1  **Heteroatom Substitution at Amide Nitrogen — Resonance Reduction and HERON**

2  **Reactions of Anomeric Amides**

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9

10  **Abstract:** This review describes how resonance in amides is greatly affected upon substitution

11  at nitrogen by two electronegative atoms. Nitrogen becomes strongly pyramidal and resonance

12  stabilisation, evaluated computationally, can be reduced to as little as 50% that of *N,N*-

13  dimethylacetamide. However, this occurs without significant twisting about the amide bond,

14  which is borne out both experimentally and theoretically. In certain configurations, reduced

15  resonance and pronounced anomeric effects between heteroatom substituents are instrumental

16  in driving the HERON (Heteroatom Rearrangement On Nitrogen)[†] reaction, in which the more

17  electronegative atom migrates from nitrogen to the carbonyl carbon in concert with heterolysis

18  of the amide bond, to generate acyl derivatives and heteroatom-substituted nitrenes. In other

19  cases the anomeric effect facilitates $S_N1$ and $S_N2$ reactivity at the amide nitrogen.

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21  **1. Introduction**

22  Amides are prevalent in a range of molecules such as peptides, proteins, lactams and many

23  synthetic polymers [1]. Generically, they are composed of both a carbonyl and an amino

24  functional group, joined by a single bond between the carbon and nitrogen. The contemporary

25  understanding of the resonance interaction between the nitrogen and the carbonyl in amides is

26  that of an interaction between the LUMO of the carbonyl, $\pi*_{C=O}$, and the HOMO of the amide

27  nitrogen ($N2p_z$) (Figure 1). This molecular orbital model highlights the small contribution of

28  the carbonyl oxygen to the LUMO, which indicates that limited charge transfer to oxygen

29  occurs, in line with the resonance model presented in Figure 2. The major factor in the

30  geometry of amides, and the restricted rotation about the amide bond, is the strong $\pi$-overlap

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[†] Named at the Third Heron Island Conference on Reactive Intermediates and Unusual Molecules, Heron Island 1994.

1    between the nitrogen lone pair and the $C2p_z$ component of the LUMO, which dominates the

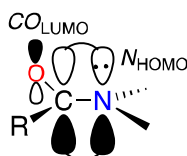2    $\pi^*_{C=O}$ orbital, on account of the polarisation in the $\pi_{C=O}$ [2, 3].

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6    **Figure 1**. The interaction between the nitrogen HOMO and the carbonyl LUMO in amides.

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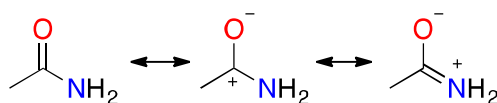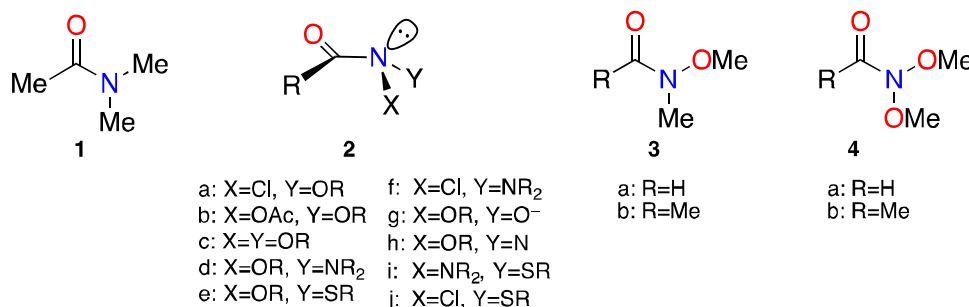9    **Figure 2**. Resonance hybrid contributions in amides, showing that the majority of charge transfer occurs

10    between nitrogen and carbon.

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14    Amide resonance can be diminished by limiting the overlap between the nitrogen lone pair, $n_N$,

15    and $\pi^*_{C=O}$ orbitals. In most instances, this can occur by twisting the amino group about the *N—*

16    *C(O)* bond and/or pyramidalising the nitrogen, which amounts to introducing "s" character into

17    the $N2p_z$ orbital.

18    Computational modelling of *N—C(O)* rotation and nitrogen pyramidalisation in *N,N*-

19    dimethylacetamide **1**, at the B3LYP/6-31G(d) level, illustrates the energetic changes (Figure

20    3) [4]. Distortion of the amide linkage can be quantified by Winkler-Dunitz parameters $\chi$ and

21    $\tau$, where $\chi = 60°$ for a fully pyramidal nitrogen, and $\tau = 90°$ for a completely twisted amide

22    where the lone pair orbital on nitrogen is orthogonal to the $C2p_z$ orbital [5, 6]. Deformation

23    from the non-twisted $sp^2$ planar ground state (Figure 3a) through rehybridisation of nitrogen to

24    $sp^3$ (Figure 3b) is accompanied by an increase in energy ($\sim 27$ kJ mol$^{-1}$), but the majority of

25    amide resonance remains intact. A much larger increase in energy ($\sim 100$ kJ mol$^{-1}$) results from

1    twisting the $N$—$C(O)$ bond through 90° whilst maintaining sp$^2$ planarity at nitrogen (Figure

2    3d), and as the nitrogen is allowed to relax to sp$^3$ hybridisation (Figure 3c), a fully twisted

3    amide devoid of resonance is obtained.  The loss of ~31 kJ mol$^{-1}$ in this final step is indicative

4    of the concomitant twisting and pyramidalisation observed in a variety of twisted amides.
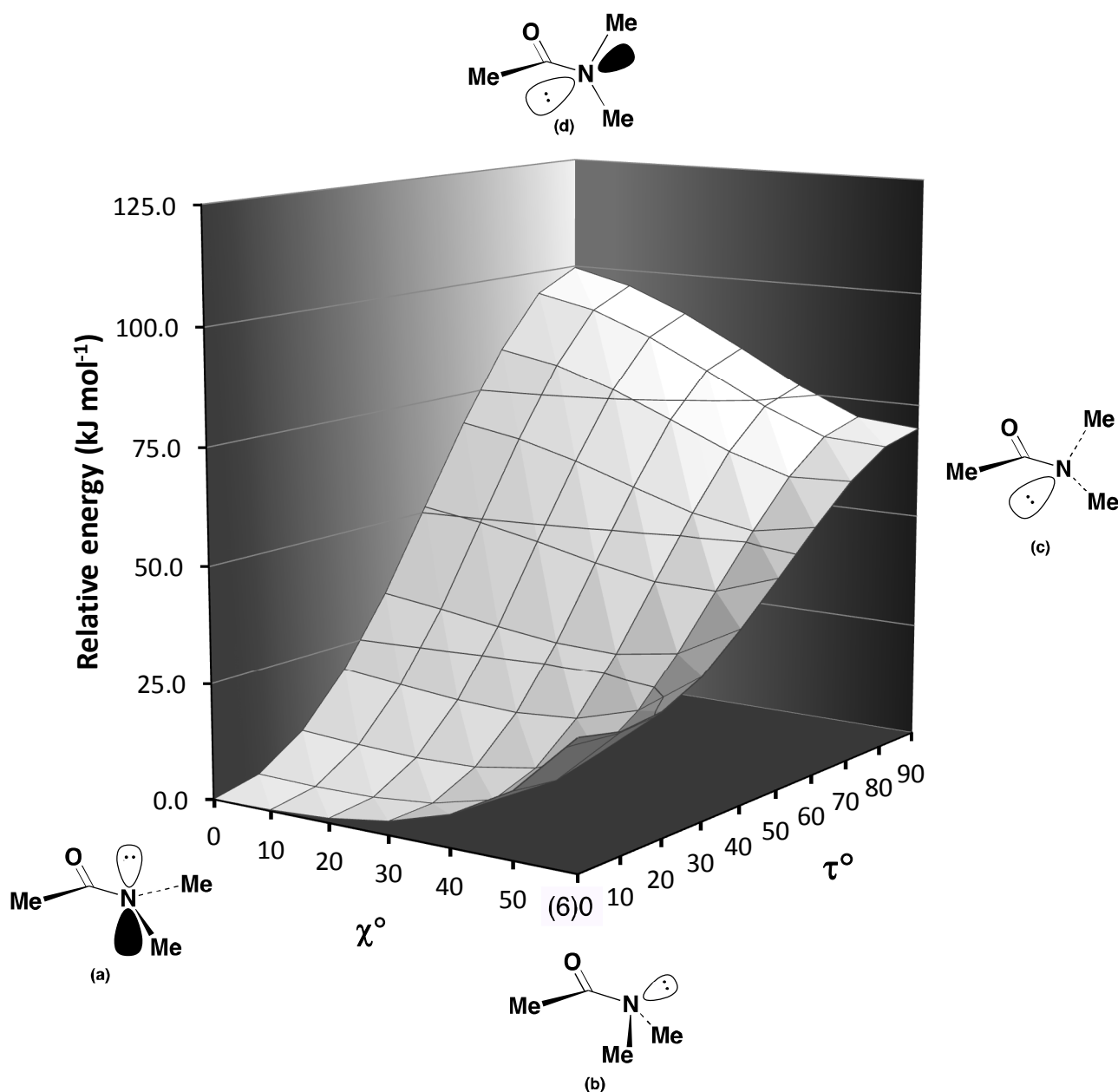
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9    **Figure 3.** A B3LYP/6-31G(d) generated energy surface for the deformation of the amide moiety in *N,N*-

10    dimethylacetamide **1** [4].  χ and τ are Winkler-Dunitz parameters for pyramidalisation and twist, respectively [5,

11    6]. (a) The ground state planar structure for *N,N*-dimethylacetamide; (b) untwisted system with sp$^3$ hybridised

12    nitrogen; (c) 90° rotation about *N—C(O)*, whilst maintaining sp$^3$ hybridisation at nitrogen; and (d) the fully twisted

13    moiety, 90° *N—C(O)* rotation and sp$^2$ hybridised nitrogen.

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1   Typically, amides exhibit restricted rotation about the *N—C(O)* bond, in the order of 67 – 84
2   kJ mol$^{-1}$, along a sigmoid pathway with little change in energy upon moderate pyramidalisation
3   ($\chi$ = 0 – 40°) and minor twisting ($\tau$ = 0 – 20°).  Clearly, rotation without pyramidalisation is
4   energetically unfavourable and many examples of twisted amides are testament to this.  The
5   shift to sp$^3$ hybridisation at the amidic nitrogen is clearly demonstrated when twisting of the
6   *N—C(O)* bond is geometrically enforced by tricyclic and bicyclic bridged lactams [7-13].
7   Kirby's "most twisted amide" 1-aza-2-adamantanone, synthesised in 1998 [10, 12], and Tani
8   and Stoltz's 2-quinuclidone, synthesised in 2006 [14], exemplify the fully twisted amide,
9   geometrically and chemically.  Intramolecular steric hindrance is another source of non-planar
10  twisted amides [15, 16], as exemplified by the thioglycolurils [17, 18] and other systems.  Ring
11  strain   in   non-twisted   amides,   such   as   1-acylaziridines   [19,   20]   and   *N*-acyl-7-
12  azabicyclo[2.2.1]heptanes [21-24] can result in pyramidality at the amide nitrogen, despite
13  retaining a noticeable $n_N – \pi^*_{C=O}$ interaction.

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15  The structural changes accompanying the loss of amide resonance include the lengthening of
16  the *N—C(O)* bond and minor shortening of the *(N)C=O* bond. Comparing the fully twisted 1-
17  aza-2-adamantanone  to an analogous unstrained tertiary δ-lactam, the *N—C(O)* bond shortens
18  from 1.475 Å to 1.352 Å, and the *(N)C=O* bond lengthens from 1.196 Å to 1.233 Å [12] [25].
19  Spectroscopically  and  chemically,  the  amide  carbonyl  trends  towards  ketonic  behaviour  at
20  large twist angles.  In tricyclic 1-aza-2-adamantanone, the carbonyl carbon $^{13}$C NMR resonance
21  is at 200.0 ppm and the IR carbonyl vibrational frequency (1732 cm$^{-1}$) is significantly higher
22  than regular amides (1680 cm$^{-1}$) [10, 12].

23

24  **2. Properties of anomeric amides**
25  *2.1 Structural properties*
26  Another way in which amides may be dispossessed of their planarity and resonance is through
27  bisheteroatom-substitution by electronegative heteroatoms at the amide nitrogen in **2**.  We
28  named this class 'anomeric amides' on account of the pronounced anomeric effects that can
29  and  do  occur  between  the  heteroatoms  [26-35].   However,  the  physical,  theoretical,  and
30  chemical properties of various congeners differ from those of conventional primary, secondary
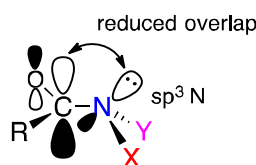31  and tertiary alkylamides.

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**Figure 4.** Reduced $n_N - \pi^*_{C=O}$ overlap due to pyramidalisation.

Electronegative atoms demand an electron density redistribution which is facilitated by a shift in the hybridisation at nitrogen towards sp$^3$, in accordance with Bent's rule [36, 37]. Reduced $n_N - \pi^*_{C=O}$ overlap due to pyramidalisation (Figure 4) together with the increased '2s' character of the lone pair on nitrogen results in structural, electronic, spectroscopic and chemical differences in comparison to traditional amides. Their unique properties of have been reviewed in recent years [31, 35].

Much of our interest into, and indeed the discovery of, anomeric amide chemistry emanates from our investigations of the biological activity, structure and reactivity of *N*-acyloxy-*N*-alkoxyamides (NAA's) **2b** [31, 38-49] a class of anomeric amides.  Readily synthesised by treatment of *N*-alkoxy-*N*-chloroamides **2a**, themselves a form of anomeric amide, with silver or sodium carboxylate salts in anhydrous solvents [45, 46, 48, 49], NAA's are direct-acting mutagens which react with nucleophilic centres in DNA [31, 39-46, 49, 50].  Additionally, they react with a variety of nucleophiles to produce other congeners, including, reactive anomeric amides in the form of *N*-alkoxy-*N*-aminoamides **2d** [44, 47, 51] and *N*-alkoxy-*N*-thioalkylamides **2e** [52].  We have also encountered several anomeric reactive intermediates through reactions of *N*-acyloxy-*N*-alkoxyamides: reaction of **2b** with base generates *N*-alkoxy-*N*-hydroxamate anions **2g** [45], and reaction with azide ultimately generates 1-acyl-1-alkoxydiazenes, which are aminonitrenes **2h** [53, 54].  We have generated *N,N*-dialkoxyamides **2c** in related studies by solvolysis of *N*-alkoxy-*N*-chloroamides **2a** in aqueous alcohols and through the reaction of hydroxamic esters with hypervalent iodine reagents in appropriate alcohols [30, 55, 56].  Other anomeric amides of theoretical interest to us are *N*-amino-*N*-chloroamides **2f** [34], as well as *N*-amino-*N*-thioalkylamides **2i** and *N*-chloro-*N*-thioalkyamides **2j**.

The impact of heteroatom substitution at amide nitrogen is clearly demonstrated by comparing *N,N*-dimethylacetamide **1** to *N*-methoxy-*N*-methylacetamide **3b** and *N,N*-dimethoxyacetamide **4b**.  In 1996, we reported on the B3LYP/6-31G(d) theoretical properties of the corresponding

1    formamides **3a** and **4a** [27].  The substitution of hydrogen by methoxyl in **3a** led to an increase

2    in *N—C(O)* bond length from 1.362 Å to 1.380 Å and a second substitution at nitrogen in **4a**

3    resulted in a similar increase to 1.396 Å; the carbonyl bond contracted marginally by 0.006 Å.

4    Nitrogen in *N*-methoxy-*N*-methylformamide and *N,N*-dimethoxyformamide becomes

5    distinctly pyramidal with average angles at nitrogen of ~114°.  With similar degrees of

6    pyramidality ($\chi$), the increased *N—C(O)* bond length in *N,N*-dimethoxyformamide could not

7    solely be attributed to deformation at nitrogen.  Energetic lowering of the lone pair electrons is

8    also responsible for reduced overlap with the adjacent $C2p_z$ orbital.  This is dramatically

9    exemplified by the rotational barriers for *N,N*-dimethylformamide, *N*-methoxy-*N*-

10   methylformamide and *N,N*-dimethoxyformamide, which were computed to be of the order of

11   75, 67 and 29 kJ mol$^{-1}$, respectively [27].

12

13   Deformation energy surfaces for *N*-methoxy-*N*-methylacetamide **3b** and *N,N*-

14   dimethoxyacetamide **4b**, for comparison with that of *N,N*-dimethylacetamide **1**, are depicted

15   in Figure 5.  In contrast to *N,N*-dimethylacetamide (Figure 3), the lowest energy forms clearly

16   deviate from planarity at nitrogen with $\chi_0$ in the region of 40° and 50° respectively.  In both

17   structures, the highest point corresponding to $\chi = 0°$, $\tau = 90°$ is metastable, and the planar fully

18   twisted, and therefore non-conjugated forms, relax to fully pyramidal conformations ($\tau = 90°$,

19   $\chi = 60°$), the energy of which reflects the B3LYP/6-31G(d) barriers to amide isomerisation in

20   each case, which are approximately 67 and 44 kJ mol$^{-1}$, respectively.  While the energy

21   lowering for *N*-methoxyacetamide is modest, the attachment of two electronegative oxygens

22   to the amide nitrogen radically lowers the isomerisation barrier by some 29 – 33 kJ mol$^{-1}$.

23   Inversion barriers at nitrogen are low on account of the gain in resonance stabilisation in the

24   planar form, though the barrier is higher for *N,N*-dimethoxyacetamide where the resonance

25   capability would be less and a six $\pi$-electron repulsive effect would operate; planarisation in

26   the hydroxamic ester is less costly than in *N,N*-dimethoxyacetamide (~6.3 vs  14.6 kJ mol$^{-1}$,
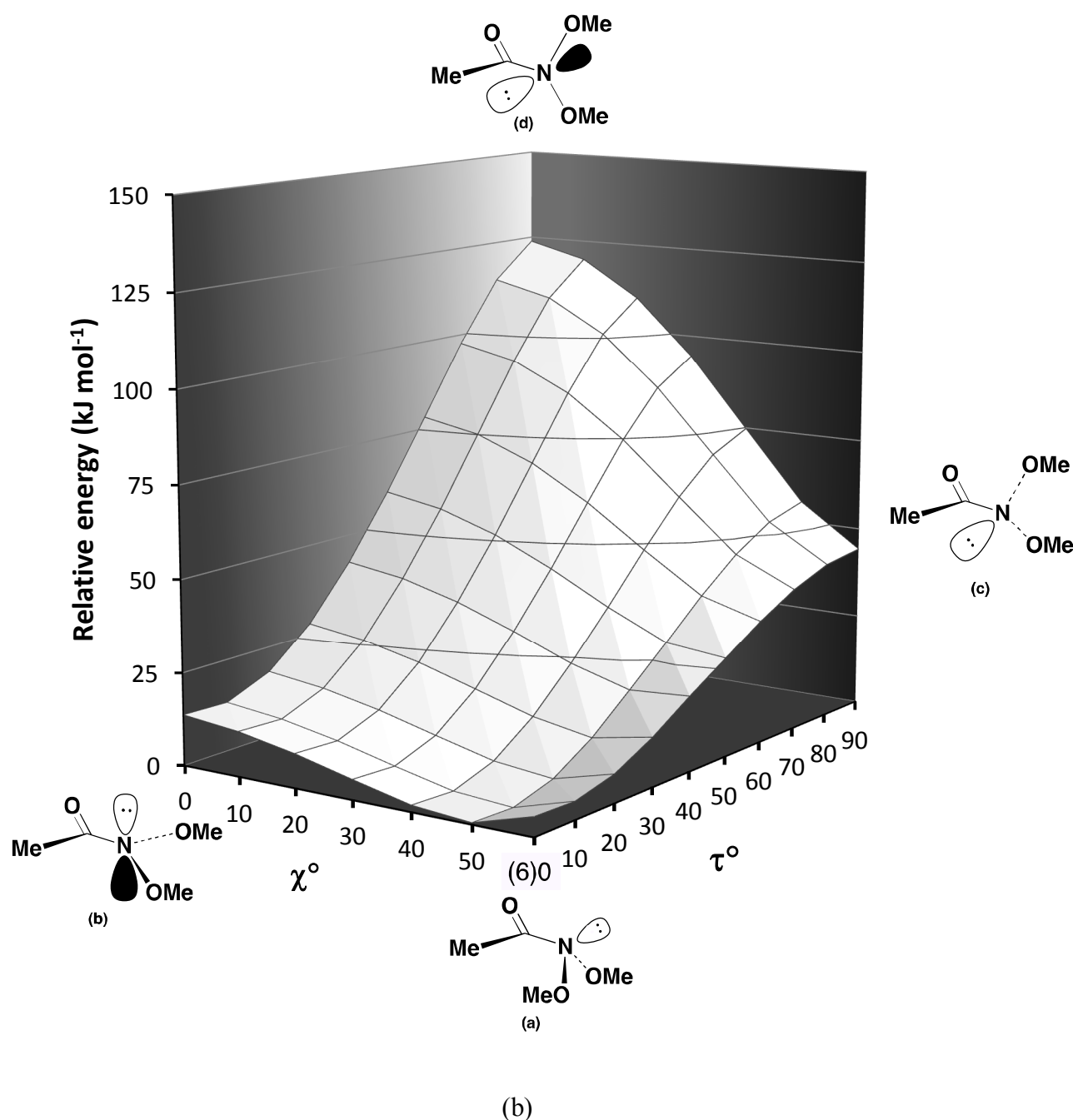
27   respectively).

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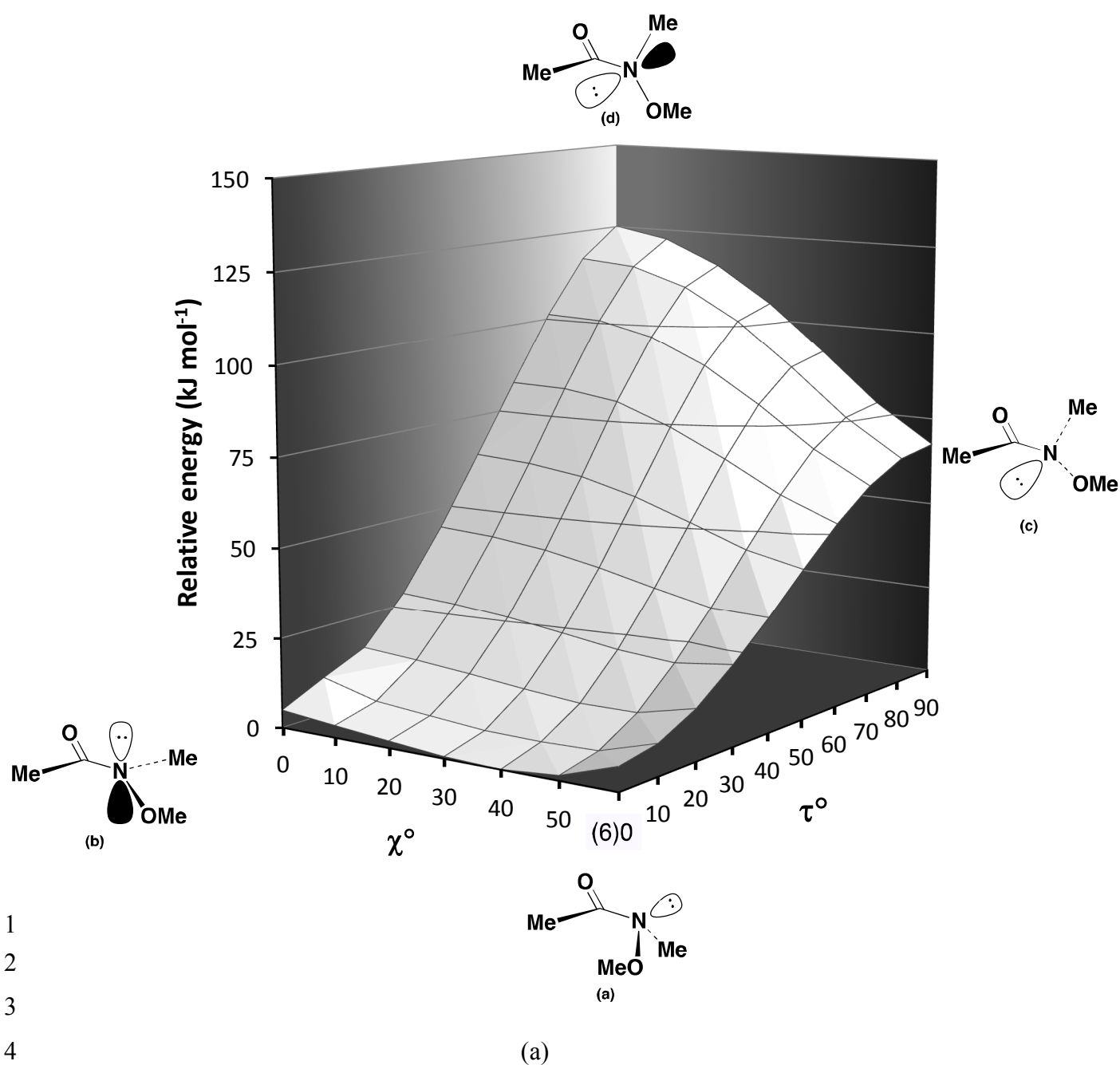
**Figure 5.** B3LYP/6-31G(d) energy surfaces for deformation of (a) *N*-methoxy-*N*-methylacetamide **3b** and (b) *N,N*-dimethoxyacetamide **4b**. (a) Untwisted system with sp$^3$ hybridised nitrogen; (b) planar untwisted structure; (c) 90° rotated structure with sp$^3$ hybridisation at nitrogen; and (d) the fully twisted moiety with sp$^2$ hybridised nitrogen.

In a recent publication, we outlined two concurring isodesmic methods for estimating the amidicity of amides and lactams [4]. Carbonyl substitution, nitrogen atom replacement (COSNAR), developed by Greenberg evaluates the energy stabilisation when the target amide is generated from corresponding ketone and amine according to isodesmic Equation 1 [57-59].

1  Steric or substituent effects are conserved throughout the reaction so steric corrections are not

2  required.

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(1)

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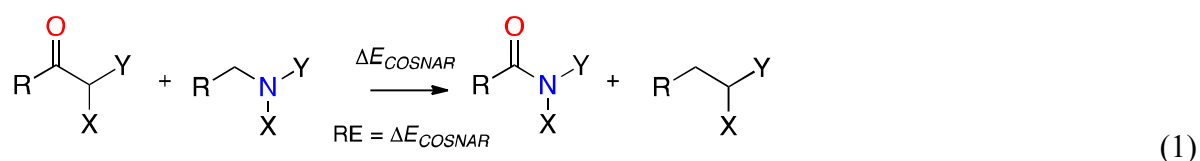
6  In the second approach, the transamidation method (TA), the energy change is determined

7  when $N,N$-dimethylacetamide **1** transfers the carbonyl oxygen to a target amine according to

8  Equation 2. The limiting energy increase for formation of fully twisted, unstrained 1-aza-2-

9  adamantanone by the corresponding reaction with 1-azaadamantane, constitutes complete loss

10  of resonance stabilisation ($\Delta E_{TA} = 76.0$ kJ mol$^{-1}$). However, where heteroatom substituents are

11  present at nitrogen, $\Delta E_{TA}$ must be corrected for any additional inductive destabilisation of the

12  carbonyl ($\Delta E_{ind}$) in the absence of resonance, which we obtain isodemically from reactions

13  such as Equation 3 [33].

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(2)

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(3)

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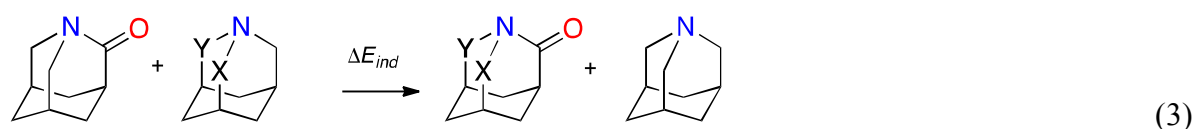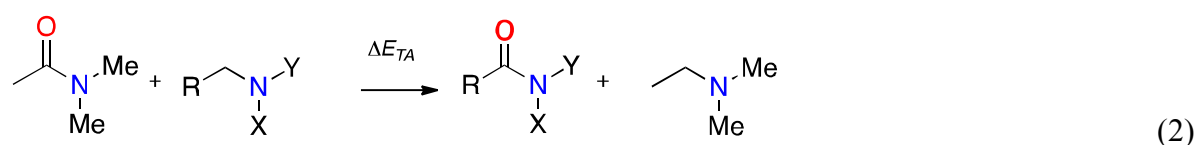
19  By the TA method, the residual resonance, RE$_{TA}$, is given by Equation 4.

20

21  $RE_{TA} = -76.0$ kJ mol$^{-1}$ + ($\Delta E_{TA} - \Delta E_{ind}$)    (4)

22

23  In both the TA and COSNAR approaches, zero point energies largely cancel and meaningful

24  results are obtained without the need for frequency calculations [58, 60]. RE by both methods,

25  the negative of the traditional representation of resonance stabilisation energy, should correlate

1   [4, 30, 33, 34, 61, 62] and RE as a percentage of $-76.0$ kJ mol$^{-1}$ (or $-77.5$ kJ mol$^{-1}$ in the case

2   of COSNAR) yields the amidicity relative to *N,N*-dimethylacetamide **1** (by definition 100%).

3   The resonance energy and amidicity of *N*-methoxy-*N*-methylacetamide **3b** has been

4   determined with COSNAR ($-62.1$ kJ mol$^{-1}$, 80% amidicity) and TA ($-61.25$ kJ mol$^{-1}$, 81%

5   amidicity) and accords nicely with the lowest rotational barrier from Figure 5(a) of 67.5 kJ

6   mol$^{-1}$.   In contrast, for the bisoxyl-substituted acetamide, the RE$_{COSNAR}$ and RE$_{TA}$ were

7   determined at $-35.9$ kJ mol$^{-1}$, respectively just 47% or 46% that of *N,N*-dimethylacetamide

8   [33].  From Figure 5(b) the rotational barrier was 44.4 kJ mol$^{-1}$ and therefore most of the barrier

9   can be accounted for by loss of resonance.

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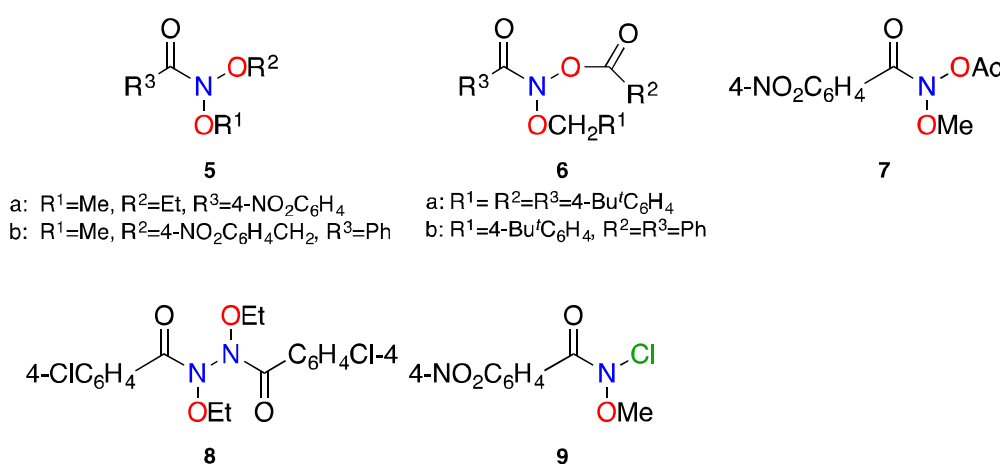
13   The unusual structure of a number of stable anomeric amides (**5-9**) has been confirmed by X-

14   ray crystallography (Figure 6) and relevant structural parameters of these are given in Table 1.

15   The X-ray structures of anomeric amides **5-9** provide clear evidence of reduced amide

16   resonance.  The data in Table 1 shows that as the combined electron demands of X and Y

17   increase, *N–C(O)* bond length and pyramidalisation at nitrogen both increase.  The reported

18   average *N–C(O)* bond length in acyclic amides is 1.359 Å (median 1.353 Å), generated from

19   Cambridge Structural Database (CSD) [29, 63], which is significantly shorter than the average

20   1.418 Å from these seven X-ray structures.   While the *(N)C=O* bond (average 1.207 Å)

21   contracts slightly compared to simple acyclic amides (1.23 Å), there is little to no correlation

22   seen between change in *(N)C=O* bond length and degree of lone pair dislocation; this may be

23   attributed to bias towards carbon in the LUMO (Figure 1) [2, 26, 35, 64].  Deviation from the

24   usual sp$^2$ hybridisation at the amide nitrogen ($\chi_N = 0$) is significant and in line with the electron

25   demands of substituents.  *N*-Acyloxy-*N*-alkoxyamides **6a**, **6b** and **7** ($\chi_N = 65.33°$, 65.62° and

26   59.7°, respectively) are pyramidalised at nitrogen to the extent of, and beyond, what is expected

1   for a pure sp$^3$ hybridisation.  The 4-nitrobenzamide **7** is less pyramidal than the benzamides **6a**

2   and **6b** presumably on account of greater positive charge at the carbonyl carbon and attendant

3   increase in nitrogen lone pair attraction.  Both *N,N*-dialkoxyamides **5a** and **5b** ($\chi_N$ = 58.3° and

4   55.6°, respectively) are also strongly pyramidalised. For Shtamburg's *N*-alkoxy-*N*-

5   chloroamide **9**, X-ray data reveals a small $\chi_N$ of 52.5°, similar to *N,N*-dialkoxyamides **5a** and

6   **5b**.  Both amide nitrogens in hydrazine **34** are the least pyramidalised with $\chi_{N1}$ and $\chi_{N2}$ of 47°

7   and 49°, respectively.

8

9   Despite high degrees of pyramidalisation in this set of anomeric amides, there is minimal twist

10  about the *N—C(O)* bond ($\tau$ = 6.7° – 15.5°). This indicates that lone pair orbital overlap with

11  the carbonyl C2p$_z$ orbital, though clearly less effective on electronic and geometric grounds,

12  remains a stabilizing influence (Table 1).  As can be seen in the B3LYP/6-31G(d) deformation

13  surface for *N,N*-dimethoxyacetamide **4b** (Figure 5(b)), the strongly pyramidal structure

14  requires twist angles ($\tau$) beyond 20° before there is significant loss of stabilization.
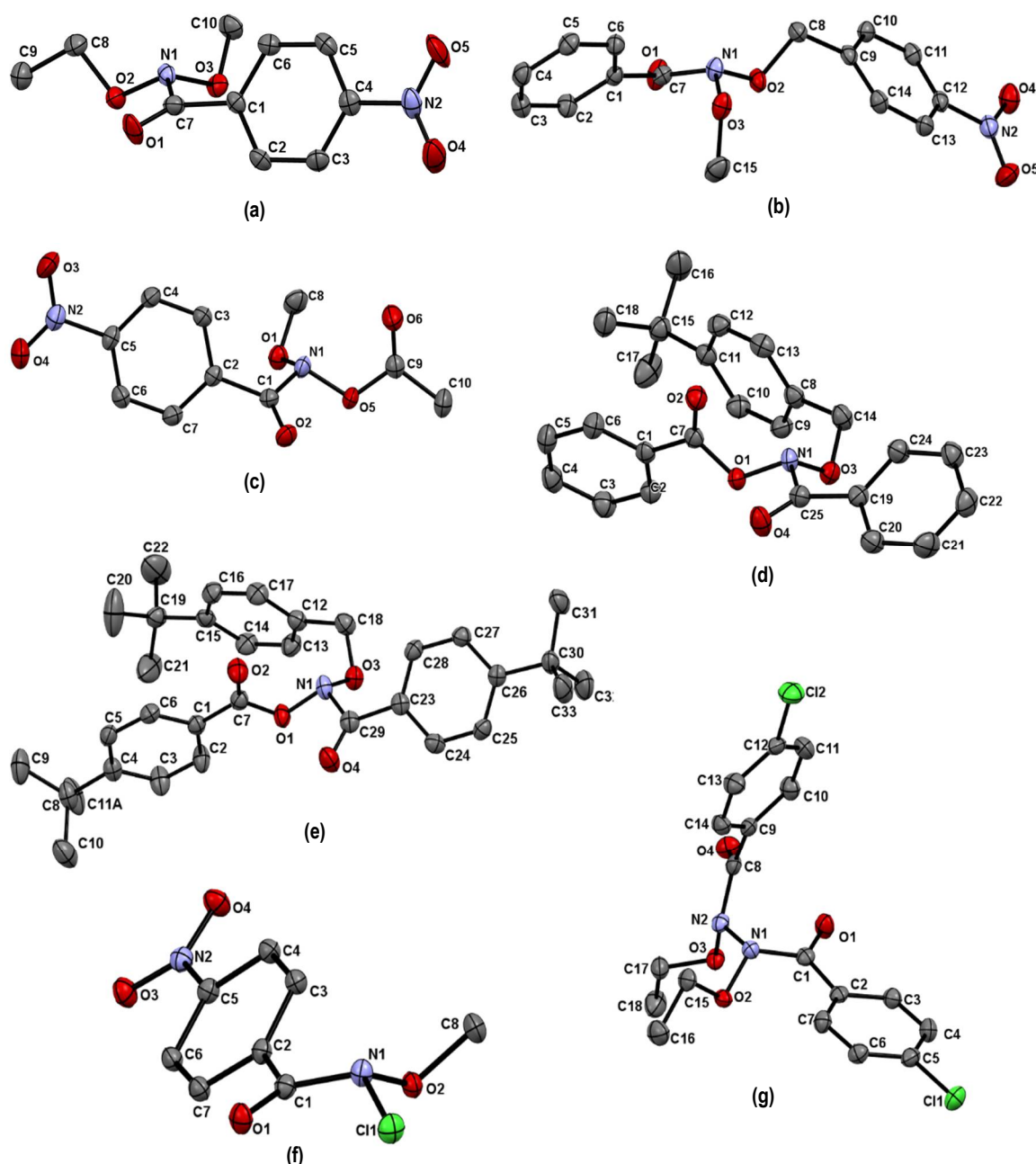
**Figure 6**. X-ray structures for (a) *N*-ethoxy-*N*-methoxy-4-nitrobenzamide **5a** [33], (b) *N*-methoxy-*N*-(4-nitrobenzyloxy)benzamide **5b** [33], (c) *N*-acetoxy-*N*-methoxy-4-nitrobenzamide **7**[65], (d) *N*-benzoyloxy-*N*-(4-*tert*-butylbenzyloxy)benzamide **6b** [29], (e) *N*-(4-*tert*-butylbenzoyloxy)-*N*-(4-*tert*-butylbenzyloxy)-4-*tert*-butylbenzamide **6a** [29], (f) *N*-chloro-*N*-methoxy-4-nitrobenzamide **9** [65] and (g) *N,N'*-4-chlorobenzoyl-*N,N'*-diethoxyhydrazine **8** [32].
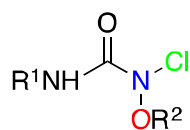
1                **Table 1.**  Selected structural data for anomeric amides **5-9** from X-ray structures (Figure 6).

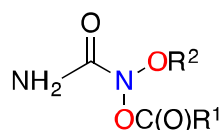| Structure | N-C(O)/Å | (N)C=O/Å | $\theta/°$ | $\chi_N/°$ | $\tau/°$ | Anomeric twist[1] $/°$ |
|---|---|---|---|---|---|---|
| **5a** [33] | 1.409(4) | 1.206(3) | 331.2 | 58.3 | 6.7 | **C10-O3-N1-O2: 95.9** <br> C8-O2-N1-O3: -114.1 |
| **5b** [33] | 1.421(2) | 1.211(2) | 334.5 | 55.6 | 13.9 | **C8-O2-N1-O3: -101.6** <br> C15-O3-N1-O2:-63.8 |
| **6a** [29] | 1.4394 | 1.2052 | 323.51 | 65.33 | 15.51 | **C18-O3-N1-O1: 96.21** <br> C7-O1-N1-O3: -141.60 |
| **6b** [29] | 1.4414 | 1.2070 | 324.14 | 65.62 | 13.93 | **C14-O3-N1-O1: 96.66** <br> C7-O1-N1-O3: -137.6 |
| **7** [65] | 1.411 | 1.203 | 330.3 | 59.7 | -14.0 | **C8-O1-N1-O5: -91.83** <br> C9-O5-N1-O1: 116.15 |
| **8(N1)** [32] | 1.412(3) | 1.213(2) | 343.2 | 47.33 | -8.49 | LP (N2)-N2 -N1-O2: 47.3 |
| **8(N2)** | 1.410(3) | 1.207(3) | 341.1 | 48.90 | -11.35 | **LP (N1)-N1-N2-O3: 178.6** |
| **9** [65] | 1.408 | 1.204 | 337.5 | 52.5 | -13.3 | **C8-O2-N1-Cl1: -84.2** |

2                            [1]Anomeric alignments in bold-face.

3

4

5    Pyramidal nitrogens and corresponding anomeric interactions have also been observed in the

6    structures of a number of urea and carbamate analogues of anomeric amides (**10-14**) studied

7    by Shtamburg and coworkers and selected structural data are presented in Table 2 [66-69].

8    Where substituent electronic effects are largely similar as in **11b** and **13**, it can be deduced that

9    the stronger conjugative effect of the α-nitrogen lone pair in the urea **11b,** relative to the α-

10   oxygen in the carbamate **13,** results in significantly less amide resonance interaction and,

11   hence, significant increase in pyramidality at the amide nitrogen.  Comparison of the ONCl
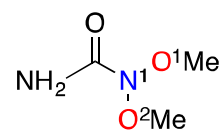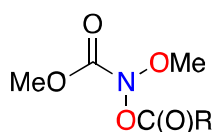
1 structures **9** and **10a** and **b**, again indicates greater pyramidality in the ureas where competing

2 acyl nitrogen resonance reduces the amide resonance interaction.



**10**

a;  R$^1$=H, R$^2$=Me
b;  R$^1$= 4-NO$_2$C$_6$H$_4$, R$^2$=C(Me)$_2$CO$_2$Me

**11**

a;  R$^1$=Me, R$^2$=Et
b;  R$^1$= 4-ClC$_6$H$_4$, R$^2$=Bu
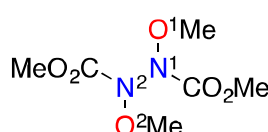
**12**

**13**

a;  R=4-ClC$_6$H$_4$

**14**

5 **Table 2.** Selected structural data for ureas **10-12** and carbamates **13-14** from X-ray structures.

| Structure | N-C(O)/Å | (N)C=O/Å | $\theta$/° | $\chi_N$/° | $\tau$/° | Anomeric twist[1] /° |
|---|---|---|---|---|---|---|
| **10a** [66] | 1.443 | 1.226 | 329.1 | 59.9 | 8.2 | **C-O-*N*-Cl: –90.9** |
| **10b** [66] | 1.472 | 1.210 | 325.8 | 61.9 | −13.4 | **C-O-*N*-Cl: –100.1** |
| **11a** [67] | 1.426 | 1.222 | 333.6 | −57.1 | −6.8 | **C-O-*N*-Oacyl: –104.0** |
| **11b** [68] | 1.441 | 1.233 | 323.7 | 64.6 | 11.8 | **C-O-*N*-Oacyl: –98.2** |
| **12** [68] | 1.438 | 1.220 | 331.8 | 57.4 | 0.8 | **C-O2-N1-O1: –89.3** <br> C-O1-N1-O2: 55.2 |
| **13** [67] | 1.424 | 1.198 | 334.2 | −56.3 | 2.9 | **C-O-*N*-Oacyl: –95.5** |
| **14** [69] (N1)/(N2)[2] | 1.408 | 1.194 | 340.0 | 59.8 | −9.4 | **LP (N1)-N1-N2-O: 189.2** |

6    [1]Anomeric alignments in bold-face; [2] Equivalent nitrogens.

8 These and other anomeric amides have been modelled at B3LYP/6-31G(d) level in the

9 simplified acetamide system and ground state models of **15a-d** systems display high degrees

10 of pyramidality, little *N—C(O)* twist, long *N—C(O)* bonds and slightly shortened *(N)C=O*

11 bonds, in line with the electron demands of substituents and, where applicable, are reasonable

12 approximations of their respective X-ray structure counterparts (Figure 7, Table 3).  ONS and

13 NNCl analogues, **15d** and **15e**, have only been generated as intermediates in reactions but their

1    theoretical structures are in line with those of anomeric systems **15a-d**; *N—C(O)* bond lengths

2    and pyramidality at nitrogen ($\chi$) are broadly in line with the gross electronegativity of

3    substituents at nitrogen.  Sulfur, with its low electronegativity, results in a less pyramidal

4    nitrogen, while the NNCl system **15e**  is completely planar (and untwisted) for steric reasons.

5    Nonetheless, its *N—C(O)* bond is comparatively long. The carbamate and the urea **16a** ($\chi$ =

6    46.3°) and **16b** ($\chi$ = 49.6°) are both more pyramidal than the corresponding acetamide **15c** ($\chi$ =

7    41.8°), presumably as a result of competing resonance from the $\alpha$-oxygen and $\alpha$-nitrogen lone

8    pairs.



**15**
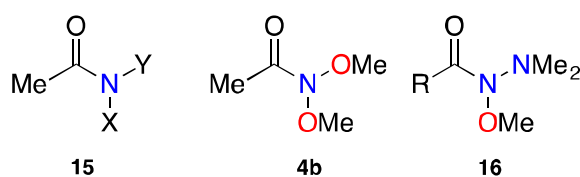
a: X=Cl, Y=OMe
b: X=OAc, Y=OMe
c: X=OMe, Y=NMe$_2$
d: X=OMe, Y=SMe
e: X=Cl, Y=NMe$_2$
f:  X=OMe, Y=O⁻
g: X=OMe, Y=N

**4b**

**16**

a: R=MeO
b: R=M$_2$N

9
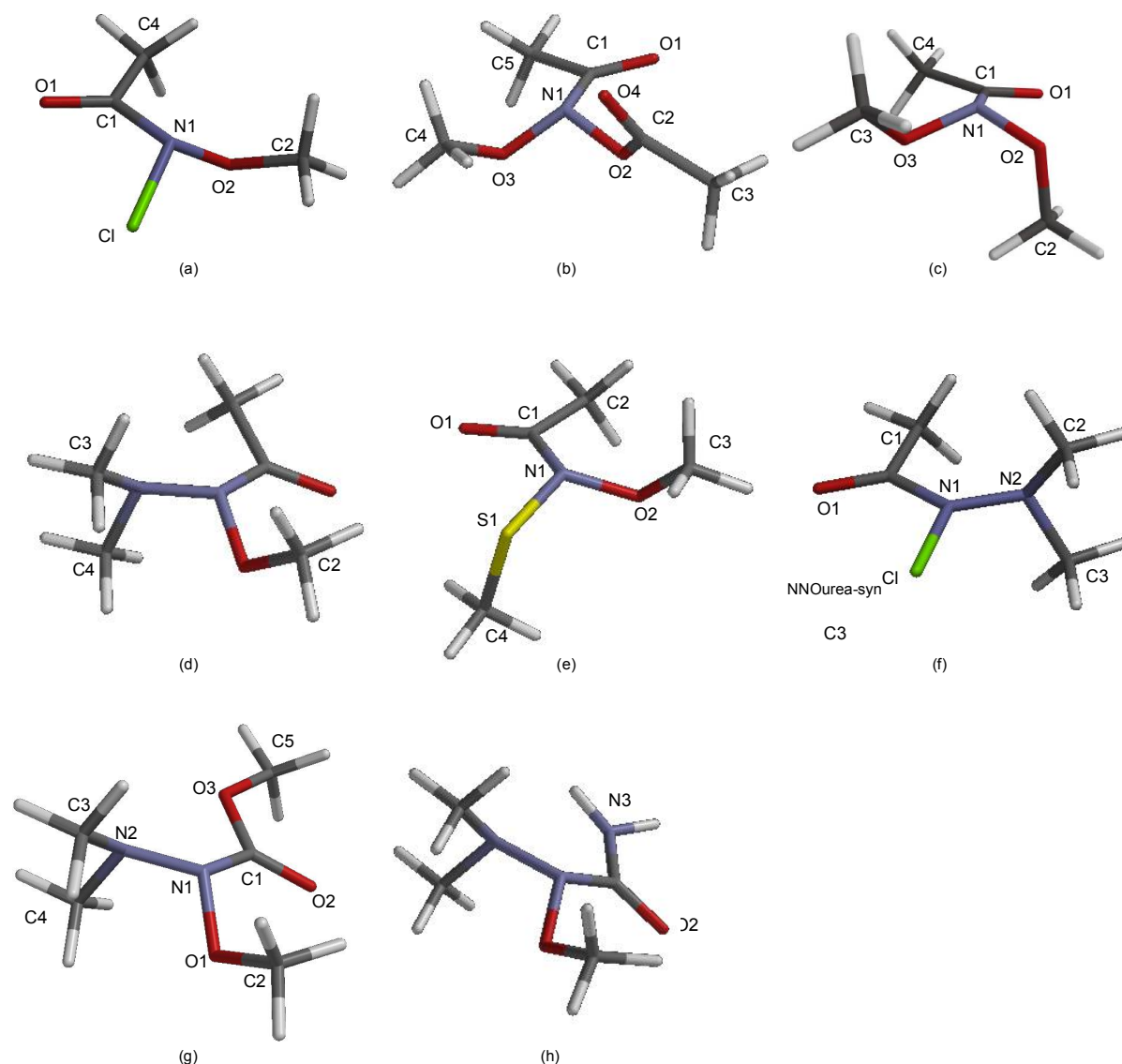
**Figure 7**. B3LYP/6-31G(d) lowest energy ground state conformers of model anomeric acetamides (a) *N*-chloro-*N*-methoxyacetamide **15a,** (b) *N*-acetoxy-*N*-methoxyacetamide **15b**, (c) *N,N*-dimethoxyacetamide **4b**, (d) *N*-methoxy-*N*-dimethylaminoacetamide **15c**, (e) *N*-methoxy-*N*-methylthiylacetamide **15d**, (f) *N*-chloro-*N*-dimethylaminocetamide **15e**, (g) *O*-methyl *N*-methoxy-*N*-dimethylaminoacetamide **16a** and (h) *N*-methoxy-*N*-dimethylaminourea **16b**.

1   **Table 3**. Selected structural data for B3LYP/6-31G(d) lowest energy conformers of model acetamides **4b**, **15a-e** and **16a,b**.

| Structure | N-C(O)/Å | (N)C=O/Å | (N-X,*N*-Y)/Å | $\theta$ /° | $x_N$ /° | $\tau$ /° | Anomeric twist angles[1] /° |
|---|---|---|---|---|---|---|---|
| **15a** ONCl [34] | 1.432 | 1.207 | Cl:1.787 O2:1.389 | 337.6 | 52.3 | −5.3 | **C2-O2-N1-Cl: 88.8** |
| **15b** ONOAc [61] | 1.429 | 1.209 | O2:1.423 O3:1.395 | 332.1 | 58.0 | 2.3 | **C4-O3-N1-O2: 101.1** |
| **4b** ONO [33] | 1.417 | 1.212 | O2:1.387 O3:1.412 | 342.9 | 48.1 | 8.5 | C2-O2-N1-O3: 66.6 **C3-O3-N1-O2: 83.8** |
| **15c** NNO [62] | 1.404 | 1.217 | O1:1.430 N2:1.387 | 346.5 | 41.8 | 5.4 | **LP (N2)-N2-N1-O1: 190** |
| **15d** ONS [61] | 1.408 | 1.215 | S1:1.717 O2:1.420 | 352.4 | 31.7 | −4.6 | C4-S1-N1-O2:–79 **C3-O2-N1-S1: –86.6** |
| **15e** NNCl [34] | 1.414 | 1.209 | Cl:1.820 N2:1.351 | 360.0 | 0 | 0 | **LP(N2)N2-N1-Cl: 180** |
| **16a** NNO **[61]** | 1.406 | 1.212 | O1:1.404 N2:1.383 | 342 | 46.3 | 0 | **LP (N2)-N2-N1-O1: 169.4** |
| **16b** NNO | 1.428 | 1.217 | O1:1.397 N2:1.428 | 340.0 | 49.6 | −1.7 | **LP (N2)-N2-N1-O1: 167.5** |

2                                         [1] Anomeric alignment in bold face

3

4   *2.2 Resonance energies and amidicities*

5   The resonance energy and the amidicity of anomeric amides **4b, 15a-e** have been calculated at

6   the B3LYP/6-31G(d) level by both the TA and COSNAR methods and by the COSNAR

7   method using dispersion corrected M06/6-311++G(d,p). $\Delta E_{COSNAR}$ (Equation 1), reaction

8   energies ($\Delta E_{TA}$) (Equation 2), inductive stabilization corrections ($\Delta E_{ind}$) (Equation 3), resultant

9   RE$_{TA}$ together with COSNAR and TA amidicities are presented in Table 4.

10

11

**Table 4**. B3LYP/6-31G(d), B3LYP/6-311++G(d,p) and M06/6-311++G(d,p) derived resonance energies and amidicities of model anomeric acetamides **4b**, **15a-e** and **16a**.

| Amide (R=Me) | $\Delta E_{COSNAR}$[1] /kJ mol⁻¹ | $\Delta E_{TA}$ /kJ mol⁻¹ | $\Delta E_{ind}$ /kJ mol⁻¹ | $RE_{TA}$[1] /kJ mol⁻¹ |
|---|---|---|---|---|
| **15a** (ONCl) [34] | –29.6(38) | 69.9 | 23.4 | –29.5(39) |
| **15a**[2] | –27.2(36) | - | - | - |
| **15a**[3] | –34.4(45) | - | - | - |
| **15b**(ONOAc) [61] | –39.7(52) | 65.3 | 29.7 | –40.5(53) |
| **15b**[3] | –39.5 (52) | | | |
| **4b**(ONO)[35] | –36.0(47) | 58.2 | 18.0 | –36.0(47) |
| **4b**[3] | –39.5(53) | | | |
| **15c**(ONN) [62] | –52.3(69) | 35.1 | 10.0 | –51.0(67) |
| **15c**[3] | –55.7(73) | | | |
| **15d**(ONS) [61] | –48.6(64) | 26.8 | 5.0 | –48.6(64) |
| **15d**[3] | –47.3(62) | | | |
| **15e**(NNCl) [34] | –28.7(38) | 64.5 | 17.6 | –29.0(37) |
| **15e**[2] | –28.6(38) | - | - | - |
| **15e**[3] | –48.7(64) | - | - | - |
| **16a** (ONN) [61] | –47.7 (63) | 31.8 | 14.6 | –50.6(67) |
| **1** | –75.9 (100) | | | |
| **1**[3] [34] | –75.9 (100) | | | |

[1]Amidicity (%) in parentheses; [2] At B3LYP/6-311++G(d,p); [3] M06/6-311++G(d,p)

The TA and COSNAR methodologies give almost identical resonance energies for all the anomeric amides (**4b**, **15a-e**) at the B3LYP/6-31G(d) level. $\Delta E_{COSNAR}$ determined at M06 with the expanded basis set yields very similar results to B3LYP/6-31G(d) for *N,N*-dimethylacetamide **1** and the anomeric amides with the exception of **15e**, where resonance is computed to be just over 60% that of *N,N*-dimethylacetamide and substantially higher than that predicted from B3LYP/6-311++G(d,p), which was identical to the B3LYP/6-31G(d) value (29 kJ mol⁻¹) [34]. The RE parity for **15a** and **15e** at B3LYP is no longer observed with M06, in line with the lower overall electronegativity of nitrogen and chlorine. These results impute the necessity for inclusion of dispersion corrections in treatments of molecules where anomeric interactions are likely to have a pronounced influence.

It is clear that resonance in anomeric amides is impaired, broadly in line with the gross electronegativity or negative inductive effect of the atoms/groups bonded to nitrogen. Interestingly, the ONN and ONS acetamides, **15c** and **15d** have very similar resonance energies despite the much lower electronegativity of sulfur. From Bent's rule, the opposite effect would

1  be expected, since s-character in the lone pair orbital should decrease with decreasing

2  electronegativity of X.  This is likely to be a manifestation of the role of orbital size since the

3  influence of second period elements is significant; nitrogen increases p-character in the bond

4  to sulfur to effect better overlap with the larger, 3p orbital of sulfur.  Consequently, the nitrogen

5  lone pair gains more "s" character relative to the amide nitrogen in the NNO acetamide **15c**,

6  resulting in less amide resonance [36, 37, 70].  Comparing the M06 values, ONCl and ONO

7  systems have about half the resonance of *N,N*-dimethylacetamide while NNO, NNCl and ONS

8  are computed to preserve some 60-70%  of the resonance of *N,N*-dimethylacetamide.

9

10  *2.3 The anomeric effect*

11  In addition to their reduced amide resonance,  anomeric amides are exemplars of XNY systems

12  featuring an anomeric effect [26, 35].  There are two possible anomeric interactions designated

13  as  $n_X - \sigma^*_{NY}$ and $n_Y - \sigma^*_{NX}$ and where X and Y are different electronegative atoms, one of

14  these interactions will be favoured over the other (Figure 8).  By analogy with anomeric carbon

15  centres [26, 35, 71-73], the relative electronegativities of heteroatoms X and Y at nitrogen and

16  the relative sizes of interacting orbitals contribute to the strength of an anomeric interaction.

17  Heteroatoms Y and X directly influence the relative energies of $n_Y$ and $\sigma^*_{NX}$, which, in turn,

18  affect the net stability gain for the lone pair electrons (Figure 9a).

19



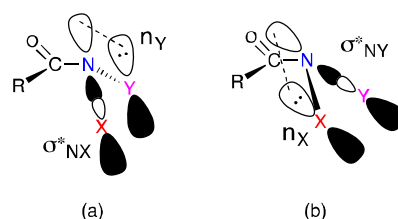20                    (a)                    (b)

21  **Figure 8.** Two possible anomeric interactions in anomeric amides (a) $n_Y - \sigma^*_{NX}$ and (b) $n_X - \sigma^*_{NY}$

22

23  As the electronegativity of X and Y increases by going across the p-block row on the periodic

24  table, $\sigma^*_{NX}$ (and $\sigma_{NX}$) decreases in energy as does $n_Y$.  Additionally, as X decreases in

25  electronegativity by going down a p-block group, $\sigma^*_{NX}$ decreases in energy due to reduced

26  orbital overlap [26, 35, 36, 71, 72].  An optimal anomeric effect can be achieved when Y is an

27  early p-block element and X is a p-block element to the right of Y on the periodic table; more

28  specifically an anomeric stabilisation will be greater when the energy gap between $n_Y$ and $\sigma^*_{NX}$

29  is lower (Figure 9b) [74, 75].  In the unusual case of anomeric amides, where the nitrogen  may

30  range between planar sp$^2$ and pyramidal sp$^3$ hybridisation, the geometry of the central nitrogen

1    atom in XNY systems also plays a role, as pyramidal nitrogen is more conducive to edge-on

2    $n_Y$ and $\sigma^*_{NX}$ overlap than is planar, sp$^2$ hybridised nitrogen (Figure 10a) [26, 35].
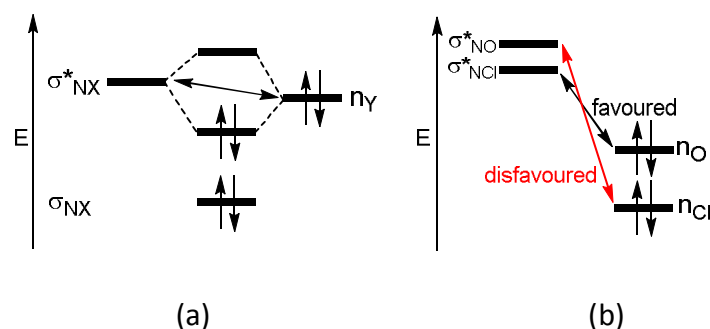
3



(a)                                    (b)

**Figure 9**. (a) Stabilisation of a lone pair through a $n_Y - \sigma^*_{NX}$ anomeric interaction; (b) the energetics of the anomeric effect in **15b**.

9

10    Similar to XCY configurations, in an XNY system, a stabilising $n_Y - \sigma^*_{NX}$ anomeric effect, for

11    example, can cause the amide to adopt a gauche conformation in which the lone pair of Y is

12    coplanar with the vicinal to *C—X* bond (Figure 10b) [71, 74]. In anomeric amides, when $n_Y$ is

13    divalent oxygen or sulfur, an *R-Y-N-X* dihedral angle close to |90°| aligns the p-type lone pair

14    on those atoms with the vicinal $\sigma^*_{NX}$ (Figure 10b).   Where the donor is $n_N$, an optimum

15    anomeric effect would need the lone pair on nitrogen to be *antiperiplanar* to X, *LP(N)-N-N-X*

16    = 180° (Figure 10c). Consequences of the $n_Y - \sigma^*_{NX}$ interaction include an increased barrier to

17    rotation about the *N—Y* bond (Figure 10d), a contraction of the *N—Y* bond and an extension of

18    the *N—X* bond as electrons from Y populate the $\sigma^*_{NX}$ orbital.

19



(a)                          (b)                          (c)                          (d)
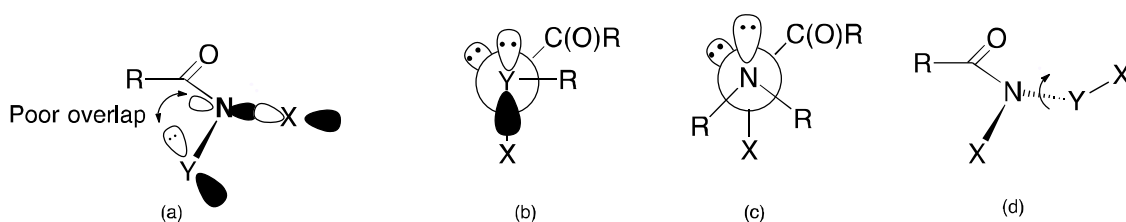
**Figure 10**. (a) sp$^2$ hybridised nitrogen hinders overlap with heteroatom Y in an $n_Y - \sigma^*_{NX}$ system; (b) optimum conformation in an $n_Y - \sigma^*_{NX}$ anomeric interaction; (c) optimum conformation in an $n_N - \sigma^*_{NX}$ anomeric interaction; (d) restricted rotation about the N–Y bond in an $n_Y - \sigma^*_{NX}$ anomeric interaction.

25

1  In each of the X-ray structures in Figure 6 there is clear evidence of these anomeric interactions

2  (Table 1, bold-face torsion angles).  On the basis of energetics, the expected anomeric

3  interactions are $n_O – \sigma^*_{NOAc}$ in **6a**, **6b** and **7**, $n_N – \sigma^*_{NO}$ in **8** and $n_O – \sigma^*_{NCl}$ in **9**.  In **5a** and **5b**

4  one $n_O – \sigma^*_{NO}$ would be expected to prevail.  Dihedral angles about the *N—O* bonds in **5-7**, **9**

5  show a preferred p-type lone pair alignment with the adjacent $\sigma^*_{NO}$, $\sigma^*_{NOAc}$ or $\sigma^*_{NCl}$ bond.  In

6  hydrazine **8**, the lone pair on N1 is almost perfectly aligned with the *N2—O3* bond while the

7  N2 lone pair makes an angle of only 47° to the *N1—O2* bond (1.403 Å), which is shorter than

8  the anomerically destabilised bond *N2—O3* (1.411 Å).  The structure is asymmetrical with a

9  donor N1 and recipient N2.  Similar anomeric interactions are observable in ureas **10-12** and

10  carbamates **13** and **14** (Table 2).

11

12  All computed structures exhibit an anomeric interaction (Table 3, bold-face torsion angles)

13  and, besides the ONO system where one $n_O – \sigma^*_{NO}$ prevails, an anomeric $n_O – \sigma^*_{NX}$ prevails in

14  ONCl, ONOAc, and ONS in line with expectations based on electronegativity.  The size of the

15  sulfur p-orbital and lower energy of the $\sigma^*_{NS}$ renders an $n_S – \sigma^*_{NO}$ anomeric interaction less

16  likely than a $n_O – \sigma^*_{NS}$ stabilisation.  Where nitrogen  is present, the $n_N – \sigma^*_{NO}$ and $n_N – \sigma^*_{NCl}$

17  interactions are clearly in evidence.

18

19  The anomeric effects not only dictate stereochemistry at nitrogen but, as will be seen, combined

20  with reduced amide resonance, they have a profound impact upon spectroscopic properties and

21  the reactivity of anomeric amides.

22

23  *2.4 Spectroscopic properties of anomeric amides.*

24  Spectroscopic properties of anomeric amides are strongly influenced by reduced resonance due

25  to electronegativity of substituents at nitrogen.  Infrared and $^{13}$C NMR data for a diverse range

26  of ONCl, ONOAcyl [26, 31, 35] and ONO systems [35, 55] have been reported as well as for

27  a number of ONN *N,N'*-dialkoxy-*N,N'*-diacylhydrazines [76-78].  Representative infrared

28  carbonyl stretch frequencies in solution  for stable anomeric amides (Table 5) are significantly

29  higher (1700 to 1750 cm$^{-1}$) [32, 47, 55, 79-81] than those of their precursor hydroxamic esters

30  (1650 to 1700 cm$^{-1}$) and primary (1690 cm$^{-1}$), secondary (1665 to 1700 cm$^{-1}$) and tertiary (1630

31  to 1670 cm$^{-1}$) alkylamides [26, 35, 82].  While there is a slight tightening of the *(N)C=O* bond,

32  the increase in $\nu_{C=O}$ has been attributed primarily to electronic destabilisation of single-bond

33  resonance form of the carbonyl as electron density is pulled towards the electronegative

1    heteroatoms on nitrogen, resulting in a more ketonic carbonyl bond [2, 64]. Likewise,

2    anomeric amides exhibit more ketonic carbonyl $^{13}$C chemical shifts (CDCl$_3$), with downfield

3    shifts of approximately 8.0 ppm from their hydroxamic ester precursors. Deshielding of the

4    carbonyl carbon is an expected consequence of the electron-withdrawing substituents.

5    However, like acid chlorides and anhydrides, the carbonyls resonate upfield of ketones, relative

6    to which the electron density at the carbonyl is increased on account of greater double bond

7    character.

8

9    **Table 5**. Typical spectroscopic data for stable anomeric alkanamides and arylamides (RC(O)NXY), and their hydroxamic

10                                                         ester precursors.

| System | X | Y | R | Amide v/cm$^{-1}$ ($\delta^{13}$C) | Hydroxamic ester v/cm$^{-1}$ ($\delta^{13}$C) |
|---|---|---|---|---|---|
| **2a** [79] | Cl | OBu | Me | 1740$^1$(175.3) | 1678 (167.9) |
| **2a** [35] | Cl | OBu | Ph | 1719 (174.2) | 1654 (165.7) |
| **2b** [79] | OAc | OBu | Me | 1746 (176.2) | 1678 (167.9) |
| **2b** [80] | OAc | OBu | Ph | 1732 (173.9) | 1654 (165.7) |
| **2c** [81] | OBu | OBu | Me | 1707 (174.1) | 1678$^1$ (167.9) |
| **2c** [55] | OMe | OMe | Ph | 1711 (174.3) | 1683 (166.4) |
| **2d** [76] | 4-MeBnONAc | 4-MeBnO | Me | 1734/1700 (171.3) | 1693 (168.0) |
| **2d** [76] | BzNOEt | OEt | Ph | 1708 (170.0) | 1685 (166.5) |

11                                                         $^1$ Neat

12

13    Common primary, secondary and tertiary amides have significant *cis-trans* isomerisation

14    barriers for rotation about the *N—C(O)* bond, due to the stabilising effect of amide resonance

15    in their ground state [2]. Restricted rotation through lone pair overlap with the adjacent

16    carbonyl C2p$_z$ orbital, as illustrated in Figure 1, often results in observation of different

17    chemical shifts of *cis* and *trans* conformers in their $^1$H NMR spectra, from which barriers to

18    isomerisation can be deduced [83, 84]. The computed surface for *N,N*-dimethylacetamide in

19    Figure 3 indicates that the barrier (difference between the completely planar and the fully

20    rotated-pyramidal forms) is of the order of 71 – 75 kJ mol$^{-1}$. Hydroxamic esters have slightly

21    less resonance and amidicity, and the rotation barrier for *N*-methoxy-*N*-methylacetamide from

22    Figure 5a is approximately 67 kJ mol$^{-1}$. Many hydroxamic esters have broadened $^1$H NMR

23    signals at ambient temperatures. Anomeric amides with lower resonance should have lower

1    *cis-trans* isomerisation barriers as exemplified in the model *N,N*-dimethoxyacetamide in Figure

2    5b.  Accordingly, the isomerisation barrier in bisoxyl-substituted amides **2b** and **2c** are too low

3    to be measured by usual dynamic NMR methods.  All proton signals of *N,N*-dimethoxy-4-

4    toluamide remained sharp down to 180 K (in $d_4$-methanol) and the ^{1}H NMR signals for *N*-

5    acetoxy-*N*-benzyloxybenzamide remained isochronous down to 190 K (in $d_8$-toluene) [26].

6    The barrier for *N*-benzyloxy-*N*-chlorobenzamide could likewise not be determined by dynamic

7    NMR [35].

8

9    Figure 11 illustrates the dramatic difference between ^{1}H NMR spectra of *N*-butoxyacetamide

10    and its *N*-chloro- or *N*-acetoxyl derivatives as a consequence of reduced resonance in the

11    anomeric structures, which clearly have much lower isomerization barriers.  At room

12    temperature, the anomeric amides are in the fast exchange region as opposed to the slow

13    exchange in the hydroxamic ester.  Earlier theoretical studies by Glover and Rauk support this

14    assertion [27, 28].  For example, a comparison of formamide **17a**, *N*-methoxyformamide **17b**

15    and *N*-chloro-*N*-methoxyformamide **17d**, calculated at the B3LYP/6-31G(d) level, showed

16    little reduction in the  *cis-trans* isomerisation barrier of 73.2 kJ mol$^{-1}$ in formamide, to 67 – 75

17    kJ mol$^{-1}$ in *N*-methoxyformamide.  However, the introduction of a second electronegative

18    heteroatom, Cl, reduced the barrier to only 32.2 kJ mol$^{-1}$, indicating that monosubstitution

19    alone is insufficient to impact upon the isomerisation barrier [27].  A theoretical isomerisation

20    barrier for *N*-methoxy-*N*-(dimethylamino)formamide, which, by analogy with typical NNO

21    systems, should retain about 70% the resonance in *N,N*-dimethylacetamide, was computed to

22    be higher at 52.7 kJ mol$^{-1}$ [28].  Such an amide isomerisation barrier in the hydrazine, *N,N′*-

23    diacetyl-*N,N′*-di(4-chlorobenzyloxy)hydrazine **19**, was measurable at $\Delta G^{\ddagger}_{278} = 54.0$ kJ mol$^{-1}$,

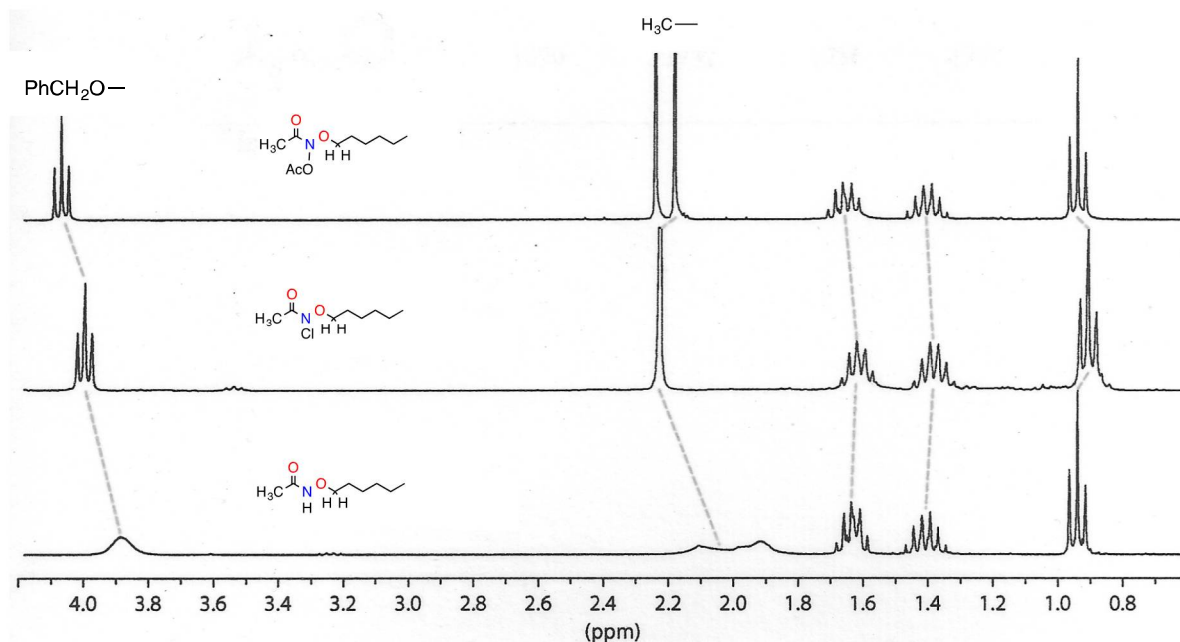24    in line with this theoretical barrier [27].

25

1

2

3   **Figure 11**. ^{1}H NMR spectra (300K, CDCl₃) of *N*-butoxyacetamide, and anomeric amides *N*-butoxy-*N*-

4   chloroacetamide and *N*-acetoxy-*N*-butoxyacetamide

5

6   The intrinsic barrier to inversion at nitrogen in bisheteroatom-substituted amides is expected

7   to be much lower than those of analogous amines.  The transition state for inversion in anomeric

8   amides is expected to be planar, where the nitrogen lone pair can interact with the carbonyl $2p_z$

9   orbital generating stabilisation (Figure 5b(b)) [35]. Several theoretical estimates put these

10  barriers at about 10 kJ mol$^{-1}$ [28].

11



12

13
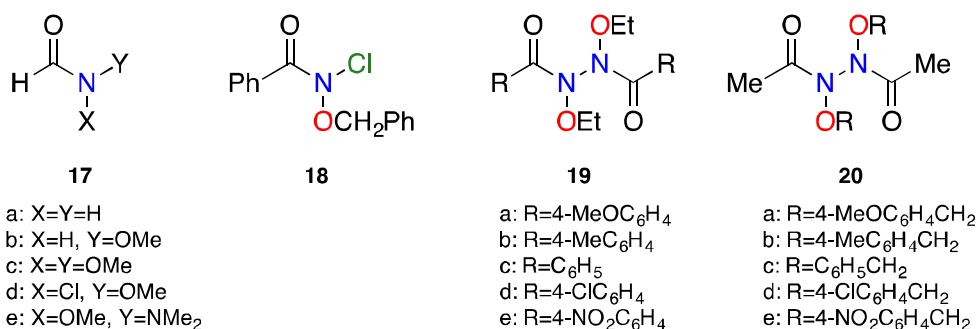
14  In anomeric systems,  strong $n_Y - \sigma^*_{NX}$ interactions should increase the bond order of the *N—*

15  *Y* bond, which should impose barriers to rotation about those bonds.   For *N*-chloro-*N*-

16  methoxyformamide **17d**, the *N—O* and *N—C(O)* rotation barriers have been estimated at the

17  B3LYP/6-31G(d) level at 44.7 and 29.2 kJ mol$^{-1}$, respectively [27], while the theoretical barrier

1    to rotation about the *N—N* bond in *N*-methoxy-*N*-dimethylaminoformamide **17e** was computed

2    at ~60 kJ mol$^{-1}$[28].  Experimental measurements for both anomerically induced barriers have

3    been made.  An *N—O* anomeric rotational barrier of $\Delta G^{\ddagger}$ = 43 kJ mol$^{-1}$ has been determined

4    for *N*-chloro-*N*-benzloxybenzamide **18**, where the benzylic methylenes become diastereotopic

5    at 217 K in $d_8$-toluene, but as no amide isomerisation could be detected, that barrier must be

6    significantly lower  [26].  An anomerically induced rotational barrier  for *N—N'* bond in a

7    number of *N,N*-diacyl-*N,N*-dialkoxyhydrazines **19a-e** and **20a-e** has been measured in dynamic

8    $^1$H NMR studies [32].  Methylene signals of *N,N'*-diethoxy **19a-e** and *N,N'*-dibenzyloxy groups

9    **20a-e**, which were diastereotopic at room temperature, as a consequence of restricted rotation

10   about the *N—N'* bond, coalesced at higher temperatures ($T_c$ = 316 – 346 K) from which

11   rotational free energy barriers of the order of 60 – 70 kJ mol$^{-1}$ could be determined [32], which

12   compares favourably with the theoretically calculated *N—N'* rotational barrier of 60 kJ mol$^{-1}$

13   [28].

14

15   **3. Reactivity of anomeric amides**

16   The reduced resonance and attendant pyramidalisation at the amide nitrogen together with

17   anomeric properties of these unusual molecules results in a plethora of amide reactivity, some

18   known, and now better understood, and others that are unique to anomeric amides.  The

19   destabilisation of the amide bond, coupled with the substitution pattern, facilitates reactivity at

20   the amide nitrogen in which the amides are usually transformed from one anomeric amide form

21   to another.  Moreover, it can induce a novel process, known as the HERON reaction, in which

22   the amide bond is broken to form acyl derivatives and heteroatom-stabilised nitrenes.  This

23   reaction is facilitated by weakened amide resonance, but is driven by $n_Y - \sigma^*_{NX}$ anomeric

24   destabilisation of the *N—X* bond.

25

26   *3.1 Reactivity at the amide nitrogen*

27   Due to their characteristic, diminished amide resonance and anomeric destabilisation, this class

28   of amide has been shown to undergo $S_N2$ reaction at nitrogen, and elimination of *N*-substituents

29   leading to $S_N1$-type processes. Several congeners undergo thermolytic homolysis to give

30   alkoxyamidyl radicals.

31

32   3.1.1 $S_N2$ Reactions

1    In XNY systems, a moderate $n_Y - \sigma^*_{NX}$ negative hyperconjugation leads, through neighbouring

2    group participation, to weakening of the *N—X* bond, which can encourage $S_N2$ reactions at

3    nitrogen [26, 31, 35]. The increased electrophilicity of nitrogen in *N*-acyloxy-*N*-alkoxyamides

4    **21** leaves them vulnerable to attack by arylamines (Scheme 1 i) [42, 44, 47, 51], azide (Scheme

5    1 ii) [54], hydroxide (Scheme 1 iii) [45], and thiols (Scheme 1 iv) [52], the outcomes from

6    which are anomerically substituted intermediates **22 – 24** and **26**  that ultimately may undergo

7    HERON reactions. Furthermore, *N*-acyloxy-*N*-alkoxyamides **21** themselves may be

8    synthesised in $S_N2$ reactions between *N*-alkoxy-*N*-chloroamides **25** and sodium or silver

9    carboxylates (Scheme 1 vi) [43, 45, 46, 48, 51, 80, 85]. *N*-alkoxy-*N*-chloroamides  **25** also react

10    bimolecularly with azide generating reactive *N*-alkoxy-*N*-azidoamides  **26** (Scheme 1 v) [54].

11



12
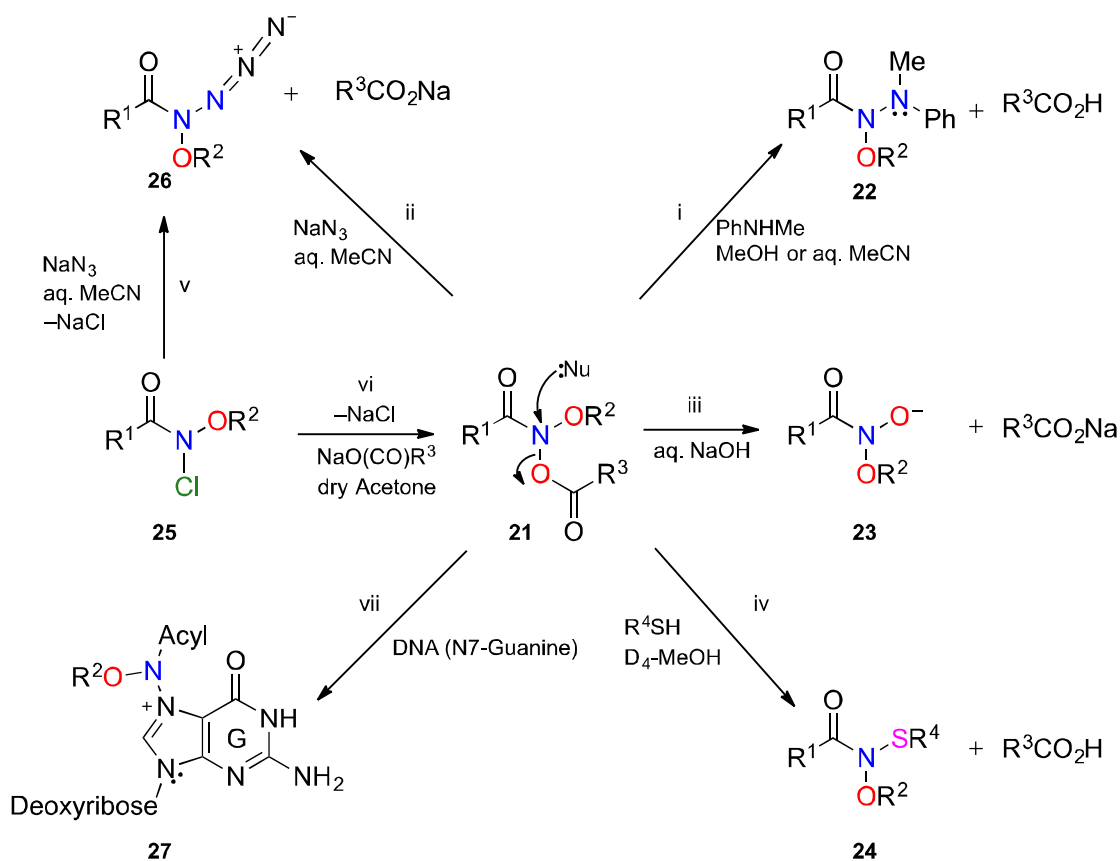
13    **Scheme 1**. $S_N2$ reactions of *N*-acyloxy-*N*-alkoxyamides **21** with: i, arylamines; ii, azide; iii, hydroxide; iv, thiols

14    and reaction of *N*-alkoxy-*N*-chloroamides **25** with v, azide and vi, sodium carboxylates.

15

16    Reactions of **21** systems with amines and thiols have been modelled at the AM1, HF/6-31G(d)

17    and pBP/DN* levels, which reveal significant charge separation in the transition states  and

18    alkoxynitrenium ion character (Figure 12) [86].  These reactions should be favoured by

1　electron-donor substituents on the nucleophile and electron-acceptor substituents on the
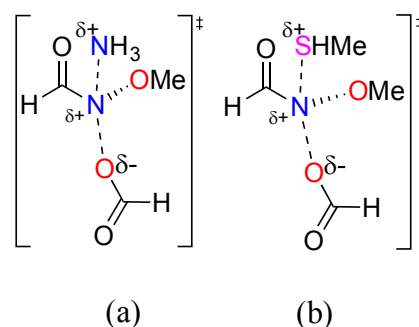
2　acyloxyl group.

3



　　　　　　　　　　　　　(a)　　　　　　　(b)

4

5　**Figure 12.** HF/6-31G* predicted charge separation in transition states for reactions of *N*-formyloxy-*N*-

6　methoxyformamide with (a) ammonia and (b) methanethiol.

7

8　The $S_N2$ reaction of *N*-methylaniline with a wide range of *N*-acyloxy-*N*-alkoxyamides **21** has

9　been studied (Scheme 1 i), and relative rate constants, Arrhenius activation energies and

10　entropies of activation are in accord with a transition state with significant charge separation

11　(Scheme 2) [31, 44, 51, 87]. $E_A$'s are of the order of $40 - 60$ kJ mol$^{-1}$. Entropies of activation

12　$(-90 - -160$ J K$^{-1}$ mol$^{-1})$ are more negative than found in $S_N2$ reactions of alkyl halides, owing

13　to a greater degree of solvation in the charge separated transition state [88]. In addition the

14　rates for reactions i, iii and iv with a series of *N-p*-substituted benzoyloxyl leaving groups

15　correlated with Hammett $\sigma$ constants with positive slope (i, $\rho = 1.7$, iii, $\rho = 0.6$ and iv, $\rho = 1.1$)

16　[44, 45, 52]. In addition, a series of anilines reacted bimolecularly and rate constants correlate

17　with Hammett $\sigma^+$ constants ($\rho = -0.9$) [44]. In most respects, the $S_N2$ reactions are

18　electronically and geometrically reminiscent of those at carbon centres and are accelerated by

19　electron-donor groups on the nucleophile and electron-withdrawing groups on the leaving

20　group. The amide carbonyl facilitates $S_N2$ reactivity in line with enhanced reactivity in

21　phenacyl bromides [89]. In particular, bimolecular reaction rates are radically impeded with

22　branching $\alpha$ to the carbonyl [50], which is analogous to the resistance to $S_N2$ reactions of $\alpha$-

23　halo ketones bearing substituents at the $\alpha'$ position [90, 91].

24

25

26　Anomeric substitution at nitrogen in *N*-acyloxy-*N*-alkoxyamides **21** renders this class of

27　amides as direct-acting mutagens. Mutagenicity towards *S. typhimurium* in the Ames reverse

1    mutation assay does not require pre-metabolic activation [92, 93]. Our DNA damage studies

2    on plasmid DNA at physiological pH, as well as extensive structure-activity relationships

3    [31, 38-41, 43, 45, 46, 48-50, 79, 80], point to binding of *NAA*'s **21**, intact, into the major

4    groove of DNA, where an $S_N2$ reaction occurs at the most nucleophilic center, the electron-

5    rich N7 in guanine (Scheme 1 vi) [94-97]. All three side chains ($R^1$, $R^2$ and $R^3$) of **21** have an

6    impact upon both DNA damage profiles as well as mutagenicity levels. An $S_N1$ mechanism,

7    yielding electrophilic *N*-acyl-*N*-alkoxynitrenium ions, was ruled out since only $R^1$ and $R^2$

8    would influence binding and reactivity. Moreover, mutagenic activity is radically reduced

9    when there is branching $\alpha$ to the carbonyl in parallel with the impaired $S_N2$ reactivity [40, 50,

10   51]. The mutagenic activity of *N*-acyloxy-*N*-alkoxyamides **21** has been used recently to show

11   how hydrophobicity and intercalating side chains impact upon DNA binding [38, 39].

12

13   3.1.2 Elimination Reactions

14   In an anomeric amide where $n_Y - \sigma^*_{NX}$ is a strong interaction, where X has a high electron

15   affinity and Y is a strong electron donor, polarisation can lead to elimination of $X^-$, leaving a

16   Y-stabilised nitrenium ion **28** (Scheme 2) [98]. The stronger the anomeric effect, the more

17   readily the elimination is expected to occur. In the case of *N*-alkoxy-*N*-chloroamides **25,**

18   elimination can be facilitated by Lewis acid complexation with X and by the use of polar

19   solvents [35]. For example, treatment of *N*-chloro-*N*-(2-phenylethyloxy)- **29a** and *N*-chloro-

20   *N*-(3-phenylpropyloxy)amides **29b** with silver tetrafluoroborate in ether, initiates a ring closing

21   reaction to form *N*-acyl-1*H*-3,4-dihydro-2,1-benzoxazines **30a** and *N*-acyl-1,3,4,5-

22   tetrahydrobenzoxazepines **30b**, respectively, via chlorine elimination to form nitrenium ions

23   (Scheme 3). *N*-Acyl-*N*-alkoxynitrenium ions are strongly stabilised by delocalisation of the

24   positive charge onto oxygen [98, 99]. This methodology has been used widely since its

25   discovery in 1984 by Glover [100, 101] and Kikugawa [102-108]. In addition, treatment of *N*-

26   alkoxy-*N*-chloroamides **25** with silver carboxylates in diethyl ether, allows the nitrenium ion

27   to be scavenged by carboxylate in a versatile reaction which has been used to synthesise a range
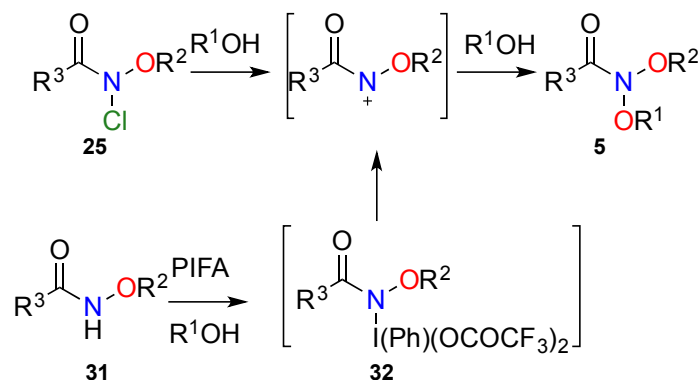
28   of *N*-acyloxy-*N*-alkoxyamides **21** [48, 80].

29



30
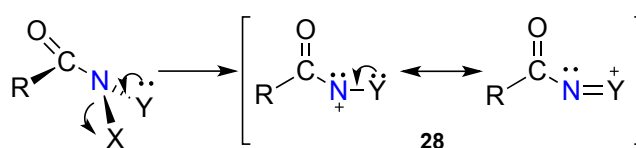
31   **Scheme 2**. Nitrenium ion formation by elimination of X due to a strong $n_Y - \sigma^*_{NX}$ interaction.

1
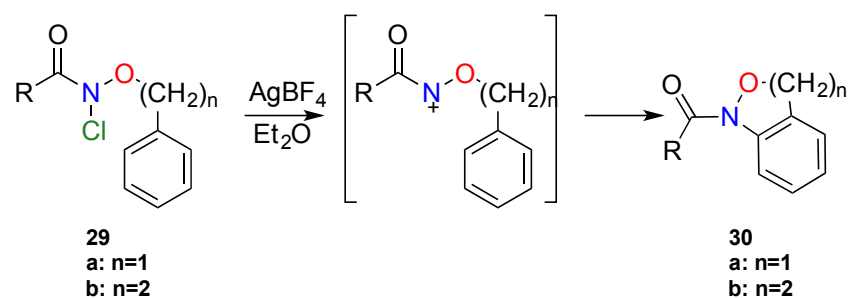


**Scheme 3**. Cyclisation by silver ion catalysed elimination reactions.

Elimination of chloride in the alcoholysis of **25** to give nitrenium ion, provided a synthetic pathway to *N,N*-dialkoxyamides **5** (Scheme 4) [55, 56].  We recently reported a more versatile synthesis effected by PIFA oxidation of hydroxamic esters **31** in appropriate alcohol, which proceeds through a reactive phenylbistrifluoroacetate derivative **32** [30, 55].  Similar hypervalent iodine oxidations have been used in nitrenium ion cyclisations onto aromatic rings [105].



**Scheme 4**. *N*-Acyl-*N*-alkoxynitrenium ion mediated syntheses of *N,N*-dialkoxyamides **5**.

*N*-Alkoxy-*N*-benzoylnitrenium ions **34** are generated through $A_{A1}1$ acid-catalysed solvolysis of *N*-acetoxy-*N*-alkoxybenzamides **33** (Scheme 5) [46, 48, 49].  Acetoxyl, upon protonation with a catalytic amount of mineral acid, is eliminated from *N*-acetoxy-*N*-alkoxybenzamides **33** and the nitrenium ions are trapped by water to form *N*-alkoxyhydroxamic acids **35**. The anomeric **35** undergoes secondary reactions to form a range of products.

**33**        **34**        **35**
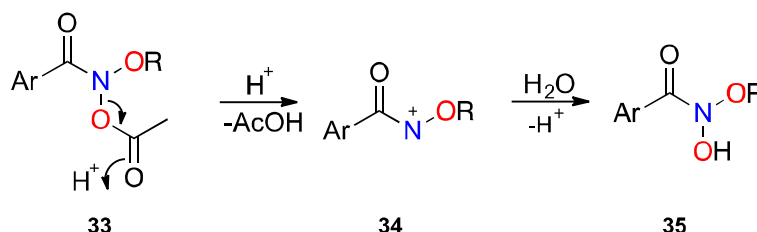
**Scheme 5**. Acid catalysed hydrolysis of *N*-acetoxy-*N*-butoxybenzamides.

The elimination reactions of *N*-alkoxy-*N*-chloroamides **25** and the acid-catalysed solvolysis reactions of **33**, both of which proceed through intermediacy of *N*-acyl-*N*-alkoxynitrenium ions, can better be re-evaluated in terms of anomeric destabilisation in combination with their reduced amidicities.

*3.2 The HERON reaction*

3.2.1 HERON reactions of *N*-amino-*N*-alkoxymides

A novel reaction of suitably constituted anomeric amides is the HERON (*He*teroatom *R*earrangement *O*n *N*itrogen) reaction [56, 109-113]. In such amides, when the X heteroatom of an anomerically destabilised *N*—*X* bond is a poor leaving group, the amide can undergo a concerted rearrangement involving the migration of X to the carbonyl carbon and the ejection of a Y stabilised nitrene (Scheme 6).
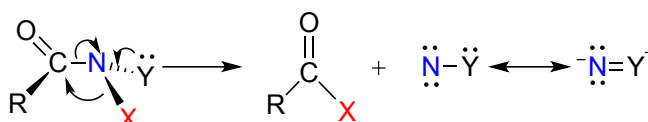


**Scheme 6**. The HERON reaction of an anomeric amide.

The HERON reaction was discovered by Glover and Campbell during research into $S_N2$ reactivity of *N*-acyloxy-*N*-alkoxyamides **21**, specifically the reaction between *N*-acetoxy-*N*-butoxybenzamide and *N*-methyl aniline according to Scheme 1 (i) [47, 111]. In a polar solvent such as methanol, *N*-methyl aniline attacks the amide nitrogen, replacing the acetoxyl side chain to form an unstable intermediate, *N*-butoxy-*N*-(*N'*-methylanilino)benzamide **36**, which undergoes the HERON reaction to form butyl benzoate **37**, and an aminonitrene, 1-methyl-1-phenyldiazene **38** (Scheme 7 i). Aminonitrenes are highly reactive intermediates with a singlet ground state, which persist long enough under reaction conditions to dimerise to tetrazenes [114-117], in this case, **39** (Scheme 7 ii) [44, 47]. *N,N'*-Diacyl-*N,N'*-dialkoxyhydrazines **40**, the only forms of *N*-alkoxy-*N*-aminoamides **2d** to have been isolated, undergo tandem HERON

1    reactions to form two equivalents of ester **41** and a molecule of nitrogen; the *N*-acyl-*N*-

2    alkoxyaminonitrenes **42**, formed in this HERON reaction, rapidly undergo a second

3    rearrangement to form a molecule of nitrogen and ester before dimerisation of the *N*-acyl-*N*-

4    alkoxyaminonitrene can occur (Scheme 8) [56, 76].  Step ii can also be regarded as a HERON

5    process, driven by a high energy electron pair on 1,1-diazene, a charge separated form of

6    aminonitrene. Barton and coworkers studied the decomposition at about the same time, and

7    both groups established the operation of three-centre mechanisms using asymmetric hydrazines

8    [77].  In addition, Barton found its concerted nature facilitated formation of a range of highly

9    hindered esters and, recently, Zhang has utilised the reaction to generate hindered esters from

10   *N,N′*-dialkoxy-*N,N′*-diacylhydrazines,  synthesised    through  *N*-bromosuccinimide  (NBS)

11   oxidation of hydroxamic esters [118].

12



13
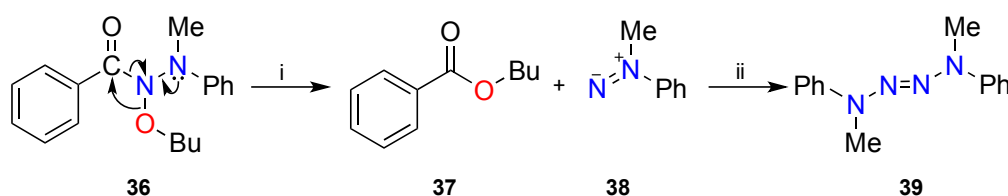
14        **Scheme 7**.  The first HERON reaction of *N*-butoxy-*N*-(*N′*-methylanilino)benzamide **36**.

15



16
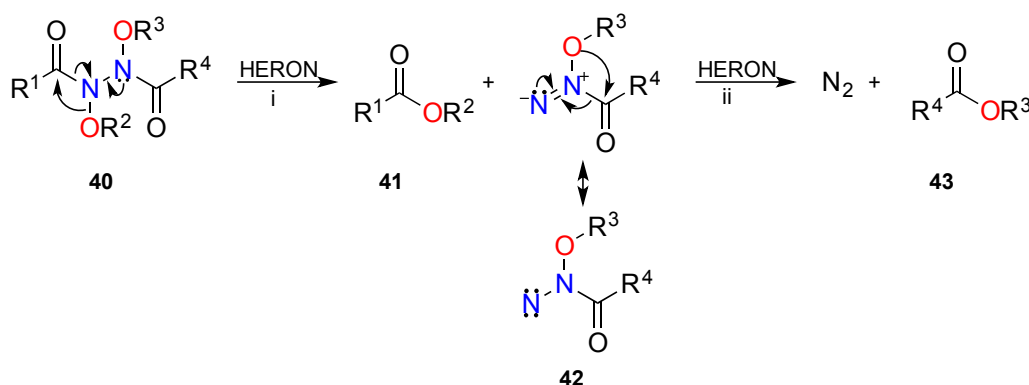
17        **Scheme 8**.  Tandem HERON reactions of *N,N′*-diacyl-*N,N′*-dialkoxyhydrazines **40**.

18

19   3.2.2 Theoretical and experimental validation of the HERON reaction

20   The HERON reaction of **22** and **40** has been modelled and validated computationally.  Initially,

21   AM1 modelling predicted that the three-centre reaction in the first HERON (Scheme 7 i) had

22   an energy barrier of 184 kJ mol$^{-1}$, while that of the second step was very low (25 kJ mol$^{-1}$) [56,

23   77].  An extensive AM1 study of HERON reactions of *N*-amino-*N*-alkoxyacetamides predicted

24   a similar barrier of 159 kJ mol$^{-1}$ in the gas phase, but a lower barrier of 126 kJ mol$^{-1}$ in solution

1  [111].  The same study also predicted lower barriers with electron-donor groups on the amino

2  nitrogen.  In a more rigorous study at the B3LYP/6-31G(d) level [76], Glover *et al.* modelled

3  the HERON reaction of *N*-methoxy-*N*-dimethylaminoformamide **17e**, a model representative

4  of *N*-(*N′*-methylanilino)-*N*-butoxybenzamide **36**, and *N,N′*-diacyl-*N,N′*-dialkoxyhydrazines **40**,

5  for which HERON reactions had been experimentally observed.  It was confirmed that the $n_N$

6  − $\sigma^*_{NO}$ anomeric destabilisation resulted in migration of the methoxyl group with an activation

7  barrier of 90 kJ mol$^{-1}$ and the reaction was exothermic by 23 kJ mol$^{-1}$.  Similar diasteromeric

8  transition states were located, but the transition state accessible from the lowest energy (*syn*)

9  conformer of **17e** was found to be that depicted in Figure 13a.  Importantly, modelling showed

10 that amide resonance in the transition state was largely lost, as migration occurs in a plane

11 perpendicular to the carbonyl, twisting the nitrogen lone pair away from alignment with the

12 $\pi^*_{C=O}$ orbital.  Anomeric destabilisation, however, remained along the reaction coordinate,

13 driving the reaction forward.  The *N—C(O)* bond is largely intact at the transition state but

14 breaks as the *O2—C* bond forms in an internal, $S_N2$-like reaction at the amide carbon.

15 Significantly, a tetrahedral intermediate is avoided by this process. Subsequent high level

16 calculations on the decomposition of anomeric hydrazines by Tomson and Hall, yielded similar

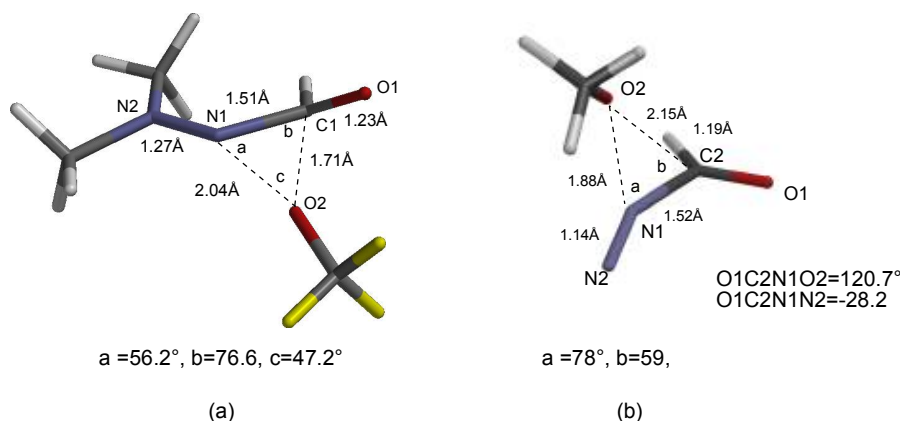17 energetics for the HERON process [119].



a =56.2°, b=76.6, c=47.2°

(a)

O1C2N1O2=120.7°
O1C2N1N2=-28.2

a =78°, b=59,

(b)

18

19 **Figure 13.** Twisted HERON transition states of (a) *N*-methoxy-*N*-dimethylaminoformamide **17e** and (b) 1-

20 formyl-1-methoxydiazene **44** (R$^1$=H, R$^2$=Me) at B3LYP/6-31G(d) level [53, 76].

21

22 Analysis of charge separation in the B3LYP/6-31G(d) transition state revealed a partial positive

23 charge of +0.5 on amino group, partial negative charge of –0.3 on the migrating methoxyl

24 group and little change in charge at the carbonyl.  This indicated that HERON in these NNO

25 systems could be assisted by polar solvents, electron-donating groups on the stationary amino

26 substituent, and electron-withdrawing groups on the migrating oxygen substituent.  The

32

1    activation barriers and charge separation in the transition state were validated experimentally

2    by Arrhenius studies and Hammett correlations from thermal decomposition of a range of

3    substituted hydrazines **19a-e** and **20a-e** in mesitylene (Table 6) [76].  In **19**, the donor ability

4    of $n_N$ is increased by electron-rich aroyl groups, leading to enhanced reaction rates and a

5    negative Hammett $\sigma^+$ correlation ($\rho = -0.35$, $R^2 = 0.978$) (Figure 14a).  However, acceptor

6    benzyloxy substituents in **20** facilitate the migration, leading to a positive Hammett $\sigma$-

7    correlation ($\rho = 1.02$, $R^2 = 0.911$) (Figure 14b). Rate constants were lower in **20** on account of

8    a negative impact at the donor nitrogen. Donor groups, on the other hand, have little impact on

9    the carbonyl in **19**.

10   **Table 6.** Hammett reaction constants, Arrhenius activation energies, entropies of activation, and rate constants for HERON

11   decomposition of **19a-e** and **20a-e** [76].

| Series | System | $E_A$/kJ mol$^{-1}$ | $\Delta S^{\ddagger}$/J K$^{-1}$ mol$^{-1}$ | $10^6 \cdot k_{298}$/s$^{-1}$ |
|---|---|---|---|---|
| | **19a** | 99.2 (4.3) | -21.2 (13) | 5.56 |
| | **19b** | 100.7 (8.2) | -19.6 (25) | 3.72 |
| Series **19**: $\sigma^+$ reaction constant $\rho = -0.35$[1] | **19c** | 100.4 (5.1) | -23.8 (15) | 2.52 |
| | **19d** | 107.7 (1.7) | 0.9 (5) | 2.50 |
| | **19e** | 104.0 (1.7) | -15.4 (5) | 1.57 |
| | | | | $10^8 \cdot k_{298}$ (s$^{-1}$) |
| | **20a** | 111.4 (0.9) | -21.1 (2) | 4.02 |
| Series **20**: $\sigma$ reaction constant $\rho = +1.02$[1] | **20b** | 125.9 (1.0) | 24.5 (3) | 2.76 |
| | **20c** | 114.1 (3.9) | -8.7 (11) | 6.21 |
| | **20d** | 125.1 (8.5) | 27.4 (24) | 5.44 |
| | **20e** | 98.8 (0.3) | -46.4 (1) | 31.9 |

12   [1] Hammett correlations using $k_{298K}$.

13



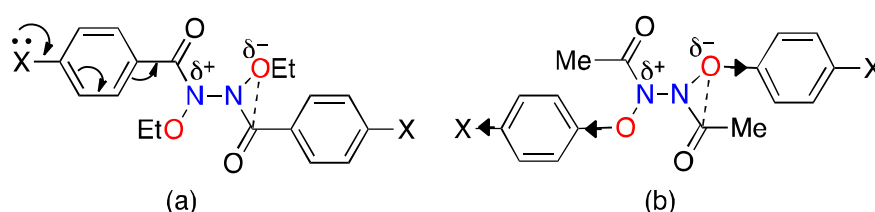(a)                                                       (b)

14

15   **Figure 14**. Influence on the HERON transition state of (a) electron-rich benzoyl groups in **19** and (b) electron-

16   deficient benzyloxy groups in **20**

17

1    3.2.3 HERON reaction of 1-acyl-1-alkoxydiazenes

2    The second step in the thermal decomposition of *N,N′*-dialkoxy-*N,N′*-diacylhydrazines **40**, **19**,

3    and **20**  has also been modelled at both B3LYP/6-31G(d) and CCSD(T)//B3P86 level using *N*-

4    formyl-*N*-methoxydiazene, and was found to have an extremely small $E_A$ of between 5 – 12 kJ

5    mol$^{-1}$ and to be highly exothermic ($\Delta E = –400$ kJ mol$^{-1}$) [53, 119].  We encountered this process

6    from the reaction of *N*-acyloxy-*N*-alkoxyamides **21** with azide (Scheme 1 ii), which generates

7    ester and two molecules of nitrogen [54].  The reaction of *N*-acyloxy-*N*-alkoxyamides with

8    azide was originally conceived in an attempt to trap and determine the lifetimes of *N*-acyl-*N*-

9    alkoxynitrenium ions, by analogy with the determination of lifetimes of arylnitrenium ions in

10   water [120, 121].  However, *N*-Alkoxy-*N*-azidoamides **26** are highly unstable intermediates,

11   losing nitrogen to generate 1-acyl-1-alkoxydiazenes **44**, which react further to nitrogen and

12   ester Scheme 9. The transition state for this reaction of *N*-formyl-*N*-methoxydiazene, modelled

13   at the B3LYP/6-31G(d) level, is depicted in Figure 13b.  Once again, the methoxyl group

14   migrates in a plane orthogonal to the *N1-C2-O1* plane in an earlier transition state with little

15   *N—C(O)* bond cleavage, which occurs in concert with *O2—C2* bond formation, again avoiding

16   a tetrahedral intermediate.  The reaction of azide with *N*-chloro-*N*-alkoxyamides **25** proved to

17   be an excellent means of generating highly hindered esters [54] – not surprisingly, in light of

18   the very low $E_A$ and extreme exothermicity born out of the entropically favourable generation

19   of two highly stable molecules (methyl formate and nitrogen) [53, 119].  Overall, the

20   decomposition of *N*-azido-*N*-methoxyformamide to two molecules of nitrogen and

21   methylformate was computed to be exothermic by some 575 kJ mol$^{-1}$ [53].  Yields of hindered

22   esters prepared by this method are given in Table 7.

23



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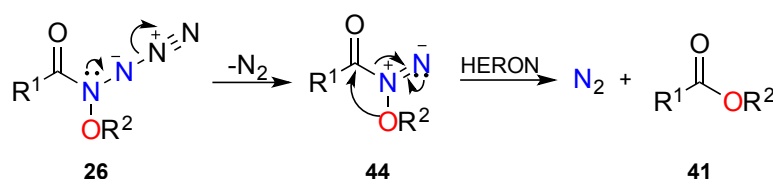
25        **Scheme 9**. Decomposition and HERON reaction of *N*-alkoxy-*N*-azidoamides **26**.

26

27

1  **Table 7**. Ester **41** ($R^1COOR^2$) formation from the reaction of *N*-alkoxy-*N*-chloroamides **25** ($R^1CONClOR^2$) with sodium
2  azide in aqueous acetonitrile.

| R | R' | Isolated crude yield / % |
|---|---|---|
| Ph | $(CH_3)_3C$ | 87 |
| $(CH_3)_3C$ | $(CH_3)_3C$ | 30 |
| 1-adamantyl | $(CH_3)_3C$ | 82 |
| $(CH_3)_3C$ | cyclohexyl | 97 |
| Ph | $(CH_3)_2CH$ | 92 |
| Ph | $PhCH_2$ | 93 |
| $CH_3$ | $PhCH_2$ | 92 |
| p-$NO_2C_6H_4$ | Et | 94 |
| Ph | Et | 94 |

3

4

5  Both Barton and recently Zhang have shown that the thermal decomposition of *N,N′*-dialkoxy-
6  *N,N′*-diacylhydrazines is a source of hindered esters. The avoidance of a tetrahedral
7  intermediate in both HERON steps of these reactions, and which is a limiting structure in Fisher
8  esterification, is critical. This, and the clear role of anomeric substitution at nitrogen in both
9  reducing amidicity, as well as promoting the rearrangement, are paramount.

10

11  3.2.4. HERON reactions of anionic systems

12  Hydroxide substitution of the acyloxyl side chain from a range of *N*-acyloxy-*N*-
13  alkoxybenzamides **21**, at room temperature in aqueous acetonitrile, generated esters and their
14  hydrolysis products [45]. Rate data and crossover experiments pointed to an $S_N2$ reaction at
15  nitrogen and the intramolecular nature of the reaction, implicating a HERON process. The
16  hydroxamic acid intermediates **45** from initial attack (Scheme 1 iii) would be converted to their
17  conjugate base **23** under basic reaction conditions, generating a strong $n_{O^-} - \sigma^*_{NO}$ anomeric
18  destabilisation of the *N—O* bond. A HERON migration of the alkoxyl side chain to the carbonyl
19  carbon results in the formation of alkyl benzoate and the ejection of the nitric oxide anion
20  (Scheme 10, $R^1$=Ph). This route to esters from hydroxamic acids in equilibrium with **23** was
21  earlier invoked to explain non-crossover ester formation in the $A_{Al}1$ solvolysis of *N*-acyloxy-
22  *N*-alkoxyamides at low acid concentrations (Scheme 5) [45, 46, 48, 49].

23
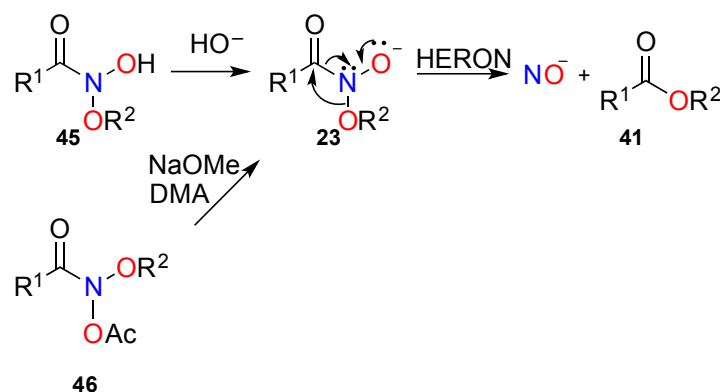
**Scheme 10**. HERON reaction of hydroxamate anion **23**.

The HERON reaction was also invoked by Shtamburg and coworkers to account for formation of ethyl benzoate **41** (R$^1$=Ph, R$^2$=Et) when *N*-acetoxy-*N*-ethoxybenzamide **46** (R$^1$=Ph, R$^2$=Et) was treated with methoxide in aprotic media. Anion **23** (R$^1$=Ph, R$^2$=Et) leading to the HERON reaction was generated by methoxide addition at the ester carbonyl (Scheme 10), while methoxide attack at the amide carbonyl lead to the formation of methyl benzoate [122].

Dialkyl azadicarboxylates, widely used in the Mitsonobu reaction, decompose vigorously with methoxide in methanol [123, 124]. **47a** afforded methyl isopropyl carbonate **49a** and isopropyl formate, **50a** in a 1:1 ratio by $^1$H NMR, and diethyl azadicarboxylate **47b** behaved similarly, though volatile ethyl formate **50b** was less prevalent in the reaction mixture (Scheme 11) [112, 125]. Since the nitrogens in **47** are the overwhelming contributors to the LUMO of azadicarboxylates [112], the most probable route to these products is methoxide addition at nitrogen and a facile HERON reaction of the anionic adducts **48**. Calculations based on the HERON reaction of dimethyl azodicarboxylate **5c**, gave an $E_A$ of 27 kJ mol$^{-1}$ and exothermicity of 59 kJ mol$^{-1}$, at the B3LYP/6-31G*//HF/6-31G(d) level [112].
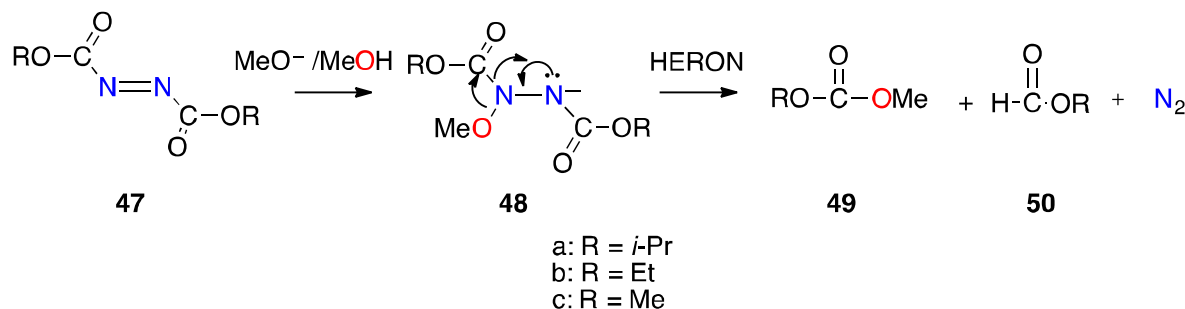


**Scheme 11**. Amide anion induced HERON reaction in reactions of azadicarboxylates with methoxide.

1    3.2.5. HERON reactions of *N*-alkoxy-*N*-aminocarbamates

2    By analogy with the HERON reactions of *N*-acyloxy-*N*-alkoxyamides, several carbamates

3    have been shown to undergo a similar reaction (Scheme 12).   *N*-Acetoxy-*O*-alkyl-*N*-

4    benzyloxycarbamates **51a-c** and *N*-methylaniline reacted bimolecularly in [D$_4$]-methanol to

5    produce the corresponding carbonates **53** and tetrazene **39**, presumably through HERON

6    reaction of the *N*-methylanilino intermediate **52** [126].

7
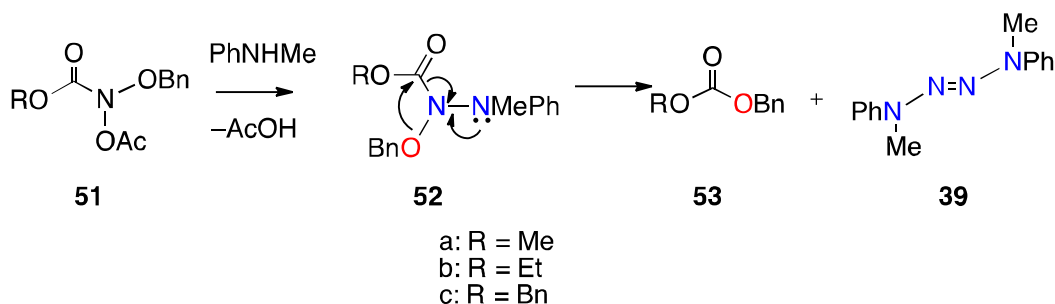


**Scheme 12**. HERON reactions of *N*-alkoxy-*N*-aminocarbamates.

10

11    3.2.6. HERON reactions of *N*-acyloxy-*N*-alkoxyamides

12    Based on RE's of models **15c** and **16a** in Table 4, the amidicity of NNO systems such as *N*-

13    alkoxy-*N*-aminoamides **2d** or *N*-alkoxy-*N*-aminocarbamates such as **52**, is likely to be reduced

14    by modest amounts (60-70% that of *N,N*-dimethylacetamide), yet these systems undergo

15    HERON reactions at room temperature, as do the 1,1-diazenes **2h** and hydroxamates **2g**.

16    However, all have in common a strong anomeric destabilisation of the *N—O* bond through

17    high energy electron pairs on the donor atom, n$_Y$, and high electronegativity of oxygen.  n$_O$ −

18    σ*$_{NO}$ systems such as *N*-acyloxy-*N*-alkoxyamides **2b** and *N,N*-dialkoxyamides **2c**, on the other

19    hand, should have lower RE's (amidicities around  50% that of *N,N*-dimethylacetamide), yet

20    they are thermally stable at room temperature on account of a weaker n$_O$ − σ*$_{NO}$ anomeric

21    interaction.  However, at elevated temperatures, *N*-acyloxy-*N*-alkoxyamides **2b** also undergo

22    HERON reactivity [85].

23

24    A tandem mass spectrometric analysis by electrospray ionisation, used in characterising

25    mutagenic *N*-acyloxy-*N*-alkoxyamides **2b**, produced, in addition to sodiated parent compounds

26    **54**, three characteristic sodiated ions, a sodiated alkoxyamidyl radical, **55**, which was generally

27    most prevalent, a sodiated anhydride, **56**, and a minor cation due to sodiated ester, **57**, which

28    was absent in the ionisation of aliphatic amides.  While the fragments formed in parallel with

29    each product ion **58-60** were undetectable, under these conditions the source of anhydrides

37

1    must be an intramolecular process and the HERON rearrangement at elevated temperature was

2    implicated.  Furthermore, the relative amounts of sodiated anhydride and ester reflected the

3    expected bias towards an $n_O - \sigma^*_{NOAc}$ anomeric stabilisation with attendant weakening of the

4    *N—OAc,* rather than the *N—OR,* bond [112].  A B3LYP/6-31G(d) computational study of

5    migration tendencies in *N*-formyloxy-*N*-methoxyformamide predicted high $E_A$'s for migration

6    of both formyloxyl and methoxyl in the gas phase (162 and 182 kJ mol$^{-1}$, respectively) [112].

7    While acyloxyl, rather than alkoxyl, migration would be energetically more favourable, in

8    solution at room temperature and particularly in polar media, the HERON reaction would not

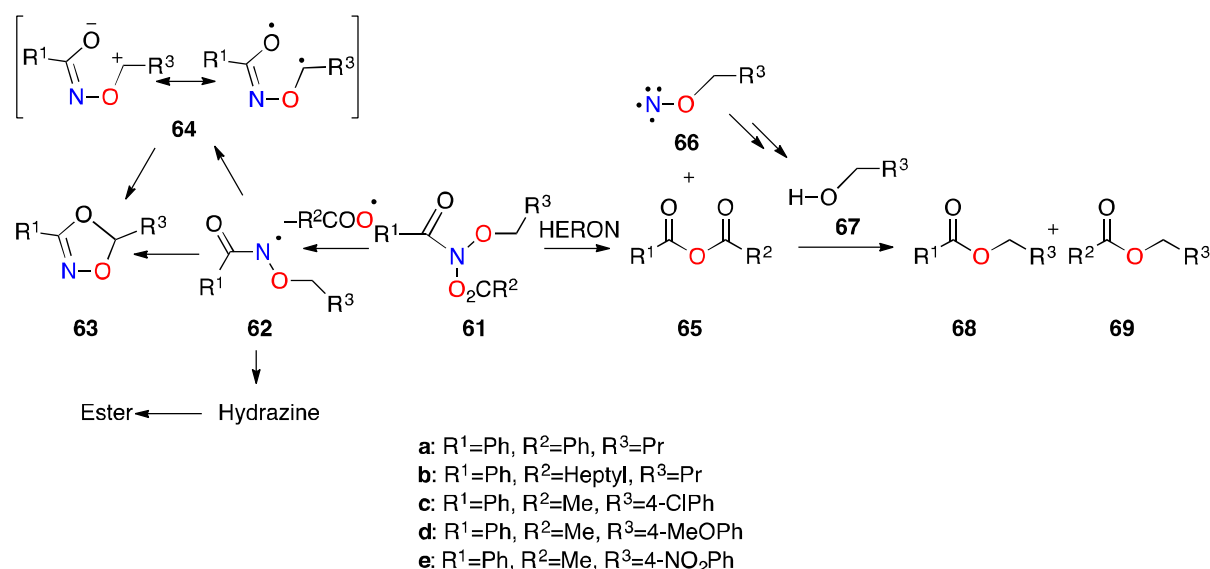9    be competitive with $S_N2$ and $S_N1$ reactions at nitrogen.

10



11
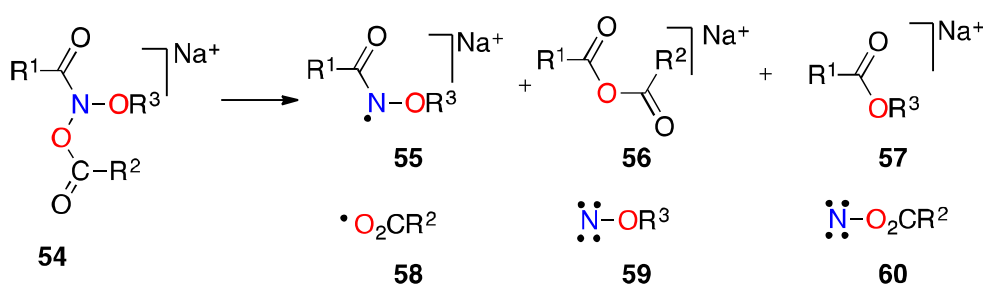
12    **Scheme 13**. Fragments from collision induced ES-MS spectra of *N*-acyloxy-*N*-alkoxyamides **2b**.

13

14    However, in toluene at 90°C, HERON reactions of **2b** have been detected in competition with

15    a homolytic decomposition pathway  and analysis of the complex reaction mixtures provides

16    further support for the driving force behind the HERON process (Scheme 14) [85].  Homolysis

17    of the *N—OAc* bond in **61** gave relatively long-lived alkoxyamidyl radicals **62**, which in solvent

18    cage reactions with product radicals generated dioxazole **63**, or upon escaping the solvent cage

19    dimerise to hydrazines leading to the expected thermal decomposition esters.  The HERON

20    reaction of **61** generates anhydrides **65** and alkoxynitrenes **66**.  Anhydrides, which in the case

21    of symmetrical benzoic anhydride from **61a** and mixed benzoyl heptanoyl anhydride from **61b**

22    were relatively stable, react further to give esters **68** and **69** with alcohols **67** generated in the

23    reaction mixture, the source of which was the alkoxynitrenes, the other HERON product.

24    Critical evidence for the HERON process derived from products of alkoxynitrenes **66**, which

25    1. could be trapped by oxygen; 2. dimerised to hyponitrites; or, 3. underwent characteristic

26    rearrangements leading aldehydes, nitriles and alcohols.  Competition between the HERON

27    and homolytic reaction pathways was evident in a comparison of products from **61c-e**.  The

28    polarity of these HERON transition states would require a build-up of positive charge on the

29    donor alkoxyl oxygen, $n_O$. This would be stabilised by electron-donor *para* substituents on the

1    benzyloxy group, but destabilised by electron-withdrawing *para* substituents.  In accord with

2    this, **61c** and **61e** generated dioxazole and esters.  Little dioxazole was formed from **61d** in

3    which the methoxyl group would lower the energy of the HERON transition state, but would

4    have little impact on the non-polar transition state for homolysis of the *N—OAc* bond (Figure

5    14).

6



**a**: R$^1$=Ph, R$^2$=Ph, R$^3$=Pr
**b**: R$^1$=Ph, R$^2$=Heptyl, R$^3$=Pr
**c**: R$^1$=Ph, R$^2$=Me, R$^3$=4-ClPh
**d**: R$^1$=Ph, R$^2$=Me, R$^3$=4-MeOPh
**e**: R$^1$=Ph, R$^2$=Me, R$^3$=4-NO$_2$Ph

8    **Scheme 14**. HERON and radical decomposition pathways for *N*-acyloxy-*N*-alkoxyamides in toluene at 90°C.

9



(a)                                    (b)
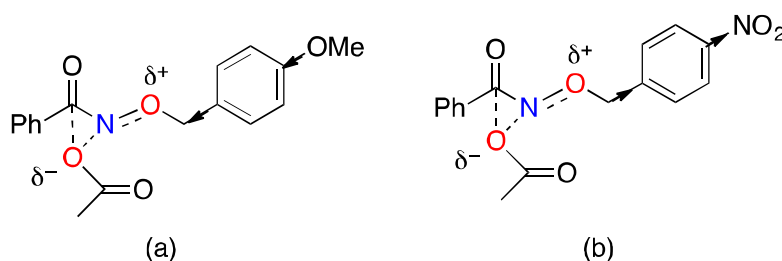
11    **Figure 15.** (a)  Stabilisation of the HERON transition state for *N*-acyloxy-*N*-alkoxyamides by *para* methoxyl

12    group and (b) destabilisation by a *para* nitro group.

13

14    3.2.7 HERON reactions of *N,N*-dialkoxyamides

15    Like *N*-acyloxy-*N*-alkoxyamides **2b**, *N,N*-dialkoxyamides **2c** possess low amidicity and they

16    are thermally unstable, but require higher temperatures (typically 155 °C in mesitylene).

17    However, their reaction proceeds exclusively by homolysis.  Secondary products from

18    alkoxynitrenes, which would be produced by the HERON pathway, were not observed for

19    acyclic *N,N*-dialkoxyamides.  Rather, they produce alkoxyamidyl radicals, which dimerise to

1    *N,N′*-dialkoxy-*N,N′*-diacylhydrazines  and ultimately esters.  In addition, they can be trapped

2    by hydrogen donors and solvent derived radicals [55].

3

4    On the other hand, room temperature HERON reactivity was found to occur exclusively in

5    several  alicyclic  ONO  systems  [30].  Cyclic  *N,N*-dialkoxyamides,  *N*-butoxy-3(*2H*)-

6    benzisoxazolone **73**, *N*-butoxyisoxazolidin-3-one **74** and *N*-butoxytetrahydro-*2H*-1,2-oxazin-

7    3-one **75,** can be synthesised by PIFA oxidation of the salicamide **70**, β- and γ-

8    hydroxyhydroxamic esters, **71** and **72**, respectively, by analogy with the synthesis of acyclic

9    *N,N*-dialkoxyamides (Scheme 4) [55].  Only *N*-butoxy-3(*2H*)-benzisoxazolone **73** is stable; *N*-

10   butoxyisoxazolidin-3-one **74** and *N*-butoxytetrahydro-*2H*-1,2-oxazin-3-one **75** both react at

11   room temperature and the reactions can be monitored by $^1$H NMR and mass spectrometry

12   (Scheme 15). The γ-oxazinolactam undergoes quantitative ring opening to a diastereomeric

13   mixture of the stable hyponitrite **76**, which must arise from dimerization of alkoxynitrene **77**,

14   a known reaction of alkoxynitrenes.  The δ-oxazinolactam, on the other hand, undergoes a

15   quantitative ring contraction to the γ-valerolactone **78** with production of butoxynitrene **79**.

16   Both are clearly HERON reactions [30].

17

18   The $E_A$ for both HERON reactions must be radically lower than that for acyclic *N,N*-

19   dialkoxyamides. Analysis of the B3LYP/6-31G(d) optimised ground state structures of *N*-

20   methoxy-γ-oxazinolactam **81** (Figure 15b) and *N*-methoxy-δ-oxazinolactam **82** (Figure 15c)

21   provide insight into this unusual difference in reactivity.  Firstly, the model γ-oxazinolactam is

22   strongly pyramidal at nitrogen (χ = 64.6°) and significantly twisted (τ = –36°), with attendant

23   loss of amide character. The *N—C(O)* bond is very long compared to *N,N*-dimethoxyacetamide

24   **4b** (1.417 Å, Table 3).  The COSNAR and TA resonance energies for **81** are –20 and –19 kJ

25   mol$^{-1}$, respectively, translating to amidicities of only 26% and 25%.  Torsion angles close to

26   90° indicate that the *endo* and *exo* oxygen lone pairs are ideally aligned for maximum $n_O$ –

27   $\sigma^*_{NO}$ stabilisation.  Low amidicity and a strong stereoelectronic effect would favour either

28   reaction but, clearly, ring opening would be more favourable than ring contraction, which

29   would give a highly strained β-lactone.
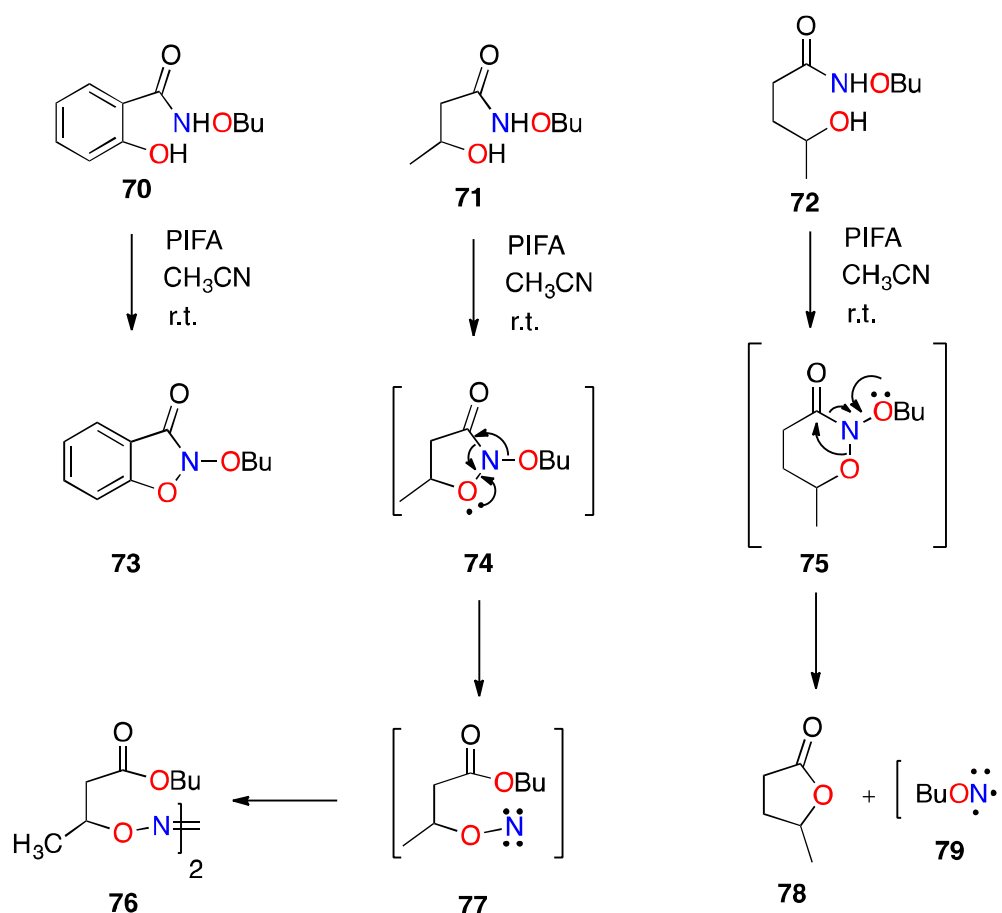
**Scheme 15.** HERON reactions of γ-oxazinolactam **71** and δ-oxazinolactam **72**.
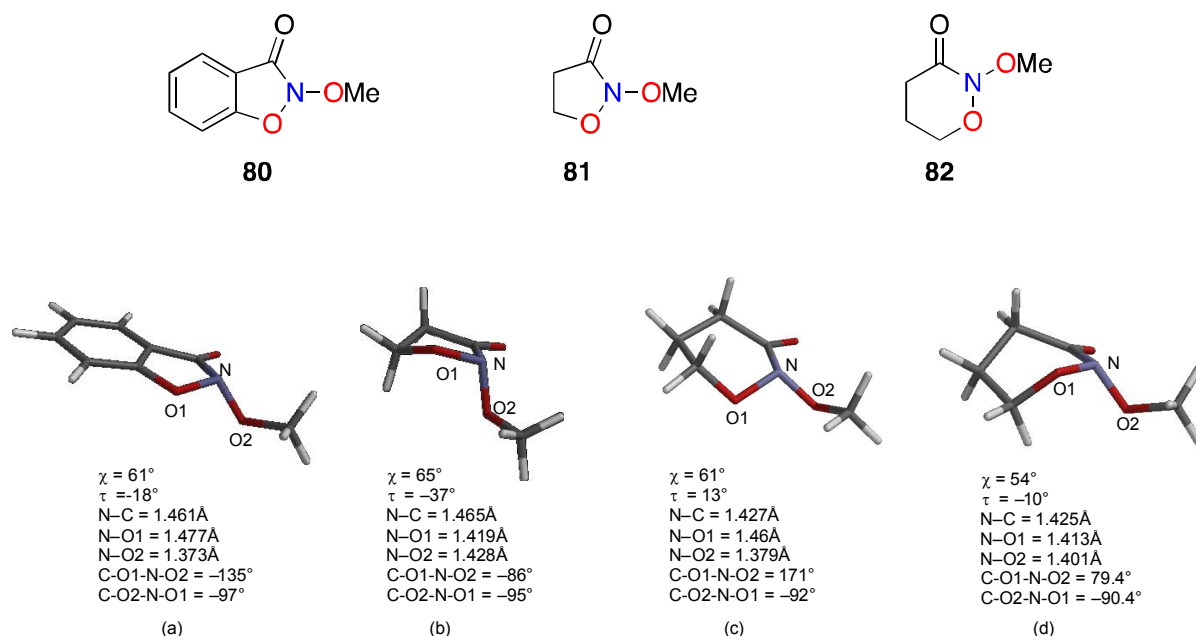




**Figure 16**. Ground state structures of models (a) *N*-methoxybenzisoxazolone **80**, (b) *N*-methoxy-γ-oxazinolactam

**81** and (c) chair and (d) boat *N*-methoxy-δ-oxazinolactam **82**.

1    The B3LYP/6-31G(d) structure of the model δ-oxazinolactam **82** ($\chi = 61°$ and $\tau = 13°$)

2    matches the experimental ($^1$H NMR) chair conformation of **75** which has a chiral nitrogen. It

3    is also more pyramidal at nitrogen and slightly more twisted than the alicyclic *N,N*-

4    dimethoxyacetamide **4b** ($\chi = 48°$ and $\tau = 9°$, Figure 7c, Table 3), but its resonance and

5    amidicity ($RE_{COSNAR} = -38$ kJ mol$^{-1}$, amidicity 49%, and $RE_{TA} = -37$ kJ mol$^{-1}$, amidicity 47%)

6    is almost identical to the open chain form. However, only an *endo* oxygen $n_{O(exo)} - \sigma^*_{NO(endo)}$

7    anomeric alignment is evident; with a torsion angle of 171°, the $n_{O(endo)} - \sigma^*_{NO(exo)}$ is completely

8    switched off. The *endo* N—O bond is nearly 0.1 Å longer than the *exo* N—O bond (the *endo*

9    bond is marginally shorter than the *exo* bond by by 0.01 Å in γ-oxazinolactam and 0.02 Å in

10   *N,N*-dimethoxyacetamide). Ring opening and ring contraction are computed to have about the

11   same $E_A$ and $\Delta H^{\ddagger}$ at B3LYP/6-31G(d) [30]. It is evident that the ring contraction of the δ-

12   oxazinolactam to γ-butyrolactone is largely driven by a strong, conformationally imposed

13   anomeric effect, a remarkable impact of anomeric substitution at an amide nitrogen [30]. While

14   the computed transition state for ring opening of model *N*-methoxy-δ-oxazinolactam is

15   marginally lower in energy, the required $n_{O(endo)} - \sigma^*_{NO(exo)}$ is only accessible from the boat

16   conformation of the δ-oxazinolactam (Figure 15d). Experimentally, accessing this

17   conformation in **75** by nitrogen inversion could be energetically unfavourable, owing to steric

18   hindrance between the axial 4-methyl and *N*-butoxy groups. However, even in the boat

19   conformation, the strong $n_{O(exo)} - \sigma^*_{NO(endo)}$, which favours ring contraction is still evident.

20

21   The γ-lactam in benzisoxazolone is stable at room temperature, though model **80** has a suitable

22   anomeric alignment for migration of O2. However, the $n_{O(endo)} - \sigma^*_{NO(exo)}$ interaction is

23   probably weakened by conjugation of the $O_{endo}$ p-type lone pair onto the aromatic ring.

24

25   3.2.8. *N*-alkoxy-*N*-alkylthiylamides

26   The combination of sulfur and oxygen attachment to amide nitrogen in *N*-methoxy-*N*-

27   methylthiylacetamide **15d** results in a similar reduction in amide resonance to that of *N*-

28   methoxy-*N*-dimethylaminoacetamide **15c**, namely about 64% vs 67% (Table 4). However, the

29   reaction of *N*-acyloxy-*N*-alkoxyamides **21** with biological thiols, glutathione and methyl and

30   ethyl esters of cysteine, which resulted in S$_N$2 displacement of carboxylate produced

31   exclusively hydroxamic esters **83** and disulfides **84** [52] (Scheme 16). The driving force for

32   HERON reactivity is not only reduced resonance, but the anomeric effect. Instead of HERON

33   reactions, the intermediate *N*-alkoxy-*N*-alkylthiylamides **24** undergo an S$_N$2 reaction at sulfur

1  by thiol. The distinction between reactivity modes for NNO and SNO systems lies in the $n_S$ –

2  $\sigma^*_{NO}$ anomeric interaction, which is much weaker than the $n_N - \sigma^*_{NO}$ of *N*-alkoxy-*N*-

3  aminoamides.

4

**21**        **24**        **83**        **84**
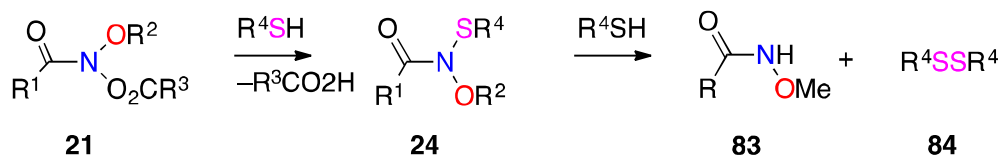
**Scheme 16**. Reaction of *N*-acyloxy-*N*-alkoxyamides with alkylthiols.

7

8  *3.3 Driving force for the HERON reaction*

9  The most accessible transition states for HERON migration of methoxyl in a number of model

10  anomeric amides, *N*-methoxy-*N*-dimethylaminoacetamide **15c**, *N,N*-dimethoxyacetamide **4b**,

11  *N*-acetoxy-*N*-methoxyacetamide **15b** and *O*-methyl-*N*-methoxy-*N*-dimethylaminocarbamate

12  **16a**, ring opening of *N*-methoxy-γ-oxazinolactam **81**, and ring contracting of *N*-methoxy-δ-

13  oxazinolactam **82**, each of which represents a class of neutral anomeric amides known to

14  undergo HERON reactions, as well as for methoxyl migration in *N*-methoxy-*N*-

15  methylthiylacetamide **15d**, *N*-methoxyacetohydroxamate **15f** and 1-acetyl-1methoxydiazene

16  **15g**, have been derived at the B3LYP/6-31G(d) level as part of several studies [30, 61, 62].

17  Transition state geometries of **4b**, **15b-d**, **f** and **g**, **16a**, **81** and **82** are presented in Figure 16.

1
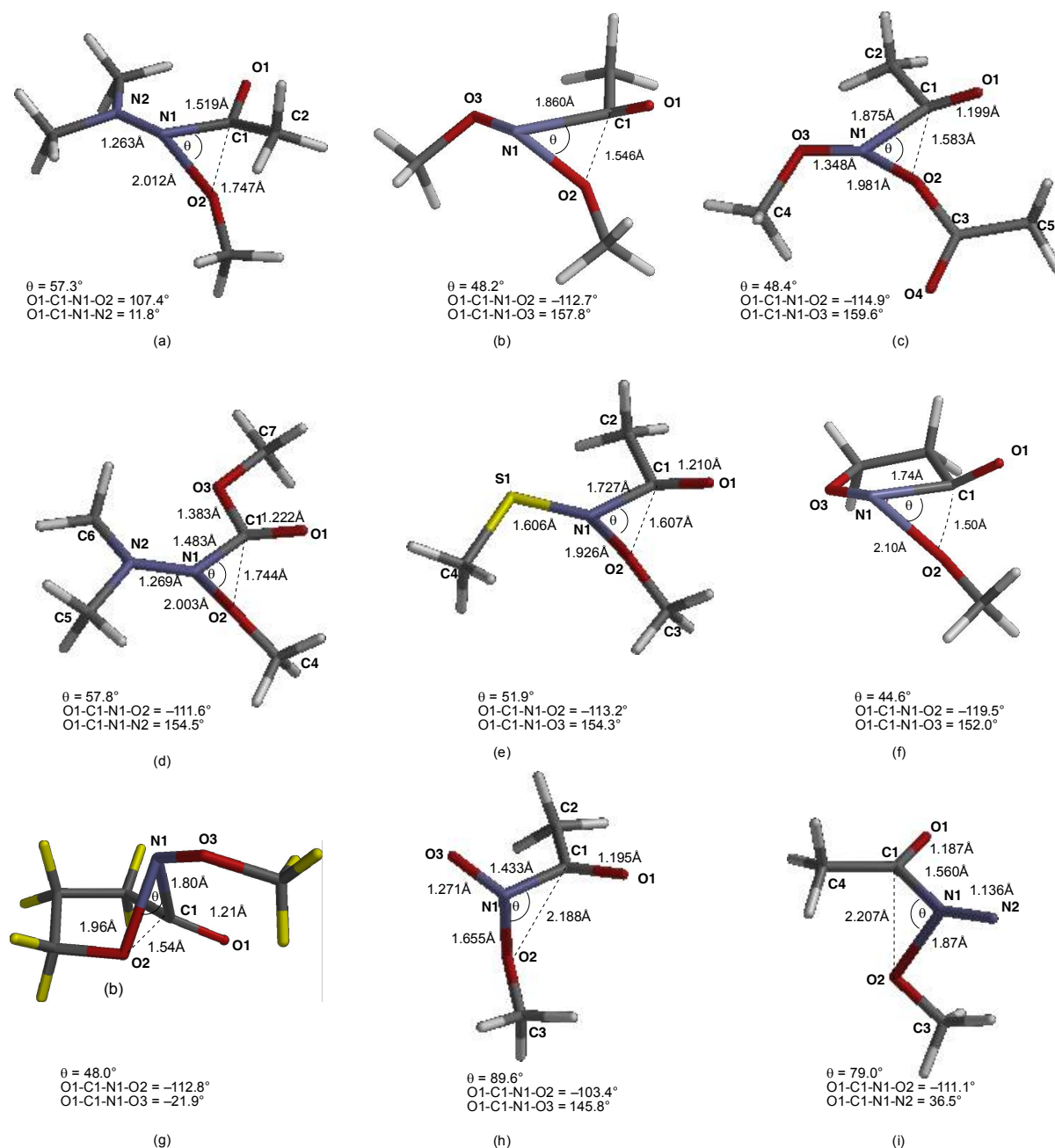


**Figure 17**. B3LYP/6-31G(d) optimised transition states of favoured HERON reactions of (a) *N*-methoxy-*N*-dimethylaminoacetamide **15c**, (b) *N,N*-dimethoxyacetamide **4b**, (c) *N*-acetoxy-*N*-methoxyamide **15b**, (d) *O*-methyl-*N*-methoxy-*N*-dimethylaminocarbamate **16a**, (e) *N*-methoxy-*N*-methylthiylacetamide **15d**, (f) *N*-methoxy-γ-oxazinolactam **81** (ring opening),   (g) *N*-methoxy-δ-oxazinolactam **82** (ring contraction), *N*-methoxyacetohydroxamate **15f** and 1-acetyl-1-methoxydiazene **15g**.

In all the transition state complexes, the migrating oxygen does so in a plane largely orthogonal to the *N1–C1–O1* plane and the donor atom n_Y, driving the migration, is largely in the *N1–C1–O1* plane.  As a consequence, the amide nitrogen  lone pair lies close to the plane and amide

resonance is largely lost in the transition state.  The resonance energy, RE is therefore a component of the overall $E_A$, the balance being the energy required for the rearrangment under anomeric assistance, $E_{rearr}$, and must reflect the relative nature of the $n_X – \sigma^*_{NO}$ driving force. It is therefore possible to approximate the influence of the anomeric substituents on the resonance interaction on the one hand, and on the migration process, on the other. Table 8 gives the $E_A$, $RE_{TA}$ and net $E_{rearr}$ data for these transition states.

Methoxyl migration in the NNO systems **15c** and **16a**, have similar RE's of around $-50$ kJ mol$^{-1}$ and therefore $E_{rearr}$ of about 40 kJ mol$^{-1}$.  The change in charge on the carbonyl carbon in the HERON transition state is negligible [76], so replacement of methyl by methoxyl has little bearing on the rearragement energies.  ONO in **4b** and ONOAc in **15b** migrations have much higher $E_A$'s despite the lower amide resonance energy.   The large difference lies in the $E_{rearr}$ which is nearly 100 kJ mol$^{-1}$ less favourable and a reflection of the relative efficacy of the $n_N – \sigma^*_{NO}$ vs the weaker $n_O – \sigma^*_{NO}$ anomeric interaction.  The difference of about 80 kJ mol$^{-1}$ between methoxy migration in the ONS **15d** and ONN  acetamides **15c** lies, again, in the much weaker $n_S – \sigma^*_{NO}$ anomeric effect. This can be accounted for by size mis-match due the larger 3p orbitals of the sulfur.  Both HERON reactions of the cyclic forms of *N,N*-dialkoxyamides **81**  and **82** have substantially lower overall $E_A$'s than *N,N*-dimethoxyacetamide **4b**.  After RE has been taken into account, $E_{rearr}$ values indicate that in the cyclic forms, reorganisation to the HERON transition state is easier.  Better stereoelectronic control in the cyclic system accounts for this.

The RE of the 1,1-diazene **15g**, is computed to be about the same as the overall $E_A$ for its HERON reaction.  This is a very early transition state in keeping with the exothermicity of the process. $E_{rearr}$ is essentially zero on account of the high energy electron-pair on the amino nitrene and the $E_A$ is essentially  equivalent to the RE that must be sacrificed.  Likewise,  the hydroxamate **15f** bears a very high energy electron pair on the anomeric donor oxygen.  While the resonance energy is similar to that of *N,N*-dimethoxyacetamide, the $E_{rearr}$ is small. This too is a very early transition state.

Overall, the decreasing order of $E_{rearr}$ of XNY systems based on  the deconvolution in Table 8, which can be regarded as the order of decreasing effectiveness of an $n_Y – \sigma^*_{NX}$ interaction and destabilisation of the *N—OMe* bond, is AcONO > SNO ~ ONO > ONN > ONO$^-$ > ONNitrene. The order of $RE_{TA}$ is ONN > ONS > AcONO > ONO > ONO$^-$ > ONNitrene and the overall

1    activation energies decrease in the order AcONO > ONS > ONO > ONN > ONO⁻ > ONNitrene.

2    Clearly, the dominant influence in HERON reactivity is the strength of the anomeric effect

3    rather than the decrease in amidicity.

4

5    Rearrangement energies, $E_{rearr}$'s, obtained by the deconvolution method represent activation

6    energies in the absence of resonance.  Relative $E_{rearr}$'s can be compared to relative $E_A$'s for

7    intramolecular rearrangement in fully twisted amides, heteroatom-substituted 1-aza-2-

8    adamantanone **85** (Scheme 17)  and 2-quinuclidone **88** (Scheme 18) and the $E_A$'s are also

9    presented in Table 8.  $\Delta E_A$'s relative to migration of oxygen to (Scheme 17, i) in **85b**, for **85a**

10   and **85c** are −88 and 5.8 kJ mol⁻¹, respectively, which correlate well with the respective

11   differences in $E_{rearr}$ of the respective acetamides, namely −77 and 5 kJ mol⁻¹.  Similarly, the

12   difference in the ease of migration of alkoxyl to form **90** and acyloxyl to form **89** in **88** (Scheme

13   18, ii and i) is 28 kJ mol⁻¹ and the difference between the corresponding $E_{rearr}$ form the *syn*

14   conformer of **15b** is 27 kJ mol⁻¹.

15

16   No transition state can be found for migration of alkoxyl group in hydroxamic ester **3d**.

17   However, **85d** can be rearranged to lactone **87** (Scheme 17, ii) with concomitant rearrangement

18   of the nitrene product to the imine.  The difference between $E_A$ for this process and the

19   rearrangement of **85a** is 184 kJ mol⁻¹.  If this translates to the difference in $E_{rearr}$ between twisted

20   *N*-methoxy-*N*-methylacetamide **3** and *N*-methoxy-*N*-dimethylaminoacetamide **15c**, for which

21   $E_{rearr}$ is 43.5 kJ mol⁻¹, the rearrangement of **3** to methyl acetate and methylnitrene would have

22   an activation energy of about 233 kJ mol⁻¹ from twisted **3** or, adding in the RE for **3** of 62 kJ

23   mol⁻¹, 295 kJ mol⁻¹ from conjugated **3**.  It is clear that hydroxamic esters do not rearrange to

24   esters and alkylnitrenes and the role of anomeric (bisheteroatom) substitution in the HERON

25   reaction is vital.

26

27

**Table 8.** B3LYP/6-31G(d) activation energies ($E_A$), resonance energies ($RE_{TA}$) and rearrangement energies ($E_{rearr}$) for HERON reactions of model anomeric amides and tricyclic anomeric amides; all values in kJ mol$^{-1}$

| Migratory mode | $E_A$ | XNY[1] | $RE_{TA}$[2] | $E_{rearr.}$ |
|---|---|---|---|---|
| MeO from *anti* **15c** | 95.0 | ONN | -51.5 | 43.5 |
| MeO from **4b** | 156.5 | ONO | -35.9 | 120.5 |
| MeO from *syn* **16a** | 92.4 | ONN | -50.7 | 41.8 |
| AcO from *syn* **15b** | 181.0 | AcONO | -40.5 | 140.5 |
| MeO from *syn* **15b** | 207.9 | ONOAc | -40.5 | 167.4 |
| AcO from *anti* **15b** | 181.5 | AcONO | -40.5 | 141.0 |
| MeO from *anti* **15b** | 182.8 | ONOAc | -40.5 | 142.3 |
| MeO from *anti* **15d** | 174.1 | ONS | -48.6 | 125.4 |
| MeO from **15f** [3] | 48.0 | ONO$^-$ | -32.4 | 15.6 |
| MeO from **15g** | 8.8 | ONNitrene | -14.8 | -6.0 |
| Ring opening **81** | 113.0 | ONO | -19.2 | 93.8 |
| Ring contraction **82** | 145.2 | ONO | -36.7 | 108.4 |
| Ring opening of **82** | 136.4 | ONO | -36.7 | 99.7 |
| Scheme 17 i X=NMe | 59.0 | ONN | 0.0 | 59.0 |
| Scheme 17 i X=O | 146.9 | ONO | 0.0 | 146.9 |
| Scheme 17 i X=S | 152.7 | ONS | 0.0 | 152.7 |
| Scheme 17 ii X=CH$_2$ | 242.7 | ONCH$_2$ | 0.0 | 242.7 |
| Scheme 18 i | 133.5 | AcONO | 0.0 | 133.5 |
| Scheme 18 ii | 161.5 | ONOAc | 0.0 | 161.5 |

[1] $n_Y$ donor to $\sigma^*_{NX}$

[2] Transamidation data (COSNAR data very similar)

[3] HF/6-31G(d) values
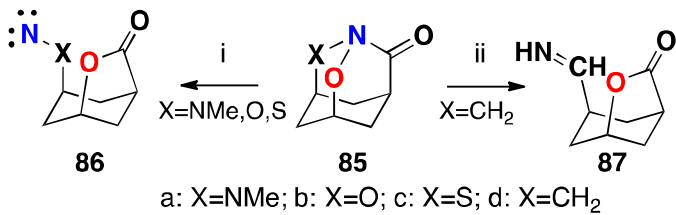


**Scheme 17**. HERON migrations of alkoxyl in the absence of resonance.

1

2



3          **89**              **88**                    **90**
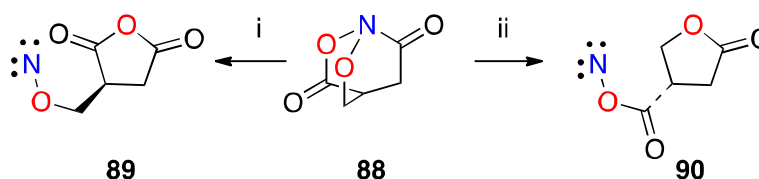
4          **Scheme 18.** HERON reactions of *N*-acyloxy-*N*-alkoxyamide in absence of resonance.

5

6     **4. Conclusion**

7     In this review we have outlined the theoretical and structural properties and the reactivity of

8     the class of anomeric amides.  Much of the data from this, and several other groups is relatively

9     recent and, while several compilations on the subject have appeared in the literature, a focus

10    on the perturbation of the amide structure is befitting this special edition. The fairly recent

11    accrual of structural data from our laboratory and that of Shtamburg has provided  experimental

12    verification of the unusual properties of bisheteroatom-substituted  amides.  Coupled with

13    extensive computational results, the effect of heteroatoms at nitrogen on amide resonance and

14    conformation at the amide nitrogen can be better understood and predicted, in particular the

15    role played by electronegativity of the bonded atoms and orbital interactions.  Ensuing from

16    the work is a clearer understanding of the energetic consequences  of distortion of the amide

17    linkage.  It is clear that spectroscopic properties of various congeners are dictated by two

18    principle concepts:  the first is impaired resonance owing to change in hybridisation bought

19    about by orbital interactions that have their foundation in Bent's, and more recently Alabugin's

20    theories of orbital interactions.   Of  particular importance is the reassignment of 2s character

21    to the amide nitrogen lone pair orbital, as consequence of both electronegativity and orbital

22    overlap considerations.  Secondly, the participating atoms in this purturbation of regular amide

23    bonding possess intrinsic orbital interactions by virtue of both their electronegativity and their

24    lone pairs. The anomeric interaction bought about by $n_Y - \sigma^*_{NX}$ overlap is pronounced in

25    anomeric amides.  What is clear is that the electronegativity induces a shift to less resonance

26    through pyramidalisation and lowering the energy of the amide nitrogen lone pair and the

27    anomeric interaction is better served by this shift to sp$^3$ character.  Stronger electronegativity

28    serves to reduce resonance as well as to promote the anomeric interaction.

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30    Regarding reactivity,  it is abundantly clear that both resonance impairment and strength of the

31    anomeric effect are definitive, but  the anomeric effect dominates in promoting both S$_N$2 and

1    elimination reactions at the amide nitrogen.  Most significant is the anomeric driving force for

2    the HERON reaction, notably in systems such as *N*-amino-*N*-alkoxyamides  (NNO systems)

3    where the energetics for anomeric weakening of the *N—O* bond are optimised, and in cyclic

4    systems such as the *N*-alkoxy-γ- and δ-oxazinolactams where conformation and configuration

5    appear to favour and enhance anomeric overlap.  The HERON reaction is unique to this class

6    of amides and has no equivalence in the literature.  It operates in the opposite sense to the well-

7    known  Curtius,  Hoffman  and  Lossen  rearrangements  in  which  an  acyl  substituent  migrates

8    from the carbonyl to the nitrogen.  Finally our studies of the HERON and those of Barton and

9    coworkers,  shed  light  on  the  well-known  decomposition  reactions  of  *N,N′*-dialkoxy-*N,N′*-

10    diacylhydrazines.  The HERON mechanism that operates in these decompositions and in those

11    of the 1-acyl-1-alkoxydizenes is critical to the synthesis of highly hindered esters.

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