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Stereochemistry of Quinolizidines. II.[1] Carbon-13 Magnetic Resonance Spectra of N-Methylquinolizidinium Ions

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The carbon magnetic resonance spectra of *trans*- (I) and *cis*-N-methylquinolizidinium ion (II) were examined in relation to the stereochemistry of these compounds. Ring inversion of the *cis*-N-methylquinolizidinium ion was observed in variable temperature experiments and results afforded $\Delta G_c^{\ddagger}=13.7$ kcal/mole. The observed carbon chemical shift difference between I and II was compared with that estimated empirically, and shown to be a measure of the stereochemical difference between the *trans*- and *cis*- forms of the quinolizidine nucleus.

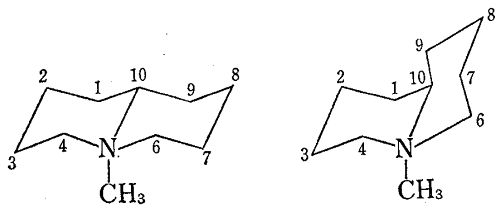
Keywords——carbon-13 chemical shift; *trans*- and *cis*-N-methylquinolizidinium ion; ring inversion; variable temperature experiment on C-13 magnetic resonance spectra; free energy of activation at coalescence

Introduction

The quinolizidine nucleus is the unique skeleton of a number of important alkaloids, whose stereochemistry has been examined in various ways.[3] Problems of ring juncture and/or ring inversion of these compounds have stimulated discussion on the stereochemistry of berberine type alkaloids.

Previously,[1] we examined the carbon-13 magnetic resonance spectra of quinolizidine, *cis*- and *trans*-4-methylquinolizidine and their quaternary salts. In that work, we discussed the substituent effects on the carbon chemical shifts by a C-4 methyl group and protonation and quaternization effects.

In this work, we measured the carbon-13 magnetic resonance spectra of the *trans*- (I) and *cis*- (II) isomers of the N-methylquinolizidinium ion and discussed the stereochemistry of these compounds. Arata, *et.al.*[3d] studied the stereochemistry of 10-substituted N-methylquinolizidinium ions by examining their carbon-13 chemical shifts. However, they did not examine the N-methylquinolizidinium ion or ring inversion of the *cis*- form.



Ia: X=I
Ib: X=Cl

IIa: X=I
IIb: X=Cl

Chart 1

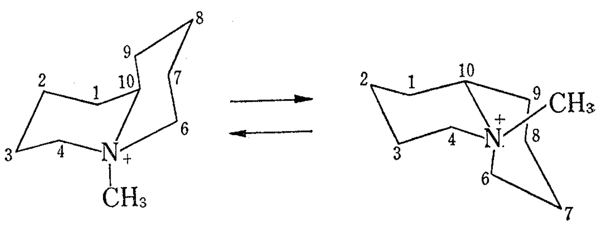


Chart 2

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[1] Part I: M. Sugiura and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **24**, 2988 (1976).

[2] Location: *a*) *Motoyama-Kitamachi, Higashinada, Kobe*; *b*) *Yamadakami 133–1 Suita, Osaka.*

[3] *a*) T.M. Moynehan, K. Schofield, R.A. Jones, and A.R. Katritzky, *J. Chem. Soc.* **1962**, 3637; *b*) C.D. John, R.A.Y. Jones, A.R. Katritzky, C.R. Palmer, K. Schofield, and R.J. Wells, *J. Chem. Soc.*, **1965**, 6797; *c*) R.T. LaLonde and T.N. Dovito, *Can. J. Chem.*, **52**, 3788 (1974); *d*) Y. Arata, T. Aoki, M. Hanaoka, and M. Kamei, *Chem. Pharm. Bull.* (Tokyo), **23**, 333 (1975).

In this work, ring inversion of *cis*-N-methylquinolizidinium ion was demonstrated in variable temperature experiments of carbon-13 magnetic resonance spectra and the thermodynamical parameters of this inversion were estimated.

Experimental

Materials

1) ***trans*-N-Methylquinolizidinium Iodide (Ia)**[3a)]——Quinolizidine was refluxed with excess CH_3I in EtOH following conventional methods,[3a)] mp>300° (Found: C, 42.6; H, 6.8. Calcd. for $C_{10}H_{20}IN$: C, 42.7; H, 7.2%).

2) ***cis*-N-Methylquinolizidinium Iodide (IIa)**[3a)]——2-4′-Ethoxybutyl-1-methylpiperidine, prepared by N-methylation of 2-4′-ethoxybutylpiperidine with HCHO and HCOOH, was cyclized with HI and K_2CO_3, by a reported method,[3a)] mp>300° (Found: C, 42.6; H, 6.9%).

3) **Conversion of IIa (iodide) to IIb (chloride)**——A solution of *cis*-N-methylquinolizidinium iodide (IIa) (*ca.* 650 mg) in MeOH was shaken with AgCl (from $AgNO_3$ *ca.* 2 g) for 30 min. The mixture was filtered and on evaporation the filtrate gave needles (*ca.* 410 mg) of a mixture of *cis*-(IIb) and *trans*-quaternary chloride (Ib) (*ca.* 3: 4). (see Fig. 2b).

Measurements of C-13 NMR Spectra

C-13 FT NMR spectra were measured with a NEVA NV-21 spectrometer at 22.6 MHz in 8 mm tubes. Samples were dissolved in CD_3OD containing TMS as an internal reference ($\tau_C = 0$) at a concentration of about 0.3—1 mole/liter. *cis*-Quaternary iodide was also dissolved in D_2O.

The conditions for FT NMR measurements were: spectral width, 5000 Hz; pulse width, 25 μsec. (flipping angle, about 30°); aquisition time, 0.8 sec; number of data points, 8192; number of transients, 1—3K.

In variable temperature experiments, temperatures were measured directly by inserting a thermometer into the probe.

Results and Discussion

1) Ring Inversion of *cis*-N-Methylquinolizidinium Ion

The C-13 NMR spectrum of *cis*-N-methylquinolizidinium iodide (IIa) is shown in Fig. 1. At room temperature (*ca.* 35°, Fig. 1b), the spectrum consists of three sharp singlets, a triplet with slight splitting into three peaks owing to coupling with nitrogen —assigned to N-methyl—, and two broad signals. At higher temperatures, the two broad signals become sharper and at *ca.* 90°, almost all the signals were observed as sharp lines (Fig. 1a). On decreasing the temperature, the two broad signals become broader, and then each devided into two separated signals (Fig. 1c).

The carbons in ring A of the *trans*-form correspond to those in ring B, and so the C-13 NMR spectra of the *trans*-isomer (I) showed four signals each corresponding to two carbons and two signals assigned to C-10 and N-methyl carbon, even when ring inversion occurred. On the contrary, the carbon atoms of the two ring in the *cis*-form (II) are not symmetrical and so are not necessarily equivalent. At room temperature, ring inversion is relatively slow in the NMR time scale and broad signals are seen as shown Fig. 1b. When ring inversion is more rapid, a single resonance line is observed, and, when it is slower, two separate signals are observed. These changes were demonstrated in variable temperature experiments, as shown in Fig. 1a—c. These NMR spectra indicate that ring inversion occurrs as shown in Chart 2.

The rates of inversion can be calculated from the observed temperature dependencies of the spectra. The free energy of activation at coalescence was calculated from equation (1)

$$\Delta G_c^{\ddagger} = 4.576T_c(10.32+\log(T_c\cdot\tau_c)) \qquad (1)$$

where T_C is the coalescence temperature and τ_C is given by (2),

$$\tau_c = \sqrt{2}/(\pi\cdot\delta\nu) \qquad (2)$$

where $\delta\nu$ is the limiting chemical shift difference.[4)]

The spectra shown in Fig. 1 were measured in deuterium oxide, so that variable temperature experiments could not be carried out at below 0°. To do this, the samples were

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[4)] T. Drankenberg and J.K. Lehn, *J. Chem. Soc. Perkin II*, **1972**, 532.

converted from the iodide to the chloride form, which is very soluble in methanol-d_4. Unfortunately, the *cis*-form was converted to the *trans*-form in the process. Mixtures of *cis*- and *trans*-N-methylquinolizidinium chloride (IIb+Ib) were difficult to separate into their components, so mixtures of the two forms were used in variable temperature experiments (see Fig. 2). The chemical shifts of the chloride were similar to those of the iodide, and the shifts were also similar in deuterium oxide and methanol-d_4.

Table I summarizes the chemical shift differences of the coalescing signals, the coalescence temperatures and the free energies of activation at the coalescence temperatures, for

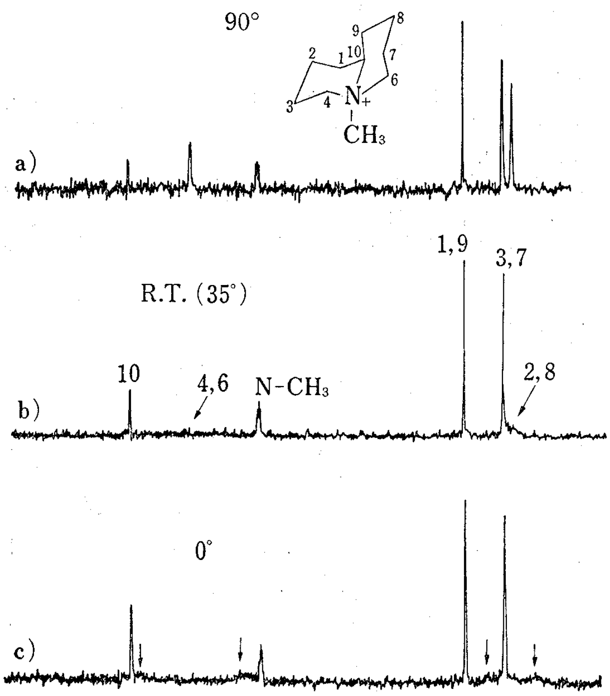


Fig. 1. Carbon-13 Magnetic Resonance Spectra of *cis*-N-Methylquinolizidinium Iodide (IIa), (a) at 90°, (b) at Room Temperature (*ca.* 35°) and (c) at 0° (in D_2O)

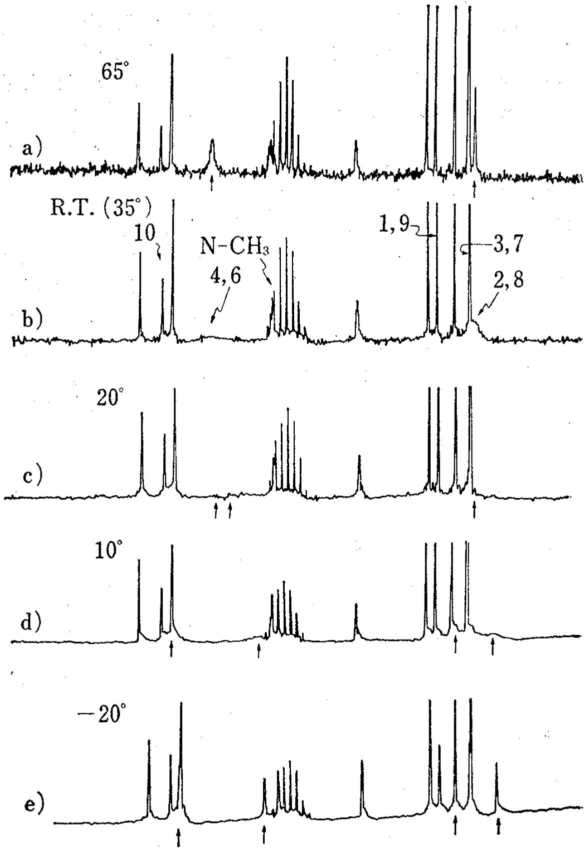


Fig. 2. Carbon-13 Magnetic Resonance Spectra of a Mixture of *cis*-(IIb) and *trans*-N-Methylquinolizidinium Chloride (Ib) at Different Temperatures (in CD_3OD)

The Signals with numbers were assigned to the *cis*-Isomer.

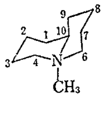
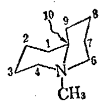


Table I. Chemical Shift Difference of Exchanging Signals, Coalescence Temperature, and Free Energy of Activation for *cis*-N-Methylquinolizidinium Ion

Position[a]	$\delta\nu$ (Hz)	T_c (°K)	$\Delta G_c^{\neq}$ (kcal/mole)
C-6, C-4	294±1	303±3	13.8±0.2
C-8, C-2	177±1	293±3	13.6±0.2

[a] The numbering is as follows:



C–6, C–4 and C–8, C–2. As shown in this Table, the free energy of activation, $\varDelta G_C^{\neq}$, calculated for C–6, C–4 and C–8, C–2 agree reasonably well.

Grant, *et. al.*[5] calculated that $\varDelta G_C^{\neq}$ was 12.6 kcal/mole for both *cis*-decaline and 9-methyl-*cis*-decaline by total line-shape analysis of results of C–13 NMR variable temperature experiments. This $\varDelta G_C^{\neq}$ value is comparable to that of *cis*-N-methylquinolizidinium ion in Table I.

The question has been raised whether the slight difference between these $\varDelta G_C^{\neq}$ values (12.6 kcal/mole and 13.7 kcal/mole) is significant. Drankenberg[4] reported that $\varDelta G_C^{\neq}$ values obtained by the coalescence temperature method are *ca.* 0.1 kcal/mole smaller than those obtained by total line-shape analysis. Thus, the observed difference, *ca.* 1 kcal/mole, seems to be significant and may be ascribed to the difference between C–CH_3 and N^+ –CH_3 bonds.

2) The Correlation between C-13 Chemical Shifts and Stereochemistry

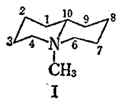
The C–13 chemical shifts of I and II and $\varDelta_{C-T}$, the chemical shift differences between I and II, are shown in Table II.

Table II. C-13 Chemical Shift[a] of *trans*- (I) and *cis*-N-Methylquinolizidinium Ion (II)

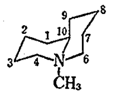
Carbon[b]	I[c]	II[d]	$\varDelta_{C-T}^{obs.}$ [e]	$\varDelta_{C-T}^{calc.}$ [f]
10	71.24	67.65	−3.59	—
4	66.15	52.96*	−13.19	−11.8
6	66.15	65.98*	−0.17	—
3	20.80	20.84	0.04	0
1	27.21	25.78	−1.43	−2.4
9	27.21	25.78	−1.43	—
7	20.80	20.84	0.04	—
2	23.01	16.64*	−6.37	−5.9
8	23.01	23.13*	0.12	—
N–CH_3	38.63	51.02	12.39	11.4

a) Relative to TMS in ppm. The minus sign means a high field shift.

b) Carbons are numbered as follows:



I



II

c) for "iodide" in CD_3OD

d) for "chloride" in CD_3OD, values with an asterisk were measurde at −20°.

e) $\varDelta_{C-T}^{obs.}$: difference between chemical shifts of II and I

f) $\varDelta_{C-T}^{calc.}$: calculated $\varDelta_{C-T}$

$\varDelta_{C-T}$ is ascribed to the difference in configuration between *trans*- and *cis*-. The large $\varDelta_{C-T}$ at C–4 (−13.19) may be attributed to the high field shift of the *cis*-form resulting from steric interference by the protons at C–9 and C–7, and the large value of $\varDelta_{C-T}$ at C–2 (−6.37) may also result from steric interference from proton at C–9. The value of $\varDelta_{C-T}$ at N-methyl carbon (12.39) is due to the low field shift of the *cis*-form because of disappearance of steric interaction with protons at C–9 and C–7, unlike in the *trans*-form. Thus, the $\varDelta_{C-T}$ for each carbon on ring A can be estimated approximately with C-methyl substituent parameter.[6] The calculated values of $\varDelta_{C-T}$, also given in Table II, show a similar trend to experimental values, although approximation were used in calculating them.

This work shows that $\varDelta_{C-T}$ values are measures of the stereochemical difference between the *trans*- and *cis*- form, and can be used as parameters of C–13 chemical shifts in discussion of the stereochemistry of quinolizidine.

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[5] D.K. Dalling, D.M. Grant, and L.F. Johnson, *J. Am. Chem. Soc.*, **93**, 3678 (1971).

[6] M. Tsuda, *Farumashia*, **9**, 756 (1973).