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Conformational Analysis of Di-tertiary Amine in Aprotic Solvent by Dielectrometric Titration. II.[1] Conformation of *l*-Sparteine-*p-tert*-butylbenzenesulfonate in Dioxane[2]

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l-Sparteine was titrated with *p-tert*-butylbenzenesulfonic acid in dioxane at room temperature and the N-formed titration curve was obtained. The moment angle between two ion-pairs of *l*-sparteine-disulfonate calculated from the titration curve was found to be 138°10′, which differed much from the value of 93°02′ calculated from the conformation of free *l*-sparteine determined by Bohlmann, *et al.* But our optical rotatory dispersion study of the solution in the titration process proved that nearly 100% inversion occurred in A-ring when *l*-sparteine-monosulfonate became its disulfonate by the titration. The moment angle of new conformation was calculated as 139°44′ which was in good agreement with the observed value of 138°10′.

Allinger, *et al.*[4] studied the equilibrium mixture of conformations of N,N′-dimethylpiperazine at room temperature in aprotic solvent and decided the molar ratio of three forms from the measurement of dipole moment of the free diamine in benzene solution, by assuming that there existed only three chair forms and the amount of non-chair form was negligible. Among these three chair forms of N,N′-dimethylpiperazine, two of them have no net dipole moment, and the other has the value of 1.55 Debye since its two methyl groups bound to the nitrogen atoms have an equatorial and an axial positions respectively. The molar fraction of this form was calculated to be 0.104 at 25°.

In the preceding paper,[1] we also have decided the ratio of three conformations of N,N′-dimethylpiperazine dielectrometrically by titrating it with *p-tert*-butylbenzenesulfonic acid in dioxane at room temperature, utilizing the fact that the change of electrical capacity depends on large dipole moment of the ion-pair generated by an acid-base reaction. The results were in good agreement with those of Allinger, *et al.*

In the present work, *l*-sparteine was titrated with *p-tert*-butylbenzenesulfonic acid in a similar manner to that described in the previous report and a unique N-formed titration curve shown in Fig. 2 was obtained. From the curve the moment angle between two lone-pairs of *l*-sparteine was calculated to be 138°10′ at 25° in dioxane, by assuming that two ion-pair moments should have an equal magnitude and the ion-pair moment should be formed towards the direction of lone-pair moment of the nitrogen atom. This moment angle unfoturnately differs much from the value of 93°02′ which was calculated from the absolute configuration of *l*-sparteine determined by Bohlmann, *et al.*[5] in 1965. However, from the measurements of optical rotatory dispersion (ORD) of the solution in the titration process, an unexpected phenomenon was found that an inversion of the conformation of disulfonate might occur at A ring system on account of its steric effect. The moment angle of this newly formed conformation by the ring inversion was calculated as 139°44′ which was nearly equal to the experimental value of 138°10′.

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[1] Part I: I. Horikoshi, M. Morii, and N. Takeguchi, *Chem. Pharm. Bull.* (Tokyo), 23, 754 (1975).

[2] Presented at the 93rd Annual Meeting of the Pharmaceutical Society of Japan at Sendai, Apr. 1974.

[3] Locaiofn: *3190 Gofuku, Toyama.*

[4] N.L. Allinger, J.G.D. Carpenter, and F.M. Karkowski, *J. Am. Chem. Soc.*, **87**, 1232 (1965).

[5] F. Bohlmann, D. Schumann, and C. Arndt, *Tetrahedron Letters*, **1965**, 2705.

Experimental

Apparatus——The apparatus for dielectrometric titration was the same to that used in the previous work. The measurement of ORD was carried out using the Spectropolarimeter (Yanagimoto, ORD-200).

Solvent and Titrimetric Operation——All were similar to those used in the previous work. The temperature of samples was kept 25° in this experiment.

Reagents——(1) *p-tert*-Butylbenzenesulfonic Acid: Approximately 0.5 mole/liter of its dioxane solution was prepared in a similar manner to that described in the preceding paper.

(2) *l*-Sparteine: In a small amount of water 25 g of *l*-sparteine sulfonate (J.P. product) was dissolved and 5 N NaOH solution was added. The liberated free *l*-sparteine was extracted with ether and the ether solution was washed twice with water. After evaporating ether, the crude extract of oily sparteine was distilled under the coexistence of KOH using a precision fractional distillator. The distillate of bp 173° at 8 Torr was obtained. The purity of *l*-sparteine was checked by a thin-layer chromatography and 0.01 mole/liter dioxane solution of *l*-sparteine was used in the titration.

Results and Discussion

Absolute Configuration of *l*-Sparteine

l-Sparteine, found in the plants of Leguminosae, is a representative lupin alkaloid which has an oxytocic effect. Its molecular equation is $C_{15}H_{26}N_2$ and it has an optical active character. As shown in Chart 1-I, *l*-sparteine is composed of four ring systems (A, B, C, and D) which are all chair forms, with di-tertiary amines (N_1 and N_{16}), and four asymetric carbons (C_6, C_7, C_9, and C_{11}). It was clarified in the 1950's that the sparteine had three conformational isomers,6,7) one of which possessed a *cis* and a *trans* ring juncture in the A/B and C/D ring systems was so-called sparteine, and two others both of which possessed two *cis* and two *trans* ring junctures were called α-iso-sparteine and β-iso-sparteine, respectively.

But recently, the studies of nuclear magnetic resonance of sparteine5) and infrared spectrum of lupin alkaloids8) proved that the ring C was in a boat conformation in the solution and that the ring juncture had *trans*-diaxial relation to its lone-pair of the nitrogens. The most reliable configuration of *l*-sparteine therefore would be like that shown in Chart 1-II.

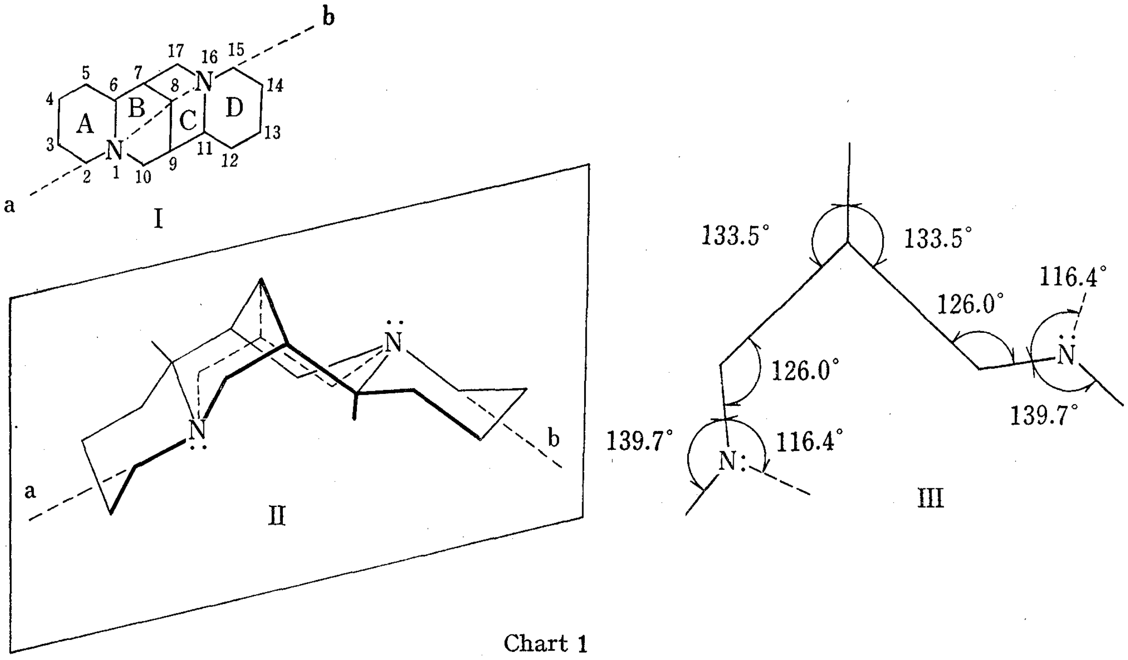

Chart 1

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6) L. Marion and N.J. Leonard, *Can. J. Chem.*, **29**, 355 (1951).

7) F. Galinovski, *Ber.*, **77B**, 132 (1944).

8) M. Wiewieorowski, O.E. Edwards, and M.D. Bratek-wiewierowska, *Can. J. Chem.*, **45**, 1447 (1967).

So we will use this configuration for *l*-sparteine to calculate the moment angle between two lone-pairs of nitrogens.

The Moment Angle between Two Lone-pairs of *l*-Sparteine

The vertical sectional view and the face angles of the configuration of *l*-sparteine along the dotted line $\overline{ab}$ were shown in Chart 1-II and 1-III. In the Chart 1-II, all face-angles projected on the vertical plane was calculated, in a similar manner to that described in the previous report, using the bond distance[9] of C-C and C-N (ring) as 1.528±0.005 Å and 1.457±0.010 Å, respectively, and the valency angles[9] of C-C-C, C-C-N, and C-N-C (ring) as 111.55±0.10°, 110.3±1°, and 114.4±1°, respectively. From the Chart 1-III, the moment angle between two lone-pairs of *l*-sparteine was easily calculated as 93°02′. Generally when the moment angle between two lone-pairs of aliphatic di-tertiary amine is smaller than 120°, tangent of the titration curve after the first equivalence point is not able to take a negative value, and the titration curve elevates continuously. However, in the case of *l*-sparteine the tangent of the titration curve after the first equivalence point took a negative value and the so-called N-formed titration curve shown in Fig. 2, which was extremely similar to that of N,N′-dimethylpiperazine, was obtained.

From the fact mentioned above, the following two cases are suggested: One is that the mixture of a few isomer exists already in the solution before the titration, and the other is that only one kind of isomer, the moment angle of which is 93°02′, exists in the solution at first and some part of it is converted to other isomer by the inversion in the process of titration. If the inversion should occur, the juncture of B/C ring system is so tight that the inversion would occur in A or D ring, and it means only to exchange the positions of a lone-pair of electrons and of N_1-C_2 (or N_{10}-C_{15}) bond with each other at N_1 (or N_{16}) atom, while two lone pairs and two N-C bonds (N_1-C_2 and N_{16}-C_{15}) are always contained in the vertical plane. Thus, there could be theoretically four conformations (a, b, c, and d) in which the moment angles were different. Uninversioned *l*-sparteine (a) has the conformation as shown in Chart 1-II and its moment angle is 93°02′. In the second conformation (b), the inversion occurrs at A ring and the conformation (a) is converted to a new isomer of its moment angle 139°44′. Only in this

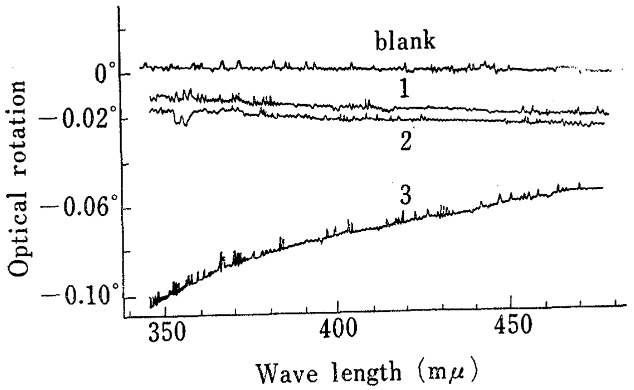

Fig. 1. Optical Rotatory Dispersion of *l*-Sparteine

Specific rotation $[\alpha]^{25}_{350}$ of free diamine (1), mono-sulfonate (2) and di-sulfonate (3) were −25.6°, −24.5° and −78.4°, respectively.

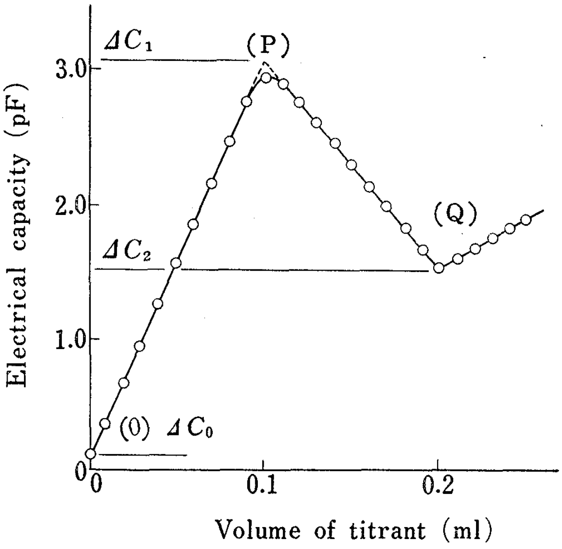

Fig. 2. Dielectrometric Titration of *l*-Sparteine with *p*-Tertiarybutylbenzene-sulfonic Acid in Dioxane at 25° and at 300 kHz

P: first equivalence point
Q: second equivalence point

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[9] M. Davis and O. Hassel, *Acta. Chem. Scand*, **17**, 1181 (1963).

conformation, it is possible to induce the N-formed titration curve. Other two conformations (c) and (d) correspond to those when the inversion occurrs in D ring and in both two rings of A and D. The moment angles in these conformations are 34°12′ and 93°02′ respectively.

When the ORD of the solution in the process of dielectrometric titration was measured, a clear-cut change of optical rotation appeared between before and after the first equivalence point as shown Fig. 1. This fact suggested that the inversion occurred undoubtedly in the ring A or D. Taking the N-formed titration curve into consideration, it is the most reasonable phenomenon that *l*-sparteine (a) will be converted to a new isomer (b) by the steric effect of ion-pairs after the first equivalence point. Now we will consider how to obtain the apparent moment angle (θ) from the values of the titration curve, which is shown in Fig. 2. In the figure, the differences of electrical capacity of the free diamine solution and of the solution at the first and second equivalence points from these of dioxane solvent are shown at point $0=\Delta C_0$, point $P=\Delta C_1$, and point $Q=\Delta C_2$, respectively. Considering the case when one molecule of *l*-sparteine is titrated, dipole moments at the point of 0, P, and Q are written in the equations (1), (2), and (3), respectively,

$$\mu_0^2 = 2\mu_x^2(1+\cos\theta_a) \tag{1}$$

$$\mu_1^2 = \mu_x^2 + \mu_y^2 + 2\mu_x\mu_y\cos\theta_a \tag{2}$$

$$\mu_2^2 = 2\mu_y^2(1+\cos\theta) \tag{3}$$

where μ_0, μ_1, and μ_2 are dipole moments of free diamine, of diamine monosulfonate and of diamine disulfonate; μ_x and μ_y are the lone-pair moment and the ion-pair moment of nitrogen atom; and θ_a and θ are the moment angle of free diamine (93°02′) and the apparent moment angle of diamine disulfonate, respectively. Using the equations (1), (2), and (3), the equation (4) is obtained.

$$2\mu_1^2 = \frac{\mu_0^2}{1+\cos\theta_a} + \frac{\mu_2^2}{1+\cos\theta} + \frac{2\mu_0\mu_2\cos\theta_a}{\sqrt{(1+\cos\theta_a)(1+\cos\theta)}} \tag{4}$$

According to Higashi's equation, there exists a simple relation between the dipole moment of a solute and the electrical capacity of its solution, *i.e.*, $\mu_0^2=k\cdot\Delta C_0$, $\mu_1^2=k\cdot\Delta C_1$, and $\mu_2^2=k\cdot\Delta C_2$. Substituting these equations into (4), the following relation is derived.

$$\cos\theta = (1+\cos\theta_a)\cdot f(\Delta C,\ \cos\theta_a) - 1 \tag{5}$$

where $f(\Delta C,\ \cos\theta_a)$ is $[\Delta C_0\Delta C_2(2\cos^2\theta_a-1)+2\Delta C_1\Delta C_2(\cos\theta_a+1)+2\sqrt{\Delta C_0\Delta C_2}\cdot\cos\theta_a\cdot\sqrt{\Delta C_0\Delta C_2(\cos^2\theta_a-1)+2\Delta C_1\Delta C_2(\cos\theta_a+1)}]/[2\Delta C_1(\cos\theta_a+1)-\Delta C_0]^2$.

The apparent moment angle (θ) calculated by the authors from the titration curve using equation (5) at 25° was 138°10′, which is very near to 139°44′ in isomer (b).

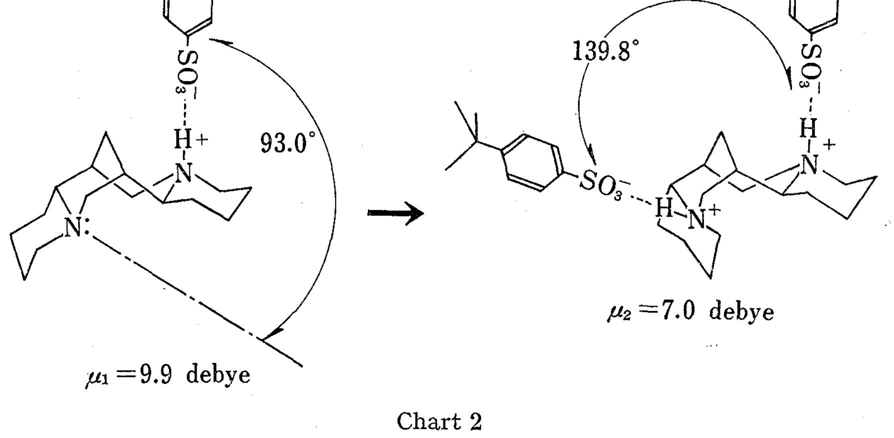

Chart 2

As the data of bond distances and of valence angles reported by Davis, *et al.*[9] has a certain extent of measuring error, the minimum and maximum values of θ calculated from those data become 134°46′ and 145°00′. Thus it will be more reasonable conclusion that when *l*-sparteine-*p*-*tert*-butylbenzene-monosulfonate becomes its disulfonate by the titration, the inversion of the conformation from (a) to (b) proceeds completely in dioxane at room temperature, the process of which is illustrated in Chart 2.