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CONFIGURATIONAL AND CONFORMATIONAL ANALYSIS OF CYCLIC AMINE OXIDES

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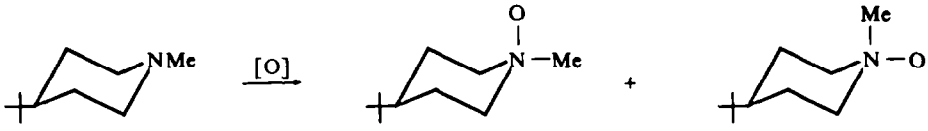
Abstract—The two stereoisomeric 4-t-butyl-N-methylpiperidine-N-oxides were prepared by oxidizing 4-t-butyl-N-methylpiperidine. They were separated, characterized and their configurations assigned. It has been established that the equatorial N-methyl in a piperidine oxide system gives rise to an NMR signal at lower magnetic field than the axial one. The conformational equilibrium of N-methylpiperidine oxide was investigated. The equilibrium constant and the conformational free energy were evaluated.

RESULTS AND DISCUSSION

THE NITROGEN ATOM of an amine oxide is known to possess a rigid tetrahedral configuration. Consequently, in a properly substituted system it may constitute a chiral center and indeed, optically active amine oxides are known.[1] The incorporation of the nitrogen atom of an amine oxide into a ring system will result in the formation of diastereomeric species. It is upon oxidation of the configurationally unstable tertiary amine that the rigid configuration of the amine oxide is obtained. We would, therefore, like to consider the stereochemical course of the oxidation of the nitrogen atom in heterocyclic systems. A further point which we have investigated is associated with the conformational aspects of cyclic amine oxides. More specifically, we were able to estimate the conformational free energy difference between an axial and an equatorial oxygen. Obviously, the conformational and configurational aspects of these compounds are two interrelated problems and were therefore studied concurrently.

The oxidation of N-alkyl piperidine and its ring-substituted derivatives may proceed *via* two energetically different transition states. The geometry of the transition states may be roughly described in terms of the oxidizing reagent approach, namely an axial or equatorial approach which are obviously diastereomerically related. The distribution of the products will reflect the relative stability of the two transition states provided two conditions are fulfilled. The first one concerns the Curtin–Hammet principle.[2] In the ring-rigid heterocyclic amine system (**1**) the conformational process which must be considered is the one due to the nitrogen inversion. The rate of exchange between the two diastereomeric conformations resulting from such an inversion is undoubtedly much faster ($1{\cdot}6\text{–}4 \times 10^2$ sec^{-1})[3] than the rate of oxidation of the tertiary amine with H_2O_2 which requires several hours for completion. Therefore, from this point of view, the distribution of products may be safely regarded as being a function of the energy difference between the two transition states. The second condition requires a kinetically controlled reaction if product distribution is to reflect the relative energies of the transition states. Indeed, an experiment will be described which establishes that the oxidation is kinetically controlled.

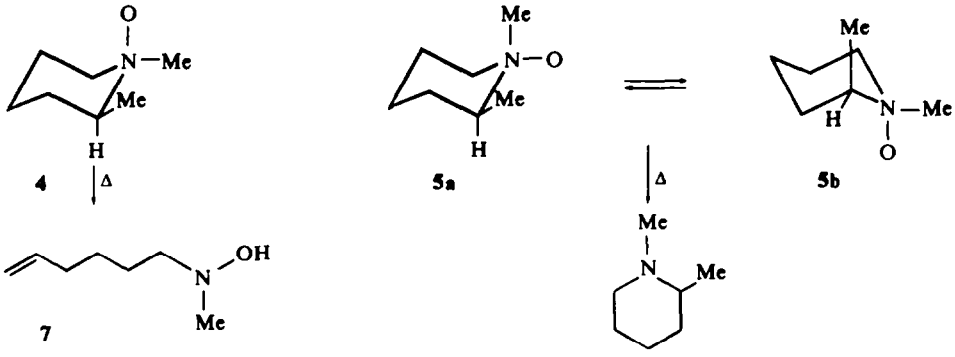
In order to discern the stereochemical consequences of the oxidation reaction, 4-t-butyl-N-methylpiperidine (**1**) was employed as a substrate. Such a system ensures that each of the two possible oxidation products (**2**, **3**) are for all practical purposes conformationally homogeneous and obviously conformational equilibration between them is excluded. Y. Kawazoe *et al.*, oxidized **1** and detected the presence of only one product.[4] However, we find that careful chromatography of the crude oxidation mixture on basic alumina yields two discrete components. The percentage composition of the mixture was determined both gravimetrically and by NMR analysis (integration of the N–Me signals areas) and was found to be 95/5 $\pm$ 2%. The picrates of the two crystalline products were prepared and their elemental analyses were consistent with the expected empirical formula ($C_{10}H_{21}NO$) for 4-t-butyl-N-methylpiperidine-N-oxide. The two are, therefore, undoubtedly stereoisomeric oxidation products of **1**.



1 **2** **3**

Next, it was necessary to assign the configuration of each of the two stereoisomers (**2** and **3**). This problem could have been solved rather simply by analyzing the relative chemical shifts of the N–Me groups in the NMR spectra of **1** and **2** (Table 1). However, a literature search reveals that no sound correlation exists between the configuration of the N–Me and its chemical shift in amine oxides of the piperidine systems.* Clearly, a comparison with carbocyclic systems is invalid since the anisotropy effect of the N—O bond on the chemical shift of the N–Me is not known. For the same reason a comparison with quaternary piperidinium salts may also be misleading. In fact, the pitfall of such comparisons has been recently pointed out by Fodor and collaborators[5] who reversed the configurational assignments of the nitrogen atom in the piperidinium system of the various tropane derivatives, and consequently all NMR correlations were also reversed. From their X-ray analysis, the above authors conclude that the axial Me resonates at a lower magnetic field than the equatorial Me, this being at variance with the situation in the carbocyclic systems. Furthermore, on the basis of X-ray study the above authors also reversed the configurational assignment of the nitrogen atom in scopolamine N-oxide hydrobromide which was previously based on empirical NMR data of the chemical shift of the N–Me group. In light of this situation we have sought an independent correlation between the chemical shift of the N–Me and the configuration of the nitrogen atom in the piperidine oxide system. To solve this problem, we turned our attention to the two stereoisomeric 1,2-dimethylpiperidine-N-oxides **4** and **5** which were prepared by A. C. Cope *et al.*[6] The configurations of **4** and **5** were determined by these authors on the basis of the thermal β-elimination reaction.

* Y. Kawazoe *et al.*[4] use NMR correlations based on the chemical shifts of quaternary piperidinium salts and carbocyclic systems.



Only one of the two isomers yields 5-hexenyl-N-methylhydroxylamine (7) in a thermal reaction, indicative of the β-elimination reaction. Consequently, this isomer was assigned[6] the *trans* configuration (4) since only 4 can attain the five-membered *cis*-planar geometry of the transition state required for the elimination. We have repeated the Cope experiment. The two stereoisomeric products were obtained in a ratio of 2:3. Separation of the two components was affected by column chromatography. While the fast running component could be easily obtained in a pure state (TLC and NMR analysis) the slow running component required additional chromatographic purifications. Each of the two components was subjected to identical thermal elimination conditions (160°/2 mm). Analysis of the distillate indicated that only the fast running component on the chromatographic column yields 5-hexenyl-N-methylhydroxylamine (7). The other component was unreactive at 160°, but upon raising the temperature (195°) 1,2-dimethylpiperidine distilled out and was identified by comparing its NMR spectrum with that of an authentic sample. On the basis of the above experimental results the *trans* configuration (4) was assigned to the fast running component (m.p. 220–222°: picrate) and the *cis* configuration (5) to the slow running component (m.p. 208–210°: picrate). With the configurational assignments on hand we have now determined the chemical shift of the N–Me signal in the NMR spectra of 4 and 5 (Table 1). The data indicate that in three solvents the axial N–Me

TABLE 1. NMR DATA OF AMINE OXIDES

Compd.[a]	Conf. of N–Me	m.p. picrate	ν_{N-Me} (c/s)[b]				
			CH_2Cl_2	$CDCl_3$	D_2O	CF_3CO_2H	$W_{\frac{1}{2}}$ (c/s)[c]
2	eq	228–229	319·1 ± 0·2	359·7	344·4	330·4	1·0 ± 0·05
3	ax	179–180	303·2	334·7	334·5	325·5	1·4
4	eq	220–222	313·3	342·0	341·0		0·65
5	eq + ax	208–210	294·5	330·0	326·6		1·0
6	eq + ax	206–207	315·7	353·5	340·6	329·6	1·3

[a] The chemical shift data for 2,3 and 6 are that of a solution of equimolar concentration (0·01 M) of the three components. The chemical shift data for 4 and 5 are that of a solution of equimolar concentration (0·07 M) of the two components.

[b] The frequency data is at 100 MHz. The shifts are relative to TMS, used internally with CH_2Cl_2 and $CDCl_3$ and octamethyltetrasiloxane used externally with D_2O and TFA.

[c] Measured in CH_2Cl_2.

resonates at higher field than the equatorial one. It should be noted that this conclusion holds regardless of any conformational equilibrium associated with either **4** or **5**. Undoubtedly, the chemical shift of **4** is that of practically pure equatorial N–Me, since it will be unreasonable to assume significant population of the trans diaxial methyl conformation. Therefore, the upfield shift of the N–Me of **5** with respect to **4** must be mainly due to the population of the axial N–Me conformer of **5**. However, the N–Me signal of **5** is a time-averaged signal arising from **5a** and **5b** which are in fast equilibrium. Therefore, the above conclusion must rest upon the assumption that the N–Me of **5b** resonates at lower field than the N–Me of **5a**. We shall argue that the chemical shifts of the equatorial N–Me of **5b** and of **4** are, in fact, almost identical. The possible difference between the two may arise from the anisotropic effect resulting from the change in the configuration of the adjacent C–Me. The magnitude of this effect may be estimated from the comparison of the chemical shifts of the methyl groups in *cis*-1,2-dimethylcyclohexane (δ 0·86 ppm) and its *trans* isomer (δ 0·89 ppm).[7] The difference, 3 c/s (at 100 MHz) reflects the maximum anisotropic effect experienced by an equatorial Me due to the change in configuration of an adjacent Me.* When extrapolating these results to the presently investigated system, it is concluded that the resonance line of the N–Me of **5b** may be shifted upfield by a maximum value of 3 c/s with respect to the corresponding signal of **4**. This should be compared with our experimental value of 18·8 c/s (CH_2Cl_2) for the difference in the chemical shifts between **4** and **5** (Table 1). Our previous conclusion is now on safe ground, and regardless of the conformational equilibrium, the upfield shift of the time averaged N–Me signal of **5** with respect to **4** is practically due only to the population of **5a** with an axial N–Me. We can now state that in the system of piperidine oxide the axial N–Me is resonating at higher field than the equatorial one.

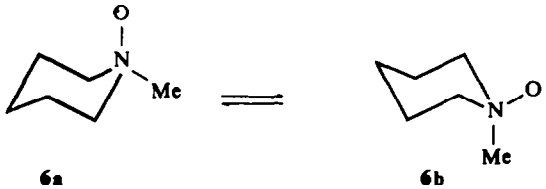
It seems to us legitimate to now apply this proposition to the configurational assignments of the two amine oxides (**2** and **3**). Thus on the basis of the relative chemical shifts of the N–Me signals in the NMR spectra of **2** and **3** (Table 1), the low field signal (equatorial Me) is assigned to **2** (m.p. 228–229° picrate); while the high field signal (axial Me) is assigned to **3** (m.p. 179–180°: picrate).

The above conclusions were further corroborated by additional experimental observations. Significant variations were noted in the width at half height ($w_{\frac{1}{2}}$) of the N–Me signal of the two pairs of stereoisomers, namely **2**, **3** and **4**, **5** (Table 1). Such variations were previously encountered in carbocyclic and heterocyclic systems.[8] They are related to changes in the unresolved long range spin coupling between the N–Me and the adjacent ring methylene protons. Any contribution from spin coupling involving the axial C-2 and C-6 protons, and the protons of an adjacent *axial* Me has been previously found to produce maximum broadening of the Me signal. From Table 1 it can be realized that $w_{\frac{1}{2}}(3) > w_{\frac{1}{2}}(2)$ and $w_{\frac{1}{2}}(5) > w_{\frac{1}{2}}(4)$. These results correspond exactly to our previous configurational assignments. Furthermore, compound (**3**) possessing an equatorial oxygen is expected to be more polar than **2** with an axial oxygen. Such behaviour is well documented in the cyclocarbinol systems with which the analogy seems pertinent.[9] Also, judging from the chromatographic behaviour of

* The recorded signal of *cis*-1,2-dimethylcyclohexane is a time-averaged signal arising from two enantiomeric conformations. Since we are interested in the chemical shift of the equatorial Me, and since the equatorial Me resonates at lower field than the axial one, the value of 3 c/s reflects the maximal anisotropic effect.

4 and **5**, for which configurational assignments are on secure grounds (see previous discussion), it was found that **5**, with an equatorial oxygen, has a larger retention time than **4** on the chromatographic column and is, therefore, the more polar isomer. Indeed, as expected, the more polar **3** (equatorial oxygen) was more strongly retained than **2** on the chromatographic column, again supporting our previous assignments.

Having assigned the configuration to the two stereoisomeric 4-t-butyl N-methylpiperidine-N-oxides, we are now in a position to analyze the conformational equilibrium in the mobile system of N-methylpiperidine-N-oxide (**6**).[6] This compound gives rise to only one N–Me signal in its NMR spectrum, its chemical shift being an average of the two fast equilibrating conformations (**6a**) and (**6b**). A convenient and



6a **6b**

simple experiment for the estimation of the above conformational equilibrium constant consists of measuring the chemical shifts of the N–Me signals of the two rigid systems (**2** and **3**) and comparing it with that of the mobile system (**6**).[10] The equilibrium constant K was calculated from the following relationship:[10]

$$K_{28^\circ} = \frac{(\mathbf{6a})}{(\mathbf{6b})} = \frac{\delta_6 - \delta_3}{\delta_2 - \delta_6}$$

It must be noted that the usual assumptions are inherent in this type of experiment and therefore the calculated values must be regarded as being only approximations. The shift values (Table 1) were determined at 28°, in three different solvents. The dependence of the chemical shift on the concentration of the various amine oxides was checked and found to be negligible. However, in order to obtain reproducible chemical shifts in organic solvents, strict precautions have to be exercised to exclude traces of H_2O or EtOH (from $CHCl_3$). This is most difficult in the case of the notoriously hygroscopic amine oxides (experimental). Therefore, the NMR shift values which were used for calculating the equilibrium constant of **6** were determined by measuring the spectrum of an equimolar concentration solution of **2**, **3** and **6** and the values are those listed in Table 1. Such spectra were determined at various concentrations and even with solutions known to contain some water. Even though the individual chemical shifts varied, the value of the equilibrium constant remained within the experimental error. The equilibrium constants for the interconversion **6b** ⇌ **6a** in the three different solvents and in TFA, and the corresponding ΔG° values are listed in Table 2.

TABLE 2. THERMODYNAMIC DATA FOR THE EQUILIBRIUM **6b** ⇌ **6a** AT 28°

	CH_2Cl_2	$CDCl_3$	D_2O	CF_3CO_2H (TFA)
K_{eq}	3·1 ± 0·1	3·0	1·6	6·2
$-\Delta G^\circ$(Kcal/mol)	0·68	0·65	0·28	1·1
$-\Delta G_{N-O}$(Kcal/mol)	1·02	1·05	1·42	0·6

These results indicate the preference of an axial oxygen *versus* an axial Me in all solvents. A solvent-solute interaction can be detected by variations in the conformational equilibrium as a function of the nature of the solvent. A hydrogen donor solvent is expected to solvate the basic oxygen of an amine oxide. For steric reasons such a solvation is expected to stabilize **6b**, possessing the equatorial oxygen, to a larger extent than **6a**, with the axial oxygen. From the similarity of the ΔG° values in CH_2Cl_2 and $CHCl_3$ it must be concluded that hydrogen bonding in $CHCl_3$ is weak and does not affect the thermodynamics of the equilibrating system. On the other hand in D_2O the decrease in the population of **6a** (axial oxygen) is consistent with the above description, namely, the axial sphere of solvation is less effective than the equatorial one.*

It will now be interesting to examine the conformational energy value of the oxygen atom in the system under consideration. On the assumption that the geometry of N-methylpiperidine-N-oxide is similar to that of the cyclohexane ring system, the value of ΔG_{CH_3} (1·7 kcal/mol) can be used to calculate $\Delta G_{N\rightarrow O}$ (Table 2). At present, such an assumption has no experimental basis. In fact it has been recently demonstrated that the conformational energy value of the N–Me group in N-methylpiperidine is significantly smaller than the corresponding value in the cyclohexane system.[11] The calculated $\Delta G_{N\rightarrow O}$ values in the first three solvents (Table 2) seem to be too large; they imply that the oxygen atom in N-methylpiperidine-N-oxide has a significantly larger effective size than the OH group in cyclohexanol (ΔG_{OH} = 0·52–0·87 kcal/mol).[12] This may be taken as an indication that the conformational energy value of the N–Me group in the piperidine oxide system is smaller than 1·7 kcal/mol, this being due to the geometrical changes in the heterocyclic system as compared to the cyclohexane system. In TFA, **6a** and **6b** are transformed into the corresponding charged conjugated acids. The data in Table 2 indicate that the protonation of the oxygen atom results in the largest equilibrium constant in this series. Since protonation must be accompanied by change in the hybridization of the oxygen atom, and in the charge density around the nitrogen atom, it seems to us that comparison of the thermodynamic data with those of the unprotonated species is invalid. Even more interesting is the magnitude of $\Delta G_{N\rightarrow O}$ in TFA (Table 2). This value (0·6 kcal/mol) is now within the range of ΔG_{OH} values of the cyclohexanol system (0·52–0·87).[11] This again may be taken as an indication that the geometry and the various non-bonded interactions in the conjugated acids of **6** are similar to those of the cyclohexane system.

Since the value of free energy difference between the Me group in the axial and equatorial conformations has been estimated, it is now possible to suggest an interpretation to the high degree of stereoselectivity (95% of **2**) encountered in the oxidation of 4-t-butyl-N-methylpiperidine. That the reaction under consideration is kinetically controlled was established by subjecting the minor oxidation component (**3**) to the oxidation reaction conditions. Formation of the stereoisomer (**2**) could not be detected and **3** was reisolated. The transition state for equatorial oxidation is associated with a shift of the N–Me group toward the axial position, while the axial approach generates 1,3-diaxial interactions between the oxidizing specie and the axial 3,5 hydrogen atoms of the piperidine ring. The energy relationship between these two

* It can also be argued that the equilibrium shift in D_2O is due to the difference in the polarity between the two stereoisomers, **6b** being more polar than **6a**.

effects is similar to that between the two equilibrating conformers **6a** and **6b**. In the latter system the oxygen atom is more stable than the Me, in the axial position. It can be deduced that a similar energy relationship also prevails in the transition state of the oxidation reaction thus accounting for the high axial stereospecifity. Of course, with the present experimental information such considerations are only of qualitative value.

Recently, the two stereoisomeric amine oxides of a tropine system were isolated.[13] Their configurational assignments were made on the basis of the relative chemical shifts of the ring protons of the two isomers. In agreement with our findings, the N-axial Me resonates at higher field than the equatorial one, as can be judged from the NMR spectra which were reproduced in the text.[13] Also, predominance of the axial oxidation product was encountered.

EXPERIMENTAL

M.ps were taken on a "Uni-melt", Thomas and Hoover Capillary apparatus and are uncorrected. NMR spectra were measured on a Varian HA-100. To ensure complete dryness of NMR samples, hydration water was first removed by azeotropic distillation with C_6H_6 and then, after having distilled the C_6H_6 out at reduced pressure and dissolved the sample in $CDCl_3$ or CH_2Cl_2, the solution was filtered through $MgSO_4$ directly into the NMR tube. Line width measurements of the N–Me signal were run at a sweep width of 50 c/s and sweep time of 500 sec using acetone as internal standard for the homogenity control. The acetone line width at half the height being equal in all cases to 0·40 ± 0·05 c/s. Special attention was paid to H_1 level in order to avoid saturation.

General procedure for the oxidation of amines. Amine oxides were prepared from the corresponding amines by oxidation with excess 30% H_2O_2 (molar ratio 1:2·5) in acetone for 48 hr at room temperature. Unreacted H_2O_2 was destroyed by catalytic decomposition with MnO_2, until no more oxygen was evolved and the filtrate proved negative to KI paper. The solution was evaporated to dryness under reduced pressure at *ca.* 60° to prevent any decomposition occurring and the residue was first flash distilled with $CHCl_3$ or C_6H_6 and then washed several times with pentane to eliminate any unreacted amine. The yield of the crude amine oxides was *ca.* 90%. Picrates were prepared in aqueous solution and crystallized from $CHCl_3$.

Cis *and* trans 4-*t-butyl*-N-*methylpiperidine*-N-*oxides.* In a typical experiment 16·5 ml (0·25 m) 30% H_2O_2 was added, dropwise, to a stirred solution of 15·4 g (0·1 m) 4-t-butyl-N-methylpiperidine dissolved in 50 ml acetone at 5°. After the addition was completed the procedure was continued as described above, yielding 15·5 g (91%) of the crude amine oxide.

Separation of trans (**2**) *and* cis (**3**) 4-*t-butyl*-N-*methylpiperidine*-N-*oxides.* From 3·45 g of the crude product, which showed only one N–Me absorption line in the NMR spectrum, 2 g of pure compound (**2**) was crystallized out ($CHCl_3$-ether) m.p. 196°. The mother liquor was evaporated, yielding 1·35 g of a mixture which, from the NMR spectrum was found to contain 83% **2** and 17% of **3**. Column chromatography of the above enriched mixture was carried out on 80 g of basic alumina (activity 2: Merck –1076) with a mixture of $CHCl_3$ (99·5%) and MeOH (0·5%) using the N–Me signals in the NMR spectrum for product control. The amine oxide having the N–Me absorption line at lower field (**2**) was eluted first, m.p. (picrate) 228°–229° (dec.). (Found: C, 47·92; H, 5·99; N, 13·89. Calc for $C_{16}H_{24}N_4O_8$: C, 48·15; H, 6·07; N, 13·57%). Further elution resulted in a second crystalline product (**3**), m.p. (picrate) 179–180° (dec). Analysis calculated as above. (Found: C, 48·28; H, 6·07; N, 13·67%).

Separation of trans (**4**) *and* cis (**5**), 1,2-*dimethylpiperidine*-N-*oxides.* The oxidation of 1,2-dimethylpiperidine according to the above procedure, gave a crude mixture with N–Me signal ratio of 2:3 in the NMR spectrum. The crude mixture (5 g) was chromatographed on basic alumina (300 g) using a mixture of $CHCl_3$ (80%) and petrol ether 40–60° (20%). Compound **4**, the major component, emerged first in a pure state, followed by fractions which were progressively enriched in 5. Fractions containing more than 70% of 5 were rechromatographed to obtain the *cis* isomer (**5**) in a pure state. M.p. of **4** (picrate) 220–222° (lit. 211–215°);[6] m.p. of **5** (picrate) 208–210° (lit. 207–211°).[6]

Thermolysis of trans-1,2-*dimethylpiperidine*-N-*oxide* (**4**). 1·6 g of 4 was dried by azeotropic distillation with C_6H_6. It was heated on an oil bath under nitrogen at 2 mm. Decomposition commenced at 160° and the

distillate was collected in dry ice traps. It was identified as 5-hexenyl-N-methyl hydroxylamine (7), NMR ($CDCl_3$): δ 1·5 (4H, m, C-2 and C-3); 2·1 (2H, m, C-4); 2·57 (3H, s, N–Me); 2·6 (2H, m, C-1); 4·76–5·16 (2H, m, C-6); 5·43–6·15 (1H, m, C-5). Oxalate, (cryst. from EtOAc) m.p. 112–114° (lit. 114–115°).[6]

Thermolysis of cis-1,2-*dimethylpiperidine*-N-*oxide* (5). 0·7 g of 5 was subjected to the identical thermolysis conditions as described for the isomer 4. No distillate could be detected at 160°. When the temperature was raised to 195° sluggish decomposition started. The small quantity of distillate collected was identified as 1,2-dimethylpiperidine by comparing its NMR spectrum to that of an authentic sample. The residue was identified as starting material. No trace of 7 could be detected.

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