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Conformational Analysis of Di-tertiary Amine in Aprotic Solvent by Dielectrometric Titration. I. Conformation of N,N'-Dimethylpiperazine-*p*-*tert*-butylbenzenesulfonate in Dioxane[1]

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The relative ratio of three forms of N,N'-dimethylpiperazine in aprotic solvent was determined at room temperature by analyzing the curve of dielectrometric titration. The molar ratios of forms I, II, and III at 30° in dioxane were 0.880, 0.116, and 0.004, respectively, which were in good agreement with those of Allinger, *et al.* had obtained from the dipole moment of free diamine in benzene solution. The use of dielectrometric titration seemed to afford a particularly simple and direct method for conformational analysis of aliphatic di-tertiary amines.

When an organic acid reacts with an organic base in a low dielectric constant solvent such as *p*-dioxane, formation of an ion-pair can be detected by the large increase of dielectric constant of the solution. A new titrimetric method was devised utilizing the difference of the dielectric constant of acid, base, and salt (ion-pair) in the solution, and was named "dielectrometric titration" in 1961 by Ishidate and his co-workers[3] including one of the present authors (I.H.).

The increase in dielectric constant of the solution depends on an ion-pair moment formed by the titration, and dipole moment of the organic salt can be calculated from the titration curve. The ion-pair moment squared is remarkably larger than the square summation of dipole moments of acid and base which form the salt, and the ion-pair behaves as if it were one molecule in the non-self-dissociating solvent.

When a diamine is titrated with an acid, two ion-pairs are formed and, if the vector additivity is set up between the two ion-pair moments, the figure of titration curve will be determined by the angle between them. If the direction of ion-pair moment is equal to that of lone pair of nitrogen atom and two ion-pair moments have the same magnitude, the angle between them can be calculated from the titration curve and thus the conformational analysis of di-tertiary amine in aprotic solvent becomes possible from dielectrometric titration.

In the present work, N,N'-dimethylpiperazine was titrated with *p*-*tert*-butylbenzenesulfonic acid which was employed in consideration of its good solubility and strong acidity in an aprotic solvent. We found some interesting phenomena, which are reported here in detail.

Experimental

Apparatus——Measurements of the change in electrical capacity (ΔC) and impedance of the solution in the process of titration were made at 300 kHz and at 30°, using a Shering type bridge (Ando Denki, TR-10C), a cell, a precision condenser (G.R., 722MD), an oscillator, and a detector. The accuracy in the measurement of ΔC is 1/100 pF, and that in the measurement of impedance, about 2% or 0.001, whichever is greater. The container of the measuring cell had a condenser of coiled nickel plates shown in Fig. 1. The electrical capacity of the empty cell was 153.3 pF. During the titration, the cell was shielded from outside air and

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[1] A part of this report was presented at the 38th Hokuriku Regional Meeting of the Pharmaceutical Society of Japan at Toyama, June 1974.

[2] Location: *3190 Gofuku, Toyama.*

[3] M. Ishidate, H. Nishizawa, H. Sano, and I. Horikoshi, *Yakugaku Zasshi*, 81, 1303 (1961); *idem, ibid.*, 81, 1307 (1961).

kept in constant temperature by circulation of water through the outer jacket, using Thermo Unit (Taiyo Kagaku, C-100).

As a titrimetric buret, Tycoon Micrometer syringe of 0.5 ml in volume was used.

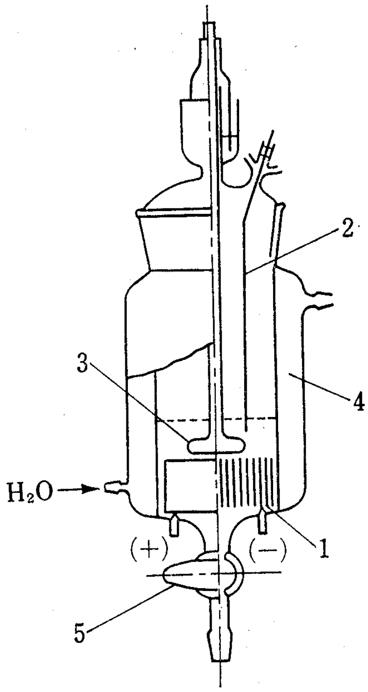

Fig. 1. Cross Section of Dielectric Cell

1. condenser (153.3 pF)
2. injector
3. stirrer
4. outer jacket
5. stop cock

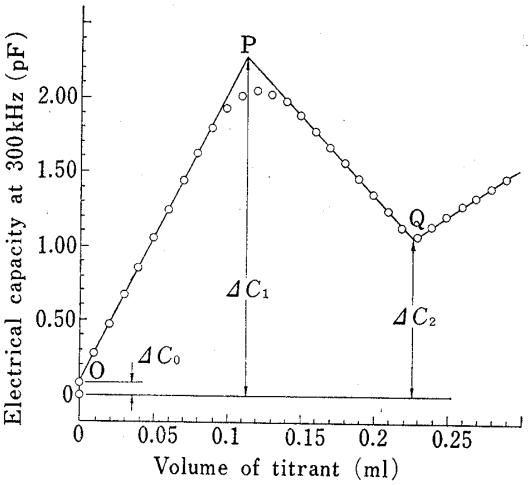

Fig. 2. Dielectrometric Titration of N, N'-Dimethylpiperazine with *p-tert*-Butylbenzenesulfonic Acid in Dioxane at 30°

P: first equivalence point
Q: second equivalence point

Reagents——(1) *p-tert*-Butylbenzenesulfonic Acid: This compound was synthesized by the following procedure. To 50 ml of conc. sulfonic acid in a 300 ml round-bottomed flask, 25 ml of *tert*-butylbenzene was added and the mixture was stirred for about 8 hr at room temperature till it was completely reacted. The end point of the sulfonation was easily found from a solubility of the reaction mixture, because the sulfonated compound has higher solubility in water. After sulfonation was completed, the reaction mixture was diluted with 100 ml of cold water, neutralized with $Ca(OH)_2$, and precipitated materials was removed by filtration. Calcium ion was removed from the salt solution using the Amberlite IR-120 resin, and free *p-tert*-butylbenzenesulfonic acid was extracted with ether. Crude crystals obtained by evaporation of the solution were recrystallized twice from benzene. As this crystal had one mole of water, it was dehydrated at 80° in vaccum of 3 Torr in a desiccator. Recrystallization from dehydrated benzene afforded anhydrous crystals of mp 112°. The purity of *p-tert*-butylbenzenesulfonic acid was checked by Differential Scanning Calorimeter (Perkin Elmer, DSC-1B).

(2) N,N'-Dimethylpiperazine: The sample of analytical grade was distilled by precision fractional distillator and the distillate of bp 120—121° was used for titration. Purity of the diamine was checked by gas chromatography.

Solvent——*p*-Dioxane: This solvent was purified by the method of Weissberger, *et al.*[4] and, after it was recrystallized at 5—10° metallic Na was added and kept in a dark room till evolution of H gas ceased. Its bp was 101.25° at 760 Torr and its density was 1.028 at 25°.

Methanol: It was distilled and the distillate of bp 65° was used.

Ether: It was dried over $CaCl_2$ and distilled, and the distillate of bp 36.5° was collected and used.

Preparation of Acid and Diamine Solutions——Approximately 0.5 mole/liter of dioxane solution of *p-tert*-butylbenzenesulfonic acid was prepared and the factor of acid concentration was determined by titration with 0.1 N Na_2CO_3 solution. A solution of 0.01 mole/liter N,N'-dimethylpiperazine was prepared.

Titration Operation——The cell and the precision condenser for compensation were connected to two ends of the bridge. After the cell was washed several times with MeOH and ether, it was dried sufficiently

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[4] A. Weissberger and E. Proskauer, "Org. Solvents," Interscience Publ Inc., New York, N.Y. 1955, p. 126.

by dry air so that the electrical capacity of the empty cell became constant and its impedance became infinity. Then 25 ml of dioxane was poured into the cell, maintained until the temperature became constant, and then the scales of electrical capacity and impedance meters were set to find the best equilibrium condition of the bridge. When the volume of solvent in the cell was more than 20 ml, no change was found in electrical capacity which is generally assumed to depend on increase of the solvent. After 5.00 ml of 0.01 mole/liter diamine solution (5×10^{-5} mole diamine) was added and stirred, the change in electrical capacity (ΔC_0) due to 5×10^{-5} mole free diamine was read. Next, 0.5 mole/liter solution of *p-tert*-butylbenzenesulfonic acid was added in portions of 0.010—0.020 ml using a micrometer cyringe. The change of electrical capacity in this titration process, ΔC_1 or ΔC_2, was plotted against titration volume. The titration was continued until about 0.2 ml was added after the second equivalence point.

Results and Discussion

When N,N′-dimethylpiperazine was titrated with *p-tert*-butylbenzenesulfonic acid in dioxane, a unique titration curve shown in Fig. 2 was obtained. Using Higashi's equation[5)] derived from Debye's equation, the dipole moments of N,N′-dimethylpiperazine-*p-tert*-butylbenzenesulfonate at the first and second equivalence points were calculated from the values of clear turning point, P and Q, in the curve, and their values were 8.3 and 5.9 Debye, respectively. It was found that the value of dipole moment at the first equivalence point was in accordance with that of the other aliphatic tertiary monoamine *p-tert*-butylbenzenesulfonates. If two ion-pair moments had an equal magnitude but different directions, the titration curve of the diamine would be varied as shown in Fig. 3. Utilizing these characteristics, the conformational analysis of diamine in aprotic solvent would become possible. Although there are various ways in which the problem of the conformation of diamine might be attacked, the present method of the use of ion-pair moments in suitable compounds seemed to afford a paticularly simple and direct method.

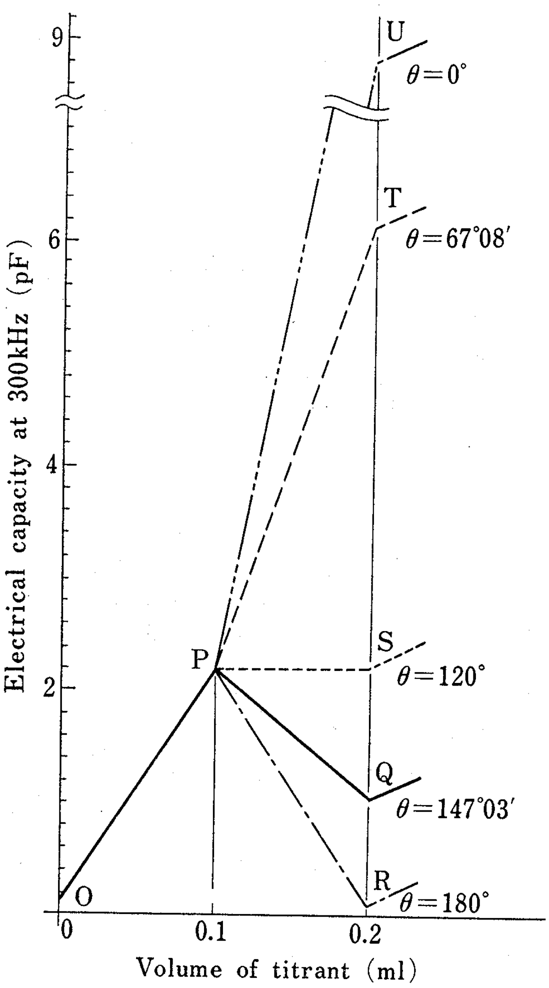

Fig. 3. Schematic Model of Titration Curves at First and Second Equivalence Points

In 1964, Allinger, *et al.*[6)] drew a conclusion that there are three conformations of N,N′-dimethylpiperazine as shown in Chart 1, from the study of its energetic preference for CH_3 group and for H on nitrogen atom, and they were convinced that boat or twist form[7)] did not exist. Hereafter, following the conclusion existing ratio of three conformations of N,N′-dimethylpiperazine, when they formed an ion-pair with *p-tert*-butylbenzenesulfonic acid in dioxane, will be discussed.

Among the three chair forms, I, II, and III, two lone-pairs in I or III have an equatorial/equatorial and an axial/axial positions and they have no net dipole moments. First, we will consider imaginary case where only I or III exists in the solution. When one lone-pair

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5) K. Higashi, *Riken Ihou*, **22**, 805 (1943).
6) N.L. Allinger, J.G.D. Carpenter, and F.M. Karkowsky, *J. Am. Chem. Soc.*, **87**, 1232 (1965).
7) M. Aroney and R.J.W. Le Fervre, *J. Chem. Soc.*, **1960**, 2161.

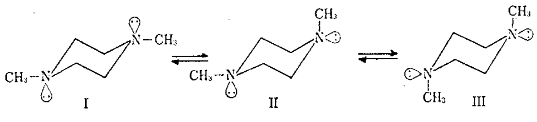

Chart 1

in a molecule becomes an ion-pair and the other in the molecule remains a lone-pair by titration before the first equivalence point, the net change in dipole moment of form I or III monosulfonate is obtained simply by substracting the lone-pair moment from the ion-pair moment. This imaginary titration would correspond with the curve $\overline{\mathrm{OP}}$ in Fig. 3. When two ion-pairs in each molecule are formed by titration, the disulfonate has no net dipole moments and this process is shown as a falling curve $\overline{\mathrm{PR}}$, where if the volume increase of solution in the cell is negligible, the electrical capacity at the second equivalence point would be reduced to that of a free diamine solution.

Second, we will consider the other imaginary case where only form II exists in the solution. The vector angle between the two ion-pair moments in form II can be calculated as 67°08′ by using the bond lengths of C-C and C-N as 1.521±0.010 Å and 1.457±0.010 Å, respectively, and the bond angles of C-C-N and C-N-C as 110°03′±1.0° and 114°00′±1.0°, respectively.[8] According to Higashi's equation, the change in electrical capacity of the solution is proportional to the square of dipole moment of the solute. Thus, if only form II existed in the solution, the imaginary titration curve after the first equivalence point would still elevate like $\overline{\mathrm{PT}}$.

However, experimental results differed from these imaginary cases. The experimental titration curve followed from $\overline{\mathrm{OP}}$ to $\overline{\mathrm{PQ}}$, and it seemed possible to clarify in the ratios of the forms I, II, and III from the titration curve. To calculate the ratio of form II to the total diamine from the titration curve, the following three hypotheses will be necessary:

(1) The magnitude of two ion-pair moments should be equal.

(2) Ion-pair should be formed towards the direction of lone-pair moment of the nitrogen atom.

(3) The inversion or reversal change of conformation of the molecule would not occur in the process of titration. If these hypotheses were to be correct, the net dipole moment of free N,N′-dimethylpiperazine would be expressed generally as

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

where μ_x is the lone-pair moment of nitrogen atom and θ is the apparent vector angle between the two lone-pair moments. Then the net dipole moments at the first and second equivalence points are written respectively as

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

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

where μ_y is the ion-pair moment. Using these three equations (1) to (3), θ can be written as

$$\cos\theta = \frac{\mu_0^2+\mu_2^2-2\mu_1^2}{2(\mu_1^2-\mu_0\cdot\mu_2)} \tag{4}$$

When the difference of electrical capacity of the free diamine solution and of the solutions at the first and second equivalence points from that of pure dioxane solvent are expressed as ΔC_0, ΔC_1, and ΔC_2, respectively, the following equations are obtained:

$$\mu_0^2 = k\cdot\Delta C_0 \tag{5}$$

$$\mu_1^2 = k\cdot\Delta C_1 \tag{6}$$

$$\mu_2^2 = k\cdot\Delta C_2 \tag{7}$$

where k is the proportional constant. Substituting equations (5), (6), and (7) into (4), the equation (8) is derived.

$$\cos\theta = \frac{\Delta C_0+\Delta C_2-2\Delta C_1}{2(\Delta C_1-\sqrt{\Delta C_0\cdot\Delta C_2})} \tag{8}$$

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

Thus, without calculating the values of μ_0, μ_1, and μ_2, the apparent vector angle, θ, between two ion-pair moments can be obtained directly from the values of ΔC_0, ΔC_1, and ΔC_2 on the titration curve.

Consideration will now be made on how to obtain the molar fraction of form II, P_B, in the solution from the value of θ obtained. N,N′-Dimethylpiperazine takes three conformations in the solution and the dipole moment of the equilibrium mixture of three chair forms is generally given by

$$\mu_{\mathrm{app.}}^2 = N_1 \cdot \mu_{\mathrm{I}}^2 + N_2 \cdot \mu_{\mathrm{II}}^2 + N_3 \cdot \mu_{\mathrm{III}}^2 \tag{9}$$

where N_i is the molar fraction and $\sum_{i=1}^{3} N_i = 1$. Since $\mu_{\mathrm{I}} = \mu_{\mathrm{III}}$, it can be regarded dielectrically that there exist only two types of conformations I or III and II, which are now called A and B groups. The dipole moment of the equilibrium mixture at the second equivalence point, μ_2, will satisfy the following equation.

$$\mu_2{}^2 = P_B \cdot \mu_{B_2}^2 + (1 - P_B) \cdot \mu_{a_2}^2 \tag{10}$$

From equation (3), $\mu_{A_2}{}^2$ and $\mu_{B_2}{}^2$ are written as

$$\mu_{A_2}^2 = 2\mu_y{}^2(1+\cos\theta_A) \tag{11}$$

$$\mu_{B_2}^2 = 2\mu_y{}^2(1+\cos\theta_B) \tag{12}$$

where θ_A and θ_B are the intramolecular bond angle between two ion-pairs in each group, P_B is the molar fraction of B, and the suffix 2 means the second equivalence point. Introducing equations (11) and (12) into (10), the next relation is obtained:

$$\mu_2{}^2 = 2\mu_y{}^2[P_B(\cos\theta_A - \cos\theta_B) + 1 + \cos\theta_B] \tag{13}$$

By solving equation (13) on P_B, it can be written as

$$P_B = \frac{u_2{}^2/2u_y{}^2 - 1 - \cos\theta_B}{\cos\theta_A - \cos\theta_B} \tag{14}$$

and, utilizing equation (3), P_B can be rewritten as

$$P_B = \frac{\cos\theta - \cos\theta_B}{\cos\theta_A - \cos\theta_B} \tag{15}$$

The apparent vector angle of the equilibrium mixture, θ, found from the titrated curve at 30° was 147°03′.

By substituting $\theta_B = 67°08'$, $\theta_A = 180°$, and $\theta = 147°03'$ into equation (15), P_B, the molar fraction of form II was calculated as 11.6% at 30°. This value closely agreed with the value of 10.4% which Allinger, *et al.*[6] had determined from the measurement of the dipole moment of free N,N′-dimethylpiperazine in benzene at 25°.

Allinger, *et al.*[6] showed the method of determining the molar fraction of forms I and III, P_{I} and P_{III}, from the theoretical entropy differences between form I and III. Following their treatment, the values of $P_{\mathrm{I}} = 0.0880$, $P_{\mathrm{III}} = 0.004$, and $P_{\mathrm{II}} = P_B = 0.116$ at 30° in dioxane were obtained. The enthalpy difference between form I and II was calculated as 1.6 kcal/mole. This value of 1.6 kcal/mole at 30° in dioxane is about the same as the value of 1.7±0.4 kcal/mole at 25° in benzene obtained by Allinger, *et al.*[6]

Finally, although a few people have recognized the importance of this dielectrometric titration method[9] from the early stage of its appearance, it is still felt that the advantage of this method is not familiar. It should be noted that the ion-pair moments, which are formed by the titration of acid with base or *vice versa* in aprotic solvents are so large that accurate titration curves can be obtained with a relatively simple apparatus, and accurate conformational informations can be found without using accurate absolute values of dipole moments of compounds.

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[9] M.M. Davis, "Acid-Base Behavior in Aprotic Organic Solvents," National Bureau of Standards Monograph 105, Washington, D.C., 1968, p. 134.