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THE ROLE OF SUBSTITUENTS IN THE HERON REACTION OF ANOMERIC AMIDES**Stephen A. Glover^{1*} and Adam A. Rosser**

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ABSTRACT

Anomeric amides, $RCON(X)(Y)$, have two electronegative atoms at the amide nitrogen, a configuration that results in greatly reduced amide resonance and strongly pyramidal nitrogen atoms. This, combined with facilitation of anomeric interactions, can result in the HERON reaction, an intramolecular migration of the more electronegative atom, X , from nitrogen to the carbonyl with production of a Y -stabilised nitrene. We have modelled, at B3LYP/6-31G(d) level, a variety of anomeric amides that undergo the HERON reaction to determine factors that underpin the process. The overriding driving force is anomeric destabilisation of the bond to the migrating group. Rotated transition states show loss of residual resonance and this is a component of the overall activation energies. However, the reduced resonance in these systems plays only a minor role. We have determined the resonance energies (RE) and HERON activation barriers, E_A , of five anomeric systems. RE for the amides have been calculated isodesmically using our calibrated *trans* amidation method and COSNAR calculations. Reduction of their overall E_A 's by the corresponding RE gives rearrangement energies, E_{rearr} , a measure of relative impact on rearrangement of substituents on nitrogen. In $CH_3CON(OMe)(Y)$ systems producing $(CH_3CO_2Me + NY)$, a loosely-bound electron pair on the donor atom, Y , in $n_Y - \sigma_{NOMe}^*$ anomeric interactions drives the reaction. E_{rearr} increases in the sequence $Y=N(\text{nitrene}) < O^-(\text{oxide}) < NMe_2 < SMe < OMe$. For the same systems, RE increases in the order $Y=N < O^- < OMe < NMe_2 \sim SMe$. Other effects such as molecular conformation, nature of the migrating group, X , as well as acyl substituents at the carbonyl carbon are discussed.

Keywords: anomeric amides, HERON reactions; reaction mechanism; pyramidal amides; amide resonance; anomeric effects

Introduction

In the course of our investigations into the biological activity of a class of direct-acting mutagens, *N*-acyloxy-*N*-alkoxyamides **1a**, we have encountered a range of unusual amides, so-called anomeric amides, which are amides bearing two electronegative atoms at the nitrogen **1**. Much has now been published concerning the unusual properties of such amides.¹⁻¹² The combined electronegativity of *X* and *Y* results in a high degree of pyramidalisation of the amide nitrogen resulting in localisation of the nitrogen lone pair in an sp³ hybrid orbital rather than the normal 2p_z orbital. The energy of the lone pair is also lowered resulting in a diminution of the degree of resonance over the amide carbonyl with attendant lengthening of the *N*—C(*O*) bond and much higher carbonyl stretch frequencies in their IR spectra, the latter due to higher pi bond character through destabilisation of the polar, single bond resonance form of the carbonyl. In addition, x-ray structural data and theoretical calculations on the ground state structures demonstrate pronounced n_Y—σ*_{NX} anomeric effects through the central amide nitrogen.

1 **2** **3**

a: X=O₂CR, Y=OR

b: X=OR, Y=NR₂

c: X=OR, Y=OH

d: X=OR, Y=O⁻

e: X=OR, Y=SR

f: X=Cl, Y=OR

g: X=OR, Y=N₃

h: X=OR, Y=N

i: X=Y=OR

Not only are there structural and spectroscopic changes, these amides undergo a variety of reactions that are not found in normal *N,N*-dialkyl, *N*-alkyl- or primary amides. With suitable substituents that can stabilise negative charge, both S_N1 and S_N2 reactions at nitrogen have been shown to occur. For instance, *N*-acyloxy-*N*-alkoxyamides **1a** undergo S_N2 reactions with arylamines to generate *N*-amino-*N*-alkoxyamides **1b**,^{7, 8, 13-16} reaction in base to give hydroxamic acids **1c**,¹⁷ which convert to

their anions **1d**, and reaction with thiols to generate intermediate *N*-alkoxy-*N*-alkylthiylamides **1e**.¹⁸ With aqueous acid catalysis they are hydrolysed to *N*-alkoxyhydroxamic acids **1c** and carboxylic acids in A_{Al}1 reactions.^{19, 20} Both *N*-acyloxy-*N*-alkoxyamides **1a** and *N*-alkoxy-*N*-chloroamides **1f** undergo S_N2 reactions with azide to give *N*-alkoxy-*N*-azidoamides **1g**, which decompose to *N*-acyl-*N*-alkoxyaminonitrenes (1-acyl-1-alkoxydiazenes) **1h** and nitrogen.²¹ *N*-Acyloxy-*N*-alkoxyamides **1a** themselves are formed by S_N2 displacement of chlorine in **1f** by carboxylates.^{16, 17, 22} Solvolysis of *N*-alkoxy-*N*-chloroamides **1f** in aqueous alcohol can generate *N,N*-dialkoxyamides **1i**,²³ which can also be generated directly from hydroxamic esters with phenyliodine bis(trifluoroacetate) (PIFA) in appropriate alcohols.¹⁰ *N*-Alkoxy-*N*-chloroamides **1f** react with Lewis acids yielding *N*-acyl-*N*-alkoxynitrenium ions, a reaction that has proven to be useful in the intramolecular addition of such ions to olefins and aryl systems.²⁴⁻³¹ Similar structural properties and reactions of the related anomeric carbamates and ureas have been studied extensively by Shtamburg and coworkers.³²⁻³⁸

Scheme 1

Fig. 1. Theoretically derived transition state for the generalised HERON reaction of an *X,Y*-substituted amide; (a) perspective drawing, (b) Newman projection along the *N*–*C*(*O*) bond.

Anomeric amides have also been found to undergo an unusual intramolecular rearrangement, now known as the HERON reaction (*H*eteroatom *R*earrangements *O*n *N*itrogen), which was first implicated in the reactions of *N*-acyloxy-*N*-alkoxyamides **1a** with *N*-methylaniline and in which the intermediate *N*-alkoxy-*N*-methylanilinoamides **1b** generate esters together with 1,1-diazenes (Scheme 1, Y=NMePh, X=OR).^{7, 8, 13, 14, 39-41} Notably, the process in this case is facilitated by a strong $n_{\text{N}}-\sigma_{\text{NOR}}^*$ anomeric interaction between the nitrogen substituents, which weakens the *N*—*OR* bond resulting in its migration from nitrogen to the carbonyl carbon concomitant with *N*—*C*(*O*) bond heterolysis. Theoretical evaluation of the rearrangement for model **2** at B3LYP/6-31G(d) level predicted a modest E_{A} of $\sim 20 \text{ kcal mol}^{-1}$ and a transition state in which the lone pair on nitrogen resides in the *N*—*C*(*O*) plane and all resonance is lost.⁴⁰ In addition, the alkoxy group migrates in a plane orthogonal to the *N*—*C*(*O*) plane (Fig. 1a and Fig. 1b, Y=NR₂, X=OR). The reaction was also studied directly in the thermal decomposition of *N,N'*-dialkoxy-*N,N'*-diacylhydrazines **3**, which decompose near room temperature and with E_{A} 's of 20-30 kcal mol⁻¹ in consecutive three-centre HERON processes giving two equivalents of ester and nitrogen; 1-acyl-1-alkoxydiazenes **1h** are intermediates.⁴⁰

Scheme 2

Scheme 3

Scheme 4

Scheme 5

Other systems undergo the HERON reaction. *N*-Acyloxy-*N*-alkoxycarbamates **4** also react at room temperature with *N*-methylaniline to form *N*-alkoxy-*N*-methylanilinocarbamates **5**, which rearrange to dialkyl carbonates **6** and the 1-methyl-1-diazenes **7** (Scheme 2).⁴² *N*-Acyloxy-*N*-alkoxyamides **1a** themselves generate anhydrides and alkoxynitrenes but at significantly higher temperatures in toluene (Scheme 3).⁴³ *N*-Acyl-*N*-alkoxy-1,1-diazenes extrude nitrogen to give esters in a facile reaction which resembles the HERON process (Scheme 4),^{5, 21, 40, 44, 45} and the conjugate anions of *N*-alkoxyhydroxamic esters **1d** readily form esters intramolecularly by a similar process (Scheme 5).¹⁷ Aminonitrenes (**7**, Scheme 2) and nitrogen (Scheme 4) are generated as singlets, but alkoxynitrenes (**9**, Scheme 3) and NO^- (Scheme 5) must relax upon formation to their more stable triplet states. The features of these reactions have been highlighted in a series of papers from our laboratory and the HERON reaction has been reviewed in this journal.⁴¹

In contrast, rather than undergoing HERON reactions, *N*-alkoxy-*N*-alkylthiylamides **1e**, formed from *N*-acyloxy-*N*-alkoxyamides **1a** and thiols (including glutathione) generate hydroxamic esters **11** and disulfides **12** (Scheme 6).¹⁸ *N,N*-Dialkoxyamides **1i**, instead, undergo thermolysis reactions

in toluene generating *N*-alkoxyamidyl radicals,¹⁰ while several cyclic forms rearrange by HERON reactions.¹¹

Scheme 6

From theoretical modelling, the transition states for all HERON reactions studied to date are similar to that calculated for **1b** in that the migrating group in each case moves in a plane orthogonal to the *N*—*C*(*O*) system and there is loss of all intrinsic resonance, with the amide nitrogen lone pair in the *N*—*C*(*O*) plane (Scheme 1, Fig. 1).^{11, 39, 40, 46}

A number of factors could influence the ease of HERON reactions:

1. The strength of the anomeric destabilising effect and therefore the nature of *X* and *Y*;
2. The degree of residual amide resonance in **1**, which varies with substituents *X* and *Y* and, since this is sacrificed at the HERON transition state, it can also dictate the overall E_A for the process;
3. The nature of the migrating group, *X*;
4. The nature of amide acyl substituents, *R*;
5. Conformation and stereoelectronic effects.

We recently showed computationally that for *N*-methoxy-*N*-dimethylaminoacetamide **13f** and *N,N*-dimethoxyacetamide **13g**, models for **1b** and **1i** respectively, deconvolution of the E_A into a resonance energy (RE) and a rearrangement energy component (E_{rearr}) is possible since the residual resonance in anomeric and many other amides and lactams can be computed by *trans* amidation,⁴⁷ and COSNAR (carbonyl substitution, nitrogen atom replacement) isodesmic studies.⁴⁸⁻⁵⁰ *N,N*-Dimethoxyacetamide **13g**, with an E_A for HERON of 37.4 kcal mol⁻¹, has a low residual resonance

energy ($RE = -8.6 \text{ kcal mol}^{-1}$) but a large rearrangement component ($E_{rearr} = 28.8 \text{ kcal mol}^{-1}$), while **13f** has a much greater degree of resonance on account of the lower combined electronegativity of the nitrogen substituents ($RE = -12.5 \text{ kcal mol}^{-1}$) but a much lower rearrangement component ($E_{rearr} = 10.4 \text{ kcal mol}^{-1}$) and consequently a much lower overall E_A of $22.7 \text{ kcal mol}^{-1}$.⁴⁶ In this comparison it is clear that the factors affecting the ease of the migration are more important than reduced resonance.

In this paper we have examined models for HERON reactions in Scheme 2-Scheme 5 as well as possible HERON reactivity of the *N*-alkoxy-*N*-alkylthiylamides **1e** to discern the relative influences of structure on the process.

Computational Methods

Fully optimised ground states of models of all structures **13a-d** and **22**, components used in calculation of *trans* amidation and COSNAR resonance energies according to eq. [1-6] and eq. [8-11], and transition states for HERON reactions of **13a-d** and **22** were computed at the B3LYP/6-31G(d) level using MacSpartan 10.⁵¹ B3LYP/6-31G(d) has been shown to perform well in determinations of structure and properties of a wide range of amides, lactams and anomeric amides,^{1, 3, 9, 11, 12, 40, 41, 46, 47} and resonance energies at this level have been demonstrated to be in relatively good agreement with those obtained with much larger basis sets and higher levels of correlation energy corrections.⁴⁷ Neither model **13e**, nor some elements required in the computation of its resonance energy were stationary points at B3LYP/6-31G(d). Calculations at B3LYP/6-31G(d,p) up to B3LYP/6-311++G(d,p) and employing dispersion-corrected M06/6-311++G(d,p) on **13e** ground state failed to resolve this problem. Resonance energy and HERON reaction data for **13e** were computed at the HF/6-31G(d) level, which performed well with these anions. Energies of model structures in isodesmic eq. [1-6] and eq. [8-11] were computed without ZPE and thermal

corrections since these largely cancel. Lowest energy twisted amides used in eq. [6] were obtained by transition state searches starting with a twisted form or were constrained to keep the lone pair in the $N-C(O)$ plane. Geometries of reactants, transition states and products as well as absolute energies for all components in these equations are provided as supplementary material. For the HERON reactions of **13a-e** and for **22**, the determination of activation energies and reaction energies with ZPE, and enthalpic corrections required full frequency calculations on all reactants, transition states and products. Transition states for HERON processes possessed one imaginary frequency and geometry optimisations at start and finish coordinates of the imaginary vibrational mode were carried out to ensure transition states were real and relaxed back to reactants before, and products after the transition state complex. Priority groups at nitrogen as determined according to the Cahn-Ingold-Prelog system are designated *syn* or *anti* to the carbonyl oxygen with respect to the $N-C(O)$ bond. In hydroxamate **13e**, O^- is by definition prioritised over OMe.

Results and discussion

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- a:** X=OAc, Y=OMe, Z = Me
b: X=OMe, Y=SMe, Z=Me
c: X=OMe, Y=N(Me)₂, Z=MeO
d: X=OMe, Y=N, Z=Me
e: X=OMe, Y=O⁻, Z=Me
f: X=OMe, Y=NMe₂, Z=Me
g: X, Y = OMe, Z=Me

The lowest energy ground state structures of model anomeric amides **13a-e** are shown in Fig. 2 and with the exception of **13d** and **13e**, the nitrogens are pyramidal at nitrogen with average angles at nitrogen of well below 120° and Winkler-Dunitz pyramidal indices, χ ,^{52, 53} in line with the total electronegativity of the two atoms attached to the amide nitrogen. *N*-Acetoxy-*N*-methoxyacetamide ($\chi = 58^\circ$) is very near to being fully sp³ hybridised at nitrogen ($\chi = 60^\circ$). The nitrogen in *N*-methoxy-*N*-methylthiylacetamide **13b** ($\chi = 31.7^\circ$) is a shallow pyramid while *N*-methoxy-*N*-dimethylaminoacetamide ($\chi = 46.3^\circ$) is moderately pyramidalised at the amide nitrogen. In the cases of **13a-c** the Winkler-Dunitz twist parameters, τ ,^{52, 53} are small, indicating good alignment of the lone pair orbital on nitrogen with the adjacent carbon 2p_z orbital and some residual resonance in each case. However, *N*—C(*O*) bonds are longer relative to *N,N*-dimethylacetamide (1.378 Å) and, based solely on *N*—C(*O*) bond lengths, **13a** would be expected to have the least residual resonance while that in **13b** and **13c** would be expected to be similar and less than that in **13a**. The 1,1-diazene **13d** is completely planar as is the hydroxamate **13e** and both of these acetamides mirror the calculated structures of the formamide systems.^{5, 41, 45} The 1,1-diazene **13d** would be expected to exhibit little resonance on account of the *N*—*N* conjugation and ammonium character of the amide nitrogen and in keeping with this, has the longest *N*—C(*O*) bond length of all five structures. *N*—C(*O*) is particularly long since both the N1 and C2 are also sp² hybridised. While the computed

structure of the hydroxamate anion **13e** has a much shorter $N-C(O)$ bond, direct comparison with the B3LYP/6-31G(d) structures is not possible since at this level it is unstable and all data for **13e** could only be computed at the HF/6-31G(d) at which it was at an electronic energy minimum. However, the electron-rich anion would be expected to exhibit significantly more resonance relative to *N,N*-dimethoxyacetamide or *N*-acetoxy-*N*-methoxyacetamide.

In **13a-c** there is evidence of ground state anomeric effects. In **13a** the C4-O3-N1-O2 dihedral aligns the 2p lone pair on O3 in the same plane as the N1-O2 σ^* orbital. In **13b** the dihedral angles predict that the p-type lone pairs located on S1 and O2 are similarly aligned with the N1-O2 and N1-S1 σ^* orbitals respectively, while from dihedral angles in **13c**, the lone pair on N2 deviates only *ca* 10 degrees from the plane of the N1-O3 σ^* orbital.

Fig. 2 Lowest energy ground state structures for **13a-d** (at B3LYP/6-31G(d)) and **13e** (at HF/6-31G(d)); χ and τ are the Winkler-Dunitz pyramidal and twist indices;^{53, 53} average angles at nitrogen are denoted by $\langle \rangle$.

Resonance effects in various anomeric amides **13a-c** including 1,1-diazene **13d** (formally an aminonitrene) and hydroxamate anions **13e** have been computed using both our *trans* amidation method (eq. [1])⁴⁷ and, for confirmation, Greenberg's COSNAR method (eq. [2]).⁴⁸⁻⁵⁰ B3LYP/6-31G(d) performed well for the neutral systems **13a-d**. In the *trans* amidation method we calculate destabilisation relative to *N,N*-dimethylacetamide **14** when anomeric amide **13** (with **16**) is generated by transfer of the carbonyl to amine **15**.

For the *trans* amidation method, the destabilisation relative to *N,N*-dimethylacetamide, ΔE_{react} , also includes an inductive effect owing to the replacement of methyl groups at nitrogen in **14** by *X* and *Y* in **13**. For **13a-c**, this can be estimated isodesmically from formation of tricyclic systems **19-21**, in which the resonance is zero, according to eq. [3] for **13a**, eq. [4] for **13b** and eq. [5] for **13c**. Reduction of the overall destabilisation from eq. [1] by the inductive quantum gives the loss of

energy relative to *N,N*-dimethylacetamide due to reduction in resonance alone. In the case of **13d** and **13e**, which have no tricyclic analogue, the inductive destabilisation can be estimated from eq. [6] in which the fully twisted forms **22** have little or no resonance. The twisted forms were obtained as rotational transition states. We have previously determined the maximum possible resonance loss, ΔE_{max} for a simple amide to be 18.16 kcal mol⁻¹ from the isodesmic reaction of *N,N*-dimethylacetamide with 1-azaadamantane to give 1-aza-2-adamantanone and *N,N*-dimethylethylamine,⁴⁷ so the residual resonance stabilisation is given by eq. [7] in each case.

Computed RE's, together with the ΔE_{react} and $\Delta E_{inductive}$ destabilisation are presented in Table 1. These values were in close agreement with the values from COSNAR, which directly measures the increase in stabilisation when substituted nitrogen in **15** and carbonyl in **17** are adjacent in **13** with the expulsion of **18**.

$$RE = -[\Delta E_{max} - (\Delta E_{react} - \Delta E_{inductive})] = -[18.16 - (\Delta E_{react} - \Delta E_{inductive})] \quad [7]$$

Resonance in the *N*-acetoxy-*N*-methoxyacetamide **13a** (52-53%) relative to *N,N*-dimethylacetamide is similar to that previously obtained by similar methods for *N,N*-dimethoxyacetamide **13g** (47%)⁹ and reflects comparable total electronegativity at the amide nitrogen. The reduced resonance also accords well with the x-ray structural properties of two *N*-acyloxy-*N*-alkoxyamides, which have *N*–*C*(*O*) bonds of 1.44 Å and similar pyramidity ($\chi = 65^\circ$ and 66°) and twist ($\tau = 14^\circ$ and 15°) to the model **13c**.^{6,7}

The *N*-methoxy-*N*-methylthiylacetamide system **13b** represents intermediates **1e** implicated in the reactions of *N*-acyloxy-*N*-alkoxyamides with thiols in Scheme 6. The reduced electronegativity of the sulfur atom results in a substantial increase in resonance delocalisation to about 71% that of *N,N*-dimethylacetamide.

Estimation of the extent of amide resonance for the carbamate **13c** was best determined by *trans* carbamation to the substituted amine according to eq. [8]. However, the maximum loss of resonance for the carbamate, ΔE_{max} , is reduced relative to *N,N*-dimethylacetamide on account of competing resonance with the acyl oxygen, but can be estimated in an analogous fashion to that for *N,N*-dimethylacetamide⁴⁷ from the increase in energy upon formation of fully twisted 3-oxa-2-quinuclidone from *N,N,O*-trimethylcarbamate and 3-oxaquinuclidine, according to isodesmic eq. [9].

Application of COSNAR (eq. [2]) to resonance in **13c** results in a very different cross-conjugated configuration with attendant configurational stabilisation, which cannot be separated from resonance effects. For comparison with the *trans* carbamation result, resonance was best determined from the difference between two isodesmic COSNAR equations generating, respectively, an unconjugated, twisted carbamate (eq. [10]) and a conjugated carbamate (eq. [11]). The residual resonance percentages are in reasonable agreement (63% and 67% of that in *N,N*-dimethylacetamide) and compare well with that obtained for *N*-methoxy-*N*-dimethylaminoacetamide (65% that of *N,N*-dimethylacetamide).⁴⁶ Interestingly, from these results, the acyl oxygen appears to provide little competitive resonance in the carbamate.

It was not possible to calculate the residual resonance in *N*-acetyl-*N*-methoxydiazene **13d** by COSNAR method on account of spontaneous nitrene insertion reaction in the 1-methoxypropyl nitrene product required for eq. [2]. However, the *trans* amidation eq. [1] was successfully applied and confirms very low resonance of just 15% that of *N,N*-dimethylacetamide.

The residual resonance in the hydroxamate **13e** could only be computed at the HF/6-31G(d) level as at the B3LYP/6-31G(d) level with inclusion of electron correlation, and even upon incorporation of expanded basis sets and with the dispersion-corrected M06/6-311++G(d,p) method, the parent *N*-methoxyacetohydroxamate and amine anions relevant to both the COSNAR and the *trans* amidation reaction are unstable, generating instead partially dissociated complexes with methoxide. However, as an approximation, HF/6-31G(d) energies afforded similar RE's of 6 kcal mol⁻¹ and 8 kcal mol⁻¹ or 36%-46% that of *N,N*-dimethylacetamide at the HF/6-31G(d) level.

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Table 1. B3LYP/6-31G(d) derived COSNAR and *trans* amidation data for anomeric amides **13a-e** from eq.'s [1–11] together with that for **13f** and **13g**

Structure	Energy (kcal mol ⁻¹) ^{a,b}
<i>N</i> -Acetoxy- <i>N</i> -methoxyacetamide 13a	
ΔE_{COSNAR} from eq. [2]	-9.5 [52%]
ΔE_{react} from eq. [1]	15.6
$\Delta E_{\text{inductive}}$ eq. [3]	7.1
RE eq. [7]	-9.7 [53%]
<i>N</i> -Methoxy- <i>N</i> -methylthiylacetamide 13b	
ΔE_{COSNAR} from eq. [2]	-13.0 [71%]
ΔE_{react} from eq. [1]	6.4
$\Delta E_{\text{inductive}}$ eq. [4]	1.2
RE from eq. [7]	-13.0[71%]
<i>N</i> -Methoxy- <i>N</i> -dimethylamino- <i>O</i> -methylcarbamate 13c	
ΔE_{COSNAR} from (eq. [11–10])	- 11.4 [63%]
ΔE_{react} from eq. [8]	7.6
$\Delta E_{\text{inductive}}$ from eq. [5]	3.5
RE from [-16.19-(eq. [8–5])]	-12.1 [67%]
1-Acetyl–1-methoxydiazene 13d	
ΔE_{COSNAR}	_c
ΔE_{react} from eq. [1]	24.1
$\Delta E_{\text{inductive}}$ from eq. [6], Y=N	9.5
RE from eq. [7]	-3.5[14.8%]
<i>N</i> -Methoxyacetohydroxamate anion 13e^d	
ΔE_{COSNAR} from eq. [2]	- 6.2 [36%]

ΔE_{react} from eq. [1]	5.4
$\Delta E_{inductive}$ eq. [6], $Y=O^-$	1.0
RE from eq. [7]	-7.8 [46%]
<i>N</i> -Methoxy- <i>N</i> -dimethylaminoacetamide 13f ^e	
ΔE_{COSNAR}	- 12.5 [69%]
ΔE_{react}	8.4
$\Delta E_{inductive}$	2.4
RE	-12.2 [67%]
<i>N,N</i> -Dimethoxyacetamide 13g ^f	
ΔE_{COSNAR}	-8.6 [47%]
ΔE_{react}	13.9
$\Delta E_{inductive}$	4.3
RE	-8.6 [47%]

^a Relative to the energy of *N,N*-dimethylacetamide

^b Amidicities in parentheses.

^c Not applicable

^d Computed at the HF/6-31G(d) level.

^e Previously published values ⁴⁶

^f Previously published values ⁹

Transition states for the HERON reactions of **13a-e** are shown in Fig. 3 and relevant ground state conformer energies, activation energies (E_A) and reaction energies (ΔE) are collated in Table 2. In all cases, the transition states possessed one imaginary frequency and relaxed to reactant and product from coordinates either side of them.

Fig. 3. B3LYP/6-31G(d) optimised transition states for migration of acetoxyl from (a) *syn* and (b) *anti* conformers of *N*-acetoxy-*N*-methoxyacetamide **13a** and migration of methoxyl from (c) *anti* and (d) *syn* conformers of *N*-acetoxy-*N*-methoxyacetamide **13a**.

Fig. 4. B3LYP/6-31G(d) optimised transition states for migration of methoxyl from (a) *syn* and (b) *anti* conformers of *N*-methoxy-*N*-methylthiylacetamide **13b** and migration of methoxyl from (c) *syn* and (d) *anti* conformers of *N*-methoxy-*N*-dimethylamino-*O*-methylcarbonate **13c**.

Fig. 5. (a) B3LYP/6-31G(d) optimised transition state for migration of methoxyl in 1-acetyl-1-methoxydiazene **13d** and (b) HF/6-31G(d) optimised transition state for migration of methoxyl in *N*-methoxyacetohydroxamate **13e**.

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Table 2. B3LYP/6-31G(d) derived relative energies of conformers, transition states and products for HERON reactions of **13a-e** and **19**.^a

Structure	E_{rel} (kcal mol ⁻¹) ^b
<i>N</i>-Acetoxy-<i>N</i>-methoxyacetamide 13a	
<i>Syn</i>	0
<i>Anti</i>	0.57 (0.6)
E_A AcO migration from <i>syn</i> (<i>i</i> 308)	43.3 (41.2)
E_A AcO migration from <i>anti</i> (<i>i</i> 314)	43.4 (41.6)
E_A MeO migration from <i>syn</i> (<i>i</i> 255)	49.6 (48.1)
E_A MeO migration from <i>anti</i> (<i>i</i> 243)	43.7 (42.4)
ΔE_C Acetic anhydride + methoxynitrene (S) complex	30.4
ΔE_S Acetic anhydride + methoxynitrene (S)	36.8 (34.3)
ΔE_T Acetic anhydride + methoxynitrene (T)	19.1 (21.7)
ΔE_C Methyl acetate + acetoxynitrene (S) complex	37.2
ΔE_S Methyl acetate + acetoxynitrene (S)	35.2 (33.0)
ΔE_T Methyl acetate + acetoxynitrene (T)	14.9 (13.2)
<i>N</i>-Methoxy-<i>N</i>-methylthiylacetamide 13b	
<i>Syn</i>	0
<i>Anti</i>	1.9 (1.8)
E_A MeO migration from <i>anti</i> (<i>i</i> 398)	41.6 (39.8)
E_A MeO migration from <i>syn</i> (<i>i</i> 368)	44.3 (42.6)
ΔE_C Methylacetate + methylthionitrene (S) complex	12.4
ΔE_S Methylacetate + methylthionitrene (S)	19.7 (18.0)
ΔE_T Methylacetate + methylthionitrene (T)	14.3 (12.4)
ΔE_S <i>S</i> -methyl ethanethioate + methoxynitrene (S)	58.8 (56.0)

ΔE_T *S*-methyl ethanethioate + methoxynitrene (T) 41.2 (43.4)

***N*-Methoxy-*N*-dimethylamino-*O*-methylcarbamate 13c**

Syn 0

Anti 0.25 (0)

E_A MeO migration from *anti* (*i* 240) 22.1 (20.5)

E_A MeO migration from *syn* (*i* 250) 24.4 (22.9)

ΔE_C Dimethyl carbonate + 1,1-dimethyldiazene complex -5.5

ΔE_S Dimethyl carbonate + 1,1-dimethyldiazene (S) 0.16 (-1.6)

1-Acetyl-1-methoxydiazene 13d

Anti 0

Syn 1.2 (1.3)

E_A Transition state (*i* 187) 2.1 (1.5)

ΔE_C Methylacetate + nitrogen complex -93.9

ΔE_S Methylacetate + nitrogen -93.6 (-93.1)

***N*-Methoxyacetohydroxamate anion 13e^c**

Anti 0

Syn 6.6 (6.4)

E_A Methoxy migration from *anti* (*i* 301) 11.5 (10.0)

ΔE Tetrahedral intermediate -15.6

ΔE_S Methyl acetate + nitroxide anion (S) 15.9 (15.2)

ΔE_T Methyl acetate + nitroxide anion (T) -33.0 (-33.8)

2',2''-Dioxa-2,3'-quinuclidione 19 0

E_A Acyloxyl migration (<i>i</i> 330)	31.9 (30.6)
E_A Alkoxyl migration (<i>i</i> 342)	38.6 (37.2)
ΔE_C Anhydride complex 27	11.1
ΔE_C Lactone complex 28	25.5

^a Absolute energies are given in the supplementary information.

^b Energies of conformers, transition states (E_A) and relaxed transition state complexes (ΔE_C) and products (ΔE , ΔE_S and ΔE_T) relative to the respective lowest energy ground state; enthalpy corrected values in parentheses.

^c Computed at HF/6-31G(d) level

Draft

Since conformers of *N*-acetoxy-*N*-methoxyacetamide **13a** are very close in energy and both nitrogen substituents are bonded through oxygen, rearrangement of both acetoxy and methoxyl were computed leading to four transition states. While acetoxy migration from the lowest energy, *syn* rotamer is more favourable by *ca* 6 kcal mol⁻¹ relative to methoxyl migration, methoxyl and acetoxy migrations from the *anti* form have similar E_A 's. Experimentally, in the limited cases studied to date, the major reaction pathways result from acyloxyl migration to give anhydrides and alkoxynitrenes together with radical homolysis.⁴³ While esters are generated in those reactions, they can be formed indirectly by either of those processes. However, their formation by HERON migration of alkoxyl groups cannot be discounted since the properties of acyloxynitrenes, which would be formed in concert with HERON migration to form esters are unknown, as are their reactivities. The significantly higher E_A calculated for rearrangements of **13a** is in line with the experimental decompositions of *N*-acyloxy-*N*-alkoxyamides in non-polar solvents, which occur at temperatures above 90 °C. The transition states are all similar and indicate breaking of the *N*—*C*(*O*) bond in concert with *O*—*C* bond formation. In step with this, double bond character in the amide carbonyls is conserved at the transition state and their lengths are virtually unchanged from that in the ground state structure Fig. 1a (1.209 Å). Both reactions, with conservation of singlet character are endothermic but relaxation of the transition states affords a complex between acetic anhydride and methoxynitrene from transition state Fig. 3a (Fig. 6a) and one between methylacetate and acetoxynitrene from Fig. 3d (Fig. 6b). The very long acyl *C*—*ON* bond (1.825 Å) in this complex suggests partial dissociation and instability of acetoxynitrene although similar lengthening to 1.99 Å is also found in the isolated gas phase structure, which is at a minimum on the potential surface of the acetoxynitrene. The complexes are endothermic by respectively 30.4 kcal mol⁻¹ and 37.2 kcal mol⁻¹ and respectively 6.4 kcal mol⁻¹ more stable and 2.0 kcal mol⁻¹ less stable than the separated gas phase products.

Fig. 6. Products and product complexes from relaxation of lowest energy transition states for HERON reactions of **13a-e** transition states.

Though *N*-alkoxy-*N*-alkylthiylamides **1e** are implicated as intermediates in the reactions of *N*-acyloxy-*N*-alkoxyamides **1a** with thiols (Scheme 6), no HERON reactivity was detected and this pathway is clearly not competitive with bimolecular substitution at sulfur. Nonetheless, sulfur and oxygen substitution at nitrogen is an unusual arrangement that could lead to either esters or *S*-alkyl alkylthioates and the corresponding nitrenes by HERON reactions (Scheme 7) and the energetics and possibilities for HERON rearrangement are interesting by way of comparison with other, similar anomeric amides.

Scheme 7

The HERON reactions of model *N*-methoxy-*N*-methylthiylacetamide **13b** can, in theory, involve migration of methoxyl or the methylthiyl substituent. However, transition states can only be found for translocation of methoxyl to give methyl acetate and methylthionitrene (Fig. 4a and b). Migration of methoxyl from the *anti* form with carbonyl oxygen and sulfur *anti* in the transition state has the lowest E_A , though the *anti* form is slightly less stable. Activation energies (E_A) of both migrations are of the same order as those for migration of acetoxyl in *N*-acetoxyl-*N*-methoxyacetamide **13a** (Table 3). Methoxyl migration is again in concert with heterolysis of the *N*—*C*(*O*) bond as evidenced by the much longer *N*—*C*(*O*) (1.72 Å) relative to the ground state (1.41 Å). Developing thiyl nitrene character is also evident in the shortening of the *S*—*N* bond from 1.717 Å to 1.59–1.6 Å). Relaxation of the methoxyl migration transition states affords either **13b** or, in the forward direction, a complex (Fig. 6c) between methyl acetate and singlet methylthionitrene which is 7.3 kcal mol⁻¹ more stable than its constituents in the gas phase. No transition state could be found for sulfur migration in either rotamer of **13b** and the reaction is predicted to be highly endothermic. *S*-Methyl ethanethioate and methoxynitrene would not appear to be a stationary point on the reaction profile.

Syn and *anti* forms of model *N*-methoxy-*N*-dimethylamino-*O*-methylcarbamate **13c** are comparable in energy, and methoxyl migration from each occurs with similar E_A 's of 24.4 kcal mol⁻¹ and 22.1 kcal mol⁻¹. These much lower activation barriers for the formation of dimethylcarbonate from *N*-methoxy-*N*-dimethylamino-*O*-methylcarbamate are in accord with their reactions in solution according to Scheme 2, which occur at room temperature and in which dialkyl carbonates **6** and 1,4-dimethyl-1,4-diaryltetrazene (from dimerisation of 1,1-diazene **7**) are generated from reaction of *N*-acyloxy-*N*-alkoxycarbamates **4** and *N*-methylarylamines.⁴² The transition state geometries (Fig. 4c and 4d) and energies (Table 2) are similar in most respects to those for migration of methoxy in *N*-methoxy-*N*-dimethylaminoacetamide ($E_A = 22.7$ kcal mol⁻¹).^{40, 46} At the lowest energy transition

state, there is appreciable lengthening of the $N-C(O)$ bond (by 0.08 Å) and shortening of the $N-N$ bond (by 0.02 Å) relative to **13c**, indicating cleavage of the $N-C(O)$ bond with developing 1,1-diazene character. Like the HERON rearrangement of **13f**, which is computed to be slightly exothermic, the carbamate reaction is computed to be almost thermoneutral. The transition state in Fig. 4c generates **13c** in the reverse direction and in the forward direction, well separated 1,1-dimethyldiazene and dimethyl carbonate (Fig. 6d), which is lower in energy by 5.5 kcal mol⁻¹ relative to the isolated nitrene and carbonate.

As has been determined computationally in several previous high-level studies on 1-formyl-1-methoxydiazene,^{5, 45} the 1-acetyl-1-methoxydiazene **13d** rearranges similarly with a minimal E_A of 2.1 kcal mol⁻¹. Only one transition state is formed from *syn* and *anti* forms and is very early along the reaction coordinate leading to nitrogen and methyl acetate in a highly exothermic process. Consequentially, there is a large CNO angle (79°) and minimal lengthening of the $N-C(O)$ bond relative to ground state (Fig. 4a). The transition state resembles reactants but reverts to the diazene or proceeds to separated methyl acetate and nitrogen (Fig. 6e) at geometries before and after the saddle point.

The transition state for rearrangement of **13e** could not be located at the B3LYP/6-31G(d) level. However, consistent with the successful calculation of resonance energy at the HF/6-31G(d) level of theory, the lowest energy form of the anion **13e** rearranges in an exothermic reaction with an early transition state that resembles reactants and with an E_A of 11.5 kcal mol⁻¹. As determined at the HF/6-31G(d) level this reaction is not a true HERON process since, while rearrangement of methoxyl from nitrogen to carbon occurs, there is no cleavage of the $N-C$ bond in concert with that migration and a tetrahedral intermediate is generated, which would presumably lead to NO⁻ and methyl acetate, according to the products observed experimentally when *N*-acyloxy-*N*-alkoxyamides **1a** are treated with base (Scheme 5).¹⁷ Shortening the $N-OMe$ bond resulted in an

intermediate rotamer of **13e** with the lone pair *syn* to the carbonyl, which is a local minimum on the amide rotational energy profile. Relaxation in the forward direction produced the tertiary alkoxide (Fig. 6f), which is thermally more stable than reactant by 16 kcal mol⁻¹. The elongated C1—O1 bond (1.274 Å) and charge on the O1 (-0.989) are consistent with its formation.

The computed E_A 's for HERON reactions is composed of the RE, which is lost in the process as well as a rearrangement component, E_{rearr} . Without deconvolution of the total E_A , the influence of various substituents on the ease of migration is unclear since substituents affect both the RE and the migration. However, reduction of the total E_A by the RE in each case provides more reliable insight into the relative influence of substituents as well as other important features of the HERON process. The nature of the migrating group, the role of acyl substituents and conformation in the ground states are also relevant factors that can affect HERON activation energies.

Activation energies (E_A), resonance energies (RE) and derived rearrangement energies (E_{rearr}) for amides **13a-e** are collated in Table 3, together with previous data for *N*-methoxy-*N*-dimethylaminoacetamide **13f**, *N,N*-dimethoxyacetamide **13g**, two lactam forms of **13g**, **23** and **24** and resonance energies of *N*-chloro analogues **25** and **26**.

Table 3. Activation energies (E_A), resonance energies (RE) and rearrangement energies (E_{rearr}) for HERON reactions of amides **13a-g**, **19**, **23-24** and resonance energies for **25** and **26**.

Migratory mode	E_A (kcal mol ⁻¹)	RE (kcal mol ⁻¹)		E_{rearr} (kcal mol ⁻¹) ^a
		<i>Trans</i> amidation	COSNAR	
AcO from <i>syn</i> 13a	43.27	-9.68	-9.48	33.59(33.79)
MeO from <i>syn</i> 13a	49.68	-9.68	-9.48	40.00(40.20)
AcO from <i>anti</i> 13a	43.39	-9.68	-9.48	33.71(33.91)
MeO from <i>anti</i> 13a	43.68	-9.68	-9.48	34.00(34.20)
MeO from <i>anti</i> 13b	41.6	-12.97	-12.97	28.63(28.63)
MeO from <i>syn</i> 13b	44.27	-12.97	-12.97	31.30(31.30)
MeO from <i>anti</i> 13c	24.42	-12.11	-11.4	12.31(3.02)
MeO from <i>syn</i> 13c	22.09	-12.11	-11.4	9.98(10.69)
MeO from 13d	2.1	-3.54	-	-1.44 (-)
MeO from 13e	11.48	-7.75	-6.17	3.73(5.31)
MeO from <i>syn</i> 13f ^b	22.7	-12.3	-12.5	10.40(10.20)
MeO from 13g ^b	37.4	-8.59	-8.58	28.81(28.82)
Acyloxyl from 19	31.9	0	0	31.9
Alkoxy from 19	38.6	0	0	38.6
Ring opening 23 ^c	27	-4.59	-4.78	22.41(22.22)
Ring contraction 24 ^c	34.7	-8.78	-8.97	25.92(25.73)
Ring opening 24 ^c	32.6	-8.78	-8.97	23.82(23.63)
25 ^d	-	-7.04	-7.07 (8.21)	-
26a ^d	-	-6.93	-6.86 (11.62)	-
26b ^d	-	-7.78	-7.78 (10.98)	-

^a *Trans* amidation data; COSNAR-derived values in parentheses

^b Previously published values ⁴⁶

^c Previously published values ^{11, 46}

^d Previously published values;¹² M06/6-311++G(d,p) COSNAR values in parentheses.

Draft

Acetoxyl migrations from either rotamer of *N*-acetoxy-*N*-methoxyacetamide **13a** have slightly higher E_{rearr} 's, to that previously computed for *N,N*-dimethoxyacetamide **13g**, for which homolysis with a lower E_{A} is the preferred mode of reaction upon thermolysis. While the difference between E_{rearr} for acetoxyl and methoxyl migrations is significant from the *syn* form, it is only marginally favoured starting from the *anti* form. The preference for acetoxyl migration in the thermal decomposition of *N*-acyloxy-*N*-alkoxyamides in non-polar solvent may also be dependent upon other factors, such as steric effects in the transition state or factors that control the *syn-anti* energies, such as steric and pi-pi stacking effects (where aromatic substituents are present); two solid-state structures for which we have x-ray structural data are both *syn* conformers with evidence for pi-pi stacking between aromatic side chains.⁶ Inspection of the computed transition states in Fig. 3 indicates that alkoxyl migration from the *syn* form shown in Fig. 3d would invoke significant steric interaction between the alkoxyl group and the acyl substituent, which would be less important in acyloxyl migrations or in the migration of alkoxyl from the *anti* conformer.

Relative migratory aptitudes of alkoxyl and acyloxyl in the absence of any resonance can also be estimated from rearrangement of the fully twisted 2',2''-dioxo-2,3'-quinoxalidione **19**, which generates anhydride **27** or lactone **28** by migration of acyloxyl and alkoxyl branches, respectively (Scheme 8). B3LYP/6-31G(d) optimised ground state **19**, transition states and relaxed products are depicted in Fig. 7 and energies are given in Table 2.

Scheme 8

Both transition states (Fig. 7b and c) resemble those for the acetamide system and relax in the forward direction to intramolecular complexes of alkoxynitrene and anhydride (**27**, Fig. 7d) and acyloxynitrene and lactone (**28**, Fig. 7d). The actual E_A values for both intramolecular HERON reactions (32 kcal mol⁻¹ and 39 kcal mol⁻¹) are very similar to those for corresponding migration of acetoxy and methoxy from the *syn* form of *N*-acetoxy-*N*-methoxyacetamide **13a** (34 kcal mol⁻¹ and 40 kcal mol⁻¹) and, in this case, acyloxy is again preferred by 6.7 kcal mol⁻¹. Both reactions are endothermic and formation of the lactone and acyloxynitrene is much less favourable.

Fig. 7 B3LYP/6-31G(d) optimised structures for (a) ground state 2',2''-dioxo-2,3'-quinuclidione **19**, transition states for (b) acyloxy and (c) alkoxy migration and relaxed transition states from (d) acyloxy and (e) alkoxy migration.

Only methoxyl migration from both conformers of *N*-methoxy-*N*-methylthiylacetamide **13b** is viable. The overall E_A is, in both cases, similar to that for acyloxy migration in **13a** but the increased resonance in this system results in lower E_{rearr} values. The reduced electronegativity of sulfur facilitates the migration process relative to the oxygen destabilisation in **13a**. However, it is far less effective at driving migration than nitrogen in **13c** or **13f**. The $n_S-\sigma^*_{\text{NO}}$ anomeric interaction is likely to be weaker than an $n_N-\sigma^*_{\text{NO}}$ effect. While the 3p orbital on sulfur is higher in energy than an oxygen 2p orbital which would benefit interaction with the low energy σ^*_{NO} , its overlap with σ^*_{NO} is likely to be weaker on account of its larger, more diffuse nature; $n_Y-\sigma^*_{\text{NX}}$ anomeric overlap is best between X and Y orbitals of similar size.^{2,8} Overall, HERON reactions of *N*-alkoxy-*N*-alkylthiylamides would be expected at similar, high temperatures to those required for

the formation of anhydrides from thermal decomposition of *N*-acyloxy-*N*-alkoxyamides. Since formation of *N*-alkoxy-*N*-alkylthiylamides upon reaction of thiols with *N*-acyloxy-*N*-alkoxyamides has low E_A 's of between 9 and 16 kcal mol⁻¹ and occurs at measurable rates at room temperature resulting in formation of disulfides and hydroxamic esters (Scheme 6),¹⁸ the HERON reaction at these temperatures is not competitive with bimolecular scavenging of these intermediates by thiols.

Migration of methoxyl from either conformer of the carbamate **13c** has a similar $E_{\text{rearr.}}$ to that of *N*-methoxy-*N*-dimethylaminoacetamide **13f**. In both the carbamate **13c** and the amide **13f** the rearrangement is driven by the availability of a loosely bound amine lone pair of electrons, which results in a strong $n_N-\sigma_{\text{NO}}^*$ anomeric interaction. Furthermore, the presence of the more electronegative methoxyl oxygen at the carbonyl in **13c**, as opposed to electron donating methyl at that position in **13f**, has no impact upon $E_{\text{rearr.}}$ It is testament to the nature of the HERON transition state in which charge at the carbonyl carbon remains similar at the transition state (*syn N*-methoxy-*N*-dimethylaminoacetamide **13f**, +0.602) to that in the ground state (*syn 13f* +0.576), since the C—*N* bond breaks in concert with C—O bond formation in an intramolecular S_N2 reaction at the carbonyl carbon.^{40, 46} Charges at the carbonyl carbon in the carbamate ground states of **13c** (*anti* +0.810, *syn* +0.807) and their rearrangement transition states (*ex anti* +0.818, *ex syn* +0.826) are also similar.

1-Acyl-1-alkoxydiazenes, formed as intermediates in the decomposition of *N,N'*-diacyl-dialkoxyhydrazines **3**^{23, 40, 44} or thermal decomposition of *N*-alkoxy-*N*-azidoamides **1g**,^{5, 21} rearrange spontaneously to esters and nitrogen at room temperature. 1-Acetyl-1-methoxydiazene **13d** is predicted to rearrange concertedly to methyl acetate and nitrogen in a highly exothermic process. A very low overall E_A of just 2 kcal mol⁻¹ is predicted, which correlates well the residual resonance between the aminonitrene and the carbonyl (-3.5 kcal mol⁻¹). This resonance is forfeited upon rotation to the transition state and $E_{\text{rearr.}}$ is essentially zero for this reaction. In this amino nitrene,

which has a singlet ground state, the amide nitrogen is strongly positively charged due to donation of the amide nitrogen lone pair to the nitrene nitrogen rather than to the carbonyl. However, in **13d** there is some residual resonance stabilisation of $-3.5 \text{ kcal mol}^{-1}$, which might well be attributed to conjugation between the $C=O$ and $N^+=N^-$ pi bonds. The facile HERON process is in this case driven by the presence of a high energy, loosely bound lone pair on the nitrene nitrogen and consequent anomeric weakening of the $N-OMe$ bond (Scheme 9).

Scheme 9

N-Alkoxyhydroxamic acid anions also possess a high energy electron pair on the *N*-oxide and this would be expected to drive the HERON reaction. Experimentally, esters have been found to be generated intramolecularly since crossover esters are not formed in mixed reactions of *N*-acyloxy-*N*-alkoxyamides **1a** with aqueous base.¹⁷ Calculations on *N*-methoxyacetohydroxamate **13e** predict a HERON-like process but with formation of a tetrahedral intermediate anion, which presumably generates ester and NO^- in a second step. HF/6-31G(d) calculations predict an overall E_A of $11.5 \text{ kcal mol}^{-1}$ but this includes resonance energy of some $6-8 \text{ kcal mol}^{-1}$, which results in a low $E_{\text{rearr.}}$ of approximately 4 kcal mol^{-1} .

It is clear from comparison of $E_{\text{rearr.}}$ for these HERON processes, together with $E_{\text{rearr.}}$ for previously-studied *N*-methoxy-*N*-dimethylaminoacetamide **13f** and *N,N*-dimethoxyacetamide **13g**, that the driving force is anomeric destabilisation of the bond between the amide nitrogen and the migrating atom. More tightly bound oxygen lone pairs at *Y* (in **13a** and **13g**) result in high overall activation energies but bis oxo-substitution in **13a** and **13g** also results in the lowest resonance energies that

must be overcome to attain the transition state. Reduced resonance is not the overriding influence. This is reinforced by a comparison of nitrogen and oxygen systems. While the reduced combined electronegativity of nitrogen and oxygen (in **13c** and **13f**) results in much higher amide resonance than in systems with two oxygens, their $E_{\text{rearr.}}$ are significantly lower. Reduced sulfur electronegativity in **13b** enhances amide resonance relative to *N,N*-bisoxo-substituted systems **13a** and **13g**, but its anomeric destabilisation is similar to that of oxygen despite its higher energy lone pair. The facile reaction of the 1,1-diazene **13d** is wholly the result of low resonance and a very strong anomeric interaction. The HF/6-31G(d) derived $E_{\text{rearr.}}$ for **13e** points predictably to strong destabilisation by an anion electron pair on Y. Comparing methoxyl migrations in **13a-g**, $E_{\text{rearr.}}$ from Table 3 increases in the sequence $Y=N < O^- \ll NMe_2 \ll SMe < OMe$. Resonance energies, RE, increase in the order $Y=N < O^- < OMe < NMe_2 \sim SMe$.

The nature of the migrating group X in promoting the rearrangement is less clear. In the comparison of acetoxyl versus methoxyl in **13a**, charge transfer to the migrating oxygen should favour acetoxyl migration. However, while acetoxyl migration is preferred over methoxyl in the *syn* conformer and acyloxyl migration is preferred over alkoxyl migration in the tricyclic analogue **19**, acetoxyl rearrangement is only marginally favoured in the *anti* conformer. A greater influence would be expected with strong electron donation from Y, and nitrogen as anomeric donor in $n_N-\sigma^*_{NO}$ interactions should lead to greater charge transfer to the migrating group. In support of this, we have shown experimentally that electron acceptor substituents at the *para* position of *N,N*-dibenzoyloxy-*N,N*-diacetyl hydrazines **3** ($R^2=Bn$, $R^1=Me$) accelerate the rate of HERON rearrangement with formation of benzylacetates (Hammett $\rho = 1.0$).⁴⁰ No HERON transition state could be found for *N*-chloro-*N*-methoxyacetamide **25** and *N*-anilino-*N*-chloroacetamides **26a** and **26b** model systems.¹² These cases resulted, instead, in heterolytic dissociation into a complex between chloride ion and methoxyl- or anilino-stabilised nitrenium ions. This would be driven by the electron affinity of

chlorine and the resonance-stabilisation in the nitrenium ion.^{8, 29, 54, 55} Strong stabilisation of charge on *X* can alter the preferred reaction pathway.

The role of conformation in promotion of the HERON process is three-fold. Firstly, concomitant with reduced resonance, owing to the more tightly bound amide nitrogen lone pair, the nitrogen tends towards sp^3 hybridisation since increased *p* character favours transfer of electron density to the *X* and *Y* substituents. However, sp^3 hybridisation also favours anomeric interactions since $n_Y - \sigma^*_{N_{sp^3}X}$ p-orbital overlap integrals are better than edge-on overlap with $n_Y - \sigma^*_{N_{sp^2}X}$ overlap.^{2, 8} Secondly, alignment and overlap of the *Y* lone pair and *NX* σ^* orbitals is essential for anomeric destabilisation of the *N—X* bond. In **13a-c** (Fig. 2) and in **13f**^{3, 40, 46} and **13g**^{1, 9, 11} conformations are adopted in the ground state structures for near ideal overlap. Conformation can actually dictate the mode of reaction. We have recently suggested that the optimal $n_{O_{exo}} - \sigma^*_{NO_{endo}}$ anomeric destabilisation of the endocyclic *N—O* bond in δ -oxazinolactam **24** leads to preferential ring contraction rather than ring opening of δ -oxazinolactam. The $n_{O_{endo}} - \sigma^*_{NO_{exo}}$ anomeric interaction is completely switched off in the ground state structure.¹¹ Thirdly, conformation can also impact upon the intrinsic RE of similarly substituted systems. The RE of *N,N*-dimethoxyacetamide **13g** (-8.6 kcal mol⁻¹, $\tau = 9^\circ$) and the relatively strain-free δ -oxazinolactam **24** (-8.8 kcal mol⁻¹, $\tau = 13^\circ$) is reduced in the ground state γ -oxazinolactam **23** (-4.8 kcal mol⁻¹) owing to substantial twisting about the *N—C(O)* bond ($\tau = -37^\circ$). HERON ring opening of both lactams **23** and **24** have a similar $E_{rearr.}$ (22.4 kcal mol⁻¹ and 23.8 kcal mol⁻¹ respectively) but there is less resonance to overcome in the twisted γ -oxazinolactam **23** thereby reducing the E_A for HERON ring-opening of **23** (27 kcal mol⁻¹) relative to that for HERON opening of **24** (33 kcal mol⁻¹).

Conclusion

The HERON reaction is peculiar to anomeric amides, amides in which the electronegative atoms adjacent to nitrogen provide the structurally important elements for the reaction, both in modifying the hybridisation at nitrogen and its resultant resonance with the amide carbonyl, and in their participation in classical anomeric interactions through the central nitrogen. Both these effects influence the ease of the HERON reaction. However, the nature of the HERON transition state, in which the lone pair on the central nitrogen resides in the amide plane and the migrating group reacts in a plane orthogonal to that plane, allows deconvolution of the overall activation energies into a resonance component (RE) and a rearrangement component (E_{rearr}). From this, it is clear that reduced resonance itself does not promote the reaction, since with two, more electronegative oxygen atoms at nitrogen, the resonance can be as low as 50% that of *N,N*-dimethylacetamide as is the case for *N*-acetoxy-*N*-methoxyacetamide **13a** and *N,N*-dimethoxyacetamide **13g**. However, activation energies for their HERON reactions are high in keeping with experimental HERON anhydride formation from **1a** at elevated temperatures at which there is competition with radical decomposition. The large E_{rearr} component to the E_A in these cases is clearly due to the tightly-bound lone pairs on the anomeric donor atom. On balance HERON rearrangement of acyloxyl group rather than the alkoxyl group is preferential although stereochemistry may play a role. Dialkoxyamides decompose homolytically without competitive HERON reactions.

When nitrogen replaces one oxygen atom, as in **13c** and **13f**, there is clear evidence that energetically the more accessible lone pair on nitrogen drives the rearrangement process to the extent that higher intrinsic amide resonance (65-70% that of *N,N*-dimethylacetamide) is readily overcome and the reactions of carbamate **13c** and, from earlier studies, *N*-methoxy-*N*-dimethylaminoacetamide **13f**, to give respectively dimethylcarbonate and methyl acetate together with 1,1-dimethyldiazene, have a much lower overall E_A and very low E_{rearr} . This is borne out of the

strong anomeric effect and destabilisation of the bond to the migrating oxygen. The calculated barriers are entirely consistent with experimental findings

The anomeric driving force for oxygen migration when sulfur is attached to nitrogen is radically diminished and with enhanced resonance (70% that of *N,N*-dimethylacetamide), on account of its lower electronegativity relative to either oxygen or nitrogen, the reaction is predicted to have a high E_A and would only occur at elevated temperatures. Despite its higher energy lone pairs, sulfur, as an anomeric donor, is not as effective as nitrogen most probably on account of disparity in orbital size. Reverse migration of thiomethyl in **13b** was not viable.

Two systems with high energy electron pairs on the anomeric donor atom, **13d** and **13e**, models for 1-acyl-1-alkoxydiazenes **1h** and *N*-alkoxyhydroxamate anions **1d** both of which undergo facile HERON reactions experimentally, rearrange with low barriers, though the hydroxamate **13d** is not a true HERON reaction. **1h** has trivial resonance energy, some 15% that of *N,N*-dimethylacetamide, and loss of this is basically the only activation energy for the reaction. The rearrangement process is extremely exothermic. It is not surprising that 1-acyl-1-alkoxydiazenes, formed from decomposition of *N*-alkoxy-*N*-azidoamides **1g** can react to form highly hindered esters in very exothermic reactions although the intrinsic cleavage of *N*—*C*(*O*) bonds at the HERON transition state also plays a role, obviating the formation of a highly hindered tetrahedral intermediate.²¹

The nature of the migrating group and its substituents can lower E_A 's but dissociation to nitrenium ions is predicted for chlorine systems **25** and **26**. The electronegative acyl methoxyl in carbamate **13c** appears not to influence reactivity relative to the acetamide **13f** in keeping with the theoretical properties of the transition state which involves concomitant *N*—*C*(*O*) bond cleavage with the migration resulting in little change in the charge at the amide carbon.

HERON reactivity is also influenced by conformation in at least three ways. Conformations about the $N-C(O)$ bond can reduce resonance and thereby HERON E_A 's. Conformation about $N-X$ and $N-Y$ bonds at the amide nitrogen should optimise $n_Y-\sigma_{NX}^*$ interactions and pyramidalicity at nitrogen would be expected to facilitate anomeric overlap.

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Figure Captions:

Fig. 1. Theoretically derived transition state for the generalised HERON reaction of an X,Y -substituted amide; (a) perspective drawing, (b) Newman projection along the $N-C(O)$ bond.

Fig. 2. Lowest energy ground state structures for **13a-d** (at B3LYP/6-31G(d)) and **13e** (at HF/6-31G(d)); χ and τ are the Winkler-Dunitz pyramidity and twist indices; average angles at nitrogen are denoted by $\langle \rangle$.

Fig. 3. B3LYP/6-31G(d) optimised transition states for migration of acetoxy from (a) *syn* and (b) *anti* conformers of *N*-acetoxy-*N*-methoxyacetamide **13a** and migration of methoxyl from (c) *anti* and (d) *syn* conformers of *N*-acetoxy-*N*-methoxyacetamide **13a**.

Fig. 4. B3LYP/6-31G(d) optimised transition states for migration of methoxyl from (a) *syn* and (b) *anti* conformers of *N*-methoxy-*N*-methylthiylacetamide **13b** and migration of methoxyl from (c) *syn* and (d) *anti* conformers of *N*-methoxy-*N*-dimethylamino-*O*-methylcarbonate **13c**.

Fig. 5. (a) B3LYP/6-31G(d) optimised transition state for migration of methoxyl in 1-acetyl-1-methoxydiazene **13d** and (b) HF/6-31G(d) optimised transition state for migration of methoxyl in *N*-methoxyacetohydroxamate **13e**.

Fig. 6. Products and product complexes from relaxation of lowest energy transition states for HERON reactions of **13a-e** transition states.

Fig. 7. B3LYP/6-31G(d) optimised structures for (a) ground state 2',2''-dioxo-2,3'-quinuclidione **19**, transition states for (b) acyloxyl and (c) alkoxy migration and relaxed transition states from (d) acyloxyl and (e) alkoxy migration.

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