Bimolecular Reactions of Mutagenic *N*-Acyloxy-*N*-alkoxybenzamides with Aromatic Amines

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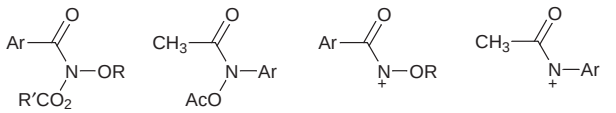
John J. Campbell and Stephen A. Glover*

Division of Chemistry, School of Physical Sciences, University of New England, Armidale, New South Wales 2351, Australia

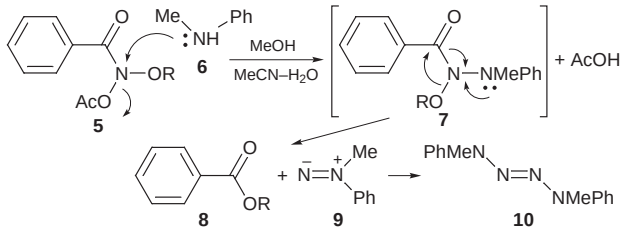
Mutagenic *N*-acyloxy-*N*-alkoxybenzamides undergo S_N2 reactions at the amide nitrogen with *N*-methylaniline and ring-substituted anilines in reactions modelling the possible mode of interaction between the mutagens and nucleic acids and which may be responsible for their biological activity.

N-Acyloxy-*N*-alkoxybenzamides **1** are mutagenic analogues of the carcinogenic metabolites **2** formed from aromatic amines.[1–5] They have been found to damage DNA primarily at guanine residues. Both classes of these biologically active compounds are sources of stabilised, electrophilic nitrenium ions **3** and **4** which could react with DNA, however, alkoxyacylnitrenium ion formation only occurs under acid catalysis.[2–5]



1 **2** **3** **4**

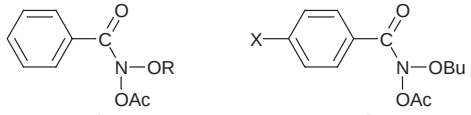
N-acyloxy-*N*-alkoxybenzamides **1** have also been found to react bimolecularly with *N*-methylaniline and the reaction led to the discovery of the HERON reaction of the intermediate *N*-amino-*N*-alkoxyamides **7** (Scheme 1).[48–51] Thus electron-rich nitrogens such as N^2 or N^7 of guanine could possibly react by displacement of acetate in a similar process.



Scheme 1

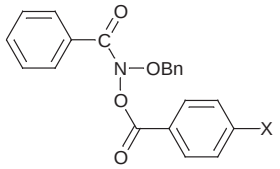
The S_N2 reactions of *N*-methylaniline with mutagens **12**–**14** in [$^2H_4$]methanol have been investigated in detail using NMR spectroscopy and here we report on factors affecting this process. Bimolecular rate constants, together with Arrhenius E_A and $\Delta S^{\ddagger}$ values, have been obtained for a wide range of substrates to explore the steric role of different alkoxy substituents (series **12**) and the electronic effect of substituents on both the benzoyl (series **13**) and benzoyloxy side-chains (series **14**). In addition, steric influences in the nucleophile have been investigated by studying the reactions of butyl *N*-acetoxybenzohydroxamate **12** (R = Bu) with *N*-methylaniline **17a**, diphenylamine **17b**, 2,6-dimethyl- **15a**, 2,6-diethyl- **15b** and 3,5-dimethylaniline **16**. Electronic effects of substituents on the nucleophile were derived from reactions of a series of *para*-substituted anilines **18**.

Branching closest to the amide nitrogen in the alkoxy series **12** (R = Pr^i, Bu^i) was found to retard the reaction relative to their straight-chain counterparts (Tables 1 and 2, Fig. 2, see full text). Steric crowding around the aniline nitrogen (**15a** and **15b**) also resulted in a reduction in rate constants by almost two orders of magnitude relative to unhindered aniline [Table 7 (see full text) and Table 8]. Bimolecular rate constants also decreased in the order of aniline **18c** > *N*-methylaniline **17a** ≫ diphenylamine **17b** (Table 8).



12
R = Et, Pr, Pr^i, Bu, Bu^i, n-C_5H_{11}, i-C_5H_{11}, n-C_8H_{17}

13
X = H, Br, Cl, NO_2, Me, OMe, Bu^t, Ph



14
X = H, Bu^t, Cl, Me, MeO

Table 8 Arrhenius activation energies, entropies of activation and rate constants at 278, 298 and 308 K for reaction of butyl *N*-acetoxybenzohydroxamate **12** with anilines in [$^2H_4$]methanol

Aniline substituent	E_A/kJ mol^{-1}	$\delta S^{\ddagger}$ J K^{-1} mol^{-1}	$10^4k_2^{308}$/ dm^3 mol^{-1} s^{-1}	$10^4k_2^{298}$/ dm^3 mol^{-1} s^{-1}	$10^4k_2^{278}$/ dm^3 mol^{-1} s^{-1}	r
None	–	–	–		89.7	–
N-Me[a]	52.83 (1.64)	−113.7 (4.3)	581.5	290.9	62.8	0.999
3,5-Me_2	50.55 (0.52)	−133.2 (0.5)	193.4		22.9	1.000
2,6-Me_2	54.22 (5.34)	−144.4 (21.1)	8.4		0.9	0.990
2,6-Et_2	64.04 (8.93)	−99.2 (18.4)	15.4		1.0	0.981
N-Ph[b]	–	–	–	1.6	–	–

[a] From Table 2. [b] Included for comparison only.

* To receive any correspondence (*e-mail:* sglover@metz.une.edu.au).

Variation in electronic effects in series **13** resulted in a weakly positive Hammett σ correlation ($\rho = +0.13$, Fig. 4, see full text). In contrast, electronic effects in the benz-

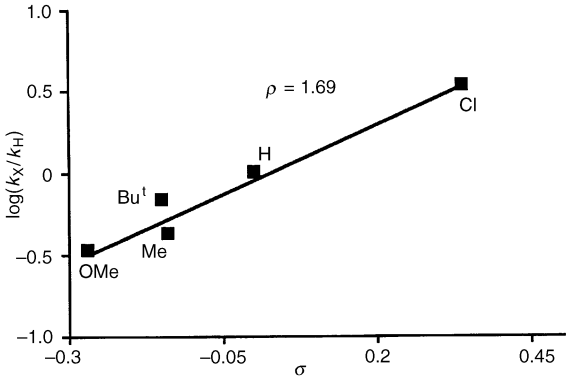


Fig. 6 Hammett correlation for the reaction of *N*-methylaniline and benzyl *N*-(*p*-substituted benzoyloxy)benzohydroxamates **14** at 308 K in [$^2H_4$]methanol. For **14** (X = H) $k_2^{308} = 260.8 \times 10^{-4}$ dm^3 mol^{-1} s^{-1}.

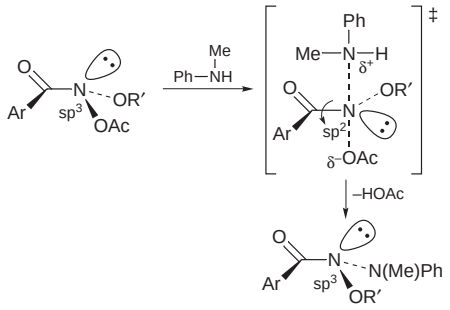


Fig. 1 Ground state and transition state geometries for the bimolecular reaction of *N*-methylaniline and alkyl *N*-acetoxybenzohydroxamates.

oyloxy group (series **14**) have a marked effect upon the reaction rate constants which correlated with Hammett σ values, but with a reaction constant of $\rho = 1.69$ (Fig. 6). Rates of reaction of *para*-substituted anilines **18** (Table 9, see full text) correlated with Hammett σ^+ with $\rho = -0.92$ (Fig. 7, see full text), somewhat smaller than the values for S_N2 reactions at alkyl or acyl halides which are typically −2 to −3.[63]

This data is consistent with a mechanism in which there is charge separation in the transition state as illustrated in Fig. 1, a fact supported by the strongly negative $\Delta S^{\ddagger}$ values (typically −100 to −160 J K^{-1} mol^{-1}), a contribution to which must be the increased ordering of solvent molecules (entropies of activation in S_N2 reactions of alkyl halides by anionic displacement involving charge delocalisation are typically −40 to −20 J K^{-1}mol^{-1} [55]). Positive, linear isokinetic relationships for series **12** (Fig. 2), **13** (Fig. 3) and **14** (Fig. 5), see full text, confirm S_N2 characteristics in that the better the overlap (lower the activation energy), the more reorganisation is required in the transition state. From studies on series **14**, and reactions with different anilines **18**, the sensitivity to electronic effects in the leaving group and the nucleophile suggests an early transition state with a significant degree of N–O cleavage. The partial nitrenium ion character at the amide nitrogen would be stabilised by the adjacent alkoxy group together with the incoming aniline nitrogen lone pair.[58]

Bisheteroatom substitution at the amide nitrogens of *N*-acyloxy-*N*-alkoxybenzamides results in pyramidality rather than planarity at the amide nitrogen leading to decreased amide conjugation (Fig. 1).[52,53] In the transition state, which involves an sp^2 amide nitrogen, the lone pair, must of necessity, lose conjugation with the amide carbonyl. A portion of the activation energy is thus likely to involve loss of the remaining conjugation present in the ground state. In addition, while reorganisation of transition state components to accommodate the incoming nucleophile together with the orientation of solvent molecules, is largely responsible for the strongly negative entropies of activation, these may be offset to a degree by increased rotation about the amide C–N bond and relief of steric compression.

Techniques used: ^{1}H and ^{13}C NMR, spectrophotometry

References: 65

Figures: 8

Tables: 9 (bimolecular rate constants and derived Arrhenius activation energies and entropies of activation)

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