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Anomeric Amides — Structure, Properties and Reactivity

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1. INTRODUCTION

Amides, geminally substituted with two heteroatoms at nitrogen, can support anomeric effects in much the same way as their carbon analogues such as acetals and aminals. To date very few such compounds have been reported in the literature and, in most instances, these have been hydroxamic ester derivatives. Rudchenko investigated the chemistry of *N*-alkoxy-*N*-chloroureas as well as *N,N*-dialkoxyureas[1,2] while we have studied the first *N,N*-dialkoxyamides and *N*-acetoxy-*N*-alkoxyamides.[3] There have been several reports of amides geminally substituted at nitrogen with both an oxygen and a nitrogen but these have, to the exclusion of all other forms, dealt with *N,N'*-dialkoxy-*N,N'*-diacylhydrazines.[4-7] Several groups have reported reactions of *N,N*-dihaloamides.[8-16] It is therefore not surprising that, to date, the unusual properties of such amides have not been described at length and this report may serve to focus attention on the unique characteristics and reactivity patterns that this configuration imparts to such amides. In short, amides in this class display quite different physical and chemical properties to those of normal amides or those with even a single heteroatom at nitrogen such as hydroxamic esters and hydrazides. In certain members of this family of amide derivatives, such intrinsic properties may be central to their biological behaviour.[3,17,18] Recently we have termed all such species *anomeric amides* although not all properties exhibited by these amides may be attributed to the operation of anomeric affects.[19] The term "*anomeric*" is rather used to describe all systems bearing two heteroatoms at nitrogen and that are thus capable of displaying anomeric effects.

2. DEFINITION

By definition, a generalised anomeric effect is observed at the carbon of an *X—C—Y* system when a molecule undergoes conformational change to optimise a secondary, stabilising electronic interaction involving overlap between the lone pair on one heteroatom with the σ* orbital of the bond between the central carbon atom and the second heteroatom.[20-23] Fig. 1a illustrates that in *X—N—Y* systems, as with anomeric carbon centres, two anomeric interactions are possible and involve either an n_Y—σ^*_{NX} or an n_X—σ^*_{NY} overlap. In either case, the result is a reduction in energy of the lone pair of electrons and a net stabilisation of the molecule (Fig. 1b). In carbon systems, such anomeric effects are well documented and, in sugars and their models, account for the well known preference for conformations which bear axial gem hydroxyl or alkoxyl groups.[24] Anomeric effects have now been invoked to explain a range of conformational preferences and even stereochemical selectivities in radical reactions.[25] They are also known for bisoxo-substituted amines and readily account for conformational preferences in *N*-alkoxy cyclic hydroxylamines. In an extensive review, Rudchenko recently dealt with this and other manifestations of anomeric effects in acyclic and cyclic *ONO* systems.[26] Anomeric interactions have also been used to explain reactivity of the *N*-alkoxy-*N*-chloroureas.[2]

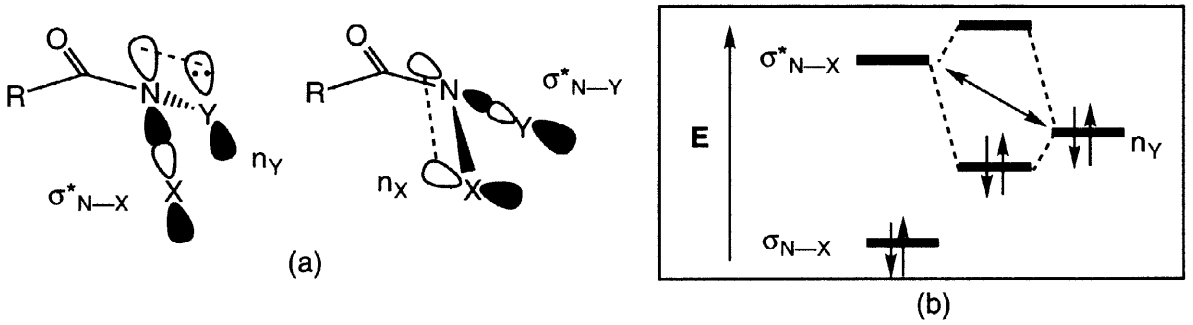


Fig. 1. (a) Anomeric interactions in bisheteroatom-substituted amides. (b) Lone pair stabilisation through an n_Y—σ^*_{NX} anomeric interaction.

In such purturbation approaches, one important factor affecting the degree of lone pair stabilisation is the relative energies of the n_Y and the antibonding *N*—*X* σ orbital. They are influenced in opposite senses by electronegativity of substituents; while σ^*_{NX} is lowered in energy (together with the σ_{NX}) as *X* becomes more electronegative along the same p-block row, [27,28] n_Y is increased in energy on less electronegative atoms (Fig. 2). As is the case for carbon systems, optimal anomeric stabilisation would be developed when *Y* belongs to an early p-block group and *X* belongs to p-block groups to the right of the periodic table.[29,30] Thus, for instance, an *NNF* system would result in significant anomeric stabilisation. *N*—*X* σ* orbitals decrease in energy as one proceeds down the periodic table and smaller overlap dominates the energy; thus anomeric effects are likely to be stronger in that order (Fig. 2).

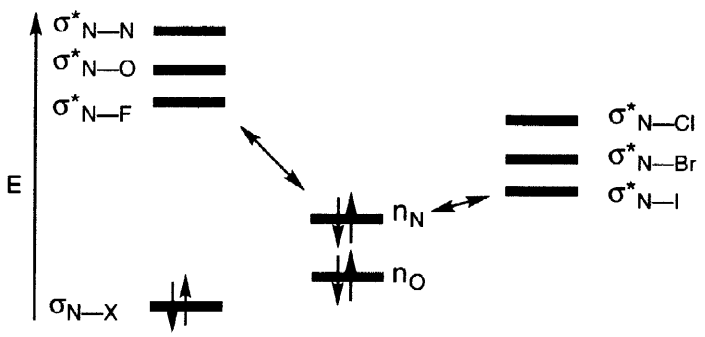


Fig. 2. Energetics governing anomeric effects.

In addition to the relative energies of the interacting orbitals, other factors can play a role. With increasing electronegativity, the *N* coefficient in the σ* orbital increases in size (the inverse of the effect upon the σ orbital) (Fig. 3). Thus anomeric π-overlap would be greater with the σ* orbital of an *N*—*F* bond than with the σ* orbital of an *N*—*N* bond.

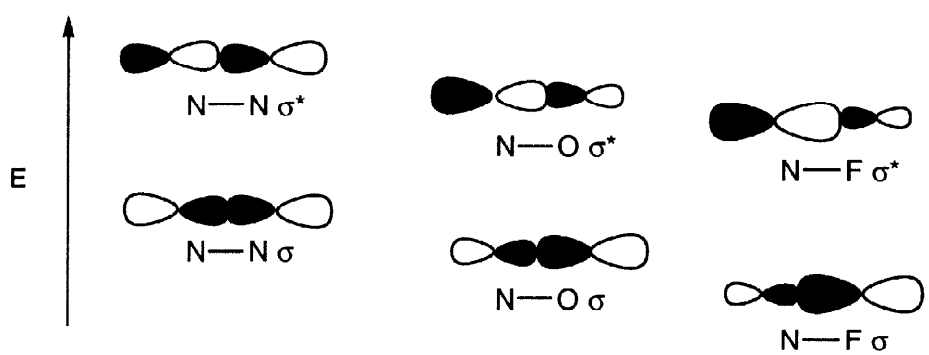


Fig. 3. Polarisation of σ_{NX} and σ^*_{NX} orbitals with increasing electronegativity of *X*.

The size of the p-orbital on *Y* may also be important. In anomeric overlap involving second or higher row elements, lone pair overlap with nitrogen would be best with second row elements. Thus in *ONCl* systems, lone pair size would favour the n_O—σ^*_{NCl} interaction (Fig. 4a) rather than the n_{Cl}—σ^*_{NO} overlap (Fig. 4b). Anomeric overlap would also be easier with sp^3 hybridisation at the central atom since the nitrogen contribution to σ^*_{NX} would possess greatest p-character. Pyramidal central atoms would also facilitate geometrical overlap of the two components; with sp^2 hybridisation at the central atom, edge-on overlap with a p-orbital lone pair on *Y* would be less effective on geometrical grounds alone (Fig. 4c).

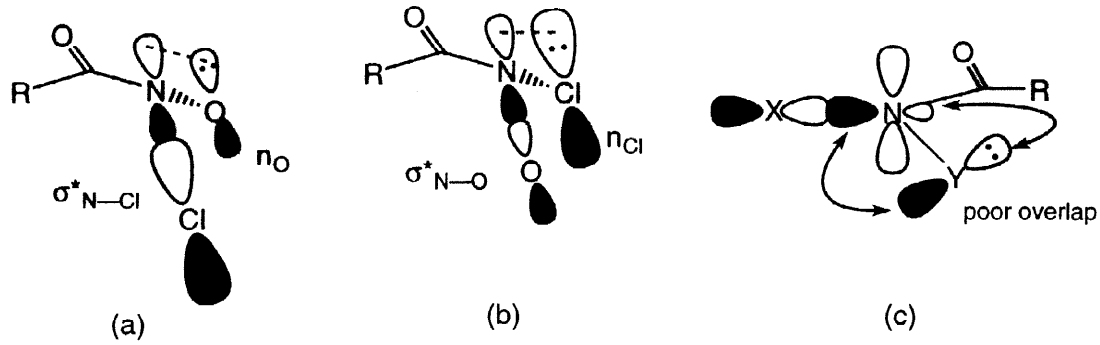


Fig. 4. (a) Orbitals of similar size favour anomeric overlap; (b) Poor anomeric overlap with a chlorine 3p lone pair; (c) Weak anomeric effect with sp^2 hybridisation at the central nitrogen.

Finally, a third, strongly electron-withdrawing substituent could reverse the polarity of *N—X* bonds and, with this, the size of the *N*-contribution to the σ^*_{NX} orbital (Fig. 5a). Anomeric overlap would thus be weaker. The natural consequence of strong anomeric interactions is a negative hyperconjugation. Thus chlorine is expected to be negative in *N*-chlorohydroxamic esters but in the corresponding sulfonohydroxamic esters, like *N*-halosulfonamides,[31,32] chlorine is likely to be more positively polarised as these are known to be positive halogen sources (Fig. 5b).[33] The sulfonyl substituent (σ_I=+0.64) is a much stronger electron-withdrawing group than an acyl (σ_I=+0.28)[34] or dialkoxyphosphoryl group (σ_I=+0.06) which, relative to acyl, is an even weaker *–I* substituent.[35]

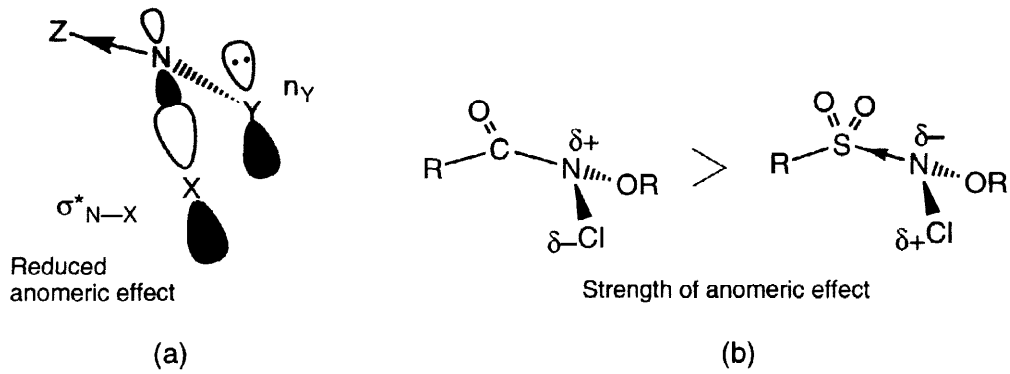


Fig. 5. (a) Effect of a third strongly electron-withdrawing substituent; (b) Reverse *N—Cl* polarities and relative strength of anomeric overlap in amides versus sulfonamides.

3. CONSEQUENCES OF BISHETEROATOM SUBSTITUTION AND THE ANOMERIC EFFECT

It is well known that atoms geminally substituted with two heteroatoms are strongly pyramidal. In qualitative terms, relative to sp^2 hybrisation, sp^3 hybridisation at the central atom and the consequent increase in p-character in the σ bonds enables electron density to be closer to the more electronegative ligands. In amines, dioxo substitution results in much higher barriers to inversion than in alkylamines.[26,36] This has also been explained in terms of an electronegativity effect; increased p-character in the σ bonds results in more s-character for the electron pair on nitrogen. The planar inversion transition state is therefore destabilised since, in it, the lone pair must develop pure p-character. This transition state is also destabilised by a six electron anti-bonding interaction between heteroatom lone pairs. In addition, the better anomeric overlap that is possible in sp^3 rather than sp^2 systems may also play a role (Fig. 6).[37] These phenomena can also be rationalised theoretically.[38,39]

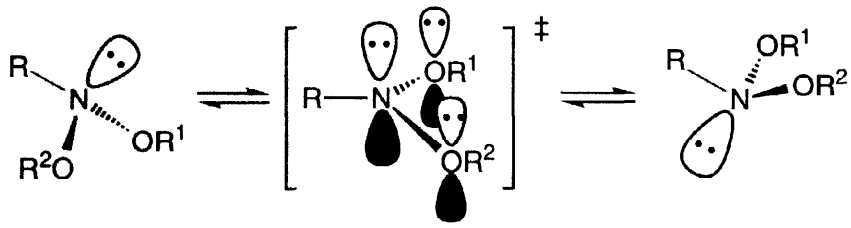


Fig. 6. Inversion in *N,N*-dialkoxyamines.

3.1 *Amide rotation barriers*

Anomeric amides should thus possess a nitrogen which deviates substantially from planarity. The increased "s"-content of the lone pair should drastically reduce lone pair delocalisation onto the carbonyl and, with this, the associated barrier to rotation about the *N—C(O)* bonds, a barrier that is significant in normal amides[40,41] and hydroxamic esters[19,42,43] and which often leads to dynamic effects in their ^{1}H n.m.r. spectra at room temperature (Fig 7a). Such amides should have longer than normal *N—C(O)* bonds and shorter carbonyl bonds resulting in higher than normal infrared carbonyl stretch frequencies. Basicity of the amide carbonyls which become more ketone-like, is likely to be lower than in alkylamides.

3.2 *Inversion at nitrogen*

The barrier to inversion at nitrogen, which would normally be higher with bisheteroatom substitution is likely to be substantially reduced in the amides since the planar transition state (Fig. 7b) can benefit from π-overlap with the carbonyl. It should however be greater than that found for hydroxamic esters, hydrazides or *N*-alkylamides. In support of this, Rudchenko has measured the inversion barriers for several *N,N*-dialkoxyureas at $\Delta G^{\ddagger}_{298}$= 38-46 kJmol^{-1} while those in acyclic dialkoxyamines are typically $\Delta G^{\ddagger}_{Tc}$ = 84-92 kJmol^{-1} (T_c =293-298 K).[26]

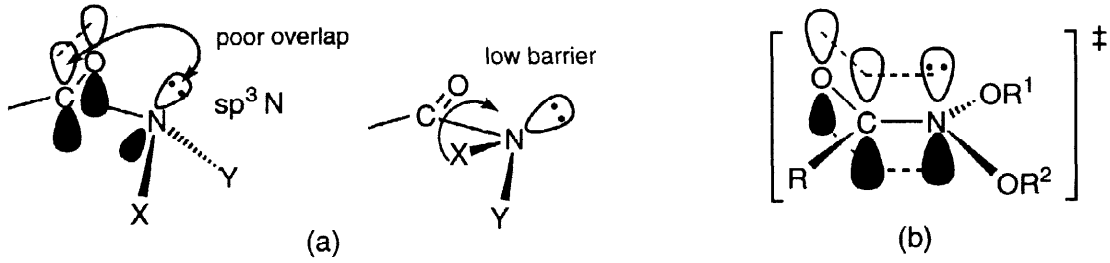


Fig. 7. (a) Facile amide rotation in anomeric amides; (b) Stabilisation of inversion transition state.

3.3 *Conformation about the Y—N bond*

The ground state structures in anomeric amides should facilitate overlap between a lone pair orbital on one heteroatom, *Y*, with a σ^*_{NX} orbital (Fig. 8). Depending upon the extent of the anomeric overlap, barriers to rotation about the *N—Y* bond can be expected to be greater than predicted by steric effects alone. Anomeric overlap should also result in shorter than normal *N—Y* bonds and longer than normal *N—X* bonds.

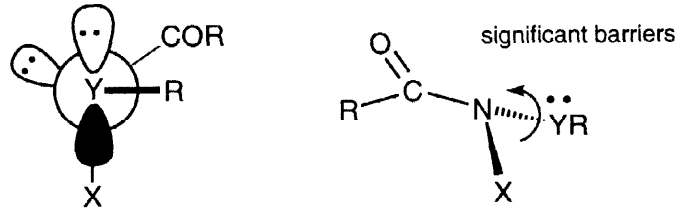


Fig. 8. Conformational preference in anomeric amides.

3.4 *Reactivity*

The ***XNY*** system should be polarised as shown in Fig. 9a. Where *Y* is a strong electron pair donor (eg nitrogen), and *X* a strongly electron attracting atom such as halogen, elimination might be expected yielding in the process a stabilised nitrenium ion. Work in these laboratories and elsewhere has established that nitrenium ions are strongly stabilised by neighbouring heteroatoms.[44-49] Such a process would be promoted by polar solvents, as well as acid or Lewis acid complexation with *X*. Thus unimolecular decomposition would be expected in strongly anomeric systems.

In S_N2 reactions, substituents at the central atom that can stabilise cationic character will also stabilise the S_N2 transition state, leading to longer bonds to both the nucleophile and the leaving group.[50-52] Thus, in systems with moderate anomeric overlap, this fact together with negative hyperconjugation and consequential weakening of the *N*—*X* bond, should promote S_N2 reactions at nitrogen leading to loss of X^- (Fig. 9b).

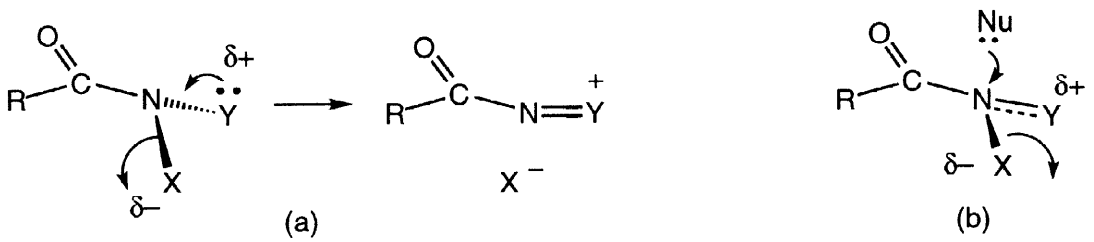
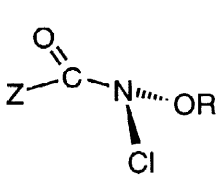


Fig. 9. (a) Anomerically induced elimination; (b) S_N2 reaction at nitrogen.

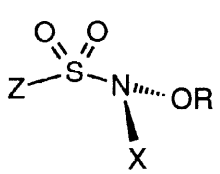
In this report, we will address the relative anomeric effects, theoretical and physical properties and reactivity of a number of different classes of bisheteroatom-substituted amides that we, and other groups have studied. Principal categories include *N*-alkoxy-*N*-haloamides (***ONX*** systems), *N,N*-dialkoxyamides (***ONO*** systems), *N*-acyloxy-*N*-alkoxyamides (***ONOAc*** systems), *N*-alkoxy-*N*-aminoamides (***NNO*** systems), *N*-amino-*N*-haloamides (***NNX*** systems) and *N,N*-dihaloamides (***XNX*** systems). In many cases, properties of known sulfonamide, phosphorylamide, urea and urethane analogues will also be discussed.

4. *N*-ALKOXY-*N*-HALOAMIDES

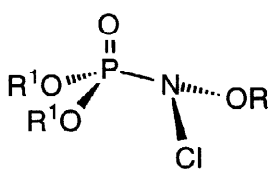
N-Alkoxy-*N*-chloroamides **1** constitute the main examples of this class of anomeric amides to have been reported in the literature.[44-49] Rudchenko and coworkers formed the analogous *N',N'*-dimethylureas **2** and urethanes **3**.[1,2,53] Sulfonamide **4**[2] and **5**[54] and phosphoramidate **6**[55] analogues are also known. Formation in all cases involved chlorination of a hydroxamic ester, usually with *tert*-butyl hypochlorite. Attempts at brominating and iodinating *N*-methoxybiphenyl-2-carboxamide with *tert*-butyl hypobromite and *tert*-butyl hypoiodite led to unstable products.[44]



1 Z=alkyl, aryl
2 Z=Me_2N
3 Z=RO



4 Z=Me_2N, X=Cl
5 Z=Ar, X=Br



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4.1 *Anomeric effect*

Anomeric effects in *ONCl* systems are n_O—σ^*_{NCl} even though oxygen is more electronegative than chlorine. Disparity in orbital size may play a role in two ways. *N* and *O* orbitals are of similar size, thereby facilitating overlap and, in addition, σ^*_{NCl} will be lower in energy than σ^*_{NO} since chlorine is a 3p element.

N—Cl σ* occupation leads to transfer of electron density to the *X* substituent and the substantially higher electron affinity of chlorine will favour this anomeric interaction rather than an n_{Cl}—σ^*_{NO} overlap.

4.2 *Theoretical properties*

Ab initio calculations at the Becke3LYP/6-31G(D) level support an n_O—σ^*_{NCl} interaction.[19] *Z* and *E* (with respect to the *CO—N* bond) ground state structures of *N*-chloro-*N*-methoxyformamide (Fig. 10a and 10b) differ in energy by only 2.5 kJmol^{-1} and possess strongly pyramidal nitrogens (average angles at nitrogen of <113.2°> and <112.0°> respectively). The *Cl—N—O—Me* dihedral angle in the lowest energy *Z* form (Fig. 10c) is almost 90° reflecting the optimum anomeric interaction between the p-type lone pair on oxygen and the *N—Cl* σ* orbital.

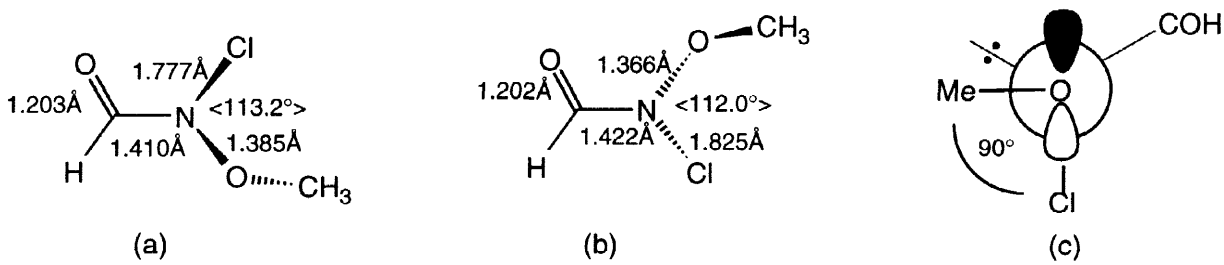


Fig. 10. (a) *Z*-form and (b) *E*-form of *N*-chloro-*N*-methoxyformamide; (c) Newman projection along the *O—N* bond in (a).

N—Cl bonds (1.777 and 1.825Å) are longer than that calculated for *N*-chloroformamide (1.735Å) while the *N—O* bond (1.385Å) is shorter than that calculated for *N*-methoxyformamide (1.405Å). The *C—N* bond (1.41Å) is significantly lengthened relative to formamide (1.362Å) and *N*-methoxy-*N*-formamide (1.38Å) reflecting a smaller degree of lone pair interaction with the carbonyl. The barrier to amide rotation has been calculated to be only 32 kJmol^{-1} but there is a considerable barrier to rotation about the *N—O* bond, a process that is complicated by inversion at nitrogen. The lowest rotation barrier corresponding to a rotamer in which chlorine and methyl are eclipsed has a barrier of 45 kJmol^{-1}. The barrier to inversion at nitrogen was calculated to be only 10.4 kJmol^{-1} and reflects stabilisation of the planar transition state by the carbonyl. Calculations on this and other anomeric amides at the density functional level indicated that, while non-planarity at nitrogen was confirmed, the role of anomeric effects in stabilising that geometry is rather small; inversion at nitrogen was usually accompanied by rotation about the *N—O* bond to optimise the anomeric overlap. However, while the anomeric interaction should be better at sp^3 as opposed to sp^2 nitrogen, stabilisation of the planar inversion transition state by conjugation with the carbonyl is the dominant factor affecting the inversion barrier.

4.3 *Physical Properties*

The extent to which lone pair delocalisation is reduced in *N*-alkoxy-*N*-chloroamides is reflected in the high infrared carbonyl absorption frequencies. Table 1 indicates that these are uniformly in a band 1720-1745 cm^{-1} and are on average about 40 wavenumbers higher than their hydroxamic ester precursors reflecting much higher double-bond character. As is the case for amides themselves, aryl amides are at the lower end of the range in keeping with conjugative effects while straight-chain amides are as high as 1740 cm^{-1}. While carbonyl stretch frequencies are strongly dependent upon solvent,[56] the infrared stretch frequency of *N*-chloroformamide in chloroform is at 1690 cm^{-1} [57] and those for *N*-chloroacetamide, *N*-chlorophenylacetamide and *N*-chlorobenzamide in chloroform are at 1709, 1699 and 1696 cm^{-1} respectively.[8,56,58] Simple aliphatic amides show two carbonyls corresponding to both the *E* and the *Z* isomers (*Z*-isomer favoured by steric effects) but the benzamides exist exclusively in the *Z*-form.[56,58] According to *ab initio* calculations at Becke3LYP/6-31G(D) level, formamide, *N*-methoxyformamide and *N*-chloroformamide are close to planar at nitrogen and observed rotation barriers as well as carbonyl stretch frequencies are rather similar.[19] The *E/Z* rotation barrier

for formamide has been calculated at 73 kJmol^{-1} which is in the region measured experimentally[59-61] while those for *N*-methoxyformamide and *N*-chloroformamide are 65 and 67–75 kJmol^{-1} respectively.[19]

It is clear that the presence of a single heteroatom at an amide nitrogen has a relatively small influence upon amide properties. However, bisheteroatom substitution results in significant changes to the amide configuration. It is likely that this reflects a critical combined electronegativity rather than the facilitation of anomeric effects alone. At total electronegativities below this critical value, stabilisation through conjugation of the p-type nitrogen lone pair is sufficient to sustain the planar or near-planar conformation at nitrogen. Substitution with a second heteroatom results in a shift of p-character from the lone pair to the *N—X* and *N—Y* σ-bonds thereby reducing resonance stabilisation. The electron demand of both heteroatoms is best accommodated if nitrogen assumes pure sp^3 or near sp^3 hybridisation. The infrared carbonyl absorption frequencies are consequently more "ester-like"; the dipolar form of the carbonyl is further destabilised by the negative inductive effect of the *XNY* group resulting in a greater *C—O* π-bond order than that found in simple ketones and aldehydes.

Table 1. Infrared Carbonyl Absorption Frequencies (cm^{-1}) for *N*-Alkoxy-*N*-chloroamides ($R^1ONClCOR^2$) and Precursor Hydroxamic Esters in Chloroform.

R^1	R^2	Amide	Ester	Source
$PhCH_2CH_2$	CH_3	1736	1685	62
$PhCH_2CH_2$	Et	1744	1693	63
$PhCH_2CH_2$	Bu	1739	1685	63
$PhCH_2CH_2$	Pr^i	1726	1685	63
$PhCH_2CH_2$	2-butyl	1730	1693	63
$PhCH_2CH_2$	3-pentyl	1731	1689	63
$PhCH_2CH_2$	Bu^t	1717	1686	63
p-$CH_3OC_6H_4(CH_2)_3$	C_6H_5	1722	1680	62
CH_3	*o*-$C_6H_4.C_6H_5$	1720	1675	44
CH_3	C_6H_5	1722	1683	64
CH_3	*p*-$CH_3OC_6H_4$	1719	1687	64
CH_3	*p*-ClC_6H_4	1727	1687	64
CH_3	*p*-$CH_3C_6H_4$	1723	1685	64
Bu	*p*-$C_6H_4.C_6H_5$	1718	1684	65
Bu	*p*-$Bu^tC_6H_4$	1724	1679	65
Bu	*o*-$NO_2C_6H_4$	1723	1693	62
Et	C_6H_5	1719	1679	65
n-Pr	C_6H_5	1720	1678	65
Pr^i	C_6H_5	1723	1684	65
Bu	C_6H_5	1719	1654	65
Bu^i	C_6H_5	1718	1684	65
Octyl	C_6H_5	1719	1684	65
p-$C_6H_5.C_6H_4CH_2$	C_6H_5	1720	1674	62
$C_6H_5CH_2$	C_6H_5	1718	1682	62
Bu	2-naphthyl	1722	1683	62
$C_6H_5CH_2$	—$(CH_2)_4$—	1728	1685	66
$C_6H_5CH_2$	—$(CH_2)_7$—	1728	1689	66
$C_6H_5CH_2$	—$(CH_2)_8$—	1735	1690	66
—$(CH_2)_6$—	C_6H_5	1726	1662	66
CH_3	Cyclohexyl	1718	-	6

We have studied the ^1H n.m.r. spectrum of *N*-chloro-*N*-benzyloxybenzamide at temperatures down to 173K in acetone-d_6 and toluene-d_8. In acetone the benzyl aromatic signal (δ7.85) separated into two signals (ratio 2:1) close to 200K corresponding to a free energy barrier of *ca* 42-46 kJmol^{-1}.[67] Since benzoyl resonances were largely unaffected, amide rotation is a faster process than *N—O* rotation. The benzyloxymethylene signal showed line broadening below 200K and appeared to become diastereotopic at 173K although this signal must consist of overlapping benzylic resonances, each corresponding to an anomerically stabilised conformation of the benzyloxy group (Fig. 11 (b)⇄(c)). In toluene-d_8, the benzyl aromatic signal separated into two at low temperature but the effect upon the benzylic methylene was dramatic. Below 217K, the benzylic singlet separated into two overlapping pairs of diastereotopic signals. At 190K, one of these was completely resolved into a clean AX spin system (Δν=119Hz, J_{AX} = 9.4Hz) and the exchange process is characterised by k_{217}=246s^{-1} and $\Delta G^{\ddagger}_{217}$ = 43 kJmol^{-1}. Topomerisation of the benzylic protons in each conformer (Fig. 11 (a)⇄(c) and (b)⇄(d)) must involve both inversion at nitrogen and rotation about the *O—N* bond and since barriers to the former process are small[19] the barrier best reflects that for rotation away from the anomeric conformation.

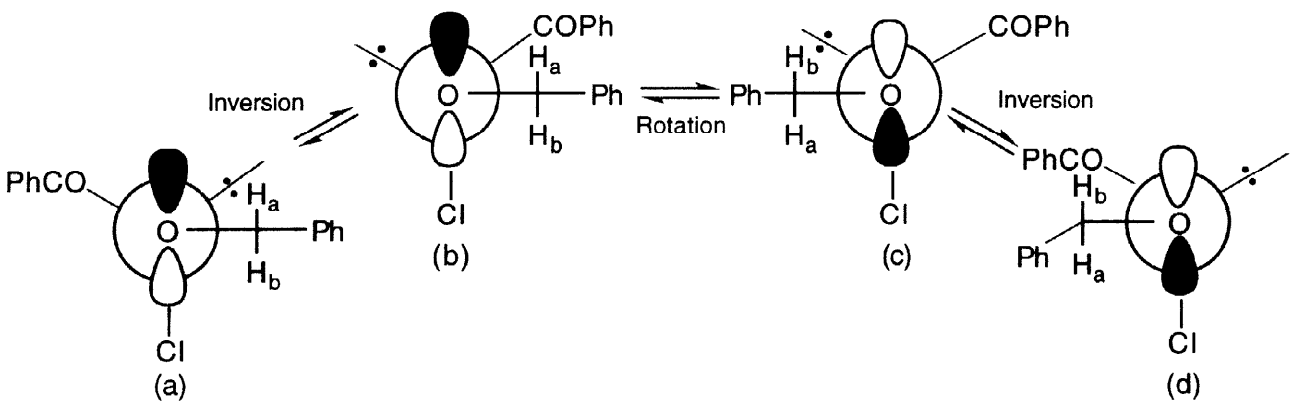
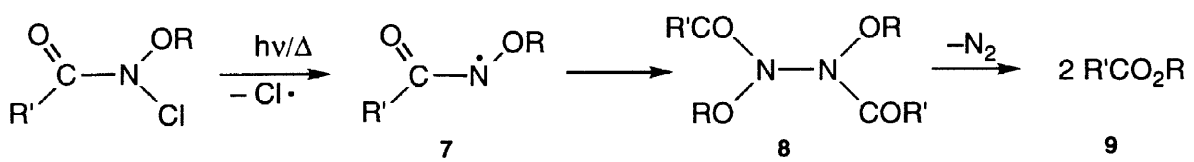


Fig. 11. Isomerisation and topomerisation in *N*-benzyloxy-*N*-chlorobenzamide.

4.4 *Reactivity*

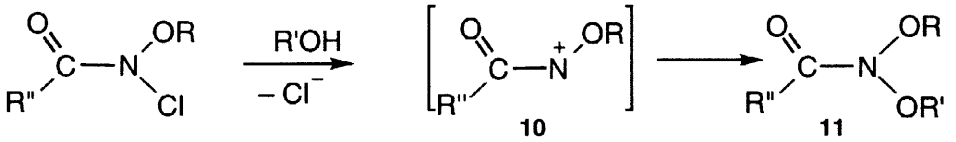
N-Alkoxy-*N*-haloamides, -halosulfonamides and -halophosphoramidates are photochemically and thermally unstable compounds. Under photolytic conditions, they have been found to be excellent sources of *N*-alkoxyamidyl radicals through homolysis of labile *N—X* bonds.[54,68,69] Unlike their parent amidyl radicals which are electrophilic in nature,[70-74] alkoxyamidyls **7** are strongly resonance stabilised leading to long lifetimes in solution and a propensity to dimerise to *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines **8**,[44,68,75] themselves a class of anomeric amides (see Section 7) (Scheme 1). Thermolysis of *N*-alkoxy-*N*-chloroamides almost always leads to the formation of the corresponding esters **9** through homolysis of the *N—Cl* bonds and intermediacy of the hydrazines **8**, which are known to rearrange to esters and nitrogen.[4-7]



Scheme 1.

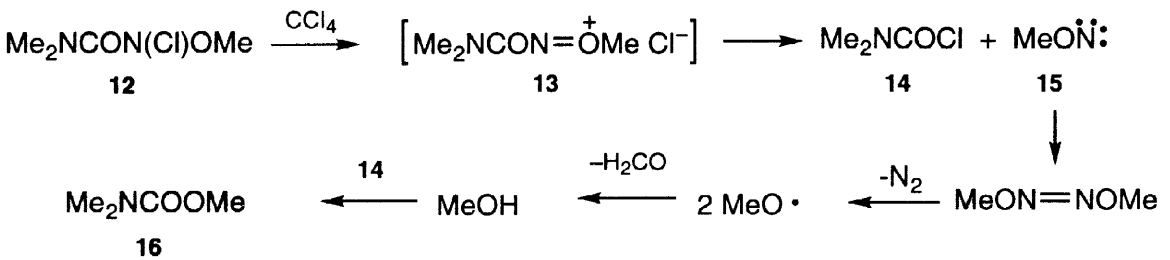
Heterolytic reactivity of *N*-alkoxy-*N*-chloroamides is influenced in a predictable fashion by the anomeric overlap n_O—σ^*_{NCl}. While this configuration at amide nitrogen is stable at room temperature in non-polar solvents, in polar media S_N1 type reactivity leading to the formation of *N*-alkoxynitrenium ion intermediates

10 is found. Thus in alcoholic or aqueous alcoholic medium, *N*-chloro-*N*-alkoxyamides undergo conversion to *N,N*-dialkoxyamides **11**[3,76] (Scheme 2) while *N*-chloro-*N*-alkoxyureas behave similarly.[2] Evidence for S_N1 solvolysis lies in the fact that in mixed aqueous/alcoholic solutions, the rates of solvolysis are linearly dependent upon the solvent polarity but otherwise independent of the alcohol concentration.[76] Both symmetrical and unsymmetrical dialkoxyamides can be synthesised, although we could not form *N*-alkoxy-*N*-*tert*-butoxy amides by this method.



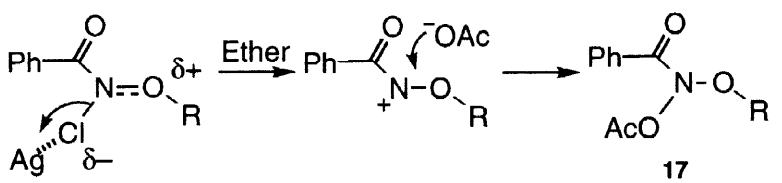
Scheme 2.

Rudchenko has found that upon prolonged standing in CCl_4, *N*-methoxy-*N*-chloro-*N',N'*-dimethylurea **12** forms the corresponding urethane **16** and has suggested initial unimolecular decomposition to alkoxynitrenium chloride **13** and methoxynitrene **15** since methanol and the acyl chloride **14** were formed as intermediates in the reaction mixture (Scheme 3).[2]



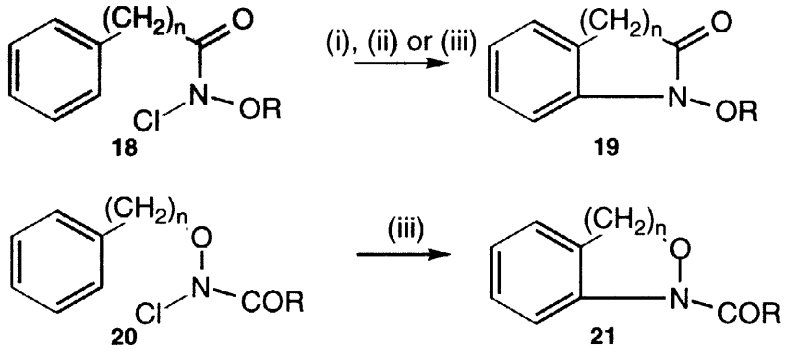
Scheme 3.

Alkoxynitrenium ion formation in hydroxylic and non-hydroxylic organic solvents has been effected by treating *N*-alkoxy-*N*-chloroamides with Lewis acids, typically silver and zinc ions.[44,45,47-49] Metal ion complexation of the chlorine can be visualised as a means of significantly lowering the energy of the σ^*_{NCl} orbital resulting in anomerically assisted elimination of metal chloride. If silver acetate is utilised, the alkoxynitrenium ion can be scavenged to yield *N*-acetoxy-*N*-alkoxybenzamides **17** (Scheme 4).[3]



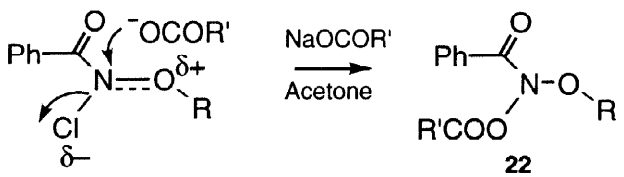
Scheme 4.

Alkoxynitrenium ions formed by this method have proven to be excellent electrophiles towards aromatic ring systems. Kikugawa and coworkers utilised silver carbonate/trifluoroacetic acid and zinc acetate/nitromethane in the synthesis of a variety of benzolactams (**19**, n=1,2,3) by cyclisation onto aryl rings on the acyl sidechain of **18**, while we have synthesised benzolactams in a similar fashion as well as novel *N*-acyl-1*H*-3,4-dihydro-2,1-benzoxazines (**21** n=2) and *N*-acyl-1,3,4,5-tetrahydrobenzoxazepines (**21**, n=3) by respective treatment of open chain *N*-chloro-*N*-(2-phenylethyloxy)- and *N*-chloro-*N*-(3-phenylpropyloxy)amides (**20**, n=2,3) with silver tetrafluoroborate in ether (Scheme 5).[44,45,47-49,63,77]



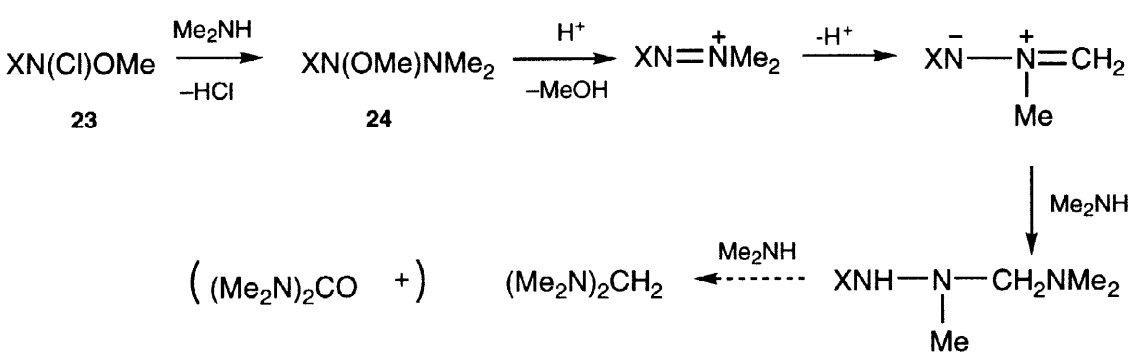
Scheme 5. (i) Ag_2CO_3/CF_3CO_2H; (ii) $Zn(OAc)_2/CH_3NO_2$; (iii) $AgBF_4/Et_2O$.

In addition to solvolysis and elimination reactions, *N*-alkoxy-*N*-chloroamides also undergo bimolecular reactions at nitrogen. Treatment with sodium carboxylates in anhydrous acetone affords *N*-acyloxy-*N*-alkoxyamides **22** by S_N2 displacement of chloride by carboxylate ions (Scheme 6). We have utilised this reaction and that in Scheme 4 in the synthesis of a wide variety of *N*-acetoxy- and *N*-benzoyloxy-*N*-alkoxybenzamides, -naphthamide and -alkylamides.[3,17,78,79] Results in these laboratories have shown that all such compounds are mutagenic[80] and, as a new class of anomeric amides, their properties and reactivities are described in Section 6.



Scheme 6. R'= alkyl, aryl.

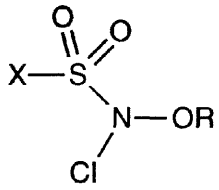
N-Alkoxy-*N*-chloroureas **23** have been reacted with nitrogen and oxygen nucleophiles resulting in S_N2 displacement of chloride. With amines, the products implicate an unstable *N*-alkoxy-*N*-amino intermediate **24** which, under the influence of hydrochloric acid formed in the reaction, decomposes to diaminomethane and other products (Scheme 7). Tetramethylurea is also a product although the exact mechanism of formation is unclear.[1] Reaction with alkoxides in alcohol affords the corresponding *N,N*-dialkoxyureas (Section 5).



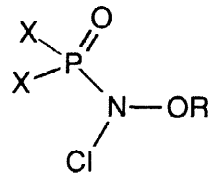
Scheme 7. X= Me_2NCO.

In contrast to *N*-alkoxy-*N*-chloroamides and ureas, the sulfonamide analogues **25** and **26**, as well as phosphorylamides **27** and **28** and urethanes **29**, exhibit quite different reactivities. *N*-Benzyloxy-*N*-chlorobenzenesulfonamide **30** is readily obtained by chlorination of the corresponding sulfonamide **33**.

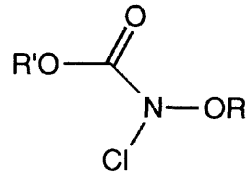
However, attempted replacement of chloride by acetate using sodium acetate in anhydrous acetone (S_N2 conditions) afforded, instead of *N*-acetoxy-*N*-alkoxysulfonamide, a mixture of chloroacetone **31**, hydroxamic ester **33** and the hydrazine dimer **34** (Scheme 8).



25 X=Ph
26 X=NMe_2, R=CH_2Ph

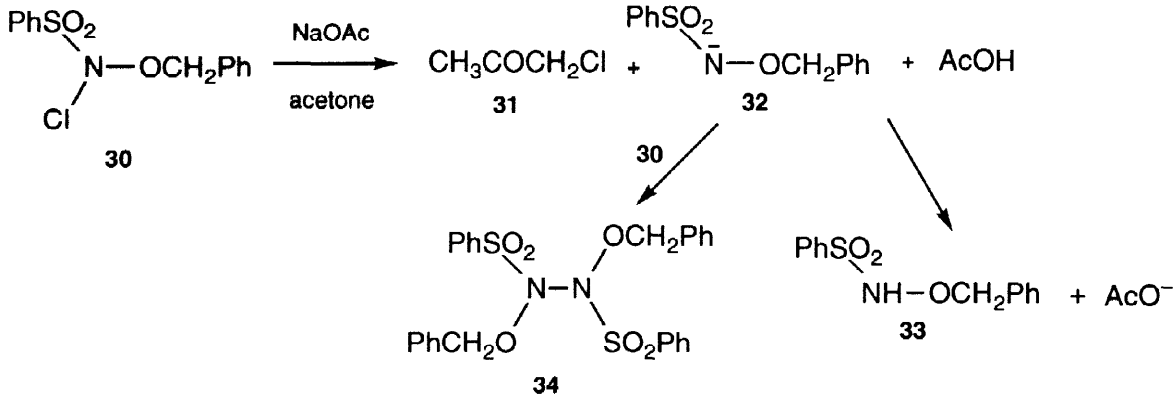


27 X=EtO, R=Me
28 X=NMe_2, R=Me, CH_2Ph



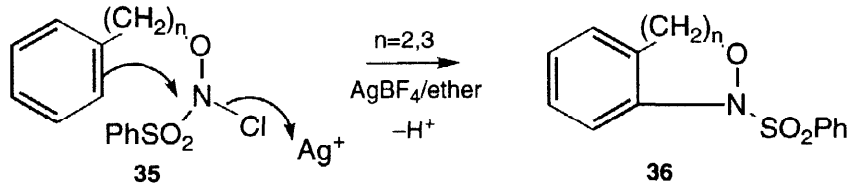
29

Under these conditions, **30** behaves as a positive chlorinating agent and this is an example where the polarity of the *N*—*Cl* bond is reversed due to the strongly electron-withdrawing effect of the sulfonyl group. Weaker anomeric overlap can be attributed to the lower *N* 2p character in the σ^*_{NCl} orbital. Interestingly, in acetone, the sulfonamide anion **32** is a weaker base but stronger nucleophile than acetate and initiates S_N2 displacement of chloride from starting material **30** to form hydrazine dimer **34**, rather than proton exchange with acetic acid giving hydroxamic ester **33**. Upon introduction of a *p*-methoxysubstituent on the benzenesulfonyl ring, only hydroxamic ester is formed indicating the reverse of the above properties.



Scheme 8.

Silver tetrafluoroborate cyclisation of *N*-chloro-*N*-(2-phenylethyloxy)- and *N*-chloro-*N*-(3-phenylpropyloxy)benzenesulfonamides (**35** , n=2,3) proceeds smoothly in ether giving the *N*-benzenesulfonyl-2,1-benzoxazine (**36** , n=2) and the *N*-benzenesulfonyl-2,1-benzoxazepine (**36** , n=3) (Scheme 9).[33,81] In spite of the electron-withdrawing ability of the sulfonyl group, complexation with silver ions results in reverse polarisation of the *N*—*Cl* bond. Although the corresponding benzamides produce the alkoxynitrenium ion intermediates, under these conditions it is likely that the cyclisation in these cases involves a concerted intramolecular S_N2 reaction.

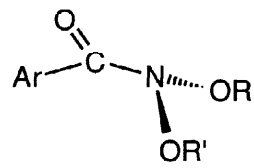


Scheme 9.

In the presence of triethylamine, *N*-benzyloxy-*N*-chlorosulfonamide **26** and *N*-chloro-*N*-methoxydialkylphosphoramidate **27** have also been found to behave as a chlorinating agent towards methanol while S_N2 displacement of Cl^- by sodium methoxide was not observed.[2] With **28**, S_N2 reaction at nitrogen was also disfavoured and with sodium methoxide, reaction at phosphorus rather than at nitrogen was observed. In contrast, the corresponding urethane **29** behaved more like amides in that they reacted with triethylamine in methanol to give hydrazines in a free radical coupling process (Scheme 1, R' = MeO).[53] Thus our results with sulfonamides and those of Rudchenko and coworkers have illustrated that the *N—Cl* polar properties can be altered significantly by the nature of the third nitrogen substituent.

5. *N,N*-DIALKOXYAMIDES

These largely unexplored species have been formed exclusively by alcoholysis of the corresponding *N*-alkoxy-*N*-chloro precursors. We first synthesised several symmetrical and mixed dialkoxyamides **37** by S_N1 solvolysis of *N*-alkoxy-*N*-chloroamides in aqueous/alcohol mixtures (Scheme 2)[3,76] while Rudchenko has made the analogous *N,N*-dialkoxy-*N',N'*-dimethylureas **38** from the S_N2 displacement of chloride with alkoxides in alcohol.[2]



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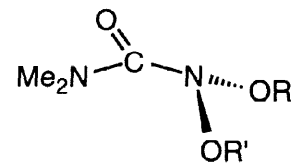


38

5.1 *Anomeric effect*

In these systems, the oxygen p-type lone pair can interact with a σ^*_{NO} orbital. Orbital overlap is optimal since both oxygen and nitrogen have similar sized p-orbitals but the higher σ^*_{NO} energy and smaller electron affinity of the alkoxy group results in a weaker anomeric interaction than is the case in *N*-alkoxy-*N*-chloroamides.

5.2 *Theoretical properties*

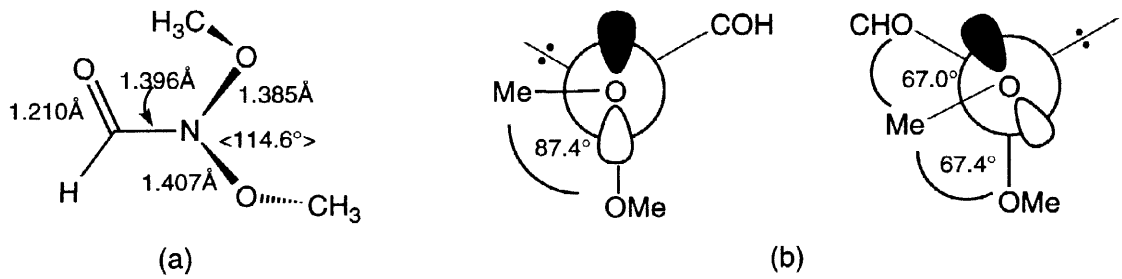


Fig. 12. (a) Lowest energy conformation of *N,N*-dimethoxyformamide; (b) Newman projections along the *N—O* bonds in (a).

Density functional *ab initio* calculations on *N,N*-dimethoxyformamide have identified several diastereomeric forms, the lowest in energy being that shown in Fig. 12a.[19] The geometry is characterised by a pyramidal nitrogen atom and one anomeric interaction in which the *N—O* bond to the methoxy group *anti* to the carbonyl is nearly orthogonal to the vicinal *N—O* bond (Fig. 12b). A mutual anomeric interaction is precluded on the basis of steric effects. The *N—CO* bond (1.396Å) is significantly lengthened relative to formamide (1.362Å) and *N*-methoxyformamide (1.38Å) and the average angle at nitrogen is <114.6°>. Reduced conjugation gives rise to an amide rotation barrier of around 29 $kJmol^{-1}$ although the process is

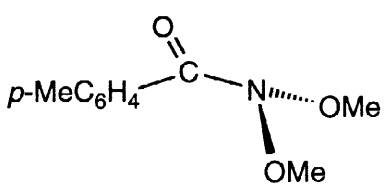
complicated by the inversion and *N—O* rotation processes which could increase the barrier up to about 42 kJmol^{-1}. The nitrogen inversion barrier is once again predicted to be only around 10 kJmol^{-1}. Rotation about the stabilising *N—O* σ bond was complicated by inversion processes but the barrier is expected to be below that for *N*-methoxy-*N*-chloroformamide.[19]

5.3 *Physical Properties*

No infrared data have been reported for *N,N*-dialkoxyureas however the infrared carbonyl stretch frequencies for a number of simple *N,N*-dialkoxyamides are presented in Table 2 and reflect an increase in absorption by betweeen 20 and 30 cm^{-1} relative to the hydroxamic esters from which they were derived. In confirmation of theoretical studies, *N—CO* double bond character is considerably less than in the hydroxamic esters although the carbonyl stretch frequencies are not as high as in the corresponding *N*-alkoxy-*N*-chloroamides. This may imply that the nitrogen lone pair in *N,N*-dialkoxyamides is more p-like although calculations suggest a similar degree of sp^3 hybridisation for both types of anomeric amides, ie the combined electronegativity of the two oxygen atoms is also greater than the critical value. The difference may lie in the extent to which the *ONO* group, as opposed to the *ONCl* group, destabilises the polar, single bond resonance form of the carbonyl.

Table 2. Infrared Carbonyl Absorption Frequencies (cm^{-1}) for *N,N*-Dialkoxyamides ($R^1ON(OR^2)COR^3$) and their Precursor Hydroxamic Esters in Chloroform.[64,82]

R^1	R^2	R^3	Amide	Ester
CH_3	CH_3	Ph	1711	1683
CH_3	CH_3	*p*-$CH_3C_6H_4$	1710	1685
CH_3	CH_3	*p*-$CH_3OC_6H_4$	1705	1687
CH_3	CH_3	*p*-ClC_6H_4	1712	1687
CH_3	Pr	Ph	1713	1678 (Pr)
CH_3	Pr^i	Ph	1714	1684 (Pr^i)
CH_3	Et	Ph	1712	1679 (Et)
Et	Et	Ph	1712	1679 (Et)
Et	Pr	Ph	1711	1678 (Pr)
Et	Pr^i	Ph	1715	1684 (Pr^i)
Bu	Bu	Ph	1710	1654



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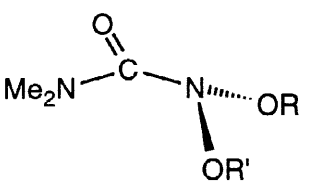

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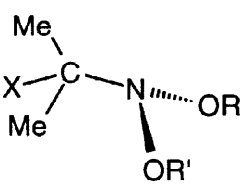


41

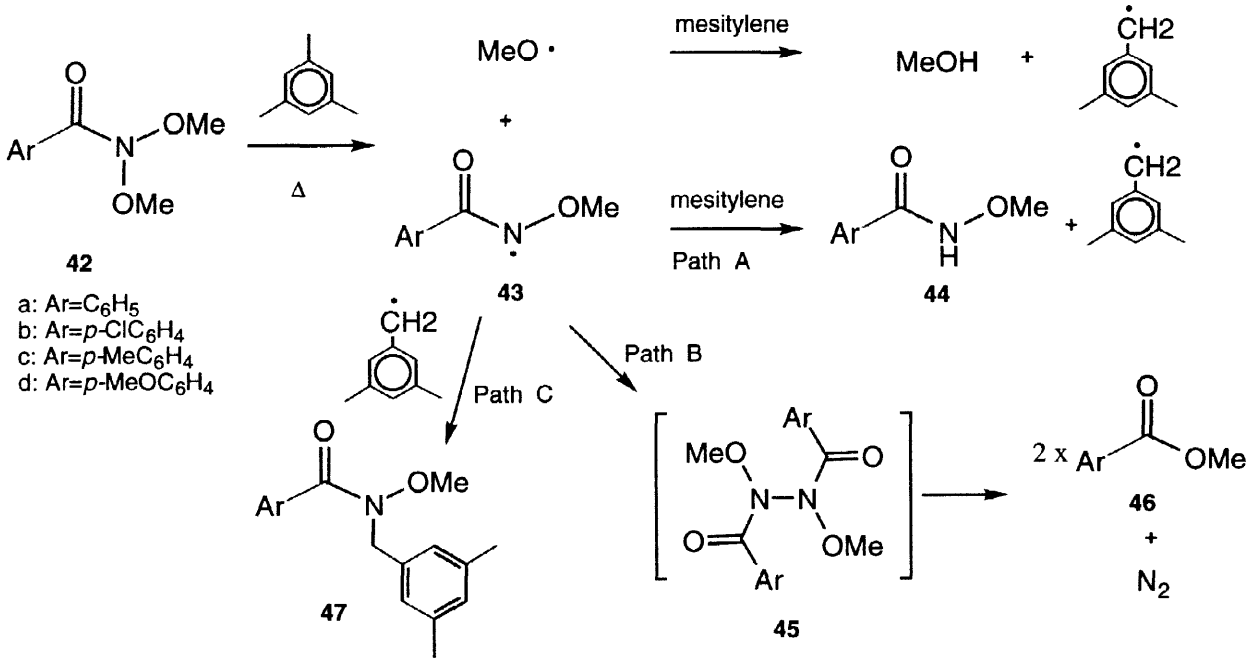
a: R=Bu^i, R'=CH_2CF_3
b: R=CH_2CHCH_2, R'=CF_3CH_2
c: R=PhCH(Me)NHCOCMe$_2$, R'=Et

Proton n.m.r. studies indicate that *N,N*-dimethoxy-*p*-toluamide **39** has a low amide rotation barrier. In the slow exchange region, this substrate should exhibit two methoxy singlets corresponding to the methoxy groups *syn* and *anti* to the carbonyl. However the methoxy methyl groups resonated together as a sharp singlet down to –90°C in methanol-d_4. In addition, the benzylic protons of *N*-methoxy-*N*-benzyloxybenzamide remain

isochronous down to the same temperature putting an upper limit of about 33 kJmol^{-1} on the barrier for any isomerisation process. The barriers to inversion ($\Delta G^{\ddagger}_{Tc}$) in some *N,N*-dialkoxy-*N'*,*N'*-dimethylureas (**40**a-c) have been measured in toluene-d_8 at between 42 and 54 kJmol^{-1} (T_c=243-298 K). These are much lower than those found under similar conditions for the configurationally stable acyclic dialkoxyamines **41** ($\Delta G^{\ddagger}_{Tc}$ = 84-92 kJmol^{-1}, T_c=293-298 K) and point to the significant role that an α-carbonyl group plays in stabilising the inversion transition state.[26] The fact that the ureas have a higher inversion barrier than that predicted for *N,N*-dialkoxyamides is in accord with the weaker electron demand of the dialkylaminocarbonyl substituent; in alkoxyureas, the amide rotation barrier for rotation about the *CO—NMe*$_2$ bond has been measured at 56-60 kJmol^{-1} indicating a significant degree of delocalisation of the adjacent nitrogen lone pair onto the carbonyl. Conjugative stabilisation of the planar transition state for inversion at the dialkoxyamine nitrogen should thus be reduced in ureas leading to higher inversion barriers than those in the dialkoxyamides where full delocalisation onto the carbonyl is possible in the nitrogen inversion transition state.

5.4 *Reactivity*

N,N-Dialkoxyamides are relatively stable at room temperature but upon prolonged standing they produce the corresponding carboxylic esters. At temperatures greater than 100°C in mesitylene, *N,N*-dimethoxy-*p*-substituted benzamides **42** undergo unimolecular decomposition giving esters **46**, *N*-mesityl-*N*-alkoxyamides **47** and the parent hydroxamic ester **44** (Scheme 10). Initial homolysis of an *N—O* bond results in formation of resonance-stabilised *N*-alkoxyamidyl radicals **43** which can abstract hydrogen (Path A) or combine with mesityl radicals formed by the abstraction by alkoxy radicals of hydrogen from solvent (Path C). The source of esters is presumably the anomeric *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines **45** formed by dimerisation of **43** (Path B) (see Section 7.4).[7,82] *N*-Alkoxyamidyls **43** are long-lived and are known to dimerise readily.[44,68,75] In the presence of the hydrogen donor, tri-*n*-butyltin hydride, **43** is trapped leading to exclusive formation of hydroxamic ester **44**. Homolytic, rather than heterolytic cleavage of *N—O* bonds is presumably a direct consequence of the low electron affinity of the alkoxy group which prevents anomerically assisted elimination of methoxide to give stabilised alkoxynitrenium ions. In these compounds σ^*_{NO} is also higher in energy than σ^*_{NCl} resulting in a weaker anomeric effect.



Scheme 10.

Table 3. Arrhenius Activation Energies, Entropies of Activation and Rate Constants at 373K for Radical Decomposition of *N,N*-Dimethoxy-*p*-substituted benzamides (**42** a-d).[64,82]

X	E_A/kJmol^{-1}	$\Delta S^{\ddagger}$/JK^{-1}mol^{-1}	$10^6 k_{373}$/s^{-1}
H	125.3±1.7	-23.3±4.1	0.69
Cl	126.5±7.6	-17.1±18.6	4.24
CH_3	132.5±1.5	-6.9±3.6	2.12
MeO	134.4±6.0	-1.2±14.6	2.24

Table 3 gives activation energies, entropies of activation and rate constants for thermal decomposition of *p*-chloro-, *p*-methyl-, *p*-methoxy- and unsubstituted *N,N*-dimethoxybenzamides. Interestingly the $\Delta S^{\ddagger}$ are rather small considering this is a homolytic process. Diacyl peroxides and dialkyl peroxides decompose with similar E_A but appreciably larger $\Delta S^{\ddagger}$ values.[83] While the anomeric effect is relatively weak in the reactant, upon homolysis, stretching of the *N—O* bond, and the reduced overlap, results in a rapid lowering of the σ^*_{NO} orbital and an enhanced anomeric overlap. This process leads ultimately to a two-centre three-electron π-bond in the alkoxyamidyl radical (Fig. 13). Significant π-overlap in the transition state imposes more constraints in the form of coplanarity of the *C(O)NOR* moiety which may account for the unusual entropies of activation.

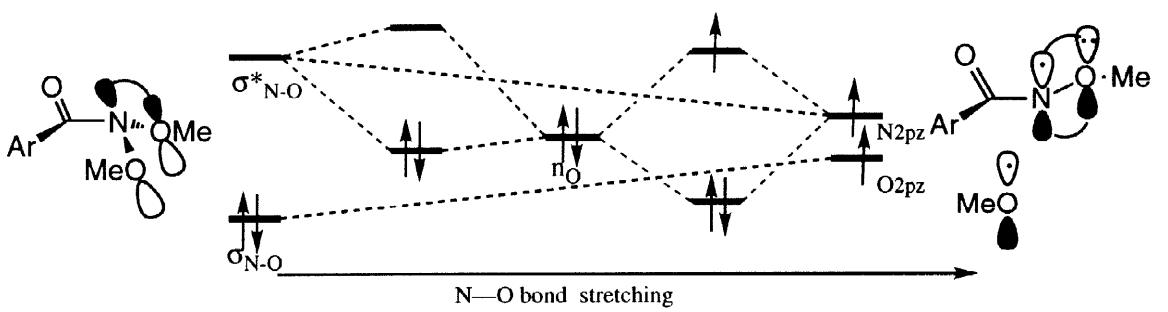
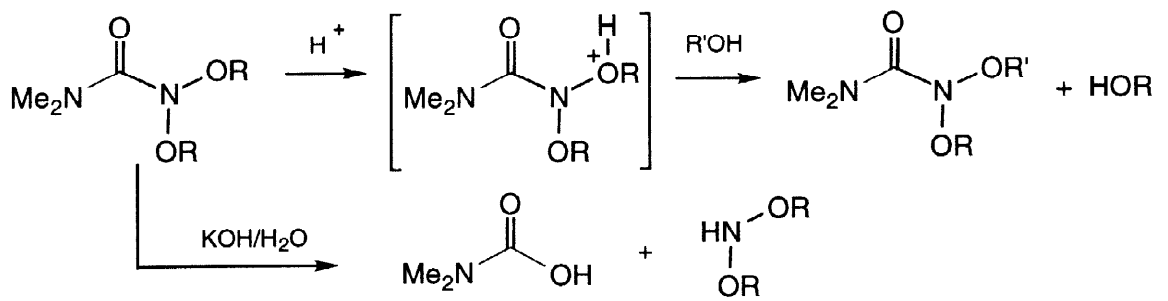


Fig. 13. Orbital interactions during *N—O* bond homolysis in *N,N*-dialkoxyamides.

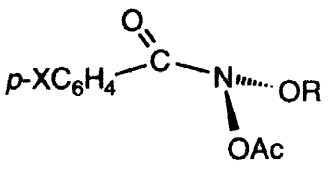
The reactions of *N,N*-dialkoxyamides with electrophiles or Lewis acids have not been investigated although Rudchenko has found that the analogous ureas undergo facile trans-esterification in acidic media (ROH/TsOH or ROH/H$^+$).[26] In this manner mixed and cyclic *N,N*-dialkoxyureas can be synthesised (Scheme 11). Under these conditions, anomerically driven elimination leading to alkoxy nitrenium ions is likely since electrophilic complexation of an oxygen would significantly lower the σ^*_{NO} orbital. In keeping with the poor leaving capacity of alkoxide, solvolysis in aqueous KOH leads to hydrolysis of the amide instead of to S_N2 displacement at nitrogen. This reaction is an excellent source of hitherto little known *N,N*-dialkoxyamines.[84]



Scheme 11.

6. *N*-ACYLOXY-*N*-ALKOXYAMIDES

N-Acetoxy-*N*-alkoxybenzamides **48** were first synthesised in 1989 by treatment of *N*-alkoxy-*N*-chloroamides with silver acetate in ether (Scheme 4) and more recently we have utilised S_N2 substitution at nitrogen using sodium salts of acids in anhydrous acetone (Scheme 6).[3,78,80] Both *N*-acetoxy- and *N*-benzoyloxyamides **48** - **50**, can be synthesised by this method.



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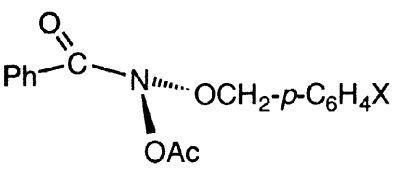

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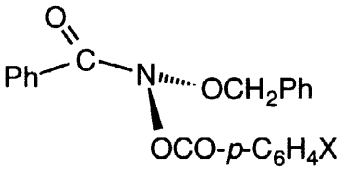
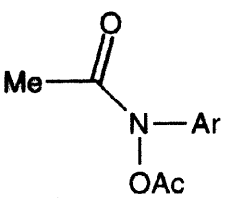


50

These *ONO* anomeric amides are analogues of the metabolites of aromatic amines, the *N*-acetoxy-*N*-arylacetamides **51** which, under solvolytic conditions, are known sources of resonance-stabilised *N*-acetyl-*N*-arylnitrenium ions **52**.[85-98] *N*-Alkoxy-*N*-acylnitrenium ions **53** and *N*-aryl-*N*-acylnitrenium ions **52** have similar stability and ease of formation[46] and we predicted that the title compounds would also be mutagenic. Initial investigations in these laboratories showed that simple *N*-acetoxy-*N*-ethoxy-, -*N*-butoxy-, -*N*-benzyloxy- and -*N*-octyloxybenzamides were indeed mutagenic toward *Salmonella* strains TA100 and TA98, both with and without metabolic activation. Since then we have synthesised some 40 such variants including both *N*-acetoxy- and *N*-benzoyloxy-*N*-alkoxyamides and all 35 of those tested to date are direct acting mutagens. In recent studies we have concentrated on the chemical reactivity of these substances with a view to uncovering their mechanism of mutagenesis.[3,17,18,78-80]



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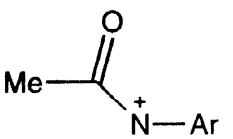

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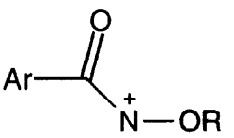

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6.1 *Anomeric effect*

Relative to *N,N*-dialkoxyamides, *N*-acetoxy-*N*-alkoxybenzamides are likely to exhibit a stronger anomeric effect. The σ^*_{NOAc} orbital would be lower in energy than σ^*_{NOR} resulting in a better n_O—σ^*_{NOAc} than n_O—σ^*_{NOR} interaction. This is manifested in their theoretical and physical properties and chemical reactivity. They undergo homolytic decomposition to give *N*-alkoxyamidyl radicals, S_N2 substitution at nitrogen with nucleophiles and acid-catalysed S_N1-type reactions leading to formation of alkoxynitrenium ions.

6.2 *Theoretical properties*

Both AM1 calculations on *N*-acetoxy-*N*-methoxybenzamide[17] and *ab initio* 6-31G* calculations on *N*-acetoxy-*N*-methoxyformamide[99] predict a strongly pyramidal nitrogen. The conformation in which the amide carbonyl and the acetoxy group are *syn* and both methyl and acetoxy acyl groups are *exo* to the nitrogen pyramid is lowest in energy (Fig. 14a). The average angle at nitrogen was 109.7° while the *CH*$_3$—*O*—*N*—*OAc* dihedral angle was 91.5° at the 6-31G* level (Fig. 14b). The *N*—*CO* (1.408Å) and amide *CO* (1.178Å) bond lengths are longer and shorter than those found in *N*-methoxyformamide (1.373Å and 1.188Å) and *N*-acetoxyformamide (1.385Å and 1.184Å) at 6-31G* reflecting decreased amide resonance. Anomeric overlap also results in a shorter methoxy *O*—*N* bond than that found for methoxyformamide (1.374Å). A comparison of bond lengths for *N*-acetoxy-*N*-methoxyformamide (Fig. 14) with those for *N,N*-dimethoxyformamide (Fig. 12) also indicates reduced amide resonance for the *N*-acetoxy species. Barriers to inversion at nitrogen and

rotation about the amide and anomeric bonds were not calculated. However, the amide rotational barrier is likely to be smaller in these substrates relative to the dialkoxyamides in light of the lower degree of amide resonance. As was the case in *N,N*-dimethoxyformamide, rotation about the *N—OMe* bonds should also be a complex process involving nitrogen inversion, although the barrier is most probably between that found for *N,N*-dimethoxyformamide and strongly anomeric *N*-methoxy-*N*-chloroformamide.[19]

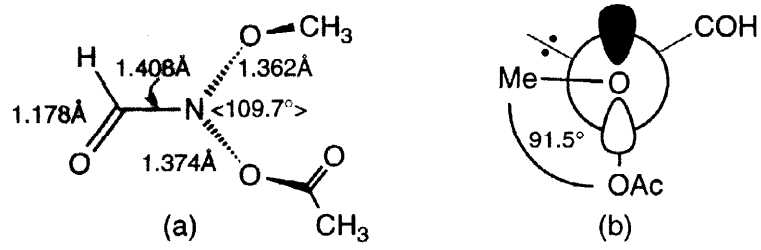


Fig. 14. (a) 6-31G* optimised geometry for *N*-acetoxy-*N*-methoxyformamide; (b) Newman projection along *MeO—N* bond.

6.3 *Physical Properties*

Infrared data have been obtained for all mutagens synthesised to date. All are characterised by two high frequency carbonyl absorptions corresponding to the stretch mode of the ester and amide carbonyls. Values in Table 4 indicate that for all *N*-acetoxy-*N*-alkoxybenzamides, the amide carbonyls were on average 43 cm^{-1} higher than the carbonyl stretch frequencies of precursor hydroxamic esters. The degree of sp^3 hybridisation at nitrogen thus resembles that of *N*-alkoxy-*N*-chloroamides. The only aliphatic substrate we have made, absorbs a further 14 cm^{-1} higher and reflects enhanced π-bond character brought about by loss of partial π-overlap with an adjacent phenyl ring. With the exception of *N*-(*p*-methoxybenzoyloxy)-*N*-benzyloxybenzamide, the amide carbonyls of the *N*-benzoyloxy series absorb even higher (55 cm^{-1}) relative to the hydroxamic esters reflecting the greater stability of benzoate relative to acetate; stronger electron-withdrawing effects result in even greater pyramidalisation at nitrogen and consequent loss of amide resonance. Interestingly, the *N*-(*p*-methoxybenzoyloxy)-*N*-benzyloxybenzamide has much lower amide and ester carbonyl absorptions which can be ascribed to destabilisation of electron transfer to benzoate by the positively mesomeric *p*-methoxy substituent. Pyramidalisation of nitrogen is therefore reduced resulting in more lone pair delocalisation onto the amide carbonyl. Infrared carbonyl stretch frequencies are clearly a sensitive monitor of electronic demand at the amide nitrogen, the properties of which are strongly dictated by the gross electron-withdrawing ability of nitrogen substituents.

Table 4. Infrared Carbonyl Absorption Frequencies (cm^{-1}) for *N*-Acetoxy-*N*-alkoxyamides ($R^1ON(OCOR^2)COR^3$) and Precursor Hydroxamic Esters in Chloroform.

R^1	R^2	R^3	Amide	Ester	Hydroxamic ester	Source
Bu	CH_3	*p*-$C_6H_4.C_6H_5$	1721	1794	1684	17
Bu	CH_3	*p*-BrC_6H_4	1731	1791	1696	17
Bu	CH_3	*p*-ClC_6H_4	1728	1792	1695	17
Bu	CH_3	*p*-$CH_3C_6H_4$	1730	1790	1695	17
Bu	CH_3	*p*-$NO_2C_6H_4$	1730	1790	1695	17
Bu	CH_3	*p*-$CH_3OC_6H_4$	1728	1790	1692	17
Bu	CH_3	*p*-$Bu^tC_6H_4$	1721	1794	1679	17
Bu	CH_3	*m*-$NO_2C_6H_4$	1727	1794	1693	62
Et	CH_3	C_6H_5	1724	1789	1679	17
n-Pr	CH_3	C_6H_5	1724	1789	1678	17

Table 4 (continued)

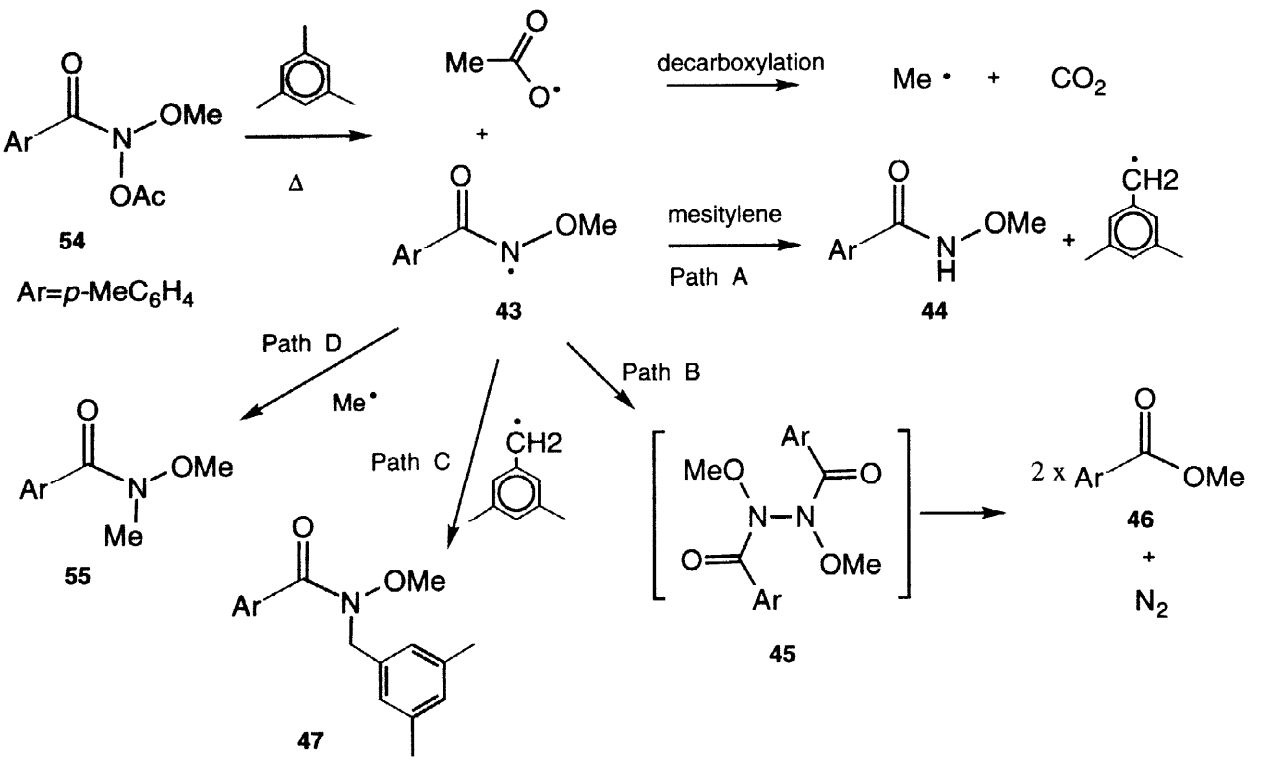
R^1	R^2	R^3	Amide	Ester	Hydroxamic ester	Source
Pr^i	CH_3	C_6H_5	1724	1788	1684	17
Bu	CH_3	C_6H_5	1732	1795	1654	3
Bu^i	CH_3	C_6H_5	1724	1790	1684	17
Octyl	CH_3	C_6H_5	1728	1798	1684	3,65
$C_6H_5CH_2$	CH_3	C_6H_5	1728	1798	1678	3
p-$BrC_6H_4CH_2$	CH_3	C_6H_5	1731	1791	1680	17
p-$ClC_6H_4CH_2$	CH_3	C_6H_5	1731	1793	1687	17
p-$NO_2C_6H_4CH_2$	CH_3	C_6H_5	1732	1793	1691	17
p-$C_6H_5.C_6H_4CH_2$	CH_3	C_6H_5	1729	1791	1674	17
p-$Bu^tC_6H_4CH_2$	CH_3	C_6H_5	1725	1790	1685	17
p-$CH_3C_6H_4CH_2$	CH_3	C_6H_5	1729	1791	1681	17
p-$PhOC_6H_4CH_2$	CH_3	C_6H_5	1725	1795	1690	17
p-$CH_3OC_6H_4CH_2$	CH_3	C_6H_5	1725	1795	1684	17
Bu	CH_3	2-naphthyl	1724	1793	1683	62
$C_6H_5CH_2$	CH_3	—$(CH_2)_7$—	1742	1794	1689	66
$C_6H_5CH_2$	CH_3	—$(CH_2)_8$—	1741	1791	1690	66
$C_6H_5CH_2$	C_6H_5	C_6H_5	1731	1758	1678	80
$C_6H_5CH_2$	p-ClC_6H_4	C_6H_5	1734	1759	1678	80
$C_6H_5CH_2$	p-$CHOC_6H_4$	C_6H_5	1735	1761/1707	1678	80
$C_6H_5CH_2$	p-$CF_3C_6H_4$	C_6H_5	1734	1765	1678	80
$C_6H_5CH_2$	p-$CH_3C_6H_4$	C_6H_5	1733	1756	1678	80
$C_6H_5CH_2$	p-$CH_3OC_6H_4$	C_6H_5	1718	1750	1678	80
$C_6H_5CH_2$	p-CNC_6H_4	C_6H_5	1732	1763	1678	80
$C_6H_5CH_2$	$pNO_2C_6H_4$	C_6H_5	1733	1764	1678	80

In stark contrast to parent hydroxamic esters which usually exhibit line broadened alkoxy group resonances in their ^1H n.m.r. spectra, at or even significantly above room temperature, [42,43] in $CDCl_3$ the alkoxy and acetoxy protons in *N*-acetoxy-*N*-alkoxybenzamides give rise to sharp signals well below room temperature. In toluene-d_8, the benzylic and acetoxy methyl resonances of *N*-acetoxy-*N*-benzyloxybenzamide showed significant line broadening below 250K but remained isochronous down to 190K.[67] These results clearly indicate that barriers to isomerisation processes are at least less than about 35 kJmol^{-1}. Like *N*-alkoxy-*N*-chloroamides, the nitrogen inversion barrier is expected to be small and the amide and anomeric rotation barriers are predicted to be only moderate. It is clear that anomeric overlap is weaker than that observed in the corresponding *N*-chloro compound in which diastereotopic benzylic protons were anisochronous at low temperature, but stronger than in *N*-benzyloxy-*N*-methoxybenzamide where no significant line broadening was observed at the same temperatures.

6.4 *Reactivity*

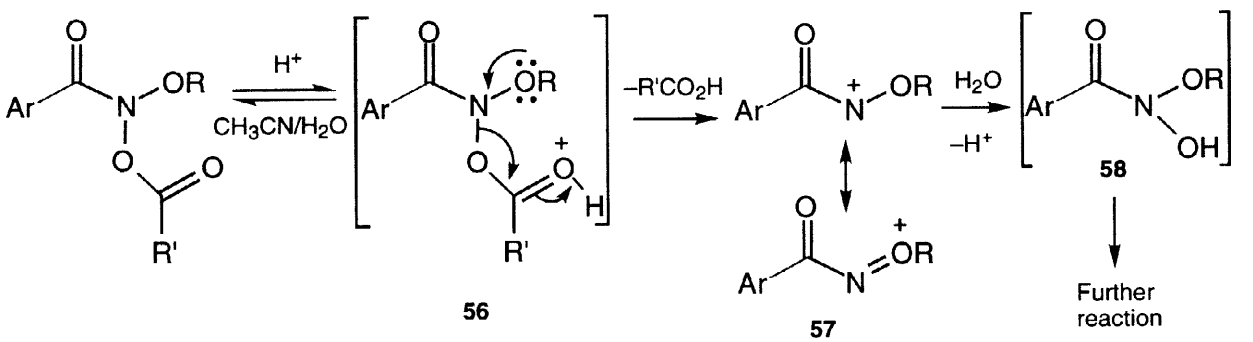
Most *N*-acyloxy-*N*-alkoxyamides are relatively stable at room temperature. They can be stored under refrigeration in an inert atmosphere for extended periods. At higher temperatures in mesitylene, *N*-acetoxy-*N*-methoxy-*p*-toluamide **54** undergoes radical homolysis of the *N*—*OAc* bond. The products included methyl *p*-toluate **46**, methyl *N*-mesityl-*p*-toluohydroxamate **47**, methyl *N*-methyl-*p*-toluohydroxamate **55** and the parent hydroxamic ester **44** (Pathways A-D, Scheme 12). These products are in keeping with a homolysis step followed by decarboxylation. Like the radical reactions of *N,N*-dialkoxyamides, esters are formed from

hydrazines **45** (see Section 7.4), the products of dimerisation of *N*-methoxy-*p*-toluamidyl radicals **43** (Pathway B). As outlined above for *N,N*-dimethoxybenzamides, homolysis here may also be regarded as an anomerically driven process. In non-polar solvents, this reaction occurs even though the formation of a resonance-stabilised nitrenium ion and acetate by heterolysis would seem to be plausible; while formation of alkoxide by such a process involving the *N,N*-dialkoxyamides is unfavourable, acetate formation would be much more likely.



Scheme 12.

In aqueous/organic medium, heterolytic processes are favoured due to stabilisation of charge separation in the transition state. *N*-Acyloxy-*N*-alkoxybenzamides react extremely slowly at room temperature, but undergo $A_{Al}1$ acid-catalysed solvolysis in acidic aqueous acetonitrile (Scheme 13).[3,17,78-80] This process involves a rapid, reversible protonation of the ester carbonyl followed by rate determining cleavage of the *N—OAc* bond in **56** resulting in the formation of a resonance-stabilised alkoxynitrenium ion **57**. Anomerically driven elimination of acetic acid is a consequence of the lowering in σ^*_{NOAc} orbital upon protonation of the ester group. Alkoxynitrenium ion formation was confirmed by solvent isotope effects, steric effects, Arrhenius activation data and Hammett reaction constants.



Scheme 13.

Rate data and activation parameters for the three series **48**, **49** and **50** are presented in Tables 5-7. Acid-catalysed solvolysis in all three substrates was characterised by positive $\Delta S^{\ddagger}$ values. Notably, the presence of the bulky *N*-isopropoxy group (**48**, R=Pr^{i}, X=H) results in a rate constant for solvolysis at 308 K *ca.* one order greater than benzamide mutagens bearing a straight-chain alkoxy substituent and, according to $\Delta S^{\ddagger}$ values, is characterised by a much looser transition state. Relief of steric compression in the transition state (sp^2 nitrogen) relative to the ground-state (sp^3 nitrogen) is in accord with the tetrahedral geometry at nitrogen as predicted by AM1 and 6-31G* calculations and confirmed by the high carbonyl stretch frequencies.

Table 5. Arrhenius Activation Energies, Entropies of Activation and Rate Constants at 308K for Acid-catalysed Solvolysis of *N*-Acetoxy-*N*-alkoxybenzamides **48**.[17,a]

48		E_A/	$\Delta S^{\ddagger}$/	$10^2 k_H^{308}$/
R	X	kJmol^{-1}	JK^{-1}mol^{-1}	Lmol^{-1}s^{-1} [b]
Et	H	114.6 (1.2)	91.5 (1.0)	3.72
Bu	H	116.9 (2.9)	96.1(9.1)	2.60
Pr^{i}	H	119.9 (5.3)	127.0 (5.6)	33.50
Bu^{i}	H	115.8 (0.8)	89.9 (0.7)	1.92
Bu	MeO	113.0(3.4)	104.7(10.7)	33.86
Bu	Bu^{t}	121.6(3.2)	117.2(10.2)	5.34
Bu	Me	120.0(0.7)	112.7(2.2)	5.88
Bu	Ph	123.3(2.8)	120.6(8.8)	3.90
Bu	Cl	110.8(6.3)	71.4(19.7)	1.45
Bu	Br	113.2(1.7)	79.0(5.2)	1.46
Bu	NO_2	95.3(2.1)	6.6(6.5)	0.25

[a] CD_3CN:D_2O, 3.8:1

[b] From Arrhenius data at 308K

Table 6. Arrhenius Activation Energies, Entropies of Activation and Rate Constants at 308K for Acid-catalysed Solvolysis of *N*-Acetoxy-*N*-(*p*-substituted benzyloxy)benzamides **49**.[17,a]

49	E_A/	$\Delta S^{\ddagger}$/	$10^2 k_H^{308}$/
X	kJmol^{-1}	JK^{-1}mol^{-1}	Lmol^{-1}s^{-1} [b]
H	128.0(3.5)	121.0(11.0)	0.50
MeO	118.8(6.9)	116.7(21.7)	14.87
PhO	106.6(7.2)	64.3(23.3)	3.16
Bu^{t}	122.5(2.5)	111.1(7.8)	1.82
Me	130.4(1.9)	138.0(5.9)	2.06
Ph	122.2(2.1)	104.2(6.5)	0.88
Cl	122.5(3.3)	95.0(10.5)	0.27
Br	117.9(1.2)	79.4(3.7)	0.24
NO_2	107.3(2.9)	33.0(9.1)	0.06

[a] CD_3CN:D_2O, 3.8:1

[b] From Arrhenius data at 308K

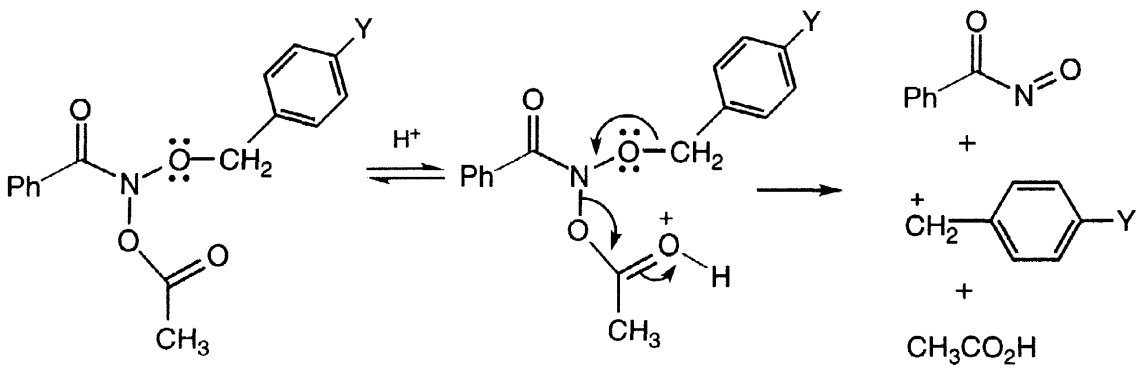
Table 7. Arrhenius Activation Energies, Entropies of Activation and Rate Constants at 308K for Acid-catalysed Solvolysis of *N*-(*p*-Substituted benzoyloxy)-*N*-benzyloxybenzamides **50**.[80,a]

50 X	E_A/ kJmol^{-1}	$\Delta S^{\ddagger}$/ JK^{-1}mol^{-1}	$10^2 k_H^{308}$/ Lmol^{-1}s^{-1}[b]
MeO	119.6 (3.5)	89.2 (11.1)	0.40
Me	118.2 (3.0)	83.9 (10.0)	0.37
H	115.1 (1.6)	74.7 (4.8)	0.41
Cl	113.4 (2.2)	69.8 (7.0)	0.42
CHO	113.2 (3.5)	71.4 (10.8)	0.58
CF_3	115.4 (3.3)	80.2 (10.0)	0.69
CN	105.6 (3.3)	47.4 (10.8)	0.63
NO_2	106.9 (4.4)	54.4 (14.1)	0.86

[a] CD_3CN:D_2O, 3.8:1

[b] From Arrhenius data at 308K

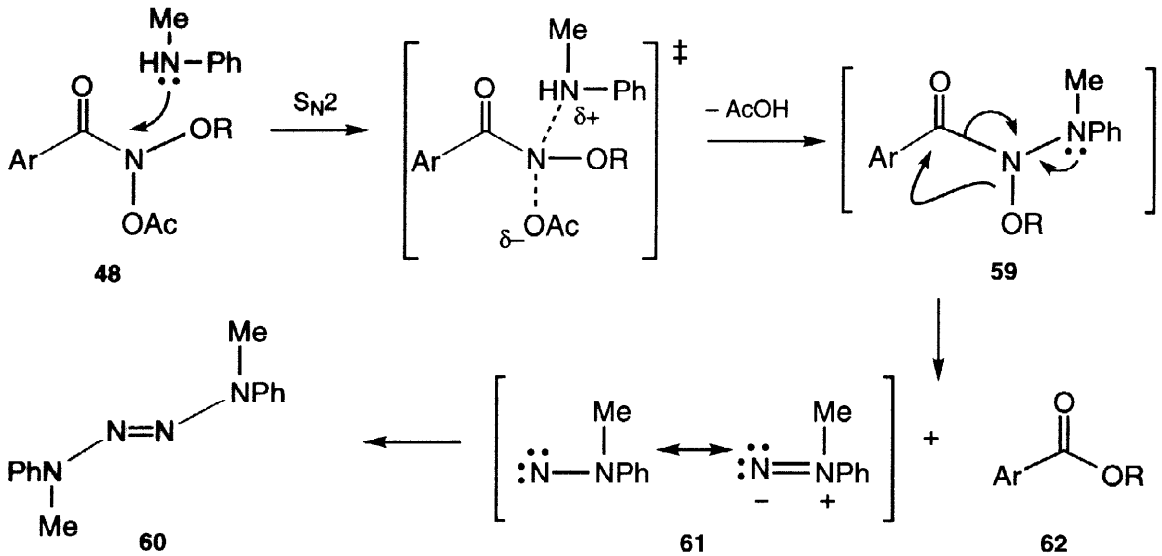
Data for acid-catalysed solvolysis of *p*-substituted *N*-acetoxy-*N*-butoxybenzamides (**48**, R=Bu) correlate with Hammett σ^+ with $\rho = -1.59$ in keeping with developing nitrenium ion character in the transition state.[17] Substituents diminishing the polar separation at the carbonyl carbon facilitate development of positive charge on the adjacent nitrogen. Evidence for oxonium character (which may be viewed as a consequence of enhanced anomeric overlap in the transition state) was found in a study of rates of acid-catalysed solvolysis of *N*-acetoxy-*N*-(*p*-substituted benzyloxy)benzamides **49**. With all but +*M* substituents, a negative Hammett σ correlation ($\rho = -1.61$) was measured and inductive stabilisation of the partial oxonium ion by electron-donor groups facilitated decomposition. With +*M* substituents, however, anomeric overlap in the transition state led to direct heterolysis to give stabilised benzyl cations and rate data correlated with Hammett σ^+ with a $\rho = -2.04$ (Scheme 14).[78] Substituent effects in *N*-(*p*-substituted benzoyloxy)-*N*-benzyloxybenzamides **50** led to a weakly positive Hammett σ correlation ($\rho = +0.3$) due to opposing electronic effects upon the pre-equilibrium protonation and heterolysis steps.[78,80]



Scheme 14. Y=Ph, OPh, MeO.

Products from all three series of reactions can be ascribed to intermediacy of anomeric *N*-alkoxy-*N*-hydroxybenzamides **58** (Scheme 13), formed by attack of solvent on the alkoxynitrenium ions. To date these intermediates have not been isolated or detected *in situ* due to their instability in an acidic aqueous/organic medium.[17,78,80]

N-Acyloxy-*N*-alkoxybenzamides are also susceptible to S_N2 reactions at nitrogen. Series **48** undergo bimolecular reactions with *N*-methylaniline in methanol and in aqueous acetonitrile.[18] The products of these reactions are esters **62** and the tetrazene **60** which are formed from unstable intermediate *N*-alkoxy-*N*-methylanilinobenzamides **59** in what is now called the HERON (**HE**teroatom **R**earrangement **O**n **N**itrogen) reaction. The 1,1-diazene **61** is also an intermediate in the reaction (Scheme 15).



Scheme 15.

N-Methylanilino-*N*-alkoxybenzamides **59** are themselves anomeric and their properties as well as the dynamics of the HERON reaction are dealt with in Section 7. Rate constants and activation parameters for the reaction of methylaniline with the benzoyl series (**48**, R=Bu) appear in Table 8. $\Delta S^{\ddagger}$ is significantly negative for all reactions while rate constants correlate with Hammett σ constants and $\rho = +0.24$. Greater electron deficiency at nitrogen with electron-withdrawing substituents leads to a marginal promotion of the substitution process. Rate constants for reaction of *N*-methylaniline with the benzoyloxy series **50** at 308K (Table 9) correlated with Hammett σ values with $\rho = +1.8$ in keeping with partial benzoate character in the transition state.[100]

Table 8. Arrhenius Activation Energies, Entropies of Activation and Rate Constants at 308K for the Bimolecular Reactions of *N*-Methylaniline and *N*-Acetoxy-*N*-butoxy-*p*-substituted benzamides(**48**, R=Bu).[18,100,a]

48 X	E_A/ kJmol^{-1}	$\Delta S^{\ddagger}$/ JK^{-1}mol^{-1}	$10^4 k_2^{308}$/ Lmol^{-1}s^{-1} [b]
H	52.83	-105.4	581.3
Br	61.31	-77.4	609.2
Cl	37.88	-100.6	678.5
NO_2	45.77	-126.7	703.7
Me	43.93	-142.3	222.4
OMe	48.51	-121.0	481.5
Bu^t	54.74	-99.1	585.4
Ph	47.21	-124.0	559.3

[a] Methanol-d_4

[b] From Arrhenius data at 308K

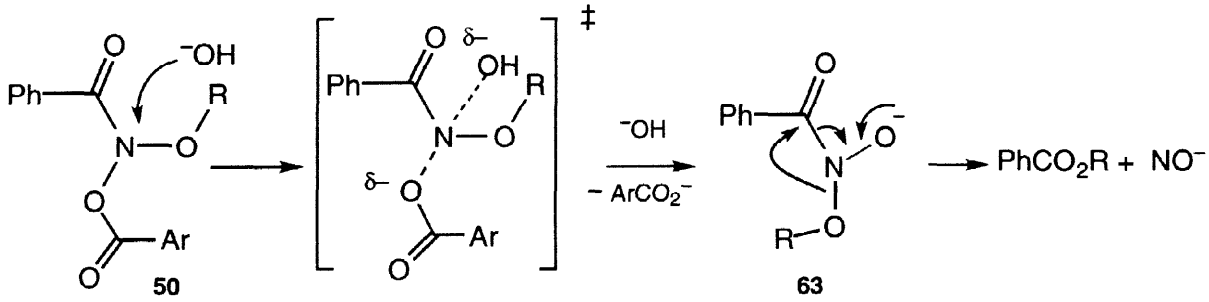
Table 9. Arrhenius Activation Energies, Entropies of Activation and Rate Constants at 308K for the Bimolecular Reaction of *N*-Methylaniline and *N*-(*p*-Substituted benzoyloxy)-*N*-benzyloxybenzamides **50**.[100,a]

50 X	E_A/ kJmol^{-1}	$\Delta S^{\ddagger}$/ JK^{-1}mol^{-1}	$10^4 k_2^{308}$/ Lmol^{-1}s^{-1}[b]
H	46.72	-131.9	260.8
Cl	56.43	-90.2	881.2
Me	26.68	-204.1	109.8
OMe	48.73	-134.4	87.7
Bu^t	64.43	-77.6	177.0

[a] Methanol-d_4

[b] From Arrhenius data at 308K

Recently the reactions of *N*-acetoxy-*N*-butoxybenzamide (**48**, X=H, R=Bu) as well as the benzoyloxy series, **50**, with sodium hydroxide have also been investigated. Under pseudo-unimolecular conditions they react to form the corresponding esters in excellent yields (Scheme 16). Esters have been shown to be formed intramolecularly since a crossover experiment between *N*-acetoxy-*N*-butoxybenzamide and *N*-acetoxy-*N*-ethoxy-*p*-toluamide afforded only butyl benzoate and ethyl *p*-toluate. The rate constants for reaction of **50** at 276K correlate with Hammett σ values with ρ = 0.55, a value that is consistent with hydroxide attack at nitrogen through the less common $B_{Al}2$ process rather than reaction through the normal $B_{Ac}2$ process of ester hydrolysis.[101] Rate constants for base-induced solvolysis of benzoate esters are much more sensitive to substituent effects and correlate with Hammett σ values with ρ = 2.0-2.4.[102] The product of hydroxide attack at nitrogen is the hydroxamic acid which in the conjugate anionic form **63** would be strongly anomeric. The excellent n_{O^-}—σ^*_{NOR} overlap that results from the high energy anionic p-electrons initiates an *N* to *C* migration of the alkoxy group in a HERON reaction to give esters (Section 7.4) and presumably NO$^-$.[80,103,104]



Scheme 16.

6.5 *Biological Activity*

The mechanism of mutagenesis and carcinogenesis of *N*-acetoxy-*N*-arylamides has been the subject of extensive studies in recent years. They can form adducts with DNA nucleotides (principally guanine) through either an S_N1 or an S_N2 processes.[85-98] *N*-Arylnitrenium ions are relatively stable in aqueous solution owing to conjugation into the adjacent aromatic ring system and Laser Flash Photolysis studies have shown that the extreme mutagenicity of 4-biphenylamine and 2-aminofluorene metabolites is most probably owing to very long nitrenium ion lifetimes due to steric hindrance to solvolysis of the delocalised charge.[95-98] We have also shown that *N*-acyloxy-*N*-alkoxybenzamides react at *N*-7 of guanine[105] and both the S_N1 and the S_N2 reaction processes are possible although the former would appear to proceed at appreciable rates only under acidic

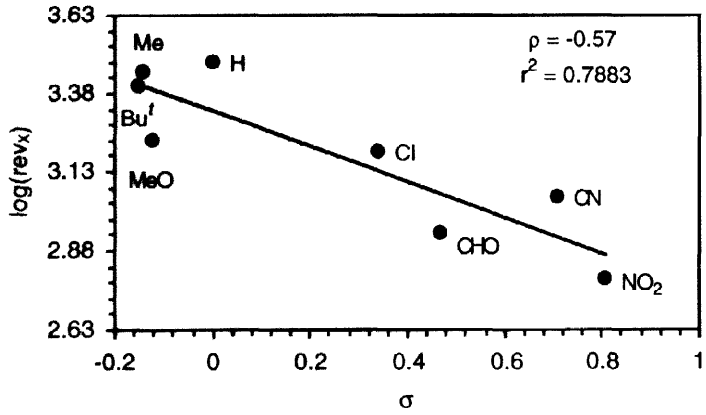
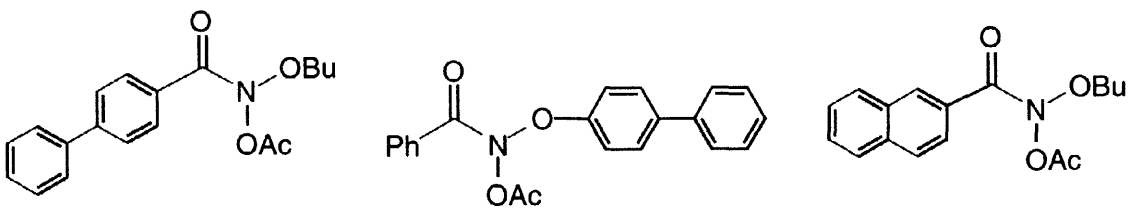


Fig. 15. Hammett correlation for Ames mutagenicities of *N*-benzoyloxy-*N*-benzyloxybenzamides **50** in *Salmonella* TA100. Rev_X are the induced revertants at 1μmol/plate.

conditions or in the presence of a Lewis acid. Ames mutagenicity data for all three series have now been obtained and in the case of the benzoyl **48** and benzyloxy **49** series, there is no obvious correlation between reactivity and mutagenicity. In the case of the benzoyloxy series **50** however, Ames mutagenicities towards TA100 at 1μmol/plate appear to correlate with Hammett σ values but with negative slope (ρ = –0.57, Fig. 15). Since both ease of S_N1 and S_N2 reactivity correlate with σ but with positive slope, mutagenicity appears to be inversely correlated with reactivity, that is, correlates with stability in this series. Low reactivity would reduce the consumption of mutagen through adventitious side-reactions in the Ames assay.

There also appears to be a correlation between the hydrophobicity and activity:

- Mutagenicities generally increase with increasing aromatic substitution, ie along the series **48<49<50**;[80]
- Mutagenicities of biphenyl containing substrates **64** and **65** are significantly elevated relative to the parent (**48**, X=H, R=Bu) and (**49**, X=H);[17,78]
- The *N*-acetoxy-*N*-butoxy-2-naphthamide **66** is more than one order more mutagenic than the benzamide analogue (**48**, X=H, R=Bu).[106]

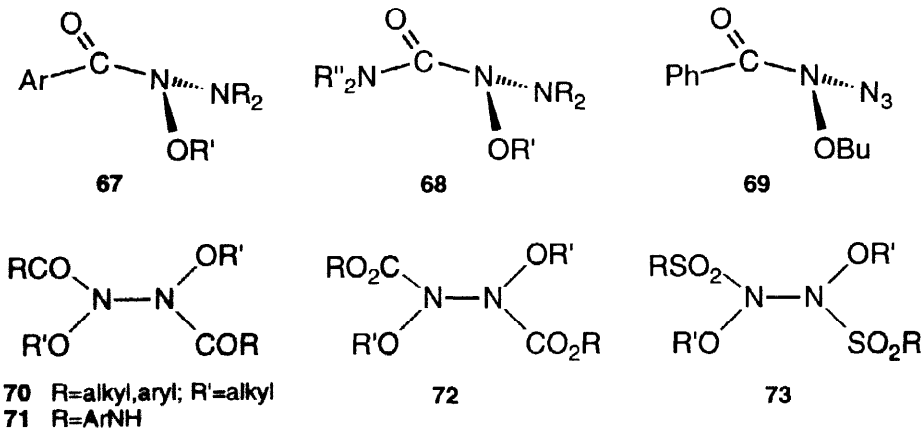


64 **65** **66**

Thus Ames mutagenicities of *N*-acetoxy-*N*-alkoxybenzamides might be elevated in those substrates with lowest chemical reactivity and which can bind hydrophobically or intercalate with DNA. While a probable binding site on DNA has been identified through DNA damage studies, the exact mode of binding has not yet been determined although anomeric weakening of the *N—OAc* bond is likely to facilitate substitution at nitrogen.

7. *N*-ALKOXY-*N*-AMINOAMIDES

Simple *N*-amino-*N*-alkoxyamides **67** are a class of anomeric amides we first encountered in the reaction of *N*-acetoxy-*N*-alkoxybenzamides with aromatic amines (Scheme 15). The products from the reaction of *N*-methylaniline with *N*-acetoxy-*N*-butoxybenzamides, *N*-methylanilino-*N*-alkoxybenzamides **59** are unstable and rearrange to 1-methyl-1-phenyldiazene **61** and benzoate esters **62**.[18] *N*-Alkoxy-*N*-chloro-*N'*,*N'*-dialkylureas also react with dialkylamines but the product *N*-dialkylamino-*N*-alkoxyureas **68** are unstable under the acidic reaction conditions.[1] *N*,*N'*-Diacyl-*N*,*N'*-dialkoxyhydrazines **70** are a class of thermally labile hydrazines that can be formed by dimerisation of alkoxyamidyl radicals formed either through oxidation of the parent hydroxamic esters[4,6,75,107] or through photolysis of *N*-halo-*N*-alkoxyamides.[68] They constitute anomeric amides in which the donor amino group is substituted with both an alkoxy and an acyl group. Sulfonamide analogues of **70**, **73**, are also known[33,75,108,109] as are *N*,*N'*-dicarboalkoxy-*N*,*N'*-dialkoxyhydrazines **72**.[53,110] A urea derivative **71** has also been reported.[111] We have recently found that *N*-azido-*N*-butoxybenzamide **69** is an unstable intermediate in the reaction of *N*-acetoxy-*N*-butoxybenzamide with sodium azide in aqueous/organic medium. **69** decomposes spontaneously to butyl benzoate and nitrogen.[62]



7.1 *Anomeric effect*

In the *NNO* systems, anomeric overlap is facilitated by both the electronegativity of oxygen, the similarity in sizes of orbitals and, most importantly, the high energy lone pair on nitrogen. In the context of anomeric interactions, second to the negative charge in anionic heteroatoms, the nitrogen lone pair is the highest in energy along the second row and should interact strongly with σ^*_{NO} orbitals in these systems. In hydrazines (**70–73**), mutual effects are possible but the n_N lone pair should be lower in energy as a consequence of both oxygen and carbonyl substitution. Azidoalkoxyamides **69** represent an interesting case. Anomeric overlap could be n_N—σ^*_{NO}, however while one resonance form (Fig. 16, II) generates anionic nitrogen adjacent to the amide nitrogen, the strongly electron-withdrawing effect of the quaternary ammonium centre in form I (Fig. 16) could both reduce the donor capacity of this nitrogen as well as result in a reverse n_O—σ^*_{NN} anomeric effect through a lowering of the *C(O)N*—*N* σ^* orbital energy.

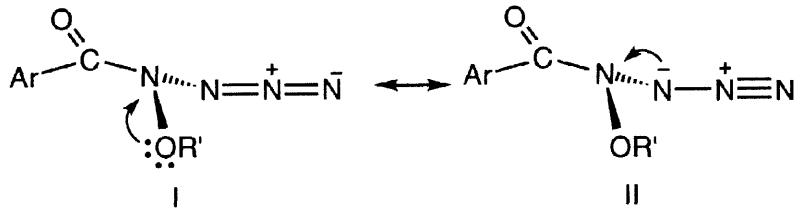


Fig. 16. Anomeric effects in *N*-azido-*N*-alkoxyamides.

7.2 Theoretical properties

Both AM1[104] and recent *ab initio* [112] calculations on models for **67** predict ground state geometries in which the lone pair on the amino nitrogen is collinear or nearly collinear with the adjacent *N—OR* bond (Fig. 17). The ground state configuration of *N*-dimethylamino-*N*-methoxyformamide at the Becke 3LYP/6-31G(D) level is shown in Fig. 17a and has the oxygen atoms *cis*. The amide nitrogen is pyramidal with an average angle at nitrogen of <116°> and *C—N—N—O* dihedral angles of 74.2 and 54.7°. The anomeric effect is clearly n_N—σ^*_{NO} (Fig. 17b) since the π-type lone pair on the methoxy oxygen subtends an angle of 40° relative to the *N—N* bond (Fig. 17c). The *N–O* (1.426Å) and *N–C* (1.387Å) bonds are both longer than those of the unsubstituted hydroxamic ester (1.40Å and 1.38Å respectively).

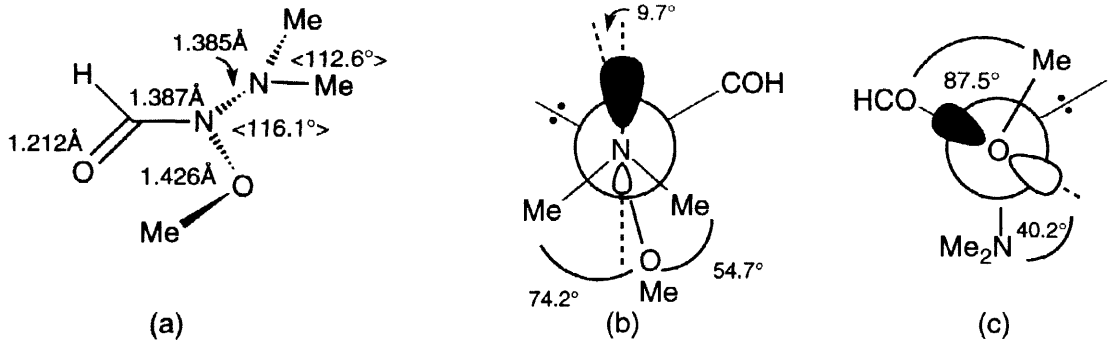


Fig. 17. (a) Becke3LYP/6-31G(D) optimised geometry for *N*-dimethylamino-*N*-methoxyformamide; (b) Newman projection along the *N—N* bond; (c) Newman projection along the *O—N* bond.

The amide nitrogen inversion barrier was essentially zero while the lowest amide rotation barrier and the barrier to rotation about the *N—N* bond were calculated to be 53 and 58 kJmol^{-1} respectively. Thus rotation about the *N—N* bond is most likely to be the slowest conformational change although both should be observable in low temperature NMR studies. The AM1 ground state geometry of *N*-dimethylamino-*N*-methoxyacetamide is similar to that of the formamide at the *ab intio* level[104] and the ground state geometries of a range of *N*-substituted amino-*N*-methoxyacetamides indicate that there is a uniform degree of coplanarity of the amino lone pair, n_N, and the σ^*_{NO} bond (Table 10, Fig. 19). The greatest deviation was found for those substrates with strongly electron-withdrawing substituents at the amino nitrogen and which therefore results in a weaker anomeric overlap.

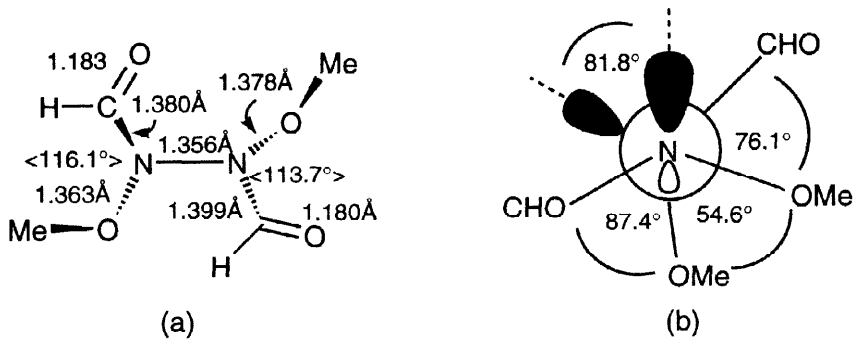


Fig. 18. (a) 6-31G* optimised geometry of *N,N'*-dimethoxy-*N,N'*-diformylhydrazine; (b) Newman projection along the *N—N* bond.

The 6-31G* optimised geometry of the lowest energy conformer of *N,N'*-diformyl-*N,N'*-dimethoxyhydrazine (**70**, R=H, R'=Me) is unsymmetrical (Fig.18a).[99] Nitrogens are pyramidal although one is

significantly shallower than the other (<116.1°> vs <113.7°>) and the lone pairs are gauche (Fig. 18b). Bipyramidal hydrazines bearing electronegative substituents, *X*, are known to prefer a gauche conformation in which maximum n_N —σ^*_{NX} overlap is possible.[113] In addition the lone pair-lone pair trans gauche rotamer is destabilised by lobal electron repulsion.[114] The gauche conformation of *N,N'*-diformyl-*N,N'*-dimethoxyhydrazine results in a mutual anomeric interaction leading to an *N—N* bond length of 1.356Å, significantly shorter than that calculated for *N*-dimethylamino-*N*-methoxyformamide (1.385Å). The *O—N* bond lengths of 1.378Å and 1.363Å reflect weaker individual anomeric effects although the disparity in bond lengths, as well as the different degrees of non-planarity at nitrogen, clearly indicate a stronger anomeric interaction in one direction. The amide *N—CO* bond to the more pyramidal nitrogen is accordingly nearly 0.02Å longer than that to the more planar (donor) nitrogen.

Table 10. The Effect of Amine Substituents, R', on the Ground-state Geometries and $\Delta H_{reaction}$ and $\Delta H_{activation}$ for the HERON Reaction of *N*-methoxy-*N*-(substituted amino)acetamides.[104,a]

R'	x/ degrees[b]	y/ degrees[b]	z/ degrees[c]	$\Delta H_{reaction}$/ kJmol^{-1}[d]	$\Delta H_{activation}$/ kJmol^{-1}
p-aminophenyl	108.0	119.7	5.8	-104	+133
phenyl	109.0	118.0	4.5	-102	+138
p-chlorophenyl	109.5	118.2	4.3	-99	+142
p-nitrophenyl	110.7	116.5	2.9	-91	+151
benzyl	96.3	120.0	11.8	-118	+104
methyl	47.0	81.0	17.0	-80	+161
acetyl, methoxy	63.4	65.4	1.0	-75	+174
acetyl	106.0	80.0	-13.0	-71	+205
succinyl (cyclic)	79.4	108.9	14.8	-37	+193
chloromethyl	26.6	116.7	45.1	-64	+182
dichloromethyl	40.0	106.2	33.1	-56	+198
trifluoromethyl	33.7	99.0	32.7	-79	+209
trichloromethyl	53.7	93.5	19.9	-81	+223
amino	66.7	64.9	-0.9	-28	+204

[a] All values were calculated for the gas phase using the AM1 Hamiltonian of MOPAC.
[b] *R'—N—N—O* dihedral angles.
[c] z=[0.5(x+y)-x] = deviation of lone pair from the *N—N—OMe* plane (see Fig. 19)

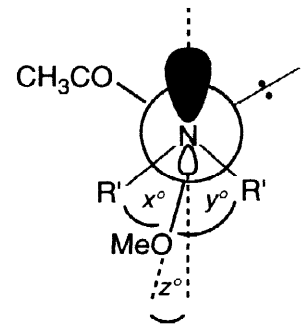


Fig. 19. Newman projection along the *N–N* bond in *N*-substituted amino-*N*-methoxyacetamides

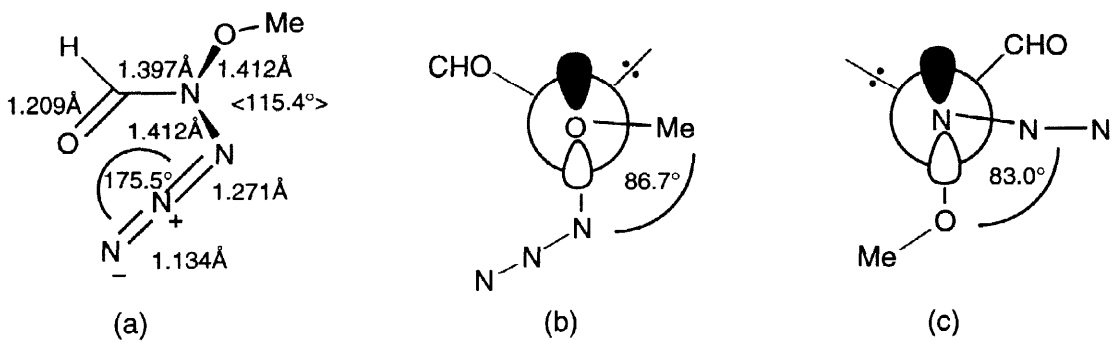


Fig. 20 (a) Becke3LYP/6—31G(D) optimised geometry for *N*-azido-*N*-methoxyformamide; (b) Newman projection along the *O—N* bond; (c) Newman projection along the *N—NC(O)* bond.

Recent *ab initio* calculations on *N*-azido-*N*-methoxyformamide (Fig. 20a) indicate that in the ground state geometry nitrogen is pyramidal (<115.4°>) and there is an anomeric overlap of the π-type lone pair on oxygen and the *N*—*N* σ* orbital (Fig. 20b).[112] The terminal *N*—*N* bond is extremely short (1.134Å) while the azido nitrogen to amide nitrogen bond is relatively long (1.412Å). The *N*–*O* bond (1.412Å) and *N*–*C(O)* bond (1.397Å) are both longer than those found in methoxyformamide (1.405 and 1.380Å respectively) at the same level of theory. This, together with the orientation of the azido group, would appear to indicate a reverse anomeric overlap between a π-type lone pair on the azide nitrogen attached to the amide and the *N*—*O* σ* orbital (Fig. 20c).

7.3 *Physical properties*

To date the only stable *N*-amino-*N*-alkoxyamides that are known are *N*,*N*'-diacyl-*N*,*N*'-dialkoxyhydrazines in which the donor amino substituent is also bonded to an acyl and an alkoxy group, or their disulfonyl and dicarboalkoxy analogues. Table 11 lists the infrared carbonyl stretch frequencies for symmetrical *N*,*N*'-diacyl-*N*,*N*'-dialkoxyhydrazines that we and others have synthesised. Where both sets of data have been reported, the amide carbonyl stretch frequencies are significantly higher than the precursor hydroxamic esters. In the benzyloxy series (last five entries) two carbonyl absorptions are present but these appear to be degenerate in the benzamide series. 6-31G* calculations of the normal modes of vibration for the model *N*,*N*'-diformyl-*N*,*N*'-dimethoxyhydrazine predict, after scaling by a factor of 0.8737,[115,116] two distinct carbonyl frequencies at 1765 and 1781 cm^{-1} corresponding to stretch modes associated with different carbonyls. The lower stretch frequency corresponds to the carbonyl attached to the (donor) more planar nitrogen which can conjugate better with its adjacent *CO* double bond. Infrared spectroscopy therefore supports the unsymmetrical nature of these hydrazines.

Table 11. Infrared Carbonyl Absorption Frequencies (cm^{-1}) for *N*,*N*'-diacyl-*N*,*N*'-dialkoxyhydrazines ($R^2CON(OR^1)N(OR^1)COR^2$) and Precursor Hydroxamic Esters and Hydrazine *N*—*N* rotation Barriers.[a]

R^1	R^2	Amide	Ester	T_c/K	$\Delta G^{\ddagger}_{Tc}$/kJmol^{-1}	Source
CH_3	Ph	1718 (neat)	-			6
Bu^t	Ph	1685 (KBr)	-			6
Bu^t	1-adamantyl	1708 (neat)	1644 (neat)			6
CH_3	Bu^t	1684(neat)	-			6
CH_3	$PhCH_2CH_2$	1725 (neat)	1685 ($CHCl_3$)			6
$PhCH_2$	$PhCH_2CH_2$	1724 (neat)	-			6
CH_3	Cyclohexyl	1711 (KBr)	-			6
Et	*p*-$CH_3OC_6H_4$	1700	1681			117
Et	*p*-$CH_3C_6H_4$	1701	1682	318	66.1($CDCl_3$)	117
Et	C_6H_5	1708	1685	319	66.1($CDCl_3$)	117
Et	*p*-ClC_6H_4	1711	1680	316	65.7($CDCl_3$)	117
Et	*p*-$NO_2C_6H_5$	1722	1692			117
p-$CH_3OC_6H_4CH_2$	CH_3	1733/1707	1693	338	71.6(toluene-d_8)	117
p-$CH_3C_6H_4$ CH_2	CH_3	1734/1700	1693			117
$PhCH_2$	CH_3	1735/1711	1682	336	69.9(toluene-d_8)	117
p-ClC_6H_4 CH_2	CH_3	1738/1715	1693	342	72.4(toluene-d_8)	117
p-$NO_2C_6H_5CH_2$	CH_3	1744/1723	1700	346	72.8(toluene-d_8)	117

[a] Chloroform unless otherwise stated.

N.m.r. data are known for a number of *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines. At room temperature, all ethoxy (**70**, R=Ar,R'=Et) and benzyloxy substrates (**70**, R=Me,R'=OCH_2Ar) displayed a single AB spin system for oxymethylenic protons which are clearly diastereotopic. In these substrates, the barrier to nitrogen inversion is likely to be similar to that calculated for other anomeric amides and it is unlikely that anomeric overlap would stabilise the pyramidal state to the extent that the inversion barrier was unattainable at room temperature. Nitrogen inversion is therefore expected to be rapid on the n.m.r. time scale. Diastereotopism is thus most likely a consequence of restricted rotation about the *N—N* bond. Methylene protons in simple bipyramidal hydrazines topomerise through inversion-rotation processes avoiding high energy eclipsing of lone pairs. Free energy barriers to these isomerisations are in the region of only 42-46 $kJmol^{-1}$ and have been attributed to the rotation rather than the inversion process.[118] Here too, inversion processes are less demanding energetically.[119,120] *N—N* rotation barriers in pyramidal-planar and biplanar hydrazines are significantly higher (typically 67-71 and 84-96 $kJmol^{-1}$ respectively) because of the unavoidable involvement of lone pair-lone pair eclipsing in rotation processes.[118,121,122] Topomerisation of methylene protons in bipyramidal *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines, **70**, clearly involves a much higher energy barrier than that found for simple bipyramidal hydrazines since the methylene protons are resolved into tight AB systems well above room temperature. Since facile inversion processes lower activation barriers to topomerisation, the origin of these high barriers is almost certainly due to the loss of mutual anomeric overlap.

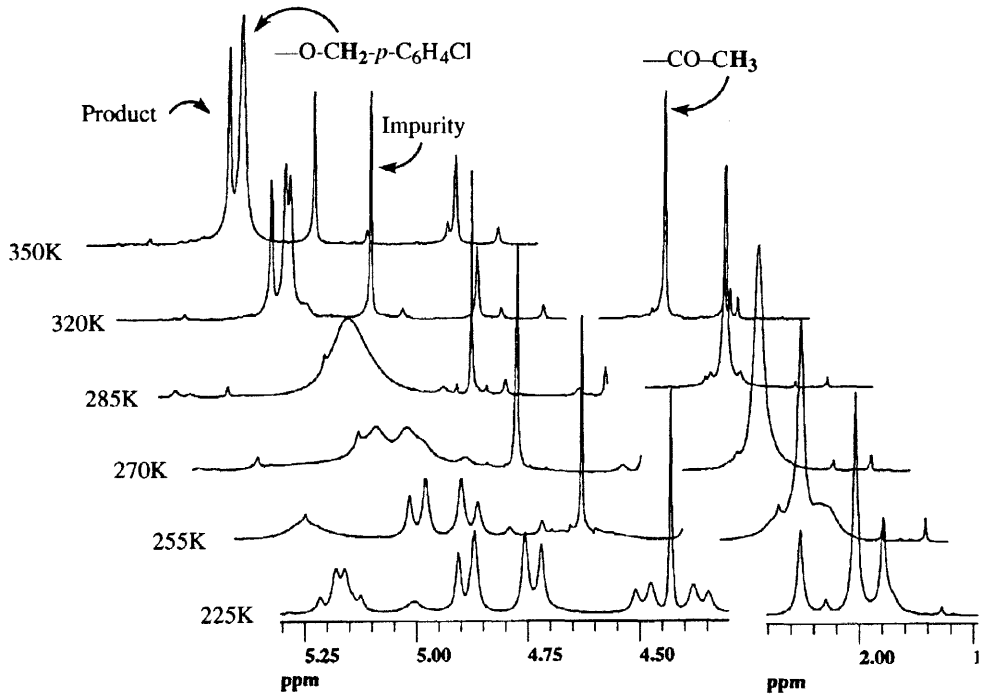
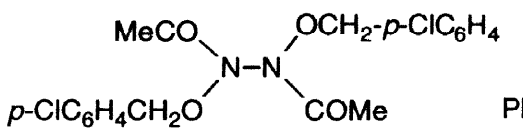


Fig. 21. Variable temperature ^1H NMR spectra of the benzylic methylene and acetyl methyl resonances of *N,N'*-diacetyl-*N,N'*-di-(*p*-chlorobenzyloxy)hydrazine **74** in toluene-d_8.

Fig. 21 illustrates coalescence, at high temperature, of the diastereotopic benzylic protons for *N,N'*-diacetyl-*N,N'*-di-(*p*-chlorobenzyloxy)hydrazine **74** in toluene-d_8. Topomerisation barriers, obtained from the coalescence temperatures of selected hydrazines, including **74**, are given in Table 11 and can be regarded as a direct measure of the strength of anomeric overlap in these *ONN* systems; the transition state corresponds to a geometry in which each nitrogen lone pair is approximately orthogonal to the adjacent *N—O* bond. In the case of *N,N'*-diacetyl-*N,N'*-di-(*p*-chlorobenzyloxy)hydrazine **74** in toluene-d_8, the diastereotopic benzylic protons were significantly broadened at room temperature. Below 278K they separated into three sets of diastereotopic

methylenes (ratio 1:2:1) while the acetyl signal also resolved into three separate resonances in similar ratio (Fig. 21). Below 278K, rotation about the amide *N—C(O)* bond becomes slow on the NMR time scale and the spectrum probably indicates the presence of gauche conformations of a major symmetrical (*E,E* or *Z,Z*) form centred on δ4.8 and 2.0 and two different benzyl and acetyl resonances of an unsymmetrical (*Z,E*) form at δ5.17, 4.42, 2.13 and 1.95). From the coalescence temperature, the barrier to amide rotation was estimated at $\Delta G^{\ddagger}_{278}$ =54 kJmol^{-1} and accords with a significant reduction in amide conjugation in these systems.



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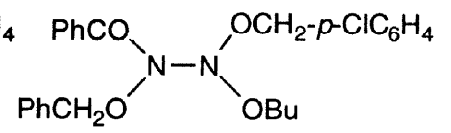

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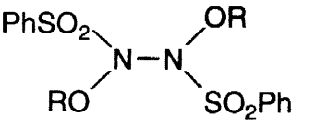


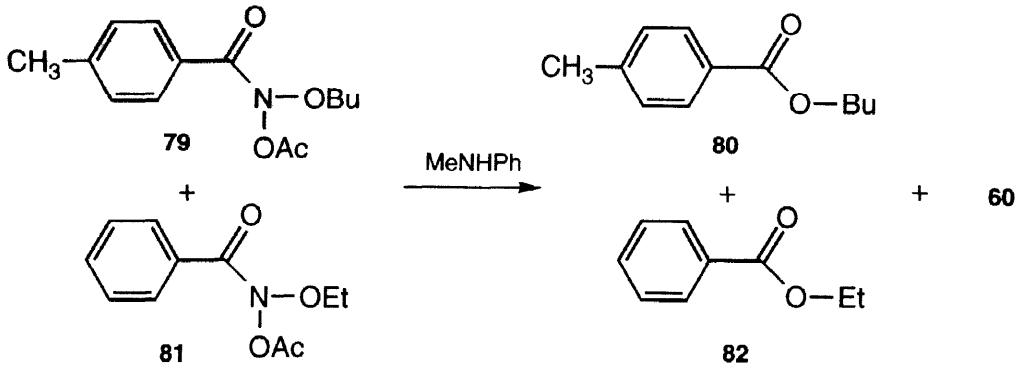
76 R=Et
77 R=CH_2Ph
78 R=$(CH_2)_3$Ph

It has been reported in the literature that *N,N'*-dibenzenesulfonyl-*N,N'*-diethoxyhydrazine **76** also shows dynamic effects in its ^{1}H n.m.r. spectrum. The ethoxy methylene protons become anisochronous at 253K and the process has a somewhat smaller barrier estimated to be *ca.* 54 kJmol^{-1}.[108] While Balaban and coworkers could not ascribe this to any particular isomerisation process, it is likely that it also corresponds to rotation about the *N—N* bond. A smaller barrier would be predicted in this instance since the strongly positive sulfonyl substituent at nitrogen is likely to lower the energy of the nitrogen lone pairs, thereby diminishing the anomeric effect. Reversed or reduced polarity in the *N—O* bonds would also be expected to disfavour the anomeric effect relative to the diacylhydrazines. We have recently confirmed Balaban's results by measuring similar barriers of 58 kJmol^{-1} in chloroform for hydrazines **77** and **78**. For **77** the benzylic methylene protons resonated as an AB system (Δν=79Hz) below 289K while below 293K, the oxymethylene protons of **78** were broadened triplets (Δν=45Hz).[33,109]

Shtamburg has reported that *N,N'*-dicarboalkoxy-*N,N'*-dialkoxyhydrazines **72** behave similarly at low temperatures and has measured a barrier to amide rotation of only 41 kJmol^{-1}.[53] Furthermore, a much weaker anomeric overlap is present in these hydrazines since benzylic methylenes were isochronous down to at least 183K. These results are in line with our observations for the diacyldialkoxyhydrazines since in carbamates, *N—C(O)* π overlap is expected to be weakened further due to the resonance demand of the alkoxy oxygen atom. In addition, relative to an acyl substituent, the more electron-withdrawing *N*-carboalkoxy substitutent would result in a lowering in energy of the donor nitrogen lone pair thereby weakening the anomeric overlap.

7.4 *Reactivity — the HERON reaction*

Simple *N*-alkylamino- or *N*-arylamino-*N*-alkoxyamides are unstable and have only been formed as intermediates in the reactions of amines and *N*-acyloxy-*N*-alkoxybenzamides or *N*-alkoxy-*N*-chloro-*N',N'*-dialkylureas. *N*-Anilino-*N*-alkoxyamides, formed by the reaction of *N*-acetoxy-*N*-alkoxybenzamides with anilines, rearrange by a novel concerted process to esters and 1,1-diazenes (Scheme 15). We were first alerted to this reaction when mutagenic *N*-acetoxy-*N*-alkoxybenzamides were subjected to S_N2 reactions with *N*-methylaniline (Section 6.4). A crossover experiment using **79** and **81** afforded butyl *p*-toluate **80** and ethyl benzoate **82** as the only detectable esters and which must therefore form intramolecularly (Scheme 17).[18] The 1-methyl-1-phenyldiazene (Scheme 15, **61**) was regarded as precursor to the tetetrazene as this is a known reaction of these stabilised nitrenes.[123-128] Thus ester formation involves an anomerically driven migration of the alkoxy group from the amide nitrogen to the carbonyl carbon and we have called this process the HERON reaction.[129] Rearrangement is clearly more appropriate than elimination in these *NNO* systems since the latter process would involve formation of unstable alkoxide ions.



Scheme 17.

Both our preliminary AM1 calculations on the HERON reaction of *N*-dimethylamino-*N*-methoxyacetamide and more recent *ab initio* calculations at the B3LYP/6-31G(D) level for the corresponding rearrangement of *N*-dimethylamino-*N*-methoxyformamide indicate that, in the gas phase, the reaction is exothermic with a moderate activation energy.[104,112] At the more rigorous *ab initio* level, a gas phase enthalpy barrier of only 90 kJmol^{-1} is predicted and the rearrangement leads directly to a complex between 1,1-dimethyldiazene and methyl formate which is marginally more stable than the separate products (Fig. 22). The calculated transition state indicates that the migration is induced by anomeric overlap of the dimethylamine nitrogen lone pair and the σ^*_{NO}. Relative to the starting material, the N1—N2 bond is shortened by 0.117Å to only 1.268Å and the alkoxy oxygen atom (O3) is 2.004Å and 1.713Å from the amide nitrogen (N2) and the carbonyl carbon (C4) respectively and in a plane orthogonal to the *NC(O)* plane. The *N—C(O)* bond (1.51Å) is largely intact but breaks as the ester bond develops.

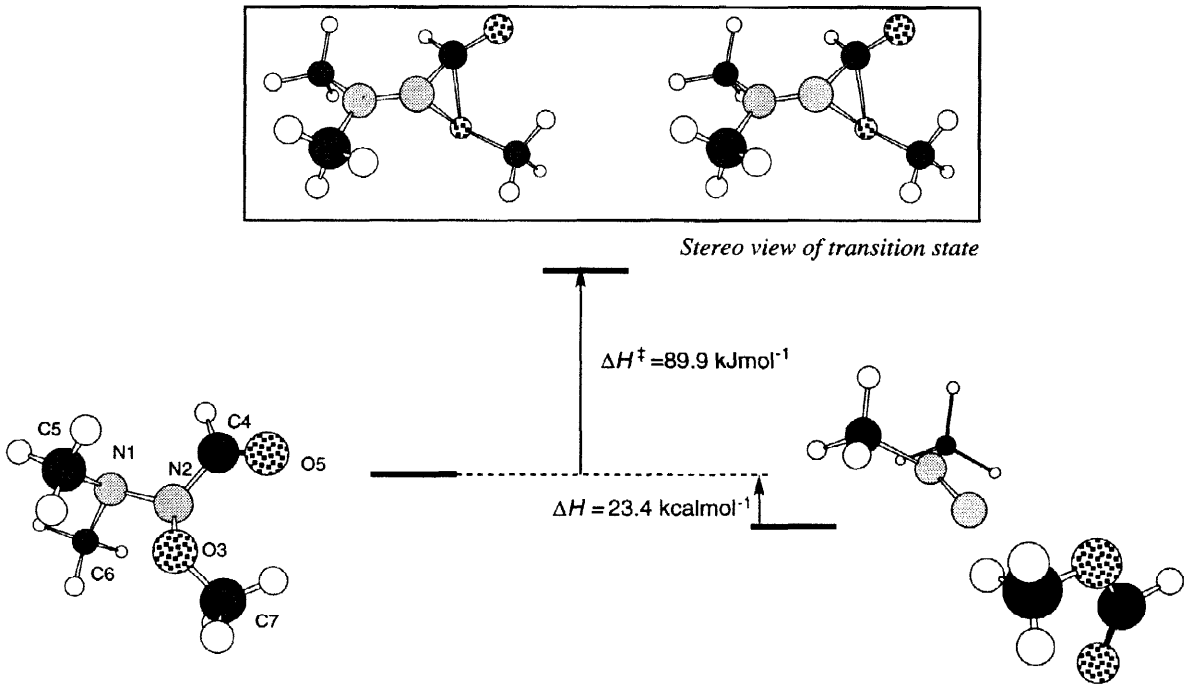


Fig. 22. *Ab initio* ground state, transition state and product energies and geometries for the HERON reaction of *N*-dimethylamino-*N*-methoxyformamide to 1,1-dimethyldiazene and methyl formate.

The 6-31G* group charges for the transition state (Table 12) indicate a significant increase in the partial positive character of the dimethylamino group and a corresponding increase in the negative character of the

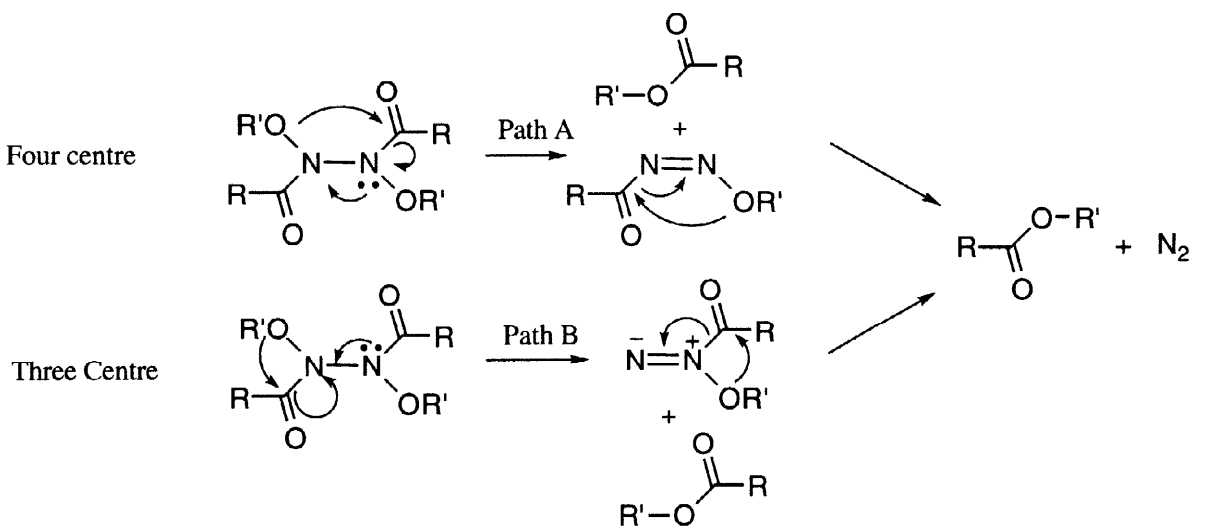
migrating group. Migration should thus be promoted with electron-donor groups at the amino nitrogen which thus facilitate anomeric overlap, and electron-withdrawing substituents on oxygen. AM1 calculations support these trends. Activation energies for methoxy migration in a wide range of *N*-amino-*N*-methoxyacetamides have been computed (Table 10) and there is a correlation between the theoretical activation energies and both the difference between the *N*—*N* π-bond orders of the ground state and the transition state as well as with the negative charge on the migrating group.[104] The polar separation in the transition state indicates that solvent effects should also be important.

Table 12. Group Charges in the Transition State for the HERON Reaction of *N*-dimethylamino-*N*-methoxyformamide to 1,1-dimethyldiazene and Methyl Formate.

Group[a]	Ground state	Transition state
—N1(CH_3)$_2$	0.00	0.51
—N2—	0.00	-0.19
CH_3O—	-0.02	-0.34
HCO—	+0.02	-0.01

[a] Numbering shown in Fig. 22 .

From the data in Table 10, *N*-acyl substituents are predicted to raise the energy barrier for the migration process and it is therefore not surprising that *N*,*N*'-diacyl-*N*,*N*'-dialkoxyhydrazines **70** are relatively stable and can be isolated at room temperature. However, it is well established that they undergo thermal decomposition to give esters and nitrogen in a concerted process which according to Cooley and coworkers, involved two consecutive four-centre rearrangements (Scheme 18, Pathway A).[4,5] Based on our results, we considered that an alternative pathway, involving two consecutive three-centre HERON processes (Scheme 18, Pathway B), would be more likely. To test this, we synthesised a mixed hydrazine **75**. Decomposition at room temperature in $CDCl_3$ afforded largely butyl *p*-chlorobenzoate and benzyl benzoate, the esters formed through the HERON reaction.[7] Similar results were obtained concurrently by Barton and coworkers who also showed that thermal decomposition of symmetrical hydrazines, formed by ceric ammonium nitrate or nickel peroxide oxidation of hydroxamic esters bearing bulky substituents gave excellent yields of highly hindered esters.[6] Using semiempirical AM1 calculations, both our groups predicted the first HERON step to be rate determining and the second HERON process of the 1-acyl-1-alkoxydiazene to be extremely fast.



Scheme 18.

Cooley first studied the rates of decomposition of *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines and reported that electron-donor groups on the acyl substituent and electron-withdrawing groups on the alkoxy group increased the rate of decomposition in keeping with acylium and alkoxide character in the cyclic four-membered transition states.[4,5] Reaction rates were monitored by molecular weight determinations but neither rate constants nor Arrhenius data were reported. In the light of the re-evaluation of the mechanism,[6,7] we recently repeated Cooley's study of substituent effects. Two hydrazine series were found to decompose unimoleculary in mesitylene giving esters and nitrogen and activation data and rate constants at 298 K are given in (Table 13).

Table 13. Arrhenius Activation Energies, Entropies of Activation and Rate Constants at 298K for Decomposition of *N,N'*-Diacyl-*N,N'*-dialkoxyhydrazines, $RCON(OR')-\frac{1}{2}$

R	R'	E_A/kJmol^{-1}	$\Delta S^{\ddagger}$/JK^{-1}mol^{-1}	$10^6 k_{298}$/s^{-1}	Source
p-$CH_3OC_6H_4$	Et	99.2	-21.2	5.564	117
p-$CH_3C_6H_4$	Et	100.7	-19.6	3.719	117
C_6H_5	Et	100.5	-23.8	2.521	117
p-ClC_6H_4	Et	107.7	0.9	2.502	117
p-$NO_2C_6H_4$	Et	104.0	-15.4	1.572	117
C_6H_5, *p*-ClC_6H_4	$C_6H_5CH_2$, Bu	101.1	-11.5	7.943	Chloroform[7]
				$10^8 k_{298}$/s^{-1}	
CH_3	*p*-$CH_3OC_6H_4CH_2$	111.4	-21.1	4.017	117
CH_3	*p*-$CH_3C_6H_4CH_2$	125.9	24.5	2.757	117
CH_3	$C_6H_5CH_2$	114.1	-8.7	6.206	117
CH_3	*p*-$ClC_6H_4CH_2$	125.1	27.4	5.436	117
CH_3	*p*-$NO_2C_6H_4CH_2$	98.8	-46.4	31.880	117

Members of the ethoxy series react about two orders faster at 298 K than the benzyloxy series. Entropies of activation are for the best part negative in keeping with a highly ordered HERON transition state. Furthermore, rate constants at 298 K correlate with Hammett σ^+ with a low but negative sensitivity of $\rho = -0.4$.[130] Thus donor groups facilitate the rearrangement in this series. The charge distribution in the model transition state for the HERON process (Table 12) indicates a significant increase in positive character at the anomeric nitrogen (N1, Fig. 22) rather than at the acyl carbon (C6, Fig. 22). In the case of the hydrazines, this would be stabilised by *para* electron-donor groups on the adjacent benzoyl group since these reduce the polarity at the carbonyl carbon (Fig. 23a). Thus Cooley's earlier assertion, that electron rich acyl groups stabilise acylium character, is incorrect. There is also an increase in negative charge in the model transition state at the alkoxy group (Table 12) and this is born out by a reasonable, positive Hammett σ correlation in the benzyloxy series ($\rho = +0.9$, Fig. 23b).

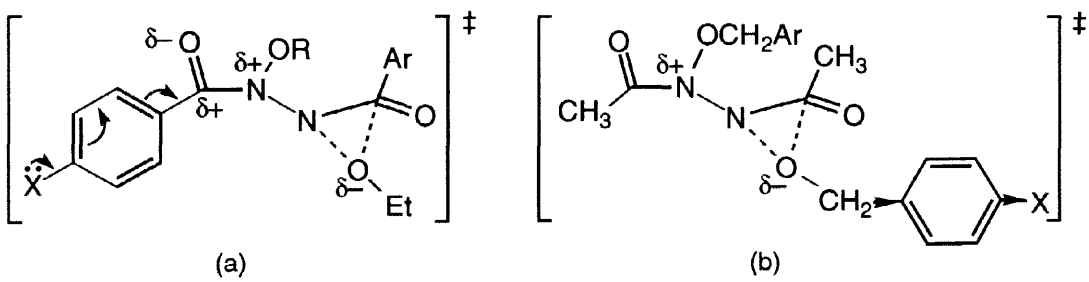
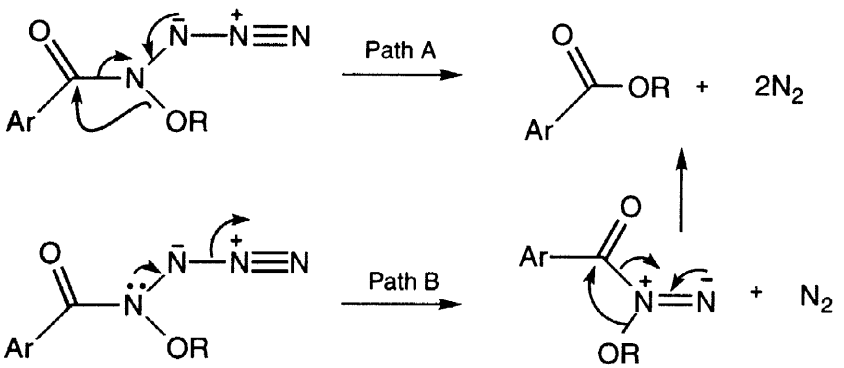


Fig. 23. Stabilisation of HERON transition states by (a) electron rich benzoyl groups and (b) electron deficient benzyloxy groups.

N-Azido-*N*-alkoxyamides, postulated intermediates in the reaction of *N*-acetoxy-*N*-alkoxyamide with sodium azide in aqueous acetonitrile, are a special case of *NNO* systems.[62] They decompose to alkyl benzoate and nitrogen. Dilatometry confirmed the evolution of two equivalents of molecular nitrogen for every equivalent of ester produced and that the reaction is bimolecular. A crossover experiment using *N*-acetoxy-*N*-ethoxy-*p*-toluamide and *N*-acetoxy-*N*-butoxybenzamide afforded exclusively the non-crossover esters, butyl benzoate and ethyl *p*-toluate. ***Ab initio*** calculations predict a mutual anomeric effect.[112] However, while formation of ester by a normal HERON process (Scheme 19, Pathway A) is feasible, the lowest energy pathway most probably involves initial loss of nitrogen to give 1-acyl-1-alkoxydiazene **83** (Scheme 19, Pathway B); Becke3LYP/6-31G(D) *ab initio* calculations on *N*-azido-*N*-methoxyformamide predict that initial loss of nitrogen to give 1-formyl-1-methoxydiazene is exothermic by 162 kJmol^{-1} and has an activation barrier of only 18 kJmol^{-1}. As outlined above, acylalkoxydiazenes are also formed from a three-centre rearrangement of *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines (Scheme 18, Pathway B) and have been calculated to proceed to ester and nitrogen through a low energy HERON process.[6,7]

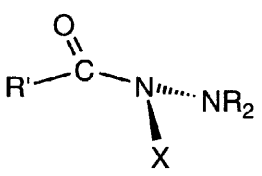


83

Scheme 19.

8. *N*-AMINO-*N*-HALOAMIDES

No examples of stable *N*-amino-*N*-haloamides **84** are known. *N*-Amino-*N*-chloroamides may however be unstable intermediates formed during the chlorination of β,β-dialkyhydrazides. Treatment of β,β-dimethylbenzhydrazide **85** with *N*-chlorinating agent *tert*-butyl hypochlorite in methylene chloride, afforded one major product in the form of *N*-dimethylaminobenzimide **89** in good yield (Scheme 20).[131] Initial formation of α-chloro-β,β-dimethylbenzhydrazide **86** as a reactive intermediate has been proposed but this must be a source of benzoylating agent which reacts with the parent hydrazide.



84

8.1 *Anomeric effect.*

ClNN systems should exhibit the strongest anomeric interaction of all neutral bisheteroatom-substituted nitrogens. A combination of the high energy amine nitrogen lone pair together with a low-lying *N—Cl* σ* orbital should result in a strong $n_N—\sigma^*_{NCl}$ interaction which could lead to heterolytic dissociation of the *N—Cl* bond. *Ab initio* molecular orbital calculations support this assertion.

8.2 *Theoretical properties*

Becke3LYP/6-31G(D) *ab initio* calculations predict *E*- and *Z*-conformational isomers of *N*-chloro-*N*-dimethylaminoformamide to lie at local minima but analysis of the structure of the lowest energy isomer (*E*) suggests that it should be relatively unstable.[19] The anomeric nitrogen lone pair is anti-coplanar with the vicinal *N—Cl* bond (Fig. 22a and b) and this model exhibits both an extremely long *N—Cl* bond (2.068Å) and short *N–N* bond (1.309Å). In addition, the amide *C—N* bond is long (at 1.418Å) when compared to *N*-chloroformamide (1.369Å). The β nitrogen is approximately planar (<116°>) but the amide nitrogen is sharply pyramidal with an average angle at nitrogen of only 112.3°. The nitrogen inversion barrier was however very low at 11 kJmol^{-1} and theoretical calculations indicate that in bisheteroatom-substituted amides, there is no obvious correlation between the strength of anomeric effects and the nitrogen inversion barriers, which are lowered because of resonance stabilisation in the planar inversion transition state.

For this model, the enthalpy barriers to rotation about the *N—CO* and *N—N* bonds were estimated at 41 and 81 kJmol^{-1} respectively and reflect a stronger anomeric interaction than that predicted for *N*-alkoxy-*N*-aminoamides (Section 7). In the twisted transition structure for amide rotation, the *N—Cl* bond was found to be 2.25Å and the *C—N—Cl* angle of 89° suggests the initial stages of the HERON rearrangement (Fig. 22c).

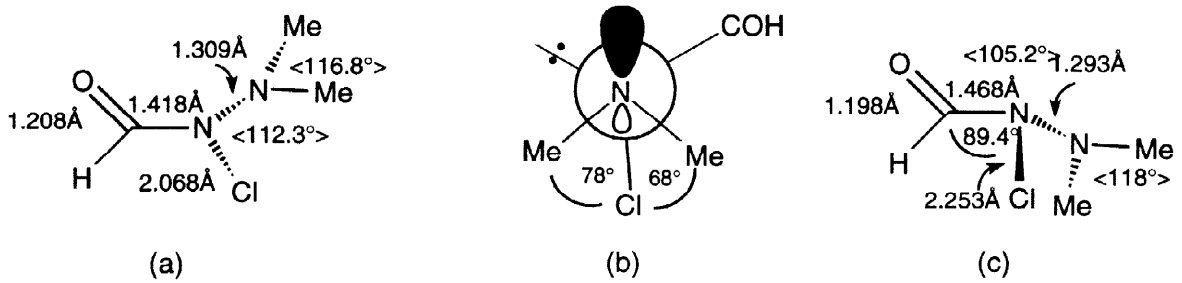
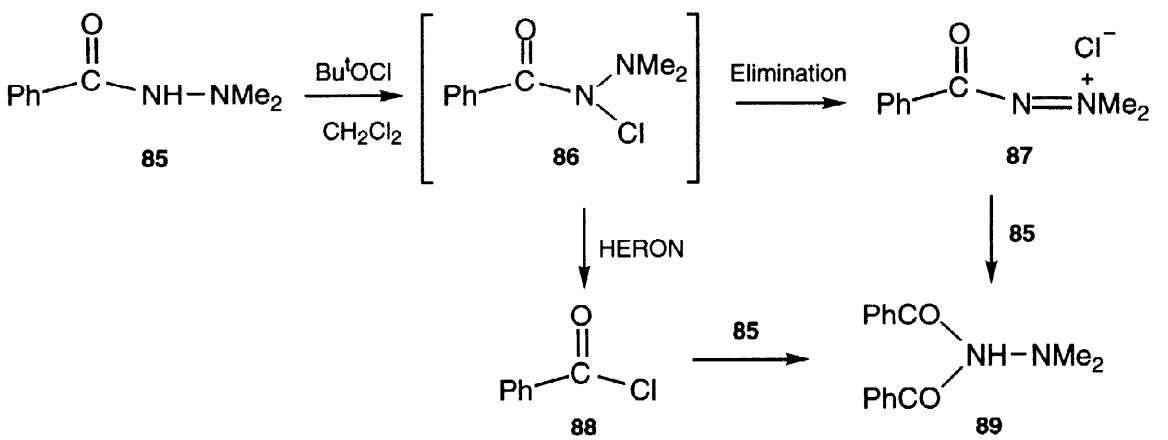


Fig. 22 (a) Becke3LYP/6-31G(D) optimised geometry for *N*-chloro-*N*-dimethylaminoformamide; (b) Newman projection along the *N—N* bond; (c) Transition state for rotation about the *N—C(O)*bond.

8.3 *Reactivity*

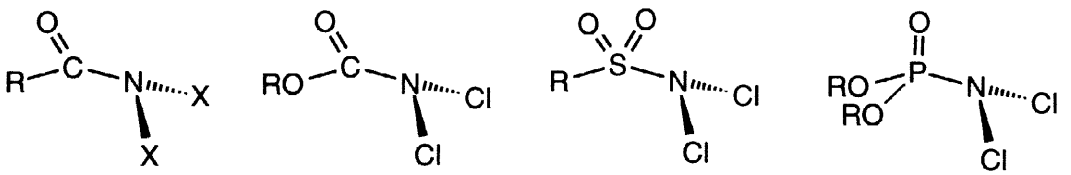
Treatment of β,β-dimethylbenzhydrazide with *tert*-butyl hypochlorite in methylene chloride afforded one major product in the form of *N*-dimethylaminobenzimide (Scheme 20).[131] Its formation can be ascribed to reaction of the starting hydrazide with an acylating agent. Theoretical calculations indicate an extremely strong anomeric interaction which could lead to elimination of chloride and the formation of the diazenium ion intermediate **87**, which could in turn act as an acylating agent. Alternatively, the strong anomeric effect could initiate a HERON reaction and chlorine migration would form the acylating agent benzoyl chloride **88**.



Scheme 20.

9. *N,N*-DIHALOAMIDES

A number of examples of *N,N*-dihaloamides **90-93** are known although most investigations have centred upon the *N,N*-dichloro compounds.[8-13] The corresponding dichlorourethanes **94**,[12,132,133] *N,N*-dichlorosulfonamides **95**,[134,135] and *N,N*-dichlorophosphoramidates **96** [136-138] have also been reported. Dibromo[14] and diiodoamides [15] are known while the synthesis of *N,N*-difluoroformamide (**93**, R=H) and *N,N*-difluorotrifluoroacetamide (**93**, R=CF_3) has also been reported.[16] Zawadzki and Zwierzak have studied *N,N*-dibromophosphoramidates.[139] In most cases, these substrates are prepared from the corresponding amides with positive halogenating agents such as molecular chlorine,[8] *N*-haloisocyanuric acids,[14,140] and sodium and calcium hypochlorite.[11,12] *N,N*-Diodoacetamide (**92**, R=Me) has been synthesised by iodine exchange with the corresponding dibromo compound.[15]



90 X=Cl
91 X=Br
92 X=I
93 X=F

94 **95** **96**

9.1 *Anomeric effect.*

These *XNX* systems should exhibit relatively weak anomeric effects since, although the *N*—*X* σ* is low in energy, the halogen lone pair will also be of low energy. Anomeric overlap will also be disfavoured by unmatched orbital sizes, particularly where *X* is bromine or iodine. Combined electronegativities should however favour sp^3 hybridisation at the amide nitrogen, although reduced electronegativity and steric repulsion may result in greater planarity for the higher halides.

9.2 *Theoretical properties*

A 6-31G* *ab initio* calculation on *N,N*-dichloroformamide predicts the planar and pyramidal forms to be minima with similar energy although the pyramidal form is lowest by 1.9 $kJmol^{-1}$. This optimised geometry is illustrated in Fig. 23. The average angle at nitrogen is 116.9° while the *N*—*C(O)* bond is longer and the *CO* bond shorter than those calculated for *N*-chloroformamide (1.369Å and 1.209Å respectively) and are indicative of a low degree of amide resonance. Like other anomeric amides, *N,N*-dichloroformamide should exhibit higher carbonyl stretch frequencies relative to amides and *N*-chloroamides. The lowest barrier to rotation about the *N*—*C(O)* bond is calculated to be 43 $kJmol^{-1}$ and corresponds to the transition state with oxygen *exo* to the pyramidal nitrogen.

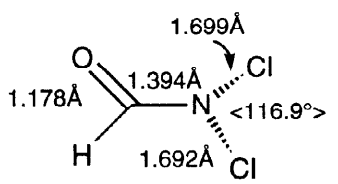


Fig. 23. 6-31G* optimised geometry for *N,N*-dichloroformamide.

9.3 *Physical properties*

Infrared data are known for some *N,N*-dichloroamides (Table 14). Carbonyl stretch frequencies for *N,N*-dichloroalkylamides are in the range expected for anomeric amides although detailed comparisons cannot be

made between spectra obtained under different conditions. Nevertheless, where data are available, the carbonyl stretch frequencies for the dichloro derivatives under the same conditions are significantly greater than those of their monochloro counterparts.

Table 14. Infrared Carbonyl Absorption Frequencies (cm^{-1}) for *N,N*-dihaloamides ($RCONX_2$) and their Precursor *N*-haloamides.

R	X	Dihaloamide	Haloamide	Source
CH_3	Cl	1742/1715 (CCl_4)	1728/1715(sh) (CCl_4)	8
		1772/1734 (vap.)	1708/1677 ($CHCl_3$)	58
$PhCH_2$	Cl	1720 (liq.)	1660 (nujol), 1699 ($CHCl_3$)	10,56
Bu	Cl	1730 (liq.)		12
$ClCH_2(CH_2)_3$	Cl	1721 (liq.)		12
IPGPO[a]$(CH_2)_2$	Cl	1740 (CCl_4)	1700 (CCl_4)	11
H	Br	1760/1615 (nujol)[b]		14
CH_3	Br	1780/1600 (nujol)[b]	1717/1700 (CCl_4)	14
Ph	Br	1710/1646 (nujol)[b]	1704 (CCl_4)	14,58
$ClCH_2$	Br	1793/1660 (nujol)[b]		14
H	I	1680 (KBr)[c]		15
EtO	Cl	1750 (CCl_4)	1724 (liq.)	12,132
Bu^tO	Cl	1765 (liq.)		12

[a] 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose.

[b] Assignments unclear.

[c] Polymeric structure

An X-ray structure of *N,N*-diiodoformamide is planar at nitrogen with typical amide bond lengths (*N—CO* =1.328Å and *C=O* = 1.213Å).[141] Interestingly, the carbonyl stretch for *N,N*-diiodoformamide is in the range expected for primary and secondary amides in which normal amide resonance is operative.[15] These data and the X-ray structure supports a polymeric crystalline form of *N,N*-diiodoformamide in which there is association between the carbonyl oxygen and a neighbouring iodine atom (Fig. 24). Such a tertiary structure accounts for its stability in the solid state and can be a consequence of the lower electronegativity of iodine and steric repulsion between the iodine atoms leading to adoption of a planar arrangement at nitrogen.

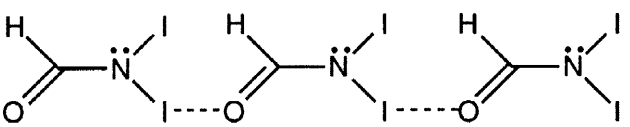
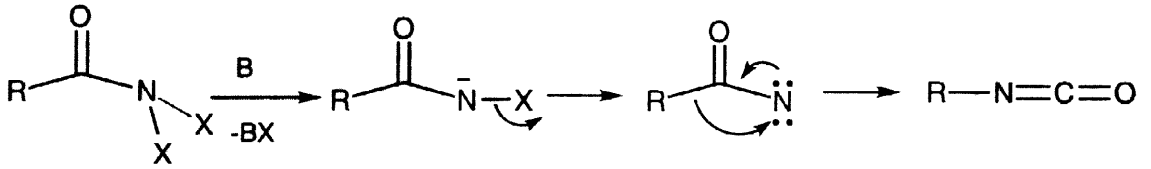


Fig. 24. Polymeric structure of *N,N*-diiodoformamide.

9.4 *Reactivity*

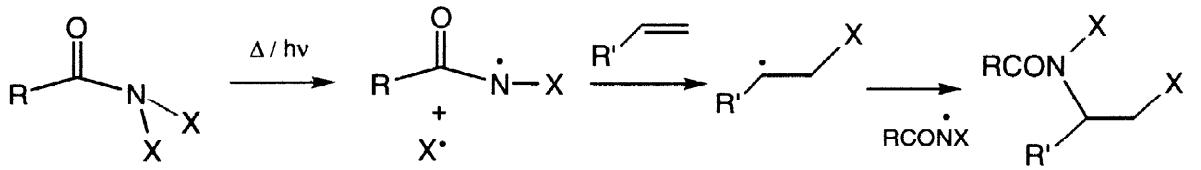
N,N-Dihaloamides are generally very unstable in solution but the variety of decomposition reactions reported to date indicate that they are unlike other anomeric amides. While reaction with Lewis acids has not been reported, there is no evidence that they generate halonitrenium ions readily. Relative to alkoxynitrenium ions, such species should be destabilised owing to poorer overlap with the larger halogen atoms, chlorine, bromine and iodine. However, there is ample evidence that the halogen atoms are labile and, if anything, *N,N*-dichloro- and *N,N*-dibromoamides are weak sources of positive halogen. *N,N*-Dibromobenzamide exchanges with benzamide giving *N*-bromobenzamide and with iodine to give *N,N*-diiodobenzamide which, in solution, itself undergoes an extrusion of iodine to give benzoylnitrene.[15] Inorganic and organic bases can

abstract halogen from *N,N*-dichloro- and *N,N*-dibromoamides resulting in Hofmann rearrangements (Scheme 21).[9,11] Strong base results in acyl substitution to give dihaloamines.[12,15]



Scheme 21.

Thermal free radical additions to alkenes are also known (Scheme 22). Miskova has described the addition of *N,N*-dichloroamides to trichloroethylene[13] while trans addition of *N,N*-dichlorophenylacetamide to cyclohexene has also been reported.[10] Like their *N,N*-dialkoxyamide counterparts, homolytic decomposition is favoured over heterolytic elimination.



Scheme 22.

N,N-Dichlorocarbamates **94** react by similar processes. Methoxide reacts with *N,N*-dichlorourethane giving ethyl methyl carbonate and dichloroamide[133] while, by analogy with Scheme 22, free radical addition of *N,N*-dichlorocarbamates to alkenes is well documented.[132] Such additions afford mainly the anti-Markovnikov addition products in reasonable yield. *N,N*-Dichloroalkyl- and arylsulfonamides **95**[134,135] as well as dialkyl *N,N*-dihalophosphoramidates **96**[136,137] also add homolytically to alkenes yielding the anti-Markovnikov products. Radical addition of dihalophosphoramidates **96** to butadiene provides a direct useful route to 1-amino-4-chloro-2-butenes and hence, by cyclisation, pyrrolidines.[138] The olefin addition reactions of **94**, **95** and **96** have previously been reviewed.[70]

10. CONCLUSION

Amides substituted with two heteroatoms at nitrogen exhibit unique characteristics. Unlike their parent amides or monoheteroatom-substituted amides, the nitrogens of this class are more amine-like resulting in unusually weak amide conjugation, as illustrated by high infrared carbonyl stretch frequencies and much lower barriers to rotation about the amide *C—N* bond. Infrared carbonyl stretch frequencies have been shown to be a sensitive measure of non-planarity at amide nitrogens and the demonstrated movements to higher frequency upon bisheteroatom-substitution provide an excellent means of monitoring the progress of such processes. Resonance stabilisation of the planar transition state for inversion at nitrogen results, nonetheless, in low barriers to this conformational isomerisation.

With appropriate substitution, and particularly in *ClNO, AcONO, ONN* and *ClNN* systems, amides can sustain strong anomeric effects at the amide nitrogen through $n_Y—\sigma^*_{NX}$ overlap resulting in high barriers to rotation about the *Y—N* bond and unusually labile *N—X* bonds. Dynamic NMR studies suggest that the anomeric effects increase in the order *ONO* < *AcONO* < *ClNO* < *ONN* systems. *XNX* systems mimic the behaviour of *ONO* systems while at the other extreme, anomeric stabilisation in *ClNN* systems is likely to be more effective than in *ONN* amides. In *ClNO* and *AcONO* systems both S_N1 and S_N2 reactions at nitrogen are observed. *AcONO* systems in the form of *N*-acyloxy-*N*-alkoxyamides are direct acting mutagens whose reaction with DNA may also be as a result of anomeric weakening of the *AcO—N* bond. In *ONN* systems,

enhanced anomeric weakening of the *N—O* bond initiates a novel, concerted rearrangement process at the amide nitrogen (the HERON reaction) involving migration of oxygen from nitrogen to the carbonyl carbon to give excellent yields of esters and 1,1-diazenes. HERON reactions in *ONN* amides, including *N*-azido-*N*-alkoxyamides, provide efficient routes to esters, even where these are highly hindered. Where substitution is with identical, strongly electronegative atoms such as in *ONO* and *ClNCl* systems, such nitrogens are also strongly pyramidal but anomeric effects are weaker. The reactivity of such systems is however characterised by anomerically assisted homolytic decomposition which, in the case of *N,N*-dialkoxyamides, results in formation of reactive alkoxyl and stable alkoxyamidyl radicals. In anomeric sulfonamides the adjacent sulfonyl group radically alters the chemical behaviour. Nitrogens in such systems are strongly affected by the electron-withdrawing properties of SO_2 and they are less able to sustain anomeric effects than their acyl counterparts.

The observations, outlined in this Report, raise the prospect of HERON reactions occurring in other α,β-unsaturated amines and, in addition, the peculiar decoupling of amide lone pairs from the amide carbonyl suggests that reactions involving the carbonyl may more resemble those of ketones and aldehydes rather than amides.

11. ACKNOWLEDGEMENTS

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Biographical sketch

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Stephen Glover received his Ph.D. in 1976 from the University of Port Elizabeth for his research into the chemistry and electronic properties of amidyl radicals and which was carried out under the direction of Prof. André Goosen. He continued to a Postdoctoral Fellowship with Prof. Sir Derek Barton at the Imperial College of Science and Technology where he worked on organotellurium chemistry. From 1977 until 1985 he was Lecturer, then Senior Lecturer at the University of Port Elizabeth where he consolidated his research into properties and reactions of *N*-haloamides and later the chemistry and properties of alkoxynitrenium ions. In 1985, after a Visiting Fellowship with Prof. Athel Beckwith at the Australian National University working on radical cyclisation reactions, he was appointed as Lecturer, then Senior Lecturer at the University of New England, Australia. He was promoted to Associate Professor in 1996. His current research interests centre on the chemical and biological properties of mutagenic *N*-acyloxy-*N*-alkoxyamides, heterocyclic chemistry, organic reaction mechanisms and computational chemistry. In 1995 he was elected to Fellowship of the Royal Australian Chemical Institute and, in 1996, was recipient of the Vice-Chancellors Award for Teaching Excellence at the University of New England.