

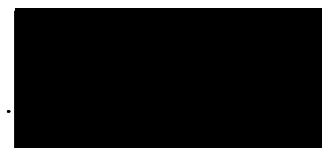
AN INVESTIGATION OF THE REACTIVITY
AND MUTAGENICITY OF
ALKYL *N*-ACYLOXYBENZOHYDROXAMATES

BY

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The work described in this thesis has never previously been submitted for a degree or diploma at any university and, to the best of my knowledge, contains no material previously published or written by another person except where due reference is made in the text.

A solid black rectangular box redacting the signature of the author.

Gerard P. Hammond

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Lastly, I would like to thank my Nan.

Preface:

Parts of this work have appeared in three publications to date:

Evidence for the formation of nitrenium ions in the acid-catalysed solvolysis of mutagenic *N*-acetoxy-*N*-alkoxybenzamides.

Campbell, J. J.; Glover, S. A.; Hammond, G. P.; Rowbottom, C. A. *J. Chem. Soc., Perkin Trans. 2*. **1991**, 2067.

Reactive intermediates from the solvolysis of mutagenic *O*-alkyl *N*-acetoxybenzohydroxamates.

Bonin, A. M.; Glover, S. A.; Hammond, G. P. *J. Chem. Soc., Perkin Trans. 2*. **1994**, 1175.

Decomposition of *N*-*N'*-diacyl-*N*-*N'*-dialkylhydrazines revisited.

Buccigross, J. M.; Glover, S. A.; Hammond, G. P. *Aust. J. Chem.* **1995**, 48, 353.

Abstract:

A new class of relatively stable compounds, alkyl *N*-acyloxybenzohydroxamates, were synthesised and found to be excellent sources of alkoxy stabilised nitrenium ions under acidic conditions. Under basic conditions the alkyl *N*-acyloxybenzohydroxamates are rapidly consumed in bimolecular reactions. All precursors were determined to be mutagenic.

In aqueous acetonitrile, butyl *N*-acetoxybenzohydroxamate decomposes *via* an Λ_{Al} mechanism to an *N*-acyl-*N*-butoxynitrenium ion and the progress of the reaction was monitored by ^1H NMR across the temperature range 298-338K. The acid-catalysed solvolysis was repeated with a number of electron-donating and electron-withdrawing *para* substituents and the Arrhenius data was obtained, which determined that nitrenium ion formation proceeds with positive entropy of activation and negative heat of enthalpy. Analysis of the Hammett plot revealed an excellent σ^+ relationship with moderate slope that reflected the separation between the ring and the developing positive charge of the nitrenium ion.

The extent of alkoxy stabilisation on the formation of nitrenium ion during acid-catalysed solvolysis was measured by synthesis of a series of *para*-substituted benzyl *N*-acetoxybenzohydroxamates. Hammett and Arrhenius relationships have been presented which indicate that nitrenium ion formation is modified by electronic effects exerted by the benzyloxy side chain. Positive mesomeric groups resulted in a change of mechanism to an acid catalysed E1 process which results in direct formation of *para*-substituted benzyl cations.

The formation of the nitrenium ion was also investigated as a function of the leaving group potential by synthesis and study of a series of benzyl *N*-(*para*-substituted benzyloxy)benzohydroxamates. Increased electron-withdrawing ability of the *para*

substituent lowered the energy required for separation of the leaving group from the precursor and favoured nitrenium ion formation.

Analysis of the solvolysis products revealed a number of complex solvolysis pathways which emanated from the acid-catalysed decomposition of the transient intermediate, alkyl *N*-hydroxybenzohydroxamate.

Alkyl *N*-acyloxybenzohydroxamates react with hydroxide ion *via* a fast B_{Al}2 mechanism, and attack at nitrogen rather than the carbonyl was confirmed by studying rates of reaction with benzyl *N*-(*para*-substituted benzoyloxy)benzohydroxamates. The reaction products were very different from those obtained under acidic conditions and were characterised by HERON reactions which lead to ester formation.

The mutagenicity of alkyl *N*-acyloxybenzohydroxamates were determined by the Ames test using TA100 *salmonella typhimurium* bacteria. No clear and conclusive relationship between electronic effects and mutagenicity levels was detected in the case of the butyl *N*-acetoxy-*para*-substituted benzohydroxamate and *para*-substituted benzyl *N*-acetoxybenzohydroxamate series but the benzyl *N*-(*para*-substituted benzoyloxy)benzohydroxamate series exhibited an inverse dependence upon reactivity. An increase in the potency as a function of the number of aromatic rings was evident suggesting that hydrophobicity is also a factor promoting biological activity.

Gerard Hammond

January 1997

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