Barriers to Nitrogen Inversion in Cyclic and Acyclic Substituted Hydroxylamines. A Theoretical Study[1]

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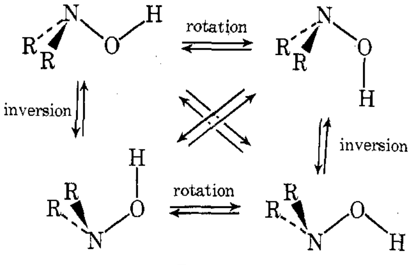
Approximate SCF-MO calculations (CNDO/2) have been used to study nitrogen inversion in *N,N*-dimethylhydroxylamine. The difference between the barriers in cyclic and acyclic substituted hydroxylamines was simulated by calculating the inversion barrier as a function of dihedral angle. Excellent agreement between calculated and experimental barriers was found. The results obtained have provided evidence for an inversion-dominated topomerization in dialkyl- and trialkylhydroxylamines and for rate retardation due to lone pair–lone pair interactions as well as the electronegativity of oxygen.

Numerous experimental investigations of barriers to conformational interchange in cyclic and acyclic hydroxylamines have been carried out[3-5] and have also been the subject of theoretical interest.[6] Chemical shift nonequivalence of diastereotopic groups in these systems can arise from slow inversion of the nitrogen pyramid or slow torsion about the nitrogen–oxygen single bond since both processes are required for topomerization (Scheme I). In cyclic hydroxylamines where the nitrogen and oxygen atoms form part of three-,[4,7] four-,[8] or five[9]-membered rings the rate-determining step must be inversion of the nitrogen pyramid, since the ring system constrains the N–O bond to a planar or nearly planar geometry, which is very close to the transition state for torsion. Very substantial barriers to nitrogen inversion are observed in these systems. The presence of the oxygen atom greatly increases the barriers, and oxaziridines exhibit the highest nitrogen inversion barriers which have been measured.

Scheme I.



The acyclic hydroxylamine derivatives represent a more ambiguous case. Here, either torsion or inversion could be the rate-determining step. It has been argued that slow nitrogen inversion is the rate-determining step in the topomerization of trialkylhydroxylamines,[10] while in other hydroxylamine systems, evidence for substantial torsional barriers has been obtained.[5,11] A third possibility which may be considered is that torsion and inversion occur synchronously rather than sequentially and that the transition state for the topomerization involves both flattening of the nitrogen pyramid and torsion about the N–O bond.

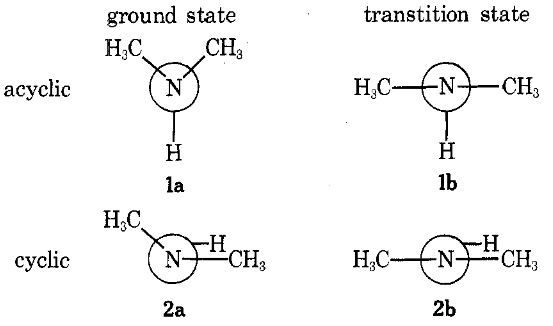
It is clear that the presence of an oxygen atom bonded to nitrogen has an important effect in raising the barrier to nitrogen inversion. However, the precise reasons for this effect are not entirely clear. The electronegativity of the oxygen atom and the presence of nonbonding valence electrons are two features of the oxygen atom which have been implicated. Both theoretical[12] and experimental[13] evidence have been obtained for increased barriers to nitrogen inversion as a function of the increased electronegativity of the atom bonded to nitrogen. Interactions between lone pairs of valence electrons on adjacent atoms might also lead to increased nitrogen inversion barriers. Overlap between filled valence level orbitals should lead to destabilization and this destabilization should be greatest in the transition state for nitrogen inversion since the increased p character of the nitrogen lone pair orbital should facilitate π overlap.

Comparison between cyclic and acyclic analogues can provide one means of distinguishing between these two possibilities. If electronegativity alone were important we would expect to find the nitrogen inversion barrier to be independent of the N–O dihedral angle since the inductive potency of the oxygen atom should not be affected by the torsion angle. If, on the other hand, π overlap between vicinal pairs of nonbonded valence electrons is most important we would expect to find that the nitrogen inversion barrier is a strong function of dihedral angle. Since the interaction is repulsive, the adoption of a geometry of minimum interaction, which is possible only for the acyclic examples, should lead to lowered nitrogen inversion barriers. Indeed, comparisons of this sort between experimentally obtained barriers for cyclic and acyclic trialkylhydroxylamines indicated that the barriers in the acyclic compounds are ca. 3 kcal/mol lower than in their cyclic analogues.[5] Barriers to nitrogen inversion in acyclic hydrazines also appear to be substantially lower than in cyclic hydrazines.[14]

These comparisons suffer from the drawback that not all parameters can be effectively controlled. Thus, steric interactions and ring strain are known to have large effects on nitrogen inversion barriers, and it is not possible to devise model cyclic and acyclic compounds in which differences in steric interactions are removed and in which ring strain effects are avoided. For this reason the conclusions based upon experimental comparisons are not completely definitive. A more conclusive comparison would have to involve cyclic and acyclic models in which all molecular parameters would be identical except for the dihedral angle associated with the nitrogen–oxygen bond. While such models are not accessible experimentally, such a comparison between calculated inversion barriers can be realized using molecular orbital calculations. This paper reports the results of such a study of barriers to nitrogen inversion in *N,N*-dimethylhydroxylamine using CNDO/2 SCF-MO calculations. The geometries used for the acyclic ground state (**1a**) and transition state (**1b**) and the cyclic ground state (**2a**) and transition state (**2b**) were those in Scheme II.

Method of Calculation. CNDO/2 calculations were carried out using the CNINDO program.[15] Geometry optimization was

Scheme II



performed for the N–O, O–H and C–N bond lengths and for the C–N–C and N–O–H bond angles in the ground state and in the transition state. The angle between the O–N bond and the C–N–C plane (nitrogen out of plane angle) was also optimized for the ground state. The geometry of the methyl hydrogens was not optimized but held fixed throughout the calculations. The methyl H–C–H and H–C–N bond angles were precisely tetrahedral, and the C–N torsion angles were such that two of the hydrogen atoms lay in the CNC plane and these atoms H–C–N–C–H traced out a W shape. The bond lengths and angles are given in Table I. The same bond lengths and angles were used for the cyclic model except for the C–N–O–H dihedral angle, which was set equal to 0° (eclipsed methyl group and hydrogen). The original parameters of the CNINDO program were used throughout the calculations.

Results and Discussion

The energies of both the pyramidal ground state and the planar transition state were calculated as a function of the torsion angle. These data are given in Table II and are plotted in Figure 1.[17] Two different representations for the torsion angle can be used: ϕ, the dihedral angle between the O–H bond and one of the N–C bonds, and θ, the dihedral angle between the O–H bond and the bisector plane of the C–N–C angle, which also corresponds to the dihedral angle between the O–H bond and the nitrogen lone pair orbital. Since the latter is of greater significance in terms of lone pair interactions, the data in Figure 1 are plotted in terms of θ.

The lone pair interactions between oxygen and nitrogen are best considered by dividing the lone pair density on oxygen into two nonequivalent lone pair orbitals. One of these orbitals is the pure p orbital which has its axis at right angles to the N–O–H plane; the other is a hybrid orbital in the N–O–H plane which has approximately sp hybridization ($sp^{0.8}$ for an N–O–H angle of 107°).[18] If we consider π overlap between the lone pair orbital on nitrogen and the lone pair orbitals on oxygen, it is clear that π overlap with the pure p orbital must be much more important than that with the hybrid orbital. Minimum overlap will then occur when the nitrogen lone pair lies within the N–O–H plane, i.e., when $\theta = 90°$.

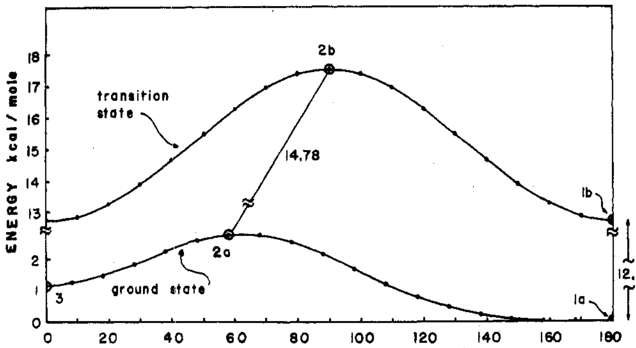


Figure 1. CNDO/2 calculated energy profiles for N–O torsion for the pyramidal (ground) and planar (transition) states of dimethylhydroxylamine.

Table I.[a] **Geometry of *N,N*-Dimethylhydroxylamine, Optimized with Respect to Minimum Energy**

	Ground state	Transition state
Bond lengths, Å		
O–H	1.04	1.04
N–O	1.30	1.29
C–N	1.42	1.41
C–H	(1.093)	(1.093)
Bond angles, deg		
N–O–H	107	108
C–N–C	107	122
Dihedral angle between N–O and C–N–C plane, deg	123	(180)

[a] Bond lengths and angles in parentheses were not adjusted to provide minimum energy.

Table II. Change of Calculated Total Energy as a Function of Dihedral Angle

Ground state			Transition state		
ϕ^a	θ^b	E^c	E^c	θ^b	ϕ^a
−58.2	0	1.16	12.74	0	90
−50	8.2	1.23	12.87	10	80
−40	18.2	1.47	13.26	20	70
−30	28.2	1.84	13.88	30	60
−20	38.2	2.24	14.64	40	50
−10	48.2	2.59	15.48	50	40
0	58.2	2.78	16.28	60	30
10	68.2	2.77	16.95	70	20
20	78.2	2.54	17.40	80	10
30	88.2	2.16	17.56	90	0
40	98.2	1.68	17.40	100	−10
50	108.2	1.21	16.95	110	−20
60	118.2	0.78	16.28	120	−30
70	128.2	0.46	15.48	130	−40
80	138.2	0.23	14.64	140	−50
90	148.2	0.1	13.88	150	−60
100	158.2	0.03	13.26	160	−70
110	168.2	0.01	12.87	170	−80
121.8	180.	0	12.74	180	−90

[a] HONC dihedral angle. [b] Dihedral angle between OH and CNC bisector. [c] Total energy (kcal/mol) relative to the energy of the minimum energy ground state conformation.

As the data indicate, both geometries exhibit torsional barriers, although these barriers are considerably smaller than those expected on the basis of the barriers measured experimentally for *N*-phenyl and *N*-acylhydroxylamines,[5,9] or obtained using ab initio calculations.[6]

In both cases energy minima are found which correspond to eclipsing of the O–H bond with the nitrogen lone pair orbital (i.e., corresponding to $\theta = 0$ and 180°), geometries of minimum π overlap between lone pair orbitals on oxygen and nitrogen. This is in accord with suggestions based upon variable temperature NMR spectra of *N*-alkoxy-2-piperidones.[5] While the curve for the planar transition state is symmetrical, that for the ground state is unsymmetrical since two geometries are possible, **1a** and **3**, in which the O–H bond eclipses the nitrogen lone pair. While both represent local minima, the

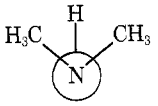


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Table III. Calculated and Experimental Nitrogen Inversion Barriers in Substituted Hydroxylamines

State	CNDO/2 barrier[a]	Exptl barriers
Acyclic	12.7	12.8[c]
Cyclic[b]	14.8	15.6[d]

[a] Difference between calculated total energies for the ground and transition states (kcal/mol). [b] The cyclic state means full eclipsing of CH_3 and H. Variation of the dihedral angle by 10° in either direction caused changes in total energy of ca. 0.2 kcal/mol. [c] Barrier for *N*,*N*-dibenzylhydroxylamine in $CDCl_3$ from ref 10c. [d] Barrier for *N*-methylisoxazolidine in $CDCl_3$ from ref 9a.

conformer **1a,** whose Newman projection resembles a Y, is of lower energy than conformer **3** (which has been referred to as the W conformer[6c]). It is noteworthy that ab initio calculations[6] on hydroxylamine itself and on the related isoelectronic anion $^-CH_2OH$ have also indicated that the Y conformer is more stable than the W conformer. An x-ray crystallographic structure determination of a related compound, a sulfenamide, similarly featured a Y conformation along the N–S bond in the Newman projection.[20]

The ground state conformation **2a** serves as a cyclic model and has dihedral angles of $\phi = 0°$ and $\theta = 58.2°$. This point lies very close to the torsional energy maximum which occurs at $\phi = 5°$, $\theta = 63°$. Thus, the judgment[5] that the geometry in cyclic compounds corresponds to a point near the torsional maximum and to a geometry of maximum repulsive interaction seems to be supported. We may note also that the calculated torsional barrier is higher for the transition state than for the ground state as predicted by the model discussed above, since increased p character in the nitrogen lone pair orbital should result in greater overlap with the oxygen lone pair p orbital in the torsional transition state.

The nitrogen inversion barriers are obtained by taking differences between points on the two curves in Table II or Figure 1. Vertical lines in Figure 1 represent inversion barriers under the constraint that θ remain a constant. This is satisfactory for **1** since both the ground state and transition state have values of $\theta = 180°$; the value of ϕ, however, changes from 121.8° in **1a** to 90° in **1b.** By contrast, the inversion of the cyclic model is characterized by a change in θ from 58.2° in **2a** to 90°, while ϕ remains unchanged at 0° for both ground and transition states. For this reason the inversion of **2** is not represented by a veritcal line in Figure 1 but by an oblique line.

The values for the inversion barriers as calculated by CNDO/2 are given in Table III. The agreement of the CNDO/2 values with experimental values is surprisingly good. The experimental barriers obtained by variable temperature NMR spectroscopy for the similar compounds *N*,*N*-dibenzylhydroxylamine[10c] and *N*-methylisoxazolidine[9a] are given in Table III for comparison purposes. We have also calculated the inversion barriers using two other semiempirical methods, INDO and the modification of CNDO developed by Mislow and co-workers for the calculation of pyramidal inversion barriers.[13b] However, the CNDO/2 optimized geometry was used with these methods, resulting in barriers which are much too low (INDO cyclic model barrier 5.2 kcal/mol; acyclic 1.6 kcal/mol. Modified CNDO cyclic model barrier 3.8 kcal/mol; acyclic 2.4 kcal/mol). Apparently this procedure is inadequate, and individual geometry optimization with each method is essential in order to obtain acceptable results. In spite of this fact, the same general trend to higher barriers for the cyclic models is evident by both of these methods, lending further support to the conclusion derived from this trend as calculated using the CNDO/2 method.

Table IV. Eigenvectors for the HOMO of 2b

Atom	Atomic orbital[a]	Eigenvector
O	p_z	0.4298
N	p_z	−0.7721
C_1	p_z	0.1142
C_2	p_z	0.1158
H-(O)	s	0
H_1	s	0
H_2	s	−0.2190
H_3	s	0.2190
H_4	s	0
H_5	s	0.2200
H_6	s	−0.2200

[a] The AO's which are not listed had zero Eigenvectors.

The mechanism for stereomutation or topomerization of substituted hydroxylamines has been a matter of some controversy. Both inversion of the nitrogen pyramid and torsion about the N–O bond are required for interconversion of a chiral hydroxylamine and its mirror image (degenerate racemization). Since either step could conceivably be the rate-determining step the topomerization can be described as rotation dominated[6e] if the reaction coordinate in the neighborhood of the transition state primarily describes torsion about the N–O bond or inversion dominated if the reaction coordinate involves predominantly changes in pyramidality at nitrogen. A number of experimental probes have been used to distinguish between rotation-dominated and inversion-dominated topomerization in the sulfur analogues of hydroxylamines, the sulfenamides.[20,21] In the sulfenamide series the experimental results have demonstrated conclusively that the topomerization is rotation dominated, except in the sulfenylaziridines where inversion-dominated topomerization is found.[22] The experimental data in the hydroxylamine system have been far more ambiguous. Initial results on substituent effects on inversion barriers in trialkylhydroxylamines seemed to favor a rotation-dominated mechanism.[23] Subsequent studies have indicated that other substituent effects favor inversion-dominated topomerization.[10c] In our view, the present close agreement between calculated and observed barriers provides further support for the assignment of an inversion-dominated mechanism for topomerization of dialkyl- and trialkylhydroxylamines.

The results rule out the possibility that inversion and rotation take place simultaneously in acyclic hydroxylamines with a common planar transition state (the diagonal path in Scheme I). Such a transition state would correspond to the cyclic conformation **2b.** The data in Table II and Figure 1 indicate that the energy of **2b** is substantially higher than that of either **1b** or **2a,** which are the transition state conformations for nitrogen inversion and N–O torsion in the acyclic molecule.

Examination of the molecular orbitals calculated for the cyclic transition state **2b** further indicates the importance of π overlap of the lone-pair p orbitals on nitrogen and oxygen. In this conformation all of the atoms except the methyl hydrogen atoms lie in the XY plane, and hence an analysis of the contribution of each of the isoalted atomic orbitals to the moelcular orbitals can be made. The highest occupied molecular orbital (HOMO) of **2b** clearly corresponds to antibonding π interaction of the p_z orbitals of the nitrogen and oxygen atoms (Table IV). This destabilizing interaction obviously becomes smaller as the dihedral angle between the p_z orbitals is changed, and the overlap reduced.

Our results also provide more convincing evidence that repulsive interactions between nonbonded valence electrons play a role in raising barriers to nitrogen inversion in cyclic hydroxylamines and, by extension, in related systems including substituted hydrazines. This is clearly not the only source of the rate retardation: the high barriers calculated and measured for acyclic hydroxylamines indicate that the electronegativity of the oxygen atom also plays a very important role.

Registry No.—*N,N*-Dimethylhydroxylamine, 5725-96-2; *N,N*-dibenzylhydroxylamine, 621-07-8; *N*-methylisoxazolidine, 22445-44-9.

References and Notes

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Regiospecific Synthesis of Unsymmetrical Azoxy Compounds (Diazene *N*-Oxides)[1a]

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A directed synthesis is described of unsymmetrical azoxy compounds by condensation of nitroso substrates with *N,N*-dihaloamino derivatives in the presence of different types of promoters. Products bearing a variety of substituents, including aryl, alkyl, carboxylate, carbonamide, and halogen groups, are produced in fair to high yield. Evidence is presented that the reaction can proceed by several mechanistic pathways, depending upon the promoter.

Until 1974 there were only two useful methods for the regiospecific synthesis of azoxyalkanes and alkylazoxyarenes.[2,3] Other methods are not regiospecific[4a,b] or are impractical when electron-withdrawing groups are present.[4c] Recently,[5] we described the regiospecific synthesis of azoxyalkanes and alkylazoxyarenes by condensation of an *N,N*-dichloro amine with a nitroso compound in the presence of caustic (eq 1)

$$\mathrm{RNCl_2 + R'NO \longrightarrow RN{=}N(O)R'} \qquad (1)$$

but the method is not useful if product or starting material is sensitive to basic conditions.

We herein report that the condensation of *N,N*-dihalo amine derivatives and tertiary alkyl or aryl nitroso compounds can be effected by a wide variety of promoters, generally in fair to excellent yields. It is probable that several mechanistic pathways pertain, depending upon the promoter.

Results and Discussion

By the condensation of a tertiary alkyl or aryl nitroso substrate with an *N,N*-dihalo amine derivative, various types of azoxy compounds (Table I) have been prepared. In addition to the base-sensitive ester (**3**), amide (**5**), and acyl derivative (**4**), we have synthesized members containing two azoxy moieties (**10** and **11**) (Table II), and the interesting compound "chloroazoxobenzene" (**8**) in a yield superior to that reported in the only other published procedure.[6]

The method also works with *N,N*-dibromo compounds as shown in Table III. Only two dibromoamino derivatives, a dibromo amide and dibromo amine, were investigated. In general *N,N*-dibromo substrates provide considerably higher yields than the corresponding *N,N*-dichloro counterparts. The *N,N*-dibromo amide, however, gave poorer results, presumably owing to its instability (decomposition even below 0 °C). This method for the synthesis of azoxy compounds is limited mainly by the availability of the nitroso precursor and the lack of success with aromatic *N*-halo amines. An attempt by us to N,N-dichlorinate *m*-nitroaniline was not fruitful, and exposure of sulfanilic acid to hypochlorite yielded the corresponding azo compound.[7]

Since primary and secondary nitrosoalkanes preferentially exist as the oxime tautomers, we were able to use only tertiary alkyl or aryl nitroso compounds. With the intent of circumventing this deficiency, we prepared the haloazoxy compounds **6** and **12** in order to replace subsequently the halogen with hydrogen. Attempted reductions with Zn, $CrCl_2$, Bu_3SnH, $NaBH_4$, and HI yielded intractable material in all cases. Sodium cyanoborohydride proved to be unreactive, even toward the azoxy moiety.

A convenient synthesis of azoxyalkenes is desirable, since several natural products[8] such as **13** contain α,β unsaturation, for which type there are only a few published syntheses.[9] Experiments aimed at producing such compounds from pre-