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Conformational Analysis of Di-tertiary Amine in Aprotic Solvent by Dielectrometric Titration. III.[1] A Molecular Orbital Study on the Structure of Protonated N,N′-Dimethylpiperazine[2]

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The relative stability of equatorial *vs.* axial for methyl groups on nitrogens in diprotonated N,N′-dimethylpiperazine was determined from the total energy differences of six possible conformers using the Unrestricted Open Shell SCF-MO INDO Method, and the result was in accord with the observed value of our previous paper obtained from the curve of dielectrometric titration. An equatorial methyl group bonded to the chair form piperazine ring was more stable than that of an axial position by an amount of 1.38 kcal/mol from computer analysis, which was fairly coincident with the observed value of 1.6 kcal/mol obtained from the dielectrometric titration.

Keywords——conformational analysis; dielectrometric titration; unrestricted open shell SCF-MO INDO method; diprotonated N,N′-dimethylpiperazine; size of lone pair; equatorial *vs.* axial preference; total energy; repulsion energy; molar ratio of conformers

A study of the equatorial (eq.) *vs.* axial (ax.) energetic preference for methyl group on nitrogen in piperazine ring is a problem of considerable current interest and has been investigated by many methods, leading to widely differing results.[4–8]

In the preceding paper,[1] we decided the molar existing ratio of conformers of diprotonated N,N′-dimethylpiperazine in dioxane at room temperature by analyzing the curves of dielectrometric titration. Assuming the equilibrium mixture of three chair conformations (I, II, III) with two methyl groups at eq.-eq., eq.-ax., and ax.-ax. positions, the relative existing ratio of each conformer was calculated to be 88.0%, 11.6%, and 0.4% respectively, which was in good agreement with those of Allinger, *et al.*[4]

However, there exists a clear difference in measuring conditions; one was calculated from the dipolemoment of the salt form of diamine di-tertiarybutylbenzene sulfonate in dioxane solution, and the other was calculated from that of free diamine in benzene solution. If both results are reliable, this good agreement suggests that no conformational change occurs in the process of dielectrometric titration.

For the purpose of supporting the validity of our dielectrometric titration method, six possible conformers of di-protonated N,N′-dimethylpiperazine were chosen for this report as shown in Fig. 1, and the total and repulsion energies of each conformer were calculated by using the Unrestricted Open Shell SCF-MO INDO Method.

From the calculated total energies the following facts were found. Conformer I was the most stable, II the second, and III was the third in order. The differences in total energies

1) Part I: I. Horikoshi, M. Morii, and N. Takeguchi, *Chem. Pharm. Bull.* (Tokyo), **23**, 754 (1975).
2) Presented at the 96th Annual Meeting of the Pharmaceutical Society of Japan at Nagoya, Apr. 1976.
3) Location: *3190 Gofuku, Toyama, 930, Japan.*
4) N.L. Allinger, J.G.D. Carpenter, and F.M. Karkowski, *J. Am. Chem. Soc.*, **87**, 1232 (1965).
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6) V.M. Gittins, P.J. Heywood, and E. Wyn-Jones, *J.C.S.* Perkin II, **1975**, 1642.
7) E.L. Eliel and F.W. Vierhapper, *J. Am. Chem. Soc.*, **97**, 2424 (1975).
8) F.A.L. Anet and Issa Yavari, *Tetrahedron Letters*, **25**, 2093 (1976).

between I and II, and between II and III were calculated to be 1.38 kcal/mol in each case, and the molar existing ratios of I, II, and III at 30° were 81.6%, 16.4%, and 0.8%, respectively. The ratios of III and of the other three conformers were all negligible. These results closely agreed with the observed values obtained from the dielectrometric titration.

Method

The method used in our calculation is the Unrestricted Open Shell SCF-MO INDO Method, developed by Pople, *et al.*,[9] details of which are not described here. This method is suitable for such molecules as radicals and ions. The parameters reported by Pople, *et al.* were used in the calculation without any alteration. The calculations were carried out using FACOM 230 45S in the computer center of Toyama University.

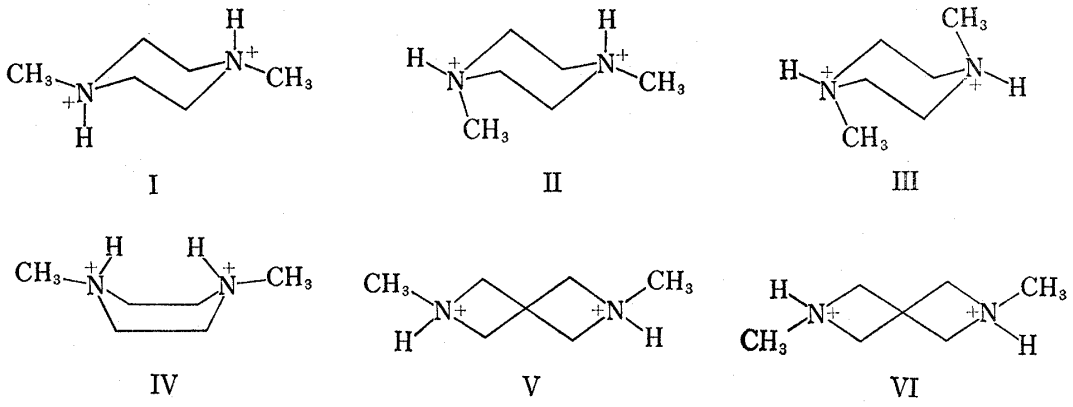
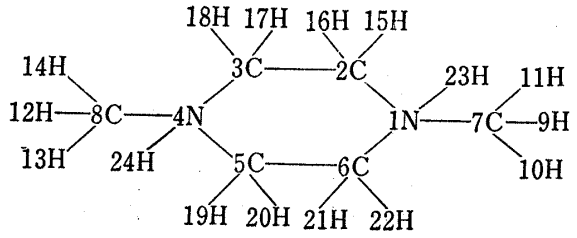


Fig. 1. Predictions for Six Possible Conformations of Diprotonated N,N′-Dimethylpiperazine

TABLE I. Coordinates of Six Possible Conformations of Diprotonated N,N′-Dimethylpiperazine



Atom	X	Y	Z
Chair form piperazine ring			
1N	1.2660	0.6062	0.0000
2C	0.7605	0.0000	−1.2247
3C	−0.7605	0.0000	−1.2247
4N	−1.2660	−0.6062	0.0000
5C	−0.7605	0.0000	1.2247
6C	0.7605	0.0000	1.2247
7C (eq.)	2.7269	0.5890	0.0000
9H	3.0804	−0.4495	0.0000
10H	3.0986	1.1018	0.8957
11H	3.0986	1.1018	−0.8957
7C (ax.)	0.9866	2.0402	0.0000
9H	−0.0985	2.2014	0.0000
10H	1.4243	2.4980	0.8957
11H	1.4243	2.4980	−0.8957
8C (eq.)	−2.7269	−0.5890	0.0000
12H	−3.0804	0.4495	0.0000

9) J.A. Pople, D.L. Beveridge, and P.A. Doboch, *J. Chem. Phys.*, **47**, 2026 (1967).

Atom	X	Y	Z
13H	−3.0986	−1.1018	0.8957
14H	−3.0986	−1.1018	−0.8957
8C (ax.)	−0.9866	−2.0402	0.0000
12H	0.0985	−2.2014	0.0000
13H	−1.4243	−2.4980	0.8957
14H	−1.4243	−2.4980	−0.8957
15H	−1.1224	−1.0333	−1.2932
16H	1.1224	0.5722	−2.0808
17H	−1 1224	1.0333	−1.2932
18H	−1.1224	−0.5722	−2.0878
19H	−1.1224	1.0333	1.2932
20H	−1.1224	−0.5722	2.0878
21H	1.1224	−1.0333	1.2932
22H	1.1224	0.5722	2.0878
23H (eq.)	0.9732	1.5937	0.0000
(ax.)	2.2900	0.4955	0.0000
24H (eq.)	−0.9732	−1.5937	0.0000
(ax.)	−2.2900	−0.4955	0.0000
Boat form piperazine ring			
4N	−1.2660	0.6062	0.0000
8C (eq.)	−2.7269	0.5890	0.0000
12H	−3.0804	−0.4495	0.0000
13H	−3.0986	1.1018	0.8957
14H	−3.0986	1.1018	−0.8957
17H	−1.1224	−1.0333	−1.2932
18H	−1.1224	0.5722	−2.0878
19H	−1.1224	−1.0333	1.2932
20H	−1.1224	0.5722	2.0878
24H	−0.9732	1.5937	0.0000
Skew boat piperazing ring			
1N	1.4522	0.0000	0.0000
2C	0.6630	0.3726	−1.1666
3C	−0.6630	−0.3726	−1.1666
4N	−1.4522	0.0000	0.0000
5C	−0.6630	0.3726	1.1666
6C	0.6630	−0.3726	1.1666
7C	2.3747	1.0792	0.3447
9H	1.8035	1.9714	0.6296
10H	3.0066	0.7659	1.1849
11H	3.0066	1.3109	−0.5216
8C (*cis*)	−2.3747	1.0792	−0.3447
12H	−1.8035	1.9714	−0.6296
13H	−3.0066	0.7659	−1.1849
14H	−3.0066	1.3109	0.5216
8C (*trans*)	−2.3747	−1.0792	0.3447
12H	−1.8035	−1.9714	0.6296
13H	−3.0066	−0.7659	1.1849
14H	−3.0066	−1.1309	−0.5216
15H	0.4712	1.4525	−1.1440
16H	1.2205	0.1192	−2.0768
17H	−0.4712	−1.4525	−1.1440
18H	−1.2205	−0.1192	−2.0768
19H	−0.4712	1.4525	1.1440
20H	−1.22.5	0.1192	2.0768
21H	−0.4712	−1.4525	1.1440
22H	1.2205	−0.1192	2.0768
23H	2.0229	−0.8168	−0.2609
24H (*cis*)	−2.0229	−0.8168	0.2609
(*trans*)	−2.0229	0.8168	−0.2609

In order to perform calculations of total and repulsion energies of di-protonated diamine, it is necessary to know the coordinates of all atoms in the molecule. Prior to calculation, six possible conformers of the di-protonated diamine were assumed to exist as shown in Fig. 1. Conformers I, II, and III have all chair form piperazine ring to which two methyl groups were bonded to nitrogens with eq.–eq., eq.–ax., and ax.–ax. positions, respectively. Conformer IV has a boat form to which two methyl groups bonded with eq.–eq. position. Conformers V and VI have both skew-boat form in which the four atoms including two carbons and two nitrogens in piperazine ring take coplanar position and two methyl groups take *cis* and *trans* configurations, respectively as shown in Fig. 1. Furthermore, all methyl groups in the six isomers were assumed to take a staggered form against the piperazine ring.

The coordinates of atoms were calculated from the results of electron diffraction analysis reported by Davis and Hassel.[10] As the data of H–C–H angle are lacked in their report, the bond angles of methyl and of methylene were all assumed as a tetrahedral angle. The N^+—H bond length was assumed to be equal to that of N–H in piperazine and this hydrogen atom was also assumed to keep an equal distance from the nearest three carbon atoms. The coordinates of six conformers of di-protonated N,N′-dimethylpiperazine were shown in Table I.

Results and Discussion

Table II shows the total energy (E_t) and the repulsion energy (E_r) for six possible conformers of di-protonated N,N′-dimethylpiperazine. The E_t is generally given by the equation (1)[11]

$$E_t = E_e + E_c \tag{1}$$

where

$$E_e = \sum\varepsilon_i + \frac{1}{2}P_iU(i) + \sum P_{ij}\mathrm{BETA(ij)} - \frac{1}{2}\sum\sum(\mathrm{AP}_i\cdot Z_j' - \mathrm{AP}_j\cdot Z_i')\cdot G(ij) \tag{2}$$

and

$$E_c = \sum_{A>B}\sum Z_A\cdot Z_B/R_{AB} \tag{3}$$

E_r is expressed by the following equation (4),[11]

$$E_r = E_c - \frac{1}{2}\sum\sum(\mathrm{AP}_i\cdot Z_j' - \mathrm{AP}_j\cdot Z_i')\cdot G(ij) \tag{4}$$

Table II. Total Energies (E_t), Repulsion Energies (E_r), and These Energy Differences (ΔE_t, ΔE) calculated for Six Possible Conformations of Di-protonated N,N′-Dimethylpiperazine

No.	Ring Conformation	Disposition of N–CH_3 Bonds	E_t (eV/mol)	ΔE_t (eV/mol)	E_r (eV/mol)	ΔE_r (eV/mol)
I	chair form	eq, eq	−2053.07	0.00	416.00	0.00
II	chair form	eq, ax	−2053.01	0.06	419.01	3.01
III	chair form	ax, ax	−2052.95	0.12	412.58	5.58
IV	boat form	eq, eq	−2052.68	0.39	417.87	1.78
V	skew-boat form	*cis*	−2052.94	0.13	417.74	1.74
VI	skew-boat form	*trans*	−2052.94	0.13	416.89	0.89

ΔE_t and ΔE_r are the difference in the energy from the corresponding value for conformer I.

E_t is a sum of the total electronic energy and of the core-core repulsion energy among atoms and is utilized to estimate the stability of molecules. The relative stability of conformers in the ground state can be expressed quantitatively with the total energy differences among conformers, ΔE_t, in Table II. On the other hand, the E_r is a sum of the total core-

10) M. Davis and O. Hassel, *Acta Chem. Scand.*, **17**, 1181 (1963).
11) Osamu Kikuchi, "Molecular Orbital Theory," Koudan-sha Co., Tokyo, 1971, p. 201.

core repulsion energy and of the total inter-electron repulsion energy belonging to each atom. The differences of the repulsion energies among conformers, ΔE_r, which are shown in Table II express only a degree of the steric hindrance of intramolecular structure qualitatively. The relative molar existing ratio was calculated from the data on ΔE_t, following the same method used by Allinger, *et al.*[4]

From the values of ΔE_t for six conformers, the following conclusion may be drawn: 1) The conformer I is the most stable one because of the smallest value of ΔE_t and ΔE_r. The relative stability of other conformers are in the order of II, III, VI, V, and IV. This result proved the validity of our assumption in the calculation of previous report that there exist only three chair forms for piperazine ring, and other conformers are negligible in dioxane solution. 2) The ΔE_t between I and II and that between II and III have an equal value of 1.38 kcal/mol (0.06 eV/mol), which means there exists no interaction between two methyl groups, and the contribution of each methyl group to E_t is additive. The value of 1.38 kcal/mol corresponds to the enthalpy difference of methyl group between eq. and ax. position and it agreed with the observed value of ours (1.6 kcal/mol)[1] and of Allinger's (1.7 kcal/mol)[4]. 3) The *cis* and *trans* skew-boat forms of V and VI are more stable than the boat form of IV, but those relative molar ratios of IV, V, and VI are found to be negligible.

Thus, the conformational preferency of six possible isomers in di-protonated N,N'-dimethylpiperazine is similar to that of cyclohexane derivatives.[12] The relative molar existing ratio of three conformers (I, II, and III) at 30° were calculated to be 81.6%, 16.4%, and 0.8%, respectively from the present data. The values of ΔE_r of conformers II and III have particlarly large steric effect than those of the other three conformers IV, V, and VI. However, it is speculated that this effect could not be large enough to exchange the relative stability of six conformers described above.

As described in the introduction, there exists a clear methodological difference between Allinger's experiment and our dielectrometric titration; the former is concerned with the preferred conformations of free diamine and the latter is with that of the salt form of diamine di-sulfonate. A fundamental difference between them is the presence of two ion pairs on piperazine ring, and we have therefore particularly been interested in the space requirement of ion pairs and their influences on the configuration of methyl group. The problem of the so-called "Size" of the lone pair on nitrogens has been discussed by many investigators.[13–15] In this case, the "Size" means the eq. *vs.* ax. energetic preferency of radicals such as lone pair, hydrogen, methyl group. At present, it is widely recognized that the methyl and the hydrogen are both "bigger" than the lone pair on nitrogen. From the good agreement of results of molecular orbital calculation with that of dielectrometric titration, the size of protonated hydrogen is considered to be nearly equal to a normal hydrogen, and the existence of ion pair ($R_3N^+H\cdots\cdots O_3S^-$-$\phi$-R) does not influence the preferred configuration of other radicals.

During the course of this work, we learned that ^{13}C nuclear magnetic resonance spectrum measurements on di-protonated N,N'-dimethylpiperazine give an enthalpy difference of 2.96 kcal/mol for the ax.-eq. N-methyl equilibrium,[8] though this large value was measured in the mixed solution of 98% H_2SO_4 and pentane, not in the dilute solutions of ours or of Allingers.

In conclusion, as to usefulness and reliability of the dielectrometric titration method in conformational analysis, we found a supporting evidence from computer analysis. Further investigation for other heterocyclic derivatives are at present being carried on.

12) *a*) Kurt Mislow, "Introduction to Stereochemistry," W.A. Benjamine, INC., New York, N.Y., 1966, p. 77; *b*) E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.B. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N.Y., 1965, p. 439.
13) N.L. Allinger and J.C. Tai, *J. Am. Chem. Soc.*, **87**, 1227 (1965).
14) J.B. Lambert, R.E. Carhart, and P.W.R. Corfield, *J. Am. Chem. Soc.*, **91**, 3356 (1969).
15) M.J. Cook, A.R. Katritzky, and M.M. Manas, *J. Chem. Soc.*, (*B*) **1971**, 1330.