Conformational Equilibria in *cis*-Decahydroisoquinoline and *C*-Methyl Derivatives: Studies using ^{13}C and ^{1}H Magnetic Resonance Spectroscopy

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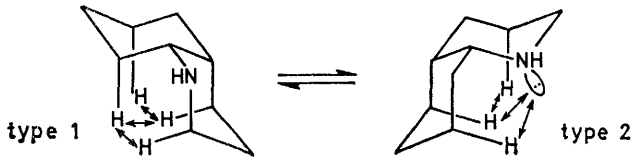
^{13}C N.m.r. spectroscopy at 215 K has demonstrated that the conformational equilibrium in *cis*-decahydroisoquinoline favours the type 1 conformation (70% ΔG° 0.37 kcal mol^{-1}) in which the nitrogen lone pair is able to occupy the ' inside ' position. The type 1 and type 2 conformations become degenerate for both *cis*-decahydroquinoline and *cis*-decahydroisoquinoline when the nitrogen atom is protonated. The two isomers of *cis*(4aH,8aH)-3-methyldecahydroisoquinoline are conformationally homogeneous with the 3-methyl substituent equatorial.

PREVIOUS work [1,2] has demonstrated that the conformational equilibrium (1) ⇌ (2) in *cis*-decahydroquinoline favours the type 2 conformation (2) by *ca.* 1.06 kcal mol^{-1} ($-\Delta G^{\circ}_{1\rightarrow 2}$), the proportions at 199 K being 93.5% (2) and 6.5% (1). Whilst conformation (2) allows the nitrogen lone pair to occupy the hindered ' inside ' position, the actual position of conformational equilibrium at the nitrogen atom is not known. If the conformational entropy difference ($\Delta S^{\circ}_{1\rightarrow 2}$) is negligible, as seems probable, then the conformational enthalpy difference ($-\Delta H^{\circ}_{1\rightarrow 2}$) is also 1.06 kcal mol^{-1}. Further, if it is assumed that the energy situation is dominated by the 1,4-interactions, the enthalpy difference between (1) and (2) is essentially the difference between *two* 1,4 hydrogen–hydrogen interactions and *two* 1,4 hydrogen–lone pair interactions.



(1) (2)

Thus 1,4 H–H − 1,4 H–lone pair = 0.53 kcal mol^{-1}. If the ring geometry of *cis*-decahydroquinoline is little different from that of *cis*-decalin, we can take 0.9 kcal mol^{-1} as the energy of the 1,4 H–H interaction, since three such interactions make up the experimentally determined enthalpy difference (2.69—2.72 kcal mol^{-1}) between *cis*- and *trans*-decalin.[3] Thus each 1,4 H–lone pair interaction in (2) accounts for (0.9—0.53 =) 0.37 kcal mol^{-1}, a value which must be regarded as rough, bearing in mind the assumptions involved in its derivation. Brignell *et al.*[4] and Kessler *et al.*[5] have deduced values of 0.5 and 0.2 kcal mol^{-1}, respectively, for this same interaction.

We now report the position of equilibrium in the related molecule *cis*-decahydroisoquinoline (3) ⇌ (4). Catalytic hydrogenation of isoquinoline gave a mixture of (3) ⇌ (4) and the *trans*-base (5), from which samples of the pure stereoisomers were obtained by preparative g.l.c. (see Experimental section). The ^{13}C n.m.r. spectrum of (5) at 293 K showed nine sharp lines and was unchanged when the temperature was lowered to

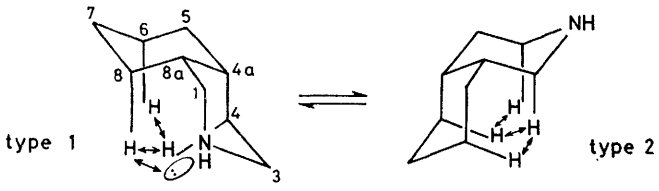
TABLE 1

^{13}C Chemical shifts for decahydroisoquinolines in $CDCl_3$ (p.p.m. downfield from Me_4Si) (calculated shifts in parentheses)

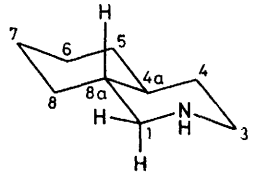
Ring fusion	*cis*	*cis*	*cis*	*trans*	*trans*	*cis*	*cis*	*trans*
Formula	(3) ⇌ (4)	(3)	(4)	(5)	(10)	(12)	(13)	(15)
T/K	321	215 [a]	215 [a]	293	293	293	293	293
C atom								
1	50.3	52.2	45.1	53.0	53.2	45.9	52.8	56.9
		(53.0)	(46.1)	(54.9)	(53.4)	(45.5)	(52.6)	(58.4)
3	45.3	47.0	40.9	47.1	52.5	46.3	52.8	47.0
		(47.5)	(41.5)	(47.4)	(52.5)	(46.3)	(52.4)	(47.5)
4	28.6	24.6	32.3	34.2 [c]	42.2	40.8	34.7	34.6
		(25.9)	(32.8)	(34.7)	(42.0)	(40.1)	(32.4)	(34.2)
5	29.9	31.9	25.1	33.5 [c]	33.5	26.6	32.1	33.9
		(32.7)	(25.8)	(34.6)	(33.5)	(25.1)	(31.9)	(33.5)
6	22.8	20.5	*b*	26.5 [d]	26.5	26.7	20.8	26.6
		(21.2)	(27.2)	(27.1)	(26.5)	(—)	(20.5)	(26.5)
7	24.9	26.5 [c]	21.2	26.2 [d]	26.3	21.7	26.7	26.5
		(27.2)	(21.2)	(27.1)	(26.2)	(21.2)	(26.5)	(26.2)
8	26.8	26.0 [c]	29.8	30.5	30.3	29.6	25.1	29.0
		(25.8)	(31.7)	(33.6)	(30.5)	(29.8)	(26.0)	(27.9) [e]
8a	36.3	35.8	35.4	43.6	42.9	35.4	35.8	49.7
		(36.4)	(36.4)	(44.0)	(43.6)	(35.4)	(35.8)	(51.4)
4a	34.5	34.1	33.8	42.4	42.2	34.9	34.7	42.1
		(34.4)	(34.4)	(42.0)	(42.8)	(34.2)	(34.5)	(42.8)
Me					22.8	22.7	23.0	20.2
					(23.1) [f]	(23.1)	(23.1)	(20.5) [e]

[a] Solvent $CFCl_3$–$CDCl_3$ (9 : 1 v/v). [b] Not seen. [c] Assignments may need to be exchanged. [d] Assignments may need to be exchanged. [e] Includes a mutual shielding of 2.6 p.p.m.[9] [f] Observed shift in 2-methylpiperidine.

220 K. On the other hand, the ^{13}C n.m.r. spectrum of (3) ⇌ (4) at 321 K showed only two sharp lines, at 34.5 and 36.3 p.p.m., the seven remaining lines being broad. The spectrum at 215 K revealed 17 sharp lines out of the 18 expected for a mixture of (3) and (4) at



(3) (4)



(5)

the slow exchange limit. The assignments of Table 1 are based on considerations of electronegativity, on signal multiplicities in off-resonance proton decoupled experiments, and on a comparison of observed shifts with 'calculated' shifts. As in the case of (1) ⇌ (2),[1] the 'calculated' shifts were derived from the ^{13}C chemical shifts in *cis*- and *trans*-decalin, modified by empirical parameters for replacement of a ring CH_2 by a nitrogen atom.

Table 2 lists ^1H n.m.r. spectral data for *cis*- and *trans*-decahydroisoquinolines at 293 K. The spectra of both (5) and (3) ⇌ (4) contain a low-field portion of four signals, well separated at 220 MHz, due to the four protons bonded to C-1 and -3. In the spectrum of (5), the almost first-order pattern allowed assignments of the signals from their multiplicities and splittings. These assignments were confirmed by iterative spectral analysis and computer simulation; for this purpose the four-bond coupling constants were ignored and the low-field signals were treated in two parts, a three-spin system for 8a-, 1eq-, and 1ax-H, and a four-spin system for 3eq-, 3ax-, 4eq-, and 4ax-H. Although it was obviously necessary to make an arbitrary choice of chemical shifts for 8a-, 4eq-, and 4ax-H, the final simulated spectrum for protons bonded to C-1 and -3 was only mildly sensitive to the exact values chosen in the range covered by the uninterpretable high-field envelope (δ 0.50—1.50), presumably due to the relatively large chemical shift differences involved. Analysis of the low-field region of the 220 MHz spectrum of the *cis*-molecule (3) ⇌ (4) was more difficult because the system is more second order, and because the chemical shifts and coupling constants are necessarily weighted averages of those in conformations (3) and (4). Nevertheless, a satisfactory match of observed and computer-simulated spectra was obtained. The values for vicinal proton–proton coupling constants, and particularly those for $J_{1,8a}$ (Table 2) confirm the assignment of conformation (5) to the *trans*-amine and the assignment of a mixture of conformations (3) and (4) to the *cis*-amine.

TABLE 2

Spectral data for protons in decahydroisoquinolines (100 or 220 MHz; $CDCl_3$)

Formula	Stereochemistry	Chemical shift (δ) 1eq-H	1ax-H	3eq-H	3ax-H	CH_3
(5)	*trans*(4aH,8aH)	2.87	2.24	3.08	2.62	
(3) ⇌ (4)	*cis*(4aH,8aH)	2.71,*	2.84 *	2.63,*	2.97 *	
(10)	*cis*(3 H,4aH) *trans*(4aH,8aH),	2.88	2.32		2.64	1.04
(12)	*trans*(3 H,4aH), *cis*(4aH,8aH)	2.61	3.00		2.81	1.00
(13)	*cis*(3 H,4aH), *cis*(4aH,8aH)	2.9 †	2.8 †		2.60	1.07
(15)	*cis*(1 H,4aH), *trans*(4aH,8aH)		2.27	3.03	2.71	1.00

Approximate coupling constants (Hz)

Formula	$J_{1eq,1ax}$	$J_{3eq,3ax}$	$J_{1eq,8a}$	$J_{1ax,8a}$
(5)	11.9	12.0	2.9	10.2
(3) ⇌ (4)	12.5	12.5	3,5 * 4.8 *	

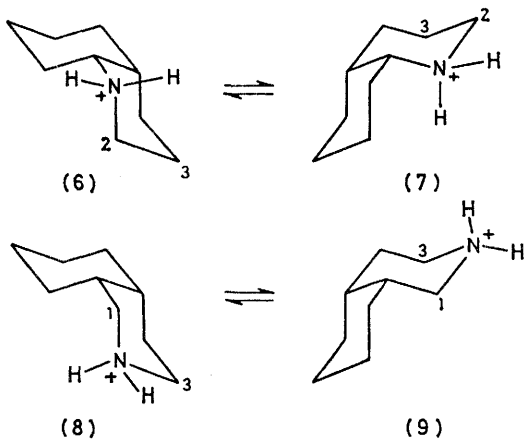
Formula	$J_{3eq,4eq}$	$J_{3ax,4ax}$	$J_{3eq,4ax}$	$J_{3ax,4eq}$
(5)	2.0	12.1	3.0	2.9
(3) ⇌ (4)	3.6,* 4.0,* 5.6,* 8.6 *			

* Stereochemical labels not appropriate, due to the averaging effects of fast ring inversion. † Approximate figures, which may also need to be exchanged.

The proportions of (3) and (4) at 215 K were obtained from the relative areas of ^{13}C signals assigned to structurally identical carbon atoms. The techniques necessary to obtain meaningful areas were fully discussed in an earlier paper.[6] The measured proportions [70.0% (3); 30.0% (4)] are equivalent to a value for $\Delta G^\circ_{3\rightarrow4}$ of 0.37 kcal mol^{-1}. It seems probable that $\Delta H^\circ_{3\rightarrow4}$ is also 0.37 kcal mol^{-1}. Now the considerations applied above to *cis*-decahydroquinoline (1) ⇌ (2) lead to the prediction that conformation (3), which allows the nitrogen lone pair to occupy an 'inside' position, should be favoured over (4), the enthalpy difference being the difference between *one* 1,4 H–H interaction and *one* 1,4 H–lone pair interaction. Thus (3) is expected to be favoured by *ca.* 0.53 kcal mol^{-1}. The discrepancy between expectation and observation is due probably to the slightly different ring geometries of decahydroquinoline and decahydroisoquinoline, resulting essentially from the different positions of the nitrogen atom with respect to the ring junction. Clearly the formally identical 1,4-interactions will not be equal in the two systems. Interestingly, the observed conformational free energy difference of 0.37 kcal mol^{-1} in (3) ⇌ (4) is in good agreement with that of 0.4 kcal mol^{-1} deduced by Aaron and Ferguson [7] from i.r. data on decahydroisoquinolinols.

The explanation advanced to account for the position of equilibria in (1) ⇌ (2) and (3) ⇌ (4) received further support from the ^{13}C n.m.r. spectra of the protonated bases. A low-temperature ^{13}C spectrum of a solution of (1) ⇌ (2) in $CDCl_3$–CH_3CO_2H showed equal proportions of the ionic conformations (6) and (7), which

are indeed expected to have almost identical geometries. The proportions of (6) and (7) at 243 K were deduced from the relative areas of the well separated ^{13}C signals for C-2 at 39.4 in (6) and 46.3 p.p.m. in (7); C-2 in (6) is expected to be considerably shielded, relative to C-2 in (7), as in the conformations of the free base.[1] A similar experiment using decahydroisoquinoline (3) $\rightleftharpoons$



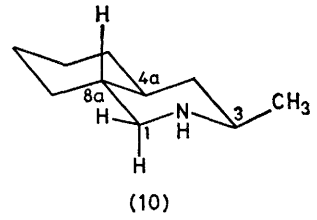
(6) (7)

(8) (9)

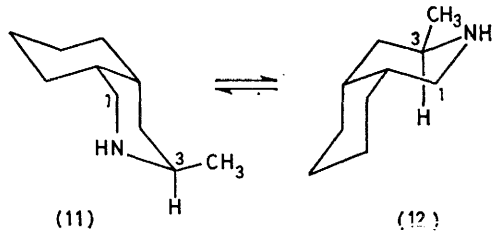
(4) also gave equal proportions for the corresponding ions (8) and (9). In the mixture of (8) and (9) at 223 K, C-1 gave signals at 51.1 for (8) and 44.2 p.p.m. for (9), whilst C-3 gave signals at 46.1 for (8) and 40.6 p.p.m. for (9).

The relatively small free energy difference between conformations (3) and (4), compared with the conformational free energy difference (1.74 kcal mol^{-1}) in methylcyclohexane,[8] leads to the firm prediction that a *C*-methyl-*cis*-decahydroisoquinoline will exist largely (>95%) in that conformation carrying an equatorial methyl group. The prediction was tested by the preparation and spectral analysis of the two isomers of *cis*-decahydro-3-methylisoquinoline. The catalytic hydrogenation of 3-methylisoquinoline gave a mixture of perhydro-bases which were separated by preparative g.l.c. into *cis*(3*H*,4a*H*),*trans*(4a*H*,8a*H*)-decahydro-3-methylisoquinoline (10), *trans*(3*H*,4a*H*),*cis*(4a*H*,8a*H*)-decahydro-3-methylisoquinoline (11) $\rightleftharpoons$ (12) and *cis*-(3*H*,4a*H*),*cis*(4a*H*,8a*H*)-decahydro-3-methylisoquinoline (13) $\rightleftharpoons$ (14). The isomer with *trans*-fused rings was readily identified from its ^{13}C n.m.r. spectrum, the signals being assigned in the normal way. The ^{13}C chemical shifts (Table 1) show good agreement with chemical shifts calculated by combining the *observed* chemical shifts in the parent (5) with the shift parameters for substitution of equatorial hydrogen in piperidine by methyl.[1] The ^1H n.m.r. spectrum of this amine (shifts in Table 2) gave the coupling constants between 8a-H and the two protons attached to C-1 as 3.0 and 9.7 Hz, values which are consistent with conformation (10) but which would not exclude the *cis*-fused conformations (12) and (14), in the absence of evidence from the ^{13}C spectrum. In a spin decoupling experiment, the multiplet due to 3-H at δ 2.75—2.53 was simplified to a doublet, separation 12 Hz, probably because 4eq-H suffered simultaneous irradiation. However, the experiment did confirm the axial character of 3-H.

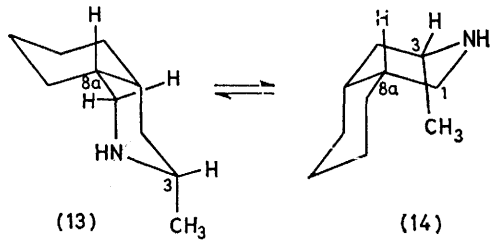
Both *cis*-fused isomers, a crystalline solid (11) $\rightleftharpoons$ (12) and a liquid (13) $\rightleftharpoons$ (14) gave ^{13}C n.m.r. spectra at 294 K in which all signals were sharp, in contrast to the parent molecule (3) $\rightleftharpoons$ (4), for which the room temperature spectrum shows broad lines for all carbons except the ring junction carbons 4a and 8a. Evidently each isomer consists largely of *one* conformation. Comparison between observed and calculated ^{13}C chemical shifts (Table 1) established beyond doubt that (a) the solid base was (11) $\rightleftharpoons$ (12), and (b) the dominant conformations were (12) for (11) $\rightleftharpoons$ (12) and (13) for (13) $\rightleftharpoons$ (14). Additional support came from the ^1H n.m.r. spectra of the two bases. In the ^1H spectrum of the solid base, the signal for 1ax-H was a triplet, with separations of 12 Hz, thus implicating either conformation (12) or (14). The complex multiplet for 3-H was simplified to a quartet on irradiation of the methyl protons at δ 1.0; since the splittings in this quartet were 9.5 and 3.7 Hz, 3-H must be axial, thus confirming (12) for the solid base. The 3-H multiplet at δ 2.60 in the spectrum of the liquid base (13) $\rightleftharpoons$ (14) collapsed



(10)



(11) (12)

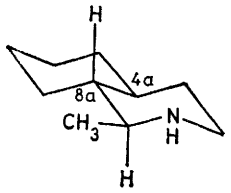


(13) (14)

to a doublet, with a separation between the rather broad signals of 10—11 Hz, establishing the *axial* nature of 3-H, as in conformation (13).

An attempt to prepare one or both of the isomers of *cis*(4a*H*,8a*H*)-decahydro-1-methylisoquinoline gave as the sole isolable product *cis*(1*H*,4a*H*),*trans*(4a*H*,8a*H*)-decahydro-1-methylisoquinoline (15), the stereo-

chemistry of which was conclusively settled from ^{13}C chemical shifts (Table 1) and from ^{1}H n.m.r. data. The multiplet for 1-H at δ 2.27 in the ^{1}H n.m.r. spectrum of



(15)

(15) collapsed to a doublet, separation 9 Hz, on irradiation at the chemical shift of the methyl protons, confirming that 1-H is axial.

EXPERIMENTAL

General details for the measurement of ^{13}C n.m.r. spectra have been given previously.[9,10] 100 MHz ^{1}H N.m.r. spectra were recorded on a JEOL-MH 100 spectrometer. 220 MHz ^{1}H N.m.r. spectra were measured on the S.R.C. Varian HR-220 spectrometer at Harwell.

cis(4aH,8aH)- *and* trans(4aH,8aH)-*Decahydroisoquinoline.*—Isoquinoline (25 g) in cyclohexane (300 cm³) was reduced with hydrogen at 60 atm. and 180° in the presence of Raney nickel (2 teaspoonfuls; T-1 grade [11]). After 3 days the mixture was filtered and distilled, the crude product (17.6 g) having b.p. 100—102° at 30 mmHg. The two isomers were separated by preparative g.l.c. (Varian Aerograph series 700) on a 12 ft × ⅜ in column of 20% Carbowax 20M on alkali-washed Chromosorb W. *cis*-(4aH,8aH)-Decahydroisoquinoline was obtained as a liquid, picrate, m.p. 152—154° (lit.,[12] 150°) (Found: C, 48.7; H, 5.5; N, 14.9. Calc. for $C_{15}H_{20}N_4O_7$: C, 48.9; H, 5.4; N, 15.2%). *trans*(4aH,8aH)-Decahydroisoquinoline was a liquid, picrate, m.p. 177.5—179.5° (lit.,[12] 177°) (Found: C, 48.8; H, 5.8; N, 14.9%).

Hydrogenation of 3-*Methylisoquinoline.*—3-Methylisoquinoline (25 g) in cyclohexane (300 cm³), was hydrogenated at 40 atm. pressure of hydrogen and 180° over Raney nickel (2 teaspoonfuls; T-1 grade). After 4 days the mixture was filtered and distilled, the crude amine (20.8 g) having b.p. 110—113° at 14 mmHg. Analytical g.l.c. (Pye series 104) using a 9 ft × ¼ in column of 20% Carbowax 20M on alkali-washed Chromosorb W, showed the presence of three major components. Preparative g.l.c. employed a Varian Aerograph series 700 and used a 12 ft × ⅜ in column of 10% OV17 silicone on acid-washed and dimethylchlorosilane-treated diatomite C. cis(3H,4aH),trans(4aH,8aH)-*Decahydro-3-methylisoquinoline*, with shortest retention time, was a crystalline solid, m.p. 42.5—44°. The derived *picrate*, from ethanol, had m.p. 173—174° (Found: C, 50.3; H, 5.9; N, 14.5. $C_{17}H_{22}N_4O_7$ requires C, 50.3; H, 5.8; N, 14.7%).

cis(3H,4aH),cis(4aH,8aH)-*Decahydro-3-methylisoquinoline* was a liquid; *picrate*, m.p. 170—171° (Found: C, 50.0; H, 6.2; N, 14.5%).

trans(3H,4aH),cis(4aH,8aH)-*Decahydro-3-methylisoquinoline*, with longest retention time, was a crystalline solid, m.p. 54.5—55.5°. The *picrate* had m.p. 187—188.5° (Found: C, 50.6; H, 6.1; N, 14.4%).

cis(1H,4aH),trans(4aH,8aH)-*Decahydro-1-methylisoquinoline.*—1-Methylisoquinoline (20 g) in cyclohexane (300 cm³) was hydrogenated at 85 atm. pressure of hydrogen and 180° over Raney nickel (2 teaspoonfuls; T-1 grade). After 6 days the mixture was filtered and distilled. Analytical g.l.c. (see preceding preparation for details) showed one major constituent, which was shown to be cis(1H,4aH),-trans(4aH,8aH)-*decahydro-1-methylisoquinoline.* The derived *picrate* had m.p. 197—199° (Found: C, 49.9; H, 5.5; N, 14.5. $C_{16}H_{22}N_4O_7$ requires C, 50.3; H, 5.8; N, 14.7%).

[8/1061 *Received*, 6*th June*, 1978]

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