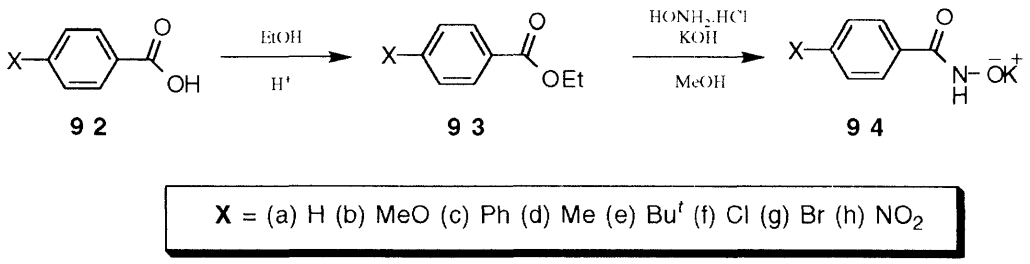
CHAPTER TWO

2. Acid-catalysed solvolysis of alkyl *N*-acyloxybenzohydroxamates

2.1 General synthesis of alkyl *N*-acyloxybenzohydroxamates

The aim of this thesis is an investigation of the reactivity of alkyl *N*-acyloxybenzohydroxamates. This new class of mutagens were first synthesised by Glover[167] by acetoxylation of alkyl benzohydroxamates with silver acetate, but this procedure was subsequently found to be unsuccessful in a number of cases. Thus a versatile synthesis of a wide range of mutagens was developed, based on work by Glover[167] and Cooley.[168] The versatility of this new synthesis arises from the ease of variation in the alkyl and acyl groups, with the potential for a wide range of "designer mutagens" to be developed.



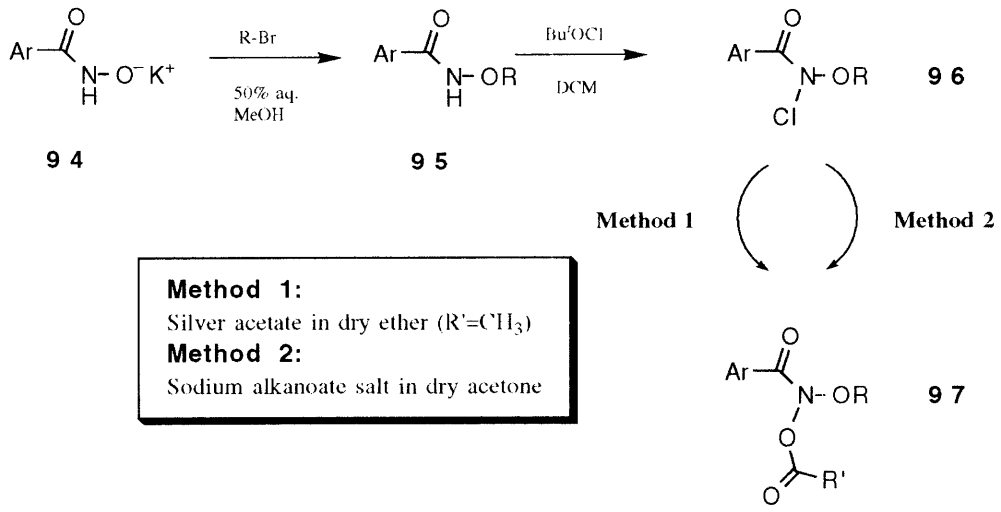
92 **93** **94**

X = (a) H (b) MeO (c) Ph (d) Me (e) Bu^t (f) Cl (g) Br (h) NO_2

Scheme 2-1 Synthesis of potassium benzohydroxamates

Potassium benzohydroxamate salts **94** were obtained through treatment of the appropriate ethyl benzoate esters **93** with hydroxylamine hydrochloride under basic conditions in methanol. The salts precipitated in moderate to good yields over time with refrigeration.

Ethyl esters **93** were obtained by classical esterification of the appropriate benzoic acids **92** with excess ethanol under acidic conditions and were purified by distillation and characterised by b.p., IR, ^1H and ^{13}C NMR spectroscopy.



Scheme 2-2 General syntheses of alkyl *N*-acyloxybenzohydroxamates

Alkyl benzohydroxamates **95** were synthesised in good yield by alkylation of the potassium benzohydroxamate salt **94** with bromoalkane in refluxing 50% aqueous methanol (Scheme 2-2). Generally, alkyl bromides were either purchased or synthesised by bromination of the corresponding alcohol using hydrobromic acid.

Simple straight chain alkyl benzohydroxamates **95** were found to be light, clear oils which were unstable and degraded over several weeks to complex mixtures. As a result, benzohydroxamic esters were usually purified by flash column chromatography immediately prior to use. Several butyl *para*-substituted benzohydroxamic esters were obtained as low melting point solid compounds that could be satisfactorily recrystallised from chloroform and hexane.

All alkyl benzohydroxamates **95** were satisfactorily characterised by b.p. or m.p., IR, microanalysis, mass spectra and NMR spectroscopy.

Alkyl benzohydroxamates **95** were first converted to their *N*-chloro derivatives **96** using a 3*M* excess of *t*-butyl hypochlorite at room temperature in dichloromethane (Scheme 2-2). Reaction times varied from 2-12 hours but ^{1}H NMR provided a convenient diagnostic test to determine the progress of the reaction. Chlorination of the alkyl benzohydroxamates **95** generally resulted in a downfield shift of approximately 0.15 ppm to the 1'-methylene protons of the alkyl moiety. Removal of solvent *in vacuo* provided the alkyl *N*-chlorobenzohydroxamates **96** as yellow oils that could not be purified by flash

chromatography but were sufficiently clean to be used immediately without further purification. Two general methods were used for acetoxylation of the *N*-chlorobenzohydroxamic esters (Scheme 2-2).

Method One developed by Glover and co-workers[167] involved treating the alkyl *N*-chlorobenzohydroxamates **96** with a 2 molar equivalent of the Lewis acid, silver acetate, in dry ether. The mechanism of acetoxylation probably proceeds *via* a silver catalysed heterolysis of the N–Cl bond to form a nitrenium ion that is trapped by the acetate anion. Where this method was successful, fair to good yields were obtained.

Method Two involved stirring **96** at room temperature with a 1.4 molar excess of anhydrous sodium alkanoate salt for 12-48 hours in anhydrous acetone. Solid NaCl crystallising above the surface of the dry acetone was an excellent indicator that the *N*-acylation was proceeding smoothly. The acylation reaction could not be allowed to stir indefinitely in dry acetone as the yield of alkyl *N*-acyloxybenzohydroxamate **97** reached a maximum and then slowly reduced. An excess of sodium acetate significantly greater than 1.4 molar generally reduced the yield of **97** and increased the amount of (principally benzoate ester) contaminants. The mechanism of acetoxylation for Method Two most probably involves an S_N2 process.[j]

The progress of *N*-acyloxylation was monitored by reverse-phase HPLC analysis or in the case of alkyl *N*-acetoxybenzohydroxamates, through ^{1}H NMR spectroscopy by observing the formation of the resonance for the *N*-acetoxy peak at δ2.05.

Filtration and removal of solvent *in vacuo* at room temperature provided the crude alkyl *N*-acyloxybenzohydroxamates which were purified by flash chromatography in fair to excellent yields. Potential instability and possible hazards precluded mass spectra and

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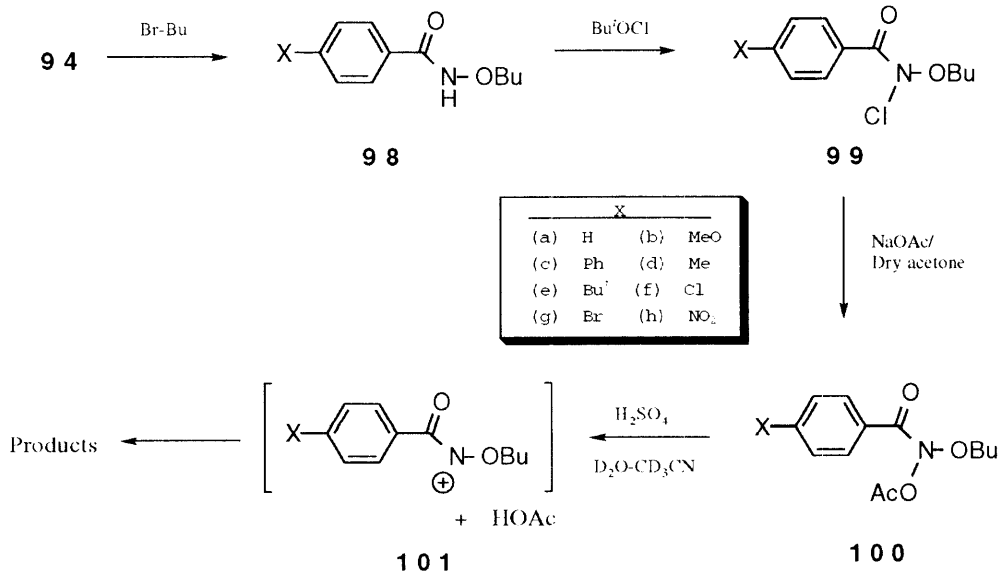
[j] Nucleophilic substitution of chlorine in ONCl compounds has been reviewed by Rudchenko.[116] Heterolysis of the chlorine is facilitated by $n_{\pi(O)}$-$\sigma^*_{N\text{-}Cl}$ interaction which destabilises the N-Cl bond allowing nucleophilic substitution to occur under mild conditions.[169,170] Glover *et al* have also found that the aqueous alcoholysis of alkyl *N*-chlorobenzohydroxamate provides good yields of alkyl *N*-alkoxybenzohydroxamates.[167]

microanalytical analysis, and **97** were satisfactorily characterised from IR, ^{1}H, gated decoupled and where needed $^{1}J_{CH}$ correlated ^{13}C spectra at 298K. The infrared spectra for alkyl *N*-acetoxybenzohydroxamates displayed two strong characteristic carbonyl absorptions at approximately 1730 cm^{-1} and 1790 cm^{-1}. The high amide carbonyl absorptions at 1730 cm^{-1} are indicative of a low amide isomerisation barrier. This has been interpreted to indicate a pyramidal nitrogen geometry and these compounds are considered to be members of the class of the so-called "anomeric amides". Anomeric effects are possible in such compounds and lead to significantly increased N–OR rotational barriers.[169,171,172]

The non-diastereotopic nature of the methylene protons NO-CH_2Ph on the alkyl side chain which was evident from the single sharp resonance at *ca.* δ 5.2 in the ^{1}H NMR is however indicative of fast nitrogen inversion for this class of hydroxamic ester. Asymmetric non-bridgehead nitrogen compounds have been reported for systems with similar geminally substituted nitrogen[169] however the pyramidal stability of ONO systems is greatly affected by the nature of the substituents and steric effects.[116] The rate determining step in the topomerization of ONO systems is the inversion at nitrogen which proceeds *via* a planar transition state in which the lone pair occupies the N_{p_z} orbital. Electronegative ligands increase the *s* character of the nitrogen non-bonding orbital, which in turn increases the energy of the inversion transition state, disfavouring a fast inversion-rotation process. For both alkyl *N*-chlorobenzohydroxamates **96** and alkyl *N*-acetoxybenzohydroxamates **97** the combined electronegativity of the alkoxy and chloro or acetoxy functional groups were clearly insufficient to restrict nitrogen inversion, resulting in the sharp oxymethylene resonances. The inversion barriers in these amide systems[116,170] are most probably lowered since in the planar transition state, conjugation is possible. These barriers were recently investigated by Rauk and Glover who found them to be in the region of 2-3 $kcal.mol^{-1}$ and that they did not vary significantly over a range of anomeric amides.[171]

Alkyl *N*-acyloxybenzohydroxamates **97** are relatively stable compounds if stored under nitrogen and refrigerated. Under these conditions they decompose to alkyl benzoate esters and acetic acid over several weeks.

2.2 Acid-catalysed solvolysis of butyl *N*-acetoxybenzohydroxamates



Scheme 2-3

2.2.1 Background

Butyl *N*-acetoxybenzohydroxamate **100a** was the first alkyl *N*-acyloxybenzohydroxamate to be synthesised and was used as the reference compound in the investigation of the mechanism of acid-catalysed solvolysis. Preliminary in-house assays to ascertain the mutagenic potential of this new class of compounds indicated that **100a** was significantly mutagenic in the Ames test, with and without metabolic activation. Subsequently, **100a** was used as the standard against which the mutagenicity levels and rates of solvolysis for all alkyl *N*-acyloxybenzohydroxamates were measured.

2.2.2 Preliminary kinetics - NMR monitoring of reaction dynamics

Butyl *N*-acetoxybenzohydroxamate **100a** was earlier found by Glover *et al*[173] to decompose slowly in aqueous acetonitrile to a mixture of products indicating quantitative formation of acetic acid. The progress of the reaction was monitored using ^{1}H NMR analysis by automatic spectral acquisition at pre-programmed intervals and measuring the disappearance of the acetoxy methyl peak at δ2.08. The acetoxy methyl protons were found to be an excellent probe for measuring the rate of reaction due to their isolation from

other overlapping resonances. The appearance of acetic acid at δ1.95 could also be used as a secondary probe but was not as suitable owing to the overlapping quintet resonance of residual protio-acetonitrile from deuterio-acetonitrile solvent (Figure 2-1).

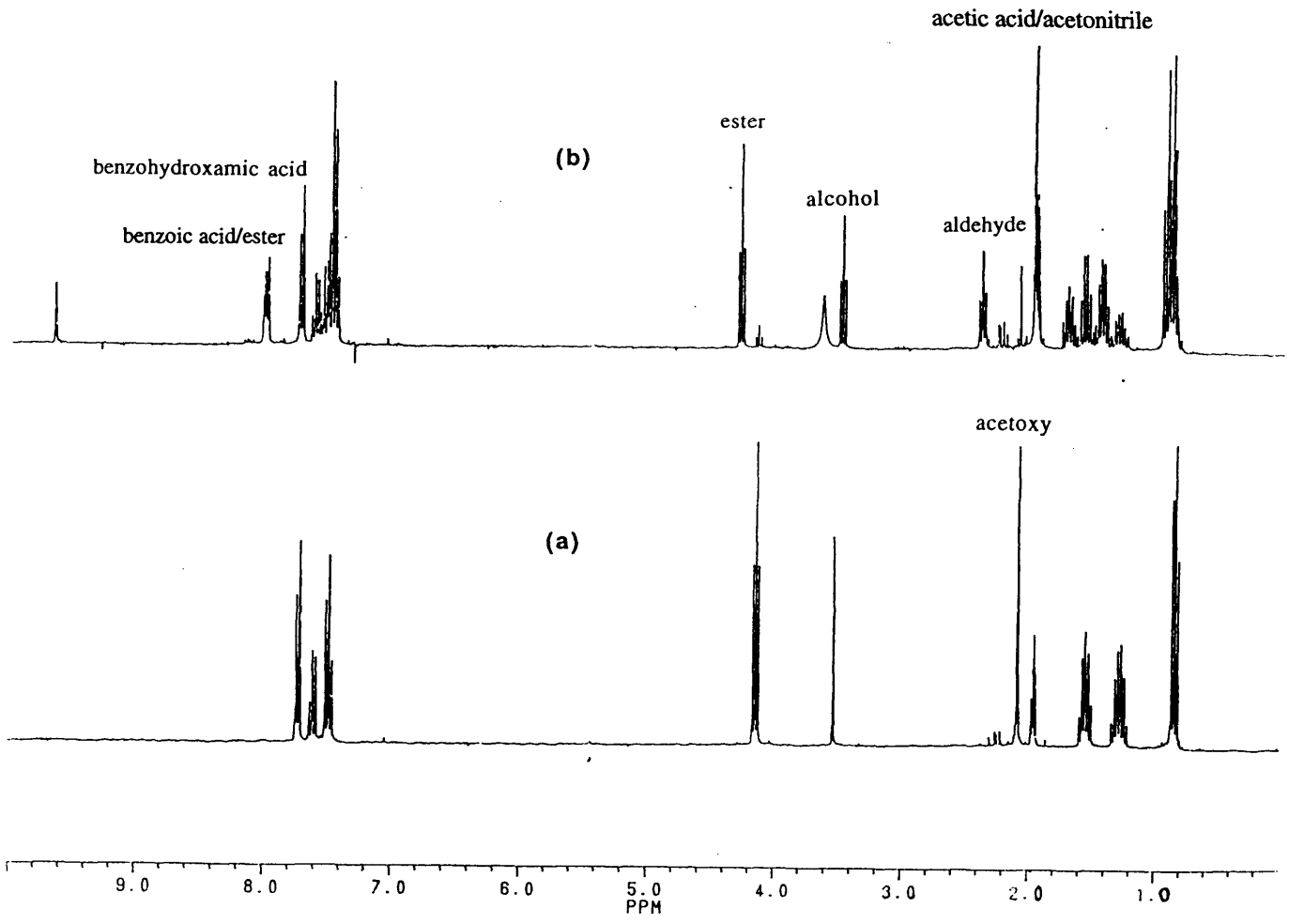


Figure 2-1 a) Butyl *N*-acetoxybenzohydroxamate **100a** in D_2O/CD_3CN at 298K.
b) Typical reaction mixture at completion of solvolysis.

b) Typical reaction mixture at completion of solvolysis.

The progress of solvolsis was determined by measuring the disappearance of the ^{1}H NMR resonance peak for the acetoxy methyl protons at δ2.08 through integration and the results are shown in Figure 2-2.

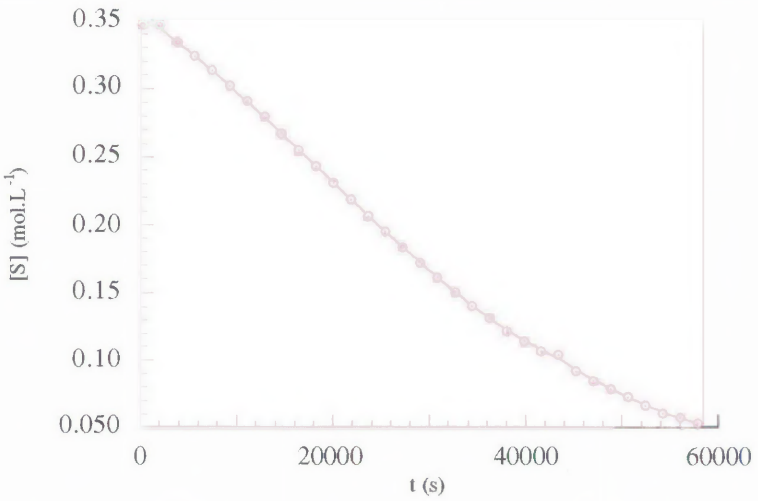


Figure 2-2 Disappearance of **100a** at 333K. [S]=concentration of **100a**

Integration and analysis of the disappearance of **100a** in acetonitrile indicated a poor correlation with unimolecular or pseudo-unimolecular kinetics but showed an excellent fit to first-order auto catalysis kinetics for the solvolysis of weak carboxylic esters. The "s" shape to the curve in Figure 2-2 is characteristic of such processes.

$$AcOH \overset{K'}{\rightleftharpoons} AcO^- + H^+ \qquad (i)$$

$$H^+ + S \overset{K}{\rightleftharpoons} SH^+ \qquad (ii)$$

$$SH^+ \xrightarrow{k} Products + AcOH \qquad (iii)$$

Scheme 2-4

Autocatalysis is found where there is an increase in the rate of a reaction through formation of reaction products and is described by the rate equation: rate = k[react][prod]. The small decrease in the pH generated by the release of acetic acid initiates the process and

accelerates the rate of solvolysis to a maximum, at which time both acetic and SH^+ are at their highest concentration, until the concentration of S (SH^+) decreases and the reaction rate slows.

$$kK\sqrt{(K'}.[S]_o t = \ln \frac{[\sqrt{[S]_o} + \sqrt{[A]_t}]}{[\sqrt{[S]_o} - \sqrt{[A]_t}]} = \ln B \quad \textbf{EQUATION 2-1}$$

The solvolysis of weak carboxylic esters (Scheme 2-4) is described by the integrated equation 2-1 in which $[S]_o$ is the initial concentration of butyl *N*-acetoxybenzohydroxamate **100a**, $[A]_t$ is the concentration of acetic acid at time t, k is the unimolecular or pseudo unimolecular rate constant, K' is the dissociation constant of acidic acid and K is the pre-equilibrium constant for protonation of butyl *N*-acetoxybenzohydroxamate.[174] The data from the solvolysis of butyl *N*-acetoxybenzohydroxamate **100a** in aqueous acetonitrile was plotted according to Equation 2-1 and is shown below (Figure 2-3).

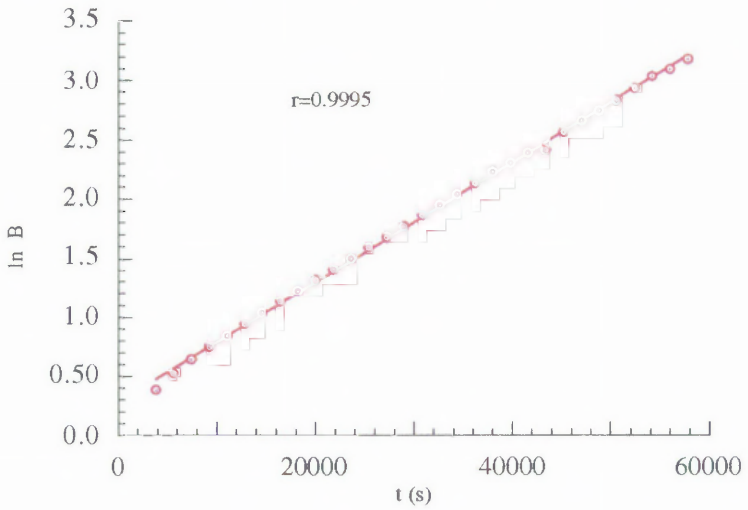


Figure 2-3 Data plotted to first-order autocatalysis kinetics

An excellent fit was evident (r^2=0.999) and the composite rate constant ($kK\sqrt{(K'}$) at 308K was found to be 8.58×10^{-5} $L^{\frac{1}{2}}mol^{\frac{1}{2}}s^{-1}$ but knowledge of the dissociation constant for acetic acid, K' and the equilibrium constant, K, under these experimental conditions are required for the derivation of first-order rate constant, k. These results were the first to

indicate that alkyl *N*-acetoxybenzohydroxamates are relatively stable to unimolecular decomposition in aqueous/organic media.

Glover noted that addition of an aliquot of standardised sulphuric acid solution resulted in pseudo first-order acid-catalysed kinetic behaviour.

$$H_3O^+ + S \underset{\text{Fast}}{\overset{K}{\rightleftharpoons}} SH^+ + H_2O \qquad \text{(i)}$$

$$SH^+ \xrightarrow[\text{Slow}]{k} \text{Products} + AcOH \qquad \text{(ii)}$$

[S] = substrate

$$K = \frac{[SH^+][H_2O]}{[S][H_3O^+]} \qquad \textbf{EQUATION 2-2}$$

$$\therefore [SH^+] = \frac{K[S][H_3O^+]}{[H_2O]}$$

$$\text{Rate} = \frac{-d[S]}{dt} = \frac{d[AcOH]}{dt} = k[SH^+]$$

$$= k\,\frac{K[S][H_3O^+]}{[H_2O]} \qquad \textbf{EQUATION 2-3}$$

$$\text{let } k' = k\,\frac{K[H_3O^+]}{[H_2O]}$$

$$\therefore \text{rate} = k'[S] \qquad \textbf{EQUATION 2-4}$$

$$k' \propto [H_3O^+]$$

but k_H, the acid independent or bimolecular rate constant can be defined as

$$k_H = \frac{k'}{[H_3O^+]} \qquad \textbf{EQUATION 2-5}$$

Scheme 2-5

The addition of mineral acid increased the concentration of the protonated substrate, SH^+, and increased the observed rate of solvolysis. The half-life of the solvolysis reaction was significantly shortened compared with that for solvolysis without the addition of the mineral acid. Under autocatalytic conditions the rate of solvolysis was determined, in part, by the dissociation of acetic acid, however the addition of sulphuric acid suppressed this pre-equilibrium resulting in pseudo first-order kinetic conditions which simplified the overall rate equation as described above.

The equilibrium equation for protonation of the substrate is given by equation 2-2 which in turn provides the concentration of the protonated intermediate. Substitution gives the rate equation for acid-catalysed solvolysis, 2-3 which can be further simplified to give equation 2-4.

$$\text{Thus} \quad \frac{-d[S]}{dt} = k'[S]$$

$$\frac{-d[S]}{[S]} = k'\,dt \quad \text{and hence}$$

$$\int_0^t \frac{-d[S]}{[S]} = -\ln\frac{[S]}{[S]_0} = \int_0^t k'dt = k't \quad \text{or}$$

$$\ln[S] = -k't + \ln[S]_0 \qquad \textbf{EQUATION 2-6}$$

The integrated rate equation for pseudo first-order solvolysis is given in equation 2-6. For acid-catalysed reactions the acid independent rate constant, k_H, was calculated by measuring the pseudo-unimolecular rate constant, k', and dividing by the concentration of hydronium ions as indicated in equation 2-5.

In these preliminary experiments and those subsequently performed by the author, the molarity of the standardised sulphuric acid/deuterium oxide solution was determined by standard laboratory procedures.[175] The general acid-catalysed solvolysis procedure was to dissolve a small quantity of alkyl *N*-acetoxybenzohydroxamate **100** in approximately 26% aqueous (D_2O) D_3-acetonitrile in an NMR tube. An appropriate aliquot of sulphuric acid (D_2O) solution was injected to initiate solvolysis and the tube was immediately inserted into

the pre-equilibrated probe of the variable temperature NMR spectrometer and allowed to equilibrate at the required temperature before automated spectral analysis was initiated.

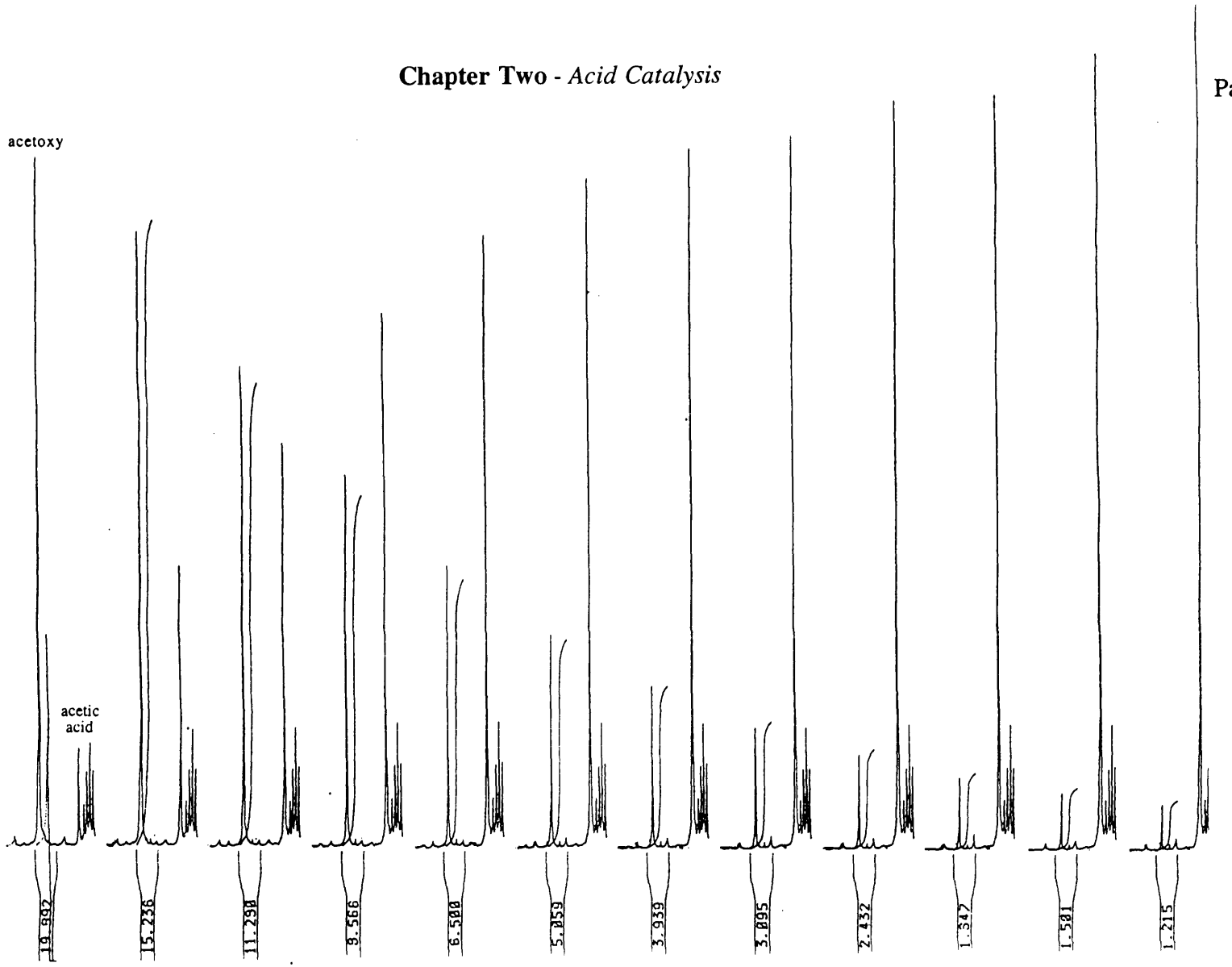


Figure 2-4 Disappearance of acetoxy and appearance of acetic acid methyl resonances at δ2.05 and δ1.95 respectively, during acid-catalysed solvolysis of butyl *N*-acetoxybenzohydroxamate **100a**

A typical acid-catalysed solvolysis reaction for butyl *N*-acetoxybenzohydroxamate as monitored by ^{1}H NMR is shown in Figure 2-4 and the data, plotted according to equation 2-6, is displayed in Figure 2-5.

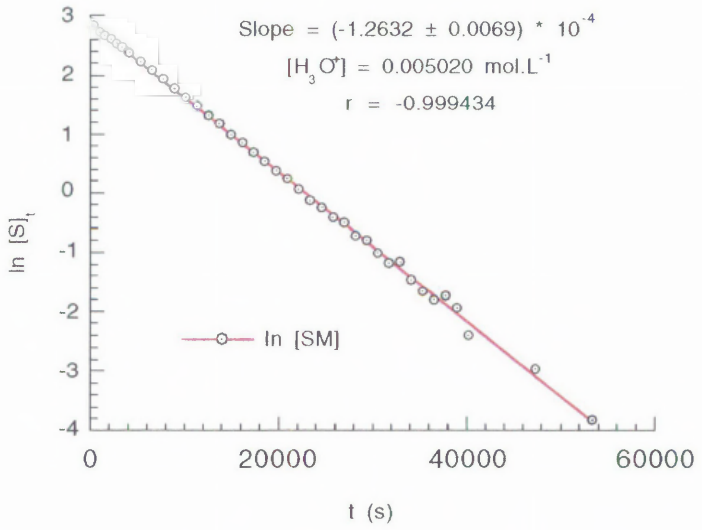


Figure 2-5 Acid-catalysed solvolysis of **100a** at 308K plotted according to Equation 2-6

The straight line relationship between $\ln[S]_t$ and time over several half-lives confirmed pseudo first-order behaviour for acid-catalysed solvolysis of butyl *N*-acetoxybenzohydroxamate. The acid independent rate of solvolysis, k_H, was obtained after dividing k' by the concentration of applied hydronium ion in the reaction mixture.

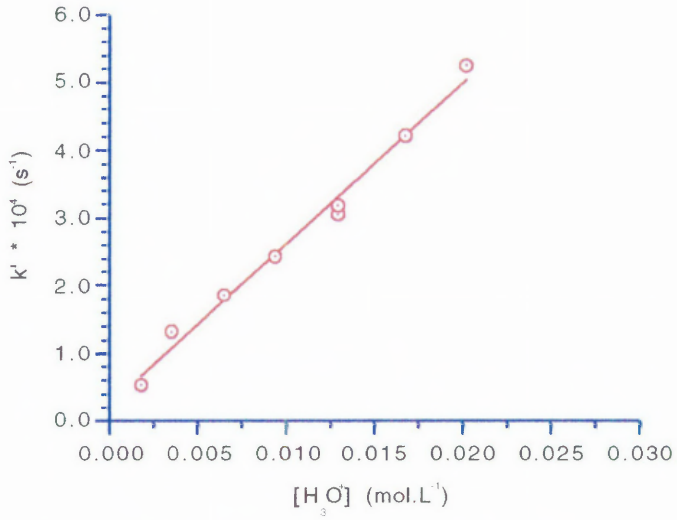


Figure 2-6 Dependence of k' on $[H_3O^+]$ at 308K

The apparent rate constant of solvolysis, k', is linearly dependent upon the concentration of acid and this relationship has been confirmed[173] by measuring the change in rate constant with varying quantities of hydronium ion (Figure 2-6).

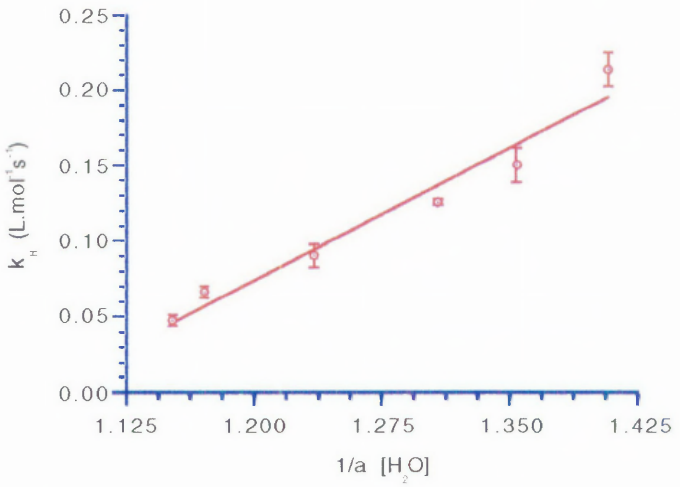


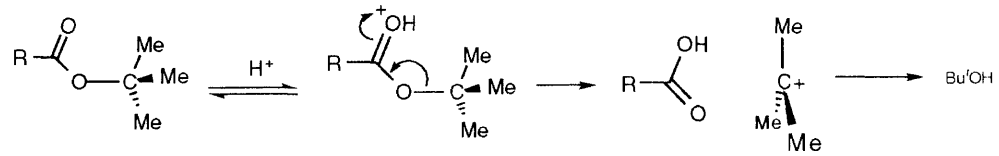
Figure 2-7 Dependence of k_H on the activity of water

Scheme 2.5 also indicates that the acid-independent rate constant for solvolysis, k_H, should be inversely proportional to the activity of water. Glover[174] *et al* subsequently showed that the rate of solvolysis is linearly dependent on the inverse of $a_{[H_2O]}$ (Figure 2-7).

In summary, initial results in these laboratories indicated that rapid reversible protonation of alkyl benzohydroxamate leads to dissociation to acetic acid and products.

2.2.3 $A_{Al}1$ solvolysis of alkyl *N*-acetoxybenzohydroxamate

A study of the solvent isotope effects[173] suggested that the $A_{Al}1$ rather than the $A_{Ac}2$ process was operating. The rate of solvolysis at different acid concentrations in D_2O-CD_3CN and H_2O-CD_3CN varied and the observed solvent KIE was 0.44 ± 0.02, which is consistent with an $A_{Al}1$ mechanism,[174] rather than the $A_{Ac}2$ process for which a larger KIE between 0.48 and 0.69 was predicted.



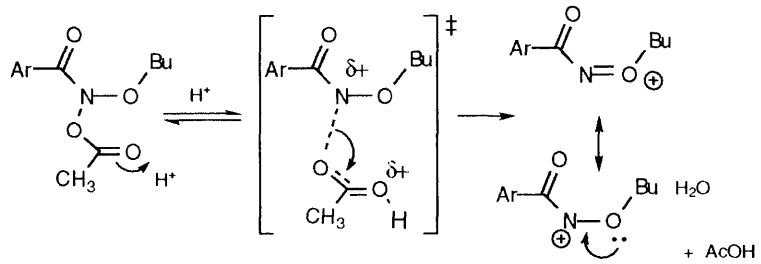
102 **103** **104** **105**

(a) R= Ph
(b) R = Et

Scheme 2-6

The unusual $A_{Al}1$ hydrolysis of *t*-butyl benzoate esters **102a** requires unimolecular ionisation of the protonated intermediated **103a** to give a carbocation **105a** derived from the alcoholic group (Scheme 2-6). The formation of a charged intermediate is facilitated by polar solvents[176] and when the carbocation is tertiary or benzylic.

The Arrhenius parameters for the $A_{Al}1$ solvolysis of *t*-butyl ethanoate **102b** have been reported.[176,177] The entropy of activation for the acid-catalysed process has been determined to be +54 kJmol^{-1}, while the enthalpy of activation was 108 kJmol^{-1}. The positive entropy of activation is consistent with an increase in the disorder of the system coincident with unimolecular dissociation. In contrast, $\Delta S^{\ddagger}$ for the normal $A_{Ac}2$ process is usually large and negative, indicative of association in the activation step.[176]



100a **101a**

Scheme 2-7 $A_{Al}1$ acid-catalysed solvolysis mechanism

Like tertiary alkyl esters, the mutagens **97** are acetic acid esters with the potential for formation of a stabilised cation, *N*-acyl-*N*-alkoxynitrenium ion. By analogy with the solvolysis of *t*-butyl benzoate esters **102a**, the mechanism for nitrenium ion formation from the acid-catalysed solvolysis of butyl *N*-acetoxybenzohydroxamate **100a** was

proposed according to Scheme 2-7. Fast, reversible protonation at the carbonyl of the acetoxy moiety increases the leaving potential of the group, resulting in N–OAc bond stretching until insufficient orbital overlap exists and the nitrenium ion **101a** and acetic acid separate. The driving force is clearly the increased stability afforded the nitrenium ion by the alkoxy moiety and solvation of this ion by the polar solvent. Such stability has been predicted theoretically by both semi-empirical and *ab initio* calculations.[95,100]

Reversible protonation of butyl *N*-acetoxybenzohydroxamate **100a** is in principle possible at the acetoxy and alkoxy ether oxygen, nitrogen, and the carbonyl oxygen of the benzoyl and acetoxy moieties. AM1 calculations, on the model methyl *N*-acetoxybenzohydroxamate (**97** R=CH_3, R'=CH_3, Ar=C_6H_5), predict that protonation at the benzamide carbonyl **107** is more favourable than the *N*-acetoxy carbonyl oxygen **106** by 21 kJmol^{-1} (Figure 2-8). However, only pre-equilibrium protonation at the acetoxy moiety can lead to ester hydrolysis and nitrenium ion formation.

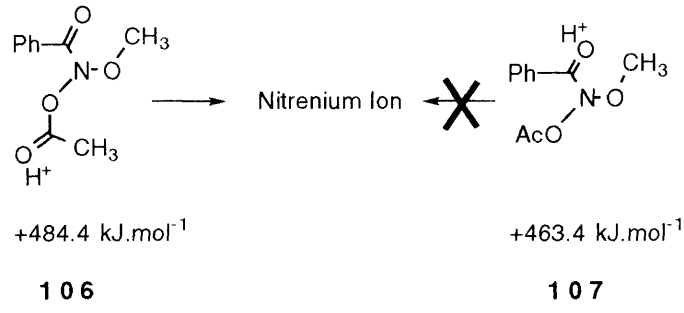


Figure 2-8 AM1 heat of formation for protonation at ester and amide carbonyls

Conclusive evidence for the $A_{Al}1$ process was obtained in this study from the Arrhenius parameters for solvolysis of butyl *N*-acetoxybenzohydroxamates as well as substituent effects.

2.2.4 Arrhenius results for butyl *N*-acetoxybenzohydroxamate

Butyl *N*-acetoxybenzohydroxamate **100a** was solvolysed over the range 298K-338K to determine the acid-independent rate constant, k_H, and the resulting Arrhenius data is given in Table 2-1.

Table 2-1 Arrhenius Data for **100a** (298K-338K)

Temp. (K)	$[H_3O^+]$ (mol^{-1})	$10^4 k'$ (s^{-1})	k_H ¶ ($Lmol^{-1}s^{-1}$)	ln k_H
298.0	0.05414	2.941	0.005433	-5.2152
303.0	0.03248	3.650	0.01124	-4.4886
308.0	0.002813	0.7229	0.02570	-3.6614
318.0	0.05393	75.65	0.1403	-1.9641
328.0	0.002819	11.21	0.3977	-0.9222
328.0	0.002781	12.26	0.4409	-0.8190
338.0	0.001718	28.50	1.6596	0.5066
338.0	0.002808	31.928	1.1372	0.1285
338.0	0.001415	22.533	1.5928	0.4655

¶ $k_H = \dfrac{k'}{[H_3O^+]}$

All solvolysis runs displayed excellent pseudo first-order kinetics ($r > 0.999$) leading to very small errors in k'. The plot of ln k_H against the reciprocal of the absolute solvolysis temperature gave an excellent Arrhenius relationship (Figure 2-9).

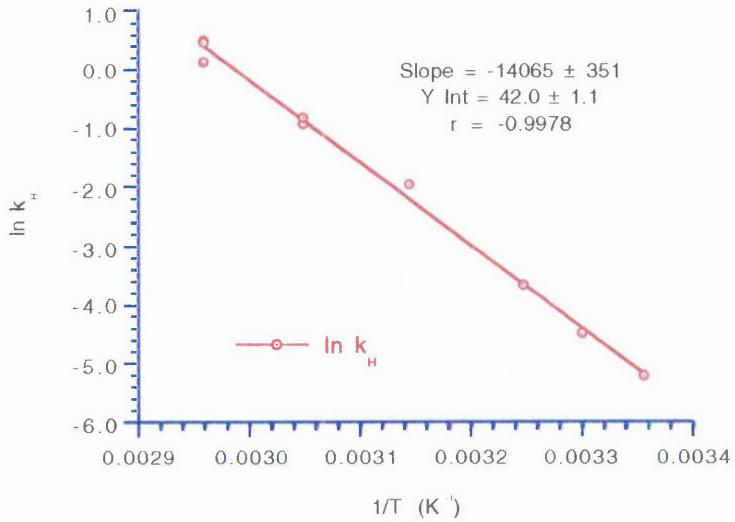


Figure 2-9 Arrhenius plot for butyl *N*-acetoxybenzohydroxamate **100a**

The linear relationship between ln k_H and the inverse of absolute temperature indicated that a consistent solvolysis mechanism operated over the temperature range and the Arrhenius parameters for that process were calculated from the slope and intercept. The energy of activation (E_a) was calculated to be 116.9±2.9 $kJmol^{-1}$ which is in the region of those cited for the acid-catalysed hydrolysis of *tertiary* alkyl diphenylmethyl and α-methylallyl esters, namely 120 $kJmol^{-1}$.[176]

From the intercept, the Arrhenius plot gives an entropy of activation ($\Delta S^{\ddagger}$) of 96.1±9.1 $JK^{-1}mol^{-1}$ which is even more positive than the ester values (*cf.* 40 $JK^{-1}mol^{-1}$) and accords with a much looser and probably later transition state with substantial alkoxy-nitrenium ion character. The substantial anomeric overlap between the filled 2p orbital on the alkoxy oxygen and the N–OAc σ* orbital accounts for this, since it would facilitate heterolysis of the N–OAc bond. Anomeric effects are strongest in $X-N-\ddot{Y}$ systems when the $\ddot{Y}$ lone pair is highest in energy and N–X σ* is lowest in energy.[116,171,172,176] Relative to RON(COR)OR and $CH_3COON(COR)OR$ the protonated intermediate $CH_3C(OH^+)ON(COR)OR$ would have a much lower O–N σ* orbital resulting in a strong anomeric weakening of the bond and a loose transition state.

The Arrhenius data is consistent with alkoxynitrenium ion formation. The transition state would thus involve considerable development of positive charge at nitrogen. The susceptibility of the heterolysis process to electronic factors is reflected in the Arrhenius parameters for solvolysis of a series of butyl *N*-acetoxy-(*para*-substituted)benzohydroxamates, **100a-h**.

2.2.5 Synthesis and reactivity of butyl *N*-acetoxy-(*para*-substituted) benzohydroxamates

Butyl *N*-chloro-(*para*-substituted)benzohydroxamic esters **99b-h**, were synthesised *via* the standard procedure and were converted to the butyl *N*-acetoxy-(*para*-substituted)benzohydroxamates **100b-h** according to method one, as shown in Scheme 2-3. The compounds were solvolysed in aqueous acetonitrile over the temperature range of 298-338K in the same manner as for the solvolysis of **100a** and the Arrhenius parameters are tabulated below (Table 2-2).

Table 2-2 Arrhenius parameters and rate constants for acid-catalysed solvolysis of butyl *N*-acetoxy-(*para*-substituted)benzohydroxamates **100a-h** at 308K.

Subst	ln A	$\Delta S^{\ddagger}$ ($JK^{-1}mol^{-1}$)	E_a/R (K)	ΔE_a ($kJmol^{-1}$)	$100k_H$ (308K) ($Lmol^{-1}s^{-1}$)	$\Delta G^{\ddagger}_{308K}$ ($kJmol^{-1}$)	r
100b MeO	43.05±1.29	104.7±10.7	13592±408	113.0±3.4	33.86	80.75	0.999
100d Me	44.01±0.13	112.7±2.2	14429±87	120.0±0.7	5.875	85.29	1.000
100e Bu^t	44.56±1.23	117.2±10.2	14628±389	121.6±3.2	5.337	85.50	0.999
100c Ph	44.92±1.06	120.6±8.8	14834±340	123.3±2.8	3.899	86.16	0.999
100a H	42.02±1.09	96.1±9.1	14065±351	116.9±2.9	2.600	87.30	0.998
100g Br	39.96±0.63	79.0±5.2	13610±199	113.2±1.7	1.455	88.87	0.999
100f Cl	39.05±2.37	71.4±19.7	13331±753	110.8±6.3	1.452	88.80	0.995
100h NO_2	31.25±0.78	6.6±6.5	11468±248	95.3±2.1	0.252	93.27	0.999

Butyl *N*-acetoxy-(*para*-substituted)benzohydroxamates **100a-h**, all solvolyse with positive entropies of activation, which is consistent with dissociation to acetic acid and nitrenium ions. The slowest compound to solvolyse **100h** had the lowest enthalpy of activation (95.3±2.1 $kJmol^{-1}$) and lowest entropy of activation (6.6±6.5 $JK^{-1}mol^{-1}$), which combine to give the highest Gibbs Free Energy of activation (93.27 $kJmol^{-1}$) at 308K. For **100h** the entropy change is only marginally positive, indicating that a smaller reorganisation of the ground state is required to generate the transition state geometry. This is confirmed by the low E_A, reflecting a relatively small loss of orbital overlap. Data in Table 2-2 shows that electron availability at nitrogen in the transition state is a determining factor. Developing positive charge at nitrogen is consequently stabilised by electron releasing substituents.

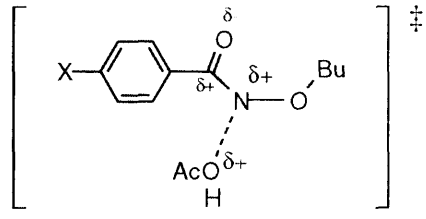


Figure 2-10

Longer N-OAc bonds for these substituents reduces orbital overlap resulting in higher activation energies. Interestingly, solvolysis must be an entropy driven process as the increase in rate constant, k_H, for substrates with electron releasing *para* substituents is clearly not promoted by the increase in the energy of activation which acts to increase the Gibbs Free Energy of activation. The concomitant rise in the entropy of activation is

favourable to the process. The magnitude of $\Delta S^{\ddagger}$ is consistent with the acid-catalysed solvolysis of *t*-butyl esters[176] and the decomposition of ω-diazoacetophenones.[178] $A_{Al}1$ solvolysis of *t*-butyl mesitoate and *t*-butyl acetate are 41 and 59 $JK^{-1}mol^{-1}$ respectively.[176]

The linear correlation between the activation enthalpy and entropy of activation across a series of related compounds, the so-called *isokinetic relationship*, has been considered at length by Good *et al*[179] and Exner.[180] While the potential artificial nature of the relationship has been debated, it is widely agreed that a linear correlation can be taken as evidence that a similar reaction mechanism is common throughout the series.

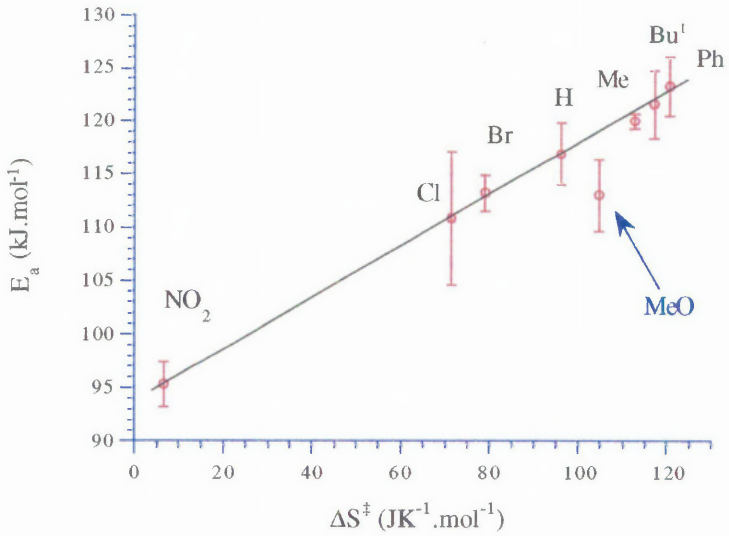


Figure 2-11 Isokinetic relationship for **100a-h**

With the exception of the *p*-methoxy substrate **100b**, the isokinetic relationship for butyl *N*-acetoxy-(*para*-substituted)benzohydroxamates **100a-h** displays an excellent correlation between the entropy and enthalpy of activation which indicates that a single mechanism is operating across this series (Figure 2-11). The *p*-nitro substrate **100h** was the slowest compound to solvolyse but had the lowest activation energy and the lowest entropy in the transition state complex with the difference in disorder between the ground state and the transition state configurations only marginally positive. With increasing electron donating substituents, up to *p*-phenyl **100c**, the rise in activation energy of the transition state complex is more than offset by an increase in the entropy of activation.

Butyl *N*-acetoxy-*p*-methoxybenzohydroxamate **100b** lies somewhat outside the isokinetic line with both the heat of formation and entropy of activation lower than the predicted trend (Figure 2-11).

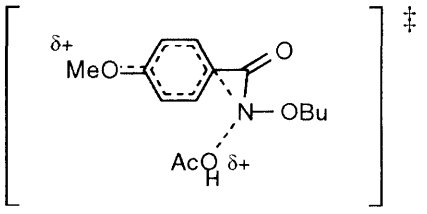


Figure 2-12 Non-classical transition state

The tighter transition state and lower activation energy may be due to a non-classical transition state providing a significant, additional supply of electron density to the reactive centre that adds extra stabilisation of the developing positive charge (Figure 2-12). A more orderly transition state with increased alignment between the leaving group, central nitrogen and the ring, would translate into a lower entropy of activation. Tsuno noted a similar discrepancy in the study of the decomposition of ω-diazoacetophenones and postulated a similar transition state to account for it.[178] In these decomposition reactions, positive charge is also developed α- to a carbonyl.

Clearly in the acid-catalysed solvolysis of **100a-h** entropy is the driving force. Electron donating substituents reduce the partial positive charge on the benzamide carbonyl carbon which facilities the formation of the adjacent nitrenium ion. This in turn leads to elongation of the N–OAc bond and an increase in the enthalpy of activation as orbital overlap between N and O decreases. Furthermore the longer N–OAc bond, not withstanding the added constraints imposed by a partially conjugated benzamide moiety, still results in an overall increase in the disorder of the system when electron donating substituents are situated on the ring.

2.2.6 Hammett correlation

The acid-independent rate constant, k_H at 308K was calculated for **100a-h** from the Arrhenius parameters and two orders of magnitude difference in rates was evident between the least and most reactive compounds. The rates were correlated with Hammett substituent constants (Figure 2-13).

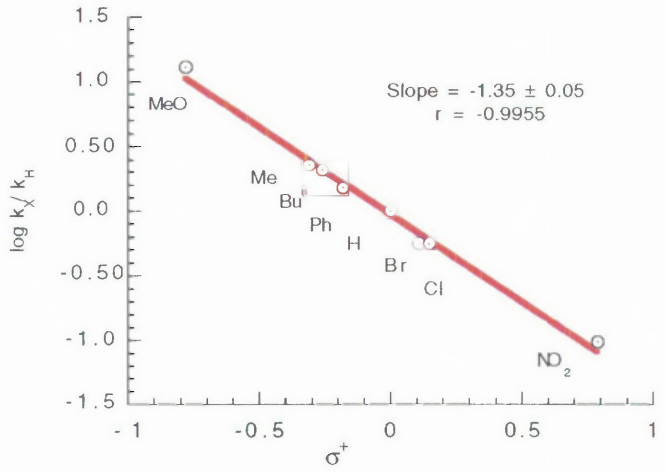


Figure 2-13 Hammett correlation for acid-catalysed solvolysis for **100a-h** at 308K

A plot of $\log(k_X/k_H)$ for **100b** to **100h** displayed a poor correlation with Hammett σ constants[176,181-186] (r = -0.885) whereas a much better relationship was found using σ^+ constants (r = -0.995) (Figure 2-13). The negative slope ($\rho = -1.35 \pm 0.05$) reflects the observed increase in rate when electron donating substituents are present on the ring.

Generally, σ^+ reactions which involve formation of a positive charge *alpha* to the ring are significantly influenced by the electronic demands placed on and transmitted through the ring. These reactions tend to have stronger, more negative ρ values than that observed for solvolysis of **100a-h**. For example, the reaction constant for the σ^+ ionisations of: a)$ArCMe_2$–Cl (90% aq. acetone, 25 °C)[185] was -4.45; and b) $ArCPh_2$–OH (H_2SO_4, 25 °C)[187,188] was -3.64. The moderate slope observed from Figure 2-13 arises from the influence of the intervening carbonyl moiety which buffers the reaction centre from the electronic effects of the ring.

For the acid-catalysed solvolysis of **100a-h**, a σ^+ correlation also indicates that the *para* substituents influence the formation of a developing positive charge at nitrogen through a conjugative interaction. *Para* substituents can interact directly with the carbonyl carbon thereby increasing or decreasing the positive charge at that centre. Such variations would clearly influence the ease of nitrenium ion formation. The moderate slope of -1.35 is consistent with development of the positive charge *beta* to the ring, as is the case for

nitrenium ion formation. The decomposition of ω-diazoacetophenones,[178] in which carbenium ion character develops α- to the carbonyl, revealed a comparable Hammett relationship with a negative slope of similar magnitude.

Protonation of the *N*-acetoxy carbonyl should not be influenced by *para* substituents on the ring. k_H is the composite of k for heterolysis of the N–O bond and K, the pre-equilibrium constant for protonation at the carbonyl. The latter is remote from the influence of *para*–substituents and K is likely to be similar across the series. Variation in k_H is thus largely due to changes in k for the unimolecular step.

2.2.7 Analysis of solvolysis products

An analysis of the ^{1}H NMR spectrum at the completion of a typical rate study run for the solvolysis of butyl *N*-acetoxybenzohydroxamate at 308K revealed the presence of a number of solvolysis products which were benzoic acid, benzohydroxamic acid, butyl benzoate, butanol and butanal. All products were readily identified in the ^{1}H spectrum and their presence was confirmed by ^{13}C spectroscopy by comparison with authentic samples under identical conditions (D_3-acetonitrile/D_2O)

2.2.7.1 Solvolysis products for butyl N*-acetoxybenzohydroxamate at 308K*

A solvolysis reaction for **100a** was initiated at 308K and the disappearance of the mutagen and formation of the products was monitored over 15 hours and is shown in Figure 2-14.

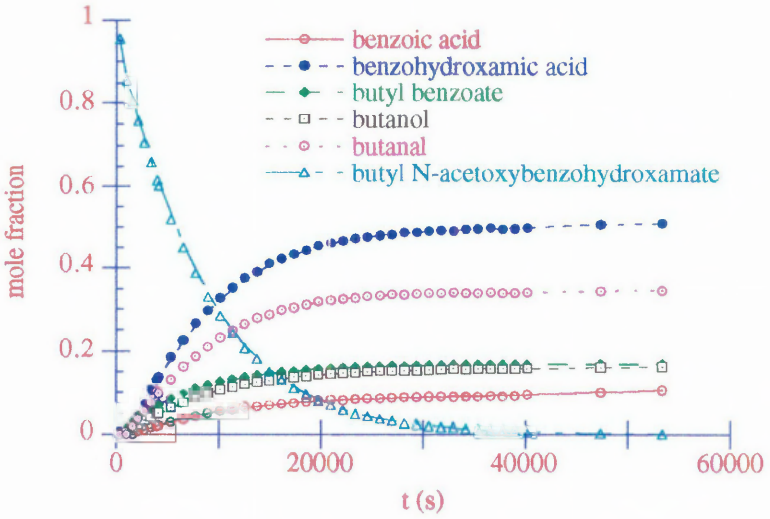


Figure 2-14 Solvolysis product formation with respect to time.

Analysis of the formation of products indicated parallel formation in concert with the disappearance of starting material. For parallel product formation from unimolecular reactions, Scheme 2-8 pertains.

$$\mathrm{A} \xrightarrow{k_1} \text{product (1)}$$

$$\mathrm{A} \xrightarrow{k_2} \text{product (2)}$$

$$\mathrm{A} \xrightarrow{k_3} \text{product (3)}$$

Scheme 2-8

Thus

$$-\frac{d\mathrm{A}}{dt} = k_1\mathrm{A} + k_2\mathrm{A} + k_3\mathrm{A} = (k_1 + k_2 + k_3)\mathrm{A}$$

$$= k\mathrm{A} \quad \text{where } k = k_1 + k_2 + k_3$$

$$\text{and } \mathrm{A} = \mathrm{A}_o e^{-kt}$$

$$\text{also } \frac{d[\text{prod}]}{dt} = k_{\text{prod}}\mathrm{A} = k_{\text{prod}}\mathrm{A}_o e^{-kt}$$

$$\text{hence} \int_0^t \frac{d[\text{prod}]}{dt} = [\text{prod}] = [\text{prod}]_o + \left(\frac{k_{\text{prod}}A_o}{k}\right)\left(1-e^{-kt}\right)$$

As the concentration of all products is zero at the start of the reaction, ie. $[\text{prod}]_o = 0$, for all products (1, 2 and 3) the following holds:

$$[\text{prod}] = \left(\frac{k_{\text{prod}}A_o}{k}\right)\left(1-e^{-kt}\right)$$

A plot of the appearance of the solvolysis species versus $\left(1-e^{-kt}\right)$ for the solvolysis of butyl *N*-acetoxybenzohydroxamate **100a** is shown in Figure 2-15. In this plot, the yield of each product has been determined from the integral of the signal in the ^{1}H NMR and has been subsequently normalised with respect to the initial concentration of the *N*-acetoxy compound. Hence, at t=0, the concentration of **100a** (also shown) is 1.0.

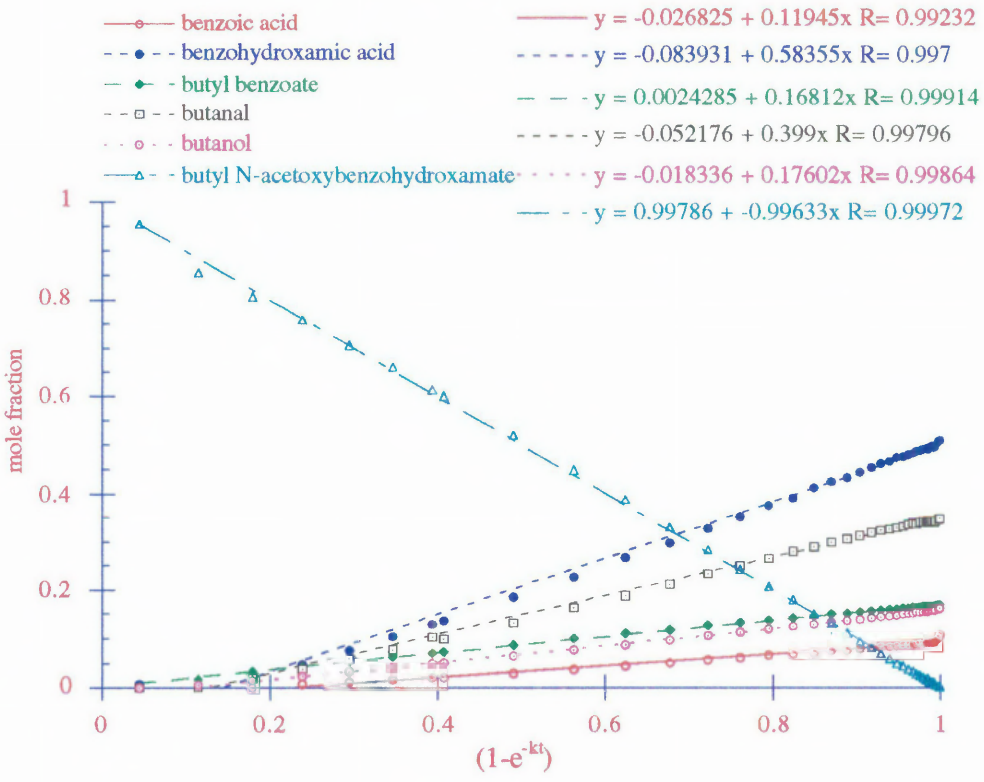


Figure 2-15 Solvolysis product formation in parallel reactions

Figure 2-15 reveals that the data for all species simplify to straight lines upon plotting the normalised concentrations against $(1-e^{-kt})$ as the abscissa and the partial rate constants for appearance of the products are obtained from the individual slopes, $\left(\frac{k_{prod}A_o}{k}\right)$. The acid independent rate of solvolysis for butyl *N*-acetoxybenzohydroxamate in this reaction was (2.51±0.02) x 10^{-2} s^{-1}. The sum of the relative rate constants for formation of butyl benzoate, benzoic acid, and benzohydroxamic acid is close to the overall rate constant, since the sum of ratios (k_{prod}:k) is almost 0.9.

Butanol and butanal must be formed in conjunction with formation of benzohydroxamic acid and benzoic acid. Butyl benzoate is not formed from butanol and benzoic acid, since the alcohol, carboxylic acid and ester are formed in parallel reactions. This is clearly seen in Figure 2-15 as the ratio of the yield of all three remain constant, signified by the straight line relationship between the concentrations of all three with respect to $(1-e^{-kt})$.

While there appears to be a delay in the formation of all products in the early stage of the reaction, which could be construed as evidence for the existence of reactive intermediates, detection limits of the NMR method are inaccurate at low concentration.

Further insight into the mechanism of decomposition was obtained from studies of the pH dependence of product formation.

2.2.7.2 Acid dependence of product distribution

Butyl *N*-acetoxybenzohydroxamate **100a** was solvolysed at five acid strengths to determine the effect of pH on the percentage yields of the solvolysis products. The results are given in Table 2-3 and plotted in Figure 2-16.

Table 2-3 Percentage yield of solvolysis products of **100a** at different pH

$[H^+]$	rate (s^{-1})	Percentage yield[a]				
		benzoic	benzohydroxamic	butyl benzoate	butanol	butanal
0.003343	0.004963	6	36	27	16	28
0.005028	0.007579	11	51	17	16	35
0.016650	0.019010	13	53	11	22	38
0.050820	0.065096	16	46	3	25	39
0.100890	0.122870	19	64	3	28	37

[a] Percentage yields were calculated by integration of appropriate resonances in the ^{1}H NMR spectrum at the completion of the reaction and comparison with the integration of the acetoxy singlet for butyl *N*-acetoxybenzohydroxamate at the start of the solvolysis.

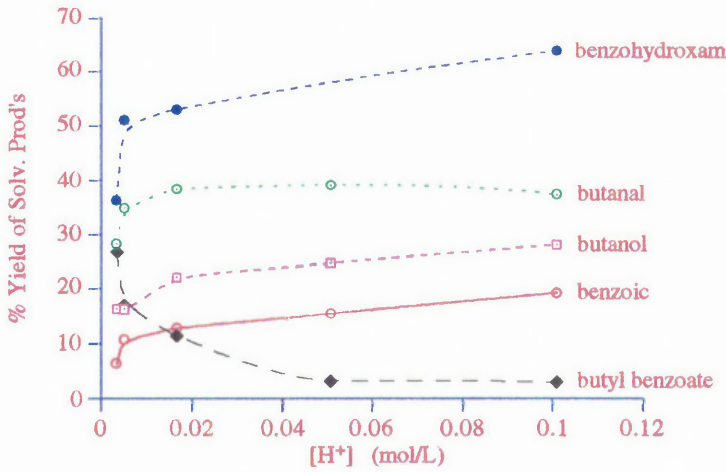


Figure 2-16 Dependence of product yields upon acid concentration for solvolysis of **100a**

Increasing sulphuric acid strength resulted in higher yields of benzoic acid, benzohydroxamic acid and butanol. The yield of butanal also increases as pH decreases but appears to reach a maximum value and then decrease slightly. This apparent maximum yield is most probably an artefact of the error associated with obtaining an accurate integral of the methylene hydrogens (*ca.* δ2.3) adjacent to the aldehyde group in the ^{1}H NMR spectrum. At high acid concentrations there was noticeable broadening of this triplet signal. While the integral of the signal should not be affected by loss of resolution brought on by line broadening, there is an increase in the error associated with the integral and hence the yield. The formation of these products has clearly been promoted by a decrease in pH.

The yield of butyl benzoate on the other hand, clearly decreases as the acidity increases, indicating that formation of the ester is an acid-independent process and thus the formation of ester does not compete with the acid-catalysed processes at higher acid concentration.

2.2.7.3 Dependence of product distribution upon electronic effects

The product distribution at the end of suitable kinetic runs was analysed for the series butyl *N*-acetoxy-*para*-substituted benzohydroxamate (*p*-MeO, *p*-Me, *p*-H, *p*-Cl, *p*-Br, *p*-NO_2) and the results are displayed in Table 2-4. While pH was not identical in each case, some important observations could be made.

Table 2-4 Products and percentage yields from acid-catalysed solvolysis of butyl *N*-acetoxybenzohydroxamates

X	MeO (100b)	Me (100d)	H (100a)	Cl (100f)	Br (100g)	NO_2 (100h)
$[H^+]/10^{-3}$ moll^{-1}	2.2	8.5	3.3	9.4	4.2	8.3
Butanol	16	22	16	25	16	22
Benzoic acid	4	4	6	17	*a*	*a*
Butanal	34	31	28	21	16	0
benzohydroxamic acid	19	21	36	32	*a*	*a*
Butyl benzoate	9	11	27	29	42	42

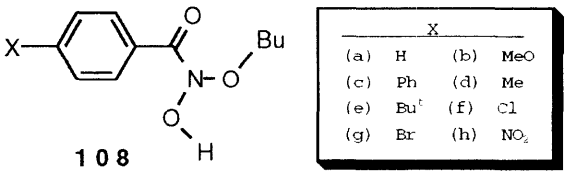
[a] Could not be determined due to overlapping resonances.

Butanol is produced in similar, moderate quantities by all *para*-substituted compounds. Benzoic acid was found in low yields with electron-donating substituents and appears to be produced in greater quantities under the influence of electron-withdrawing substituents, although data for *p*-bromo and *p*-nitro substrates could not be obtained. Conversely, butanal is produced in fair yields with electron-donating substituents but the yield is reduced with electron-withdrawing substituents and, significantly, is zero with *p*-nitro. Benzohydroxamic acid is found in moderate yields across the series and in yields at least similar to those of butanal in the case where measurement was possible. The yield of butyl benzoate was markedly influenced by the *para* substituents and is formed preferentially where electron-withdrawing groups are present.

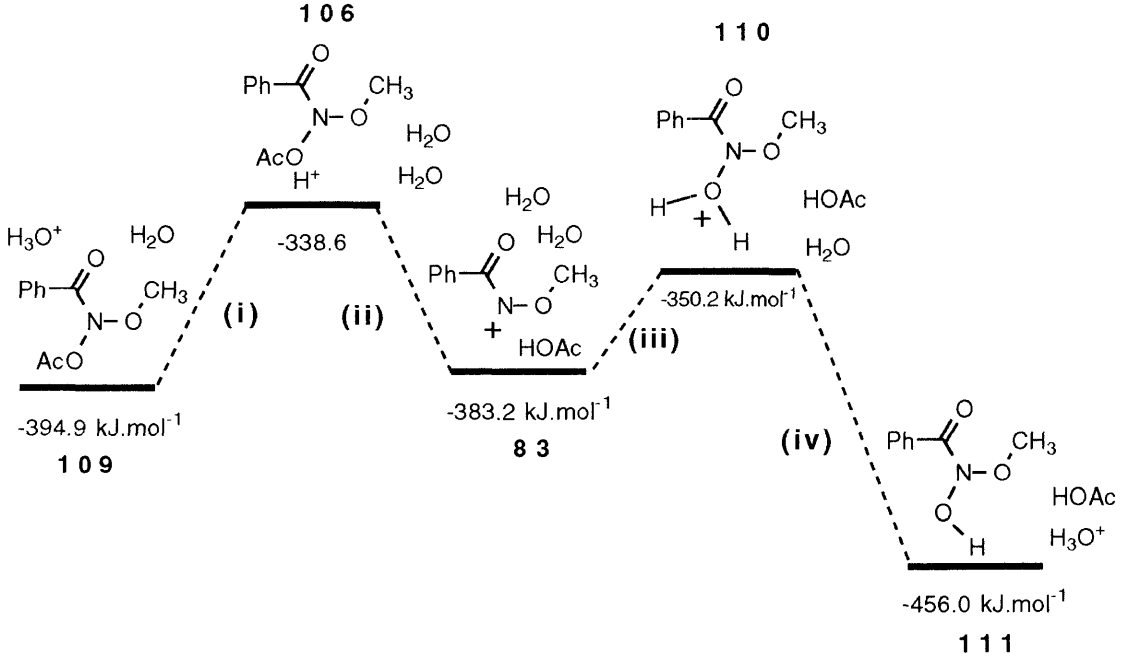
2.2.8 Solvolysis mechanisms

In aqueous acetonitrile, rate determining formation of nitrenium ion is most probably followed by a rapid solvolysis of the positively charged nitrenium ion intermediate.

Subsequent loss of a hydrogen ion would provide the hitherto unknown intermediate, *N*-butoxybenzohydroxamic acid **108**.

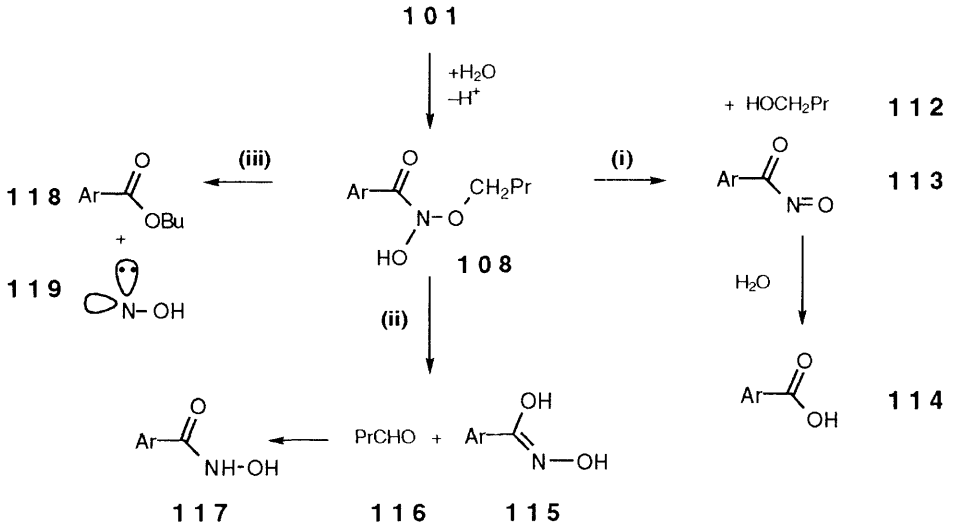


AM1 heats of formation for important intermediates along this pathway for the model methyl *N*-acetoxybenzohydroxamate **109** are depicted in Scheme 2-9.



Scheme 2-9 AM1 energy profile for acid-catalysed solvolysis of **109**

AM1 calculations on methyl *N*-acetoxybenzohydroxamate **109** indicated that acid-catalysed nitrenium ion formation was possible. Rate determining formation of the activated complex occurs upon reversible protonation of the *N*-acetoxy carbonyl carbon **106** which subsequently loses acetic acid to form the reactive intermediate nitrenium ion **83**. According to these semi-empirical calculations, hydrolysis of the nitrenium ion appears to be a favourable process. These results indicate that the heterolysis is essentially a thermoneutral process and that overall formation of *N*-methoxybenzohydroxamic acid **111** is strongly exothermic (Scheme 2-9).

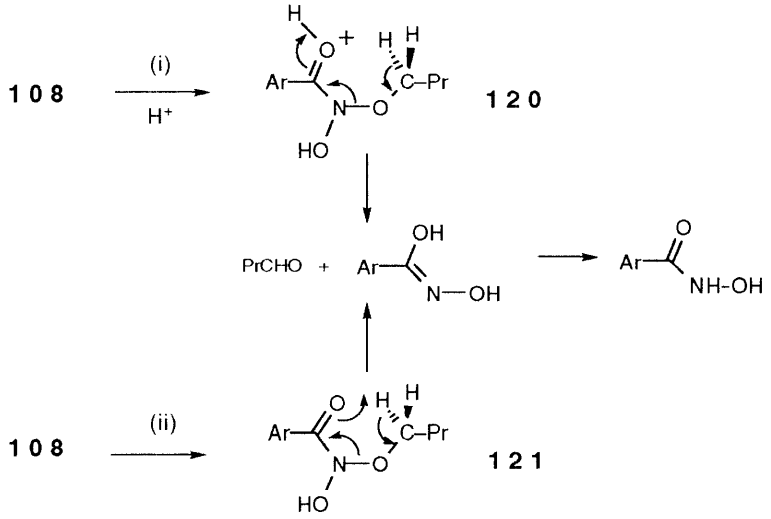


Scheme 2-10 Possible solvolysis pathways for nitrenium ions **101**

N-butoxybenzohydroxamic acid **108** could not be isolated from the reaction mixture, however unequivocal evidence for its formation was provided by ^{18}O isotope studies described in Section 2.2.10. Nor could it be detected *in situ* during the reaction rate studies which were monitored continually by NMR. The decomposition pathways proposed for **108** are illustrated in Scheme 2-10 and, together, satisfactorily account for all the products as well as the effects of acid concentration and *para* substituents.

Acid catalysis could lead to the formation of butanol **112** and nitrosocarbonylbenzene **113** in a similar process to acid-catalysed decomposition of hemiacetals[189] (Scheme 2-10i). Nitrosocarbonylbenzene could then be the source of benzoic acid **114** through reaction with water. Alternatively, protonation at the benzoyl carbonyl could lead to loss of butanal **116** and oxime **115** which would rearrange to the more stable tautomer, benzohydroxamic acid **117** (Scheme 2-10ii). The conjugate anion of the alkoxy benzohydroxamic acid intermediate could also result in the formation of ester through a novel internal rearrangement releasing hydroxynitrene as a reactive by-product (Scheme 2-10iii). All three possible mechanisms are addressed below.

2.2.9 Butanal and benzohydroxamic acid



Scheme 2-11 Possible mechanisms for butanal/benzohydroxamic acid formation

Butanal and benzohydroxamic acid, while difficult to quantify accurately by ^{1}H NMR, appear to be generated together in an acid-catalysed elimination reaction (Table 2-3 and Figure 2-16). The yields of products (estimated by ^{1}H NMR) from the solvolysis of butyl *N*-acetoxybenzohydroxamate **100a** at different acid concentrations are illustrated in Figure 2-16. There is an increase in both aldehyde and hydroxamic ester formation with increasing acid strength in accord with acid-catalysis. Two possible mechanisms for the formation of butanal and benzohydroxamic acid are shown in Scheme 2-11. Scheme 2-11(i) is an acid catalysed reaction in which the protonated intermediate *N*-butoxybenzohydroxamic acid **120** rearranges to give the required products. As an acid catalysed process, the reaction will be favoured with a decrease in pH. Scheme 2-11(ii) is an acid independent mechanism where rearrangement occurs *via* the formation of a six-membered transition structure **120** allowing internal transfer of a proton between butoxy and carbonyl moieties. An increase in acid concentration would favour other acid catalysed solvolysis processes over this mechanism and thus the yield of butanal and benzohydroxamic acid would have decreased.[k]

---

[k] A third method for the formation of butanal is possible through direct elimination of benzoyl nitrene from the nitrenium ion. This mechanism is unlikely to be the source of butanal since aniline, which would be the result of the Curtius- or Lossen- type rearrangement, was not detected.

The yield of both solvolysis products increases as the concentration of hydronium ion increases, indicating that Scheme 2-11(i) holds over both Scheme 2-11(ii) and direct elimination from the free nitrenium ion.

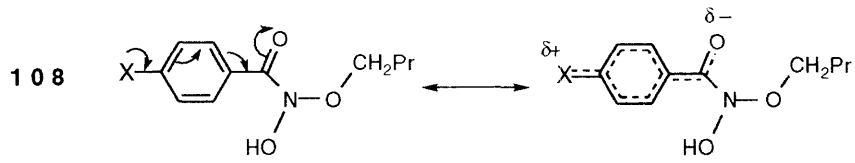
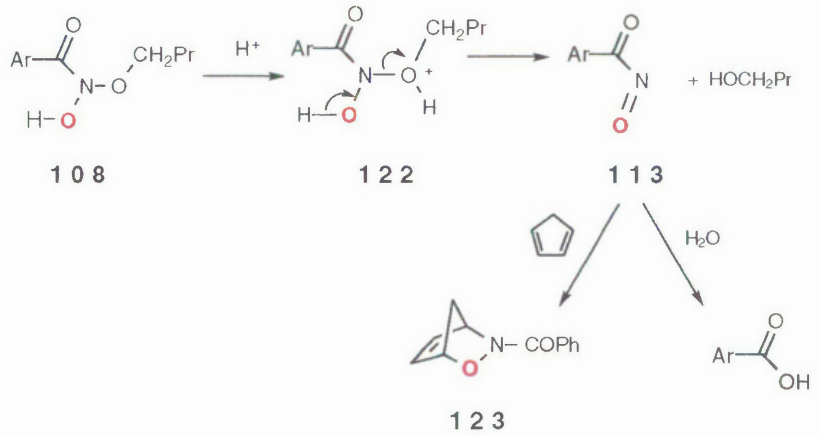


Figure 2-17 Resonance interaction with +*M* *para* substituents

The basicity of the benzoyl oxygen will be influenced through mesomeric and inductive interactions from substituents on the benzoyl ring. Electron-donating substituents *para* to the carbonyl group will reduce the partial positive charge associated with the normal carbonyl polarisation and increase the basicity of the carbonyl oxygen (Figure 2-17). Positive mesomeric groups will also increase the electron density on the carbonyl oxygen through direct resonance interactions across the ring and into the carbonyl moiety.

From Table 2-4 the yield of butanal is greatest (34%) with a *para*-methoxy substituent **100b**. The data for benzohydroxamic acid is incomplete due to the overlap of benzoic and benzohydroxamic acid resonances in the ^{1}H NMR spectrum and errors in ^{1}H NMR integrations were appreciable. Nevertheless, butanal and hydroxamic acid are formed in relatively similar yields. The yield of butanal progressively decreased as the electron-donating ability of the *para* substituent diminished. This is most evident when *p*-nitro **100h** was present on the ring in which case the yield of butanal dropped to zero. Clearly, the ring substituent influences the basicity of the carbonyl oxygen which controls the mechanism leading to formation of butanal and benzohydroxamic acid.

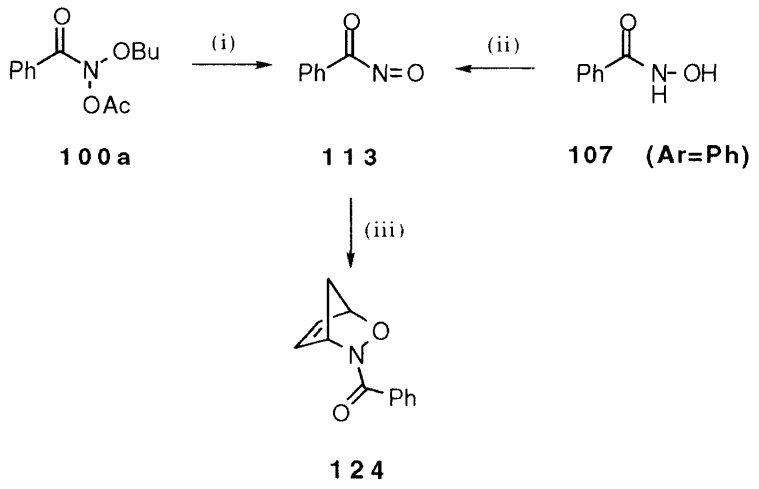
2.2.10 Butanol and nitrosocarbonylbenzene



Scheme 2-12

The source of butanol is most likely acid-catalysed decomposition of *N*-butoxybenzohydroxamic acid **108** to the nitrosocarbonylbenzene **113** intermediate which, like acyl chlorides, reacts with water[190] to give the benzoic acid (Scheme 2-12). The yields of benzoic acid and alcohol for butyl *N*-acetoxybenzohydroxamate **100a** also improve with increasing acid concentration (Table 2-3). Protonation of the butoxy oxygen **122** would be expected occur at higher acid concentration thus promoting formation of butanol and nitrosocarbonylbenzene.

The formation of nitrosocarbonylbenzene **113** as a key intermediate in the solvolysis reaction was confirmed by selectively trapping the nitrosocarbonylbenzene intermediate, as a Diels-Alder adduct, from the solvolysis mixture.



100a **113** **107 (Ar=Ph)**

124

Scheme 2-13 Reagents: (i) H^+, 25% H_2O–CH_3CN; (ii) NBS, CH_2Cl_2; (iii) cyclopentadiene.

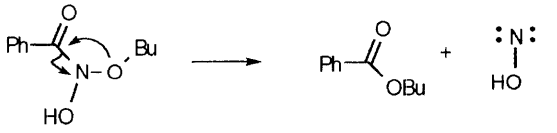
Nitrosocarbonylbenzenes are transient intermediates formed by oxidation of benzohydroxamic acids and are excellent dienophiles[191-200] Addition of cyclopentadiene to the reaction mixture for the acid-catalysed solvolysis of butyl *N*-acetoxybenzohydroxamate **100a** in 25% aqueous acetonitrile led to the formation, albeit in low yield, of *N*-benzoyl-2,3-oxazabicyclo[2.2.1]hept-5-ene **124** (Scheme 2-13i). This was detected by both NMR and HPLC and was identical (NMR and retention time) to authentic material prepared by oxidation of benzohydroxamic acid with *N*-bromosuccinimide in dichloromethane in the presence of cyclopentadiene (Scheme 2-13ii).[192] The authentic material was subjected to a number of NMR studies (^1H, ^{13}C, Gated decoupled, COSY and NOESY) to confirm its structure. 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 25% (10% ^{18}O enriched) aqueous acetonitrile 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 at natural abundance 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 to give *N*-butoxyhydroxamic

acid **108** and subsequent hemiacetal-like acid-catalysed decomposition to the nitrosocarbonylbenzene **113**. While the yields of benzoic acid **114** are erratic, those for butanol are relatively similar across the *para*-substituted series (Table 2-4). Substituents would not be expected to influence the protonation step involved in this process. Poor yields of benzoic acid might be ascribed to both difficulties in NMR measurement across the series as well as other, hitherto undetected reactions of the nitrosocarbonylbenzene intermediate.

2.2.11 Butyl benzoate

Esters **118** are not formed from alcohol and benzoic acids, since alcohols and esters are formed in parallel processes (Figure 2-15).[174] In addition, Figure 2-16 indicates that there is a large reduction in ester formation with increasing acid concentration in accordance with a non acid-catalysed process in competition with acid-catalysed pathways. From these observations it appears plausible that esters are formed in a concerted, intramolecular rearrangement resulting in the formation of hydroxynitrene **119** (Scheme 2-14).

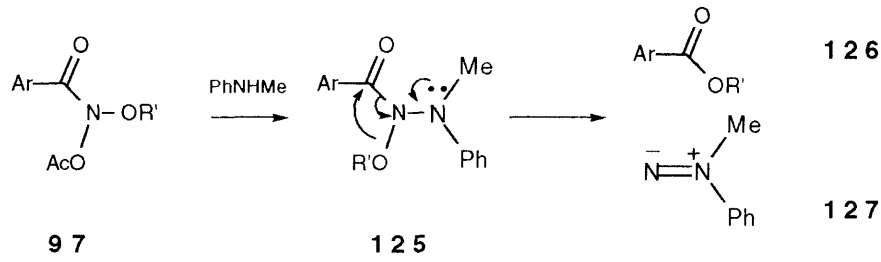


108 **118** **119**

Scheme 2-14 Intramolecular butyl benzoate formation

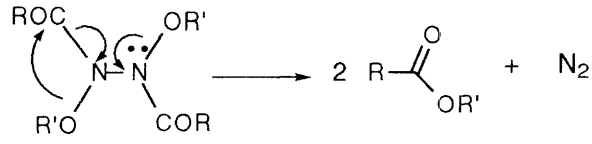
Several precedents for this type of process have been discovered in these laboratories and the process appears to be a general one for *N,N*-bishetereoatomsubstituted amides

177.[201] Called the HERON[1] reaction, it is favourable in most RCONXY systems where the lone pair on Y can lead to an anomeric weakening of the N-X bond.[202] Such interactions are best with high energy lone-pairs (n_Y) and low energy $\sigma^*_{N\text{-}X}$ orbitals and the HERON reaction was first discovered when alkyl *N*-acetoxybenzohydroxamates **97** were reacted with *N*-methylaniline.[203] The product of S_N2 reactions at nitrogen **125** undergoes concerted N to C migration of the alkoxy group leading to formation of the ester and aminonitrene (Scheme 2-15).



Scheme 2-15

This process is driven by the strong anomeric effect of the high energy nitrogen lone pair in **125**. A similar example of this type of rearrangement is found in the thermal decomposition of *N,N'*-dialkoxy-*N,N'*-diacylhydrazines **128** which also give esters (Scheme 2-16).



128

Scheme 2-16

Evidence for consecutive HERON processes in such compounds is presented in Section 2.2.11.1

Thus by analogy with the above reactions, butyl benzoate **118** could form from the *N*-butoxybenzohydroxamic acid intermediate **108** through alkoxy migration together with

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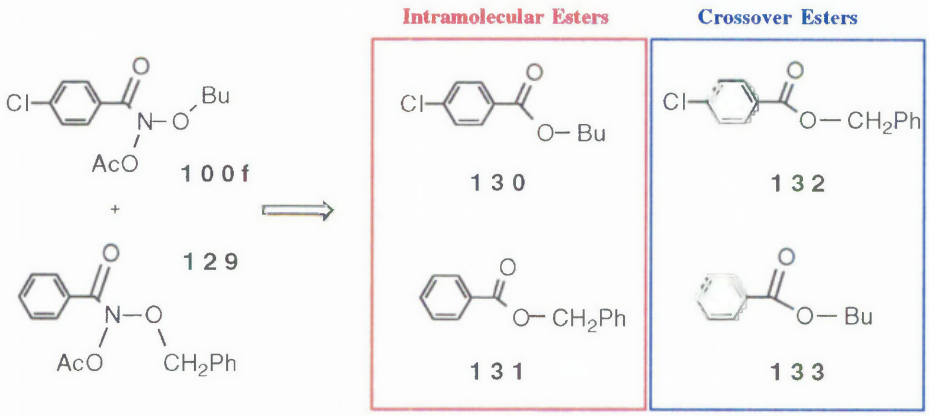
[1] HEteroatom Rearrangement On Nitrogen

simultaneous release of hydroxynitrene **119** in a non-catalysed process. To test for intramolecular formation of ester, a crossover experiment involving two different alkyl *N*-acetoxybenzohydroxamates was performed. To ensure optimum ester conversion a low acid concentration was used to initiate the reaction at 298K.



Scheme 2-17

In the joint solvolysis of equimolar quantities of benzyl *N*-acetoxybenzohydroxamate **129** and butyl *N*-acetoxy-*p*-chlorobenzohydroxamate **100f**, neither of the mixed, crossover esters **132** and **133** were detected (by ^{1}H NMR) but significant quantities of butyl *p*-chlorobenzoate **130** and benzyl benzoate **131** were detected. The results were confirmed by HPLC analysis (Table 2-5).

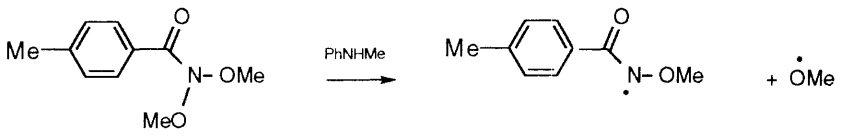
Table 2-5 Acid-catalysed ester crossover reaction at 298K

Product	Percentage Yield†
benzyl benzoate	54
benzyl *p*-chlorobenzoate	0
butyl benzoate	0
butyl *p*-chlorobenzoate	36

† Determined by analytical HPLC.

If the observed esters had formed from acid-catalysed esterification from the carboxylic acid and alkanol, butyl benzoate **133** and benzyl *p*-chlorobenzoate **132** should have been formed. The total lack of these crossover esters indicates that while crossover esterification is possible from the solvolysis products available in the solution, the rate of esterification is very slow under these reaction conditions. Clearly the esters **118** form intramolecularly from the hydroxylated nitrenium ion **108**.

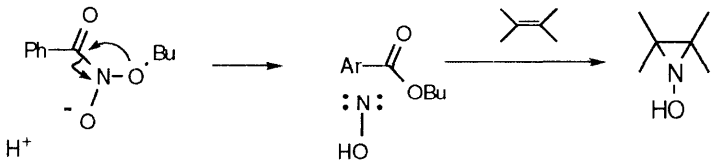
Preliminary semi-empirical AM1 calculations by the author and subsequently by Buccigross and Glover[172] indicated that such migrations (Scheme 2-14) are concerted and lead to simultaneous formation of ester **118** and hydroxynitrene **119**. The activation energies for such migrations are however considerably higher than those involving a nitrogen lone pair; the anomeric driving force of an oxygen lone pair, which is more tightly bound, is considerably weaker. In evidence, Glover found that *N,N*-dimethoxy-*p*-toluamide **134** decomposes thermally into alkoxyamidyl **135** and methoxyl **136** radicals at temperatures greater than 110 °C.[204]



134 **135** **136**

Scheme 2-18

Buccigross found however, that the conjugate anion of the hydroxamic acid **137** rearranges both smoothly and with low activation energy to ester and nitric oxide anion which in acid would give hydroxynitrene.

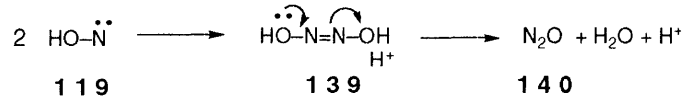


137 **138**

Scheme 2-19

The oxide anion in **137** behaves as a high energy lone pair which results in excellent $\sigma^*_{N\text{-}O}$ anomeric overlap. Thus it is proposed that the conjugate anion of **108** leads to ester formation in a HERON reaction. This is supported by reactions of butyl *N*-acetoxybenzohydroxamate **100a** in base (See Chapter 3.1) as well as the fact that ester formation drops off dramatically with decreasing pH (Figure 2-16). While hydroxyl migration and formation of butoxynitrene cannot be excluded, the driving force would be low and, like neutral ONO systems, it would be expected to have a high activation energy.

Under neutral or slightly acidic conditions, the by-product of this concerted intramolecular rearrangement would be hydroxynitrene **119**. Hydroxynitrenes would be expected to be transient species that dimerise to 1,2-dihydroxydiazene **139**.

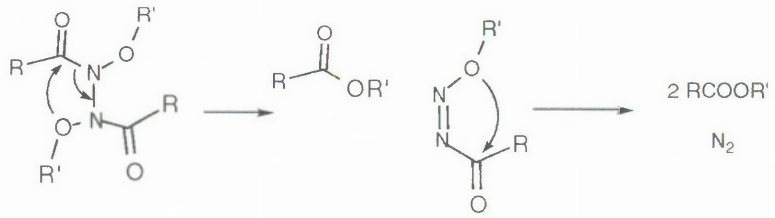


Scheme 2-20

In acid this would most likely decompose to nitrous oxide **140** and water (Scheme 2-20).[189] One method for trapping nitrenes is by addition to double bonds to form aziridines **130** (Scheme 2-19). Several potential problems were envisaged with trapping hydroxynitrene in this manner. These were the low yields expected, and the susceptibility of *N*-hydroxyaziridines **138** to acid: aziridines, like epoxides, are catalytically opened by acids to form β-amino ethers by alcoholysis,[189] a not improbable scenario under these conditions. Nevertheless, attempts were made at trapping hydroxynitrene under conditions conducive to formation of ester in high yield, but neither the aziridine nor products derived therefrom could be isolated or identified. Efforts to identify products derived from hydroxynitrene are continuing in these laboratories.[204]

2.2.11.1 HERON reactions - crossover reaction with N-p-chlorobenzoyl-N-butoxy-N'-benzoyl-N'-benzyloxyhydrazine.

As outlined in Section 2.2.11, the HERON reaction is found to occur readily in ONN amides and was first encountered in concerted decomposition of *N*-anilino-*N*-alkoxybenzamides formed from S_N2 reactions of mutagens with anilines (Scheme 2-15). Subsequent calculations confirmed a low activation energy for this process together with exothermicity brought about by the stability of 1,1-diazenes as well as the esters formed in the process. A report by Cooley *et al*[205] that *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines **141** decompose *via* a concerted four-centre mechanism to ester and nitrogen attracted our attention (Scheme 2-21).



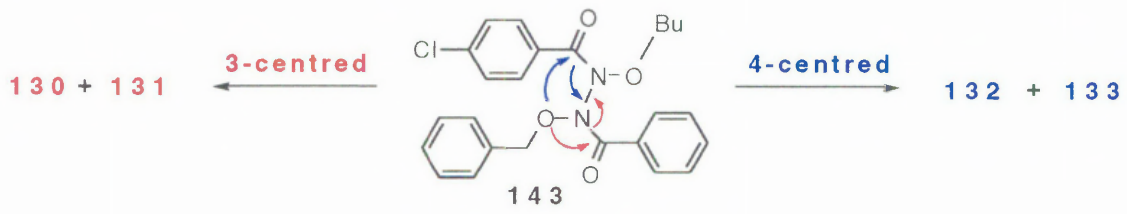
141 **142**

Scheme 2-21 Four-centred decomposition of *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines

The similarity of the decomposition of these *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines **141** to that for *N*-anilino-*N*-alkoxybenzamides **125** as well as the proposed decomposition of *N*-alkoxy benzohydroxamic acid **108** justified a brief review[201] of Cooley's work.

N,N'-diacyl-*N,N'*-dialkoxyhydrazines **141** are formed from the oxidation of hydroxamic esters[205] or recombination of *N*-alkoxy amidyl radicals.[206] Cooley postulated that these compounds decompose through two consecutive four-centred process, Scheme 2-21, to give esters and molecular nitrogen with the transition state displaying incipient alkoxide and acylium character. The reaction is favoured by electron-withdrawing substituents on the alkoxy side chain and electron-donating substituents on the acyl-side chain. Since the hydrazine **141** is a special case of a NNO system, the author considered that consecutive three-centred mechanisms would best account for ester formation.

To confirm which pathway was most favourable, an asymmetrical hydrazine, *N-p*-chlorobenzoyl-*N*-butoxy-*N'*-benzoyl-*N'*-benzyloxyhydrazine **143** was synthesised by lead tetraacetate oxidation of butyl *p*-chlorobenzohydroxamate **98f** and benzyl benzohydroxamate **98a** in dichloromethane.[207] The asymmetric hydrazine **143** was isolated by flash chromatography from two symmetric products and decomposed thermally in chloroform.



143

Figure 2-18

The yields of esters so produced are given in Table 2-6 and clearly indicate that the favoured process involves a three-centred mechanism, the major products being the benzyl benzoate and butyl *p*-chlorobenzoate esters. Minor esters may be formed by the four-centred mechanisms but alternatives cannot be ruled out.

Table 2-6 Percentage yield of products from decomposition of **143** in chloroform at 308K

Product	% Yield†
benzyl benzoate **131**	57
benzyl *p*-chlorobenzoate **132**	9
butyl benzoate **133**	6
butyl *p*-chlorobenzoate **130**	41

† Determined by analytical HPLC.

N-*p*-chlorobenzoyl-*N*-butoxy-*N'*-benzoyl-*N'*-benzyloxyhydrazine **143** was decomposed at 318K in 20% aqueous acetonitrile (D_2O-CD_3CN) and the progress of the reaction was monitored by ^1H NMR through integration of the peaks for the diastereotopic benzyl methylene proton at δ5.05.

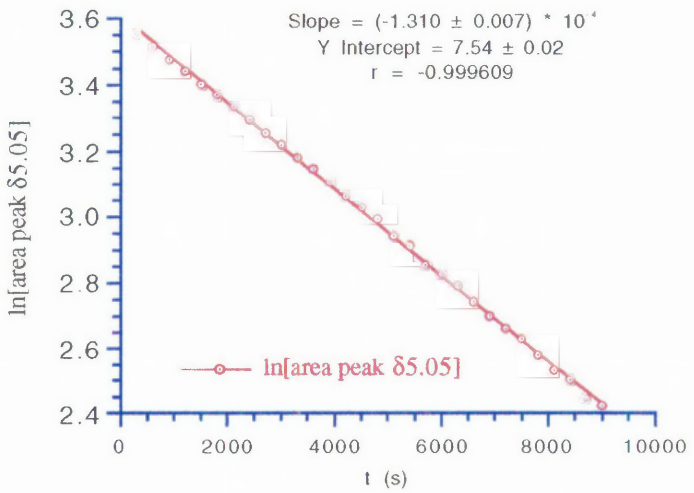


Figure 2-19 First-order decomposition of **143**

N-*p*-chlorobenzoyl-*N*-butoxy-*N'*-benzoyl-*N'*-benzyloxyhydrazine **143** decomposed under first order kinetic control as evident from Figure 2-19. The solvolysis reaction was repeated at 298K, 308K, and 331.5K and the results of the Arrhenius study are given in Table 2-7.

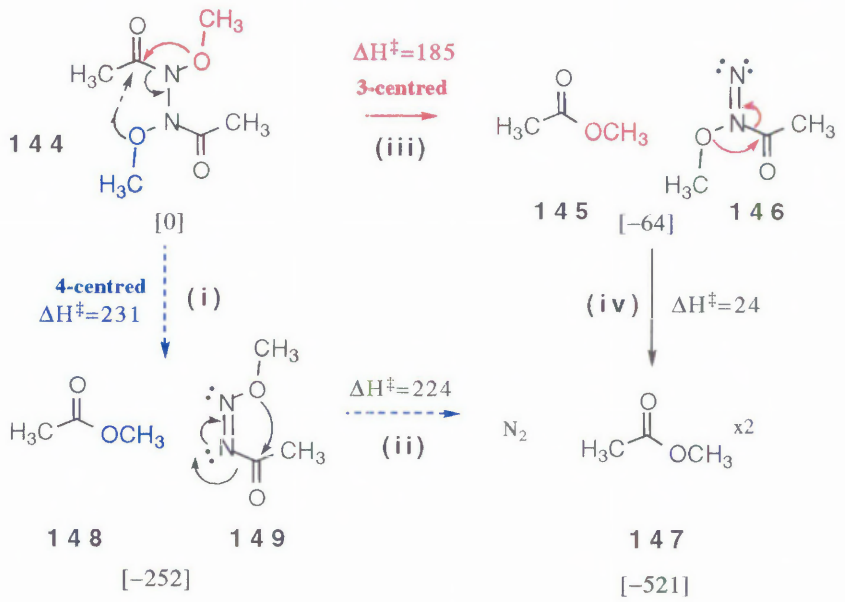
Table 2-7 Arrhenius data for solvolysis of **143**

Temp. (K)	$10^3 \frac{1}{T}$ (K^{-1})	10^6 Rate (s^{-1})
298.0	3.35570	6.623 (0.016)
308.0	3.24675	34.27 (0.48)
318.0	3.14465	131.0 (0.7)
331.5	3.04878	431.4 (8.6)

The Arrhenius parameters were calculated from a weighted least squares analysis of the data in Table 2-7 (r=0.9990) and the enthalpy of activation was found to be 112.9±3.6 $kJmol^{-1}$ and the entropy of activation was 26.9±11.6 $JK^{-1}mol^{-1}$. This is the first evaluation of the energetics of a HERON reaction process for which a $\Delta H^{\ddagger}$ of approximately 90 $kJmol^{-1}$ has recently been calculated using state-of-the-art *ab initio* methods.[208]

Interestingly, the small positive entropy change indicates that the transition state is not significantly more disordered than the ground state even though this is a dissociative reaction. This is in accord with a concerted process involving a cyclic transition state in which bond formation and bond breaking is concurrent.

2.2.11.2 AM1 analysis of 3- centred versus 4- centred pathways



Scheme 2-22 3- and 4-centred rearrangements for *N,N'*-dimethoxy-*N,N'*-diacetylhydrazine.[m]

An analysis of the two possible rearrangement pathways for *N,N'*-methoxy-*N,N'*-diacetylhydrazine **144** was undertaken at the semi-empirical AM1 level. Scheme 2-22 illustrates the possible decomposition pathways by which *N,N'*-dimethoxy-*N,N'*-diacetylhydrazine **144** forms 2 moles of methyl esters **147** and nitrogen gas.

In depth AM1 investigations of the 3- and 4-centred decomposition pathways were carried out as part of this study and later confirmed in a wider investigation of HERON process by Buccigross and Glover.[172,201]

The 4-centred reaction involves a concerted attack from the opposite methoxy moiety across the N–N linkage with concomitant N=N double bond formation (Scheme 2-22(i)). This rearrangement was modelled by decreasing the distance between the alkoxy oxygen and the carbonyl carbon and this ultimately lead to the formation of a stable 1,2-diazene intermediate (Scheme 2-22(i)). An AM1 reaction profile on this molecule was set up such that the energy of the system was determined as the second alkoxy oxygen was set closer to the acyl carbonyl. This did not provide a smooth reaction path but rather the energy

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[m] AM1 heats of formation relative to the hydrazine are given together with the $\Delta H^{\ddagger}$ in kJmol^{-1}.

rose to a very high level until the molecule snapped to give the products as outlined in Scheme 2-22(ii). This indicated that while the first intramolecular rearrangement was possible, the second step would be unlikely at room temperature and pressure.

A reaction profile analysis on the 3-centred reaction mechanism was conducted using a similar methodology. The bond distance between the alkoxy oxygen and the acyl carbonyl carbon on the same end of the N–N bond was shortened. This resulted in a smooth reaction profile to give the 1,1-diazene (Scheme 2-22iii) which in turn decomposed to ester and N_2 (Scheme 2-22iv). The latter process required very little activation energy. Semi-empirical methods indicated that the 3-centred, two step process was more likely and required less energy than the single step, 4-centred reaction.

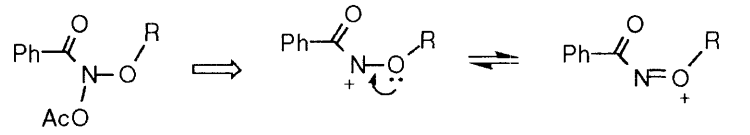
This novel rearrangement is similar to the N to C migrations in *N*,*N*-bisheteroatom-substituted amides which undergo the "HERON" rearrangement. *N*,*N*-bisheteroatom-substituted amides R–CO–NXY undergo a 3-centre rearrangement in which an electronegative atom (X) migrates from the nitrogen to the carbonyl carbon producing an acyl derivative (R–CO–X) and a substituted nitrene (N–Y). The reaction in these cases appears to be driven by an anomeric effect involving interaction between the lone pair on Y and the X–Nσ^* orbital. The energy of the transition states for migration is lowered with electron donor substituents on the amide amino substituent and the rearrangement displays high double bond N–N character as well as a build up of charge on the migrating group.

The experimental and theoretical outcomes of this study have subsequently been corroborated by a concurrent investigation by Barton and co-workers who explored this reaction as an effective means of synthesising hindered esters.[209]

2.3 Acid-catalysed solvolysis of benzyl *N*-acetoxybenzohydroxamate

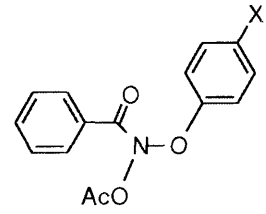
2.3.1 Background

Theoretical and experimental studies in these laboratories[95,100,164,165] have indicated that alkoxy stabilised nitrenium ions should also exhibit substantial oxonium ion character (Scheme 2-23) and so an investigation into the influence of oxygen substituents on oxonium/nitrenium ion formation was undertaken.



Scheme 2-23

Several series of compounds were considered for the study, two of which were phenyl *N*-acetoxybenzohydroxamates **148** and benzyl *N*-acetoxybenzohydroxamates **151** (Scheme 2-24). Both series were considered to have excellent potential to change the electronic environment of the oxonium ion through substitution of a range of electron donating and withdrawing *para* substituents, and hence influence the rate of formation of the nitrenium ion.



148

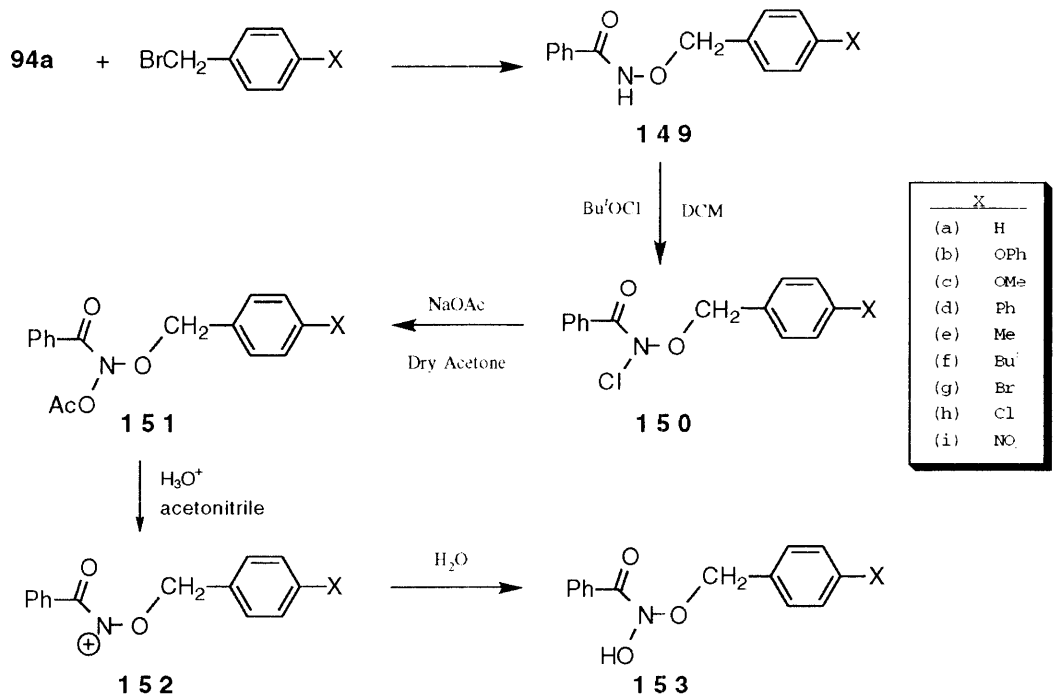
Figure 2-20

Para-substituted phenyl *N*-acetoxybenzohydroxamates **148** would allow direct resonance interactions through the ring onto the alkoxy oxygen. The synthesis of aryl benzohydroxamates (**95**, R=Ar) is non-trivial and only a small number of compounds of this type have being reported. The synthesis of phenyl benzohydroxamate (**95**, Ar= C_6H_5, R=C_6H_5) from potassium benzohydroxamate **94a** and diphenyliodonium bromide has been reported in low yield[210] and improved by Taylor and Kienzle who reacted

thallium(I) benzohydroxamate with diphenyliodonium chloride.[211] The synthesis of diaryliodonium salts[212,213] is limited in scope and similarly non-trivial.[214-217]

From these considerations, the synthesis of phenyl *N*-acetoxybenzohydroxamates **148** was not attempted in the initial phase of the experiments. Benzyl benzohydroxamates **149**, on the other hand, could readily be prepared by simple alkylation of potassium benzohydroxamate with benzyl bromides and were found in practise to be easily and conveniently synthesised.

While in these substrates no conduit exists for direct resonance between the *para* substituents on the ring and the benzyloxy oxygen, inductive effects transmitted through the benzyloxy methylene should be sufficient to influence the electron density on the oxygen and therefore affect the rate of nitrenium ion formation.



Scheme 2-24

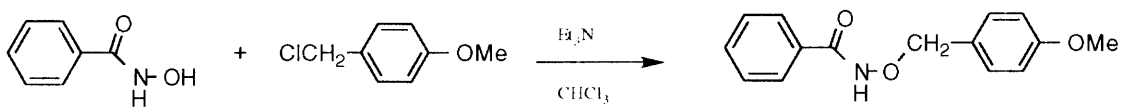
Accordingly a series of *para*-substituted benzyl *N*-acetoxybenzohydroxamates **151a-i** were synthesised (Scheme 2-24) in an attempt to measure the electronic effect of the alkoxy side chain upon the ease of nitrenium ion **152** formation.

2.3.2 Synthesis of benzyl *N*-acetoxybenzohydroxamates

Benzyl benzohydroxamates (**149**, (c) excepted) were synthesised by the standard method (Scheme 2-2) and were obtained as stable, colourless crystalline materials which could be stored for several months without noticeable degradation.

The substitution reaction involving *p*-methoxy benzyl bromide or *p*-methoxy benzyl chloride and potassium benzohydroxamate **94a** under a variety of solvent conditions (10% aq. MeOH, 50% aq. MeOH, 100% Dry THF) did not provide *p*-methoxybenzyl benzohydroxamate **149c**. An alternative synthesis was devised that endeavoured to bypass the hydroxamic ester and lead directly to the mutagen *p*-methoxybenzyl *N*-acetoxybenzohydroxamate **151c**.

O-acetyl-*N*-benzoylhydroxylamine was synthesised from benzohydroxamic acid and acetic anhydride in dry ether. *N*-chlorination of the hydroxylamine was achieved by treatment with a 3*M* excess of *t*-butyl hypochlorite in dry chloroform and was confirmed by NMR spectroscopy. The sodium salt of *p*-methoxybenzyl alcohol was obtained by treatment of *p*-methoxybenzyl alcohol with a 1 molar equivalent of sodium in anhydrous ether under nitrogen and isolated by filtration (under anhydrous conditions). A 1.4 molar excess of the salt in dry acetone was allowed to react with *N*-acetoxy-*N*-chlorobenzamide but after stirring at room temperature for 12 hours there was no evidence for the formation of the required product. A third method for the production of the hydroxamic ester, *p*-methoxybenzyl benzohydroxamate was successfully developed. The nature of the reaction products from the normal alkylation reaction of the potassium salt and benzyl bromide (*p*-methoxybenzyl methyl ether and *p*-methoxybenzyl alcohol) indicated that under the reaction conditions resonance stabilised *p*-methoxybenzyl carbenium ion was formed which was trapped by solvent rather than the potassium salt. Consequently, the reaction conditions were altered to favour S_N2 reaction and disfavour the S_N1 formation of the benzyl carbenium ion.



117 **154** **149c**

Scheme 2-25

Hence, benzohydroxamic acid **117**, *p*-methoxy benzyl chloride **154** and triethylamine were dissolved and refluxed for 2 hours in dry $CHCl_3$. Workup provided **149c** in moderate yield.

N-chlorination of the benzyl benzohydroxamates proceeded smoothly in DCM, with the exception of *p-tert*-butylbenzyl benzohydroxamate **149f** which required 50% DCM/$CHCl_3$ to fully dissolve. Complete *N*-chlorination was complete within 20-120 minutes.

2.3.3 Acetoxylation of benzyl *N*-acetoxybenzohydroxamates

Acetoxylation of the *N*-chloro compounds **150a-i** was best accomplished using Finkelstein-like conditions[189] *via* Method 2 (Scheme 2-2, NaOAc in acetone) in preference to Method 1 (Scheme 2-2, AgOAc in ether) as side products were reduced leading to increased yields (Table 2-8).

Table 2-8 Comparison of yields of **151** via Method **1**: AgOAc/Ether and Method **2**: NaOAc/Acetone

Substrate		Method 1 (%)	Method 2 (%)
151e	**Me**	5[a]	60[b]
151a	**H**	30[b]	87[b]
151g	**Br**	25-30[a]	94[b]
151h	**Cl**	45[a]	96[b]
151i	**NO_2**	0[b]	93[b]

a Approximate yield based on ^1H NMR of final reaction mixture.
b Quantitative analysis by HPLC.

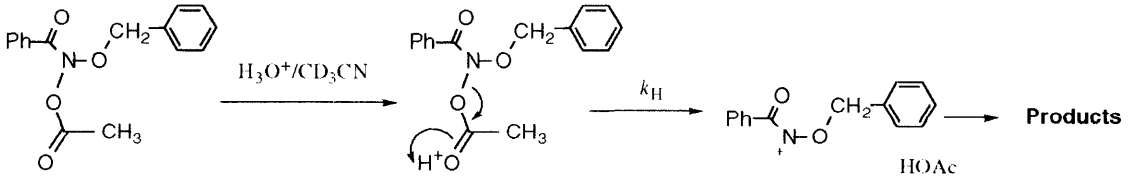
For instance, treatment of *p*-nitrobenzyl *N*-chlorobenzohydroxamate **150i** with silver acetate in ether failed to provide the *N*-acetoxy substrate even after stirring at room temperature for 48 hours, but resulted in the partial formation of *p*-nitrobenzyl benzohydroxamate **149i**. It was thought that the Lewis acid may be insufficiently activating to heterolyse the N–Cl bond in this case and consequently the reaction conditions were adjusted to favour a bimolecular reaction with acetate anion. When *p*-nitrobenzyl *N*-chlorobenzohydroxamate **150i** was treated with a 1.4 molar excess of anhydrous sodium acetate in dry acetone and stirred at room temperature for 12-48 hours, excellent yields of *p*-nitrobenzyl *N*-acetoxybenzohydroxamate **151i** were obtained. A molar excess greater than 1.4 appeared to reduce the conversion to *N*-acetoxy substrates **151**. Sodium acetate is only slightly soluble in acetone but Le Chateliers principle

ensures that sufficient soluble acetate anion is available for the S_N2 reaction with the *N*-chloro substrate **150** as the reaction progresses.

Crystallisation of solid sodium chloride above the level of solvent in the reaction vessel flask provided a convenient qualitative indicator that acetoxylation was proceeding smoothly.

Acetoxylation of the benzyl *N*-chlorobenzohydroxamates **150** resulted in a 0.11 ppm downfield shift for the oxymethylene resonance to about δ5.2 which could also be used to monitor the progress of the reaction.

2.3.4 Acid-catalysed solvolysis of benzyl *N*-acetoxybenzohydroxamates



151a **155** **152a**

Scheme 2-26

Under acidic conditions in aqueous acetonitrile, benzyl *N*-acetoxybenzohydroxamate **151a** solvolysed following pseudo first-order kinetics giving acetic acid and various solvolysis products (Scheme 2-26). The acid-dependent rate constants of solvolysis at 308K was measured at four acid concentrations and the results are recorded in Table 2-9.

Table 2-9 The rate constants for solvolysis of **151a** at different acid concentrations

$[H^+]$ (mol.L^{-1})	$10^4 k'$ (s^{-1})
0.007040	0.5667
0.01358	0.8056
0.02181	1.3221
0.02739	1.6852

The acid-independent rate constants for solvolysis at 308K was calculated to be $(5.59\pm0.45)\times10^{-3}$ s^{-1} (r=0.9936) from the plot of rate constant, k' against hydronium ion concentration.

The rate constant for non-catalysed solvolysis, as given by the intercept, was $(1.20\pm0.86)\times10^{-5}$ s^{-1} which is at least two orders of magnitude smaller than the rate constant for acid-catalysis.

The Arrhenius parameters were calculated for the acid-catalysed solvolysis of a series of *para*-substituted benzyl *N*-acetoxybenzohydroxamates **151a-i** over the temperature range, 298K-338K and the results are given in Table 2-10. k' was obtained at a single $[H_3O^+]$ for each temperature and k_H calculated according to the equation 2-5.

Table 2-10 Arrhenius parameters and rate constants for solvolysis for **151a-i** at 308K

Subst.	ln A	$\Delta S^{\ddagger}$ ($JK^{-1}mol^{-1}$)	E_a/R (K)	E_a ($kJmol^{-1}$)	$100k_H$ (308K) ($Lmol^{-1}s^{-1}$)	$\Delta G^{\ddagger}_{308}$ ($kJmol^{-1}$)	r
151c MeO	44.5(2.6)	116.7(21.7)	14286(825)	118.8(6.9)	14.87	82.86	0.99334
151b PhO	38.19(2.8)	64.3(23.3)	12827(872)	106.6(7.2)	3.16	86.80	0.99314
151e Me	47.06(0.71)	138.0(5.9)	15690(223)	130.4(1.9)	2.062	87.90	0.99969
151f Bu^t	43.82(0.94)	111.1(7.8)	14731(298)	122.5(2.5)	1.821	88.28	0.99939
151d Ph	42.99(0.78)	104.2(6.5)	14700(247)	122.2(2.1)	0.876	90.11	0.99958
151a H	45.01(1.32)	121.0(11.0)	15400(421)	128.0(3.5)	0.499	90.73	0.99889
151g Br	40.01(0.45)	79.4(3.7)	14181(144)	117.9(1.2)	0.239	93.44	0.9999
151h Cl	41.89(1.26)	95.0(10.5)	14731(397)	122.5(3.3)	0.265	93.24	0.99889
151i NO_2	34.43(1.09)	33.0(9.1)	12903(350)	107.3(2.9)	0.0573	97.14	0.99817

All compounds solvolysed with a significant activation energy and a positive entropy of activation. Increasing electron donating ability of the *para* substituent increased the overall rate of solvolysis. The least reactive compound, *p*-nitrobenzyl *N*-acetoxybenzohydroxamate **151i**, solvolysed with only a small increase in the disorder of the transition state, and with the smallest activation energy. Increasing electron donating ability of the *para* substituent increased both the energy of activation and entropy of activation. Clearly, the rise in $\Delta S^{\ddagger}$ is a significant driving force for the reaction, as was the case with the acid-catalysed solvolysis of the butyl *N*-acetoxybenzohydroxamate **100** series of compounds.

2.3.5 Enthalpy vs entropy relationship

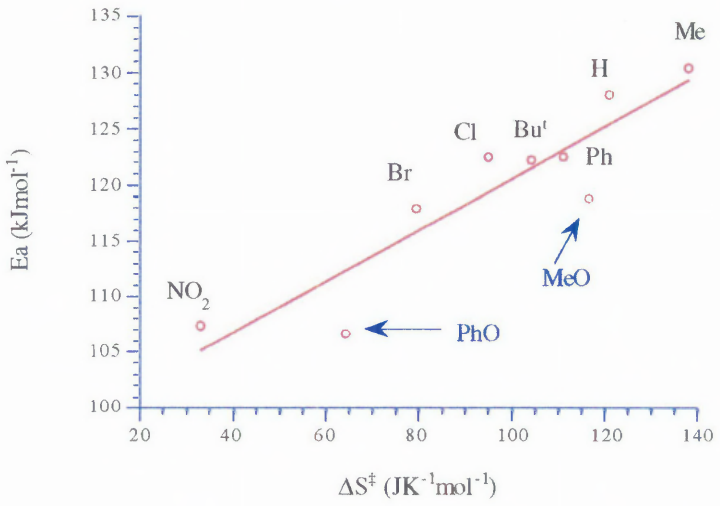


Figure 2-21 Enthalpy vs. Entropy

An excellent correlation was obtained when the activation energy of the compounds from *p*-nitro to *p*-methyl was plotted against the entropy of activation (r=0.988), however two substrates *p*-methoxy and *p*-phenoxy deviated significantly from the expected trend (Figure 2-21). These substituents, with powerful electron donating ability, underwent the fastest solvolysis even though the disorder in the system is lower than expected. As solvolysis to a nitrenium ion is an entropy driven process, a more ordered transition state should result in a slower reaction however this was not observed.

Figure 2-21 indicated that an alternative solvolysis mechanism may be operating when powerful electron donating substituents were present on the benzyl ring. The possibility of an alternative mechanism of solvolysis was supported by an unusual Hammett relationship. When the log of relative rates at 308K (Table 2-10) was plotted, the data revealed an excellent, and unexpected, σ^+ correlation (ρ=-1.56; r=0.9797). A σ^+ relationship normally indicates that *para* substituents have direct inductive and resonance access, through the molecular framework, to a developing positive charge and the magnitude of the slope of the Hammett plot, ρ, reflects the ability of the *para* substituents to influence that charge.

In this system, rates of nitrenium ion-oxonium ion formation should not result in σ^+ correlation as the influence of mesomeric *para* substituents must be radically reduced by the intervening benzyloxy methylene group.

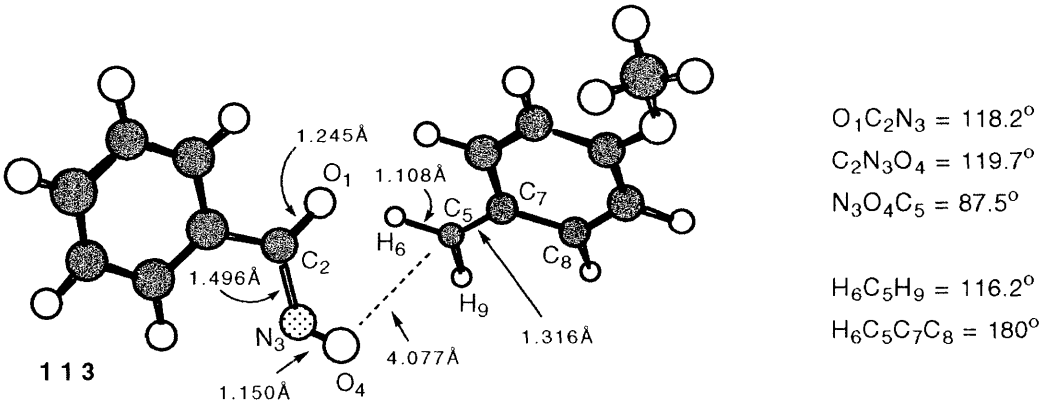


Figure 2-22 Attempted gas-phase AM1 optimisation of **152c**

Gas-phase AM1 optimisation of *para*-methoxybenzyloxynitrenium ion **152c** (ΔH_f=719 kJmol^{-1}) resulted in fragmentation to a complex of *para*-methoxy benzyl carbocation (ΔH_f=929 kJmol^{-1}) and nitrosocarbonylbenzene (ΔH_f=27 kJmol^{-1}) (Figure 2-22). A similar result was obtained using COSMO which simulates a solvated ion. Interestingly, AM1 anticipated a similar decomposition for nitrenium ions **152a** (ΔH_f=1805 kJmol^{-1}) and **152i** (ΔH_f=1959 kJmol^{-1}).

Thus preliminary theoretical analysis indicated that benzyloxy stabilised nitrenium ions may fragment to benzyl cation easily suggesting that, in the case of *p*-methoxy **151c** and *p*-phenoxy **151b** substrates, the initial step may involve direct fragmentation to *p*-methoxybenzyl cation and *p*-phenoxybenzyl cation. Evidence for such a mechanistic switch was evident from an analysis of the solvolysis products.

2.3.6 Analysis of solvolysis products

The products from the acid-catalysed solvolysis of **151a-e** and **151h-i** are given in Table 2-11. Since acid strengths were different in each case direct comparisons cannot be made. The range of products from the solvolysis of **151a, 151e** and **151h** was however similar to those obtained from the butyl *N*-acetoxybenzohydroxamate with the exception that small quantities of benzoic anhydride were also detected. This is presumably a consequence of reaction of the nitrosocarbonylbenzene **113** intermediate with the benzoic acid **114** it generates with water. Esters are formed in modest but not dissimilar yields from each of **151a, 151e, 151d, 151h** and **151i.**

Table 2-11 Percentage yields[a] of solvolysis products from the acid-catalysed[b] solvolysis of **151a-e** and **151h-i.**

	X						
	MeO	PhO	Ph	Me	H	Cl	NO_2
Product	**151c**	**151b**[c]	**151d**[c]	**151e**	**151a**	**151h**	**151i**
Benzaldehyde	<1	*d*	4	4	8	13	16
Benzohydroxamic acid	0	*d*	*d*	1	7	3	<5
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
Benzoic anhydride	20	17	9	6	2	0.3	0

a Yields from HPLC.

b Typically 5-20 μL of a 1.0 $mol.L^{-1}$ solution of H_2SO_4 was required for complete conversion over a 24 hour period.

c Estimated from the final ^1H NMR spectrum of a typical kinetic run.

d Could not be accurately determined

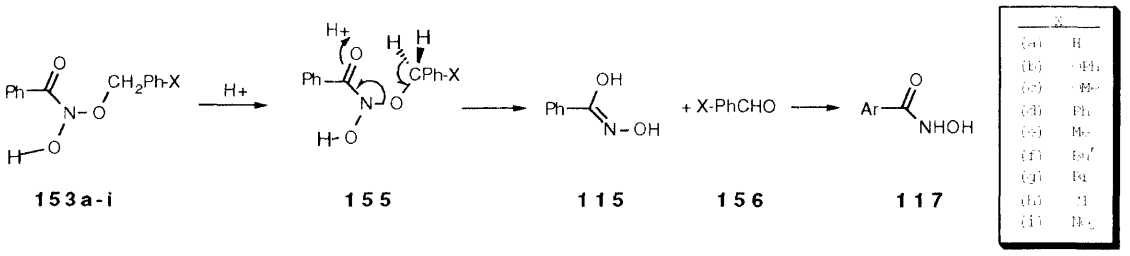
At the completion of solvolysis of the *p*-methoxy substrate **151c**, the ^1H NMR spectrum was significantly less complex when compared to all other substrates and was dominated by 3 major compounds: benzoic acid; benzyl alcohol; and benzoic anhydride. Benzaldehyde, benzohydroxamic acid and benzyl benzoate were not detected.

Of particular note was the total lack of ester which implied the absence of the *N*-(*p*-methoxybenzyl) benzohydroxamic acid **153c**; a fundamental intermediate in the proposed mechanism for the solvolysis of all alkyl *N*-acetoxybenzohydroxamates to alkoxynitrenium ions. For phenoxy substrate **153b** the yield of ester was also lower than normal, however both substrates produced significant quantities of benzoic acid anhydride.

A discussion of the results from Table 2-11 has been broken up in the following sub-sections.

2.3.7 Benzaldehyde and benzohydroxamic acid

From Table 2-11 the yield of benzaldehyde appears to increase with increasing electronegativity of the *para* substituent from a negligible yield recorded for *p*-methoxy to a low to moderate yield recorded for *p*-nitro. From Scheme 2-12, aldehyde is proposed to be formed together with hydroxamic acid from the rearrangement of the protonated alkoxy benzohydroxamic acid intermediate.



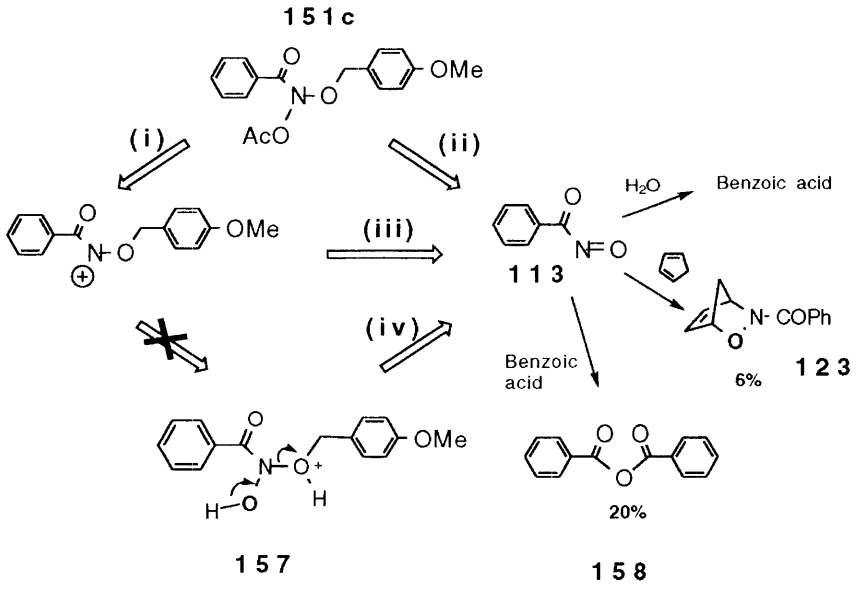
Scheme 2-27

As described previously, this is an acid-catalysed process and the critical point for rearrangement is likely to be protonation of the carbonyl to give **155** and loss of a single benzylic proton to the solution as the molecule reorganises to form the aldehyde and the oxime (Scheme 2-27). As the yield of these products is relatively small, it appears that the *para* substituents have little of influence over this rearrangement due to their remoteness from the site of protonation. From the yields (Table 2-11) this reaction pathway is clearly overshadowed by other reaction processes.

2.3.8 Benzoic acid, benzyl alcohol and benzoic anhydride

For the benzyloxy series **151a-i**, benzoic acid was formed in moderate to good amounts but the yields reveal no definitive trend (Table 2-11). On the other hand, the yield of benzyl alcohol tends to increase consistently with increasing electron donor capacity of the *para* substituent.

The *p*-methoxy substrate **151c** gave only 3 major products: benzoic acid; benzyl alcohol and benzoic anhydride. While the formation of nitrosocarbonylbenzene **113** was indicated by the formation of these products, the absence of ester, benzaldehyde and benzohydroxamic acid suggests that *N*-(*p*-methoxybenzyl) benzohydroxamic acid **153c** is not an intermediate in the reaction.



Scheme 2-28

By analogy with the acid-catalysed solvolysis of butyl *N*-acetoxybenzohydroxamate **100a** (Section 2.2.7) *N*-(*p*-methoxybenzyl) benzohydroxamic acid **153c** should rearrange to *p*-methoxybenzyl benzoate at low acid concentrations or to benzaldehyde and benzohydroxamic acid at higher acid concentrations. The lack of these products indicates that the hydroxamic ester is not produced and this in turn indicates that formation of nitrenium ion intermediates in the reaction was questionable. The formation of benzoic anhydride **158** in significant yield suggests that nitrosocarbonylbenzene **113** is generated in substantial quantities, either by fast fragmentation of the nitrenium ion intermediate prior to attack by water solvent (Scheme 2-28(iii)), or through direct elimination from the *N*-acetoxy starting material (Scheme 2-28(ii)).[190]

The presence of nitrosocarbonylbenzene as a solvolysis product was once again confirmed by trapping the intermediate **113** with cyclopentadiene as the Diels-Alder cycloadduct, 3-benzoyl-2,3-oxazabicyclo[2.2.1]hept-5-ene **123**.

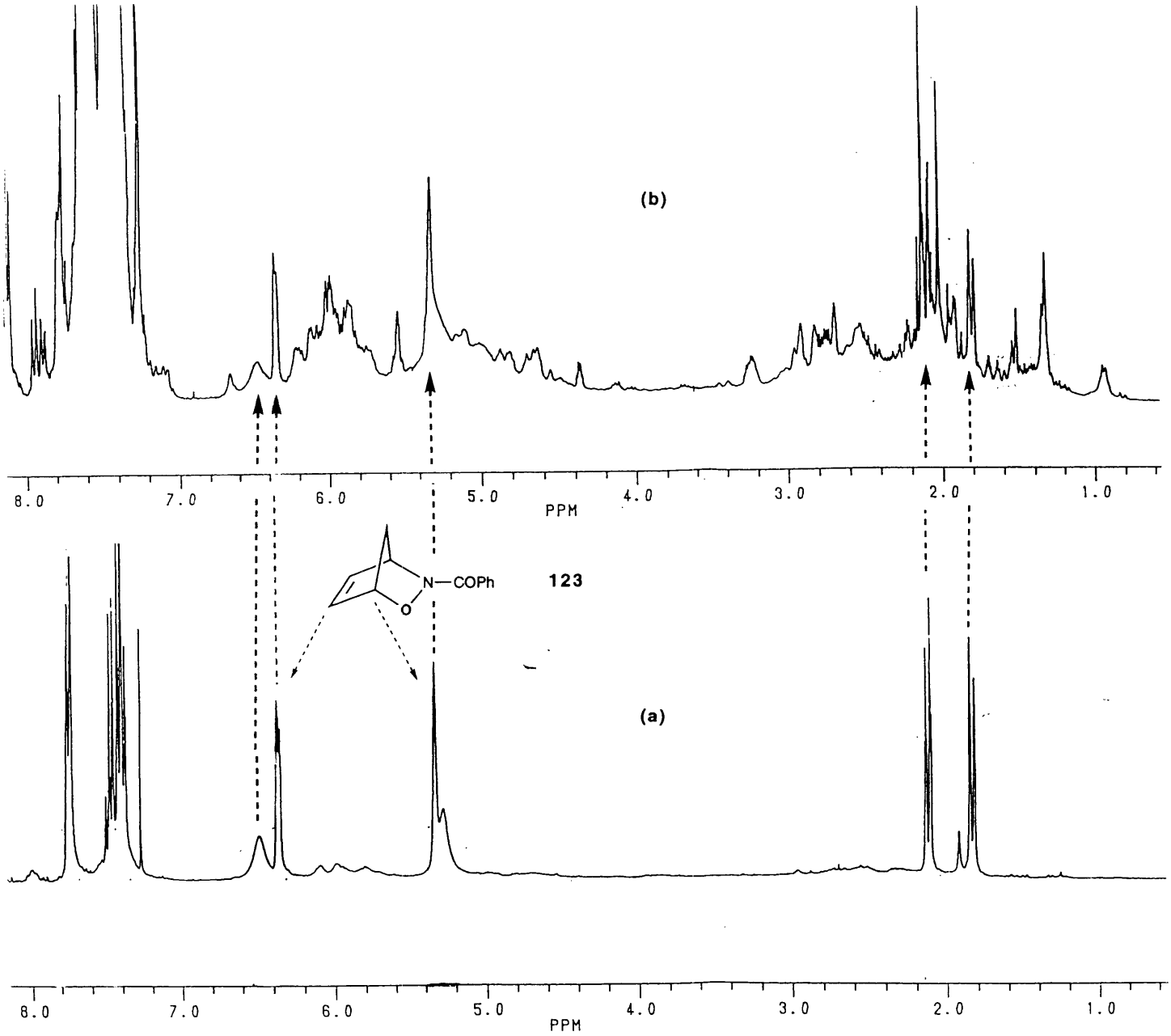
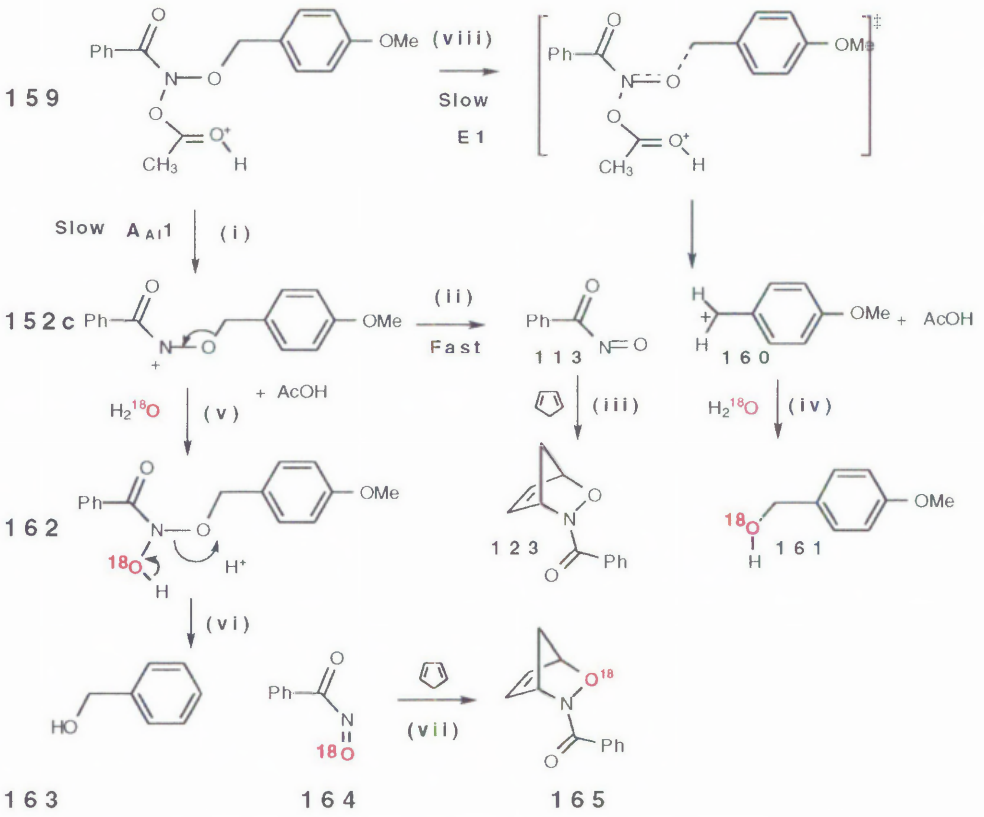


Figure 2-23 a) 3-benzoyl-2,3-oxazabicyclo[2.2.1]hept-5-ene **123** **b)** Solvolysis of **151c** with cyclopentadiene in 25% aqueous acetonitrile.

Cyclopentadiene was dissolved in a solution of **151c**, in 25% aqueous acetonitrile, and an acid-catalysed solvolysis reaction was initiated with sulphuric acid at 308K. NMR analysis of the products at completion of the reaction indicated that a similar quantity of benzyl alcohol was produced to the amount that was generated in the absence of the diene. The Diels-Alder cycloadduct, 3-benzoyl-2,3-oxazabicyclo[2.2.1]hept-5-ene **123** was also identified in the mixture by ^{1}H (Figure 2-23b), ^{13}C NMR and was detected in 6% yield by analytical HPLC.



Scheme 2-29

Scheme 2-29 illustrates alternative mechanisms for the decomposition of **159** to give 3-benzoyl-2,3-oxazabicyclo[2.2.1]hept-5-ene **123.** The rate determining step could involve concerted release of acetic acid, *p*-methoxybenzyl carbocation **160** and nitrosocarbonylbenzene **113** in an acid-catalysed E_1 process (pathway (viii)). Alternatively, rate determining $A_{Al}1$ formation of a nitrenium ion **152** could be followed by a fast, highly competitive elimination of *p*-methoxybenzyl carbocation **160** (pathway (i-ii)). Neither mechanism invalidates the kinetics of the reaction as both processes produce a positively charged intermediate in a pseudo first-order fashion.

Since the nitrosocarbonylbenzene **113** 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 2-29(iii)). On the other hand, benzyl alcohol **161** that would be formed by trapping of the benzyl cation should be enriched with ^{18}O (Scheme 2-29 (iv)).

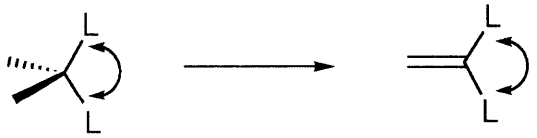
Pathway v-vii, involves hydrolysis of the nitrenium ion **152** and based on the study of solvolysis products which revealed the absence of ester, is unlikely to occur. Like solvolysis of butyl *N*-acetoxybenzohydroxamate **100a**, normal acid-catalysed hemi-acetal like decomposition of the hydroxamic acid intermediate **162**, Scheme 2-29(vi), would lead to unlabelled benzyl alcohol **163** and labelled nitroso intermediate **164** as well as ^{18}O labelled Diels-Alder adduct **165**, Scheme 2-29(vii) in ^{18}O enriched water.

Accordingly, the solvolysis of **151c** was repeated in 10% ^{18}O-enriched aqueous acetonitrile (1:4) in the presence of cyclopentadiene. *N*-benzoyl-2,3-oxazabicyclo[2.2.1]hept-5-ene **123** and benzyl alcohol were then isolated by preparative HPLC. The $(M+2)^+$:M^+ ratio for the adduct 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 10% ^{18}O-enriched water (0.122) and an order greater than that for unlabelled *p*-methoxybenzyl alcohol (0.007). Clearly nitrosocarbonylbenzene **113** is formed by either pathway (i) then (ii) or pathway (viii) but not via acid-catalysed decomposition of the hydroxamic acid **162** (Scheme 2-29(vi)).

The distinction between these pathways was made on the basis of deuterium isotope effects. Unlike pathway (i), pathway (viii) leads to a transition state in which there is a change in hybridisation 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.[176]

Replacement of one or more atoms with their heavier isotopes can bring about a change in the rate in a reacting system and is known as the kinetic isotope effect. Isotopic substitution does not affect the potential energy surface of the molecule, but only influences those properties which are dependant on the atomic masses, such as vibrational frequencies. The extent to which the reaction rate is affected by isotopic substitution is greatest for those of hydrogen H D and T, and has been measured for other isotopes

including carbon[218-223] ^{12}C, ^{13}C and ^{14}C. Since the maximum isotopic rate ratio is approximately the square root of the inverse ratio of isotopic masses, the isotopic effect for atoms heavier than hydrogen becomes very small. A *secondary isotope kinetic effect* (SKIE) is observed when the rate of the reaction is changed when an atom is replaced by its isotope at a bond which is not broken during a reaction. In a solvolytic reaction, a carbon undergoing a change from sp^3 to sp^2 hybridisation will benefit from a reduction in the vibrational energy of the bending mode and will favour the reaction as well as favouring hydrogen over deuterium.

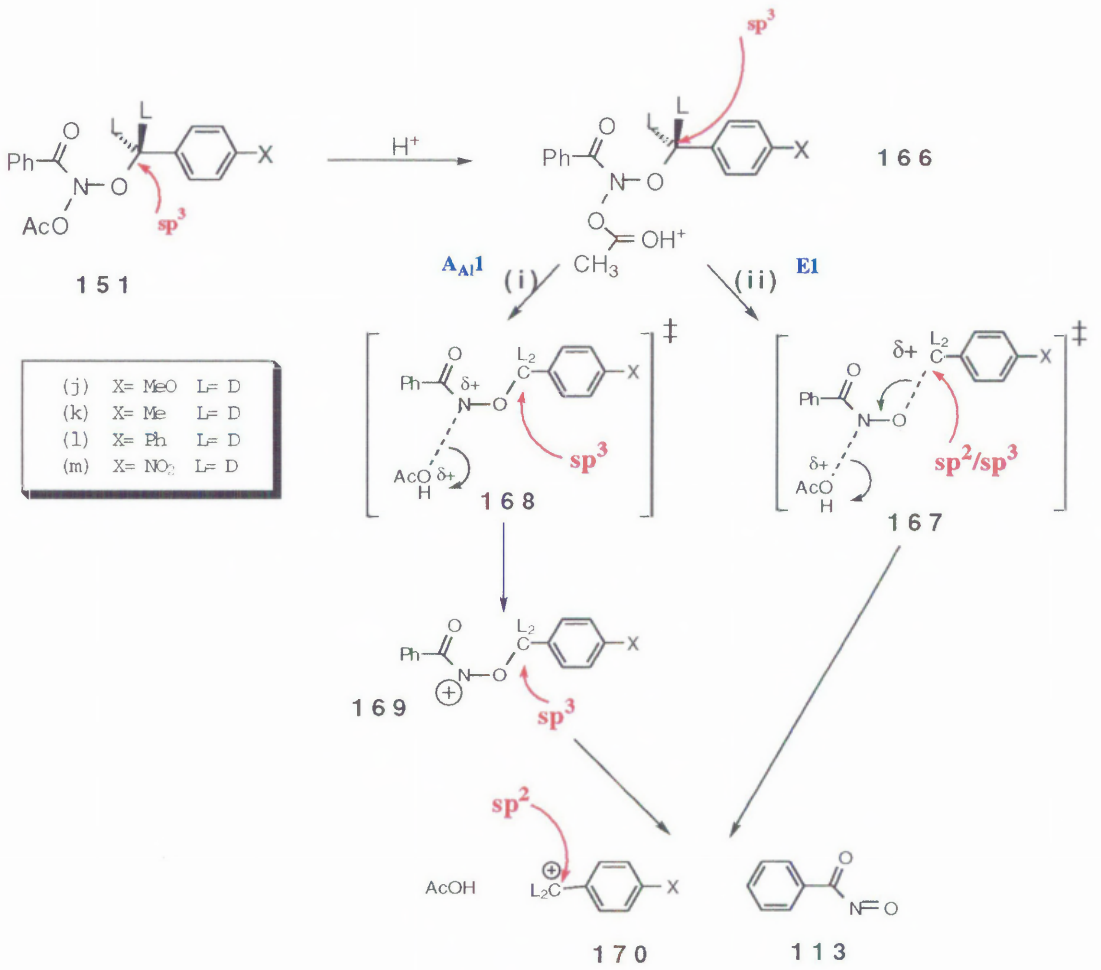


L = H	1340 cm^{-1}	800 cm^{-1}
L = D	957 cm^{-1}	571 cm^{-1}

Figure 2-24

For hydrogen, the reduction in the C-H bending frequency for a carbon undergoing sp^3 to sp^2 hybridisation (Figure 2-24) is 540 cm^{-1} compared to deuterium which is 386 cm^{-1}, which gives $\frac{k_H}{k_D}$ to be approximately 1.4.

Acid independent rate constants for acid-catalysed solvolysis of **151c**, **151e**, **151d** and **151i** and their *bis*-deuterated analogues **151j**, **151k**, **151l** and **151m** were obtained from the rates of solvolysis at different sulfuric acid concentrations (Scheme 2-30).



Scheme 2-30

Rate determining acid-catalysed elimination of *p*-methoxybenzyl carbocation **170** involves a change in the hybridisation of the benzyloxy methylene moiety from sp^3 in the starting material to sp^2 hybridisation in the carbocation (Scheme 2-30(ii)). On the other hand, $A_{Al}1$ solvolysis to the nitrenium ion **169** does not involve a change in hybridisation for this methylene (Scheme 2-30(i)).

The rate of acid-catalysed solvolysis for the protio and deuterio species are recorded in Table 2-12 below.[224]

Table 2-12 Rate constants and secondary kinetic isotope effects for *para*-substituted benzyl *N*-acetoxybenzohydroxamates at 308K

Subst.	k_H^{308} / 10^{-2} L.mol^{-1}s^{-1}	*r*	k_D^{308} / 10^{-2} L.mol^{-1}s^{-1}	*r*	k_H^{308}/k_D^{308}
NO_2[f]	0.0624 (0.0017)	0.9981	0.0609 (0.0028)	0.9979	1.02 (0.06)
Me[*]	2.2917 (0.0033)	1.0000	2.3228 (0.0097)	0.9954	0.99 (0.01)
Ph[¶]	0.8662 (0.0044)	0.9961	0.7346 (0.0154)	0.9993	1.18 (0.03)
MeO[#]	14.96 (0.54)	0.9981	11.35 (0.50)	0.9970	1.32 (0.08)

[*]Me, k_H from **151e** and k_D from **151k**; [¶]Ph, k_H from **151d** and k_D from **151l**; [f]NO_2,k_H from **151i** and k_D from **151m**; [#]MeO, k_H from **151c** and k_D from **151j**;

p-Nitrobenzyl *N*-acetoxybenzohydroxamate did not show any significant difference in the rate constants for solvolysis (k_H/k_D=1.02±0.06). Clearly, the rate determining step is well removed from the influence of this carbon, indicating that nitrenium ion formation proceeds *via* the normal $A_{Al}1$ mechanism. Interestingly, a similar result was observed when α,α-dideuterio-*p*-methylbenzyl *N*-acetoxybenzohydroxamate was solvolysed (k_H/k_D=0.99±0.01). While elimination of *p*-nitrobenzyl carbocation from *p*-nitrobenzyl *N*-acetoxybenzohydroxamate would be considered unlikely, the positively inductive methyl moiety should increase the possibility for carbocation formation, however this was clearly not the case as the rate constant for the reaction remained the same for both protio and deuterio substrates.

While a *para* phenyl substituent is more +*M* but less +*I* than a *para*-methyl substituent, the overall effect is to be slightly less electron donating than the methyl moiety. However, the SKIE was determined to be 1.18±0.03, which is consistent with the partial heterolysis of the C–O bond in the rate determining elimination step. Importantly elimination was confirmed for solvolysis of *p*-methoxybenzyl *N*-acetoxybenzohydroxamate as the ratio of the slopes gives a k_H/k_D, of 1.32±0.08, which is close to the theoretical maximum of 1.4[176] and is indicative of a transition state with substantial sp^2 character at the benzylic carbon (Scheme 2-30(ii)).

The change in mechanism found for *p*-methoxybenzyl *N*-acetoxybenzohydroxamate is undoubtedly a consequence of resonance stabilisation imparted to 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 (Scheme 2-30(i)).

It was envisaged that a change in mechanism from $A_{Al}1$ to E1 would occur with increasing electron donor capacity of the *para* 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 in varying the *para* substituent from methyl ($k_H/k_D = 0.99 \pm 0.02$) to *p*-phenyl ($k_H/k_D = 1.18 \pm 0.07$). 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 by mesomeric stabilisation of the benzyl cation.

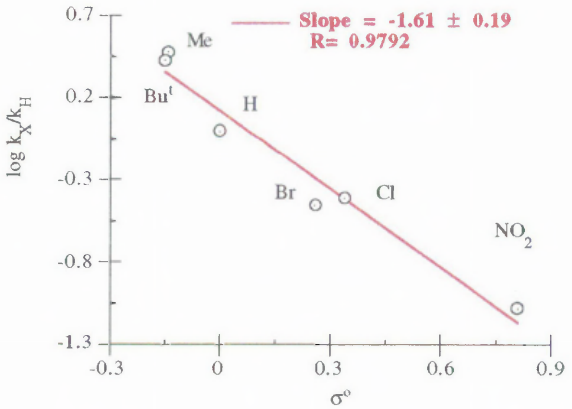


Figure 2-25 Hammett relationship for acid-catalysed solvolysis of *para*-substituted benzyl *N*-acetoxybenzohydroxamates (**151a,e-i**) to benzylnitrenium ions ($A_{Al}1$ mechanism)

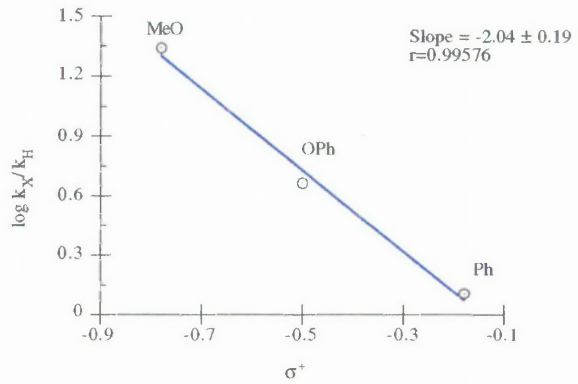


Figure 2-26 Hammett relationship for acid-catalysed solvolysis of *para*-substituted benzyl *N*-acetoxybenzohydroxamates (**151b-d**) to benzyl carbocations (E1 Mechanism)

The Hammett data for the benzyloxy series is thus best represented by two independent correlations; one for substrates **151a**, **151e-i** (Figure 2-25) which correlate with Hammett σ substituent constants (ρ= -1.61 ± 0.19) and one for substrates **151b, 151c** and **151d** (Figure 2-26) 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. (Scheme 2-30, E1 pathway)

The entire series of substrates have been shown to be significantly mutagenic without metabolic activation (Section 4.3). These are thus direct acting mutagens. Recent results of DNA damage studies[225] have indicated that the mutagens modify DNA at N-7 of guanine, the most nucleophilic centre of all the nucleotides. The results in this section have important implications for the mechanism of mutagenesis. Either alkyl *N*-acyloxy amides behave as molecular electrophiles towards DNA which nucleophilically displaces the acyloxy substituent, or the mutagens generate acylalkoxynitrenium ions. There is a precedent for S_N2 displacement of acyloxy group in the work of Campbell and Glover[203] who investigated the bimolecular reactions of mutagenic *N*-acetoxy-*N*-alkoxybenzamides and *N*-methylaniline. The S_N1 process is however extremely slow and requires an acid catalyst to generate electrophilic nitrenium ions. Under such conditions however, the mutagens **151b, 151c** and **151d** are likely to yield benzyl cations directly. Thus if catalysed S_N1 processes are involved, mutagenicity would have to arise by either alkoxyamidation of nucleotides by nitrenium ions or alkylation of nucleotides by benzyl cations.

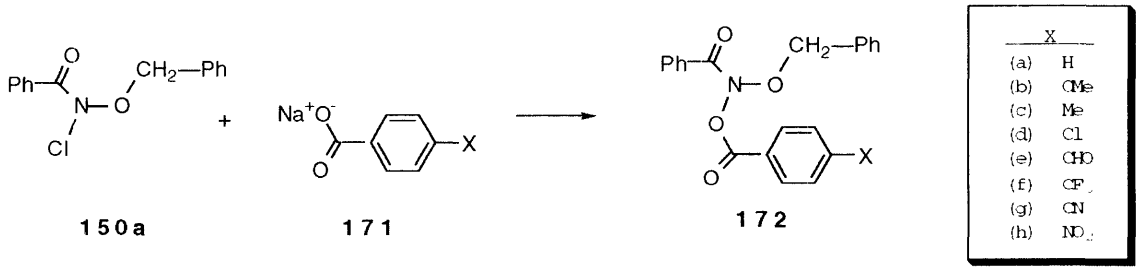
2.4 Acid-catalysed solvolysis of benzyl *N*-benzoyloxybenzohydroxamates

2.4.1 Background

In the previous sections, nitrenium ion formation has been shown to be moderately influenced by electronic factors[173,174,224] and steric factors have also been shown to play a small role.[174] Electronic effects in butyloxy series **100** and benzyloxy series **151** are moderate, according to the results adumbrated thus far and they operate on the positive charge in the transition state for acid-catalysed solvolysis. A third series of compounds, benzyl *N*-benzoyloxybenzohydroxamates, was designed to investigate the electronic effects that substituents on the leaving group exert upon nitrenium ion formation.

2.4.2 Synthesis of benzyl *N*-benzoyloxybenzohydroxamates

Benzyl *N*-benzoyloxybenzohydroxamates were prepared according to the general Method 2 described previously except that sodium benzoate salts were used instead of sodium acetate (Scheme 2-31).



150a **171** **172**

Scheme 2-31

The sodium benzoate salts **171a-h** were generated from the appropriate benzoic acids with a 0.9 molar equivalent of sodium hydroxide solution, and the filtrate was collected

from the suspension[n] and thoroughly dried in an oven at 58°C before use. Pure benzyl *N*-benzoyloxybenzohydroxamates **172a-h** were obtained by flash chromatography (hexane/ethyl acetate) in good to excellent yields. They were clear, viscous oils and could be stored under a blanket of nitrogen under refrigeration. Some crystallised over time. The compounds were however susceptible to hydrolysis and decomposed over several weeks. Thus they were used immediately after purification. Characterisation was through ^{1}H and ^{13}C NMR as well as IR spectroscopy.

2.4.3 Kinetic results

Benzyl *N*-benzoyloxybenzohydroxamate **172a** was solvolysed under acidic conditions in aqueous acetonitrile and in this series the progress of the reaction was monitored by integrating the disappearance of the benzyl methylene resonance over time according to the general ^{1}H NMR method.

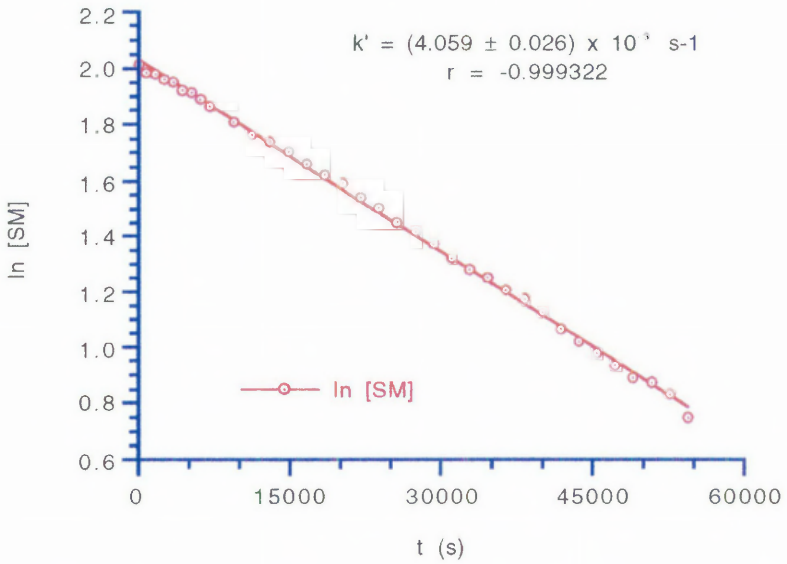


Figure 2-27 First-order acid-catalysed solvolysis of benzyl *N*-benzoyloxybenzohydroxamate **172a** at 308K

Benzyl *N*-benzoyloxybenzohydroxamate **172a** decomposed by first-order kinetics as evidenced by the excellent relationship between ln[SM] and time (Figure 2-27). The acid-

[n] Residual sodium hydroxide in the crystalline structure of the sodium salt was avoided to ensure that hydroxide ion did not hydrolyse the benzyl *N*-benzoyloxybenzoxamates formed after mixing with benzyl *N*-chlorobenzohydroxamates.

independent rate constants for the acid-catalysed solvolysis were determined from the kinetic runs over the temperature range 298-338K and an excellent Arrhenius plot was obtained (Figure 2-28).

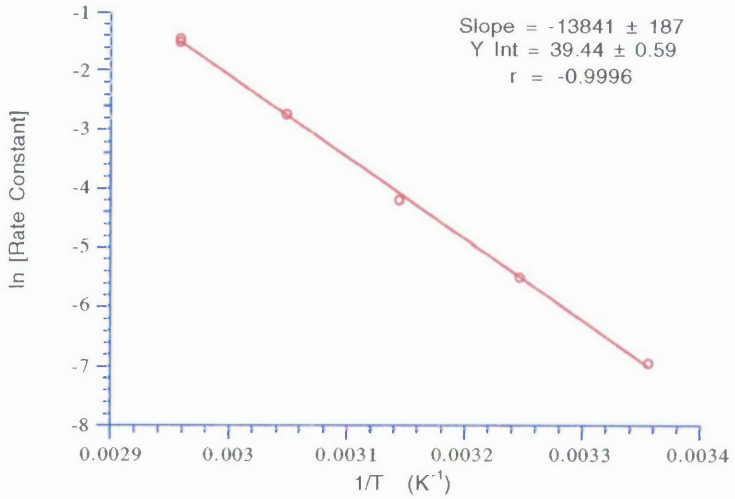
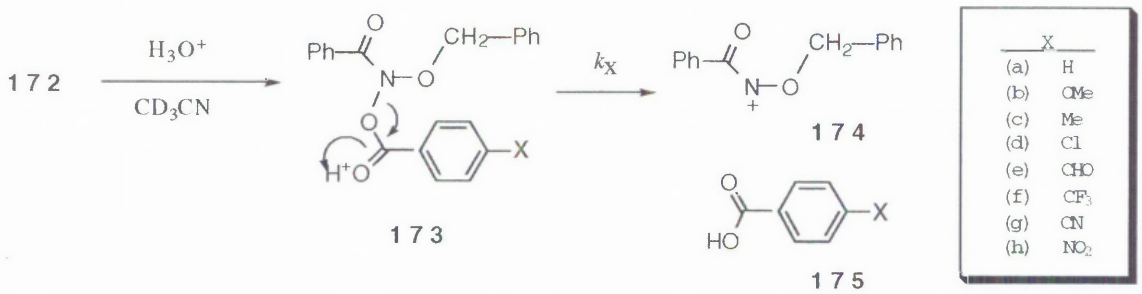


Figure 2-28 Arrhenius plot for benzyl *N*-benzoyloxybenzohydroxamate **172a**

A least squares analysis of the solvolysis data gave the intercept as 39.44±0.59 which yielded a $\Delta S^{\ddagger}$ of +74.7±4.8 $JK^{-1}mol^{-1}$. The positive entropy change is consistent with release of benzoic acid concomitant with nitrenium ion formation (Scheme 2-32) but the change is lower than that found for the release of acetic acid from benzyl *N*-acetoxybenzohydroxamate (121±11 $JK^{-1}mol^{-1}$, see Section 2.3.4).



Scheme 2-32

All members of the series of benzyl *N*-(*para*-substituted benzoyloxy) benzohydroxamates **172** were solvolysed under acidic conditions and the Arrhenius parameters were obtained from the acid-catalysed rate constants over the temperature range 298-338K. The results are reported in Table 2-13.

Table 2-13 Arrhenius parameters and rate constants for acid-catalysed solvolysis[∂] of benzyl *N*-(*para*-substituted benzoyloxy) benzohydroxamates **172a-h**.

Subst	ln A	$\Delta S^{\ddagger}$ ($JK^{-1}mol^{-1}$)	E_a/R (K)	E_a ($kJmol^{-1}$)	$100k_H$ (308K) ($Lmol^{-1}s^{-1}$)	$\Delta G^{\ddagger}_{308}$ ($kJmol^{-1}$)	r
172b MeO	41.2 (1.3)	89.2 (11.1)	14390 (421)	119.6 (3.5)	0.395 (0.018)	92.13	0.9987
172c Me	40.5 (1.2)	83.9 (10.0)	14214 (365)	118.2 (3.0)	0.369 (0.015)	92.36	0.9990
172a H	39.44 (0.58)	74.7 (4.8)	13840 (187)	115.1 (1.6)	0.411 (0.008)	92.09	0.9996
172d Cl	38.83 (0.84)	69.8 (7.0)	13642 (267)	113.4 (2.2)	0.424 (0.010)	91.90	0.9994
172e CHO	39.1 (1.3)	71.4 (10.8)	13614 (422)	113.2 (3.5)	0.578 (0.031)	91.21	0.9986
172f CF_3	40.1 (1.2)	80.2 (10.0)	13886 (391)	115.4 (3.3)	0.689 (0.030)	90.70	0.9988
172g CN	36.2 (1.3)	47.4 (10.8)	12698 (400)	105.6 (3.3)	0.630 (0.035)	91.00	0.9985
172h NO_2	37.0 (1.7)	54.4 (14.1)	12855 (530)	106.9 (4.4)	0.863 (0.076)	90.14	0.9975

[∂] Rate constants were obtained from single runs after adjusting for $[H_3O^+]$

Unlike the previous *para*-substituted benzyloxy series **151**, $\Delta S^{\ddagger}$ and E_A gave an excellent isokinetic relationship consistent with a single mechanism of solvolysis across the entire series.

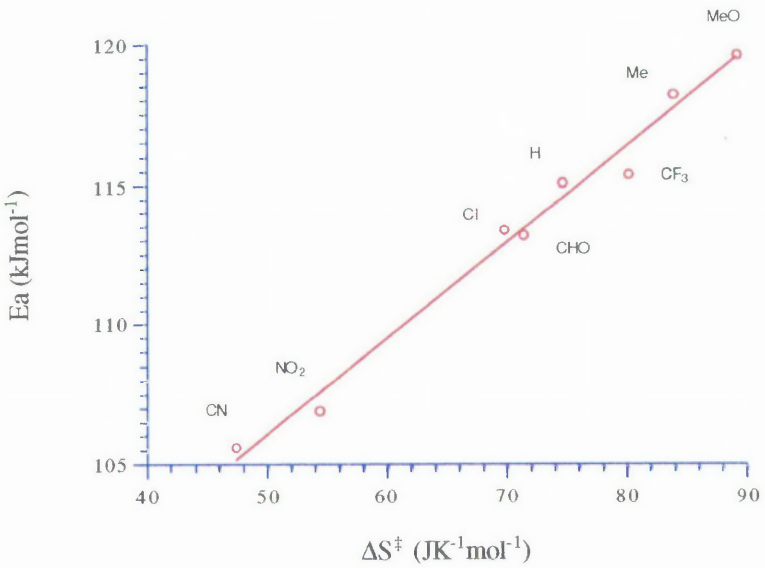


Figure 2-29 Isokinetic relationship for acid-catalysed solvolysis of **172**

The positive $\Delta S^{\ddagger}$ is in contrast to $A_{Ac}2$ hydrolysis of benzoate esters[176] which show a strongly negative $\Delta S^{\ddagger}$ (acid-catalysed solvolysis of *p*-X-$C_6H_4CO_2Et$ in aqueous/organic medium are typically -100 to -120 $JK^{-1}mol^{-1}$). An increase in the electron-withdrawing ability of the *para* substituent led to an increase in the rate of solvolysis but the rate acceleration was not as great when compared to the effect of substituents on the solvolysis rates for the series of butyl *N*-acetoxybenzohydroxamates **100** (Table 2-2).

This is most probably a consequence of the hybrid nature of k_H ($k_H = kK$), the bimolecular rate constant. Substituent effects work in opposite senses for the protonation and heterolytic steps. While electron donor groups shift equilibrium protonation to the right, they would be expected to lower k_H by destabilising a build-up of negative charge in the transition state. Conversely, electron-withdrawing substituents which would facilitate heterolysis would be expected to disfavour pre-equilibrium protonation. These counter electronic effects are reflected in the Hammett correlation.

2.4.4 Hammett correlation

The Arrhenius data was used to calculate the rate constants for solvolysis for each compound at 308K (Table 2-13). The data was found to give a poor correlation with σ^+ values (r= 0.862) but a reasonable relation with σ was evident (Figure 2-30).

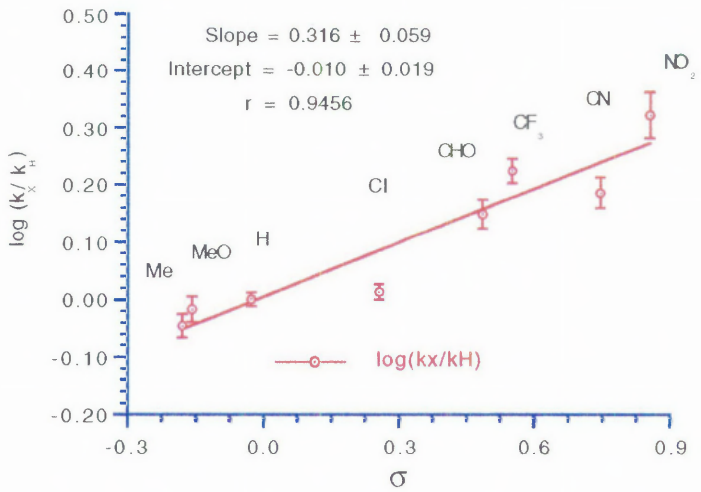


Figure 2-30 Hammett correlation for **172a-h** at 308K

The positive slope is indicative of a transition state in which there is a developing negative charge on the leaving group. Heterolysis is promoted by electron-withdrawing groups.

Since the slope is positive, the influence of substituents upon the heterolytic steps is greater than upon the protonation step. Based upon the protonation at carbonyl of benzoic acids, ρ for this step should be in the region of -1 (although the solvent systems are different[176]). Hence a reaction constant for the heterolytic step would be in the region of +1.3 and entirely consistent with the build-up of negative charge at a centre indirectly conjugated to the substituent. The classical Hammett reaction constant for the benzoic acid-benzoate equilibrium is strongly solvent dependent, but in 50% aqueous ethanol is +1.52. Thus these results suggest a significant degree of benzoic acid character in the transition state which has less partial positive charge on the acyl carbon than the starting ester.[176]

Finally, a positive reaction slope is further evidence against the normal $A_{Ac}2$ hydrolysis of the starting material involving attack of water at the protonated carbonyl moiety of the leaving group. Acid-catalysed hydrolysis of ethyl benzoates in aqueous ethanol proceeds with a similar insensitivity to substituents but ρ is a negative value.[176] A bimolecular reaction involving solvent would be facilitated by electron-donating substituents which is clearly not the case.

2.5 Acid-catalysed solvolysis summary

It is clear that benzyl *N*-benzoyloxybenzohydroxamates undergo $A_{Al}1$ solvolyses to give benzyloxynitrenium ions by analogy with *N*-acetoxy compounds. Arrhenius and Hammett data support this mechanism. Thus the $A_{Al}1$ process appears to be general for alkyl *N*-acyloxybenzohydroxamates except where substituents on the alkyl group can strongly stabilise a benzyl carbenium ion (*p*-methoxy-, *p*-phenoxy-, *p*-phenybenzyl) in which case direct elimination of the nitrosocarbonylbenzene occurs preferentially.