Ring Inversion Equilibria in 4-Chloro-, 4-Bromo-, and 4-Methoxy-1-alkylpiperidines in a Non-polar Solvent

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The position of ring inversion equilibrium (axial R ⇌ equatorial R) in 4-R-*N*-alkylpiperidines (R = Cl, Br, or OMe), dissolved in $CFCl_3$–$CDCl_3$, has been determined by ^{13}C n.m.r. spectroscopy at low temperatures. In all three series, change of NH to NMe produces a marked increase in the proportion of conformation with axial R. When R is OMe, further alterations in the *N*-substituent from Me to Et, Pr^i, and CH_2CF_3 do not affect the equilibrium significantly, but the significant changes observed when R is halogen can be related to the inductive effect of the *N*-substituent. ^{13}C Chemical shifts, proportions of conformations, and conformational free energy differences are recorded for all systems studied.

The position of ring inversion equilibria in molecules which lack polar groups can generally be understood, in qualitative terms, by reference to the van der Waals (' steric ') repulsions between non-bonded atoms. The presence of a single polar group does not alter the situation substantially, unless the molecule forms bonds with the solvent [1] or with itself.[2]

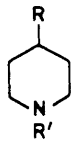
When the molecule possesses two polar groups, the factors already listed will continue to operate, but in addition there is likely to be an intramolecular dipole–dipole interaction between the two polar groups.[3,4] The energy due to dipolar interactions will be a minimum in that conformation allowing the minimum overall dipole moment, provided that a non-polar solvent is used.[5] A polar solvent, on the other hand, is expected to stabilise a more polar conformation.[3]

The purpose of the present study was to assess the contribution made by intramolecular coulombic effects to the conformational free energy differences ($\Delta G^\circ_{4a\rightarrow 4e}$) of 1-alkylpiperidines bearing Cl, Br, or OMe in the 4-position [(1)—(16)]. Most of the piperidines appeared to be stable over a six-month period at 273 K. Exceptions were 4-chloro- (1) and the 4-bromopiperidine (6), which were therefore studied immediately after their release, at −78 °C, from the hydrochloride and hydrobromide, respectively.

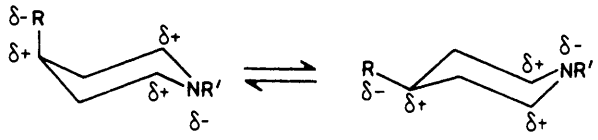
The conformational equilibria (17*a*) ⇌ (17*e*), (18*a*) ⇌ (18*e*), and (19*a*) ⇌ (19*e*) were studied in the range 182—205 K by integration of ^{13}C n.m.r. signals. Signals were assigned by determination of the numbers of attached protons from multiplicities in off-resonance proton-decoupled spectra, and by comparisons of observed shifts at lowest temperatures with shifts calculated from those observed for piperidine (C-2,6 : 47.51; C-3,5 : 27.30; C-4 : 25.31) and tripropylamine,[6] together with the substituent chemical shift parameters for methoxy,[7] and for the groups listed in Table 1.

The ^{13}C shifts thus predicted give chemical shift *differences* for carbon atoms involved in exchange. The room temperature (averaged) signals may be assigned by observation of the temperatures at which broadening commences as the temperature is lowered. Since the rate constant for exchange at coalescence is directly proportional to the chemical shift difference (in Hz) between the appropriate signals, a signal which shows early broadening (*i.e.* at relatively high temperature *T*), as *T* is reduced, must be correlated with a relatively large chemical shift difference. This method is valuable but time-consuming, because it requires spectra at several temperatures. Although it is easy to calculate room temperature shifts as a weighted average of the observed low temperature shifts (the mole fractions are known from the integration), this method is often frustrated by a marked temperature dependence of some ^{13}C signals.

The process being slowed at low temperatures was undoubtedly ring inversion, which has for piperidines an activation energy (ΔG^*) of about 10 kcal mol^{-1}. The nitrogen inversion half-barrier relevant to low temperature work is much lower (*ca.* 6 kcal mol^{-1}; *cf.* refs. 8 and 9).



(1) R = Cl, R′ = H
(2) R = Cl, R′ = Me
(3) R = Cl, R′ = Et
(4) R = Cl, R′ = Pr^i
(5) R = Cl, R′ = CH_2CF_3
(6) R = Br, R′ = H
(7) R = Br, R′ = Me
(8) R = Br, R′ = Et
(9) R = Br, R′ = Pr
(10) R = Br, R′ = Pr^i
(11) R = Br, R′ = CH_2CCl_3
(12) R = Br, R′ = CH_2CF_3
(13) R = MeO, R′ = H
(14) R = MeO, R′ = Me
(15) R = MeO, R′ = Et
(16) R = MeO, R′ = Pr^i



(17*a*) R = Cl (17*e*)
(18*a*) R = Br (18*e*)
(19*a*) R = OMe (19*e*)

As in earlier work [10,11] involving quantitative ^{13}C Fourier transform n.m.r., pulse repetition times were generous (at least 2 s) and equilibrium constants were obtained by comparing the integrals of carbon atoms in identical structural environments. However, as a further precaution ^{13}C spin–lattice relaxation times were measured at 192 K, by the inversion-recovery method, for a typical molecule, 4-chloro-1-methylpiperidine (17*a*) ⇌ (17*e*) (R = Me). The T_1 values obtained (seconds) were:

C-2,6	0.9 in (17*a*); 0.9 in (17*e*)
C-3,5	0.8 in (17*a*); 0.9 in (17*e*)
C-4	1.5 in (17*a*); 1.5 in (17*e*)
N–CH_3	0.7 in (17*a*); 0.8 in (17*e*)

The values determined at 294 K were 4.2 (C-2,6), 4.1 (C-3,5), 8.6 (C-4), and 3.2 (N–CH_3). Evidently the relaxation times of structurally identical carbon atoms are not significantly different in the two conformations.

^{13}C Chemical shifts for bromo-compounds (6)—(12) and

Table 1. ^{13}C Chemical shift parameters * for substituents in piperidines (p.p.m.; positive shifts downfield)

Substituent	α_a †	β_a	γ_a	δ_a	α_e	β_e	γ_e	δ_e
4-Cl	31.8	6.2	−7.4		31.8	10.3	−1.4	
4-Br	27.5	8.1	−6.3		25.0	11.3	0.7	
1-Me		‡	‡	‡		9.1	−1.2	−1.4
1-Et		‡	‡	‡		7.4	−0.5	0.1
1-Pr^i		‡	‡	‡		2.3	−0.7	−0.3
1-CH_2CCl_3		‡	‡	‡		9.2	−0.9	−0.8
1-CH_2CF_3		‡	‡	‡		8.3	−1.5	−0.4

[a] J. M. Bailey, H. Booth, and J. R. Everett, unpublished work. [b] H. Booth and J. M. Bailey, *J. Chem. Soc., Perkin Trans. 2*, 1979, 510. [c] H. Booth and H. A. R. Y. Al-Shirayda, unpublished work.

* Change in chemical shift on replacement of H by substituent, deduced from the chemical shifts of piperidine, 4-bromo- and 4-chloropiperidine, 1-alkylpiperidines,[a] *cis*-decahydroisoquinoline,[b] *cis*-1-(2,2,2-trichloroethyl)decahydroisoquinoline,[c] and *cis*-(1-2,2,2-trifluoroethyl)decahydroisoquinoline.[c] † α, β, γ, and δ refer to the substituent positions. ‡ All the 1-alkyl substituents are largely equatorial.

Table 2. ^{13}C Chemical shifts (δ values; p.p.m. downfield from Me_4Si) for 4-bromo-1-alkylpiperidines in $CFCl_3$–$CDCl_3$

Formula *	(6)	(6*a*)	(6*e*)	(7)	(7*a*)	(7*e*)	(8)
T/K	298	192	192	298	205	205	297
C Atom							
2,6	45.3	40.5	47.3	54.2	50.0	56.4	52.1
3,5	37.4	33.3	38.5	36.5	33.9	37.4	36.8
4	50.0	51.9	50.2	49.0	51.3	48.5	49.6
CH_3N				46.0	46.4	46.0	
CH_2N							52.5
CHN							
CH_3C							12.3
CF_3							
CCl_3							

Formula *	(8*a*)	(8*e*)	(9)	(9*a*)	(9*e*)	(10)	(10*a*)
T/K	203	203	290	202	202	297	203
C Atom							
2,6	47.8	54.2	52.5	48.2	54.6	47.6	43.2
3,5	34.0	37.4	36.8	33.9	37.3	37.0	34.2
4	51.4	48.9	49.9	52.1	49.1	50.5	52.8
CH_3N							
CH_2N	52.7	52.3	60.7	61.1	60.6		
CHN			20.4 [a]	20.2 [a]	20.4 [a]	54.7	54.8
CH_3C	12.3	12.5	11.9	12.1	12.1	18.4	18.2
CF_3							
CCl_3							

Formula *	(10*e*)	(11)	(11*a*)	(11*e*)	(12)	(12*a*)	(12*e*)
T/K	203	285	192	192	298	190	190
C Atom							
2,6	49.5	53.0	49.6	55.6	52.3	49.1	54.9
3,5	37.6	36.3	34.6	37.2	36.3	33.8	37.0
4	49.6	49.2	51.8	48.7	48.8	51.2	48.1
CH_3N							
CH_2N		75.2	74.1	75.0	58.6	58.6 [b]	58.6 [b]
CHN	54.3						
CH_3C	18.2						
CF_3					125.6	125.6 [c]	125.6 [c]
CCl_3		100.9	100.5	100.5			

* *a* and *e* refer to the orientation of bromine.

[a] C–CH_2–C. [b] q, $^2J_{CF}$ 30.5 Hz. [c] q, $^1J_{CF}$ 280 Hz.

chloro-compounds (1)—(5) are listed in Tables 2 and 3, respectively. Tables 4 and 5 give proportions of conformations, equilibrium constants, and conformational free energy differences ($\Delta G^\circ_{a\rightarrow e}$) for the 4-bromo- and 4-chloro-1-alkylpiperidines, respectively. The equilibria in 4-chloro- (2) and 4-bromo-1-methylpiperidine (7) have been studied previously. For the chloro-compound (2), Remane *et al.*[12] obtained an equilibrium constant (*a*/*e*) of 0.2 from n.m.r. measurements in CCl_4. However, from measurements of the dipole moment in benzene, and two different calculations of the dipole moments of the individual conformations, values of 1.1 and 1.5 were obtained. The same authors [13] used two kinds of i.r. measurement to deduce equilibrium constants (*a*/*e*) of 0.5 and 1.4 in iso-octane. For the bromo-compound (7) the same i.r. techniques gave *K* values of 0.7 and 0.6, again in iso-octane.[13]

It is clear that the trends in *K* and ΔG° which follow changes in *N*-substitution are identical in the 4-chloro and 4-bromo series. Thus, change of NH to NMe causes a marked increase

Table 3. ^{13}C Chemical shifts (δ values; p.p.m. downfield from Me_4Si) for 4-chloro-1-alkylpiperidines in $CFCl_3$–$CDCl_3$

Formula *	(1)	(1*a*)	(1*e*)	(2)	(2*a*)	(2*e*)	(3)	(3*a*)	(3*e*)	(4)	(4*a*)	(4*e*)	(5)	(5*a*)	(5*e*)
T/K	273	196	196	278	185	185	278	191	191	275	192	192	298	202	202
C Atom															
2,6	45.1	40.5	46.5	53.5	49.4	55.4	51.2	47.2	53.2	46.8	42.6	48.4	51.5	48.4	53.9
3,5	37.4	33.9	38.0	35.9	33.5	36.5	35.9	33.5	36.5	36.5	33.9	36.9	35.7	33.5	36.4
4	57.6	57.7	57.7	56.6	56.2	56.8	57.1	56.9	57.2	57.6	57.4	57.6	56.3	56.6	56.3
CH_3N				46.2	46.5	45.9									
CH_2N							52.4	52.2	52.7				58.6 [a]	58.8 [a]	57.9 [b]
CHN										54.7	54.9	54.3			
CH_3C							12.4	12.3	12.6	18.4	18.2	18.2			
CF_3													125.7 [c]	125.4 [d]	125.4 [d]

* *a* and *e* refer to the orientation of chlorine.
[a] q, $^2J_{CF}$ 30.5 Hz. [b] q, $^2J_{CF}$ 29.3 Hz. [c] q, $^1J_{CF}$ 280.5 Hz. [d] q, $^1J_{CF}$ 279.5 Hz.

Table 4. Proportions of conformations, equilibrium constants, and conformational free energy differences for ring inversion (18*a*) ⇌ (18*e*) in 4-bromo-1-alkylpiperidines

Formula	R′	*T*/K	[%*a* *]	[%*e* *]	*K* (*e*/*a*)	$-\Delta G°_{a \rightarrow e}$/kcal mol^{-1}
(6)	H	192	31.0	69.0	2.23 ± 0.13	0.30 ± 0.03
(7)	Me	205	39.6	60.4	1.53 ± 0.06	0.17 ± 0.02
(8)	Et	203	39.4	60.6	1.54 ± 0.08	0.17 ± 0.02
(9)	Pr	202	37.2	62.8	1.69 ± 0.07	0.21 ± 0.02
(10)	Pr^i	203	34.1	65.9	1.93 ± 0.10	0.26 ± 0.03
(11)	CH_2CCl_3	182	42.4	57.6	1.36 ± 0.07	0.11 ± 0.02
(12)	CH_2CF_3	190	47.6	52.4	1.10 ± 0.06	0.04 ± 0.02

* *a* and *e* refer to the orientation of bromine.

Table 5. Proportions of conformations, equilibrium constants, and conformational free energy differences for ring inversion (17*a*) ⇌ (17*e*) in 4-chloro-1-alkylpiperidines

Formula	R′	*T*/K	[%*a* *]	[%*e* *]	*K* (*e*/*a*)	$-\Delta G°_{a \rightarrow e}$/kcal mol^{-1}
(1)	H	196	32.0	68.0	2.13 ± 0.11	0.30 ± 0.02
(2)	Me	185	41.0	59.0	1.44 ± 0.10	0.13 ± 0.02
(3)	Et	191	35.3	64.7	1.83 ± 0.13	0.23 ± 0.03
(4)	Pr^i	192	32.7	67.3	2.06 ± 0.14	0.28 ± 0.03
(5)	CH_2CF_3	202	45.0	55.0	1.22 ± 0.05	0.08 ± 0.02

* *a* and *e* refer to the orientation of chlorine.

in the proportion of conformation with halogen axial, but subsequent change of NMe to NEt and finally NPr^i causes a decrease in the proportion of this conformation. Finally, however, change of NMe to NCH_2CX_3 (X = halogen) causes a marked increase in percentage of axial conformation. These trends are readily explained in terms of van der Waals non-bonded repulsive interactions, and intramolecular coulombic interactions.

In the equilibrium (18*a*) ⇌ (18*e*), van der Waals non-bonded interactions are dominated by the *syn*-axial repulsions between the 4-axial bromine and the 2- and 6-axial hydrogen atoms in (18*a*), which is therefore destabilised with respect to (18*e*). The unexpectedly weak destabilisation of axial bromocyclohexane relative to equatorial bromocyclohexane in bromocyclohexane ($\Delta G°_{a \rightarrow e}$ −0.48 kcal mol^{-1} at 192 K)[14] is a direct result of the relatively long carbon–bromine bond (0.191 nm). The same situation should hold for 4-bromopiperidines. Furthermore, the non-bonded repulsions involving the halogen will be approximately constant within a series, such as (1)—(5) or (6)—(12), and need not be considered when making comparisons. The intramolecular coulombic interactions (including dipolar interactions) arise from the presence in (18*a*) and (18*e*) of partial charges, as shown, which result from the inductive effects in C–N and C–halogen bonds. The coulombic interactions may be divided into 2 types: (1) those which are *identical* in (18*a*) and (18*e*), namely the attraction of C-4 and N, and the repulsion of C-4 and C-2 and C-6; (2) those which *differ* in (18*a*) and (18*e*), namely, the attraction of Br and C-2 and C-6, and the repulsion of Br and nitrogen.

Type (2) interactions are clearly the only ones which will affect the position of equilibrium, and a brief study of the molecular geometries leads to the conclusions that (*a*) the distance from axial Br to C-2 in (18*a*) is much less than the distance of equatorial Br to C-2 in (18*e*); and (*b*) the distance of axial Br to N in (18*a*) is much less than the distance of equatorial Br to N in (18*e*). Thus the axial conformation has attractive charges closer together, and repulsive charges closer together, than the equatorial conformation.

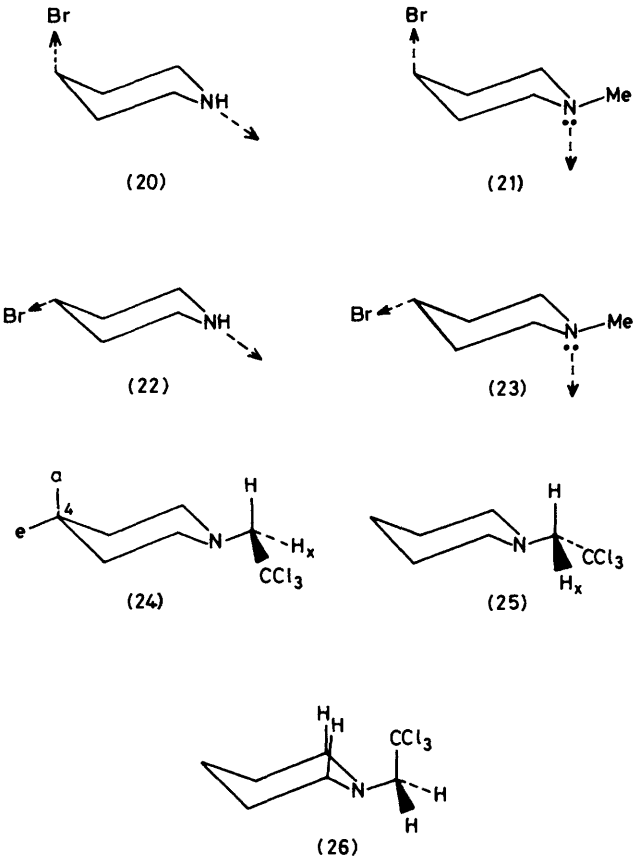
Now the conformational equilibrium in bromocyclohexane is determined entirely by steric effects, as intramolecular coulombic effects are absent. As the 4-bromopiperidine equilibrium (31% axial at 192 K) gives greater stability to the axial conformation than does the bromocyclohexane equilibrium [14] (22% axial at 192 K), it is reasonable to assume that the attractive forces Br/C-2 outweigh the repulsive forces Br/N in 4-bromopiperidine (20) ⇌ (22).

The situation for the comparable chloro-compounds is the same: 32% axial chlorine in 4-chloropiperidine at 196 K and 20% axial chlorine in chlorocyclohexane [14] at 192 K. In fact

Table 6. ^{13}C Chemical shifts (δ values; p.p.m. downfield from Me_4Si) for 4-methoxy-1-alkylpiperidines in $CFCl_3$–$CDCl_3$

Formula *	(13)	(13*a*)	(13*e*)	(14)	(14*a*)	(14*e*)	(15)	(15*a*)	(15*e*)	(16)	(16*a*)	(16*e*)
T/K	294	194	194	278	192	192	278	192	192	294	192	192
C Atom												
2,6	44.7	40.8	45.1	53.5	50.2	54.4	50.9	47.9	51.9	46.5	43.1	46.9
3,5	33.0	29.7	32.8	31.3	29.3	31.5	31.0	29.1	31.3	32.0	29.5	31.6
4	77.0	73.2	77.9	76.3	71.9	77.4	76.7	72.5	77.8	77.3	72.9	78.1
CH_3N				46.3	46.7	46.1						
CH_2N							52.6	52.9	52.3			
CHN										54.8	54.9	54.2
CH_3C							12.5	12.4	12.7	18.6	18.3	18.3
CH_3O	55.0	55.4	54.9	55.2	54.9	55.4	55.3	55.4	55.4	55.2	55.4	55.4

* *a* and *e* refer to the orientation of OCH_3.



our experimental results for 4-bromo- and 4-chloro-piperidine are closely similar to those reported by Schrooten *et al.*[15] for 4-bromo- and 4-chloro-1-oxacyclohexane.

In 4-bromopiperidine (20) ⇌ (22) the preferences of N–H and N–lone pair for the equatorial orientation are similar, following those of piperidine itself.[8] Consequently, the overall moment due to the C(2)–N and C(6)–N bonds will lie in a direction approximately midway between axial and equatorial, as illustrated in the diagrams for (20) and (22). On the other hand *N*-methylpiperidines favour strongly the conformation which has N–Me equatorial,[16] and which therefore has a moment which is axial in direction, as in diagrams (21) and (23). In this case a much smaller overall dipole moment will result if the bromine is axial, as in (21), than if it is equatorial as in (23). This argument predicts an increase in the percentage of axial conformation on moving from NH to NMe. However, a second effect is involved when NH is changed to NMe, namely the inductive effect of Me, which (relative to H) should increase electron density on nitrogen. The resultant increase in Br/N repulsion is stronger for axial bromine than equatorial bromine owing to the smaller distance involved. Consequently this effect promotes a decrease in percentage of axial conformation. Since a marked increase in percentage of axial conformation is observed (Table 4), it is clear that the favouring of axial, due to a minimisation of overall dipole moment, outweighs the disfavouring due to the inductive effect.

When the *N*-alkyl group is changed successively from Me to Et, Pr, and Pr^i, the lone pair orientation remains unaltered, and no further advantage accrues to the axial conformation from a minimisation of the overall molecular dipole moment. However, the increased inductive effect of the *N*-alkyl group will cause increased electron density on nitrogen, leading to a decrease in percentage of axial conformation, as already argued, and as observed (Table 4). If the explanation is correct, the replacement of NCH_3 by the electron-attracting groups NCH_2CCl_3 and NCH_2CF_3 should cause an increase in the percentage of axial conformation and this, too, is observed (Table 4). The effect of CH_2CF_3 is greater than that of CH_2CCl_3, in agreement with the stronger electron-withdrawing effect of the lighter atom. It should be noted that the direction of the additional dipole introduced by the use of the groups CH_2CCl_3 and CH_2CF_3 is *not* a factor causing any change in the position of conformational equilibrium in (17*a*) ⇌ (17*e*) or (18*a*) ⇌ (18*e*). The reason is as follows. The *N*-trichloroethylpiperidines will exist in two enantiomeric (and therefore equi-energetic) conformations (24) and (25), with respect to rotation about the N–C bond. The rotamer (26) will make a negligible contribution because it suffers *two* repulsive interactions between CCl_3 and 2- and 6-axial hydrogens. Therefore the dipole associated with the C–CCl_3 bond will effectively bisect the Cl_3C–C–H_x angle, as shown in diagram (24). Since this direction passes through C-4 and bisects the *a*–C(4)–*e* angle, the dipole moment associated with N–CH_2CCl_3 acts equally on an axial or an equatorial halogen atom at C-4. Consequently the use of CH_2CCl_3 (or CH_2CF_3) as a substituent on nitrogen will not contribute an additional dipole–dipole factor which could affect the equilibrium (17*a*) ⇌ (17*e*) or (18*a*) ⇌ (18*e*). The sole influence of the substituent, therefore, is that to be ascribed to the inductive electron-attracting effect of the three halogen atoms.

The results for the 4-chloro-compounds (Table 5) follow exactly those for the 4-bromo-compounds (Table 4) and can be explained in a similar manner.

Finally, results from the analyses of conformational equilibria (19*a*) ⇌ (19*e*) in a series of 1-alkyl-4-methoxypiperidines (13)—(16) are summarised in Tables 6 and 7. There was a possibility that the ΔG° values of Table 7 concealed

Table 7. Proportions of conformations, equilibrium constants, and conformational free energy differences for ring inversion (19*a*) ⇌ (19*e*) in 4-methoxy-1-alkylpiperidines

Formula	R′	*T*/K	[%*a* *]	[%*e* *]	*K* (*e*/*a*)	$-\Delta G°_{a \rightarrow e}$/kcal mol^{-1}
(13)	H	194	14.4	85.6	5.94 ± 0.70	0.69 ± 0.06
(14)	Me	192	24.3	75.7	3.11 ± 0.30	0.43 ± 0.04
(15)	Et	182	21.6	78.4	3.64 ± 0.16	0.47 ± 0.02
(15)	Et	192	23.3	76.7	3.28 ± 0.20	0.45 ± 0.03
(15)	Et	199	23.3	76.7	3.28 ± 0.18	0.47 ± 0.03
(16)	Pr^{i}	192	23.4	76.6	3.27 ± 0.13	0.45 ± 0.02

* *a* and *e* refer to the orientation of OCH_3.

a substantial entropy contribution [17] due to the different preferences, in equatorial and axial orientations, for conformations with respect to rotation about the C(4)–O bond. However, at approximately identical temperatures the entropy contribution $T\Delta S$ is not expected to change within the series (13)—(16). The change in measured equilibrium constant (Table 7), on conversion of NH into NMe, is again interpreted as a consequence of the alteration in direction of the C–N bond moment (see earlier). Subsequent changes of NMe to NEt and NPr^{i} cause virtually no change in equilibrium constant. Evidently the *syn*-axial repulsions between the C-4 axial substituent and the C-2 and 6 -axial hydrogen atoms are dominant in the case of a 4-methoxy group (as compared with the case of a 4-halogen atom) probably because of the relatively short carbon–oxygen bond (0.143 nm). This dominance is also encouraged by the weaker polarity of a C–O bond as compared with a C–halogen bond, lessening the intramolecular coulombic interactions.

Experimental

^{1}H N.m.r. spectra were recorded with JEOL MH-100, Varian HR-220, and Bruker WM-250 spectrometers. ^{13}C N.m.r. spectra were measured in the Fourier transform mode, with generous repetition times, at 25.15 MHz (JEOL PS-100 spectrometer interfaced to Nicolet 1085 computer) and at 62.90 MHz (Bruker WM-250 spectrometer). Experiments at 25.15 MHz used 8 K data points over a width of 4 000 Hz; experiments at 62.90 MHz used 16 or 32 K data points over a width of 10 000 Hz. The JEOL variable temperature controller was calibrated over the range 150—270 K using a chromel–alumel thermocouple, and quoted temperature figures are considered accurate to within ±2 K. Temperatures indicated by the Bruker thermocouple are considered to be accurate to within ±3 K. The solvent was an 85 : 15 (v/v) mixture of $CFCl_3$ (ε 2.28) and $CDCl_3$ (ε 4.81).

Relative areas in ^{13}C n.m.r. spectra were obtained by measurements on integral traces corresponding to structurally identical carbon atoms in the two conformations. Error limits for the equilibrium constants (*K*) are believed to be generous, and were deduced from a consideration of the minimum and maximum possible values for the measurements on the integral traces.

4-*Chloro*-1-*methylpiperidine*.—A solution of 4-chloro-1-methylpiperidine hydrochloride (Aldrich) (6 g) in water (15 cm^3) was cooled in ice and treated with 30% sodium hydroxide solution (10 cm^3). Extraction with ether, drying ($MgSO_4$) of the extracts, and evaporation gave 4-chloro-1-methylpiperidine as a pale yellow liquid, suitable for n.m.r. analysis.

4-*Chloro*-1-*ethylpiperidine*.—A mixture of 4-chloropiperidine [18] (3 g), sodium carbonate (8 g), water (5 cm^3), and methanol (50 cm^3) was cooled to 0 °C, stirred, and treated with iodoethane (4.68 g) during 15 min. After 2 h at room temperature the mixture was filtered and heated under reduced pressure to remove ethanol. The residue was treated with water (30 cm^3) and extracted into chloroform (4 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered, and evaporated. The residual liquid was treated with dry ether (50 cm^3), decanted, and evaporated to give 4-chloro-1-ethylpiperidine as an orange oil (1.51 g, 40%). The crude amine was purified by preparative g.l.c. [12 ft × ⅜ in column of OV17 phenylsilicone (15%) on acid-washed and dimethylchlorosilane-treated diatomite C]. The *picrate* (ethanol) had m.p. 167—168.5 °C (Found: C, 41.3; H, 4.6; N, 15.1. $C_{13}H_{17}ClN_4O_7$ requires C, 41.5; H, 4.3; N, 14.9%).

4-*Chloro*-1-*isopropylpiperidine*.—The preceding method was repeated using 4-chloropiperidine (8.5 g), sodium carbonate (21.3 g), propan-2-ol (100 cm^3), water (10 cm^3), and 2-iodopropane (14.5 g). The product, 4-chloro-1-isopropylpiperidine (2.3 g, 20.0%), was purified by preparative g.l.c. as before. The *picrate* (ethanol) had m.p. 200—201 °C (Found: C, 42.9; H, 5.0; N, 14.4. $C_{14}H_{19}ClN_4O_7$ requires C, 43.0; H, 4.9; N, 14.3%).

4-*Chloro*-1-(2,2,2-*trifluoroethyl*)*piperidine*.—A mixture of piperidin-4-ol (10 g), dry benzene (50 cm^3), and trifluoroethyl methanesulphonate (14 g) was heated to boiling, and treated with triethylamine (12 cm^3) during 15 min. Heating was continued for 24 h, after which the mixture was cooled and shaken successively with water (2 × 40 cm^3) and 2M-hydrochloric acid (2 × 50 cm^3). The acid extracts were combined, washed with ether (2 × 30 cm^3), cooled in ice, and basified with ice-cold sodium hydroxide solution (20%). The liberated amine was extracted into ether (4 × 40 cm^3), and the combined extracts were dried ($MgSO_4$) and evaporated, giving crude 1-(2,2,2-trifluoroethyl)piperidin-4-ol (6 g, 33%) as a red oil, δ_H ($CDCl_3$; 100 MHz) 1.4—2.0 (m, 3,5-H), 2.40 (m) and 2.82 (m) (2,6-H), 2.88 (q, J_{HF} 10 Hz, CH_2CF_3), 3.60 (sept, *J ca.* 4 Hz, 4-H), and 2.2 (s, OH). A mixture of this product (4.2 g) and dry benzene (60 cm^3) was heated under reflux with freshly distilled thionyl chloride (4 cm^3). After 2 h the mixture was cooled and evaporated under reduced pressure. The residual oil was dissolved in water (50 cm^3) and extracted with chloroform (3 × 40 cm^3). The combined extracts were dried ($MgSO_4$), filtered, and evaporated, leaving 4-chloro-1-(2,2,2-trifluoroethyl)piperidine as a pale yellow oil (3 g, 65%), δ_H ($CDCl_3$; 100 MHz) 1.68—2.20 (m, 3,5-H), 2.55 (m) and 2.80 (m) (2,6-H), 2.88 (q, J_{HF} 8 Hz, CH_2CF_3), and 3.92 (sept, *J* 4 Hz, 4-H). The *picrate* (ethanol) had m.p. 126—128 °C (Found: C, 36.1; H, 3.4; N, 12.8. $C_{13}H_{14}ClF_3N_4O_7$ requires C, 36.3; H, 3.3; N, 13.0%).

4-*Bromopiperidine*.—Piperidin-4-ol (10 g) was added slowly to cold aqueous hydrogen bromide (130 cm^3; 48%) and the mixture was heated under reflux for 12 h. Water was

removed under reduced pressure and the crystalline residue was recrystallised from propan-2-ol, giving 4-bromopiperidine hydrobromide (18 g, 81%), m.p. 190—191 °C (lit.,[19] 192—193 °C) (Found: C, 24.7; H, 4.9; N, 6.0. Calc. for $C_5H_{11}Br_2N$: C, 24.7; H, 4.6; N, 5.8%). The hydrobromide (10 g), in a conical flask cooled in acetone–solid CO_2, was treated with an excess of ice-cold sodium hydroxide (20%), and the solution was then allowed to warm to room temperature and saturated with sodium chloride. The free base was extracted into $CDCl_3$ and a portion of the extract, dried ($MgSO_4$) and then diluted with $CFCl_3$, was used without delay for a determination of the ^{13}C n.m.r. spectrum. In a separate experiment extraction of the free base with $CHCl_3$, drying ($MgSO_4$), and removal of solvent gave 4-bromopiperidine as a pale yellow oil (3.9 g, 81% from hydrobromide) (Found: M^+ 162.9982. Calc. for $C_5H_{10}{}^{79}BrN$: M, 162.9997), δ_H ($CDCl_3$; 250 MHz) 1.80 (m) and 2.00 (m) (3,5-H), 2.54 [t (separations 9.5 Hz) of d (3 Hz)] and 2.92 [d (13 Hz) of t (4.5 Hz)] (2,6-H), 4.11 [sept (4.3 Hz), 4-H], and 2.4 (s, NH).

4-*Bromo*-1-*methylpiperidine*.—A mixture of 1-methylpiperidin-4-ol (Aldrich) (5 g) and aqueous hydrogen bromide (80 cm³; 48%) was heated under reflux for 16 h and then evaporated to near dryness under reduced pressure. The residue was cooled in acetone–solid CO_2 and basified with an excess of aqueous sodium hydroxide (20%). The mixture was allowed to warm to room temperature, saturated with sodium chloride, and extracted with $CHCl_3$ (4 × 50 cm³). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to give a yellow oil (4.8 g, 63%). The product, contaminated with 3,4-didehydro-1-methylpiperidine, was purified by chromatography on silica gel with light petroleum (b.p. 40—60 °C) as eluant, and obtained finally as a pale yellow liquid, δ_H ($CDCl_3$; 100 MHz) 1.6—2.4 (m, 3,5-H), 2.4—2.9 (m, 2,6-H), 2.28 (s, NCH_3), and 4.12 (sept, 4-H). The *picrate* (ethanol) had m.p. 207—209 °C (Found: C, 35.8; H, 3.7; N, 13.7. $C_{12}H_{15}BrN_4O_7$ requires C, 35.5; H, 3.7; N, 13.8%).

4-*Bromo*-1-*ethylpiperidine*.—4-Bromopiperidine (3.5 g), dissolved in dry benzene (60 cm³), was treated with ethyl methanesulphonate (2.68 g) and the solution was heated to boiling under reflux. Triethylamine (8 cm³) was added during 15 min. Heating was continued for 48 h, after which the mixture was cooled to room temperature and shaken successively with water (2 × 40 cm³) and 2M-hydrochloric acid (2 × 50 cm³). The combined acid extracts were washed with ether (2 × 30 cm³), cooled in acetone–solid CO_2, and basified with sodium hydroxide solution (20%). The solution was saturated with NaCl and extracted with $CHCl_3$ (3 × 30 cm³). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to leave an orange oil (2.50 g, 61%). Chromatography (see preceding preparation) gave 4-bromo-1-ethylpiperidine as a pale yellow oil, δ_H ($CDCl_3$; 250 MHz) 1.01 (t, J 7 Hz, CH_3), 2.20 (m) and 2.15 (m) (3,5-H), 2.15 (m) and 2.66 (m) (2,6-H), 2.35 (q, J 7 Hz, CH_2CH_3), and 4.14 (m, 4-H). The *picrate* (ethanol) had m.p. 159—162 °C (Found: C, 36.8; H, 3.7; N, 13.4. $C_{13}H_{17}BrN_4O_7$ requires C, 37.1; H, 4.1; N, 13.3%).

4-*Bromo*-1-*propylpiperidine*.—The foregoing method, applied to 4-bromopiperidine (3.8 g), propyl methanesulphonate (3.4 g), and triethylamine (12 cm³) gave the crude product as a yellow oil (3.5 g, 47%). After chromatography on silica gel, pure 4-bromo-1-propylpiperidine was obtained as a pale yellow oil, δ_H ($CDCl_3$; 100 MHz) 0.86 (t, J 7 Hz, CH_3), 1.44 (m, CH_2CH_3), 2.0—2.4 (m, $CH_2CH_2CH_3$, four hydrogens of 3,5-H and two of 2,6-H), 2.7 (m, two hydrogens of 2,6-H), and 4.10 (sept, J *ca.* 4 Hz, 4-H). The *picrate* (ethanol) had m.p. 123—124 °C (Found: C, 38.6; H, 4.5; N, 13.1. $C_{14}H_{19}BrN_4O_7$ requires C, 38.7; H, 4.4; N, 12.9%).

4-*Bromo*-1-*isopropylpiperidine*.—The foregoing method was applied to 4-bromopiperidine (3 g), isopropyl methanesulphonate (2.5 g), and triethylamine (10 cm³) to give, after chromatography on silica gel, 4-bromo-1-isopropylpiperidine as a pale yellow oil (2.2 g, 58%), δ_H ($CDCl_3$; 100 MHz) 1.0 (d, J 7 Hz, CH_3), 1.98—2.40 (m, four hydrogens of 3,5-H and two of 2,6-H), 2.68—2.80 (m, two hydrogens of 2,6-H), 2.60 (sept, J 7 Hz, Me_2CH), and 3.95—4.16 (m, 4-H). The *picrate* (ethanol) had m.p. 183—185 °C (Found: C, 38.9; H, 4.6; N, 13.2. $C_{14}H_{19}BrN_4O_7$ requires C, 38.7; H, 4.4; N, 12.9%).

4-*Bromo*-1-*trichloroacetylpiperidine*.—To a stirred mixture of 4-bromopiperidine (6 g) and tetrahydrofuran (60 cm³) was added hexachloroacetone (10.5 g), with cooling in ice. The mixture was stirred at room temperature for 24 h, filtered, and evaporated to a thick red oil. Extraction with hot light petroleum (b.p. 60—80 °C) (3 × 50 cm³), followed by drying ($MgSO_4$), filtering, and evaporation gave a yellow oil. Crystallisation from light petroleum (b.p. 40—60 °C) gave 4-*bromo*-1-*trichloroacetylpiperidine* as white crystals, m.p. 60—61 °C (5.2 g, 55%) (Found: C, 27.3; H, 3.1; N, 4.6. $C_7H_9BrCl_3NO$ requires C, 27.4; H, 2.9; N, 4.6%), δ_H ($CDCl_3$; 100 MHz) 2.40 (m, 3,5-H), 3.72 (m, 2,6-H), and 4.24 (sept, J *ca.* 4 Hz, 4-H).

4-*Bromo*-1-(2,2,2-*trichloroethyl*)*piperidine*.—Diborane–tetrahydrofuran complex (27 cm³) was added, with nitrogen purging, to a solution of 4-bromo-1-trichloroacetylpiperidine (5 g) in dry tetrahydrofuran (40 cm³). The mixture was heated under reflux for 16 h, cooled to room temperature, and treated dropwise with water (2 cm³), then with more water (30 cm³). The solution was extracted with $CHCl_3$ (3 × 30 cm³) and the combined extracts were dried ($MgSO_4$), filtered, and evaporated to leave 4-bromo-1-(2,2,2-trichloroethyl)-piperidine as a yellow oil (3 g, 53%), δ_H ($CDCl_3$; 250 MHz) 1.9—2.3 (m, four hydrogens of 3,5-H and two of 2,6-H), 2.80 (m, two hydrogens of 2,6-H), 2.88 (s, CH_2CCl_3), and 4.18 (sept, J *ca.* 4 Hz, 4-H). The *picrate* (ethanol) had m.p. 123—124 °C (Found: C, 30.1; H, 2.8; N, 10.7. $C_{13}H_{14}BrCl_3N_4O_7$ requires C, 29.9; H, 2.7; N, 10.7%).

4-*Bromo*-1-(2,2,2-*trifluoroethyl*)*piperidine*.—1-(2,2,2-Trifluoroethyl)piperidin-4-ol (3.8 g, prepared as described earlier), was dissolved in cold aqueous hydrogen bromide (130 cm³; 48%), and the mixture was heated under reflux for 12 h. Most of the water was removed by evaporation under reduced pressure. The residual solution was cooled in acetone–solid CO_2, basified with an excess of aqueous sodium hydroxide (20%), saturated with sodium chloride, and extracted with chloroform (3 × 25 cm³). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to leave 4-bromo-1-(2,2,2-trifluoroethyl)piperidine as a yellow oil (3.2 g, 63%), δ_H (100 MHz; $CDCl_3$) 1.6—2.2 (m, 3,5-H), 2.4—2.7 (m, two hydrogens of 2,6-H), 2.7—3.0 (m, two hydrogens of 2,6-H), 2.88 (q, J 10 Hz, CH_2CF_3), and 4.12 (sept, J *ca.* 4 Hz, 4-H). The *picrate* (ethanol) had m.p. 134—136 °C (Found: C, 33.2; H, 3.1; N, 12.0. $C_{13}H_{14}BrF_3N_4O_7$ requires C, 32.9; H, 3.0; N, 11.8%).

4-*Methoxypiperidine*.—4-Methoxypyridine [20] (5 g), dissolved in cyclohexane (20 cm³), was hydrogenated over rhodium–active carbon (0.5 g) at 90 °C and 40 atm during 3 days. The mixture was filtered and heated under reduced pressure to remove cyclohexane. The residue of crude 4-methoxypiperidine (4.5 g) was purified by preparative g.l.c. on a 12 ft × $\frac{3}{8}$ in

column of Carbowax 20M (20%) on alkali-washed Chromosorb W. The ^{1}H n.m.r. spectrum ($CDCl_3$; 100 MHz) showed δ 1.40 [q (separations 13.4 Hz) of d (3.6 Hz), 3,5-axial H], 1.72 (br s, NH), 1.90 [d (13 Hz) of q (3.7 Hz), 3,5-equatorial H], 2.59 [t (9.3 Hz) of d (3.5 Hz), 2,6-axial H], 3.07 [d (12.8 Hz) of t (4.6 Hz), 2,6-equatorial H], 3.23 [t (9 Hz) of t (4 Hz), 4-H], and 3.32 (s, OCH_3). The *picrate* (ethanol) had m.p. 106—108 °C (Found: C, 41.7; H, 4.8; N, 16.1. $C_{12}H_{16}N_4O_8$ requires C, 41.9; H, 4.7; N, 16.3%).

4-*Methoxy*-1-*methylpiperidine*.—An ice-cold solution of 4-methoxypyridine (2 g) in dry acetonitrile (50 cm^3) was treated with dry, freshly distilled iodomethane (3 g). The mixture was stirred at 30 °C for 72 h and then heated under reduced pressure to remove acetonitrile. The crystalline residue was triturated with dry ether and filtered, leaving bright yellow crystals (4.4 g, 97%) of 4-methoxy-1-methylpyridinium iodide, δ_H (CD_3OD; 100 MHz) 4.18 (s, OCH_3), 4.32 (s, NCH_3), 7.58 (d, *J* 7.5 Hz, 3,5-H), and 8.78 (d, *J* 7.5 Hz, 2,6-H). The salt (2.5 g), dissolved in dry methanol (50 cm^3), was hydrogenated over PtO_2 (0.5 g) at 20 °C and 760 mmHg, until uptake of hydrogen ceased. The mixture was filtered and heated under reduced pressure to remove methanol. The residual crystalline solid was treated with aqueous 30% sodium hydroxide (20 cm^3) and extracted with ether (4 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated, leaving 4-methoxy-1-methylpiperidine as a colourless liquid (0.9 g, 70%). Preparative g.l.c. (see preceding preparation) afforded a sample which gave unsatisfactory results in elemental microanalysis, but which was estimated by ^{1}H and ^{13}C n.m.r. spectroscopy to be ≥ 97% pure. The ^{1}H n.m.r. spectrum ($CDCl_3$; 100 MHz) showed δ 1.6—2.3 (m, 3,5-H and two protons of 2,6-H), 2.6—2.8 (m, two protons of 2,6-H), 3.1—3.3 (m, 4-H), 2.25 (s, NMe), and 3.16 (s, OCH_3).

1-*Ethyl*-4-*methoxypiperidine*.—4-Methoxypyridine (2 g), dissolved in ethanol (300 cm^3), was hydrogenated over Raney nickel (grade T-1) (5 g) at 150 °C and 50 atm initial pressure of hydrogen. After 3 days the mixture was filtered and heated at 35 °C under reduced pressure (20 mmHg) to remove ethanol. The residue was treated with aqueous sodium hydroxide (20 cm^3; 20%) and extracted with ether (4 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered, and evaporated, leaving 1-ethyl-4-methoxypiperidine as a pale yellow liquid (2.1 g, 80.2%). The sample for spectroscopic examination was purified by preparative g.l.c. (see preceding preparation). The ^{1}H n.m.r. spectrum (220 MHz; $CDCl_3$) showed δ 1.61 (m, two protons of 3,5-H), 1.87—2.0 (m, two protons of 3,5-H), 2.07—2.19 (m, two protons of 2,6-H), 2.71—2.81 (m, two protons of 2,6-H), 3.23 (sept, 4-H), 1.09 (t, *J* 7 Hz, CH_3–C), 2.41 (q, *J* 7 Hz, NCH_2CH_3), and 3.34 (s, OCH_3). The *picrate* had m.p. 108—110 °C (Found: N, 15.1. $C_{14}H_{20}N_4O_8$ requires N, 15.1%).

4-*Methoxy*-1-*isopropylpiperidine*.—4-Methoxypyridine (2 g), dissolved in propan-2-ol (300 cm^3), was hydrogenated over Raney nickel (grade T-1) at 150 °C and 50 atm initial pressure of hydrogen. Work-up according to the preceding preparation gave 4-methoxy-1-isopropylpiperidine as a yellow liquid (2.4 g, 83%). The sample for spectroscopic examination was purified by preparative g.l.c. (see preceding preparation). The ^{1}H n.m.r. spectrum ($CDCl_3$; 220 MHz) showed δ 1.50—1.68 (m, two protons of 3,5-H), 1.86—2.0 (m, two protons of 3,5-H), 2.18—2.32 (m, two protons of 2,6-H), 2.72—2.82 (m, two protons of 2,6-H), 3.18 (sept, 4-H), 2.72 (sept, *J* 6.5 Hz, Me_2CH), 1.0 (d, *J* 6.5 Hz, CH_3–C), and 3.34 (s, OCH_3). The *picrate* had m.p. 133—135 °C (Found: N, 14.7. $C_{15}H_{22}N_4O_8$ requires N, 14.5%).

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