Barriers to Rotation about the Nitrogen–Oxygen Single Bond in Substituted Hydroxylamines[1]

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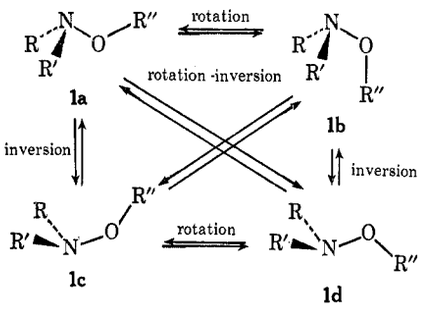
Substituted hydroxylamines have occupied a central position in Dnmr studies of barriers to nitrogen inversion and barriers to rotation about nitrogen–heteroatom bonds.[2] One of the earliest reports of slow nitrogen inversion described chemical shift nonequivalence in a cyclic hydroxylamine, an oxaziridine.[3a] The oxaziridine system also furnished the first example of an optically active compound whose optical stability was due to slow inversion of a nitrogen pyramid.[3b] Recently, substantial barriers to nitrogen inversion have been observed in other cyclic hydroxylamines, where the nitrogen and oxygen atoms form part of a four[4]- or five[5]-membered ring. Chemical shift nonequivalence and barriers to conformational interchange have also been studied in tetrahydrooxazines,[5a,b] although, as Lambert has pointed out, it is difficult to distinguish nitrogen inversion from ring reversal in six-membered ring systems.[2d]

Chemical shift nonequivalence and coalescence of signals from diastereotopic nuclei have also been observed in acyclic trialkyl hydroxylamines and, in fact, these initial reports attributed these phenomena to slow nitrogen inversion.[6,7] Subsequently, it was pointed out that the observed phenomena might have originated from slow rotation about the N–O single bond instead of slow nitrogen inversion.[8,9] If the ground state conformation of hydroxylamines and their derivatives is represented by **1a** or **1b** (Scheme I) coalescence of diastereotopic benzyl methylene protons or isopropyl methyl groups must be associated with a degenerate racemization: **1a** ⇄ **1d**, or **1b** ⇄ **1c**. As illustrated in Scheme I, both rotation and inversion are required for topomerization, and the question at issue is the specification of the rate-determining step as either inversion or rotation.[10] A third possibility

SCHEME I

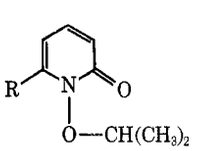


which may be considered is that torsion and inversion occur synchronously rather than sequentially and that the transition state for the topomerization involves both flattening of the nitrogen pyramid and torsion about the N–O bond.

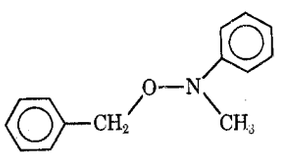
This paper describes conformational interchanges associated with N–O torsional barriers in compounds in which nitrogen must be planar, or inverting rapidly, and, consequently, for which slow nitrogen inversion may be excluded as a possible rate determining step in the topomerization.

Results

Conjugation of the nitrogen lone pair with a carbonyl group or a phenyl ring is known to lower nitrogen inversion barriers very considerably. The replacement of an *N*-alkyl group in aziridines by phenyl lowers the nitrogen inversion barrier by 8 kcal/mol,[11] while the barrier in *N*-acylaziridines is apparently too small to be measured (less than 5 kcal/mol). Substituted hydroxylamines **2a**, **2b**, and **3** containing both structural features were examined. All three compounds showed line broadening as torsion about



2a, R = H
b, R = Cl



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the N–O bond became slow on the nmr time scale. Alkoxypyridone **2b** exhibited line broadening at a much higher temperature than did **2a**. The transition state for topomerization in **2b** probably involves steric crowding of the isopropyl group with either the oxygen or chlorine atom. The rate constant for torsion at the coalescence temperature was obtained by complete line shape analysis and afforded the free energy of activation ($\Delta\nu$ = 23 Hz, T_c = −73.5°, $\Delta G^{\pm}$ = 10.0 kcal/mol). Although we were unable to measure the low temperature limit spectra for **2a** and **3**, we were able to obtain ranges for their free energies of activation using complete line shape analysis. The spectra were measured at temperatures at which line broaden-

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(10) Although the interconversion **1a** ⇄ **1b**, or **1c** ⇄ **1d** could be effected by "planar inversion" at divalent oxygen, this process very probably requires a great deal more energy and need not be considered in systems where torsion is a possible alternative: A. J. Gordon and J. P. Gallagher, *Tetrahedron Lett.*, 2541 (1970).

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ing was substantial and were matched with theoretical spectra. A range of values was used for the chemical shift difference, $\Delta\nu$, and each value of $\Delta\nu$ afforded a different value for the first-order rate constant and subsequently for the free energy of activation. Thus we obtained in each case a range for k and for $\Delta G^{\ddagger}$, corresponding to a range for $\Delta\nu$: **2a**, $\Delta\nu$ = 15–50 Hz, k = 45–340 sec^{-1}, T = −86°, $\Delta G^{\ddagger}$ = 8.6–9.4 kcal/mol; **3**,[12] $\Delta\nu$ = 25–50 Hz, k = 90–320 sec^{-1}, T = −93°, $\Delta G^{\ddagger}$ = 8.3–8.7 kcal/mol. A "best estimate" for the rate constant and free energy of activation for **2a** was obtained by assuming a comparable value of $\Delta\nu$ to that measured for **2b**. The values (**2a**, k = 51 sec^{-1}, $\Delta G^{\ddagger}$ = 9.3 kcal/mol) fall in the ranges quoted above. Although the free energies could not be measured precisely, the ranges obtained are fairly narrow and are sufficient for further discussion.

Discussion

Slow rotation about bonds between heteroatoms bearing nonbonding valence electrons is a fairly well documented phenomenon, and torsional barriers have been measured by Dnmr spectroscopy[2c] for P–N,[13] S–N,[14] N–N,[15] and S–S[16] bonds. Our results confirm that substantial barriers to rotation about N–O single bonds do exist as well and that we may suppose that comparable barriers exist in other compounds containing N–O single bonds. In this respect they support, in a qualitative sense at least, the *ab initio* calculations on hydroxylamine by Pedersen and Morokuma which indicated a torsional barrier of 9.9 kcal/mol.[17]

There has been considerable disagreement concerning the rate-determining step in the topomerization of acyclic trialkylhydroxylamines. Some workers have argued that the rate-determining step is slow nitrogen inversion.[18,19] Others have suggested that slow rotation about the N–O single bond can account as well or better for the experimental observations of chemical shift nonequivalence and coalescence of signals from diastereotopic groups.[8,9,20] One approach to this problem has been to examine compounds in which either of these processes can be excluded.

In cyclic trialkylhydroxylamines the torsional process can be excluded when both heteroatoms are part of a three-, four-, and five-membered ring. Experiments in this area have indicated that nitrogen inversion is indeed slowed by the presence of the oxygen atom. In evaluating experiments on cyclic compounds as predictors for similar trends in acyclic compounds it is of crucial importance to determine whether retardation of the inversion rate derives from the electronegativity of the oxygen atom or the presence of nonbonding valence electrons. If electronegativity alone is important, we would expect comparable rate retardation in cyclic and acyclic compounds, since the inductive potency of oxygen should be only a weak function of torsion angle. If, on the other hand, interactions between vicinal electron pairs are dominant, we may expect to find that the magnitude of the rate retardation is a strong function of dihedral angle. Unlike the cyclic examples, the acyclic molecules are free to adopt a geometry of minimum interaction. Our results for **2** and **3** indicate that the ground state for these hydroxylamines, like their sulfur analogs, the sulfenamides, must be chiral. Given the planarity of the pyridone ring in **2**, we may conclude that the NOC plane approximately bisects the bond angle formed by the other two ligands at nitrogen.[5c] The geometry in the cyclic compounds approximates that in the transition state for torsion about the N–O bond. If repulsive interactions do indeed contribute substantially to torsional barriers, as has been suggested, it is necessary that the magnitude of the interaction be greater in a geometry approximating that in the transition state for torsion than it is when the molecule is free to achieve a geometry of minimum interaction.

The strongest evidence that electronegativity is important has been the finding, in both experimental investigations and studies using molecular orbital calculations, that the electropositive elements silicon, germanium, and tin lower barriers to pyramidal inversion.[2,21] On the other hand, experimental investigations have indicated that the barriers to nitrogen inversion in acyclic hydrazines are substantially lower than in cyclic analogs. This apparent dependence of the barrier increase due to heteroatom substitution at nitrogen does not seem to be consistent with the sole importance of electronegativity. It is more difficult to make such a comparison in the hydroxylamine series. However, the barriers to nitrogen inversion in acyclic trialkylhydroxylamines can be no higher than 12–13 kcal/mol, *i.e.*, lower than those in cyclic analogs. If we take *N*-benzyl-*N*,*O*-dimethylhydroxylamine and *N*-methylisoxazolidine as comparable acyclic and cyclic compounds the difference amounts to 3.3 kcal/mol.[5a,7] This comparison suggests a significant dihedral angle requirement and a contribution to the inversion rate diminution from the interaction between electron pairs on neighboring heteroatoms. When all of the evidence is taken together it seems most likely that both electronegativity and lone pair interactions contribute to increases in inversion barriers, although it does not seem possible, at this time, to make a definitive conclusion about the relative importance of these two factors.

The present study, as well as a previous investigation of *N*,*O*-diacylhydroxylamines,[18] deal with compounds in which conjugation lowers nitrogen inversion barriers enough that the barriers observed must be torsional. Further the *N*-alkoxy pyridone system is one in which there can be no confusion between tor-

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sion about an amide linkage and torsion about the N–O bond.

On the one hand, the observation of barriers to rotation in **2** and **3** makes the suggestion that torsional barriers may account for the observed nonequivalence in other hydroxylamine derivatives seem reasonable. On the other hand, it may be argued[18] that the magnitude of the barriers observed for **2** and **3** suggests that the somewhat higher barriers observed for trialkylhydroxylamines derive from another hindered conformational interchange, namely nitrogen inversion. However, we note that torsional barriers as well as inversion barriers seem to be subject to substituent effects. In particular the torsional barriers in *N,N*-(dialkyl)trichloromethanesulfenamides are lowered by about 3 kcal/mol when the two alkyl groups are replaced by the diacyl succinimide ring.[14d] If the replacement of the *N*-alkyl groups by the pyridone ring were to result in a comparable lowering of the N–O torsional barrier we would expect the torsional barriers in trialkylhydroxylamines to be about 11–12 kcal/mol, which is very close to the barriers observed. Because of these, as yet poorly understood, substituent effects on torsional barriers we do not believe that comparisons of this sort offer convincing evidence concerning the nature of the rate-determining step in topomerization of trialkylhydroxylamines in the absence of confirming evidence.

We do not believe that it is possible, at this time, to definitively assign the barriers to topomerization in trialkylhydroxylamines to either slow inversion or slow rotation. The evidence accumulated thus far seems to indicate that both inversion and rotation barriers are substantial in compounds containing N–O single bonds. Given the probability that substituents and solvents can affect the shape of the conformational energy surface it seems possible that subtle changes in structure and medium should be capable of shifting from a torsional transition state for topomerization to an inversional one or vice versa.

Experimental Section

Elemental analyses were performed by Midwest Microlab, Inc. Nmr spectra were measured on a Varian A-60A spectrometer, in toluene-d_8 solution. Temperatures were calibrated using methanol spectra as described in the Varian manual. Melting points were measured on a Thomas–Hoover melting point apparatus. *N*-Benzyloxy-*N*-methylaniline (**3**) was prepared as described in the literature.[22] Both *N*-isopropoxy-2(1*H*)-pyridones were prepared in a manner similar to that described by Paquette.[23]

***N*-Isopropoxy-2(1*H*)-pyridone (2a).**—Pyridone **2a** was synthesized from 2-ethoxypyridine *N*-oxide[24] by treatment of the latter with excess 2-bromopropane and heating under reflux for 4 days. The mixture was distilled under reduced pressure and a fraction boiling at 69–72° (0.2 mm) was collected (80%). This material was shown by its nmr spectrum to be a 5:2 mixture of **2a** and *N*-ethoxy-2(1*H*)-pyridone which resulted from rearrangement of the starting material. Chromatography of 0.30 g of distillate on 25 g of silica gel (3:1 hexane–acetone eluent) afforded 0.20 g of pure **2a**.

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.28; H, 7.52; N, 8.98.

2-Chloro-6-ethoxypyridine *N*-Oxide (4).—2-Chloro-6-ethoxypyridine *N*-oxide (4) was synthesized from commercial 2-chloro-6-ethoxypyridine by hydrogen peroxide–trifluoroacetic acid oxidation, using a procedure described for the oxidation of substituted pyridines.[25] The crude oxide was purified by chromatography on alumina (chloroform eluent), and then crystallized from a benzene–hexane mixture, mp 93.5–95°.

Anal. Calcd for $C_7H_8ClNO_2$: C, 48.43; H, 4.65; Cl, 20.42; N, 8.07. Found: C, 48.21; H, 4.72; Cl, 20.26; N, 8.03.

***N*-Isopropoxy-6-chloro-2(1*H*)-pyridone (2b).**—Oxide **4**, (0.5 g) was dissolved in 10 ml of 2-bromopropane, and the mixture was refluxed for 24 hr. The excess alkyl bromide was removed under vacuum, and chromatography of the remaining dark oil on 25 g of silica gel (3:1 hexane–acetone eluent) afforded 0.10 g of **2b**.

Anal. Calcd for $C_8H_{10}ClNO_2$: C, 51.21; H, 5.37; N, 7.47. Found: C, 51.45; H, 5.60; N, 7.49.

Registry No.—**2a**, 32846-47-2; **2b**, 32846-48-3; **4**, 32846-49-4.

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A Comparison of the Electronic Effects of Substituents Bonded to Annular Nitrogen and Carbon Atoms

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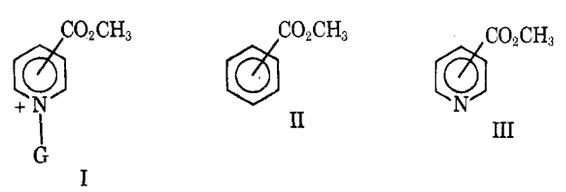
Much is known about the electronic effects exerted by meta and para substituents bonded to carbon.[2] By comparison, very little is known about the electronic effects exerted by the same groups bonded to an annular nitrogen atom.[3]

We have determined the rates of hydroxide ion catalyzed hydrolysis of esters I where the N substituents, CH_3O, CH_3, and O^-, are meta and para to the reactive center.[4] Comparison of our results with those for esters II[5] provides an insight into the ability of a positively charged annular nitrogen atom to transmit resonance and inductive effects.



I II III

Kinetic studies were carried out using a pH-Stat. In the case of the para *N*-methyl ester, the hydroxide ion concentration was varied by a factor of 8 and the second-order rate constant, k_2, was found to be given

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