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Stereochemistry of Quinolizidines. IV.[1] Conformation of Benzo[*a*]quinolizidines and Their ^{13}C Chemical Shifts

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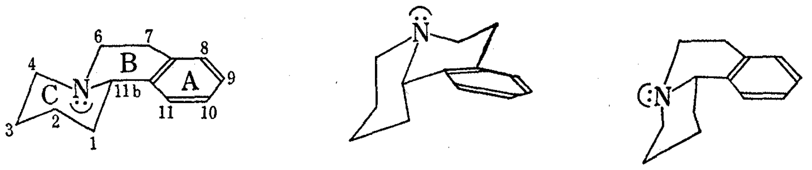
The equilibriums "*trans*⇄*cis*"*a*"" of some benzo[*a*]quinolizidine derivatives were investigated by three different approaches; ^{13}C chemical shift of C-6 and ^{13}C paramagnetic shift induced by Ni(AA)$_2$ as well as Bohlmann bands of infrared spectra. By means of these approaches, the equilibrium states of these derivatives were determined, and the displacement of C-6 chemical shift was approved as a guide to estimate the state of the equilibrium and to indicate the relative weight of each conformer.

Keywords——benzo[*a*]quinolizidine derivatives; conformational equilibrium; ^{13}C chemical shift; ^{13}C paramagnetic shift; IR Bohlmann band

Introduction

Conformational equilibrium with the inversion of the nitrogen atom and/or of the ring is one of the most interesting subject of the nitrogen containing six-membered ring system. In recent years, with the development of ^{13}C nuclear magnetic resonance (NMR) spectroscopy, many approaches of the above subject using this technique were extended. For example, several studies have been reported concerning the inversion of the nitrogen,[3] in addition to the ring inversion of piperidine[4] and *cis*-decahydroquinoline derivatives,[5] *etc.* These results were confirmed by the variable temperature experiment and by the comparison of the observed shifts with those of the estimated values from the additivity of the empirical parameter. Variable temperature experiment, however, is restricted by the feasible temperature range of the solvent, and for the latter a suitable model compound is necessary.



trans *cis* "*a*" *cis* "*b*"

Chart 1

Previous work of this series[1] has shown that ^{13}C chemical shifts of benzo[*a*]quinolizidines well reflect their conformations, and, especially, chemical shifts of C-6 and C-7 are approved as the indications to distinguish the conformers. As illustrated in Chart 1, for benzo-

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[1] Part III: M. Sugiura, N. Takao, K. Iwasa, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 1168 (1978).

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

[3] *a*) E.L. Eliel and F.W. Vierhapper, *J. Am. Chem. Soc.*, **97**, 2424 (1975); *b*) E.L. Eliel and F.W. Vierhapper, *J. Org. Chem.*, **41**, 199 (1976); *c*) Y. Takeuchi, P.J. Chivers, and T.A. Crabb, *J.C.S. Perkin II*, **1975**, 51; *d*) S.F. Nelsen and G.R. Weismann, *J. Am. Chem. Soc.*, **98**, 1842 (1976).

[4] D.J. Loomes and M.J. T. Robinson, *Tetrahedron*, **33**, 1149 (1977).

[5] *a*) H. Booth and D.V. Griffiths, *J.C.S. Perkin II*, **1973**, 842; *b*) H. Booth and D.V. Griffiths, *J.C.S. Perkin II*, **1975**, 111; c) H. Booth, D.V. Griffiths and M.L. Jozefowicz, *J.C.S. Perkin II*, **1976**, 751; *d*) F.W. Vierhapper and E.L. Eliel, *J. Org. Chem.*, **42**, 51 (1977).

[*a*]quinolizidines, three possible conformations convertible from each other through the ring inversion and/or the nitrogen inversion are expected, and the favoured conformation is the one with the least interference between the non-bonded atoms. So far, ^{1}H chemical shift of 11b-H has been applied to distinguish these three conformations. But this approach is not necessarily available because the signal of 11b-H is often ambiguous and some exceptions have been found. For example, IIb, with the 11b-H shift of ca.0.4 ppm higher than 3.8 ppm reported as the measure of the *cis* conformation,[6] prefers rather *cis*"*a*"-conformer.[1]

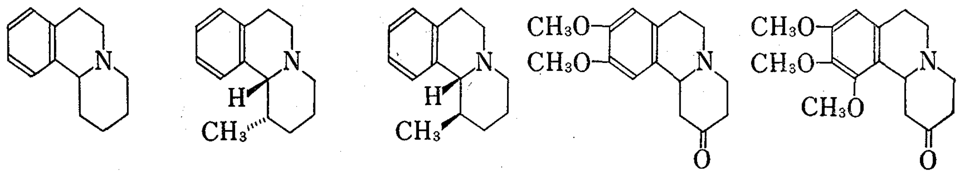
As shown in Table I, ^{13}C chemical shifts of C-6 and C-7 exhibit the characteristic values for each conformation and the *cis*"*a*" conformation is distinguished from the others by C-6 as well as C-7 chemical shifts for the *cis*"*b*" conformation.[1]

Table I. Characteristic ^{13}C Chemical Shifts (ppm) for Three Conformers of Benzo[*a*]quinolizidine Derivatives

	C-6	C-7
trans	50.8—53.4	28.6—30.2
cis "*a*"	<46	28.9—30.3
cis "*b*"	50.9—51.4	<26

In solution, these derivatives do not always exist only in one conformation. The expression that "prefers *trans* conformation" represents that "the preferred conformation is the *trans*," namely, that "the equilibrium lies to the *trans* side." Therefore, it is interesting to investigate to what extent these derivatives contain the *trans*-conformer or to determine the contribution of the *cis*-conformer, in solution. Nevertheless, in the variable temperature experiments of these derivatives, signal splittings are not observed up to the temperature range of the freezing point of solvent (*ca.* −90°) though signal broadenings are observed.

In this work, therefore, this problem is discussed by the following approaches; C-6 chemical shift and the induced paramagnetic shift by $Ni(AA)_2$ as well as the Bohlmann band of infrared (IR) spectrum. The correlations among above experiments are investigated, and furthermore the states of equilibrium due to the nitrogen inversion—"*trans*$\rightleftarrows$*cis*"*a*""—of each compound are discussed.



I IIa IIb IIIa IIIb

Chart 2

Experimental

1) **Materials**——1,2,3,4,6,7,11b-heptahydro-benzo[*a*]quinolizine (I), *trans*- and *cis*-1-methyl-1,2,3,4,6,7, 11b-heptahydro-benzo[*a*]quinolizine (IIa and IIb) and 9,10-dimethoxy-2-oxo-1,2,3,4,6,7,11b-heptahydrobenzo[*a*]quinolizine (IIIa) were prepared as described in the preceding paper.[1]

9,10,11-Trimethoxy-2-oxo-1,2,3,4,6,7,11b-heptahydro-benzo[*a*]quinolizine (IIIb) was synthesized by the condensation of 6,7,8-trimethoxy-3,4-dihydroisoquinoline (IV) with methylvinylketone and followed by the cyclization,[7] where IV was prepared from methyl 3,4,5-trimethoxybenzoate *via* eight steps by the

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[6] M. Uskoković, H. Bruderer, C. von Planta, T. Williams and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3364 (1964).

[7] D. Beke and C. Szàntay, *Chem. Ber.*, **95**, 2132 (1962).

similar way of the synthesis of 6-benzoyloxy-7,8-dimethoxy-3,4-dihydroisoquinoline.[8] IIIb: mp 105,° Mass spectrum *m/e*: 290, 291 (M^+), 221, 248. Picrate: mp 125° (Found C, 50.50; H, 4.59. Calcd. for $C_{22}H_{24}N_4O_{11}$; C, 50.77; H, 4.62%).

Commercially available $Ni(AA)_2$ was dried *in vacuo* over 30 hr. at 60° before use.

2) **Measurements of ^{13}C NMR Spectra**——^{13}C FT NMR Spectra were measured with a NEVA NV-21 spectrometer at 22.6 MHz in 8 mm tubes. For the normal measurements, samples were dissolved in $CDCl_3$ containing TMS as an internal reference ($\tau_c = 0$) at a concentration about 0.3—0.7 mol/l. Conditions of the FT NMR measurements were: spectral width, 5000 Hz; pulse width, 25—30 μsec. (flipping angle, about 30—35°); aquisition time, 0.8 sec; number of data points, 8192; number of transient, 1—3K.

For I, IIa and IIb, spectra were taken by the successive addition of $Ni(AA)_2$. The molar ratio of reagent/ligand ([R]/[L]) is varied from 0.01 to 0.1. The observed paramagnetic shifts are expressed relative to the free ligand.

3) **Measurements of IR Spectra**[9]——Spectra were obtained with a HITACHI EPI-G2 spectrometer in $CHCl_3$ at a concentration range of 0.15—0.1 mol/l using an expanded frequency scale of 1 cm^{-1}/0.19 mm. KRS Cell with a 0.5 mm path length was used. Apparent molecular absorptivity, ε, was estimated from Eq. (1)

$$\varepsilon = \frac{1}{b \cdot c} \log \left(\frac{T_0}{T}\right)_\nu \qquad (1)$$

where T_0 and T=apparent intensities of the incident and transmitted radiation, ν=a frequency of measurement, b=a cell length (cm) and c= a concentration of the solute (mol/l). Apparent integrated intensity, B, was calculated by means of the measurement of the area occupied by the wave number-molecular absorptivity curve.

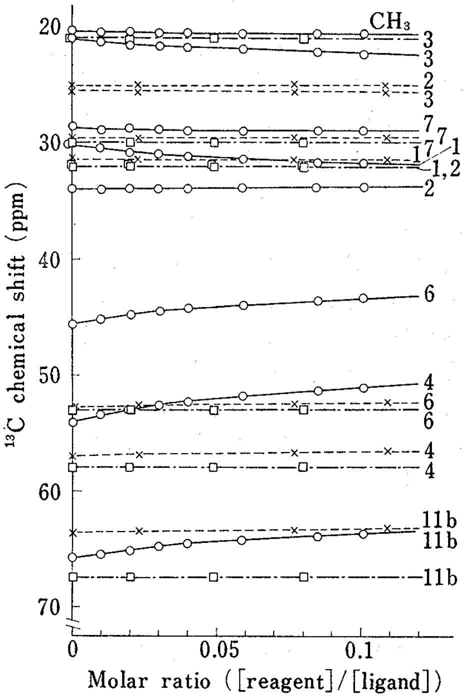

Fig. 1. Plots of ^{13}C Chemical Shifts in the Presence of $Ni(AA)_2$ for IIb (○—○), I (×----×) and IIa (□—·—□)

Results and Discussion

1) Paramagnetic Shift Induced by $Ni(AA)_2$

Figure 1 summarized the variations of chemical shifts of I, IIa and IIb by the successive addition of $Ni(AA)_2$, and the induced paramagnetic shifts are evident for IIb, but less evident for I and not for IIa, respectively. These are the paramagnetic shifts induced by the coordination of $Ni(AA)_2$ to the nitrogen atom.

It was already shown[10] that the ^{13}C paramagnetic shifts of the $Ni(AA)_2$ complex are related mainly to the contact interaction induced by the transfer of the electron spin on carbon, where the manner of an attenuation of the shift is dependent on the orientation of the nitrogen lonepair and also the contribution of the through-space spin transfer on the planar zigzag arrange-

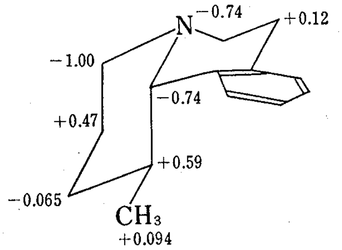

Chart 3. Relative Value of ^{13}C Paramagenetic Shift of IIb

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8) Y. Inubushi and K. Fujitani, *Yakugaku Zasshi*, **78**, 486 (1958).

9) N. Takao and K. Iwasa, *Chem. Pharm. Bull.* (Tokyo), **24**, 3185 (1976).

10) *a*) I. Morishima, K. Okada, T. Yonezawa and K. Goto, *J. Am. Chem. Soc.*, **93**, 3922 (1971); *b*) I. Morishima, K. Yoshikawa and K. Okada, *J. Am. Chem. Soc.*, **98**, 3787 (1976).

ment of σ-skeleton is allowed. The former is evident especially on the β-carbon shift, and the latter on the γ-carbon shift.

The relative values for each carbon of a ligand are obtained from the slopes of the linear plots of the induced paramagnetic shift *vs.* reagent/ligand molar ratio ([R]/[L]), with the value for C-4 normalized to -1.00 (up field). These relative shifts of IIb are summarized in Chart 3 and are interpreted by means of the properties of paramagnetic shifts as pointed out above. The variation of the shift of β-position (C-1=0.59 ppm, C-3=0.47 ppm and C-7=0.12 ppm) is ascribed to the difference of the orientation of the nitrogen lone-pair with respect to ring B and C. In ring C with an equatorial lone-pair, electron spin reaches on the carbon through a "zigzag path"[10a)], while, in ring B with an axial lone-pair, the odd electron distributes itself on the ligand carbon along a "folded path"[10a)]. The observed values are consistent with the relative values of the calculated electron spin densities[10a)] of the β position, which are $+0.56$ for equatorial and $+0.20$ for axial lone-pair, normalized $\alpha=-1.00$. A low field shift of C-methyl carbon, in contrast to the high field shift of C-2, supports the contribution of a through space spin transfer in the planer arrangement. These features of the ^{13}C paramagnetic shifts by Ni(AA)$_2$ support the preference of *cis*"*a*"-conformer for IIb with an axial nitrogen lone-pair for ring B and equatorial for ring C.

Figure 1 shows that no change is induced by the addition of Ni(AA)$_2$ to IIa. Since the same result was observed for quinolizidine of the *trans* conformation,[11)] it is deduced that this result arises from the *trans* conformation of IIa, where, compared with the *cis* conformation, the nitrogen lone-pair is sterically crowded and an access of reagent is hindered. This fact means that IIa exists almost in the *trans* conformation or with little contribution of the *cis*-conformer. These facts that Ni(AA)$_2$ affords the induced paramagnetic shifts for *cis*-conformer but not for *trans* one are of interest for the conformational analyses of these quinolizidine derivatives.

As shown in Fig. 1, a little induced shift is observed in I. This fact, from above discussion, supports a little contribution of *cis*-conformer in I. In Table II, the actual induced paramagnetic shifts of IIb and I under several [R]/[L] ratios are summarized. The values under [R]/[L]=0.023 of IIb are estimated by the extrapolating the above two values ([R]/[L]= 0.0203 and 0.0294). A comparison of these values with those of I under [R]/[L]=0.0230 shows that the tendencies of alternation in sign and the magnitude of attenuation are the same from each other, though the net shifts of I are of 10% of IIb. Consequently, the *cis*-conformer contained in I requests the same conformation preferred for IIb—*cis*"*a*"-conformer—, and the contribution of this conformer in I is determined about an extent of 10% of that in IIb, when the equilibrium constants of Ni(AA)$_2$ complex formation for these derivatives are about the same degree from each other.

TABLE II. Observed ^{13}C Paramagnetic Shift (ppm) for *cis*-1-Methyl-1,2,3,4,6,7,11b-heptahydro-benzo[*a*]quinolizine (IIb) and 1,2,3,4,6,7,11b-Heptahydro-benzo[*a*]quinolizine (I) with Ni(AA)$_2$

	[R]/[L]	1	2	3	4	6	7	11b	C–CH$_3$
IIb	0.0203	0.65	−0.06	0.53	−1.11	−0.81	0.14	−0.81	0.10
	0.0294	0.86	−0.11	0.67	−1.45	−1.08	0.16	−1.08	0.14
	0.023[a)]	0.71	−0.07	0.57	−1.21	−0.89	0.15	−0.89	0.11
I	0.0230	0.06	0	0.05	−0.12	−0.09	0.02	−0.10	

a) These values are estimated by extrapolation of above two values.

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11) The private information from Dr. K. Yoshikawa (Tokushima University, College of General Education), and we confirmed this conclusion experimentally.

2) Bohlmann Band of IR Spectra

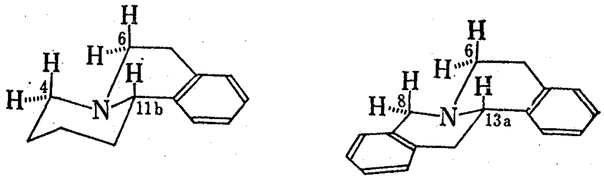
In Table III, the apparent molecular absorptivities (ε) at *ca.* 2750 and *ca.* 2800 cm^{-1} and the apparent integrated intensity (B) at 2600—2830 cm^{-1} of IIa, I, IIIa and IIIb are summarized. In IIIa and IIIb, an accurate determination of intensity is unable because of the overlapping of the C-H streching vibration due to methoxyl groups, and also an absorption band of IIb at *ca.* 2800 cm^{-1} is not detected.

TABLE III. Apparent Molecular Absorptivity (ε; $\text{mol}^{-1}\cdot\text{l}\cdot\text{cm}^{-1}$) and Apparent Integrated Intensity (B; $\text{mol}^{-1}\cdot\text{l}\cdot\text{cm}^{-2}$) of the Bohlmann Bands of Benzo[*a*]quinolizidines

Compound	ε		B
	ca. 2750 cm^{-1}	*ca.* 2800 cm^{-1}	2600—2830 cm^{-1}
IIa	92.19	87.82	7630
I	80.38	82.92	7036
IIIa	62.08	58.83	—[a]
IIIb	20.09	—[a]	—[a]

a) Undetected due to OMe groups.

The Bohlmann band has been extensively studied for the determination of the conformational preferences of the nitrogen bridgehead compounds,[12] and the more quantitative treatments were carried out on a number of spartein-type quinolizidine alkaloids using selectively deuterated compounds.[13] And, recently, the detailed examination[9] on the Bohlmann band using deuterated tetrahydroprotoberberine-type alkaloids presented the following conclusions; two bands at *ca.* 2750 and *ca.* 2800 cm^{-1} of these alkaloids are ascribed to the streching vibration of the axial C-H bond α to the nitrogen atom and *trans* to the nitrogen lone-pair ($\nu_{C\alpha-H}$), and the band at *ca.* 2750 cm^{-1} is assigned to $\nu_{C\alpha-H}$ at C-8 and C-13a and the band at *ca.* 2800 cm^{-1} comes from $\nu_{C\alpha-H}$ at C-6. In addition, and an apparent integrated intensity (B) at 2600—2830 cm^{-1} (or 2600—2810 cm^{-1}) is proportional to the content of the *trans*-conformer.



benzo[*a*]quinolizidines

tetrahydroprotoberberine-type alkaloids

Chart 4

Since benzo[*a*]quinolizidine derivatives are of the analogous steric features, especially around the nitrogen atom, of tetrahydroprotoberberine-type alkaloids (*cf.* Chart 4), above conclusions should be applied to benzo[*a*]quinolizidines. Then, in these derivatives, the band at *ca.* 2750 cm^{-1} is assigned to $\nu_{C\alpha-H}$ of C-4 and C-11b and that at *ca.* 2800 cm^{-1} to $\nu_{C\alpha-H}$ of C-6. Table III shows that IIIb has a small band at *ca.* 2750 cm^{-1}. Since, in *cis*"*a*"-conformer, the axial hydrogens at both C-4 and C-11b are not *trans* to the nitrogen lone-pair, this small band is also ascribed to the *trans* conformation. Consequently, this observation suggests a slight contribution of *trans*-conformer for IIIb. Under the assumption that IIa exist in an almost 100% *trans* conformation, which is accepted from the discussion of the preceding section, the contribution of 22% *trans*-conformer is assumed from the ε at *ca.* 2750 cm^{-1} of IIIb.

In a similar manner, the contributions of *trans*-conformer of IIIa and I are estimated from two ε's or B's, and these results are summarized in the second column of Table IV.

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12) T.A. Crabb, R.F. Newton and D. Jackson, *Chem. Rev.* **71**, 109 (1971).

13) *a*) M. Wiewiorowski, O.E. Edwards and M.D. Bratek-Wiewiorowska, *Can. J. Chem.*, **45**, 1447 (1967); *b*) J. Skolik, P.J. Krueger, and M. Wiewiorowski, *Tetrahedron*, **24**, 5439 (1968).

TABLE IV. Populations of *trans*-Conformers of Benzo[*a*]quinolizidines estimated from Three Different Approaches

Compound	A[a]	B[b]	C[c]
IIa	100%	(100%)[d]	(100%)[d]
I	92	92	93
IIIa		67	74
IIb	(24)[d]		24
IIIb		22	(22)[d]

[a] A: from the ^{13}C paramagnetic shift by Ni(AA)$_2$.
[b] B: from IR Bohlmann bands.
[c] C: from ^{13}C Chemical shift of C-6.
[d] Values in parentheses were tentatively assumed for each calculation.

TABLE V. ^{13}C Chemical Shifts of C-6 and C-7, and ^{1}H Chemical Shifts of 11b-H of Benzo[*a*]quinolizidines (ppm)

Compound	C-6	C-7	11b-H
IIa	53.39	30.16	3.29
I	52.67	29.60	<3.4
IIIa	50.78	29.39	3.53
IIb	45.84	28.85	3.43
IIIb	45.41	30.25	4.09

3) ^{13}C Chemical Shift of C-6 and Population of the *trans*-Conformer

As shown in Table I, ^{13}C chemical shift of C-6 is utilized to distinguish the *cis*"*a*" conformation from another (*trans* or *cis*"*a*" conformation).[1] In Table V, C-6 chemical shifts of some benzo[*a*]quinolizidines are summarized together with C-7 and 11b-H ^{1}H chemical shifts, where these C-6 chemical shifts suggest that IIa, I and IIIa prefer the *trans* conformation and, in IIb and IIIb, the equilibrium displaces to the *cis*"*a*"-conformer. IIb And IIIb prefer rather the *cis*"*a*" to avoid the steric interference between an equatorial methyl group at C-1 and C-11 hydrogen of the former or the methoxyl group at C-11 and an equatorial hydrogen at C-1 of the latter. However, as shown in the last column of Table V, ^{1}H chemical shifts do not necessarily afford a clear information on the conformation of these derivatives. On the other hand, C-6 signals are shifted to the higher field in the order of IIIb>IIb>IIIa>I >IIa. This order corresponds to the decrease of the contribution of the *trans*-conformer, or is related to an equilibrium "*trans*⇄*cis*"*a*"". The validity of this conclusion is justified by the following discussion.

On the above presumption, the estimation of the contribution of *trans*-conformer was carried out. From the facts that IIa exists in almost 100% *trans* conformation obtained in section 1) and from the contribution of 22% *trans*-conformer of IIIb suggested by IR spectra, the populations of *trans*-conformer of I, IIIa and IIb were calculated as given in the last column of Table IV. From these results, C-6 chemical shift of the derivative of 100% *cis* conformation is presumed at *ca.* 43.4 ppm, but this value is unreliable because the compound of 100% *cis* conformation is not available.

Furthermore, from the value of 24% estimated for IIb, the contribution of *ca.* 8% *cis*"*a*"-conformer for I is concluded, as the contribution of *cis*"*a*"-conformer in I was estimated about 10% of that in IIb as shown in section 1), which deduces also 92% *trans*-conformer as shown in Table IV.

Table IV shows that the contributions of *trans*-conformer estimated by these three methods are of the similar magnitudes from each other. The results from the variation of C-6 chemical shift are consistent with those of the paramagnetic shifts induced by Ni(AA)$_2$ and Bohlmann band of IR spectra. Therefore, it is concluded that C-6 chemical shift of benzo[*a*]quinolizidines reflects the equilibrium "*trans*⇄*cis*"*a*"" and indicates the equilibrium state for each compound.

In conclusion, ^{13}C chemical shift provides the quantitative information for the conformational analysis, which has been discussed hitherto rather qualitatively by ^{1}H magnetic resonance, and these approaches will become available for this series.