Molecular Orbital Studies of Novel N to C Migrations in *N,N*-Bisheteroatom-substituted Amides—HERON Rearrangements

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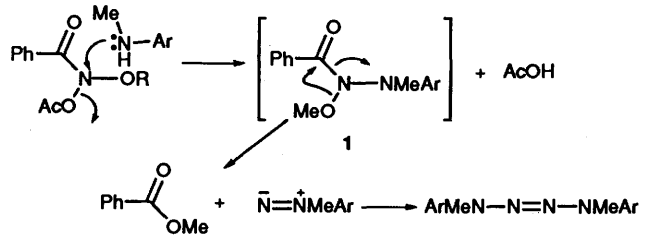
Bisheteroatom-substituted amides (R–CO–NXY) can undergo a novel rearrangement of the more electronegative atom from nitrogen to the carbonyl carbon producing acyl derivatives (R–CO–X) and substituted nitrenes (N–Y). Such reactions have been observed chemically. AM1 molecular orbital calculations on *N*-substituted acetamides support the concerted nature of this process and predict that amino substituents ($Y = NR_2$) promote the rearrangement of similarly or more electronegative nitrogen substituents ($X = NR_2$, Cl, OR). Migration appears to be driven by an anomeric effect involving interaction between the lone pair on Y and the X–N σ^* orbital. Favourable transiton states display a significant increase in N–Y double bond character, negative charge on the migrating substituent and little RCO–N heterolysis. 6-31G* *ab initio* calculations on migration of the hydroxy group in *N*-amino-*N*-hydroxyformamide largely accord with the AM1 findings for this model compound.

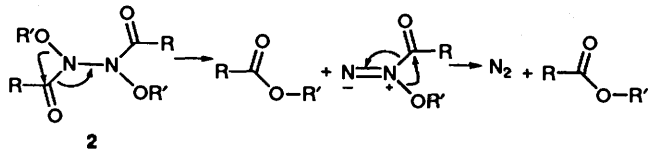
N-Alkoxy-*N*-aminobenzamides are intermediates in the bimolecular reaction of mutagenic *N*-acetoxy-*N*-alkoxybenzamides and arylamines. S_N2 reaction at the amide nitrogen and displacement of acetate results in the formation of *N*-anilino-*N*-alkoxybenzamides (**1**) which are unstable and undergo concerted migration of the alkoxy group to form a benzoate ester and a 1,1-diazene (Scheme 1).[1] Ester formation is an



Scheme 1

intramolecular process as shown by a crossover experiment and the process is a rapid one since the intermediates **1** cannot be observed by ^1H NMR spectroscopy. Only starting material, ester and the products from dimerisation of 1,1-diazenes, tetrazenes, can be detected during the course of the reaction.

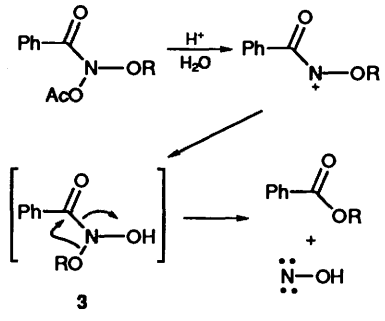
The rearrangement may be typical of *N*-aza-*N*-oxo substituted amides. We have recently shown that the thermal decomposition of *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines (**2**) to



Scheme 2

esters and nitrogen[2] occurs predominantly through two three-centre rearrangements rather than the previously proposed four-centre process (Scheme 2).[3] These dimers are analogues of **1** where the *N*-amino group bears both an acyl and an alkoxy group.

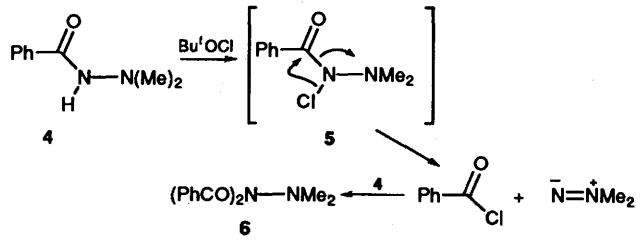
The reaction may not be confined to *N*-aza-*N*-oxo systems however. Earlier results indicate that *N*-alkoxy-*N*-hydroxy amines (**3**) formed as intermediates in the acid-catalysed solvolysis of *N*-acetoxy-*N*-alkoxybenzamides undergo a similar



Scheme 3

reaction to produce alkyl benzoates and hydroxynitrene (Scheme 3). This reaction appears not to be acid-catalysed and a crossover experiment has shown that it is also an intramolecular process.[4] The fate of hydroxynitrene though has never been established.

In other studies, we have shown that chlorination of β,β-dimethylbenzhydrazide **4** gives, instead of the α-chloro intermediate **5**, *N,N*-dibenzoyl-*N',N'*-dimethylhydrazine (**6**) as the sole product in high yield. Rapid rearrangement of α-chloro-β,β-dimethylbenzhydrazide (**5**) to benzoyl chloride and 1,1-dimethylaminonitrene followed by reaction with the starting material is a possible source of the imide (Scheme 4) although



Scheme 4

other mechanisms cannot be ruled out at this time.[5] We have called these novel reactions of amides involving *he*teroatom *r*earrangements *on n*itrogen, HERON rearrangements.†

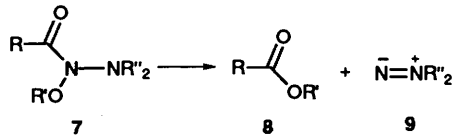
† These findings were presented to the Second Heron Island Conference on Unusual Molecules and Reactive Intermediates.

Table 1 $\Delta H_{reaction}$ and $\Delta H_{activation}$ for migration of MeO in **7a** and HO in **7d** as depicted in Scheme 5

Substrate	Method	$\Delta H_{reaction}$/ kJ mol^{-1}	$\Delta H_{activation}$/ kJ mol^{-1}
7a	AM1 gas phase	−80	+161
	AM1 solution phase[a]	−140	+126
7d	AM1 gas phase	−62	+155
	AM1 solution phase[a]	−130	+125
	6-31G* gas phase	−3	+176
	6-31G* solution phase[b]	−47	—

[a] Values were calculated with AM1 using the COSMO option of MOPAC. [b] Values were calculated with 6-31G* using the SCRF option of GAMESS.

The rearrangement of **1** as shown in Scheme 1 has been modelled by AM1 semiempirical molecular orbital calculations on **7a**[1,6] and in this paper we report in detail on those results as well as those for compounds similar to **1**, **3** and **5** to ascertain whether this type of migration is predicted whenever there are two hetero atoms on an amide nitrogen. In addition, compounds **7b** and **7c**, with various R′ and R″ groups have been modelled to try to determine the factors which influence the activation energy for these migrations. A comparison has also been made between 6-31G* *ab initio* and AM1 results for rearrangement of the model *N*-amino-*N*-hydroxyformamide (**7d**).



7 **8** **9**

a; R = R′ = R″ = Me
b; R = R′ = Me, R″ variable
c; R = R″ = Me, R′ variable
d; R = R′ = R″ = H

Scheme 5

Results and Discussion

AM1 predicts the rearrangement of *N*-dimethylamino-*N*-methoxyacetamide (**7a**) (Scheme 5) to be exothermic in the gas phase (Table 1). This is a consequence of the stability of methyl acetate (**8a**) and resonance delocalisation in dimethylaminonitrene (**9a**). The N–N bond length and bond order for **9a** are computed to be 1.22 Å and 1.90, respectively. There is a charge of *ca.* −0.3 on the terminal nitrogen and aminonitrenes are clearly best described as 1,1-diazenes.

The potential energy surface for the rearrangement [Fig. 1(*a*)] indicated a saddle point with relatively little C(O)–N bond elongation. The optimised transition state geometry is depicted in Fig. 1(*b*). The methoxy oxygen is *ca.* 1.85 Å from the amide carbon and nitrogen and lies in a plane approximately perpendicular to the NCO plane. The N–C(O) bond length (1.48 Å) is marginally longer than the corresponding bond in the starting configuration (1.46 Å) however the N–N bond is significantly shortened (1.4 to 1.26 Å) indicating overlap with the dimethylamino nitrogen lone pair as the methoxy group migrates. The driving force for the rearrangement can therefore be ascribed to a strong interaction between the dimethylamino nitrogen lone pair and the low-lying N–O σ* orbital which weakens the methoxy–nitrogen bond. Such anomeric effects have been postulated to give rise to the conformational stability in O–N–O systems; barriers to inversion in acyclic dialkoxyamines are significantly higher than those in alkoxyamines.[7] In X–N–Ÿ systems, whenever the non-bonding orbital on Y and the X–N σ* orbital approach closely in energy, the interaction may be sufficiently strong so as to weaken the X–N σ-bond leading to heterolysis. The n_N–σ^*_{NO} interaction in the case of O–N–N systems is likely to be stronger than that found in O–N–O systems (n_O–σ^*_{NO}) owing to the higher energy of the nitrogen lone pair relative to the oxygen lone pair of electrons.

Rather than simple heterolysis, the outcome in this case is a concerted methoxy migration though. The difference between the two systems is supported by the fact that, while *N*-methylanilino-*N*-alkoxybenzamides are reactive intermediates, dialkoxybenzamides[3] and dialkoxyureas[8] can actually be isolated at room temperature. Although there is no obvious increase in N–N bond order, the ground state geometry for the molecule supports an anomeric effect analogous to that which controls conformations in acetals;[9] a conformation is adopted which would facilitate an n_N–σ^*_{NO} overlap (Fig. 2).‡

The N–C(O) bond is virtually intact at the transition state and only dissociates in concert with MeO–C(O) bond formation. The carbonyl bond is 0.01 Å longer in the transition state and the carbonyl oxygen bears an additional 0.1 negative charge (−0.29 in the ground state and −0.38 in the transition state). However a careful search of the potential energy surface failed to detect a zwitterionic intermediate corresponding to addition of methoxide to the carbonyl.

Solution-phase Rearrangement.—The rearrangement of *N*-dimethylamino-*N*-methoxyacetamide (**7a**) to methyl acetate and 1,1-dimethyldiazene (Scheme 5) was also modelled in solution using the COSMO facility in MOPAC with a molecular radius and relative permittivity for methanol.[10] The migration was predicted to be significantly more exothermic in the solution phase and the $\Delta H^{\ddagger}$ was reduced by some 35 kJ mol^{-1} (Table 1). This stabilisation is in accord with greater charge separation in the transition state than in the ground state (*vide supra*). Stabilisation of the products is also to be expected in methanol as the 1,1-diazene is a strongly dipolar entity. The geometries for the ground state and transition structure in the solution phase were similar to those found in the gaseous phase.

Ab Initio *Results.*—The migration of the hydroxy group in *N*-amino-*N*-hydroxyformamide (**7d**) to give formic acid (**8d**) and aminonitrene (**9d**) (Scheme 5) was studied in detail using both the semiempirical AM1 Hamiltonian of MOPAC and the *ab initio* 6-31G* basis set of GAMESS.[11] While the actual values of the calculated heats of reaction differ between the two methods, the *ab initio* results were in reasonable agreement with the semiempirical findings, both methods predicting the hydroxy migration to be thermodynamically favourable in both gas phase and solution phase and for the solution-phase rearrangement to be significantly more exothermic than the gas-phase reactions (Table 1). A solution-phase *ab initio* transition state could not be located, however the gas-phase barriers were similar. The transition state geometries (Fig. 3) were almost identical; N–N bond lengths and bond angles reflected those properties previously determined using AM1 for *N*-dimethylamino-*N*-methoxyacetamide.

‡ While *N*-amino-*N*-alkoxybenzamides rearrange at room temperature and have not been detected as intermediates in our experiments, hydrazine dimers can be isolated. We have recently found that in their ^{1}H NMR spectra, they exhibit diasteriotopism for the resonances of alkoxy methylenes adjacent to the O, which must arise through high barriers to inversion of the nitrogen atoms caused by the anomeric effect. At around room temperature these dimers also undergo 1,2-alkoxy group migration to the acyl carbon.[3]

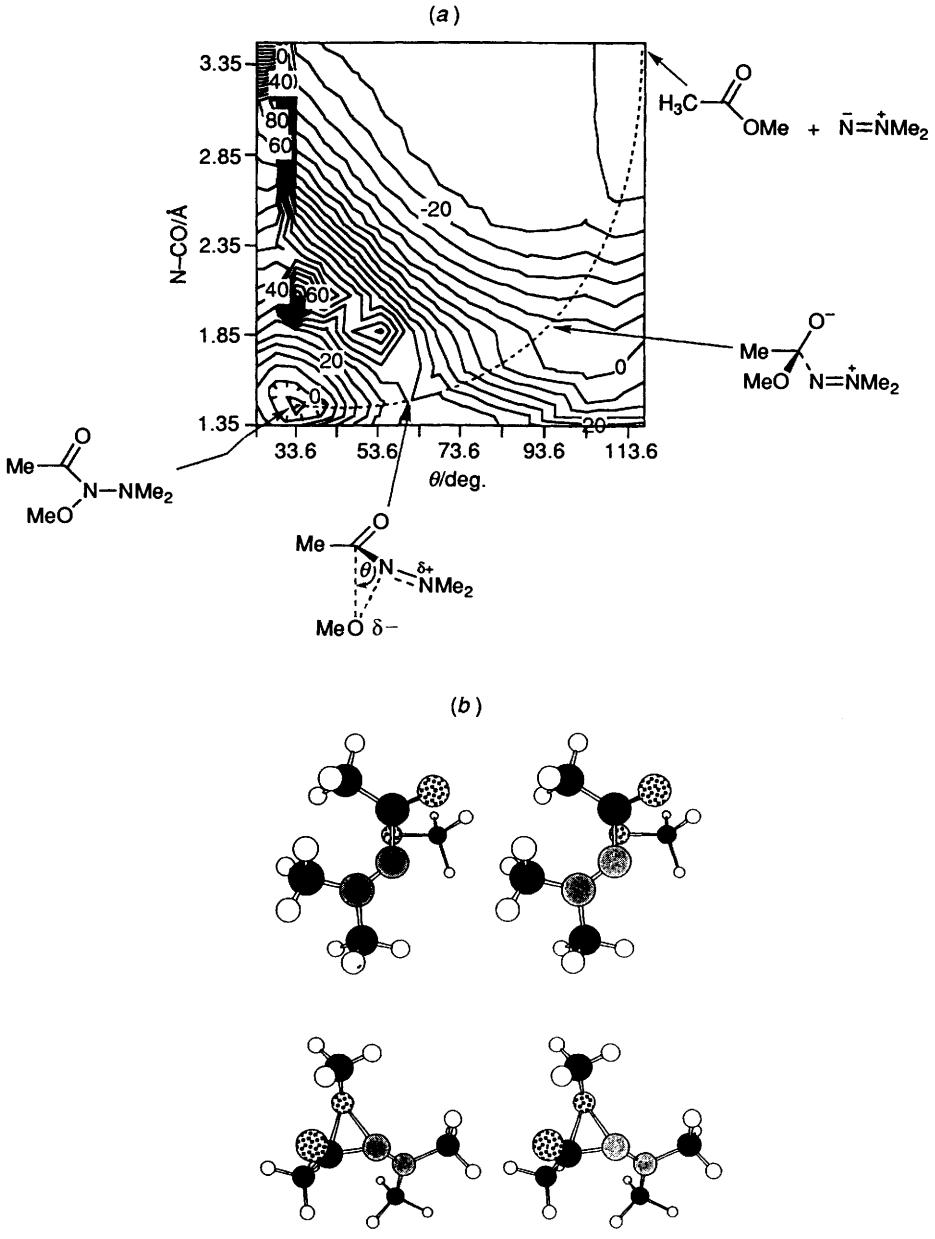


Fig. 1 (*a*) Reaction surface in kcal mol^{-1} for the concerted rearrangement of **7a** to methyl acetate and 1,1-dimethyldiazene; (*b*) stereoviews of the transition state for methoxy migration

Effect of Different Amino Substituents upon the Migration of Methoxy in (**7b**) (Scheme 5).—Our initial AM1 study for rearrangement of the methoxy group in **7a** indicated significant N–N π-bond order, as well as negative charge upon the methoxy oxygen in the transition state. AM1 calculations on a series of molecules were carried out to explore further these facets of the migration. Table 2 gives gas-phase enthalpies of reaction as well as activation barriers for (**7b**). All reactions were predicted to be exothermic, the degree of exothermicity being roughly related to the electron donor capacity of the amino substituents (R″). Correspondingly, activation barriers reduced with increasing exothermicity in accordance with the Hammond postulate. Several trends are predicted. Firstly $\Delta H^{\ddagger}$ values increase through R″ = CH_3, CH_2Cl, $CHCl_2$ and CCl_3 or CF_3 in accord with the increasing group electronegativity. This increase would significantly lower the energy of the lone pair electrons on the amino nitrogen atom. Similarly, there is an increase in $\Delta H^{\ddagger}$ with the electron withdrawing ability of *para*-phenyl substituents (*p*-NH_2, H, Cl and NO_2). In addition, relative to dimethyl or dibenzyl substitution, acyl substitution in the form of methoxyacetyl, succinyl and diacetyl also raises the activation barrier for the rearrangement. It is notable that AM1 correctly predicts that rearrangement of hydrazine dimers **2** requires a higher enthalpy of activation than rearrangement of **1**; while the dimers are unstable, they can be isolated[2,3] whereas *N*-anilino-*N*-alkoxybenzamides have not been detected experimentally.[1]

For the substrates in Table 2 there is a correlation between the $\Delta H^{\ddagger}$ and the difference between the N–N bond order in the transition states and ground states. Higher bond orders correlate with lower activation energies and are found for those substituents with lowest electron withdrawing ability [Fig. 5(*a*)]. From our original AM1 study for rearrangement of **7a**, such N–N overlap should also correlate with incipient negative charge on the methoxy group in the transition state. Indeed, there is a similar correlation between $\Delta H^{\ddagger}$ values and the group charge on the methoxy group; lowest activation energies are found with greatest negative charge on the migrating group

Table 2 The effect of amine substituents, R″, on the $\Delta H_{reaction}$, $\Delta H_{activation}$ and ground-state geometries of *N*-methoxy-*N*-aminoacetamides, **7b** in Scheme 5[a]

R″	$\Delta H_{reaction}$/kJ mol^{-1}	$\Delta H_{activation}$/kJ mol^{-1}	*x*/deg[b]	*y*/deg[b]	*z*/deg[c]
p-Aminophenyl	−104	+133	108.0	119.7	5.8
Phenyl	−102	+138	109.0	118.0	4.5
p-Chlorophenyl	−99	+142	109.5	118.2	4.3
p-Nitrophenyl	−91	+151	110.7	116.5	2.9
Benzyl	−118	+104	96.3	120.0	11.8
Methyl	−80	+161	47.0	81.0	17.0
Acetyl and methoxy	−75	+174	63.4	65.4	1.0
Acetyl	−71	+205	106.0	80.0	13.0
Succinyl (cyclic)	−37	+193	79.4	108.9	14.8
Chloromethyl	−64	+182	26.6	116.7	45.1
Dichloromethyl	−56	+198	40.0	106.2	33.1
Trifluoromethyl	−79	+209	33.7	99.0	32.7
Trichloromethyl	−81	+223	53.7	93.5	19.9
Amino	−28	+204	66.7	64.9	0.9

[a] All values were calculated using the AM1 Hamiltonian of MOPAC. Only gas-phase values were compiled. [b] R″–N–N–O dihedral angles. [c] Deviation of bisector from the vicinal N–O plane (see Fig. 4).

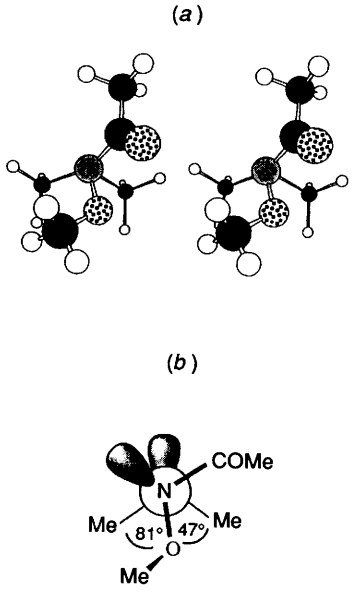


Fig. 2 (*a*) Stereoviews of *N*,*N*-dimethylamino-*N*-methoxyacetamide looking along the N–N bond; (*b*) Newman projection along the N–N bond

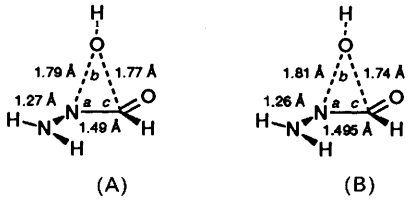


Fig. 3 Gas-phase transition states for migration of OH in **7d** as determined by (A) AM1 (MOPAC) where $a = 65.1°$, $b = 49.5°$ and $c = 65.1°$, and (B) 6-31G* (GAMESS) where $a = 63.3°$, $b = 48.2°$ and $c = 68.5°$

[Fig. 5(*b*)]. $\Delta H^{\ddagger}$ values also correlate inversely with the MeO–N bond length [Fig. 5(*c*)]. Examination of these correlations thus confirms that both large N–N bond order and negative charge build-up on the methoxy group are observed when the R groups are more electron donating. This makes sense if these groups inductively donate electron density to the amino nitrogen, raising the energy of the amide nitrogen lone pair in the ground state of the reactant and resulting in a better n_N–σ^*_{NO} anomeric interaction. Experimental evidence for these substituent effects has been reported for the decomposition of dimers (Scheme 2) where electron withdrawing groups on the

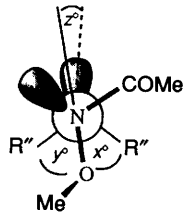


Fig. 4 Newman projection along the N–N bond in **7b**

alkoxy group (R′) and electron rich aromatics on the acyl functionality (R) promote decomposition.[2] The influence of the latter is more likely to be felt in promoting the anomeric interaction by raising the energy of the nitrogen lone pair since the computed transition states show virtually no increase in positive charge at the acyl carbon to which methoxy migrates.

While steric factors must play some role in determining the lowest energy rotamers (about the N–N bond), there is surprising consistency across the series **7b**. Analysis of dihedral angles in the optimised ground-state geometries (Fig. 4, Table 2) indicates a significant degree of coplanarity between the N-lone pair orbital and the N–Oσ (σ*)-bond. Greatest deviation was found for chloro-, dichloro- and trichloro- and trifluoromethylamino substrates whose group electronegativities would result in a weaker anomeric effect. Dihedral angles (Fig. 4) and deviations from the N–O σ* plane for the series are given in Table 2.

The Effect of Different Migrating Oxo Substituents.—The methyl substituent on the migrating oxygen disfavours migration relative to hydrogen and acetyl in accord with its $+I$ effect (Table 3). The rearrangement of an acetoxy group has the lowest $\Delta H^{\ddagger}$ of all the rearrangements we have simulated. This could in part be attributed to the ability of the acetyl carbonyl group to stabilise negative charge on the migrating oxygen. Furthermore, in the perturbation approach, $\sigma^*_{N\text{-}OAc}$ would be lower in energy than $\sigma^*_{N\text{-}OH}$ or $\sigma^*_{N\text{-}OMe}$ thus enhancing the interaction with the dimethylamino nitrogen lone pair. However the $\Delta H^{\ddagger}$ for migration of acetate is anomalously low and analysis of the transition-state properties reveals an N–OAc separation of 2.0 Å (bond order 0.22), a C(O)–OAc separation of 2.3 Å (bond order 0.03) and a total charge of −0.73 on the acetate group. Bond orders from the acetate carbon to the acetate oxygens are 1.32 and 1.56 which is indicative of anion delocalisation and the migration might best be depicted as shown in Scheme 6 where the transition state (Fig. 6) resembles more a diazenium–acetate ion pair. The high N–N bond order (1.59) also supports this proposal.

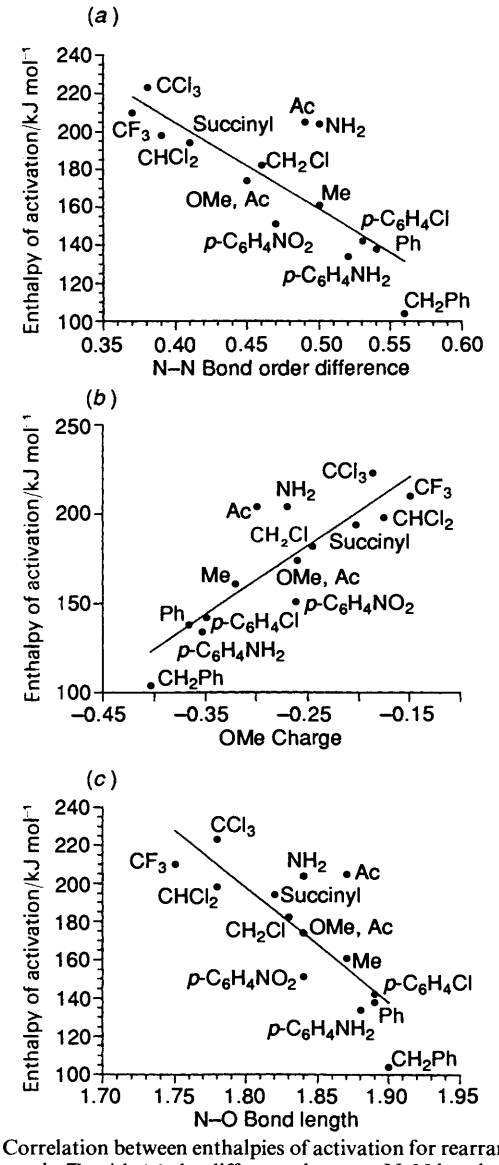
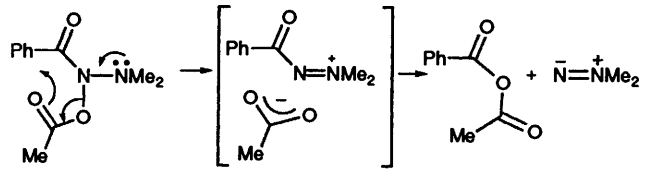


Fig. 5 Correlation between enthalpies of activation for rearrangement of methoxy in **7b** with (*a*) the difference between N–N bond orders of ground state and transition states; (*b*) methoxy-group charge in the transition states; (*c*) N–OMe bond length in the transition states



Scheme 6

Table 3 AM1 computed energies and transitition-state properties for the migration of oxo substituents in **7c**

Substrate (**7c**) R'	Gas phase $\Delta H_{reaction}$/ kJ mol^{-1}	Gas phase $\Delta H_{activation}$/ kJ mol^{-1}	Bond order N–N	Bond order N–C	OR charge
Me	−80	+161	1.45	0.81	−0.32
H	−117	+150	1.37	0.82	−0.28
Ac	−85	+57	1.59	0.88	−0.73

The Effect of Different Hetero Substituents upon Methoxy Migration.—The migration of methoxy should also be disfavoured by more electronegative heteroatom substituents on the amide nitrogen. Table 4 gives the enthalpies of reaction and activation enthalpies for series **10a–d** (Scheme 7) and indicates this to be the case; barriers to rearrangement are uniformly high when the atom bearing the lone pair is oxygen or chlorine. Such lone pairs would be lower in energy and therefore less likely to interact with the MeO–N σ* orbital. Similarly, hydroxy (**10c**) and acetoxy (**10d**) migrations are disfavoured when the other amide substituent is methoxy rather than the dimethylamino group. In the case of **10d** (X = OMe), the transition state for migration of acetoxy has much less acetate character as evidenced by the lower charge of −0.45 on the migrating group and bond orders from the acetoxy carbon to the acetoxy oxygens of 1.1 and 1.75. The migrating oxygen reverts to the 'normal' position; similar distances from the amide nitrogen and carbon and below the amide plane.

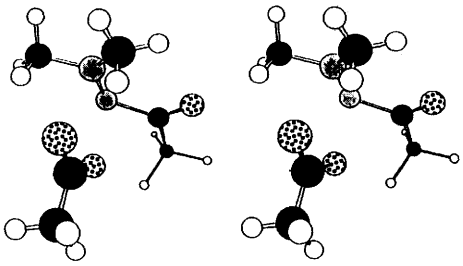
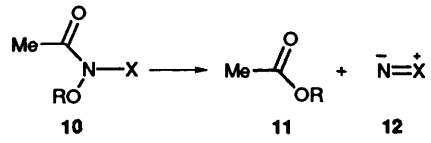


Fig. 6 Stereoviews of the transition state for acetoxy migration in **7c** (R' = Ac)



10 **11** **12**

a; R = Me, X = $N(Me)_2$, OEt, OAc, OH, Cl
b; R = Et, X = OMe
c; R = H, X = $N(Me)_2$, OMe
d; R = Ac, X = $N(Me)_2$, OMe

Scheme 7

The high barriers to rearrangement with two alkoxy substituents (**10a**, X = OEt and **10b**) on the amide nitrogen are supported by our observation that *N*,*N*-dialkoxybenzamides are relatively stable at room temperature and can be isolated from the solvolysis of *N*-alkoxy-*N*-chlorobenzamides in aqueous alcoholic solution.[3,5] They decompose thermally to give esters above 100 °C, however we have recently shown this to involve homolysis of the alkoxy O–N bond giving alkoxy and alkoxyamidyl radicals.[3] The latter are known to dimerise leading to intermediates (*e.g.*, **2**) which decompose to esters.

Interestingly, the migration of methoxy in **10a** (X = OH) and hydroxy group in **10c** (X = MeO) is disfavoured (Table 4) although results in these laboratories suggest that *N*-alkoxy-hydroxamic acids do rearrange intramolecularly to esters (Scheme 3).[4] We have also shown that the rearrangement is not acid-catalysed. Furthermore, the product of solvolysis of mutagenic *N*-acetoxy-*N*-alkoxybenzamides in alkaline aqueous/organic solution is exclusively ester and their formation has been shown to be intramolecular by crossover experiments.§[,12] The rearrangement of *N*-alkoxy-*N*-hydroxyamides to esters therefore most probably occurs in the conjugate base form of the hydroxamic acid. While the lone pair in the hydroxamic

§ Base solvolysis of a mixture of benzyl *N*-acetoxybenzohydroxamate and butyl *N*-acetoxy-*p*-chlorobenzohydroxamate in aqueous acetonitrile gives only benzyl benzoate and butyl *p*-chlorobenzoate as product esters.

Table 4 $\Delta H_{reaction}$, $\Delta H_{activation}$ for migration of oxo substituents in **10a–d** which have different heteroatom substituents on the amide nitrogen

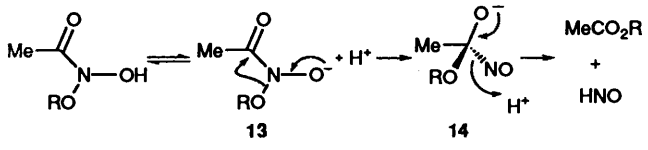
Substrate (**10**)		Gas phase		Solution phase	
R	X	$\Delta H_{reaction}$/kJ mol^{-1}	$\Delta H_{activation}$/kJ mol^{-1}	$\Delta H_{reaction}$/kJ mol^{-1}	$\Delta H_{activation}$/kJ mol^{-1}
Me	$N(Me)_2$	−80	+161	−140	+126
	OEt	+22	+215	−14	+197
	OAc	+51	+251	+17	+236
	OH	+58	+273	+25	+220
	Cl	+167	+280	+131	+265
	O^-	+64	+26	*a*	*a*
Et	OMe	+33	+232	−7	+208
H	$N(Me)_2$	−116	+150	−159	+130
	OMe	+20	+237	+3	+226
Ac	$N(Me)_2$	−85	+58	−137	+43
	OMe	+21	+195	+3	+142

[a] Not determined.

Table 5 $\Delta H_{reaction}$, $\Delta H_{activation}$ for migration of other hetero-substituents in **15a–c**

Substrate (**15**)		Gas phase		Solution phase	
X	Y	$\Delta H_{reaction}$/kJ mol^{-1}	$\Delta H_{activation}$/kJ mol^{-1}	$\Delta H_{reaction}$/kJ mol^{-1}	$\Delta H_{activation}$/kJ mol^{-1}
$N(Et)_2$	$N(Me)_2$	−39	+170	−102	+130
$N(Me)_2$	$N(Et)_2$	−45	+164	−108	+126
	SMe	+59	+215	−30	+215
	Cl	+239	+305	+210	+298
	OAc	+70	+170	+40	+165
	OH	+47	+159	+26	+158
	OMe	+45	+164	+23	+158
Cl	$N(Me)_2$	+9	+96	−33	+29
	OMe	+62	+194	+51	+141
	SMe	+62	+137	−15	+77
SMe	Cl	+356	+417	+335	+411
	$N(Me)_2$	+124	+211	+76	+176

acid hydroxy oxygen would be tightly bound (leading to a weak n_{OH}–σ^*_{MeO-N} interaction), the anion would possess a high energy pair of electrons thus enhancing the anomeric effect. In support of this, rearrangement of the anion **13** to intermediate **14** is predicted to be exothermic by 60 kJ mol^{-1} and to proceed with a low activation barrier of just 26 kJ mol^{-1} (Scheme 8).

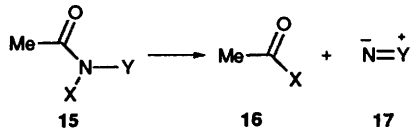


13 **14**

Scheme 8

Participation of the anionic species accords with our observation that ester formation in acidic conditions only competes with acid-catalysed reaction pathways at low acid concentrations.[4c] It also explains why benzoic acids, formed through the alternative rearrangement in these species, namely N-to-C-migration of hydroxy, have not been observed as a significant product in either acid-catalysed solvolysis[4b] or base hydrolysis reactions of *N*-acetoxy-*N*-alkoxybenzamides.[12]

Migration of Other Heteroatom Substituents.—Chlorination of β,β-dialkylbenzhydrazides with *tert*-butylhypochlorite results in acylation of the hydrazide at the α-nitrogen atom (Scheme 4). This suggests that α-chlorination results in the formation of an acylating agent such as benzoyl chloride. Like the rearrangement of *N*-amino-*N*-alkoxyamides, the rearrangement shown in Scheme 4 would also be facilitated by the n_N–σ^*_{Cl-N} anomeric interaction. AM1 calculations support this assertion. While the rearrangement of α-chloroacethydrazide **15b** (Y = NMe_2) to acetyl chloride and 1,1-diazene is predicted to be endothermic in the gas phase, it has a lower $\Delta H^‡$ than the migration of methoxy (Table 5). The reaction is predicted to be exothermic in solution phase with a low activation barrier of only 29 kJ mol^{-1}. The transition-state geometry for the migration is similar to those found for oxygen migration; while the N–Cl and Cl–C(O) bonds are longer, the bond orders to both atoms are significant (*ca.* 0.25). By AM1 the amino lone pair assistance is predicted to result in rearrangement rather than simple heterolysis to the diazenium chlorides. The pathway indicated in Scheme 9 is predicted to be the source of α,α-diacyl-



15 **16** **17**

a; X = NMe_2, Y = NEt_2, SMe, Cl, OAc, OH, OMe
b; X = Cl, Y = NMe_2, OMe, SMe
c; X = SMe, Y = Cl, $N(Me)_2$

Scheme 9

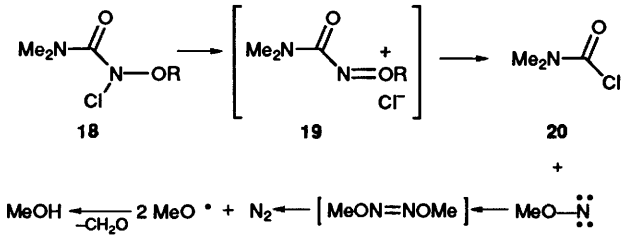
Table 6 Important transition state geometrical parameters for the migrations of X in CH_3CONXY

X	Y	N–C(O) bond length/Å	N–X bond length/Å	C(O)–X bond length/Å	X–N–C(O) angle/deg	N–C(O)–X angle/deg	N–X–C(O) angle/deg	N–Y bond length/Å	N–Y bond order
OMe	$N(benzyl)_2$	1.47	1.90	1.92	68.1	66.5	45.4	1.26	1.50
	$N(p\text{-aminophenyl})_2$	1.48	1.88	1.91	68.1	66.0	45.9	1.27	1.45
	$N(phenyl)_2$	1.48	1.89	1.86	65.7	67.7	46.6	1.27	1.47
	$N(p\text{-chlorophenyl})_2$	1.48	1.89	1.86	65.7	67.7	46.6	1.27	1.46
	$N(p\text{-nitrophenyl})_2$	1.49	1.84	1.81	65.0	66.8	48.1	1.28	1.39
	$N(methyl)_2$	1.48	1.87	1.84	65.6	67.4	47.0	1.27	1.45
	N-acetyl-N-methoxy	1.49	1.84	1.80	64.4	67.5	48.1	1.28	1.39
	$N(chloromethyl)_2$	1.50	1.83	1.76	63.0	67.8	49.2	1.27	1.39
	N-succinyl	1.51	1.82	1.72	61.2	68.3	50.4	1.28	1.33
	$N(dichloromethyl)_2$	1.51	1.78	1.72	62.3	66.8	50.9	1.28	1.33
	$N(acetyl)_2$	1.50	1.87	1.76	61.9	69.2	48.9	1.27	1.41
	$N(amino)_2$	1.50	1.84	1.75	62.2	68.6	49.2	1.28	1.42
	$N(trifluoromethyl)_2$	1.54	1.75	1.70	61.7	65.5	52.8	1.27	1.33
	$N(trichloromethyl)_2$	1.52	1.78	1.73	62.8	66.1	51.1	1.28	1.33
	OEt	1.51	1.78	1.64	59.2	68.4	52.4	1.22	1.43
	OAc	1.56	1.76	1.56	55.4	68.8	55.8	1.23	1.36
	OH	1.59	1.79	1.55	54.3	69.6	56.1	1.24	1.37
	O^-	2.30	2.08	1.49	78.3	62.3	39.4	1.17	
	Cl	1.91	1.41	1.54	52.8	46.5	80.7	1.67	1.00
OEt	OMe	1.55	1.76	1.59	56.9	68.1	55.0	1.25	1.34
OH	NMe_2	1.49	1.77	1.82	67.3	63.7	49.0	1.28	1.37
	OMe	1.53	1.73	1.58	57.8	67.3	54.9	1.23	1.39
OAc	NMe_2	1.48	2.00	2.34	83.4	57.8	38.8	1.26	1.59
	OMe	1.51	1.96	1.75	58.7	73.6	47.7	1.20	1.60
NEt_2	NMe_2	1.59	1.83	1.49	51.0	72.8	56.2	1.25	1.50
NMe_2	NEt_2	1.58	1.80	1.50	52.0	71.5	56.4	1.26	1.53
	SMe	2.55	1.79	1.46	34.0	43.3	102.8	1.47	1.76
	Cl	2.72	2.08	1.43	31.1	48.6	100.3	1.59	1.31
	OAc	2.62	1.91	1.45	32.7	45.3	102.0	1.20	1.55
	OH	2.60	1.85	1.45	32.9	43.8	103.3	1.21	1.49
	OMe	2.58	1.79	1.46	33.3	42.3	104.4	1.21	1.52
Cl	NMe_2	1.49	2.35	2.29	69.3	73.4	37.3	1.25	1.60
	OMe	1.59	2.49	2.02	53.8	86.7	39.5	1.20	1.64
	SMe	1.43	2.25	2.35	76.0	67.9	36.1	1.43	1.65
SMe	Cl	1.44	2.40	1.89	52.1	91.0	36.9	1.63	1.11
	NMe_2	1.79	2.57	1.87	46.7	89.1	44.2	1.22	1.79

β,β-dialkylhydrazines. It is likely though that diazenium chlorides, if formed in solution would also behave as acylating agents.

By analogy with alkoxy migration, chlorine migration in **15b** is disfavoured by amide substituents of greater electronegativity than nitrogen, such as oxygen; methoxy substitution results in a higher activation enthalpy and the reaction is predicted to be more endothermic. This is consistent with the fact that *N*-chlorohydroxamic esters are readily isolated from the treatment of hydroxamic esters with chlorinating agents such as *tert*-butyl hypochlorite. These intermediates are used in the synthesis of mutagenic *N*-acetoxy-*N*-alkoxybenzamides.[4] Rudchenko and co-workers[8] have reported that *N*-alkoxy-*N*-chloroureas (**18**) are relatively stable but decompose slowly in CCl_4 to carbamoyl chlorides (**20**) and methanol. These authors proposed initial formation of **19** which decomposes to the acyl chloride and methoxynitrene according to Scheme 10, however our calculations suggest that intramolecular rearrangement of chlorine from N to C is more likely. The influence of thiomethyl upon chlorine migration is less clear.

Migration of amino groups in *N*,*N*-diaminoacetamides is predictably a favourable process. Migrations are found to be exothermic with similar activation energies to those for the migration of alkoxy groups in *N*-amino-*N*-alkoxyamides. The



Scheme 10

activating effect diminishes with *N*-chloro substitution. This accords with the fact that chloro most probably migrates in preference to amino upon chlorination of β,β-dialkylhydrazides. Surprisingly, while being thermodynamically much less favourable, gas-phase migration of dimethylamino in **15a** (Y = OMe and OH) is predicted to be competitive with methoxy and hydroxy migration (Table 3). However, COSMO predicts the latter migrations to be significantly more facile in solution state.

The results with thiomethyl are difficult to interpret. It is clear though that chlorine would migrate in preference to thiomethyl in **15** (X = Cl, Y = SMe) but the preference for thioester or

amide formation from migrations in **15** (X = SMe, Y = NMe_2) would appear to be dependent upon the phase.

Conclusions

The migration of heteroatom substituents from nitrogen to carbon in *N,N*-bisheteroatom-substituted amides is predicted to be favourable whenever the substituent not migrating is an amino group. Under these circumstances, oxo and chloro substituents are predicted to migrate in accordance with experimental findings.

The migration probably involves overlap between a lone pair of electrons on the non-migrating group with the σ* orbital between N and the migrating group. This is energetically most favourable when the interacting orbitals are closest in energy, as is the case with a nitrogen lone pair and the σ* orbital between the amide nitrogen and a more electronegative atom such as oxygen and chlorine. Conformational preferences in the ground state of the *N,N*-bishetero-substituted amides appear to favour this orbital overlap and anomeric effect.

The energy of the transition states for migration is clearly lowered with electron donor substituents on the amide amino substituent; transition states of favourable rearrangements display high N–N double-bond character as well as a build-up of negative charge on the migrating group and have little 1,1-diazene character.

Calculations on *N,N*-dioxo-substituted amides show that for this class of compounds the migration is disfavoured. The conjugate base of *N*-alkoxyhydroxamic acids is thus more likely to be the origin of rearrangement in these species.

Since the carbonyl appears to play a minor role in these reactions, HERON rearrangements may also be possible with other π-systems and we intend investigating such processes by both experimental and theoretical means.

Experimental

Semiempirical calculations were performed using the AM1 Hamiltonian of MOPAC 93.[6] Force calculations were run on all calculated geometries of reactants and products to ensure

Table 7 AM1 ΔH_f for ground states of reactants and products, and transition states for rearrangement of CH_3CONXY to CH_3COX and N–Y

		Ground state		Transition state		CH_3COX		N–Y	
X	Y	Gas phase ΔH_f/kJ mol^{-1}	Solution phase[a] ΔH_f/kJ mol^{-1}	Gas phase ΔH_f/kJ mol^{-1}	Solution phase[a] ΔH_f/kJ mol^{-1}	Gas phase ΔH_f/kJ mol^{-1}	Solution phase[a] ΔH_f/kJ mol^{-1}	Gas phase ΔH_f/kJ mol^{-1}	Solution phase[a] ΔH_f/kJ mol^{-1}
OMe	$N(benzyl)_2$	231.30		335.44		−381.34	−438.17	494.48	
	$N(p\text{-aminophenyl})_2$	264.28		397.71				541.58	
	$N(phenyl)_2$	280.13		418.32				559.35	
	$N(p\text{-chlorophenyl})_2$	221.12		363.34				503.59	
	$N(p\text{-nitrophenyl})_2$	315.07		466.28				605.82	
	$N(Me)_2$	−29.44	−74.79	131.81	51.01			271.47	223.09
	N-acetyl-N-methoxy	−183.41		−9.15				123.31	
	$N(chloromethyl)_2$	−105.45		76.77				212.00	
	N-succinyl	−299.59		−106.41				45.05	
	$N(dichloromethyl)_2$	−134.71		63.10				190.46	
	$N(acetyl)_2$	−302.70		−97.58				7.22	
	$N(amino)_2$	163.32		367.49				517.03	
	$N(trifluoromethyl)_2$	−1233.58		−1024.10				−931.17	
	$N(trichloromethyl)_2$	−94.70		128.10				205.79	
	OEt	−249.25	−290.50	−33.82	−93.61			153.79	134.13
	OAc	−381.76	−447.30	−131.07	−210.89			50.48	8.06
	OH	−262.24	−318.00	10.72	−97.48			177.22	145.26
	O^-	−343.53		−317.38				101.89	
	Cl	−85.86	−127.00	194.04	137.68			462.94	442.43
OEt	OMe	−249.25	−290.50	−17.71	−82.54	−405.04	−464.08	188.62	166.77
OH	NMe_2	−43.12	−98.93	107.25	31.44	−431.12	−481.42	271.47	223.09
	OMe	−262.24	−318.00	−24.84	−91.84			188.62	166.77
OAc	NMe_2	−192.33	−250.70	−134.46	−207.56	−549.29	−611.19	271.47	223.09
	OMe	−381.76	−447.30	−186.55	−305.14			188.62	166.77
NEt_2	NMe_2	89.12	61.21	258.80	191.28	−221.28	−263.56	271.47	223.09
NMe_2	NEt_2	89.12	61.21	252.63	186.74	−173.30	−218.61	217.23	171.83
	SMe	−17.42	−59.80	197.36	154.73			215.15	128.50
	Cl	50.53	14.02	355.17	311.89			462.94	442.43
	OAc	−192.33	−250.69	−22.24	−85.51			50.48	8.06
	OH	−43.12	−98.93	115.86	58.94			177.22	145.26
	OMe	−29.44	−74.79	134.86	83.25			188.62	166.77
Cl	NMe_2	50.53	14.02	146.12	43.05	−212.17	−242.39	271.47	233.09
	OMe	−85.96	−127.00	108.52	14.48			188.62	166.77
	SMe	−58.88	−99.24	77.90	−22.32			215.15	128.50
SMe	Cl	−58.88	−99.24	357.76	311.59	−165.42	−206.95	462.94	442.43
	NMe_2	−17.42	−59.80	193.69	116.56			271.47	223.09

[a] Solution-phase energies determined using the COSMO option within MOPAC.

that they corresponded to energy minima on the potential energy surface (all real force constants).

The approximate transition state for the rearrangement of *N*-dimethylamino-*N*-methoxyacetamide to 1,1-dimethyldiazene and methyl acetate was located on the potential energy surface through a grid search in which the angle O–C(O)–N and the C(O)–N bond were the reaction coordinates. Refinement was completed using the TS routine within MOPAC (TS will find the transition-state structure if a sufficiently good guess is used as the initial geometry[13]). Most other transition states were located by first starting with the optimised 'reactant' structure and restricting the important bond lengths and angles to values similar to those observed for the transition state from the initial study. The restricted structure was optimised to produce a 'guess' for the transition state which was refined with all restrictions removed using the TS routine of MOPAC. This procedure has been reported to be more reliable than routines such as SADDLE for locating transition states.[13b]

When the above method failed to locate a transition state, the X–N–CO bond angle (X being the migrating atom) was altered systematically and the resulting structures were examined to try to locate a better 'guess' structure, which could be optimised with TS. When compared with other internal coordinates the X–N–C bond angle change going from 'reactant' structure to transition-state structure was significant and so was used to represent an approximate reaction coordinate. Altering the reaction coordinate is an accepted method for locating the transition state.[13b] In the few cases where this method also failed to locate a transition state, both the bond angle and the N–C bond length were varied producing a variety of structures from which to choose 'guess' structures, however this method was not always successful and transition states for some reactions could not be modelled. All transition-state structures were verified by force calculations to have exactly one imaginary force constant.

Gas-phase calculations were done for all compounds. The COSMO routine available in MOPAC was also used for some compounds to calculate the geometry and energies in a solution-like environment. COSMO models the solvent as a uniform dielectric medium with the solute in a solvent-accessible cavity.[10] A relative permittivity of 32 and a solvent radius (RSOLV) of 1.4 were used to simulate properties in methanol. The corresponding gas-phase geometry was used as the starting structure for the COSMO optimisation for both stable states and transition states. COSMO calculations can lead to unacceptably large values for the gradient norms (greater than 5), however these were for most part less than unity and in only two instances were they greater than two (2.9 and 3.3). ΔH_f for ground states, products and transition states are presented in Table 7, while important transition state geometrical parameters are listed in Table 6.

The $\Delta H_{reaction}$ for hydroxy migration in *N*-hydroxy-*N*-aminoformamide, **7d** of Scheme 5, was also modelled by *ab initio* methods at the 6-31G* level using GAMESS. Hessian calculations were run on these structures to ensure that local minima or saddle points had been located. The solution environment was modelled using the SCRF routine available in GAMESS which models the solvent environment as a uniform dielectric medium with a spherical cavity for the solute molecule. The size of the cavity was determined using the greatest internuclear distance as described by Wiberg[14] and a relative permittivity for methanol of 32 was used. The gas-phase transition state for the methoxy migration was also modelled.

Acknowledgements

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