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Stereochemistry in Solution. IV.[1] Conformational Preference of the Non-bonded Electron Pair of Nitrogen in Piperidine Derivatives. Effective Size of the Lone Paired Electrons

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From the IR spectrum in C–D stretching region of 2,6–dideuterated piperidine, N–methylpiperidine, and N–isopropylpiperidine, quantitative evaluation was made about conformational preference of the non–bonded electron pair of nitrogen. Thirty percent of the lone pair was proved to exist in equatorial position in piperidine molecule in carbon tetrachloride.

There has been much interest in determining the effective size of the non–bonded electron pair of nitrogen in connection with its conformational preference in a piperidine or piperazine ring. It is reasonable to consider a less space–demanding group to be preferentially oriented in axial position of a chaired cyclohexane ring. Therefore, assuming that the effective size of the lone pair of nitrogen is sufficiently smaller than that of hydrogen, the lone pair electrons in piperidine would exist in the axial position and the N–H hydrogen in the equatorial. In 1958, Aroney and LeFèbre suggested from the molar Kerr constant measurements of piperidine and N–methylpiperidine that the effective size of the lone pair was considerably larger than that of a bonded hydrogen.[3,4] However, evidence has since been accumulated[5–14] for the reverse conclusion that the lone pair is somewhat smaller than a bonded hydrogen, although a supporting indication was also reported.[15,16] To begin with, the fact that the rotational barriers about CH_3–CH_3, CH_3–NH_2, and CH_3–OH bonds are 2.9, 1.9 and 1.1 kcal/mole, respectively,[17] may allow a presumption to be made regarding the effective size of the lone pair. Thus, the height of the barrier to rotation of the methyl group increases by about 1 kcal/mole with increase in the number of hydrogen attached to the hetero atom, suggesting that a hydrogen may be a more space–demanding group than the lone pair of nitrogen or oxygen.

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Now, we provide in this paper an additional conclusive evidence for the latter conclusion by demonstrating that 70% of the lone pair in piperidine is axially oriented, using the infrared spectroscopy, the energy difference between the conformers involving the axial and equatorial lone pairs being 0.47 kcal/mole.

Results and Discussion

In quinolizidine derivatives, it is well known that infrared absorptions in the 2700—2800 cm^{-1} region, the so-called Bohlmann band,[18,19] are correlated with the presence of at least two hydrogens on carbons attached to the nitrogen, both of which are oriented *anti* (or *trans*) to the lone pair. This correlation has been widely applied to the stereochemical problems of quinolizidine derivatives,[6,20–25] although some caution should be taken when it is applied to the ring systems having substituents or ring strain.[20,26,27] Since this characteristic band shift must arise from a type of interactions between the lone pair and the *anti* C–H bond,[28] as shown in Fig. 1, this structural correlation may be

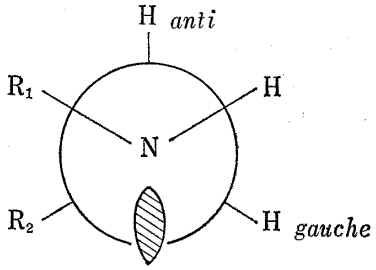

Fig. 1.

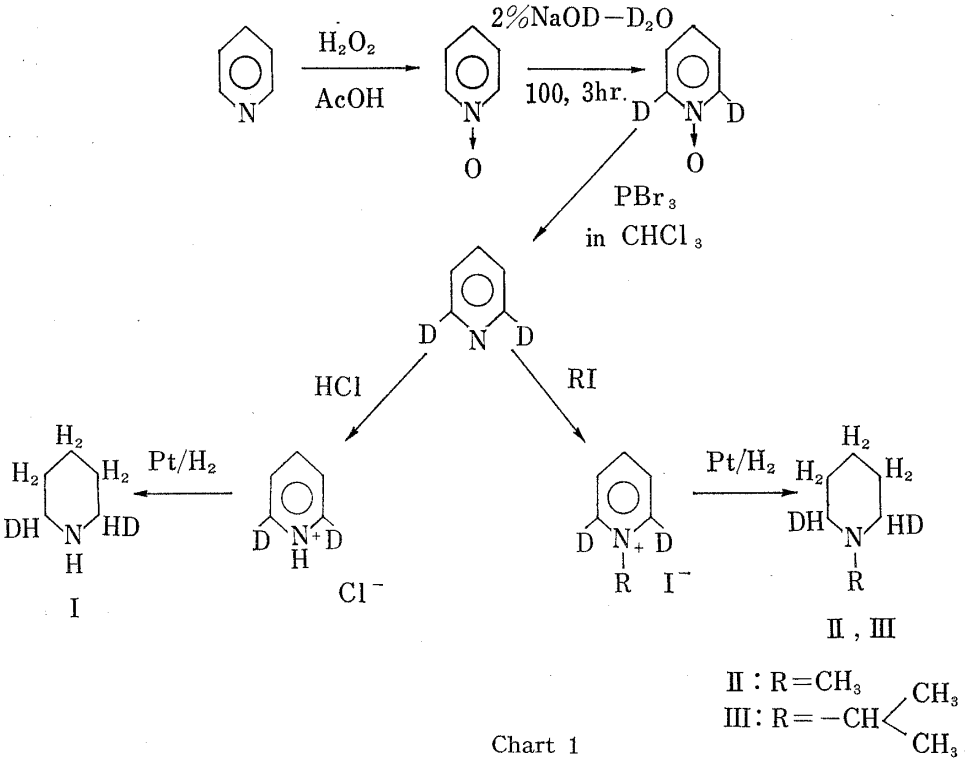

Chart 1

18) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957).
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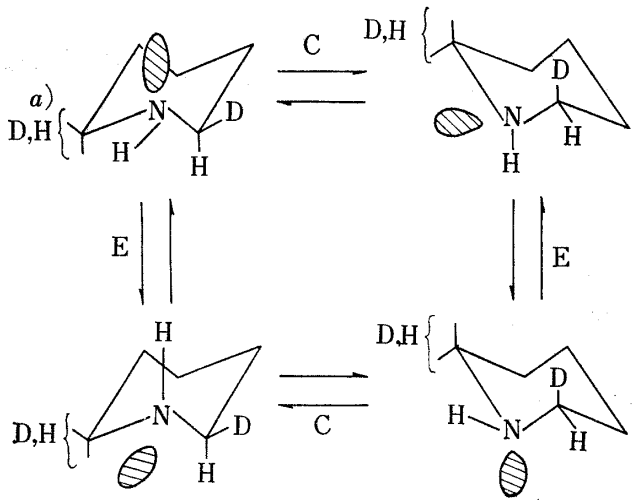
expected to be generally applicable to the system shown in Fig. 1, regardless of other moiety of the molecule.

We applied in the present study this criterion to piperidines in order to estimate how much of the lone pair is axially oriented in these molecules. The compounds chosen for this purpose were the 2,6-dideuterated derivatives of piperidine, N-methylpiperidine, and N-isopropylpiperidine (I, II, and III, respectively). Quantitative comparisons were made between the absorption intensities of C–D stretching vibrations of the normal and the relevant *anti* C–D bonds, the latter being expected to give an absorption in lower frequency region than the former. Our choice may be advantageous for the following two reasons: (i) To observe the absorptions due to C–D bonds next to the nitrogen atom separately from those due to all other C–H bonds and (ii) to avoid the complexity owing to the signal splitting into symmetric and asymmetric bands by using –N–CDH– compounds instead of –N–CH_2– or –N–CD_2– ones. These model compounds were prepared by hydrogenation of N-substituted 2,6-dideuterated pyridinium iodides, as shown in Chart 1. With regard to stereochemistry of the deuteriums substituted at 2- and 6-positions in these derivatives, it can be concluded that each deuterium atom has exactly the same possibility in orienting axially or equatorially, since the two interconvertible chair forms are without doubt at the same free energy level. In addition to the ring conversional equilibrium, these piperidine derivatives are also in an epimeric equilibrium in respect to the nitrogen, which can be achieved by interconversion of N-substituent and lone pair of electrons, as indicated in Chart 2. As a result, statistical populations of the axial and equatorial deuteriums are exactly the same, regardless of the presence or absence of the stereospecificity in hydrogenation of the pyridinium ions.



a) Geometrical configuration, *cis* and *trans*, of the deuterium atoms at 2- and 6-positions need not be taken into consideration in the present study.
E: epimerization C: ring conversion

Chart 2

Here, we made an assumption that the conformational free energy difference of the N-isopropyl group is large enough to maintain it almost exclusively in the equatorial position in piperidine molecule. On the basis of this reasonable assumption, it can be concluded that the number of deuterium which is situated in *anti* (or *trans*) orientation is almost the same as that of the deuterium which is *gauche* to the lone pair. The IR spectrum of III measured in carbon tetrachloride is reproduced in Fig. 2c and Fig. 3 which constitute the two well-separated C–D absorptions. According to Bohlmann's work,[18,19] the lower frequency signal (2075—2030 cm^{-1}), should be assigned to the stretching vibration of the *anti* C–D bond and the higher one (2170—2150 cm^{-1}) assigned to that of the *gauche* C–D bonds.[29] An interesting feature of this spectrum is that the integral intensity[30] of these peaks is not equal, the peak due to the *anti* C–D bond being 1.18 times more intense than that of the *gauche* C–D bond. This inequality might be considered to arise from the difference in polarity between *anti* and *gauche* C–D bonds. This may tentatively be explained from an assumption that the hydrogen

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30) The integral intensities were compared after the absorption scale of the spectrum was transferred from the percentage transmittance (I) to the optical density (A), following the formula $A=\log_{10} I_0/I$.

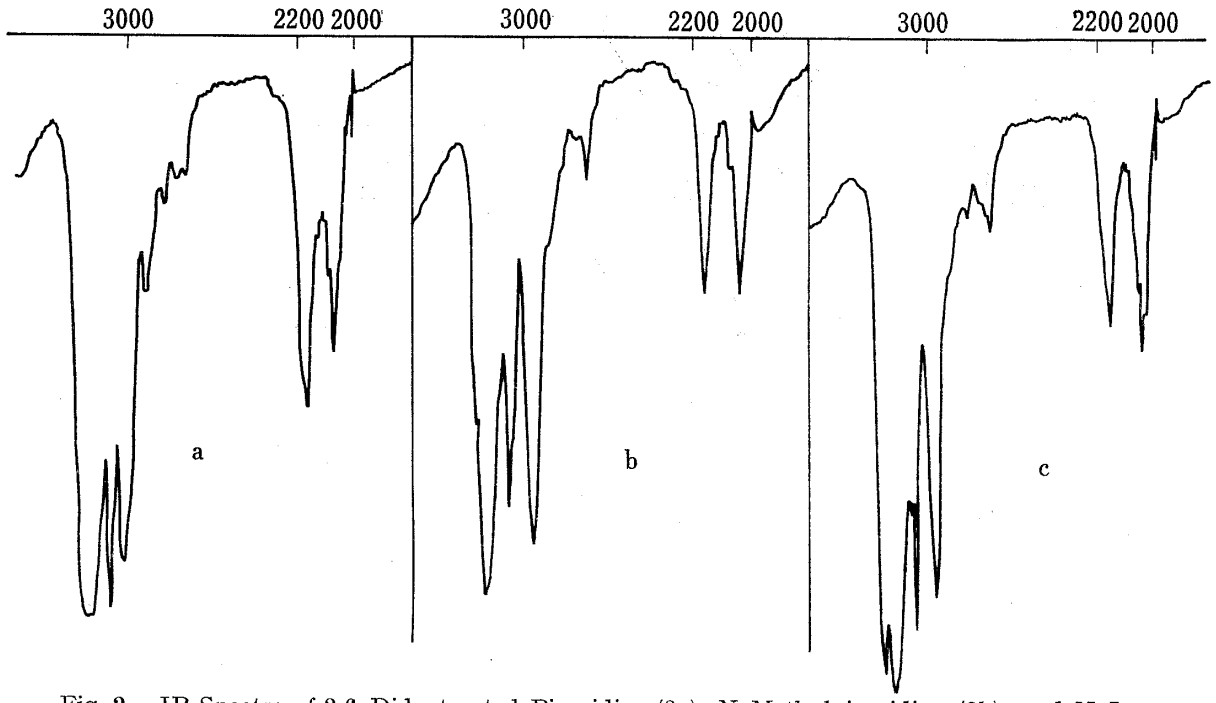

Fig. 2. IR Spectra of 2,6–Dideuterated Piperidine (2a), N–Methylpiperidine (2b), and N–Isopropylpiperidine (2c) in CCl_4

anti to the lone pair is more acidic than the *gauche* due to the stereoelectronic effect of the nitrogen atom.

Another assumption was made here that the intensity ratio, 1.18, obtained for N–isopropyl derivatives (III) can be applied to piperidine (I) itself and N–methylpiperidine (II). The IR spectra of I and II are reproduced in Fig. 2a and 2b. From the comparison of the integral intensity ratios referred to that of N–isopropyl derivative (III),[31] population of the axial lone pair of the epimerically equilibrated piperidines can be obtained according to Eq. 1.

$$x=2A/(1.18+A) \qquad \text{(Eq. 1)}^{32}$$

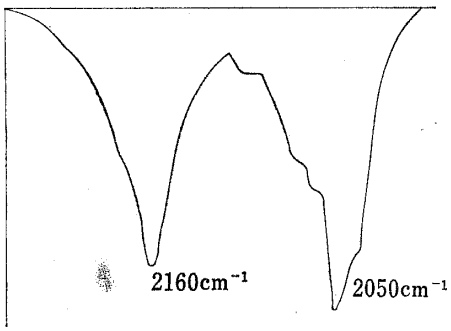

Fig. 3. IR Spectrum of 2,6–Dideuterated N–Isopropylpiperidine in C–D Stretching Region, measured in CCl_4 with 10–times expanded Transversal Coördinate

The Longitudinal Coördinate is calibrated with the optical density.

where x is the molar fraction of the axially oriented lone pair of electrons and A is the observed integral intensity ratio[30] of the peak due to the *anti* C–D bond (*ca.* 2050 cm^{-1}) to that due to the *gauche* one (*ca.* 2150 cm^{-1}).

Values of 0.62 and 1.05 were obtained as the A values in carbon tetrachloride for piperidine (I) and N–methylpiperidine (II), respectively. It can be deduced from these A values and Eq. 1, that the molar fractions of the axially oriented lone paired electrons in I and II molecules are 0.69 and 0.94, respectively, as illustrated in Chart 3. These results indicate a good coincidence with those stated in the literature of Ref. (5) to (11). Almost the same results

31) The comparison of the integral intensity was carried out by using the 10–times expanded spectra where the optical density was taken as the longitudinal coördinate.

32) The molar ratio of *anti*–D to *gauche*–D in the equilibrating mixture are x to $x+2(1-x)=2-x$. Then, the observed intensity ratio (A) can be written as $f \cdot x/(2-x)$, where f is a factor due to inequality in the intrinsic signal intensity between C–D_{anti} and C–D_{gauche} bonds and was tentatively evaluated to be 1.18 by introducing the data from N–isopropylpiperidine as a reference criterion. The molar fraction of the conformer having the axial lone pair of electrons can, therefore, be formulated as $2A/(f+A)$.

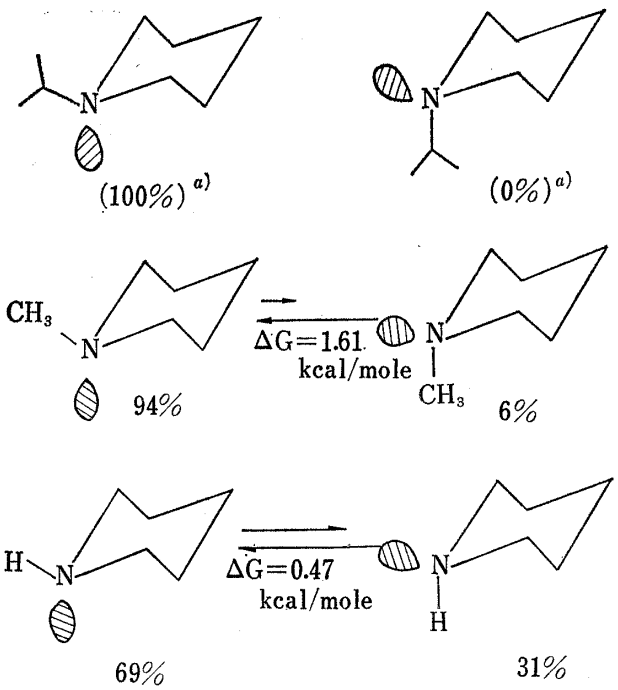

Chart 3. Epimeric Equilibrium of N-Substituted Derivatives in CCl_4

a) These values are not the experimental but are tentatively assumed ones.

were also obtained with neat liquids and the chloroform solutions of these compounds. In a protic solvent, on the other hand, such as methanol, water, or acidic medium, the so-called Bohlmann band around 2050 cm^{-1} collapsed, the peaks being transferred to a higher frequency field and the intensity appearing decreased. It is to be noted that the result obtained in protic solvents as mentioned above would be unreliable for determining the population ratio between the epimers with regard to the lone-pair electrons, because hydrogen bonding interaction between the lone pair and hydroxylic hydrogen may make the Bohlmann correlation invalid to a serious extent.

In any way, as a conclusion, the effective size of the lone-pair electrons of nitrogen is somewhat smaller than the hydrogen bonded to nitrogen in nonpolar solvents and also in neat state. More definite evidence for this conclusion should be derived with N-*tert*-butylpiperidine instead of N-isopropyl derivative as the reference compound having the lone pair in the axial position exclusively. This is now under investigation.

It should be mentioned at the end of this paper that each of the C-D stretching signals has a fine structure as seen in Fig. 2 and Fig. 3. This is still in question although one possibility may be due to the rotational isomerism in the vicinity of N-C-D group.

Experimental

2,6-Dideuterated Pyridine 1-Oxide——Ten grams of freshly distilled pyridine 1-oxide was dissolved in 50 ml of 2% NaOH-D_2O and heated under reflux for 4 hr. The reaction mixture was concentrated *in vacuo* to *ca.* 20 ml, to which 50 ml of fresh D_2O was added. The reaction mixture was heated under reflux for another 4 hr. After most of the solvent was removed *in vacuo* at room temperature, the residue was extracted thoroughly with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and concentrated to 100 ml in volume. Then, 23 ml of PBr_3 was added to this solution under ice-cooling and the reaction mixture was warmed under gentle reflux for 1 hr. After an excess of PBr_3 was decomposed by addition of 30 ml of H_2O, $CHCl_3$ was evaporated *in vacuo*. The residual aqueous solution was made alkaline with Na_2CO_3 and saturated with $(NH_4)_2SO_4$ for the salting out. The 2,6-dideuterated pyridine thus separated was extracted with ether. After removal of the solvent, deuteriopyridine was distilled. bp 115°. Yield, 6.0 g. The deuterium content of the product was verified to be more than 95 D-atom % by proton magnetic resonance spectrum.

Catalytic Reduction——One gram of 2,6-dideuterated pyridine hydrochloride, N-methylpyridinium iodide, or N-isopropylpyridinium iodide was hydrogenated in H_2O with 100 mg of Adams' PtO_2 catalyst under atmospheric condition. After H_2-uptake was completed, the catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was made alkaline with a minimum volume of conc. KOH solution. The separated oil was distilled under a moderately reduced pressure and after the distillate was dried over KOH pellets, it was redestilled. Yields were 60 to 70% for the three compounds studied.

IR Measurements——The spectra were obtained with an infrared spectrometer Model DS-402G (Japan Spectroscopic Co., Ltd.). The cells used for the solutions were 0.1 mm in width and made of NaCl.

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