The HERON reaction — Origin, theoretical background, and prevalence[1]

Stephen A. Glover, Arvi Rauk, Jeanne M. Buccigross, John J. Campbell, Gerard P. Hammond, Guoning Mo, Luke E. Andrews, and Ashley-Mae E. Gillson

Abstract: The origin of the HERON reaction is reviewed from a historical perspective and shown to have its foundation in the unusual properties of bisheteroatom-substituted amides, so-called anomeric amides. The reaction involves migration of anomerically destabilized oxo-substituents on an amide nitrogen to the amide carbon and dissociation of the amide bond. Computational work providing a theoretical basis for the reaction is presented, together with physical organic measurements that support results therefrom. The rearrangement has been observed in a number of chemical transformations of *N*-alkoxy-*N*-aminoamides, reactions of 1-acyloxy-1-alkoxydiazenes, *N*-alkoxy-*N*-aminocarbamates, *N*-alkoxyhydroxamic acids, as well as in the gas-phase reactions of *N*-acyloxy-*N*-alkoxyamides.

Key words: HERON reaction, anomeric amides, rearrangements, hindered esters, concerted reactions.

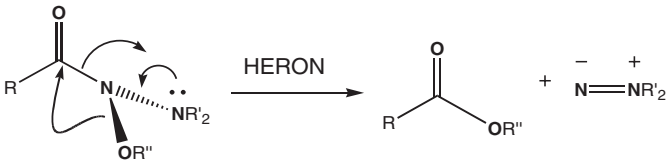
Résumé : On a fait une revue historique de l'origine de la réaction HERON et on montre que sa base réside dans les propriétés inhabituelles des amides portant des substituants bishétéroatomiques, les amides dits anomères. La réaction implique la migration de substituants oxo anomériquement déstabilisée de l'azote d'un amide vers le carbone de l'amide accompagnée d'une dissociation de la liaison amide. On présente un ensemble de calculs théoriques qui sert de base pour expliquer la réaction ainsi que des mesures de chimie organique physique qui supportent les résultats de ces calculs. Le réarrangement a été observé dans un certain nombre de transformations chimiques de *N*-alkoxy-*N*-aminoamides, dans les réactions de 1-acyloxy-1-alkyoxydiazènes, de *N*-alkoxy-*N*-aminocarbamates et d'acides *N*-alkoxyhydroxamiques ainsi que dans les réactions en phase gazeuse de *N*-acyloxy-*N*-alkoxyamides.

Mots clés : réaction HERON, amides anomères, réarrangements, esters stériquement empêchés, réactions concertées.

Introduction

The HERON reaction (Scheme 1) was conceived during our investigations into the reactions of a highly unusual class of mutagenic amides, the *N*-acyloxy-*N*-alkoxyamides (1, 2). It was annointed at the Second Heron Island Conference on Reactive Intermediates and Unusual Molecules, which was held on Heron Island in 1994, and, more recently, confirmed as a named reaction in the 13th edition of *The Merck Index* (3). *N*-Acyloxy-*N*-alkoxyamides are members of the class of anomeric amides that bear two heteroatoms bonded to the amide nitrogen (4). These highly unusual amides are direct-acting mutagens in that they mutate *Salmonella typhimurium* in the Ames test without the need for metabolic activation. Since the initial discovery (5, 6), we have synthesized well over 70 examples and nearly all those that we have tested are mutagenic (7). The direct mutagenicity of this class of amides has led to a quantitative structure–activity relationship (QSAR) from which we can predict the mutagenic activity of virtual congeners, but, equally as interesting, we can identify and quantify unusual molecular interactions of structural elements with DNA (8).

Scheme 1.



Structure of anomeric amides

N-Acyloxy-*N*-alkoxyamides, as with all anomeric amides, possess pyramidalized nitrogen atoms (4). Early computational work at the AM1 level confirmed a tendency to highly developed sp^3 hybridization at nitrogen (2, 4), and, subsequently, so too have more rigorous ab initio calculations at both the HF/6-31G* and the B3LYP/6-31G* density functional theory (DFT) levels of theory (9–11). This conformational

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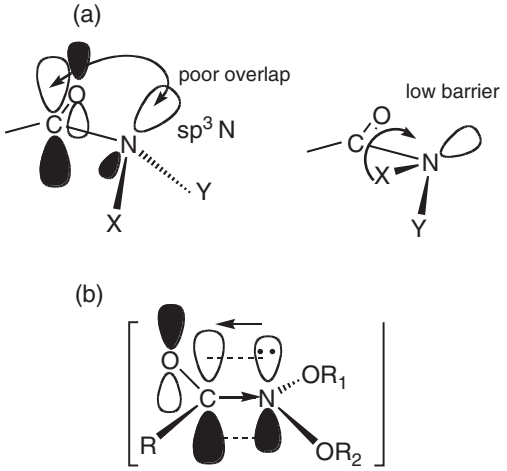
Fig. 1. (*a*) Facile amide isomerism in anomeric amides. (*b*) Stabilization that raises isomerization barriers in planar amides.



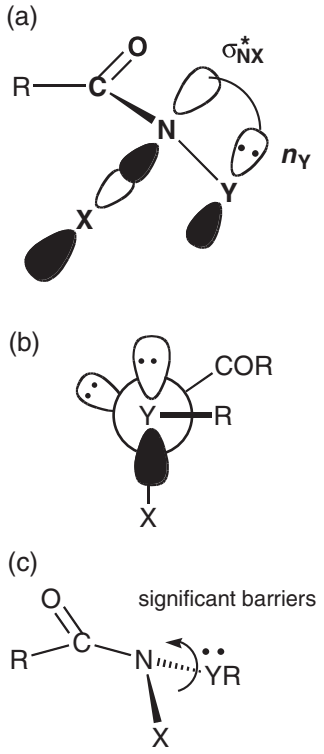
change is readily interpreted in terms of electronegativity of the nitrogen substituents.

It is well-known that atoms geminally substituted with heteroatoms tend towards pyramidality. In qualitative terms, relative to sp^2 hybridization, sp^3 hybridization at the central atom and the consequent increase in p character in the σ bonds enables electron density to be closer to the more electronegative ligands. Thus, anomeric amides possess a nitrogen that substantially deviates from planarity and the increased "s" content of the lone pair drastically reduces lone pair delocalization onto the carbonyl. The intrinsic barrier to rotation about the N—C(O) bonds (Fig. 1*a*), a barrier that is significant in normal amides (12) and hydroxamic esters, (9, 13) and which often leads to dynamic effects in their ^1H NMR spectra at room temperature, is largely lost. Wiberg (14) recently argued that the barrier in "normal" amides is a combination of a π type HOMO–LUMO overlap between the lone pair on nitrogen and the $\pi^*_{C=O}$ molecular orbital combined with a synergistic σ type back donation to the electronegative sp^2 nitrogen (Fig. 1*b*). In anomeric amides both effects disappear on account of the sp^3 hybridization at nitrogen and barriers to isomerization have been found to be drastically reduced or are too low to be measured by dynamic NMR methods (4, 10). Ab initio calculations confirm these properties (4, 9, 10, 15).

N-Acyloxy-*N*-alkoxyamides amides should have longer than normal N—C(O) bonds and shorter carbonyl bonds resulting in higher than expected IR carbonyl stretch frequencies. This has been experimentally determined in that all *N*-acyloxy-*N*-alkoxyamides exhibit amide carbonyl stretch frequencies between 1710 and 1760 cm^{-1} (4). In addition, these amides sustain anomeric effects through the amide nitrogen by which the lone pair on one heteroatom (Y) interacts with the σ* orbital between nitrogen and the other heteroatom X (Fig. 2*a*), thus shortening the Y—N bond and weakening the N—X bond. The ground-state conformations in anomeric amides should facilitate this overlap and, depending upon its strength, barriers to rotation about the N—Y bond can be expected to be greater than predicted by steric effects alone (Figs. 2*b* and 2*c*).

The structural features outlined above have been verified by X-ray crystallography. We recently published the structures of the "most pyramidal" amides, both *N*-acyloxy-*N*-alkoxyamides, which verify the conformational effects previously described (Fig. 3*a*) (16). Not only do they exhibit highly pyramidal nitrogens (avg. angle ~ 108°) and very long N—C bonds, their alkoxy O—N bonds are shortened while the N—O acyl bond is long. Similarly, the related *N*,*N*′-dialkoxy-*N*,*N*′-diacylhydrazine possesses pyramidal nitrogens, long N—C bonds and a short N—N bond (Fig. 3*b*). Both structures exhibit a conformational preference that clearly optimizes either the n_O— σ^*_{NO} or the n_N—σ^*_{NO} overlap (15, 16).

Fig. 2. (*a*) Anomeric overlap, (*b*) conformational preference, and (*c*) rotationally restricted bond in anomeric amides.

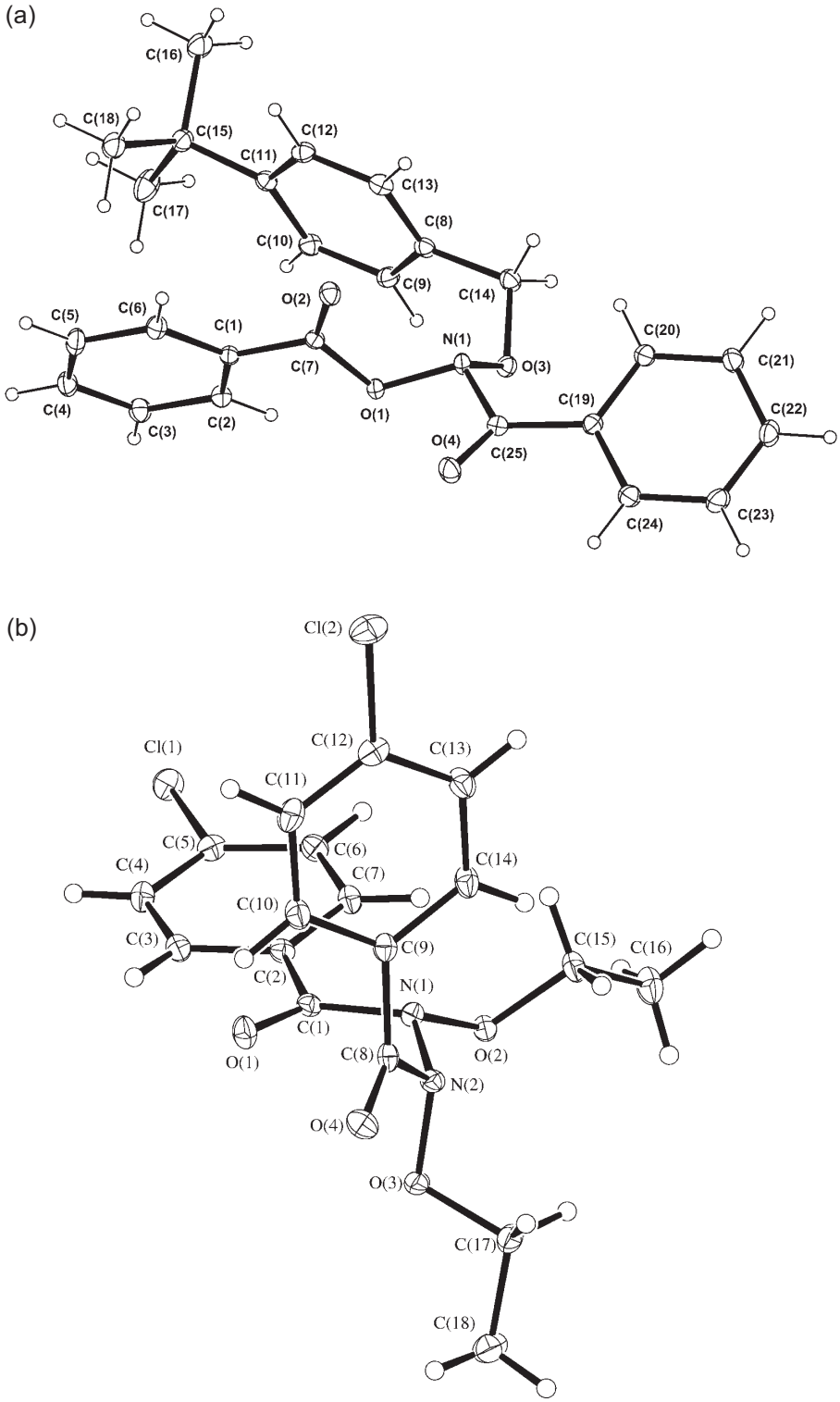


Reactivity of anomeric amides

The XNY system should be polarized as shown in Fig. 4. Where Y is a strong electron pair donor (e.g., nitrogen), and X a strongly electron affinic atom such as halogen or in the case of *N*-acyloxy-*N*-alkoxyamides, the acyloxy oxygen, elimination might be expected yielding in the process a stabilized nitrenium ion (Fig. 4*a*). Work in these laboratories and elsewhere has established that nitrenium ions are strongly stabilized by neighbouring heteroatoms (17–28). Such a process would be promoted by polar solvents as well as acid or Lewis acid complexation with X. Thus, unimolecular decomposition would be expected in strongly anomeric systems.

In S_N2 reactions, substituents at the central atom that can stabilize cationic character will also stabilize the S_N2 transition state leading to longer bonds to both the nucleophile and the leaving group (29–31). Thus, in systems with moderate anomeric overlap, this together with negative hyperconjugation and anchimeric assisted weakening of the N—X bond should promote S_N2 reactions at nitrogen leading to loss of X^- (Fig. 4*b*).

Fig. 3. ORTEP depictions of: (*a*) *N*-benzoyloxy-*N*-(4-*tert*-butylbenzyloxy)benzamide and (*b*) *N*,*N*′-di(*p*-chlorobenzoyl)-*N*,*N*′-diethoxyhydrazine with thermal ellipsoids depicted at the 20% and 25% levels, respectively.

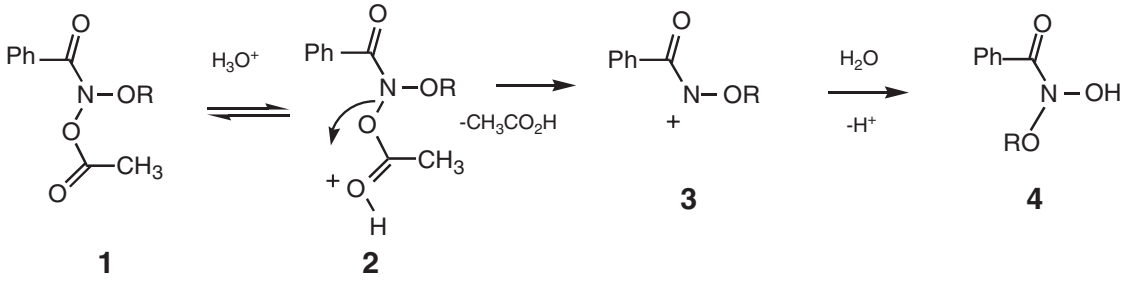


Discussion

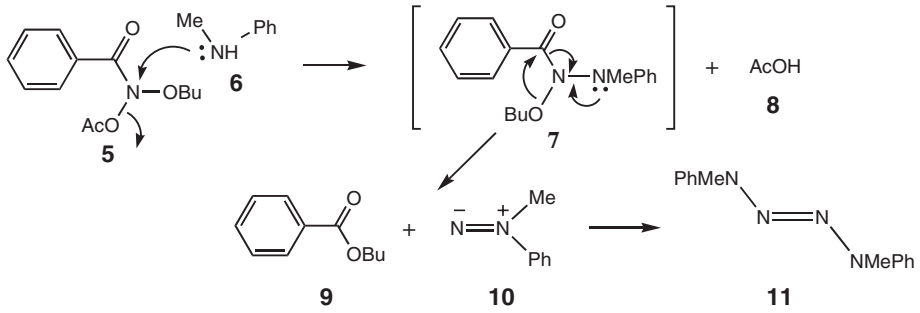
The HERON reaction

As a part of an investigation into the mechanism of their mutagenic action we subjected *N*-acetoxy-*N*-alkoxybenzamides **1** to a range of solvolytic studies and reactions with potential biological nucleophiles (1, 4, 6, 11, 21, 32–34). They hydrolyse very slowly at neutral pH, but, as predicted, upon protonation on the acetoxy group **2** with acid catalysis in aqueous acetonitrile, they undergo rapid decomposition by the unusual $A_{Al}1$ mechanism leading to *N*-acyl-*N*-alkoxynitrenium ions **3**, which react rapidly with water leading to

Scheme 2.



Scheme 3.



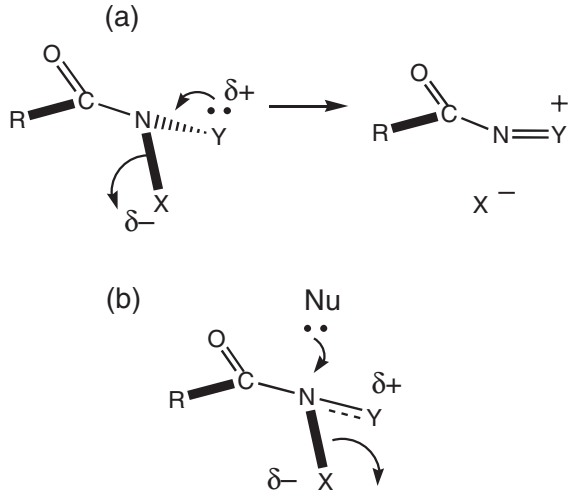
N-alkoxyhydroxamic acids **4** and a variety of secondary products (Scheme 2).

However, a fundamental difference between these and all other conventional amides is that they are susceptible to S_N2 reactions at the amide nitrogen. Treatment of *N*-acyloxy-*N*-alkoxybenzamides with aromatic amines in methanol results in S_N2 displacement of the acyloxy group to give, as intermediates, *N*-alkoxy-*N*-arylaminobenzamides (1, 11, 35). These too are strongly anomeric on account of a high energy lone pair on nitrogen and the electronegative oxygen of the alkoxyl group. With *N*-methyl aniline (**6**) in methanol or aqueous acetonitrile, *N*-acetoxy-*N*-butoxybenzamide (**5**) afforded an excellent yield of butyl benzoate (**9**) and acetic acid (**8**). Close examination of these highly coloured reaction mixtures indicated the presence of crystals of *N*,*N*′-dimethyl-*N*,*N*′-diphenyl tetrazene (**11**) (Scheme 3). A crossover experiment using a mixture of *N*-acetoxy-*N*-butoxy-*p*-toluamide and *N*-acetoxy-*N*-ethoxybenzamide afforded clean yields of butyl *p*-toluate and ethyl benzoate, thus pointing to an intramolecular rearrangement.

In Scheme 3, the S_N2 reaction leads to the intermediate *N*-butoxy-*N*-(*N*′-methylanilino)benzamide (**7**). Anomeric weakening of the N—O bond in **7** results not in heterolysis to alkoxide ion, which would be energetically unfavourable, but rather migration of the butoxyl group from the amide nitrogen to the carbonyl carbon and heterolysis of the N—C bond. This reaction results in the formation of 1-methyl-1-phenyldiazene (**10**), which under the reaction conditions dimerizes to the tetrazene **11**. These rearrangement processes are characterized by a transition state in which the alkoxyl group migrates from the amide nitrogen to the carbonyl carbon (Fig. 5*a*) and therefore involves heteroatom rearrangements on nitrogen, the HERON reaction[3] (2).

Thus, the HERON reaction, as well as the unique properties of *N*-acyloxy-*N*-alkoxyamides, can be ascribed to the configuration at nitrogen, namely bisheteroatom substitution.

Fig. 4. (*a*) Anomerically induced elimination. (*b*) S_N2 reaction at nitrogen.

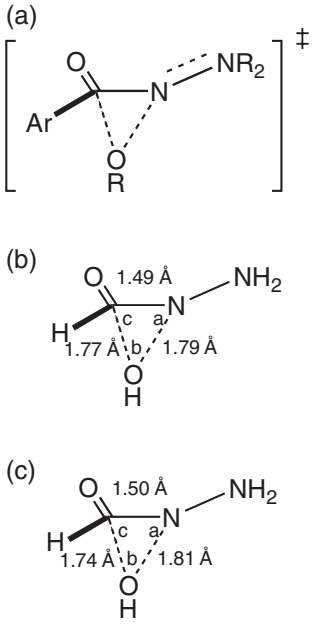


Computational verification of the HERON reaction

This reaction, though published in the early 1990s, was named in the literature in a 1995 paper in which we presented a semiempirical molecular orbital treatment of the HERON reactions of a range of anomeric amides (2). AM1 predicted, adequately, the ground-state properties of various anomeric amides, as well as the relative propensity for HERON migration of a variety of geminal heteroatom substituents on nitrogen. In general, the activation energy was lowered with an amino substituent and more electronegative migrating atoms or electron-deficient groups. In the case of

[3] Presented to the 2nd Heron Island Conference on Reactive Intermediates and Unusual Molecules. The authors are grateful to Professor Richard Wong who suggested that the reaction deserved to be named.

Fig. 5. (*a*) Transition state for a HERON reaction of an *N*-alkoxy-*N*-aminoamide. Computed transition states for the migration of hydroxyl in *N*-amino-*N*-hydroxyformamide at: (*b*) AM1 (a = 65°, b = 45°, and c = 65°) and (*c*) HF/6-31G* (a = 63°, b = 48°, and c = 69°) levels.

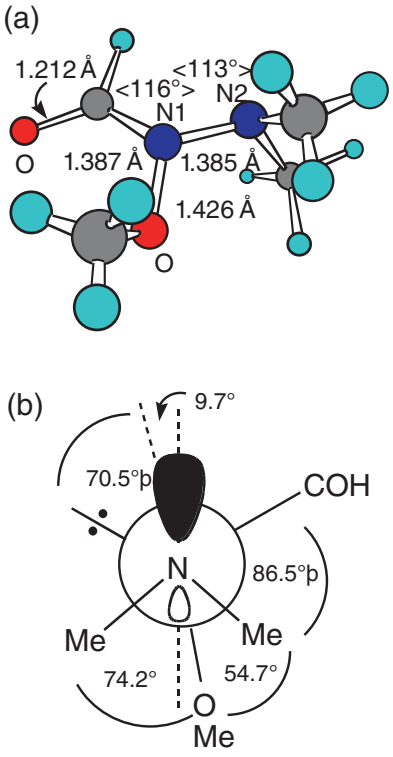


N-alkoxy-*N*-aminoamides, we attributed this to better anomeric weakening of the N—OR bond through a favourable interaction between a high energy nitrogen lone pair and a low energy N—OR σ* orbital. A transition state was predicted that indicated partial bonding between the migrating oxygen and both the amide nitrogen and carbon atoms in a plane perpendicular to that of N-C=O (Fig. 5*b*). The amide bond was largely unaltered. A similar result was obtained from HF/6-31G* calculations (Fig. 5*c*).

In a comprehensive study using DFT, we showed that anomeric substitution can be expected to lead to the conformational changes outlined in Fig. 2 in a wide range of amides (9). At this more reliable computational level, bis-heteroatom substitution leads to pyramidal amide nitrogens, lengthened N—CO bonds, shortened Y—N bonds, conformations about which optimize n_Y— σ^*_{NX} overlap. A subsequent, detailed B3LYP/6-31G* investigation of the congener, *N*-methoxy-*N*-dimethylaminoformamide, a model for the intermediate **7** in the HERON reaction indicated all these features (Fig. 6*a*) (10) and predicted: a strongly pyramidal nitrogen (avg. angles at nitrogen of 116°); a long N—C bond of 1.39 Å (computed to be 1.36 Å in formamide); a short N—N bond of 1.38 Å (1.45 Å in hydrazines); an extraordinarily low barrier of 13 kcal mol^{-1} (1 cal = 4.184 J) to E–Z isomerization about the N—C bond (typically 19–24 kcal mol^{-1} in conventional amides); a remarkably high barrier of 14 kcal mol^{-1} to rotation about the formally single N—N bond; an orientation of the amino substituent that optimized the anomeric overlap with the vicinal N—O bond (Fig. 6*b*).

A DFT evaluation of the HERON reaction of *N*-methoxy-*N*-dimethylaminoformamide to give methyl formate and 1,1-dimethyldiazene confirmed the earlier predictions at the AM1 and HF/6-31G* level (Fig. 7). The activation energy in

Fig. 6. (*a*) Lowest energy conformation of *N*-methoxy-*N*-dimethylaminoformamide (< x > = avg. angle). (*b*) Newman projection along the N—N bond.



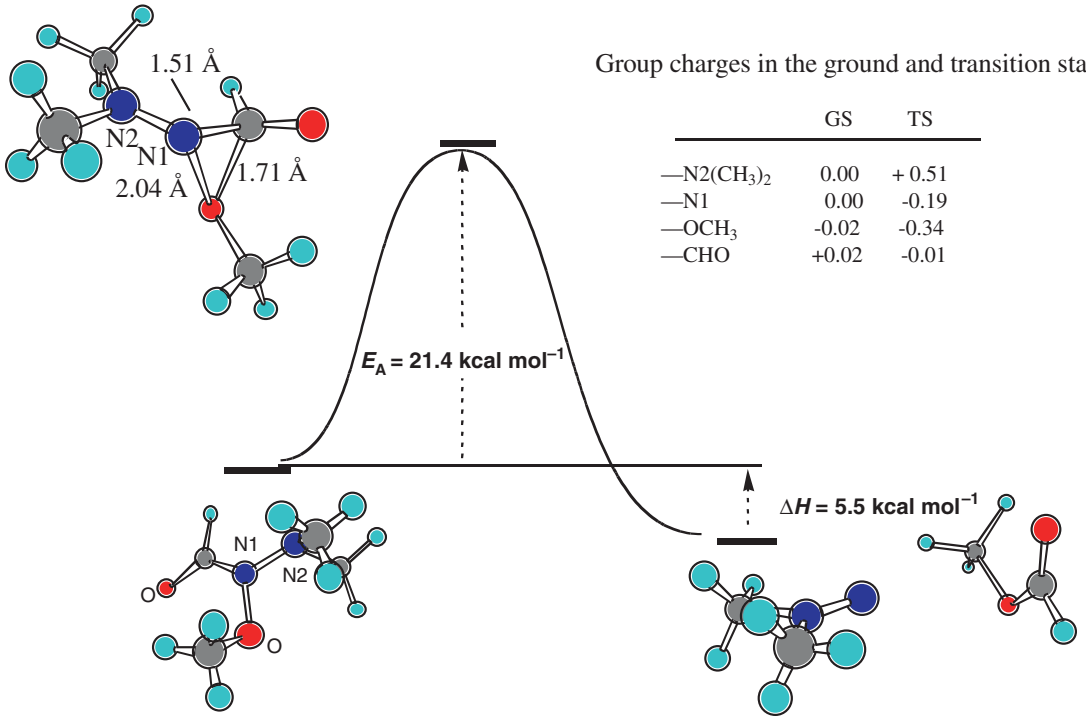
the gas phase is modest at 21.4 kcal mol^{-1}, and the rearrangement is predicted to be exothermic by some 5.5 kcal mol^{-1} (36). The transition-state geometry shows that the N—C bond is intact, and the carbonyl bond is virtually unaltered. An intrinsic reaction coordinate study indicated that the N—C bond cleaves in concert with O—C bond formation after the transition state. In essence, this reaction represents an intramolecular S_N2 reaction on the amide carbonyl. Further analysis of the computed transition state indicates the charge redistribution (Fig. 7). Predictably, N2 becomes more positive at the transition state, while N1 and the migrating group develop negative charge. Electron-releasing groups on the donor nitrogen and electron-withdrawing groups on the migrating oxygen should lower the energy of the transition state, which should also proceed better in polar solvents that can stabilize this charge separation. Interestingly, there is no appreciable change in charge at the carbonyl and neither electron-donor groups nor electron-withdrawing groups at this position should exert a major influence upon the energetics of the reaction.

Experimental evidence in support of these computational results has accrued from a number of reactivity studies.

The HERON reaction of *N*-amino-*N*-alkoxyamides

We have routinely used the S_N2 reaction of *N*-acyloxy-*N*-alkoxyamides and *N*-methylaniline as a measure of their susceptibility to nucleophilic attack at nitrogen, and hence, to possible reactions with nucleophilic centres in DNA. The reactions can be followed in d_4-methanol and can be monitored through the disappearance of the mutagen or aniline and the formation of ester and tetrazene. HERON

Fig. 7. Energetics and transition-state properties for the HERON reaction of *N*-methoxy-*N*-dimethylaminoformamide to 1,1-dimethyldiazene and methyl formate.



rearrangement of the intermediate *N*-alkoxy-*N*-(*N*-methylanilino)benzamides proceeds with a low activation energy in methanol as it has never been detected under these reaction conditions, even at temperatures well below ambient (34). This is not surprising as the B3LYP/6-31G* activation energy for the model reaction in the gas phase is an upper limit and it would probably be significantly lower in solution.

A related class of analogues, the *N*,*N*′-diacyl-*N*,*N*′-dialkoxyhydrazines **12**, are readily generated by oxidative dimerization of hydroxamic esters (37–40) and by dimerization of alkoxyamidyl radicals formed upon oxidation of hydroxamic esters or photolysis of *N*-alkoxy-*N*-haloamides (41, 42). In a recent study we have demonstrated that these hydrazines exhibit all the hallmarks of anomeric amides (15). Their carbonyl stretch frequencies in solution are in the range of 1700–1744 cm^{-1}, while those of their precursor hydroxamic esters are in the range 1680–1690 cm^{-1} (4, 15). This accords with pyramidal nitrogen atoms, and in the case of *N*,*N*′-diacetyl-*N*,*N*′-di(*p*-chlorobenzyloxy)hydrazine, dynamic NMR methods afforded a low amide isomerization barrier of just 12.9 kcal mol^{-1}. For a range of such *N*,*N*′-diacyl-*N*,*N*′-dialkoxyhydrazines, we also obtained barriers for isomerization about the N—N bond that were in the range of 15–17 kcal mol^{-1}, which is indicative of a strong NNO anomeric interaction (15). Furthermore, from IR studies, these hydrazines appear to be unsymmetrical in both the solution and the solid phase, displaying two carbonyls;[4] one-half of the hydrazine can be regarded as a donor substituent on the other anomerically substituted nitrogen.

This spectroscopic evidence is supported by the X-ray structure of *N*,*N*′-di(*p*-chlorobenzoyl)-*N*,*N*′-diethoxyhydrazine (Fig. 3*b*). This *N*,*N*′-diacyl-*N*,*N*′-dialkoxyhydrazine is asymmetrical in nature and both nitrogens are strongly pyramidal with avg. angles at N(1) and N(2) of 113.6° and 114.4°, respectively. Furthermore, there is evidence for an anomeric interaction in the direction of N(2). The N(2)—O(3) bond nearly bisects the C(1)-N(1)-O(2) angle with torsion angles of 69.4° and –66.7° to N(1)—C(1) and N(1)—O(2) bonds, respectively, while the N(2)—O(3) bond is nearly 0.01 Å longer then the N(1)—O(2) bond. Both could be accounted for by overlap between the N(1) lone pair and the N(2)—O(3) antibonding orbital.

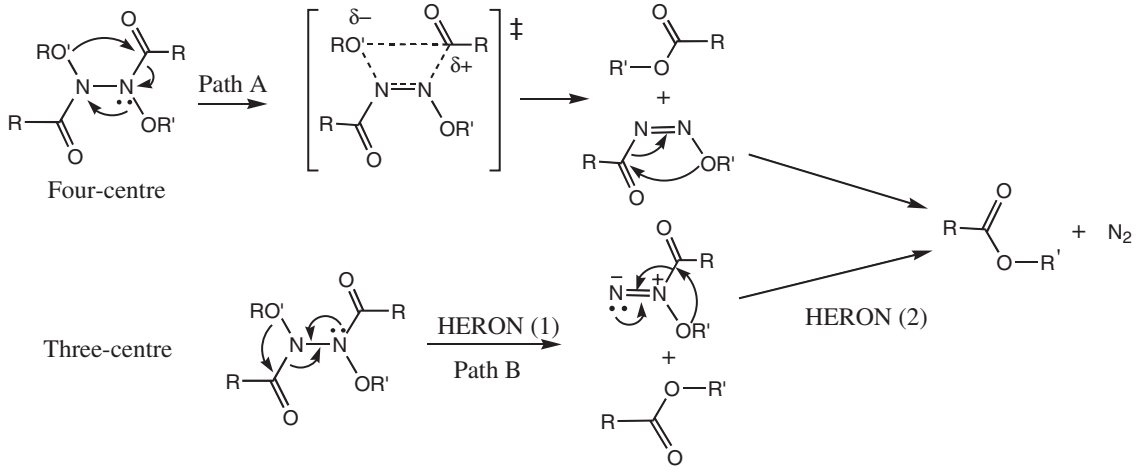
Upon mild heating, *N*,*N*′-diacyl-*N*,*N*′-dialkoxyhydrazines were known to decompose intramolecularly to 2 equiv. of ester and nitrogen by a reaction mechanism originally purported to involve two, four-centre rearrangements (Scheme 4, path A). Rate-enhancing donor acyl substituents were believed to stabilize intrinsic acylium character in the first, rate-determining step (39, 43).

The discovery of the HERON reaction process instigated a reevaluation of the mechanistic details of this reaction by our group (44) and, coincidentally, by Barton and co-workers (40). Both studies involved the synthesis and thermal decomposition of an asymmetrical hydrazine. In our study, *N*-benzoyl-*N*-benzyloxy-*N*′-butoxy-*N*′-(*p*-chlorobenzoyl)hydrazine (**12a**) decomposed at room temperature in $CDCl_3$ affording largely benzyl benzoate (**13a**) and butyl *p*-chlorobenzoate (**13b**) from two, three-centre processes (Scheme 4, path B). Similarly, Barton and co-workers exclusively rearranged **12b** to a 1:1 mixture of **13c** and **13d** (40).

AM1 calculations carried out by both ourselves (44) and Barton's group (40), and subsequent high level calculations

[4] These are due to symmetrical and asymmetrical coupled stretch modes rather than individual frequencies for each carbonyl (15).

Scheme 4.

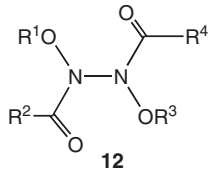


carried out by Thomson and Hall (45) on **12d**–**12f**, supported this mechanism in which the second step, also a HERON-type reaction, has a very low activation barrier. For hydrazine model **12d**, they calculated an activation barrier of 25 kcal mol^{-1} at the CCSD(T)//B3P86 level for HERON (1) in Scheme 4, a step that was exothermic by 13 kcal mol^{-1}. At the B3P86//B3P86 level, activation barriers for **12d**, **12e**, and **12f** were 24, 23, and 35 kcal mol^{-1}, respectively. The second HERON reaction (HERON (2), Scheme 4) of the diazene intermediate is computed to have a low activation barrier of just 2 kcal mol^{-1} and the extrusion of nitrogen is exothermic by 104 kcal mol^{-1}! Similar results were obtained for HERON (2) for the methylated models **12e** and **12f**. They also reported that a concerted pathway to two molecules of ester and nitrogen was not viable.

The transition state for HERON (1), computed for the rearrangement of methoxyl in **12f**, resembled that previously computed for the HERON reaction of *N*-methoxy-*N*-dimethylaminoformamide to give methyl formate and 1,1-dimethyldiazene (36). The transition state for the second step was very early in accordance with the exothermic nature of this step. B3LYP/6-31G*calculations from our group for a similar rearrangement of 1-formyl-1-methoxydiazene confirmed this and will be dealt with later in this review (46).

The initial, rate-determining step in the HERON reaction of hydrazines **14a**–**14e** and **15a**–**15e** proceeds with modest activation barriers of between 22 and 30 kcal mol^{-1} and negative entropies of activation (36). Thus, the experimental values are in excellent agreement with our activation energy for the HERON reaction of *N*,*N*-dimethylamino-*N*-methoxyformamide (21 kcal mol^{-1}, Fig. 7) and those computed by Thomson and Hall (45) for models **12d**–**12f**.

The unimolecular rate constants at 298 K for decomposition of a series of *N*,*N*′-di(*p*-substituted benzoyl)-*N*,*N*′-diethoxyhydrazines (**14a**–**14e**) in mesitylene correlated with Hammett σ^+ constants with $\rho = -0.35$, reflecting the stabilization of the transition state by electron-releasing acyl substituents adjacent to the donor nitrogen (Fig. 8*a*). The rates constants at 298 K for a series of *N*,*N*′-diacetyl-*N*,*N*′-di(*p*-substituted benzyloxy)hydrazines (**15a**–**15e**) correlated with Hammett σ constants, but with positive slope ($\rho = 1.02$), thus reflecting the stabilization of the transition state by electron-withdrawing alkoxyl substituents (Fig. 8*b*). Both results con-



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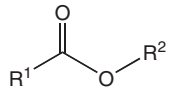
a: $R^1 = C_6H_4CH_2$, $R^2 = C_6H_5$ $R^3 = Bu$, $R^4 = p\text{-}ClC_6H_4$
b: $R^1 = CH_3$, R^2 = cyclohexyl $R^3 = C_6H_5(CH_2)_2$, $R^4 = C_6H_5CH_2$
c: $R^1 = R^3 = Bu^t$, $R^2 = R^4$ = 1-adamantyl
d: $R^1 = R^2 = R^3 = R^4 = H$
e: $R^2 = R^4 = CH_3$, $R^1 = R^3 = H$
f: $R^1 = R^2 = R^3 = R^4 = CH_3$



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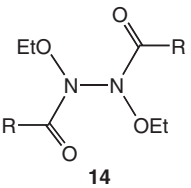
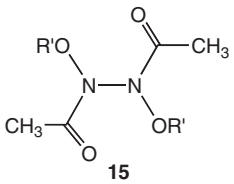
a: $R^1 = C_6H_5$, $R^2 = C_6H_5CH_2$
b: $R^1 = p\text{-}ClC_6H_4$, $R^2 = Bu$
c: R^1 = cyclohexyl, $R^2 = CH_3$
d: $R^1 = C_6H_5CH_2$, $R^2 = C_6H_5(CH_2)_2$
e: R^1 = 1-adamantyl, $R^2 = Bu^t$
f: $R^1 = R^2 = H$
g: $R^1 = CH_3$, $R^2 = H$
h: $R^1 = R^2 = CH_3$



14

a: $R = p\text{-}CH_3OC_6H_4$
b: $R = p\text{-}CH_3C_6H_4$
c: $R = C_6H_5$
d: $R = p\text{-}ClC_6H_4$
e: $R = p\text{-}NO_2C_6H_4$



15

a: $R' = p\text{-}CH_3OC_6H_4CH_2$
b: $R' = p\text{-}CH_3C_6H_4CH_2$
c: $R' = C_6H_5CH_2$
d: $R' = p\text{-}ClC_6H_4CH_2$
e: $R' = p\text{-}NO_2C_6H_4CH_2$

firmed the charge distribution at the transition state for the HERON rearrangement (Fig. 7) (36). Furthermore, members of the benzoyl series react about two orders of magnitude faster at 298 K than the benzyloxy series (typically 3×10^{-6} vs. 5×10^{-8} L mol^{-1} s^{-1}). This can be understood since, in the benzoyl series, a donor group facilitates development of positive charge at the donor nitrogen but has little effect upon the acyl carbon in the migration, since this accrues little charge in the transition state (Figs. 7 and 8*a*). However, while an electron-withdrawing group on the alkoxyl group will stabilize negative charge in the migrating group, it will destabilize the developing positive charge on the adjacent donor nitrogen (Figs. 7 and 8*b*).

Thus, the thermal rearrangement of *N*,*N*′-diacyl-*N*,*N*′-dialkoxyhydrazines to esters and nitrogen is a HERON reac-

Scheme 5.

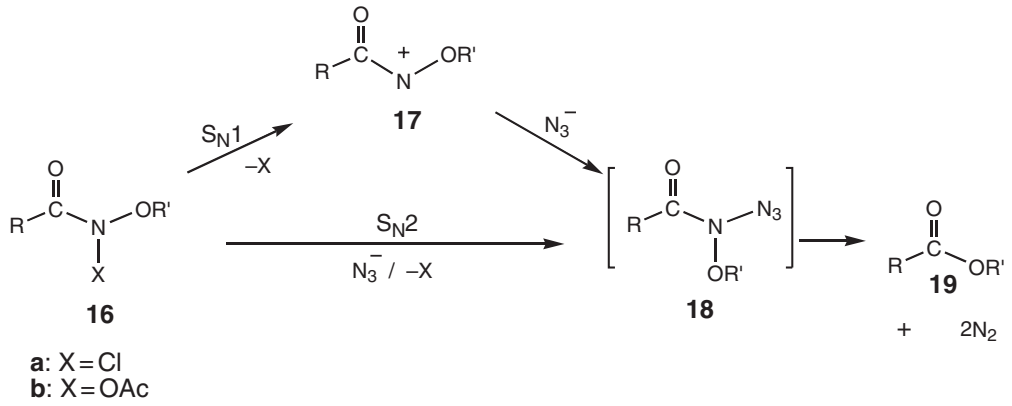
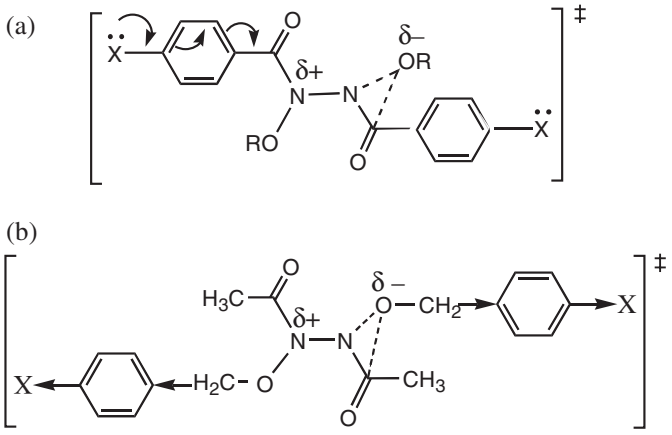


Fig. 8. Influence on the HERON transition states of: (*a*) electron-rich benzoyl groups in **14**; and (*b*) electron-deficient benzyloxy groups in **15**.



tion and their reduced rates of reactivity (probably on account of weaker donor capacity of one nitrogen because of acyl substitution) enabled us to confirm the theoretical transition-state properties.

This concerted reaction was flagged by Barton and coworkers (40) as an excellent synthesis of sterically hindered esters. For example, decomposition of **12c** afforded *tert*-butyl 1-adamantanecarboxylate (**13e**) in 87% yield.

The HERON reaction of 1-acyl-1-alkoxydiazenes

N-Alkoxy-*N*-chloroamides (**16a**) and *N*-acetoxy-*N*-alkoxyamides (**16b**) react with sodium azide at room temperature giving the ester **19**, derived from the alkoxyl and acyl groups of the hydroxamic ester, as well as nitrogen. In the case of both *N*-alkoxy-*N*-chloroamides and *N*-acyloxy-*N*-alkoxyamides, crossover experiments indicated that the reaction exclusively yields the carboxylic ester derived from the corresponding alkoxyl and acyl group (35). Both an S_N1 process involving the nitrenium ion **17** and direct S_N2 mechanism are possible under these conditions (Scheme 5). The reactions are extremely fast in aqueous organic solvents but can be monitored dilatometrically at 295 K and have been found to proceed by the bimolecular process yielding 2 equiv. of nitrogen, with rate constants of around 2 L mol^{-1} s^{-1}. Bimolecular reactions of *N*-acyloxy-*N*-alkoxyamides with *N*-methylanilines (34) and glutathione or L-cysteine methyl ester[5] are slower by two to three orders of magnitude. *N*-Alkoxy-*N*-azidoamides **18** are believed to form as reactive intermediates (35, 46).

Calculations on the lowest energy structure for *N*-azido-*N*-methoxyformamide (**20**) at HF/6-31G* (35) and B3LYP/6-31G* (46) indicate that the azido adduct lies at a potential energy minimum and is typically anomeric with avg. angles at nitrogen of 112° and 113° (Fig. 9*a*), and a conformation that supports one anomeric overlap, that being between the oxygen lone pair and the N1—N2 bond (Figs. 9*b* and 9*c*).

Production of methylformate and two molecules of nitrogen can occur by three routes. The first possibility involves a HERON reaction yielding ester **21** and tetrazene **22**, which is the source of 2 equiv. of nitrogen (Scheme 6, path A). Alternatively, an initial loss of nitrogen could give 1,1-diazene (Scheme 6, path B), which undergoes a HERON reaction producing ester and a second equivalent of nitrogen (Scheme 6, path C). The latter process is identical to the HERON (2) step in the decomposition of *N*,*N*′-diacyl-*N*,*N*′-dialkoxyamides (Scheme 4). A concerted rearrangement with loss of nitrogen (Scheme 6, path D) is also possible. Once again, we have used computational methods to determine the most likely reaction mechanism. All three reactions are highly exothermic (137 kcal mol^{-1}), but neither path A nor path D was found to be a viable competitor to the stepwise dissociation into 1,1-diazene (**23**) and nitrogen (Scheme 6, paths B and C). The azidonitrene in path A decomposes with zero activation energy to two molecules of nitrogen and no transition state for the concerted pathway could be found without prior loss of nitrogen as occurs in path B. Loss of nitrogen from *N*-azido-*N*-methoxyformamide in path B is exothermic by between 42 and 44 kcal mol^{-1} depending upon the ground-state geometry and has very low activation barriers of between 5 and 8 kcal mol^{-1}. The transition states all show stretching of the N4—N5 bonds of about 0.24 Å and sp^2 hybridization at the amide nitrogen. In addition, the N3—N4 bonds shorten by about 0.11–0.13 Å. The connected ground-state, transition-state, and 1,1-diazene ge-

[5] At 308 K, gluthione reacted in d_6-DMSO–D_2O with bimolecular rate constants of around 2.6 × 10^{-2} L mol^{-1} s^{-1}; at 303 K in d_4-methanol, L-cysteine methyl ester reacted with a rate constant of 1.6 × 10^{-2} L mol^{-1} s^{-1}.

Scheme 6.

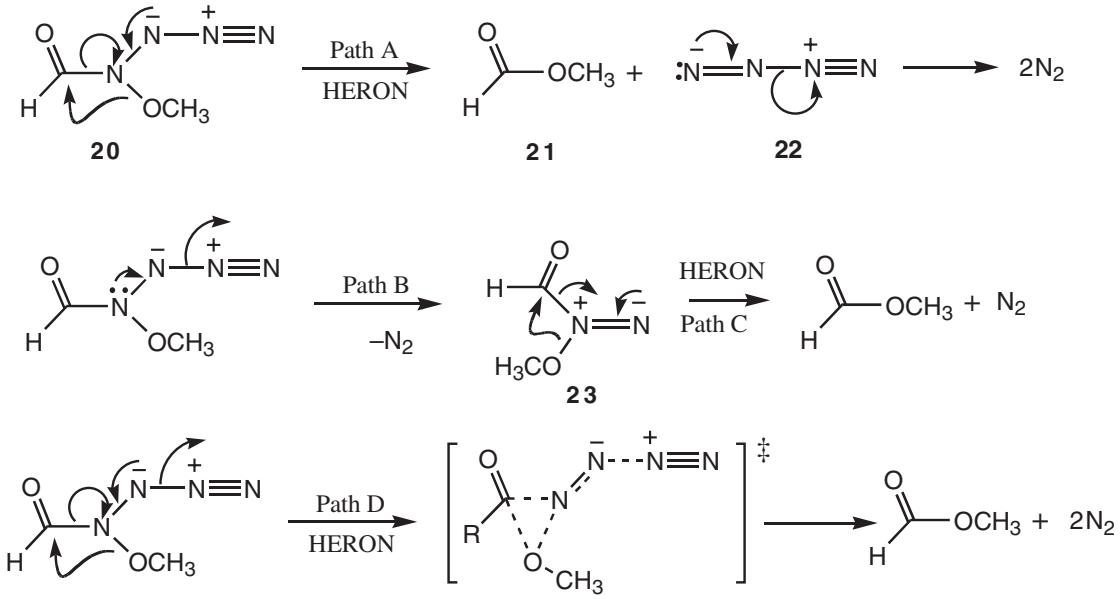
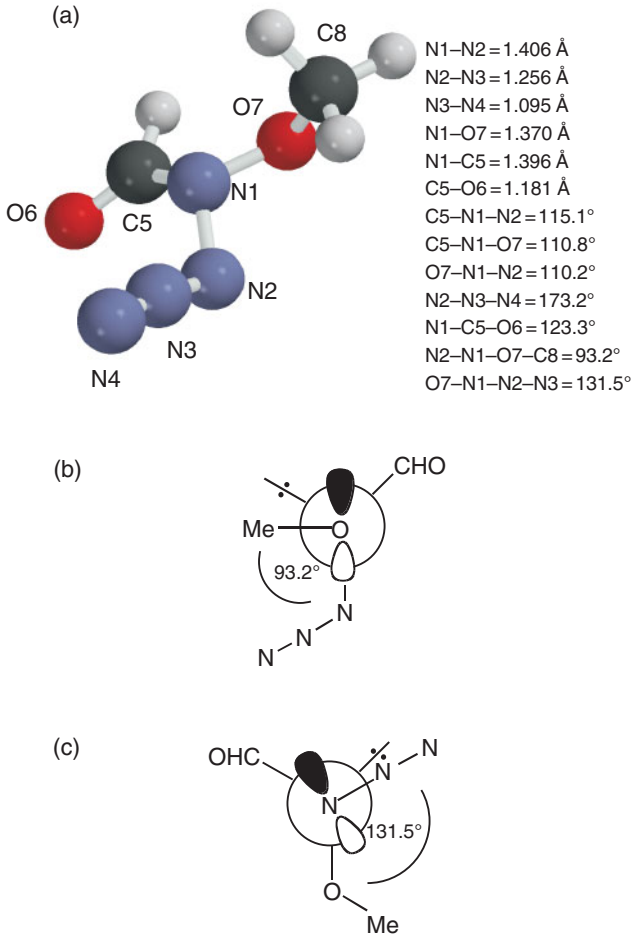


Fig. 9. (*a*) HF/6-31G* geometry of *N*-azido-*N*-methoxyformamide. (*b*) Newman projection along the O7—N1 bond. (*c*) Newman projection along the N2—N1 bond.



ometries from the lowest energy conformer of *N*-azido-*N*-methoxyformamide are given in Fig. 10.

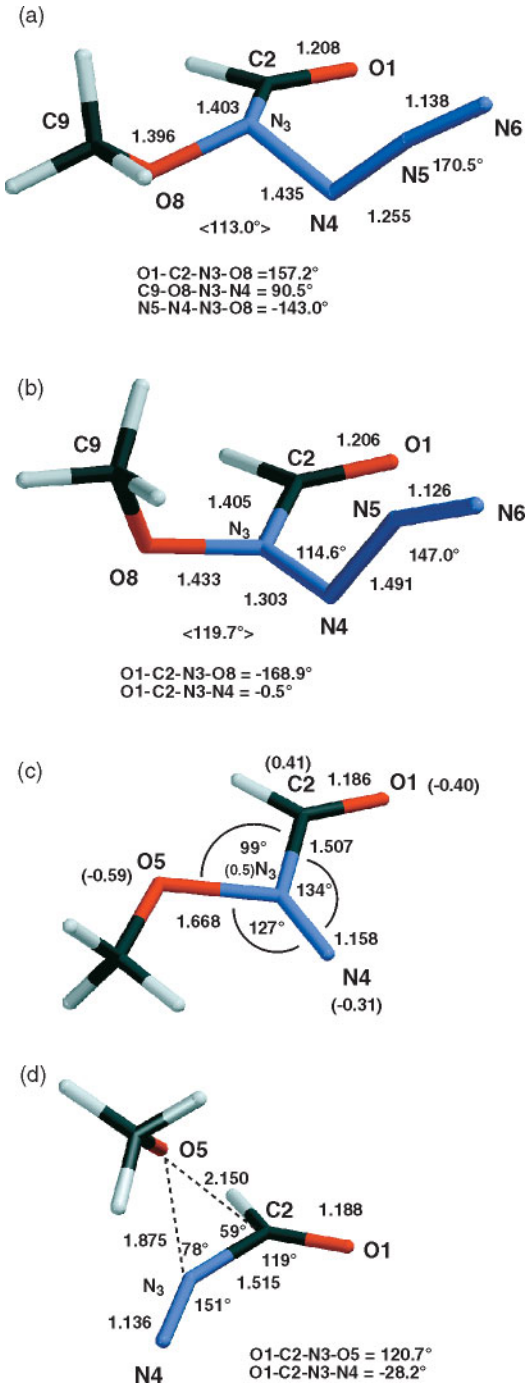
Rearrangement of 1-formyl-1-methoxydiazene to nitrogen and methylformate (Scheme 6, path C) is a HERON reaction and is an identical process to the second step for the thermal decomposition of *N*,*N*′-diacyl-*N*,*N*′-dialkoxyhydrazines. At the B3LYP/6-31G* level, the transition state (Fig. 10*d*) is early with an activation barrier of only 2.8 kcal mol^{-1}, and the second step is overall exothermic by approximately 95 kcal mol^{-1}. Our result is completely in line with that of Hall and Thomson's (45), previously described for the simpler system (E_A = 2 kcal mol^{-1}, ΔE = 104 kcal mol^{-1}).

We have utilized the favourable energetics and concerted rearrangement of *N*-alkoxy-*N*-azidoamides to esters and nitrogen in the facile synthesis of highly hindered esters from *N*-chlorohydramic esters (Table 1). Yields rival those of Barton's group (40) from HERON decomposition of the hydrazines. Precursors for both syntheses are the hydroxamic esters, but the hydrazine method involves prior oxidative dimerization, whereas the intermediates in our synthesis are the *N*-chlorohydroxamic esters that are very readily generated from hydroxamic esters in quantitative yield using *tert*-butyl hypochlorite.

The HERON reaction in alcoholysis of dialkyl azodicarboxylates

Azodicarboxylates **24** are a class of nitrogen electrophiles that have been used widely in the Mitsunobu reaction, an effective synthetic protocol for activating alcohols to esterification (largely with inversion of configuration) (47–49). Reactions in alcohols have produced both symmetrical and unsymmetrical dialkylcarbonates as side products or as the major product (50, 51). Direct alcoholysis of azodicarboxylate esters has been described by several groups (38, 52–54). Azodicarboxylates **24** were reported to be stable in ethanol, but vigorously decomposed upon addition of bases such as alkoxides and sodium acetate (52). The hydrazines **25** were believed to be unstable intermediates, although reports are contradictory. Galynker and Still (55) reported that

Fig. 10. (*a*) Ground-state geometry for *N*-azido-*N*-methoxyformamide. (*b*) First transition state for the loss of nitrogen (Scheme 6, path B). (*c*) Ground-state geometry of 1-formyl-1-methoxydiazene. (*d*) Transition state for the HERON reaction of 1-formyl-1-methoxydiazene (Scheme 6, path C).



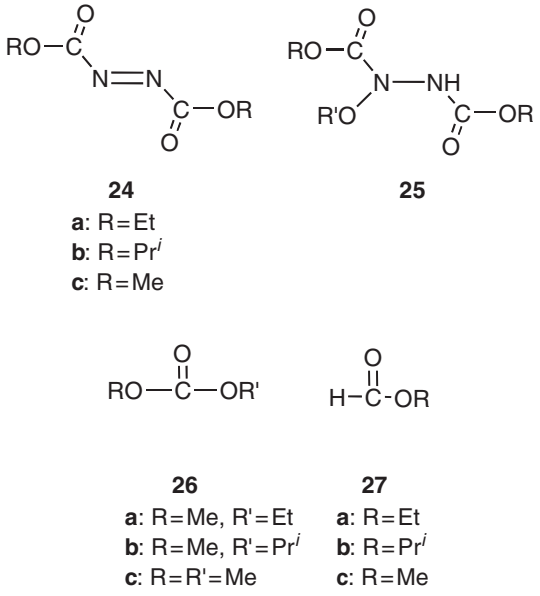
they were major, stable side products from Mitsonobu tosylation reactions. However, based on our observations azodicarboxylates **24** are most likely to undergo a HERON rearrangement upon nucleophilic addition.

In support of this, we found that diethyl azodicarboxylate (**24a**) and diisopropyl azodicarboxylate (**24b**) were completely stable in methanol, but upon addition of sodium methoxide, sodium acetate, or sodium hydroxide, they decomposed with a spontaneous evolution of an equivalent of nitrogen, liberation of heat, and a change of colour from the characteristic yellow of the azodicarboxylates to pink. The products of decomposition in a methanolic solution of sodium methoxide or sodium acetate were identified spectroscopically and by GLC as ethyl methyl carbonate (**26a**) and ethyl formate (**27a**), and in the case of the reaction of **24b**, ^{1}H NMR analysis of the reaction mixture indicated the presence of methyl isopropyl carbonate (**26b**) and isopropyl formate (**27b**) in an approximate ratio of 1:1.

Table 1. Ester (RCOOR′) formation from the reaction of alkyl *N*-alkoxy-*N*-chloroamides (RCONClOR′) with sodium azide in aqueous acetonitrile.

Ester	R	R′	Crude yield (%)
19a	Ph	$(CH_3)_3C$	87
19b	$(CH_3)_3C$	$(CH_3)_3C$	30[a]
19c	1-Adamantyl	$(CH_3)_3C$	82[b]
19d	$(CH_3)_3C$	Cyclohexyl	97
19e	Ph	$(CH_3)_2CH$	92
19f	Ph	$PhCH_2$	93
19g	CH_3	$PhCH_2$	92
19h	*p*-$NO_2C_6H_4$	Et	94
19i	Ph	Et	94

[a]GLC analysis; reaction accompanied by formation of pivalic acid (29%).
[b]Traces of adamantane carboxylic acid were also detected.



24 **25**

a: R=Et
b: R=Pr^i
c: R=Me

26 **27**

26
a: R=Me, R'=Et
b: R=Me, R'=Pr^i
c: R=R'=Me

27
a: R=Et
b: R=Pr^i
c: R=Me

In support of this, we found that diethyl azodicarboxylate (**24a**) and diisopropyl azodicarboxylate (**24b**) were completely stable in methanol, but upon addition of sodium methoxide, sodium acetate, or sodium hydroxide, they decomposed with a spontaneous evolution of an equivalent of nitrogen, liberation of heat, and a change of colour from the characteristic yellow of the azodicarboxylates to pink. The products of decomposition in a methanolic solution of sodium methoxide or sodium acetate were identified spectroscopically and by GLC as ethyl methyl carbonate (**26a**) and ethyl formate (**27a**), and in the case of the reaction of **24b**, ^{1}H NMR analysis of the reaction mixture indicated the presence of methyl isopropyl carbonate (**26b**) and isopropyl formate (**27b**) in an approximate ratio of 1:1.

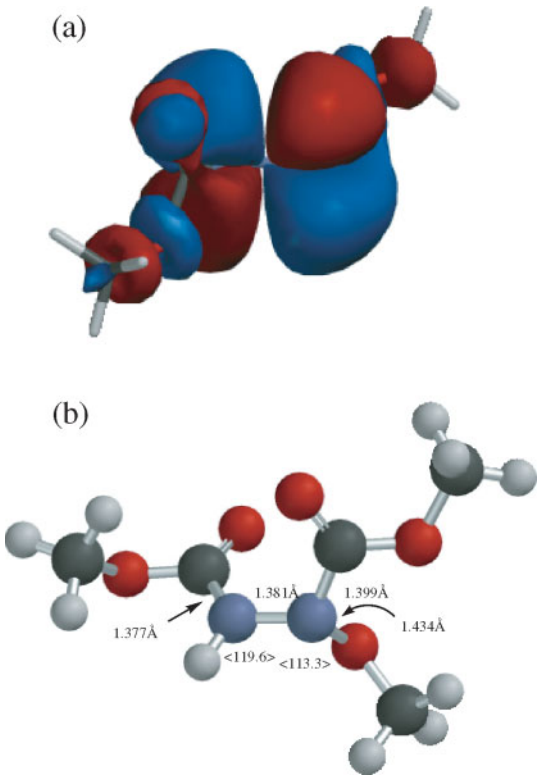
Formation of mixed carbonates might be rationalized by carbonyl addition followed by acyl cleavage. However, there is ample evidence from Mitsonobu chemistry that azodicarboxylates undergo nucleophilic attack at nitrogen. The HF/6-31G* computed lowest energy conformer of dimethyl azodicarboxylate has the ester groups orthogonal to the nitrogen double bond and the LUMO of **24c** is essentially a pure $\pi^*_{N=N}$ orbital (Fig. 11*a*). The second lowest unoccupied orbital possesses $\pi^*_{C=O}$ character, but is nearly 2.5 eV higher in energy. Nucleophiles, including methoxide, would be pre-

Table 2. Computed B3LYP/6-31G*//HF/6-31G* energies for reactants and products from the reaction of dimethyl azodicarboxylate (**32**) and methoxide ion.

Structure	HF/6-31G* (au)	B3LYP/6-31G*//HF/6-31G* (au)	SM5.4 (kcal mol^{-1}) (ref. 56)
Carbonyl adduct (**28**)	–677.72754	–681.52136	–59.1
Azo adduct (**29**	–677.71817	–681.51338	–65.0
HERON t.s. (**32**, R = Me)	–677.68059	–681.50298	–56.6
Carbonate (**26c**)	–341.70052	–343.60391	–0.9
Acyl anion (**34**, R = Me)	–227.13615	–228.41052	–67.7
Nitrogen	–108.94395	–109.52189	0.6
Reaction energies (kcal mol^{-1})	HF/6-31G*	B3LYP/6-31G*//HF/6-31G*	SM5.4 (ref. 56)
E_A	23.6	6.5	8.4
ΔE_{HERON}[a]	–5.9	–5.0	6.0
ΔE_{React}[b]	–39.2	–14.4	–3.0

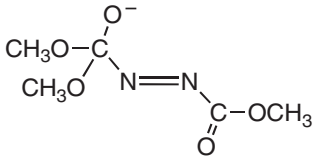
[a]Reaction energy for the transformation of **29** into **28**.
[b]Reaction energy for the transformation of **29** into **26c**, **34** (R = Me), and nitrogen.

Fig. 11. (*a*) HF/6-31G* LUMO orbital of dimethyl azodicarboxylate (**24c**). (*b*) HF/6-31G* geometry of *N,N′*-dicarbomethoxy-*N*-methoxyhydrazine.

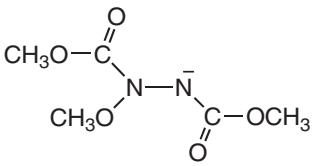


dicted to attack azodicarboxylates exclusively at the nitrogen atoms. In addition, while the anionic carbonyl adduct **28** is slightly more stable than the azo adduct **29** in the gas phase, it is slightly less stable if aqueous solvation is incorporated (Table 2).

Scheme 7 depicts possible mechanisms for the conversion of dialkyl azodicarboxylates into mixed carbonates. Attack at the azo group would result in the intermediate **30** in which the neighbouring nitrogen has anionic character. The anion could be protonated giving **31** (Scheme 7, path A) or, alternatively, could undergo a HERON reaction (Scheme 7, path B) with the formation of the mixed dialkyl carbonate **26** and



28



29

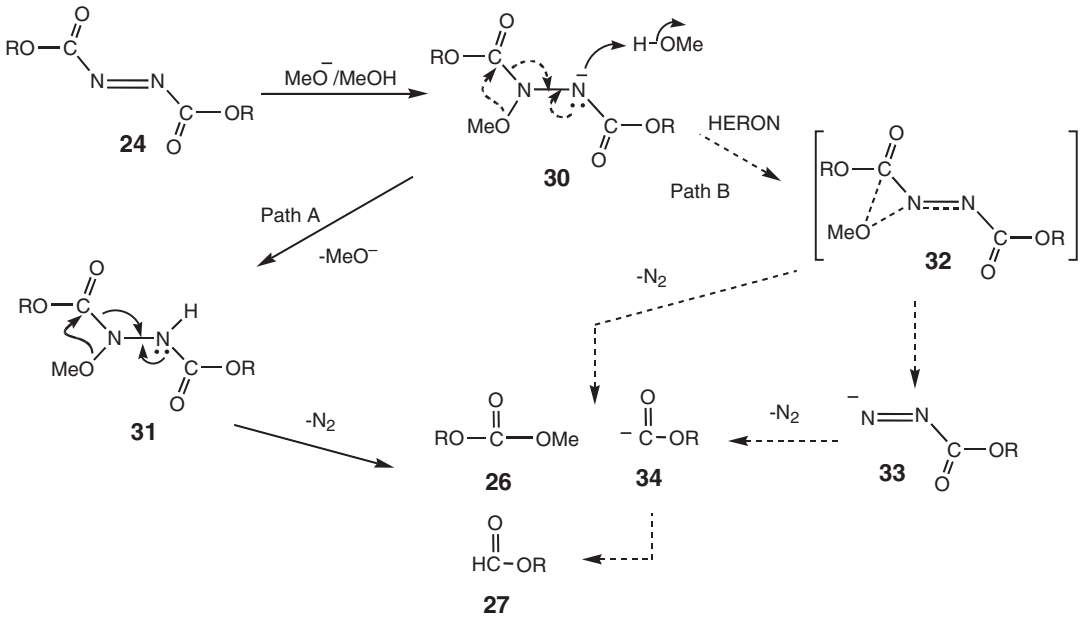
alkyl formate anion **34**, which ultimately leads to alkyl formate **27**.

However, path A followed by HERON reaction of **31** is less likely. Firstly, methoxide must be a stronger base than **30**, and secondly, **31** is likely to be much more stable than the *N,N′*-diacyl-*N,N′*-dialkoxyhydrazines; according to HF/6-31G* calculations (Fig. 11*b*), the amide lone pair is strongly conjugated with the carbonyl, since the nitrogen is largely sp^2 at the protonated nitrogen (avg. angle at nitrogen 119.6°). Compared to the *N,N′*-diacyl-*N,N′*-dialkoxyhydrazines, which are computed to have N—N bond lengths of around 1.355 Å (15), this "half-anomeric" hydrazine has a much longer N—N bond (1.381 Å), reflecting poor anomeric overlap. In keeping with this, we could not locate a transition state for a HERON reaction of this structure.

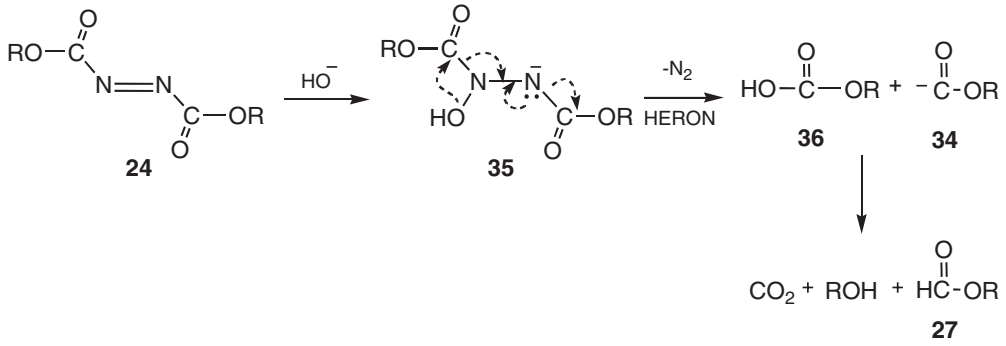
In **30**, the anionic lone pair is very high in energy resulting in a strong anomeric overlap and driving force for the rearrangement. The process has an analogy in the previously reported, facile HERON reaction of the conjugate anion of *N*-alkoxyhydroxamic esters described in the following example (33).

Table 2 gives calculated energies for the reactant, transition state, and products from the HERON reaction of *N,N′*-dicarbomethoxy-*N*-methoxy anion (**29**). In the gas phase, the rearrangement has an extremely low E_A of 6.5 kcal mol^{-1} (14.8 kcal mol^{-1} with solvation), and in this case, leads initially to the carbonyl adduct **28**, which is similar in energy and is a stationary point. It is proposed that **28** directly decomposes to nitrogen and an acyl anion, which scavenges a proton from methanol. The methoxycarbonyldiazene anion (**33**) (R = Me) that would be formed by cleavage of the amide bond is computed to be a metastable point on the energy surface and spontaneously rearranges to an acyl anion and nitrogen. Overall, the reaction is exothermic by 14.4 kcal mol^{-1} (17.4 kcal mol^{-1} with solvation).

Scheme 7.



Scheme 8.



In a methanolic solution of potassium hydroxide, **24a** and **24b** exothermically decomposed with immediate evolution of nitrogen and formation of ethyl and isopropyl formate. In the case of **24b**, isopropanol was isolated as a product. Reaction according to Scheme 7 would result in formation of the alkyl hydrogen carbonate **36**, which under the basic reaction conditions, would probably decompose to alcohol and carbon dioxide (Scheme 8).

The formation of alkyl formate by this reaction represents a more acceptable route than that proposed by Vederas and co-workers (57) for the formation of steroidal formate ester (**39**) from *N*-bromosuccinimide oxidation of chiral diazane (**37**) (Scheme 9). The intermediate azodicarboxylate **38** was thought to react with water giving **40** by attack at carbonyl. Decarboxylation and radical decomposition of **40** via **41** completed the process. Homolytic decomposition of **40** to give **41** is considered by the author to be a highly unlikely process as is the reaction of water at the carbonyl of **38**.

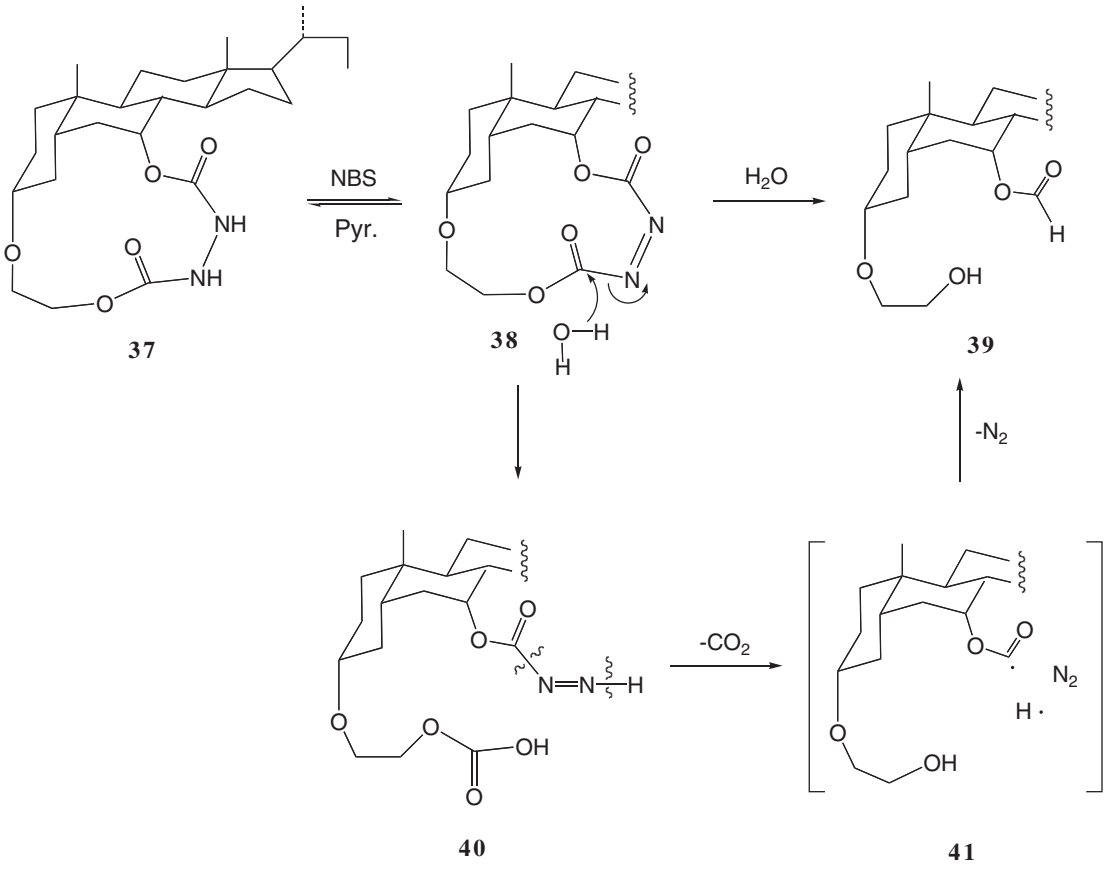
The HERON reaction of *N*-alkoxyhydroxamic acids

Treatment of *N*-acyloxy-*N*-alkoxybenzamides (**42a**) with dilute aqueous sodium hydroxide, at room temperature, resulted in the rapid formation of alkyl benzoates **19** (33). A crossover experiment using *N*-acetoxy-*N*-butoxy-*p*-chlorobenzamide and *N*-acetoxy-*N*-benzyloxybenzamide resulted in the exclusive formation of butyl *p*-chlorobenzoate (46%) and benzyl benzoate (43.3%) esters along with the hydrolysis products, *p*-chlorobenzoic and benzoic acid. This result indicates that ester formation involves an intramolecular process.

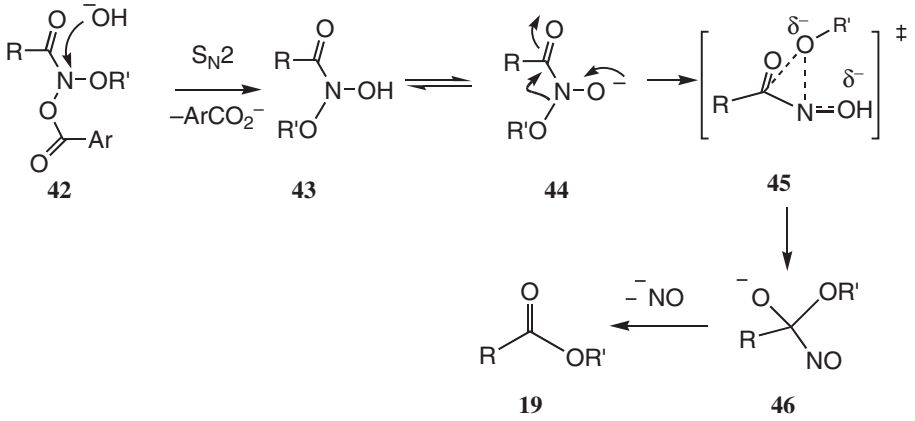
Using a series of *N*-(*p*-substituted benzoyloxy) mutagens, it was shown to occur by S_N2 reaction of hydroxide at nitrogen, which gives hydroxamic acid (**43**) as an intermediate (Scheme 10) (33). The presence of excess base would ensure conversion of the hydroxamic acid intermediate into the conjugate anion **44** resulting in a HERON reaction and formation of ester **19** and presumably NO^-. The formation of noncrossover esters in the acid-catalysed solvolyses of *N*-acetoxy-*N*-alkoxyamides **1** at low acid concentrations, according to Scheme 2, has also been observed. Such reactions produce the *N*-alkoxy-*N*-benzoylnitrenium ion **3** from **2** and, by solvolysis, *N*-alkoxyhydroxamic acid (**4**) directly (32).

While the lone pair on the hydroxy oxygen of hydroxamic acid (**43**) would be tightly bound, resulting in a weak n_{OH}—σ^*_{N-OR} interaction, the anion **44** would possess a high energy pair of electrons, thus enhancing the anomeric effect

Scheme 9.



Scheme 10.



a: R = Ph, R' = Bn
b: R = R' = Me

in a similar fashion to the amide anion **30** previously described and which drives that HERON reaction. Calculations on the rearrangement of *N*-methoxy-*N*-methanohydroxamate anion (**44b**) (Fig. 12*a*) to methyl formate (**19b**) indicated an early transition state (**45b**) (Fig. 12*b*) that leads to the tetrahedral alkoxide intermediate (**46b**) (Fig. 12*c*), which presumably decomposes by elimination of NO^-. B3LYP/6-31G*//HF/6-31G* results (Table 3) gave an activation energy for the HERON step of only 5.3 kcal mol^{-1} (10.0 kcal mol^{-1} including solvation effects). Formation of the tetrahedral intermediate was exothermic by 10.7 kcal mol^{-1} and the overall reaction was endothermic by 21 kcal mol^{-1} with solvation, which suggests reversibility of the HERON step in this case.

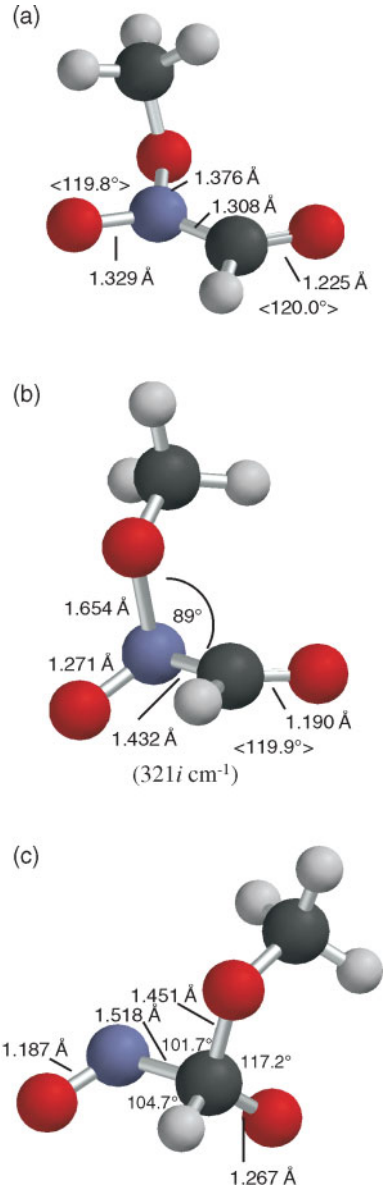
Recently, Shtamburg et al. (58) studied the methanolysis of a variety of *N*-acetoxy-*N*-alkoxy derivatives of carbamate **47a**, urea **47b**, and benzamide **50** and found that, with the exception of the benzamide, acyloxy substitution at nitrogen

Table 3. Computed B3LYP/6-31G*//HF/6-31G* energies for reactants and products from the rearrangement of *N*-methoxymethanohydroxamate anion (**44b**).

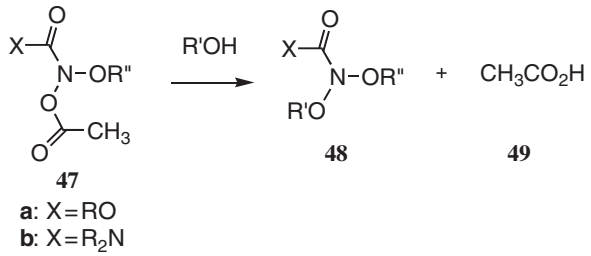
Structure	HF/6-31G* (au)	B3LYP/6-31G*//HF/6-31G* (au)	SM5.4 (kcal mol^{-1}) (ref. 56)
Hydroxamate (**44b**)	–356.95534	–358.93375	–67.4
HERON t.s. (**45b**)	–356.93625	–358.9252	–62.8
Alkoxide (**46b**)	–356.98422	–358.95114	–67.2
Methyl formate (**19b**)	–227.77945	–229.05208	–3.5
NO^-	–129.13602	–129.80825	–88.5
Reaction energies (kcal mol^{-1})	**HF/6-31G***	**B3LYP/6-31G*//HF/6-31G***	**SM5.4 (ref. 56)**
E_A	12.0	5.4	4.6
ΔE_{HERON}[a]	–18.1	–10.9	0.3
ΔE_{React}[b]	25.0	46.1	–24.5

[a]Reaction energy for the transformation of **44b** to **46b**.
[b]Reaction energy for the transformation of **44b** to **19b** and NO^-.

Fig. 12. HF/6-31G* geometries for: (*a*) the ground state of *N*-methoxymethanohydroxamate (**44b**); (*b*) HERON transition state **45b**; and (*c*) tetrahedral intermediate **46b**.



Scheme 11.



and loss of acetic acid was a useful means of obtaining the corresponding symmetrical and asymmetrical *N*,*N*-dialkoxy derivatives **48** (Scheme 11).

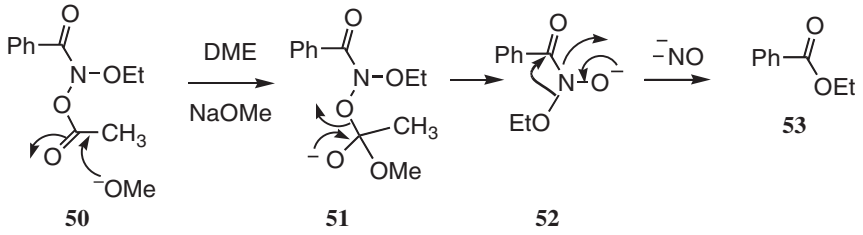
The reaction with *N*-acetoxy-*N*-ethoxybenzamide (**50**) did not result in substitution at nitrogen and a reaction in an aprotic medium with sodium methoxide afforded methyl and ethyl benzoates. They attributed the formation of methyl benzoate to methoxide reaction at the amide carbonyl and the formation of ethyl benzoate (**53**) to a HERON reaction. Presumably, in this medium, attack at the carbonyl of the acetoxyl group would directly lead, by fragmentation of **51**, to the conjugate anion of the *N*-ethoxybenzohydroxamic acid (**52**), followed by the HERON migration of the ethoxy substituent from nitrogen to the benzamide carbonyl (Scheme 12).

The HERON reaction of *N*-acyloxy-*N*-alkoxyamides in the gas phase

HERON rearrangement of *N*-acyloxy-*N*-alkoxyamides has not been observed. In polar solvents (aqueous acetonitrile) anomeric weakening of the AcO—N bond favours heterolysis over migration of the acyloxy substituent. Migration would yield anhydrides, which have never been observed as side products from the $A_{Al}1$ or S_N2 reactions of *N*-acyloxy-*N*-alkoxyamides of our group (1, 6, 21, 32–34) or Shtamburg's recent studies (58).

ESI-tandem mass spectrometric studies on a number of *N*-acyloxy-*N*-alkoxyamides indicated that under these conditions, free from solvent, the sodiated parent ion can be detected, which fragmented under collision-induced dissociative conditions into three sodiated product ions (Table 4). These products exhibited masses corresponding to the sodiated *N*-alkoxyamidyl radical (**54**), which in most cases was the

Scheme 12.



Scheme 13.

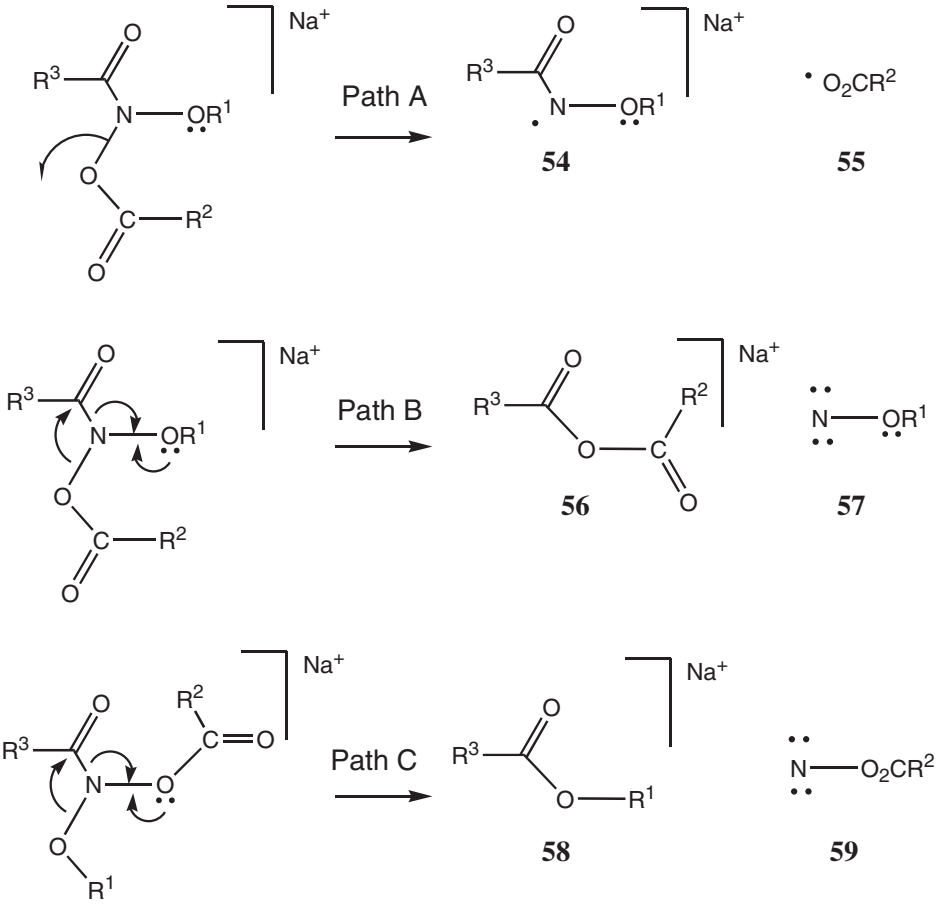


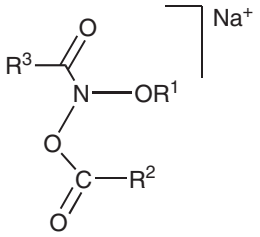
Table 4. Values of *m*/*z* for sodiated ions from the ESI-MS of *N*-acyloxy-*N*-alkoxyamides **60a–60l**.

Structure	**60**	**54**	**56**	**58**
a	274	215	187	201
b	302	243	215	229
c	362	303	275	—
d	404	345	317	—
e	370	249	249	235
f	426	305	249	291
g	336	215	249	—
h	288	167	201	Trace
i	302	181	215	—
j	394	273	307	—
k	316	195	229	—
l	330	209	243	—

Note: ESI conditions in positive ion mode: H_2O–MeOH, drying gas 350 °C, capillary = 30 V, CID = –5 to –30 eV.

major pathway (Scheme 13, path A), but the second most intense product ion was the sodiated anhydride **56** formed through HERON rearrangement of the acyl group (Scheme 13, path B). The alternative ester **62** that would be formed through a HERON migration of the alkoxy group (Scheme 13, path C) was a weak product ion in all cases where it was present and absent in the fragmentations of all aliphatic amides (**60h–60l**). The fragments from the reaction processes are presumed to be acyloxyl radical (**55**), alkoxynitrene (**57**), and acyloxynitrene (**59**).

According to B3LYP/6-31G*//HF/6-31G* calculations on **60m** and its HERON rearrangement products in the gas phase, migration of the acyloxyl group is favoured over the alkoxyl group by about 4 kcal mol^{-1} (Table 5). The transition states (Figs. 13*b*–13*d*) are relatively similar with the migrating oxygen perpendicular to the ONC(O) plane, though the HERON transition state for acyl appears looser (Fig. 13*b*), which would be expected because of the polarities involved.



60

a: R^1=Bu, R^2=Me, R^3=Ph
b: R^1=Bu, R^2=Me, R^3=3,5-diMeC_6H_3
c: R^1=Bu, R^2=Me, R^3=fluoren-1-yl
d: R^1=Bu, R^2=Me, R^3=2-anthraquinon-2-yl
e: R^1=R^2=R^3=Ph
f: R^1=4-Bu^t, R^2=R^3=Ph
g: R^1=Bu, R^2=R^3=Ph
h: R^1=Bu, R^2=Ph, R^3=n-Pr
i: R^1=Bu, R^2=Ph, R^3=Bu^i
j: R^1=Bu, R^2=Ph, R^3=1-Ad
k: R^1=Bu, R^2=Ph, R^3=Bu^t
l: R^1=Bu, R^2=Ph, R^3=neopentyl
m: R^1=Me, R^2=R^3=H

Table 5. Computed energies for ground state and migration transition states for **60m**.

Structure	B3LYP/6-31G* (au)	Relative energy (kcal mol^{-1})	Frequency (cm^{-1})
Fig. 13*a*	–472.851865	0.0	
Fig. 13*b*	–472.790221	38.7	271*i*
Fig. 13*c*	–472.782035	43.4	210*i*
Fig. 13*d*	–472.783513	42.9	282*i*

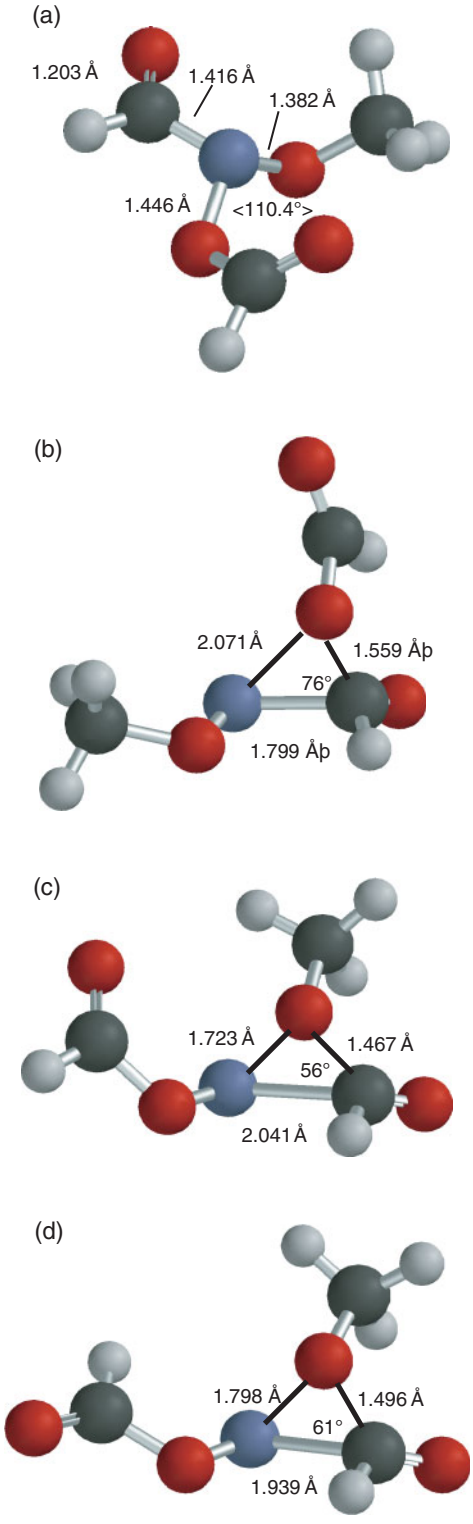
Two conformations of the transition state for methoxyl migration (Figs. 13*c* and 13*d*) were found with very similar energies.

The magnitude of the activation energies indicates that such migrations are unlikely to compete with heterolysis of the N—OAc bond, particularly in polar solvents. While the influence of the spectator sodium ion on these reactions is unknown, clearly, the ESI-MS–MS data reflects the expected migration tendencies of acyl vs. alkoxyl moieties in these substrates. The alkoxyl oxygen, though much more electronegative than nitrogen, is a better donor atom than the acyloxy oxygen, which is bonded to an electron-withdrawing carbonyl carbon, and hence, the acyl group migration would be preferred.

Conclusions

The HERON reaction is one of the newest named reactions (3). In this review we have outlined the discovery of this reaction, theoretical support for the process, as well as instances where there are good grounds to expect its participation. Certainly, it is involved in the reactions of NNO anomeric amides that have tetrahedral amide nitrogens, which is a consequence of the favourable anomeric interaction in those configurations. These reactions, which involve migration of groups from an amide nitrogen to an amide carbonyl carbon, contrast with the known migrations in the reverse direction that are exemplified by the well-documented Hoffman (59), Lossen (60), and Curtius (61) reactions. The reaction is also found in the conversion of 1-acyl-1-alkoxydiazenes, a second step in the thermal decompositions

Fig. 13. B3LYP/6-31G* geometries for: (*a*) the ground state of *N*-formyloxy-*N*-methoxyformamide (**60m**), and transition states for the migration of: (*b*) acyloxyl; and (*c*) and (*d*) alkoxyl groups.



of *N*,*N*′-diacyl-*N*,*N*′-dialkoxyhydrazines and *N*-alkoxy-*N*-azidoamides that are formed by S_N2 reactions of azide with *N*-chloro- and *N*-acyloxy-*N*-alkoxyamides. The mechanism is also implicated in the reactions of some ONO anomeric amides as exemplified by the rearrangements of alkoxyl groups in basic or weakly acidic solutions of *N*-alkoxyhydroxamic acids, and, most recently, in the gas-phase rearrangements of *N*-acyloxy-*N*-alkoxyamides. In the future, other anomeric amides such as *N*-alkoxy-*N*-haloamides or *N*-amino-*N*-haloamides may well be found to undergo HERON processes.

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