N-Hydroxy-compounds as Acyl Transfer Agents. Part 1. Kinetics and Mechanism of Nucleophilic Displacements on 1-Hydroxybenzotriazole Esters and Crystal and Molecular Structure of 1-Benzoyloxybenzotriazole

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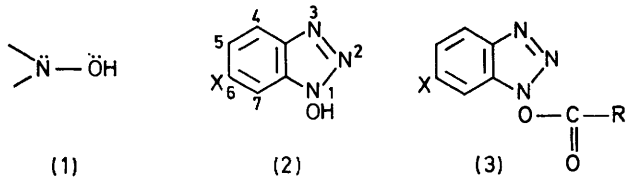
1-Hydroxybenzotriazole esters (3) show surprisingly rapid acyl transfer to HO^-, H_2O, and to primary amines; the reactions are *ca.* 10^3-fold faster than with *p*-nitrophenyl esters where the leaving group has a similar pK_a. The acylating ability of (3) is therefore akin to that of anhydrides or *N*-acylimidazoles. No evidence however was found to indicate that the esters exist in the *N*-acyl form (9) or (10) and an *X*-ray crystallographic study on (3; X = H, R = Ph) shows the *O*-acyl structure; in solution this ester retains the spectral characteristics of the solid. The ρ value for HO^- attack on (3; X = H), is +1.83 while electron-withdrawing substituents in the hydroxybenzotriazole leaving group also enhance the reactivity of the ester (ruling out a nitrenium ion mechanism). For aminolysis β_{Nuc} = 0.80 (primary amines) and 0.92 (α-effect amines). For water attack on (3; R = Ar), the Hammett ρ = +1.39, while k_{H_2O}/k_{D_2O} = 2.2 and general base catalysis by acetate ion and by tertiary amines (where β = 0.46) is observed. Carbonate esters (3; R = PhO) show similar enhanced reactivity as do *N*-protected amino-acid esters (3; R = $CH_2NHCO_2CH_2Ph$ or $CH_2NHCOPh$); the i.r. spectrum of the N-benzoyloxycarbonylglycine ester is unusual however in that no carbonyl absorptions >1 800 cm^{-1} were observed in the solid or solutions.

COMPOUNDS containing the *N*-hydroxy-functional group (1) have been widely used as acyl transfer agents in peptide synthesis. Thus, esters of 1-hydroxybenzotriazole [1] (2; X = H), 1-hydroxypiperidine,[2] *N*-hydroxysuccinimide,[3] and *N*-hydroxyphthalimide [4] react with amine nucleophiles under mild conditions to give peptides in high yields. It has also been found that addition of equimolar quantities of these materials to the conventional dicyclohexylcarbodi-imide (DCC) peptide coupling reaction increases the optical purity of the products, and inhibits formation of *N*-acylurea side products. The nucleophilic properties can be attributed to the fact that these materials are ' α-effect ' nucleophiles.[5] By analogy with the corresponding *C*-hydroxy compounds it would be expected that the leaving group ability of *N*-hydroxy-compounds would be determined to a great extent by the acidity of the O–H bond. Little kinetic data is available on the deacylation of *O*-acylhydroxylamine derivatives and the available data [6] do not permit general conclusions to be drawn on the leaving ability of the N–OH group.

A wide range of biological activities has been reported for substances containing the N–OH group.[7] This

[1] W. Konig and R. Geiger, *Chem. Ber.*, 1970, **103**, 788.
[2] B. O. Handford, J. H. Jones, G. T. Young, and T. F. N. Johnson, *J. Chem. Soc.*, 1965, 6814.
[3] G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, 1964, **86**, 1964.
[4] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, New York, 1967, vol. 1, p. 485.
[5] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, 1962, **84**, 16.
[6] (*a*) J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, 1964, **86**, 837; (*b*) P. G. Gassman and G. D. Hartman, *J.C.S. Chem. Comm.*, 1972, 853.
[7] R. T. Coutts, *Canad. J. Pharm. Sci.*, 1967, **1**, 27.

includes antitumour, antimalarial, and herbicide detoxification properties [8] for hydroxamic acid derivatives. In addition, the carcinogenic properties of certain amines and amides are attributed to initial *N*-hydroxylation.[9] This is followed by formation of an *N*-sulphate ester which on decomposition yields derivatives (possibly nitrenium ions) which induce tumour growth.[10] With a view to establishing the general reactivity of *O*-acylhydroxylamine derivatives in aqueous media we have investigated the kinetics of nucleophilic displacements on esters of 1-hydroxybenzotriazole (2; X = H) and report the crystal and molecular structure of 1-benzoyloxybenzotriazole (3; X = H, R = Ph).



(1) (2) (3)

RESULTS AND DISCUSSION

The esters (3) were synthesised by Schotten–Baumann acylation of 1-hydroxybenzotriazole with the corresponding benzoyl chloride in aqueous sodium hydroxide or by the dicyclohexylcarbodi-imide method. In aqueous dioxan at 25° rapid hydrolysis of the esters (3) occurs to give the corresponding benzoic acid and 1-hydroxybenzotriazole (2) over the pH range studied. A plot of the log of the pseudo-first-order rate constant (k_{obs}) against pH shows two distinct regions. Above pH 7 log k_{obs} is directly proportional to pH, and from pH 0—7 log k_{obs} is independent of pH (Figure 1).

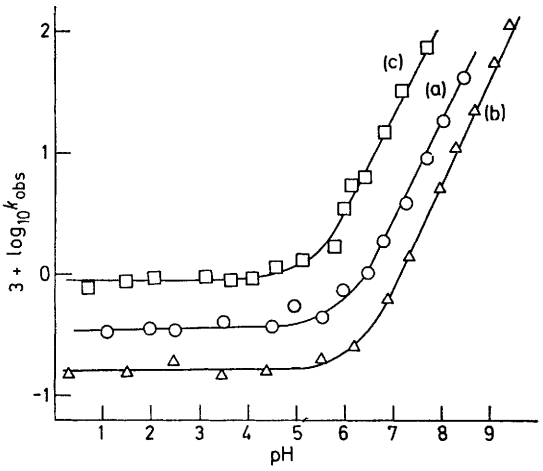


FIGURE 1 Plot of log k_{obs} against pH for hydrolysis of (3; X = H); (a) R = *p*-ClC$_6$H$_4$; (b) R = OPh; (c) R = CH$_2$NHCO$_2$CH$_2$Ph. The points are experimental and the curves are derived, drawn using equation (1) and the following values of the rate constants: (a) k_0 0.335 × 10^{-3}; k_2 16 × 10^3, (b) k_0 0.16 × 10^{-3}; k_2 3.63 × 10^3; (c) k_0 0.85 × 10^3 s^{-1}; k_2 1.15 × 10^5 l mol^{-1} s^{-1}

At high pH (>7) the rate of reaction increases with increasing electron-withdrawing power of substituents in the benzoate portion of the molecule (Table 1). A plot of log k_{obs} *versus* the σ values of McDaniel and Brown [11] gives ρ +1.83 (*r* 0.997). Thus at high pH rate-determining attack of hydroxide ion on the ester is occurring. This is comparable to the Hammett ρ values of 1.98—2.04 which have been observed for alkaline hydrolysis of phenyl-substituted benzoates.[12] Electron-withdrawing substituents in the 6-position of the fused aryl ring also increase the rate of hydroxide attack on the ester. At pH 8.3 k_{obs} for hydrolysis of (3; R = Ph, X = Br and NO_2) are 10^{-2} s^{-1} and 6 × 10^{-2} s^{-1} respectively.

TABLE 1

Observed first-order rate constants (s^{-1}) for the hydrolysis of substituted benzoyloxybenzotriazoles (3; X = H, R = Ar) in 1 : 4 dioxan–water at 25 °C (μ = 1.0; $NaClO_4$)

Ar	*p*-CH$_3$C$_6$H$_4$	Ph	*p*-ClC$_6$H$_4$
10^3k_{obs} [a]	2.18	3.96	12.6
10^3k_{obs} [b]	0.07	0.15	0.355
Ar	*m*-ClC$_6$H$_4$	*m*-NO$_2$C$_6$H$_4$	*p*-NO$_2$C$_6$H$_4$
10^3k_{obs} [a]	16.0	90.3	102.4
10^3k_{obs} [b]	0.51	1.58	2.0

[a] In 10^{-2}M-borax at pH 8.3; buffer catalysis was not observed under these conditions. [b] At pH 3.5 in the absence of buffers using Cary 14 pH stat assembly.

Over the entire pH range studied, the rates of hydrolysis of the esters (3) can be represented by equation (1), where k_{obs} = pseudo-first-order rate constant for the pH independent reaction and k_2 is the second-order rate constant for hydroxide attack on (3).

$$k_{obs} = k_o + k_2K_w/a_H \quad (1)$$

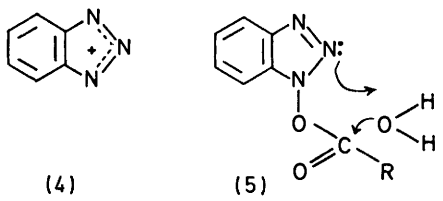
The carbonate ester (3; X = H, R = Ph) reacts faster with hydroxide ion than the benzoate ester by a factor of 1.3 (k_2 3 600 l m^{-1} s^{-1}). However this difference is much smaller than observed by Cooper for diphenyl carbonate which reacted faster than phenyl benzoate with hydroxide ion by a factor of 20.[13]

An interesting feature of the results obtained is the substantial pH independent rate of hydrolysis of esters (3) (Figure 1). For acyl benzoates this has been shown to involve general base catalysed water attack on the ester, and this type of mechanism is only found in esters possessing electron-withdrawing substituents in the acyl rather than the alcohol portion of the molecule.[14] At least three mechanisms can be considered for the pH independent reaction: (*a*) rate-determining cleavage of the N–O bond in the ester to give a nitrenium ion (4) and benzoate anion followed by fast reaction of (4) with water to give (2); (*b*) intramolecular catalysed water

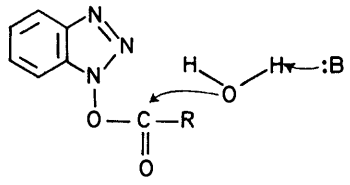
[8] N. I. Nakano, E. E. Smissman, and R. L. Schowen, *J. Org. Chem.*, 1973, **38**, 4396.
[9] J. L. Radomski, G. M. Conzelman, jun., A. A. Roy, and E. Brill, *J. Nat. Cancer Inst.*, 1973, **50**, 989.
[10] L. N. Ferguson, *Chem. Soc. Rev.*, 1975, **4**, 289.
[11] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420.
[12] (*a*) J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, 1968, **33**, 127; (*b*) W. P. Jencks and M. Caplow, *Biochemistry*, 1962, **1**, 883.
[13] G. D. Cooper and B. Williams, *J. Org. Chem.*, 1962, **27**, 3717.
[14] T. C. Bruice and S. Benkovic, 'Bio-organic Mechanisms,' Benjamin, New York, 1966, vol. 1, p. 30.

attack with the nitrogen in the 2-position acting as a general base (5); and (*c*) intermolecular (B = H_2O) general base catalysed water attack on the ester (6).

Formation of (4) can be discounted since product analysis for the hydrolysis of (3; X = NO_2, R = Ph) showed that the only products were (2; X = NO_2) and benzoic acids. 1-Hydroxy-5-nitrobenzotriazole which

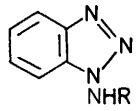


(4) (5)



(6)

could be formed by water attack on the nitrenium ion was not detected. Furthermore product analysis from the analogous aminolysis reaction (see below) showed that the 1-aminobenzotriazole derivative (7) was not present. The 6-nitro-ester (3; X = NO_2, R = Ph) (k_o = 0.32 × 10^{-3} s^{-1}) reacts faster than the unsubstituted compound (3; X = H, R = Ph). The opposite behaviour would be expected for formation of (4). From variation of substituents in the benzoate leaving group a Hammett ρ of 1.39 was obtained for k_o (Table 1). This value would support any of the mechanisms proposed.



(7)

When the reaction medium was changed to 1 : 4 dioxan–D_2O, a reduction in the rate of reaction by a factor of 2.2 was observed (3; X = H, R = *p*-ClC_6H_4 and *p*-$NO_2C_6H_4$). This indicates that one or more water molecules are involved in the transition state for the pH independent reaction as in (5) or (6). If N(2) is participating as an efficient general base (5), it might be expected that this is a basic site which could be protonated at an appropriate pH. However scans of the u.v. spectrum of the unchanged ester over the pH range 0—9 indicated no spectral change with pH. Moreover other general bases, acetate, triethylenediamine monocation, and *N*-ethylmorpholine were found to be efficient catalysts for the hydrolysis of (3; X = H, R = Ph and OPh). If N(2) is participating as a neighbouring group to catalyse water attack it is unlikely that the other base catalysts would be able to compete efficiently with it, due to the higher ' effective concentration ' of the former.[15] In the case of acetate catalysis for the benzoate ester (k_B 7 × 10^{-3} l mol^{-1} s^{-1}) a solvent deuterium effect of 1.9 was obtained. This indicates general base catalysis of water attack. The carbonate esters (3; X = H, R = OPh and $OC_6H_4NO_2$) show similar behaviour except that the rate of hydrolysis is faster than that of the benzoates by a factor of three. This increase, which can be attributed to the inductive effect of the extra oxygen atom, is much less than previously observed for water attack on phenyl benzoate and diphenyl carbonate.[13] A solvent isotope effect of 2.7 was observed consistent with previous reports that carbonate ester hydrolysis generally gives higher solvent isotope effects than benzoate esters for water attack.[16] A more detailed investigation of general base catalysis gave a Brønsted β of 0.46 (r 0.998). In the Brønsted plot (Figure 2) the point for water fits well on the line for the other general bases.

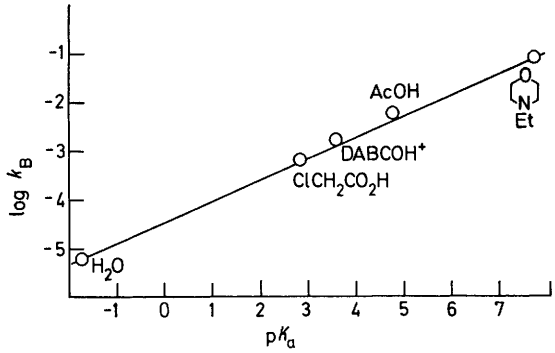


FIGURE 2 Brønsted plot of log k_B against pK_a of conjugate acid of catalyst for general base catalysed hydrolysis of (3; X = H, R = OPh). The slope (β) is 0.46

Aminolysis Reactions.—1-Benzoyloxybenzotriazole (3; X = H, R = Ph) reacts rapidly with primary amines in aqueous solution to give the corresponding amides and (1). In the present study six amines were used, three normal, primary amines and three ' α-effect ' amines. Studies were conducted over the range 0.01—0.1M at a pH equal to the pK_a of the conjugate acid of the amines. However with ethylenediamine monocation and glycine ethyl ester, because of their higher reactivity, lower concentration of amine (10^{-3}—10^{-2}M) and lower pH values, 6.85 and 7.1, respectively, were used. In addition phosphate buffers were used to maintain constant pH for these two aminolysis reactions. Separate studies showed that for all the amines the rate of reaction increased with pH indicating that the free amine and not its conjugate acid was the species reactive towards the ester. The first-order rate constants were directly proportional to the total amine buffer concentration and no second-order term in amine concentration was

[15] W. P. Jencks, ' Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969, p. 8.

[16] (*a*) T. H. Fife and D. M. McMahon, *J. Amer. Chem. Soc.*, 1969, **96**, 7481; (*b*) T. H. Fife and D. M. McMahon, *J. Org. Chem.*, 1970, **35**, 3699.

observed.[17] Rate constants for the aminolysis reactions are given in Table 2 and in the Brønsted plot (Figure 3)

TABLE 2

Second-order rate constants for reaction of (3; X = H, R = Ph) with primary amines in 1 : 4 (v/v) dioxan–water at 25 °C (μ = 1.0; $NaClO_4$)

Amine	pK_a	k/l mol^{-1} s^{-1}
Ethyl carbazate	3.43 [b]	0.383
Semicarbazide	3.76 [b]	0.054
Methoxyamine	4.75 [b]	3.25
Trifluoroethylamine	5.84 [c]	1.0
Ethylenediamine [a]	7.42 [c]	64.6
Glycine ethyl ester	7.90 [c]	52.48

[a] Monocation. [b] pK_a from A. Williams and W. P. Jencks, *J.C.S. Perkin II*, 1974, 1753. [c] pK_a from ref. 18.

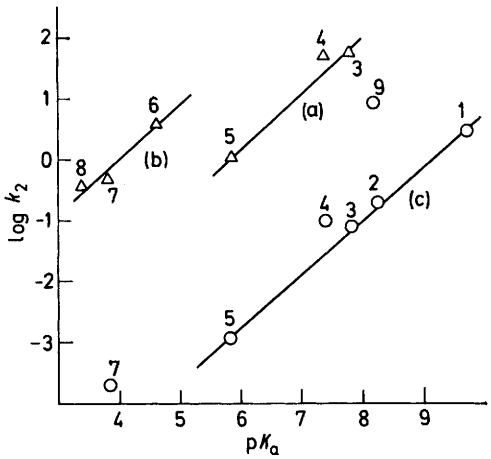


FIGURE 3 Brønsted plot of log k_2 against pK_a for reaction of (3; X = H, R = Ph) with primary amines: (a) normal primary amines, (b) ' α-effect ' amines, (c) reaction of primary amines with *p*-nitrophenyl acetate (data from ref. 18). Amines: 1, glycine; 2, glycylglycine; 3, glycine ethyl ester; 4, ethylenediamine monocation; 5, trifluoroethylamine; 6, methoxyamine; 7, semicarbazide; 8, ethyl carbazate; 9, hydrazine

the data are compared with those for the reaction of primary amines with *p*-nitrophenyl acetate.[18] It is immediately clear that the three ' α-effect ' amines react much faster than the other amines with (1). Brønsted β values of 0.92 and 0.8, respectively, were obtained for the two groups of amines. The difference between the two β values may be due to the small number of data points taken; however Bruice and Dixon [19] have observed a correlation between the ' α-effect ' and the magnitude of the β value for these nucleophiles. Figure 3 also shows that 1-benzoyloxybenzotriazole reacts much faster than *p*-nitrophenyl acetate with the same amines. This difference in reactivity is 10^3 for the normal amines and 2.2×10^3 for the ' α-effect ' amines. The magnitude of the β values obtained indicates that the aminolysis of (3; X = H, R = Ph) involves approximately the same degree of carbon–nitrogen bond formation in the transition state for aminolysis as for *p*-nitrophenyl acetate.[18]

Nature of the Active Acylating Species.—From the data presented it is clear 1-hydroxybenzotriazole is a very efficient acyl transfer agent comparable in reactivity with acetic anhydride and acetylimidazole. On the basis of the reported pK_a for (2; X = H) it would be expected that the esters of (2; X = H) would have a reactivity similar to *p*-nitrophenyl acetate or *p*-nitrophenyl benzoate. The alkaline hydrolysis of phenyl acetates exhibits a leaving group sensitivity $\beta_{l.g.}$ of −0.33.[6a] It would not be expected that 1-hydroxybenzotriazole would lie exactly on the line for phenoxide leaving groups since the former is structurally and electronically different from phenoxides. However in cases where *N*-hydroxy-leaving groups have been compared with phenoxide leaving groups of the same pK_a positive deviations of the >N–OH compounds from the Brønsted line have been observed.[18] These deviations generally correspond to a 10—20 fold rate difference. Thus *ON*-diacetyl-*N*-methylhydroxylamine reacts 15 times faster with hydroxide ion than an aryl acetate where the leaving group has the same pK_a as the *N*-hydroxy-compound. The pK_a reported (7.88) for (1; X = H) corresponds to that for the ionization of a mixture of (1; X = H) and its tautomer benzotriazole *N*-oxide.[20] However from the tautomeric equilibrium constant (K_t) and the fraction of each tautomer present at equilibrium, pK_a values of 7.39 and 8.05 can be calculated for the *N*-hydroxy and *N*-oxide tautomers respectively.* This correction of the observed pK_a does not greatly influence the position of (2; X = H) relative to phenoxide leaving groups.

In view of the extreme reactivity of esters of (2), alternative mechanisms for the deacylation of (3) must be sought. Nucleophilic attack on N-3 to give 1,3 elimination of benzoate can be excluded on the basis of product analysis for the hydrolysis of (3; X = NO_2, R = Ph) and aminolysis of (3; X = H, R = Ph). Konig and Geiger [1] report that the carbonyl stretching frequencies of the ester carbonyl group in benzoyloxycarbonyl amino-acid esters of (2) depend on the medium of measurement. Thus the glycine ester (1; X = H, R = $CH_2NHCO_2CH_2Ph$) showed carbonyl absorptions at 1 745 and 1 715 cm^{-1} in the solid state (KBr) and on dissolving in dioxan these changed to 1 820 and 1 725 cm^{-1}. To account for this change they suggest that in the solid state the ester is in the *N*-acyl form (9) or (10) and in solution it isomerises to the *O*-acyl form (3). High carbonyl stretching frequencies in the i.r. have been reported for *O*-acylhydroxylamine derivatives.[21] Thus we found that 1-acetoxybenzotriazole (3; X = H, R = CH_3) and 1-benzoyloxybenzotriazole showed carbonyl absorptions at 1 805 and 1 785 cm^{-1} (KBr),

* The tautomeric equilibrium constant is dependent on the solvent used. The calculations here have taken the data reported for pure water as solvent,[20] although the kinetics were obtained in the present work in 1 : 4 dioxan–water.

[17] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1966, **88**, 104.

[18] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622.

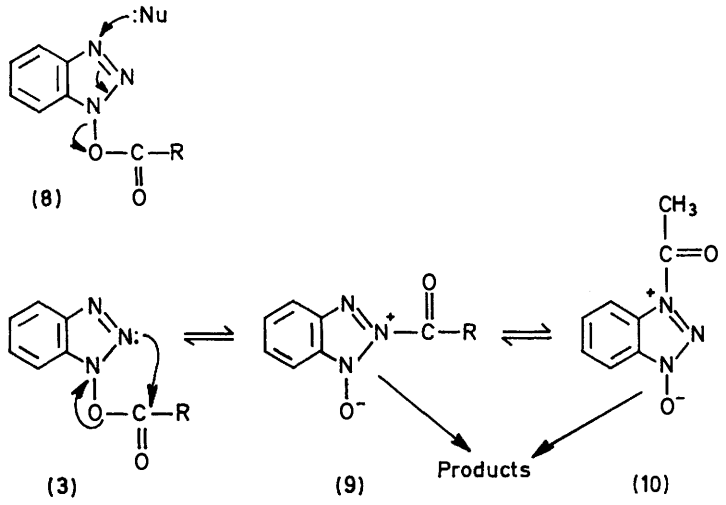
[19] J. E. Dixon and T. C. Bruice, *J. Amer. Chem. Soc.*, 1972, **94**, 2052.

[20] F. T. Boyle and R. A. Y. Jones, *J.C.S. Perkin II*, 1973, 160.

[21] J. P. Freeman, *J. Amer. Chem. Soc.*, 1958, **80**, 5954.

respectively. In solution (CCl_4 or dioxan) they did not change appreciably. We repeated the preparation of (3; X = H, R = $CH_2NHCO_2CH_2Ph$) and found that the solid showed the same carbonyl stretching frequencies as found by Konig and Geiger [1] and given above. However on dissolving this compound in dioxan no change in the i.r. spectrum was found, even on standing for a long period or on heating. It is interesting that the hippurate ester (3; X = H, R = $CH_2NHCOPh$) showed the same behaviour, ν(C=O) 1 745 and 1 650 cm^{-1} in solid or solution state. We also investigated whether the structure of the ester depends on how the compound is prepared, rationalising that under Schotten–Baumann conditions the more nucleophilic $N-O^-$ would give *O*-acylation. Under the conditions of the dicyclohexylcarbodi-imide reaction (tetrahydrofuran or ethyl acetate), the oxygen of (1) would be fully protonated and the nitrogen would be more nucleophilic under these conditions. We prepared the benzoate ester of (2; X = H) by the dicyclohexylcarbodi-imide method and found it to be identical (i.r., m.p., t.l.c.) with that prepared in basic solution. Kinetic studies on the hydrolysis of (3; X = H, R = $CH_2NHCO_2CH_2Ph$) were conducted under the same conditions as for the benzoate esters. An identical log k_{obs}–pH profile was obtained for this compound except that the pH independent (0.85×10^{-1} s^{-1}) and the hydroxide-catalysed reactions ($k_2 = 1.15 \times 10^5$ l mol^{-1} s^{-1}) were faster than for the benzoate esters. These rate increases are probably due to the lower steric effect of the methylene group (relative to the aryl group) adjacent to the ester carbonyl group.

If the *N*-acylated species (9) and (10) are the active acyl transfer agents in aqueous solution, then in a correlation of log k_{HO}^- against pK_a of leaving group, 1-hydroxybenzotriazole would not be expected to lie on the line for phenoxide leaving groups. Structures (9) and (10) are similar to those of *N*-acetylimidazolium or *N*-acetyl-*N*-methylimidazolium ions and indeed the rates of reaction of (3) with nucleophiles are of the same order of magnitude as those for the imidazole derivatives.[22] These structures would also explain why the rates of water and hydroxide ion attack on the carbonate



SCHEME

TABLE 3

Atomic co-ordinates of non-hydrogen atoms of 1-benzoyloxybenzotriazole (estimated standard deviations in parentheses) and anisotropic temperature factors ($Å^2 \times 10^4$)

Atom	*x/a*	*y/b*	*z/c*	U_{11}
N(1)	0.380 5(10)	0.377 5(7)	0.341 3(11)	515(27)
N(2)	0.350 2(10)	0.280 5(8)	0.359 5(13)	692(34)
N(3)	0.438 7(11)	0.231 9(8)	0.294 4(14)	720(34)
O(1)	0.296 9(8)	0.447 8(6)	0.393 3(10)	603(25)
O(2)	0.180 3(8)	0.426 0(6)	0.154 4(10)	628(29)
C(4)	0.639 7(13)	0.281 8(11)	0.151 4(16)	754(43)
C(5)	0.695 2(14)	0.361 5(11)	0.102 8(17)	820(46)
C(6)	0.656 0(13)	0.457 7(11)	0.132 1(15)	726(41)
C(7)	0.549 9(11)	0.476 4(9)	0.213 4(14)	604(36)
C(8)	0.484 9(11)	0.393 1(8)	0.259 9(13)	470(32)
C(9)	0.525 7(12)	0.296 8(9)	0.233 5(15)	575(37)
C(10)	0.191 3(11)	0.468 1(9)	0.276 1(15)	496(34)
C(11)	0.112 3(10)	0.545 8(8)	0.335 0(13)	389(30)
C(12)	0.139 8(11)	0.590 9(8)	0.482 3(13)	470(34)
C(13)	0.056 8(12)	0.664 0(9)	0.533 3(16)	594(37)
C(14)	−0.052 4(12)	0.689 8(9)	0.430 8(14)	553(36)
C(15)	−0.082 2(13)	0.645 7(8)	0.285 1(15)	578(37)
C(16)	0.000 1(11)	0.572 1(9)	0.236 7(15)	569(35)

Calculated atomic co-ordinates of the hydrogen atoms of 1-benzoyloxybenzotriazole (see text for method of refinement)

Atom *	*x/a*	*y/b*	*z/c*
H(4)	0.677 4(13)	0.209 2(11)	0.130 2(16)
H(5)	0.778 5(14)	0.351 9(11)	0.034 9(17)
H(6)	0.710 2(13)	0.518 9(11)	0.089 6(15)
H(7)	0.518 3(11)	0.550 9(9)	0.239 2(14)
H(12)	0.225 6(11)	0.569 7(8)	0.559 3(13)
H(13)	0.077 4(12)	0.699 9(9)	0.648 5(16)
H(14)	−0.117 5(12)	0.746 8(9)	0.467 4(14)
H(15)	−0.168 0(13)	0.666 8(8)	0.207 9(15)
H(16)	−0.022 4(11)	0.535 2(9)	0.122 7(15)

* The hydrogen atoms are numbered according to the number of the carbon atom to which they are attached and have fixed temperature factors of 0.070.

[22] (*a*) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, 1959, **234**, 1272; (*b*) R. Wolfenden and W. P. Jencks, *J. Amer. Chem. Soc.*, 1961, **83**, 4390.

esters are much less sensitive than expected to the extra oxygen atom in the ester group.

Crystal Structure of 1-*Benzoyloxybenzotriazole*.—In order to establish the structure of the hydroxybenzotriazole esters [*i.e.* whether (3), (9), or (10)], at least in the solid state, the structure of the benzoate ester was determined by crystallographic methods.

The molecular structure of 1-benzoyloxybenzotriazole shown in Figure 4 establishes that the acyl linkage is

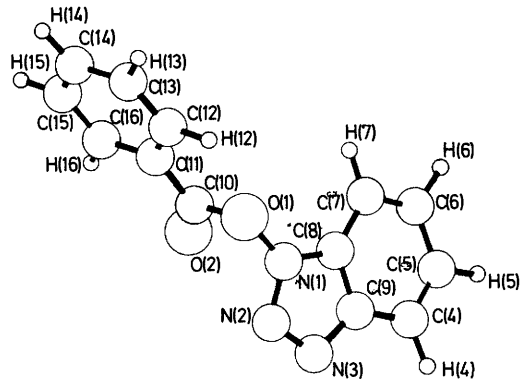


FIGURE 4 Molecular structure and atomic labelling scheme for 1-benzoyloxybenzotriazole

through oxygen rather than nitrogen [N(2) or N(3)]. There is nothing unusual in the bond length and bond angle data of Table 4 and both aromatic rings are reasonably planar (Table 5). The ester group [O(1)–C(10)–O(2) plane] is inclined 5° from the plane of the C(11)–C(16) phenyl group. Within the triazole ring system N(1) is essentially trigonal coplanar but it is lifted a significant distance [0.040(8) Å] out of the plane of O(1), N(2), C(8). The planes of the two aryl groups are almost at right angles (96.1°) with the result that the potentially nucleophilic N(2) and the carbonyl group C(10) are separated by 3.027 Å.

TABLE 4

Molecular geometry

(*a*) Bond lengths (Å)

N(1)–N(2)	1.365(13)	C(7)–C(8)	1.388(15)
N(1)–O(1)	1.383(11)	C(10)–O(1)	1.418(13)
N(1)–C(8)	1.342(12)	C(10)–O(2)	1.161(12)
N(2)–N(3)	1.286(13)	C(10)–C(11)	1.447(15)
N(3)–C(9)	1.386(14)	C(11)–C(12)	1.378(14)
C(9)–C(8)	1.397(16)	C(11)–C(16)	1.397(14)
C(9)–C(4)	1.429(16)	C(12)–C(13)	1.402(14)
C(4)–C(5)	1.306(17)	C(13)–C(14)	1.397(15)
C(5)–C(6)	1.396(17)	C(14)–C(15)	1.363(16)
C(6)–C(7)	1.363(15)	C(15)–C(16)	1.395(15)

(*b*) Bond angles (°)

O(1)–N(1)–N(2)	118.4(9)	N(1)–C(8)–C(9)	101.5(10)
O(1)–N(1)–C(8)	127.0(10)	C(10)–O(1)–N(1)	112.1(9)
N(2)–N(1)–C(8)	114.3(10)	O(1)–C(10)–O(2)	120.8(12)
N(1)–N(2)–N(3)	105.6(10)	O(1)–C(10)–C(11)	109.0(11)
N(2)–N(3)–C(9)	109.7(10)	O(2)–C(10)–C(11)	130.2(12)
N(3)–C(9)–C(8)	108.9(10)	C(10)–C(11)–C(12)	123.6(11)
N(3)–C(9)–C(4)	132.4(13)	C(10)–C(11)–C(16)	116.5(11)
C(4)–C(9)–C(8)	118.8(12)	C(12)–C(11)–C(16)	119.9(11)
C(9)–C(4)–C(5)	115.8(15)	C(11)–C(12)–C(13)	120.4(12)
C(4)–C(5)–C(6)	125.4(15)	C(12)–C(13)–C(14)	118.3(13)
C(5)–C(6)–C(7)	121.3(14)	C(13)–C(14)–C(15)	122.0(13)
C(8)–C(7)–C(6)	114.7(13)	C(14)–C(15)–C(16)	119.1(14)
N(1)–C(8)–C(7)	134.5(12)	C(15)–C(16)–C(11)	120.2(12)
C(7)–C(8)–C(9)	123.9(11)		

TABLE 5

The equation of some mean planes given in the form $lx + my + nz = p$, with the deviations (Å) of the next relevant atoms from the planes given in square brackets (where $x = a^*$, $y = ca^*$, and $z = c$)

	l	*m*	*n*	*p*
Plane 1: O(1), O(2), C(10)—C(16)				
	0.541 9	0.691 9	−0.477 1	4.455 0
[O(1) −0.022 8, O(2) −0.024 3]				
Plane 2: O(1), O(2), C(10)				
	0.532 1	0.717 3	−0.449 9	4.637 8
Plane (3): C(11)—C(16)				
	0.532 7	0.695 7	−0.481 9	4.471 5
Plane 4: N(1), N(2), O(1), C(8)				
	0.556 5	0.002 1	0.830 8	4.206 0
[N(1) −0.028 2, N(2) −0.009 0, O(1) −0.009 8, C(8) −0.009 5]				
Plane 5: N(1)—N(3), C(4)—C(9)				
	0.571 4	0.002 6	0.820 7	4.249 6

Some relevant angles between planes: 2–3, −2.21°; 1–5, −95°.

Conclusions.—These results, taken with the absence of a spectral change on the dissolution of (3; X = H, R = Ph) indicate that the major form of the ester present in solution is also the *O*-acyl form. Intermolecular *N*-acylation [*i.e.* conversion into (9) or (10) which then acts as the active species] can be ruled out by the observed kinetics. We cannot however rule out the presence of a small equilibrium concentration of (9) [or perhaps (10)] which undergoes very rapid deacylation. This is however unlikely in view of the low nucleophilicity of N(2) and the unfavourable orientation of the carbonyl group relative to N(2). Moreover the nitro-ester (3; X = NO_2) is *more* reactive than (3; X = H) whereas the equilibrium would be expected to be shifted towards the *O*-acyl isomer by the electron-withdrawing group. We conclude therefore that these esters react in the *O*-acyl form. The high reactivity shown is then best attributed to activation of the starting esters by the electron-withdrawing benzotriazole ring acting to reduce the normal resonance stabilization in the ester group.

EXPERIMENTAL

General.—M.p.s were determined on a Thomas Unimelt apparatus and are uncorrected. Combustion analyses were performed by the Microanalytical Laboratory, University College, Cork. All inorganic materials were AnalaR grade. Liquid amines were distilled once before use. Deionized water was twice distilled from alkaline potassium permanganate. Deuterium oxide (99.8% D) was obtained from Stohler Isotope Chemicals. Dioxan–water solvent mixtures were prepared by diluting one volume of dioxan (AnalaR grade) with four of water at room temperature. I.r. spectra were recorded on a Perkin-Elmer 257 spectrophotometer. ^{1}H N.m.r. spectra were recorded on a Perkin-Elmer R20-H spectrometer at 60 MHz, with tetramethylsilane as internal standard.

Kinetic Method.—Kinetic data were obtained spectrophotometrically in the u.v. region. Where buffer solutions were used either a Perkin-Elmer 124 or Unicam SP 800 spectrophotometer were used, both equipped with thermostatted cell blocks and external recorders. In the absence of buffers a Cary 14 spectrophotometer equipped with a pH stat was used.[23] Pseudo-first-order rate constants were calculated graphically either from the experimental infinity value or by the method of Guggenheim, and were reproducible to within 4% of the mean. Ionic strength was maintained at unity with sodium perchlorate. The pH values quoted in the text are those measured directly for the dioxan–water solutions without further corrections being applied. A Radiometer model PHM 26 pH meter with a Metrohm EA 125 U glass combination electrode was used, the latter being standardised in Radiometer standard buffer solutions. Prior to each kinetic run, the electrode was equilibrated for 30 min in the dioxan–water solution. Kinetic runs were initiated by addition of 1 drop of a stock solution of the substrate (10^{-2}M) in dioxan to the reaction solution in a quartz cuvette placed in the spectrophotometer. The change in optical density at suitable wavelengths was then followed.

Substrates.—1-Hydroxybenzotriazole monohydrate was obtained from *o*-nitrophenylhydrazine and potassium hydroxide.[24] The anhydrous compound was obtained by recrystallising the monohydrate from absolute ethanol three times. 1-Hydroxy-6-nitrobenzotriazole was similarly obtained from 2,4-dinitrophenylhydrazine.

1-(*Benzoyloxy*)*benzotriazole* was prepared by the method of Brady and Reynolds [25] and recrystallised from benzene–light petroleum (b.p. 60—80°) (1 : 1), m.p. 77—78° (Found: C, 65.4; H, 3.7; N, 17.6. $C_{13}H_9N_3O_2$ requires C, 65.3; H, 3.8; N, 17.6%). Similarly prepared were 1-(p-*nitrobenzoyloxy*)*benzotriazole*, m.p. 144—146° [benzene–chloroform (1 : 1)] (Found: C, 54.8; H, 2.7; N, 19.8. $C_{13}H_8N_4O_4$ requires C, 54.9; H, 2.8; N, 19.7%); 1-(m-*nitrobenzoyloxy*)-*benzotriazole*, m.p. 148—149° (benzene) (Found: C, 54.9; H, 2.8; N, 19.7%); 1-(p-*chlorobenzoyloxy*)*benzotriazole*, m.p. 127—129° (benzene) (Found: C, 57.1; H, 3.0; N, 15.2; Cl, 13.1. $C_{13}H_8ClN_3O_2$ requires C, 57.4; H, 2.9; N, 15.4; Cl, 13.0%); 1-(m-*chlorobenzoyloxy*)*benzotriazole*, m.p. 129—130° (benzene) (Found: C, 57.3; H, 3.18; N, 15.7; Cl, 12.5%); 1-(p-*methylbenzoyloxy*)*benzotriazole*, m.p. 82° [benzene–light petroleum (1 : 1)] (Found: C, 66.8; H, 4.55; N, 16.7. $C_{14}H_{11}N_3O_2$ requires C, 66.4; H, 4.35; N, 16.6%); 1-(m-*methylbenzoyloxy*)*benzotriazole*, m.p. 114—115° [benzene–light petroleum ether (1 : 1)] (Found: C, 66.65; H, 4.3; N, 16.5%); and 1-*benzoyloxy*-6-*nitrobenzotriazole*, m.p. 155—157° (benzene) (Found: C, 54.5; H, 2.8; N, 19.1. $C_{13}H_8N_4O_4$ requires C, 54.9; H, 2.8; N, 19.7%).

1-*Benzoyloxy*-6-*bromobenzotriazole* was prepared from *N*-α-bromobenzylidene-*N'*-(4-bromo-2-nitrophenyl)hydrazine by the method of Gibson,[26] m.p. 115—116° (lit.,[26] 115—116°) (Found: C, 49.2; H, 2.7; N, 12.8; Br, 25.5. Calc. for $C_{13}H_8BrN_4O_4$: C, 49.1; H, 2.5; N, 13.2; Br, 25.2%).

Benzotriazol-1-*yl Phenyl Carbonate.*—Phenyl chloroformate (0.75 g) was added to a solution of 1-hydroxybenzotriazole (0.5 g) in water (20 ml) containing sodium hydroxide (0.16 g). The mixture was shaken vigorously for 10 min and the precipitate collected, washed with water (20 ml) and cold ethanol (10 ml), and dried (P_2O_5). The crude solid was recrystallised twice from chloroform–pentane (1 : 1), m.p. 177—179° (Found: C, 60.9; H, 3.7; N, 16.4. $C_{13}H_9N_3O_3$ requires C, 61.2; H, 3.5; N, 16.5%).

Benzotriazol-1-*yl* p-*Nitrophenyl Carbonate* was prepared similarly, m.p. 189—190° [benzene–chloroform (1 : 1)] (Found: C, 51.9; H, 2.8; N, 18.45. $C_{13}H_8N_4O_5$ requires C, 52.1; H, 2.7; N, 18.7%).

N-*Benzoyloxycarbonylglycine Ester of Hydroxybenzotriazole.*—This compound was prepared by the method of Konig and Geiger,[1] m.p. 142° (lit.,[2] 147°) (Found: C, 59.05; H, 4.6; N, 17.5. Calc. for $C_{16}H_{14}N_4O_4$: C, 58.9; H, 4.3; N, 17.2%), δ[$(CD_3)_2CO$] 7.6 (9 H, m), 5.16 (2 H, s), and 4.55 (2 H, d, *J* 6 Hz).

N-*Benzoylglycine Ester of* 1-*Hydroxybenzotriazole.*—A similar procedure gave the *ester*, m.p. 122—125° [$CHCl_3$–pentane (1 : 1)] (Found: C, 60.6; H, 4.4; N, 19.0. $C_{15}H_{12}N_4O_3$ requires C, 60.8; H, 4.0; N, 18.9%), δ[$(CD_3)_2CO$] 7.55 and 7.9 (9 H, m) and 4.73 (2 H, d, *J* 4.5 Hz).

1-*Acetoxybenzotriazole* was prepared by the above method, m.p. 94—95° [benzene–hexane (1 : 1)] (lit.,[25] 98°), δ[$(CD_3)_2CO$] 2.7 (3 H, s) and 7.65 (4 H, m).

Product Analysis.—Products of hydrolysis and aminolysis reactions were determined by comparing the u.v. spectra of the solutions at the end of a kinetic run with the spectra of authentic samples run under the same conditions and at the same concentration. In addition the kinetic experiments were carried out on a preparative scale and the products isolated.

(a) *Hydrolysis of* 1-*Benzoyloxy*-6-*nitrobenzotriazole.*—The ester (3; X = NO_2, R = Ph) (0.25 g) in dioxan (1 ml) was added to an aqueous solution of 1N-NaOH (4 ml). The solution turned deep red and was stirred at room temperature for 1 h. Acidification of the mixture with 2N-HCl, and cooling in an ice-bath gave a yellow precipitate (120 mg, 83%). This was recrystallised from absolute ethanol. The compound was identical with 1-hydroxy-6-nitrobenzotriazole [m.p., mixed m.p., t.l.c. (silica; Merck HF_{254} methanol–acetone 9 : 1)]. Extraction of the aqueous solution with ether (2 × 50 ml) gave a further quantity (6 mg) of the above compound. On further acidification (12N-HCl) and concentration to a small volume, the aqueous portion gave benzoic acid.

(b) *Hydrolysis of* 1-*Benzoyloxybenzotriazole.*—Treatment by the above method, and t.l.c. analysis [on silica gel, eluant ethyl acetate–light petroleum (b.p. 60—80°) (1 : 1)] of the aqueous product mixture after acidification showed that the only products were benzoic acid and 1-hydroxybenzotriazole.

(c) *Aminolysis of* 1-*Benzoyloxybenzotriazole with Glycine Ethyl Ester.*—1-(Benzoyloxy)benzotriazole (0.15 g) in dioxan (1 ml) was added to an aqueous solution of glycine ethyl ester hydrochloride (0.5M, 10 ml) at pH 7.9. The solution was stirred at room temperature for 2 h, then acidified to litmus with 2N-HCl. The aqueous solution was then extracted with ether (3 × 50 ml); evaporation of the dried (Na_2SO_4) ethereal extracts gave an oil which solidified on cooling. T.l.c. analysis of the oil [silica, ether–pentane (3 : 2)] showed that it contained 1-hydroxybenzotriazole

[23] A. F. Hegarty, C. N. Hegarty, and F. L. Scott, *J.C.S. Perkin II*, 1975, 1166.
[24] (*a*) J. Nietzki and E. Braunschweig, *Ber.*, 1894, **27**, 3381; (*b*) T. Zincke and P. Schwarz, *Annalen*, 1900, **311**, 332.
[25] O. L. Brady and C. V. Reynolds, *J. Chem. Soc.*, 1928, 193.
[26] I. T. Barnish and M. S. Gibson, *J. Chem. Soc.* (*C*), 1968, 8.
[27] 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965, vol. 3, p. 1622.
[28] 'International Tables for *X*-ray Crystallography,' Kynoch Press, Birmingham, vol. 1, 1969.

and *N*-benzoylglycine ethyl ester. The solid was redissolved in ether and extracted with 10% $NaHCO_3$ solution until all the 1-hydroxybenzotriazole was removed (t.l.c.). The ethereal solution gave on evaporation a solid which was recrystallised from ether to give *N*-benzoylglycine ethyl ester, m.p. 66° (lit.,[27] 67.5°).

(d) *Aminolysis of 1-Benzoyloxybenzotriazole with Aniline.*—A similar procedure using 0.5M-aniline solution at pH 5.0, gave after acidification and pouring into ice–water, benzanilide (71%) which on recrystallisation from benzene was identical with a commercial sample.

Crystal Data on 1-Benzoyloxybenzotriazole.—Single crystals of the ester were grown from benzene–light petroleum (b.p. 40—60°) (1 : 1). $C_{13}H_9N_3O_2$, $M = 239.14$. Monoclinic, $a = 10.290$, $b = 13.579$, $c = 8.34$ Å, $\beta = 95.50°$, $U = 1\ 160.38$ Å^3, $D_m = 1.364$ (by flotation), $Z = 4$, $D_c = 1.369$ g cm^{-3}, $F(000) = 496$, $\mu = 7.02$ cm^{-1} (for Cu-K_α radiation). Space group $P2_1/c$ (C_{2h} No. 14).

The space group and unit cell data were determined from zero and first layer precession photographs measured up all three axes. The intensity data were collected photographically using the equi-inclination Weissenberg technique; the layers collected were: *hk*0–*hk*6 and *h*1*l*–*h*3*l*. Non-integrated reflections were used and the intensities were estimated by the S.R.C. Microdensitometer Service, Harwell; 574 unique reflections were estimated. The intensities were corrected for Lorentz and polarisation effects and were placed on a common arbitrary scale by internal correlation; no correction was applied for absorption or extinction. Literature values [28] for the atomic scattering factors were used and all calculations were carried out using the SHELX program of Dr. G. M. Sheldrick and the PLUTO program of Dr. S. Motherwell.

Solution and Refinement of the Structure.—The structure was solved using the automatic ' black box ' direct methods programme included in the SHELX program and yielded directly the positions of all of the non-hydrogen atoms. Five cycles of a full matrix least-squares refinement using isotropic temperature factors yielded an R value of 0.155 0 where $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$ and the subsequent difference map showed the position of six of the nine hydrogen atoms present. The overall scale factor was then refined and fixed (R 0.120 6). The positions of the nine hydrogen atoms were calculated assuming a fixed C–H bond distance of 1.08 Å plus trigonal bond angles and their positional parameters were allowed to float on those of the carbon atom to which the hydrogen atom were attached, with a fixed isotopic temperature factor of 0.07 (R 0.094 1). Three further cycles of least squares refinement reduced the shift/least square deviation of all parameters to <0.03 and three further cycles reduced it to <0.01 with a final R value of 0.093 9.

The final atomic co-ordinates and thermal parameters, together with their estimated standard deviations are given in Table 3; Table 4 lists the final bond distances and bond angles and Table 5 reports some relevant mean planes. Figure 4 illustrates the overall molecular geometry and the numerical labelling scheme used. Observed and calculated structure factors are in Supplementary Publication No. SUP 21851 (5 pp.).*

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* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1976, Index issue. Items less than 10 pp. are supplied as full-size copies.