^{1}H Spin–Lattice Relaxation Times of Quaternary Piperidinium Salts

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Spin–lattice relaxation times of the *N*-methyl protons of quaternary piperidinium salts, as well as piperidine bases as references, were measured in various solvents and for various concentrations. These relaxation times reflect overall molecular rotation rather than internal rotation of the methyl groups. Furthermore, the results are related to the dissociation equilibrium of the quaternary salts, and the dissociation equilibrium constants (*K*) were determined in some solvents.

Spin–lattice relaxation times (T_1) are a powerful tool which can yield new chemical and molecular structural data which are either difficult or impossible to obtain from other kinds of studies. They have been widely applied to organic compounds as a result of the development of pulsed and Fourier transform techniques.

In this paper, as a part of studies of the application of T_1 to alkaloids, ^{1}H T_1 values of piperidines are reported. Since many alkaloids are known to exist as quaternary salts *in vivo*, we report the ^{1}H T_1 values of the *N*-methyl signals of some quaternary piperidinium salts (*N*-methyl-, *N*-alkyl-piperidinium iodide) as well as piperidine bases as references.

$$B^+ + X^- \underset{}{\overset{K}{\rightleftharpoons}} B^+X^- \qquad (1)$$

Since a quaternary salt is in a dissociation equilibrium in solution, the observed T_1 (T_1^{obs}) can be represented by equation (2) where $T_1(B^+)$ and $T_1(B^+X^-)$ are the intrinsic T_1 values of

$$(T_1^{obs})^{-1} = P_{B^+}\cdot(T_1[B^+])^{-1} + P_{B^+X^-}\cdot(T_1[B^+X^-])^{-1} \qquad (2)$$

the components B^+ and B^+X^-, respectively and P_{B^+} and $P_{B^+X^-}$ are the proportions of each component. The dissociation equilibrium as shown in equation (1) should be affected by the solvent and concentration and the observed T_1 should be changed by these conditions.

Spin–lattice relaxation rates (T_1^{-1}) involving several relaxation mechanisms can be assumed to be additive, as shown in equation (3) where T_1^{DD} is dipole–dipole relaxation, T_1^{quad}

$$T_1^{-1} = (T_1^{DD})^{-1} + (T_1^{quad})^{-1} + (T_1^{CA})^{-1} + (T_1^{SC})^{-1} + (T_1^{SR})^{-1} \qquad (3)$$

quadrupole relaxation, T_1^{CA} relaxation *via* chemical shift anisotropy, T_1^{SC} scalar relaxation, and T_1^{SR} spin–rotation relaxation. Although the contributions of T_1^{CA}, T_1^{SC}, T_1^{SR}, and T_1^{DD} should be taken into account for the overall ^{1}H T_1 value, the first three factors can be neglected in our case for reasons given below, and dipole–dipole relaxation can be taken as dominant. (a) Few instances of the relaxation *via* chemical shift anisotropy have been reported for ^{1}H T_1, (b) all the *N*-methyl signals measured are not broad and, for the ^{13}C signals of *N*-methyl groups of quaternary salts, the ^{14}N–^{13}C splittings can be observed,[1] and (c) the observed T_1 values are found to increase with increasing temperature. (Two typical examples are shown in Figure 1). For ^{1}H dipole–dipole relaxation (T_1^{DD}), both contributions should be considered, intramolecular rotation and intermolecular interaction as shown in equation (4). In a

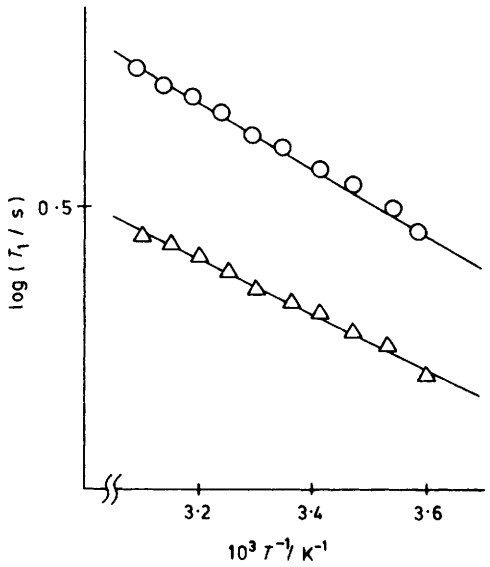


Figure 1. Temperature dependence of T_1: (1) ○; (7) △ in CD_3OD

$$(T_1^{DD})^{-1} = [T_1^{DD}(\text{inter})]^{-1} + [T_1^{DD}(\text{intra})]^{-1} \qquad (4)$$

low concentration solution of deuteriated solvent, the intermolecular contribution should become negligibly small.

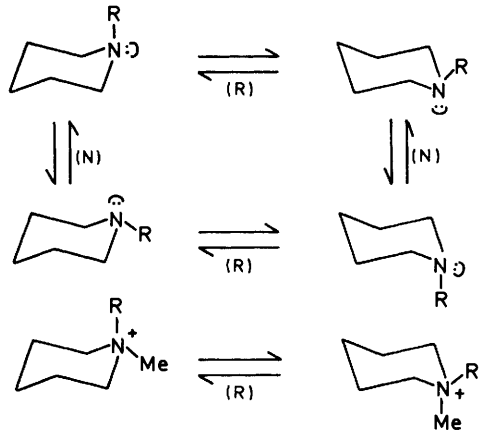
If rotational reorientation is isotropic or if internal motion is absent, ^{1}H T_1^{DD}(intra) is represented by equation (5), and the correlation time for overall molecular reorientation (τ_R) is related to the viscosity of solution (η) and the effective molecular radius (a), as shown in equation (6).

$$[T_1^{DD}(\text{intra})]^{-1} = 3/2N\gamma^4\hbar^2\tau_R r^{-6} \qquad (5)$$

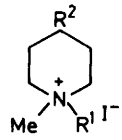
$$\tau_R = 4\pi\eta a^3(3kT)^{-1} \qquad (6)$$

In these conditions, T_1^{DD} should have a linear correlation with molecular size or solution viscosity. But if internal motion must be considered, the total correlation time for reorientation (τ_C) is given by equation (7) where τ_G is the correlation time for internal motion. This is the case for T_1 of the *N*-methyl group.

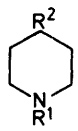
$$\tau_C^{-1} = \tau_R^{-1} + \tau_G^{-1} \qquad (7)$$



Scheme.



	R^1	R^2
(1)	Me	H
(2)	Et	H
(3)	Pr^i	H
(4)	Bu^i	H
(5)	Bu^n	H
(6)	Me	Bu^t



	R^1	R^2
(7)	Me	H
(8)	Me	Bu^t

In piperidine derivatives, the conformations can be interconverted by two distinct processes, ring inversion and nitrogen inversion, and the quaternization of nitrogen prevents the latter inversion leaving only the ring inversion, as shown in the Scheme. Since the rates of both inversions are slower (*ca.* 10^4—10^5 s^{-1})[2] than that of total reorientation, these processes are not expected to affect spin–lattice relaxation.

Experimental

The quaternary piperidinium iodides (**1**)—(**6**) and 4-t-butyl-*N*-methylpiperidine (**8**) were prepared as described previously,[1] and *N*-methylpiperidine (**7**) was of commercial origin.

Samples were dissolved in each solvent at a concentration of 0.01 mol l^{-1} except for the variable-concentration experiments and sealed in 5 mm n.m.r. tubes after bubbling in argon gas for several minutes.

^1H N.m.r. spectra were observed on a Varian XL-200 spectrometer operating at 200.06 MHz and 25 °C. Spin–lattice relaxation times were measured using the inversion-recovery (180°–τ–90°–*t*) method, in which 9—14 τ values were usually included. The standard deviations of T_1 values were *ca.* 5%. Spectra were obtained using 16 K data points over a 1 kHz spectral width. The mean values of three measurements were taken as the observed T_1 values.

Calculations for the analysis of the concentration dependence of T_1^{-1} values[3] were done on a NEAC S-900 computer at the Computation Center, Osaka University.

Results and Discussion

Spin–Lattice Relaxation Times of N-*Methyl Protons.*—^1H Relaxation times (T_1) of the *N*-methyl groups of (**1**)—(**8**) in some different solvents are listed in Table 1. Some observed ^1H T_1 values in CD_3OD give a linear correlation with the corresponding ^{13}C T_1^{DD}[4] (data for C-3, -5 obtained from the measurements of ^{13}C T_1 and n.O.e.) in the same solvent (CD_3OD, 0.05 mol l^{-1}) as shown in Figure 2, which suggests that these observed ^1H T_1 values are contributed mainly by dipole–dipole relaxation or that the contribution of this relaxation mechanism is of the same order for these derivatives ($T_1^{obs} \simeq T_1^{DD}$ or $T_1^{obs} \propto T_1^{DD}$).

Plots of the observed ^1H T_1 in CD_3OD *versus* the corresponding molecular length (the rough estimated length of the cation part from the Dreiding models) yield a linear correlation for all compounds except (**5**) (see Figure 3). This relation suggests that these relaxation times reflect the overall molecular rotational motion rather than the internal rotation of methyl groups. Similar features can be seen in other solvents. In any solvent studied here, the observed T_1 becomes smaller as the molecular size increases, as can be seen from Table 1. This means that τ_G is negligibly small or constant in equation (7) ($\tau_C \simeq \tau_R$ or $\tau_C \propto \tau_R$). This observation is consistent with the results[5] for *N*-methyl-1,2,3,4-tetrahydroisoquinoline derivatives in which internal rotational diffusion rates of *N*-methyl groups [$D_i = (6\tau_G)^{-1}$] are almost constant regardless of molecular size.

The deviation of (**5**) from the linear correlation of Figure 3 is probably due to an overestimation of the molecular length. That is, we estimated the length of the n-butyl group as a stretched pattern which may be not true in solution due to its free segmental motion.

In our previous study of ^{13}C chemical shifts of quaternary piperidinium salts,[1] it was concluded that larger *N*-alkyl substituents shift the ring-inversion equilibrium shown at the bottom in the Scheme to the right and that ring inversion of salt (**6**) is stopped by the bulky substituent on C-4. The observed ^1H T_1 values, however, are not affected by these conformational changes but relate only to their molecular sizes.

Solvent Effects.—In Figure 4, T_1^{-1} is plotted against the solvent viscosity (η)* for two bases (**7**) and (**8**) and two quaternary salts (**1**) and (**2**). The bases give linear correlations except for [$^2H_6$]DMSO but the quaternary salts show scattered patterns. The linear correlations show that τ_G is negligibly small or constant in equation (7) ($\tau_C \simeq \tau_R$ or $\tau_C \propto \tau_R$) and equations (6) and (5) are satisfied. The deviation for [$^2H_6$]DMSO may be due to the special and/or strong solvation.

The scattered patterns are seen not only for the two examples in Figure 4b but also for all the quaternary salts, for which some linear correlations can be seen in solvents with low polarity [$(CD_3)_2C{=}O$, CD_2Cl_2, and $CDCl_3$] but higher polarity solvents show smaller T_1^{-1} values.

In solution, a quaternary salt is in a dissociation equilibrium as shown in equation (1). The polarity of the solvent should change the equilibrium constant *K* and the proportion of ion and ion-pair (B^+/B^+X^-). A change in the proportion of B^+ and B^+X^- should affect T_1 value in two ways, since the observed T_1 is represented by equation (2). One is the effect of the anion ($X^- = I^-$) and the other is the change of apparent molecular size. It may not be necessary to take the former effect into account since all the signals did not broaden and relaxation

* Although the solution viscosity should be used, solvent viscosities were taken for convenience.

Table 1. Spin–lattice relaxation times of *N*-methyl protons (T_1/s)[a]

Solvent	Quaternary salts (1)	(2)	(3)	(4)	(5)	(6) ax.	(6) eq.	Tertiary bases (7)	(8)
D_2O	4.59	3.04	2.98		1.46	1.74	1.52	2.43	1.12
CD_3OD	4.09	3.15	2.98	2.00	1.88	1.99	1.90	4.59	2.15
$[^2H_6]$DMSO	1.38	1.16	1.24		0.63	0.85	0.63	3.94	1.61
$(CD_3)_2C{=}O$	3.56	2.72	2.86		1.99	2.08	2.04	11.43	4.32
CD_2Cl_2	2.27	2.12	2.26		1.31	1.36	1.29	6.19	3.06
$CDCl_3$	1.41	1.33	1.56	0.85	0.78	0.90	0.71	4.28	2.25

[a] At 25 °C, 0.01 mol l^{-1}.

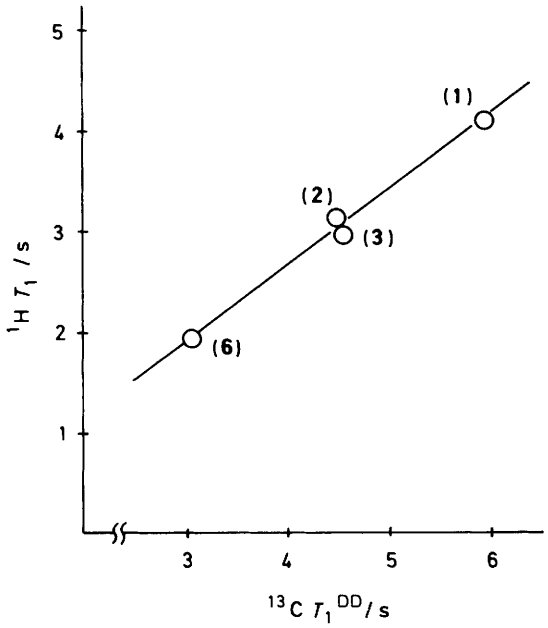


Figure 2. Correlation of the observed ^1H T_1 value of the *N*-methyl group (0.01 mol l^{-1} in CD_3OD) with the ^{13}C T_1^{DD} value of C-3, −5 (0.5 mol l^{-1} in CD_3OD)[4]

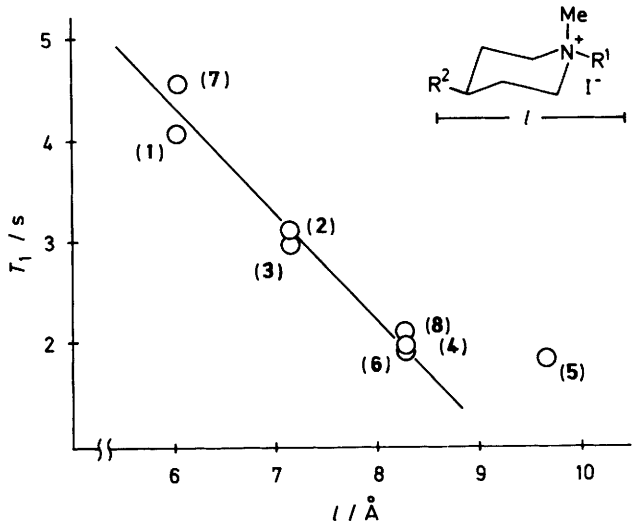


Figure 3. Plots of the observed ^1H T_1 value of the *N*-methyl group in CD_3OD against the rough estimated molecular length (*l*)

mechanisms other than dipole–dipole relaxation have been neglected. Since, in the absence of solvation, the molecular size of ion (B^+) is smaller than that of the ion-pair (B^+X^-), $T_1(B^+)$ should be longer then $T_1(B^+X^-)$. The polar solvent should shift the equilibrium of equation (1) to the left and then be expected to make the observed T_1 longer (smaller T_1^{-1}). This seems to be the reason for the scattered patterns of Figure 4b.

Dissociation Equilibrium Constants of Quaternary Salts in Various Solvents.—To investigate the relation between the dissociation equilibrium and the T_1 value in quaternary salts discussed above, variable-concentration experiments of T_1 were performed in several solvents. The quaternary salt (**2**) was chosen for its higher solubility. As shown in Figure 5, some deviations were seen at higher concentrations (0.03 and 0.05 mol l^{-1}), suggesting the contribution of the intermolecular interaction.

In D_2O and $[^2H_6]$DMSO, T_1 values do not change for concentrations below 0.02 mol l^{-1}. Since D_2O is a polar solvent, a quaternary salt dissociates completely into ions and no change in the T_1 value is expected. Thus, its T_1 value can be taken as the intrinsic value of the ion [$T_1(B^+)$]. On the other hand, in spite of its low polarity, T_1 values in $[^2H_6]$DMSO also do not change with concentration. This indicates strong and/or special solvation of this solvent. Solvation of this solvent may be too strong to change the dissociation equilibrium.

In other solvents, CD_3OD, CD_2Cl_2, and $(CD_3)_2C{=}O$, the values of T_1^{-1} decrease for low concentrations, which shows the quaternary salts to be in a dissociation equilibrium. If a quaternary salt is in the dissociation equilibrium as shown in equation (1), the equilibrium constant K is given by equation (8), where C_{B^+}, C_{X^-} and $C_{B^+X^-}$ are the concentrations of each

$$K = \frac{C_{B^+X^-}}{C_{B^+}C_{X^-}} = \frac{C_{B^+X^-}}{(C_{B^+})^2} = \frac{C^0_{B^+X^-} - C_{B^+}}{(C_{B^+})^2} \qquad (8)$$

component of solution, B^+, X^-, and B^+X^-, respectively, and usually $C_{B^+} = C_{X^-}$. $C^0_{B^+X^-}$ is the initial concentration of the salt. In addition, P_{B^+} and $P_{B^+X^-}$ in equation (2) can be rewritten as C_{B^+} and $C^0_{B^+X^-} - C_{B^+}$, respectively. The optimum values of K and $T_1(B^+X^-)$ can be determined in such a way that T_1^{calc}, T_1 calculated from equations (8) and (2), becomes very similar to the observed T_1 value, $T_1^{obs.}$, using procedures similar to the analysis of other n.m.r. data.[3] In this analysis, $T_1(B^+)$ should be obtained by extrapolation of the observed T_1^{-1} values to zero concentration. For $(CD_3)_2C{=}O$ and CD_2Cl_2, however, $T_1(B^+)$ cannot be determined from the observed values for the limiting concentration and thus suitable values were estimated as follows. Since the product of $T_1(B^+)$ and the viscosity of the solution [$T_1(B^+)\cdot\eta$] should be constant for each solvent from equations (5)—(7) (if τ_G is constant), $T_1(B^+)$ can be obtained from the $T_1(B^+)\cdot\eta$ value (2.54 s cp) of the D_2O solution and the solution viscosity for each solvent.

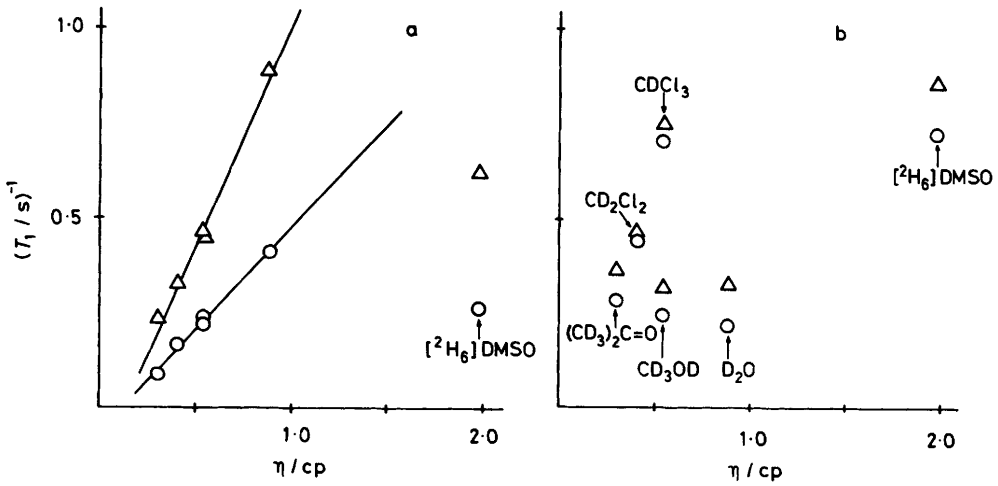


Figure 4. Relationship between T_1^{-1} and solvent viscosity (η) for (a) tertiary bases (**7**), ○, and (**8**), △, and (b) quaternary salts (**1**), ○, and (**2**), △

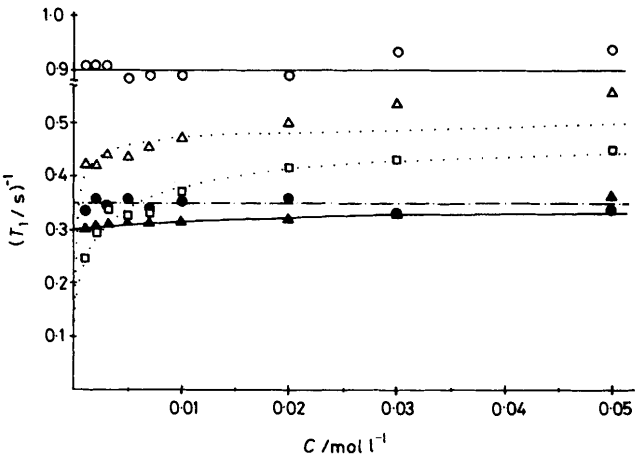


Figure 5. Concentration dependence of T_1^{-1} for (**2**) on different solvents: ○ $[^2H_6]$DMSO; △ CD_2Cl_2; □ $(CD_3)_2C=O$; ● D_2O; ▲ CD_3OD

The K and $T_1(B^+X^-)$ values obtained by this analysis are listed in Table 2 and plots of T_1^{-1} *versus* concentration are also depicted in Figure 5. Although the absolute values of K may have to be checked by another approach because of the relatively low precision of the measured T_1 values and the limit applied by the concentration, qualitative discussion about relative value of K is not a problem. The K values determined

Table 2. Dissociation constants (K)[a] and the intrinsic T_1 values of the ion-pair $[T_1(B^+X^-)]$[a]

	log K	$T_1(B^+X^-)$/s
In CD_3OD	1.30 ± 0.20	2.49
In $(CD_3)_2C=O$	2.68 ± 0.13	1.96
In CD_2Cl_2	3.31 ± 0.34	1.96

[a] At 25 °C

are reasonable in terms of the polarity of each solvent. As the solvent polarity becomes smaller, the value of K becomes larger. The largest K value in CD_2Cl_2 shows that, in this solution, a large portion of the quaternary salt exists as a ion-pair and the dissociation equilibrium (1) lies far to the right.

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