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Conformational Analysis. XXX.[1] Conformational Equilibrium of the *N*-Methyl Group in *N*-Methyl-*trans*-decahydroquinoline. The *N*-Methylpiperidine Problem

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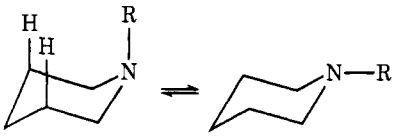
Abstract: The ^{13}C NMR signals of the methyl groups in *N*-methyl-*trans*-decahydroquinoline and some of its analogs with "mobile" *N*-methyl groups are compared with corresponding signals of *N*-methyl groups which are constrained, sterically, to remain in either the equatorial or the axial position. From these data, the conformational equilibrium *N*-methyl (axial) $\rightleftharpoons$ *N*-methyl (equatorial) is evaluated; the conformational energy $-\Delta G^\circ$ is between 1.8 and 2.45 kcal/mol in chloroform and possibly somewhat larger in benzene. The appropriateness of the conformationally biassed (anancomeric) models is discussed. A less reliable value of $-\Delta G^\circ$ = 1.35–1.77 kcal/mol in chloroform was determined for the *N*-methylpiperidine equilibrium (Me-a $\rightleftharpoons$ Me-e), for which no suitable model for the Me-axial conformation is available.

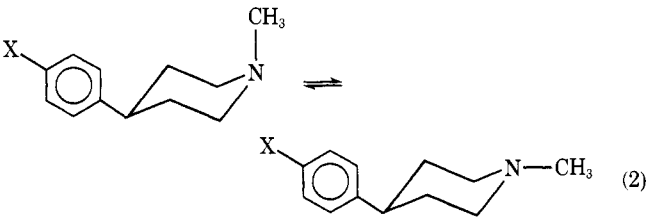
The question as to the position of the N-H equilibrium in piperidine (eq 1, R = H) has been discussed extensively in the literature;[2] yet the answer is still controversial with



(1)

values reported ranging from +0.6 to −0.4 kcal/mol. Much less attention has been given to the *N*-methylpiperidine problem (eq 1, R = Me), even though the values reported, from −0.65 kcal/mol[3] to −1.61 kcal/mol,[4,5] span about the same range as those for the N-H compound (though they do not bracket the magic value of zero). Yet the widespread occurrence of *N*-methylpiperidines and their polycyclic homologs makes it very desirable to know whether 25 or 5% of their molecules exist in the conformation with axial *N*-methyl.

The most extensive studies of equilibrium 1 have involved studies of dipole moments as shown in (2).[3,6] In the original work,[6a] X was chlorine; later supporting experiments with X = NO_2 were reported.[6b] Since evaluation of the equilibrium shown in (2) from dipole moments depends on accurate calculation of the moments of the two conformers shown, which, in turn, depends on an accurate knowledge of the molecular geometry, later studies[3] included an optimization



(2)

of molecular geometry by molecular mechanical calculation; however, the refinement of the data produced thereby was relatively minor. Other studies of the equilibrium (eq 1) have involved infrared absorption intensity measurements of Bohlmann bands,[4] evaluation of the ratio of the protonated species formed when *N-cis*-3,5-trimethylpiperidine [a system similar to that in (1) but with ring reversal prevented by the methyl substituents] is quenched into trifluoroacetic acid,[2b] and an evaluation of the chemical-shift difference of the axial and equatorial protons at C-2,6 in variously substituted *N*-methylpiperidines.[2c] These studies have been subjected to various criticisms: the infrared study[4] on grounds that the *N*-isopropyl homolog, used as a standard for the intensity measurements of the Bohlmann bands, did not, itself, appear to be conformationally homogeneous (equatorial);[6b] the quenching study on grounds that the reaction may have been diffusion controlled, and partial equilibration of the salts may have occurred during

Table I. Values for the *N*-Methylpiperidine Equilibrium (eq 1, R = CH_3) from the Literature[8]

$-\Delta G°$, kcal/mol	Solvent	Method	Ref
0.39	Benzene	Dipole[a]	6a
0.42	Cyclohexane	Dipole[a]	6a
0.53	Benzene	Dipole[a]	6b
0.57	Benzene	Dipole[a]	6b
0.59	Cyclohexane	Dipole[a]	6b
0.67	Cyclohexane	Dipole[b]	6b
0.55	Cyclohexane	Dipole[a,c]	6b
0.66	Cyclohexane	Dipole[b,c]	6b
0.60	Dioxane	Dipole[a]	6b
0.81	Dioxane	Dipole[b]	6b
0.65	Cyclohexane	Dipole[a,d]	3
1.61	Carbon tetrachloride	Ir′	4
>1.6	Neat	Quenching	2b[e]
2.7	Cyclohexane	Quenching	5

[a] 4-*p*-Chlorophenyl compound. [b] 4-*p*-Nitrophenyl compound. [c] 4-Spirodioxolane compound used as comparison sample. [d] Optimized geometry. [e] See also J. McKenna, *Tetrahedron*, 30, 1555 (1974).

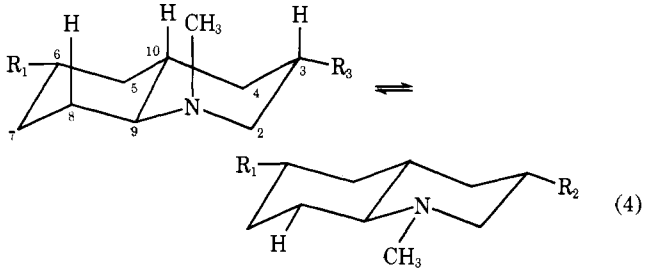
quenching.[5,7] The NMR method as published[2c] does not yield quantitative results but merely suggests that the preference for equatorial *N*-methyl is substantial. The data in the literature for the *N*-methylpiperidine equilibrium (eq 1) are summarized in Table I.[8]

Results

Since it is known that large ^{13}C chemical-shift differences are observed between equatorial and axial methyl groups in cyclohexanes,[9] similar differences might be expected in the equatorial and axial conformations of *N*-methylpiperidines (eq 1). If the shift of the *N*-methyl group in the equatorial conformation is δ_e and that in the axial conformation δ_a, then the observed average shift will be[10]

$$\delta = n_e\delta_e + n_a\delta_a \qquad (3)$$

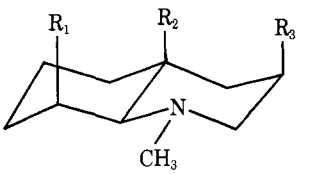
where n_e and n_a are the mole fractions of the equatorial and axial conformations, respectively (eq 1). Since δ is readily measured and $n_e + n_a = 1$, the two mole fractions can be evaluated if models for measuring δ_e and δ_a can be found, and if these two shifts are substantially different from each other and from δ. While the problem of constructing suitable model compounds could not be totally solved in the case of *N*-methylpiperidine, it did prove amenable to solution in the homologous *N*-methyl-*trans*-decahydroquinoline (**1**, R = H) (eq 4).



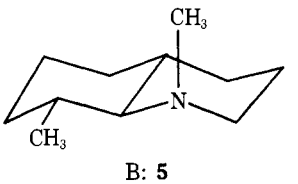
(4)

1, $R_1 = R_2 = H$
6, $R_1 = H$; $R_2 = CH_3$
7, $R_1 = CH_3$; $R_2 = H$

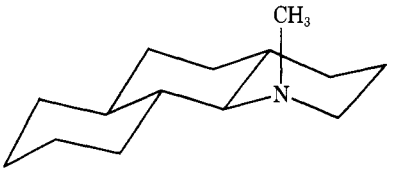
Inspection of eq 4 indicates **1** has three syn-axial CH_3/H interactions in the N-axial conformation instead of the two found in *N*-methylpiperidine (eq 1). However, the extra interaction is hopefully offset by the peri interaction in the N-equatorial conformation, assuming that, as a close approximation, peri and syn-axial interactions are equivalent. Suitable models, both with equatorial (A) and with axial methyl (B) are readily conceived and, thanks to a newly developed synthesis of the N-H precursors,[11] readily synthesized by N-methylation of the latter. The synthesis[11] also led to two additional mobile systems (**6, 7**; eq 4) and to three additional anancomeric model compounds (**8–10**) in the tricyclic series.



A: **2**, $R_1 = CH_3$; $R_2 = R_3 = H$
3, $R_2 = CH_3$; $R_1 = R_3 = H$
4, $R_3 = CH_3$; $R_1 = R_2 = H$



B: **5**



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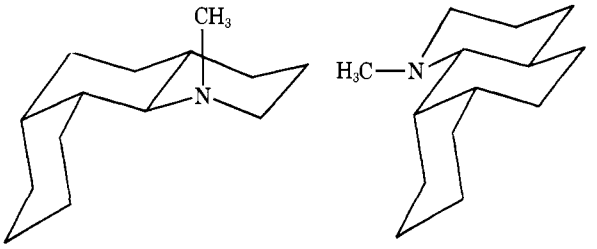


9 **10**

The *N*-methyl resonances of compounds **1–10** are summarized in Table II.[12] The assignment of the equatorial and mobile N-Me signals (compounds **1–4, 6, 7, 10**) proved simple since these compounds displayed only a few well-separated signals below 40 ppm among which the methyl group was readily discerned by off-resonance decoupling. Off-resonance decoupling also permitted assignment of the axial *N*-methyl resonances of compounds **5, 8,** and **9** but, since these N-Me signals occurred in a relatively crowded region of the spectrum, the result for **5** was confirmed by synthesizing the corresponding $N\text{-}CD_3$ analog. In this compound, the signal assigned to N-Me disappeared through a combination of the absence of a strong nuclear Overhauser effect and the dissipation of the signal intensity into a heptet.

From the data reported in Table II, one may compute, in $CDCl_3$: δ_e = 42.99 (average of **3** and **4**[13]); δ = 42.54 (average of **1, 6,** and **7**); δ_a = 33.08 (average of **5, 8,** and **9**); whence (eq 3) K = 21.0 and $-\Delta G°$ = 1.80 kcal/mol (eq 4). Similarly, in benzene, δ_e = 42.88, δ = 42.68, δ_a = 33.23 (value for **5**), whence K = 47.25 and $-\Delta G°$ = 2.28 kcal/mol. Indeed, the value of K is so large[14] as to be difficult to determine with accuracy, since δ is so close to δ_e. Confirmatory evidence for a large K comes from measurement of the C-3 chemical shift; this shift differs greatly in the N-Me-axial model **5** (19.41 ppm) and the N-Me-equatorial **2** (25.76 ppm, all shifts in $CDCl_3$) because of the steric compression[9] in the former. For the mobile species **1** and **7**, C-3 resonates at 25.76 and 25.88 ppm, respectively, i.e., virtually at the same frequency as in the equatorial model **2.**

Discussion

Adequacy of the Models. In any conformational analysis based on model studies, one must be very concerned about the adequacy of the models. The problem is greatly aggravated in the present case where δ is so close to δ_e so that

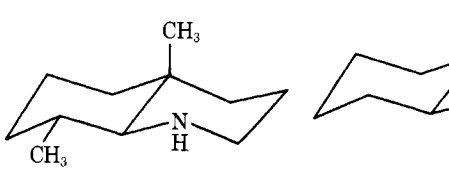
Table II. *N*-Methyl ^{13}C Resonances[a,b]

Compd:	1	2	3	4	5	6	7	8	9	10
$\delta_{N\text{-}Me}$[c]	42.52	42.22	43.04	42.94	33.18	42.32	42.77	33.10	32.97	42.27
$\delta_{N\text{-}Me}$[d]	42.66	42.26	42.86	42.90	33.23	42.54	42.85	Nr[e]	Nr[e]	Nr[e]

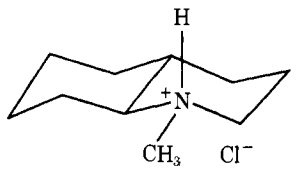
[a] In parts per million downfield from Me_4Si. [b] The data here reported are slightly different from those in the preliminary communication [E. L. Eliel and F. W. Vierhapper, *J. Am. Chem. Soc.*, 96, 2257 (1974)] because of the attachment of a pulse-shaping network to our instrument which eliminated small calibration errors contained in the preliminary paper. [c] In solvent $CDCl_3$. [d] In solvent benzene-d_6. [e] Not recorded.

even a minor decrease of δ_e or a minor increase in δ would lead to a much increased K and $-\Delta G°$. Under the circumstances, it is difficult if not impossible to define an upper reasonable limit for K and $-\Delta G°$. Fortunately, in the context of the history of the *N*-methylpiperidine problem, it is more important to define a *lower* reasonable limit, and we shall, in the main, concentrate on this objective.

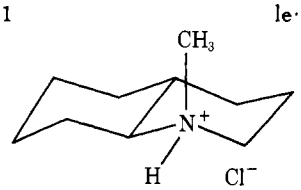
To investigate whether the *C*-methyl substituents employed as conformational holding groups in this study would have an important effect on the *N*-methyl ^{13}C NMR signal, we prepared a *C*-dimethyl-substituted model [the 8,10-dimethyl-*trans*-decahydroquinoline (**11**)], and we also converted compounds **1, 2, 3,** and **5** to their respective hydrochlorides. It should be noted that compound **1** can give rise to two diastereomeric hydrochlorides, **1e**·HCl and **1a**·HCl, and that, by pulsing for a long enough time, the ^{13}C NMR spectra of both isomers in a mixture can be recorded, even though **1a** comprises only 8% of the total.



11



1e·HCl



1a·HCl

Compound **11** showed the signal for the 10-methyl group at 16.72 ppm and that for the 8-methyl group at 18.91 ppm. These values should be compared with that for the 10-Me group in the N-H analog of **3** (15.57 ppm) and with that for the 8-Me group in the N-H analog of **5** (18.56 ppm). It appears that the two methyl groups do have a reciprocal effect on each other's signals which amounts to 0.35 ppm for Me-8 and 1.15 ppm for Me-10. The latter effect may also be seen (but now with an *N*-methyl group rather than a *C*-methyl group as the cause) when one compares the 10-Me group of **3** (17.32 ppm) with that of its N-H analog (15.57 ppm); in this case, the effect amounts to 1.75 ppm. One might argue that the effect of Me-10 on Me-8 would also express itself in compound **3** as an effect of Me-10 on Me-N, and that the observed Me-N value of 43.04 should thus be reduced by 0.35 ppm to 42.69. This would change K (calculated from the data for **3** plus the average δ and δ_a listed above) from 19 to 63. While this change is perturbingly large, it is in the direction of making K even larger than calculated earlier and would raise $-\Delta G°$ to 2.45 kcal/mol which we consider to be an upper limit.

The shifts for the hydrochlorides measured are summarized in Table III. The signals for the axial *N*-methyl groups in **1a**·HCl and **5**·HCl are coincident within the limits of experimental error. The same is not true for the equatorial *N*-methyl groups. Those in **1e**·HCl and **3**·HCl are sufficiently different to suggest a substantial distortion caused, possibly, by the syn-axial interaction of the N-H and 10-Me in **3**·HCl. It should be noted, however, that, if even part of this correction applied to **3** itself, its effect would be to make the earlier used N-Me shift value of **3** too large, thus lowering the true δ_e and increasing K in the calculation (ii) (vide supra). The opposite is true for **2,** and one is tempted to increase the value for $\delta_{N\text{-}Me}$ for **2** in Table II by 0.30 ppm (the difference between the $N\text{-}CH_3$ shift in **1e**·HCl and **2**·HCl, Table III). The effect of that adjustment, however, would merely be to bring $\delta_{N\text{-}Me}$ for **2** (now corrected to 42.52) into a reasonable range for δ_e, though it would still be at the low end of that range; we recall that the raw value of 42.22 was so low that we had to reject it in the compution of the average δ_e.[13] If this corrected value of $\delta_{N\text{-}Me}$ for **2** is included in the average for δ_e, the average becomes 42.83 giving $K = 32.6$ and $-\Delta G° = 2.07$ kcal/mol.[15]

Table III. ^{13}C Chemical Shifts for Amine Hydrochlorides[a]

Compd:	1e	1a	2	3	5
$N\text{-}CH_3$ Shift	40.35[b]	32.77[b]	40.05	41.70	32.66[b]

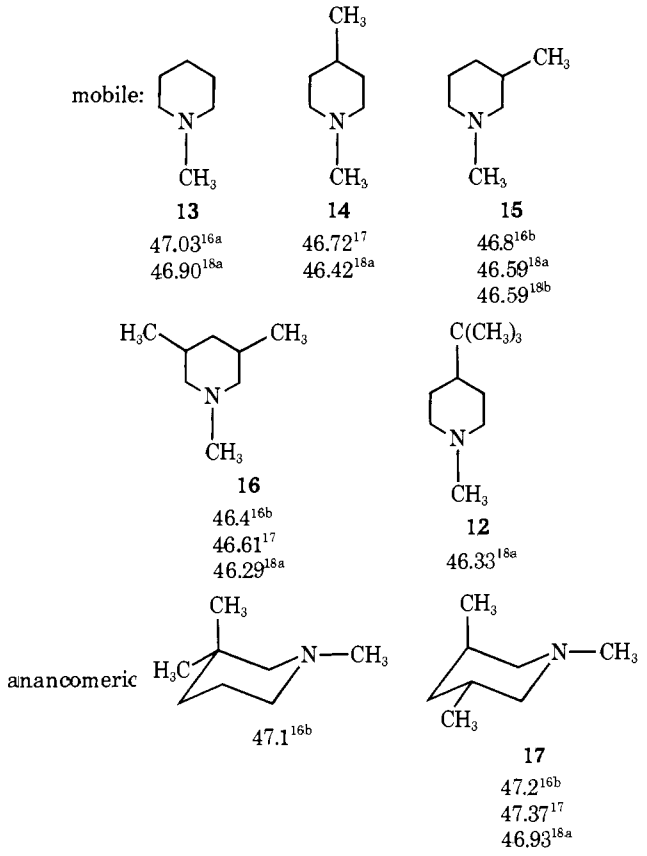
[a] In parts per million from Me_4Si, $CDCl_3$. [b] $N\text{-}CH_3$ signal assigned from ^{13}C NMR spectrum of $N\text{-}CD_3$ analog, see text.

In summary, even though our models are expectedly imperfect, any reasonable correction applied on this score would have the effect of making $-\Delta G°_{N\text{-}Me}$ even larger than 1.80 kcal/mol, the maximum reasonable value in $CDCl_3$ being 2.45 kcal/mol.

The *N*-Methylpiperidine Problem. No suitable model for the axial N-Me group in *N*-methylpiperidine (eq 1) has as yet been devised. Mobile systems and systems with equatorially biassed methyl groups are, of course, readily available and are shown in Chart I along with the pertinent *N*-methyl ^{13}C shifts (in parts per million relative to Me_4Si), many of them from the literature. It is immediately obvious that the difference between the purely equatorial and the mobile *N*-methyl groups is less than 1 ppm, the average for the mobile N-Me groups being 46.66 and that for the equatorial groups 47.15 ppm.[20]

There are several ways in which one may calculate a likely value for axial $N\text{-}CH_3$. Comparison of Table III with Table II shows that, in the *trans*-decahydroquinoline series, formation of the hydrochloride produces an upfield shift of 2.17 ppm for equatorial N-Me (compound **2**) and an upfield shift of 0.52 ppm for axial N-Me (compound **5**). When *N*-methyl-4-*tert*-butylpiperidine (**12,** Chart I) is converted to the hydrochloride, both the stereoisomer with axial $N\text{-}CH_3$ (**12a**·HCl) and that with equatorial $N\text{-}CH_3$ (**12e**·HCl) are seen in the ^{13}C NMR spectrum, the equatorial isomer predominating by far. The N-Me shift in **12e**·HCl is 43.59 ppm, which is upfield by 2.74 ppm from the corresponding shift in the free base **12.** Considering that **12** is not conformationally homogeneous, a better comparison might be that of **12e**·HCl with the average value for equatorial N-Me in the free bases given above as 47.15; in that case, the upfield shift on salt formation is 3.56 ppm. Since **12e** behaves similarly to **2** upon protonation, one might assume that the same is true for **12a** in comparison with **5**

Chart I



and, on that basis, the calculated N-Me shift for **12a** would be 37.60 + 0.52 = 38.12. Putting this value into eq 3 as δ_a along with δ_e = 47.15 and δ = 46.61 (vide supra) gives K = 15.7 and $-\Delta G^\circ$ = 1.63 kcal/mol.[21] As an alternative, one might try to correct the difference between **5**·HCl by a correction factor of 1.68, this being the ratio of the protonation shifts of **12e**·HCl and **2**·HCl (3.63/2.17). If one proceeds thus, the adjusted difference becomes 0.52 × 1.68 = 0.87, and δ_a is then 37.60 + 0.87 = 38.47, yielding K = 15.1, $-\Delta G^\circ$ = 1.61 kcal/mol. The adjustment is evidently quite minor. A slightly larger adjustment results if one uses only the shifts found in the present work.[20b] In that case, δ_e = 46.93, δ = 46.51, K = 19.98, $-\Delta G^\circ$ = 1.77 kcal/mol.

An alternative way of calculating δ_a is to assume that the change of frequency of the axial N-Me signal in going from the piperidine to the *trans*-decahydroquinoline series is the same as for the equatorial (making the assumption that the downfield shift of the N-Me signals in the decahydroquinoline series is due to the extra syn-axial hydrogen for the axial N-Me and to the peri hydrogen in the case of the equatorial N-Me, and that the shifts engendered by these two interactions may be considered equal in a first approximation). Now the difference between the equatorial signals (average value) is 47.15-42.99 = 4.16 ppm. If one adds this value to the average value of δ_a in *N*-methyl-*trans*-decahydroquinoline (33.08 ppm), one obtains a calculated δ_a for *N*-methylpiperidine of 37.24 ppm. This value is lower than the value calculated above and leads (eq 3) to K = 17.4, $-\Delta G^\circ$ = 1.69 kcal/mol.

Another rather appealing method of calculating the missing δ_a is to start from the difference between the equatorial and axial methyl ^{13}C NMR frequencies in cyclohexane, reported[22] as 4.30 ± 0.40. Because of the disparity of C-Me and N-Me geometry, this difference cannot be directly transferred to equatorial and axial *N*-methyl, but a correction suggests itself on the basis of the models shown in Chart II. It is immediately evident from the data shown in

Chart II

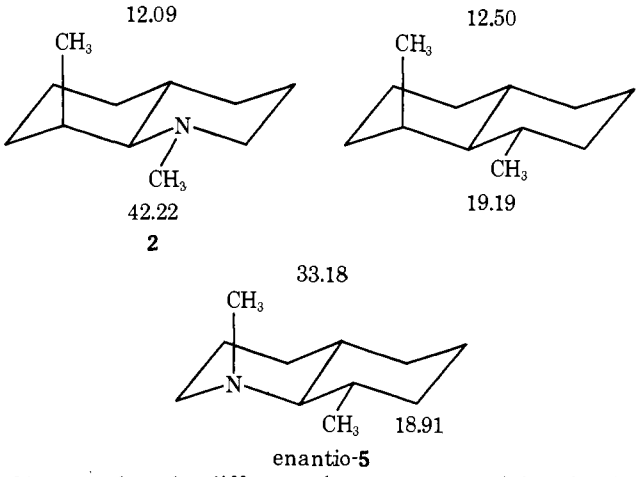


Chart II that the difference between equatorial and axial *N*-methyl in conformationally fixed *N*-methyl-*trans*-decahydroquinolines (9.04 ppm) is considerably larger than the corresponding difference in equatorial and axial *C*-methyl groups in 1,8-dimethyl-*trans*-decalin[23] (6.69 ppm), the ratio of the two differences being 1.35. If one corrects the difference of 4.30 in the methylcyclohexanes (vide supra) by this factor, the calculated difference between equatorial and axial *N*-methyl groups in *N*-methylpiperidines is 4.30 × 1.35 = 5.81. From this, δ_a = 47.15-5.81 = 41.34, whence K = 9.8 and $-\Delta G^\circ$ = 1.35 kcal/mol. We consider this value a lower limit.

From all these considerations, it appears that $-\Delta G^\circ$ (eq 1) is between 1.35 and 1.77 kcal/mol. This value is considerably higher than values derived from dipole measurements,[3,6,24] close to those derived from infrared[4] or the earlier quenching[2b] experiments, and appreciably lower than that most recently reported from quenching results.[5]

After this paper was submitted, a communication[5] appeared reporting a value of $-\Delta G^\circ$ in *N*-methylpiperidine of 2.70 kcal/mol (corresponding to 99% of equatorial methyl) on the basis of refined quenching experiments. A solution of *N,cis*-3,5-trimethylpiperidine in cyclohexane was extracted with dilute hydrochloric acid and the concentration of the two diastereomeric hydrochlorides formed analyzed by NMR in the aqueous phase. If one accepts (in the absence of experimental detail) that 1% of the hydrochloride with axial N-Me can in fact be accurately analyzed by NMR, the quenching result indicates that N-Me in *N*-methylpiperidine prefers the equatorial position by about 1 kcal/mol more than it does in the corresponding piperidinium salt, or than C-Me does in methylcyclohexane. Even allowing for the uncertainty of the models, the small difference of δ_e and δ in the present investigation (cf. Chart I) and the absence of a firm value for δ_a, we feel that the present investigation is not compatible with a value for $-\Delta G^\circ_{N\text{-}Me}$ as large as −2.7 kcal/mol in chloroform solution. It is, of course, possible that the value in solvent cyclohexane[5] is substantially larger than that in chloroform since chloroform may bias the equilibrium slightly in favor of axial methyl by preferentially hydrogen-bonding to an equatorial lone pair.[25]

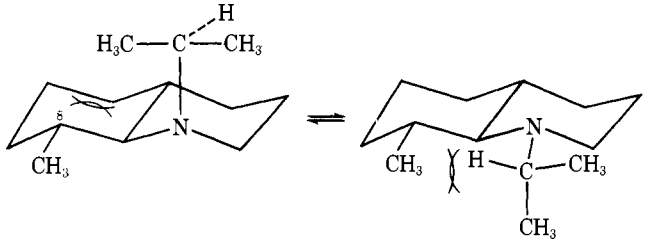
Higher Alkyl Groups. Rather low ΔG° values are reported in the literature[3] also for the *N*-alkyl groups in *N*-ethylpiperidine (1.03 kcal/mol) and *N*-isopropylpiperidine (1.58 kcal/mol). In the present work, we have prepared several *N*-ethyl- and *N*-isopropyl-*trans*-decahydroquinolines, namely the *N*-ethyl and *N*-isopropyl homologs of **1** and **6** (eq 4) and **2**, **3**, and **5**. The shifts for N-CH_2-CH_3 and N-$CH(CH_3)_2$ are summarized in Table IV. Using the average of **1**-Et and **6**-Et for δ, **5**-Et for δ_a, and **3**-Et for δ_e,[26] one obtains K = 47 and $-\Delta G^\circ$ = 2.1 kcal/mol, for the conforma-

Table IV. ^{13}C NMR Signals for α-Carbon Atoms in *N*-Ethyl- and *N*-Isopropyl-*trans*-decahydroquinolines[a]

Compd:	1-R[b]	2-R[b]	3-R[b]	5-R[b]	6-R[b]
N–CH_2CH_3	46.22	45.51	46.34	36.57	46.05
N–$CH(CH_3)_2$	45.89	44.83	45.79	45.28	45.72

[a] In $CDCl_3$, parts per million downfield from Me_4Si. [b] Upper line of figures, R = CH_2CH_3, lower line, R = $CH(CH_3)_2$.

tional energy of *N*-ethyl, a value which is, as expected[27] slightly higher than the corresponding value for *N*-methyl and much higher than the literature value (1.03 kcal/mol) for N-Et.[3] The data for the isopropyl methine carbons in Table IV unfortunately cannot be used to calculate a conformational energy value for *N*-isopropyl since the shift of this carbon in **5**-$CH(CH_3)_2$ is about the same as the shifts for the other compounds shown. Model considerations show that the isopropyl group in **5**-$CH(CH_3)_2$ cannot avoid serious steric compression for, if it is axial and assumes the most likely position (with the methyl groups outside the ring), a serious syn-axial interaction of one of the methyl groups with C-8 ensues. This may lead to the isopropyl group being at least partly in the equatorial conformation, despite the very severe peri interaction this would involve (eq 5). The literature value[3] for N-*i*-Pr, 1.58 kcal/mol, is less than our value for N-Et.



(5)

Results from Dipole Moments. In view of the extensive amount of work which has been done on the *N*-methylpiperidine problem with the dipole moment method (cf. eq 2), a somewhat detailed discussion of this work, which has uniformly given low values for $-\Delta G^\circ$ for *N*-methylpiperidine (eq 1), as shown in Table I, would seem appropriate. In principle, the dipole moment method is unassailable since it is based on the theoretically correct equation $\mu^2 = \Sigma_i n_i \mu_i^2$ where μ is the dipole moment of a conformationally heterogeneous substance, n_i are the mole fractions of the i contributing conformations, and μ_i their dipole moments. In practice,[28] there is a difficulty in measuring the μ_i's; this must either be done on model compounds (which may or may not be adequate) or, if appropriate model compounds are not available, the dipole moments of the individual conformations must be obtained by a priori calculations which are known to be fraught with uncertainties.

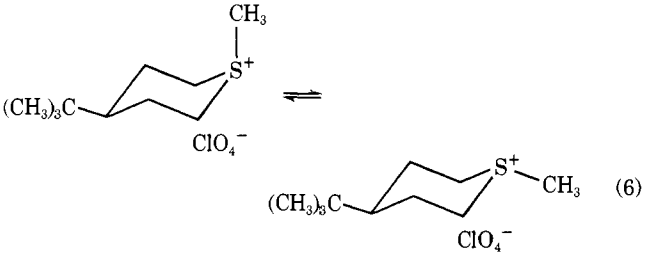
One of the conditions[28] for the model study discussed earlier and summarized in eq 2 to be successful is that the *p*-chlorophenyl (or *p*-nitrophenyl) holding group does not change the N-Me(a) $\rightleftharpoons$ N-Me(e) equilibrium. This assumption was suspect since it is known that molecules tend to minimize their dipole moments because of dipole-dipole repulsion[29] which, in the present case, would tend to favor the N-CH_3(a) conformation with its lower overall moment. We therefore measured the N-CH_3 ^{13}C NMR frequency of *N*-methyl-4-(*p*-chlorophenyl)piperidine (eq 2, X = Cl, sample kindly provided by Dr. N. L. Allinger) and found it to be 46.29 ppm. This value is appreciably below the average value of $\delta_{N\text{-}Me}$ (46.61 ppm); a calculation with δ = 46.29, δ = 47.15, δ = 41.34 (the highest value used earlier) gives K = 5.76, $-\Delta G^\circ$ = 1.04 kcal/mol, much lower than the lowest reasonable value (1.35 kcal/mol) for *N*-methylpiperidine but still substantially above the values of K = 3, $-\Delta G^\circ$ = 0.75 kcal/mol reported earlier.[6] (The discrepancy would become larger were one to use the smaller values for δ_a discussed above.) It would thus appear that part but not all of the problem with the dipole-derived ΔG° values can be blamed on dipole–dipole interaction. A rather likely alternative source of difficulty (which is, however, hard to pinpoint) is the difficulty of calculating the dipole moments of the models (eq 2) with the required accuracy.

Conclusion

The value for $-\Delta G^\circ_{N\text{-}Me}$ (in $CDCl_3$) for *N*-methyl-*trans*-decahydroquinoline (**1**, eq 4) lies between 1.8 and (at the extreme) 2.45 kcal/mol; i.e., it is somewhat in excess of the value of 1.7 kcal/mol for C-Me in cyclohexane[27] and close to the value for 1-methyl-*trans*-decalin which may be computed from published[30] equilibrium data to be 1.85 kcal/mol.

The value of 1.35–1.77 kcal/mol for *N*-methylpiperidine (eq 1) is on somewhat less firm ground because a model for axial methyl is not available. It would seem reasonable that this value is somewhat smaller than that for **1** since the methylcyclohexane value (vide supra) is somewhat smaller than the methyldecalin value. The value of 0.75 kcal/mol previously reported[6] is quite incompatible with our findings, and the recently reported[5] value of 2.7 kcal/mol also seems to be incompatible, though it must be stressed that the latter value was determined in cyclohexane whereas our measurement refers to chloroform-*d*.

It has recently been speculated that the 1.7 kcal/mol preference for equatorial methyl in methylcyclohexane is due not to steric interaction of the axial methyl but to steric interaction of the equatorial tertiary hydrogen in the axial conformer.[31a] The low $-\Delta G^\circ$ value, 0.27 kcal/mol,[32] for S-Me in *S*-methylthianium salts (eq 6) might have been



(6)

considered to support this hypothesis, but the much higher and essentially "methylcyclohexane-like" value in *N*-methylpiperidine does not bear it out.[31b] More likely the variation in $-\Delta G^\circ_{Me}$ reflects differences in bond lengths (C-S > C-C > C-N), torsional angles (the heterocyclic systems are puckered in the vicinity of the heteroatom[32,33]), and ease of outward bending of the methyl group (deformation potential). Deformation is remarkably facile in the thianium system (eq 6)[32] but apparently not at all so in *N*-methylpiperidine, contrary to earlier assumption.[6b] This point and two others (comparison of *N*-alkylpiperidines with *N,N'*-dialkylhexahydropyrimidines and the question of equivalency of peri and syn-axial interactions) are discussed in the Appendix.[34]

Experimental Section

NMR spectra were recorded on a Varian XL-100 pulsed Fourier transform nuclear magnetic resonance spectrometer. Internal deuterium or fluorine lock was used for both ^1H and ^{13}C spectra, the solvent ($CDCl_3$ or CF_3COOH) providing the lock signal. Proton spectra were recorded in 5-mm diameter tubes, ^{13}C spectra in 10-mm diameter tubes. Me_4Si (2%) was added to the samples as an internal reference. Synthesis, purification, and ^1H-NMR spec-

Table V

Compd[a]	^{1}H-NMR signal[b,c]				N–CHR′R″[a]			
	H-2-e	H-2-a	H-9	H	R′[e]	R″[e]	C–CH_3[e]	Picrate, mp[d] (lit.), °C
1	2.88_5	*f*	*f*	2.25_5				172 (173[35b])
2	2.88_5	*f*	*f*	2.17_3			0.95_3 (7.0)	186 – 187
3	2.87_5	*f*	*f*	2.15_5			0.98	240 – 241 (dec)
4	2.66	*f*	*f*	2.19_5			1.16 (7.0)	*g*
5	2.98_5	2.89_5	1.98	2.31_5			0.95 (6.0)	141 – 142
6	2.79	*f*	*f*	2.22_0			0.82_5 (6.0)	194 – 195
7	2.86_5	*f*	*f*	2.24_6			0.86_6 (6.0)	187.5 – 188.0
8	2.95_5	2.87	*f*	2.27_5				140.5 – 141.5
9	3.00_5	2.94	*f*	2.31_5				*g*
10	2.88_7	*f*	*f*	2.17_2			0.96[h]	176 – 177
11	3.14_5	2.61_5	1.85				0.85_5[i]	220 – 221
12	2.93[j]	*f*		2.26			0.87[k] 1.01[h]	*l*
13	2.95_5	2.88_5	2.04	2.40_4			0.91_5[i]	215.5 – 2116.5
1-Et	2.90	*f*	*f*	2.80_3[m]	2.59[m]	0.96_5 (7.0)[m]		112 – 113 (112 – 114[36])
2-Et	2.92	*f*	1.79_5	2.76[m]	2.40_5[m]	0.96_5 (7.0)[m]	0.95 (7.0)	182 – 182.5
3-Et	2.84	2.23	*f*	2.69[m]	2.59[m]	0.90 (7.0)[m]	0.95	128 – 128.5
5-Et	3.21	2.61_5	2.02	2.56		1.04_5 (6.5)	0.94 (6.0)	139.5 – 140.5
6-Et	2.85	*f*	*f*	2.82[m]	2.63[m]	0.97 (7.0)[m]	0.85 (6.0)	134 – 134.5
1-iPr	2.90	*f*	*f*	3.37[n]	1.10 (7.0)[n]	0.81_7 (7.0)[n]		169 – 169.5
2-iPr	2.89	*f*	*f*	3.24[n]	1.08_8 (6.5)[n]	0.81_3 (6.5)[n]	0.93_5 (7.0)	162
3-iPr	2.88	1.98	*f*	3.14[n]	1.04_8 (6.5)[n]	0.76_3 (6.5)[n]	0.94	260–261 (dec)[o]
5-iPr	3.25_5	2.57	2.03	3.23_5[n]	1.12 (6.5)[n]	1.08 (6.5)[n]	0.93_7 (6.0)	122 – 124
6-iPr	2.85	*f*	*f*	3.40[n]	1.12_5 (7.0)[n]	0.82 (7.0)[n]	0.85 (6.0)	171

[a] N-Substituent CH_3 (R′ = R′ = H) if not otherwise indicated. [b] Recorded at 100 MHz, solvent $CDCl_3$. Shifts downfield from Me_4Si (δ) in parts per million. [c] H-2-e indicates equatorial proton at C_2, H-2-a axial proton at C_2, H-9 proton at C_9 (see eq 4). A detailed discussion of the proton spectra will be given elsewhere[11]. [d] Recrystallized from ethanol if not otherwise indicated. [e] Coupling constants in hertz, in parentheses. [f] Not resolved. [g] Because of the very small amounts of material available, no picrate was prepared. [h] CH_3(10). [i] CH_3(8). [j] Equatorial protons at $C_{2,6}$. [k] CH_3 of *tert*-butyl group. [l] Hydrochloride, mp 252–253° (lit. 252–254°; R. A. Y. Jones, A. R. Katritzky, and P. G. Mente, *J. Chem. Soc. B*, 1210 (1970). [m] N–CHH′CH_3; R′ = H; R″ = CH_3. The ABX_3 pattern was resolved by decoupling the CH_3 protons. For details, see ref 11. [n] N = $CH(CH_3)_2$; R′ = R″ = CH_3. [o] Recrystallized from glacial acetic acid.

tra of the NH precursors of the majority of the model compounds used are described elsewhere.[11] *N*-Methyl derivatives were prepared by the standard Clarke-Eschweiler procedure[35] with HCOOH and HCHO. *N*-Ethyl compounds were obtained by acetylating the secondary amines with acetic anhydride and reducing the acetamides with $LiAlH_4$.[36] *N*-Isopropyldecahydroquinolines were prepared by stirring the NH precursors with 2-iodopropane and potassium carbonate in refluxing acetone for 48 hr,[37] except in the case of 8α-methyl-*trans*-decahydroquinoline.[38] Use of hexamethylphosphoric triamide (HMPT) as a solvent and prolonged reaction times (6 days) led to *N*-isopropyl-8α-methyl-*trans*-decahydroquinoline in high yield (see below for deuterio analog). Pertinent ^{1}H-NMR data and melting points of picrates of the model compounds used are collected in Table V. The melting points were determined on a Sargent "Mel-Temp" variable-temperature heating block. N–CD_3 analogs of **1** and **5** were prepared as described for *N*-trideuteriomethyl-*trans*-decahydroquinoline.

***N*-Trideuteriomethyl-*trans*-decahydroquinoline.** To 700 mg of *trans*-decahydroquinoline dissolved in 10 ml of ether and 18 ml of H_2O and stirred at +5°, CH_3OCOCl (473 mg) in 7.5 ml of anhydrous ether was slowly added. After addition of the first 3 ml, a solution of 200 mg of NaOH in 3.5 ml of H_2O was added simultaneously. When addition was complete, the mixture was stirred for 1 more hr at 5°; then the ether phase was separated, the aqueous phase was extracted with ether, and the ether phases were combined, washed twice with dilute HCl, and dried over $MgSO_4$. After evaporation of the solvent, the product was distilled in a Kugelrohr apparatus and dissolved in 5 ml of freshly distilled THF. The solution was slowly added to a suspension of $LiAlD_4$ (300 mg) in THF and the mixture heated to reflux for 12 hr. The excess $LiAlD_4$ was carefully decomposed with H_2O, the reaction mixture was repeatedly extracted with ether, the ether extracts were dried, and the solvent was evaporated. Distillation of the residue in a Kugelrohr apparatus gave 535 mg of *N*-trideuteriomethyl-*trans*-decahydroquinoline, pure by VPC. N–CD_2CD_3 and N–$CD(CD_3)_2$ analogs of some of the model compounds were prepared in a way similar to the proton analogs.

***N*-Pentadeuterioethyl-8α-methyl-*trans*-decahydroquinoline.** 8α-Methyl-*trans*-decahydroquinoline (430 mg) and 540 mg of $(CD_3CO)_2O$ were heated to reflux in 30 ml of dry acetone over K_2CO_3 (1 g) for 12 hr. After that time, the mixture was diluted with ether, the salts were filtered off, the solvent was evaporated, and the residue was dissolved in anhydrous ether and slowly added to a suspension of 300 mg of $LiAlD_4$ in anhydrous ether. The mixture was heated to reflux for 12 hr. The excess of $LiAlD_4$ was decomposed with water, the ether phase separated, the aqueous phase repeatedly extracted with ether, the ether phases were united and dried, and the solvent was evaporated. The residue was distilled in a Kugelrohr apparatus. The product, *N*-pentadeuterioethyl-8α-methyl-*trans*-decahydroquinoline (410 mg), was tested by VPC and showed only small amounts of impurity with low retention time.

***N*-Heptadeuterioisopropyl-8α-methyl-*trans*-decahydroquinoline.** Isopropyl-d_7 iodide [1.55 g; prepared from isopropanol-d_8 (Merck and Co.) and hydriodic acid], 765 mg of 8α-methyl-*trans*-decahydroquinoline, and 1.4 g of K_2CO_3 were mixed with 7 ml of HMPT and stirred at ~50° for 6 days. After that time, the mixture was poured on 50 ml of water, made acidic with HCl, and extracted repeatedly with ether. The aqueous phase was made basic with a concentrated solution of NaOH and extracted five times with hexane. The hexane extracts were combined, washed two times with water, and dried. The solvent was evaporated and the residue distilled in a Kugelrohr apparatus. The product, 620 mg, showed only traces of HMPT as impurity by VPC.

Hydrochlorides of model compounds were prepared by passing a stream of dry HCl gas into the ethereal solution of the amine and distilling off the solvent.

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Supplementary Material Available. Appendix A (Deformation Potential for N–Me and Comparison with *N,N′*-Dialkylhexahydropyrimidines) and Appendix B (Comparison of peri and syn-

axial Interactions) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 200236. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JACS-75-2424.

References and Notes

(1) Paper XXIX: E. L. Eliel and W. F. Bailey, *J. Am. Chem. Soc.*, **96**, 1798 (1974).

(2) The literature is too vast to be summarized here, not being directly pertinent to the subject matter of this paper. For recent references, see (a) R. A. Y. Jones, A. R. Katritzky, A. C. Richards, R. J. Wyatt, R. J. Bishop, and L. E. Sutton, *J. Chem. Soc. B*, 127 (1970); (b) H. Booth and J. H. Little, *J. Chem. Soc., Perkin Trans. 2*, 1846 (1972); (c) J. B. Lambert, D. S. Bailey, and B. F. Michel, *J. Am. Chem. Soc.*, **94**, 3812 (1972).

(3) I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J. Chem. Soc., Perkin Trans. 2*, 332 (1973).

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(6) (a) R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc. B*, 493 (1967); (b) R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc. B*, 122 (1970).

(7) J. McKenna and J. M. McKenna, *J. Chem. Soc. B*, 644 (1969).

(8) To minimize confusion, we have deliberately excluded from the table data which are manifestly incorrect. The first report of the equilibrium was one by M. Aroney and R. J. W. Le Fèvre, *J. Chem. Soc.*, 3002 (1958), based on Kerr constant measurements, which gave $\Delta G^\circ = 0$. Neither the result nor the methodology is accepted today. The preliminary report of R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, and A. R. Katritzky, *Proc. Chem. Soc., London*, 257 (1964), using the procedure of (2) and giving $-\Delta G^\circ = 1.63$ kcal/mol was based on an erroneous value of the reference moment (*p*-chlorophenylcyclohexane) and is corrected in the full paper.[6a] A similar report of N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski [*Tetrahedron Lett.*, 3345 (1964); *J. Am. Chem. Soc.*, **87**, 1232 (1965)], giving $-\Delta G^\circ = 1.7$ kcal/mol, although never withdrawn, seems to suffer from use of the same erroneous reference moment. A subsequent molecular mechanical calculation [N. L. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Lett.*, 3729 (1967)] is no longer considered dependable since the disregard of the "steric effect" of the unshared electron pair assumed in that work is probably not justified (N. L. Allinger, personal communication). Results based on the use of paramagnetic shift reagents [T. Yonezawa, I. Morishima, and Y. Ohmori, *J. Am. Chem. Soc.*, **92**, 1267 (1970); I. Morishima, K. Okada, T. Yonezawa, and K. Goto, *ibid.*, **93**, 3922 (1971); I. Morishima, K. Okada, M. Ohashi, and T. Yonezawa, *Chem. Commun.*, 33 (1971)] are vitiated by the fact that the two conformational isomers do not complex equally with the cobalt and nickel acetonylacetates employed so that the equilibrium is changed on complexation: I. D. Blackburne, A. R. Katritzky, and Y. Takeuchi, *J. Am. Chem. Soc.*, **96**, 682 (1974).

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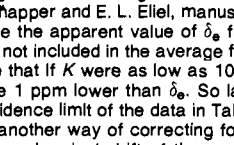
(11) F. W. Vierhapper and E. L. Eliel, submitted to *J. Org. Chem.*

(12) The complete ^{13}C NMR spectra of these compounds, with evidence for assignment of the ring carbon atoms, will be published elsewhere: F. W. Vierhapper and E. L. Eliel, manuscript in preparation.

(13) Since the apparent value of δ_e for **2** and **10** is below the value for δ, it was not included in the average for δ_e. This point is discussed later.

(14) Note that if K were as low as 10 ($-\Delta G^\circ = 1.4$ kcal/mol), δ would have to be 1 ppm lower than δ_e. So large a difference is entirely outside the confidence limit of the data in Table II.

(15) Yet another way of correcting for the effect of the axial 8-methyl group on the chemical shift of the equatorial *N*-methyl is to use the shifts in the (conformationally rigid) 1β-methyl-*trans*-decalin (I) and 1β,8α-dimethyl-*trans*-decalin (ii):[23]



R = H; δ_{CH_3} = 19.74 ppm (i)
R = CH_3; δ_{CH_3} = 19.19 ppm (ii)

If it is assumed that the difference of 0.55 ppm engendered by the axial 8-methyl group also applies to the nitrogen analog **2**, the corrected *N*-methyl shift for the latter would be 42.77 ppm. (A similar correction would apply to the shift in **10**.) Using this value plus those for **3** and **4** gives δ_e (average) 42.92, $K = 24.9$, $-\Delta G^\circ = 1.89$ kcal/mol.

(16) (a) M. W. Duch, Ph.D. Thesis, University of Utah, Salt Lake City, Utah, 1970, neat liquid; see also ref 19; (b) D. W. Cochran, Ph.D. Thesis, Indiana University, Bloomington, Ind., 1971; L. D. Kopp, Ph.D. Thesis, University of Notre Dame, Ind., 1973, solvent $CHCl_3$; see also ref 19.

(17) H. Booth and D. V. Griffith, *J. Chem. Soc., Perkin Trans. 2*, 842 (1973). Solvent C_6D_6.

(18) (a) Determined in this work, solvent $CDCl_3$; (b) J. B. Stothers, personal communication; solvent CD_2Cl_2, at 40°.

(19) See also E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975); specifically the microform supplement to this paper.

(20) (a) In comparing the values for the anancomeric (N-Me equatorial) system with those of the mobile system, we have made no effort to correct for a possible δ effect of the axial *C*-methyl on the equatorial *N*-methyl group in the anancomeric model. Comparison of the axial *C*-methyl frequencies in *cis*-1,3-dimethylcyclohexane and *cis*-1,3,5-trimethylcyclohexane (23.13 ppm)[9] with those of *r*-1-, *cis*-3-, *trans*-5-trimethylcyclohexane (23.36 ppm[9]) and 1,1,3-trimethylcyclohexane (23.46 ppm)[9] would suggest that such a correction would, if anything, make δ_e smaller and therefore (see below) $-\Delta G^\circ_{N\text{-}Me}$ larger. (b) We must also point out that (perhaps because of solvent and referencing differences) values obtained in our laboratory are systematically upfield from those obtained elsewhere.

(21) One can also base the argument on ^{13}C NMR spectra of solutions of the amines in trifluoroacetic acid which we have measured: trifluoroacetate of **2**, N–Me, 41.86; of **5**, 34.13; of **12e**, 45.32; of **12a**, 39.4 ppm. Here upon protonation, the N–Me shift in **2** moves upfield by 0.36 ppm, that in **5** downfield by 0.95 ppm, that in **12e**, upfield by 1.01 (compared with **12**) or 1.91 ppm (compared with average δ_a). If one applies the 0.95 ppm downfield correction of the axial N–Me (model **5**) to **12a** trifluoroacetate, the signal for **12a** base is calculated to be at 38.45 ppm. This leads to a K of 15.1, $-\Delta G^\circ = 1.61$ kcal/mol.

(22) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **94**, 5318 (1972).

(23) D. K. Dalling, D. M. Grant, and E. G. Paul, *J. Am. Chem. Soc.*, **95**, 3718 (1973).

(24) To obtain a value of K as low as 3 (as given in ref 3) with $\delta_e = 47.15$ and $\delta = 46.61$, δ_a would have to be 44.99 ppm, differing by only 2.16 ppm from δ_e. Such a small difference is highly unlikely in the light of existing ^{13}C NMR data.

(25) After learning of the results reported in ref 5, we repeated the ^{13}C NMR measurements for compounds **12–17** in Chart I in benzene-d_6 as solvent, the following values for the N–Me signals being obtained: **12**, 46.60; **13**, 47.06; **14**, 46.67; **15**, 46.76; **16**, 46.45; average of five δ-values 46.71 (the corresponding average in $CDCl_3$ is 46.51 ppm). The δ_e value for **17** in C_6D_6, 46.94 ppm, is virtually the same as in chloroform. Thus $\delta_e - \delta$ (using the values listed here) changes from 0.42 in $CDCl_3$ to 0.23 in C_6D_6 corresponding to a factor of 2. Assuming that the change in $\delta - \delta_a$ is of the same magnitude, it may be safely disregarded (since $\delta - \delta_a$ is of the order of 5–8 ppm so that the variation is less than 5%), and it is concluded that $K = (\delta - \delta_a)/(\delta_e - \delta)$ increases by a factor of about 2 when the solvent is changed from chloroform to benzene, with a concomitant increase in $-\Delta G^\circ$ of 0.42 kcal/mol. (This increase is similar to that of 0.48 kcal/mol earlier computed for *N*-methyl-*trans*-decahydroquinoline.) It follows that the solvent variation, while contributing to the difference between the reported value[5] and ours, still does not make the two values compatible. The remaining discrepancy would appear to be due either to difficulties in accurate NMR measurement of the reported[5] value, or to inadequacies of the models used in the present work, or to a combination of both causes.

(26) As in the case of the *N*-methyl compounds, the signal for **2**-Et could not be used since it falls outside the axial–equatorial range. No attempt was made to correct for the influence of the biassing group on the chemical shift.

(27) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1965, pp 43–44.

(28) The limitations in this regard are clearly stated in ref 5 and 6.

(29) Cf. ref 27, pp 69, 159, 461. In the present case (eq 2), the effect may be small, however, since the two dipoles (C–Ar and N pair) are rather far from each other in space.

(30) A. W. Weitkamp, *Adv. Catal.*, **18**, 1 (1968).

(31) (a) D. H. Wertz and N. L. Allinger, *Tetrahedron*, **30**, 1579 (1974). (b) Professor Allinger has informed the authors that, because of differences in geometry, comparison of *N*-methylpiperidine with methylcyclohexane may be inappropriate. However, since the literature[2b,5,7] suggests that the $-\Delta G^\circ$ value for *N*-methylpiperidine hydrochloride (whose geometry is similar to that of *N*-methylpiperidine) is nearly the same as that for methylcyclopiperidine, our argument, in our view, still applies.

(32) E. L. Eliel, R. L. Willer, A. T. McPhail, and K. D. Onan, *J. Am. Chem. Soc.*, **96**, 3021 (1974).

(33) Cf. J. B. Lambert and S. A. Featherman, *Chem. Rev.*, in press.

(34) See paragraph at end of paper regarding supplementary material.

(35) (a) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933); (b) M. Ehrenstein and W. Bunge, *Ber.*, **67**, 1728 (1934).

(36) J. McKenna, J. M. McKenna, A. Tulley, and J. White, *J. Chem. Soc.*, 1711 (1965).

(37) D. R. Brown, R. Lygo, J. McKenna, J. M. McKenna, and B. G. Hutley, *J. Chem. Soc. B*, 1184 (1967).

(38) Nomenclature: β means on the same side as CH_3 or H at C-10, α on the opposite side. This nomenclature is different from that used in the preliminary communication: F. W. Vierhapper and E. L. Eliel, *J. Am. Chem. Soc.*, **96**, 2256 (1974).