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Conformational Analysis of 1,1a,6,10b-Tetrahydrodibenzo[*b*, *f*]-cycloprop[*d*]azepine Derivatives

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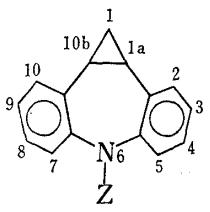
Detailed inspection of the nuclear magnetic resonance spectra of 1, 1a,6,10b-tetrahydrodibenzo[*b*, *f*]cycloprop[*d*]azepines (**1**) in $CDCl_3$ solutions has revealed that the state of conformational equilibrium falls into the following five categories according to the nitrogen substituent Z: 1) There exists a slow equilibrium between conformers I and IV, conformers II and III being either involved in a fast process or not involved at all. 2) Thre eexists a slow (much slower than category 1) equilibrium between conformers I and IV, conformers II and III being either involved in a fast process or not involved at all. 3) Conformer I is the sole one that is present, conformer III being either involved in a fast process or not involved at all. 4) Conformer IV (≡II) is the sole one that is present. 5) There exists a fast equilibrium between conformers I and IV, conformers II and III being either involved in a fast process or not involved at all.

1,1a,6,10b-Tetrahydrodibenzo[*b*, *f*]cycloprop[*d*]azepines (**1**) are compounds of a novel condensed ring system, which have been synthesized recently by the present authors.[2] Conformational analysis of these substances is described in the present paper.

The possible conformations I, II, III and IV for **1** are shown in Chart 1. The equilibria I⇌II and III⇌IV are due to the inversion of the central seven-membered ring,[3] the cyclopropane ring being in pseudoaxial (for conformers I and III) or in pseudoequatorial (for conformers II and IV) conformations.[4] On the other hand, the equilibria I⇌III and II⇌IV



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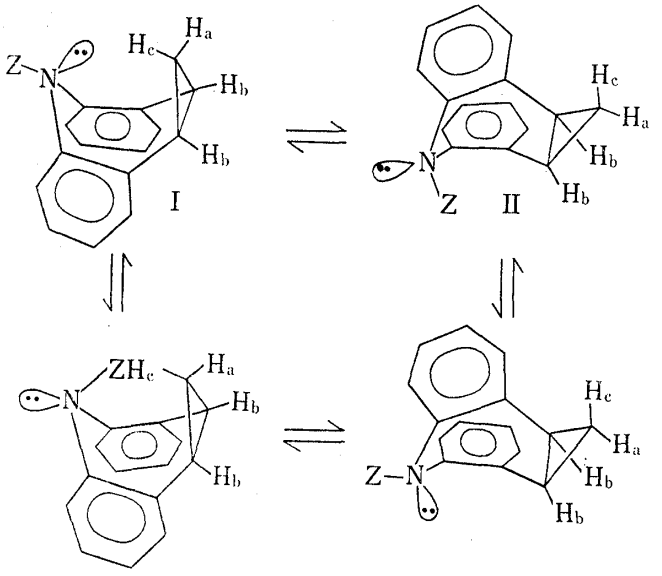


Chart 1

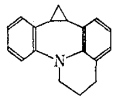
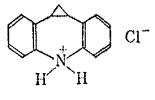
1) Location: *17–85, Juso-honmachi 2-chome, Yodogawa-ku, Osaka, 532, Japan.*
2) K. Kawashima and Y. Kawano, *Chem. Pharm. Bull.* (Tokyo), **24**, 2751 (1976).
3) W. Tochtermann, *Fortschritte Chem. Forsch.*, **15**, 378 (1970).
4) R.F. Childs, M.A. Brown, F.A.L. Anet, and S. Winstein, *J. Am. Chem. Soc.*, **94**, 2175 (1972).

are due to the nitrogen inversion.[5] Detailed inspection of the NMR spectra of these compounds revealed that the actual position of the conformational equilibria and the rate of conversion between the conformers are greatly influenced by the kinds of substituent Z on the nitrogen atom. The following discussions demonstrate that all the compounds synthesized fall into five categories according to the kind of substituent Z as shown in Table I.

Category 1 represents a slow[6] equilibrium between conformers I and IV, conformers II and III being either involved in a fast[6] process or not involved at all. In the NMR spectrum[7]

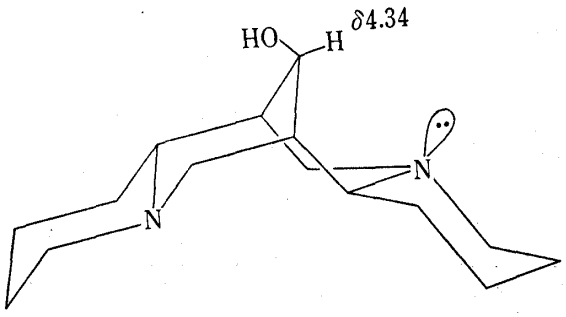
Table I. Conformational Equilibria of 1,1a,6,10b-Tetrahydrodibenzo-[*b*,*f*]cycloprop[*d*]azepines (**1**)

Category	Substituent Z	Compd. No.	Conformational[c] equilibrium
1	$-CH_3$	**2**	I ⟷ II (slower); I ⇅ III (fast); II ⇅ IV (fast); III ⌣ IV
	$-CH_2CH{=}CH_2$	**3**	
	a)	**4**	
2	$-CH_2CH_2CH_2Cl$	**5**	I ⟷ II (slower); I ⇅ III (fast); II ⇅ IV (fast); III ⌣ IV
	$-CH_2CH_2CH_2Br$	**6**	
	$-CH_2CH_2N^+H(CH_3)_2\cdot$ fumarate	**7**	
	$-CH_2CH_2CH_2N^+H(CH_3)_2\cdot$ fumarate	**8**	
3	$-CH_2CH_2N(CH_3)_2$	**9**	I ⌒ III (fast); III ⌣ I
	$-CH_2CH_2N(C_2H_5)_2$	**10**	
	$-CH_2CH_2CH_2N(CH_3)_2$	**11**	
4	*b*)	**12**	II ‖ IV
5	$-H$	**13**	I ⟷ II (fast); I ⇅ III (fast); II ⇅ IV (fast); III ⌣ IV
	$-CHO$	**14**	
	$-CONH_2$	**15**	

a)  *b*)  Cl^- *c*) The terms "fast" and "slow" are relative to NMR time scale.

5) J.M. Lehn, *Fortschritte Chem. Forsch.*, **15**, 311 (1970); J.B. Lambert, "Topics in Stereochemistry," Vol. 6, ed. by N.L. Allinger, and E.L. Eliel, Wiley-Interscience, New York, 1971, p. 19.
6) The terms "fast" and "slow" are relative to nuclear magnetic resonance (NMR) time scale.
7) NMR spectra were taken with Varian HR-100 model, the chemical shifts being expressed in ppm relative to internal tetramethylsilane (TMS) (δ) in $CDCl_3$ solutions. In order to inspect the δ 0—1 region in detail, chloroform or benzene locked spectra were measured as well as the ordinary TMS locked spectrum. The sample solutions were shaken with D_2O when necessary.

of 6-allyl-1,1a,6,10b-tetrahydrodibenzo[*b*, *f*]cycloprop[*d*]azepine (**3**) at 30° (Fig. 1c) the sharp signals at δ 0.97, 2.12, and 3.57 are assigned to H_a, H_b and H_c, respectively (J_{ab}=9, J_{ac}=4, J_{bc}=6 Hz, Table II). Since coupling constants for *cis* protons in cyclopropanes are generally larger than that for *trans* protons,[8] the signal at δ 0.97 is assigned to H_a, which is in the *cis* position to the benzylic protons H_b and couples to the latter with the larger coupling constant of 9 Hz. These coupling interactions are ascertained by the double resonance experiment with the N-methyl deivative **2**. The fact that the signal for H_c appears at δ 3.57, which is an abnormally low-field value for a cyclopropane proton,[8] and that the shift difference between H_a and H_c is as large as 2.60 ppm could be accounted for by assuming that these signals originate from conformer I. A possible anisotropic effect of the two benzene rings, when estimated by the method of Johnson and Bovey,[9] will shift all of the cyclopropane protons to a lower field whichever the conformation might be. In fact, the empirical estimation indicates that H_c is more deshielded than H_a by 0.15 ppm with conformers I or III, and 0.41 ppm with conformers II or IV. Accordingly, the observed chemical shift difference (2.60 ppm) cannot be accounted for only by the ring current effect of the benzene rings. The effect of the nitrogen atom should now be considered. It has been claimed[10] that nitrogen lone pair electrons deshield a proton which is located in close proximity to the lobe of lone pair electrons; the chemical shift difference of 0.93 ppm for the carbinyl hydrogens in epimeric sparteines **16** and **17** has been attributed to the nitrogen anisotropy.[11] The high degree of deshielding effect



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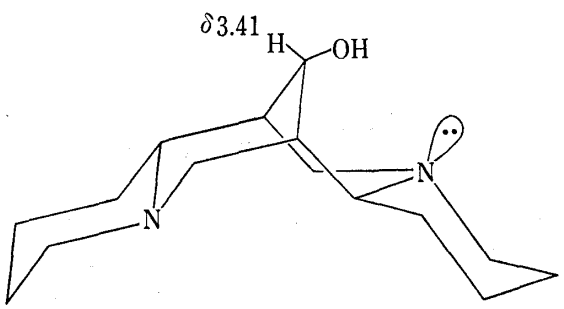

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exerted on H_c of **3** would therefore be ascribed to the very short distance between H_c and nitrogen atom, and location of H_c on the axis of the lobe of the nitrogen lone pair electrons in conformation I.

The temperature-dependent NMR spectra of **3** (Fig. 1) revealed that the broad signals at δ 0.50, 1.44 and 2.37 are originated from the conformer IV. The sharp signal at δ 2.12 for benzylic protons coalesces with the broad signal at δ 2.37 with concomitant broadening upon temperature elevation, the coalescence temperature being *ca.* 70° (Fig. 1b). Further elevation of temperature sharpens the signal and a single double-doublet is observed at 105° (Fig. 1a). Similarly, the signal at δ 0.97 for H_a coalesces with a broad signal at δ 1.44 and begins to be sharpened at 105°. It is to be noted that the counterpart signal of the H_c signal at δ 3.57 appears at δ 0.50, the coalesced signal being very broad at as high temperature as 105° in accord with the large shift difference. Inspection of the spectrum at −12° made the situation more clear. That is, the broad signals at higher temperatures now exhibit themselves as

8) J.W. Emsley, J. Feeney, and L.H. Sutchiffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press Ltd., New York, 1966, p. 690.
9) J.W. Emsley, J. Feeney, and L.H. Sutchiffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1. Pergamon Press Lrd., New York, 1965, p. 595.
10) S. Yamaguchi, S. Okuda, and N. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **11**, 1465 (1963). For an objective view-point see J.L. Sudmeier, *J. Phys. Chem.*, **72**, 2344 (1968).
11) F. Bohlmann, D. Schumann, and C. Arndt, *Tetrahedron Letters*, **1965**, 2705.

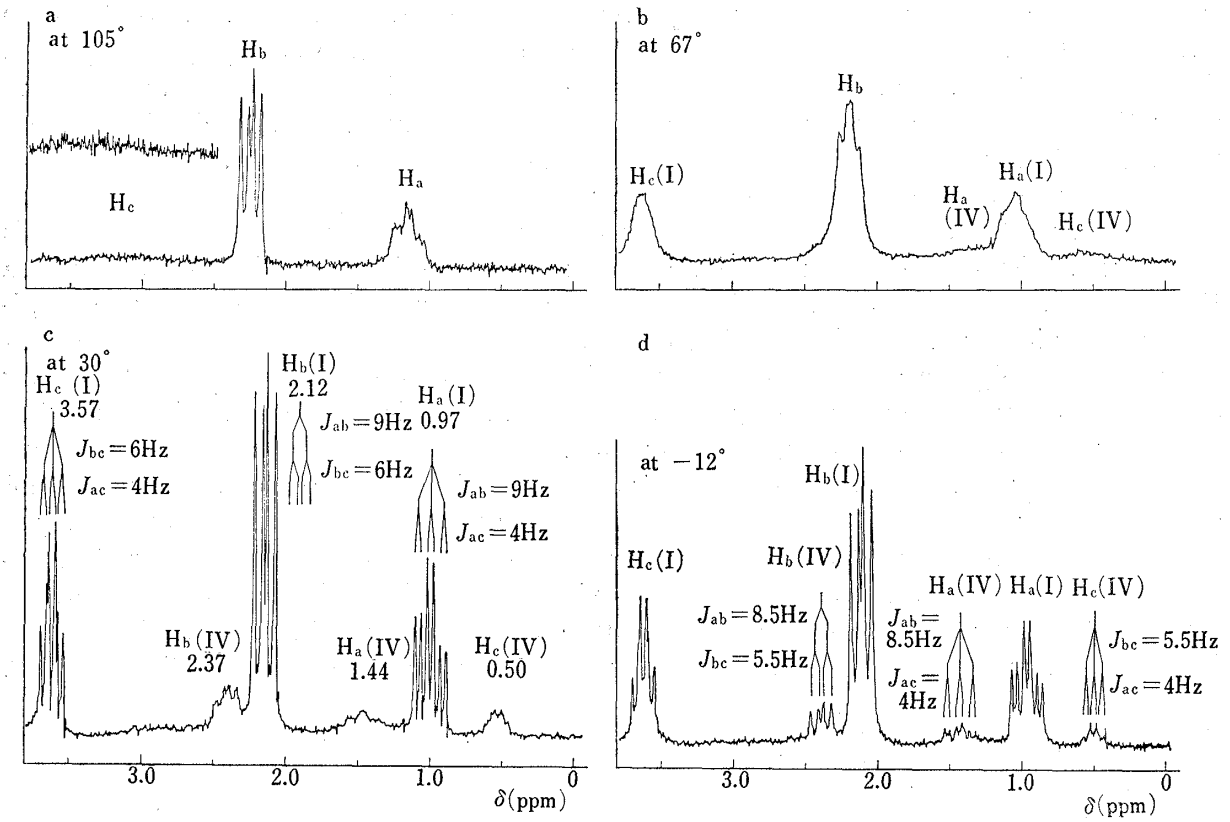


Fig. 1. NMR Spectra of 6-Allyl-1,1a,6,10b-tetrahydrodibenzo[*b*,*f*]cycloprop-[*d*]azepine (3) at Various Temperatures in $CDCl_3$ Solutions at 100 MHz

sharp signals and the coupling patterns led us to establish the following assignments: signals at δ 0.97 and 1.44 for H_a, signals at δ 2.12 and 2.37 for H_b, and signals at δ 3.57 and 0.50 for H_c. Accordingly, the conformer I is in equilibrium with another conformer, which is assumed to be either II or IV because the signal for H_c appears at a normal position[8] of δ 0.50. The broad signals assigned to the second conformer may suggest that the equilibrium II⇌IV is a slow one. However, this possibility is ruled out for two reasons: firstly, the nitrogen inversion in ordinary tertiary amines takes place fast and the coalescence temperatures are considerably lower than room temperature,[5] and secondly the signals to be assigned to the conformer IV of **4**, in which the conformer II is excluded owing to the presence of an additional ring, are broad at room temperature (Chart 2). It has been well documented[12] that when a proton is in an exchange equilibrium between states A and B the signal for state A of smaller probability of existence becomes broader in preference to that for state B on temperature elevation. Although it is most reasonable to assume a rapid equilibrium between conformers II and IV,

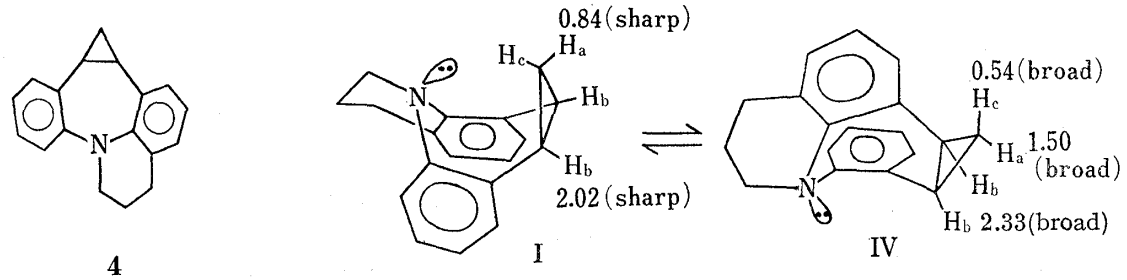
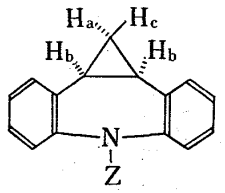


Chart 2

12) T. Nakagawa, *Bull. Chem. Soc. Japan*, **39**, 1006 (1966); *Idem*, *Ann. Rept. Shionogi Res. Lab.*, 13, 60 (1963).

TABLE II. NMR Parameters for 1,1a,6,10b-Tetrahydrodibenzo[*b*,*f*]cycloprop[*d*]azepines (1) in $CDCl_3$ Solutions at 100 MHz



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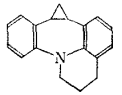
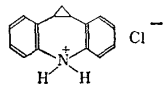
Category	Substituent Z	Compd. No.	Conformation I: Chemical shift[c] H_a	H_b	H_c	Conformation I: Coupling constant[d] J_{ab}	J_{ac}	J_{bc}	Conformation IV: Chemical shift[c] H_a	H_b	H_c	Conformation IV: Coupling constant[d] J_{ab}	J_{ac}	J_{bc}	Conformational equilibrium I: IV
1	$-CH_3$	**2**	0.95	2.10	3.41	9	4	6	1.47[e]	2.39[e]	0.52[e]	*f*)	*f*)	*f*)	7: 3
	$-CH_2CH{=}CH_2$	**3**	0.97	2.12	3.57	9	4	6	1.44[e]	2.37[e]	0.50[e]	8.5[g]	4[g]	5.5[g]	8: 2
	a)	**4**	0.84	2.02	*f*)	9	4	6	1.50[e]	2.33[e]	0.54[e]	*f*)	*f*)	*f*)	9: 1
2	$-CH_2CH_2CH_2Cl$	**5**	0.98	2.12	3.47[h]	8.5	4	6	1.38	2.32	0.46	9	4	5.5	8: 2
	$-CH_2CH_2CH_2Br$	**6**	0.99	2.1[f]	3.5[f]	9	4	*f*)	1.44	2.34	0.47	9	4	5.5	7: 3
	$-CH_2CH_2N^+H(CH_3)_2\cdot$ fumarate	**7**	1.06	2.16	4.0[f]	9	4	6	1.50	2.34	0.48	9	4	5	6: 4
	$-CH_2CH_2CH_2N^+H(CH_3)_2\cdot$ fumarate	**8**	1.07	2.16	3.7[f]	9	4	6	1.50	2.36	0.48	9	4	5	7: 3
3	$-CH_2CH_2N(CH_3)_2$	**9**	0.96	2.1[f]	3.7[f]	9	4	6							10: 0
	$-CH_2CH_2N(C_2H_5)_2$	**10**	0.9[f]	2.09	3.7[f]	9	*f*)	6							10: 0
	$-CH_2CH_2CH_2N(CH_3)_2$	**11**	0.95	2.1[f]	3.6[f]	9	4	6							10: 0
4	*b*)	**12**							1.60	2.73	0.66	9	4	6	0:10

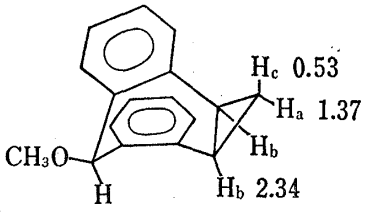
Category	Substituent Z	Compd. No.	Conformation I ⇄ IV: Chemical shift H_a	H_b	H_c	Coupling constant J_{ab}	J_{ac}	J_{bc}	Conformational equilibrium I: IV
5	$-H$	**13**	1.55	2.1[f]	2.4[f]	9	4	*f*)	*ca.* 1: 1
	$-CHO$	**14**	1.39	2.2[f]	2.3[f]	9	5	*f*)	*ca.* 1: 1
	$-CONH_2$	**15**	1.43	1.99	2.31	9	5	6	*ca.* 1: 1

a) 

b) 

c) expressed in ppm relative to internal TMS (δ). *d*) expressed in Hz. *e*) broad signad. *f*) Exact values can not be read because of broadening, overlapping, or inapplicability of the first-order analysis. *g*) values at −12° *h*) measured by the double-resonance technique

the possibility of the sole existence of either of the two conformations is not excluded. Irrespective of the truth, the conformer IV will be considered in the following discussion for convenience. The NMR signal assignments receives support from the fact that the chemical shift values assigned to the conformer IV of **3** are in good agreement with the values (in CS_2) for compounds **18** and **19**, which are carbon analogs of **1** and have been established to exist in the conformations as shown below.[4]



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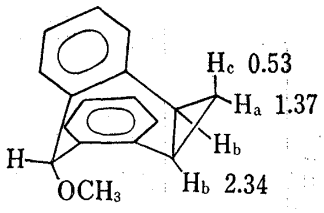

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Because the signals assigned to the conformer I are sharp at room temperature, it follows that either the conformer III is not involved owing to the high degree of steric hindrance, or an equilibrium I⇌III is a fast one if it is present. If the latter is the case, a van der Waals interaction[13] between H_c and the allyl substituent on nitrogen would result in an anormalous low field chemical shift of the H_c proton.

The equilibrium ratio for **3** at room temperature can be estimated by the integral intensities of the NMR signals to be I: IV=8: 2. The rate constant and the activation energy[3] of the ring inversion of the seven-membered ring at 70° can be calculated, taking the coalescence temperature of 70° for the H_b signal, to be $k \simeq 60$ sec.$^{-1}$ and $\Delta G^* \simeq 18$ kcal/mole, respectively.

Similarly, for the N-methyl derivative (**2**) both the sharp signals assigned to the conformer I and the broad signals assigned to the conformer IV are observed, the equilibrium ratio being I: IV=7: 3 (Table II). The relationship among H_a (I), H_b (I) and H_c (I) was substantiated by the double resonance experiment. The results indicated that the changes in coupling patterns were in good accord with the anticipated patterns.

Category 2 represents a slow (much slower than category 1) equilibrium between conformers I and IV, conformers II and III being either involved in a fast process or not involved at all. To this category belong derivatives with such N-substituents as haloalkyl and protonated dialkylaminoalkyl groups. For example, in the NMR spectrum of **7** (Fig. 2) are observed two sets of signals to be assigned to the conformers I and IV; the signal assignable to H_c (I) is not observ d clearly because of overlapping with other signals. The only difference from category 1 is that H_a (IV), H_b (IV) and H_c (IV) represent themselves as sharp signals even at room temperature at δ 1.50, 2.34 and 0.48, respectively; the ring inversion is slow enough to allow the protons of the minor conformer to exhibit sharp signals.

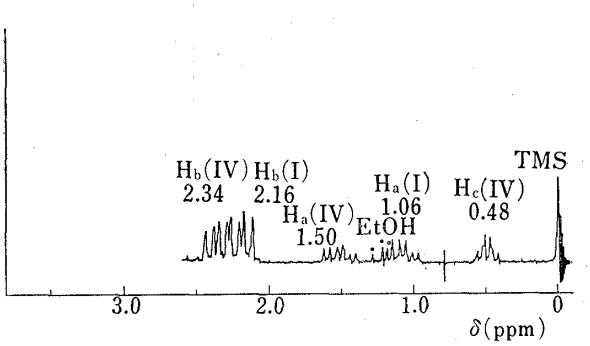


Fig. 2. NMR Spectrum of 6-[2-(Dimethylamino)ethyl]-1,1a,6,10b-tetrahydrodibenzo-[*b*,*f*]cycloprop[*d*]azepine maleate (1:1) (**7**) in $CDCl_3$ Solution at 100 MHz

Similarly, slow equilibria in **5**, **6** and **8** are also evident from their NMR spectra. Double resonance experiments on each of the two groups of protons H_a (I), H_b (I) and H_c (I), and H_a (IV), H_b (IV) and H_c (IV) in **5** supported the validity of the assignments described above.

13) S. Winstein, P. Carter, F.A.L. Anet, and A.J.R. Bourn, *J. Am. Chem. Soc.*, **87**, 5247 (1965).

Category 3 includes analogs, in which the conformer I is the sole species, the conformer III being either involved in a fast process or not involved at all. To this category belong dialkylaminoalkyl groups as the N-substituent Z. For example, the NMR spectrum of **9** (Fig. 3) shows the signal for H_a (I), but the signals to be assigned to H_c (IV) and H_a (IV) are

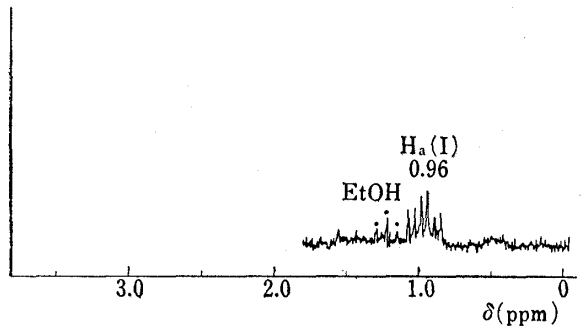


Fig. 3. NMR Spectrum of 6-[2-(Dimethylamino)ethyl]-1,1a,6,10b-tetrahydrodibenzo-[*b*,*f*]cycloprop[*d*]azepine (**9**) in $CDCl_3$ Solution at 100 MHz

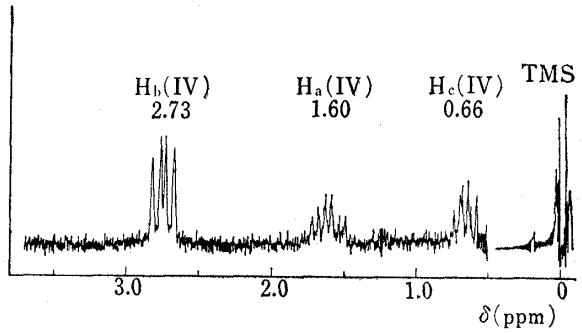
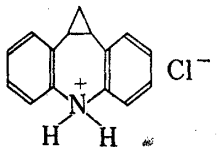


Fig. 4. NMR Spectrum of 1,1a,6,10b-Tetrahydrodibenzo[*b*,*f*]cycloprop[*d*]azepinium chloride (**12**) in $CDCl_3$ Solution at 100 MHz

not discernible. Accordingly, it is concluded that **9** exists in a single conformation I or a fast equilibrium I⇌III exists. The same is true with compounds **10** and **11** (Table II).

Category 4 represents the case where the conformer IV (≡II) is the sole species. The only example which belongs to this category is the hydrochloride (**12**) of 1,1a,6,10b-tetrahydrodibenzo[*b*, *f*]cycloprop[*d*]-azepine. In the NMR spectrum (Fig. 4) of **12** the signal for H_c appears at δ 0.66 but not around δ 3.5, and its integral intensity is equal to that for the H_a signal at δ 1.60. Therefore, the conformation of **12** is likely represented by IV but not I. As the lone pair electrons of the nitrogen atom in **12** is protonated, the conformer IV is identical with the conformer II.



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Category 5 represents a fast equilibrium between conformers I and IV, conformers II and III being either involved in a fast process or not involved at all. Compounds having hydrogen atom or an acyl group as an N-substituent Z belong to this category, 1,1a,6,10b-tetrahydrodibenzo[*b*, *f*]cycloprop[*d*]azepine (**13**) being an example. In the NMR spectrum (Fig. 5) of **13**, H_c represents itself as a sharp signal even at room temperature at δ 2.4, an intermediate position between δ 3.5 and δ 0.5 expected for the conformers I and IV, respectively. Therefore, it is concluded that **13** exists as a mixture of the fast equilibrium between conformers I and IV, the populations of which are nearly equal. The conformers II and III are either involved in a fast process or not involved at all. The same is true for N-formyl (**14**) and N-carbamoyl (**15**) derivatives (Table II).

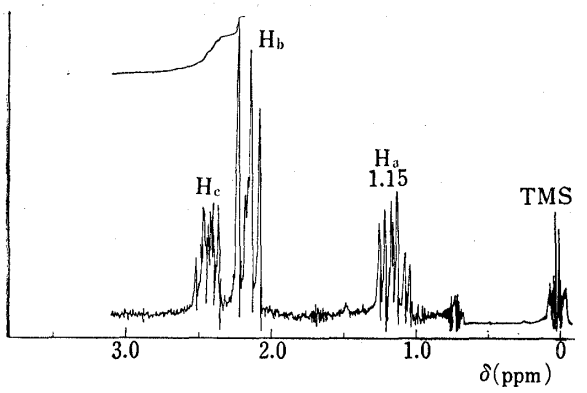
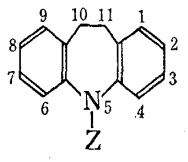


Fig. 5. NMR Spectrum of 1,1a,6,10b-Tetrahydrodibenzo[*b*,*f*]cycloprop[*d*]azepine (**13**) in $CDCl_3$ Solution at 100 MHz

However, another interpretation might be possible for these N-acyl derivatives (**14** and **15**), because in these compounds the lone pair electrons on the nitrogen atom should be partially withdrawn toward the carbonyl group and the deshielding effect on H_c is thus

weakened. The observed chemical shift for H_c, therefore, might be accounted for by assuming the predominant presence of the conformer I.

The conformational equilibria of **1** are greatly influenced by the kinds of N-substituent Z as discussed above in detail. Abraham and co-workers[14] have recently carried out conformational analysis of 5-substituted-10,11-dihydro-5*H*-dibenz[*b*, *f*]azepines (**20**) by the NMR method. They found that inversion of the central seven-membered ring is fast when the substituent Z is methyl, whereas it is slow when Z is acetyl (T_c=112°, $\Delta G^{\ddagger}$=19.5 kcal/mole). To interpret this difference they invoked a steric interaction between the abutting C4- and C6-hydrogens and a planar amide group, in the transition state of ring inversion. It is interesting to note that an entirely reverse relationship holds for compounds **1**, the inversion being slow for alkyl substituents (categories 1 and 2) and fast for acyl substituents (category 5). The difference in conformational behavior should be ascribed to an electronic factor, because the molecular models indicate that steric interrelations between the substituent Z and peri-hydrogens (C4- and C6-H for **20**, and C5- and C7-H for **1**) are similar for these two classes of compounds. In this connection, it should be pointed out that the cyclopropane ring in **1** could conjugate with the benzene rings.[2] This conjugation would be greater when the N-substituent Z is an acyl than when Z is an alkyl group, since it has been known[15] that the more electron-withdrawing is a substituent on phenyl, the larger the phenylcyclopropane conjugation. In addition, the sp^5 electrons of the cyclopropane ring would overlap with the π-electrons of the benzene rings more effectively when the compound takes a planar seven-membered ring in a transition state of ring inversion than when it takes puckered conformations in the ground states according to the theory of the angle dependence of phenylcyclopropane conjugation.[15] This kind of conjugation would result in reduced activation energy of the ring inversion for **1** with an acyl group as an N-substituent, which is consistent with the observation.



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It is worthy to note that **1** exists as an equilibrium mixture of the conformers I and IV, whereas the exclusive conformation for **18** and **19**, the carbon analogs of **1**, is the one corresponding to IV.[4] Furthermore, the population of conformer I is equal to (category 5) or larger (categories 1—3) than that of conformer IV in the 1,1a,6,10b-tetrahydrodibenzo[*b*, *f*]cyclopropa[*d*]azepine series. The reason for this might be explained as follows: Although there is a profound steric hindrance between H_c and the C6-methoxy group (or C6-hydrogen) in the conformation corresponding to I of the compound **18** (or **19**), there exists only a limited interaction between the lone pair electrons of the nitrogen and H_c. These arguments also account for the fact that the conformer IV is the exclusive one in category 4. As for the conjugative interaction between the cyclopropane and the benzene rings,[15] the electron overlapping in conformation I is far more favored than that in conformation IV.

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