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181. Yutaka Kawazoe and Mitsuhiro Tsuda*1 : Stereochemistry in Solution. III.*2 Stereoselectivity in N-Quaternization and N-Oxygenation of α-Substituted Piperidines.

(*National Cancer Center Research Institute**1)

Stereoselectivities in salt formation, N-methylation, N-ethylation, and N-oxygenation of α-substituted piperidines were examined in connection with the free energy-difference between the reaction intermediates in the axial and equatorial approaches of the reagent.

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Several studies have been reported on the stereochemistry and stereoselective salt formation of piperidine derivatives. Steric course of quaternization of this class of cyclic amines was discussed by several workers using a nuclear magnetic resonance technique,[1~3] and the conformational analysis of the lone-pair electrons of piperidine ring was discussed from the consideration of molar Kerr constant, dipole moment, and nuclear magnetic resonance.[4] As one of our serial studies on stereochemistry of piperidine derivatives in solution, this paper describes the substituent effect of α-substituents on the steric course of protonation, quaternization, and N-oxygenation of alkylpiperidine derivatives.

Results and Discussion

Let us consider the protonation process of α-substituted N-methylpiperidines such as 2-methyl, 2-ethyl, *cis*-2,6-dimethyl, and *cis*-2-methyl-6-ethyl derivatives. These compounds are protonated into *cis* and *trans* configurations in reference to the α-substituents to produce a pair of epimers. Since the epimeric salts thus produced readily reach chemical equilibrium at room temperature, the free energy difference between the epimers can be expressed by

$$-\Delta G = RT \ln K$$

where K is the equilibrium constant between epimers bearing N-methyl group in *cis* and *trans* configuration (I and II in Table I) to the α-substituents. The values "K" and "$-\Delta G$" of the hydrochlorides of these derivatives were obtained in their aqueous solutions at room temperature (23°) by measuring the areal intensity-ratios of N-methyl proton signals in their nuclear magnetic resonance spectra. They are listed in Table I. The signal assignments and, consequently, the stereochemical assignment presented in Table I are based on the earlier studies of this class of compounds.[5~8]

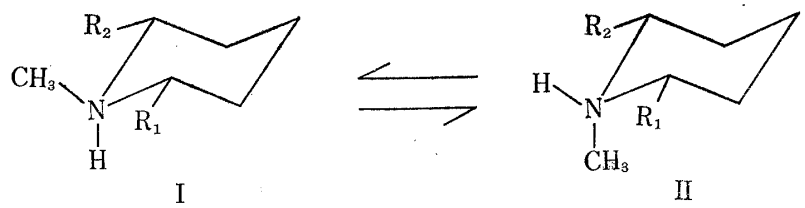
These data clearly indicate that the thermodynamic stability of the equatorial N-methyl (*i.e.*, axial NH) isomer decreases as the bulkiness of α-substituents increases,

*1 Tsukiji, Chuo-ku, Tokyo (川添 豊, 津田充宥).

*2 Part II. This Bulletin, **15**, 214 (1967).

1) H. O. House, B. A. Tefertiller, C. G. Pitt : J. Org. Chem., **31**, 1073 (1966), and literatures cited therein.
2) J. McKenna, J. M. McKenna, A. Tulley, J. White : J. Chem. Soc., **1965**, 1711, and literatures cited therein.
3) J. McKenna, J. M. McKenna, A. Tulley : J. Chem. Soc., **1965**, 5439.
4) J. B. Lambert, R. G. Keske : J. Am. Chem. Soc., **88**, 620 (1966), and literatures cited therein.
5) Y. Kawazoe, M. Tsuda, M. Ohnishi : This Bulletin, **15**, 51 (1967).
6) Y. Kawazoe, M. Tsuda : *Ibid.*, to be published.
7) J. C. N. Ma, E. W. Warnhoff : Canad. J. Chem., **43**, 1849 (1965).
8) J. K. Becconsall, R. A. Y. Jones, J. McKenna : J. Chem. Soc., **1965**, 1726.

Table I. Equilibrium Constants (K) and Free Energy Differences (ΔG) between the N-Epimeric Hydrochlorides of α-Substituted N-Methylpiperidines in Water at 23°



I ⇌ II

R_1	R_2	$K=I/II$	$-\Delta G$ (cal./mol.)[a]
CH_3	H	4.00	820
C_2H_5	H	3.00	650
CH_3	CH_3	1.85	360
CH_3	C_2H_5	0.78	−140

a) Positive values of $-\Delta G$ mean that the epimer I is more stable than epimer II.

and finaly axial N-methyl conformer becomes more favorable than the equatorial one in 1,2-dimethyl-6-ethylpiperidinium hydrochloride. It is worth noting that the stability difference between these epimers are insensitive toward the kind of counter anions and concentration of the solutes in the aqueous solutions although they are considerably dependent on them in non-polar solvents.

Next, let us consider the reaction processes of N-quaternization and N-oxygenation, where there is no chemical interconversion between the products under mild conditions.[3,9] In general, when two or more isomeric components of a single compound, which are in rapid interconversion, undergo a reaction and each of these isomers produces its own characteristic product, the ratio of the products is independent of the molar fractions of the isomers at the initial state, *i.e.*, independent of the free energy difference between the two isomeric starting materials, but does depend solely on the relative energy levels at the transition states through which the products are formed, provided that the activation energy for the interconversion of the isomeric starting materials is small compared to the activation energy for the product formation. The latter conclusion, which is known as the Curtin-Hammett principle,[10] may be readily understood by considering that the species of A, E, A*, and E* in Fig. 1 are in thermodynamic equilibrium and that, therefore, [A*]/[E*] is determined only by the difference in the free energy between A* and E*, but independent of those of the starting isomers, A and E. N-Alkylation and N-oxygenation of N-methylpiperidines are of this case, so that the isomeric ratio of the products, $[P_A]/[P_E]$, is related, as seen in equation (1), to the energy difference between the reaction intermediates at the transition states, A* and E* in Fig. 1, through which the reaction proceeds.

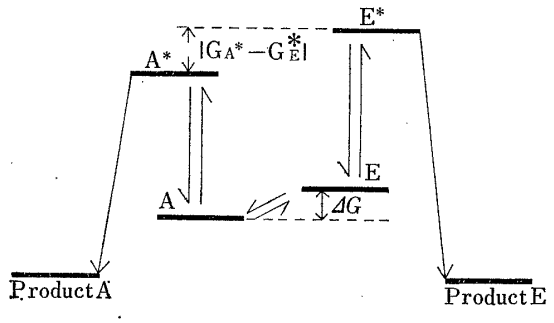


Fig. 1. Schematic Presentation of N-Alkylation and N-Oxygenation Reactions

9) J. McKenna, J. M. McKenna, J. White : J. Chem. Soc., **1965**, 1733.
10) E. L. Eliel : "Stereochemistry of Carbon Compounds," p. 149~156, 237~239 (1962). McGraw-Hill Book Company, Inc., New York.

$$G_A^* - G_E^* = -RT \ln [P_A]/[P_E] \quad (1)$$

As illustrated in Chart 1, the product P_A may be regarded as being produced by the axial attack of the alkylating reagent and the product P_E be produced by the equatorial attack. Quaternizations were carried out with methyl-d_3 iodide (CD_3I) and with ethyl iodide in acetone solutions at room temperature. N-Oxygenation was carried out with aqueous 30% H_2O_2 solution at room temperature. Isomeric ratios were determined by measuring the areal intensity ratio of the N-methyl proton singnals and are listed in Table II. One of the spectra is reproduced in Fig. 2. The signal assignments are based

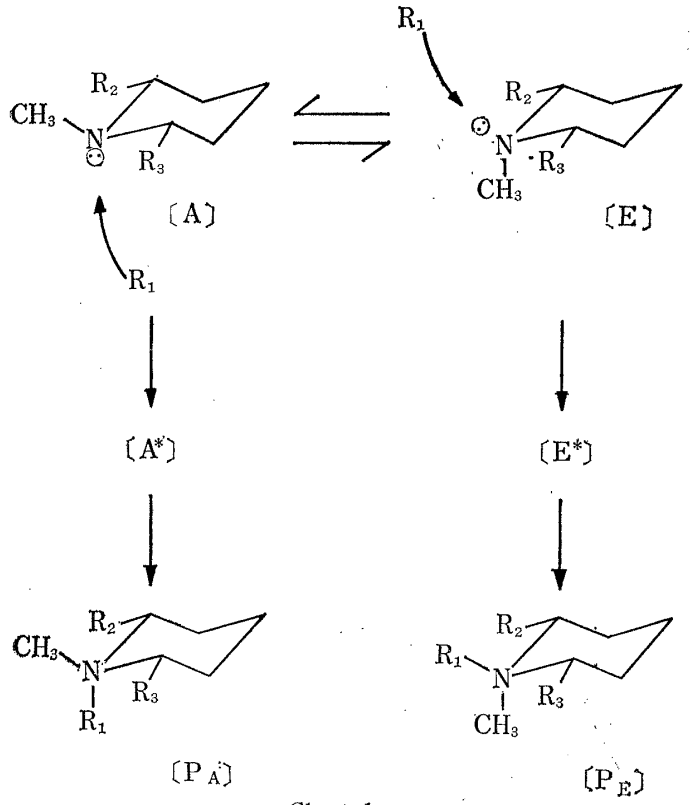


Chart 1.

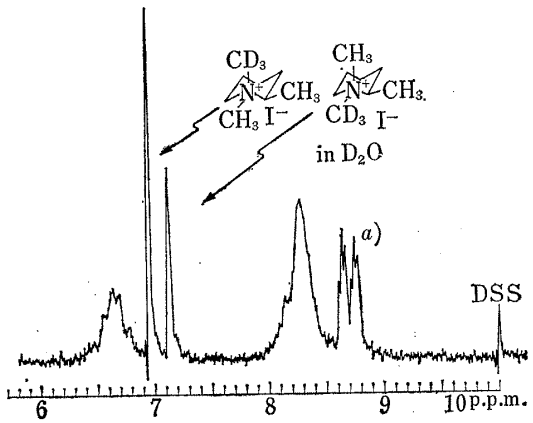


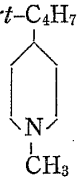
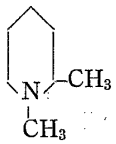
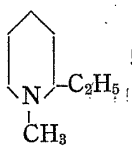
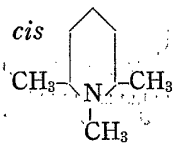
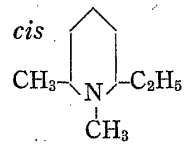
Fig. 2. NMR Spectrum of N-Quaternization Products of 1,2-Dimethylpiperidine with CD_3I in acetone at 23°

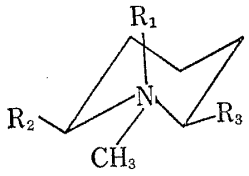
a) Triple splitting is due to spin-coupling with N^+ nucleus. See This Bulletin, **15**, 214 (1967).

on the earlier studies of this class of compounds.[1,6,8] The values, $G_A^* - G_E^*$, listed in the same table are the free energy differences between the transition states in both reaction processes, which are estimated from the product ratios according to equation (1). Table II includes the data reported by House, *et al.*[1] on the methylation of 4-*tert*-butylpiperidine with methyl-d_3 tosylate. These data reveal that α-substituents affects the stability of the reaction intermediates at the transition state, and that the axial approach of the alkylating agent becomes more difficult to proceed than the equtorial approach. The substituent effect seems to be amplified in the order of methylation, oxygenation, and ethylation.

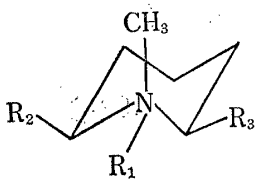
Another finding was obtained on the solvent effect on the steric course in quaternization. Methylation was carried out with methyl-d_3 iodide in various kinds of solvents, from aqueous methanol to nonpolar solvents such as cyclohexane. The ratios of the epimeric quaternary salts thus produced, which are listed in Table III, revealed that there was only a slight dependence of the steric course of the reaction on the kind of solvents but not so much. The substituent effect of α-alkyl groups tends to be rather large in nonpolar solvents compared with that in polar solvents.

Table II. The Ratios of the Epimeric Products obtained from Methylation, Ethylation and Oxygenation of α-Substituted N-Methylpiperidines and the Free Energy Differences at the Transition Stated between Axial and Equatorial Approach Processes

	Methylation[a]			Ethylation[b]			Oxygenation[c]		
	product ratio		$-(G_A^*-G_E^*)$[e] (cal/mol.)	product ratio		$-(G_A^*-G_E^*)$[e] (cal/mol.)	product ratio		$-(G_A^*-G_E^*)$[e] (cal/mol.)
	P_A	P_E		P_A	P_E		P_A	P_E	
tert-C_4H_7 	87	13[d]	1120	83	17[d]	933			
	66	34	390	43	57	−170	64	36	340
	56	44	140	36	64	−340	50	50	0
cis 	44	56	−140	11	89	−1230	39	61	−260
cis 	34	66	−390	9	91	−1360	19	81	−850



P_A



P_E

R_1=$-CD_3$, $-C_2H_5$, or $-O$
R_2, R_3=$-H$, $-CH_3$, or $-C_2H_5$

a) They reacted with CD_3I in acetone at 23°. b) They reacted with C_2H_5I in acetone at 23°.
c) They reacted with 30% aqueous H_2O_2 at 23°. d) Ref. 1).
e) Positive values mean that the axial attack which yields Product A is more preferable to the equatorial attack which yields Product E. Negative values mean the reverse preferrence in the reaction cource.

Table III. Solvent Effect on Steric Course in Quaternization of 1,2-Dimethylpiperidine with Methyl-d_3 Iodide[a]

Reaction Medium	Product Ratio (%)		Reaction Medium	Product Ratio (%)	
	Product A	Product E		Product A	Product E
Methanol-water (3:1 v/v)	71	29	Ethyl ether	66	34
Methanol	69	31	Dioxan	63	37
Chloroform	69	31	Benzene	63	37
Acetone	66	34	Cyclohexane	64	36

a) As shown in Chart 1, Product A is the product by axial attack of the reagent and Product E is the one by equatorial attack of the reagent.

Temprature dependence of the product ratio was also clearly shown by the data from reactions at an elevated temperature, about 70°, as shown in Table Ⅳ. The thermodynamic analyses of the results from these reactions will be discussed in a forthcoming paper in connection with the molecular structures of these amines at the transition state.

Table Ⅳ. Temperature Dependence on Steric Course in N-Alkylation and N-Oxygenation of N-Methylpiperidine Derivatives

Compound	Reaction	Product ratio $[P_A]/[P_E]$[a] 23°	70°
2-Methyl	N-oxygenation	1.78	1.22
2-Methyl	N-methylation	2.22	1.86
2-Ethyl	N-ethylation	0.56	0.67
cis-2,6-Dimethyl	N-ethylation	0.12	0.14

a) As shown in Chart 1, P_A is the product by axial attack of the reagent and P_E is the one by equatorial attack of the reagent.

Experimental

α-Substituted N-Methylpiperidines——α-Substituted pyridine methiodides were catalytically hydrogenated with Adams' platinum at the atmospheric pressure and afforded the corresponding N-methylpiperidine derivatives. The products were once isolated as their hydriodides, from which the free bases were liberated by addition of conc. NaOH solution and its extraction with ether. 2,6-Dialkyl derivatives were separated into *cis* and *trans* isomers by column chromatography, eluted with ether. The stereoisomeric assignments were made on the basis of the fact that the N-dimethylpiperidinium salts of the *cis* isomers should show two separated $N-CH_3$ signals in the nuclear magnetic resonance (NMR) spectra, whereas those of the *trans* should show only one singlet for two $N-CH_3$ groups.[5] In both cases of 2,6-dimethyl- and 2-methyl-6-ethyl derivatives, the *cis* isomers were predominantly produced (in *ca.* 80% yield). The melting points of the derivatives of these amines are summarized in Table Ⅴ.

Table Ⅴ. Melting Points of the Methiodides and Picrates of α-Substituted N-Methylpiperidines

	Methiodide (°C)	Picrate (°C)
2-Methyl[a]	314 ~ 6	233 ~ 5 (decomp.)
2-Ethyl[b]	267 ~ 9	166 ~ 7
cis-2,6-Dimethyl[c]	280 ~ 2 (decomp.)	225 ~ 7
trans-2,6-Dimethyl[d]	300 ~ 1 (decomp.)	244 ~ 5
cis-2-Methyl-6-ethyl	213 ~ 5	132 ~ 5
trans-2-Methyl-6-ethyl	268~270	169~170

a) Ber., **59**, 2337; Ann., **289**, 229. b) Ber., **33**, 3517.
c) J. Am. Chem. Soc., **79**, 5279. d) Chem. Abstr., **47**, 9325.

N-Oxygenation of the Amines——The amines were dissolved in 30% H_2O_2 solution and kept standing at room temperature over night. After decomposition of the excess of H_2O_2 by the addition of PtO_2, the solvent was removed by vacuum evaporation. The hygroscopic crystalline residue was dried in a vacuum desiccator and used for NMR measurements. The melting points and analytical data of the picrates of these N-oxides are summarized in Table Ⅵ. As shown in Table Ⅱ, these N-oxides are mixtures of stereoisomers with regard to the ring nitrogen.

Reagents——CD_3I was purchased from the Canada Merck Co. (99 D-atom %).

NMR Measurements——The spectra were obtained with a JNM-3H-60 spectrometer (Japan Electron Optics Lab. Co., Ltd.), operating at 60 Mc.p.s.

Table Ⅵ. Melting Points and Elemental Analysis Data of Mixtures of Epimeric N-Oxides' Picrates of α-Substituted N-Methylpiperidines

	m.p. (°C)	Analysis (%)			
		Calcd.		Found	
		C	H	C	H
2-Methyl	178 ~ 182	43.57	5.06	44.06	5.25
2-Ethyl	130 ~ 136	45.16	5.41	44.45	5.14
cis-2,6-Dimethyl	166 ~ 172	45.16	5.41	45.21	5.06
cis-2-Methyl-6-ethyl	157 ~ 160	46.63	5.74	46.71	5.66

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