^{13}C Spin-lattice Relaxation Times of Piperidines. Molecular Motions and Interactions with Solvents

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^{13}C Spin-lattice relaxation times have been measured for piperidine (**1**) and *N*-methylpiperidine (**2**) in several different solvents [$CDCl_3$, CD_3OD, D_2O, $(CD_3)_2CO$, C_6D_{12}, $C_6D_5NO_2$, and $(CD_3)_2SO$], and have been analysed in terms of anisotropic molecular motion. The results of these calculations show that these solvents can be divided into three types according to the hydrogen-bonded solute–solvent interaction involved: (i), C_6D_{12}, $C_6D_5NO_2$, and $(CD_3)_2SO$, which have no effect on molecular rotation; (ii), $CDCl_3$, CD_3OD, and D_2O, in which hydrogen-bonded interactions between solute and solvent molecules caused by the nitrogen lone-pair are expected (these affect the apparent size and anisotropy of the solute molecule, depending on the orientation of the lone-pair); and (iii), $(CD_3)_2CO$, in which the carbonyl group interacts with the solute NH proton.

The ^{13}C spin-lattice relaxation time (T_1) gives useful information about the rate and also the anisotropy of molecular rotation. This information can then be correlated with the stereochemistry, the configuration and/or the conformation of the molecule.

We have discussed previously the ^{13}C T_1 values of *N*-methyl-1,2,3,4-tetrahydroisoquinoline and several of its quaternary salts in connection with their molecular anisotropic motion.[1] The 1,2,3,4-tetrahydroisoquinoline system is the fundamental skeleton of the isoquinoline alkaloids and the orientations of the major axes of molecular rotation reflect the subtle differences between the conformations of these derivatives. A study of the piperidines, (a fundamental skeleton of many more kinds of alkaloid), has now been taken up. This basic study of solvent effects on the ^{13}C T_1 values of these simple compounds is relevant to a discussion of the ^{13}C T_1 values for many alkaloids. In solution, piperidine (**1**) and *N*-methylpiperidine (**2**) are in equilibrium between two processes, a nitrogen inversion and a ring inversion (Scheme). At room temperature, the equilibria are shifted to the preferred conformation. Thus (**1**) and (**2**) exist mainly in the *E* (the nitrogen lone-pair is oriented to the equatorial position) and *A* forms respectively.

In this work, the ^{13}C T_1 values of (**1**) and (**2**) have been measured in seven different solvents and an estimation of the molecular motional anisotropy has been performed using these data. The molecular rotation reflects the overall molecular form, including solvation or the interaction with solvent.[2] The solvation or solvent interaction depends on the properties of the solvent and on the molecular conformation.

Experimental
Piperidine (**1**) and *N*-methylpiperidine (**2**) were of commercial origin and were used without further purification. Samples were dissolved in each solvent (0.3 mol dm^{-3}) and the solutions were degassed and sealed under vacuum.

^{13}C N.m.r. spectra were measured with a Varian XL-200 spectrometer operating at 50.3 MHz at 25 °C. The spin-lattice relaxation times (T_1) were obtained using the inversion-recovery ($180° - \tau - 90° - t$) method. The standard deviation of the T_1 values was $\pm 5\%$. The T_1 measurements were carried out twice and the mean values were taken as the observed T_1 values. Nuclear Overhauser effect (n.O.e.) values were measured
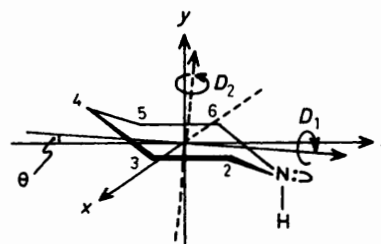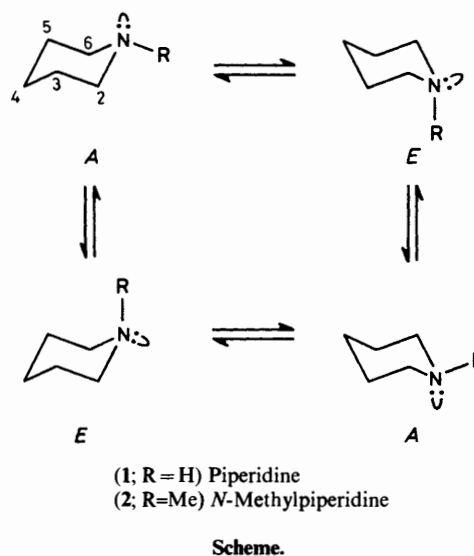

(**1**; R = H) Piperidine
(**2**; R=Me) *N*-Methylpiperidine

Scheme.

Figure 1. Co-ordinates used for the calculation.

using a gated decoupling technique. The experimental error in the n.O.e. was $\pm 20\%$.

Calculations were carried out on an NEC ACOS-1000 computer at the Computation Center, Osaka University, following the procedure described previously.[1,3] The co-ordinates of the molecules were taken as those shown in Figure 1, in which the conformation was fixed by assuming tetrahedral angles for all aliphatic carbons and bond distances of 1.5 Å for aliphatic C–C, 1.1 Å for C–H, and 1.5 Å for C–N bonds. The other angles were

Table 1. ^{13}C Spin-lattice relaxation times $(T_1/s)^a$ and n.O.e. values (in parentheses) for piperidine (1) and N-methylpiperidine (2).
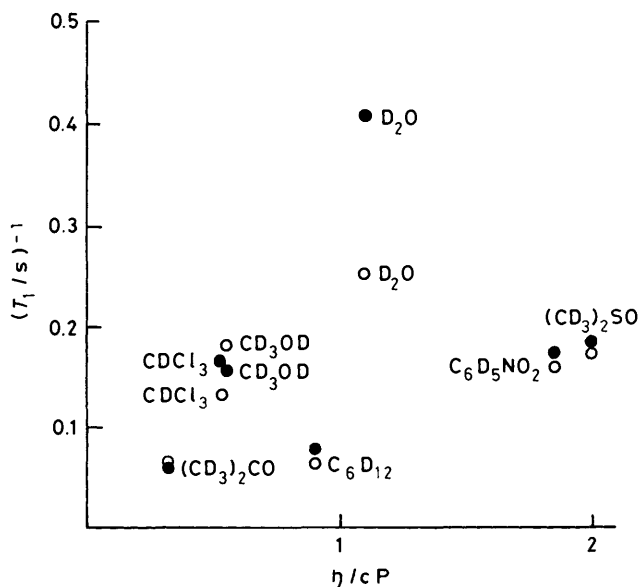
Solvent	(1)			(2)			
	C-2,-6	C-3,-5	C-4	C-2,-6	C-3,-5	C-4	N-CH$_3$
CDCl$_3$	7.59	7.56	6.16	6.20	6.04	5.68	4.98
	(1.82)	(1.72)	(1.81)	(1.88)	(1.83)	(1.87)	(1.85)
CD$_3$OD	5.79	5.53	4.31	6.62	6.35	6.15	5.26
	(1.65)	(1.90)	(1.87)	(1.74)	(1.68)	(1.70)	(1.81)
D$_2$O	4.03	3.95	3.03	2.56	2.46	2.22	2.48
	(1.69)	(1.85)	(1.95)	(2.05)	(2.07)	(2.07)	(2.04)
(CD$_3$)$_2$CO	15.90	15.67	15.41	16.19	16.35	14.43	11.55
	(1.82)	(1.64)	(1.83)	(1.68)	(1.70)	(1.87)	(1.78)
C$_6$D$_{12}$	16.44	16.53	b	13.35	b	11.12	10.29
	(1.74)	(1.91)		(1.84)		(1.61)	(1.86)
C$_6$D$_5$NO$_2$	6.48	6.40	5.62	6.02	5.79	4.93	4.71
	(1.93)	(1.87)	(2.02)	(1.99)	(1.98)	(2.03)	(2.01)
(CD$_3$)$_2$SO	5.88	5.87	5.23	5.72	5.65	4.88	4.66
	(1.88)	(1.82)	(1.88)	(1.87)	(1.86)	(1.77)	(2.09)

^{a} Recorded at 25 °C, 0.3 mol dm^{-3}. ^{b} Could not be obtained because signal is overlapped by those of the solvent.

Table 2. Calculated values of geometric factor of the major axis ($\theta = 0°$) and the rotational diffusion rate (D_1 and D_2).^{a}

Solvent	(1)			(2)		
	D_1/D_2	$10^{-10}D_1/$ s^{-1}	$10^{-10}D_2/$ s^{-1}	D_1/D_2	$10^{-10}D_1/$ s^{-1}	$10^{-10}D_2/$ s^{-1}
CDCl$_3$	2.20	8.45	3.84	1.34	5.29	3.95
CD$_3$OD	2.74	7.04	2.57	1.23	5.38	4.37
D$_2$O	2.78	5.00	1.80	1.61	2.38	1.48
(CD$_3$)$_2$CO	1.08	12.23	11.32	1.70	15.57	9.16
C$_6$D$_{12}$				2.06	14.46	7.02
C$_6$D$_5$NO$_2$	1.70	6.31	3.71	2.00	6.26	3.13
(CD$_3$)$_2$SO	1.58	5.53	3.50	1.81	5.74	3.17

^{a} See Figure 1.

Figure 2. Relationship between T_1^{-1} (C-3,-5) and solvent viscosity (η) for (1) (○) and (2) (●).

determined from molecular models. The T_1 values of the N-CH$_3$ carbon on (2) were not used for the calculation. The

observed T_1 values $(T_1^{obs.})$ were taken as the T_1^{dd} values (assuming $\eta_{C=H} = 1.99$) and were used directly in the calculation.

Results and Discussion

The ^{13}C spin-lattice relaxation times (T_1) and n.O.e. values of (1) and (2) in seven different solvents are shown in Table 1. Since almost all n.O.e. values are close to 1.99 within experimental error, these observed relaxation times depend mainly on the dipolar interaction mechanism.[4]

Assuming the isotropic molecular rotation on the extreme narrowing condition ($\omega_0\tau_c \ll 1$), the ^{13}C dipolar relaxation time (T_1^{dd}) is expressed as equation (1):[5]

$$1/T_1^{dd} = n\gamma_C^2\gamma_H^2\hbar^2 r_{CH}^{-6}\tau_c \qquad (1)$$

where γ_C and γ_H are the gyromagnetic ratios of ^{13}C and ^1H, respectively, $\hbar = h/2\pi$, h is Planck's constant, r_{CH} is the C–H internuclear distance, n is the number of directly adjacent protons, and τ_c is the rotational correlation time of the molecule which is related to the viscosity (η) of the solute and the molecular radius a as shown by equation (2):[6]

$$\tau_c = 4\pi\eta a^3/3kT \qquad (2)$$

A plot of $1/T_1$ values for C-3,-5 against solvent viscosity gives a scattering for both compounds, as shown in Figure 2. From equation (2) the correlation with the solution viscosity should be taken into consideration but a rough linear relationship between τ_c and the solvent viscosity has been reported for small molecules.[7] This observation suggests that the molecular motions are anisotropic and that there is the possibility of solvation or solvent interaction for some solvents. In fact, the T_1 values for the C-4 atom of both compounds are relatively lower than other ring carbons (C-2,-6 or C-3,-5) in every solvent, which suggests that the molecular rotation is anisotropic.

For an anisotropic molecular motion with ellipsoid tumbling about two axes at different rates, T_1^{dd} is written as in equation (3)[8]

$$1/T_1^{dd} = n\gamma_C^2\gamma_H^2\hbar^2 r_{CH}^{-6}[(A/6D_2 + B/(D_1 + 5D_2) + C/(4D_1 + 2D_2)] \qquad (3)$$

$$A = 0.25 (3\cos^2\Delta - 1)^2$$
$$B = 0.75 \sin^2 2\Delta$$
$$C = 0.75 \sin^4\Delta$$

instead of equation (1), where D_1 and D_2 are the rotational diffusion rates about the major axis and the axis perpendicular to the major axis, respectively, and Δ is the angle between the C–H vector and the major axis.

The calculation was performed using a computer program[1,3] by fitting the T_1 data to equation (3) in order to determine the diffusion rates (D_1 and D_2) and the orientation of the major axis (defined by the angle θ between the major axis and the z-axis, see Figure 1). The co-ordinate and geometry used in the calculation are indicated in Figure 1 and the results (D_1, D_2, and θ) are summarised in Table 2. The calculated θ values are 0° in all cases, that is, the major axis coincides with the z-axis, which is the symmetric axis on the plane bounded by C-2,-3,-5, and -6. The presence of the N-methyl group has no effect on the orientation of the major axis. This result supports the equatorial orientation of the methyl group on (2). An axial methyl group would cause the major axis to deviate from the z-axis in the N-axial direction.

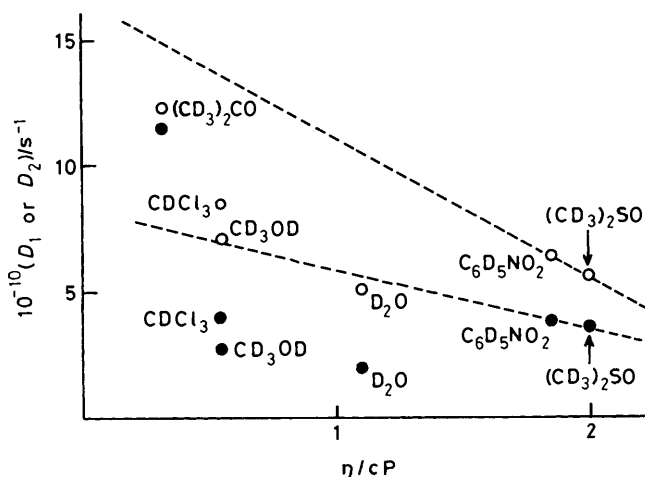For both compounds, the D_1/D_2 ratio varies with solvent, which suggests solvation or solvent interaction for some

Figure 3. Relationship between the rotational diffusion rates, D_1 ($\bigcirc$) and D_2 ($\bullet$) and the solvent viscosity (η) for (1).
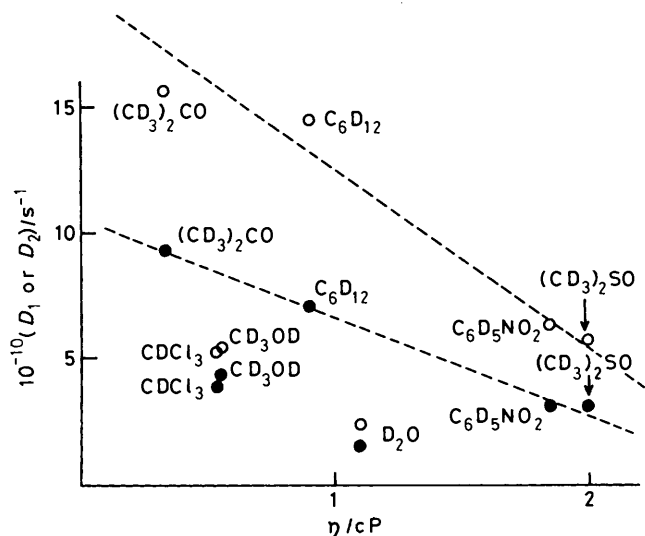

Figure 4. Relationship between the rotational diffusion rates, D_1 ($\bigcirc$) and D_2 ($\bullet$), and the solvent viscosity (η) for (2).

solvents. From molecular models, the ratios (length of the long axis)/(length of the short axis) are *ca.* 1.7 and 2.0 for (1) and (2), respectively. For (1), the D_1/D_2 values in $C_6D_5NO_2$ and $(CD_3)_2SO$ are relatively close to 1.7, and (2) has a D_1/D_2 value close to 2.0 in C_6D_{12}, $C_6D_5NO_2$, and $(CD_3)_2SO$. The relationship between the rotational diffusion rates (D_1 and D_2) and solvent viscosity for (2) shows a linear correlation in C_6D_{12}, $C_6D_5NO_2$, $(CD_3)_2SO$ and $(CD_3)_2CO$ for both D_1 and D_2 (see Figure 4). For (1), similar relationships are expected [except in the case of $(CD_3)_2CO$], though this is impossible to confirm owing to a lack of data for C_6D_{12} (see Figure 3). This suggests that these compounds rotate with little solvent effect in C_6D_{12}, $C_6D_5NO_2$, and $(CD_3)_2SO$, *i.e.* there is no solvation or solvent interaction in these solvents to affect the overall size and/or the anisotropy of the molecules. However, in $CDCl_3$, CD_3OD, and D_2O, the values of D_1 and D_2 are lower than those expected from the appropriate solvent viscosity. The plots for these solvents shown in Figures 3 and 4 deviate down from the lines showing ideal relationships (the dotted lines). These observations suggest that the molecular rotations are slower in these solvents, which means that there are changes in the overall size and/or the anisotropy owing to solvent interactions. The ratio D_1/D_2 in these solvents is larger than that expected (1.7) for (1)

whereas those for (2) are less than 2.0. The interaction with these solvents seems to influence the molecular rotations of (1) and (2) in different ways. With (1), solvation increases the anisotropy, whereas (2) rotates less anisotropically. These observations can be accounted for by hydrogen-bonding between the solvent proton with the nitrogen lone-pair.[7] (In fact, as deuteriated solvents were used it is the deuteron, not the proton, which interacts with the lone-pair). The lone-pair of (1) is equatorially oriented and (2) is axially oriented. The hydrogen-bonding with the nitrogen lone-pair should lead to a much greater increase in anisotropy for (1) and a decrease for (2).

In $(CD_3)_2CO$, the ratio D_1/D_2 for (1) is the smallest and closest to 1.0, suggesting a spherical molecule. The solvent effect of $(CD_3)_2CO$ for compound (1) must be different from other solvents. Hydrogen-bonding such as $NH \cdots O{=}C$ could be proposed, which would make the molecular shape of (1) more isotropic. On the other hand, as compound (2) does not possess an NH proton to interact with the carbonyl group of $(CD_3)_2CO$, this same solvent effect does not take place. In fact, the D_1/D_2 value for (2) in $(CD_3)_2CO$ is not so different from the expected value, 2.0, and the plots for this solvent do not deviate from the linear correlation line (Figure 4).

Conclusions

The ^{13}C spin-lattice relaxation times of (1) and (2) were measured in seven different solvents. From the results of the calculation estimating the anisotropy of the molecular rotation using these ^{13}C T_1 data, these solvents can be divided into three types.

The first includes C_6D_{12}, $C_6D_5NO_2$, and $(CD_3)_2SO$, in which the molecule rotates without solvent interaction. Normally, $(CH_3)_2SO$ or $(CD_3)_2SO$ are known to exhibit strong solvation; in this case, however, $(CD_3)_2SO$ does not affect the apparent molecular size or the anisotropy of the molecule.

For the second type ($CDCl_3$, CD_2OD, and D_2O), interaction is expected between the solute and the solvent. In these solvents, protons (or deuterons) of the solvent interact with the nitrogen lone-pair by hydrogen bonding. The apparent molecular size thus lengthens in the direction of the lone-pair; equatorial lone pair for (1) and the axial for (2). The preferred conformations in solution [E for (1) and A for (2), as shown in the Scheme] are confirmed by these observations.

The last type is $(CD_3)_2CO$, which interacts with the solute NH proton through the carbonyl group. Only (1), which has an NH proton, is subject to this solvent effect.

References

1 M. Sugiura, T. Sai, N. Takao, and H. Fujiwara, *J. Chem. Soc., Perkin Trans.* 2, 1983, 907.
2 I. D. Campbell, R. Freeman, and D. L. Turner, *J. Magn. Reson.*, 1975, 20, 172.
3 H. Fujiwara, T. Takagi, M. Sugiura, and Y. Sasaki, *J. Chem. Soc., Perkin Trans.* 2, 1983, 903.
4 J. R. Lyerla, Jr., and G. C. Levy, 'Topics in Carbon-13 NMR Spectroscopy,' ed. G. C. Levy, Wiley, New York, 1974, vol. 1, p. 79.
5 A. Abragam, 'Principles of Nuclear Magnetism,' Clarendon Press, Oxford, 1961, ch. 8.
6 P. Debye, 'Polar Molecules,' Dover, New York, 1945.
7 A. Maliniak, J. Kowalewski, and I. Panas, *J. Phys. Chem.*, 1984, 88, 5628; A. Maliniak and J. Kowalewski, *ibid.*, 1986, 90, 6330.
8 J. B. Lambert, R. J. Nienhuis, and J. W. Keepers, *Angew. Chem., Int. Ed. Engl.*, 1981, 20, 487, and references cited therein.