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Stereochemistry of Quinolizidines. V.[1] Protonation of Benzo[*a*]quinolizidines and Determination of Their Nitrogen Inversion Rates

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The nitrogen inversion rate of 1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (I) is determined by means of line broadening of ^{13}C FT nuclear magnetic resonance under the successive alteration of pD. The k_{trans} thus obtained was confirmed to be reasonable but k_{cis} was presumed to be smaller than the actual one, which is responsible to the difference of pK_a between *trans*- and *cis*"a"-conformer. Actually, it was realized for benzo[*a*]-quinolizidines that *trans*-conformer takes lower pK_a than that of *cis*"a"-conformer because of the steric effect.

Keywords——benzo[*a*]quinolizidines; ^{13}C FT NMR; nitrogen inversion rate; "*trans*⇄*cis*"a" " equilibrium; conformational dependence of pK_a

Introduction

In the previous report,[1] the details of the stereochemistry and ^{13}C chemical shift of benzo-[*a*]quinolizidine derivatives were examined, and ^{13}C chemical shifts of C–6 and C–7 were approved as the guide to distinguish the three possible conformations (*cf.* Chart 1)[3] and, particularly, the displacement of C-6 chemical shift reflected on the state of an equilibrium "*trans*⇄*cis* "a" ".[1]

The determination of the nitrogen inversion rate of the system equilibrated as "*trans*⇄*cis*" is interesting, because the rate is a very important thermodynamic parameter, and further-

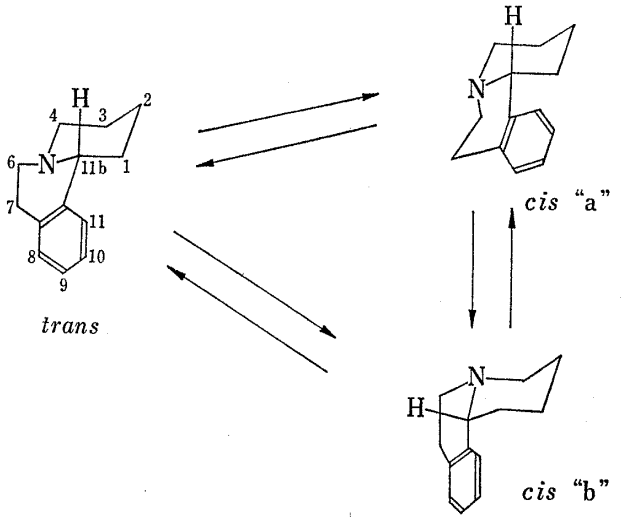


Chart 1

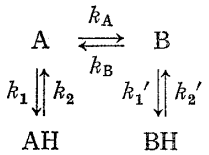


Chart 2

1) Part IV: M. Sugiura, N. Takao, K. Iwasa, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 1901 (1978).
2) Location: *a) Motoyamakita-machi 4–19–1, Higashinada-ku, Kobe 658, Japan*; *b) Yamadakami 133–1, Suita, Osaka 565, Japan.*
3) M. Sugiura, N. Takao, K. Iwasa, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 1168 (1978).

more, in the system as shown in Chart 2, the ratio k_A/k_B corresponds to that of the population p_A/p_B. Nevertheless the nuclear magnetic resonance determination of the nitrogen inversion rate of N-heterocyclic amine involves two difficulties[4]: high rate value and additional effects of the ring and nitrogen inversion. For the system as shown in Chart 2, Delpuech, *et al.*[4] determined k_A and k_B from the observation of the signal broadening of ^{1}H NMR during the protonation process.

In this work, as an extension of Delpuech's method to ^{13}C FT NMR, the nitrogen inversion rate of 1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (I) was determined. The ^{13}C NMR spectra were measured at pD *ca.* 0.54—7.5 and, from the variation of the signal line width, the nitrogen inversion rates of the equilibrium "*trans*⇄*cis* "a" ", k_{trans} and k_{cis}, were determined. The values obtained for k_{trans} are reasonable and, the validity of this conclusion has been well confirmed. But, the underestimation of k_{cis} than the actual value is presumed, and the pK_a difference between the *trans*- and *cis*"a"-conformer was probably responsible for this estimation. And, in fact, the *trans*-conformer takes lower pK_a than the *cis*"a"-conformer because of the steric hindrance, and this assumption has been confirmed.

Experimental

1) **Materials**——1,2,3,4,6,7-Hexahydro-11b*H*-benzo[*a*]quinolizine (I), *trans*-1-methyl-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (II) and *cis*-1-methyl-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (III) were prepared as described in the previous paper.[3]

1,2,3,4,6,7-Hexahydro-11b*H*-benzo[*a*]quinolizine hydrochloride (I·HCl) was obtained by refluxing I in MeOH with an excess amount of conc.HCl, and after evaporating the solvent and acid, the residue was recrystallized from $(CH_3)_2C{=}O$+MeOH, mp 209—211°.

2) **Measurements of NMR Spectra**——^{13}C FT NMR Spectra were measured with a NEVA NV-21 spectrometer at 22.6 MHz. Unless otherwise stated, the conditions of FT NMR measurements are: spectral width 5000 Hz; pulse width, 25—30 μsec (flipping angle, about 30—40°); acquisition time, 0.8 sec, number of data [Base] was varied points, 8192.

^{13}C NMR Measurement of I in the Successive Addition of Trifluoroacetic Acid TFA: For a solution of I in CD_3OD (*ca.*1.4 mol/l), spectra were taken by the successive addition of TFA. Molar ratio of [H$^+$]/[Base] was varied from 0—5.28.

Plot of ^{13}C chemical shift against [H$^+$]/[Base] for each aliphatic carbon was shown in Fig. 1.

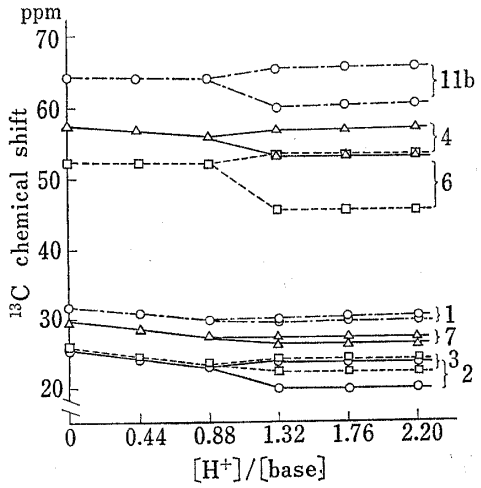


Fig. 1. Plot of ^{13}C Chemical Shift *vs.* Molar Ratio [H$^+$]/[Base] of I

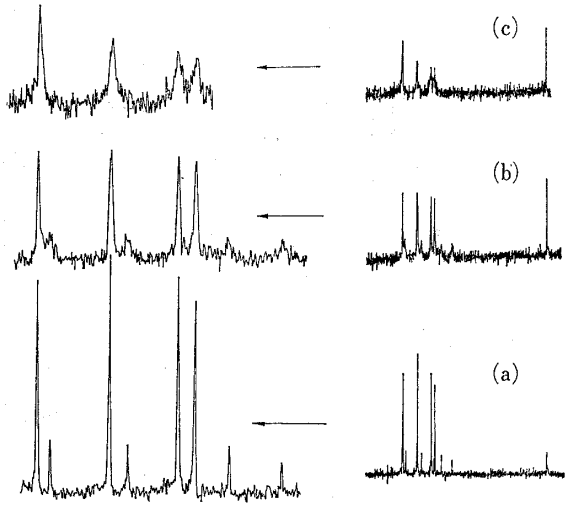


Fig. 2. ^{13}C NMR of I in D_2O, (a) pD=0.54, (b) pD=5.55 and (c) pD=6.00

The left hands are the five-times expanded spectra of the right.

4) J.J. Delpuech and M.N. Deschamps, *Chem. Comm.*, **1967**, 1188.

^{13}C NMR Measurement of I·HCl at Variable Acidity: I·HCl was dissolved in D_2O (*ca.* 0.6 mol/l), and pD was adjusted by DCl or NaOD. Spectra were taken at optional pD by the following conditions: spectral width, 3000 Hz and horizontal scale is expanded at 5 times; Hz/point, 0.76 Hz (*cf.* Fig. 2). Correction of pD scale was achieved by adding 0.40 to the pH meter reading.[5]

^1H NMR Measurement of II and III at Variable Acidity: ^1H NMR Spectra were measured with a NEVA NV-21 spectrometer at 90 MHz with CW mode. For each solution of II and III of CD_3OD (*ca.* 0.1 mol/l), spectra were taken by the successive addition of DCl at optional pD. The apparent pD values were not corrected.

Plots of 11b-H chemical shifts against apparent pD's were shown in Fig. 3.

3) **Determination of pK_a of I**——The pK_a of I was determined by a potentiometric titration[6] with a Hitachi-Horiba pH meter, model F-5, equipped with a combination pH electrode. The observed value was 8.73±0.03 at 0.01 mol/l.

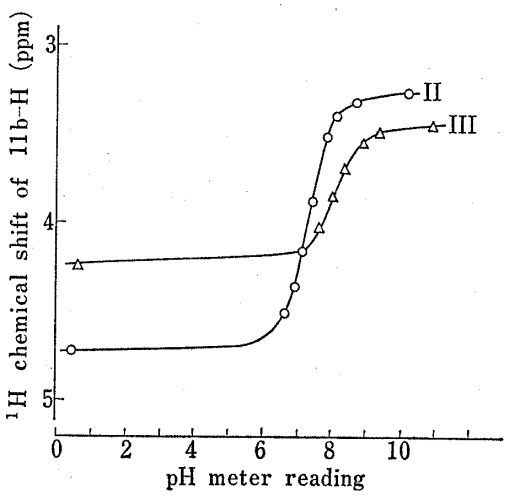
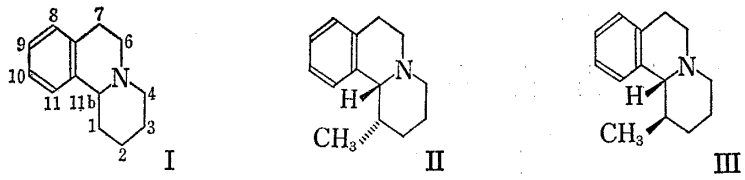


Fig. 3. Plot of 11b-H Chemical Shift *vs.* pD for II and III

Results and Discussion

1) Protonation of Benzo[*a*]quinolizidines

When an excess amount of TFA is added in the $CDCl_3$ or CD_3OD solution of 1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (I), *trans*-1-methyl-1,2,3,4,6,7-hexahydro-11b*H*-



benzo[*a*]quinolizine (II) and *cis*-1-methyl-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (III), their ^{13}C NMR spectra showed different patterns from each other. Except a few carbons, in aliphatic region, large high field shifts are observed for II and III. In contrast, though I shows high field shifts with a small amount of TFA, all signals separate into two with the successive increase of TFA (*cf.* Fig. 4). The variations of ^{13}C chemical shifts on the successive addition are illustrated in Fig. 1, and these show that each signal separates in the region of molar ratio $[H^+]/[\text{Base}]>1$ and shifts little beyond this region.

In Table I, ^{13}C chemical shifts of I, II and III with an excess amount of TFA, as well as the differences of shifts from the free bases of aliphatic carbons, are summarized. When an excess amount of TFA is added, the nitrogen inversion is stopped and the equilibrium "*trans*⇄*cis*"a"" is diminished, where the observed shifts are regarded to those of the protonated salts and the differences from the free bases are to the protonation shifts.

Since the free base II exists as almost 100% *trans*-conformer in solution,[1] its salt should be protonated to the *trans* configuration. The protonation shifts of II are comparable to those of quinolizidine (IV)[7] summarized in Table I for reference, and this fact supports the *trans* configuration of the protonated salt of II.

5) M. Davis, H.M. Hügel, R. Lakhan, and B. Ternai, *Aust. J. Chem.*, **29**, 1445 (1976).
6) A. Albert and E.P. Serjeant, "Ionization Constants of Acids and Bases, A Laboratory Manual," Methuen and Co., Ltd., London, 1962, Chapter 2.
7) M. Sugiura and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **24**, 2988 (1976).

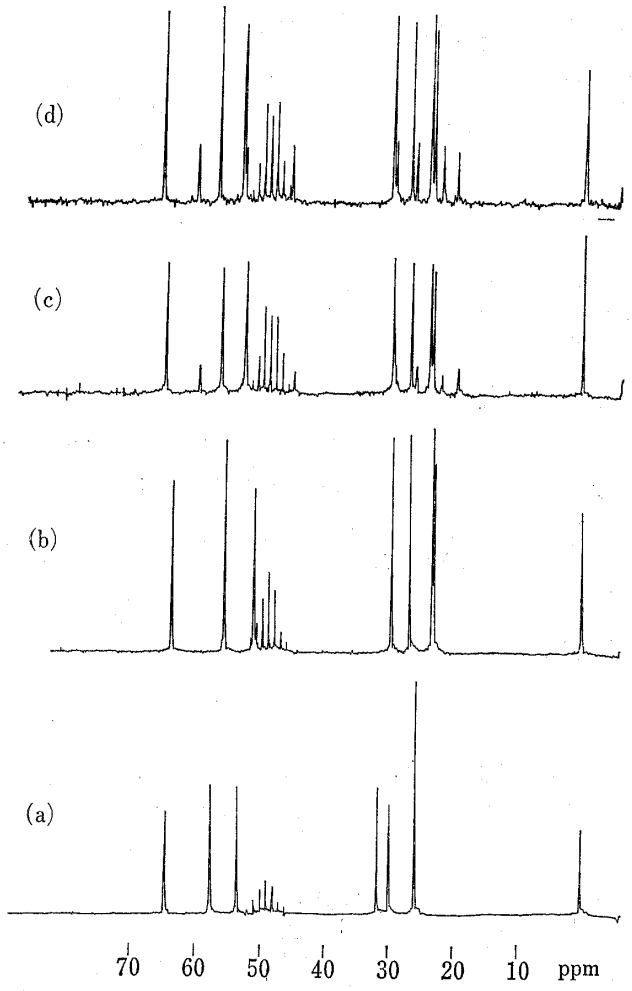
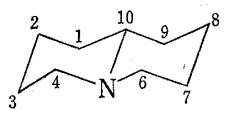


Fig. 4. ^{13}C NMR Spectra of I (a) CD_3OD, (b) in CD_3OD+TFA ([H^+]/[Base]=0.88), (c) in CD_3OD+TFA ([H^+]/[Base]=1.32), and (d) in CD_3OD+Large Excess of TFA



IV

Although the free base III in solution has a contribution of *ca.* 20% *trans*-conformer, the protonated salt of III affords the spectral pattern of one species of salt. In comparison of its chemical shifts with those of protonated salt of II, the higher field shift of C–6 is noted, which suggests the *cis*"a" configuration of the salt of III. This high field shift arises from the gauche interaction between C–6 and C–3,[3] which is confirmed by the high field shift of C–3 of the salt of III. On the other hand, the high field shift of C–3 of the salt of II is due to the γ-effect of the axial methyl. Consequently, in spite of some contribution of the *trans*-conformer of the free base, the protonated salt of III takes the *cis*"a" configuration. As shown above, a large difference of C–6 chemical shifts is observed between the salts of II and III as well as of the free bases. This results shows that the utility of the C–6 chemical shift to dis-

Table I. ^{13}C Chemical Shifts[a] of Protonated Salts of I, II and III, and Protonatin Shifts (ΔH^+)[b]

Carbon	I		II	ΔH^+(II)[b]	III	ΔH^+(III)[b]	ΔH^+(Qu)[c]
	trans	*cis* "a"					
1	28.81	28.35	30.94	−1.22	31.72	1.41	−2.88
2	22.74	20.59	29.09	−3.07	30.84	−3.36	−2.35
3	22.98	19.63	18.70	−2.44	18.64	−2.43	−2.56
4	56.50	51.50	58.45	−0.01	53.73	−0.69	−0.75
6	52.74	45.71	53.87	0.48	45.26	−0.58	−0.75
7	26.16	24.95	26.51	−3.65	25.29	−3.56	−2.56
11b	65.29	59.35	69.76	1.78	67.00	0.78	2.44
8	129.26	129.37	130.03		129.79		
9	128.76	127.82	129.58		129.15		
10	127.70	126.42	128.77		127.00		
11	124.86	128.76	125.11		129.79		
7a	130.93	129.69	129.20		129.96		
11a	131.14	131.44	131.44		130.25		
C–CH_3			10.98	−2.01	18.64	−1.93	

a) Relative to TMS in ppm.
b) ΔH^+=the difference of chemical shift between free base and protonated salt. The minus sign means a high field shift.
c) Protonation shifts of quinolizidine,[7] corresponding to each carbon of benzo[*a*]-quinolizidines.

tinguish the conformation—*trans* or *cis* "a"—of the free base is also available for the protonated salt.

Because, for the free base I, an equilibrium "*trans*⇄*cis*"a" " includes *ca.* 90% *trans*-conformation,[1] the observed two signals at protonated species are regarded as of the two salts —*trans* and *cis*"a". From these chemical shifts, refering to those of the salts of II and III, the major salt is the *trans* and the minor is the *cis*"a".

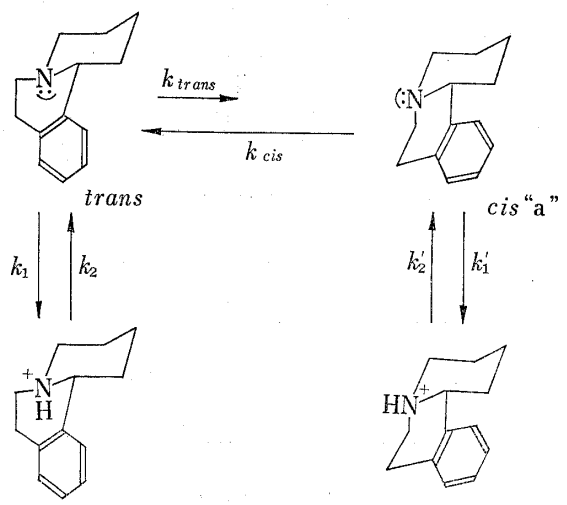


Chart 3

As shown in Fig. 1, when [Base]>[H⁺], only one kind of signal is observed. In this condition, the presence of the free bases of the *trans*- and *cis*"a"-conformer as well as the *trans* and *cis*"a" salts are expected. And, these species are reached to a rapid equilibrium as shown in Chart 3, where the observed chemical shifts are averaged in the NMR time scale and are also the weighed average of these species.

2) Nitrogen Inversion Rate of 1,2,3,4,6,7-Hexahydro-11b*H*-benzo[*a*]quinolizine (I)

Delpuech, *et al.*[4] determined the nitrogen inversion rate of piperidine derivative having two kinds of protonated salts from ^{1}H NMR under the alteration of pH. In the system as shown in Chart 2, while two different sharp signals are observed for some protons at the complete protonation, the equilibriums depicted as k_1 and k_2 as well as k'_1 and k'_2 are gradually established with the progressive increase of pH, and the two different signals become broad by the exchange, thus bringing a coalescence.[4] k_A and k_B are approximated as below;

$$\frac{1}{\tau_{AH}} = \frac{K_i \cdot k_A}{[H^+]} \quad \text{and} \quad \frac{1}{\tau_{BH}} = \frac{K_i \cdot k_B}{[H^+]} \qquad (1)^{4)}$$

where K_i is the acid dissociation constant, and τ_{AH} and τ_{BH} are the life times of isomer AH and BH on the exchange, as determined by a NMR line-broadening as represented in Eq. (2).

$$\frac{1}{\tau_{AH}} = \pi \cdot \Delta W_{AH} \quad \text{and} \quad \frac{1}{\tau_{BH}} = \pi \cdot \Delta W_{BH} \qquad (2)$$

In Eq. (2), ΔW is the increment of the width in Hz at half-height of each signal by the exchange. For the salts of the system as shown in Chart 2, when NMR spectra are measured with the successive increase of pH from the acidic side and the variations of half-height width are measured for each signal, k_A and k_B are determined from Eq. (1) and (2) when pK_a is known.

Since Chart 3 is replaced by Chart 2, above treatments are available for I. Therefore, these treatments were applied to ^{13}C NMR of I·HCl. ^{13}C NMR of I·CHI in D_2O solution was measured under the alteration of pD, and parts of the spectra were reproduced in Fig. 2. On the dissolution in D_2O (pD=0.54), a I·HCl gave sharp signals (*cf.* Fig. 2(a)), which became broad with the increase of pD (*cf.* Fig. 2(b)), and at pD=*ca.*6.00 the signals corresponding to the *cis* "a" salt became unobservable in the noise (Fig. 2 (c)). From the observation of the signals shown in Fig. 2, the averages of the increment of the half-height width for each signal between pD=5.55 or 6.00 and *ca.* 0.54 were measured, and the results determined k_{trans} and k_{cis}. From Eq. (1) and (2), k_{trans} and k_{cis} are represented by Eq. (3).

$$k_{trans} = \frac{\pi \cdot \Delta W_{trans \cdot H^+} \cdot [H^+]}{K_i} \qquad (3)$$

$$k_{cis} = \frac{\pi \cdot \Delta W_{cis \cdot H^+} \cdot [H^+]}{K_i}$$

The results of each salt are summarized in Table II. Two values of k_{trans} given at two conditions —pD=5.55 and 6.00— are similar from each other. This fact supports the validity of this treatment. The nitrogen inversion rate[8] of N-methyl-1,2,3,4-tetrahydroisoquinoline[5] is comparable to the k_{trans} determined in this work.

Table II. Difference of the Width at Half-height of the Peak (ΔW) and Calculated Nitrogen Inversion Rates (k_{trans} and k_{cis}) of I

	pD	$\Delta\overline{W}$ (Hz)	k (sec^{-1})
trans	6.00±0.01	6.17±0.7	10.4 (±0.4) × 10^3
	5.55±0.01	1.97±0.7	9.35(±0.4) × 10^3
cis	5.55±0.01	4.77±0.7	22.6 (±0.4) × 10^3

It is obvious from Chart 3 that the ratio of the population for each conformer is inversely proportional to the ratio of the inversion rate, namely.

$$p_{trans}/p_{cis} = k_{cis}/k_{trans} \quad (4)$$

consequently, from the values of k at pD=5.55, $p_{trans}/p_{cis} \fallingdotseq 7/3$, which suggests a *ca.* 70% population of the *trans*-conformer of the free base, is obtained. Fot I, however, a 92—93% population of the *trans*-conformer was concluded by means of the Bohlmann band of IR and the induced paramagnetic shift by $Ni(AA)_2$ as well as the ^{13}C chemical shift of C-6.[1] This discrepancy is probable from the difference of K_i in Eq. (3) for the conformer *trans* or *cis* "a". Though only one value was given for pK_a of I by the potentiometric titration, the possibility of the presence of two pK_a of the *trans*- and *cis*"a"-conformer is expected. In this experiment, the same K_i in Eq. (3) is used for the estimation of k_{trans} and k_{cis}. In order to obtain p_{trans}/p_{cis} ($=k_{cis}/k_{trans}$)$\fallingdotseq$9/1, K_i of the *cis*-conformer should be smaller than that of the *trans* and it is expected that $K_i(cis)=1/(3—4)\cdot K_i(trans)$, namely pK_a (*cis*)=pK_a (*trans*) +*ca.*0.5—0.6. Since, in the free base, the equilibrium "*trans*$\rightleftarrows$*cis* "a" " lies rather to the *trans*-site, pK_a obtained from the potentiometric titration-8.73- is assigned to the *trans*-conformer. Consequently, pK_a of the *cis*-conformer is expected to be higher than that of the *trans* by 0.5—0.6 unit.

3) Conformational Dependence of pK_a

In the preceding section, two conformers of I-*trans* and *cis* "a"- were expected to afford the different pK_a from each other. This difference is ascribed to the steric factor, when other situation is similar between these two conformers. In the *trans*-conformer, the surroundings of the nitrogen lone-pair are more crowded by β axial protons. Previously,[1] we have observed that II with a 100% *trans* conformation was not coordinated by the paramagnetic shift reagent $Ni(AA)_2$, while III showed significant paramagnetic shift, and these observations are provably attributed to the steric hindrance of the *trans*-conformer. However, since the steric requirement of proton is known to be smaller,[9] the similar situation of the addition of $Ni(AA)_2$ is not available.

In order to elucidate the conformational dependence of pK_a, the difference of pK_a between II and III have been examined. ^1H Chemical shifts of II with a 100% *trans* conformation[1] and III with a 80% *cis* conformation[1] were measured under the successive alteration of pD. 11b-H Chemical shifts of both compound are readily observable because of the absence of overlapping and its marked shift. Then, the variations of the 11b-H chemical shifts of CD_3OD solution at several acidities are represented in Fig. 4, which indicate the clear difference between

8) =1.0(±0.2) × 10^4 sec^{-1}.
9) H.C. Brown, D.H. McDaniel, and O. Häfliger, "Determination of Organic Structures by Physical Methods," ed. by E.A. Braude and F.C. Nachod, Academic Press Inc., New York, 1955, p. 603.

II and III. The roundings of the two curves are due to the protonation of each base, and their midpoints are regarded as an apparent pK_a. Therefore, for III, the higher pK_a by nearly one unit than II is obvious.

Although this experiment is carried out in CD_3OD and does not afford the real pK_a, the difference between these two derivatives is significant. In the preceding section, the assumption of pK_a(*cis*)=pK_a(*trans*)$^+$(0.5—0.6) has been postulated to resolve the conflict of the experiments. This conclusion is also supported by the above observation even though the difference of solvent, *etc.* are taken into account.

It is concluded that two conformers of benzo[*a*]quinolizidines-*trans* and *cis*"a"- have the different pK_a, and the value of the *cis* "*a*"-conformer is higher than that of the *trans*-conformer by 0.5—1 unit. This difference is attributed to the conformational difference and reflects the stability of the salt including the effect of solvent and ion-pair, since the steric requirement of proton is negligible.

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