^{13}C Spin–Lattice Relaxation Times and Molecular Motion in N-Alkyltetrahydroisoquinoline Derivatives

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^{13}C Spin–lattice relaxation times have been measured for N-methyl-1,2,3,4-tetrahydroisoquinoline and several quaternary N-methyl-N-alkyl-1,2,3,4-tetrahydroisoquinolinium salts, and have been analysed in terms of an anisotropic molecular motion. The calculated orientations of the major axes of molecular overall rotation reflect well the delicate differences in conformation of these derivatives. In quaternary salts, the longer alkyl chain restricts the rotational motion about the major axis more than that about the perpendicular axis, and brings the molecular motion close to the isotropic rotational one. Internal rotations of N-methyl groups are also discussed. In these derivatives, the values of the barrier to methyl rotation, V_0, resemble one another, as well as the rotational diffusion rates, D_i, and are quite large owing to steric hindrance by the lone pair or by the N-alkyl groups.

The 1,2,3,4-tetrahydroisoquinoline system is the fundamental skeleton of the isoquinoline alkaloids, and data relating its stereochemistry and molecular motion are therefore of interest. In this system, conformational inversion can occur by two distinct processes, ring inversion and nitrogen inversion, as for piperidines (Scheme 1), and variation of substituents and/or their configuration will shift the equilibria of these two processes. As shown in Scheme 2, nitrogen quaternization prevents nitrogen inversion, and allows ring inversion to be observed separately.

Spin–lattice relaxation times (T_1) can yield chemical and molecular structural data that are either difficult or impossible to obtain from other kinds of study.[1] There have been many studies of molecular motion by use of ^{13}C spin–lattice relaxation times,[2] analysed by application of Woessner's theory. When the molecular motion is anisotropic, analyses of ^{13}C T_1 data in terms of an ellipsoid tumbling about two axes at different rates $(D_1 \neq D_2 = D_3)$ are of interest in connection with the stereochemistry.

In this work, ^{13}C T_1 data of some quaternary tetrahydroisoquinolinium salts, the N-methyl-N-alkyl-1,2,3,4-tetrahydroisoquinolinium iodides (2)—(5), as well as of N-methyl-1,2,3,4-tetrahydroisoquinoline (1) for comparison, are reported, and are analysed in terms of an anisotropic molecular motion; thus molecular rotational diffusion rates, motional anisotropy (characterized by D_1/D_2), and the orientation of the major axis of ellipsoid tumbling have been determined. The results have been correlated with the conformations of the molecules. The influence of the N-alkyl groups on molecular rotation and the internal motions of the N-methyl groups are discussed.

Experimental

*Materials.*—N-Methyl-1,2,3,4-tetrahydroisoquinoline (1)[3] was prepared by reducing N-methylisoquinolinium iodide with NaBH$_4$ in EtOH. The N-methyl-N-alkyl-1,2,3,4-tetrahydroisoquinolinium iodides (2)—(5) were prepared by N-alkylation of the isoquinoline (1) with the corresponding alkyl iodide.

Measurements.—Samples were dissolved in CD$_3$OD (concentration 0.3 mol l^{-1}) and sealed in 10 mm n.m.r. tubes after bubbling argon gas for several minutes.

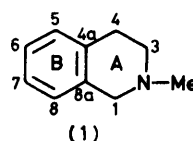^{13}C N.m.r. spectra were measured with a Varian XL-200 spectrometer operating at 50.3 MHz at 35 °C. The spin–

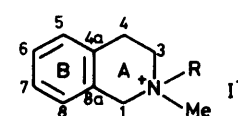Scheme 1.

conformer a'   conformer e'
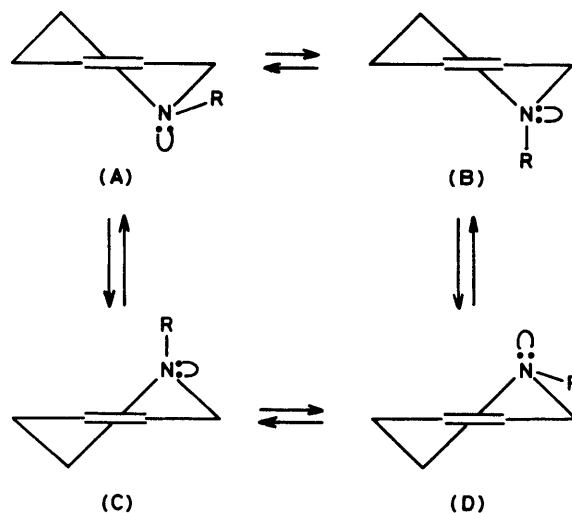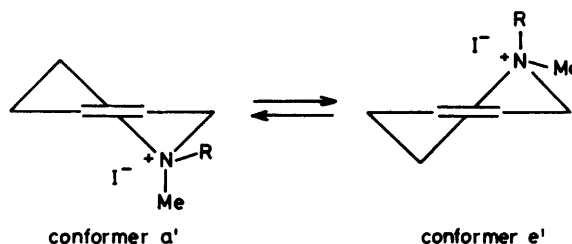
Scheme 2.

(1)

(2) R = Me
(3) R = Et
(4) R = Pr^n
(5) R = Bu^n

Table 1. Spin–lattice relaxation times T_1 and n.O.e. values η_{C-H}

	Ring carbon															
	C-1		C-3		C-4		C-5		C-6		C-7		C-8		NMe	
Compound	T_1/s	η_{C-H}	T_1/s	η_{C-H}	T_1/s	η_{C-H}	T_1/s	η_{C-H}	T_1/s	η_{C-H}	T_1/s	η_{C-H}	T_1/s	η_{C-H}	T_1/s	η_{C-H}
(1)	4.05	1.9	3.46	2.0	3.60	2.0	8.37	1.8	6.95	1.8	7.02	1.9	8.02	1.7	3.08	1.6
(2)	3.37	2.0	3.22	2.0	3.17	2.0	6.40	2.0	4.51	2.0	4.71	2.0	5.79	1.8	2.31	2.0
(3)	2.60	2.0	2.56	2.0	2.64	2.0	5.37	2.0	3.80	1.9	4.34	2.0	5.43	2.0	2.22	a
(4)	1.78	1.8	1.63	1.8	1.92	1.9	3.89	1.9	2.91	2.0	3.29	2.0	3.85	2.0	1.81	a
(5)	1.59	2.0	1.59	2.0	1.78	1.8	3.53	1.8	2.81	1.8	2.99	1.9	3.30	1.7	b	a

	Alkyl carbon							
	C-1′		C-2′		C-3′		C-4′	
	T_1/s	η_{C-H}	T_1/s	η_{C-H}	T_1/s	η_{C-H}	T_1/s	η_{C-H}
(3)	2.94	2.0	4.12	2.0				
(4)	1.75	2.0	2.50	2.0	3.63	1.8		
(5)	1.71	1.9	2.31	1.9	3.15	2.0	4.05	1.6

[a] An accurate η_{C-H} value cannot be determined, because the signal is small and slightly split into a triplet by coupling with ^{14}N. [b] An accurate observed T_1 value cannot be measured because of overlap with the solvent signals.

lattice relaxation times were measured using the inversion-recovery method. The standard deviations of the T_1 values were $\sim 5\%$. The spectra were obtained using 16 K data points over a 7 kHz spectral width. The mean values of two time measurements were taken as the observed T_1 values. Nuclear Overhauser effect (n.O.e.) values were measured using a gated decoupling technique. The experimental errors in the n.O.e. values were $\sim 20\%$.

The assignments of the carbon signals were made using off-resonance decoupling and comparisons of chemical shifts, as well as the comparisons of T_1 values.

Calculation of Anisotropic Molecular Motion and of Internal Rotation of Methyl Groups.[4]—The dipolar relaxation time for carbon on the rigid backbone in anisotropic motion is given by equation (1), in which A, B, and C are geometric factors

$$1/T_1^{DD} = N\hbar^2\gamma_H^2\gamma_C^2 r_{C-H}^{-6} [A/6D_2 + B/(D_1 + 5D_2) + C/(4D_1 + 2D_2)] \quad (1)^2$$

determined by the angle Δ between the C–H vector and the major axis, and D_1 and D_2 are rotational diffusion rates about the major axis and the axis perpendicular to the major axis, respectively. The geometric constants are given by equations (2a—c).

$$A = 1/4 (3\cos^2\Delta - 1)^2 \quad (2a)$$

$$B = 3/4 \sin^2 2\Delta \quad (2b)$$

$$C = 3/4 \sin^4\Delta \quad (2c)$$

If the internal motion of the methyl group is independent of the overall motion, and D_i is now the methyl rotational diffusion rate in jumps s^{-1}, modification of equation (1) to include internal rotation gives equation (3), in which the nine

$$A_1 = 1/8 (1 - 3\cos^2\alpha)^2 (3\cos^2\Delta - 1)^2$$
$$A_2 = 9/16 \sin^2 2\alpha \cos^2 2\Delta$$
$$A_3 = 9/16 \sin^4\alpha \sin^4\Delta$$
$$B_1 = 3/8 \sin^2 2\alpha (3\cos^2\Delta - 1)^2$$
$$B_2 = 3/4 (\cos^2 2\alpha + \cos^2\alpha) \sin^2 2\Delta \quad (4)$$
$$B_3 = 3/4 (\sin^2\alpha + 1/4 \sin^2 2\alpha) \sin^4\Delta$$
$$C_1 = 3/8 \sin^4\alpha (3\cos^2\Delta - 1)^2$$
$$C_2 = 3/4 (\sin^2\alpha + 1/4 \sin^2 2\alpha) \sin^2 2\Delta$$
$$C_3 = 3/16 [(1 + \cos^2\alpha)^2 + 4 \cos^2\alpha] \sin^4\Delta$$

The calculations for the rigid parts of the molecules and for the methyl groups were done separately, and the orientation of the major axes (defined by the angles θ, between the major axis and the Z axis, and ψ, between the X axis and the projection of the major axis on the XY plane; see footnote to Table 2) and the diffusion rates (D_1, D_2, and D_i) were determined from a computer program[4] by fitting the T_1^{DD} data to equations (1) and (3).

The co-ordinates of the molecules were taken as 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, 1.4 Å for aromatic C–C, 1.1 Å for C–H, and 1.5 Å for C–N bonds. The other angles were determined from Dreiding models.

For the calculations on the rigid part, ^{13}C T_1 values of the six fixed ring carbons, C-1, -4, -5, -6, -7, and -8 were used. The N-methyl group of (1) was assumed to be pseudoequatorial and for the quaternary salts the N-methyl groups were fixed as pseudoaxial. Compounds (2) and (5) are omitted in the calculation of methyl internal rotation because the two methyl signals of (2) are indistinguishable as a result of ring inversion, and an accurate observed T_1 value for the N-methyl group of (5) cannot be measured because the signal overlaps with the solvent signals.

$$1/T_1^{DD} (Me) = 3\hbar^2\gamma_H^2\gamma_C^2 r_{C-H}^{-6}\{1/2[A_1/6D_2 + A_2/(6D_2 + 3D_i/2) + A_3/(6D_2 + 3D_i/2) + B_1/(D_1 + 5D_2) + B_2/(D_1 + 5D_2 + 3D_i/2) + B_3/(D_1 + 5D_2 + 3D_i/2) + C_1/(4D_1 + 2D_2) + C_2/(4D_1 + 2D_2 + 3D_i/2) + C_3/(4D_1 + 2D_2 + 3D_i/2)]\} \quad (3)^2$$

constants are given by equations (4), and α is the angle between the axis of internal rotation and the major axis of the ellipsoid.

The observed T_1 values (T_1^{obs}) were taken as the T_1^{DD} values ($\eta_{C-H} \simeq 1.988$) and were used directly for the calculation.

Table 2. Calculated values of the orientation of the major axes (θ, ψ) * and diffusion rates (D_1, D_2, D_t)

Compound	θ *	ψ *	D_1/D_2	D_t/D_2	$10^{-10}\ D_2/s^{-1}$	$10^{-10}\ D_t/s^{-1}$	$10^{-10}\ D_t/s^{-1}$
(1)	0—2°	0°	1.25	1.12	2.5	3.1	2.8
(2)	3°	0°	2.45		1.5	3.7	
(3)	10—15°	0°	2.35	2.38	1.3	3.1	3.1
(4)	20°	−70 to −80°	1.90	3.30	1.0	1.9	3.3
(5)	10°	0°	1.50		1.0	1.5	

* The orientation of the major axis can be defined by two kinds of angle, θ and ψ on XYZ co-ordinates: θ is the angle between the major axis and the Z axis; ψ is the angle between the X axis and the projection of the major axis on the XY plane.
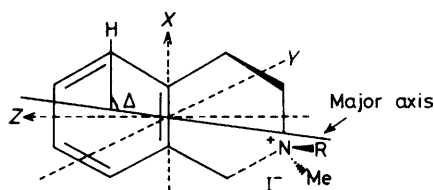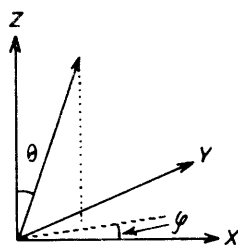
Figure 1. Co-ordinates for the calculation

Results and Discussion

The ^{13}C relaxation times T_1 and the values of the nuclear Overhauser enhancement η_{C-H} of all the carbon atoms except the quaternary ones are shown in Table 1. Since in almost all cases the n.O.e. values can be taken as 1.988 within experimental error, the observed relaxation times (T_1) can be taken as the dipolar relaxation times (T_1^{DD}). For the methyl groups of compounds (3), (4), and (5), accurate n.O.e. values could not be obtained because the signals are small and slightly split into triplets by coupling with ^{14}N. Nevertheless, the influence of these splittings on the ^{13}C T_1 values may not be a problem, since semilogarithmic plots of these N-methyl signals, log ($A - A_0$) vs. t, showed good linearity.

Table 2 summarises the determined values of D_1, D_2, and D_t and the orientations of the major axes (defined by the angles θ and ψ), as well as D_1/D_2 and D_t/D_2.

Although ring A of 1,2,3,4-tetrahydroisoquinolines is subject to both nitrogen and ring inversion, as mentioned earlier, both inversions are slower (ca. 10^4—10^5 s^{-1}) [3,5] than the overall molecular rotation or internal methyl rotation. Neither ring inversion nor nitrogen inversion, therefore, is expected to affect the spin–lattice relaxation.

The Orientation of the Major Axes.—The major axes of molecular rotation defined by the angles θ and ψ in Table 2 can be illustrated as in Figure 2.

In compounds (1) and (2), the major axis nearly coincides with the Z axis. Compound (1) is known to exist in the equilibrium shown in Scheme 1 (R = Me), where a conformer with the N-methyl group pseudoequatorial (A or D) may predominate. Since A and D are mirror images, it is natural that the major axis should be in the plane of the aromatic ring. Although the quaternary salt (2) is different from the free base in that nitrogen inversion is prevented, the two conformers in
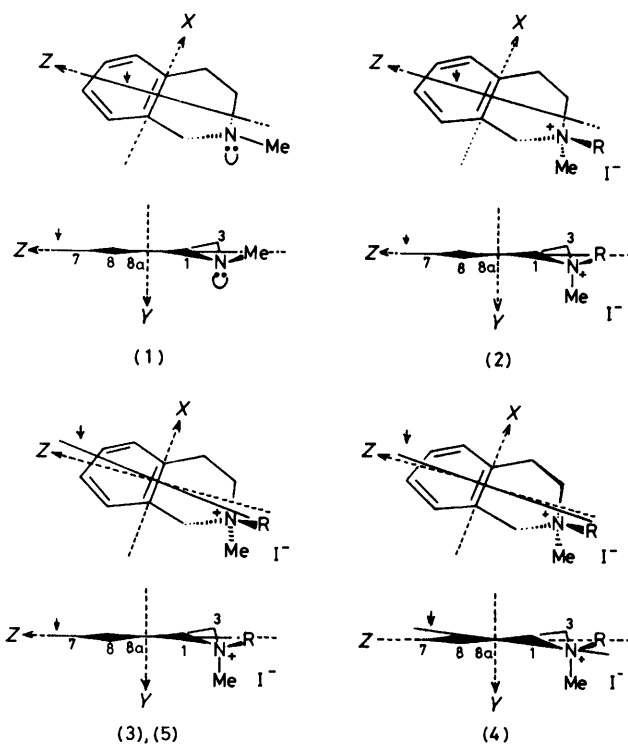
Figure 2. The major axes of molecular rotation

Scheme 2 (R = Me) are equivalent, and so this structure is also expected to have the major axis in the plane of the aromatic ring. The results for (1) and (2) suggest that the difference in size between the C-3 methylene system and the N(2)Me system is not so large as to incline the major axis from the Z axis, although a slight movement of the centre of gravity to the nitrogen atom would be expected.

On the other hand, the major axis of compound (3) inclines slightly (10—15°) from the Z axis towards the nitrogen in the plane of the aromatic ring. This is an effect of the N-ethyl substitution. The ring inversion equilibrium of this salt is expected to lie on the side of conformer a' in Scheme 2
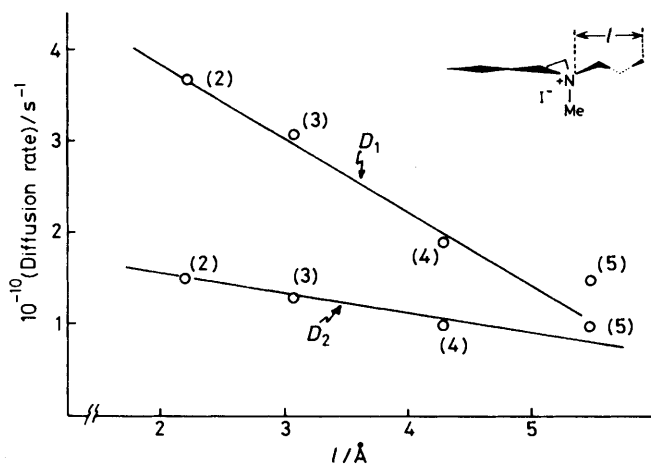
Figure 3. Correlation between rotational diffusion rates (D_1, D_2) and length of alkyl chain (l)

(R = Et), in which the major axis might be moved out of the plane of the aromatic ring. This effect becomes clear in the *N*-propyl derivative (4). The major axis of (4) passes through the centre of the bond between C-4a and C-8a but is not in the plane of the aromatic ring. Furthermore it is inclined slightly towards the nitrogen. These observations are thought to reflect the contribution of conformer a′ in the equilibrium in Scheme 2 (R = Pr^n).

In compound (5), the major axis is on nearly the same line as that of (3). At first sight this is unexpected, but the overall molecular form of (5) cannot be fixed because of the random motion of the long n-butyl chain in the solvent, even if the ring inversion equilibrium shifts toward conformer a′.

Thus it is seen that the differences in orientation of the major axis reflect the delicate differences in conformation of these derivatives.

Rotational Diffusion Rates of Rigid Ring Parts.—In the quaternary salts, lengthening of the alkyl chain might be expected to increase the anisotropy of the molecular motion. However, this is not the case in the present study: in fact D_1/D_2 falls off as the alkyl group is made longer (see Table 2). Plots of D_1 and D_2 *versus* the length of the alkyl group in pseudoequatorial orientation projected on the major molecular axis show linear correlations (Figure 3) except for compound (5), and the longer alkyl groups are seen to restrict and slow down the molecular motion. In these plots, the slope for D_1 is larger than that for D_2; thus D_1/D_2 decreases with increasing length of alkyl group. In ellipsoidal molecules, an increase of the component around one axis may restrict molecular rotational motion along the other axis. However, when the alkyl chain is elongated in the quaternary salts treated here, the longer alkyl group can act to suppress the rotation not only around the axis perpendicular to the major

axis but also around the major axis, by increasing the moment of inertia along the latter axis as a result of segmental motion of the alkyl chain. It is probable that such effect of the elongated alkyl chain is partly masked in the rotation around the perpendicular axis, for which the tetrahydroisoquinoline framework itself is larger in dimension. This effect is thought to make the longer alkyl groups restrict rotational motion about the major axis more than that about the perpendicular axis, diminishing the anisotropic molecular motion. However, the restriction of the rotational motion seems to be not necessarily linearly proportional to the length of alkyl chain, as can be seen for compound (5), which deviates slightly from the linear correlations for both D_1 and D_2. For still longer alkyl chains, the plots of D_1 and D_2 as in Figure 3 are expected to become close to horizontal lines.

Internal Rotation of N-*Methyl Groups.*—Although the D_i/D_2 values differ for compounds (1), (3), and (4), the D_i values resemble one another, indicating similar values of the barrier to methyl rotation.

The barrier to methyl rotation, V_0, is calculated from the experimental value of D_i using D_{i0} as in equation (5).[2] This

$$D_i = D_{i0} \exp(-V_0/RT) \qquad (5)$$

parameter D_{i0} is the jump rate for zero barrier height and is given by equation (6), where I_{Me} is the moment of inertia of

$$D_{i0} = (kT/I_{Me})^{1/2} \qquad (6)$$

a methyl group, 5.35×10^{-40} g cm^2.[6] Substitution of the calculated D_{i0} value and the values of D_i in Table 2 permits the calculation of values V_0 from equation (5): (1) 14.7; (3) 14.5; (4) 14.3 kJ mol^{-1}. These values are larger than those of methylnaphthalenes (8.8—11.7 kJ mol^{-1})[6] and of methyl-benzofurans (4.4—7.9 kJ mol^{-1}),[4,7] perhaps as a result of steric hindrance by the lone pair [in (1)] or by the alkyl group on the same nitrogen atom [in (3) and (4)].

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