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6. Yutaka Kawazoe, Mitsuhiro Tsuda and Masako Ohnishi : Stereochemistry in Solution. I. Stereochemistry of Symmetrically Substituted Dimethylpiperidinium Salts in Aqueous Solutions.

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The *cis-trans* assignment of methyl groups of symmetrically disubstituted piperidines was done by inspection of NMR spectra of their N,N-dimethyl derivatives. The conformation of N-methyl group of N-monomethyl derivatives was discussed in taking account of the intermolecular interaction with solvent molecule in addition to the intramolecular steric hindrances.

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Many studies have been done on the stereochemistry of tertiary nitrogens of alicyclic amines bearing lone paired electrons. Thus, the conformation and effective size of the lone pair of electrons have been discussed with helps of dipole moment, infrared, nuclear magnetic resonance (NMR) techniques and so on.[1~8] In addition, stereochemical studies on tetravalent cationic nitrogens of alicyclic amines are also of interest in connection with the ring conversion and the inversion of N-alkyl group.[2,3,9~11]

Now, this paper concerns the configuration of C-methyl and N-methyl groups of symmetrically disubstituted N-methylpiperidinium salts, *i.e.*, 2,6- and 3,5-lupetidine derivatives, in aqueous solutions. Classically, the assignment of configuration to the *cis* and the *trans* isomers of symmetrically disubstituted alicyclic amines has been based on resolution of the *trans* isomer into its optical antipodes. This method is, however, of no use in those cases in which the *trans* isomer does not form crystalline, separable salts with the resolving acid. Recently, Hill and Chan[12] established an elegant method to assign the *cis* and *trans* configurations by nuclear magnetic resonance technique. This method is based on the magnetic non-equivalent character of two methylene protons of N-benzyl derivatives of the *trans* isomer. But, since this non-equivalence is caused by the dissymmetry of the proximity of the nitrogen function, this method can not be applicable to such a case as 3,5-dimethylpiperidine where the asymmetry at the β-carbon atom is too far removed from the benzylic methylene protons to perturb their magnetic environment. We describe in this paper another simple method to assign the configuration to the *cis* and the *trans* by means of nuclear magnetic resonance technique in taking account of their stereochemistry in solution. In addition, with regard to the conformation of NH^+-CH_3 group of these cyclic amines, many factors which may affect the stereochemical stability of both epimers, such as

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kind of the counter anions, concentration of the solutes, pH of the solution, etc., were examined from their resonance spectra, taking account of ring conversion and proton exchange of NH group.

Results and Discussion

cis and *trans* 2,6-dimethylpiperidinium derivatives

The assignment of configuration of two C-methyls in N-methyl-2,6-dimethylpiperidine molecules was effectively carried out by considering the stereochemical stability of their N,N-dimethyl derivatives and their nuclear magnetic resonance spectra. Thus, with regard to the *cis* isomer, two chair conformations are possible; one has two equatorial methyl groups and the other has two axial ones. As the latter conformation is absolutely unfavored, no ring conversion occurs, both C-methyl groups being fixed in equatorial conformation. On the other hand, two chair conformers of the *trans* isomer, where one methyl is equatorial and the other is axial in either chair forms, are of completely same stability, so that the ring conversion can be expected to occur as easily as that of a cyclohexane ring. It is well known that one can not distinguish between the states going back and forth rapidly enough for the requirement of the uncertainty principle. The ring conversion of the *trans* isomer is supposed to be of this case in the proton magnetic resonance spectroscopy at room temperature. As a result, one can expect a serious difference in N-methyl resonance region between the isomers. Thus, in the *cis* molecule two singlets must be observed for two N-methyls, whereas, in the *trans* molecule, two of N-methyls are alternating in the conformational situation as rapidly as not to be detected by nuclear magnetic resonance spectroscopy. As a result, one can observe only one singlet for six N-methyl protons. Now the spectra were measured of two isomers and the results were just as expected above,[*2] the chemical shift data being shown in Table I.

Table I. Chemical Shifts of 1,1,2,6- and 1,1,3,5-Tetramethylpiperidinium Iodides

Compound \ Solvent		N-CH_3		C-CH_3	
		D_2O[b]	$CHCl_3$[a]	D_2O[b]	$CHCl_3$[a]
1,1,2,6-tetramethylpiperidinium iodide	*cis*	7.28 6.98	7.12 6.67	8.64	8.53
	trans	7.00	6.72	8.64	8.50
1,1,3,5-tetramethylpiperidinium iodide	*cis*	6.95 6.90	6.62 6.45	9.08	8.98
	trans	6.92	6.51	8.92	8.82

a) Tetramethylsilane was used as the internal reference, represented as τ-values.
b) Sodium dimethylsilapentasulfonate (DSS) was used as the internal reference, represented just like τ-values.

Next, let us consider N-monomethyl piperidinium salts such as hydrogen halides, perchlorate, picrate, etc., where the nitrogen is also epimeric in addition to two of C-methyls. The chemical exchange of the N^+-H hydrogen in these salts was proved not to be so rapid in neutral or acidic solutions since the resonance signal of N^+-CH_3 protons appeared as a doublet spin-coupled with the N^+-H proton. The chemical shift data are shown in Table II and the spectra of the *cis* isomer in H_2O and D_2O are reproduced in Fig. 1, for example. C-Methyl signal of the *trans* isomer consisted of two doublets,[*3] each areal intensity being same. It can be regarded that one doublet

[*2] The same observations were found in other solvents such as chloroform, pyridine, etc.

Table II. Chemical Shifts of 1,2,6- and 1,3,5-Trimethylpiperidine Hydrochlorides

Compound		N-CH_3		C-CH_3	
	Slovent	H_2O[b]	$CHCl_3$[a]	H_2O[b]	$CHCl_3$[a]
1,2,6-trimethylpiperidine-HCl	*cis*	7.42 7.17	7.54 7.25	8.73 8.64	8.65 8.45
	trans	7.27	7.24	8.72 8.72	8.64 8.50
1,3,5-trimethylpiperidine-HCl	*cis*	7.20	7.22	9.07	9.03
	trans	7.22	7.20	9.08 8.90	9.07 8.61

a) Tetramethylsilane was used as the internal reference, represented as τ-values.
b) Sodium dimethylsilapentasulfonate (DSS) was used as the internal reference, represented just like τ-values.

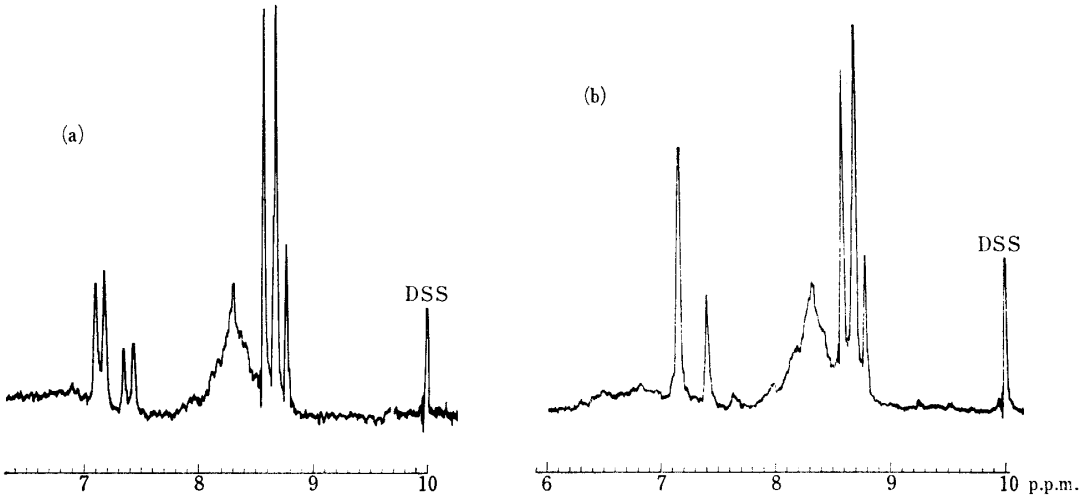

Fig. 1. Nuclear Magnetic Resonance Spectra of *cis*-1,2,6-Trimethylpiperidinium Hydrochloride (a) in H_2O and (b) in D_2O (30 mg. of the sample in 0.5 ml. of the solvent)

DSS was used as the internal standard for spectral calibration as analoguously as in τ-scale.

is due to *cis* methyl relative to N-methyl and the other is due to *trans* one. N-methyl signal consisted of only one doublet which did not split further any more even in chloroform or benzene solutions. These facts can be reasonably explained by considering that there exists rapid ring conversions between epimers with regard to N-methyl group. The spectrum of the *cis* isomer in water consisted of two doublets for two C-methyls and two doublets for N-methyl. The areal-intensity ratio of two doublets of each pair is not unity but 66% to 34%. This should represent the proportion of equatorial and axial isomers with regard to N-methyl group. Since the lower doublet of N-methyl signals can be assigned to equatorial N-methyl protons,[*4,10,11] it can be concluded that the population of the equatorial N-methyl isomer is 66% and the residual 34% is the axial N-methyl isomer.[*5] According to the Maxwell-Boltzmann's

[*3] In aqueous solution, these two doublets are accidentally overlapped with each other.
[*4] The reason for this assignment is as follows : i) More intense signal which locates in the lower field than the weaker must be expected due to more stable equatorial one. ii) In 1,2-dimethylpiperidinium salts in water, the intense signal became more intense and the weak signal became weaker compared with 1,2,6-trimethyl derivative. When no methyl group was, in turn, substituted at α position, only one N-methyl signal was observed, showing that equatorial conformation was one-sided.
[*5] These values may include an experimental error of $\pm 2\%$.

distribution law, the conformational free energy difference (ΔG) between these isomers can be evaluated as 0.39 ± 0.05 kcal/mol.

Then, the factors which may influence the free energy difference between the isomers will be discussed.

Sort of the counter anion

Various salts of the *cis* isomer were prepared; hydrochloride, hydrobromide, perchlorate, tosylate, picrate and hydroxide. No dependency was observed in aqueous solution at all on the sort of the counter anions examined, as shown in Table Ⅲ.

Table Ⅲ. Equatorial-axial Ratios of N-Methyl Groups in Aqueous Solutions of *cis*-1,2,6-Trimethylpiperidinium Salts

Counter anion	mg./0.5 ml.	Ratio (%)		Relative shift of N-methyl groups (p.p.m.)
		Equatorial	Axial	
Cl^-	15	66	34	0.25
	30	68	32	
	50	66	34	
	100	67	33	
Br^-	19	68	32	0.25
	32	67	33	
	38	67	33	
	64	68	32	
I^-	20	67	33	0.25
ClO_4^-	40	66	34	0.25
	80	66	34	
CF_3COO^-	45	66	34	0.25
picrate	30	67	33	0.25
tosylate	30	69	31	0.25

pH of the solution

The hydrochloride and the hydrobromide were examined. No difference was observed at all on the spectra between the neutral solution and the concentrated hydrogen halide solutions. It is, however, worth noting that the exchange rate decreased to a great extent with increase of acid concentration.

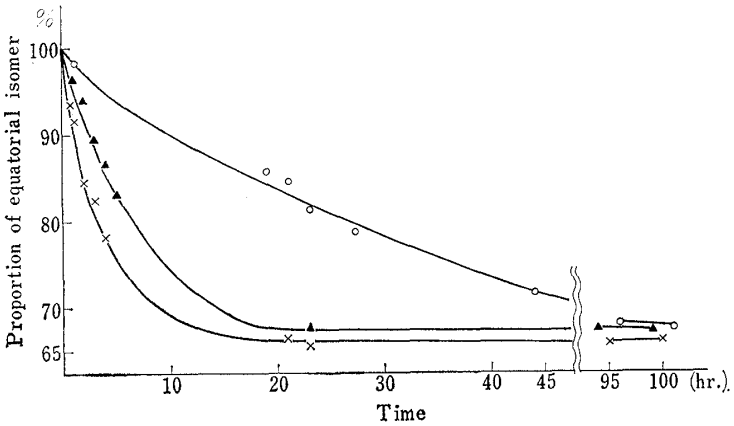

Fig. 2. Conformational Equilibration of $N\text{-}CH_3$ Group of *cis*-1,2,6-Trimethylpiperidinium Hydrochloride in Aqueous Solutions at Room Temperature

× 30 mg. in 0.5 ml. H_2O ▲ 30 mg. in 0.5 ml. D_2O
○ 100 mg. in 0.5 ml. HCl aq. (pH 2)

Concentration of the solute

No dependency was found again. The ratios are same within an experimental error, as shown in Table Ⅲ. Fig. 2 shows the plots of the proportion (%) of the equatorial signal against time at room temperature, upto reaching to the inversional equilibrium. To be of a great notice, the figure is telling that N-methyl group is equatorial in all at $t = 0$, that is, in solid state. This means that, although axial-equatorial proportion does not

depend on the concentration of the solute, they do consist only of the equatorial N-methyl isomer in their crystalline state as illustrated in Chart 1. This was proved to be true for 1,2-dimethylpiperidinium salt, too.

The solvent nature

The solvent used for the present study was water only. But when organic solvents such as chloroform and pyridine were employed, different results were encountered with. Thus, in organic solvents the intensity difference seemed to be enhanced in some cases and to be diminished in other cases depending on the concentration of the solute, the sort of the counter anions, etc. The behaviors in organic solvents will be discussed in a forthcoming paper.

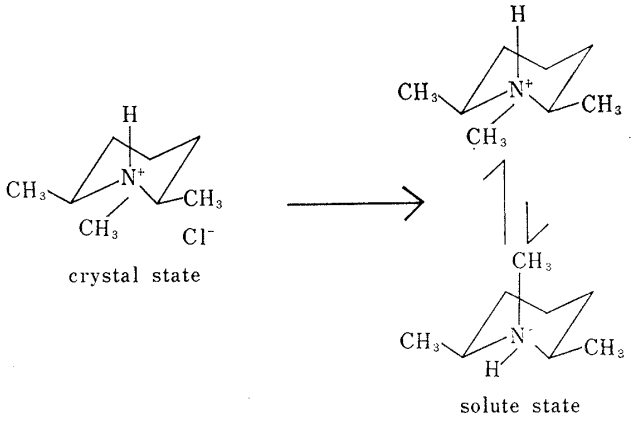

Chart 1.

***cis*- and *trans*-3,5-dimethylpiperidinium derivatives**

In order to determine the *cis* and the *trans* configurations of N-methyl-3,5-dimethylpiperidine, the spectra of its quaternary methyl iodides was inspected just as in case of 2,6-dimethyl isomer. Since one of the isomers gave two singlets and the other gave only one singlet in the N-methyl proton region, the former was assigned to the *cis* and the latter was assigned to the *trans* isomer, where rapid ring conversions made two epimeric N-methyls time-averaged out to give only one singlet signal. The chemical stift data are shown in Table I.

Let us consider 1,3,5-trimethylpiperidinium salts such as the hydrochloride, picrate, etc., where another epimeric center is in their molecules. Chemical shift data are included in Table II. It can be concluded from spectrum-inspection that the *cis* isomer, where no ring conversion occurred, N-methyl was one-sidedly situated in equatorial conformation and that the *trans* isomer consisted of a pair of racemates, where N-methyl was equatorial with no ring conversion.

Conclusion

The *cis-trans* assignment of methyl groups of symmetrically disubstituted piperidines was easily carried out by a simple inspection of the proton magnetic resonance spectra of their N,N-dimethyl derivatives. The conformation of N-methyl group of N-monomethyl derivatives was discussed in taking account of the intermolecular interaction with solvent molecule in addition to the intramolecular steric hindrances. As far as their aqueous solutions are concerned, no remarkable dependence was observed on sort of the counter anion, concentration of the solute nor pH of the solution. But in crystalline state of 2-methyl and 2,6-dimethyl derivatives, it was proved that equatorial N-methyl is predominantly favored. This must be due to the interaction with the crystal field.

Experimental

Catalytic Reduction of 1,2,6-Trimethylpyridinium Iodide

Ethanolic solution of 5 g. of 1,2,6-trimethylpyridinium iodide was hydrogenated in presence of Adams' Platinum under the atmospheric pressure at room temperature. The reduction products were once isolated as a mixture of their hydrochlorides and then made free from acid residue and extracted with ether. The

cis-trans ratio of the reduced products in the ether extract was determined as 85 to 15 by gaschromatography. The preparative separation of this mixture was carried out by alumina column chromatography, an eluting solvent being ether. The *cis* isomer was eluted first and then the *trans* one came out.

Catalytic Reduction of 1,3,5-Trimethylpyridinium Iodide

Hydrogenation of 1,3,5-trimethylpyridinium iodide was carried out in the same way as in case of 1,2,6-trimethyl derivative. The *cis-trans* ratio was determined as 80 to 20 by gaschromatography. Column chromatographic separation as in case of the 1,2,6-trimethyl derivative gave pure *cis* and *trans* isomers, the latter being eluted first with ether.

Derivatives of the Reduction Products

TABLE Ⅳ. Melting Points of Trimethylpiperidine Derivatives

	m.p. (°C)	
	picrate	methiodide
cis-1,2,6-trimethylpiperidine	225～227[a]	280～282 (decomp.)[b]
trans-1,2,6-trimethylpiperidine	244～245 (decomp.)	300～301 (〃)[b]
cis-1,3,5-trimethylpiperidine	147～148	275～276
trans-1,3,5-trimethylpiperidine	149～150	236～238

a) N. J. Leonard, F. D. Hauck, Jr.: J. Am. Chem. Soc., **79**, 5279 (1957).
b) R. Lukes, J. Jizba: Chem. Listy, **46**, 622 (1952); C. A., **47**, 9325 (1953).

NMR Spectra

The spectra were obtained by a JNM 3H-60 (Japan Electron Optics Laboratory Co., Ltd.) spectrometer operating at 60 Mc.p.s.

We are gratefully indebted to Dr. Waro Nakahara of Director of this Institute for his encouragement throughout this work.

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7. Tetsuji Kametani, Ryobun Yanase,*1 Shinzo Kano, and Kuniyoshi Sakurai*2: Bisbenzylisoquinoline Alkaloids and Related Compounds. Ⅺ.*3 Total Synthesis of Stereoisomeric Mixture of Magnoline.*4

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The diamide (Ⅸ) was prepared by Schotten-Baumann reaction of 2-(3-methoxy-4-hydroxyphenyl)ethylamine with the diacid chloride (Ⅴ), followed by ethoxycarbonylation. Cyclization gave the bisdihydroisoquinoline (Ⅺ), the dimethiodide of which, on reduction, gave a stereoisomeric mixture of magnoline or berbamunine (Ⅰ).

(Received March 7, 1966)

Magnoline, $C_{36}H_{40}O_6N_2$, m.p. 179°, occurs in the leaves of *Magnolia fuscata* ANDR., which grows on the Caucasian shores of the Black Sea. It is a yellow crystalline,

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*3 Part Ⅹ: T. Kametani, *et al.*: J. Heterocyclic Chem., **3**, 239 (1966).
*4 This forms Part CLX of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.