Conformation of Piperidine and of Derivatives with Additional Ring Heteroatoms

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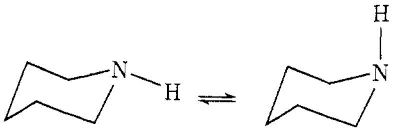
The conformational equilibrium[1a,b] of piperidine ($1 \rightleftharpoons 2$) has been the subject of considerable controversy. By 1970, extensive work and reinterpretation of earlier evidence indicated[2] that all known facts except δ_{ae} were in agreement with the preference of the equatorial NH form (**1**) in the equilibrium $1 \rightleftharpoons 2$, with $\Delta G° = 0.4 \pm 0.2$ kcal/mol for the gas phase and solutions in nonpolar solvents.



1 **2**

This situation still holds, but it needs reassertion in view of recent papers which still assume NH-axial preference[3-5] or hold that the preferred NH conformation is not yet known[6] and are based in our opinion on an incomplete survey of the preceding evidence. Other recent papers[7] which purport to deduce NH-axial preference neglect, as discussed below, vital considerations which vitiate the conclusions. The sole remaining uncertainty is the possibility that the equilibrium may be solvent sensitive and favor the NH-axial form for solutions in polar hydroxylic solvents.

Early discussion of the conformational equilibrium became entangled with the concept of the relative "sizes" or "steric requirements" of the lone pair of electrons and the hydrogen atom—it being assumed that the "smaller" moiety would prefer the axial position. It is now recognized that this whole concept of size is dangerous; despite attempts at the definition of size,[8] there is no unique distance of approach at which interactions become repulsive. Any discussion of steric interactions must consider *both* the moieties involved in the interaction, together with their distance and relative orientation; such interactions can be attractive as well as repulsive.

In this Account we summarize the published evidence for the conformational equilibrium of piperidine, and also discuss the effect of the substitution of further heteroatoms in piperidine at the 2, 3, and 4 positions.

Piperidine: Early Skirmishes and Apparent Victory for NH-Equatorial

Consideration of the equilibrium between the piperidine conformers **1** and **2** is a topic of nearly two decades standing which has attracted considerable theoretical and experimental interest. In 1956, Barton and Cookson[9a] by analogy with the stereochemistry of carbanions predicted a predominance of the NH-axial conformer. The first quantitative assessments appeared shortly after: Aroney and Le Fèvre[9b] examined molecular polarizabilities and concluded that the NH-axial conformer of piperidine was preferred to the extent of more than 80% in benzene solution. Accordingly, they suggested that in the usual conformational sense the lone pair exhibits a greater steric requirement than the hydrogen atom. In 1964, Claxton[10] attributed this NH-axial preponderance to more effective overall electron binding when the lone pair axis is directed toward the center of the molecule as in **2**; Claxton also cautioned on the sensitivity of lone pair "size" to environment.

However, in the early sixties other experimentation was leading to conflicting conclusions regarding lone pair "size". The preferred conformations of

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(1) (a) Boat forms for the six-membered heterocycles of this paper are not considered (see ref 1b for a summary of evidence against them). (b) F. G. Riddell, *Q. Rev., Chem. Soc.*, **21**, 364 (1967).

(2) 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).

(3) R. G. Lett, L. Petrakis, A. F. Ellis, and R. K. Jensen, *J. Phys. Chem.*, **74**, 2816 (1970).

(4) C. C. Price, *Tetrahedron Lett.*, 4527 (1971).

(5) I. Morishima, K. Yoshikawa, K. Okada, T. Yonezawa, and K. Goto, *J. Am. Chem. Soc.*, **95**, 165 (1973).

(6) N. L. Allinger and S. P. Jindal, *J. Org. Chem.*, **37**, 1042 (1972).

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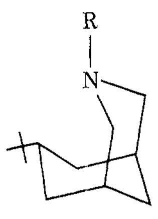
(8) M. A. Robb, W. J. Haines, and I. G. Csizmadia, *J. Am. Chem. Soc.*, **95**, 42 (1973).

(9) (a) D. H. R. Barton and R. C. Cookson, *Q. Rev., Chem. Soc.*, **10**, 44 (1956); (b) M. Aroney and R. J. W. Le Fèvre, *J. Chem. Soc.*, 3002 (1958).

(10) T. A. Claxton, *Chem. Ind.* (*London*), 1713 (1964).

methylquinolizidines were explained at the time with the now no longer recommended concept of lone pairs "smaller" than hydrogen atoms of methine or methylene groups;[11] Bohlmann bands[12] in the infrared spectrum of the bicyclic compound 3 (R = H) indicated an anticoplanar H–C–N–lone pair conformation, and hence a similar preference for placement of a lone pair rather than a hydrogen atom in the rather hindered N-axial position of this bicyclic piperidine.[13]



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Several groups joined in criticism of the Kerr constant measurements on the grounds of the assumptions of molecular parameters inherent in the treatment,[14,15] and overall reliability.[2] This lack of confidence in the Kerr constant work was increased by the unlikely conclusions that the *N*-methyl axial–equatorial equilibrium constant for *N*-methylpiperidine is ca. unity and that 1,4-dimethylpiperazine existed in the boat form:[16] the latter conclusion was soon to be proved incorrect by electron diffraction[17] and the former more recently disproved by dipole moments[18] and NMR.[19] The original prediction[9a] of NH-axial preference for piperidine was based on the conformation of carbanions which were solvent stabilized and hence did not apply to free piperidine, as was pointed out in 1964.[20]

Contemporaneously two groups began dipole moment measurements. Jones, Katritzky, Sutton, and their coworkers investigated 4-(*p*-chlorophenyl)piperidine and initially[21] concluded that the NH-equatorial conformer was favored by 1.2 kcal/mol. Nonhomogeneity of the (*p*-chlorophenyl)cyclohexane model[22,23] necessitated revision of this result to 0.4 kcal/mol in favor of the NH-equatorial conformer.[2] Such calculations were based on predicted dipole moments of individual contributing conformers and originally required a number of geometrical approximations. However, many of these were subsequently justified when recalculations based on the optimized geometry of piperidine[24] produced negligible change in the results.

Allinger and coworkers[25] measured the dipole moments of *N*-alkylpiperazines and determined an NH-equatorial preference of ca. 0.4 kcal/mol. These results provided experimental support for semiempirical calculations by the same group;[15] van der Waals' considerations of the approach of a helium atom to ammonia, considered by the authors at the time to be a valid model for H vs. lone-pair interactions in piperidine, demonstrated that (at distances below 3 Å) approach toward a hydrogen atom is less favorable than approach to the lone pair, and quantum mechanical calculations[15] were in excellent agreement. Thus, in the sense of an equatorial preference, hydrogen is "bigger" than a lone pair and Allinger concluded that there was no basis for expecting any anomalous behavior of the lone pair on nitrogen.

By the end of 1965 the situation appeared to have been clarified, and NH-equatorial preference for piperidine was widely accepted.

Piperidine: The NH-Axial Counterattack and the Confusion of 1967–1968

However, a persuasive protagonist for NH-axial was about to enter the field. In 1966/67 Lambert[26] first applied nuclear magnetic resonance spectroscopy to the problem. As the inversion about nitrogen in piperidine is fast on the NMR time scale at all the temperatures so far investigated, an indirect technique had to be used. The significance of the results obtained by this technique, that of geminal chemical shift differences, has been the most disputed of all those applied to the analysis of the NH-conformational equilibrium. The results they yielded in favor of an NH-axial preference were largely responsible for the creation of the piperidine "controversy".

The chemical shift difference (δ_{ae}) between the axial and equatorial protons of cyclohexane is 0.4–0.5 ppm, with the axial protons at higher field.[27] Considerably larger values of δ_{ae} were observed for methylene groups adjacent to tertiary ring nitrogen atoms.[28] It was suggested[28] that electronic interaction between axial CH groups and a vicinal axial lone pair leads to differential shielding of the former; i.e., an enhanced value of δ_{ae} should occur only for compounds with an equatorial substituent on nitrogen. The observation that $\delta_{ae}(\alpha)$ is 0.44 ppm for piperidine but 0.94 ppm for *N*-methylpiperidine led Lambert and coworkers[26] to conclude that the NH group is predominantly axial and the NCH_3 group equatorial. Significantly, protonation of both piperidine and *N*-methylpiperidine in methanol gives values of $\delta_{ae}(\alpha)$ (0.40, 0.44 ppm, respectively) close to that of cyclohexane. (All values of $\delta_{ae}(\alpha)$ in this Account refer to

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(11) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962). For recent theoretical treatment, see ref 8.

(12) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

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(14) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1965, p 180.

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(17) M. Davis and O. Hassel, *Acta Chem. Scand.*, **17**, 1181 (1963).

(18) R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc. B*, 122 (1970).

(19) H. Booth and J. H. Little, *J. Chem. Soc., Perkin Trans. 2*, 1846 (1972). See also E. L. Eliel and F. W. Vierhapper, *J. Am. Chem. Soc.*, **96**, 2257 (1974); P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *J. Chem. Soc. Chem. Commun.*, 825 (1974).

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(22) 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).

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(25) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *J. Am. Chem. Soc.*, **87**, 1232 (1965).

(26) J. B. Lambert and R. G. Keske, *J. Am. Chem. Soc.*, **88**, 620 (1966); J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *ibid.*, **89**, 3761 (1967).

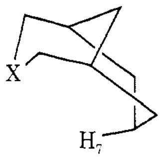
(27) F. R. Jensen, D. S. Noyce, C. H. Sederholm, and A. J. Berlin, *J. Am. Chem. Soc.*, **82**, 1256 (1960); *ibid.*, **84**, 386 (1962); N. Muller and W. C. Tosche, *J. Chem. Phys.*, **37**, 1167 (1962).

(28) H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964).

methanol.)

However, concurrent studies by Booth[29] demonstrated the complexities involved in the shielding of axial protons. Averaged chemical shifts for 2-methylene protons of 1-alkylpiperidines occurred at progressively lower fields in the series Me, Et, *i*-Pr and *t*-Bu, whereas the proportion of lone-pair axial, and hence the incidence of any differential shielding of the axial CH, should increase along this series. The orientation of the *N*-alkyl group is therefore an additional influence on δ_{ae} in a manner similar to the *C*-alkyl analogs.[30]

Lambert's conclusion[26] was criticized by Robinson,[31] who argued that it was not permissible to extrapolate results from the *N*-alkyl series to the NH compound. Robinson cited[31] contradictory observations in the 3-azabicyclo[3.3.1]nonane systems (**4**, X = NH). Endo-H_7 shielding was comparable with that for the thia- (**4**, X = S) and oxa- (**4**, X = O) analogs (and not observed in the quaternized compound) and clearly required an appreciable proportion of axial lone pair. Further, conformational change induced in **4** by addition of methanol gave no evidence for the dependence of δ_{ae} on conformation.



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Lambert's reply[32] contended that lone-pair shielding outweighs the *N*-alkyl effect. The difference ($\Delta\delta_{ae}$) between the values of $\delta_{ae}(\alpha)$ in the unprotonated and the protonated compound was proposed as a control to distinguish lone-pair and *N*-alkyl effects, as protonation removes the lone pair but has no effect on the presence of an *N*-alkyl group. For piperidine, $\Delta\delta_{ae}(\alpha)$ = 0.04 ppm was considered to show that the lone pair is predominantly equatorial (NH axial) and has little influence on δ_{ae} in the unprotonated form, whereas $\Delta\delta_{ae}(\alpha)$ = 0.50 ppm for *N*-methylpiperidine indicates a predominantly axial lone pair (NCH_3 equatorial). As δ_{ae} must be measured in the same solvent for both the amine base and salt, $\Delta\delta_{ae}$ is so far limited to methanol.

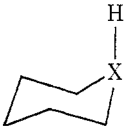
Lambert also investigated[33] δ_{ae} values in methanol for 3,3-dimethylpiperidines in which the 3-axial methyl group should drive the equilibrium toward the NH-equatorial form. For 1,3,3-trimethylpiperidine, which must possess NCH_3-equatorial on account of the methyl–methyl interactions in the NCH_3-axial form, δ_{ae} = 1.11 ppm, and for 3,3-dimethylpiperidine, δ_{ae} = 0.61 ppm. For the protonated species δ_{ae} is near 0.45 ppm for both NCH_3 ($\Delta\delta_{ae}$ = 0.64 ppm) and NH ($\Delta\delta_{ae}$ = 0.18 ppm). The increase in δ_{ae} from 0.44 ppm in piperidine to 0.61 ppm in the 3,3-dimethyl derivative, without a concurrent increase in the protonated form, is evidence for a shift in the equilibrium toward NH equatorial. The NH-axial preference in piperidine was attributed to an attractive NH···CH 1,3-diaxial interaction[33] and operation of the gauche effect,[34–36] maximizing the gauche interactions between the lone-pair and the vicinal C–H bonds. The hydrogen-bonding properties of the solvent methanol could also favor the NH-axial form, since the equatorial lone pair is more available for complexation.

Other workers have recently applied the δ_{ae} criterion to piperazine,[3] concluding that the lone pair favors the equatorial position, while from a very simple conformational treatment of acyclic ethers and amines[4] it was concluded by extrapolation that piperidine favored the lone-pair equatorial form. In each case, however, the studies did not fully consider *N*-alkyl contributions.

The initial NMR work of Lambert converted many to the NH-axial doctrine. Allinger and his coworkers were stimulated to reinvestigate the problem and in 1967 communicated[37] Westheimer–Hendrickson–Wiberg type calculations which, contrary to their earlier[15] calculations, indicated for piperidine an NH-axial conformational preference of 0.6 kcal/mol. Full details have not yet appeared, but the method presumably ignored explicit lone-pair interactions for the authors chose to consider the lone pair simply as part of the nitrogen atom.

Further confusion was engendered by preliminary microwave results which appeared to support the predominance of the NH-axial[38] conformer. On completion of the microwave work the opposite conclusion was reached[39] (see later).

The strength of the NH-axial counterattack may be measured by the conclusions of an authoritative review: in 1967 Riddell[1b] wrote: "It seems clear from the bulk of the reliable experimental evidence, that in simple heterocycles an unhindered hydrogen on the heteroatom prefers the axial conformation". This conclusion has indeed been since substantiated for the compounds **5** with X = P,[40] S^+,[41] Se^+,[41a] and Te^+.[41a]



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Piperidine: Recent Work and How the NH-Equatorial View Finally Prevailed

The "conformational rivalry between the nonbond-

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(29) H. Booth and J. H. Little, *Tetrahedron*, **23**, 291 (1967).

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(36) J. A. Mosbo and J. G. Verkade, *J. Am. Chem. Soc.*, **95**, 4665 (1973).

(37) N. L. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Lett.*, 3729 (1967).

(38) C. C. Costain, P. J. Buckley, and J. E. Parkin, personal communication to F. G. Riddell, quoted in ref 1b.

(39) P. J. Buckley, C. C. Costain, and J. E. Parkin, *Chem. Commun.*, 668 (1968). Although the full details of this work have still not appeared, we understand from J. E. Parkin that this in no way is due to any subsequent doubt as to the validity of the conclusion reported.

(40) J. B. Lambert, W. L. Oliver, Jr., and G. F. Jackson, III, *Tetrahedron Lett.*, 2027 (1969); J. B. Lambert and W. L. Oliver, Jr., *Tetrahedron*, **27**, 4245 (1971).

(41) (a) J. B. Lambert, R. G. Keske, and D. K. Weary, *J. Am. Chem. Soc.*, **89**, 5921 (1967); (b) J. B. Lambert, D. S. Bailey, and C. E. Mixan, *J. Org. Chem.*, **37**, 377 (1972).

ing electron pair and the proton on nitrogen" (phraseology from ref 26) around 1967/68 prompted a great deal of novel work using other physical techniques. The experimental concepts are of variable reliability, but apart from other NMR work[7] the basis of which has since been discounted,[42] results are in unanimous agreement with an NH-equatorial preference for piperidine at least for the vapor phase and nonpolar solvents. The sole uncertainty now remaining is the δ_{ae} evidence of Lambert which suggests NH axial for methanol solution and which is further discussed below.

In 1967, semiempirical quantitative analysis by Masamune and Takasugi[43] of the Bohlmann infrared bands of perhydroquinolines and -acridines in carbon tetrachloride gave the NH-equatorial conformer preference by 0.5 kcal/mol. Masamune deduced[44] a qualitative NH-equatorial preference from the hydrogen bonding of perhydroacridines with butanol. An independent study[45] of intramolecular hydrogen bonding in 2-hydroxyalkylpiperidines also concludes that the NH-equatorial conformation of piperidine predominates.

Quantitative intensity measurements on the ν C–D infrared absorptions of 2,6-dideuteriopiperidines indicated a preference of 0.5 kcal/mol for the NH-equatorial conformer.[46] 1-Isopropylpiperidine was used as the model for an axial lone pair to give the ratio of extinction coefficients for Bohlmann-type and normal C–D absorptions. The assumption that 1-isopropylpiperidine is essentially completely *N*-alkyl equatorial may be corrected using more accurate data for the conformational equilibrium,[24] but the preference indicated[46] for piperidine changes little, to 0.3 kcal/mol in favor of NH equatorial.

The NH-equatorial preference indicated by these experiments was conclusively confirmed by detailed rotational and vibrational analyses which followed.[39,47–49] The infrared spectra (vapor phase) of piperidine, morpholine, and derivatives in the first NH-overtone region 6000–7000 cm^{-1} show two resolved bands.[47,48] Qualitative and quantitative comparison of their contours with those predicted by theory enabled these to be assigned to the NH-equatorial and NH-axial conformers. The temperature dependence of the intensity ratios of these bands shows piperidine to possess an NH-equatorial preference of 0.5 kcal/mol. In CCl_4 solution, two bands are well resolved in this region, and can be assigned by reference to the vapor phase: a similar temperature variability study gave 0.6 kcal/mol preference for NH equatorial in both piperidine and morpholine. Similar treatment of the NH fundamental stretching frequencies, with supporting arguments for the band assignments, indicated 0.4 kcal/mol preference for NH equatorial in CCl_4 solution.[50] Analysis of the microwave spectrum of piperidine gave the preference for NH equatorial as 0.2 kcal/mol.[39] A more recent molecular vibrational analysis[49] of piperidine in the vapor state demonstrated that it exists predominately in the NH-equatorial conformation and from calorimetric data an energy difference of ca. 0.6 kcal/mol favoring the NH-equatorial conformer was found. Crystalline piperidine was shown to exist exclusively in the NH-equatorial form.[49]

From NMR stereochemical examination of deuteronated piperidinium salts formed by dissolving piperidines in CF_3CO_2D Booth[51] deduced a preference for the NH-equatorial conformer of 0.1 kcal/mol: the error was unstated, but may be of a similar magnitude. The views were expressed[2,52] that these conclusions were valid only if (a) deuteronation is fast with respect to conformational inversion, (b) exchange of H^+ (or D^+) during the mixing period was unimportant, and (c) exchange of H^+ (or D^+) in piperidinium salts dissolved in CF_3CO_2D was very slow. This author has recently described further NMR data establishing these requirements.[19] From an examination of *cis*-decahydroquinoline at 100 and 220 MHz, Booth[53] concluded that the hindered "inside" position was preferentially occupied by the lone pair.

Yonezawa et al.[7] examined the isotropic NMR shifts of piperidine derivatives in the presence of the shift reagents cobalt(II) and nickel(II) acetylacetonates and concluded that the NH-axial conformer predominated by ca. 87%. An implicit assumption in their calculations was that axial and equatorial lone pairs were equally complexed by the shift reagent. An alternative treatment[42] taking into consideration potentially unequal complexation has been carried out and indicates that, subject to uncertainty in the geometry of the piperidine-shift-reagent complexes, the ratio of the equilibrium constants for complexation of equatorial and axial lone pairs, K_e/K_a, is ca. 20 for *N*-ethyl- and ca. 11 for *N*-methylpiperidines. To assume in conformational arguments for piperidine itself that $K_e = K_a$ without supporting evidence is clearly inadmissible. The results of the second treatment suggest that, for 60% NH equatorial in piperidine, K_e/K_a is of the order of 2. It should be reiterated that application of shift reagents to conformational equilibria is extremely tenuous unless specific consideration is given to preferential complexation of one of the equilibrating species.

van Binst and Tourwe[54] find from ^{13}C–H coupling constants that *trans*-decahydroquinoline exists mainly in the NH-equatorial form (in $CHCl_3$).

To summarize, the following afford quantitative, experimental evidence for the preponderance of the NH-equatorial form in the piperidine conformational equilibrium: infrared intensities of NH overtone bands (ΔH: +0.5 kcal/mol for vapor, +0.6 kcal/mol for CCl_4 solution)[48] dipole moment of 4-(*p*-chlorophenyl)piperidine (ΔG: +0.4 kcal/mol for C_6H_{12} solution),[2] calorimetric data (0.6 kcal/mol),[49] microwave analysis (+0.2 kcal/mol in vapor),[39] infrared intensities of C–D Bohlmann absorptions (+0.3 kcal/mol in CCl_4 solution),[46] and deuteronation behavior of pi-

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(42) I. D. Blackburne, A. R. Katritzky, and Y. Takeuchi, *J. Am. Chem. Soc.*, **96**, 682 (1974).

(43) T. Masamune and M. Takasugi, *Chem. Commun.*, 625 (1967).

(44) T. Masamune, *Chem. Commun.*, 244 (1968).

(45) L. P. Kuhn, R. A. Wires, W. Ruoff, and H. Kwart, *J. Am. Chem. Soc.*, **91**, 4790 (1969).

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

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peridines (+0.1 kcal/mol).[19,51] The dipole moment studies of 1-methylpiperazine (ΔG: +0.4 kcal/mol in C_6H_6 solution)[25] and infrared Bohlmann band intensities of perhydroquinolines and -acridines (+0.5 kcal/mol in CCl_4 solution)[43] constitute additional evidence from analogous systems. This quantitative work is supported by the qualitative conclusion of an NH-equatorial preference from hydrogen bonding in 2-hydroxyalkylpiperidines[45] and perhydroacridines and from NMR examination of *cis*-[53] and *trans*-decahydroquinoline.[54]

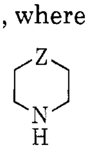
The reliable evidence thus clearly points to an NH-equatorial preference of ca. 0.2-0.5 kcal/mol, and current experimental opposition to this concensus can be claimed to rest solely on the δ_{ae} results, in itself a controversial technique. Some investigators feel δ_{ae} is a reliable indicator of lone-pair orientation,[3,4,33] but other workers have (i) established that the situation is complicated by an *N*-alkyl effect,[29,31,55,56] (ii) found irregularities in δ_{ae} for the normal alkyl group order (e.g., Me $\approx$ *i* -Pr < Et < *t*-Bu),[57] and (iii) believe no simple correlation exists between this parameter and lone-pair orientation.[55,58] The most likely conclusion is perhaps that, whereas δ_{ae} provides a qualitative indication of the orientation of lone pairs, it is as yet not a quantitative criterion for the conformational equilibrium of piperidine. Alternatively, if the δ_{ae} argument is accepted, it would indicate a considerable dependence of the NH equilibrium on phase: the δ_{ae} data derived from polar solvents while the other evidence cited was for solutions in nonpolar solvents or the gas phase.

$J_{ae}(\alpha)$, the coupling constant between α-axial and α-equatorial protons, has not previously been used as a criterion for the conformation of piperidine, and the dangers in using $J_{ae}(\alpha)$ have been emphasized;[55] however, variations in $J_{ae}(\alpha)$ are suggestive (see conclusion of this article). Two further papers do not provide evidence in either direction. Yousif and Roberts[59] from a variable temperature ^{19}F NMR study of the NH inversion, in acetone, of 4,4-difluoropiperidine concluded that the "free energy difference between the forms with NH hydrogen axial and equatorial appears to be 0.42 kcal/mol with uncertain sign". Ansell et al.[60] found NH-axial preference in 1,4-dimethylhexahydro-*s*-tetrazine, but this is no model for the piperidine case because of additional interactions (see later). It is unfortunate that NH–CH coupling constants have never been measured for piperidine derivatives,[61,62] since the *J* value would give direct evidence of the *N*-proton orientation.

Piperidine Derivatives with Additional Ring Heteroatoms

Conformational equilibria in six-membered cyclic systems are determined by the overall resultant of attractive and repulsive forces within the molecule. The principal interactions influencing conformation are those of the 1,3-diaxial- and gauche-vicinal types, and structural changes affecting these parameters in particular have been shown to exert predominant control over conformational equilibria. The host of examples available include such phenomena as the "anomeric effect" of carbohydrate chemistry. Piperidine analogs with additional ring heteroatoms exhibit such changes, and their conformational behavior may eventually provide the lead to a fuller understanding of the relative N–H and N–lone-pair steric and electronic preferences.

Additional ring heteroatoms follow three types of substitution, **6**, **7** and **8**, and the available evidence on each will be considered for the cases where X = O, NR, and, where possible, S.



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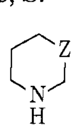

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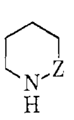

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(i) Heteroatoms in the 4 Position. Morpholine (**6**, Z = O) has been examined by the Kerr constant[63] and the NH-infrared overtone techniques,[48] and in each case the $\Delta G°$ value obtained clearly followed the piperidine conformational equilibrium. Since, as described, the Kerr constant interpretation for piperidine is contrary to the concensus and the method itself is open to criticism, it is likely that the morpholine measurement suffers comparable errors. On the ir intensity criterion morpholine (**6**, Z = O) exhibits an NH-equatorial preference of $\Delta H° = 0.63$ kcal/mol in the gas phase,[48] and this is borne out by the apparent predominance[64] of lines in the microwave spectrum characteristic of this conformation.

Similar conclusions were reached[25,65] for *N*-alkylpiperazines (**6**, Z = NR) from dipole moment evidence. *N*-Methylpiperazine, for which a large[18] *N*-methyl conformational preference was used (1.7 kcal/mol), indicated the NH-equatorial form favored by 67% in benzene,[25] but the later work[65] on *N-tert*-butylpiperazine did not greatly change this (67% in cyclohexane). Qualitative support is found from the NH-overtone contours in the infrared.[65] Photoelectron spectra of piperazines are consistent with a mixture of NH(eq)/NH(ax) and NH(eq)/NH(eq) conformations.[65a]

The results indicate that the introduction of a heteroatom into the 4 position of piperidine has no appreciable influence on the conformational equilibrium. The introduced groups (O, NR) are remote from the NH region and nonbonded, and electronic interactions are expected to be negligible. A potential source of disturbance lies in perturbation of the ring geometry by the additional heteroatom which may transmit steric interactions to the NH region. Significant perturbation, however, was not found in calculations[24] of optimized ring geometries for oxans and azans which supports the observed facts, although

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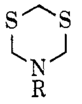
this may not apply to the perturbed 1,4-thiazine for which conformational data are not yet available.

(ii) Heteroatoms in the 3 Position. In spite of a considerable amount of research into hexahydropyrimidine systems and a certain amount into tetrahydro-1,3-oxazines, only limited data are available on the conformations of the NH compounds. Booth and Lemieux[61] examined the NH–CH coupling constants for **7** (Z = O and NMe) at low temperatures and found NH-axial to be the dominant, or sole, conformation. Recent dipole moment and infrared data support the NH-axial assignment.[65] 1-*tert*-Butylhexahydropyrimidine was determined from dipole moments to exist only as 34% in the NH-equatorial conformer; the proportion for the oxazine (**7,** Z = O) was 38% and for the thiazine (**7,** Z = S) was 22%. Some doubts surround the latter two values largely because of the uncertainty of the partial group moment for O and S in these compounds, but in each case NH-overtone infrared contours provide good qualitative support for the predominance of the NH-axial form.[65]

The replacement of the 3-methylene group of piperidine by a heteroatom should affect appreciably the NH-conformational equilibrium. Conformational energies for ring inversion and substituent preference of 1,3-diheterane systems are well known to show substantial deviations from analogous cyclohexane values (see, for example, ref 66). This behavior is clearly attributable to interactions with the heteroatom. The origins of such behavior, which includes the anomeric effect[67] and the generalized anomeric effect[68] (formerly[66] sometimes described as the "rabbit-ear" effect), are, however, not clear. Initially dipole–dipole repulsions were invoked to account for preferred conformations,[1b] and the "rabbit-ear" effect (1,3-diaxial lone pair–lone pair repulsion) provided a visually appealing explanation of the preference for a hexahydropyrimidine-NR group axial. More recently[34,35] attempts to place these phenomena on a theoretical basis suggested that they are encompassed by a more general "gauche" effect whereby interactions of bonded electrons override those of nonbonded electrons and are maximal for a "gauche" arrangement. In terms of this concept the NH-axial preference of 1,3-oxazines and hexahydropyrimidines (**7**) is explained as stabilization by attractive interaction between the polar NH and C_2–Z bonds (*gauche*), these interactions dominating lone-pair–lone-pair and lone-pair–NH effects. Which effect, however, predominates in the case of **9** where even R = *tert*-butyl displays an axial preference[69] awaits development of the "gauche" theory; certainly all act in the desired direction. The dipole moment results for **7,** Z = S, which differ somewhat from Z = O or NR, undoubtedly reflect differences in the ring geometry manifesting in changes in these interactions.



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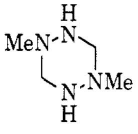
(iii) Heteroatoms in the 2 Position. Quantitative data on **8** are currently not available. Dipole moment measurements are complicated by an uncertain N–O bond moment and, since insufficient data are available on heteroatom–heteroatom force constants, uncertain geometry. However, infrared overtone measurements[65,70] suggest that in tetrahydro-1,2-oxazine the NH-equatorial conformer predominates, attributable perhaps to maximal NH–O lone-pair overlap in this arrangement. The solid-state conformation of 1,4-dimethylhexahydro-*s*-tetrazine (**10**)[60] suggests an interesting interaction of heteroatoms in the 2 and 3 positions. X-Ray data reveal the methyl groups equatorial and both NH groups axial, and this would indicate the more powerful influence of the 3-heteroatom. However the authors did suggest that some hydrogen bonding could be involved.



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General Conclusions

We thus conclude that, for the gas phase and for the noninteracting solvents CCl_4 and cyclohexane, the piperidine equilibrium is displaced in favor of NH equatorial by ca. 0.4 kcal/mol. The individual methods are of variable reliability, and in several reasonable error limits would embrace a ΔG value of zero; however, for independent methods the likelihood of error varies with the product of the error limits. A thorough discussion of errors is beyond the scope of this review, but taken overall an NH equatorial preponderance of 0.4 ± 0.2 kcal/mol must be highly likely.

However the position for hydrogen-bonding solvents such as methanol is less clear, and the δ_{ae} criterion does provide some evidence for an NH-axial preference under these conditions. Indeed this is supported by variations found in $J_{ae}(\alpha)$, the coupling constant between α-equatorial and α-axial protons. $J_{ae}(\alpha)$ in general decreases with greater contribution from adjacent lone-pair axial conformations; conformational variations of ca. 2 to 4 Hz are known in a single compound. Piperidine has $J_{ae}(\alpha)$ values of 10.2 (cyclopropane), 11.9 (methanol), and 12.3 Hz (methylene chloride) while the *N*-methyl analog shows variations of only 11.2, 11.4, and 11.2 Hz for the same solvents, respectively.[26] Such a variation in conformation could arise from hydrogen bonding or other less specific solute–solvent interactions. We emphasize that further study is needed in this area.

The piperidine equilibrium is relatively unaffected by a second heteroatom at the 4 position, but a heteroatom at the 3 position swings it to favor the NH-axial form, while an oxygen atom at the 2 position probably favors again the NH-equatorial situation. These swings induced by a second heteroatom can be qualitatively understood, but in reality the reasons

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for the conformational preference of piperidine with NH equatorial are unknown, and various explanations advanced[2,33,37] in favor of either conformer remain, as yet, unproven speculation.

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(71) For Lambert's present position, see J. B. Lambert and S. I. Featherman, *Chem. Rev.*, **75**, 611 (1975).

Carbon-13 Nuclear Magnetic Resonance and the Conformations of Biological Molecules[1]

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Carbon-13 is not an abundant isotope; it represents only 1.11% of the carbon in natural abundance. Its magnetic moment is smaller than that of ^{1}H; in a magnetic field of 23 kG it resonates at 25 MHz, compared to 100 MHz for ^{1}H. For equal numbers of nuclei, its intrinsic sensitivity is only 1.59% of that of ^{1}H. Thus, at natural abundance it is roughly 10^4 times harder to detect than ^{1}H. Nevertheless, with the development of Fourier transform techniques[2] and large sample tubes it has become possible to detect ^{13}C routinely in compounds of carbon in natural abundance at concentrations as low as 10^{-2} *M*.

Due to the larger number of surrounding electrons, the chemical shift range of ^{13}C is roughly 200 ppm, compared to 10 ppm for protons.[3-9] Couplings to ^{1}H make ^{13}C spectra very complex, but they can be removed by broad-band irradiation at the ^{1}H resonance frequency (noise decoupling). The decoupling operation gives an increase in signal-to-noise ratio by collapse of multiplets, as well as by the ^{1}H–^{13}C cross-relaxation mechanism known as the nuclear Overhauser effect.[10] Carbon-13 resonances are comparable in width to those of ^{1}H in the same compound—they appear narrower due to the wider chemical shift range and due to the simplification gained by decoupling all protons. As molecular weights increase, the rate of molecular reorientation decreases and the ^{13}C resonances become broader. If a high degree of local motion is present, the broadening will not be as great as expected from consideration of the molecular size alone; this has been found to occur for a wide variety of polymers.

Carbon-13 nuclear magnetic resonance has become almost an everyday tool in the hands of the practicing chemist. Large amounts of data on an enormous variety of compounds are available,[3-9] and can be effectively used as a means of identification or location of substituents.

Reliable information on conformation has been somewhat slower in coming, but chemical shifts are now used routinely to determine anomers, epimers, and other geometric isomers. Rotational isomers about single bonds are presently being investigated by means of ^{13}C spin–spin coupling to ^{1}H,[11] ^{13}C,[12] and ^{31}P.[13,14] Such information is also apparently present in the ^{13}C chemical shifts of carbohy-

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Harold J. Jennings and Roxanne Deslauriers are Associate Research Officer and Assistant Research Officer, respectively, in the NRC Division of Biological Sciences. Dr. Jennings was born in London. He received the Ph.D. degree from Queen's University, Kingston, Ontario, and was NATO postdoctoral fellow at Bristol University in 1964. At NRC, he studies structure-specificity relationships of bacterial antigens. Dr. Deslauriers is native of Canada, and received her Ph.D. from the University of Ottawa.

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