Conformational Stereochemistry of the HERON Amide, *N*-Methoxy-*N*-dimethylaminoformamide: A Theoretical Study

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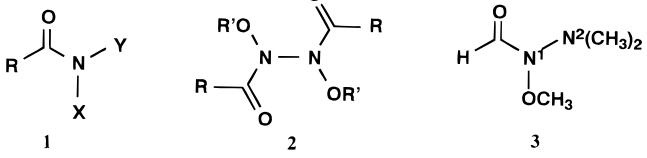
The stereochemistry and energetics of conformational interconversions of the bisheteroatom-substituted (HERON) amide, *N*-methoxy-*N*-dimethylaminoformamide **3**, have been investigated by ab initio methods at the B3LYP/6-31G* level. Four diastereomeric minima and 17 transition structures for conformational interchange were located. Ranges for barriers, in kJ mol^{-1}, are as follows: N−CO rotation, 53−60; N−N rotation, 51−60; N−O rotation, 27−50; amino N inversion, 19−27. The factors determining the structural details and barrier heights, namely, acyl conjugation, substituent electronegativity, four-electron repulsions, and anomeric effects, are discussed.

Introduction

Amides which are substituted by two electronegative heteroatoms at nitrogen, **1**, have physical and chemical properties quite different than those of normal amides or amides, such as hydroxamic acids, bearing one heteroatom. The properties of such amides are largely a consequence of three electronic features, and these affect both the structure of the amides and their reactivity. Two influences control the pyramidality at nitrogen; the normal tendency to delocalize the lone pair into the carbonyl which is best served by sp^2 hybridized nitrogen is opposed by the combined electronegativity of the heteroatom substituents. The electronic demand of X and Y is best satisfied by sp^3 hydridization at nitrogen since this places covalent electron density closer to their nuclei. Such amides should exhibit a lower degree of amide resonance and therefore display higher carbonyl stretch frequencies in their infrared spectra, as well as reduced barriers to *E*/*Z* isomerization. In addition to the above-mentioned effects, the XNY configuration may support



1 **2** **3**

anomeric effects, otherwise known as negative hyperconjugation; a nonbonded electron pair of one heteroatom may donate into the low-lying antibonding orbital of the other heteroatom's bond to the nitrogen and vice versa (Figure 1). If Y is the donor, this should lead to a weaker and longer N−X bond and a shorter N−Y bond. It is noteworthy that the two anomeric effects are in competition; lengthening of the N−X bond reduces the donor ability of X, and shortening the N−Y bond raises its antibonding orbital, thereby decreasing the acceptor ability of the N−Y bond. In general, the stronger donor, say Y, will dominate the anomeric interaction. This also results in increased barriers to rotation about the N−Y

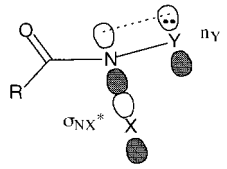


Figure 1. Anomeric overlap in XNY systems.

bond. Furthermore, where such anomeric donation is strong, elimination of X or reactions involving rearrangement of X may be observed. We have explored theoretically (B3LYP/6-31G*) the structural characteristics of several members of this class of amides and have confirmed the operation of anomeric effects as well as pyramidalization at nitrogen.[1] In a comprehensive review, we recently focused on the relative anomeric effects and theoretical, spectroscopic, and chemical properties of a number of different classes of bisheteroatom-substituted amides including *N*,*N*-dialkoxyamides (ONO systems), *N*-acyloxy-*N*-alkoxyamides (AcONO systems), *N*-alkoxy-*N*-haloamides (ONX systems), *N*-amino-*N*-chloroamides (ClNN systems), and *N*-alkoxy-*N*-aminoamides (NNO systems).[2] NNO amides form a particularly interesting member of this series. The *N*-alkoxy-*N*-methylanilinobenzamides, **4**, were first encountered in the reaction of mutagenic *N*-acetoxy-*N*-alkoxybenzamides and *N*-methylaniline (Scheme 1).[3] In methanol, S_N2 reaction at the amide nitrogen and displacement of acetate results in the formation of **4** which are unstable intermediates and which undergo a concerted migration of the alkoxy group to form benzoate esters and a 1,1-diazene. We have called these novel reactions, involving HEteroatom Rearrangements On Nitrogen, HERON rearrangements.[4] Amides of the type **1** which can undergo this rearrangement may collectively be called HERON amides.

Extensive molecular orbital studies have been carried out which support the concerted nature of the process

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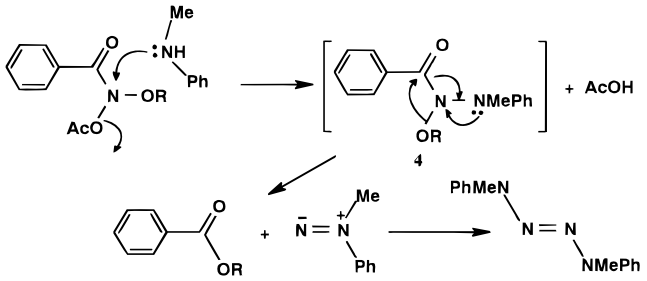
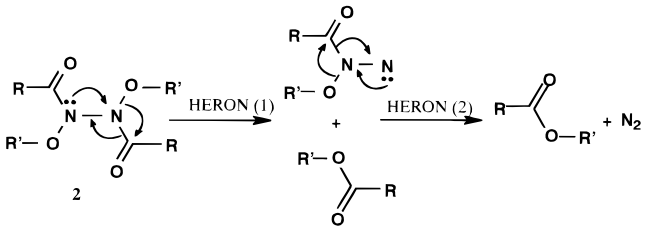
Scheme 1



Scheme 2



and point to the important structural elements that are necessary for it to occur.[4,5] The rearrangement is driven by the strength of the anomeric overlap of the high energy nitrogen lone pair, n_N, and the low energy antibonding orbital σ_{NO}*.

The analogues of **4**, *N*,*N*′-diacyl-*N*,*N*′-dialkoxyhydrazine derivatives, **2**, where the *N*-amino group bears both an acyl and an alkoxy group are more stable but undergo two consecutive HERON reactions (Scheme 2) giving two molecules of ester and a molecule of nitrogen.[5−7] In addition to this unusual reactivity, the hydrazines exhibit uniformly high carbonyl stretch frequencies in their infrared spectra as well as high N−N and low N−CO rotational barriers, both of which can be measured by dynamic NMR spectroscopy. The series of *N*,*N*′-diacetyl-*N*,*N*′-dibenzyloxyamides (**2**, R = CH_3, R′ = CH_2Ar) exhibit two carbonyls, one in the range of 1700−1723 cm^{-1} and one at higher frequency between 1733 and 1744 cm^{-1}.[2] Free energy barriers for rotation about the N−N and N−CO bonds are estimated to be in the range of 70 and 54 kJ mol^{-1}, respectively.[2,8] These spectroscopic measurements support the qualitative predictions outlined above.

In an extension of our previous studies,[1,2] density functional calculations have been used to fully explore the stereoisomerism in the model NNO system, *N*-(dimethylamino)-*N*-methoxyformamide **3**, with a view to evaluating the barriers to conformational change and other stereochemical features; in addition to reduced amide isomerization barriers and restricted rotation about the N−N bond through the anomeric effect, NNO amides may also invert at both nitrogens as well as rotate about the N−O bond.

Methods

All structures were fully optimized at the B3LYP/6-31G* level of theory using procedures implemented in Gaussian 94.[9] Harmonic frequency analysis was performed to provide zero point energy corrections to the relative energies and to verify the nature of each stationary point as a minimum (all real frequencies) or as a transition structure (exactly 1 imaginary frequency).

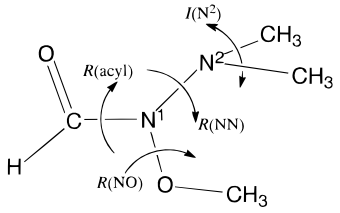


Figure 2. Definitions of the conformational interconversions discussed in the text.

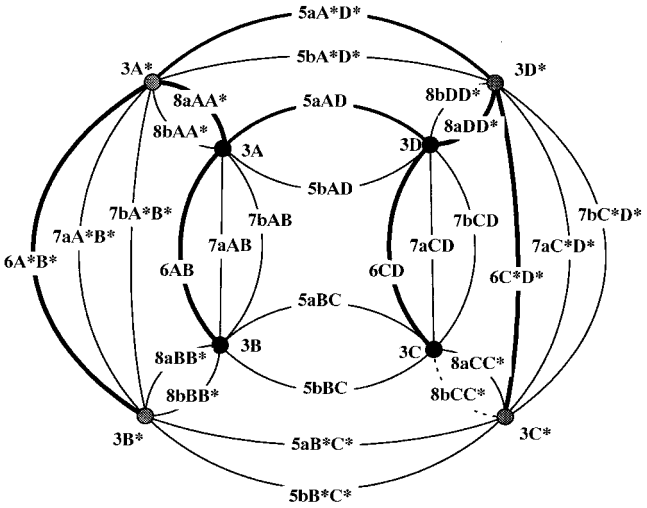


Figure 3. Total graph of interconversions. Structure labels at vertexes indicate minima (Figure 4); labels on connecting lines are transition structures (Figures 5−8). Heavy lines denote lowest energy pathways.

Results and Discussion

Stereochemistry. *N*-Dimethylamino-*N*-methoxyformamide **3** has four largely independent conformational degrees of freedom (see Figure 2): *R*(acyl), the rotation about the acyl C−N bond; *R*(NN), rotation about the N−N bond; *R*(NO), rotation about the N−O bond; and *I*(N^2), inversion at the N atom of the dimethylamino group. There is a possible fifth degree of freedom, inversion at the acylated N atom, N^1. This center is a shallow pyramid and is formally the only stereogenic center in **3**. However, *I*(N^1) is coupled to *R*(NO) and does not give rise to additional conformations. *R*(NN) and *I*(N^2) connect the same two conformations, albeit via different transition structures. One therefore expects that there are a maximum of eight stereoisomers consisting of four enantiomeric pairs of diastereomers. The complete graph of pathways interconnecting the eight stereoisomers of **3** is shown in Figure 3. The structures of the four diastereomers which have the (*R*) absolute configuration

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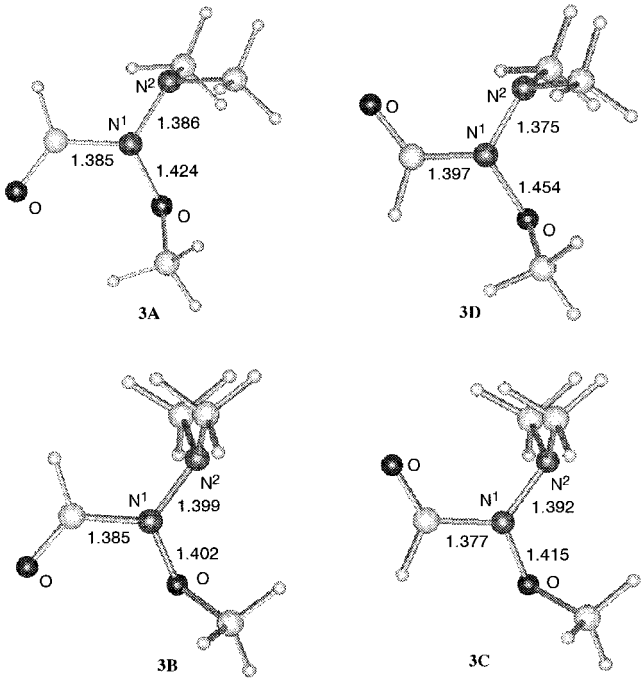


Figure 4. Minimum energy structures of **3**: large and small white balls are C and H, respectively. Bond lengths are in Å.

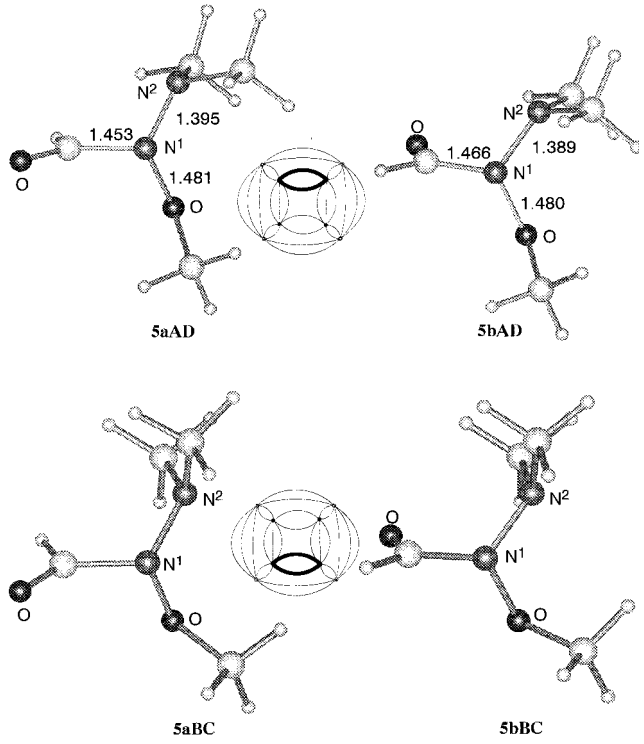


Figure 5. Transition structures for N−CO rotation (*R*(acyl)): large and small white balls are C and H, respectively. Bond lengths are in Å.

at N^1 are shown in Figure 4 and are labeled **3A**, **3B**, **3C**, and **3D**. These are designated by the filled black circles in Figure 3. Their enantiomers are designated **3A***, **3B***, **3C***, and **3D***, respectively, in Figure 3. The transition structures generated by *R*(acyl) are designated **5aAD**, **5bAD**, **5aBC**, and **5bBC** in Figure 3 and are shown in Figure 5. The lower case **a** and **b** identify the lower and higher energy pathways, respectively, and the pair of

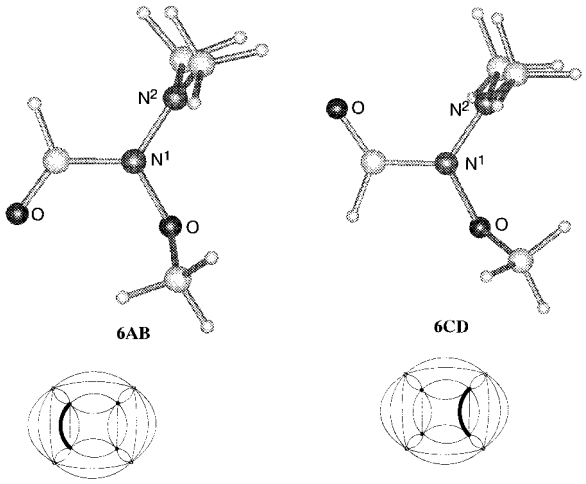


Figure 6. Transition structures for pyramidal inversion at N^2 ($I(N^2)$): large and small white balls are C and H, respectively.

capital letters indicate that, for instance, **5aBC** connects structures **3B** and **3C** (by the less hindered pathway). $I(N^2)$ generates two transition structures, **6AB** and **6CD**, where again the capital letters denote the pair of minima separated by the transition structures. The structures are shown in Figure 6 and the pathways are so labeled on the graph in Figure 3. *R*(NN) connects the same pair of diastereomers as $I(N^2)$ but by two diastereomeric pathways. It generates transition structures **7aAB**, **7bAB**, **7aCD**, and **7bCD**, which are shown in Figure 7. *R*(NO) interconnects pairs of enantiomers (through rotation and inversion at N^1) by structures **8aAA***, **8bAA***, **8aBB***, **8bBB***, **8aCC***, **8bCC***, **8aDD***, and **8bDD***, shown in Figure 8.

The total B3LYP/6-31G(D) energies in hartrees of the four stable structures and 18 transition structures are listed in Table 1, together with the relative energies in kJ mol^{-1}. These are discussed in greater detail below.

Stable Conformations: 3A, 3B, 3C, and 3D (Figure 4). All stable conformations of **3** have the following in common: the formyl group is turned into conjugation with the amide nitrogen atom, N^1, which forms a shallow pyramid; the more strongly pyramidal dimethylamino nitrogen atom, N^2, is oriented so as to place the nonbonded electron pairs of the two nitrogen atoms into each other's nodal plane; and the methoxy group is oriented so that the C−O bond is quasiperpendicular to the average plane at N^1 with the methyl group turned *exo* to the pyramid rather than *endo* to it. The quasiperpendicular geometry of the methoxy group also places the higher lone pair of the oxygen atom into the nodal plane of the lone pair at N^1. Thus the equilibrium structures are determined by the requirement to maximize the stabilizing conjugation of the electron pair at N^1 with the acyl group and to minimize the destabilizing lone pair−lone pair interactions between N^1 and N^2 and between N^1 and O (of methoxy). The most stable structure is **3A**. Structures **3C** and **3D** are higher by 5.5 and 6.4 kJ mol^{-1}, respectively. The least stable is **3B** (+22.2 kJ mol^{-1}). An important secondary stabilizing interaction is apparent in the structures, namely, an $n-\sigma^*$, or *anomeric*, interaction between a nonbonded electron pair, n, of a donor atom and the empty antibonding σ orbital, σ^*, α to the donor. In **3**, two such interactions are possible, $n_N-\sigma_{NO}^*$ and $n_O-\sigma_{NN}^*$. The former is preferred since n_N is a better

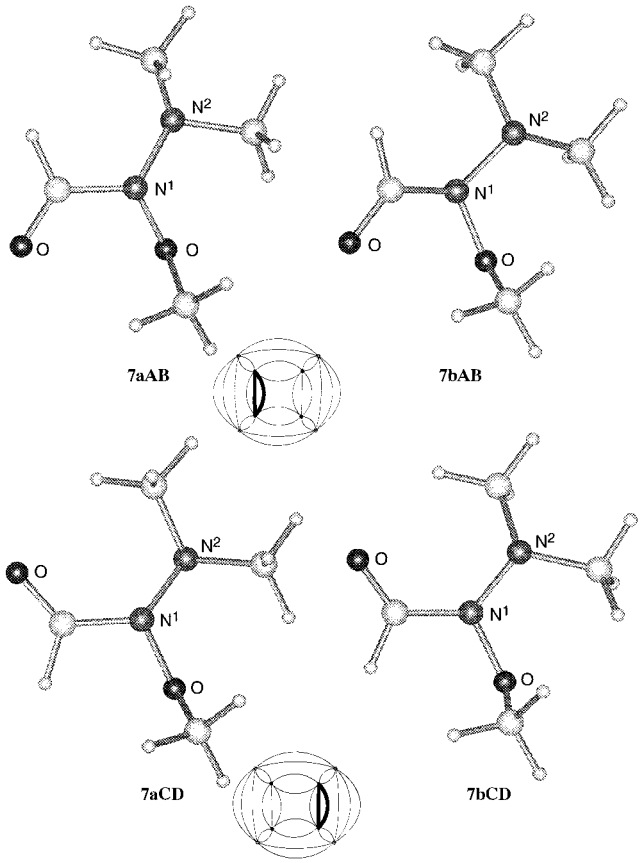
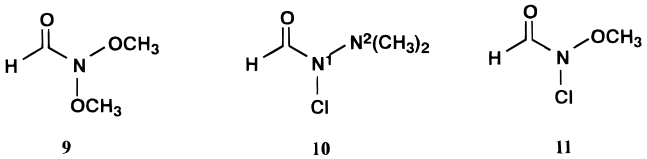


Figure 7. Transition structures for rotation about the N−N bond (*R*(NN)): large and small white balls are C and H, respectively.

donor than n_O and σ_{NO}* is a better acceptor than σ_{NN}*. In structures **3A** and **3D**, n_N (of N^2) is aligned in the favorable *anti* orientation to the N^1−O bond. The dominance of the $n_N-\sigma_{NO}$* interaction is apparent in the elongated N^1−O bond and shortened N^1-N^2 bond. In structures **3B** and **3C**, the alignment of n_N (of N^2) is the less desirable *syn* orientation to the N^1−O bond. As a consequence, the dominant anomeric interaction is $n_O-\sigma_{NN}$*, with concomitant shortening of N^1−O and lengthening of N^1-N^2.

Analysis of the properties of the lowest energy conformation with those previously reported for *N*,*N*-dimethoxyformamide **9**, *N*-dimethylamino-*N*-chloroformamide **10**, and *N*-methoxy-*N*-chloroformamide **11**, at the B3LYP/6-31G* level indicates that the amide nitrogen is slightly less pyramidal <116°> than in **9** <115°>, **10** <112°>, and **11** <113°>. The N−CO bond length (1.385 Å) is consequently shorter than that of **9** (1.396 Å), **10** (1.418 Å), and **11** (1.410 Å). Formamide has a calculated bond length of 1.362 Å, close to the experimentally determined



value of 1.352 Å[10] and a twisted, nonconjugated amide with a fully sp^3 hybridized nitrogen atom has recently been reported to have an N−CO bond length of 1.475 Å.[11] Thus anomeric (HERON) amides **3** and **9**−**11** should all exhibit significantly reduced though not complete loss of conjugation. Relative to **9** (1.407 Å), the N−O bond (1.424 Å) is significantly longer and is reflective of the stronger $n_N-\sigma_{NO}$* interaction. The N−N bond of **10** (1.309 Å) is shorter than that of **3** (1.386 Å), confirming that the anomeric interaction of **3** lies between that in **9** and **10**. The donor amino nitrogen N^2 in **10** ⟨117°⟩ is also more planar than that in **3** ⟨113°⟩.

Interconversions. By *R*(acyl): (*exo*,*Z*,*R*)-3A ⇆ (*exo*,*E*,*R*)-3D and (*endo*,*Z*,*R*)-3B ⇆ (*endo*,*E*,*R*)-3C. There are two pathways for the interconversion of (*exo*,*Z*,*R*)-**3A** and (*exo*,*E*,*R*)-**3D** by *R*(acyl), depending on whether the acyl group rotates clockwise or counterclockwise. The two transition structures, **5aAD** and **5bAD**, are shown in Figure 5, and the energies are listed in Table 1. Relative to (*exo*,*Z*,*R*)-**3A**, the respective pathways require 52.8 and 61.9 kJ mol^{-1} activation energy. The lowest barrier is higher than those computed for **9**−**11** (30−50 kJ mol^{-1})[1] but significantly smaller than those for formamide (75 kJ mol^{-1}) or methoxyformamide (67 kJ mol^{-1}). The experimentally determined $\Delta G^{\ddagger}$ for amide isomerization in the related hydrazines **2** is ∼54 kJ mol^{-1}.[2,8] There are also two pathways for the interconversion of (*endo*,*Z*,*R*)-**3B** and (*endo*,*E*,*R*)-**3C** by *R*(acyl), with activation barriers of 65.0 and 69.8 kJ mol^{-1} (relative to **3C**), via transition structures identified as **5aBC** and **5bBC** in Table 1 and Figure 5. In each case, the lower energy pathway has the formyl H atom in the *endo* position relative to the shallow pyramid at N^1. One might expect that for bulkier acyl groups than formyl the acyl-*O*-*endo* pathways, via **5bAD** and **5bBC**, may be more representative of acyl rotation barriers. Thus acyl rotation barriers in the range 60−70 kJ mol^{-1} are expected. These are somewhat lower than those found in normal amides where barriers in the range 75−90 kJ mol^{-1} have been determined. Thus B3LYP/6-31G* calculated barriers to *E*/*Z* isomerization in NNO systems also reflect a reduced degree of amide resonance which should result in higher carbonyl stretch frequencies as has been observed for the hydrazine analogues of **2**.[2,8] Selected geometric parameters are given for the *R*(acyl) TSs, **5aAD** and **5bAD**, in Figure 5. Although the sp^3 hybridization is responsible for increases in all of the bonds to N^1, the larger increases calculated for the N−CO and N−O bonds are due to loss of acyl conjugation and increased anomeric interaction, respectively. Indeed, the geometry is positioned for the HERON rearrangement which begins with acyl rotation and proceeds with only an additional 18 kJ mol^{-1}.[5]

By *I*(N^2): (*exo*,*Z*,*R*)-3A ⇆ (*endo*,*Z*,*R*)-3B and (*exo*,*E*,*R*)-3C ⇆ (*endo*,*E*,*R*)-3D. The transition structure, **6AB**, which interconverts (*exo*,*Z*,*R*)-**3A** and (*endo*,*Z*,*R*)-**3B** by *I*(N^2) is shown in Figure 6. It lies 26.6 kJ mol^{-1} above (*exo*,*Z*,*R*)-**3A** and only 3.5 kJ mol^{-1} above (*endo*,*Z*,*R*)-**3B**. Similarly, (*exo*,*E*,*R*)-**3C** and (*endo*,*E*,*R*)-**3D** are interconverted by *I*(N^2) via **6CD** with an activation barrier of 13.1 kJ mol^{-1} relative to **3C**. In each TS, N^2 is essentially planar and oriented so as to place the nonbonded lone pair simultaneously into the nodal plane of the lone pair at N^1 and into negative hyperconjugation with the low-lying σ_{NO}* orbital.

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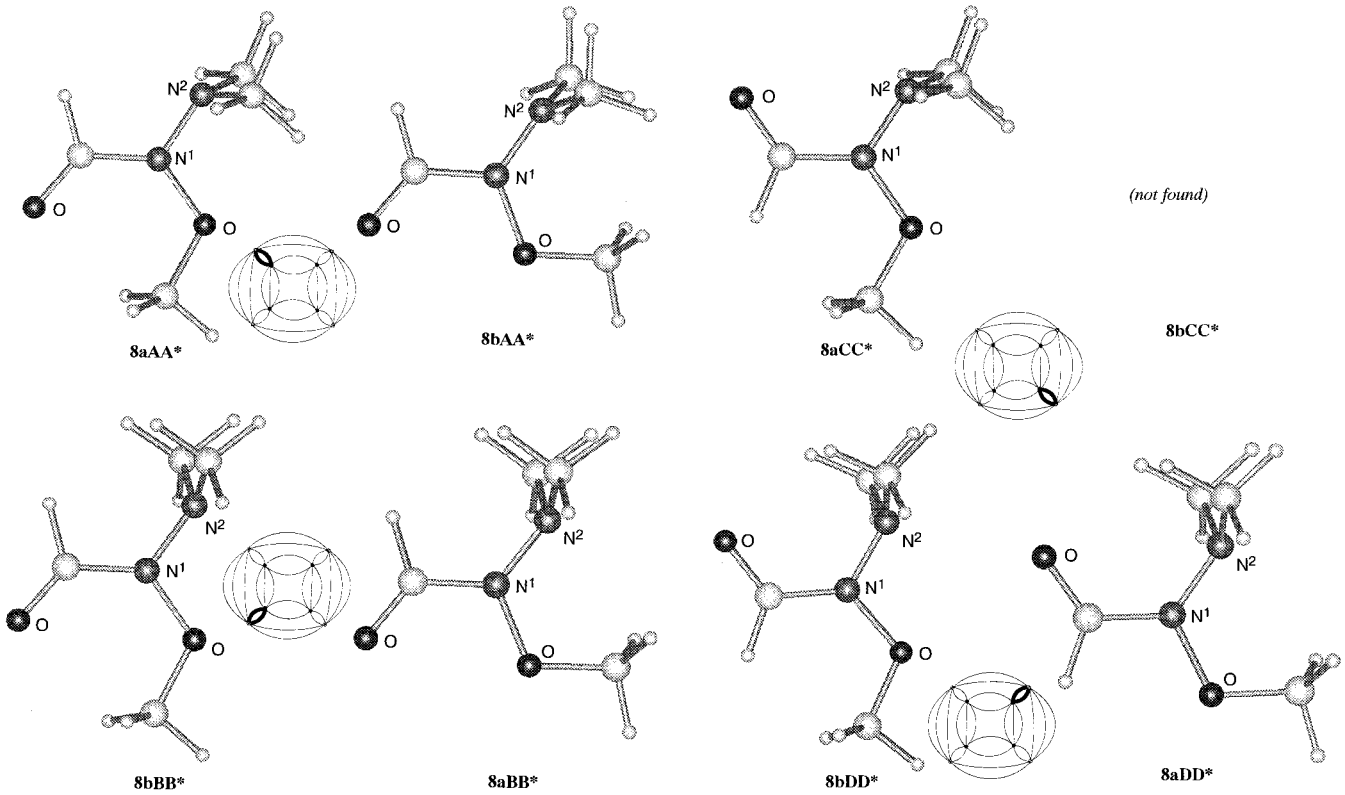

Figure 8. Transition structures for rotation about the N−O bond (*R*(NO)): large and small white balls are C and H, respectively.

Table 1. All Structures: B3LYP/6-31G* Energies, Zero Point Energies, and Relative Energies

structure	energy, hartrees	ZPE,[a] kJ mol^{-1}	ΔE, kJ mol^{-1}
	Minima		
3A-(*exo,Z,R*)[b]	−418.29799	397.2	0.0
3B-(*endo,Z,R*)[b]	−418.28921	396.3	22.2
3C-(*endo,E,R*)[b]	−418.29589	397.3	5.5
3D-(*exo,E,R*)[b]	−418.29529	396.5	6.4
	Transition Structures for Conformational Interconversion		
R(acyl)[c]			
5aAD	−418.27648	393.0 (132i)	52.8
5bAD	−418.27288	393.0 (266i)	61.9
5aBC	−418.26947	392.7 (171i)	70.5
5bBC	−418.26773	393.0 (224i)	75.3
I(N^2)[d]			
6AB	−418.28644	393.4 (175i)	26.6
6CD	−418.28956	393.6 (184i)	18.6
R(NN)[e]			
7aAB	−418.27595	397.0 (82i)	59.8
7bAB	−418.27513	397.5 (86i)	60.3
7aCD	−418.27869	397.4 (62i)	50.9
7bCD	−418.27840	397.8 (85i)	52.0
R(NO)[f]			
8aAA*	−418.28743	396.4 (152i)	27.1
8bAA*	−418.27802	394.7 (173i)	50.3
8aBB*	−418.27898	394.7 (173i)	47.7
8bBB*	−418.27802	395.1 (156i)	50.4
8aCC*	−418.28165	395.6 (152i)	41.3
8bCC*	became **8aDD*** (N^2 inverted spontaneously)		
8aDD*	−418.28618	395.6 (176i)	29.4
8bDD*	−418.28053	396.2 (130i)	44.8

[a] Number in parentheses is the imaginary frequency in cm^{-1}. [b] Figure 4. [c] Figure 5. [d] Figure 6. [e] Figure 7. [f] Figure 8.

By *R*(NN): (*exo,Z,R*)-3A ⇆ (*endo,Z,R*)-3B and (*exo,E,R*)-3C ⇆ (*endo,E,R*)-3D. (*exo,Z,R*)-**3A** and (*endo,Z,R*)-**3B** are also interconverted by *R*(NN) by two pathways, depending upon the direction of rotation. At each TS, **7aAB** or **7bAB** (Figure 7), both nitrogen atoms are pyramidal with the directed lone pairs in a staggered *anti* orientation relative to each other. The activation barriers are almost identical, 59.8 and 60.3 kJ mol^{-1}, respectively, relative to **3A**. In an absolute sense, the *R*(NN) TSs, **7aCD** and **7bCD**, which connect (*exo,E,R*)-**3C** and (*endo,E,R*)-**3D**, are lower in energy, 50.9 and 52.0 kJ mol^{-1}, respectively. This difference is likely to be much larger for derivatives of amides other than formamide, due to increased steric crowding of the dimethylamino group and a group other than H at the acyl position. It should be noted that the absolute configuration at N^1 has been inverted prior to reaching **7bAB** or **7bCD**. The analogous barrier that we computed for the ClNN system **10** was higher by ∼20 kJ mol^{-1} and once again reflects a stronger anomeric interaction in this system relative to aminoalkoxyamides. This can nicely be accounted for by the lower energy σ_{NCl}*. Hydrazines **2** with oxymethylene groups show line broadened diastereotopic protons in their room temperature ^{1}H NMR spectra which we have ascribed to restricted rotation about the N−N bond. The barriers to topomerization ($\Delta G^{\ddagger}$ between 66 and 73 kJ mol^{-1}) thus reflect the strength of anomeric overlap in these systems.

By *R*(NO): (*exo,Z,R*)-3A ⇆ (*exo,Z,S*)-3A*, (*endo,Z,R*)-3B ⇆ (*endo,Z,S*)-3B*, (*endo,E,R*)-3C ⇆ (*endo,E,S*)-3C*, and (*exo,E,R*)-3D ⇆ (*exo,E,S*)-3D*. In principle, each of the four structures, **3A**, **3B**, **3C**, or **3D** (Figure 2), may be converted to its enantiomeric form, **3A***, **3B***, **3C***, **3D***, respectively, by a rotation about the N−O bond over either of two transition structures, for a total of eight transition structures. In fact, there are seven TSs associated with *R*(NO). These are shown in Figure 8 and listed in Table 1. All have C_s symmetry, or are nearly planar at the amidyl nitrogen, N^1, with the methyl of the

methoxy group either eclipsing the acyl group or the dimethylamino group. The two lowest of these, **8aAA*** and **8aDD***, are at 27.1 and 29.4 kJ mol^{-1}, respectively, above **3A** (or **3A***). The least stable *R*(NO) TSs, **8bAA***, **8aBB***, and **8bBB***, have the methyls of the pyramidal dimethylamino group buttressed against the H of the acyl group or the methyl of the methoxy group. In the first, the steric interaction is sufficiently severe that the geometry at N^2 is close to planar, and in what would have been the eighth structure (**8bCC***), N^2 undergoes spontaneous inversion.

Conclusions

N-Methoxy-*N*-dimethylaminoformamide **3** exists as four enantiomeric pairs of diastereomers separated by moderately high barriers. The structural features are due to a number of electronic factors. The prime influence, as in normal amides, is the tendency to delocalize the amide nitrogen lone pair into the acyl group. This factor which is best accommodated by a planar nitrogen atom and normally leads to N−CO rotation barriers in the range 75−90 kJ mol^{-1} is in competition with the combined electronegativity of the two heteroatoms which shift the amide nitrogen atom toward sp^3 hybridization and reduce the N−CO rotation barrier into the range 53−60 kJ mol^{-1}, about 30 kJ mol^{-1} lower than normal. The orientations of the methoxy group and the dimethylamino group are determined by the necessity of reducing four-electron two-orbital repulsive interactions. Thus the methyls of the methoxy and dimethylamino groups adopt positions above and below the average plane of the amide. The precise torsional angles are determined by a strong anomeric interaction in which the lone pair of the amino nitrogen is delocalized into the σ antibonding orbital of the N−O bond. This attractive anomeric interaction is maximized if the N−O bond lies *anti*-coplanar to the amino nitrogen's lone pair, i.e., in the plane of the bisector of the C−N−C angle. The combined four-electron repulsive and anomeric attractive influences result in N−N rotation barriers which are comparable to the (lowered) N−CO barriers. The enantiomeric forms are interconverted by the N−O rotation which is accompanied by inversion at the amide nitrogen, formally the only stereogenic center in the molecule. The lowest pathway for epimerization corresponds to the lowest barrier for N−O rotation, 27 kJ mol^{-1}. The combination of lowered acyl rotation barriers and enhanced anomeric interactions is the driving force for the facile HERON rearrangement in this and related systems,[5] collectively termed HERON amides.

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