the solvent was removed to give 0.025 g (87%) of 3-hydroxy-2,3-diphenylindoline: ir max ($CHCl_3$) 3650 (OH), 3450 (NH), and 1620 cm^{-1} ($PhNCR_2$); λ_{max}^{EtOH} 242 and 305 mμ; nmr δ 3.17 (br s, NH-1 OH-1), 4.92 (s, 2-benzylic H), and 7.02 (br m, 14-Ar H).

This compound dehydrated very rapidly upon standing or during attempted crystallization from ethanol–water. Treatment with warm acetic acid caused complete dehydration, giving 2,3-diphenylindole. The ultraviolet spectrum and tlc of the dehydrated product were identical with those of authentic material.

Treatment of 3-Hydroxy-2,3-diphenylindolenine with Sodium Periodate.—A sample of 3-hydroxy-2,3-diphenylindolenine (0.005 g, 1.75×10^{-5} mol) was dissolved in methanol (4.5 ml), water (1.5 ml), and 0.488 *M* sodium periodate (0.5 ml) and refluxed for 12 hr. After cooling the mixture was treated in the usual manner to provide nearly white solid (0.005 g, 95%).

Comparison (ir, tlc) with authentic material demonstrated that this material was *o*-benzamidobenzophenone containing a little 2,2-diphenylindoxyl.

Registry No.—**1**, 23740-95-6; **2**, 23740-96-7; **3**, 23740-97-8; **4**, 23740-98-9; 2-methylindole, 95-20-5; N,O-diacetyl-2-methylindoxyl, 23741-00-6; N,O-diacetylindoxyl, 16800-67-2; 2-methylindole-3-aldehyde, 5416-80-8; 2,3-diphenylindole, 3469-20-3; 3-hydroxy-2,3-diphenylindoline, 23829-47-2.

Stereochemistry at Trivalent Nitrogen. VIII. Steric and Solvent Effects on Slow Nitrogen Inversion in an Isoxazolidine[1a]

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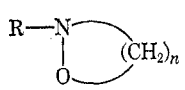
Chemical-shift nonequivalence arising from slow nitrogen inversion in *cis*-1,8-dimethyl-2-oxa-1-azabicyclo-[3.3.0]octane (**2**) was observed. An assignment of the configurations at nitrogen in the two diastereomers observed in low-temperature nmr spectra can be made on the basis of steric and solvent effects on the equilibrium constant, and on the effect of the orientation of the lone pair of electrons on chemical shifts. The nitrogen inversion barrier was determined using complete line-shape methods, and its dependence on solvent and steric factors is discussed.

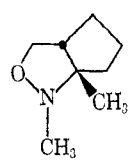
Numerous reports have appeared in recent years describing temperature dependence in the nmr spectra of amine derivatives which have a heteroatom (especially nitrogen, oxygen, or sulfur) directly bonded to the nitrogen atom. This behavior results from conformational interchange which is slow on the nmr time scale. Two classes of compounds which have received considerable attention in this respect are the cyclic and acyclic trialkylhydroxylamines. Although earlier papers[2,3] postulated a substantial barrier to inversion of the nitrogen pyramid as the origin of chemical-shift nonequivalence of diastereotopic nuclei in acyclic trialkylhydroxylamines, more recent work has indicated that the results observed more probably reflect the existence of a substantial barrier to torsion about the N–O bond.[4] By contrast to the acyclic compounds, chemical-shift nonequivalence in the cyclic systems **1** can be unequivocally ascribed to slow nitrogen inversion when the size of the heterocyclic ring is small enough to eliminate ring inversion as a possible process. When this work was begun, reports of



1, n = 1, 2, 3, 4

slow nitrogen inversion had appeared for oxaziridines[5–7] (**1**, n = 1) and a substituted 1,2-oxazetidine[8] (a derivative of **1**, n = 2) in which the heteroatoms are part of strained rings. However, a dihydro-1,2-oxazine (an unsaturated derivative of **1**, n = 4) was reported to exhibit chemical-shift equivalence resulting from more rapid nitrogen inversion.[8] Hence, it was of interest to determine whether the presence of a strained ring was a requirement for the observation of slow nitrogen inversion or whether the presence of the oxygen atom would slow nitrogen inversion in isoxazolidines (**1**, n = 3) so that chemical-shift nonequivalence could be observed. Most recently, chemical-shift nonequivalence in isoxazolidines (**1**, n = 3) and tetrahydro-1,2-oxazines (**1**, n = 4) has been described[9,10] indicating that a strained ring is not a prerequisite for a measurable nitrogen inversion barrier.

The bicyclic isoxazolidine **2** represents an additional example of a molecule which exhibits chemical-shift



2

nonequivalence due to hindered stereomutation at nitrogen. Comparison of the barrier to nitrogen inversion in **2** with those in other examples of the isoxazolidine system indicates that a significant steric effect on the inversion rate obtains.

(1) (a) Part VII: E. Carlson, F. B. Jones, Jr., and M. Raban, *Chem. Commun.*, 1235 (1969). (b) University Fellow, 1969–1970.

(2) D. L. Griffith and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 4089 (1965).

(3) R. E. Banks, M. G. Barlow, R. N. Haszeldine, and M. K. McCreath, *J. Chem. Soc.*, 7203 (1965).

(4) M. Raban and G. W. J. Kenney, Jr., *Tetrahedron Lett.*, 1295 (1969).

(5) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957).

(6) S. J. Brois, *ibid.*, **90**, 506 (1968).

(7) F. Montanari, I. Moretti, and G. Torre, *Chem. Commun.*, 1694 (1968).

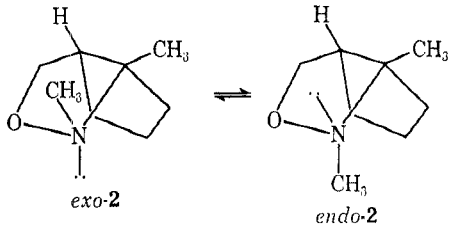
(8) J. Lee and K. G. Orrell, *Trans. Faraday Soc.*, **61**, 2342 (1965).

(9) (a) F. G. Riddell, J. M. Lehn, and J. Wagner, *Chem. Commun.*, 1403 (1968); (b) D. L. Griffith and B. L. Olson, *ibid.*, 1682 (1968).

Results and Discussion

The internal 1,3-dipolar addition of the nitrone dipole to a double bond provides a convenient entry into the isoxazolidine ring system.[10] Thus, condensation of N-methylhydroxylamine with 6-hepten-2-one followed by *in situ* 1,3-dipolar cyclization of the resulting nitrone affords **2** in high yield.

The room-temperature nmr spectrum of **2** in toluene-d_8 (Figure 1A) is consistent with the occurrence of rapid stereomutation at nitrogen. Chemical-shift nonequivalence is observed for the diastereotopic methylene protons in the heterocyclic ring which appear as two multiplets at δ 3.25 and 3.83.[11] However, this nonequivalence is not a consequence of slow nitrogen inversion but rather may be ascribed to the adjacent asymmetric carbon atoms. By contrast, the low-temperature nmr spectrum (Figure 1B) provides evidence of the existence of the nitrogen invertomers, *exo*-**2** and *endo*-**2**. Thus, two singlets at δ 0.90 and 1.00 are observed for the C-methyl groups in the two epimers since the two groups are diastereotopic by external comparison.[12] On the other hand, the diastereotopic N-methyl groups exhibit apparent chemical-shift equivalence and a sharp singlet is observed at δ 2.45 in the low-temperature spectrum as well as in the room-temperature spectrum. This event is understandable upon detailed examination of the difference in the environments of the diastereotopic methyl groups in the two epimers. The environments of the two C-methyl groups differ considerably; in *endo*-**2** the C-methyl group is *cis* to the nitrogen lone pair of electrons, while in *exo*-**2** it is *cis* to the N-methyl group. The N-methyl group, on the other hand, is *cis* to



exo-**2** *endo*-**2**

either a methyl group (in *exo*-**2**) or to a methylene group (in *endo*-**2**), and apparently this less significant difference in environments is not sufficient to make the chemical-shift difference large enough to be observable.

When the temperature is raised, the C-methyl signals broaden, coalesce (T_c = −24°), and collapse to a sharp singlet as stereomutation at the conformationally labile chiral center becomes rapid on the nmr time scale. Since the bulk composition of the sample does not change as inversion of the nitrogen pyramid becomes rapid, the epimerization is, in a sense, degenerate.

We assign the less intense low-field C-methyl singlet to the less abundant *endo*-**2** on the basis of relative

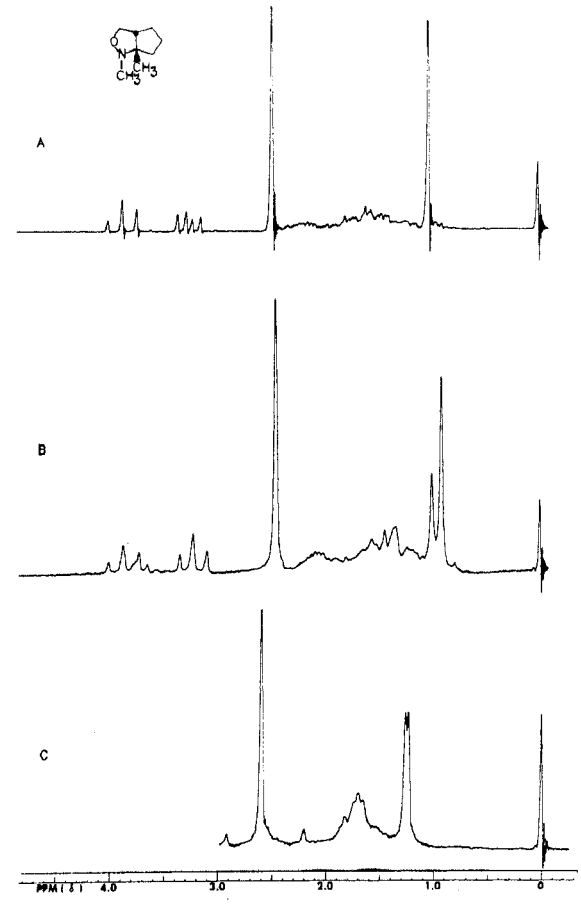


Figure 1.—Nmr spectra of isoxazolidine **2**: (A) toluene-d_8, room temperature; (B) toluene-d_8, −50°; (C) methanol–water (4:1), −40°.

chemical shifts, the equilibrium constant, and the effect of hydrogen-bonding solvents on the equilibrium constant.

Although the question of the "size"[13,14] of the lone pair of electrons remains a topic of lively controversy, most authors agree that the conformational preference of a methyl group for a less hindered environment is greater than that of the lone pair.[14] Thus, we may assign the more intense signal to *exo*-**2** where the methyl group is in the less congested *exo* position and the lone pair is in the more congested *endo* region. Additional evidence of the correctness of this assignment is based on the proposition that the effect of hydrogen-bonding solvents on the equilibrium between the two invertomers will be to stabilize the isomer in which hydrogen bonding can occur more readily, *viz.*, *endo*-**2**. Examination of the low-temperature nmr spectrum in methanol–water (Figure 1 C) indicates that the low-field signal is augmented and hence must arise from *endo*-**2**.

Alternatively, we might express this result by noting that the conformational preference of the methyl group is greatly diminished in hydrogen-bonding solvents since the solvation shell of the lone pair of electrons effectively increases its steric bulk until it is

(10) N. A. LeBel, M. E. Post, and J. J. Whang, *J. Amer. Chem. Soc.*, **86**, 3759 (1964).

(11) The two multiplets represent the M and A portions of an AMX spin system since both H_A and H_M are coupled to the methine proton. First-order analysis gave J_{AX} = 8 Hz, J_{MX} = 5 Hz, and J_{AM} = 8 Hz. On this basis we assign the high field multiplet (H_M) to the *exo* proton since it has the lower vicinal coupling constant and must be *cis* to the methine proton.

(12) K. Mislow and M. Raban in "Topics in Stereochemistry," Vol. 1, E. L. Eliel and N. L. Allinger, Ed., Wiley-Interscience, New York, N. Y., 1967, Chapter 1.

(13) We use this term as a convenient means of describing the conformational preference of the lone pair and without prejudice concerning the detailed reasons for this conformational preference.

(14) (a) F. G. Riddell, *Quart. Rev.* (London), **21**, 364 (1967); (b) N. L. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Lett.*, 3729 (1967); (c) J. B. Lambert, R. G. Keske, R. E. Cathcart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, **89**, 3761 (1967); (d) M. J. T. Robinson, *Tetrahedron Lett.*, 1153 (1968); (e) R. W. Baldock and A. R. Katritzky, *ibid.*, 1159 (1968).

TABLE I
SOLVENT EFFECTS ON INVERTOMER EQUILIBRIUM CONSTANT AND NITROGEN INVERSION BARRIER IN **2**

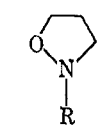
Solvent	$\Delta\nu$,[a] Hz	T_c, °C	K[b]	k_c (approx)[c]	k_c (cls)[d]	ΔG_c^* (approx),[c] kcal/mol	ΔG_c^* (cls),[d] kcal/mol
Neat	3.0	−32	0.6	6.7	4.6	13.1	13.3
Toluene-d_8	5.5	−24	0.4	12	9.5	13.3	13.4
Carbon disulfide	2.7	−32	0.4	5.9	4.3	13.2	13.3
Chloroform-d	3.0	−21	0.5	6.7	4.5	13.7	13.9
Methylene chloride	2.6	−25	0.4	5.8	4.2	13.6	13.7
Acetone-d_6	3.1	−28	0.4	6.8	4.6	13.3	13.5
Methanol–water (4:1)	1.6	−18	1.0	3.6	2.5	14.2	14.4
Acetic acid–acetone (1:1)	5.3	−5	1.4	12	10	14.3	14.4

[a] Chemical-shift difference for C-methyl protons. [b] Ratio of intensities of low-field to high-field C-methyl signals determined at low temperature. [c] Approximate rate and free energy of activation at T_c calculated using the equation $k_c = \pi\Delta\nu/\sqrt{2}$. [d] Rate and free energy of activation for conversion of less stable to more stable isomer obtained using complete line shape.

comparable in size with a methyl group.[15] Finally, we can assign configuration based on the deshielding of spatially contiguous nonvicinal protons by the lone pair of electrons on nitrogen. This effect has been noted in bicyclic piperidines and in related compounds.[14d] Our assignment, on this basis, that the low-field singlet arises from *endo*-**2** in which the lone pair is *cis* to the C-methyl group is in accord with the judgment above made on the basis of steric considerations and the effect of hydrogen-bonding solvents.

The rates of conformational interchange (k_c) and the free energies of activation (ΔG_c^*) at the coalescence temperatures in a variety of solvents were calculated using the expression[16a] $k_c = \pi\Delta\nu/\sqrt{2}$ and are given in Table I. Although this approximate expression is based on the equally populated, two-site, AB spin system, it has been widely used in cases, like the present example, where the assumptions made in its derivation are not valid. Recently, this approach has been severely criticized as unreliable and inaccurate, and the exclusive use of complete line-shape analysis has been recommended.[16b] In order to evaluate the validity of this expression, we have used a complete line-shape analysis spectrum simulator program (CLASS) to determine k_c for a range of values of $\Delta\nu$ (1–40 Hz) and K (0.33–3.0).[16c] We used a reasonable value of T_2 of 0.4 sec corresponding to a half band width ($W_{1/2}$) of 0.8 Hz for these calculations. These values of k_c were compared with those obtained using the approximate equation. The discrepancy between the two results varied. In general, the approximate equation resulted in larger errors for very small values of $\Delta\nu$, because of overlap due to natural broadness of peaks and magnet inhomogeneity and for values of K markedly different from unity. However, if a discrepancy of *ca.* 100% in k_c corresponding to a difference of only *ca.* 0.3 kcal/mol in ΔG_c^* is considered tolerable, the approximate equation gives acceptable results when $\Delta\nu$ is larger than 2 Hz, K lies between 1 and 3, and T_2 is not markedly different from 0.4. To exemplify our findings, we have included the results of both the approximate equation and the complete line-shape method for **2** in Table I. As is evident, the error introduced by using the approximate expression is relatively small in comparison with experimental errors.

Comparison of the barriers to conformational interchange in **2** with those in isoxazolidines previously reported allows a judgment concerning the effect of



3a, R = CH_3
b, R = $CH(CH_3)_2$
c, R = CH_2OCH_3

steric bulk on the free energy of activation for inversion of the nitrogen pyramid. Isoxazolidines **3a**, **3b**, and **2** form a series with groups of increasing bulk attached to the nitrogen atom; the most bulky substituent is primary in **3a**, secondary in **3b**, and tertiary in **2**. As the data in Table II indicates, the increase in steric bulk results in a decrease in coalescence temperature (T_c) and free energies of activation. The decrease in the barrier to pyramidal inversion is the result of greater steric destabilization in the ground state where the CNC angles are *ca.* 109°, than in the transition state where the CNC angles are *ca.* 120°. Such steric acceleration of pyramidal inversion has been previously described for aziridines[17,18] and oxazetidines.[8]

TABLE II
STERIC DEPENDENCE OF THE BARRIER TO NITROGEN INVERSION IN ISOXAZOLIDINES

Compound	Solvent	T_c, °C	ΔG_c^*, kcal/mol	Ref
3a[a]	Chloroform-d	+42	15.6	9a
3b[a]	Methylene chloride	+5	14.8	9b
3c[a]	Methylene chloride	−74	10.3	9b
2[b]	Methylene chloride	−25	13.7	

[a] ΔG_c^* calculated using the expression $k_c = \pi\Delta\nu/\sqrt{2}$. [b] ΔG_c^* obtained using complete line shape.

(15) K. Brown, A. R. Katritzky, and A. J. Warring, *Proc. Chem. Soc.*, 257 (1964).

(16) (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959; (b) G. Binsch, "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Wiley-Interscience, New York, N. Y., 1967, Chapter 2; (c) A Similar treatment has been reported: A. Jaeschke, H. Muensch, H. G. Schmid, H. Friebolin, and A. Mannschreck, *J. Mol. Spectrosc.*, **31**, 14 (1969).

(17) S. J. Brois, *J. Amer. Chem. Soc.*, **89**, 4242 (1967).

(18) R. G. Kostyanovsky, Z. E. Samojlova, and I. I. Tchervia, *Tetrahedron Lett.*, 3025 (1968); V. F. Bystrov, R. G. Kostyanovskii, O. A. Panshin, A. U. Stepanyants, and O. A. Iuzhakova, *Opt. Spectrosc.*, **19**, 122 (1965).

We note that the substantially lower barrier of **3c**, with respect to **3b**, does not arise from steric factors. Presumably, the presence of the electronegative oxygen atom is responsible.[18]

Although solvent dielectric constant does not appear to exert a significant influence on the free-energy barrier, hydrogen bonding by solvent results in an increase in the barrier.[19] The change in the free energy of activation accompanying change of solvent from chloroform to methanol–water for **2** ($\Delta\Delta G_c^* = 0.4$ kcal/mol) is in the same direction but smaller than that reported for the monocyclic analog **3a** ($\Delta\Delta G_c^* = 1.3$ kcal/mol).[9a] When acetic acid–acetone (1:1) is used, the increase in ΔG_c^* is comparable. Inspection of Table I suggests that some hydrogen bonding may be occurring even in chloroform and methylene chloride.

The steric acceleration in the rate of stereomutation observed in cyclic hydroxylamines may be compared with the behavior of acyclic amines bearing heteroatoms attached to nitrogen for which steric deceleration has been observed and torsional barriers about the nitrogen heteroatom postulated.[20–23]

Although the attachment of an atom with nonbonded electrons can augment the barrier to nitrogen inversion in cyclic hydroxylamines, this does not necessarily account for chemical-shift nonequivalence in acyclic compounds. It is possible that the CNXC (X = heteroatom) dihedral angle must be small in order for electron repulsion between the nitrogen lone pair and that on the heteroatom to be significant enough to cause the maximum increase in the inversion barrier. The ground-state geometry in acyclic compounds is one of minimum interaction with a large dihedral angle, and, in this geometry, torsional barriers appear to be more substantial than those to inversion of the nitrogen pyramid.[20–23]

(19) The increase in the free energy of activation upon dissolution in hydrogen bonding solvents observed in **2** and **3a** is not observed for acyclic hydroxylamines, a further reflection of the difference in the mechanism of stereomutation (unpublished result).

(20) A. H. Cowley, M. J. S. Dewar, and W. R. Jackson, *J. Amer. Chem. Soc.*, **90**, 4185 (1968).

(21) J. M. Lehn and J. Wagner, *Chem. Commun.*, 1298 (1968).

(22) M. Raban, F. B. Jones, Jr., and G. W. J. Kenney, Jr., *Tetrahedron Lett.*, 5055 (1968); M. Raban, G. W. J. Kenney, Jr., and F. B. Jones, Jr., *J. Amer. Chem. Soc.*, **91**, 6677 (1969).

(23) J. R. Fletcher and I. O. Sutherland, *Chem. Commun.*, 706 (1969).

Experimental Section

Variable-temperature nmr spectroscopy was performed on a Varian A-60A spectrometer equipped with a Varian variable-temperature probe using *ca.* 20% solutions. Temperatures were determined using methanol spectra as described in the Varian Manual. Each coalescence temperature was measured three to five times and the results were averaged. In general, duplicate measurements were within ±2°.

Theoretical spectra were generated by an IBM 360/65 computer and plotted on a Calcomp plotter using a program based on the solution to the exchange-modified Block equations.[16a] The rate at coalescence (k_c) was assigned to the lowest rate at which the minimum between two resonances disappeared, *i.e.*, became a saddle point or maximum. Plots of k_c as a function of $\Delta\nu$ and K were constructed from which k_c could be determined for intermediate values of $\Delta\nu$ and K. The value of T_2 chosen was based on the observed width at half-height at the slow exchange limit, and tetramethylsilane was used as a standard for magnet inhomogeneity as well as chemical shift.

***cis*-1,8-Dimethyl-2-oxa-1-azabicyclo[3.3.0]octane.**—A solution of 5.52 g (0.05 mol) of 6-hepten-2-one[10] in 200 ml of toluene was heated to reflux in a flask to which was attached a Stark water separator. A solution of 5.0 g (0.1 mol) of N-methylhydroxylamine in 50 ml of toluene and 10 ml of absolute methanol was added dropwise over a period of 2 hr. The theoretical amount of water was collected and the mixture was heated under reflux for an additional 16 hr. The cooled solution was extracted with six 35-ml portions of 10% hydrochloric acid. The acid extract was washed with ether and then basified with 20% sodium hydroxide solution; the organic product was extracted with ether. The combined ether extract was washed with water, dried, and concentrated. Distillation gave 5.58 g (80%) of the isoxazolidine **2**, bp 87–88° (40 mm), $n^{25}D$ 1.4627. Gas chromatography showed one component.

Registry No.—**2** (*exo*), 23884-98-2; **2** (*endo*), 23884-99-3.

Acknowledgment.—This work was supported by the U. S. Public Health Service (Grant No. GM16600-01 to M. R.) and the National Science Foundation (Grant No. GP-6393 to N. A. L.).