quence. First, the ground state is probably the imidate with the trimethylsilyl groups trans to one another. Only in this conformation is the nitrogen lone pair accessible to the *O*-Si$(CH_3)_3$ group. Moreover, when R is not large this conformation seems to minimize steric repulsions.

Second, if this is indeed the mechanism, the migration step is rate determining. This follows from the argument that the free energy of activation for rotation in the intermediate should be about the same as or lower than that of compound I (*vide supra*). Since the free energies of activation for the exchange processes are considerably higher, they must correspond to the rate-determining migration step.

Finally, an examination of space-filling models reveals that an increase in the *size* of the carbonyl substituent R probably results in slightly greater steric hindrance in the imidate ground state than in the intermediate amide. Therefore, an increase in size of R should destabilize the ground state more than the intermediate, thereby resulting in a slight decrease in activation energy. Indeed, when R = $C(CH_3)_3$ the hindrance in the trans imidate conformation is so severe that the ground state may become the cis isomer. Migration of $Si(CH_3)_3$ would probably be preceded by rotation about the C=N bond to produce the reactive trans isomer. This may account for the high $\Delta G^{\ddagger}$ for this derivative. (The low 1.3 Hz $\Delta\nu_e$ for V produces an error of no more than 0.4 kcal/mol for $\Delta G^{\ddagger}$.[8])

Acknowledgments. The authors are indebted to the Camille and Henry Dreyfus Foundation for partial support of this work.

Conformational Analysis by Lanthanide Induced Shifts. *N*-Nitrosopiperidines

T. P. Forrest,* D. L. Hooper, and S. Ray

Contribution from the Department of Chemistry, Dalhousie University, Halifax, Nova Scotia, Canada. *Received August 13, 1973*

Abstract: A method of conformational analysis based on measured lanthanide induced shifts (LIS) for a series of compounds is proposed and shown to give acceptable conformational analyses for the *N*-nitroso derivatives of piperidine, 4-methylpiperidine, 2-methylpiperidine, 2-ethylpiperidine, and 2-propylpiperidine. The method uses LIS Δ values relative to an internal standard common to all members of a series, and these relative Δ values are used to calculate the equatorial and axial populations of a given proton signal, taking the relative Δ values of the proton in an axial and equatorial orientation from a conformationally rigid model compound.

Lanthanide induced shift (LIS) values observed in the nmr spectra of complexes between organic substrates and lanthanide shift reagents have been extensively used[1] in determination of the molecular geometry of conformationally rigid systems; however, the use of LIS values in the quantitative stereochemical analysis of a conformationally mobile system has not been reported. Two approaches to the problem of interpreting experimental LIS values for molecules known to exist as mixtures of conformers have been proposed. The first method[2] uses the known or estimated population of the different conformers to calculate an average value of *G*, the geometric factor in the McConnell equation, which is then used to calculate LIS values. In cases where the position of the conformational equilibrium is unknown, a comparison of observed shifts with those calculated for different conformers, assuming a value of the metal–ligand distance, is used[3-6] to determine the preferred conformation. Several authors[7,8] have pointed out the possibility that the addition of the lanthanide shift reagent may alter the position of the conformational equilibrium. We wish to report a method by which a quantitative estimate of the population of different conformers can be made directly from observed LIS values. This method has been applied to the conformational analysis of a number of *N*-nitrosopiperidines, some of which had been subjected to conformational analysis by other nmr methods.

Rationale of the Method

In a conformationally mobile system the observed Δ value (slope of a plot of the lanthanide induced shift *vs.* molar ratio of shift reagent to substrate) for a proton is the weighted average of the Δ values of this proton in the contributing conformers, where N_i is the mole fraction of conformer *i* and Δ_i is the Δ value of this proton in conformer *i*. For six-membered rings, such as cyclohexanes and piperidines, where there are only two major conformers, eq 1 reduces to

$$\Delta = \Sigma_i N_i \Delta_i \quad (1)$$

$$\Delta = N_e\Delta_e + N_a\Delta_a \quad (2)$$

where (e) refers to the conformation in which the proton

(1) B. C. Mayo, *Chem. Soc. Rev.*, 2, 49 (1973).
(2) R. von Ammon and R. D. Fischer, *Angew. Chem., Int. Ed. Engl.*, 11, 675 (1972).
(3) L. Ernst, *Chem.-Ztg.*, **95**, 325 (1971).
(4) M. R. Willcott, R. E. Lenkinski, and R. E. Davis, *J. Amer. Chem. Soc.*, **94**, 1742 (1972).
(5) R. E. Davis and M. R. Willcott, *J. Amer. Chem. Soc.*, **94**, 1744 (1972).
(6) I. M. Armitage, L. D. Hall, A. G. Marshall, and L. G. Werbelow, *J. Amer. Chem. Soc.*, **95**, 1437 (1973).
(7) D. Horton and J. K. Thomson, *Chem. Commun.*, 1389 (1971).
(8) P. Kristiansen and T. Ledaal, *Tetrahedron Lett.*, 2817 (1971).

is equatorial and (a) the conformation in which it is axial. The mole fraction N_e of the conformers with this proton equatorial can be calculated directly from eq 3 if Δ_a and Δ_e are known.

$$N_e = (\Delta - \Delta_a)/(\Delta_e - \Delta_a) \quad (3)$$

An obvious way of obtaining Δ_a and Δ_e for use in eq 3 is to use the Δ_a and Δ_e measured for the axial and equatorial protons of a conformationally rigid model compound, but the direct use of Δ values from model compounds could be justified only if the equilibrium constant for complex formation with the shift reagent were the same for the model compound and the conformationally mobile compound. It is unlikely that this would be true. However, the ratio (Δ') of the induced shift of a proton to that of another proton within the same molecule is independent of the substrate complex equilibrium constant. Therefore, the ratios could be used (eq 4) to calculate the position of the conformational equilibrium provided that the Δ value used as the reference in each molecule is that of the same proton (*i.e.*, at the same position and in the same axial or equatorial orientation).

$$N_e = (\Delta' - \Delta_a')/(\Delta_e' - \Delta_a') \quad (4)$$

An ideal reference proton would be one for which the Δ value is independent of the position of the conformational equilibrium, as would be indicated by equality of the Δ values for the corresponding axial and equatorial protons of the model compound. If, however, measurements on the model compound show that the axial and equatorial orientations of the reference proton will have different Δ values, the ratios must be obtained by dividing by the Δ value for the reference proton in the same orientation as the reference proton of the model compound. For the conformationally mobile compounds the Δ value of the reference proton (r) in the chosen orientation must itself be calculated from the observed Δ value, which will have contributions from both axial and equatorial orientations.

$$\Delta^r = N_a^r\Delta_a^r + N_e^r\Delta_e^r \quad (5)$$

The ratio (x) of Δ_e^r to Δ_a^r is that of the Δ values of the equatorial and axial protons on the corresponding carbon of the model compound. Thus, by substituting $x\Delta_a^r$ for Δ_e^r and $(1 - N_a^r)$ for N_e^r an expression (eq 6) is obtained for the Δ of the reference proton in an axial orientation.

$$\Delta_a^r = \Delta^r/(N_a^r - xN_a^r + x) \quad (6)$$

If the Δ for the axial orientation of the reference proton is chosen to calculate Δ' values, eq 4 becomes

$$N_e = \frac{(\Delta/\Delta^r)(N_a^r - xN_a^r + x) - \Delta_a'}{\Delta_e' - \Delta_a'} \quad (7)$$

Similar equations would be obtained if the equatorial orientation of the reference proton were used to calculate the ratios.

If the probe proton has, in each conformer, the opposite orientation to the reference proton (*i.e.*, probe is axial when the reference is equatorial) then N_e for the probe proton equals N_a^r and eq 7 becomes

$$N_e = \frac{\Delta_a' - x\Delta/\Delta^r}{\Delta_a' - \Delta_e' + (\Delta/\Delta^r)(1 - x)} \quad (8)$$

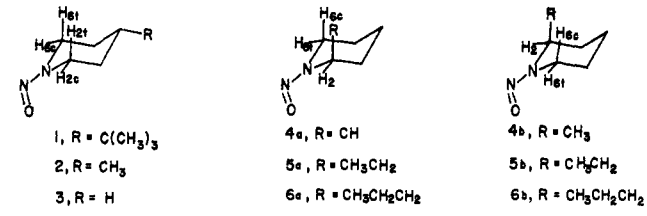

Figure 1.

For the case where the probe proton and the reference have the same orientation in a conformer, then $N_a^r = 1 - N_e$ and eq 7 becomes

$$N_e = \frac{\Delta_a' - (\Delta/\Delta^r)}{\Delta_a' - \Delta_e' - (\Delta/\Delta^r)(1 - x)} \quad (9)$$

The determination of the N_e thus requires, apart from the determination of Δ_a', Δ_e', and x from a model compound, only the measurement of the Δ value for the probe proton and for the reference proton. In most cases more than one probe proton will be available so results from several determinations may be possible from one set of spectra.

Experimental Section

Nitrosamines used in this work were prepared by nitrosation of commercially available piperidines. The shift reagent was tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)europium-(III), $Eu(fod)_3$, which was used as received from Norrell Chemical Co. The spectra were recorded on a Varian T-60 spectrometer for solutions prepared by adding weighed amounts of shift reagent to a $CDCl_3$ solution of the substrate. Since only relative shifts were required, it was not necessary to attempt to determine accurate bound shifts.[9,10]

Δ values were obtained by linear regression analysis over linear portions of the plots of LIS as molar ratio of shift reagent to substrate. For different protons, even in a single molecule, the range over which a separate resonance is observed differs depending on overlap by other signals in the spectra. All the plots which were used in the calculations were linear, the result of using only relatively small ratios of shift reagent to substrate, with the maximum value of the molar ratio less than 0.35 in each case.

Results and Discussion

The nitrosopiperidines studied and the measured Δ values for the protons α to the nitrogen and either syn or anti to the nitroso group are listed in Table I. For each of the 2-alkylnitrosamines, two isomers are observed, one with the nitroso group syn to the 2-alkyl group (**4a**, **5a**, and **6a**, Figure 1), the other with the

Table I. Observed Δ Values (in Hz) for Protons of *N*-Nitrosamines

Compd	Proton			
	2-cis	2-trans	6-cis	6-trans
1	882	505	365	340
2	846	515	349	339
3	781		404	
4a	848		353	369
4b	353		702	680
5a	1063		426	462
5b	396		885	669
6a	941		378	409
6b	356		775	620

(9) D. R. Kelsey, *J. Amer. Chem. Soc.*, **94**, 1764 (1972).
(10) J. Reuben in "Nuclear Magnetic Resonance Shift Reagents," R. E. Sievers, Ed., Academic Press, New York, N. Y., 1973, pp 341–352.

nitroso group anti to the 2-alkyl group (**4b**, **5b**, and **6b**, Figure 1) and a separate set of Δ values is given for each isomer.

In those compounds (**1**, **2**, **4a**, **5a**, and **6a**) in which two anti protons are observed, little difference is found in the Δ values of these two protons. The anti protons are thus quite insensitive to changes in the position of the conformational equilibrium, and therefore are used as reference protons. On the other hand, a wide range of values is observed for the α protons syn to the nitroso group, indicating that these protons are suitable as the probe protons in the determination of the position of the conformational equilibrium.

In *N*-nitroso-4-*tert*-butylpiperidine, the conformationally rigid model compound, the induced shifts of the α protons increase in the order axial anti proton < equatorial anti proton < axial syn proton < equatorial syn proton (*i.e.*, $H_{6t} < H_{6c} < H_{2t} < H_{2c}$ in formula 1).

The Δ value of the anti proton in the axial orientation is used as the internal standard to calculate the Δ′ values. In the conformationally mobile compounds, the proton with the lowest Δ value, hence having the greatest contribution from the axial orientation, is chosen as the reference proton.

The method of the analysis is illustrated for the isomers of *N*-nitroso-2-ethylpiperidine. From the model compound one obtains: (a) $\Delta_a' = 1.49$, the ratio of the Δ value of the syn axial proton to the Δ value of the anti axial proton; (b) $\Delta_e' = 2.59$, the ratio of the Δ value of the syn equatorial proton to the Δ value of the anti axial proton; (c) $x = 1.07$, the ratio of the Δ value of the anti equatorial proton to the Δ value of the anti axial proton.

The measured Δ values for the α protons of **5a** are 426, 462, and 1083 Hz. The reference proton (anti and predominantly axial) then has $\Delta^r = 426$ Hz, while the probe proton with $\Delta = 1063$ Hz is predominantly equatorial. Since the probe and reference protons have opposite orientations, eq 8 is used to calculate N_e. This yields a value of 0.93 for the mole fraction of the conformer with the probe proton equatorial (*i.e.*, with the alkyl group axial) (Table II).

Table II. Calculated Mole Fractions for the Conformer with the Probe Proton Equatorial and Derived Mole Fraction for the Conformer with the Alkyl Group Equatorial

Compd	Probe proton	N_e	Probe proton	N_e	N_e (alkyl)
2	2-cis	0.93	2-trans	0.97	0.95 ± 0.07
3	2	0.47	2	0.46	
4a	2	0.85			0.15 ± 0.06
4b	6-trans	0.47	6-cis	0.52	0.50 ± 0.06
5a	2	0.93			0.07 ± 0.06
5b	6-trans	0.26	6-cis	0.78	0.24 ± 0.06
6a	2	0.92			0.08 ± 0.06
6b	6-trans	0.30	6-cis	0.73	0.29 ± 0.06

The measured Δ values for the α protons of **5b** are 396, 669, and 885 Hz. In this case there is only one α anti proton (H_2) which can be used for the reference proton and two syn protons which can be used as the probe protons. The chemical shift and splitting pattern of the reference proton show it to be predominantly equatorial, hence the Δ value of 885 (belonging to the syn proton (H_{6c}), which is also seen to be mainly equatorial) must be used in eq 9. The other Δ value, 669, belonging to the proton (H_{6t}) which has the opposite orientation to the reference proton must be used in eq 8. These calculations yield mole fractions of $N_e = 0.78$ for H_{6c} and $N_e = 0.26$ for H_{6t} which correspond to values of 0.22 and 0.26 for the mole fraction of the conformer with the alkyl group equatorial.

The spectra of *N*-nitroso-2-propylpiperidine isomers indicate approximately the same conformational preference as found in the 2-ethyl compound. This preference for axial-2-alkyl groups has been observed[11] in cyclohexanones and *N*-nitrosopiperidines having an α-carboxyl group; the ring exits almost exclusively in the conformation with the carboxyl group axial in both the syn and anti isomers.[12]

For the 2-methyl compound with the nitroso group syn to the methyl group (**4a**), the syn proton (H_2) yields a value of $N_e = 0.85$, indicating a strong preference for the axial orientation of the methyl group. This agrees with the conclusion,[13,14] based on analysis of chemical shift and coupling constant data, that this isomer has the methyl group in the axial orientation. In the other isomer (**4b**), with the alkyl group anti to the nitroso group, the calculations from both of the probe protons indicate an approximately equal distribution of the alkyl group in the axial and equatorial conformations. This is in agreement with the qualitative conclusion of Harris and Spragg,[13] that even in this isomer a high proportion of the molecules have an axial orientation of the methyl group.

There is good self-consistency in the results for compounds, or isomers, where conformational populations could be measured from two different protons. The sum of the mole fractions of the two syn protons must be 1.00, while the observed totals are: 1.00 (**2**), 0.93 (**3**), 0.99 (**4b**), 1.04 (**5b**), 1.03 (**6b**). This self-consistency, combined with the determination of conformational preference in agreement with theory (for *N*-nitrosopiperidine) and previous nmr measurements (for *N*-nitroso-2-methylpiperidine), appears to justify the use of relative LIS values in the calculation of equilibrium constants for conformational equilibria. The method proposed is particularly applicable to series of compounds such as these nitrosamines which are otherwise inaccessible to quantitative stereochemical studies by nmr. Although there is no proof that the position of the equilibrium has not been shifted by complex formation, the results obtained for the compounds in this study are certainly reasonable.

Acknowledgment. The financial assistance of the National Research Council of Canada is acknowledged.

(11) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 113.
(12) W. Lijinsky, L. Keefer, and J. Loo, *Tetrahedron*, **26**, 5137 (1970).
(13) R. K. Harris and R. A. Spragg, *J. Mol. Spectrosc.*, **23**, 158 (1967).
(14) Y. L. Chow and C. J. Colon, *Can. J. Chem.*, **46**, 2827 (1968).