Configurational Prevalence at the Nitrogen Atom in Chiral, Open Chain, Secondary Amines

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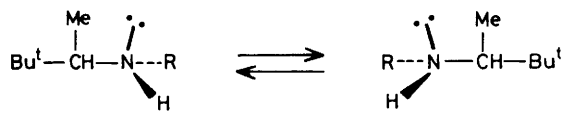
The stereochemistry of chiral, open chain, secondary amines has been studied by means of low-temperature ^1H and ^{13}C n.m.r. spectroscopy and by PCILO molecular-orbital calculations. The chiral nitrogen assumes a strongly prevalent configuration under the asymmetric induction of a vicinal asymmetric carbon atom. In the most probable conformation of the secondary amine the lone pair of the nitrogen is placed in the most crowded position.

In principle a nitrogen atom bearing three different substituents will have a preferred configuration when adjacent to an asymmetric centre. Thus, the equilibrium constant for interconversion between the two diastereoisomers of a chiral secondary amine, as shown in Scheme 1, is different from unity. It should be possible to confirm that such an equilibrium exists by means of dynamic n.m.r. spectroscopy. The nitrogen inversion process may be slowed down sufficiently to display separate signals for the isomers and measuring the concentration of the above reported diastereoisomers should yield the equilibrium constant.

The barrier to nitrogen inversion in Me_2NH,[1] the simplest secondary amine, is 4.4 ± 1.1 kcal mol^{-1}. As has been pointed out for cyclic [2] and other amine derivatives,[3] steric bulkiness at the nitrogen atom tends to decrease this value, so that slowing down of the nitrogen inversion process is expected at temperatures lower than −150 °C in both (1) and (2).

Low-temperature ^{13}C and ^1H n.m.r. spectra of (1) and (2), in Freon 22 as the solvent, were recorded down to −155 °C. Carbon spectra are the most useful at detecting the presence of exchange because of the larger chemical-shift differences between the different isomeric species. These spectra showed a progressive, but different, broadening of all resonances of the carbon atoms present in the molecules (Figures 1 and 2). Below −140 °C the C–Bu^t signals split into two signals with intensities in the ratio 2 : 1. A line-shape analysis for these two signals in the temperature range −110 to −150 °C gave ΔG = 4.9 ± 0.3 and 5.9 ± 0.3 kcal mol^{-1}, for (1) and (2), respectively. The two signals observed for the C–Bu^t cannot, however, be attributed to the diastereoisomers, because we observed the same process in the corresponding primary amine (R = H), where the nitrogen atom is not an asymmetric centre. Thus, a slow inversion at nitrogen is probably not the cause of these



Scheme 1. (1) R = Me; (2) R = Bu^t

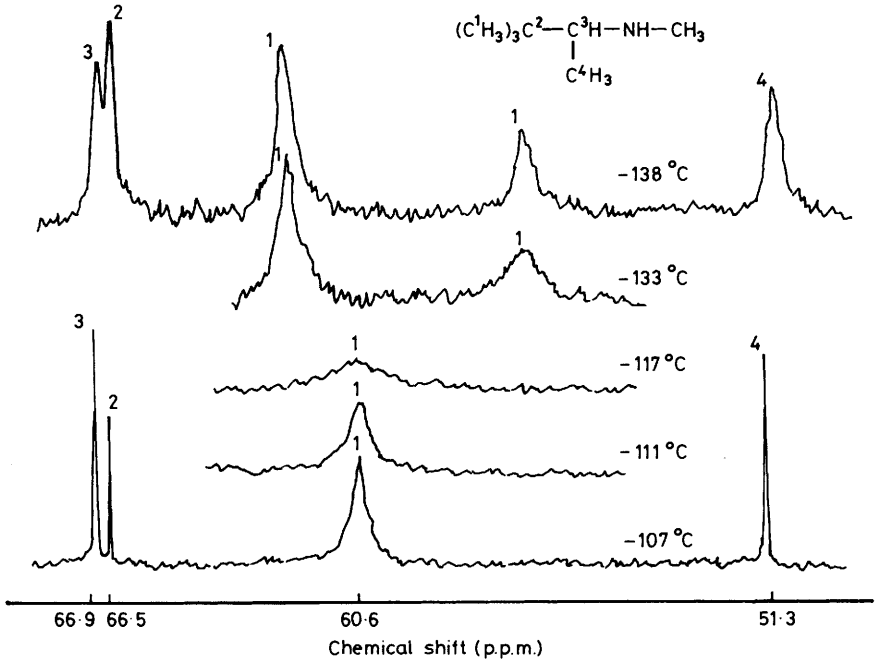


Figure 1. The 25.2 MHz ^{13}C n.m.r. spectra of (1) in Freon 22, at different temperatures (chemical shifts in p.p.m. from Me_4Si)

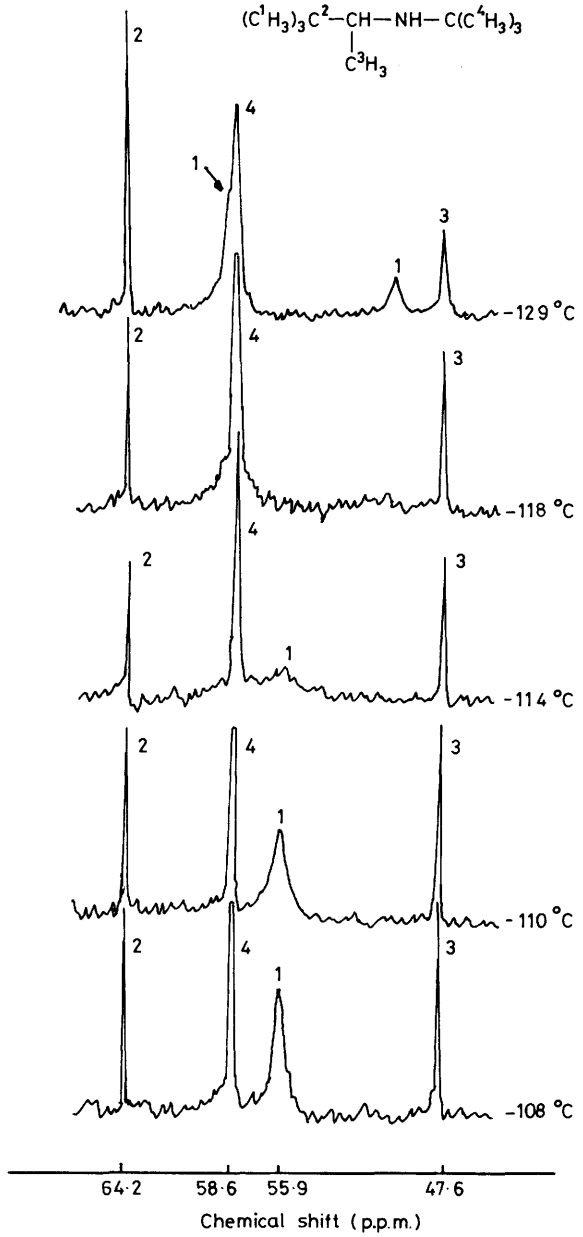
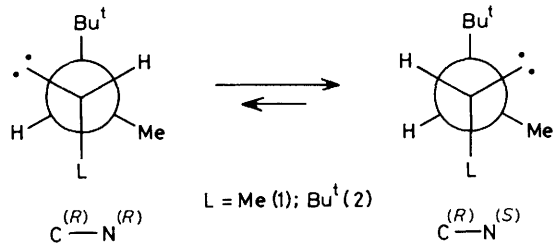


Figure 2. The 25.2 MHz ^{13}C n.m.r. spectra of (2) in Freon 22, at different temperatures (chemical shifts in p.p.m. from Me_4Si)

separate C–Bu^t signals; in fact this effect is due to a slow rotation about the C–C bond. This should give three different Me resonances and the observation of only two signals must arise from an accidental equivalence of two of the methyls. Such an intensity ratio in the case of ' locked ' Bu^t groups has been found in other compounds and was attributed to an accidental coincidence of chemical shifts.[4] A doublet of signals with relative intensities 2 : 1 has been observed for the methyl group of Bu^t in the ^1H n.m.r. spectra of Me_3CCMe_2X.[4b] In the case of (2), a slow rotation of the N–Bu^t group is not observed.

However, by lowering the temperature, useful information on the stereochemistry of secondary amines in solution could be obtained from the values of J_{HCNH} determined by ^1H n.m.r. spectroscopy, provided that proton exchange at the nitrogen atom was slow enough with respect to the n.m.r. time scale.

The exchange of the N–H proton is slow enough at about



Scheme 2.

$Bu^t—CH_2NH—Bu^t$

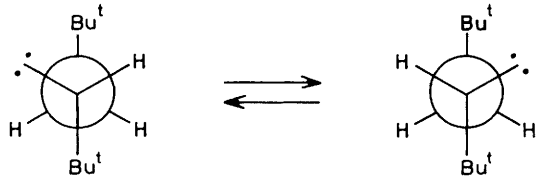
(3)

−100 °C for the C–H protons to show two quartets in the 100 MHz proton spectrum. The J_{HCNH} coupling constant is 3.0 and 3.8 Hz for (1) and (2), respectively, and does not vary on decreasing the temperature,* only a broadening of the C–Bu^t proton signals having been observed without any coalescence–decoalescence phenomenon.

The ^1H n.m.r. data can afford interesting conclusions with the aid of conformational analysis. Quantum mechanical conformational analysis has been performed on (1) and (2), using the semi-empirical method PCILO, which, owing to the aliphatic character of the molecule, should be particularly appropriate.[5] Standard bond distances and angles, with all bonds of the group Bu^t–CH–Me fixed in a staggered position, and the (*R*) absolute configuration for the asymmetric carbon atom were assumed in order to calculate the atomic co-ordinates. In practice only the torsions around the C–N bond for (1) and the C–N and N–Bu^t bond for (2) were studied starting from the zig-zag planar conformation in which the Bu^t group bonded to the asymmetric carbon atom was *trans* to the N–Me or N–Bu^t group in (1) and (2), respectively. The calculations indicate a conformation, where the largest group (C–Bu^t and N–Me or N–Bu^t) is in a quasi-*trans* position, which is the most stable (Scheme 2). Only small oscillations around the equilibrium position are allowed in (2), owing to the steric hindrance to the C–N torsion exerted both by the C–Me and the C–Bu^t groups, whereas larger oscillations are allowed in the case of (1). Torsion around the N–Bu^t bond for each of the above conformations cannot decrease the energy of (2) any further. As a consequence the limit conformations reported in Scheme 2 can be assumed for the two diastereo-isomers obtained by nitrogen inversion.

These two different conformations can be distinguished by means of the J_{HCNH} value. A vicinal diaxial CH_{ax}–NH_{ax} coupling constant of about 13 Hz has been measured[6] in 1-methyl-1,3-diazane, whereas the value reported for $J_{HC_{eq}NH_{ax}}$ is about 3 Hz in the same compound. Therefore a value of less than 4 Hz found for J_{HCNH} in both (1) and (2) supports a *cisoid* situation for the H–C–N–H fragment and then the large prevalence of the $C^{(R)}$–$N^{(S)}$ or $C^{(S)}$–$N^{(R)}$ diastereoisomer. In order to check this conclusion we have studied the ^1H n.m.r. spectrum of compound (3) at low temperatures. Because of nitrogen inversion two CH_2 protons are equivalent and only the average value of J_{HCNH} is measured. Moreover, the two CH_2 protons share, with equal probability, the two *cisoid* and *transoid* positions with respect to the N–H proton (Scheme 3). Indeed the measured value of $J = 7$ Hz

* It is noteworthy that a slowing down of the proton exchange occurs at −60 °C in isopentane and at <75 °C in CD_2Cl_2. The same values of J_{HCNH} for (1) and (2) have however been obtained.



Scheme 3.

agrees with the average value of 13 Hz for the *transoid* and about 3 Hz for the *cisoid* situation.*

The n.m.r. and PCILO results are consistent with a stereochemistry of the amine in which the most bulky groups on the carbon and nitrogen atoms are in the *anti*-position. The configurational prevalence on the nitrogen atom, which is very high at the low temperatures examined, is related to the difference in the steric hindrance of the H-atom and the lone pair, assuming the latter to be in the most crowded position.

In the investigation of the axial–equatorial N–H equilibrium in piperidine the H-atom is reported [8] to assume a predominantly equatorial position, *i.e.*, the less hindered one.

Experimental

The g.l.c. was carried out on a Perkin-Elmer F30 A instrument, equipped with 200 × 0.29 cm dual columns packed with 20% silicon gum rubber (SE-30) on 80—100 mesh Chromosorb W.

^1H and ^{13}C n.m.r. spectra were recorded, with Freon 22 as the solvent, on a Varian XL-100 instrument, equipped with a standard low-temperature device, using ^{19}F as the external lock. The temperature was monitored with a thermocouple inserted in a dummy tube before and after each series of accumulations.

N-*Methyl*-1,2,2-*trimethylpropylamine* (1).—8.2 g (0.08 mol) of 1,2,2-trimethylpropylamine, obtained by hydrogenation of 3,3-dimethylbutan-2-one oxime [9] with Raney Ni in ammonia–ethanol, were treated in ether and water with 9 g (0.08 mol) of ethyl chloroformate and with 3.6 g (0.09 mol) of sodium hydroxide in 50 ml of water.[10] 13.2 g (0.075 mol) of ethyl 1,2,2-trimethylpropylcarbamate were isolated, b.p. 106 °C at 19 mmHg, n_D^{25} 1.3570, d_4^{25} 0.9303. The latter was reduced with 5 g (0.15 mol) of $LiAlH_4$ in THF to give, in 62.5% yield, 5.75 g (0.05 mol) of (1) having b.p. 114 °C, d_4^{25} 0.7553, n_D^{25} 1.4106 (lit.,[11] b.p. 108—111 °C, n_D^{25} 1.4110).

N-*t-Butyl*-1,2,2-*trimethylpropylamine* (2).—Using the Leuckart–Wallach reaction,[12] 25.1 g (0.55 mol) of formic acid and 22.14 g (0.03 mol) of t-butylamine were kept at 170 °C until no more water condensed. Then 9.1 g (0.06 mol) of t-butyl methyl ketone and 3 g (0.06 mol) of formic acid were added and the mixture was refluxed for 8 h. After the addition of 25 ml of HCl (10N) the refluxing was continued for 3 more hours. The mixture was cooled, extracted with ether, and basified with 40% aqueous solution of KOH. Isolation with ether and distillation gave 3.2 g (0.02 mol) of (2), chemically pure by gas-chromatographic analysis, b.p. 99—100 °C at 25 mmHg (Found: C, 76.35; H, 14.9; N, 8.7. $C_{10}H_{23}N$ requires C, 76.43; H, 14.65; N, 8.92).

N-*t-Butyl*-2,2-*dimethylpropylamine* (3).—Using the above procedure, from 7.83 g (0.09 mol) of 2,2-dimethylpropionaldehyde and 22.14 g (0.31 mol) of t-butylamine compound (3) was obtained, in 55.5% yield (7.8 g, 0.05 mol), b.p. 30—31 °C at 19 mmHg, with chemical purity, as determined by gas chromatography, 99% (Found: C, 75.5; H, 14.75; N, 9.75. $C_9H_{21}N$ requires C, 75.52; H, 14.68; N, 9.8%).

Conformational-energy calculations were carried out by means of a standard PCILO program.[13]

* A similar use of coupling constants has been made, for instance, in the conformational investigation of aliphatic ethers.[7]

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