from benzene/petroleum ether. The physical properties, elemental analysis and IR and NMR data are given in Tables 1 and 2.

N,N-*Diethylmorpholine-4-carboxamide* **13**: *N,N*-Diethyl carbamoyl chloride (2.6 ml, 20 mmol) was added to a solution of morpholine (3.5 ml, 40 mmol) dissolved in methylene chloride (5 ml) at 0°C. The reaction mixture was stirred for 3 hours at room temperature. It was diluted with 80 ml methylene chloride and then washed with saturated sodium bicarbonate solution (2 × 10 ml), saturated sodium chloride solution (2 × 10 ml) and water (2 × 10 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by column (ethyl acetate/hexane, 1 : 2). The physical properties, elemental analysis and IR and NMR data are given in Tables 1 and 2.

Kinetic measurements

The kinetics of **9**, **10** and **11** with morpholine in acetonitrile (CH_3CN) were measured spectrophotometrically using a Shimadzu (UV-160A) spectrophotometer in conjunction with a Shimadzu thermo bath (TB-85). Temperature control (± 0.1°C) was attained by circulating water through cell compartments. The kinetic runs were carried out at four temperatures (30–45°C) in acetonitrile. The rate constants for the reactions of **9–11** with morpholine were measured spectrophotometically by following the formation of 7-HOAt, HOBt and 4-HOAt anions **14**, **15** and **16** at λ = 286, 317 and 275 nm respectively. All reactions were carried out under pseudo-first-order conditions, with various concentrations of morpholine (0.794-1.587 mol dm^{-3}) and concentrations of substrates **9**, **10** or **11** of 5×10^{-4} mol dm^{-3}. The pseudo-first-order rate constants k_Ψ were determined by applying Eq.(4).

$$\log(A_t - A_\infty) = \frac{-k_\Psi t}{2.303} + \log (A_0 - A_\infty) \qquad (4)$$

Where A_0, A_t and A_∞ are the values of absorbance at zero time, time t, and at the end of the reaction. The A_∞ for each run was taken as the experimentally determined value, and k_Ψ is the pseudo-first-order rate constant. Second-order rate constants, k_2, were obtained from the slope of a plot of k_Ψ vs [morpholine] with more than five concentrations of morpholine.

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