RESEARCH FRONT

Full Paper

CSIRO PUBLISHING

Aust. J. Chem. **2009**, *62*, 700–710

www.publish.csiro.au/journals/ajc

S_N2 Substitution Reactions at the Amide Nitrogen in the Anomeric Mutagens, *N*-Acyloxy-*N*-alkoxyamides

Katie L. Cavanagh,[A] *Stephen A. Glover,*[A,B] *Helen L. Price,*[A] *and Rhiannon R. Schumacher*[A]

[A]Department of Chemistry, School of Science and Technology, University of New England, Armidale, NSW 2351, Australia.

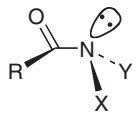
[B]Corresponding author. Email: sglover@une.edu.au

N-Acyloxy-*N*-alkoxyamides **1a** are unusual anomeric amides that are pyramidal at the nitrogen because of bis oxyl substitution. Through this configuration, they lose most of their amide character and resemble α-haloketones in reactivity. They are susceptible to S_N2 reactions at nitrogen, a process that is responsible for their mutagenic behaviour. Kinetic studies have been carried out with the nucleophile *N*-methylaniline that show that, like S_N2 reactions at carbon centres, the rate constant for S_N2 displacement of carboxylate is lowered by branching β to the nitrogen centre, or bulky groups on the alkoxyl side chain. Branching or bulky groups on the carboxylate leaving group, however, do not impact on the rate of substitution, which is mostly controlled by the pK_A of the departing carboxylate group. These results are in line with computed properties for the model reaction of ammonia with *N*-acetoxy-*N*-methoxyacetamide but are in contrast to the role of steric effects on their mutagenicity.

Manuscript received: 19 March 2009.
Final version: 14 May 2009.

Introduction

N-Acyloxy-*N*-alkoxyamides **1a** are a class of mutagenic amides that react as electrophiles towards DNA without the need for metabolic activation.[1–10] Structure–activity studies and DNA damage studies point to an S_N2 displacement of carboxylate by attack of guanine-N7 at the amide nitrogen.[7,10] Compounds **1a** are members of the wider class of anomeric amides **1** (Scheme 1) in which the nitrogen is substituted with two electronegative atoms that can interact anomerically.[11–15] This configuration has been shown to radically alter the amide properties. On account of the electron demand of these atoms, the nitrogen becomes sp^3 hybridized with loss of much of the classical amide resonance, which in conventional amides and peptides is responsible for restricted rotation about the N–C bond, and other manifestations such as low carbonyl stretch frequencies in their infrared spectra.[11,13,14,16,17] In effect, such amides behave more as *N*-acylamines. The structural, spectroscopic and chemical properties of **1a**–**d** and **1f** have recently been reviewed.[15]



1a X = OAcyl, Y = OR
1b X = Cl, Y = OR
1c X = Y = OR
1d X = NR_2, Y = OR
1e X = Y = Halogen
1f X = SR, Y = OR

Scheme 1.

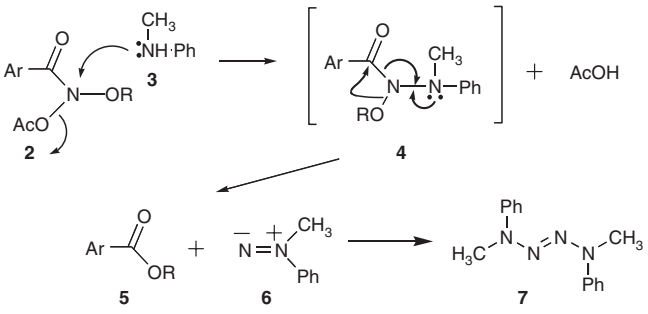
Accompanying this changed configuration, some of these amides are susceptible to both S_N1[2–5] and S_N2 reactions at the amide nitrogen and, in many respects, the chemistry of **1a** and **1b** resembles that of α-haloketones.[9,10,15,18–22] In particular, *N*-acyloxy-*N*-alkoxyamides **1a** undergo facile S_N2 replacement of the acyloxyl group at nitrogen by a variety of nucleophiles including neutral aromatic amines and thiols as well as negatively charged azide and hydroxide ions.[5,10,19,20,22]

In a series of studies aimed at understanding the underlying structural features controlling their mutagenicity, we have demonstrated that *N*-acyloxy-*N*-alkoxyamides **2** react bimolecularly with aromatic amines such as *N*-methylaniline **3** in methanol, generating intermediate *N*-alkoxy-*N*-(*N*′-methylanilino)amides **4** that themselves are anomeric but that undergo a novel rearrangement, the HERON reaction[¶] (Scheme 2).[10,15,17,22–27] In this reaction, the loosely bound lone pair on nitrogen drives migration of the alkoxyl group from nitrogen to the carbonyl carbon. The N–C bond breaks in concert with the migration, yielding esters **5** and the 1,1-diazene **6** in what is, in effect, an S_N2 reaction at the acyl carbon. Under these conditions, the diazene **6** dimerizes to the tetrazene **7**.

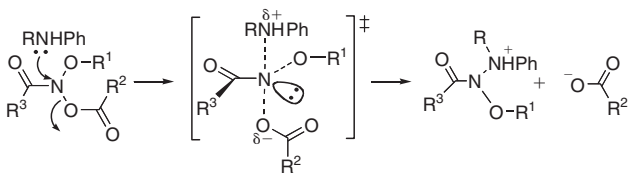
The S_N2 reaction of anilines with a wide range of *N*-acyloxy-*N*-alkoxyamides has been studied and relative rate constants, Arrhenius activation energies and entropies of activation are in

[¶]*He*teroatom *r*earrangements *on nitrogen*; first presented to the 2nd Heron Island Conference on Reactive Intermediates and Unusual Molecules, Heron Island, Australia, 1994.

10.1071/CH09166 0004-9425/09/070700



Scheme 2.



Scheme 3.

accord with bimolecular attack at nitrogen leading to a transition state with significant charge separation (Scheme 3).[9,10,19,20] Entropies of activation are more negative than found in S_N2 reactions of alkyl halides owing to a greater degree of solvation in the transition state.[28] These reactions have been modelled computationally by the reaction of ammonia with *N*-formyloxy-*N*-methoxyformamide and ammonium ion and carboxylate ion character is significant at the transition state.[10,15,21]

The reactions have an analogy in the S_N2 reactions of α-haloketones such as phenacyl bromides.[29] These are facilitated by the carbonyl substitution at the reactive centre, which has been attributed to conjugation of the p-orbital on the α-carbon in the S_N2 transition state with the carbonyl π-bond,[29–32] and stabilization of ionic character at the central carbon as outlined by Pross,[30,33] as well as electrostatic attraction of the nucleophile to the carbonyl carbon.[31] Although there are no comparative rate data for reactions on amines or alkoxyamines, these arguments could also apply to substitution at the amide nitrogen in *N*-acyloxy-*N*-alkoxyamides.

S_N2 in α-haloketones is also strongly impeded sterically by branching at the α′-carbon and S_N2 reactions in general are hindered by substitution β to the reactive centre.[34,35] *N*-Acyloxy-*N*-alkoxyamides behave similarly. We have shown from studies on series **8** (Scheme 4) that branching α to the amide carbonyl completely prevents their reaction with *N*-methylaniline.[9] Interestingly, to a degree the mutagenic behaviour of these hindered *N*-acyloxy-*N*-alkoxyamides follows the rates of reactivity, suggesting that the attack by DNA is also an S_N2 process.

The computed transition state also suggests that steric effects on the alkoxyl group should be important and there is limited evidence from relative rates of reaction of the alkoxyl series **9** that branching α to the oxygen on the alkoxyl group also slows S_N2 reactivity relative to straight-chain analogues, as to a lesser extent does branching further along an alkyl chain.[10,19,20]

Electronic effects of *para* substituents in series **10** with benzoyloxyl leaving groups support the predicted transition state properties as rate constants at 308 K correlated with Hammett σ constants with $\rho = +1.7$.[10,19,20] However, to date we have not investigated the influence of steric factors on the leaving group. The steric effect of branching γ to the reactive nitrogen would be expected to be less important on this side chain relative to the amide and alkoxyl side chains because the predicted transition state is similar to that known for classical S_N2 reactions at carbon; the nitrogen is sp^2 hybridized and the leaving the group is *anti* to the incoming nucleophile.

In the present paper, we report further evidence that branching at the β-position on the alkoxyl group, as well as bulky benzyloxy substituents, have an influence on the S_N2 reaction at nitrogen. Furthermore, we show that in contrast to the amide and alkoxyl side chains, steric effects on the leaving group are far less significant in support of the classical S_N2 transition state for reaction at nitrogen.

Results and Discussion

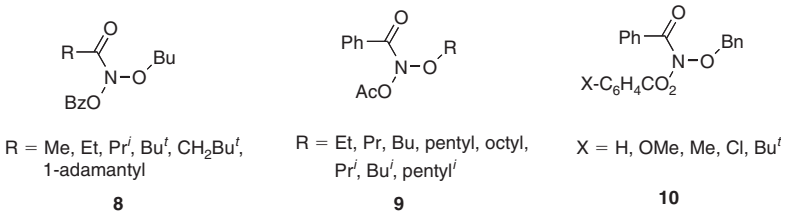
Reactions of *N*-acyloxy-*N*-alkoxyamides with *N*-methylaniline leading to HERON reactions can be conveniently carried out in the probe of the NMR spectrometer and followed in [D4]methanol by monitoring the disappearance of the methyl signal of either an *N*-acetoxyl group or an oxymethylene resonance of the substrate, together with the *N*-methyl resonance of aniline, and their transformation to the corresponding ester and tetrazene. They conform to classical bimolecular kinetics, being first-order with respect to both mutagen and *N*-methylaniline.[9,18–20,36]

The classical S_N2 transition state (Scheme 3) has been supported by computational modelling that confirms the charge separation in the transition state and the likely impact of steric effects.[21] In addition to branching on the amide side chain, which strongly impedes S_N2 reaction with *N*-methylaniline, the inclusion of steric bulk on the alkoxyl group should also, to a degree, hinder the incoming amine.

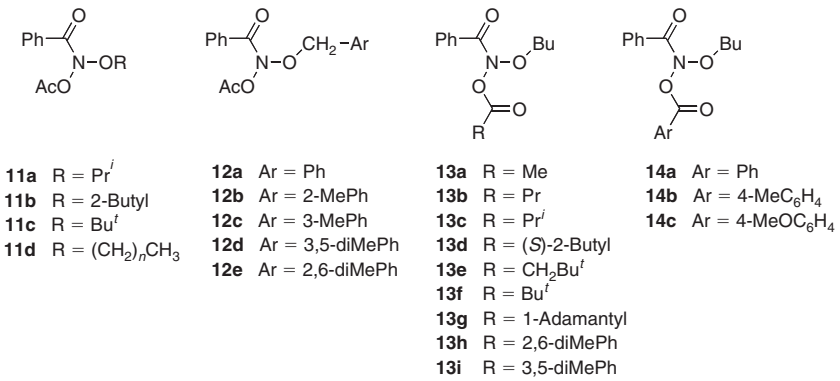
Rate constants for reaction of *N*-methylaniline with some *N*-acetoxy-*N*-alkyloxyamides **11** and *N*-acetoxy-*N*-benzyloxyamides **12** (Scheme 5), at 303 K, are given in Table 1. Earlier work from our laboratory showed that relative to an ethoxyl group, the isopropoxyl group in **11a** hindered S_N2 reactivity with *N*-methylaniline.[10,20] This result has been confirmed in a repeat study with **11a** reacting with a rate constant approximately one-fifth of the ethoxy substrate **11d** ($n = 1$). In addition, 2-butyloxyl behaves similarly, reducing the rate constant for reaction of **11b** to approximately one-tenth that of the propoxyl, butoxyl and pentoxyl substrates **11d** ($n = 2$–4). The *tert*-butyloxyl group strongly inhibits reaction with *N*-methylaniline as no rate constant could be obtained for **11c** at similar temperatures. At higher temperatures, it decomposed via other pathways in a non-second-order fashion.

Rate constants for the benzyloxy substrates also pointed to a steric effect. Substrates bearing the benzyl (**12a**), 3,5-dimethylbenzyl (**12d**), and 2- and 3-methylbenzyl (**12b**, **12c**) groups reacted with relatively similar rate constants, but with dual methylation on the *ortho* positions in the 2,6-dimethylbenzyloxy substrate **12e**, the bimolecular rate constant was significantly reduced.

Table 1 gives Arrhenius data for a series of mutagens for which a range of rate constants could be measured, together with relevant data previously published by our group. Activation energies were similar to those obtained previously for *N*-methylaniline reaction with a wide selection of such compounds and reflect the balance between bond-formation and



Scheme 4.



Scheme 5.

Table 1. Arrhenius data and bimolecular rate constants at 303 K for the reaction of *N*-methylaniline with *N*-acyloxy-*N*-alkoxybenzamides 11 and 12, 13f and 14a in [D4]methanol

Compound (R, Ar)	ln A	$\Delta S^{\ddagger}_{298}$ [J K^{-1} mol^{-1}]	E_A [kJ mol^{-1}]	$10^4 k_2^{303}$ [L mol^{-1} s^{-1}]	r^2
11a (Pr^i)	18.9 ± 2	−110 ± 16	59 ± 4	52	0.984
11a (Pr^i)[A]	19.5 ± 2	−100 ± 13	62 ± 4	66	0.986
11b (2-Butyl)	13.4 ± 1	−150 ± 6	49 ± 2	38.0	0.997
11d (Et)[A]	15.9 ± 2	−130 ± 14	50 ± 4	276	0.988
11d (Pr)[A]	19.5 ± 2	−100 ± 15	57 ± 4	435	0.984
11d (Bu)[A]	17.8 ± 1	−114 ± 14	53 ± 2	414	0.998
11d (Pent)[A]	19.9 ± 1	−96 ± 11	60 ± 3	442	0.990
11d (Oct)[A]	13.9 ± 1	−145 ± 10	44 ± 7	273	0.983
12a (Ph)[B]	14.7 ± 2	−139 ± 14	48 ± 4	114	0.986
12b (2-MePh)	17.1 ± 1	−119 ± 6	55 ± 2	78	0.997
12c (3-MePh)	20 ± 0.1	−95 ± 1	62 ± 0.3	97	1.000
12d (3,5-diMePh)	16.3 ± 0.5	−126 ± 4	53 ± 1	102	0.999
12e (2,6-diMePh)	15.1 ± 1	−136 ± 5	53 ± 1	26	0.999
13f (Bu^t)	13.5 ± 1	−149 ± 8	48 ± 2	34	0.993
14a (Ph)[B]	18.6 ± 3	−105 ± 22	51 ± 7	1844	0.970

[A] Data taken from refs [10,20,21].
[B] Data taken from refs [7,36].

bond-breaking at the transition state.[10,20] The $\Delta S^{\ddagger}$ values were similarly large and more negative than are observed in S_N2 reactions involving negatively charged nucleophiles, which we have previously attributed to a transition state that is not only subject to the spatial demands of both the nucleophile and substituents around the central nitrogen, but also to the degree of charge separation and resultant solvent organization. $\Delta S^{\ddagger}$ is rendered more negative by both steric interactions, which result in the requirement for a more ordered transition state, and also the extent of overlap, because a well-developed transition state results in more charge separation and solvation than a less advanced one. Thus, steric inhibition cannot readily be signalled by strongly negative entropies of activation alone.

The isokinetic plot in Fig. 1 presents clear evidence for the steric impact of branching β to the amide nitrogen. Data for straight chain *N*-acetoxy-*N*-alkoxybenzamides (**11d**, open circles) fit a straight line (r = 0.991) but the averaged data for the isopropoxy substrate and that for the 2-butyloxy system (**11a** and **11b**, closed circles) deviate significantly and similarly from the line of best fit. These plots are open to two interpretations; for a similarly developed transition state (similar E_As) $\Delta S^{\ddagger}$ is much more negative than it would be with a straight-chain alkoxyl

[‡] Electron density-electrostatic potential energy surface.

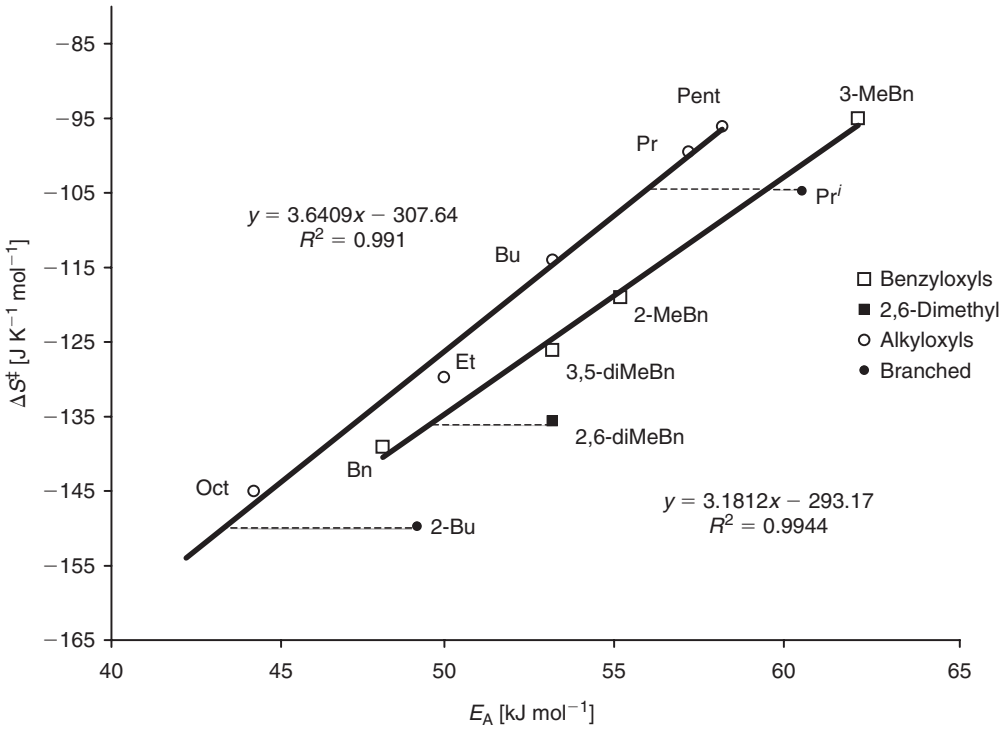


Fig. 1. Isokinetic plot for the reaction of *N*-methylaniline with *N*-acetoxy-*N*-alkoxyamides **11** and *N*-acetoxy-*N*-benzyloxyamides **12**.

group. Alternatively, a straight-chain substrate with a similar $\Delta S^{\ddagger}$ would form with a much lower E_A.

Isokinetic analysis of the benzyloxy substrates **12** differentiates similarly between the unmethylated, mono- and 3,5-dimethylated benzyloxyl side chains (in **12a**–**d**; Fig. 1, open squares) and the sterically more demanding 2,6-dimethylated substrate (**12e**; Fig. 1, closed square). It is noteworthy that the 2-methylated benzyloxy group in **12b** exerts a similar influence to the 3-methylated ring in **12c** and 3,5-dimethylated ring in **12d**. Presumably, one *ortho* methyl group can be turned away from the approaching nucleophile whereas such steric avoidance is more difficult with two *ortho* methyl substituents.

Steric effects of branching on the acyloxyl side chain are insignificant. Table 2 gives relative rate constants for the reaction of *N*-methylaniline with a range of *N*-butoxy-*N*-alkanoyloxybenzamides **13a**–**g** in [D4]methanol at 303 K, and the corresponding data for *N*-butoxy-*N*-benzoyloxybenzamides **14a**–**c** together with pK_As and molar refractivities of the leaving-group carboxylic acid. Comparison of rate constants for straight-chain (**13a** and **13b**) and branched substrates (**13c**–**g**) clearly indicates that steric influences are minimal. The range of pK_As for series **13** is relatively small. However, when plotted with the previously reported rate data for *N*-benzoyloxy-*N*-butoxybenzamide **14a** and new data for the *N*-butoxy-*N*-(4-methyl)- and -(4-methoxybenzoyloxy) benzamides **14b** and **14c**, it is clear that the logarithm of the bimolecular reaction rate constant yields a good linear correlation with pK_A (Eqn 1), which supports the theoretical transition state properties in which substantial charge transfer to the carboxyl group takes place. It is also consistent with the positive Hammett correlation for the series of *N*-benzoyloxy-*N*-benzyloxybenzamides **10**.[20]

The correlation is improved marginally by inclusion of a steric factor in the form of calculated molar refractivities (MR) of the carboxylic acid corresponding to the leaving group (Eqn 2).[37]

Table 2. Bimolecular rate constants for the reaction of *N*-methylaniline with *N*-acyloxy-*N*-butoxybenzamides 13 and 14 in [D4]methanol at 303 K

Substrate (R, Ar)	$10^4 k^{303}$ [L mol^{-1} s^{-1}]	pK_A[A]	MR [cm^3 mol^{-1}][A]
13a (CH_3)	175[C]	4.76	11.96
13b (Pr)	122	4.82	21.3
13c (Pr^i)	91	4.85	21.63
13d ((*S*)-2-Butyl)	97	4.80	26.22
13e (CH_2Bu^t)	78	4.79[B]	30.48
13f (Bu^t)	34	5.03	26.17
13g (1-Adamantyl)	61	4.86[B]	47.47
14a (Ph)	1844	4.20	32.09
14b (4-MeC_6H_4)	818	4.34	37.99
14c (4-$MeOC_6H_4$)	469	4.47	39.24

[A] pK_A and MR[38] of departing carboxylic acid.
[B] Calculated value.[39]
[C] Slightly lower but within experimental error similar to Campbell's data.[20] For Fig. 2, an averaged rate constant of 294×10^{-4} L mol^{-1} s^{-1} was used.

pK_A is poorly correlated with molar refractivity (r = 0.115). Fig. 2 shows the predicted and observed rate constants determined by both regression analyses. Eqn 2 behaves well but the small negative dependence on MR suggests that bulky carboxylic acid side chains impede rather than promote transition-state formation. However, the rate retardation is negligible when compared with the impact of branching on both the amide and alkoxyl side chains.

$$\ln k^{303} = -4.7(\pm 0.3)\mathrm{p}K_A + 18(\pm 1)\ (\mathrm{r} = 0.986) \quad (1)$$

$$\ln k^{303} = -4.9(\pm 0.2)\mathrm{p}K_A - 0.017(\pm 0.005)\mathrm{MR} + 19.6(\pm 0.9)\ (\mathrm{r} = 0.995, \mathrm{s} = 0.14, F = 367) \quad (2)$$

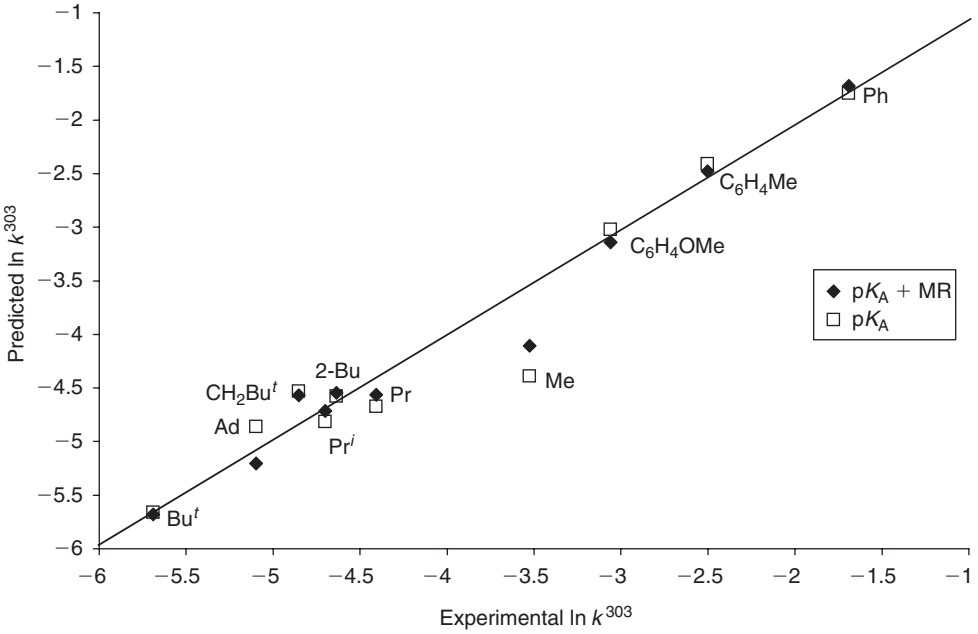
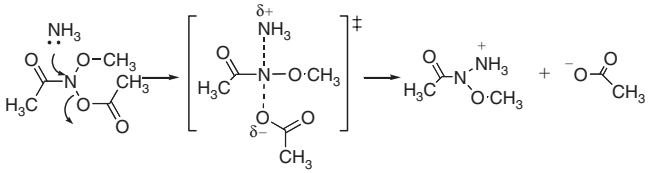


Fig. 2. Predicted (Eqns 1 and 2) versus experimental bimolecular rate constants for the reaction of *N*-methylaniline with *N*-alkanoyloxy-*N*-butoxybenzamides **13** and *N*-benzoyloxy-*N*-butoxybenzamides **14**.



Scheme 6.

To gauge the spatial requirements of substituents at the amide nitrogen, the reaction has been modelled at the *HF/6–31G(d)* level by the reaction of ammonia on *N*-acetoxy-*N*-methoxyacetamide according to Scheme 6. The lowest unoccupied molecular orbital (LUMO) of *N*-acetoxy-*N*-methoxyacetamide **15** exhibited both C=O π* and N–OAc σ* character. However, although approach of ammonia to the carbonyl carbon does not lead to a stationary point on the energy surface, attack at the amide nitrogen leads to substitution of the acetoxyl by ammonia and formation of **17** and **18**.

The transition state **16** for the reaction is depicted in Fig. 3a and is similar in most respects to that computed at *HF/6–31G(d)* for the corresponding reaction of ammonia and *N*-formyloxy-*N*-methoxyformamide.[21] The structure is characteristic of an S_N2 process. Nitrogen is sp^2 hybridized with long bonds to both the leaving group and nucleophile, which are largely *trans* to one another, subtending an angle of 158°. Relative to the ground-state reactants, the group charges on ammonia ($\Delta q = +0.4$) and acetate ($\Delta q = -0.73$) are indicative of the expected charge separation in the transition state. The rest of the charge is on the central nitrogen ($\Delta q = 0.13$) and the methoxyl group ($\Delta q = 0.14$), indicating partial alkoxynitrenium ion character. At the *B3LYP/6–31G(d)//HF/6–31G(d)* level in the gas phase, the reaction has an activation energy of 127 kJ mol^{-1} but this reduces to 57 kJ mol^{-1} when aqueous solvation energies are incorporated. Overall, the reaction is endothermic by 540 kJ mol^{-1} in the gas phase but by only 18 kJ mol^{-1} with solvation energies. The stabilization of the transition state and the products in aqueous solution relative to the gas phase reflects partial and complete charge separation respectively.

The methoxy group, amide nitrogen, and acetyl group are largely in plane in support of a conjugative interaction between the central nitrogen $2p_z$ orbital, partially overlapping with the ammonia and acetate, and both the carbonyl carbon $2p_z$ and the $2p_z$ methoxyl oxygen lone pair. We have previously shown that the presence of methoxyl as opposed to methyl at the amide nitrogen radically reduces the E_A for reaction with ammonia.[21] It is clear from the density surface (Fig. 3b) that branching α to the alkoxyl oxygen or α to the amide carbonyl would present significant steric interactions to a large incoming nucleophile. However, although dependent on the nature and conformation of the alkoxyl group, bulky groups on the acyloxyl group should have much less of a steric effect on the reaction.

The minor and negative influence of bulk in the leaving group in these unusual S_N2 reactions at nitrogen indicates that there is also no relief of steric compression at the transition state. Although the transition state for these S_N2 reactions in most respects resembles that for S_N2 substitution at primary and secondary carbons, the lone pair, in place of a fourth atom at the reactive centre (Scheme 3) may negate this effect. Indeed, the nucleophile and the leaving group are bent towards the lone pair in the transition state.

Conclusion

Bis oxygen functionalization at nitrogen in *N*-acyloxy-*N*-alkoxyamides **1a**, as with other anomeric amides, renders the amide quite atypical in structure, properties, and reactivity. Structural effects on the bimolecular reaction of *N*-methylaniline with *N*-acyloxy-*N*-alkoxyamides are predictable based on the known properties of S_N2 reactions at saturated carbon. The combination of the anomerically destabilizing alkoxyl oxygen and

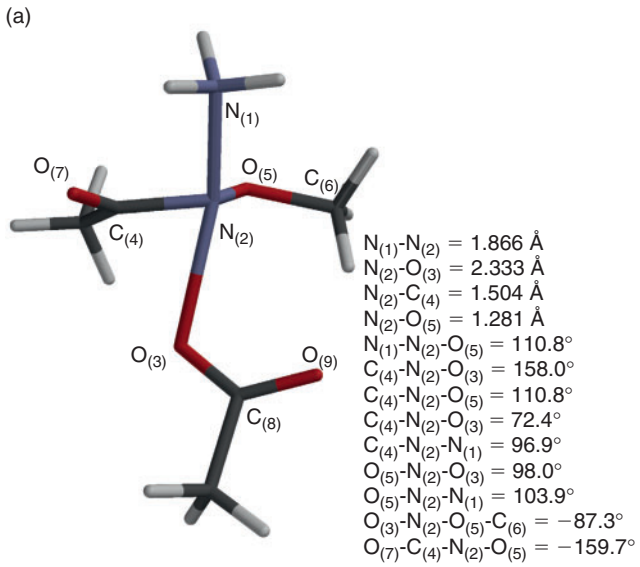


Fig. 3. (a) *HF/6–31G(d)* transition state for the reaction of ammonia with *N*-acetoxy-*N*-methoxyacetamide (*i* 446.7 cm^{-1}); and (b) associated EDEP‡ surface.

the acyloxyl leaving group in this case likens the reactivity to that of α-haloketones, which undergo accelerated S_N2 displacement of halogen. However, like such reactions at carbon α to a carbonyl, S_N2 reactions at amide nitrogen are also affected by branching β to the reactive centre, either as previously demonstrated on the amide in **8**,[9] or as shown in the present study, by branching on the alkoxyl side chain in **11a**–**c**. This is reinforced by the reduced rate of S_N2 reactivity for **12e**.

Bulky groups on the carboxoyloxyl side chain in **13** appear to influence S_N2 reactivity almost exclusively on the basis of changes to the pK_A of the leaving carboxylic acid.

The mutagenic activity of some 80 *N*-acyloxy-*N*-alkoxyamides has been determined by the Ames test and a quantitative structure–activity relationship based on 50 of these allows prediction, with some accuracy, of the activity of other congeners.[8,10] Importantly, activity is dependent on pK_A of the leaving carboxylic acid in a *positive* sense, which indicates that the better the leaving group, the more reactive is the mutagen to adventitious S_N2 reactivity that decreases the concentration of the active material in the assay.

Branching at the α-carbon on the amide side chain in **8** has previously been shown to impede, strongly, both S_N2 reactivity at nitrogen as well as mutagenicity.[9] Experimental and predicted mutagenic activity for *N*-acyloxy-*N*-alkoxyamides used in the current kinetic study will be presented elsewhere. However, it is interesting that although S_N2 reactivity is decreased with isopropoxy or 2,6-dimethylbenzyloxy on the alkoxyl side chain, these effects do not reduce mutagenic activity to a measurable extent, both substrates being well predicted by our quantitative structure–activity relationship.[10] In addition, like the amide series **8**, the activity of mutagens **13b**–**g** is strongly and adversely affected by branching and bulkiness on the leaving group. All but the butanoyloxy substrate **13b** reduced activity by nearly an order of magnitude. A 2,6-dimethylbenzoyloxyl group in **13h**, and to some extent a 3,5-dimethylbenzoyloxyl substituent in **13i** had a similarly influence.[10]

Clearly the factors controlling S_N2 reactivity and biological activity are different where these side chains are concerned. Branching and bulkiness close to nitrogen on the alkoxyl side chain, which impedes S_N2 reactivity, hinder neither binding to DNA nor reactivity at guanine-N7. Steric demands of the leaving group do not greatly influence S_N2 reactivity at nitrogen, but the carboxylic acids have higher pK_As than acetic or benzoic acids, which should favour mutagenic activity. As the opposite is found, these bulky side chains most probably hinder binding to DNA or the attainment of the transition state for reaction with guanine. Though with branching α to the amide carbonyl, binding to DNA is possible, any S_N2 reaction, including that at guanine-N7 in the major groove of DNA, is impeded.[9]

Experimental

Materials and Methods

Infrared spectra were recorded on a Perkin–Elmer 1600 series Fourier-transform (FT)-IR spectrophotometer as chloroform solutions. Mass spectra were recorded on a Varian 1200L liquid chromatograph-mass spectrometer. All samples for analysis were carried out at a 30-V capillary voltage and 350°C, 138 kPa drying gas temperature and pressure, in HiPerSolv acetonitrile. Nuclear magnetic resonance spectra were recorded on a Bruker Avance 300P FT NMR spectrometer with a 5-mm ^1H inverse/Broad Band probe with a z-gradient, operating at 300.13 MHz (^1H), 75.46 MHz (^{13}C), or 30.42 MHz (^{15}N). ^1H and ^{13}C samples studied for structural analysis were run in $CDCl_3$, ^{15}N NMR shifts were measured indirectly using a gradient enhanced heteronuclear multiple bond correlation pulse sequence (inv4 gplplrnd) optimized for $^3J_{NH} = 8$ Hz. Values were referenced relative to nitromethane (0 ppm).

Kinetic Studies

Rate constants for the bimolecular reaction between *N*-methylaniline and various mutagens were determined using ^1H NMR spectroscopy. Mutagen (2–10 mg weighed out accurately) in [D4]methanol (400 μL) in an ultra-high-precision NMR tube was equilibrated at the required temperature in the probe of an NMR spectrometer. The sample was shimmed, removed from the

‡Electron density-electrostatic potential energy surface.

probe, and a microsyringe was used to add a minimum of twice the molar equivalent of *N*-methyl aniline (2–20 μL). The exact time of mixing and the initial concentrations of both compounds were noted. After brief shimming, a series of acquisitions were accumulated at a preset time interval, and the extent of reaction was monitored by analysing the disappearance of both starting materials according to peak integrals of characteristic signals in the mutagen and the *N*-methyl resonance of the *N*-methylaniline, using the integral of the methyl hydrogens of [D4]methanol as an internal constant. Initial substrate concentrations were obtained by back-extrapolation of concentration plots for both reagents to the initial time of mixing, t_o.

Computational Methods

Structures were optimized at the *HF/6–31G(d)* level using *Spartan 04*.[40] Ground state structures for reactants and transition state for reaction of ammonia with *N*-acetoxy-*N*-methoxyacetamide were verified by frequency calculations. Density functional energies were determined on the stationary points using the *B3LYP/6–31G(d)//HF/6–31G(d)* method. Aqueous solvation energies were estimated using the SM5.4 method of Cramer and coworkers.[41]

The cartesian coordinates of the transition state, reactants and products from reaction of *N*-acetoxy-*N*-methoxyacetamide with ammonia, their absolute energies, solvation energies and group electrostatic charges are provided as an Accessory Publication.

Synthesis of *N*-acetoxy-*N*-butoxybenzamide **13a** and *N*-acetoxy-*N*-isopropoxybenzamide **11a** has been described previously.[1,3]

2,6-Dimethylbenzyl Alcohol[42]

2,6-Dimethylbenzoic acid (0.75 g, 4.99 mmol) was added to ethereal $LiAlH_4$ (0.21 g, 5.49 mmol) in dry diethyl ether (30 mL) at such a rate that the reaction mixture boiled gently. Following addition, the reaction was refluxed (48 h). The reaction flask was placed in an ice-bath and moist diethyl ether (20 mL) was added dropwise before filtration and washing with 0.1 M HCl followed by aq. Na_2CO_3. The solution was then dried over Na_2SO_4 and solvent was removed under reduced pressure affording 2,6-dimethylbenzyl alcohol (0.21 g, 1.54 mmol, 31%) as colourless crystals. Mp 82.5–83.5°C (Lit. mp 82.5–83.5°C[42]). $\nu_{max}(CHCl_3)/cm^{-1}$ 3691.4 (free OH), 3607.0 (bonded OH). δ_H 2.46 (6H, s), 4.78 (2H, s), 7.06 (2H, d, *J* 7.4), 7.12 (1H, t, *J* 7.4). δ_C 19.4, 59.3, 128.1, 128.4, 136.6, 137.4.

3,5-Dimethylbenzylbromide

3,5-Dimethylbenzyl alcohol (1.12 g, 8.22 mmol) was added to a mixture of conc. HBr (4 mL), conc. H_2SO_4 (0.6 mL), and diethyl ether (55 mL). Further H_2SO_4 (0.6 mL) was added and the mixture refluxed (3 h). The mixture was extracted with $CHCl_3$, then washed successively with HCl, H_2O, 10% aq. Na_2CO_3, and H_2O. The solution was dried over Na_2SO_4 and concentration under reduced pressure to afford a pale yellow oil. Purification by centrifugal chromatography with 10% ethyl acetate/petroleum spirit afforded pure 3,5-dimethylbenzyl bromide (1.01 g, 5.07 mmol, 62%) as a pale yellow semi-solid at room temperature (Lit. mp 37.5–38°C[43]). $\nu_{max}(CHCl_3)/cm^{-1}$ 1606, 1462 (C=C, str). δ_H 2.34 (6H, s), 4.47 (2H, s), 6.96 (1H, s), 7.04 (2H, s). δ_C 21.1, 33.9, 126.8, 130.2, 137.6, 138.4.

2,6-Dimethylbenzylbromide

2,6-Dimethylbenzyl alcohol (0.21 g, 1.52 mmol) was added to a mixture of conc. HBr (2 mL), conc. sulfuric acid (0.3 mL), and diethyl ether (30 mL). Further H_2SO_4 (0.3 mL) was added and the mixture then refluxed (2.5 h). Diethyl ether (25 mL) was added before the mixture was washed with HCl, H_2O, 10% aq. Na_2CO_3, and H_2O. The solution was dried over Na_2SO_4; concentration under reduced pressure to afford pure 2,6-dimethylbenzyl bromide (0.21 g, 1.06 mmol, 70%) as a pale yellow semi-solid at room temperature (Lit. mp 37.5–38.5°C[44]). $\nu_{max}(CHCl_3)/cm^{-1}$ 1588, 1472 (C=C, str). δ_H 2.44 (6H, s), 4.6 (2H, s), 7.04 (2H, d, *J* 7.4), 7.11 (1H, t, *J* 7.4). δ_C 19.3, 29.4, 128.5, 128.6, 134.1, 137.5.

N-(2-Butoxy)benzamide (General Procedure)[45]

Potassium benzohydroxamate (1.0 g, 92 mmol), 2-butylbromide (18.8 g, 137 mmol), and sodium carbonate (10.64 g, 0.1 mol) were stirred overnight at room temperature in 50% aqueous methanol (250 mL) and refluxed (2 h). Excess methanol was removed under reduced pressure and the mixture extracted with dichloromethane, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Flash chromatography with 10% ethyl acetate/petroleum spirit afforded *N*-(2-butoxy)benzamide (13.5 g, 69.9 mmol, 51%) as a brown oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 3221br (NH), 1686 (C=O). δ_H 0.96 (3H, t, *J* 7.3), 1.28 (3H, d, *J* 6.2), 1.50–1.85 (2H, split m), 4.04 (1H, sextet, *J* 6.4), 7.40 (2H, t, *J* 7.3), 7.49 (1H, t, *J* 7.6), 7.74 (2H, d, *J* 7.1), 8.77 (1H, br s). δ_C 9.6, 17.9, 27.5, 83.4, 127.1, 128.6, 131.9, 132.4, 166.9 (C=O). δ_N −199.9 ± 0.7. *m/z* 194.1 (M + 1), 216.1 (M + 23).

N-(2-Methylbenzyloxy)benzamide

Potassium benzohydroxamate (6.1 g, 34.7 mmol), (2-methylbenzyl)bromide (6.42 g, 34.7 mmol), and sodium carbonate (4.05 g, 3.82 mmol) were combined according to the general procedure. Centrifugal chromatography with 10% ethyl acetate/petroleum spirit afforded *N*-(2-methylbenzyloxy) benzamide (5.1 g, 21.2 mmol, 61%) as pale orange crystals. Mp 62–64°C. $\nu_{max}(CHCl_3)/cm^{-1}$ 3203br (NH), 1684 (C=O). δ_H 2.46 (3H, s), 5.07 (2H, s), 7.19–7.34 (3H, m), 7.3–7.5 (3H, m), 7.47 (1H, t, *J* 7.7), 7.69 (2H, d, *J* 7.03), 9.13 (1H, br s). δ_C 19.0, 76.5, 125.9, 127.1, 128.4, 128.6, 129.0, 130.5, 130.7, 132.0, 133.2, 138.2, 166.5 (C=O). *m/z* 264.2 (M + 23).

N-(3-Methylbenzyloxy)benzamide

Potassium benzohydroxamate (3.39 g, 19.3 mmol), (3-methylbenzyl)bromide (3.56 g, 19.3 mmol), and sodium carbonate (2.24 g, 2.12 mmol) were combined according to the general procedure. Centrifugal chromatography with 10% ethyl acetate/petroleum spirit afforded *N*-(3-methylbenzyloxy) benzamide (2.46 g, 10.3 mmol, 53%) as pale orange crystals. Mp 62–64°C. $\nu_{max}(CHCl_3)/cm^{-1}$ 3403br (NH), 1684 (C=O). δ_H 2.39 (3H, s), 5.03 (2H, s), 7.19 (1H, d, *J* 7.5), 7.22–7.34 (3H, m), 7.41 (2H, t, *J* 7.9), 7.51 (1H, t, *J* 7.3), 7.67 (2H, d, *J* 7.9), 8.49 (1H, br s). δ_C 21.3, 77.5, 126.2, 127.1, 128.4, 128.5, 129.3, 129.9, 131.0, 133.4, 136.0, 138.3, 165.6 (C=O). δ_N −195.9 ± 1.6. *m/z* 242.5 (M + 1), 264.0 (M + 23).

N-(3,5-Dimethylbenzyloxy)benzamide

Potassium benzohydroxamate (0.86 g, 4.84 mmol), (3,5-dimethylbenzyl)bromide (0.96 g, 4.84 mmol), and sodium carbonate (0.57 g, 5.32 mmol) were combined according to the

general procedure. Centrifugal chromatography with 10% ethyl acetate/petroleum spirit afforded *N*-(3,5-dimethylbenzyloxy) benzamide (0.69 g, 2.73 mmol, 56%) as a brown oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 3405br (NH), 1686 (C=O). δ_H 2.35 (6H, s), 5.00 (2H, s), 7.03 (1H, s), 7.08 (2H, s), 7.41 (2H, t, *J* 7.3), 7.51 (1H, t, *J* 7.3), 7.67 (2H, d, *J* 7.3), 8.44 (1H, br s). δ_C 21.2, 78.4, 125.7, 127.1, 128.6, 130.4, 131.9, 135.2, 137.9, 138.2, 166.0 (C=O). δ_N -202.0 ± 0.3. *m/z* 256.2 (M + 1), 278.1 (M + 23).

N-*(2,6-Dimethylbenzyloxy)benzamide*

Potassium benzohydroxamate (0.19 g, 1.05 mmol), (2,6-dimethylbenzyl)bromide (0.21 g, 1.04 mmol), sodium carbonate (0.12 g, 1.14 mmol) were combined according to the general procedure. *N*-(2,6-Dimethylbenzyloxy)benzamide crystallized from orange oil on standing. Recrystallization from benzene/petroleum spirit afforded pure *N*-(2,6-dimethylbenzyloxy)benzamide (0.18 g, 0.71 mmol, 68%) as a low-melting solid. $\nu_{max}(CHCl_3)/cm^{-1}$ 3406br (NH), 1684 (C=O). δ_H 2.50 (6H, s), 5.22 (2H, s), 7.07 (2H, d, *J* 7.9), 7.16 (1H, t, *J* 7.9), 7.42 (2H, t, *J* 7.3), 7.52 (1H, t, *J* 7.3), 7.69 (2H, d, *J* 7.3), 8.46 (1H, br s). δ_C 19.7, 72.4, 127.0, 128.3, 128.5, 128.7, 129.0, 131.4, 132.0, 139.1, 166.7 (C=O). δ_N -202.4 ± 0.6. *m/z* 255.9 (M + 1), 278.2 (M + 23).

N-*(*tert*-Butoxy)benzamide*

O-(*tert*-Butyl)hydroxylamine hydrochloride (0.26 g, 2.07 mmol) was added to dry diethyl ether (40 mL) in a two-necked round-bottom flask in an ice bath. While stirring, triethylamine (0.42 g, 4.14 mmol) was added. Over a period of 1 h, a mixture of benzoyl chloride (0.29 g, 2.07 mmol) in dry diethyl ether (10 mL) was added dropwise such that the temperature did not rise above 5°C, and the reaction mixture was left to stir overnight at room temperature. The mixture was washed with sat. $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. Recrystallization from benzene/petroleum spirit afforded pure *N*-(*tert*-butoxy)benzamide (0.16 g, 0.80 mmol, 39%) as colourless crystals. Mp 118–120°C. $\nu_{max}(CHCl_3)/cm^{-1}$ 3384br (NH), 1686 (C=O). δ_H 1.37 (9H, s), 7.42 (2H, t, *J* 7.5), 7.51 (1H, t, *J* 7.3), 7.75 (2H, d, *J* 7.5), 8.25 (1H, br s). δ_C 26.4, 82.3, 127.0, 128.6, 131.8, 132.4, 167.9 (C=O). *m/z* 194.1 (M + 1), 216.1 (M + 23).

N-*(*tert*-Butoxy)*-N-*chlorobenzamide (General Procedure)*

N-(*tert*-Butoxy)benzamide (0.10 g, 0.52 mmol) and *tert*-butyl hypochlorite (0.28 g, 2.6 mmol) were stirred in the dark at room temperature and monitored by TLC until complete conversion. Excess *tert*-butyl hypochlorite was removed under reduced pressure to give *N*-(*tert*-butoxy)-*N*-chlorobenzamide (0.10 g, 0.44 mmol, 84%) as a yellow oil, which was used without further purification. $\nu_{max}(CHCl_3)/cm^{-1}$ 1729 (C=O). δ_H 1.39 (9H, s), 7.43 (2H, t, *J* 7.3), 7.54 (1H, t, *J* 7.3), 7.82 (2H, d, *J* 7.1).

N-*(2-Butoxy)*-N-*chlorobenzamide*

N-(2-Butoxy)benzamide (0.62 g, 3.21 mmol) and *tert*-butyl hypochlorite (1.35 g, 1.24 mmol) were combined according to the general procedure, to give *N*-(2-butoxy)-*N*-chlorobenzamide (0.67 g, 2.84 mmol, 91%) as a yellow oil, which was used without further purification. $\nu_{max}(CHCl_3)/cm^{-1}$ 1724 (C=O). δ_H 0.90 (3H, t, *J* 7.5), 1.29 (3H, d, *J* 6.4), 1.50–1.80 (2H, m), 4.24 (1H, m), 7.43 (2H, t, *J* 7.3), 7.54 (1H, t, *J* 7.5), 7.80 (2H, d, *J* 7.3). δ_N -164.5 ± 0.3.

N-*Chloro*-N-*(2-methylbenzyloxy)benzamide*

N-(2-Methylbenzyloxy)benzamide (1.50 g, 6.22 mmol) and *tert*-butyl hypochlorite (3.19 g, 29.4 mmol) were combined according to the general procedure, to give *N*-chloro-*N*-(2-methylbenzyloxy)benzamide (1.65 g, 56.9 mmol, 96%) as a yellow oil, which was used without further purification. $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O). δ_H 2.28 (3H, s), 5.13 (2H, s), 7.16–7.31 (4H, m), 7.39 (2H, t, *J* 7.67), 7.53 (1H, t, *J* 7.1), 7.68 (2H, d, *J* 7.5). δ_C 18.8, 74.5, 126.1, 128.3, 129.3, 129.6, 130.5, 131.2, 131.3, 132.8, 138.3, 174.1 (C=O). δ_N -161.7 ± 0.3.

N-*Chloro*-N-*(3-methylbenzyloxy)benzamide*

N-(3-Methylbenzyloxy)benzamide (0.66 g, 2.74 mmol) and *tert*-butyl hypochlorite (1.6 g, 14.7 mmol) were combined according to the general procedure, to give *N*-chloro-*N*-(3-methylbenzyloxy)benzamide (0.73 g, 2.63 mmol, 96%) as a yellow oil, which was used without further purification. $\nu_{max}(CHCl_3)/cm^{-1}$ 1723 (C=O). δ_H 2.33 (3H, s), 5.07 (2H, s), 7.07 (2H, m), 7.15–7.28 (2H, m), 7.40 (2H, t, *J* 8.1), 7.54 (1H, t, *J* 7.1), 7.70 (2H, d, *J* 7.8). δ_N -162.2 ± 0.5.

N-*Chloro*-N-*(3,5-dimethylbenzyloxy)benzamide*

N-(3,5-Dimethylbenzyloxy)benzamide (0.54 g, 2.13 mmol) and *tert*-butyl hypochlorite (1.16 g, 10.6 mmol) were combined according to the general procedure, to give *N*-chloro-*N*-(3,5-dimethylbenzyloxy)benzamide (0.58 g, 3.03 mmol, 94%) as a yellow oil, which was used without further purification. $\nu_{max}(CHCl_3)/cm^{-1}$ 1717 (C=O). δ_H 2.29 (6H, s), 5.02 (2H, s), 6.86 (2H, s), 6.98 (1H, s), 7.40 (2H, t, *J* 8.1), 7.54 (1H, t, *J* 7.3), 7.70 (2H, d, *J* 7.8).

N-*Chloro*-N-*(2,6-dimethylbenzyloxy)benzamide*

N-(2,6-Dimethylbenzyloxy)benzamide (0.123 g, 0.48 mmol) and *tert*-butyl hypochlorite (0.26 g, 2.4 mmol) were combined according to the general procedure, to give *N*-chloro-*N*-(2,6-dimethylbenzyloxy)benzamide (0.135 g, 0.47 mmol, 97%) as pale crystals, which were used without further purification. $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O). δ_H 2.30 (6H, s), 5.20 (2H, s), 7.02 (2H, d, *J* 7.5), 7.15 (1H, t, *J* 7.5), 7.41 (2H, t, *J* 7.5), 7.54 (1H, t, *J* 7.1), 7.73 (2H, d, *J* 7.5). δ_C 19.5, 70.6, 128.4, 129.3, 129.5, 129.7, 131.5, 132.7, 139.2, 174.0 (C=O).

N-*Butanoyloxy*-N-*butoxybenzamide* ***13b*** *(General Procedure)*

N-Butoxy-*N*-chlorobenzamide (0.3 g, 1.29 mmol) was stirred in the dark with sodium butyrate (0.2 g, 1.81 mmol) in dry acetone and monitored by TLC until all *N*-chloro compound had been consumed. Filtration and concentration under reduced pressure yielded the crude product. Centrifugal chromatography with 10% ethyl acetate/petroleum spirit afforded *N*-butanoyloxy-*N*-butoxybenzamide as a light brown oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1773.7 (ester C=O), 1721.4 (amide C=O). δ_H 0.92 (6H, 2 × t, *J* 7.3), 1.38 (2H, sextet, *J* 7.7), 1.6–1.7 (4H, m), 2.33 (2H, t, *J* 7.5), 4.19 (2H, t, *J* 6.8), 7.43 (2H, t, *J* 7.9), 7.54 (1H, t, *J* 7.5), 7.78 (2H, d, *J* 7.9). δ_C 13.4, 13.7, 18.2, 19.0, 30.1, 34.0, 75.4, 128, 128.2, 129.0, 132.6, 170.9 (ester C=O), 174.4 (amide C=O).

N-*Butoxy*-N-*(2-methylpropanoyloxy)benzamide* ***13c***

N-Butoxy-*N*-chlorobenzamide (0.74 g, 3.24 mmol) and sodium isobutyrate (0.5 g, 4.54 mmol) were combined according to

the general procedure. Purification by centrifugal chromatography with 5% ethyl acetate/petroleum spirit afforded *N*-butoxy-*N*-(*2*-methylpropanoyloxy)benzamide as a light brown oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1775.2 (ester C=O), 1721.1 (amide C=O). δ_H 0.92 (3H, t, *J* 7.3), 1.12 (6H, d, *J* 6.8), 1.39 (2H, sextet, *J* 7.4), 1.67 (2H, quin, *J* 7.3), 2.55–2.63 (1H, septet, *J* 6.6), 4.19 (2H, t, *J* 6.6), 7.42 (2H, t, *J* 8.1), 7.54 (1H, t, *J* 7.3), 7.76 (2H, d, *J* 8.0). δ_C 13.7, 18.5, 19.0, 30.1, 32.4, 75.4, 128.1, 129.2, 132.1, 132.5, 174.3 (amide C=O), 174.5 (ester C=O).

N-*Butoxy*-N-*((S)-(+)-2-methylbutanoyloxy)benzamide* **13d**

N-Butoxy-*N*-chlorobenzamide (0.26 g, 1.15 mmol) and sodium (*S*)-(+)-2-methylbutyrate (0.2 g, 1.61 mmol) were combined according to the general procedure. Purification by centrifugal chromatography with 5% ethyl acetate/petroleum spirit afforded *N*-butoxy-*N*-(*S*)-(+)-2-methylbutanoyloxybenzamide as a light brown oil. $[\alpha]_D^{25}$ 11.53° in $CHCl_3$. $\nu_{max}(CHCl_3)/cm^{-1}$ 1773.7 (ester C=O), 1725 (amide C=O). δ_H 0.86 (3H, t, *J* 7.3), 0.93 (3H, t, *J* 7.1), 1.10 (3H, d, *J* 6.8), 1.36–1.45 (3H, m), 1.65–1.70 (3H, m), 2.42 (1H, m), 4.18 (2H, t, *J* 6.8), 7.42 (2H, t, *J* 7.3), 7.54 (1H, t, *J* 7.5), 7.77 (2H, d, *J* 7.3). δ_C 13.7, 11.3, 16.3, 19.0, 26.4, 30.1, 39.4, 75.4, 128.1, 129.0, 132.1, 132.5, 173.9 (ester C=O), 174.5 (amide C=O).

N-*Butoxy*-N-*(3,3-dimethylbutanoyloxy)benzamide* **13e**

N-Butoxy-*N*-chlorobenzamide (0.59 g, 2.59 mmol) and sodium 3,3-dimethylbutyrate (0.5 g, 3.62 mmol) were combined according to the general procedure. Purification by centrifugal chromatography with 10% ethyl acetate/petroleum spirit afforded *N*-butoxy-*N*-(3,3-dimethylbutanoyloxy)benzamide as a light brown oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1778.1 (ester C=O), 1721.4 (amide C=O). δ_H 0.92 (3H, t, *J* 7.1), 1.01 (9H, s), 1.39 (2H, sextet, *J* 6.7), 1.62 (2H, quin, *J* 7.3), 2.24 (2H, s), 4.18 (2H, t, *J* 7.0), 7.42 (2H, t, *J* 7.8), 7.52 (1H, t, *J* 7.5), 7.78 (2H, d, *J* 7.8). δ_C 13.7, 19.0, 29.4, 30.1, 31.0, 45.4, 75.3, 128.2, 129.1, 132.1, 132.5, 169.5 (ester C=O), 174.4 (amide C=O).

N-*Butoxy*-N-*(2,2-dimethylpropanoyloxy)benzamide* **13f**

N-Butoxy-*N*-chlorobenzamide (0.66 g, 2.88 mmol) and sodium pivalate (0.5 g, 4.03 mmol) were combined according to the general procedure. Purification by centrifugal chromatography with 5% ethyl acetate/petroleum spirit afforded *N*-butoxy-*N*-(2,2-dimethylpropanoyloxy)benzamide as a light brown oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1770.5 (ester C=O), 1721.8 (amide C=O). δ_H 0.93 (3H, t, *J* 7.1), 1.15 (9H, s), 1.40 (2H, sextet, *J* 8.1), 1.68 (2H, quin, *J* 7.5), 4.18 (2H, t, *J* 7.5), 7.44 (2H, t, *J* 7.5), 7.55 (1H, t, *J* 7.5), 7.73 (2H, d, *J* 7.5). δ_C 13.7, 19.0, 26.7, 30.0, 38.4, 75.4, 127.9, 128.1, 129.4, 132.8, 174.7 (amide C=O), 175.4 (ester C=O).

N-*(Adamantane-1-carboxoyloxy)*-N-*butoxybenzamide* **13g**

N-Butoxy-*N*-chlorobenzamide (0.44 g, 1.94 mmol) and sodium adamantane-1-carboxylate (0.55 g, 2.72 mmol) were combined according to the general procedure. Purification by centrifugal chromatography with 5% ethyl acetate/petroleum spirit afforded a light brown oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1767.4 (ester C=O), 1722.5 (amide C=O). δ_H 0.93 (3H, t, *J* 7.3), 1.39 (2H, sextet, *J* 7.7), 1.63–1.87 (8H, m), 1.83 (6H, br s), 1.99 (3H, br s), 4.17 (2H, t), 7.41 (2H, t, *J* 7.5), 7.53 (1H, t, *J* 7.3), 7.74 (2H, d, *J* 7.5). δ_C 13.7, 19.0, 27.7, 30.2, 36.2, 38.3, 40.5, 75.3, 128.1, 129.0, 132.1, 132.4, 174.4, 174.7.

N-*Acetoxy*-N-*(2-butoxy)benzamide* **11b**

N-(2-Butoxy)-*N*-chlorobenzamide (0.50 g, 2.20 mmol) and sodium acetate (0.25 g, 3.07 mmol) were combined according to the general procedure. Purification by centrifugal chromatography with 10% ethyl acetate/petroleum spirit afforded pure *N*-acetoxy-*N*-(2-butoxy)benzamide (0.34 g, 1.36 mmol, 62%) as an orange-brown oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1790 (ester C=O), 1720 (amide C=O). δ_H 0.91 (3H, t, *J* 7.5), 1.30 (3H, d, *J* 6.2), 1.53–1.79 (2H, split m), 2.05 (3H, s), 4.25–4.35 (1H, m), 7.40 (2H, t, *J* 7.7), 7.51 (1H, t, *J* 7.0), 7.76 (2H, d, *J* 7.6). δ_C 9.5, 18.5, 18.7, 27.7, 83.4, 128.2, 128.9, 132.0, 132.4, 168.3 (ester C=O), 174.9 (amide C=O). δ_N −126.9 ± 0.6. *m/z* 274 (M + 23).

N-*Acetoxy*-N-*(*tert-*butoxy)benzamide* **11c**

N-(*tert*-Butoxy)-*N*-chlorobenzamide (0.48 g, 2.11 mmol) and sodium acetate (0.26 g, 3.16 mmol) were combined according to the general procedure. Purification by centrifugal chromatography with 5% ethyl acetate/petroleum spirit afforded *N*-acetoxy-*N*-(*tert*-butoxy)benzamide (0.31 g, 1.23 mmol, 58%) as an orange oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1786 (ester C=O), 1707 (amide C=O). δ_H 1.37 (9H, s), 1.97 (3H, s), 7.38 (2H, t, *J* 7.7), 7.48 (1H, t, *J* 7.3), 7.77 (2H, d, *J* 7.0). δ_C 18.7, 27.0, 83.8, 127.9, 129.1, 131.9, 132.4, 168.4 (ester C=O), 174.9 (amide C=O). *m/z* 274.1 (M + 23).

N-*Acetoxy*-N-*(2-methylbenzyloxy)benzamide* **12b**

Sodium acetate (0.67 g, 8.17 mmol) and *N*-chloro-*N*-(2-methylbenzyloxy)benzamide (1.61 g, 5.84 mmol) were combined according to the general procedure. Purification by centrifugal chromatography with 5% ethyl acetate/petroleum spirit afforded *N*-acetoxy-*N*-(2-methylbenzyloxy)benzamide (0.96 g, 3.21 mmol, 55%) as pale yellow oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1792 (ester C=O), 1726 (amide C=O). δ_H 2.07 (3H, s), 2.35 (3H, s), 5.21 (2H, s), 7.17–7.34 (3H, m), 7.33 (1H, d, *J* 7.0), 7.39 (2H, t, *J* 7.7), 7.52 (1H, t, *J* 7.5), 7.73 (2H, d, *J* 7.7). δ_C 18.7, 18.9, 75.7, 125.9, 128.1, 128.3, 129.0, 129.1, 130.4, 130.7, 131.8, 132.7, 138.0, 168.1 (ester C=O), 174.2 (amide C=O). δ_N −123.3 ± 0.5. *m/z* 322 (M + 23).

N-*Acetoxy*-N-*(3-methylbenzyloxy)benzamide* **12c**

Sodium acetate (0.31 g, 3.68 mmol) and *N*-chloro-*N*-(3-methylbenzyloxy)benzamide (0.73 g, 2.63 mmol) were combined according to the general procedure. Purification by centrifugal chromatography with 10% ethyl acetate/petroleum spirit afforded *N*-acetoxy-*N*-(3-methylbenzyloxy)benzamide (0.55 g, 1.84 mmol, 70%) as an orange-brown oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1792 (ester C=O), 1729 (amide C=O). δ_H 2.09 (3H, s), 2.35 (3H, s), 5.16 (2H, s), 7.1–7.25 (3H, m), 7.28 (1H, s), 7.40 (2H, t, *J* 7.6), 7.53 (1H, t, *J* 7.5), 7.74 (2H, d, *J* 7.6). δ_C 18.7, 21.3, 77.7, 126.2, 128.3, 128.4, 129.1, 129.4, 129.9, 131.7, 132.7, 134.5, 138.2, 168.1 (ester C=O), 174.2 (amide C=O). δ_N −123.6 ± 0.5. *m/z* 322.1 (M + 23).

N-*Acetoxy*-N-*(3,5-dimethylbenzyloxy)benzamide* **12d**

Sodium acetate (0.30 g, 3.70 mmol) and *N*-chloro-*N*-(3,5-dimethylbenzyloxy)benzamide (0.77 g, 2.64 mmol) were combined according to the general procedure. Purification by centrifugal chromatography with 5% ethyl acetate/petroleum spirit afforded *N*-acetoxy-*N*-(3,5-dimethylbenzyloxy)benzamide (0.48 g, 1.56 mmol, 59%) as a yellow oil. $\nu_{max}(CHCl_3)/cm^{-1}$

1791 (ester C=O), 1728 (amide C=O). δ_H 2.06 (3H, s), 2.30 (6H, s), 5.07 (2H, s), 6.95 (2H, s), 6.98 (1H, s), 7.44 (2H, t, *J* 7.7), 7.57 (1H, t, *J* 7.1), 7.75 (2H, d, *J* 7.7). δ_C 18.7, 21.2, 77.7, 127.0, 128.2, 129.1, 130.3, 131.8, 132.7, 134.4, 138.0, 168.1 (ester C=O), 174.1 (amide C=O). δ_N -122.1 ± 0.3. *m/z* 336 (M + 23).

N-*Acetoxy*-N-*(2,6-dimethylbenzyloxy)benzamide* **12e**

Sodium acetate (0.052 g, 0.63 mmol) and *N*-chloro-*N*-(2,6-dimethylbenzyloxy)benzamide (0.12 g, 0.42 mmol) were combined according to the general procedure. Purification by centrifugal chromatography with 5% ethyl acetate/petroleum spirit afforded *N*-acetoxy-*N*-(2,6-dimethylbenzyloxy)benzamide (0.09 g, 0.30 mmol, 71%) as a yellow oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1791 (ester C=O), 1729 (amide C=O). δ_H 2.12 (3H, s), 2.36 (6H, s), 5.28 (2H, s), 7.02 (2H, d), 7.14 (1H, t), 7.43 (2H, t, *J* 7.7), 7.55 (1H, t, *J* 7.5), 7.76 (2H, d, *J* 7.7). δ_C 18.6, 19.4, 71.3, 128.3, 128.6, 129.0, 129.1, 130.6, 131.9, 132.7, 139.0, 168.1 (ester C=O), 174.2 (amide C=O). δ_N -123.5 ± 0.5. *m/z* 336 (M + 23).

N-*Butoxy*-N-*(*p*-methylbenzoyloxy)benzamide* **14b**

N-Butoxy-*N*-chlorobenzamide (0.5745 g, 2.523 mmol) and sodium toluate (1.1692 g, 7.3939 mmol) were combined according to the general procedure. Purification by centrifugal chromatography with 10% ethyl acetate/petroleum spirit afforded *N*-butoxy-*N*-(*p*-methylbenzoyloxy)benzamide as a yellow oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1756 (ester C=O), 1733 (amide C=O). δ_H 0.88 (3H, t, *J* 7.6), 1.36 (2H, sextet, *J* 7.1), 1.65 (2H, quin, *J* 7.6), 2.39 (3H, s), 4.27 (2H, t, *J* 6.6), 7.22 (2H, d, *J* 8.1), 7.39 (2H, t, *J* 7.3), 7.5 (1H, t, *J* 7.6), 7.82 (2H, d, *J* 7.4), 7.88 (2H, d, *J* 8.1). δ_C 13.8, 19.0, 21.8, 30.1, 75.5, 124.5, 128.3, 129.0, 129.4, 130.0, 131.9, 132.66, 145.0, 164.4 (amide C=O), 174.6 (ester C=O). *m/z* 350.1 (M + 23).

N-*Butoxy*-N-*(*p*-methoxybenzoyloxy)benzamide* **14c**

N-Butoxy-*N*-chlorobenzamide (0.6872 g, 3.018 mmol) and sodium anisate (1.39 g, 7.983 mmol) were combined according to the general procedure. Purification by centrifugal chromatography with 10% ethyl acetate/petroleum spirit afforded *N*-butoxy-*N*-(*p*-methoxybenzoyloxy)benzamide as a yellow oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1751 (ester C=O), 1723 (amide C=O). δ_H 0.88 (3H, t, *J* 7.3), 1.36 (2H, sextet, *J* 8.2), 1.66 (2H, quin, *J* 7.6), 3.85 (3H, s), 4.26 (2H, t, *J* 6.2), 6.91 (2H, d, *J* 7.8), 7.39 (2H, t, *J* 7.5), 7.5 (1H, t, *J* 7.3), 7.82 (2H, d, *J* 7.5), 7.96 (2H, d, *J* 7.8). δ_C 13.8, 19.0, 30.2, 55.5, 75.5, 113.9, 119.4, 125.3, 128.2, 129.1, 131.9, 132.2, 132.6, 164.3 (ester C=O), 174.7 (amide C=O). *m/z* 366.1 (M + 23).

Accessory Publication

DFT computational data: structures, energies and electrostatic group charges are available on the Journal's website. NMR spectra are also available.

Acknowledgement

The authors are grateful to Dr David Tucker for assistance with recording of ^{15}N NMR spectra.

References

[1] R. G. Gerdes, S. A. Glover, J. F. Ten Have, C. A. Rowbottom, *Tetrahedron Lett.* **1989**, *30*, 2649. doi:10.1016/S0040-4039(00)99089-0

[2] J. J. Campbell, S. A. Glover, C. A. Rowbottom, *Tetrahedron Lett.* **1990**, *31*, 5377. doi:10.1016/S0040-4039(00)98076-6

[3] J. J. Campbell, S. A. Glover, G. P. Hammond, C. A. Rowbottom, *J. Chem. Soc., Perkin Trans. 2* **1991**, 2067. doi:10.1039/P29910002067

[4] A. M. Bonin, S. A. Glover, G. P. Hammond, *J. Chem. Soc., Perkin Trans. 2* **1994**, 1173. doi:10.1039/P29940001173

[5] A. M. Bonin, S. A. Glover, G. P. Hammond, *J. Org. Chem.* **1998**, *63*, 9684. doi:10.1021/JO980863Z

[6] A. M. Bonin, T. M. Banks, J. J. Campbell, S. A. Glover, G. P. Hammond, A. S. Prakash, C. A. Rowbottom, *Mutat. Res.* **2001**, *494*, 115.

[7] T. M. Banks, A. M. Bonin, S. A. Glover, A. S. Prakash, *Org. Biomol. Chem.* **2003**, *1*, 2238. doi:10.1039/B301618H

[8] L. E. Andrews, T. M. Banks, A. M. Bonin, S. F. Clay, A.-M. E. Gillson, S. A. Glover, *Aust. J. Chem.* **2004**, *57*, 377. doi:10.1071/CH03276

[9] L. E. Andrews, A. M. Bonin, L. Fransson, A.-M. E. Gillson, S. A. Glover, *Mutat. Res.* **2006**, *605*, 51.

[10] S. A. Glover, in *Advances in Physical Organic Chemistry* (Ed. J. Richard) **2008**, Vol. 42, p. 35 (Elsevier: London).

[11] A. Rauk, S. A. Glover, *J. Org. Chem.* **1996**, *61*, 2337. doi:10.1021/JO9521817

[12] S. A. Glover, *Tetrahedron* **1998**, *54*, 7229. doi:10.1016/S0040-4020(98)00197-5

[13] S. A. Glover, G. Mo, A. Rauk, D. Tucker, P. Turner, *J. Chem. Soc., Perkin Trans. 2* **1999**, 2053. doi:10.1039/A904575I

[14] S. A. Glover, A. Rauk, *J. Org. Chem.* **1999**, *64*, 2340. doi:10.1021/JO982048P

[15] S. A. Glover, in *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids, Part 2* (Eds Z. Rappoport, J. F. Liebman) **2009**, p. 839 (Wiley: Chichester).

[16] A.-M. E. Gillson, S. A. Glover, D. J. Tucker, P. Turner, *Org. Biomol. Chem.* **2003**, *1*, 3430. doi:10.1039/B306098P

[17] S. A. Glover, A. Rauk, *J. Chem. Soc., Perkin Trans. 2* **2002**, 1740. doi:10.1039/B204232K

[18] J. J. Campbell, S. A. Glover, *J. Chem. Soc., Perkin Trans. 2* **1992**, 1661. doi:10.1039/P29920001661

[19] J. J. Campbell, S. A. Glover, *J. Chem. Res. (S)* **1999**, *8*, 474. doi:10.1039/A903555I

[20] J. J. Campbell, S. A. Glover, *J. Chem. Res. (M)* **1999**, *8*, 2075.

[21] S. A. Glover, *Arkivoc* **2001**, *xii*, 143.

[22] S. A. Glover, G. Mo, *J. Chem. Soc., Perkin Trans. 2* **2002**, 1728. doi:10.1039/B111250N

[23] J. M. Buccigross, S. A. Glover, *J. Chem. Soc., Perkin Trans. 2* **1995**, 595. doi:10.1039/P29950000595

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

[25] S. A. Glover, G. Mo, A. Rauk, *Tetrahedron* **1999**, *55*, 3413. doi:10.1016/S0040-4020(98)01151-X

[26] S. A. Glover, A. Rauk, J. M. Buccigross, J. J. Campbell, G. P. Hammond, G. Mo, L. E. Andrews, A.-M. E. Gillson, *Can. J. Chem.* **2005**, *83*, 1492. doi:10.1139/V05-150

[27] S. A. Glover, in *Merck Index, Organic Name Reactions ONR-43* (Ed. M. J. O'Neil) **2006** (Merck & Co., Inc.: Whitehouse Station, NJ).

[28] N. S. Isaacs, *Physical Organic Chemistry* **1995**, p. 422 (Longman Scientific and Technical: New York, NY).

[29] W. Forster, R. M. Laird, *J. Chem. Soc., Perkin Trans. 2* **1982**, 135. doi:10.1039/P29820000135

[30] A. Pross, *Theoretical and Physical Principles of Organic Chemistry* **1995**, p. 142 (John Wiley & Sons, Inc.: New York, NY).

[31] F. A. Carrol, *Perspectives on Structure and Mechanism in Organic Chemistry* **1998**, p. 489 (Brooks/Cole Publishing Company: New York, NY).

[32] A. Halvorsen, J. Songstad, *J. Chem. Soc. Chem. Commun.* **1978**, 327. doi:10.1039/C39780000327

[33] D. J. McLennan, A. Pross, *J. Chem. Soc., Perkin Trans. 2* **1984**, 981. doi:10.1039/P29840000981

[34] N. De Kimpe, R. Verhé, *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines* (Eds S. Patai, Z. Rappoport) **1988**, p. 38 (John Wiley & Sons: Chichester).

[35] J. W. Thorpe, J. Warkentin, *Can. J. Chem.* **1973**, *51*, 927. doi:10.1139/V73-137

[36] T. M. Banks, *PhD Thesis: Reactivity, mutagenicity and DNA damage of N-acyloxy-N-alkoxyamides* **2003**, University of New England, Armidale.

[37] C. Hansch, A. J. Leo, *Exploring QSAR, Fundamentals and Applications in Chemistry and Biology, Part I* **1995**, p. 78 (American Chemical Society: Washington, DC).

[38] *ChemDraw Ultra*, Version 7.01 for Macintosh (CambridgeSoft Corporation: Cambridge, MA).

[39] ACD/Log P Web Service 5.0 (Advanced Chemistry Development Inc: Toronto).

[40] *Spartan '04* for Macintosh, **2004**. 1.1.1 (Wavefunction Inc.: Irvine, CA).

[41] C. C. Chambers, G. D. Hawkins, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem.* **1996**, *100*, 16385. doi:10.1021/JP9610776

[42] P. L. Beaulieu, P. C. Anderson, D. R. Cameron, G. Croteau, V. Gorys, C. Grand-Maître, D. Lamarre, F. Liard, W. Paris, L. Plamondon, F. Soucy, D. Thibeault, D. Wernic, C. Yoakim, *J. Med. Chem.* **2000**, *43*, 1094. doi:10.1021/JM990336N

[43] W. Q. Beard, D. M. van Eenam, C. R. Hauser, *J. Org. Chem.* **1961**, *26*, 2310. doi:10.1021/JO01351A039

[44] N. Löfgren, U. Ragnarsson, K. Sjöberg, *Acta Chem. Scand.* **1963**, *17*, 1252. doi:10.3891/ACTA.CHEM.SCAND.17-1252

[45] J. H. Cooley, W. D. Bills, J. R. Throckmorton, *J. Org. Chem.* **1960**, *25*, 1734. doi:10.1021/JO01080A014