Carbon-13 Magnetic Resonance Studies of Cyclic Compounds. Part I. Piperidines and Decahydroquinolines

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Details are reported for proton decoupled ^{13}C spectra of *N*-methyl- and *C*-methyl-piperidines, measured by the pulsed Fourier transform technique. The results yield chemical shift parameters, for ring carbons in six-membered rings, corresponding to the replacement of CH_2 by NH, of CH_2 by CHMe, and of NH by NMe. The predicted ^{13}C shifts of *trans*-decahydroquinoline, and of both major and minor conformations of *cis*-decahydroquinoline, agreed well with the experimental data obtained at room temperature (*trans*) and at −74° (*cis*), where signals for both major (93·5%) and minor (6·5%) conformations of the *cis*-molecule were observed.

APPLICATIONS of proton magnetic resonance spectra to the conformational analysis of cyclic compounds have benefited greatly from the use of chemical shift parameters deduced from the spectra of compounds with known configuration and conformation. The expectation that carbon-13 chemical shift parameters would prove equally valuable encouraged us to measure the proton decoupled ^{13}C spectra of a series of substituted piperidines. Spectral interpretation proved relatively simple. Thus, C-2 and -6 were expected to give signals at lowest field. C-3, -4, and -5 were assigned from the relative intensities of signals, in symmetrically substituted piperidines, and in other cases by assuming that the effect of a *C*-methyl substituent on ^{13}C shifts would be roughly similar to those already reported for cyclohexanes.[1] The ^{13}C shifts for piperidine, 4-methylpiperidine, and 1,4-dimethylpiperidine are close to those given by Morishima *et al.*,[2] despite the difference in solvent. Carbon-13 shifts for piperidines are summarised in Table 1. Table 2 gives chemical shift parameters which have been calculated from the details of Table 1. The nomenclature used here is similar to that employed by Dalling and Grant.[1] For example, $\alpha_e(3)$ is the effect, on the shift of the carbon α to the substituent, caused by replacement of a 3-equatorial hydrogen by a methyl substituent. Effects associated with equatorial substituents were deduced directly from the ^{13}C shifts of the conformationally homogeneous *cis*-2,6- and *cis*-3,5-dimethylpiperidines. Effects associated with axial methyl substituents were deduced from the ^{13}C shifts of *trans*-2,6- and *trans*-3,5-dimethylpiperidines through simple calculations based on the supposition that these molecules exist as 1 : 1 mixtures of two conformations, in each of which one methyl substituent is axial and one is equatorial.

The calculations required two assumptions. The first assumption was that replacement of a 3-equatorial hydrogen by a 3-equatorial methyl group exerted a negligible effect on C-5. This assumption, that $\gamma_e(3)$ is zero, is reasonable in view of the facts (*a*), that $\gamma_e(2)$ was only 0·43 p.p.m., (*b*) that $\gamma_e(4)$ was zero, and (*c*) that γ_e in cyclohexanes is $0 \pm 0{\cdot}6$.[1] The second assumption was that $\gamma_a(3)$ was identical to $\gamma_a(2)$.

In addition to the parameters listed in Table 2 calculations also gave the ^{13}C chemical shifts of the methyl carbons in axial methyl groups attached to piperidines as 18·7 p.p.m. (2- and 6-Me) and 17·9 p.p.m. (3- and 5-Me). The discrepancy between the ^{13}C shifts for an axial 3-methyl group, calculated on the one hand from *trans*-3,5-dimethylpiperidine (17·9 p.p.m.) and on the other hand from 1,*t*-3,*r*-5-trimethylpiperidine (16·3 p.p.m.), is not unexpected in view of differing positions of conformational equilibrium about the nitrogen atom and, associated with this, differing 1,3-diaxial interactions.

As an example of the use of these parameters, the ^{13}C

TABLE 1

^{13}C Chemical shifts for piperidines in C_6D_6 (p.p.m. downfield from Me_4Si)

Piperidine	C-2	C-6	C-3	C-5	C-4	C-Me	N-Me
(Parent)	47·90	47·90	27·73	27·73	25·89		
2-Methyl	53·63	48·34	36·03	27·51	26·22	23·42	
3-Methyl	56·01	47·90	33·34	27·95	34·95	19·96	
4-Methyl	47·90	47·90	36·90	36·90	32·58	22·98	
1,4-Dimethyl	56·53	56·53	35·18	35·18	30·96	22·12	46·72
cis-2,6-Dimethyl	53·73	53·73	35·50	35·50	26·32	23·53	
trans-2,6-Dimethyl	46·50	46·50	33·34	33·34	20·06	20·93	
cis-3,5-Dimethyl	55·03	55·03	33·01	33·01	43·70	19·86	
***trans*-3,5-Dimethyl**	54·17	54·17	**28·16**	28·16	40·46	18·88	
1,*c*-3,*r*-5-Trimethyl	64·42	64·42	**31·72**	31·72	42·62	19·74	46·61
1,*t*-3,*r*-5-Trimethyl	63·77	63·77	28·16	28·16	39·39	18·02	47·37

[1] D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, 1967, **89**, 6612.

[2] I. Morishima, K. Okada, T. Yonezawa, and K. Goto, *J. Amer. Chem. Soc.*, 1971, **93**, 3922.

shifts in 2-*c*,4-*c*,6-*r*-trimethylpiperidine were calculated from the data of Table 2. The results in δ values (p.p.m. from Me_4Si) were converted into δ values (p.p.m. from CS_2), using 193·1 p.p.m. as the ^{13}C shift of CS_2 from Me_4Si. The shifts which emerged: 139·0 (C-2, C-6), 149·8 (C-3, C-5), 159·7 (C-4), 169·9 (2-Me, 6-Me), and 170·1 (4-Me) compared favourably with the experimentally determined values of 140·5, 149·0, 160·8, 169·0, and 170·0 p.p.m. respectively.[3]

TABLE 2

Effects on ^{13}C shifts in piperidines caused by replacement of ring hydrogens by methyl substituents (p.p.m., positive ≡ increasing downfield shift)

Position, orientation of methyl	Ring carbon affected	Description of effect	Effect
1	2	β(N)	9·01
1	3	γ(N)	−1·50
1	4	δ(N)	−0·84
2e	2	$\alpha_e(2)$	5·40
2e	3	$\beta_e(2)$	7·77
2e	4	$\gamma_e(2)$	0·43
2a	2	$\alpha_a(2)$	−2·54
2a	3	$\beta_a(2)$	3·39
2a	4	$\gamma_a(2)$	−6·23
3e	3	$\alpha_e(3)$	5·28
3e	2	$\beta_e(3)$	7·13
3e	4	$\beta_e(3)$	8·91
3e	5	$\gamma_e(3)$	0 *
3a	3	$\alpha_a(3)$	1·91
3a	2	$\beta_a(3)$	5·41
3a	4	$\beta_a(3)$	5·66
3a	5	$\gamma_a(3)$	−6·23 †
4e	4	$\alpha_e(4)$	6·69
4e	3	$\beta_e(4)$	9·17
4e	2	$\gamma_e(4)$	0

* Assumed zero (see Discussion section). † Assumed equal to $\gamma_a(2)$ (see Discussion section).

It must be emphasised that many of the parameters of Table 2 are based on a single example, albeit one of indisputable stereochemistry; refinements are therefore to be expected as further examples come to light. The parameters for 4-methyl substitution are similar to those reported by Ellis and Jones.[4]

The proton-decoupled ^{13}C spectrum of *trans*-decahydroquinoline (1) (details in Table 3) showed eight signals, two resonances being superimposed. In the undecoupled spectrum, all signals were triplets except those centred on 62·8 and 43·7 p.p.m. (C_6D_6), which are therefore due to the ring junction C-4a and C-8a. C-8a, being adjacent to nitrogen, is expected to lie at lowest field and therefore the signal at 62·8 p.p.m. is assigned to this carbon. For the same reason the lowest field triplet in the undecoupled spectrum, centred on 47·9 p.p.m., is assigned to C-2. This assignment was confirmed by the relatively high value of the ^{13}C–H coupling constant, 133 Hz, as compared with 127—129 Hz for the remaining signals; values of $J_{^{13}C-H}$ for methylamine and methane are 133 and 126 Hz respectively. The remaining assignments were based on comparisons of observed and calculated shifts, the latter being derived in the following way. The ^{13}C spectrum of *trans*-decalin (2) in C_6D_6 shows the expected three lines, the shifts being 43·88, 34·63, and 27·10 p.p.m. The weakest line, at 43·88 p.p.m., was assigned to the ring junctions C-4a and C-8a. The *trans*-decalin system may be considered to be a cyclohexane (shift 26·5 p.p.m.), substituted in at C-1 and -2 by equatorial methylene groups. If the methylene substituents behave similarly to methyl substituents (*cf.* ref. 1), C-1, -4, -5, and -8 are expected to be appreciably downfield of C-2, -3, -6, and -7. Consequently, the signal at 34·63 p.p.m. is assigned to C-1, -4, -5, and -8; the signal at 27·10 p.p.m. is assigned to C-2, -3, -6, and -7. Next, it was required to estimate the effect of replacing

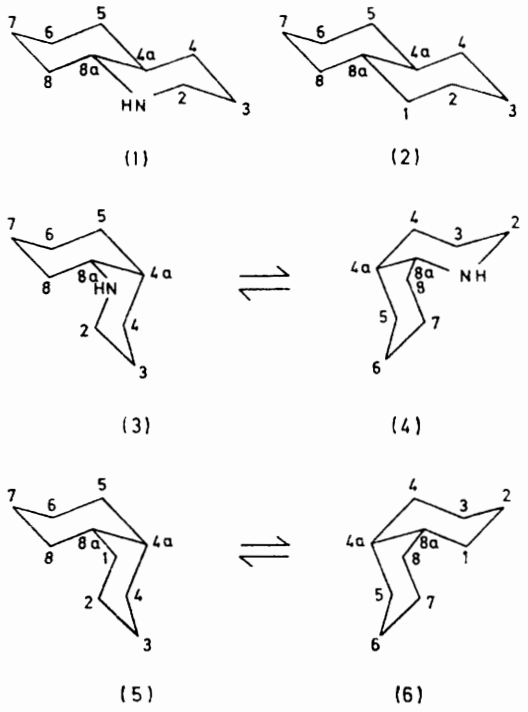

TABLE 3

Carbon-13 spectral data for *trans*-decahydroquinoline (25°)

Carbon	Carbon-13 Shifts (p.p.m. from Me_4Si) Found $CDCl_3$	Found C_6D_6	Calculated	$J_{^{13}C-H}$/Hz (neat)
2	47·6	47·9	48·5	132·8
3	27·6	27·9	28·3	127·0
4	32·9	33·2	34·0	128·0
5	32·9	33·2	34·0	128·0
6	26·5	26·9	27·1	127·0
7	25·9	26·2	26·5	127·0
8	34·1	34·4	35·8	127·0
8a	62·5	62·8	65·3	127·0
4a	43·45	43·7	45·1	129·0

the 1-CH_2 group in *trans*-decalin (2) by the NH group. A comparison of ^{13}C shifts in cyclohexane and piperidine (Table 1) shows that such a replacement affects the shifts of carbon atoms α, β, and γ to the replacement centre by +21·4, +1·2, and −0·6 p.p.m. respectively. These parameters, taken in conjunction with the observed

[3] D. Wendisch, H. Reiff, and R. Schubart, *Org. Magnetic Resonance*, 1972, **4**, 427.
[4] G. Ellis and R. G. Jones, *J.C.S. Perkin II*, 1972, 437.

shifts of *trans*-decalin, gave the calculated ^{13}C shifts for *trans*-decahydroquinoline listed in Table 3.

As expected from the *trans*-fusion of the rings in *trans*-decahydroquinoline, the ^{13}C spectrum of *trans*-decahydroquinoline showed no change when recorded at temperatures down to −80°. This experiment also demonstrated that, for such compounds, nitrogen inversion is a relatively fast process within the range of temperature studied. Of interest, too, is the relatively small effect on ^{13}C shifts of changing the solvent from C_6D_6 to $CDCl_3$ (Table 3).

The proton decoupled ^{13}C spectrum of *cis*-decahydroquinoline (3) ⇌ (4) showed eight lines at room temperature, but line broadening occurred on lowering the temperature. Since nitrogen inversion is expected to be relatively fast, the line broadening was due to a slowing of the ring inversion process (3) ⇌ (4). At −74°, 15 sharp lines were seen (Table 4), nine of which were

TABLE 4

Carbon-13 spectral data for *cis*-decahydroquinoline ($CDCl_3$) (shifts in p.p.m. from Me_4Si)

	(3) ⇌ (4)		(3)		(4)	
	^{13}C		^{13}C Shift		^{13}C Shift	
Carbon	Shift (25°)	$J_{^{13}C-H}$/ Hz	Found (−74°)	Calculated	Found (−74°)	Calculated
2	46·8	132·3	39·3	42·6	47·9	48·6
3	22·3	127·5	29·4	28·4	21·2	22·4
4	30·3	*	23·9	25·2	30·7	32·1
5	26·0	*	31·6	32·1	25·0	25·2
6	26·1	*	†	21·2	26·3	27·2
7	21·2	*	†	26·6	20·4	20·6
8	32·5	127·5	†	27·0	32·8	33·9
8a	54·6	128·5	54·0	57·7	54·9	57·7
4a	35·8	*	35·6	37·5	35·2	37·5

* Not accurately measurable. † Not seen.

attributed to conformation (4), which is known to be the dominant conformation from the ^1H spectrum,[5] and six of which were attributed to the minor conformation (3). It seems probable that the three signals for conformation (3) which were not observed, were masked by the stronger signals for conformation (4). The relative proportion of the conformations (93·5%, 6·5%) was estimated from comparisons of the integrated areas of signals; these comparisons were made for carbon atoms carrying the same numbers of hydrogens, and situated at identical positions (structurally) in the two conformations, in an attempt to counteract intensity distortions caused by differing T_1 values. In the case of the room temperature spectrum of *cis*-decahydroquinoline, assignment of lines to C-2, -4a, and -8a followed the method used for the corresponding *trans*-base. Assignment of the lines in the low temperature spectrum utilised ^{13}C shifts calculated from the observed ^{13}C shifts in *cis*-decalin (5) ⇌ (6), modified by the aforementioned shift parameters associated with replacement of CH_2 by NH. Carbon-13 shifts for *cis*-decalin at room temperature and at −50° are summarised in Table 5. The low temperature spectrum shows five lines of equal intensity due to the carbon atoms indicated [labels refer to conformation (5)]: line 1, C-1 and -5 [equivalent, respectively, to C-4 and -8 in (6)]; line 2, C-4 and -8 [equivalent, respectively, to C-1 and -5 in (6)]; line 3, C-2 and -6 [equivalent, respectively, to C-3 and -7 in (6)]; line 4, C-3 and -7 [equivalent, respectively, to C-2 and -6 in (6)]; and line 5, C-4a and -8a [equivalent to C-4a and -8a in (6)].

TABLE 5

Carbon-13 shifts in *cis*-decalin (5) (p.p.m. from Me_4Si)

Carbon	Room temperature (C_6D_6)	−50° (neat) *
1,5	29·74	32·7
4,8	29·74	25·8
2,6	24·20	21·2
3,7	24·20	27·2
4a,8a	36·73	36·3

* Taken from '^{13}C Fourier Transform N.M.R. Spectra Catalogue,' JEOL Ltd., vol. 2, Tokyo, 1971.

At room temperature, relatively rapid interconversion occurs between the enantiomeric conformations (5) and (6), which are equivalent in n.m.r. terms. As a result, the room temperature spectrum shows merely three lines: one (the weakest) for C-4a and -8a, one for the average of C-1 and -5 (line 1, above, in low temperature spectrum) and C-4 and -8 (line 2), and one for the average of C-2 and -6 (line 3) and C-3 and -7 (line 4). As in the case of *trans*-decalin, assignments were based on the assumption that ^{13}C shifts in (5) could be roughly calculated from the shift of cyclohexane carbons, modified by the effect of equatorial and/or axial CH_2 substitution, this being considered equivalent to substitution by a methyl group (*cf.* ref. 1).

EXPERIMENTAL

The preparations of piperidines [6] and decahydroquinolines [5] have been reported. Pulsed Fourier transform ^{13}C spectra were obtained using Bruker (22·63 MHz), JEOL (25·4 MHz) and Varian (25·4 MHz) equipment.

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[5] H. Booth and A. H. Bostock, *J.C.S. Perkin II*, 1972, 616.
[6] H. Booth and J. H. Little, *Tetrahedron*, 1967, **23**, 291; H. Booth, J. H. Little, and J. Feeney, *ibid.*, 1968, **24**, 279; H. Booth and J. H. Little, *J.C.S. Perkin II*, 1972, 1846.