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CONFORMATIONAL EFFECTS IN COMPOUNDS WITH 6-MEMBERED RINGS—XII

THE CONFORMATIONAL EQUILIBRIUM IN *N*-METHYLPIPERIDINE

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Abstract—The conformational equilibrium at nitrogen in *N*-methylpiperidines has been determined in the gas phase ($\Delta G^\circ_{298} \simeq 13.2 \pm 0.4$ kJ mol^{-1}) and for dilute solutions in several solvents (ΔG°_{293} ranging from 12.5 ± 0.4 in dodecane to 10.1 ± 0.4 in chloroform) by kinetically controlled protonation of anancomeric model compounds **6** and **8** at the interface between the piperidine-containing phase and an immiscible strong acid. The conformational energy for *N*-methylpiperidine determined by this method is strikingly higher than earlier estimates based on less direct methods but is supported by independent evidence from the temperature dependence of ^{13}C NMR chemical shifts. Reconsideration of the more important of the earlier methods indicates that these involved invalid or unproven assumptions and that the low values of ΔG° for *N*-methylpiperidine derived from them are not reliable.

The conformational equilibria at nitrogen in piperidines have been studied extensively for nearly twenty years since Aroney and LeFèvre[1] first compared experimental Kerr constants with values calculated for the possible conformers of a number of saturated heterocycles. Their results are no longer considered reliable but later and supposedly more reliable methods have resulted in a truly spectacular range of values, greatly exceeding the quoted probable errors, for the free energy difference ΔG° for the equilibrium at nitrogen in *N*-methylpiperidine **1** and various anancomeric derivatives (Fig. 1). The position of the equilibrium at nitrogen in piperidine itself is also not completely certain, in spite of even more extensive experimentation[2] and will be considered in a separate paper. The published results are only briefly summarised in Table 1 because Eliel and Vierhapper[3] have recently given a detailed listing of the apparently valid results together with a critical evaluation of the clearly unacceptable methods, i.e. item 1,[1] a method that has been frequently unsatisfactory;[15] invalid[16] use of shift reagents (item 3);[5] early erroneous results[17] from electric dipole moments, *not* included in item 4, that were later corrected;[6] and molecular mechanics calculations[10] based on an inadequate model[3c] (item 6). Our purpose in this paper is to consider the remaining methods, 2, 4, 5 and 7–13 in Table 1, in order to come to as firm a conclusion as possible about the equilibrium at nitrogen in *N*-methylpiperidine.

We have investigated the equilibrium in **1** using (a) ^{1}H and ^{13}C NMR chemical shifts and (b) kinetically controlled protonation of anancomeric derivatives, as well as uncovering, in other work, possible sources of error in the use of electric dipole moments in one of the most intensively studied methods (Table 1, item 4), and believe we can point to most of the probable causes of the discrepancies between various methods. For convenience in discussion we will assume that $\Delta S^\circ = 0$, a reasonable approximation for a symmetrical substituent and for solvents of low polarity, and that twist conformers may be neglected. At the end of the paper we briefly consider the possible significance of the errors arising from these assumptions.

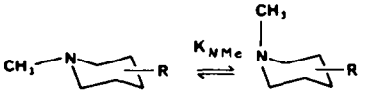


Fig. 1. Conformational equilibrium at nitrogen in *N*-methylpiperidines.

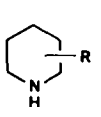
^{1}H *and* ^{13}C NMR *chemical shifts* (*Table* 1, *items* 2, 9 *and* 11)

As yet it has not been possible to observe separate NMR spectra for the axial and equatorial conformers of any unhindered *N*-methylpiperidine, in contrast to many other heterocyclic systems[18] and to *N*,2,2,6-tetramethylpiperidine.[19] It has been necessary to use relation (1)[20]

$$K_{NMe} = (\delta_e - \delta)/(\delta - \delta_a) \qquad (1)$$

where δ is an observed weighted average chemical shift or shift difference and δ_e and δ_a are the corresponding values, which must be estimated, for the individual conformers. Because $K_{NMe} < 1$ errors in estimating δ_e are more important than errors in δ_a.

The first use of NMR chemical shifts was made by Lambert (Table 1, item 2),[4] who concluded conservatively that K_{NMe} is considerably less than 1. We have briefly investigated the temperature dependence of the ^{1}H spectra of the anancomeric piperidines **8** and **11** and find essentially *no change* from 173 to 323 K (in $SiMe_4$) for **8** and **11** and from 303 K to 413 K (neat) for **11**. Unfortunately chemical shifts for the axial 2(6)-protons can not be determined at 90 MHz in **8** (spectra are simplified at 270 MHz[21]) but if one assumes that differences in chemical shifts for C-2(6)-ax and -eq protons of **11E** and **11A** and of analogous heterocyclic compounds[22] are similar then the temperature invariance of the spectrum of **11** to ± 0.05 ppm is consistent with $\Delta H^\circ > 8$ kJ mol^{-1}.



1:	R = H	**7**:	R = 3,3-Me_2	**13**:	X = H_2
2:	2-Me	**8**:	*cis*-3,5-Me_2	**14**:	X = O
3:	3-Me	**9**:	*trans*-3,5-Me_2		
4:	4-Me	**10**:	*cis*-2,6-Me_2		
5:	4-C_6H_4X(para)	**11**:	*cis*-3,5-di-t-Bu		
6:	4-t-Bu	**12**:	*trans*-3,5-di-t-Bu		

Table 1. Summary of estimates of equilibrium constants, K_{NMe}, and free energy differences,[a] ΔG°_{NMe} (1E → 1A), for the conformational equilibrium at nitrogen in N-methylpiperidine (1) in solvents of low polarity

Method	Solvent	K_{NMe}	ΔG°_{NMe} (kJ mol^{-1})	Ref.
1 Kerr constants		≈1	≈0	1
2 NMR: ^{1}H δs		<1[b]	>0	4
3 NMR: Shift reagents[c]	$CDCl_3$	≫1	≫0	5
4 Dipole moments[d]	C_6H_{12}	0.33	2.7	8
	Various	0.5 0.25	1.6 3.4	6–8
5 Ultrasonic absorption	None		(3.7)	9
6 Molecular mechanics[e]	Gas phase		(3.3)	10
7 IR intensities			(6.7)	11
8 Protonation[e]	None	0.06	6.7	12
9 NMR: ^{13}C δs	$CDCl_3$	0.1 0.05	5.6—7.4[f]	3
	C_6D_6	0.05 0.025	7.4—9.2[f]	3
10 Kinetic protonation (^{1}H NMR)	C_6H_{12}	0.009	11.3±0.8[g]	13a
11 VTNMR: ^{13}C δs	n-$C_{12}H_{26}$		(11—13)[h]	This paper
12 Nitrene addition	$C_2F_3Cl_3$	<0.01	>11.2	14
13 Kinetic protonation (^{13}C NMR)	Gas	0.004_5	13.2±0.5[j,k]	
	n-$C_{12}H_{26}$	0.006	12.6±0.3[j,l]	This paper,
	C_6H_6	0.0125	10.5±0.3[j,l]	13b
	$CDCl_3$	0.015	10.1_5±0.3[j,l]	

[a]Usually near 298K; the temperature variation of ΔG°_{NMe} is small (see text and Table 8). [b]No lower limit set. [c]See text. [d]Early values [7] were invalidated by an experimental error[6] and are therefore omitted. [e]Based on mixing neat amine with excess of strong acid. [f]A reconsideration of the assumptions made (see text) suggests that the δs used are consistent with $\Delta G^{\circ}_{NMe} < 9$ kJ mol^{-1}, with no upper limit. [g]The necessity for relatively high final concentrations casts doubt on whether strict kinetic control was achieved (see text); any error of this type *lowers* the apparent value of ΔG°_{NMe}. [h]No firm estimate of systematic errors can be made but $\Delta H^{\circ} < 9$ kJ mol^{-1} (using $\delta_e - \delta_a \approx 5$ ppm, i.e. at the *lower* end of the range considered reasonable by Eliel and Vierhapper[3]) requires that the errors in δ_e based on using **9** as a model are >8 times as large as the difference between the models **7** and **9** (see Fig. 3 and text); if **7** were used for δ_e then estimates of ΔH° would be raised by ~0.5 kJ mol^{-1}. [j]Uncorrected for possible effects of twist conformers (see text and Table 8). [k]Based on one compound (**6**) but with experimental error increased in view of differences between **6** and **8** in solvents (see Table 8). [l]Error includes an allowance for differences between **6** and **8** (see Table 8).

Values used in equation (1):

Mobile:	**1**	**3**	**4**	**6**	**8**	Ref. 3	Here
δ($^{\circ}CDCl_3$):	**46.90**	46.59	46.42	46.33	46.29	46.66	**46.90**
Anancomeric:	**7**	**9**	[Corrections				**46.98** ± 0.10
δ_e($CDCl_3$):	(47.1)	**46.93**	+0.30 − 0.25]			47.15	
	13	**14**	[Indirect estimates				
δ_a($CDCl_3$):	**41.19**	**41.19**	37.24–41.34[3]			37.24–41.34	**41.2**
			K			0.1–0.05	0.03–0

Scheme 1. Derivation of δ, δ_e and δ_a for use in equation 1. Bold numerals indicate the values we prefer (with corrections for C-methyl groups in **7** and **9**; see text) based on Eliel and Vierhapper's data[3] for δ and δ_e (essentially similar conclusions follow from our own data based on comparisons using mixtures; see Table 2). The latter[3] used *averages* of their own and published data:[25,26] by ill-chance the additional data tend to *lower* δ and *raise* δ_e, partly through systematic substituent effects (see δ values and the δ_e (**7**) value above) and partly experimental errors (see Ref. 3 for scatter in published data).

Conformational effects on ^{13}C NMR chemical shifts in cyclohexane derivatives are large and additive.[23] Surprisingly, Eliel and Vierhapper[3,24] alone have previously applied them in the study of **1** using equation 1 (see Scheme 1 and ref. 3 for the detailed arguments). Their principal conclusion that ΔG° (1E → 1A) cannot be as low as many earlier estimates is clearly correct but we question their choice of values of δ, δ_e and δ_a, and do not agree that ^{13}C chemical shifts exclude our higher values of ΔG^{c13} (and very recent independent results[14]). We suggest

Table 2. ^{13}C NMR chemical shifts (in ppm downfield from internal Me_4Si) of *N*-methyl groups in *N*-methylpiperidines and related compounds (1M)

Compound	n-$C_{12}H_{26}$[a]	n-$C_{12}H_{26}$[b]	C_6H_{12}[c]	C_6H_6[d]	$CDCl_3$[a]
NMe_3	-	-	-	-	47.71
1	47.17	0.000	47.08	46.98	46.97
3	46.92	-0.25_3	46.82	46.70	46.73
4	46.78	-0.39_2	46.67	46.59	46.58
5 (X=H)	46.79	-0.38_0	46.69	46.57	46.60
6	46.68	-0.49_5	46.58	46.55	46.47
7	47.08	-0.08_8	-	-	-
8	46.61	-0.56_0	46.50	46.40	46.43
9	47.06	-0.11_3	-	-	-
11	-	-	-	-	46.35
12	-	-	-	-	47.10
13	41.42	-5.76	-	-	41.19
14	-	-	-	-	41.19

[a]Digitisation 0.02 ppm. [b]Chemical shift differences relative to N-methyl in 1 determined from mixtures at ~0.1 M: uncertainties ~0.003 ppm. [c]Absolute values ±0.05 ppm, differences ±0.02 ppm. [d]Digitisation 0.05 ppm.

that **13** and **14** (pseudopelletierine) (Table 2), in which the *N*-methyl group must be axial to one ring, may be used as models for **1A** (compare δs for NMe_3 and **1**, and the related ions, for the trans-γ effect of $-(CH_2)_3-$ chains, and compare **13**-$\overset{+}{H}$ with other ions with hindered NMe, e.g. **6E**–$\overset{+}{H}$) so that δ_a is probably close to 41.2 ppm, near the upper end of the wide range previously used.[3] Eliel and Vierhapper used *average* values of δ and δ_e (see Scheme 1). *Either* the average values of δ_e (average 47.15, range 46.93–47.37)[3] have wide error limits *or*, as we prefer, the variations in δ are treated as C-alkyl *substituent effects* and not as random errors (which they are not). In the latter case one uses δ = 46.90 ppm (for **1**) and estimates δ_e = 46.98 (for **1E**: see Scheme 1). In either case $\delta_e - \delta = 0$ within the uncertainties in the data and assumptions and *there is no upper limit to* $\Delta G°$ (**1E** → **1A**) and ^{13}C NMR chemical shift data are consistent with our high values of $\Delta G°$ from kinetic protonation.

Since the use of eqn (1) is always open to doubt when K is very large or very small we have also determined the temperature dependence of the ^{13}C NMR chemical shifts of several piperidines. Adequate precision could not be achieved using ^{13}C at natural abundance.[28] The preparation of **1**, **3**, **4**, **5** (X = H) and **6–9** with 85–90% ^{13}C in the *N*-methyl groups (Scheme 2), however, allowed mixtures of three or four of these compounds to be studied with high precision (see Fig. 2, Table 3 and Experimental) as dilute solutions in dodecane (b.p. 216°), which can also be used for kinetic protonations (see later). We have assumed that $d\delta$ (**7** or **9**)/$dT = d\delta_e/dT$ for **1E**, **3E**, **4E**, **5E** (R = H), **6E** and **8E** (note the very close agreement between **7** and **9** in Fig. 2) and that **13** may be used as a model for δ_a (±20% error in $\delta_e - \delta_a$ leads to only ±0.4 kJ mol^{-1} error in $\Delta H°$). The temperature dependence of δ, relative to **7** or **9** may then be compared with values for

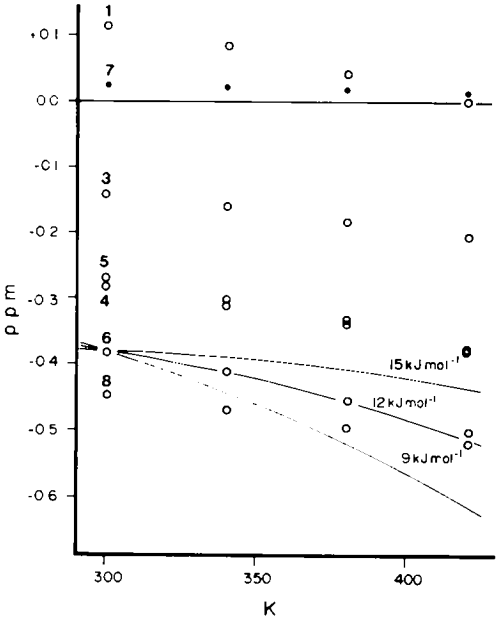
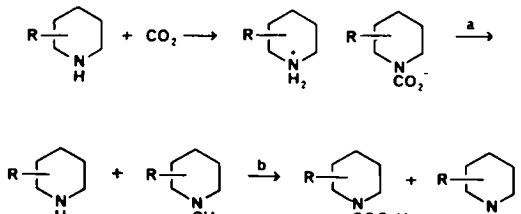


Fig. 2. Temperature dependence of the ^{13}C NMR chemical shifts of *N*-methyl groups in **1**, and **3–8** relative to **9**, in dodecane (○ for mobile compounds, ● for anancomeric compound, **7**); the calculated curves a-c for **6** assume $\Delta H° = 15$(a), 12(b), and 9(c) kJ mol^{-1}, with $\delta_e - \delta_a$ based on **9** and **13** as models, and illustrate how well defined $\Delta H°$ is for a given value of $\delta_e - \delta_a$.

Table 3. Estimates of $\Delta H°_{NMe}$ (**1E** → **1A**) (kJ mol^{-1}) derived from temperature dependence of ^{13}C NMR chemical shifts[a] of *N*-methyl groups[b] in *N*-methylpiperidines (~0.1 M in n-dodecane) using **9** for $d(\delta_e)/dT$ and **13**[d] for δ_a

Compound:	**1**	**3**	**4**	**5**	**6**	**8**
$\Delta H°_{NMe}$						
(uncorr.)[e]	$12._7$	$14._5$[f]	$13._5$	$12._7$	$12._3$	14
(corr.)[f,g,h]	$12._7$	$13._5$	$12._7$	-	$12._3$	$12._7$

[a]^1H NMR chemical shifts merely set a lower limit ~8 kJ mol^{-1} (see text) and results will not be given in detail. [b]Enriched in ^{13}C. [c]If **7** is used as a model for **1E** then estimates of $\Delta H°_{NMe}$ are slightly higher (<0.5 kJ mol^{-1}). [d]δ(13) is near the *upper* extreme of the probable values[3] for δ_a: *lower* estimates of δ_a lead to *higher* values of $\Delta H°_{NMe}$. [e]No correction for possible effects of C-alkyl substituents on δ_a. [f]Corrected (from ~15 kJ mol^{-1}) for the C-methyl conformational equilibrium.[13b,28] [g]Corrected for C-alkyl substituent effects on δ_a (3(5)-Me, +0.8 ppm; 4-Me, +0.6 ppm; 4-t-Bu, ~0 ppm), using shifts substituent effects observed in two series of derivatives of *N*-methylpiperidines. [h]An error of ±25% in $\delta_{300K} - \delta_{420K}$ (resulting from, e.g. imperfections in the model for δ_e) corresponds to ~±1 kJ mol^{-1} in $\Delta H°_{NMe}$: the very close agreement between several of the values must be regarded as an amusing coincidence.



Scheme 2. Synthesis of N-^{13}C-methylpiperidines from $^{13}CO_2$ (from $Ba^{13}CO_3 + PbCl_2$):[27b] a, $LiAlH_4 + AlCl_3$, Et_2O(2d.); b, PhCOCl + KOH, Et_2O/H_2O.

varying $\Delta H°$ (assuming $\Delta S° = 0$), as is shown explicitly for **6** in Fig. 2, leading to the estimates in Table 3. More consistent results follow if one corrects δ_a for C-alkyl substituent effects, which have been found to be relatively large for 3(5)-methyl groups and significant for 4-alkyl groups in three series of derivatives of **1E** (see Table 4 and Ref. 27). If one uses lower values of δ_a[3] (*larger* $\delta_e - \delta_a$) $\Delta H°$ *increases*. In contrast, if one adjusts δ_a to suit low estimates of $\Delta H°$ then $\delta_e - \delta_a$ becomes implausibly low *and* the fit between calculated and observed δ becomes poor. The good agreement of various estimates of $\Delta H°$ ($\simeq \Delta G°$) (Table 3) supports the assumptions made.

The results for **5** (X = H) deserve comment. Eliel and Vierhapper, assuming that "molecules tend to minimise their dipole moments because of dipole–dipole repulsion",[3] have suggested that dipole–dipole interactions in **5** (X = Cl or NO_2) destabilise **5E** and so lower $\Delta G°$, thereby accounting (in part) for the low $\Delta G°$ (**1E** → **1A**) estimated from electric dipole moments of **5** (X = Cl or NO_2).[6-8,17] They noted that δ(NMe) for **5**(X = Cl), 46.29 ppm, is less than the *average* δ (46.66 ppm, see above and Scheme 1) and derived $\Delta G°$(**5**(X = Cl)) = 4.35 kJ mol^{-1}. We do not agree with this analysis because (a) δs for **5**(X = Cl or H) are almost identical to δ for **4** or **6** (Table 2), which have *non*-polar 4-substituents, (b) our VT ^{13}C NMR results for **5**(X = H) are very similar to those for **1**, **3**, **4**, **6** and **8** (Table 3), and (c) calculations of electrostatic interactions in **5** do not support Eliel's assumption. These calculations, irrespective of details of the assumptions, show that such interactions are barely significant if the group moments are located at N and the para position in aryl (**5**) and *slightly favour equatorial N-methyl* in **5**. A slightly larger effect (still < 1 kJ mol^{-1}) in the same sense is found if account is taken of the polarity of the C(4)-Aryl bond, which is small ($\simeq$ 0.6 D, see phenylcyclohexane[6]) but close to the N-methyl group.

We conclude that ^{1}H and ^{13}C NMR measurements are uniformly consistent with high values of $\Delta H°$ and $\Delta G°$ and agree with Eliel and Vierhapper[3,24] that ^{13}C chemical shifts exclude low values (Table 1, items 4 and 5; see conclusion in Ref. 3).

Table 4. ^{13}C NMR chemical shifts[a] (ppm) for *N*-methylpiperidinium ions (1 M)[b] in 81% sulphuric acid relative to internal $\underline{Me}_3CNH_3^+$ (0.5 M) at 300 K

Ion	C-2	C-3	C-4	C-5	C-6	N–Me	Other C
$Me_3\overset{+}{N}H$	-	-	-	-	-	+18.86	-
1E-H$^+$	+29.06	-3.84	- 6.34	-3.84	+29.06	+17.17	-
3E-H$^+$	+34.11	-2.76	+ 2.20	-3 89	+28.23	-17.14	-9.04
3A-H$^+$						+15.64	
4E-H$^+$	+28.62	-4.30	+ 0.69	+4.30	+28.62	+16.95	-6.41
4A-H$^+$	+24.67	-0 35	- 1.90	+0.35	+24.67	+14.44	-9.17
6E-H$^+$	+29.27	-2.31	+15.84	-2.31	+29.27	+17.01	+4.62[c] -0 49[d]
6A-H$^+$	+26 42	-8 07	(+15.84)	-8.07	+26.42	+16.94	+4.81[c] -0.55[d]
7 -H$^+$	+38 36	+3 58	+ 5.47	-7.31	+28.93	+17.76	+1.12[e] -4.73[f]
8E-H$^+$	+33.85	+2.57	+11.05	+2.57	+33.85	+17.23	-9.03
8A-H$^+$	+31.04	-3.19	+12.11	-3.19	+31.04	+12.52	-9.19
10 -H$^+$	+36.35	+5.22	- 5.05	+5.22	+36.35	+10.30	-8.76
10A-H^{+g}	+34.02	-2.78	- 4.95	-2.78	+34.02	- 2 07	-9.54
13-H^{+h}	[C-1,5 +29.16	C-2,4 -5.72	C-3 - 9.28[h]	C-6,8 +2 68	C-7 - 9.78[h]	N-Me +12 15]	

[a]Digital resolution 0.02 ppm. [b]Solutions containing single diastereomeric ions (mainly or exclusively eq-NMe for 3–10) were prepared from crystalline chlorides. Solutions containing 1:1 mixtures (Scheme 4) were used to obtain spectra of 3A–H$^+$, 4A–H$^+$, 6A–H$^+$ and 8A–H$^+$ and concentrations could not be controlled precisely. [c]$\underline{C}Me_3$. [d]$C\underline{Me}_3$. [e]Eq 3-Me. [f]Ax 3-Me. [g]See Experimental for preparation of mixture of 10E–H$^+$ and 10A–H$^+$. [h]N–Me assigned as *syn* to the *lower* numbered carbon chain; the assignments for C-3 and C-7 are uncertain.

Electric dipole moments

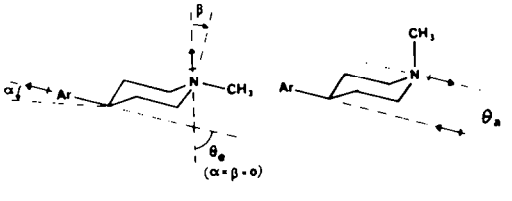
Katritzky, Sutton *et al.*[6-8,17] in an unusually thorough study have used eqn (2)

$$K_{NMe} = (\mu_e^2 - \mu^2)/(\mu^2 - \mu_a^2) \qquad (2)$$

to interpret the experimental dipole moments μ of **5** (X = Cl or NO_2). This requires that the values of μ_e for **5E** and of μ_a for **5A** be calculated as the vector sums (see eqn 3) of group moments derived from *N*-methylpiperidine (μ_A) and p-chloro- or p-nitro-phenylcyclohexane (μ_B) (Fig. 3).

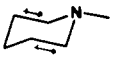
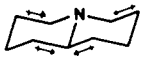
$$\mu_i^2 = \mu_A^2 + \mu_B^2 + 2\mu_A\mu_B \cos\theta_i \qquad (3)$$

By far the most crucial variable is θ_e because the observed μ is not very different from μ_e. The angle θ_e must be calculated assuming directions of the group moments relative to the calculated molecular framework (angle α and β in Fig. 3). Katritzky *et al.*[6] assumed $\alpha = 0°$ but we have determined this angle to be probably within the range +3 to +5° in the course of other work on electric dipole moments.[29] The angle $\theta_e = 66.5°$[6] or 68.5°[8] was set by assuming that the *N*-methylpiperidine moment is "equally inclined to the *N*-Me and the two N–C ring bonds".[6] In effect this ignores the 3-, 4- and 5-methylene groups and any induced moments, and is potentially a serious source of error (cf the *measured* angles between μ and C–F, ~10°, in both conformers of cyclohexyl fluoride[30]). If the difference in magnitude of μ between NMe_3 (0.86D)[31] and quinuclidine (1.27D)[32] is attributed to polarisation of the C_α–C_β bonds then equal polarisations in the corresponding C–C bonds in **1E** (Scheme 3) will have little effect on the magnitude but a large effect (~17°) on the direction of the moment. Clearly corrections as large as 17° in β, added to the probable error in α, could raise θ_e from the values assumed[6,8] to ~90° at which $\mu_e = \mu$



μ_e = 2.61D[6] (θ_e = 66.5°, $\alpha = \beta$ = 0°): K = 0.37
= 2.58D[8] (θ_e = 68.5°, $\alpha = \beta$ = 0°): K = 0.33
= 2.33D ($\theta_e \simeq$ 90°, α = 4°, β = 17°): K = ~0
μ_a = 1.43D[6] (+0.08D for ±20° change in θ_a)
μ = 2.34D[6]

Fig. 3. The sensitivity of K (eqn 3) for (X = Cl) to changes in the calculated value of μ_e caused by changes in estimated shape of the compound and by changes in assumptions about α and β (see text). Variations in θ_a by ±20° change K by ~9%.

	Obs	calc
	0 86D	–
	0 80	0 80
	0.76	0 71
	1 27	1.25

Scheme 3. Electric dipole moments of tertiany amines[6,31-33] calculated from the moment for NMe_3 and an assumed induced moment of 0.13D in each C_α–C_β bond: the induced moments change the *direction* of the total moment for *N*-methylpiperidine by ~17° but have little effect on the magnitude, whereas in quinuclidine the *magnitude* is changed but the direction is not (the value 0.13D is chosen purely to fit these four molecules and to show that large changes in direction may be caused by quite small induced moments).

so that K becomes very small and very sensitive to errors in the measured dipole moments. We conclude that, notwithstanding the numerous checks carried out by Katritzky *et al.*, the results of electric dipole moment work do *not* exclude very low values of K_{NMe}.

Intensities of infrared bands

One of the higher estimates of ΔH° in Table 1 was that determined by Tsuda and Kawazoe[11] who measured the temperature dependence of the intensities of the IR "Bolhlmann" bands of *N*-methylpiperidine in the infrared. The results were criticised by Katritzky *et al.*[7] but while the correction suggested[7] *reduces* ΔH° other possible errors, e.g. the assumption that the molar extinction coefficients of the two conformers have the same temperature dependence and the possibility of other absorption bands coinciding with the bands measured, increase the error limits, based on the precision of the measurements, given by Tsuda and Kawazoe so that these measurements are probably consistent with high values of ΔH°.

Ultrasonic relaxation (*Table* 1, *item* 5)

Wyn-Jones *et al.*[9] have recently used ultrasonic relaxation[34] in piperidines to estimate both ΔH° (**1E**→**1A**) = 3.7 kJ mol^{-1} and activation parameters (for **1A**→**1E**), using a newly developed method of analysing the data.[34b] As yet there are too few examples of this new method of treating ultrasonic relaxation data for its reliability to be evaluated but it now appears to be the only technique yielding low values of ΔH° or ΔG° that has not been shown to be in error.

Conformer trapping by fast chemical reactions

Very fast chemical reactions, e.g. protonation of an amine by a strong acid (Fig. 4), that convert the conformers of a compound in a specific and known way irreversibly into an analysable mixture of stereoisomeric compounds† (circumventing the Curtin–Hammett Principle[35]) may be used to study conformational equilibria if a number of rather stringent conditions, recently discussed by McKenna,[36] can be met. The rate of protonation of amines by strong acids is diffusion controlled[37] and therefore much faster than inversion at nitrogen at high concentrations of acids.[38]

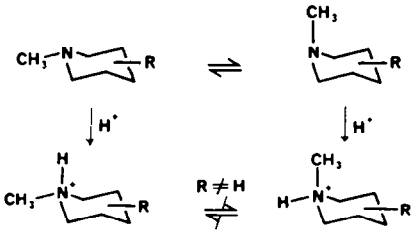


Fig. 4. Relationship between conformers of an *N*-methylpiperidine with large C-alkyl substituents and the diastereomeric ions formed by kinetically controlled protonation.

It is known, furthermore, from rates of exchange of protons between piperidium ions and acids compared with the rates of interconversion of diasteromeric ions such as **10E**–$\overset{+}{H}$ and **10A**–$\overset{+}{H}$,[39] that this protonation is stereospecific with retention of configuration at nitrogen. In the first attempt to apply kinetically-controlled protonation Booth[40] simply mixed liquid **15**, a model for piperidine itself, with an excess of rapidly stirred $CF_3{\cdot}CO_2D$ to give a mixture of isotopically distinct ions. This technique has been criticised[36,41] and defended[12] and its validity for **15** is as yet undecided. It has also been applied to **8**, a model for **1**,[12] but in this instance it is invalid[13a] because the ratio of concentrations of diasteromeric ions, $R = [\mathbf{8E}\text{–}\overset{+}{H}]/[\mathbf{8a}\text{–}\overset{+}{H}]$, *varies with the acid used* and can not be a valid measure of the conformational equilibrium in the amine (see broken lines A′ and B′ in Fig. 5). Trifluoroacetic acid, apparently always used by Booth *et al.*, appears to be one of the least suitable acids. For example, mixing the enamine **16** and CF_3CO_2H by Booth's method gives

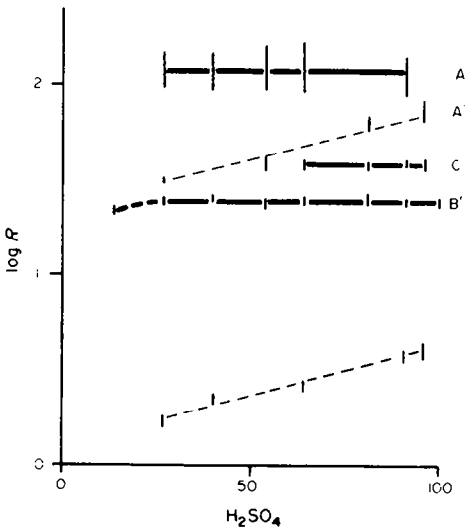
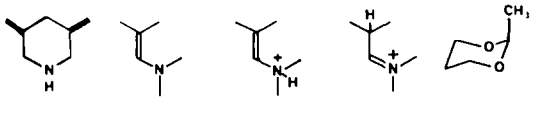


Fig. 5. Ratios of diasteromeric ions (*R*) formed by protonation of **8** and **10** as a function of sulphuric acid at 239K for varying conditions (see Experimental for details): *A* and *B*, **8** and **10** in cyclohexane; *A′* and *B′*, **8** and **10** as neat liquids; C, **10** as vapour (only a lower limit, $R \lesssim 200$, could be set for **8** as vapour in this series of experiments). Analysis by ^1H NMR.

†It is necessary for the configurations to be known but the assignments for the piperidinium ions in the present work are not controversial (see Table 4 and Experimental).

almost exclusively **18** (by C-protonation), the thermodynamically stable ion[28] (see below).

At the interface between a neat amine and a concentrated strong acid there will be a transient region in which amine and ammonium ion will coe-exist briefly allowing very rapid proton transfer between the two species. If the amine molecules and ammonium ions on average remain within this interfacial region for a time comparable with the half-life for inversion at nitrogen, then a substantial amount of equilibration will take place and R will lie between the values for strict kinetic protonation and for equilibrium (in a very concentrated trialkylammonium salt solution, a medium of low acidity but high polarity). The barrier to inversion at nitrogen in **1** is in dispute[42] and estimates of $\Delta G^{\ddagger}$ or $\Delta H^{\ddagger}$ range from 24 to 40 kJ mol^{-1} for solvents of low polarity, while Delpuech and Deschamps[39] estimate $k_{inv} \sim 500\ s^{-1}$, for **10**(E→A) in aqueous solution at 33°. Partial equilibration will be avoided only if amine molecules are protonated *and* then dispersed into the bulk acid before meeting with other amine molecules in the interfacial region. This can be achieved by protonating isolated amine molecules, dispersed either as a dilute solution in an inert immiscible solvent or in the gas phase, at the surface of an immiscible or involatile strong acid (a variety of unsuccessful methods are briefly summarised in the Experimental, together with details of the two reliable methods). That this leads to kinetic control of protonation is shown by the N-protonation of **16** to **17** (reaction at the surface between cyclohexane and H_2SO_4, 40–80%) followed by slow isomerisation in the more dilute acids to the thermodynamically stable C-protonated ion **18**.[28] A similar result has been obtained recently for *N,N'*-dimethylpiperazine.[43] The interconversion of diastereomeric piperidinium ions is too slow, however, for equilibration to be observed in the acids required for kinetic protonation and we rely on the constancy of R, at acidities above some limiting value for a given amine and conditions (see Fig. 5 for examples),† as evidence that protonation is kinetically controlled. Kinetic protonations were also carried out at elevated temperatures, using sealed ampoules for cyclohexane at 100° and dodecane at 100° and 156° at atmospheric pressure (see Experimental). The use of high temperatures made it easier to analyse the mixtures from **8** by raising the concentration of the minor ion from ~1% at 20° to ~5% at 156°.



15 **16** **17** **18** **19**

Since R is constant over wide ranges of concentration of sulphuric acid it is not plausible to suppose that there is selectivity in the protonation of the conformers of an *N*-methyl-piperidine at the acid surface because such selectivity would have to be independent of the character of the acid, which varies from a concentrated ionic aqueous solution at the lower concentrations through a molten salt ($H_3O^+ HSO_4^-$)[44] at 80–90% to a very polar but largely covalent compound at 100% H_2SO_4. Below the limiting concentrations R falls off as the concentration of acid is reduced and clearly such values can not be used to estimate K_{NMe}. It should be noticed that, down to 13% sulphuric acid, at least for **10**, the falling off in R is due to partial equilibration during protonation and *not* to slow equilibration in the acid medium between the completion of protonation and the analysis by NMR.

McKenna's discussion of the use of fast chemical reactions in studying conformational equilibria[36] does not include reactions at interfaces between fluid phases. The only important difference between homogeneous and interfacial reactions is that in diffusion controlled reactions both the quenching agent and substrates diffuse in the former whereas only the conformers of the substrate, e.g. **6**E and **6**A, diffuse in the latter. It seems unlikely, however, that differences in rates of diffusion are significant for such similar molecules. McKenna suggested that in kinetically controlled protonations proton tunnelling could lead to "cross-products"[36] but this only applies to *N*H-piperidines because it is the N-substituent that must "tunnel the conformer-inversion barrier",[36] not the proton probe; in derivatives of **1** protonation and deprotonation are known to be stereospecific.[39]

The series of experiments summarised in Fig. 5, Table 5 and in the Experimental were the culmination of work with ^{1}H NMR and could not usefully be taken much further for amines with unhindered *N*-methyl groups. In particular the high concentrations of sulphuric acid and relatively low final concentrations of salts desirable to ensure clean kinetic protonation were inconsistent with accurate analysis for very large values of R (for **6** and **8**). This was because the viscosity of the sulphuric acid at

Table 5. Ratios (R) of diastereomeric ions formed from piperidines **8** and **10** by protonation at the surface of sulphuric acid, as a function of concentration of acid (analyses by ^{1}H NMR)[a]

Solvent or phase	Temp. (K)	Conc. H_2SO_4[b] (% w/w)	Ratio of ions (R)[c,d]	ΔG°_{NMe}[e] (kJ mol^{-1})
Piperidine **8**				
Liquid[f]	~293[f]	27—96 100[g]	25—75 22	- -
Vapour	288	91	>200	>12
C_6H_{12}	288 373	27—91 91,96	120±30 37±1	11.5±0.5[h] 11.2±0.1
Piperidine **10**				
Liquid	~293[f]	27—96 100[g]	1.8—4.2 1.5	-
Vapour	288	64—100	42.4 ± 3.1	9.15±0.18
C_6H_{12}	288	27—100 13	25.0 ± 1.1 22.4	7.70±0.11 -

[a]See experimental for method and ranges of concentration of **8** and **10** and of the resulting ions. Early experiments, using a Perkin Elmer R14 spectrometer, on **2**–**4**, **8** and **10** gave results following the same pattern qualitatively as those given in this table but with much lower precision and sensitivity, and will not be reproduced here. [b]When a range of values is given the individual values are indicated in Fig. 6. [c]Ratio of major to minor product. [d]Where a range of values is given R varies with the concentration of acid; a mean and standard deviation are given when R is independent of the concentration of acid, within the limits given. [e]Calculated assuming that the ring is adequately locked in one chair so that $R = K^{-1}$ (E→A), without correction for possible twist conformers. [f]It was not possible to control the temperature when neat liquid amine was mixed with acid. [g]Trifluoroacetic acid used in place of sulphuric acid.

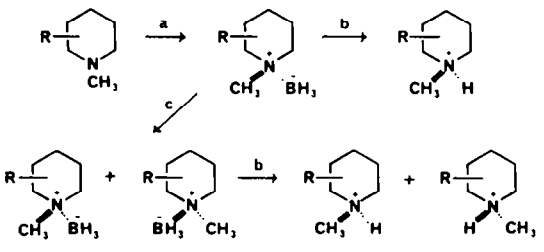
†Our experiments began with **2** and **10** because the *N*-methyl signals are readily detected in ^{1}H NMR spectra but this early work was carried out with a relatively poor spectrometer and the results will not be detailed.

concentrations >50% broadens the ^{1}H NMR bands for the N-Me groups, thereby exaggerating difficulties in resolving the overlapping bands, and it was necessary to dilute the aqueous sulphuric acid solutions with trifluoroacetic acid with a consequent decrease in concentration of **6**–H$^+$ and therefore in S/N in the spectra. We suspect now that *R* for **6** in cyclohexane was slightly *lower* than it would have been for complete kinetic control of protonation (compare results in Tables 5 and 8) because the concentrations of amine and ions, based on experience with **10**, may have been high enough to allow a very small proportion (0.2–0.4%) of **8**E–H$^+$ to isomerise to **8**A–H$^+$. If more dilute solutions were used, however, the decreased S/N in the spectra would have prevented **8**A-H$^+$ from being detected in ^{1}H NMR spectra. We accordingly turned to pulse Fourier transform ^{13}C NMR spectroscopy. The large differences in ^{13}C NMR chemical shifts between axial (relatively shielded) and equatorial methyl groups on six-membered rings[23] (in relation to line widths in ^{1}H-decoupled spectra) makes ^{13}C NMR vastly superior to ^{1}H NMR spectroscopy in this important respect (see also Table 4). The inherently low sensitivity of ^{13}C NMR, even with pulse Fourier transform (PFT) operation, may be removed very simply using ^{13}C isotopic enrichment in the *N*-methyl groups of the amines **3**–**9** (Scheme 2 and Experimental). Although ^{13}C enrichment overcomes the problem of low sensitivity adequately there remain difficulties in the quantitative use of ^{13}C band areas, e.g. errors resulting from differences in spin-lattice relaxation times (T_1), nuclear Overhauser effects (NOE), and variation of the radiofrequency power over the spectral width. In order to study possible effects of such factors on the integrated band areas of signals for axial and equatorial NH·CH$_3$ groups we required solutions containing high concentrations of both ions in each diastereomeric pair E–H$^+$ and A–H$^+$ (Fig. 4) because many of the measurements would be prohibitively time consuming at the concentrations of the minor components in the mixtures available from *either* kinetically *or* thermodynamically controlled protonation (except for the atypical amine **10**[12,13a,39]). Although separable solid diastereomeric salts have been obtained from **10**[45] such pairs of salts are unknown for the amines, **3**–**6** and **8**, of principal concern in this work. We accordingly devised preparations of ~1:1 mixtures of pairs of diastereomeric ions fromed from each of the amines **3**,[13b] **4**,[13b] **6** and **8** (Scheme 4).[27b]

With ~1:1 mixtures of diastereomeric ions (^{13}C enriched in *N*-methyl for **3**, **4**, **6** and **8** as well as the natural abundance) derived from **3**, **4**, **6**, **8** and **10** available conditions suitable for quantitative ^{13}C NMR analysis of mixtures from kinetic protonations were determined (see Experimental). Two aspects deserve comment. The spin lattice relaxation times T_1 were found to be surprisingly different for axial and equatorial NH–Me groups (see Table 6). The short T_1 times in 81% sulphuric acid are attributable to the high viscosity and are *helpful* for quantitative analysis using ^{13}C NMR spectra because reasonably short repetition times, $\lesssim 5T_1$, between 90° pulses can be used. This contrasts with ^{1}H NMR spectra in which viscosity causes unacceptable loss of resolution (see above). Using **6**E–H$^+$ we found that band areas were closely proportional to relative numbers of atoms and that isotopic enrichment calculated from comparing band areas for N–^{13}CH$_3$ with band areas for other carbon atoms at natural abundance agreed with the enrichment in the Ba^{13}CO$_3$ used. Similarly, for the well separated bands, the band areas for **6**A–H$^+$ (~1:1 mixture with **6**E–H$^+$) were proportional to numbers of atoms (Table 7).

Tables 5 and 8 (see also Ref. 13b) summarise our results on kinetic protonation. All our measurements for **6** and **8** are consistent with $\Delta G^\circ_{293} \lesssim 12$ kJ mol^{-1} for **1**E→**1**A for solutions in saturated hydrocarbons: if the more precise ^{13}C NMR results only are considered then $\Delta G^\circ_{293} \lesssim 12$ kJ mol^{-1}, a result fully consistent with the single temperature (Table 1, item 9) and variable temperature (item 11) data for ^{13}C NMR chemical shifts but dramatically higher than the estimates given by most other methods (Table 1, notably items 4 and 5). Very recently McKenna *et al.*[14] have studied **6**E⇌**6**A using a photochemically generated nitrene and find $K \gtrsim 0.01$, in agreement with our results.

The agreement between **6** and **8** indicates that these are good models for **1**, but ΔG°_{293} is so high that it is necessary to consider the possible importance of twist conformers. Qualitatively the decrease in ΔG° with increase in temperature points to a significant contribution from twist conformers, some of which give rise to **6**A–H$^+$ or **8**A–H$^+$ on protonation, because the alternative explanations, a large positive value of ΔS°(**1**E→**1**A) or the onset of partial equilibration during kinetic protonation at high temperatures (note that consistent results were obtained with different mixing techniques: see Experimental) are both implausible. The chair-twist equilibrium has not yet been studied for piperidine but is



Scheme 4. Preparation of ~1:1 mixtures of diastereomeric ions from *N*-methylpiperdines **2**–**6**, **8** and **10**: a, $Me_2S{\cdot}BH_3$, ≳20° (predominantly axial borane adduct formed; b, 64% H_2SO_4 stirred with borane-amine adduct(s) in inert solvent; c, 80° for 1–4 h (cf. Ref. 46).

Table 6. Spin-lattice relaxation times T_1 (s)[a] for carbon atoms in N-methyl groups in *N*-methylpiperidinium ions in (~90% ^{13}C in *N*-methyl), ~0.1 M in each ion,[b] in 81% sulphuric acid at 300K

	Piperidine	n[c]	T_1(s)[a] E–H$^+$	T_1(s)[a] A–H$^+$
3		7	0.47±0.03	0.65±0.01
4[d]		9	0.52±0.01	0.83±0.01
		7	0.53±0.01	0.86±0.02
6		8	0.30±0.01	0.84±0.02
8		8	0.38±0.02	0.64±0.02

[a]Data collected and processed by Nicolet B-NC 12 computer program T1PRGM using intensities. [b]Prepared as in Scheme 4. [c]Number of points excluding "infinity" values (τ = 5s) at beginning and end of experiment. [d]Duplicate experiments on the same solution.

Table 7. Relative integrated intensities[a] of ^{13}C NMR absorption bands in **6E**–H^{+b} and in **6E**–H^+ + **6A**–H^{+c} as tests of validity of method used for quantitative analysis

Carbon atoms	Relative integrated intensities		
	6E–H^{+b}		**6E**–H^+ + **6A**–H^{+c}
	Total = 10[d]	Total = 8[e]	Total = 10[d,f]
N-Me	1.01_5	$1.00_7(81._5)$[g]	0.9_4
C-2,6	1.99_2	1.97_6	1.9_6
C-3,5	1.98_6	1.97_0	2.2_0
C-4	0.97_2	-	0.9_1
$\underline{C}Me_3$	0.96_0	-	0.9_7
$C\underline{Me}_3$	3.07_2	$3.05_0(3.00)$[g]	3.0_2

[a]Based on height × width at half height ($w_{1/2}$) for bands broadened to $W_{1/2} \simeq 3$–5 Hz and plotted at 1–2 Hz cm^{-1}, using 90° pulses at 10 s intervals. [b]1 M solution prepared from crystalline salt and 81% sulphuric acid. [c]1:1 mixture, ~1 M total concentration, prepared as in Scheme 4. Because certain pairs of signals are not well resolved the areas were added together for each type of atom in the two ions. [d]Sum of intensities of *all* C-atoms normalised to 10.00. [e]Sum of intensities *excluding* methine and quaternary C-atoms normalised to 8.00. [f]Overlap of bands seriously reduces the precision of these relative areas. [g]Comparison of *enriched* N-methyl and *natural abundance* $-CMe_3$: ratio calculated from enrichment in the $Ba^{13}CO_3$ used (Scheme 3) is 80.1:3.00.

probably similar to that in cyclohexane.[47,48] If $\Delta H^\circ \simeq 20$ kJ mol^{-1} and $\Delta S^\circ \simeq 15$ J mol^{-1} K^{-1} for **1** (ch→tw) then the results for **6** and **8** are consistent with $\Delta G^\circ \simeq \Delta H^\circ \simeq 13$ kJ mol^{-1} for **1E**→**1A**, i.e. a little higher than the uncorrected estimate of ΔG° derived directly from R at 20°. The variable temperature ^{13}C NMR results do *not* require a similar correction for twist conformers because (a) the ^{13}C δs for *N*-methyl on chair (equatorial) and twist conformers probably differ little (Table 2: compare **11** and **12**, the latter probably having a twist ring[49]) and (b) chair⇌twist equilibria are unlikely to be very different for any of the amines **3**–**9**, so that the temperature dependence of the *relative* δs should be insensitive to the chair⇌twist equilibrium.

Solvent effects on the equilibrium **1E**⇌**1A** may be derived by comparing the value of ΔG° for the gas phase with values for various solvents. In all instances **1A**, with an unhindered unshared pair on nitrogen, is more solvated as would be expected, and the difference increases with the polarity of the solvent and with the possibility of hydrogen bonding.

The high value of $\Delta G^\circ(\simeq \Delta H^\circ)$ now established for **1E**⇌**1A** requires comment. Katritzky *et al.*[6–8] rationalised the low value of $\Delta G^\circ \simeq 2.7$ kJ mol^{-1} found from electric dipole moments by reference to the relatively low barrier to inversion at nitrogen. This was taken to imply easier outward bending of an axial *N*-methyl group compared with an axial *C*-methyl group but there is no reason to suppose that the bonding force constants for ∠CNC will be less than for ∠CCC for small displacements simply because they are less for large displacements (see also Ref. 14). The axial *N*-methyl group in **1A**, furthermore, will be more crowded by the *syn*-axial hydrogens on C-3 and C-5 than the axial methyl group on a cyclohexane ring because C–N bonds are shorter than C–C bonds (cf the large strain, ~17 kJ mol^{-1}, associated with the axial 2-methyl group in **19**[50]). There is evidence from structural studies that bond angles at N⟨ are not larger than HC⟨ (cf NMe_3, ∠CNC = 110.6 ± 0.6°;[51] $HCMe_3$, ∠CCC = 110.9 ± 0.2°,[52] by the same technique, electron diffraction) in more or less unstrained molecules; if Me–Me repulsions are significant in NMe_3 ($r_{Me\text{-}Me}$ = 2.42 Å) and $HCMe_3$ ($r_{Me\text{-}Me}$ = 2.53 Å) then the former has the greater strain so that the hypothetical unstrained ∠CNC is significantly less than the unstrained ∠CCC. There seems no reason for surprise at the high ΔG° for **1**(E → A).

The highly biased equilibrium in *N*-methylpiperidine has important consequences for, e.g. the interpretation of rates and ratios of products in the quaternisation of piperidines which we hope to develop later.

Table 8. Ratios (R) of diastereomeric ions formed from piperidines **6** and **8** (~90% ^{13}C in N–CH_3 groups) by protonation at the surface of 81% sulphuric acid (analysis by ^{13}C NMR)[a] and derived free energy differences, ΔG°_{NMe} (kJ mol^{-1})[b]

Temp. (K)	Gas phase		$n\text{-}C_{12}H_{26}$		$CHCl_3$		C_6H_6	
	R	ΔG°_{NMe}	R	ΔG°_{NMe}	R	ΔG°_{NMe}	R	ΔG°_{NMe}
Piperidine **6**								
293	223	13.2±0.4	170	12.5±0.3	61	10.0±0.3	79 25[c]	10.6±0.3 7.8±0.4[c]
373			40.4	11.5±0.3				
429			23.6	11.3±0.3				
Piperidine **8**								
293			178	12.6±0.4	66	10.2±0.3	70	10.3±0.3
333			66	11.6±0.3[d]				
373			40	11.4±0.3[d]				
429			19.5	11.0±0.3				

[a]See Experimental. [b]General reproducibility of analyses and of estimates of $R \leq 100$ for different processing of a given FID gave errors of 0.1–0.2 kJ mol^{-1} but errors have been rounded up to a minimum of 0.3 kJ mol^{-1}, corresponding to ~10% uncertainty in K (assumed equal to R^{-1}), because far fewer analyses could be carried out with ^{13}C NMR (times for accumulation varied from 1 to 16 h) than with ^1H NMR (Table 7, although the presence of signal overlap makes the latter far less reliable for $R > 25$. [c]For solutions with mole ratio **6**: PhOH = 2.5–5.0 ([PhOH] ≯ 0.5 M): the reproducibility was poor and there must be doubt about whether protonation was kinetically controlled. [d]Single experiment.

EXPERIMENTAL

C-*Alkylpiperidines*

Piperidine, 2-, 3- and 4-methyl-4-phenyl- and *cis*-2,6- and 3,3-dimethylpiperidine were commercial samples. 3-Methylpiperidine was purified by crystallisation of its hydrochloride from methanol-ether. 4-t-Butylpiperidine, obtained by reducing 4-t-butylpyridine with sodium and ethanol followed by hydrogenation of the hydrochloride of the product (a mixture of tetrahydro- and hexahydro-derivatives) in acetic acid over PtO_2, was purified by crystallisation of the hydrochloride. *Cis*- and *trans*-3,5-dimethylpiperidine were prepared by reduction of 3,5-dimethylpyridine, by the method used for the 4-t-butyl analogue, and were separated by repeated crystallisations of hydrochlorides and picrates.

N-*Methylpiperidines*

The above piperidines were methylated by the Eschweiler–Clark method o give **1–4**, and **6–10**, all of which were purified by crystallisation of their hydrochlorides following distillation or steam distillation. Pseudopelletierine **14** was reduced by the Huang-Minlon variant of the Wolff–Kishner method to give **13**, purified by distillation and crystallisation of its hydrochloride. The amines **6** and **8/9** were also prepared by reducing the appropriate pyridinium methiodides with $NaBH_4$ in ethanol followed by hydrogenation in acetic acid over PtO_2. The amines **11** and **12** were available from another study.[49] The amine **5**(R = H) was only prepared in the form with ~90% ^{13}C in the N–Me group (see below).

^{13}C-*Enriched* N-*methylamines*

The following general method was used. $^{13}CO_2$ (85–90% ^{13}C, from $Ba^{13}CO_3$, 1.00 g, and $PbCl_2$, ~3 g, heated until $^{13}CO_2$ was no longer evolved) was condensed on the surface of a secondary amine (15 mmoles) in ether (15 ml) at −190°. After warming to ~0° the mixture was gently swirled (~1 min), cooled again in liquid N_2 and allowed to warm to ~−10° before air was admitted. The carbamate was treated with $LiAlH_4$ (0.40 g), with *great care to cool the flask as soon as a vigorous reaction set in*, after which $AlCl_3$ (2.0 g) was added and the mixture was boiled under reflux (2 days). Secondary amines were removed from the resulting mixtures of amines by benzoylation and the N-$^{13}CH_3$ amine was isolated by steam distillation. The distillate was neutralised with 1M HCl (usually 2.5–3.5 ml, i.e. 50–70% yield) and volatile material was removed *in vacuo* until the residue, the hydrochloride of the *N*-methylated amine, was dry and constant in weight. The amine hydrochlorides were characterised by comparing their ^1H and ^{13}C NMR spectra with those of samples with natural ^{13}C abundance but were not purified. The only significant impurity was **8** in **9**, in greater proportion than in the starting amine.

The ^{13}C-enriched amines were liberated from the hydrochlorides by treatment with 50% KOH. If required free from solvent, e.g. for protonations from the vapour phase or from alkali sensitive solvents, the amine was micropipetted from the aqueous layer and dried with solid KOH, otherwise it was taken up in a solvent and the solution was dried over KOH.

Preparation of solutions of diasteromeric pairs of ions

The crystalline salts of **3–6**, **8** and **10** were the most stable of each diasteromeric pair and corresponded to the major products in kinetic protonations; in solutions in H_2SO (64% or 81%, followed by dilution with an equal volume of $CF_3{\cdot}CO_2H$ for ^1H NMR spectra) or in $CF_3{\cdot}CO_2H$ the less stable diasteromer could not be detected. These salts were assigned the E–H configuration on the basis of (a) ^{13}C chemical shifts (Table 4: correlation of N-Me shifts with **7**-H and **9**-H; γ-shielding effects in A-H isomers[23]); (b) ^1H chemical shifts (2(6)-axial protons are relatively deshielded when N–Me is axial[19,53]); (c) resolvable ^3J(2(6)ax-H, NH) couplings, large when NH is axial.[54] When (**10**–H) Cl dissolved in water at ~80° was very slowly treated with 93% H_2SO_4 so as to give 1M (total salts) solutions in 64 or 81% H_2SO_4 the ions were present in the proportions [**10**E–H]:[**10**A–H] ≅ 1.5:1. The piperidines **2–4**, **6** and **8** (at ^{13}C natural abundance, 4 mmoles; at 85–90% ^{13}C enrichment in N–Me groups, ~0.2 mmoles) in cyclohexane (~2 ml) were each treated with a small excess of $BH_3{\cdot}Me_2S$, sealed in an ampoule under N_2, and heated at 100°/2 h. The chilled ampoules were opened with care (excess pressure) and each solution was stirred with 81% H_2SO_4 (4 ml or 1 ml) for 1 day/20°. The cyclohexane was removed by pipette followed by evacuation leaving solutions (~1 M for ^{13}C natural abundance, ~0.2 M for ^{13}C-enriched samples) of the diasteromeric ions. Solutions in 81% sulphuric acid were stable at 20° (>6 months) and at 156° (>15 min) as judged by the constancy of *R* for **4**-H, using solutions with $R \simeq 1$ and 20.

Kinetically-controlled protonations

At room temperature: for mixtures to be analysed by ^1H NMR. Sulphuric acid (1 ml; arbitrarily chosen concentrations form 13–100%, w/w) was pipetted into the bottom of a narrow test tube fitted with a ground glass stopper, avoiding acid contacting the side of the tube. The acid was covered with the chosen inert solvent (1 ml) and then the solution of the amine (preferably ≯0.25 M, ≮4 ml, giving ≯1 M in the acid for ^1H NMR analysis, usually 0.01–0.05 M, 4–8 ml, giving 0.05–0.2 M in the acid for ^{13}C NMR analysis) was added so as to avoid contact with the acid before the tube was stoppered before being shaken by hand (30 s) either at ambient temperature or in a thermostat. The layers were allowed to settle, the organic phase was removed by pipette followed by evaporation (cyclohexane and other volatile solvents) or by washing with cyclohexane which was then removed as before (dodecane). The more concentrated H_2SO_4 (>50%) solutions were diluted with CF_3CO_2H.

For mixtures to be analysed by ^{13}C NMR it was unnecessary to remove the organic solvent and the kinetic protonations were carried out in NMR sample tubes using 0.5 ml H_2SO_4 in 5 mm tubes (spiral Pt wire stirrer, 2–3 strokes/s) and 1.0 ml H_2SO_4 in 10 mm tubes (PTFE rod with two PTFE discs, one located initially in the H_2SO_4 layer, the other in a layer of pure solvent so as to act as a baffle hindering the amine solution diffusing or convecting to the acid surface before stirring, ~1 stroke/s).

Above room temperature the methods using NMR tubes at room temperature were adapted to higher temperatures with dodecane as solvent by heating the tubes directly in a vapour bath (usually steam or bromobenzene, b.p. 156°), the temperature rising to within 1° of the vapour temperature in <1 min, thereby minimising the chance of the amine reaching the acid before stirring begins. Less conveniently the acid and pure solvent were stirred at the required temperature and the amine solution was added very slowly down the side of the vapour-jacketed tube. Protonations at 100° using cyclohexane as solvent were carried out in sealed tubes containing the amine solution and a thin-walled bulb of H_2SO_4 (usually 81%), with a heavy glass collar, resting on a glass bead. The tubes, strapped to a vertical reciprocal shaker rod, were heated in a vapour-jacketed air bath (2 hr) before being shaken (~4 strokes/s, ~10 cm movement) to break the bulb and mix the contents.

Vapour phase

The only consistently satisfactory protonations were achieved using a very small flask, e.g. a 2 ml volumetric flask with a fairly sharp shoulder, to contain the acid (say, 1 ml). It was vital that (a) the acid meniscus should reach the shoulder, (b) the stirring was rapid, constant and free from splashing or surges carrying acid above the shoulder, and (c) the amine was suspended above the acid surface such that 0.5 mmole of **8** or **10** evaporated in ≮4 h. The latter was achieved with the liquid amine on a 5 mm diam. glass sinter suspended ~10–20 mm above the acid. For the less volatile amine **6** the sinter had to be lowered to within 3–4 mm of the surface of the acid *after* a stable vortex had been established and evaporation of ~0.4 mmole required ~16–20 h. H_2SO_4 less than ~50% could not be used because a barely perceptible fog then formed at the surface and *R* varied erratically.

Unsuccessfully methods for kinetic protonations included (a) variations based on injecting a very fine jet of amine (e.g. 1 mmole in ~1 min) through a fine capillary under pressure into rapidly

stirred acid (see Fig. 5 for examples of variation of R). (b) spraying H_2SO_4 from an atomiser into a very dilute amine vapour in dry air, (c) passing a stream of amine vapour in air or N_2 through several different patterns of bubbler into acid, and (d) allowing amine vapour to diffuse to a relatively large surface area (10–20 cm^2) of H_2SO_4, with or without stirring, in a container with *vertical* sides. The last method gave moderately reproducible results but from time to time a line of solid amine salts formed at the edge of the meniscus, where there was a thin film of more or less static acid, showing that very high concentrations of salts, with the possibility of partial equilibration, could occur.

NMR *spectra*

Spectrometers: ^1H, Perkin Elmer R32 (90 MHz, ^1H lock); ^{13}C Bruker WH90 (^{13}C 22.63 MHz, ^2H lock). Spectra run at ambient temperature used $SiMe_4$ as lock (R32) and internal reference (R32, WH90) whenever possible. With aqueous H_2SO_4 solutions or VT NMR C-methyl signals in the solute were used as a lock for ^1H spectra and external D_2O (using concentric 5 and 10 mm tubes) or $(CD_3)_2SO$ for ^{13}C spectra, with $(\underline{C}H_3)_4\dot{C}NH_3$ (0.25M) as internal reference. Temperatures were controlled to ±1 K and the control units were checked to ±2 K with methanol and ethylene glycol samples. Variable temperature ^{13}C spectra were run with solutions in dodecane (~0.1 M in each of four amines, 85–90% ^{13}C in the *N*-methyl groups) in 5 mm tubes with $(CD_3)_2SO$ as lock in the concentric 10 mm tube; N–$\underline{C}H_3$ shifts were measured relative to N–$\underline{C}H_3$ in **7**, using **8** as a secondary standard at 300, 340, 380 and 420 K for three mixtures (**1**, **3**, **6**, **8**; **3**, **4**, **8**, **9**; **3**, **5**(R = H), **7**, **8**). FIDs were accumulated into 4 K addresses and 4K zeros were added before FT. No line broadening was used for VT on mixtures of ^{13}C enriched amines. Sweep widths were either 2000 Hz (quantitative analysis and all spectra at natural abundance, giving a digital resolution of 0.488 Hz ≡ 0.0216 ppm) or 1000 Hz (VT on ^{13}C enriched compounds, with differences in peak maxima, < 20 Hz, estimated to ≥ 0.1 Hz = 0.005 ppm from expanded spectra at ~1 cm/Hz; digital resolutions 0.244 Hz).

Analysis of mixtures

Mixtures from kinetic protonations were analysed by ^1H NMR using N–Me peak heights with a correction factor (always close to 1) determined from expanded spectra, in which peak widths could be determined, run on mixtures containing high concentrations of both diastereomeric ions. For A–$\dot{H}$ only one line in the N–Me doublet was usable and this, superimposed on the sharply rising signal of 8E–$\dot{H}$, had to be divided by eye from the rapidly rising 'background' absorption: at R = 100 reproducibility is at best ±25% but at R ≤ 200 (as in protonations of vapour of **8**) the signal merges into the noise even when the spectrum is mis-phased in order to level off the tail of the 8E–$\dot{H}$ signals.

Analyses using ^{13}C spectra were based on relative peak areas estimated from peak height times peak width. Spectra were measured using 90° pulses, delay times > 5 × T_1 (for N–Me), and FIDs were processed with large line broadening (1–4 Hz). It was found that relative areas were unaffected by variations in (a) the delay time, > 5T_1, between pulses, (b) the line broadening, (c) whether the spectrometer offset was set to low or high field of the signals, (d) the phase correction, provided this was not visibly incorrect, and (e) the NOEs (by comparing continuous with gated decoupling). Line widths for $\dot{N}$–$^{13}CH_3$ signals were determined on 1:1 mixtures of ions so that possible sources of error, resulting from overlap with impurities or spurious signals, in quantitative analyses involving very small N–Me signals might be detected by anomalies in line width.

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