2-Dimethylamino-5-phenylpyrazine——Pale yellow needles of mp 96—98° (MeOH). *Anal.* Calcd. for $C_{12}H_{13}N_3$: C, 72.33; H, 6.58; N, 21.09. Found: C, 72.30; H, 6.57; N, 21.27. MS *m/e*: 199 (M^+). UV $\lambda_{max}^{95\% EtOH}$ nm (log ε): 223 (3.95), 293 (4.35), 362 (3.90). NMR ($CDCl_3$) δ: 3.20 (6H, s).

2-Dimethylamino-3,5-diphenylpyrazine——Pale yellow needles of mp 95—96° (MeOH). *Anal.* Calcd. for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.41; 6.31; N, 15.40. MS *m/e*: 275 (M^+). UV $\lambda_{max}^{95\% EtOH}$ nm (log ε): 231 (4.21), 309 (4.22), 368.5 (3.96). NMR ($CDCl_3$) δ: 2.82 (6H, s).

2-Dimethylamino-3,6-diphenylpyrazine——Yellow prisms of mp 79° (EtOH–H_2O). *Anal.* Calcd. for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.67; H, 6.20; N, 15.18. MS *m/e*: 275 (M^+). UV $\lambda_{max}^{95\% EtOH}$ nm (log ε): 235.5 (4.26), 270 (4.18), 372.5 (4.07). NMR ($CDCl_3$) δ: 2.84 (6H, s).

2,6-Bis-dimethylamino-3,5-diphenylpyrazine——Pale yellow prisms of mp 160° (MeOH). *Anal.* Calcd. for $C_{20}H_{22}N_4$: C, 75.44; H, 6.96; N, 17.60. Found: C, 75.24; H, 7.05; N, 17.77. MS *m/e*: 318 (M^+). UV $\lambda_{max}^{95\% EtOH}$ nm (log ε): 242 (4.25), 331.5 (4.07), 381 (4.20). NMR ($CDCl_3$) δ: 2.83 (6H, s).

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On the Relationship between C-13 Nuclear Magnetic Resonance Chemical Shift and Stability of Molecule in Methyl-Substituted N,N-Dimethylpiperidinium Salts[1]

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Among positional and conformational isomers of mono- and di-methyl derivatives of N,N-dimethylpiperidinium ions, a linear relationship was found between the sum of C-13 nuclear magnetic resonance chemical shifts of all the constituent carbons of molecule and the total energy of molecule calculated by MINDO/2 method.

Keywords——methylpiperidinium salts; total C-13 chemical shift; total energy; MINDO/2; conformation

Attention has recently been paid to the correlation of the C-13 NMR chemical shifts of all the carbons constituting the molecule (total chemical shift, $\sum_n \delta_n$) with the conformational stability of molecule.[3-7] Although a linear relationship has been found in some classes of compounds such as methylcyclohexanes,[3] cyclohexanols,[4,5] and chain alkanes,[6] its applicability to stereochemical problems has not fully been demonstrated. This paper shows the correlation between the total chemical shift and the configurational and/or conformational

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1) This paper constituents Part VII of a series entitled "Stereochemistry in Solution." Part V: M. Tsuda and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **18**, 2499 (1970). Part VI: *idem*, *ibid.*, **22**, 809 (1974).

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3) A.S. Perlin and H.J. Koch, *Canad. J. Chem.*, **48**, 2639 (1970).

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stability of N,N-dimethyl derivatives of methylpiperidines. As far as isomers are concerned, the stability of molecule is represented by its total energy; a high total energy reflects instabilization due to non-bonding repulsive interaction between constituent CH functions.

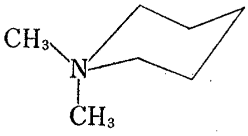
Experimental

The compounds used in the present study were N,N-dimethyl quaternary ammonium iodides of 2-, 3-, and 4-methylpiperidines and those of *cis* and trans isomers of six isomeric dimethylpiperidines.[8] They were chosen as the model compounds since the geometries of molecule can easily be drawn without ambiguity and, in addition, since a series of stereoisomers were available to test the closeness of the correlation. Carbon-13 NMR spectra were measured in 10—50% aqueous solution at room temperature with a JEOL spectrometer (JMN-PS-100/PFT-100) operating at 25.2 MHz. The chemical shift was almost independent of the concentration or the kind of counter anion in aqueous solution as far as we examined. The shift values were calibrated in reference to the chemical shift of the tetramethylsilane. Total energies were calculated by the MINDO/2 MO method.

Results and Discussion

The sums of the chemical shift values of all the carbons of each molecule are shown in Table I. In the third column of the table are shown the differences in the total chemical shift relative to that of the 3-methyl isomer for monomethylpiperidinium ions and to that of the *cis*-3,5-dimethyl isomer for dimethylpiperidinium ions, respectively. These reference molecules do not involve any gauche interactions between the substituent C-methyl groups

Table I

	 $\}(-CH_3)_n$ $n=0-3$ N,N-Dimethyl derivative of[a]	Total chemical shift[b] (ppm)		Total energy[c] (a.u.)	
		$\sum_n \delta_n$	$\Delta\sum_n \delta_n$	T.E.	ΔT.E.
[I]	Piperidine [$C_7H_{16}N^+$]	306		−49.4381	Reference
	Methylpiperidines [$C_8H_{18}N^+$]				
[II]	3(eq)-	346	Reference	−55.2997	−5.8616
[III]	4(eq)-	346	0	−55.2993	−5.8612
[IV]	2(eq)-	335	11	−55.2900	−5.8519
	Dimethylpiperidines [$C_9H_{20}N^+$]				
[V]	3(eq), 5(eq)-*cis*-	394	Reference	−61.1611	−11.7230
[VI]	2(eq), 4(eq)-*cis*-	376	18	−61.1510	−11.7129
[VII]	2(eq), 5(eq)-*trans*-	374	20	−61.1514	−11.7133
[VIII]	2(eq), 3(eq)-*trans*-	372	22	−61.1452	−11.7071
[IX]	2(ax), 5(eq)-*cis*-	361	33	−61.1438	−11.7057
[X]	2(ax), 4(eq)-*trans*- (2(eq), 4(ax)-*trans*-)	360	34	−61.1439 (−61.1361)	−11.7058 (−11.6980)
[XI]	2(eq), 6(eq)-*cis*-	355	39	−61.1415	−11.7034
[XII]	3(eq), 4(ax)-*cis*-	348	46	−61.1391	−11.7010
[XIII]	2(ax), 3(eq)-*cis*-	347	47	−61.1379	−11.6998
[XIV]	2(eq), 6(ax)-*trans*-	338	56	−61.1344	−11.6963
	Trimethylpiperidine [$C_{10}H_{22}N^+$]				
[XV]	2(eq), 4(eq), 6(eq)-*cis,cis*-	375		−67.0023	−17.5642

a) The salts used were iodides. (eq): equatorial; (ax): axial.
b) The sum of the chemical shifts of all the constituent carbons calibrated to that of the carbons of tetramethylsilane.
c) Calculations were made on the basis of the geometry of the molecule using the Dreiding Molecular Models.

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8) M. Tsuda and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **18**, 2499 (1970).

and the skeletal constituents of N,N-dimethylpiperidine ring. In the last two columns of the table are shown the total energies of molecule and the energy-differences referred to that of N,N-dimethylpiperidinium ion. Figure 1 shows the relationship between the total energy and the total chemical shift of the derivatives, which indicates a linear proportionality between the total energy and the total shift of the reference compounds, I, II, and V. Thus, one additional methylene brought about an energy gain of –5.86 a. u. and an additional shielding of 44 ppm in the total shift (II referred to I and V referred to II). In contrast, it is of interest that increase in gauche interactions in the isomeric molecules did not bring about so large an energy gain (instabilization) but produce a remarkable increase in shielding in the total shift. The C-13 chemical shift seems to be very sensitive to changes in non-bonding repulsive interactions of the constituent C-H functions.[9] In order to examine the effect of the non-bonding interaction on the total shift of molecule, the total energy of isomers were plotted on an expanded scale of the ordinate *versus* the total shift for the ten kinds of dimethyl isomers ($C_9H_{20}N^+$). This plot is shown in Fig. 2, and reveals a linear proportionality between these values. It is worth emphasizing that the changes in total chemical shift among the isomers sensitively and quantitatively reflect the non-bonding repulsive interactions involved in the molecules. It is of interest to note that the linear relationship shown in Fig. 2 predicts the conformation of 2,4-*trans*-dimethyl derivative (X) to be the 2-axial-4-equatorial structure but not the 2-equatorial-4-axial one.[7]

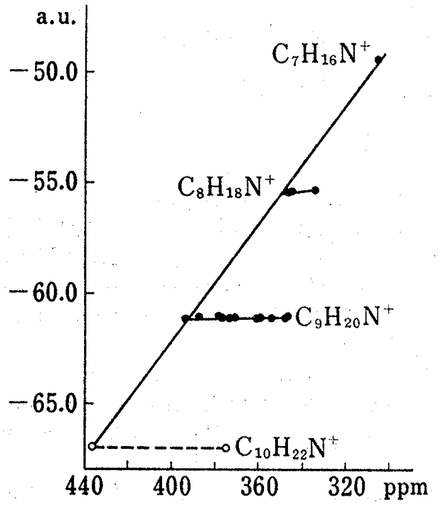

Fig. 1. Plots of Total Energy Calculated by MINDO/2 Method *versus* Sum of Chemical Shifts (from TMS) of All the Constituent Carbons of Methyl-Substituted N,N-Dimethylpiperidinium Iodides

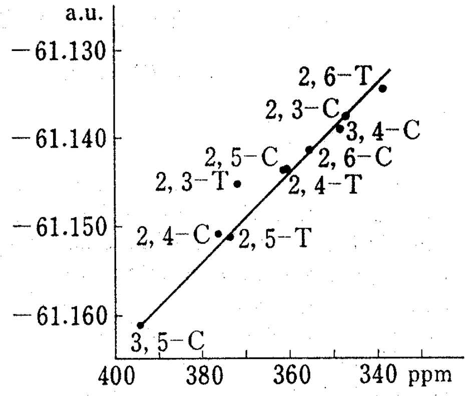

Fig. 2. Plot of Total Energy *versus* Sum of the Chemical Shifts of All the Constituent Carbons of N,N-Dimethyl-dimethylpiperidinium Iodides ($C_9H_{20}N^+I^-$)

(The ordinate is more expanded than that in Fig. 1.)

Even though a linear correlation was found for the total chemical shift, the value for the individual carbons are not directly correlated with any MO parameter of the carbon concerned.[6] The electronic perturbation induced by non-bonding interaction at a certain locus in the molecule probably decreases through successive chemical bonds, just as does the inductive effect.

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