[Chem. Pharm. Bull. 22(4) 809—817 (1974)]

UDC 547.551.2.03 : 543.422.25

Solvent- and Concentration-Dependent Shifts in Proton Magnetic Resonance of Quaternary Ammonium Salts

Mitsuhiro Tsuda, Masako Tsuda, Yutaka Kawazoe,[1a]
Alan F. Casy,[1b] and Mahmoud M.A. Hassan[1c]

National Cancer Center Research Institute,[1a] School of Pharmacy, Liverpool Polytechnic,[1b] and Faculty of Pharmacy, University of Riyadh[1c]

(Received August 1, 1973)

Proton magnetic resonance spectra of some methylpiperidinium salts were taken in various solvents and at various concentrations. Chemical shifts of the N-methyl protons were strongly dependent on solvent and concentration. Those at the infinite dilution were dependent on solvent but not on the counter anion, indicating that the free cation exists as a solvated form. Those of the ion-paired forms were also dependent on solvent. The effects of the solvent and counter ion on the chemical shift are discussed.

Proton magnetic resonance spectroscopy has been proved a useful tool for the conformational analysis of flexible alicyclic compounds in solution. The chemical shift of protons of the ring and substituents strongly reflect not only the electronic and steric structure of the molecule, but also intermolecular or interionic interactions with the solvent and solute molecules or ions present in the solution. In the course of our study of the stereochemistry of quaternary cyclic amines in solution,[2,3] it was noticed that the proton chemical shifts of quaternary piperidinium salts were significantly dependent on the kind of solvent used for the measurement. This paper deals with chemical shift changes caused in N,N-dimethylpiperidinium ions by intermolecular interaction in solution.

In general, it has been proposed from various physical means[4–6] that quaternary ammonium salts exist in solution in an equilibrium between the free (or solvated) ions, R_4N^+ and X^-, and the ion-pair, $R_4N^+X^-$, as shown below.

$$R_4N^+ + X^- \overset{Ka}{\rightleftarrows} R_4N^+X^- \qquad (1)$$

The association constant, Ka, may be dependent on the nature of the ions and solvent.[7–9] In nuclear magnetic resonance (NMR) spectroscopy, on this assumption, the observed chemical shift, δ_{obs}, of the ammonium ion is expressed by the following equation, where δ_i is the chemical shift of the free (or solvated) ion, δ_p is that of the ion-paired species, and α is the mole fraction of the ion-pair in the solution examined.

$$\delta_{obs} = (1-\alpha)\delta_i + \alpha\delta_p$$

The derivatives used in the present study are suitable to evaluate the dependence of chemical shift on intermolecular interactions such as ion-pairing and solvation, separately from

1) Location: *a) 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104, Japan,* to whom correspondence should be addressed; *b) Liverpool, L3 3AF, U. K.; c) Riyadh, Saudi Arabia.*
2) M. Tsuda and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **18**, 2499 (1970) and literatures cited therein.
3) A.F. Casy, "PMR Spectroscopy in Medical and Biological Chemistry," Academic Press, London, 1971, p. 384 and literatures cited therein.
4) P.L. Mercier and C.A. Kraus, *Proc. Nat. Acad. Sci.*, **41**, 1033 (1955).
5) R.L. Buckson and S.G. Smith, *J. Phys. Chem.*, **68**, 1875 (1964).
6) D.W. Larsen and A.C. Wahl, *Inorg. Chem.*, **4**, 1281 (1965).
7) J.B. Hyne, *J. Am. Chem. Soc.*, **85**, 304 (1963).
8) S. Winstein, G. Savedoff, S. Smith, I.D.R. Stevens, and J.S. Gall, *Tetrahedron Letters*, **1960**, 24.
9) G. Fraenkel and J.P. Kim, *J. Am. Chem. Soc.*, **88**, 4203 (1966).

the effect due to change in the electronic and steric structure of the cation itself. Such is not the case for amines having acyclic side chains because their rotamer population is significantly dependent on the solvent, while the tetramethylammonium ion (no rotational factor) gives only a limited amount of information since it provides only one proton magnetic resonance (PMR) signal. All derivatives used in this study, *e.g.*, N,N,2,*cis*-4,*cis*-6-pentamethylpiperidinium ion (I), display pronounced conformational preferences, hence all the protons are effectively fixed sterically except those of substituent C-methyl and N-methyl groups which, nevertheless, are held in axial or equatorial environments. Hence all intramolecular electric and magnetic shielding effects experienced by each proton in the cation may be regarded as constant and unaffected by the nature of the solvent and concentration of the solute. Since cation aggregation is improbable under the conditions of the present study, it may be assumed that the variations of chemical shift of protons in these ions caused by change of solvent, counter ion, and concentration, are due to the electric and/or magnetic field effects of changing the extents of ion-pairing and solvation.

Experimental

Compounds——The compounds used are listed in Table I. N,N,2,*cis*-4,*cis*-6-Pentamethylpiperidinium iodide (I) was prepared by catalytic hydrogenation of 2,4,6-trimethylpyridine methiodide over PtO_2 under an ordinary pressure of H_2 at room temperature, followed by quaternization with methyl iodide. The iodide was once changed into the hydroxide through an Dowex-1 (OH^- form) column, followed by neutralization with hydrochloric acid and *p*-toluenesulfonic acid to afford the chloride and tosylate, respectively. The iodide melted at 212—214°. Synthetic methods and physical constants of the other compounds were already reported.[2)]

NMR Measurements——Spectra were taken with a JNM-4H-100 spectrometer, operating at 100 MHz at 23°. Chemical shifts in organic solvents are presented in δ (ppm) calibrated from the internal signal of tetramethylsilane (TMS) and those in D_2O were calibrated from the internal signal of sodium dimethylsilapentasulfonate (DSS).

Result

General Profile of Solvent-Dependent Shift

The chemical shift of N-methyl protons were strongly dependent on the kind of the solvent used, whereas those of protons distant from the cationic nitrogen were not markedly affected. The chemical shifts of equatorial and axial N-methyl protons of the derivatives measured in $CDCl_3$, D_2O, and CD_3SOCD_3 at a concentration of about 0.2M are shown in Table I. Considerable differences were found between chemical shifts measured in $CDCl_3$ and those in D_2O or CD_3SOCD_3 with both axial and equatorial N-methyl resonances moving up-field in the more polar solvents. Shifts were larger for equatorial groups and this fact is probably related to the greater accessibility of equatorial as compared with axial substituents to solvent molecules. The magnitude of the shift difference depends on the extent of substitution at positions alpha to the cationic nitrogen, *i.e.*, on the steric bulk around nitrogen. As seen in Table II, whereas the sum of the shift differences, $\Delta\delta$, of the protons of axial and equatorial N-methyl groups was almost constant in all the derivatives examined unless they had equatorial C-methyl groups in the α-position, it was reduced by substitution of an α-equatorial methyl group and further reduced when nitrogen was flanked by a pair of α-methyl substituents. The reduction in shielding casued by α-equatorial methyl was similar for axial and equatorial N-methyl as expected from the similar (*gauche*) α-Me/eq.-N-Me and α-Me/ax.-N-Me spatial relationships. When axial α-methyl was present, however, only the equatorial N-methyl protons suffered a significant fall in solvent shielding, while small increases in the shielding of the further removed axial N-methyl group occurred.

These solvent-induced chemical shift changes probably arise as a result of the long range effects of the intermolecular association of solvent molecules and/or counter ion with the cationic center of the piperidine derivatives. Variation in the substituent effect of α-methyl

TABLE I. PMR Chemical Shifts of N-Methyl Protons in N,N-Dimethylpiperidinium Iodides and Their Solvent–Dependent Shift Changes[a)]

Substituents[b)]		Chemical shift (ppm) measured in			Solvent-dependent shift change	
		D_2O	DMSO-d_6	$CDCl_3$	$\delta_{CDCl_3}-\delta_{D_2O}$	$\delta_{CDCl_3}-\delta_{DMSO-d_6}$
Without α-methyls						
4(e)-Me	ax. N-Me	3.08	3.09	3.375	0.295	0.285
	eq. N-Me	3.14	3.15	3.55	0.41	0.40
3(e)-Me	ax. N-Me	3.05	3.09	3.35	0.30	0.26
	eq. N-Me	3.12	3.15	3.55	0.43	0.40
cis-3(e)-4(e)-diMe	ax. N-Me	3.08	3.08	3.43	0.35	0.35
	eq. N-Me	3.14	3.16	3.61	0.47	0.45
cis-3(e)-4(a)-diMe[c)]	ax. N-Me	3.10	3.12	3.46	0.36	0.34
	eq. N-Me	3.15	3.22	3.655	0.505	0.435
cis-3(e)-5(e)-diMe	ax. N-Me	3.08	3.095	3.375	0.29	0.28
	eq. N-Me	3.14	3.15	3.55	0.41	0.40
4(e)-*t*-butyl	ax. N-Me	3.03	3.05	3.33	0.30	0.28
	eq. N-Me	3.13	3.17	3.65	0.52	0.48
With equatorial α-methyls						
trans-2(e)-3(e)-diMe	ax. N-Me	2.95	2.965	3.20	0.25	0.235
	eq. N-Me	3.12	3.15	3.51	0.39	0.36
cis-2(e)-4(e)-diMe	ax. N-Me	2.93	2.90	3.14	0.21	0.24
	eq. N-Me	3.11	3.10	3.51	0.40	0.41
trans-2(e)-5(e)-diMe	ax. N-Me	2.91	2.94	3.175	0.265	0.235
	eq. N-Me	3.08	3.11	3.475	0.395	0.365
cis-2(e)-6(e)-diMe	ax. N-Me	2.76	2.725	2.925	0.165	0.20
	eq. N-Me	3.05	3.06	3.37	0.32	0.31
cis,cis-2(e)-4(e)-6(e)-triMe	ax. N-Me	2.76	2.68	2.89	0.13	0.21
	eq. N-Me	3.03	3.03	3.38	0.33	0.35
2(e)-Me	ax. N-Me	2.88	2.91	3.15	0.27	0.24
	eq. N-Me	3.07	3.13	3.45	0.38	0.32
With axial α-methyls						
cis-2(a)-3(e)-diMe	ax. N-Me	3.22	3.21	3.57	0.35	0.36
	eq. N-Me	3.07	3.05	3.41	0.34	0.36
trans-2(a)-4(e)-diMe[d)]	ax. N-Me	3.17	3.18	3.61	0.44	0.43
	eq. N-Me	3.00	2.96	3.34	0.34	0.39
cis-2(a)-5(e)-diMe	ax. N-Me	3.18	3.21	3.57	0.39	0.36
	eq. N-Me	3.01	3.01	3.40	0.39	0.39

a) Assignments of axial and equatorial N-methyl protons are based on PMR studies of normal methiodides and those formed from CD_3I, and the assumption of a preferred axial approach of alkyl halide in the quaternization of cyclic six-membered bases. The equatorial signal has the lower field position except when an α-axial methyl substituent is present. (Y. Kawazoe and M. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **15**, 1405 (1967); A.F. Casy, "PMR Spectroscopy in Medical and Biological Chemistry," Academic Press, London, 1971, p. 155)

b) Substituents are written in an abbreviated form; *cis*-2(a)-3(e)-diMe: *cis*-2(axial), 3(equatorial)-dimethyl-N, N-dimethylpiperidinium iodide.

c) not iodide but chloride

d) This derivative was proved to exist as this conformer to about 70% by C-13 NMR spectroscopy (M. Tsuda, Y. Kawazoe, M. Imanari, and M. Takeuchi, to be published).

groups upon the chemical shifts of axial and equatorial N-methyl groups according to solvent (Table III) may be attributed to the same causes. The last results may be understood by assuming that the nature of association with the solvent molecule and/or the counter anion is sterically perturbed by introduction of a substituent in the neighbourhood of the cationic nitrogen, resulting in changes both or either in the intermolecular electric and magnetic effects on the N-methyl protons and/or in the association constant, *K*a. Thus, in polar solvents, the shielding influences of an α-equatorial methyl substituent (as established in $CDCl_3$) are offset by a reduction in up-field shift caused by solvent/counter ion-solute interactions.

Table II. Averaged Solvent-Induced Shifts ($\Delta\delta$) of N-Methyl Protons[a]

		Averaged solvent-induced shift ($\Delta\delta=\delta_{CDCl_3}-\delta_{D_2O}$)		Sum of $\Delta\delta_{eq.}$ and $\Delta\delta_{ax.}$ (ppm)
		eq. N-Me (ppm)	ax. N-Me (ppm)	
Without α-methyls				
	(6)[b]	0.46±0.05	0.32±0.03	0.78±0.08
With an equatorial α-methyl				
	(4)	0.39±0.01	0.25±0.03	0.64±0.03
With equatorial α,α′-dimethyls				
	(2)	0.32±0.01	0.15±0.02	0.47±0.02
With an axial α-methyl				
	(2)	0.36±0.02	0.37±0.02	0.74±0.04

a) Deviation of the chemical shift measured in $CDCl_3$ from that in D_2O. The former always resonates in lower field than the latter.
b) The number of the derivatives examined.

Table III. Substituent Effects of α-Methyl Group on N-Methyl Proton Chemical Shifts

		Solvent	
		D_2O (ppm)	$CDCl_3$ (ppm)
	eq. C-Me, eq. N-Me	0.02	0.08
	eq. C-Me, ax. N-Me	0.13	0.20
	ax. C-Me, eq. N-Me	0.08	0.18
	ax. C-Me, ax. N-Me	−0.15[a]	−0.22[a]

a) Negative values mean lower field shift.

Concentration-Dependent Shift

NMR spectra were taken of the chloride, iodide, and tosylate of compound I in D_2O, $CDCl_3$, CD_3SOCD_3, CD_3OD, CD_3COCD_3, and CD_3CN at concentrations ranging from 0.005 to 0.4M in each solvent at room temperature. The spectra of the salts of *cis*-3,5-dimethyl derivative were also measured in some of the solvents described above. It was shown that the chemical shifts of N-methyl protons were dependent on the concentration of salts, the kind of counter ion, and the kind of solvent, whereas those of distant protons such as C-methyls remote from the cationic nitrogen showed much less dependence. It is worth noting that the chemical shift of protons of cyclohexane was practically independent of the concentration of solute (0.16—3.3M) or the kind of solvents (CCl_4, $CDCl_3$, CD_3SOCD_3, CD_3OD, CD_3COCD_3, and CD_3CN). Attention will, therefore, be focussed on the N-methyl protons in the discussion, unless otherwise noted.

As far as the chlorides (halides, in general) and the tosylates of our derivatives are concerned, the following general trends were revealed for the dilution effect on N-methyl protons. The chemical shifts were progressively shifted toward higher or lower field by successive dilution of the solution and those of the tosylate always resonated in higher fields than those

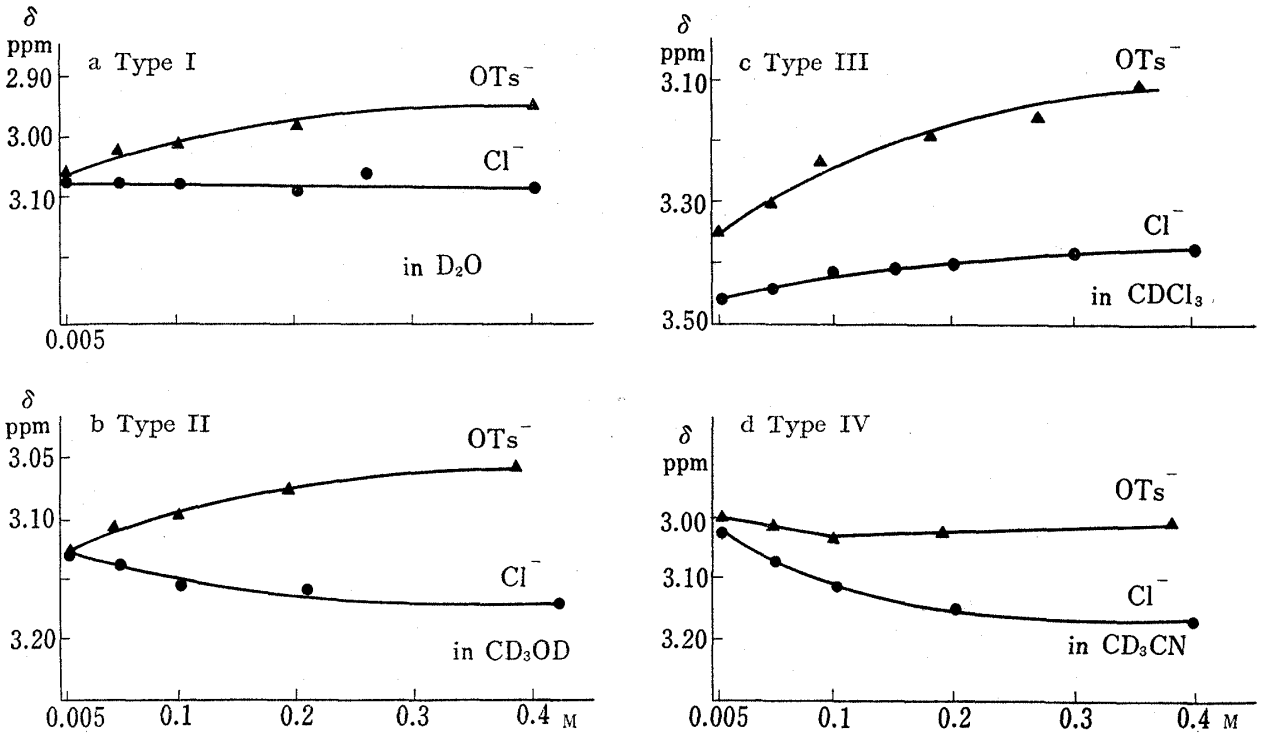


Fig. 1. Dilution Shifts for Equatorial N-Me Protons of N,N,2,*cis*-4,*cis*-6-Pentamethylpiperidinium Salts (I) in Various Solvents

TABLE IV. Methyl Proton Resonances of the Chlorides and Tosylates of N,N,2,*cis*-4,*cis*-6-Pentamethylpiperidinium and N,N,3,*cis*-5-Tetramethylpiperidinium Ions in Various Solvents

Solvent		Chemical shift (ppm)					Type of dilution shift[a]
		infinite dilution	0.005M		0.2M		
			chloride	tosylate	chloride	tosylate	
N,N,2,*cis*-4,*cis*-6-Pentamethylpiperidinium salt							
	eq. N-Me	3.08	3.08	3.04	3.09	2.98	I
D_2O	ax. N-Me	2.76	2.76	2.72	2.76	2.64	I
	4-Me	0.94	0.94	0.92	0.95	0.89	I
	eq. N-Me	3.13	3.13	3.13	3.16	3.08	II
CD_3OD	ax. N-Me	2.80	2.80	2.80	2.82	2.75	II
	4-Me	1.01	1.01	1.00	1.02	0.97	I
	eq. N-Me	3.02	3.02	3.00	3.07	2.99	II
CD_3SOCD_3	ax. N-Me	2.67	2.68	2.67	2.71	2.65	II
	4-Me	0.88	0.88	0.88	0.88	0.86	I
	eq. N-Me	3.02	3.02	3.00	3.15	3.02	IV
CD_3CN	ax. N-Me	2.67	2.68	2.67	2.74	2.65	II
	4-Me	0.95	0.95	0.95	0.96	0.91	I
	eq. N-Me	~3.36	3.40	3.32	3.46	3.28[b]	II
CD_3COCD_3	ax. N-Me	2.97	2.97	2.97	3.01	2.90[b]	II
	4-Me	0.97	0.97	0.96[c]	1.00	0.94[b]	II
	eq. N-Me	>3.46	3.46	3.35	3.40	3.19	III
$CDCl_3$	ax. N-Me	2.72	2.72	2.71	2.84	2.68	III
	4-Me	0.96	0.96	0.95	0.95	0.88	I
N,N,3,*cis*-5-Tetramethylpiperidinium salt							
	eq. N-Me	3.17	3.17	3.15	3.17	3.09	I
D_2O	ax. N-Me	3.12	3.12	3.09	3.11	3.02	I
	3,5-Me	0.95	0.95	0.94	0.95	0.91	I

(continued)

Solvent		Chemical shift (ppm) infinite dilution	0.005M chloride	0.005M tosylate	0.2M chloride	0.2M tosylate	Type of dilution shift[a)]
CD_3SOCD_3	eq. N-Me	3.10	3.10	3.10	3.19	3.10	IV
	ax. N-Me	3.06	3.06	3.05	3.12	3.05	IV
	3,5-Me	0.86	0.86	0.88	0.86	0.85	I
$CDCl_3$	eq. N-Me	>3.65	3.65	3.53	3.61	3.41	III
	ax. N-Me	>3.46	3.46	3.34	3.43	3.24	III
	3,5-Me	>1.04	1.04	0.99	1.01	0.90	III

a) refer to Fig. 1 *b*) 0.1M solution *c*) 0.01M solution

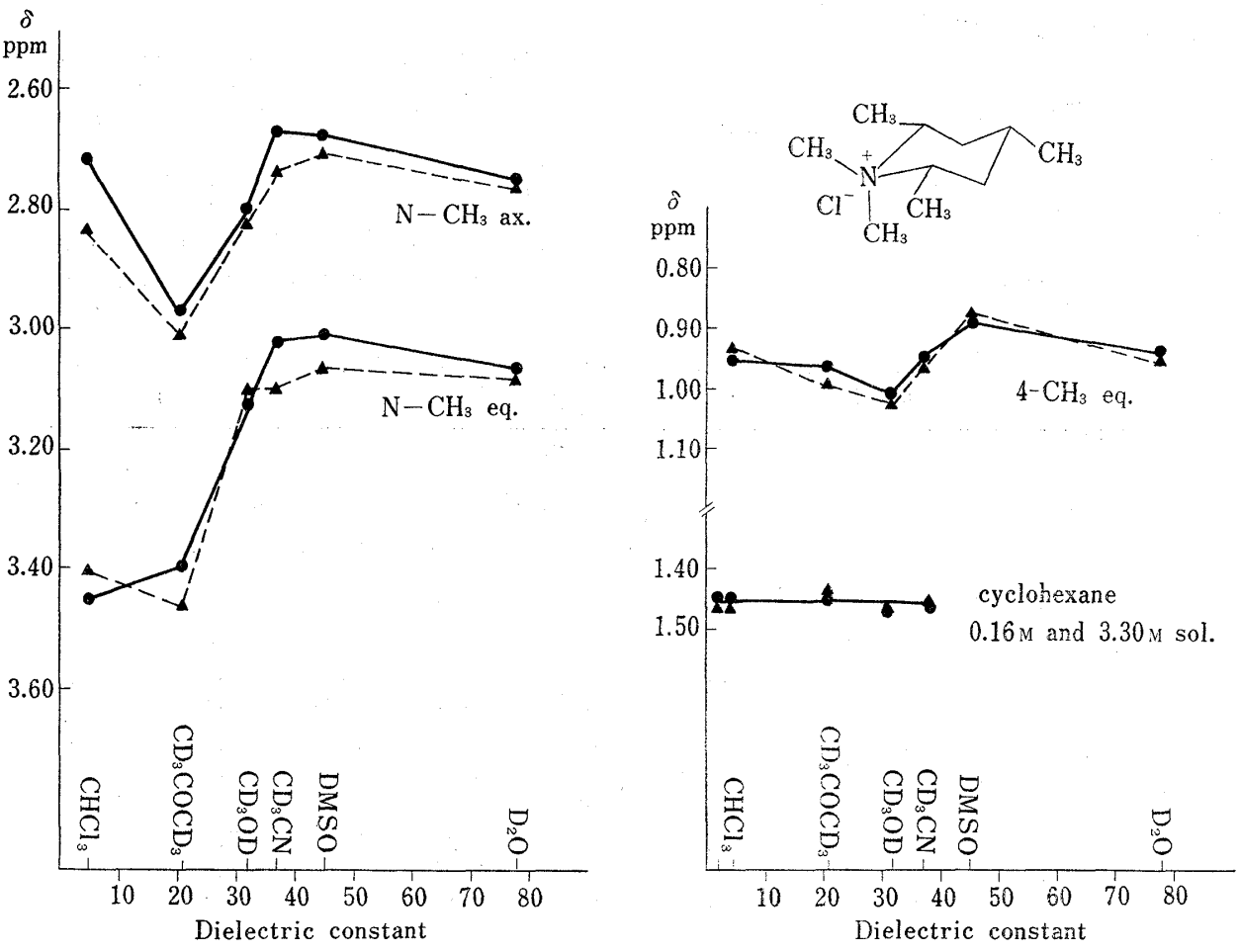


Fig. 2. Plots of δ's *vs.* Dielectric Constants of Solvents

—●—: for the 0.005M and ---▲---: for 0.2M solution

of the chlorides in all the derivatives examined. In plots of δ against concentration, curves of tosylates and chlorides approached each other as solute dilution increased and in some cases converged at the lowest concentration range examined. The mode of the dilution effect observed with our derivatives is tentatively classified into four patterns, namely types I, II, III, and IV. In type I, II, and III, whereas tosylates showed lower field shifts on dilution in all types, they are distinguished by the dilution effect of the chlorides in terms of no shift, higher field shift, and lower field shift, respectively, as exemplified in Fig. 1a, 1b, and 1c. The mode of type IV involves higher field shifts for both tosylate and chloride, as exemplified in Fig. 1d. The classification of the experimental data is shown in the last column of Table IV.

The trend of the convergence of the curves observed in all the cases indicates that the chemical shift at the convergence point is that at the infinite dilution of the salt (δ_i), where the cation is free from the influence of the counter anion and affected only by the surrounding solvent molecules.

It is further noted that the chemical shifts at infinite dilution thus obtained depend on the solvent, indicating that they aries from the solvated cation rather than the free ion, although nothing can be said in detail of the solvated structure. Some values of δ_i obtained in this way are shown in Table IV, which includes the chemical shift data obtained at concentions of 0.005 and 0.2M. The δ values were plotted *versvs* the dielectric constants of the solvents used but no correlation was found, as shown in Fig. 2. The solvent-dependence of the

Table V. Estimated Chemical Shifts of Ion-Pairs and Association Constants

Anion	Solvent		δi(ppm)[a]	δp(ppm)[b]	Ka[c]
N,N,2,*cis*-4,*cis*-6-Pentamethylpiperidinium ion (I)					
Chloride	CD_3SOCD_3	eq. N-Me	3.02	3.22	2.1
		ax. N-Me	2.67	2.81	2.3
Tosylate	D_2O	eq. N-Me	3.07	2.80	4.6
		ax. N-Me	2.75	2.40	3.0
N,N,3,*cis*-5-Tetramethylpiperidinium ion					
Chloride	CD_3SOCD_3	eq. N-Me	3.09	3.30	12.0
		ax. N-Me	3.05	3.21	14.6
Tosylate	D_2O	eq. N-Me	3.16	3.02	10.9
		ax. N-Me	3.10	2.92	9.2

a) chemical shifts at infinite dilution
b) estimated chemical shifts of the ion-pairs. Refer to Fig. 3.
c) association constants. Refer to Fig. 3.

δ_i values may, therefore, be induced by the magnetic anisotropy effect and electric field effect of the solvent molecules surrounding the cationic nitrogen. If the concentration-dependent shift were mainly due to disruption of ion-pairing with the counter anion, there would not be produced such large differences in δ_i values between different solvents and, in addition, the concentration-dependent shift would be in the same direction in every solvents. Such is not the case for experimental data, especially with the chlorides.

Using the concentration-dependent shift changes, the association constants in equilibrium (1) were estimated with some of the samples according to the method by Buckson and Smith,[5] the results being shown in Table V and Fig. 3. The *K*a values thus estimated agree with those previously obtained by other methods.[4,6] The data indicate that the 3,5-dimethyl derivative which has no methyl group in the α-position exists mainly as the ion-paired form in D_2O, whereas compound I, in which the cationic center is sterically blocked by the

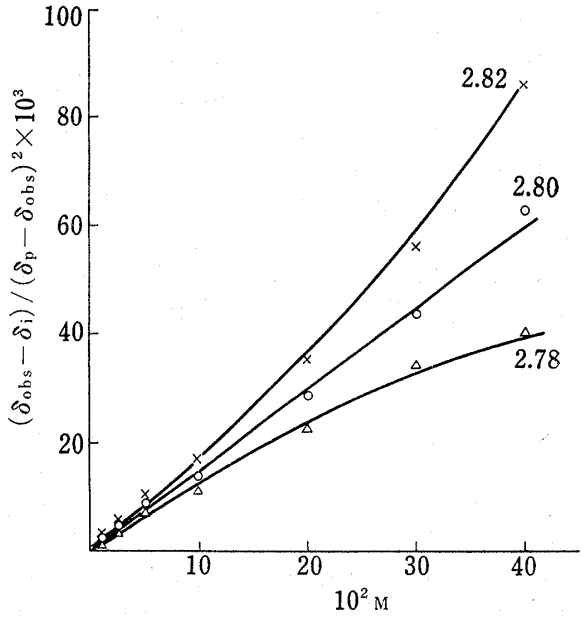


Fig. 3. Plots of $(\delta_{obs}-\delta_i)/(\delta_p-\delta_{obs})^2$ versus Concentration of the Substrate according to the Following Equation: $C(Mole)=(\delta_p-\delta_i)/Ka\cdot(\delta_{obs}-\delta_i)/(\delta_p-\delta_{obs})^2$

This figure shows the plots for eq. N-methyl protons of N,N,2,*cis*-4,*cis*-6-pentamethylpiperidinium tosylate measured in D_2O at 23°, when δp is supposed to be 2.78, 2.80, and 2.82 ppm, respectively (δi=3.07 ppm).

presence of α- and α'-methyl groups, has considerably smaller Ka value in the same solvent. This also suggests that the extent of ion-pairing is dependent on the steric bulk around the cationic nitrogen.

It is worth emphasizing that solvent molecules may participate also in the ion-pair formation, because the chemical shifts of the chloride of compound I at higher concentrations were definitely dependent on the solvent nature (See Table IV and Fig. 1).

Discussion

It is concluded that the cation exists in a solvated state at infinite dilution since the chemical shift δ_i was clearly solvent-dependent. The effect of solvation on the cation can be considered to be due mainly to the magnetic anisotropy, and partly to the electric field effect, of the solvent molecules, so that it probably depends on the solvated structure of cation. With regard to the solvents used in the present study, the chemical shift of N-methyl protons of compound I at the infinite dilution are shifted to higher field in the following solvent order.
axial N-CH_3

$$CD_3COCD_3 \longrightarrow CD_3OD \longrightarrow D_2O \longrightarrow CDCl_3 \longrightarrow CD_3CN \longrightarrow CD_3SOCD_3$$

equatorial N-CH_3

$$CDCl_3 \longrightarrow CD_3COCD_3 \longrightarrow CD_3OD \longrightarrow D_2O \longrightarrow CD_3CN \longrightarrow CD_3SOCD_3$$

It is worth noting that solvation, especially with $CDCl_3$, produces a different size of shift change in an equatorial N-CH_3 resonance from that in an axial one. This may mean that the steric requirement in solvation or collision complexing is specific for each solvent concerned and also for steric bulk around the cationic nitrogen.[10]

Participation of the solvent to the ion-pair may be understood in two ways. One possibility is that one or more solvent molecules are included in the ion-pair complex to form a solvent-separated ion-pair.[6,11,12] The alternative explanation involves the influence of the local electric field on the structure of the tight ion-pair which affects the distance between the cation and anion, leading to changes in the equilibrium constant.

In contrast to solvation, the influence of ion-pairing upon N-methyl chemical shifts must involve an important contribution from the electric field effect in addition to the anisotropy of the counter ion. The electric field due to the approach of the anion should shift the N-methyl resonances to a lower field position, taking into account the fact that the negatively charged anion repells the C-H bonding electrons with consequent deshielding of the proton.[13–15]

The modes of type of I, II, III, and IV may be understood in term of the magnitudes of δ_i, δ_p, and the association constant, Ka, in the following equation.

$$R_4N^+/Sol + X^-/Sol \overset{Ka}{\rightleftharpoons} R_4{}^+X^-/Sol$$

In cases where the curves of the tosylate and chloride do not converge within the concentration range examined, Ka may be larger than those in the other cases.

Since the tosylate anion is largely anisotropic due to its aromatic pi-electron system, it may affect the protons in the cation to produce a lower field shift on dilution, regardless of whether ion-pair are formed or the anion surrounds the cation non-specifically. The fact that no concentration dependence was shown by chlorides measured in D_2O may be understood

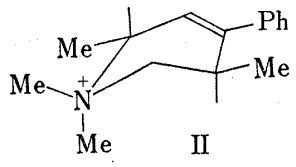
10) R.D. Green and J.S. Martin, *J. Am. Chem. Soc.*, **90**, 3659 (1968).
11) D.W. Larsen, *J. Am. Chem. Soc.*, **91**, 2920 (1969).
12) R.P. Taylor and I.D. Kuntz, Jr., *J. Am. Chem. Soc.*, **92**, 4813 (1970).
13) A.D. Buckingham, *Can. J. Chem.*, **38**, 2300 (1960).
14) E. Schaschel and M.C. Day, *J. Am. Chem. Soc.*, **90**, 503 (1968).
15) H.E. Zaugg, J.F. Ratakezyk, J.E. Leonard, and A.D. Schaefer, *J. Org. Chem.*, **37**, 2249 (1972).

by assuming that the cation is separated far enough to make the electric effect of the anion negligible even in the ion-pair due either to the large dielectric nature of water or to participation of one or more water molecules in forming the ion-pair. Alternatively, δi and δp might be equal in D_2O accidentally.

The quantitative discussion of the mechanism of solvation of the cation and for ion-pair formation, as well as the anisotropy effect of the solvent molecules and the electric field effect of the counter anion require further investigation. The solvent- and concentration-dependences of other protons such as CH groups alpha to the cationic nitrogen might aid their evaluation and a study along this line is now being pursued in our laboratories.

Note on Application

It is evident from the results of this study that due consideration of solvent should be made in the interpretation of the spectra of quaternary salts of cyclic derivatives especially if comparison between spectra recorded in polar and non-polar solvents are being made. For example, the reversal of the relative resonance positions of axial and equatorial N-methyl signals in *cis* and *trans*-4-*t*-butyl-N-methylpiperidinium chlorides when $CDCl_3$ is replaced by D_2O (axial N-methyl is higher field in $CDCl_3$ but lower field in D_2O) may be explained by the more extensive solvent-induced shielding of the equatorial group.[16] The present findings may find some application to stereochemical problems. Thus, $\delta_{CDCl_3}-\delta_{D_2O}$ shift of axial N-methyl (0.28 ppm) and equatorial N-methyl (0.40 ppm) for the tetrahydropyridine quaternary salt (II) are typical of those induced by an α-equatorial methyl group (Table II), confirming the *trans* stereochemistry and conformation of the molecule.[17]



II

16) A.T. Botini and M.K. O'Rell, *Tetrahedron Letters*, **1967**, 429.
17) A.J. Jones, A.F. Casy, and K.M.J. McErlane, *J. Chem. Soc.*, Parkin I, **1973**, 2576.