Reactive Intermediates from the Solvolysis of Mutagenic *O*-Alkyl *N*-Acetoxybenzohydroxamates

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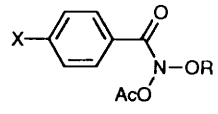
Mutagenic *O*-(*para*-substituted benzyl) *N*-acetoxybenzohydroxamates undergo acid-catalysed solvolysis in aqueous acetonitrile but there is a change in mechanism from $A_{A1}1$ to E1 on going from *para* electron-withdrawing substituents to *para* +*M* electron-donating groups. The former permit the formation of a discrete nitrenium ion intermediate whereas the latter promote a concerted elimination of a resonance stabilized benzyl carbocation.

Recently we described a new class of compounds, *O*-alkyl *N*-acetoxybenzohydroxamates (**1**), which were found to be mutagenic in the Ames test.[1-3] The mutagenicity is thought to originate either from the ability of these compounds to form a highly reactive, electrophilic nitrenium ion (**2**) or through their



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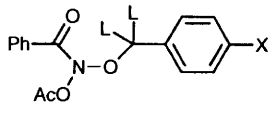
behaviour as electrophiles themselves; nucleophilic substitution at nitrogen has been reported in their reaction with aromatic amines and this mode of reactivity with nucleotides cannot be excluded.[4] Either way the alkyl *N*-acetoxybenzohydroxamates can be considered as ultimate mutagens since they do not require metabolic activation for their attack on DNA.

Extensive solvolysis studies in acetonitrile–water have indicated that *O*-alkyl *N*-acetoxybenzohydroxamates are sources of alkoxy-stabilized nitrenium ions (**2**), but only under acid-catalysis (the $A_{A1}1$ mechanism).[3] As such the intermediacy of **2** in mutagenesis is unlikely at cellular pH. We have now found that in the case of certain mutagens in the series **3** where X is an electron-donating group, nitrenium ions are not generated even under acid-catalysis. Instead unimolecular decomposition leads to a resonance-stabilised benzyl cation in an acid-catalysed E1 process.

A comparison of the rates of acid-catalysed solvolysis of the *para*-substituted series (**3**; L = H) indicated a linear correlation with Hammett σ^+ values with low sensitivity ($\rho = -1.59$). This correlation was surprising since, in the case of **3a** and **3b**, there is no resonance conduit to the nitrenium/oxonium centre. The $\Delta S^{\ddagger}$ and E_A for the reaction of these two substrates were also less positive than expected while the enthalpy–entropy relationship for *O*-(*para*-substituted benzyl) *N*-acetoxybenzohydroxamates **3a–i** revealed that in the case of **3a** and **3b** there was a significant deviation from the isokinetic trend (Fig. 1).[3] A less obvious deviation was also evident for **3e**.

The tighter transition states for **3a** and **3b** were first thought to arise through non-classical structures as depicted in Fig. 2. A more satisfactory explanation for these observations has now been found; experiments have shown that when +*M* substituents are present there is a change in mechanism from



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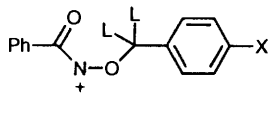

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a; L = H, X = OMe
b; L = H, X = OPh
c; L = H, X = Me
d; L = H, X = *t*-Bu
e; L = H, X = Ph
f; L = H, X = H
g; L = H, X = Cl
h; L = H, X = Br
i; L = H, X = NO_2
j; L = D, X = OMe
k; L = D, X = Ph
l; L = D, X = Me
m; L = D, X = NO_2

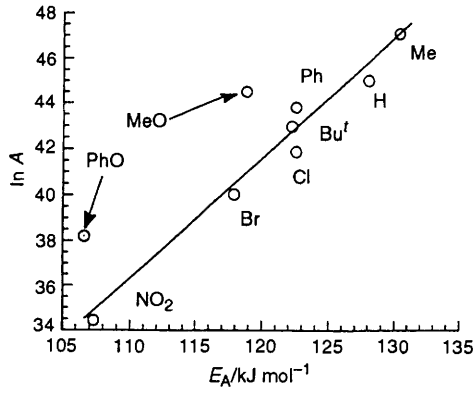


Fig. 1 Isokinetic relationship for **3a–i**

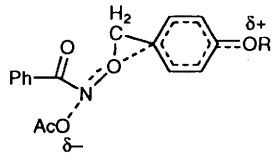


Fig. 2 Non-classical transition-state structure for **3a** and **3b**

$A_{A1}1$ to a concerted E1 process involving the simultaneous loss of acetic acid and benzyl cation.

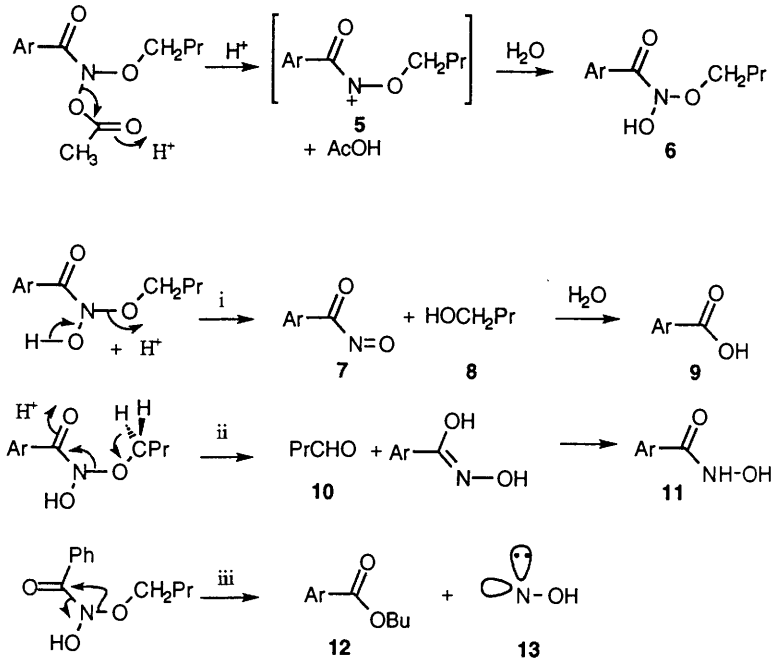
Results and Discussion

The products resulting from an acid-catalysed solvolysis of *O*-butyl *N*-acetoxybenzohydroxamates **1** (R = Bu) have been determined by ^{1}H NMR spectroscopy and are given in Table 1. These are acetic acid, butyl benzoates (**12**), butanol (**8**), benzoic acids (**9**), benzohydroxamic acids (**11**) and butanal (**10**). All of these products except acetic acid are derived from the *N*-hydroxy-*N*-butoxybenzamide intermediate **6** which is formed by capture of the nitrenium ion **5** by water (Scheme 1).[3]

Table 1 Products and yields[a] (%) from acid-catalysed solvolysis of *O*-butyl *N*-acetoxybenzohydroxamates **1** (R = Bu)

X =	MeO	Me	H	Cl	Br	NO_2
$[H^+]/10^{-3}$ mol dm^3 =	2.2	8.5	3.3	9.4	4.2	8.3
Benzoic acid (**9**)	4	4	6	17	*b*	*b*
Benzohydroxamic acid (**11**)	19	21	36	32	*b*	*b*
Butanal (**10**)	34	31	28	21	16	0
Butanol (**8**)	16	22	16	25	16	22
Butyl benzoate (**12**)	9	11	27	29	42	42

[a] Yields from ^1H NMR spectroscopy. [b] Not determined.



Scheme 1

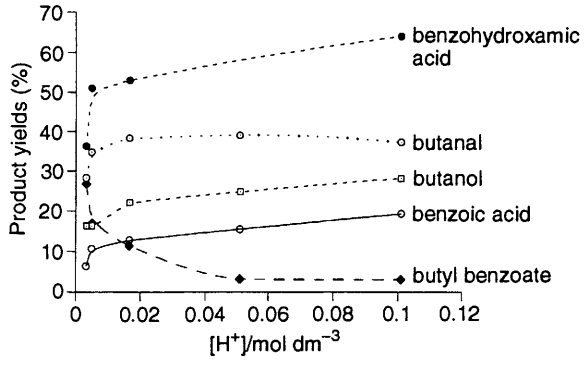


Fig. 3 Dependence of product yields upon acid concentration for solvolysis of **1** (R = Bu, X = H) in aqueous acetonitrile

Aldehyde **10** and the hydroxamic acids **11** appear to be generated together in an acid-catalysed elimination reaction (Scheme 1ii). The yields of products (estimated by ^1H NMR spectroscopy) from the solvolysis of *O*-butyl *N*-acetoxybenzamide **1** (R = Bu, X = H) at different acid concentrations are illustrated in Fig. 3. There is an increase in both aldehyde and hydroxamic ester formation with increasing acid strength in accord with acid-catalysis.

Esters **12** are not formed from alcohol **8** and benzoic acids **9**, since alcohols and esters are formed in parallel reactions.[3] In addition, Fig. 3 indicates that there is a rapid reduction in ester formation with increasing acid concentration in accord with a non acid-catalysed process. Esters are probably formed in a concerted rearrangement concomitant with the formation of the hydroxynitrene **13** (Scheme 1iii); while there is no evidence to date for the formation of hydroxynitrene, a crossover experiment at low acid concentration (optimum conversion into ester) has shown that ester is formed by an intramolecular process. Joint solvolysis of equimolar quantities of **3f** and **1** (R = Bu, X = Cl) afforded none of the mixed esters but significant quantities of butyl *p*-chlorobenzoate (36%) and benzyl benzoate (54%).* We have recently reported a similar rearrangement for the *N*-(*N*-methylanilino)-*N*-alkoxybenzamides which gives the corresponding alkyl benzoates and resonance stabilised 1,1-diazenes.[4]

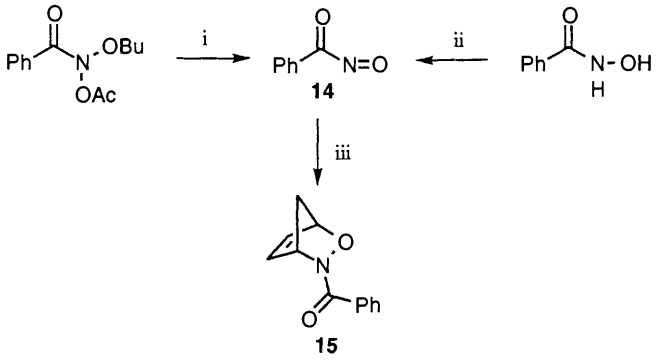
The source of alcohol **8** is most likely acid-catalysed hydrolysis of **6** to the nitrosocarbonylbenzene intermediates **7** which, like acyl chlorides, react with water to give benzoic acids **9** (Scheme 1i).[5] The yields of benzoic acid and alcohol also improve with increasing acid concentration (Fig. 3). Nitrosocarbonylbenzenes are transient intermediates formed by oxidation of benzohydroxamic acids.[5–7] They are excellent dienophiles and several studies have proved their intermediacy as well as their versatility in Diels–Alder reactions.[7–16] Addition of cyclopentadiene to the reaction mixture for the acid-catalysed solvolysis of **1** (R = Bu, X = H) in aqueous acetonitrile (1:4) led to the formation, albeit in low yield, of *N*-benzoyl-2-ox-3-azabicyclo[2.2.1]hept-5-ene **15** which was

* A similar result would be found if **7** reacted with **8** or butoxide (formed from the conjugate base of **6**) faster than diffusion rates. We prefer the concerted pathway for which we now have support from AM1 molecular orbital calculations.

Table 2 Yields[a] of products (%) from the acid-catalysed[b] solvolysis of *p*-substituted benzyl *N*-acetoxybenzohydroxamates **3a–c**, **3e–g** and **3i**

	X						
Product	MeO (**3a**)	PhO (**3b**)[c]	Ph (**3e**)[c]	Me (**3c**)	H (**3f**)	Cl (**3g**)	NO_2 (**3i**)
Benzaldehyde	<1	*d*	4	4	8	13	16
Benzyl benzoate	0	9	14	18	21	16	25
Benzyl alcohol	79	55	44	54	40	33	22
Benzoic acid	47	25	*d*	68	21	26	23
Benzohydroxamic acid	0	*d*	*d*	1	7	3	<5
Benzoic anhydride	20	17	9	6	2	0.3	0

[a] Yields from HPLC. [b] Typically 5–20 μl of a 1.0 mol dm^{-3} solution of H_2SO_4 was required for complete conversion over a 24 h period. [c] Estimated from the final ^1H NMR spectrum of a typical kinetic run. [d] Not determined.



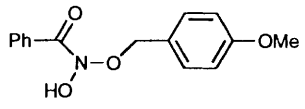
Scheme 2 *Reagents:* i, H^+, 25% H_2O–CH_3CN; ii, NBS, CH_2Cl_2; iii, cyclopentadiene

detected by both NMR spectroscopy and HPLC and was identical (NMR and retention time) with authentic material prepared by oxidation of benzohydroxamic acid with *N*-bromosuccinimide in dichloromethane and in the presence of cyclopentadiene (Scheme 2).[9] The adduct was isolated by preparative HPLC (1.4%) and displayed an extremely weak $(M + 2)^+$ ion in its mass spectrum. A similar trapping reaction in 10% ^{18}O-enriched aqueous acetonitrile (1:4) afforded the adduct which displayed an increased intensity for the $(M + 2)^+$ ion. Here the $(M + 2)^+ : M^+$ ratio was 0.148 in its mass spectrum. While the error in this ratio is quite large, since the adduct displayed a very weak molecular ion under electron impact (only 2.7% of base peak), best estimates of the corresponding ratio in the pure standard adduct were 0.023 (based on an M^+ of 4.3%) and 0.024 (based on an M^+ of 4.2%) in two independent measurements while the theoretical value is only 0.0126.

The extent to which ^{18}O is incorporated provides clear evidence for both the trapping of the nitrenium ion intermediate by solvent water molecules and subsequent hemiacetal-like hydrolysis to the nitrosocarbonylbenzene **14**.

The products from the acid-catalysed solvolysis of **3a–c**, **3e–g** and **3i** are given in Table 2. Since acid strengths were different in each case direct comparisons cannot be made. The range of products from the solvolysis of **3c**, **3f** and **3g** was, however, similar to those obtained from the *O*-butyl *N*-acetoxybenzamides **1** (R = Bu) with the exception that small quantities of benzoic anhydride were also detected. This is presumably a consequence of reaction of the nitrosocarbonylbenzene intermediate **7** with the benzoic acid **9** it generates with water. Esters are formed in modest but not dissimilar yields from each of **3c**, **3e–g**, and **3i**.

In contrast, an analysis of the solvolysis products for **3a** revealed that neither ester, benzaldehyde, nor benzohydroxamic acid was produced in the reaction. Instead, substantial quantities of benzoic anhydride, benzyl alcohol and benzoic acid were generated indicating that an alternative solvolysis mechanism could be operative in this case. While the formation of nitrosocarbonylbenzene was indicated by the formation of these products, the absence of ester, benzaldehyde and benzohydroxamic acid suggests that *N*-(*p*-methoxybenzyl) benzohydroxamic acid **16** was not an intermediate in the reaction.



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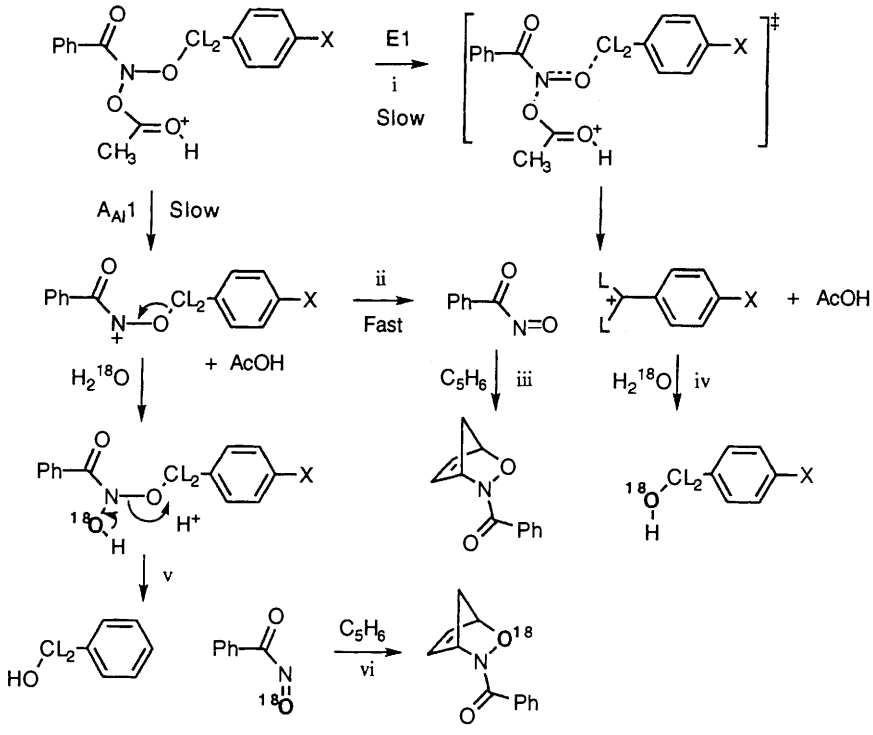
Cyclopentadiene was dissolved in a solution of **3a** in 20% aqueous acetonitrile, and the reaction was initiated with sulfuric acid at 308 K. NMR analysis of the products on completion of the reaction indicated that a similar quantity of benzyl alcohol was produced to the amount which was generated in the absence of the diene. Furthermore, the Diels–Alder cycloadduct, 3-benzoyl-2-oxa-3-azabicyclo[2.2.1]hept-5-ene **15** was detected in 6% yield (HPLC) and was identified in the mixture by ^1H and ^{13}C NMR spectroscopy.

Scheme 3 illustrates alternative mechanisms for the decomposition of **3a** to give **14**. The rate-determining step could involve concerted release of acetic acid, *p*-methoxybenzyl carbocation and nitrosocarbonylbenzene in an acid-catalysed E_1 process (pathway i). Alternatively, rate-determining formation of a nitrenium ion ($A_{A1}1$) could be followed by a fast, highly competitive elimination of *p*-methoxybenzyl carbocation (pathway ii). Neither mechanism invalidates the kinetics of the reaction as both processes produce a positively charged intermediate in a first-order fashion.

Since the nitrosocarbonylbenzene produced by either mechanism would contain the oxygen originating from the benzyloxy substituent, the Diels–Alder adduct that would be formed in the presence of ^{18}O-enriched aqueous acetonitrile ought not to display an enhanced $M^+ + 2$ molecular ion in its mass spectrum (Scheme 3iii). On the other hand, benzyl alcohol that would be formed by trapping of the benzyl cation should be enriched with ^{18}O (Scheme 3iv). Like solvolysis of *O*-butyl *N*-acetoxybenzohydroxamate, normal hemiacetal hydrolysis of the hydroxamic acid intermediate (Scheme 3v) would lead to unlabelled benzyl alcohol and a labelled nitroso intermediate as well as the Diels–Alder (Scheme 3vi). Accordingly, the acid-catalysed solvolysis of **3a** was repeated in 10% ^{18}O-enriched aqueous acetonitrile (1:4) in the presence of cyclopentadiene. *N*-Benzyl-2-oxa-3-azabicyclo[2.2.1]hept-5-ene **15** and benzyl alcohol were then isolated by preparative HPLC. The $(M + 2)^+ : M^+$ ratio for **15** was less than 0.01 (based on an M^+ of 5.2%). The $(M + 2)^+ : M^+$ ratio for the benzyl alcohol of 0.103 was similar to that obtained for labelled benzyl alcohol obtained from the hydrolysis of *p*-methoxybenzyl bromide in ^{18}O-enriched water (0.122) and an order greater than that for



Scheme 3

Table 3 Rates and secondary kinetic isotope effects at 308 K for *O*-(*p*-substituted benzyl) *N*-acetoxybenzohydroxamates **3a**, **3e**, **3c** and **3i**

Substrates (X)	$k_H^{308}/10^{-2}$ dm^3 mol^{-1} s^{-1}	r	$k_D^{308}/10^{-2}$ dm^3 mol^{-1} s^{-1}	r	k_H^{308}/k_D^{308}
3i, **3m** (NO_2)	0.0624 (0.0017)	0.9981	0.0609 (0.0028)	0.9979	1.02 (0.06)
3c, **3l** (Me)	2.2917 (0.0033)	1.0000	2.3228 (0.0097)	0.9954	0.99 (0.01)
3e, **3k** (Ph)	0.8662 (0.0044)	0.9961	0.7346 (0.0154)	0.9993	1.18 (0.03)
3a, **3j** (MeO)	14.96 (0.54)	0.9981	11.35 (0.50)	0.9970	1.32 (0.08)

unlabelled *p*-methoxybenzyl alcohol (0.007). Clearly nitrosocarbonylbenzene **14** is formed by either pathway i or pathway ii but not *via* the hydroxamic acid, v.

Secondary Kinetic Isotope Effects.—The distinction between these pathways was made on the basis of deuterium isotope effects. Unlike pathway ii, pathway i leads to a transition state in which there is a change in hydridisation from sp^3 to sp^2 at the benzylic carbon. Accordingly a secondary deuterium isotope effect of up to *ca.* 15% per deuterium is expected.[17] Second-order rate constants for acid-catalysed solvolysis of **3a**, **3c**, **3e** and **3i** and their *bis*-deuteriated analogues **3j**, **3l**, **3k** and **3m** were obtained from the rates of solvolysis at different sulfuric acid concentrations and are given in Table 3. For **3a** and **3j** the ratio of the slopes gives a k_H/k_D value of 1.32 ± 0.08, which is close to the theoretical maximum of 1.4,[17] and is indicative of a transition state with substantial sp^2 character at the benzylic carbon.

The change in mechanism found for **3a** is undoubtedly a consequence of the resonance stabilisation of the benzyl cation by the *p*-methoxy substituent. In contrast, a *p*-nitro substituent would be expected to disfavour a concerted decomposition and favour reaction by the normal $A_{Al}1$ mechanism. A comparison of the rates of solvolysis of **3i** and **3m** supported this since no kinetic isotope effect was observed (Table 3).

It was envisaged that a change in mechanism from $A_{Al}1$ to E1 would occur with increasing electron-donor capacity of the *p*-substituent. A comparison of secondary deuterium isotope effects for some other substrates in the series indicates that this is the case. However there is a clear switch in mechanism on varying the *p*-substituent from methyl (k_H/k_D = 0.99 ± 0.02) to phenyl (k_H/k_D 1.18 ± 0.07). Thus the switch from the $A_{Al}1$ to the E_1 mechanism is driven not only by electron-donor capacity of the substituents but also the necessity for the benzyl carbocation to be resonance delocalised into the *para* substituent.

The Hammett data for series **3** is thus best represented by two independent correlations; one for substrates **3c**, **3d**, **3f**–**3i** [Fig. 4(*a*)] which correlate with Hammett σ substituent constants (ρ = −1.61 ± 0.19) and one for substrates **3a**, **3b** and **3e** [Fig. 4(*b*)] which correlate with σ^+ (ρ = −2.04 ± 0.19). The modest sensitivity in the first case is in accord with the inductive interactions with the developing nitrenium/oxonium character at nitrogen and oxygen in the transition state. In the σ^+ correlation, the sensitivity is in accord with a transition state in which there is a significantly developed positive charge at the benzylic position.

Mutagenesis Studies.—All the substrates we have tested in series **3** are significantly mutagenic in Salmonella strain TA100 without metabolic activation. Of particular relevance is the mutagenicity of **3f**, **3a**, **3b** and **3e**. At 0.25 μmol per plate, the induced revertant levels were 304, 286, 630 and 1093, respectively, and **3e** is one of the most potent mutagens of this class that we have subjected to the Ames test. The failure of substrates **3a**, **3b** and **3e** to form nitrenium ions, even under acid-catalysis therefore lends additional weight to the non-intermediacy of these ions in their mutagenesis. While benzyl cations are also electrophilic species and might be expected to react as such with nucleic acids, our recently reported finding[4]

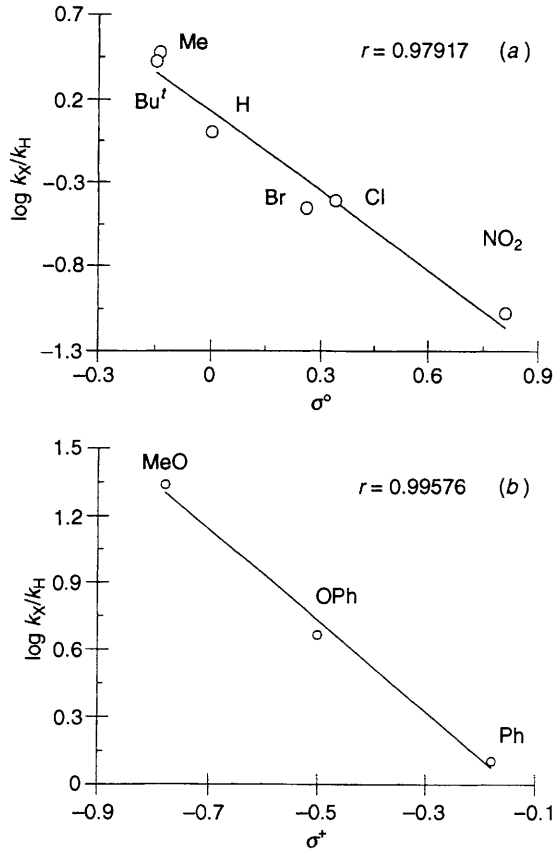


Fig. 4 Hammett relationships for acid-catalysed solvolysis of (*a*) **3c**, **3d**, **3f**–**3i** ($A_{A1}1$ mechanism); (*b*) **3a**, **3b** and **3e** (E1 mechanism)

that nucleophilic amines react at the amide nitrogen at rates some two orders faster than comparative acid-catalysed solvolysis,[3] indicates that at neutral pH, and in the presence of nucleophiles, $A_{A1}1$ and E1 solvolysis are unlikely to compete even though they both lead to electrophilic intermediates. Of significance though is the increased genotoxicity observed with increasing aromatic substitution (**3f** to **3b** and **3e**). A similar trend was found when comparing the metagenicities at 0.25 μmol per plate of *O*-butyl *N*-acetoxybenzamide **1** (R = Bu, X = H, 93 revertants) and *O*-butyl *N*-acetoxybiphenyl-4-carboxamide **1** (R = Bu, X = Ph, 258 revertants). These results suggest that mutagenicity is related to the overall hydrophobicity of these substrates and intercalation with DNA prior to their reaction with nucleosides may be important. A full report on the mutagenicity of alkyl *N*-acetoxybenzohydroxamates will be presented elsewhere.

Experimental

Melting points were determined on a Reichert Microscopic hotstage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1725X FT instrument. 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra were recorded on a Bruker AC-300P FT spectrometer. HPLC analyses were performed on a Waters 510 Analytical instrument using a model 481 UV absorbance detector linked to a Waters 740 data module. Mass spectral data was obtained on a Kratos MS902 spectrometer through the Mass Spectroscopy Unit of Sydney University. Microanalytical data was obtained from The Research School of Chemistry at Canberra. Ames tests were carried out in the Department of Environmental Toxicology at the National Institute of Occupational Health and Safety in Sydney. Acetonitrile used was HiPerSolv, 'Far UV' grade (BDH). Ether refers to anhydrous diethyl ether stored over sodium wire. Dichloromethane (DCM) and acetone were distilled and dried over 4 Å molecular sieve. Ethyl acetate (EtOAc) and methanol (MeOH) were distilled before use. Light petroleum (LP) refers to hexane of the boiling range 60–70 °C. Hydrogen bromide solution was 48% w/w. Anhydrous sodium sulfate or calcium chloride was used for drying all organic mixtures. Flash chromatography was executed on columns loaded with Kieselgel 60 (Merck). Thin layer chromatography was performed on aluminium sheets precoated with 0.2 mm of silica gel 60 F_{254} (Merck). *p*-Nitrobenzyl bromide, *p*-phenoxyacetophenone, *para*-substituted benzoic acids, trideuterioacetonitrile (CD_3CN), 99.5%, deuterium oxide (D_2O), 99.8% and H_2O (10% ^{18}O) were purchased from Aldrich.

General Synthesis Alkyl Benzohydroxamates.—*O*-Butylbenzohydroxamate was prepared according to a literature procedure.[18] The general synthesis of *para*-substituted benzyl benzohydroxamic esters from potassium hydroxamate and the appropriate benzyl bromide has been described.[19] Dideuteriated *p*-substituted benzyl bromides were prepared by reduction of the appropriate carboxylic acid by $LiAlD_4$ in dry THF, followed by bromination of the alcohol with HBr in ether. Dideuteriation of *para*-substituted benzyl alcohol and *para*-substituted benzyl bromides was confirmed by comparison of the ^{1}H and ^{13}C spectra with those of the protio species, as well as the presence of a quintet resonance for the methylene carbon in the ^{13}C spectra. Deuteriated hydroxamates were identified by comparison of their ^{1}H, ^{13}C and mass spectra with the protio species.[3] The alkylation reaction involving *p*-methoxybenzyl bromide and potassium benzohydroxamate did not provide the hydroxamic ester and hence an alternative method is described below.

α,α-*Dideuterio*-p-*methylbenzyl alcohol.* *p*-Toluic acid (3.0 g; 22.1 mmol) was reduced by being refluxed with $LiAlD_4$ (1.01 g, 15 mmol) in dry THF (20 cm^3) for 24 h. Work-up with D_2O provided pure α,α-dideuterio-*p*-methylbenzyl alcohol (99%). $\delta_H(CDCl_3)$ 2.27 (3 H, s), 7.03 (2 H, d) and 7.10 (2 H, d); $\delta_C(CDCl_3)$ 20.92 (q), 63.82 (qt), 126.94 (d), 128.58 (d), 136.88 (s) and 137.68 (s)

α,α-*Dideuterio*-p-*methylbenzyl bromide.* α,α-Dideuterio-*p*-methylbenzyl alcohol (0.85 g, 14.6 mmol) was refluxed in hydrobromic acid (10 cm^3) and sulfuric acid (2 cm^3) for 1 h. Work-up provided pure α,α-dideuterio-*p*-methylbenzyl bromide (75%) which was identical with the protio species by ^{1}H and ^{13}C NMR spectroscopy. $\delta_H(CDCl_3)$ 2.39 (3 H, s), 7.17 (2 H, d) and 7.31 (2 H, d); $\delta_C(CDCl_3)$ 21.13 (q), 33.61 (qt), 128.84 (d), 129.42 (d), 134.74 (s) and 138.19 (s).

α,α-*Dideuterio*-p-*methoxybenzyl alcohol.* *p*-Methoxybenzoic (6 g, 39.4 mmol) acid was reduced by being refluxed with $LiAlD_4$ (0.63 g, 15 mmol) in dry ether (50 cm^3) for 24 h. Work-up with D_2O provided pure α,α-dideuterio-*p*-methoxybenzyl alcohol (76%). $\delta_H(CDCl_3)$ 3.77 (3 H, s), 6.63 (2 H, d) and 7.22 (2 H, d); $\delta_C(CDCl_3)$ 55.24 (q), 63.87 (qt), 113.73 (d), 128.74 (d), 133.04 (s) and 158.94 (s).

α,α-*Dideuterio*-p-*methoxybenzyl bromide.* α,α-Dideuterio-*p*-methoxybenzyl alcohol (2.0 g, 14.6 mmol) was stirred in hydrobromic acid (6 cm^3) and sulfuric acid (0.5 cm^3) for 1 h. Work-up provided pure α,α-dideuterio-*p*-methoxybenzyl bromide (2.82 g, 95%). $\delta_H(CDCl_3)$ 3.77 (3 H, s), 6.91 (2 H, d) and 7.31 (2 H, s); $\delta_C(CDCl_3)$ 55.28 (q), 114.11 (d), 129.88 (s), 130.03 (d) and 159.66 (s).

α,α-*Dideuterio*-p-*phenylbenzyl alcohol.* Biphenyl-4-carboxylic acid (10.0 g, 50.5 mmol) was reduced by being refluxed with $LiAlD_4$ (1.0 g, 25 mmol) in dry ether (70 cm^3) for 30 h. Work-up with D_2O provided pure α,α-dideuterio-*p*-phenylbenzyl alcohol (53%). $\delta_H(CDCl_3)$ 7.41 (1 H, t), 7.47 (4 H, m) and 7.64 (4 H, d); $\delta_C(CDCl_3)$ 64.4 (qt), 127.05 (d), 127.28 (d), 127.45 (d), 128.75 (d), 139.73 (s), 140.59 (s) and 140.78 (s).

α,α-*Dideuterio*-p-*phenylbenzyl bromide.* α,α-Dideuterio-*p*-

phenylbenzyl alcohol (3.4 g, 12.8 mmol) was refluxed in hydrobromic acid (10 cm^3) and sulfuric acid (1 cm^3) for 3 h. Work-up provided pure α,α-dideuterio-*p*-phenylbenzyl bromide (72%). $\delta_H(CDCl_3)$ 7.3 (1 H, t), 7.4 (4 H, m) and 7.5 (4 H, m); $\delta_C(CDCl_3)$ 32.89 (qt), 127.08 (d), 127.34 (d), 127.49 (d), 128.61 (d), 129.28 (d), 136.55 (s), 140.49 (s) and 141.06 (s).

*α,α-Dideuterio-*p*-nitrobenzyl alcohol.* *p*-Nitrobenzoic acid (15 g, 90 mmol) was treated with PCl_5 (18 g) to give *p*-nitrobenzoyl chloride in 85% yield. Reduction of the acyl chloride by $NaBD_4$ in dioxane gave, upon work-up, α,α-dideuterio-*p*-nitrobenzyl alcohol (80%). $\delta_H(CDCl_3)$ 7.30 (2 H, d) and 8.04 (2 H, d); $\delta_C(CDCl_3)$ 63.27 (qt), 123.48 (d), 126.87 (d), 146.98 (s) and 148.45 (s).

*α,α-Dideuterio-*p*-nitrobenzyl bromide.* α,α-Dideuterio-*p*-nitrobenzyl alcohol (2.67 g, 17.3 mmol) was refluxed in hydrobromic acid (10 cm^3) and sulfuric acid (1 cm^3) for 12 h. Work-up provided pure α,α-dideuterio-*p*-nitrobenzyl bromide (0.4 g, 11%). $\delta_H(CDCl_3)$ 7.41 (2 H, d) and 8.06 (2 H, d); $\delta_C(CDCl_3)$ 30.71 (qt), 123.85 (d), 129.80 (d), 144.59 (s) and 147.47 (s).

*α,α-Dideuterio-*p*-nitrobenzyl benzohydroxamate.* Refluxing potassium benzohydroxamate (0.32 g, 1.8 mmol), α,α-dideuterio-*p*-nitrobenzyl bromide (0.4 g, 1.84 mmol) and sodium carbonate (0.2 g) in MeOH–H_2O (20 cm^3:20 cm^3) for 2 h provided pure α,α-dideuterio-*p*-nitrobenzyl benzohydroxamate (0.342 g, 65%) after work-up and recrystallisation ($CHCl_3$–LP). M.p. 159–161 °C, $\delta_H(CDCl_3)$ 7.41 (2 H, t), 7.54 (1 H, t), 7.62 (2 H, d), 7.69 (2 H, d), 8.22 (2 H, d) and 8.78 (1 H, br); $\delta_C(CDCl_3)$ 77.20 (qt), 123.79 (dd), 127.00 (d), 128.84 (d), 129.53 (d), 131.40 (fine t), 132.46 (dt), 142.45 (s), 148.08 (s) and 167.02 (s); *m*/*z* 274 (M^+, 6%), 138 (15, $CD_2C_6H_4NO_2^+$), 105 (100), 77 (38) and 51 (15).

p-*Nitrobenzyl benzohydroxamate.* Potassium benzohydroxamate (4.05 g, 23.1 mmol), *p*-nitrobenzyl bromide (5.0 g, 23.1 mmol) and sodium carbonate (3.0 g, 28 mmol) provided the crude hydroxamate *via* the general procedure. Pure *p*-nitrobenzyl benzohydroxamate (5.92 g, 94%) was obtained as pale yellow crystals upon recrystallisation ($CHCl_3$–LP), m.p. 159–161 °C (Found: C, 61.4; H, 4.3; N, 10.05. $C_{14}H_{12}N_2O_4$ requires C, 61.76; H, 4.44; N, 10.29%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3393 (NH) and 1691 (CO); $\delta_H(CDCl_3)$ 5.14 (2 H, s), 7.42 (2 H, t, J = 7 Hz, *m*-Ar), 7.51 (1 H, t, J = 7 Hz, *p*-Ar), 7.62 (2 H, d, J = 7 Hz, *o*-Ar), 7.65 (2 H, d, J = 8.4 Hz, *o'*-Ar), 8.22 (2 H, d, J = 6.9 Hz, *m'*-Ar) and 8.79 (1 H, br); $\delta_C(CD_3CN)$ 77.39 (t), 124.46 (dd), 128.04 (dt), 129.58 (d), 130.86 (d), 132.91 (dt), 133.18 (s), 144.62 (s), 148.99 (s) and 166.59 (s); *m*/*z* 272 (M^+, 5%), 136 (12, $CH_2C_6H_4NO_2^+$), 121 (25), 105 (100), 91 (25) and 77 (45).

*α,α-Dideuterio-*p*-phenylbenzyl benzohydroxamate.* Potassium benzohydroxamate (1.0 g; 5.7 mmol), α,α-dideuterio-*p*-phenylbenzyl bromide (1.4 g, 5.6 mmol) and sodium carbonate (1.4 g) in refluxing dry THF provided pure α,α-dideuterio-*p*-phenylbenzyl benzohydroxamate (1.01 g, 59%) after work-up and recrystallisation ($CHCl_3$–LP). M.p. 177–179 °C, $\delta_H(CDCl_3)$ 7.38–7.53 (8 H, m), 7.58 (4 H, m) and 7.67 (2 H, d); $\delta_C(CDCl_3)$ 126.12 (d), 126.34 (s), 126.67 (s), 127.68 (dd), 128.11 (d), 128.98 (s), 130.45 (s), 130.98 (dt) and 164.91 (s); *m*/*z* 290 (25%, M − 15^+), 181 (20), 169 (60, $CD_2C_6H_4C_6H_5^+$), 152 (32), 105 (100) and 77 (60).

p-*Phenylbenzyl benzohydroxamate.* Potassium benzohydroxamate (2.4 g, 13 mmol), *p*-phenylbenzyl bromide (2.4 g, 13 mmol) and sodium carbonate (3.0 g, 28 mmol) provided pure *p*-phenylbenzyl benzohydroxamate (0.62 g, 16%) after work-up and recrystallisation ($CHCl_3$–hexane), m.p. 177–179 °C (Found: C, 79.05; H, 5.85; N, 4.35. $C_{20}H_{17}NO_2$ requires C, 79.19; H, 5.65; N, 4.62%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3320 (NH) and 1674 (CO); $\delta_H(CD_3COCD_3)$ 5.03 (2 H, s), 7.22 (1 H, t), 7.39 (4 H, m), 7.42 (1 H, t), 7.49 (2 H, d), 7.58 (4 H, d), 7.63 (2 H, d) and 9.62 (1 H, br); δ_C(50% $CDCl_3$–CD_3CN) 126.05 (d), 126.20 (s), 126.66 (s), 127.68 (dd), 128.03 (d), 128.94 (s), 130.62 (s), 130.92 (dt) and 164.91 (s); *m*/*z* 303 (M^+, 5%), 288 (55), 286 (50), 182 (65), 181 (85), 167 (100, $CH_2C_6H_4H_5^+$), 152 (50), 121 (40), 105 (60) and 77 (60).

*α,α-Dideuterio-*p*-methylbenzyl benzohydroxamate.* Potassium benzohydroxamate (0.60 g, 3.43 mmol), α,α-dideuterio-*p*-methylbenzyl bromide (0.64 g, 3.42 mmol) and sodium carbonate (1.1 g, 10.3 mmol) were reluxed for 3 h in dry THF. Work-up and recrystallisation ($CHCl_3$–LP) provided pure α,α-dideuterio-*p*-methylbenzyl benzohydroxamate (0.62 g, 75%). $\delta_H(CDCl_3)$ 2.33 (3 H, s), 7.11 (2 H, d), 7.27 (2 H, d), 7.34 (2 H, t), 7.45 (1 H, t) and 7.69 (2 H, d); $\delta_C(CDCl_3)$ 21.11 (q), 127.07 (d), 128.42 (d), 129.08 (d), 129.30 (d), 131.65 (dt), 131.77 (s), 131.99 (s), 138.39 (s) and 166 (s); *m*/*z* 205 (35%), 121 (15), 107 (100, $CD_2C_6H_4CH_3^+$), 105 (38), 91 (30), 77 (42) and 51 (41).

p-*Methylbenzyl benzohydroxamate.* Potassium benzohydroxamate (7.33 g, 42 mmol), *p*-methylbenzyl bromide (7.74 g, 41.9 mmol) and sodium carbonate (5.55 g, 51.9 mmol) provided pure *p*-methylbenzyl benzohydroxamate (5.92 g, 59%) *via* the general procedure after work-up and recrystallisation ($CHCl_3$–hexane), m.p. 106–107 °C (Found: C, 74.35; H, 6.25; N, 5.55. $C_{15}H_{15}NO_2$ requires C, 74.67; H, 6.27; N, 5.80%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3200 (NH) and 1681 (CO); $\delta_H(CDCl_3)$ 2.33 (3 H, s), 4.93 (2 H, s), 7.11 (2 H, d, J 7.8 Hz), 7.29 (2 H, d, J 7.8 Hz), 7.34 (2 H, t, J 7.6 Hz, *m*-Ar), 7.45 (1 H, t, J 7.6 Hz, *p*-Ar), 7.68 (2 H, d, J 7 Hz, *o*-Ar) and 9.62 (1 H, br); $\delta_C(CDCl_3)$ 21.09 (q), 77.96 (t), 127.07 (dt), 128.40 (dd), 129.06 (d), 129.24 (d), 131.74 (dt, *p*-Ar), 131.85 (s), 132.14 (fine t), 138.33 (s, *p'*-Ar) and 166.24 (s); *m*/*z* 240 (5%), 136 (13), 121 (25), 105 (100, $CH_2C_6H_4CH_3^+$), 77 (70) and 51 (40).

*α,α-Dideuterio-*p*-methoxybenzyl benzohydroxamate.* Benzohydroxamic acid (2.4 g, 14.7 mmol), α,α-dideuterio-*p*-methoxybenzyl bromide (2.03 g, 14.7 mmol) and triethylamine (3 g) were stirred at room temperature in ether (30 cm^3) for 20 h. Work-up and recrystallisation (EtOH–H_2O) provided pure α,α-dideuterio-*p*-methoxybenzyl benzohydroxamate (0.50 g, 13%). M.p. 115–118 °C, $\delta_H(CDCl_3)$ 3.79 (3 H, s), 6.86 (2 H, d), 7.33 (2 H, d), 7.38 (2 H, t), 7.54 (1 H, t) and 7.66 (2 H, d); $\delta_C(CDCl_3)$ 55.11 (q), 113.76 (d), 127.04 (d), 127.16 (s), 128.46 (d), 130.92 (d), 131.79 (d), 131.86 (s), 159.81 (s) and 166.23 (s); *m*/*z* 259 (M^+, 1%), 242 (60), 123 (100, $CD_2C_6H_4OCH_3^+$), 105 (40), 77 (53) and 51 (20).

p-*Methoxybenzyl benzohydroxamate.* Benzohydroxamic acid (1.4 g, 10 mmol), *p*-methoxybenzyl chloride (1.6 g, 10 mmol) and triethylamine (3.0 g, 30 mmol) were refluxed in $CHCl_3$ (30 cm^3) for 2 h. After being washed consecutively with 10% aq. sodium carbonate and dilute HCl, the organic layer was dried and the solvent removed *in vacuo* to afford the crude hydroxamate. Recrystallisation (EtOH–H_2O) provided pure *p*-methoxybenzyl benzohydroxamate (0.48 g, 19%), m.p. 119–121 °C (Found: C, 70.2; H, 6.05; N, 5.4. $C_{15}H_{15}NO_3$ requires C, 70.02; H, 5.88; N, 5.44%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3407 (NH) and 1684 (CO); $\delta_H(CDCl_3)$ 3.75 (3 H, s), 4.92 (2 H, s), 6.62 (2 H, d, J 9 Hz, *m'*-Ar), 7.31 (2 H, d, J 9 Hz, *o'*-Ar), 7.34 (2 H, t, J 7 Hz, *m*-Ar), 7.43 (1 H, t, J 7 Hz, *p*-Ar) and 7.68 (2 H, d, J 7 Hz, *o*-Ar); $\delta_C(CDCl_3)$ 55.15 (q), 77.78 (t), 113.80 (d, *m'*-Ar), 127.05 (d, *o*-Ar), 127.33 (s), 128.48 (d, *m*-Ar), 130.94 (d, *o'*-Ar), 131.79 (d, *p*-Ar) and 159.83 (s); *m*/*z* 257 (M^+, 55%), 135 (40), 121 (100, $CH_2C_6H_4OCH_3$), 105 (50), 77 (60) and 51 (50).

N-*Chlorination of benzohydroxamic Esters.*—By analogy with the protio compounds,[3] *N*-chlorination was affected quantitatively upon treatment of the benzohydroxamic esters with a 3 mol dm^{-3} excess of *tert*-butyl hypochlorite in DCM or $CHCl_3$ at room temperature for 4–12 h. The *N*-chloro compounds were isolated by removal of solvent and excess *tert*-butyl hypochlorite under reduced pressure and used without further purification.

O-(*α,α-Dideuterio-*p*-methylbenzyl*) N-*chlorobenzohydroxa-*

mate. The title compound was prepared by dissolving the solid *O*-(α,α-dideuterio-*p*-methylbenzyl) benzohydroxamate (0.56 g, 1.85 mmol) in acetonitrile (50 cm^3) and DCM (50 cm^3). Stirring in the dark with *tert*-butyl hypochlorite for 2 h, and removal of the solvent under reduced pressure provided the title compound which was used without further purification.

General Synthesis of O-(p-*Substituted Benzyl*) N-*Acetoxybenzohydroxamates.*—*O*-(*p*-Substituted benzyl) *N*-chlorobenzohydroxamates were stirred in the dark with 1.4 mol equiv. of anhydrous sodium acetate in dry acetone, at room temp., for 12–72 h. The progress of the reaction was monitored by formation of the acetoxy peak in the ^1H NMR spectrum. Filtration and concentration provided the *N*-acetoxy derivatives which were purified by chromatography. Apart from the absence of benzylic signals at *ca.* δ 5.1 in the ^1H NMR spectrum and the reduced intensity or absence of a quintet at 76–77 ppm in the ^{13}C NMR spectrum, the spectra were essentially identical with the protio species.[3]

O-(α,α-*Dideuterio*-p-*nitrobenzyl*) N-*acetoxybenzohydroxamate* **3m**. Anhydrous sodium acetate (0.12 g, 1.4 mmol) was added in one portion to a stirred solution of *O*-(α,α-dideuterio-*p*-nitrobenzyl) *N*-chlorobenzohydroxamate (0.31 g, 1 mmol) in dry acetone (20 cm^3). After being stirred at room temperature for 24 h, the mixture was filtered. Removal of the solvent *in vacuo* and flash chromatography (90% LP–10% EtOAc) provided the title compound as a yellow solid in 87% yield. $\delta_H(CDCl_3)$ 2.04 (3 H, s), 7.40 (2 H, t), 7.54 (1 H, t), 7.57 (2 H, d), 7.69 (2 H, d) and 8.16 (2 H, d); $\delta_C(CDCl_3)$ 18.41 (q), 75.40 (qt), 123.35 (dd), 128.22 (d), 128.65 (d), 129.15 (d), 131.08 (fine t), 132.85 (dt), 142.04 (s), 147.66 (s), 168.01 (s) and 173.98 (s).

O-(α,α-*Dideuterio*-p-*methylbenzyl*) N-*acetoxybenzohydroxamate* **3l**. Anhydrous sodium acetate (0.17 g, 2.1 mmol) was added to *O*-(α,α-dideuterio-*p*-methylbenzyl) *N*-chlorobenzohydroxamate (0.41 g, 1.49 mmol) in dry acetone. Stirring at room temperature for 36 h followed by filtration and removal of solvent *in vacuo* provided the crude mixture. Purification by flash chromatography (90% LP–10% EtOAc) provided the pure compound (48%) as a pale yellow oil. $\delta_H(CDCl_3)$ 2.04 (3 H, s), 2.34 (3 H, s), 7.13 (2 H, d), 7.3 (2 H, d), 7.41 (2 H, t), 7.52 (1 H, t) and 7.76 (2 H, d); $\delta_C(CDCl_3)$ 18.68 (q), 21.21 (q), 128.23 (d), 129.05 (d), 129.12 (d), 129.25 (d), 131.57 (s), 131.65 (s), 132.68 (d), 138.50 (s), 168.14 (s) and 174.09 (s).

O-(α,α-*Dideuterio*-p-*phenylbenzyl*) N-*acetoxybenzohydroxamate* **3k**. Anhydrous sodium acetate (0.21 g, 2.59 mmol) was added to *O*-(α,α-dideuterio-*p*-phenylbenzyl) *N*-chlorobenzohydroxamate (0.63 g, 1.85 mmol) in dry acetone. Stirring in the dark at room temperature for 24 h followed by filtration and removal of solvent *in vacuo* provided the crude mixture. Purification by flash chromatography (92% LP–8% EtOAc) provided the title compound (60%) as a viscous oil. $\delta_H(CDCl_3)$ 2.10 (3 H, s), 7.39–7.6 (8 H, m), 7.62 (4 H, d) and 7.81 (2 H, d); $\delta_C(CDCl_3)$ 18.43 (q), 126.84 (dd), 126.94 (dd), 127.29 (dt), 128.08 (d), 128.60 (d), 128.82 (d), 129.51 (d), 131.43 (s), 132.57 (dt), 133.37 (s), 140.28 (s), 141.34 (s), 167.91 (s) and 173.96 (s).

O-(α,α-*Dideuterio*-p-*methoxybenzyl*) N-*acetoxybenzohydroxamate* **3j**. *O*-(α,α-Dideuterio-*p*-methoxybenzyl) *N*-chlorobenzohydroxamate (0.38 g, 1.29 mmol) was stirred with sodium acetate (0.15 g, 1.82 mmol) in the dark in dry acetone at room temperature for 14 h. Filtration and removal of the solvent *in vacuo* provided the crude product. Purification by flash chromatogrphy (85% LP–15% EtOAc) provided the title compound (44%) as a pale yellow oil. $\delta_H(CDCl_3)$ 2.06 (3 H, s), 3.77 (3 H, s), 6.83 (2 H, d), 7.27 (2 H, d), 7.38 (2 H, t), 7.51 (1 H, t) and 7.69 (2 H, d); $\delta_C(CDCl_3)$ 18.64 (q), 55.13 (q), 113.75 (d), 126.50 (s), 128.15 (dd), 128.94 (dt), 130.91 (dq), 131.58 (fine t), 132.62 (dt), 159.92 (s), 168.06 (s) and 174.07 (s).

Ester Crossover Experiment.—A solution of butyl *N*-acetoxy-*p*-chlorobenzohydroxamate[3] (0.01282 mmol) and benzyl *N*-acetoxybenzohydroxamate (0.01172 mmol) in 25% aq. acetonitrile (50.00 cm^3) was equilibrated for 1 h at 298 K. Dilute aq. H_2SO_4 (1.31 cm^3, 2.55 mol dm^{-3}) was added and the reaction was stirred for 15 h. Analytical HPLC analysis of the complex reaction mixture revealed the presence of benzyl benzoate (54%), butyl *p*-chlorobenzoate (33%) and a complete lack of the crossover esters, benzyl *p*-chlorobenzoate and butyl benzoate.

Kinetic Studies.—The acid-catalysed solvolysis of the *N*-acetoxy substrates were monitored in the probe of a Bruker AC300P NMR spectrometer at 308 K. 10–40 mg of substrate in CD_3CN (400 mm^3) were diluted with D_2O such that after addition of an appropriate volume (2-15 mm^3) of a solution of sulfuric acid in D_2O (typically 0.5–1.5 mol dm^{-3}), the ratio of $CD_3CN:D_2O$ was constant at 3.81:1. The acid solution was agitated into the mixture to initiate reaction immediately prior to insertion into the probe. ^1H NMR spectra were acquired automatically at pre-programmed intervals and the peak areas for the acetoxy methyl singlet were obtained by integration. Yields of products from the solvolysis of **1** (R = Bu) (Table 1) were determined by integration and comparison with the signal for the acetoxy methyl singlet at the start of the solvolysis. Similar reaction mixtures involving **3** were analysed by HPLC after complete conversion into products (Table 2).

Acid concentrations and pseudo-first-order rate constants obtained in determining secondary kinetic isotope effects are given below:

3a (MeO/H)		**3j** (MeO/D)		**3c** (Me/H)		**3l** (Me/D)	
$[H^+]/10^{-2}$ mol dm^{-3}	$k/10^{-3}$ s^{-1}	$[H^+]/10^{-2}$ mol dm^{-3}	$k/10^{-3}$ s^{-1}	$[H^+]/10^{-2}$ mol dm^{-3}	$k/10^{-4}$ s^{-1}	$[H^+]/10^{-2}$ mol dm^{-3}	$k/10^{-4}$ s^{-1}
3.472	5.143	3.455	3.930	2.962	6.979	2.962	7.015
2.285	3.195	2.276	2.831	2.088	4.980	2.088	4.844
1.717	2.331	1.678	2.052	0.431	1.179	1.289	3.158
1.135	1.502	1.136	1.393			0.431	1.082
0.572	0.844	0.569	0.674				
3e (Ph/H)		**3k** (Ph/D)		**3i** (NO_2/H)		**3m** (NO_2/D)	
$[H^+]/10^{-2}$ mol dm^{-3}	$k/10^{-4}$ s^{-1}	$[H^+]/10^{-2}$ mol dm^{-3}	$k/10^{-4}$ s^{-1}	$[H^+]/10^{-2}$ mol dm^{-3}	$k/10^{-5}$ s^{-1}	$[H^+]/10^{-2}$ mol dm^{-3}	$k/10^{-5}$ s^{-1}
8.500	7.408	8.500	6.229	10.298	6.604	10.304	6.508
6.375	5.6468	6.375	4.6319	6.860	4.185	6.694	3.946
4.250	4.2418	4.250	2.958	2.950	1.773	3.402	2.194
2.763	2.4518	2.763	1.911	2.705	1.610	1.085	0.841
1.063	0.943	1.063	0.810	1.705	1.298		
				1.355	0.891		
				0.556	0.482		

Oxidation of Benzohydroxamic Acid in the Presence of Cyclopentadiene.—Benzohydroxamic acid was generated by acidification and crystallisation of potassium benzohydroxamate (20 g) in glacial acetic acid.[20] Recrystallisation from EtOAc provided the pure compound, m.p. 126–128 °C. Cyclopentadiene was prepared by distillation according to a standard literature procedure.[21]

Trapping Experiments with Cyclopentadiene.—*3-Benzoyl-2-oxa-3-azabicyclo*[2.2.1]*hept-5-ene.* The title compound was prepared according to a literature procedure.[9] *N*-Bromosuccinimide (1.78 g, 10 mmol) was added over 10 min to a stirred solution of benzohydroxamic acid (1.37 g, 10 mmol), pyridine (0.79 g, 10 mmol) and cyclopentadiene (3.5 cm^3) in DCM (50 cm^3). After the solution had cleared, the organic layer was washed consecutively with water, sat. Na_2CO_3 and water, dried ($CaCl_2$) and then concentrated *in vacuo*. Flash chromatography ($CHCl_3$) and normal-phase preparative chromatography ($CHCl_3$), provided pure 3-benzoyl-2-oxa-3-azabicyclo-[2.2.1]hept-5-ene (1.55 g, 77%) as a gummy oil. The structure was characterized from ^1H, COSY, gated decoupled and $^1J_{CH}$ correlated ^{13}C spectra at 323 K. $\delta_H([^2H_6]Me_2SO)$ 1.77 (1 H, d), 1.99 (1 H, dd), 5.26 (1 H, s), 5.41 (1 H, s), 6.38 (1 H, d), 6.51 (1 H, s), 7.39 (2 H, t), 7.54 (1 H, t) and 7.72 (2 H, d); $\delta_C([^2H_6]Me_2SO)$ 47.75 (t), 63.99 (s), 83.91 (s), 127.83 (d, *m*), 128.09 (d, *o*), 131.03 (d, *p*), 132.94 (d), 134.15 (s), 135.01 (s) and 171.02 (s); *m*/*z* 203 (M^+ + 2, 0.1%), 201 (M^+, 4.2), 122 (58), 105 (100), 77 (90) and 51 (41). A second independent experiment gave: *m*/*z* 203 (M^+ + 2, 0.1%) and 201 (M^+, 4.3).

Bicycloadduct from solvolysis of **1** (R = Bu, X = H) *in* H_2O–CH_3CN.—*O*-Butyl *N*-acetoxybenzohydroxamate (125 mg, 0.49 mmol) was stirred for 6 h at 308 K in an acidified solution (H_2SO_4, 170 mm^3; 0.5 mol dm^{-3}) of freshly prepared cyclopentadiene (198 mg, 3 mmol) in acetonitrile (4.0 cm^3) and water (1.0 cm^3). The solvent was removed under reduced pressure and washed with Na_2CO_3 (10%) and water and extracted with DCM. 3-Benzoyl-2-oxa-3-azabicyclo[2.2.1]-hept-5-ene was separated by normal-phase preparative HPLC (1.4 mg, 1.4%). *m*/*z* 203 (M^+ + 2, *ca.* 0.0%), 201 (M^+, 4.5), 105 (100), 77 (45) and 51 (20).

Bicycloadduct from solvolysis of **1** (R = Bu, X = H) *in* H_2-^{18}O–CH_3CN.—*O*-Butyl *N*-acetoxybenzohydroxamate (324.2 mg, 1.084 mmol) was stirred for 4 h at 308 K in an acidified solution (H_2SO_4, 70 mm^3; 0.4 mol dm^{-3}) of freshly prepared cyclopentadiene (143 mg, 2.17 mmol) in acetonitrile (3.5 cm^3) and water (0.92 cm^3; 10% ^{18}O-labelled). The solvent was removed under reduced pressure and the residue was treated with Na_2CO_3 (10%), water and extracted with DCM. 3-Benzoyl-2-oxa-3-azabicyclo[2.2.1]hept-5-ene was separated by normal-phase preparative HPLC. *m*/*z* 203 (M^+ + 2, 0.4%), 201 (M^+, 2.7), 105 (100), 77 (75) and 51 (25).

Bicycloadduct from Solvolysis of **3a**.—*O*-(*p*-Methoxybenzyl) *N*-acetoxybenzohydroxamate **3a** (210 mg, 0.817 mmol) was stirred for 6 h at 308 K in an acidified solution (H_2SO_4, 50 mm^3; 0.25 mol dm^{-3}) of freshly prepared cyclopentadiene (0.054 g, 0.628 mmol) in acetonitrile (4 cm^3) and water (10% ^{18}O-labelled, 1 cm^3). After removal of the solvent *in vacuo*, the residue was washed with Na_2CO_3 (10%) and water and extracted with DCM. Concentration afforded the crude reaction mixture from which 3-benzoyl-2-oxa-3-azabicyclo[2.2.1]-hept-5-ene was separated by normal-phase preparative HPLC (6%, based on **3a**). *m*/*z* 203 (M^+ + 2, *ca.* 0.0%), 201 (M^+, 5.2), 105 (100), 77 (30) and 51 (8). ^{18}O-Labelled *p*-methoxybenzyl alcohol was also isolated, *m*/*z* 140 (M^+ + 2, 10.3%), 138 (M^+, 100), 137 (71.8), 121 (58), 109 (64), 77 (35) and 51 (10).

^{18}O-*Labelled* p-*Methoxybenzyl Alcohol* via *an Alternative Method.*—*p*-Methoxybenzyl bromide (0.5 g, 3.6 mmol) was stirred in approximately 25% aqueous acetonitrile (10% ^{18}O-water) for 64 h. The solution was reduced *in vacuo* and rediluted with DCM. Washing with 5% w/v sodium carbonate, water and removal of solvent *in vacuo*, provided pure *p*-methoxybenzyl alcohol. The ^1H and ^{13}C spectra were identical with authentic *p*-methoxybenzyl alcohol. *m*/*z* 140 (M^+ + 2, 10.3%), 138 (M^+, 85), 137 (84.3), 121 (100), 109 (58), 77 (44) and 51 (15).

p-*Methoxybenzyl Alcohol without* ^{18}O.—Reduction of *p*-methoxybenzaldehyde with sodium borohydride in ethanol–water provided the title compound as a clear oil, *m*/*z* 140 (M^+ + 2, 0.7%), 138 (M^+, 100), 137 (74.5), 121 (93), 109 (63), 77 (40) and 51 (15).

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References

1 J. J. Campbell, S. A. Glover and C. A. Rowbottom, *Tetrahedron Lett.*, 1990, **31**, 5377.
2 R. G. Gerdes, S. A. Glover, J. F. Ten Have and C. A. Rowbottom, *Tetrahedron Lett.*, 1989, **30**, 2649.
3 J. J. Campbell, S. A. Glover, G. P. Hammond and C. A. Rowbottom, *J. Chem. Soc., Perkin Trans. 2*, 1991, 2067.
4 J. J. Campbell and S. A. Glover, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1661.
5 J. E. Rowe and A. D. Ward, *Aust. J. Chem.*, 1968, **21**, 2761.
6 G. W. Kirby, 'Electrophilic *C*-nitroso-Compounds', *Chem. Soc. Rev.*, 1977, 1.
7 G. W. Kirby and J. G. Sweeny, *J. Chem. Soc., Chem. Commun.*, 1973, 704.
8 J. E. T. Corrie, G. W. Kirby and J. W. M. Mackinnon, *J. Chem. Soc., Perkin Trans. 1*, 1985, 883.
9 L. H. Dao, J. M. Dust, D. Mackay and K. N. Watson, *Can. J. Chem.*, 1979, **57**, 1712.
10 J. E. T. Corrie, G. W. Kirby and R. P. Sharma, *J. Chem. Soc., Chem. Commun.*, 1975, 915.
11 G. W. Kirby and J. W. M. Mackinnon, *J. Chem. Soc., Chem. Commun.*, 1977, 23.
12 D. L. Boger and M. Patel, *J. Org. Chem.*, 1984, **49**, 4098.
13 J. E. T. Corrie, G. W. Kirby and J. W. M. Mackinnon, *J. Chem. Soc., Perkin Trans. 1*, 1985, 883.
14 A. Defoin, C. Schmidlin and J. Streith, *Tetrahedron Lett.*, 1984, **25**, 4515.
15 H. Iida, Y. Watanabe and C. Kibayashi, *J. Org. Chem.*, 1985, **50**, 1818.
16 G. Just and L. Cutrone, *Can. J. Chem.*, 1976, **54**, 867.
17 N. S. Isaacs, *Physical Organic Chemistry*, Longman, Harlow, UK, 1987, pp. 263–268.
18 A. T. Fuller and H. King, *J. Chem. Soc.*, 1947, 963.
19 J. H. Cooley, W. D. Bills and J. R. Throckmorton, *J. Org. Chem.*, 1960, **25**, 1734.
20 *Org. Synth.*, Coll. Vol. II, ed. A. H. Blatt, Wiley, New York, 1963, p. 67.
21 A. I. Vogel, *A Text Book of Practical Organic Chemistry*, 2nd edn., Longmans Green, London, 1951, p. 67.

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