The Application of Low Temperature ^{13}C Nuclear Magnetic Resonance Spectroscopy to the Determination of the *A* Values of Amino-, Methylamino-, and Dimethylamino-substituents in Cyclohexane

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Determinations of nuclear Overhauser enhancements and spin–lattice relaxation times of carbon atoms in *cis*-2,4-dimethylpiperidine have shown that the measured integrals in a pulsed Fourier transform ^{13}C spectrum recorded below 220 K are an accurate indication of the molecular proportions involved, provided (a) the comparison is between protonated carbons carrying the same number of protons, and (b) the pulse repetition time is at least 2 s. The variable temperature ^{13}C spectra of *cis*-4-methylcyclohexylamine, *cis*-4,*N*-dimethylcyclohexylamine, and *cis*-4,*NN*-trimethylcyclohexylamine have been measured and interpreted, yielding ^{13}C chemical shift parameters for conformations with equatorial and axial NH_2, NHMe, and NMe_2 groups attached to cyclohexane. The proportions of conformations obtained from the low-temperature spectra have given the following *A* values, in kcal mol^{-1}: NH_2 1.45 ($CFCl_3$–$CDCl_3$) and 1.49 ([$^2H_8$]toluene); NHMe 1.29 ($CFCl_3$–$CDCl_3$) and 1.11 ([$^2H_8$]toluene); and NMe_2 1.53 ($CFCl_3$–$CDCl_3$) and 1.31 ([$^2H_8$]toluene). The *A* values are discussed with reference to previously reported values, and to the trend in the series NH_2, NHMe, and NMe_2. An *A* value for Me of 1.78 ± 0.12 kcal mol^{-1}, at 193 K, was deduced from the low temperature ^{13}C spectrum of methyl *cis*-4-methoxycyclohexyl ether.

THE *A* values of substituents attached to cyclohexane {also frequently referred to as $-\Delta G°$ values, where $-\Delta G° = RT \ln K$ and $K = [(2)]/[(1)]$} are important because they reflect the fundamental forces of attraction and repulsion between nuclei and electrons, forces which remain ill defined and the subject of continued speculation. Hitherto, 'conformational analysis', relying largely on the assumption that van der Waals forces of repulsion between non-bonded atoms were primarily responsible for differences in free energy, has been remarkably successful in predicting preferred conformations and in explaining the stereoselectivity of many reactions.

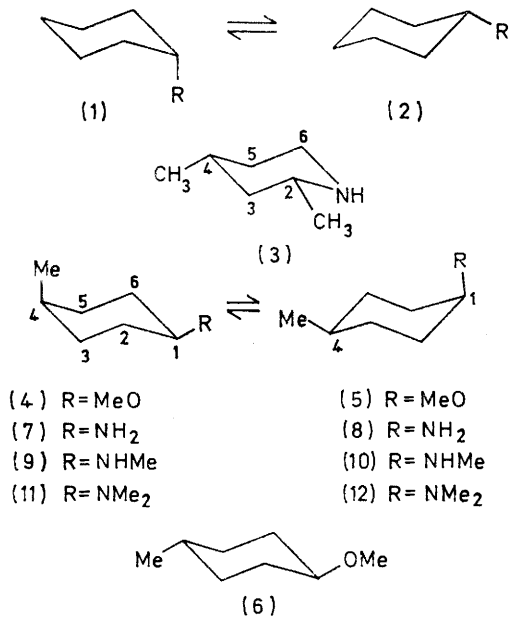
The preferred conformations of many cyclohexanes, in solution, are now relatively easy to determine by application of n.m.r. techniques.[1-4] Exact bond lengths and bond angles are not obtained however, and computer-assisted calculations of strain energies are unlikely to prove satisfactory until solvent effects are understood more clearly, and until general agreement is reached on the parameters to be employed. The van der Waals radius of hydrogen has long been taken as 1.2 Å and if the value of 1.4—1.7 Å, suggested recently by Wertz and Allinger,[5] is correct, a considerable part of classical conformational analysis will require reinterpretation.

Methods of determining *A* values have been summarised,[1] and the early work on NH_2, NHMe, and NMe_2 substituents is given in Table 1. Of particular interest was the report [6] that the *A* value of NHMe (in $CHCl_3$) was smaller than that of NH_2 (in CCl_4). Moreover, Brignell *et al.*,[7] using parameters deduced from several determinations of conformational equilibria, calculated *A* values of 1.08, 0.96, and 0.87 kcal mol^{-1} for NH_2, NHMe, and NMe_2 respectively. The same authors used the n.m.r. chemical shift method to determine *A* values of 1.2 and 1.0 kcal mol^{-1} for NH_2 and NHMe respectively in CCl_4 at 298 K; a reliable value for NMe_2 was not obtained.

The most direct, and probably the most satisfactory, method of determining *A* values in cyclohexanes is by integration of the signals assigned to individual conformations in the spectrum observed at low temperature, where ring inversion is relatively slow. The papers by Jensen and Bushweller (*e.g.* ref. 8) using low temperature ^1H n.m.r. spectroscopy, are typical of sound work in this

[1] F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.*, 1971, **3**, 140.
[2] H. Booth, *Progr. N.M.R. Spectroscopy*, 1969, **5**, 255.
[3] E. L. Eliel, *Angew. Chem. Internat. Edn.*, 1965, **4**, 761.
[4] N. C. Franklin and H. Feltkamp, *Angew. Chem. Internat. Edn.*, 1965, **4**, 774.
[5] D. H. Wertz and N. L. Allinger, *Tetrahedron*, 1974, **30**, 1579.
[6] H. Feltkamp, N. C. Franklin, K. D. Thomas, and W. Brügel, *Annalen*, 1965, **683**, 64.
[7] P. J. Brignell, K. Brown, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1968, 1462.
[8] F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Amer. Chem. Soc.*, 1969, **91**, 344.

area. Bushweller and his co-workers [9] were able to observe the α-proton signal of the axial conformation of [*NN*,2,2,6,6-$^2H_6$]cyclohexylamine and were thus able to determine the A value of ND_2 at 180 K as 1.2 (pyridine–C_2H_3Cl) and 1.4 kcal mol^{-1} (CD_3OD).



For a number of reasons, ^{13}C n.m.r. spectroscopy is well suited to the determination of conformational equilibria. Proton noise-decoupled spectra show a simplicity which is ideal for studies at variable temperature. In addition, the relatively large chemical shifts characteristic of ^{13}C nuclei in different environments represent a considerable advantage, since they generally allow a detection of exchange processes at temperatures higher than is the case for ^1H nuclei in the same molecule. Finally, ^{13}C chemical shift parameters are proving to be additive to a remarkable degree,[10-14] a consequence of which is that the interpretation of a ^{13}C spectrum can be remarkably easy. Set against these advantages are the basic disadvantages of the low sensitivity of ^{13}C at natural abundance, and the difficulties of interpretation of ^{13}C integrals, caused by the disturbances introduced into a ^1H noise-decoupled spectrum by differential nuclear Overhauser enhancements, and by differential spin–lattice relaxation times (T_1). Since accurate measurements of the relative proportions of conformations were essential in the present investigation, we undertook several experiments to demonstrate convincingly our ability to draw valid conclusions from the measured integrals in a low-temperature ^{13}C spectrum.

The compound chosen was *cis*-2,4-dimethylpiperidine (3), a molecule typical of the cyclic amines studied in our investigations, and one which is largely confined to a chair conformation possessing equatorial methyl groups. Nuclear Overhauser enhancements (n.O.e.) were determined by the technique of gated decoupling, which allowed ^1H irradiation to be applied only during acquisition of the free induction decay. The n.O.e. builds up during data acquisition, but the integrals of the ^{13}C signals in the transformed spectrum depend only on the initial amplitude of the free induction decay, at which point the n.O.e. is zero. A comparison of the measured integrals, with those obtained in a normal noise-decoupled spectrum (*i.e.* with ^1H irradiation applied continuously) is given in Table 2. Integrals were obtained

TABLE 1

Measured A values of NH_2, NHMe, and NMe_2

Substituent	A/kcal mol^{-1}	T/K	Solvent	Method	Ref.
NH_2	1.1	(Room)	CCl_4	N.m.r. shifts	*a*
NH_2	1.1—1.2	(Room)	Iso-octane	N.m.r. shifts	*b*
NH_2	1.2	298	CCl_4	N.m.r. shifts	7
NH_2	1.2	180	C_5H_5N–C_2H_3Cl	N.m.r. areas	9
NH_2	1.22—1.30	(Room)	$CHCl_3$	N.m.r. shifts	6
NH_2	1.23	(Room)	$CHCl_3$	N.m.r. band-width	6
NH_2	1.2—1.3	(Room)	$CDCl_3$	N.m.r. shifts	*b*
NH_2	1.3	293	C_6H_6	N.m.r. coupling	*c*
NH_2	1.38	(Room)	$CDCl_3$	N.m.r. shifts	*a*
NH_2	1.4	180	CD_2Cl_2–toluene	N.m.r. areas	9
NH_2	1.4	180	CD_3OD	N.m.r. areas	9
NH_2	1.7	293	80% Methyl cellosolve	pK	20
NH_2	1.8	298, 330	98% EtOH	Kinetic	*a*
NHMe	0.9	(Room)	$CHCl_3$	N.m.r. band-width	6
NHMe	1.0	298	CCl_4	N.m.r. shifts	7
NHMe	1.0—1.1	(Room)	$CHCl_3$	N.m.r. shifts	6
NMe_2	0.4—1.0	298	CH_3CN	Kinetic	7
NMe_2	2.1	298	80% Methyl cellosolve	pK	20

[a] E. L. Eliel, E. W. Della, and T. H. Williams, *Tetrahedron Letters*, 1963, 831. [b] G. Ransbotyn, J. C. Celotti, R. Ottinger, J. Reisse, and G. Chiurdoglu, *Tetrahedron*, 1968, **24**, 3647. [c] H. Booth, *Tetrahedron*, 1964, **20**, 2211.

[9] C. H. Bushweller, G. E. Yesowitch, and F. H. Bissett, *J. Org. Chem.*, 1972, **37**, 1449.
[10] D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, 1967, **89**, 6612.
[11] D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, 1972, **94**, 5318.
[12] H. Booth and D. V. Griffiths, *J.C.S. Perkin II*, 1973, 842.
[13] H. Booth and D. V. Griffiths, *J.C.S. Perkin II*, 1975, 111.
[14] N. K. Wilson and J. B. Stothers, *Topics Stereochem.*, 1974, **8**, 1.

accurately, but tediously, by expanding signals to a reasonable width (*e.g.* 1 Hz mm^{-1}) and using a planimeter. Reasonably accurate integrals were also obtained from a plotted integral curve, but the integral print-out seemed much less reliable, and frequently gave enhancements in excess of the theoretical maximum of 199% (see Table 2). Despite the fact that the sample was not degassed, the n.O.e. were high, possibly because the amine itself acts as an efficient scavenger of oxygen. It was encouraging to note that the enhancements were similar for carbons carrying the same number of protons, an expected result if ^{13}C relaxation (T_1) is dominated by dipole–dipole interaction with directly attached protons.

Spin–lattice relaxation times (T_1) for carbons in (3), determined by the inversion-recovery method, are given in Table 3. Carbons holding the same number of protons have similar T_1 values. The marked decrease in T_1 as the temperature is lowered indicates the high contribution of dipolar effects to the total T_1. More important, the actual T_1 values at 206 K are short compared to the pulse repetition time of 2—2.2 s used routinely in our experiments at variable temperature. Consequently, any differences in spin–lattice relaxation times of protonated carbons will not distort the measured integrals in the low-temperature spectrum. Summarising, provided a comparison is made of the integrals of carbons carrying the same numbers of protons, the measured integrals in a ^{13}C spectrum determined with noise-decoupling by the pulsed Fourier transform method at 220 K, or lower, give an accurate indication of the molecular proportions involved.

TABLE 2

Nuclear Overhauser enhancements of ^{13}C carbon atoms in *cis*-2,4-dimethylpiperidine (3) (solvent $CDCl_3$, not degassed)

	Nuclear Overhauser enhancement (% increase)	
Carbon	*via* Print-out	*via* Planimeter
2	169	169
4	170	168
3	215	193
5	195	199
6	234	183
CH_3 (both)	174	160

Spectral width 2 500 Hz; pulse width 4 μs (33°); data points 8 K; repetition time 30 s.

TABLE 3

^{13}C Spin–lattice relaxation times (T_1) of carbon atoms in *cis*-2,4-dimethylpiperidine (3) (solvent $CDCl_3$, not degassed)

	T_1/s		
T/K	294	230	206
Carbon			
2	4.4	1.1	0.43
4	5.1	1.2	0.43
3	2.8	0.75	0.26
5	2.8	0.80	0.29
6	2.5	0.74	0.26
2-CH_3	2.7	0.79	0.32
4-CH_3	2.7	0.81	0.32

Spectral width 2 500 Hz; pulse width 11 μs (90°); data points 8 K; repetition time 30 s.

Several attempts to identify the minor conformation (with substituent axial) in the low temperature ^{13}C spectrum of cyclohexylamine, *N*-methyl-, and *NN*-dimethyl-cyclohexylamine proved unsuccessful, despite the acquisition of sufficient pulses to enable the required signal to noise to be reached, and on the assumption that only 1—2% of the minor conformation was present. The reason for these failures is not understood. Schneider and Hoppen [15] reported similar results for both cyclohexylamine and cyclohexanol, and ascribed the failures to an increase in size (and therefore A value) resulting from the molecular association occurring at the relatively high concentrations needed to obtain acceptable signal to noise ratios. However, at temperatures down to 165 K we have also failed to detect the axial conformation of nitrocyclohexane (A value 1.1), where association is unlikely to occur. Now whilst entropy differences between axial and equatorial conformations may be significant for groups such as NHMe and NMe_2, this fact should *assist* the detection of the minor conformation as the temperature is lowered. For example, an axial NMe_2 group has two conformations, with respect to rotation about the N–ring carbon bond, in which an inward pointing methyl group suffers strong repulsive interactions with *syn*-axial hydrogen atoms, a situation which does not apply to an equatorial NMe_2. Since the number of rotational possibilities for axial NMe_2 is *less* than that for equatorial NMe_2, the former has the lower entropy. Thus $\Delta S(ax \longrightarrow eq)$ is positive. Since $\Delta H(ax \longrightarrow eq)$ is negative, the consequence is that $\Delta G(= \Delta H - T\Delta S)$ is more negative at the higher temperature, *i.e.* the A value is increased at the higher temperature and decreased at the lower temperature, by this effect. Therefore any conformational entropy difference is likely to facilitate (rather than hinder) the observation of the minor conformations at reduced temperatures. This conclusion is invalidated if $\Delta S(ax \longrightarrow eq)$ is negative, and it is worth noting that negative ΔS values have been reported,[1] *e.g.* for OH and OCOMe.

The determination of A values for NH_2, NHMe, and NMe_2 was accomplished indirectly, by assessment of the conformational equilibrium in a *cis*-4-methyl-1-R-cyclohexane (R = NH_2, NHMe, or NMe_2), followed by a correction for the A value of the methyl group. The assumption that A values are additive is justified for 1,4-disubstituted cyclohexanes carrying substituents not prone to intramolecular interaction. The A value of the methyl group is generally taken as 1.7 kcal mol^{-1} at room temperature.[16,17] The only determination at low temperature is that of Anet *et al.*,[18] who successfully identified a ^{13}C signal due to the axial conformer of methylcyclohexane at 198 K. The proportion of this conformer

[15] H.-J. Schneider and V. Hoppen, *Tetrahedron Letters*, 1974, 579.

[16] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965.

[17] J. A. Hirsch, *Topics Stereochem.*, 1968, **1**, 199.

[18] F. A. L. Anet, C. H. Bradley, and G. W. Buchanan, *J. Amer. Chem. Soc.*, 1971, **93**, 258.

(1%) led to an A value of 1.6 kcal mol^{-1}, a value which can only be approximate in view of the difficulties of making an accurate assessment of 1% from a spectrum with a high noise level. We have determined the A value of Me by assessment of the equilibrium at 193 K in methyl *cis*-4-methylcyclohexyl ether [(4) ⇌ (5)] by low temperature ^{13}C spectroscopy. The proportions of conformations [96% (5), 4% (4)] correspond to a free energy difference of 1.23 ± 0.1 kcal mol^{-1} and lead to an A value for Me of 1.78 ± 0.12 kcal mol^{-1}, at 193 K, after taking what we believe to be the most reliable value (0.55 ± 0.02 kcal mol^{-1}) for the A value of OCD_3 at 191 K.[8] A calculation by Allinger *et al.*[19] gave 1.81 kcal mol^{-1} for Me in the gas phase. Consequently, we consider the generally accepted 1.7 kcal mol^{-1} to be a reasonable value for the methyl group at *ca.* 200 K, as well as at room temperature. Carbon-13 shifts for (4) ⇌ (5), and the corresponding *trans*-isomer (6), are given in Table 4. The parameters for equatorial OCH_3,

TABLE 4

^{13}C Chemical shifts (p.p.m. downfield from Me_4Si) for methyl *cis*-4-methylcyclohexyl ether (4) ⇌ (5) and methyl *trans*-4-methylcyclohexyl ether (6) (solvent $CFCl_3$–$CDCl_3$)

	(4) ⇌ (5)	(4)	(5)	(6)
T/K	283	193	193	293
Carbon				
1	75.4	80.0	74.5	79.6
2, 6	29.6	26.3	29.2 [a]	31.9
3, 5	29.6	30.2	28.9 [a]	33.4
4	32.3	[b]	32.5	32.2
MeO	55.3	[b]	55.6	55.5
Me	22.4	17.2	23.0	22.0

[a] Assignments may need to be exchanged. [b] Not seen.

available from the room temperature spectrum of (6), were invaluable since they allowed a calculation of the shifts to be expected for carbons in the minor conformation (4).

The ^{13}C spectra of *cis*-4-methylcyclohexylamine (7) ⇌ (8), *cis*-4,*N*-dimethylcyclohexylamine (9) ⇌ (10), and *cis*-4,*NN*-trimethylcyclohexylamine (11) ⇌ (12) were determined in $CFCl_3$–$CDCl_3$ (9 : 1 v/v) and in [$^2H_8$]toluene at room temperature and at several lower temperatures. In all three cases, selective broadening of spectral lines occurred, followed by a sharpening of lines when the rate of ring inversion became relatively slow. Line assignments rested on considerations of electronegativity, and on off-resonance and specific proton-decoupling experiments. The assignment of signals in the low temperature spectra involved application of the ^{13}C shift parameters for Me;[10,11] in addition, the exact pairing of signals from a given carbon in the two conformations was assisted by the observation of selective broadening at intermediate temperatures. The relative proportions of conformations were obtained by measurement of the areas of expanded signals, corresponding to the same carbon, using a planimeter. ^{13}C Chemical shifts of *cis*-4-methylcyclohexylamine (7) ⇌ (8) are given in Table 5. At 187 K in $CFCl_3$–$CDCl_3$, the mixture of conformers contained 34% (7) and 66% (8), equivalent to a free energy difference of 0.25 kcal mol^{-1}. The corresponding figures for [$^2H_8$]toluene are 36.5% (7), 63.5% (8), and 0.21 kcal mol^{-1}. Taking into account the A value of Me, we arrive at A values for NH_2 of 1.45 ($CFCl_3$–$CDCl_3$) and 1.49 kcal mol^{-1} ([$^2H_8$]toluene) (Table 8). Shifts for *cis*-4,*N*-dimethylcyclohexylamine (9) ⇌ (10) and *cis*-4,*NN*-trimethylcyclohexylamine (11) ⇌ (12) are listed in Tables 6 and 7 respectively, and the corresponding equilibrium constants, free energy differences, and A values are given in Table 8. The A values are expected to be accurate to ±0.06 kcal mol^{-1}, the limiting factor being the errors involved in measurements of the signal areas.

TABLE 5

^{13}C Chemical shifts (p.p.m. downfield from Me_4Si) for *cis*-4-methylcyclohexylamine (7) ⇌ (8)

	$CFCl_3$–$CDCl_3$			[$^2H_8$]Toluene		
	(7) ⇌ (8)	(7)	(8)	(7) ⇌ (8)	(7)	(8)
T/K	263	187	187	274	193	193
Carbon						
1	47.4	51.4	44.9	47.3	51.0	45.0
2, 6	32.9	30.7	33.0	31.7	30.2	32.6
3, 5	29.7	30.7	28.5	29.5	30.7	28.5
4	31.1	26.2	33.0	30.8	26.5	33.1
CH_3	21.2	17.4	23.1	21.1	17.4	23.3

TABLE 6

^{13}C Chemical shifts (p.p.m. downfield from Me_4Si) for *cis*-4-*N*-dimethylcyclohexylamine (9) ⇌ (10)

	$CFCl_3$–$CDCl_3$			[$^2H_8$]Toluene		
	(9) ⇌ (10)	(9)	(10)	(9) ⇌ (10)	(9)	(10)
T/K	294	195	195	294	193	193
Carbon						
1	55.7	58.7	53.5	55.4	58.8	53.4
2, 6	29.9 [a]	27.0	29.0 [a]	29.4 [a]	26.3	29.0 [a]
3, 5	29.8 [a]	30.0	29.8 [a]	28.8 [a]	31.1	29.8 [a]
4	31.7	27.1	33.0	32.6	26.3	33.2
CCH_3	21.4	17.3	23.1	21.5	17.3	23.3
NCH_3	34.1	34.2	33.8	33.7	33.2	34.1

[a] Assignments may need to be exchanged.

TABLE 7

^{13}C Chemical shifts (p.p.m. downfield from Me_4Si) for *cis*-4,*NN*-trimethycyclohexylamine (11) ⇌ (12)

	$CFCl_3$–$CDCl_3$			[$^2H_8$]Toluene		
	(11) ⇌ (12)	(11)	(12)	(11) ⇌ (12)	(11)	(12)
T/K	294	183	183	294	183	183
Carbon						
1	62.5	64.3	60.8	61.8	63.1	60.0
2, 6	27.3	22.9	28.9 [a]	27.8	22.8	29.1 [a]
3, 5	30.4	31.0	29.3 [a]	30.3	31.0	29.7 [a]
4	31.0	26.6	33.3	31.5	28.0	33.4
CCH_3	20.7	17.3	22.9	21.2	17.2	23.5
NCH_3	42.9	41.7	43.9	42.9	41.5	43.6

[a] Assignments may need to be exchanged.

The A value of NH_2 (1.45—1.49) is substantially the same in $CFCl_3$–$CDCl_3$ as in [$^2H_8$]toluene, and is in good agreement with that of 1.4 kcal mol^{-1} for ND_2, determined at 180 K from a ^{1}H n.m.r. spectrum in CD_2Cl_2–[$^2H_8$]toluene (1 : 1 v/v).[9] The A values of NHMe and NMe_2 are significantly lower in [$^2H_8$]toluene than in $CFCl_3$–$CDCl_3$. At the same time, in both solvents, the A value of NHMe is smaller than that of NH_2 whilst that of

[19] N. L. Allinger, M. A. Miller, F. A. VanCatledge, and J. A. Hirsch, *J. Amer. Chem. Soc.*, 1967, **89**, 4345.

NMe_2 is comparable with that of NH_2. As the trend in the series NH_2, NHMe, NMe_2 is similar in both solvent systems, a specific solvent interaction cannot in itself explain the trend. The trend may result from the interplay of several factors, which are to some extent interdependent.

TABLE 8

Conformational equilibria, conformational free energy differences ($-\Delta G°$) in *cis*-4-methylcyclohexylamine (7) ⇌ (8), *cis*-4,*N*-dimethylcyclohexylamine (9) ⇌ (10), and *cis*-4,*NN*-trimethylcyclohexylamine (11) ⇌ (12), and *A* values for NH_2, NHMe, and NMe_2

R	Solvent	T/K	% Minor	% Major	K [a]	$-G°$/ kcal mol^{-1}	*A* value (*R*) [b]/ kcal mol^{-1}
NH_2	$CFCl_3$–$CDCl_3$	187	34	66	1.95	0.25	1.45
NHMe	$CFCl_3$–$CDCl_3$	195	25.5	74.5	2.90	0.41	1.29
NMe_2	$CFCl_3$–$CDCl_3$	183	38.5	61.5	1.61	0.17	1.53
NH_2	[$^2H_8$]-Toluene	193	36.5	63.5	1.74	0.21	1.49
NHMe	[$^2H_8$]-Toluene	193	18	82	4.67	0.59	1.11
NMe_2	[$^2H_8$]-Toluene	183	25	75	3.0	0.39	1.31

[a] K = equilibrium constant = % major/% minor. [b] *A* value (*R*) = *A* value (CH_3) − ($-G°$); estimated error in *A*: ±0.06 kcal mol^{-1}.

(a) *Size and Shape of the Unassociated Substituent.*—The size and shape of the unassociated group will inevitably influence the attractive and repulsive forces experienced in equatorial and axial environments. The effective size of the nitrogen lone pair is difficult to assess.

(b) *Number of* N–H *Bonds.*—Increase in the number of N–H bonds (*e.g.* NMe_2 ⟶ NHMe ⟶ NH_2) will increase the degree of association through hydrogen bonding, and lead to an increase in the effective size of the group and, therefore, of its *A* value.

(c) *Basicity of Nitrogen.*—In the solvent systems employed, the basicity of the nitrogen is expected to increase along the series NH_2, NHMe, NMe_2. The more basic the amine, the greater is the dipolar interaction with a solvent molecule containing carbon–halogen bonds; such an interaction is expected to increase the effective size of the group, and, therefore, its *A* value.

Another factor, possibly of importance, is the probability that the conformational free energy of NHMe and NMe_2 are more temperature-dependent than that of NH_2, due to considerations of entropy. As pointed out earlier, for NHMe and NMe_2 there are more admissible conformations for the equatorial conformation than for the axial conformation. Consequently, $\Delta S(ax \longrightarrow eq)$ is expected to be positive and ΔG will be less negative (*i.e. A* value will be smaller) at a low temperature than at a high temperature, due to this effect. Thus, any differences between $A(NH_2)$ and A(NHMe), or between $A(NH_2)$ and $A(NMe_2)$ will be reduced at a relatively low temperature. In fact, however, the *A* value of NHMe at 195 K in $CFCl_3$–$CDCl_3$ is rather larger than the earlier recorded values of 0.9—1.1 ($CHCl_3$) [6] and 1.0 (CCl_4),[7] obtained using n.m.r. methods at room temperature. On the other hand, the *A* values of 1.31 and 1.53 for NMe_2 are considerably smaller than the 2.1 obtained at room temperature by the p*K* method, although a straight comparison is not possible because the p*K* determination used 80% 2-methoxyethanol as solvent.[20]

The *A* values of NH_2, NHMe, and NMe_2 invite comparison with the values for Me, CH_2Me, and $CHMe_2$. For Me, CH_2Me, and $CHMe_2$ Hirsch [17] gives 1.7, 1.75, and 2.15 kcal mol^{-1} respectively, as the 'best' *A* values, whilst Allinger *et al.*[21] determined *A* values of 1.87, 1.80—1.86, and 2.10—2.11 kcal mol^{-1}, respectively, at 298 K. The fact that the *A* value of NH_2 is smaller than that of CH_3 reflects the expectation that the interaction H–N (lone pair) in the conformation with axial NH_2 is smaller than the corresponding interaction H–CH in cyclohexane substituted by axial CH_3. However, whereas the *A* value of CH_2Me is not substantially different from that of Me, that of NHMe is significantly smaller than that of NH_2, in both solvents employed, in agreement with the prediction of Brignall *et al.*[7] However, the further prediction [7] that the conformational preference of NMe_2 would be smaller than that of NHMe is not borne out by our results, which show that NMe_2 has about the same *A* value as NH_2. Interestingly, recent work [22] has shown that PMe_2 has the same *A* value as PH_2, although a detailed comparison with the nitrogen analogues would involve a consideration of the differences in the length of the bonds joining the heteroatom to the ring carbon.

The finding that NHMe has a smaller *A* value than NH_2 or NMe_2 recalls earlier studies on the conformational preferences of alkyl groups at various positions in six-membered reduced heterocycles.[23] Thus, ethyl has a smaller *A* value than methyl and isopropyl when substituted at the 5-position of 2-t-butyl-1,3-dioxan (*A* values: Me 0.8, CH_2Me 0.67, $CHMe_2$ 0.98), at the 2-position of *cis*-4,6-dimethyl-1,3-dithian (*A* values: Me 1.72, Ch_2Me 1.54, $CHMe_2$ 1.95) and at the 2-position of 4-methyl-1,3-dithian (*A* values: Me 1.26, CH_2Me 1.15, $CHMe_2$ 1.45). A possible reason for these trends is evident from models. When the ethyl substituent is equatorial one of the conformations possessing a staggered arrangement about each C–C bond, (13), is energetically unfavourable because it leaves two of the hydrogens of the methyl group within 2 Å of the axial hydrogens at positions 2 and 6. These interactions can be reduced by rotation of the CH_3–CH_2 bond, but only at the expense of causing eclipsing about this bond. The close approach of the C–H to the axial 3- and 5-hydrogens

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[21] N. L. Allinger and S. Hu, *J. Amer. Chem. Soc.*, 1962, **84**, 370; N. L. Allinger, L. A. Freiburg, and S. Hu, *ibid.*, p. 2836; N. L. Allinger and S. Hu, *J. Org. Chem.*, 1962, **27**, 3417.

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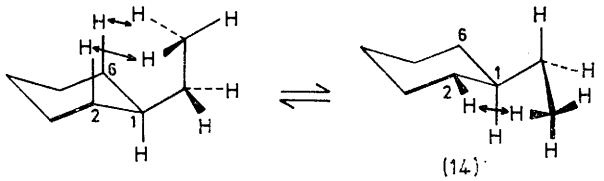
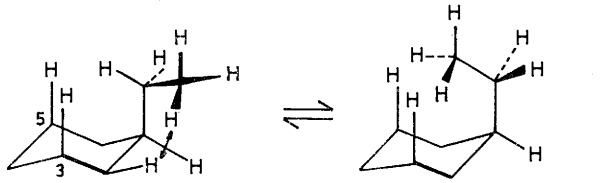
at 3, in the axial conformation (15) should lead to interactions similar to those in axial methylcyclohexane. Conformation (16) is extremely unfavourable and can be ignored. Consequently, relative to the situation in methylcyclohexane, the equatorial ethylcyclohexane (13) ⇌ (14) may be slightly destabilized. Although in each of the energetically equivalent conformations (14)



(13) (14)



(15) (16)

and its enantiomer, there is a close approach of one of the hydrogens of the methyl to an equatorial ring hydrogen, this is exactly balanced by a similar interaction in the axial conformation (15), and its enantiomer. Set against these arguments are the detailed calculations of Allinger *et al.*,[19] which give 2.01 kcal mol^{-1} as the A value of CH_2Me at 298 K, compared with 1.81 for Me. However, it may be worthwhile to reinvestigate, at variable temperature, the conformational free energies of methyl, ethyl, and isopropyl substituents attached to cyclohexane. As with NHMe and NMe_2, conformational entropy differences are significant for CH_2Me and $CHMe_2$ (*cf.* ref. 21), leading to a significant temperature dependence of the A values.

TABLE 9

^{13}C Chemical shift parameters (p.p.m., positive ≡ increasing downfield shift)

Description of effect [a]	Effect (NH_2)	Effect (NHMe)	Effect (NMe_2)
α_e	24.0 [b]	31.7	37.3
β_e	9.6 [b]	6.3	2.2
γ_e	−1.9 [b]	−2.5	−1.5
δ_e	−1.6 [b]	−1.4	−1.9
α_a	18.0	26.6	33.9
β_a	5.8	2.6 or 1.8	1.7 or 2.9
γ_a	−7.6	−6.3 or −7.1	−7.2 or −6.8
δ_a	−0.1	−0.1	0.2

[a] See ref. 12 for nomenclature. [b] An average of effect in (7) and effect in *trans*-4-methylcyclohexylamine.[24]

Finally, ^{13}C chemical shift parameters for equatorial and axial NH_2, NHMe, and NMe_2 were calculated and are listed in Table 9. These values are based on the ^{13}C shifts in Tables 5—7, on the shift of 27.1 p.p.m. for cyclohexane (this work) in $CDCl_3$, and on the parameters for axial and equatorial Me given in ref. 11. The parameters for NH_2 are revised from those of the preliminary communication,[24] where there was an error of assignment, an error which was established from the ^{13}C shifts of *cis*- and *trans*-3,5-dimethylcyclohexylamine.[25] The signals at 29.7 p.p.m. in the spectrum of (7) ⇌ (8) at 263 K, and at 28.5 p.p.m. at 187 K are correctly assigned to C-3 and -5, whilst the signals at 32.9 p.p.m. from (7) ⇌ (8) at 263 K, and at 33.0 p.p.m. at 187 K are due to C-2 and -6. It is noteworthy that the α parameters (whether axial or equatorial) increase along the series NH_2, NHMe, NMe_2. The β_e parameter, on the other hand, decreases along the same series, whilst the β_a parameter decreases from NH_2 to NHMe but is little changed when NHMe alters to NMe_2. The γ_e,δ_e, and γ_a parameters change little with increasing methylation of the nitrogen and the same applies to δ_a, which is always close to zero.

EXPERIMENTAL

^{13}C Spectra were measured at 25.15 MHz in the pulsed mode on a JEOL PS-100 spectrometer interfaced to a Nicolet 20 K 20-bit 1085 computer. Free induction decays were accumulated over 2 500 or 4 000 Hz using a pulse width of 4 μs (33° tip) and were sampled using 8 K data points. The JEOL temperature controller was calibrated using a thermocouple immersed in a stationary sample tube (8 mm) containing $CFCl_3$.

Preparative g.l.c. employed Varian Aerograph series 712 and Varian Aerograph Autoprep (A-700) instruments. A Pye series 104 instrument was used for analytical g.l.c.

cis-2,4-*Dimethylpiperidine*.—2,4-Dimethylpyridine (20 g) in cyclohexane (200 ml) was hydrogenated over Raney nickel (*ca.* 1 teaspoonful) at 200 °C and 100 atm during 7 days. Filtration and distillation gave a mixture of *cis*- and *trans*-2,4-dimethylpiperidine. Preparative g.l.c. at 120°, using a 35 ft × ¼ in. column of Carbowax 20 M (20%) on alkali-washed Chromosorb W, gave pure *cis*-2,4-dimethylpiperidine as the fraction of shorter retention time. The ^{1}H n.m.r. spectrum was identical with that given by Silhankova *et al.*[26]

Methyl cis-4-*Methylcyclohexyl Ether and Methyl* trans-4-*Methylcyclohexyl Ether*.—Commercial samples of *cis*- and *trans*-4-methylcyclohexanol were separately converted by the Williamson method [27] into methyl *cis*-4-methylcyclohexyl ether and methyl *trans*-4-methylcyclohexyl ether (*cf.* ref. 28). Both isomers were purified by preparative g.l.c. using a 12 ft × ⅜ in column of Carbowax 20 M (20%) on alkali-washed Chromosorb W at 100 °C.

cis- and *trans*-4-methylcyclohexylamine were prepared as previously described.[29]

cis-4,N-*Dimethylcyclohexylamine*.—The literature method [7] gave a colourless liquid, b.p. 100° at 40 mmHg. A partial separation of *cis*- and *trans*-amines was achieved by preparative g.l.c. using a 12 ft × ⅜ in column of OV 17 phenylsilicone (10%) on diatomite C (acid washed; dimethylchlorosilane treated) at 110 °C. The collected

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[25] H. Booth, unpublished work.
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[27] *Cf.* ' Organicum,' ed. P. A. Ongley, Pergamon, Oxford, 1973, p. 208.
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fraction, an 80% *cis*- and 20% *trans*-isomer, was used directly in the n.m.r. experiments.

cis-4,NN-*Trimethylcyclohexylamine*.— NN-Dimethyl-*p*-toluidine (10.2 g) was hydrogenated over platinum oxide (700 mg) in glacial acetic acid (50 ml) at room temperature and atmospheric pressure. After 12 h the solution was filtered and basified with sodium hydroxide (40%). Extraction with ether gave the crude, fully reduced product (10.6 g). Preparative g.l.c. at 115° used a 35 ft × ¼ in column of Carbowax 20 M (20%) on alkali-treated Chromosorb W and gave, as the first fraction, a pure sample of *cis*-4,*NN*-trimethylcyclohexylamine (*cf.* ref. 7).

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