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A Computational Investigation of the Stereoisomerism in Heteroatom-Substituted Amides

Arvi Rauk

Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4

Stephen A. Glover*

Department of Chemistry, University of New England, Armidale, N.S.W, Australia 2351

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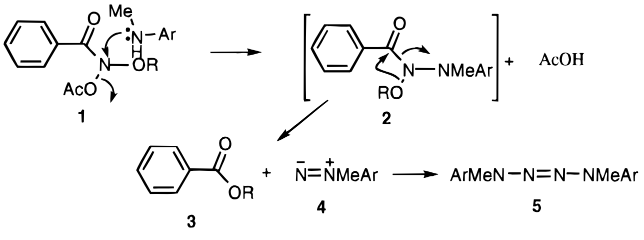
Equilibrium and transition structures for conformational interconversions in formamide (**8**), *N*-chloroformamide (**9**), *N*-methoxyformamide (**10**), *N*-chloro-*N*-methoxyformamide (**11**), *N*,*N*-dimethoxyformamide (**12**), and *N*-chloro-*N*-(dimethylamino)formamide (**13**) were determined at the Becke3LYP/6-31G(D) hybrid Hartree−Fock−density functional theoretical level. The structure and rotational barrier of formamide **8** agree well with experimental values. The computations suggest that in **9** and **10** the acyl nitrogen atom is planar after vibrational motion is considered. The barriers to acyl C−N rotation are lowered by 1−2 kcal/mol relative to normal amide barriers to about 16 kcal/mol and N−O rotation barriers in **10** are 5.6 and 7.4 kcal/mol, lower by 4−5 kcal/mol compared to those in simple hydroxylamines. The equilibrium and transition structures of the bisheteroatom-substituted formamides, **11**, **12**, and **13**, are influenced by inductive effects, repulsive lone pair−lone pair interactions, and anomeric effects. The consequences of the anomeric interactions are the following: N−Cl bonds longer than normal by 0.05−0.35 Å in the equilibrium structures of **11** and **13**; the N−O and N−N bonds are shortened by 0.04−0.14 Å in **11** and **13**, the larger deviations occurring in **13**; in each of the equilibrium and transition structures, except the transition structures to N−O and N−N bond rotation, the donor (X) and acceptor (N−Y) groups are always oriented so as to place the donor n_X orbital in an approximate anti-coplanar arrangement relative to the acceptor N−Y bond. The anomeric interaction does not appear to have a specific contribution to lowering of acyl−C−N rotation barriers which are in the range 8−10 kcal/mol for all three bisheteroatom-substituted systems, nor to the magnitude of the inversion barriers which are constant at about 2−3 kcal/mol. However it significantly increases the magnitude of barriers to rotation about N−O and N−N bonds, bringing the N−O barriers in **11** back to normal values for hydroxylamines, thereby countering the effect of acyl substitution and raising the N−N rotation barrier in **13** to almost 20 kcal/mol.

Introduction

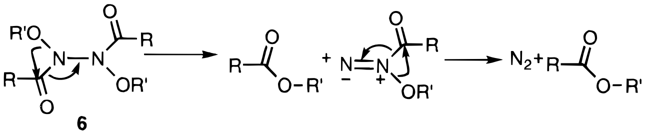
Recent investigations have revealed unusual chemistry in amides that are geminally substituted at nitrogen with alkoxy and amino groups. Mutagenic *N*-acetoxy-*N*-alkoxybenzamides[1−3] **1** undergo a facile S_N2 reaction at nitrogen with *N*-methylanilines which results in the loss of acetic acid and the formation of reactive intermediates, *N*-alkoxy-*N*-(*N*′-methylanilino)benzamides **2**. These rearrange in concerted fashion to alkyl esters **3** and 1-methyl-1-phenyldiazene **4**, which dimerizes to the tetraazene **5** (Scheme 1).[4]

A similar mechanism has recently been shown to explain the products from decomposition of *N*,*N*′-dialkoxy-*N*,*N*′-diacylhydrazines **6**; esters are formed intramolecularly through two three-center processes[5] rather than the previously proposed four-center mechanisms (Scheme 2).[6]

Scheme 1



Scheme 2



AM1 semiempirical molecular orbital studies and limited *ab initio* calculations have confirmed the concerted nature of these HEteroatom Rearrangements On Nitrogen, the so-called HERON reactions, and they are predicted to occur whenever hydrazides are substituted at the α-nitrogen with an amino, oxo, or halo substituent (Y).[7] Migration is promoted by donor groups at the

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* Author to whom correspondence should be addressed.

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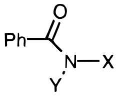
β-nitrogen, by increased electronegativity of the migrating atom or by withdrawing groups on the migrating group. Furthermore, these studies have suggested that part of the driving force for the reaction may be an anomeric weakening of the NY bond through a $n_N-\sigma^*_{NY}$ stabilization. Ground state geometries favor such overlap in all cases where rearrangement is predicted to be facile. There is evidence too that HERON rearrangements occur in *N*-alkoxyhydroxamic acids **7a** under neutral or basic conditions.[3] Since facile alkoxy migration is not predicted by AM1 calculations, the driving force is presumably an $n_O{}^{-}-\sigma^*_{NO}$ anomeric interaction which operates in the conjugate anion of **7a**. Our calculations support this pathway.[7] *N*,*N*-Dialkoxybenzamides **7b** are stable to this rearrangement but undergo thermolysis above 100 °C to give alkoxyl and alkoxyamidyl radicals, a process that would be promoted by weakening of an NO bond through an $n_O-\sigma^*_{NO}$ anomeric effect.[5] Interestingly, earlier studies in these laboratories showed that α-chloro-*β*,*β*-dialkyl hydrazides **7c** are unstable and the product from chlorination of *β*,*β*-dimethylbenzohydrazide **7c** (R=Me) with *tert*-butyl hypochlorite was *N*-(dimethylamino)benzimide which might be envisaged as forming from the starting material and benzoyl chloride.[8] The latter could have been generated through the HERON rearrangement of α-chloro-*β*,*β*-dimethyl hydrazide which is predicted to occur readily by AM1 calculations.[7]



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a; X=OH, Y=OR
b; X, Y= OR
c; X=NR$_2$, Y=Cl
d; X=OR, Y=H
e; X=OR, Y=Cl

Compounds with the general structure **7** have not been subjected to systematic and rigorous theoretical investigation. We begin here with such a study of the structures and stereochemical features of representative species. The following considerations emphasize the novel aspects.

The stereoisomerism associated with a tricoordinated nitrogen atom originates with nonplanarity and relatively facile pyramidal inversion at nitrogen. In ammonia and simple alkyl-substituted amines, this process is hindered by a barrier of approximately 6 kcal/mol.[9] It is well-known that substitution by more electronegative heteroatoms raises the barrier to inversion. The origin of the heteroatom effect is complex. The higher electronegativity of the heteroatom induces a redistribution of the electrons of the σ bond and a concommitant rehybridization of the nitrogen bonding orbitals to higher p character (and therefore the nonbonded orbital to higher s character), according to ideas first put forth by Pauling. In addition, the heteroatom usually also bears one or more pairs of electrons in p-like orbitals. If a $\pi-\pi^*$-like interaction cannot be avoided (say by torsion about the bond to the heteroatom) during the course of the inversion, the planar transition state will be destabilized by the unfavorable four-electron two-orbital interaction leading to a higher barrier. Both the σ inductive effect and the lone-pair effect operate in the same direction and are difficult to disentangle.

The presence of two or more heteroatoms on the nitrogen atom (−NXY) will accentuate the single-substituent effects and will also permit the operation of an anomeric effect[10] due to interaction of the nonbonded electrons of the X substituent (n_X) with the antibonding orbital of the N−Y bond (σ^*_{NY}).[11] The $n_X-\sigma^*_{NY}$ interaction, which we will refer to as the *anomeric interaction*, will be most important if Y is more electronegative than X and if the orientation of n_X can be coplanar to σ^*_{NY} (anti-coplanar if n_X is an sp hybrid orbital). Since the alignment of the n_X and σ^*_{NY} orbitals should be as π-like as possible (i.e., as much p character as possible in both orbitals), it is expected that a pyramidal geometry at N would be more favorable than planar to the operation of the anomeric effect. Thus the anomeric interaction should also increase the magnitude of the inversion barrier, but its importance compared to the other effects is not known.

Conjugating substituents and π-electron-withdrawing substituents on the other hand reduce the magnitude of the barrier to pyramidal inversion since π conjugation is most effective when the nitrogen atom is planar. Our emphasis will be on acyl substitution, that is, on amides. Thus simple amides (unsubstituted, or substituted by alkyl groups) are planar at nitrogen, or very nearly so. The combined effects of *N*-acyl- and *N*-heteroatom substitution on the structure and energetics at nitrogen are not well-known although high barriers observed in *N*-acyl hydrazines and hydroxylamines have been attributed to hindered rotation rather than inversion.[12]

Substitution by acyl groups at bis-substituted amines introduces an additional element of stereochemistry, namely orientation about the acyl C−N bond. In *N*,*N*-dialkyl amides in the gas phase, the barrier to acyl C−N bond rotation is in the range 15−19 kcal/mol.[13−15] When the amide nitrogen atom contains two different substituents, diastereomeric forms which may be labeled *E* and *Z* arise. The larger substituent will adopt the position *syn* to the carbonyl oxygen atom, possibly for simple steric considerations since the NCO angle (125°) is appreciably more open than the NCR angle (110°). Except in formamides where steric considerations are minimized, the *syn* (to C=O) orientation of the larger substituent may be favored by several kcal/mol.[16] In nonplanar amides, the barrier hindering rotation about the C−N bond is reduced. The effect of the presence of one or two heteroatom substituents on nitrogen on the magnitude of the barrier to hindered rotation about the acyl C−N bond is unknown. In particular, it is not clear how the operation of an anomeric interaction in amides substituted at N by two heteroatoms will affect the magnitude of the acyl C−N rotation barrier. That amide isomerism is affected in compounds in this class is borne out from infrared carbonyl stretch frequencies as well as ^{1}H NMR studies.

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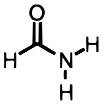
Table 1. Total and Relative Energies, Dipole Moments, and Carbonyl Stretching Frequencies (Becke3LYP/6-31G(D))

structure[a]	energy, hartrees	ZPE, kcal/mol	ΔE[b], kcal/mol	μ, D	$\nu_{C=O}$ (cm^{-1}) calcd	$\nu_{C=O}$ (cm^{-1}) scaled[c]
8	−169.88884	28.4	0.0	3.833	1839	1747
$[\mathbf{8}\text{rts}]_{\text{exo}}$	−169.85702	27.8	19.4 (19.3)	3.664	1869	1776
$[\mathbf{8}\text{rts}]_{\text{endo}}$	−169.86030	28.0	17.5 (18.1)	1.281	1831	1739
E-**9**	−629.43693	22.6	0.0	1.914	1817	1726
Z-**9**	−629.43619	22.6	0.5	3.664	1843	1751
$[E\text{-}\mathbf{9}\rightarrow\underline{E\text{-}\mathbf{9}}]$	−629.43652	22.3	0.0	2.170	1813	1722
$[Z\text{-}\mathbf{9}\rightarrow\underline{Z\text{-}\mathbf{9}}]$	−629.43596	22.3	0.3	3.783	1839	1747
$[E\text{-}\mathbf{9}\rightarrow Z\text{-}\mathbf{9}]_{\text{exo}}$	−629.41161	22.2	15.5	3.074	1871	1777
$[E\text{-}\mathbf{9}\rightarrow Z\text{-}\mathbf{9}]_{\text{endo}}$	−629.41151	22.1	15.5	1.590	1842	1750
E-**10**	−284.35255	49.1	0.0	3.494	1822	1731
Z-**10**	−284.35056	49.2	1.3	3.200	1835	1743
$[E\text{-}\mathbf{10}\rightarrow\underline{E\text{-}\mathbf{10}}]_{\text{NO}}$	−284.34299	48.7	5.6	4.019	1815	1724
$[Z\text{-}\mathbf{10}\rightarrow\underline{Z\text{-}\mathbf{10}}]_{\text{NO}}$	−284.34038	48.9	7.4	2.442	1813	1722
$[E\text{-}\mathbf{10}\rightarrow Z\text{-}\mathbf{10}]_{\text{CN}}$	−284.32689	48.7	15.7	2.064	1861	1768
Z-**11**	−743.90785	42.6	0.0	3.867	1838	1746
E-**11**	−743.90686	42.6	0.6	2.232	1835	1743
Z-**11′**	−743.90413	42.6	2.3	3.667	1827	1736
$[Z\text{-}\mathbf{11}\rightarrow\underline{Z\text{-}\mathbf{11'}}]$	−743.90373	42.5	2.5	3.976	1817	1726
$[Z\text{-}\mathbf{11}\rightarrow\underline{E\text{-}\mathbf{11}}]_{\text{exo}}$	−743.89554	41.9	7.0	2.188	1871	1777
$[Z\text{-}\mathbf{11}\rightarrow\underline{E\text{-}\mathbf{11}}]_{\text{endo}}$	−743.88991	41.9	10.6	3.095	1870	1776
NX-**12**	−398.82623	69.2	0.0	3.333	1818	1727
XN-**12**	−398.82437	69.0	1.0	3.043	1828	1737
XX-**12**	−398.82446	69.0	0.9	3.604	1828	1737
$[\text{NX-}\mathbf{12}\rightarrow\text{XN-}\mathbf{12}]_{\text{exo}}$	−398.80547	68.1	10.2	3.356	1873	1779
$[\text{XX-}\mathbf{12}\rightarrow\underline{\text{XX-}\mathbf{12}}]_{\text{exo}}$	−398.81309	68.3	7.1	2.833	1876	1782
E-**13**	−763.39030	68.5	0.0	3.399	1798	1708
Z-**13**	−763.38679	68.5	2.2	5.034	1829	1738
$[E\text{-}\mathbf{13}\rightarrow\underline{E\text{-}\mathbf{13}}]_{\text{inv}}$	−763.38560	68.1	2.6	3.143	1805	1715
$[E\text{-}\mathbf{13}\rightarrow\underline{E\text{-}\mathbf{13}}]_{\text{NN}}$[d]	−763.35949		19.3[e]	2.564		
$[E\text{-}\mathbf{13}\rightarrow Z\text{-}\mathbf{13}]_{\text{CN}}$[d]	−763.37488		9.7[e]	6.729		

[a] See Figure 1; square brackets indicate transition structures; underlined symbols refer to the enantiomer. [b] Numbers in parentheses are Becke3LYP/6-311+G(2D. P)//6-31G(D) values. [c] Scale factor = 0.95. [d] Approximate transition structure; optimized with constraint. [e] Does not include ZPE correction.

Typically, hydroxamic esters **7d** absorb at *ca.* 1685 cm^{-1} in the carbonyl region.[2,3,17] In many examples that we have synthesized, there is also clear evidence of *E*/*Z* isomerism at room temperature. In particular, protons α to the carbonyl and alkoxy oxygen often exhibit significant line broadening or are even resolved into signals due to the different geometrical isomers. Upon chlorination at nitrogen to give **7e**, carbonyl stretch frequencies are increased by 30−40 cm^{-1} which is indicative of significantly increased double-bond character.[17,18] In addition, in their ^{1}H NMR spectra at room temperature, there is no evidence of line broadening which is consistent with rotationally averaged chemical environments. Carbonyl vibrational frequencies for *N*,*N*-dialkoxybenzamides **7b** are also significantly higher (1710 cm^{-1}) when compared to the parent hydroxamic esters **7d**.[5] In the few examples known to date, these too appear to have rotationally averaged NMR spectra. Finally, while no stable *N*-alkoxy-*N*-aminobenzamides have been isolated, the *N*,*N*′-dialkoxy-*N*,*N*′-diacylhydrazines (e.g. **6)** are relatively stable at room temperature. Infrared spectra have been recorded in several cases, and the carbonyl stretch frequencies are in the region of 1720 cm^{-1} which once again reflects the low degree of conjugation in these species.[19] Interestingly, methylenic protons adjacent to oxygen in these dimers are diasteriotopic which has been attributed to the presence of high barriers to inversion,[5] but which may also be due to high rotational barriers.

We present here an *ab initio* computational investigation of the structures and energy barriers of amides with one or two heteroatom substituents on nitrogen. The structure and barriers of formamide **8** were determined for comparison at the present theoretical level. The primary focus will be on *N*-chloroformamide (**9**), *N*-methoxyformamide (**10**), *N*-chloro-*N*-methoxyformamide (**11**), *N*,*N*-dimethoxyformamide (**12**), and *N*-chloro-*N*-(dimethylamino)formamide (**13**).



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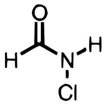

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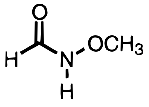

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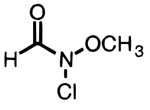

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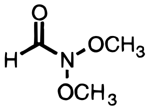

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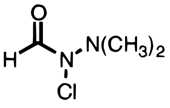

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Results and Discussion

The structures of all compounds were optimized at the Becke3LYP/6-31G(D) level (see Computational Methods) and are shown in Figure 1, together with selected geometric data. The average value of the bond angles at nitrogen, encased in pointed brackets, provides a measure of the pyramidal character. For reference, ammonia and alkylamines have values in the range ⟨107°⟩ to ⟨110°⟩. Energies, dipole moments, and selected vibrational data are listed in Table 1. In Figure 1, Table 1, and the discussion below, enantiomeric forms are identified by underlining and transition structures are

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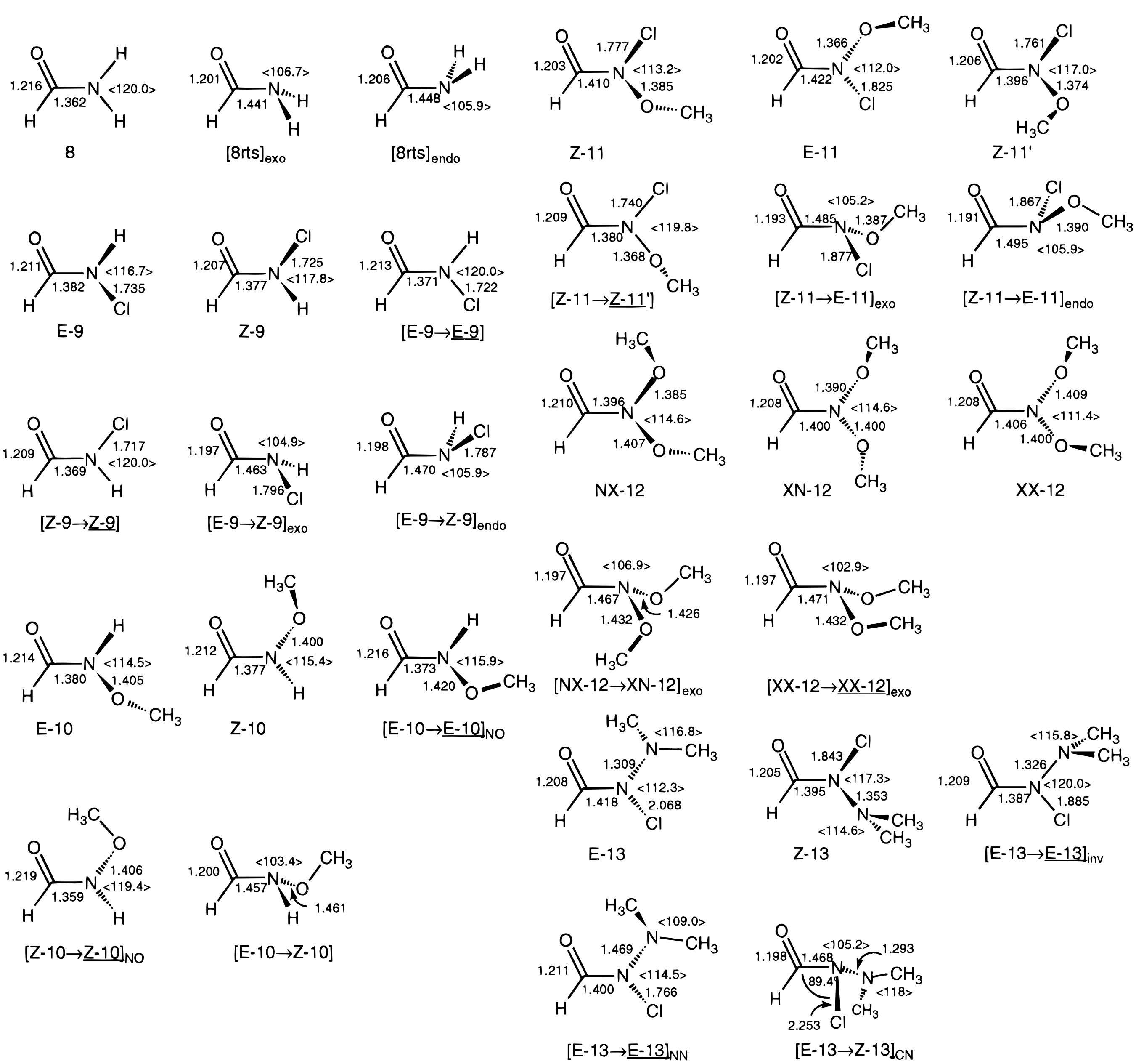

Figure 1. Selected structures of **8**–**13** optimized at Becke3LYP/6-31G(D) level: square brackets denote transition structures; underlining denotes the enantiomeric form; bond lengths in angstroms, angles in degrees, pointed brackets denote the average of the three bond angles.

enclosed in square brackets and identify the transformation (**[..→..]**). We discuss the compounds individually prior to drawing conclusions of a more general nature.

Formamide (8). This compound has been well-characterized experimentally and studied theoretically[20] and serves as a reference for the performance of the Becke3LYP/6-31G(D) method and for structural and energetic changes predicted for the derivatized systems. The predicted geometry of **8** is intermediate to the experimental MW[21] and electron diffraction[22] geometries. It has not been determined experimentally whether or not the nitrogen atom is planar.[21,23] At the present theoretical level, the geometry at N is planar.

The geometry about the nitrogen atom of **8** becomes more typically pyramidal during rotation about the C–N bond as acyl conjugation is removed. The rotation coordinate passes through two diastereomeric rotational transition structures (rts) differentiated by the orientation, *endo* or *exo*, of the carbonyl oxygen relative to the pyramid at nitrogen.[24] The calculated barrier over the lower transition structure **[8**rts**]**$_{exo}$ (Figure 1) is 17.5 kcal/mol (18.1 at Becke3LYP/6-311+G(2DF,P)//6-31G(D)). The alternate transition structure **[8**rts**]**$_{endo}$ is less than 2 kcal/mol higher. The calculated value is in the range of values (17–19 kcal/mol) determined from dynamic ^{1}H NMR experiments on solutions of ^{15}N-enriched formamide.[25]

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The same range of barrier heights is also found in gas phase NMR measurements on a variety of *N*,*N*-dialkylformamides.[13,14]

Harmonic vibrational frequencies of **8** calculated at the Becke3LYP/6-31G(D) level are too high but are brought into good agreement with experimental values if uniformly scaled by 0.96.[26] The scale factor suitable for carbonyl stretching frequencies is slightly smaller, 0.95.[26] For example, ν_{CO}(calcd, scaled) = 1747 cm^{-1}, ν_{CO}(expt) = 1740 cm^{-1}.[21]

***N*-Chloroformamide (9).** The *N*-chloro derivative exists in two diastereomeric forms, *Z*-**9** and *E*-**9** (Figure 1). The *E* form is more stable by 0.5 kcal/mol. In both forms, the geometry at N forms a shallow pyramid on the vibrationless potential surface for inversion. The barrier to pyramidal inversion from either diastereomer vanishes after inclusion of the zero-point vibrational energy estimate. For all intents and purposes, **9** may be regarded as existing in two quasiplanar diastereomeric forms. The dipole moment of the less stable *Z* form, 3.664 D, is substantially higher than that of the more stable *E* isomer, 2.170 D, suggesting that solvation may influence the equilibrium ratio. The activation energy for C−N rotation via either $[E\text{-}\mathbf{9}\rightarrow Z\text{-}\mathbf{9}]_{\mathrm{exo}}$ or $[E\text{-}\mathbf{9}\rightarrow Z\text{-}\mathbf{9}]_{\mathrm{endo}}$, is the same, 15.5 kcal/mol.

The carbonyl stretching frequency of **9** in $CHCl_3$ solution has been reported[27] to be 1690 cm^{-1}. The calculated and scaled (by 0.95) frequencies (Table 1) for the two diastereomers are both significantly higher than this and differ from each other by 25 cm^{-1}. It is possible that aggregation due to hydrogen bonding in solution is responsible for the anomalously low C═O stretching frequency.

***N*-Methoxyformamide (10).** *N*-Methoxyformamide exists in two diastereomeric forms, *E*-**10** and *Z*-**10** (Figure 1), both of which are chiral. *E*-**10** is more stable than *Z*-**10** by 1.3 kcal/mol. In each, the nitrogen forms a shallow pyramid and the methyl group adopts a position exo to the pyramid. Inversion at nitrogen in each of the two forms would potentially yield an additional structure with the methyl group endo to the pyramid. However, these are not local minima on the potential energy hypersurface of **10**. Racemization of either *E*-**10** or *Z*-**10** is accomplished by rotation about the N−O bond by either of two diastereomeric rotational transition structures in which the C−O bond is either quasi-coplanar with the N−H bond $[E\text{-}\mathbf{10}\rightarrow\underline{E\text{-}\mathbf{10}}]_{\mathrm{NO}}$ or quasi-coplanar with the N−C bond $[Z\text{-}\mathbf{10}\rightarrow\underline{Z\text{-}\mathbf{10}}]_{\mathrm{NO}}$. The rotation barrier in each case is approximately 6 kcal/mol. Rotation about the N−O bond is accompanied by spontaneous inversion at nitrogen.

In the rotational transition structures which interconvert *E*-**10** and *Z*-**10**, the nitrogen is strongly pyramidal and the C═O bond may adopt an orientation exo or endo to the pyramid. The transition structures $[E\text{-}\mathbf{10}\rightarrow Z\text{-}\mathbf{10}]_{\mathrm{exo}}$ and $[E\text{-}\mathbf{10}\rightarrow Z\text{-}\mathbf{10}]_{\mathrm{endo}}$ are 16 and 18 kcal/mol, respectively, higher in energy than *E*-**10**. The acyl C−N rotation barrier therefore is not significantly affected by the presence of a single alkoxy substituent at N.

***N*-Chloro-*N*-methoxyformamide (11).** *N*-Chloro-*N*-methoxyformamide (**11**) exists in two chiral diastereomeric forms, designated *Z*-**11** and *E*-**11**. *Z*-**11** is more stable than *E*-**11** by 0.6 kcal/mol. Each form displays evidence of operation of the anomeric effect, namely shortening of the N−O bond, lengthening of the N−Cl bond, and a Cl−N−O−C dihedral angle of approximately 90°. The effect is more pronounced in the less stable isomer *E*-**11** in which the N−Cl bond is almost 0.1 Å longer than that found in *E*-**9** and the N−O bond is 0.03 Å shorter than that in *Z*-**10**. There is reduced involvement of the nitrogen in acyl group conjugation, a consequence of a more pyramidal geometry at N. The C═O bond is 0.01 Å shorter and the C−N bond 0.04 Å longer than the corresponding bonds in formamide **8**.

The rotation barrier about the acyl C−N bond is also sharply reduced, the lower energy transition structure $[Z\text{-}\mathbf{11}\rightarrow E\text{-}\mathbf{11}]_{\mathrm{exo}}$ being only 7.7 kcal/mol above *Z*-**11**. This transition structure has the C═O bond in the exo orientation relative to the nitrogen pyramid. The endo-oriented rotational transition structure is 10.6 kcal/mol higher in energy than *Z*-**11**.

The full potential curve for the rotation about the N−O bond of *Z*-**11** is displayed in Figure 3, as a function of the C−N−O−C dihedral angle and is discussed in detail below.

***N*,*N*-Dimethoxyformamide (12).** *N*,*N*-Dimethoxyformamide (**12**) exists in three disteromeric forms, distinguished by the orientation, exo or endo, of the C−O bonds relative to the pyramid at nitrogen. We abreviate these as X (exo) and N (endo). In the most stable form, the C−O bond which is *Z* to C═O is in the endo (N) orientation and the *E* C−O bond is in the exo (X) orientation. We call this form NX-**12** (the first label refers to the *Z* C−O bond and the second to the *E* C−O bond). The XN form, in which the orientations of the *Z* and *E* C−O bonds are reversed, is 1.0 kcal/mol less stable. XX-**12**, in which both methyl groups occupy the exo positions, is 0.9 kcal/mol less stable than NX-**12**. Attempts to locate an NN-**12** form by starting the geometry optimization by rotating each of the C−O bonds of XX-**12** through 180° resulted in inversion at nitrogen and yielded the enantiomer of XX-**12**. We conclude that NN-**12** is not a local minimum on the potential energy hypersurface of **12**.

In NX-**12** there is some evidence of an anomeric effect in that the CO_ENO_Z dihedral angle is close to 90°. The effect of the anomeric interaction on N−O bond lengths is however unclear. There is significant lengthening of the N−CO bond (relative to **8**) which, together with some shortening of the C═O bond, suggests reduced amide resonance. Amide isomerism is however more complicated than in **11**.

***N*-Chloro-*N*-(dimethylamino)formamide (13).** Two stable structures, *E*-**13** and *Z*-**13** (Figure 1), were located for *N*-chloro-*N*-(dimethylamino)formamide. The *E* isomer is more stable than the *Z* diastereomer by 2.2 kcal/mol. In each of these, the orientation of the dimethylamino group is such as to place the lone pair hybrid orbital in an anti-coplanar arrangement with the N−Cl bond. An attempt to locate a second stable structure of the *Z* diastereomer with the nitrogen lone pair syn-coplanar to the N−Cl bond resulted in spontaneous inversion of configuration at the nitrogen atom of the dimethylamino group and optimization to $\underline{Z\text{-}\mathbf{13}}$. This result suggests that the *Z* diastereomer (and probably the *E*-form) will not exhibit rotational isomerism about the N−N bond. The more stable structure, *E*-**13**, exhibits the longest N−Cl bond, 2.068 Å, of all of the structures as well as a very short N−N separation, 1.309 Å. The nitrogen atom of the dimethylamino group is nearly flat, with an average

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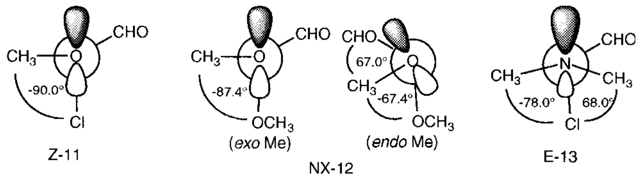

Figure 2. Newman projections of *Z*-**11**, NX-**12**, and *E*-**13** showing the anomeric effect.

bond angle of ⟨116.8°⟩. The amide nitrogen has the sharpest pyramid of all of the present stable structures, with the average of the bond angles at the nitrogen atom being ⟨112.3°⟩ and the acyl C−N bond the longest, 1.418 Å. Both factors suggest the *least* involvement of the acyl group in conjugation with the nitrogen atom. Rotational transition structures for N−N and acyl C−N rotation were not located by analytical methods. Rather, the structures, $[E\text{-}\mathbf{13}\rightarrow\underline{E\text{-}\mathbf{13}}]_{NN}$ and $[E\text{-}\mathbf{13}\rightarrow Z\text{-}\mathbf{13}]_{CN}$ shown in Figure 1 were obtained by optimization with constraints. In the former, the nitrogen lone pair orbital of the dimethylamino group was constrained to be perpendicular to the N−Cl bond in order to remove the anomeric interaction. In the latter, the lone pair orbital of the acyl nitrogen was constrained to be syn-coplanar to the C=O bond to remove the possibility of π conjugation. The structures and energies of these species should be comparable to the actual transition structures which we were unable to obtain by conventional transition structure searches because of complications originating from methyl rotations and the extreme lability of the N−Cl bond. The approximate transition structure, $[E\text{-}\mathbf{13}\rightarrow\underline{E\text{-}\mathbf{13}}]_{NN}$ (Figure 1), is 19 kcal/mol higher than *E*-**13**. By contrast, $[E\text{-}\mathbf{13}\rightarrow Z\text{-}\mathbf{13}]_{CN}$, which approximates the acyl C−N rotational transition structure, is 10 kcal/mol higher than *E*-**13**.

The structure of $[E\text{-}\mathbf{13}\rightarrow Z\text{-}\mathbf{13}]_{CN}$ requires further comment. The long N−Cl bond (2.25 Å) and contracted C−N−Cl angle (89°) suggest the initial stages of the HERON rearrangement, as has already been found by AM1 calculations.[7] Further theoretical and experimental studies are underway to verify the existence of the HERON rearrangement in the highly reactive *N*-chloro-*N*-dialkylamino amide system.

Structural and Energetic Consequences of the Anomeric Interaction. The anomeric interaction occurs when a central atom is bonded to two atoms, one of which bears a nonbonded pair of electrons and the other of which is more electronegative than it is. The orbital basis for the anomeric effect is the energetically favorable donor−acceptor interaction between the orbital containing the nonbonded pair and the σ^* orbital of the bond to the more electronegative atom.[10] The nonbonded pair must be in a p or sp^n orbital and the attractive interaction is maximized when the nonbonded orbital is (anti)-coplanar to the σ^* orbital. The anomeric interaction may also be represented in terms of resonance structures as a type of negative hyperconjugation: $:X{-}N{-}Y \leftrightarrow {}^{+}X{=}N\ Y^{-}$. A lengthening of the acceptor bond, a contraction of the bond to the donor atom, and specific torsional orientations are expected. These constitute the anomeric *effect*. The specific consequences of the anomeric interaction on the equilibrium structures, *Z*-**11**, NX-**12**, and *E*-**13**, are shown as Newman projections in Figure 2. Since the higher nonbonded orbital, n_O, of a dicoordinated oxygen atom is a p orbital oriented perpendicular to the plane of the σ bonds, the optimum structures of the methoxy compounds have a perpendicular arrangement of the C−O and acceptor (N−O or N−Cl) bonds. For steric reasons, the optimum orientation is not achievable for the "N" (endo) methoxy group of NX-**12** but is available for the "X" (exo) methoxy group. In the case of the dimethylamino compound, *E*-**13**, the anti-coplanar arrangement of n_N requires that the N−Cl bond adopt a position endo to the nitrogen pyramid, more or less in the plane of the bisector of the C−N−C angle. In the case of *E*-**13**, the deviation from the bisecting plane is only 5°.

Bond Lengths. The lengths of bonds to nitrogen vary as a function of the degree of nonplanarity since rehybridization occurs. A measure of pyramidal nature is reported in Figure 1 as the average value of the bond angles at N. From inspection of the data for compounds **9** and **10**, the following generalization regarding "normal" values may be made: at planar N ((⟨~120°⟩)), $r_{NCl} = 1.72$ Å and $r_{NO} = 1.40$ Å; at pyramidal N ((⟨~104°⟩)), $r_{NCl} = 1.79$ Å and $r_{NO} = 1.46$ Å. The length of a typical N−N single bond may be taken as 1.45 Å, the value in hydrazine ((⟨110°⟩)).[28] Values significantly outside of the normal range provide evidence of extra stereoelectronic effects. The anomeric effect would lead to shortening of the N−O bond in **11** and the N−N bond in **13**. Concomitant lengthening of the N−Cl bond in both compounds is expected. In **12** where there are two opposing anomeric interactions, the effect, if any, on the N−O bonds is uncertain. From elementary orbital interaction considerations,[29] the anomeric effect will be strongest in **13**, intermediate in **11**, and weakest in **12**, since n_N will be higher in energy than n_O and σ^*_{NCl} will be lower in energy and more polarized than σ^*_{NO}. Indeed, average N−Cl bond lengths decrease in the series **13** ($r_{NCl} = 1.96$ Å), **11** ($r_{NCl} = 1.80$ Å), **9** ($r_{NCl} = 1.73$ Å, no anomeric effect). The set of five structures associated with **13** (Figure 1) provide a direct correlation between lengthening of the N−Cl bond and shortening of the N−N bond due to the anomeric interaction (r_{NCl}, r_{NN}): $[E\text{-}\mathbf{13}\rightarrow Z\text{-}\mathbf{13}]_{CN}$ (2.253, 1.293 (maximum anomeric effect)), *E*-**13** (2.068, 1.309), $[E\text{-}\mathbf{13}\rightarrow\underline{E\text{-}\mathbf{13}}]_{inv}$ (1.885, 1.326), *Z*-**13** (1.843, 1.353), $[E\text{-}\mathbf{13}\rightarrow\underline{E\text{-}\mathbf{13}}]_{NN}$ (1.766, 1.469 (no anomeric effect)). The effect of the anomeric interactions on the N−O bonds in **12** is expected to be minimal since each oxygen can donate electrons into the σ^* orbital of the other. The associated geometric changes are in opposition and should largely cancel, leaving the N−O bond lengths at the values expected for a nearly planar nitrogen without any anomeric effect, i.e., as in **10**. In fact the small variations in the N−O bond lengths in NX-**12** are not in the direction expected for the dihedral angles (Figure 2), but are so in the case of XN-**12**. It is likely that in the case of **12,** where the anomeric effects are weakest and in opposition, features of the bonding other than anomeric interactions determine the bond lengths. For instance the data in Figure 1 reveals the tendency of the N−X bond *cis* to the C=O to be shorter than the equivalent bond in the *trans* orientation.

Degree of Nonplanarity of the Acylated Nitrogen. The presence of the acyl group complicates assessment of the effect of the anomeric interaction on the geometry at the nitrogen atom bearing the heteroatoms since it exerts a flattening effect. Nevertheless, inspection of the

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stable structures in Figure 1 reveals that the presence of the anomeric interaction tends to increase the sharpness of the nitrogen pyramid: *Z*-**11** ⟨113.2°⟩, *E*-**11** ⟨112.0°⟩; NX-**12** ⟨114.6°⟩, XN-**12** ⟨114.6°⟩, XX-**12** ⟨111.4°⟩; *E*-**13** (⟨112.3°⟩), *Z*-**13** ⟨117.3°⟩. These values are to be compared with those in the corresponding rotational transition structures in which the anomeric interaction is absent to a large degree: **[*Z*-11→*Z*-11′]** ⟨119.8°⟩; **[*E*-13→*E*-13]**$_{NN}$ ⟨114.5°⟩. The reason for the large value for *Z*-**13** is not obvious; both the CO–N–N and N–N–Cl bond angles are large, 120.0° and 118.0°, respectively.

Degree of Nonplanarity of the Dimethylamino Nitrogen. The $n_N-\sigma^*_{NCl}$ conjugation is improved if the nitrogen pyramid is flattened, increasing the p character of n_N. The average bond angle at the dimethylamino nitrogen atom may be correlated with r_{NCl} in the five structures of **13**, listed in order of decreasing N–Cl bond length (in Å): (2.253, ⟨118.0°⟩), (2.068, ⟨116.8°⟩), (1.885, ⟨115.8°⟩), (1.843, ⟨114.6°⟩), (1.766, ⟨109.0°⟩ (no anomeric effect)).

Barriers to Stereoisomerism. Stereoisomerism of the compounds of interest may take place in principle by three distinct mechanisms, pyramidal inversion at N, rotation about the acyl C–N bond, and rotation about the N–X bond (in the case of X = methoxy or X = dimethylamino). These are discussed separately below.

Inversion at Nitrogen. All of the present compounds are *N*-acylated. The effect of the acyl group is to lower or eliminate the barrier to nitrogen inversion. Indeed, formamide (**8**) is found to be planar at the present level of theory. The presence of electronegative heteroatoms on N tends to raise the inversion barrier. However, while the Born–Oppenheimer surface for N inversion of *N*-chloroformamide (**9**) has a double-minimum potential well with a barrier which is less than 0.3 kcal/mol, the barrier vanishes after inclusion of the ZPE correction. Therefore, **9** may be regarded as being planar at N as well. The same appears to be true in the case of *N*-methoxyformamide (**10**). The presence of two heteroatoms on the acyl nitrogen atom yields a non-zero inversion barrier. Two inversion transition structures were located for *N*-chloro-*N*-methoxyformamide (**11**), both 2.5 kcal/mol above the respective minimum structures, *E*-**11** and *Z*-**11**. Several inversion transition structures may be postulated for *N*,*N*-dimethoxyformamide (**12**). Only one was located, 2.4 kcal above the most stable diastereomeric form, NX-**12**. Likewise, for **13**, only a single (acyl) nitrogen inversion transition structure was located (**[*E*-13→*E*-13]**$_{inv}$, 2.6 kcal/mol above *E*-**13**. In this structure the long N–Cl bond (1.89 Å) and short N–N bond (1.33 Å) suggest that the anomeric interaction is maintained throughout the inversion process, at least in the N,Cl case. Since the last three compounds all experience the anomeric effect to different extents but have virtually identical (acylated) nitrogen inversion barriers, it is apparent that the modest raising of the nitrogen inversion barriers is only marginally attributable to the specific electronic interactions which constitute the anomeric interaction.

Rotation about the Acyl C–N Bond. Rotation about the acyl C–N bond in formamide (**8**) and simple dialkyl amides is hindered by a barrier of about 18 kcal/mol. The barrier in the *N*-chloro system, **9**, is 15.5 kcal/mol *via* either the O-exo or O-endo transition structure. In the *N*-methoxy system **10**, the lower of the two barriers is similar, 15.7 kcal/mol. It appears that the presence of a single heteroatom on the nitrogen atom reduces the acyl rotation barrier by 1–2 kcal/mol. The presence of the second heteroatom on the nitrogen atom further lowers the barrier. In the chloromethoxy species **11**, the lower of the two barriers is only 7.0 kcal/mol, the higher being 11.3 kcal/mol relative to *Z*-**11**. In the lower acyl rotational transition structure, **[*Z*-11→*E*-11]**$_{exo}$, both the carbonyl oxygen atom and the methyl group adopt an exo orientation with respect to the pyramid at N. In the dimethoxy derivative **12**, four rotation transition structures were located. The lowest of these, **[XX-12→XX-12]**$_{exo}$, is 7.1 kcal/mol above NX-**12** and has the carbonyl oxygen atom and both methyl groups in exo orientations relative to the nitrogen pyramid. The remaining three transition structures (not shown in Figure 1 or Table 1), in which at least one of the groups is endo to the pyramid, are significantly higher in energy, 12.1, 12.7, and 13.2 kcal/mol, relative to NX-**12**. The lowest acyl rotational transition structure, **[XX-12→XX-12]**$_{exo}$, is *directly* achievable only from XX-**12** and poses a barrier of only 6.2 kcal/mol. Rotation along this coordinate is accompanied by pyramidal inversion at N and interconverts XX-**12** and its enantiomer. Thus in the absence of rotation about the N–O single bonds, rotation about the acyl C–N bond of the dimethoxy system requires at least 12 kcal/mol. We did not explicitly locate any of the four (or more) distinct acyl C–N rotational transition structures of the chlorodimethylamino system **13**. The approximate structure, **[*E*-13→*Z*-13]**$_{CN}$ (Figure 1), should be representative. It is 9.7 kcal/mol higher than *E*-**13**. Like the acylated nitrogen inversion barriers, the acyl C–N rotational barriers of the bisheteroatom-substituted systems all have similar values, in the range 6–10 kcal/mol. It must be concluded that the lowering of the acyl C–N rotational barriers is a consequence of the pyramidal stabilization due to the electronegative heteroatoms, which is accompanied by increased s character (decreased p character) of n_N and lower π conjugation. The specific influence of the anomeric interaction, which differs significantly in the last three compounds, on the acyl C–N rotational barriers is small.

Rotation about the N–O Bond of 11 and the N–N Bond of 13. Rotation about these bonds involves loss of and provides a direct measure of the anomeric effect. Rotation about the N–O bond in simple hydroxylamines is hindered by barriers of 10–11 kcal/mol.[12,30] The barrier originates predominantly as a result of the unfavorable four-electron interaction between the lone pair orbitals of the heteroatoms. In **10**, four separate transition structures to N–O rotation were located, the lowest being 5.6 kcal/mol above the global minimum energy conformer, *E*-**10**, from which it may be reached directly by rotation about the N–O bond by approximately 90°. It appears that the presence of the acyl group lowers the the N–O rotation barrier by 4–5 kcal/mol.

The presence of the second heteroatom in **11**, **12**, and **13** introduces *two* anomeric interactions. The nonbonded electron pair of either heteroatom may undergo an attractive two-electron interaction with the σ^*_{NX} orbital of the other. The chloro systems **11** and **13** are simpler since one of interactions ($n_O-\sigma^*_{NCl}$, $n_N-\sigma^*_{NCl}$) will dominate. The effects of the $n_O-\sigma^*_{NCl}$ interaction are expected to be more pronounced than those of the $n_O-\sigma^*_{NO'}$ interaction in **12**, and the $n_N-\sigma^*_{NCl}$ interaction will be the strongest of the three. We examine in detail the

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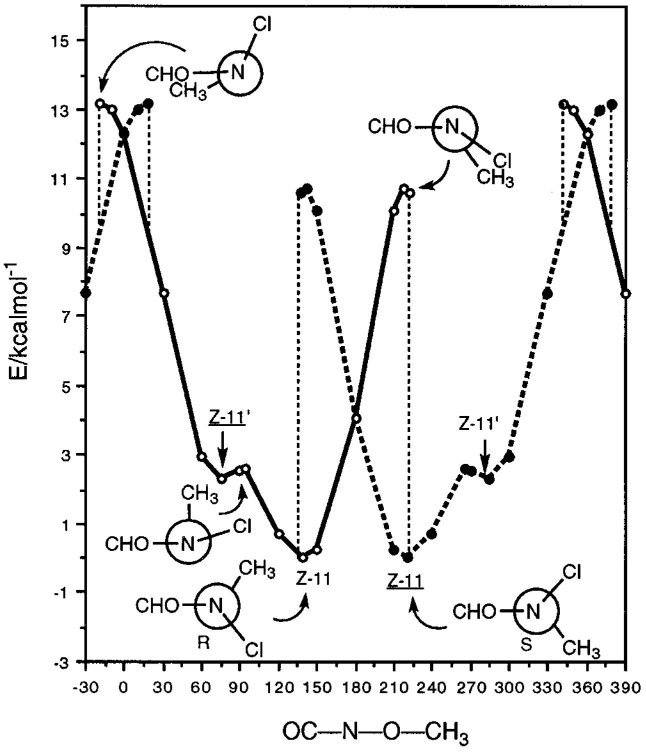

Figure 3. Potential curves for rotation about the N–O bond of *Z*-**11**. Transitions between the two overlapping curves occur in the regions of the vertical dashed lines and are accompanied by pyramidal inversion and large changes in the Cl–N–O–C dihedral angle.

intermediate system **11** since it it does not have the additional complication of stereoisomerism at a second nitrogen atom as in **13**. The relaxed vibrationless potential energy profile for the rotation about the N–O bond of *Z*-**11** as a function of the C–N–O–C dihedral angle is shown in Figure 3. Since the geometry at nitrogen is very labile, rotation stepped along the C–N–O–C coordinate is accompanied by large fluctuations in the Cl–N–O–C dihedral angle which, according to the anomeric effect, has an optimum value of 90°. This is the value found at the potential energy minimum which occurs at C–N–O–C = 138.5° if the absolute configuration at N is *R* and at C–N–O–C = 221.5° if the absolute configuration at N is *S*. Indeed, the N–O rotation is accompanied by spontaneous pyramidal inversion at N at several points (near 20°, 95°, 140°, 220°, 265°, and 340°) as the Cl–N and O–C bonds attempt to adopt a perpendicular orientation in accordance with the anomeric effect. The pair of enantiomeric rotational transition structures at 142.7° and 217.3° correspond to the lower potential energy barriers to N–O rotation, 10.7 kcal/mol, and occur as the methyl group is passing the chlorine atom. Eclipsing of the methyl group and the formyl group poses a barrier of 13.2 kcal/mol. At both barriers, the anomeric interaction is lost. These values represent a reversal of the lowering of the N–O rotation barrier due to acyl substitution. Since the barrier to acyl C–N rotation is 7.0 kcal/mol, *E*,*Z* isomerization will be rapid compared to isomerization due to N–O rotation. We have not explored the rotational potential profile for *E*-**11** but expect that it will be similar to that for *Z*-**11**. Neither have we examined in detail the significantly more complex dimethoxy system **12**. It is reasonable to expect that N–O bond rotational barriers in **12** will be *lower* than in **11** since the anomeric effect is greater in **11** than in **12**.

The rotational potential profile for simple hydrazines has two barriers, an *anti* barrier of about 3–4 kcal/mol and a *syn* barrier (in which all groups including lone pairs are eclipsed) of 11–13 kcal/mol.[30,31] The latter is similar to that measured experimentally in ^{1}H NMR experiments.[32] In order to obtain an estimate of the N–N rotational energy barrier of *E*-**13**, we carried out an optimization with the constraint that the N–Cl bond be kept perpendicular to the plane bisecting the dimethylamino group (and therefore the nitrogen lone pair). In this geometry, the anomeric effect is minimized. The resulting structure, **[*E*-13→*E*-13]**$_{NN}$ (Figure 1) is 19.3 kcal/mol less stable than *E*-**13**. It is likely that the highest barrier to stereoisomeric interconversion in **13** is rotation about the N–N bond, a direct consequence of loss of the anomeric interaction.

Conclusions

The structure and rotational barrier of formamide **8** are well reproduced by the hybrid Hartree–Fock–density functional theoretical level based on Becke's three-parameter functional and the 6-31G(D) basis set (Becke3LYP/6-31G(D)). The computations suggest that single heteroatom (Cl or OCH_3) substitution on the acyl nitrogen does not alter the planarity of the nitrogen atom after vibrational motion is considered and lowers the barriers to acyl C–N rotation by 1–2 kcal/mol to about 16 kcal/mol. Considered as an acylated hydroxylamine, the presence of the acyl group lowers the barriers to N–O rotation in *N*-methoxyformamide (**10**), by 4–5 kcal/mol to 5.6 and 7.4 kcal/mol.

The equilibrium and transition structures of the bisheteroatom-substituted formamides **11**, **12**, and **13** are dictated by inductive effects of the electronegative substituents, repulsive lone pair–lone pair interactions, and anomeric effects. The specific consequences of the anomeric interactions are that the N–Cl bonds are longer by 0.05–0.35 Å than normal in the equilibrium structures of **11** and **13**; the N–O and N–N bonds are shortened by 0.04–0.14 Å in **11**, **12**, and **13**, the larger deviations occuring in **13**; for **11**, **12**, and **13**, in each of the equilibrium and transition structures, except the transition structures to N–O and N–N bond rotation, the donor and acceptor groups are always oriented so as to place the donor n_X orbital in an approximate anticoplanar arrangement relative to the acceptor N–Y bond. The anomeric interaction does not appear to have a specific contribution to lowering of acyl C–N rotation barriers which are in the range of 8–10 kcal/mol for all three bisheteroatom-substituted systems, nor to the magnitude of the inversion barriers which are constant at about 2–3 kcal/mol. The anomeric effect does increase the magnitude of N–O and N–N rotation barriers, bringing the N–O barriers in **11** back to normal values for hydroxylamines (countering the effect of acyl substitution) and raising the N–N rotation barrier in **13** to almost 20 kcal/mol. The C–N, N–O, and N–N rotational barriers are predicted to be in the energy range conveniently studied in dynamic high-field NMR experiments.

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Computational Methods

All structures were fully optimized using procedures standard to the Gaussian 92/DFT system of computer programs[33] and the internal 6-31G(D) basis set. In all cases, the hybrid Hartree−Fock (HF)−density functional theoretical (DFT) approach based on Becke's three-parameter functional[34] was employed (Becke3LYP). The functional form is

$$(1 - a_O)E_X^{LSDA} + a_O E_X^{HF} + a_X \Delta E_X^{B88} + a_C E_C^{LYP} + (1 - a_C)E_C^{VWN}$$

where the energy terms are the Slater exchange, the Hartree−Fock exchange, Becke's 1988 exchange functional correction,[35] the gradient-corrected correlation functional of Lee, Yang, and Parr,[36] and the local correlation functional of Vosko, Wilk, and Nusair,[37] respectively. The values of the coefficients determined by Becke are

$$a_O = 0.20, \quad a_X = 0.72, \quad a_C = 0.81$$

Harmonic vibrational analysis was performed to verify the nature of the stationary point as minimum or transition structure and to provide zero-point energy (ZPE) correction and infrared (IR) frequency information. For the latter two purposes, the vibrational frequencies were scaled by 0.95.

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