

Conformational Analysis of Saturated Heterocycles. LIV.¹ The Conformation of Piperidine as Determined by Paramagnetic Shifts in the Nmr

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Abstract: Cobalt(II) acetylacetonate induced shifts in the phenyl proton nuclear magnetic resonance of N-substituted 4-phenylpiperidines disclose differential complexation of equatorially and axially oriented N lone pairs with the shift reagent. Previous applications of this technique to the NH conformational equilibrium of piperidine are invalid, and our previous conclusion of the NH-equatorial preference for piperidine stands. We caution that shift-reagent applications to equilibria must specifically consider differential complexing of equilibrating species.

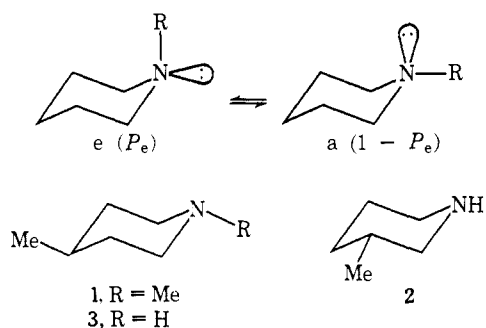
We claim² that all reliable evidence indicates the equatorial NH conformation of piperidine to be preferred by *ca.* 0.4 kcal mol⁻¹, but some original proponents of the NH-axial preference continue to waver³ or dissent.⁴ In particular, recent papers⁵⁻⁷ purport to demonstrate the NH-axial preference of piperidines using the paramagnetic shift reagents cobalt(II) and nickel(II) acetylacetonates. We contend that the interpretation⁵⁻⁷ of these experimental data needs modification and we wish to report our own theoretical and experimental work on this topic.

The earlier work⁵ on paramagnetic shifts in piperidines was based on eq 1 where $(\Delta\nu_{ax})_{obsd}$ is the observed

$$\frac{(\Delta\nu_{ax})_{obsd}}{(\Delta\nu_{eq})_{obsd}} = \frac{P_e(\Delta\nu_{ax})_e + (1 - P_e)(\Delta\nu_{ax})_a}{P_e(\Delta\nu_{eq})_e + (1 - P_e)(\Delta\nu_{eq})_a} \quad (1)$$

shift of an α -axial proton, $(\Delta\nu_{ax})_e$ and $(\Delta\nu_{ax})_a$ are the individual shifts of α -axial protons in the e and a conformers (Scheme I; "a" and "e" refer throughout to

Scheme I



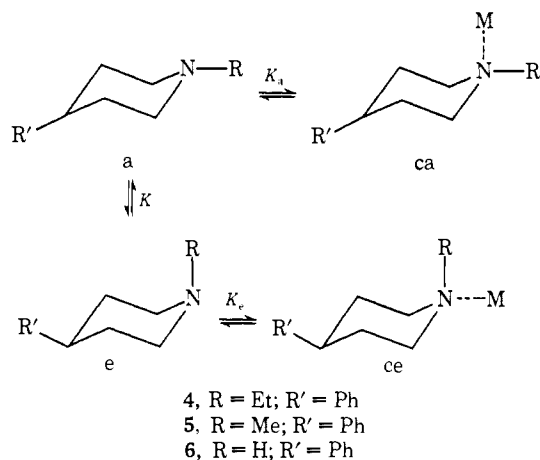
the lone pair; thus the "a" conformer of 1-methylpiperidine denotes the conformer with the equatorial

methyl group (and the axial lone pair), P_e and $1 - P_e$ are the mole proportions of those conformers, etc. Using data from 1,4-dimethylpiperidine (1) for the left-hand side, eq 1 was solved⁵ for 3- (2) and 4-methylpiperidine (3) giving P_e 0.87 and 0.88, respectively, a preference for the NH-axial conformer of *ca.* 1.2 kcal mol⁻¹.

Equation 1 assumes that an observed shift of a proton is proportional to a weighted average of the paramagnetic shifts of that proton in the equatorial and axial complexes. However, for such a weighting to reflect the free base, conformational equilibrium required the unlikely assumption that the a and e conformers *complex equally* with the added paramagnetic reagent.

We have examined the corresponding 4-phenyl derivatives. As ring inversion is absent, the equilibrium between free base forms and complexed conformers is as illustrated in Scheme II. The species with lone

Scheme II



pair equatorial and lone pair axial are denoted by e and a, respectively, and the corresponding complexes by ce and ca. The mole proportions of the compounds of the equilibrium are denoted by P_e , P_a , P_{ce} , and P_{ca} , respectively. Initially, before the addition of the shift reagent, $M(AA)_2$, let P_e equal x and P_a equal $1 - x$. On addition of $M(AA)_2$, denote P_e by y , and from the equilibrium constants P_a , P_{ce} , and P_{ca} follow as $y(1 - x)/x$, $y[M]K_e$, and $[y(1 - x)/x][M]K_a$. (The equi-

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Table I. Typical Values of Geometric Factors for Phenyl Protons

Complex	Proton	Geometric factors				
		Case A N-Co 1.9 Å, α 49°	Case B N-Co 2.5 Å, α 49°	Case C N-Co 2.2 Å, α 59°	Case D N-Co 1.9 Å, α 69°	Case E N-Co 2.5 Å, α 69°
Axial	Ortho	-0.00761690	-0.00638446	-0.01071738	-0.00998765	-0.01522616
	Meta	-0.00228653	-0.00218370	-0.00269774	-0.00216297	-0.00284618
	Para	-0.00168947	-0.00147991	-0.00205807	-0.00208403	-0.00233815
Equatorial	Ortho	0.00593266	0.00470899	0.00508663	0.00525564	0.00426464
	Meta	0.00253612	0.00211887	0.00224124	0.00224374	0.00191428
	Para	0.00198806	0.00167049	0.00175515	0.00173764	0.00149921

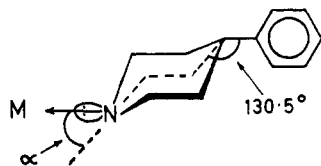


Figure 1. Geometry of the 4-phenylpiperidine complexes.

librium constants K_e and K_a for complexation of equatorial and axial lone pairs respectively are defined as $K_e = P_{ce}/[M]P_e$ and $K_a = P_{ca}/[M]P_a$, where $[M]$ refers to the concentration of shift reagent $M(AA)_2$. The initial chemical shift of an observed proton is given by eq 2 where ν_e and ν_a represent the chemical shifts of

$$\nu_{init} = x\nu_e + (1 - x)\nu_a \quad (2)$$

that proton in the respective conformers. At equilibrium after addition of $M(AA)_2$ the chemical shift of the proton is described by eq 3 where ν_{ce} and ν_{ca}

$$\nu_{equil} = y\nu_e + [y(1 - x)/x]\nu_a + y[M]K_e\nu_{ce} + [y(1 - x)/x][M]K_a\nu_{ca} \quad (3)$$

have meanings similar to the above. Thus, the shift induced by the added $M(AA)_2$, $\Delta\nu$, is given by eq 4.

$$\Delta\nu = \nu_{equil} - \nu_{init} = (y - x)\nu_e + (1 - x)(y/x - 1)\nu_a + y[M]K_e\nu_{ce} + [y(1 - x)/x][M]K_a\nu_{ca} \quad (4)$$

Added $M(AA)_2$ did not exceed 5 mol %; hence x and y may be equated and $\Delta\nu$ simplifies to eq 5. By observa-

$$\Delta\nu = x[M]K_e\nu_{ce} + (1 - x)[M]K_a\nu_{ca} \quad (5)$$

tion of the ratio of induced shifts of any two of the ortho, meta, and para protons of the phenyl ring, equations of the type in (6) may be set up.

$$\frac{\Delta\nu^o}{\Delta\nu^m} = \frac{xK_e\nu_{ce}^o + (1 - x)K_a\nu_{ca}^o}{xK_e\nu_{ce}^m + (1 - x)K_a\nu_{ca}^m} \quad (6)$$

Since $Ni(AA)_2$ has a negligible effect on the phenyl protons, the contact contribution to the isotropic shift is zero. Hence the $Co(AA)_2$ -induced shifts in this instance are pseudocontact in origin.⁸⁻¹¹ A pseudocontact shift is described by the relationship⁸ $\Delta\nu = kg$ where k is a function of g tensor anisotropy (for given operating conditions and metal complex) and g is the geometric factor, $(3 \cos^2 \theta - 1)/r^3$, of the proton under

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consideration. The resonance of a proton in the $Co(AA)_2$ -piperidine complex is therefore given by eq 7, and eq 6 follows as eq 8, where g_{ce}^o is the geometric

$$\nu_{complex} = kg_{complex} + \nu_{free\ ligand} \quad (7)$$

$$\left(\frac{\Delta\nu^o}{\Delta\nu^m}\right)_{obsd} = \frac{xK_e(kg_{ce}^o + \nu_e^o) + (1 - x)K_a(kg_{ca}^o + \nu_a^o)}{xK_e(kg_{ce}^m + \nu_e^m) + (1 - x)K_a(kg_{ca}^m + \nu_a^m)} \quad (8)$$

factor of the ortho protons in ce, etc.

Geometric factors of the phenyl protons of 4-phenylpiperidine were calculated using the energy-minimized geometry of piperidine¹² and assuming the lone pair directed at an angle of from 49 to 69° to the C_1-N-C_6 plane (α) and the N-Co bond length 1.9 to 2.5 Å.⁵ The phenyl ring adopts¹³ the "equatorial parallel" conformation shown in Figure 1 (*cf.* also work on ethylbenzene^{14,15}). The geometric factors used for the ortho and meta protons were thus averages for the two respective positions, "up" and "down," and typical values are given in Table I. The sign of the geometric factors determines the direction of induced shift, to high or low field.⁹ Prediction of the shift for a particular sign of the geometric factor requires knowledge of the g tensors parallel and perpendicular to the ligand field axis of the complex, and these are not known. However, from Table I it can be seen that the individual equatorial and axial complexes of the piperidines under investigation should exhibit different directions of induced shift and that the resultant shift depends on the relative amounts of the complexed forms, *i.e.*, on the magnitudes of K_e and K_a .

From eq 8 pairs of simultaneous equations may be set up for $(\Delta\nu^o/\Delta\nu^m)_{obsd}$ and $(\Delta\nu^m/\Delta\nu^p)_{obsd}$ in which k , k_e , and K_a , and x are variable factors. These may be solved uniquely for k and, for a given value of x , for K_e/K_a using the data in Table II. See paragraph at

Table II. Ratios of Induced Shifts of the Phenyl Protons

Compd	Ratios of induced shifts		
	Ortho/meta	Meta/para	Ortho/para
4	2.27	2.44	5.54
5	2.08	1.91	3.95
6	2.68	1	2.68

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Table III. Results Obtained from Eq 8

Compd	Geometric factors (see Table I)	k	K_e/K_a for $x =$					
			0.6	0.4	0.25	0.2	0.15	0.04
N-Et (4)	A	-12333	1.2	2.7		7.3	10	43
	B	-15301	1.1	2.5		6.6	9.0	40
	C	-9384	2.5	5.5		15	20	89
	D	-10335	2.7	6.0		16	22	96
	E	-8563	5.2	12		31	44	186
N-Me (5)	A	-13493	1.2	2.8	5.0	7.4		44
	B	-15442	1.1	2.5	5.0	6.6		40
	C	-10621	2.5	5.7	11	15		90
	D	-12952	2.7	6.2	12	16		98
	E	-9928	5.3	12	24	32		191
N-H (6)	A	-10457	0.73	1.6		4.4		26
	B	-15216	1.1	2.4		6.3		28
	C	-5996	0.88	2.0		5.3		32
	D	-3263	0.1	0.23		0.62		3.7
	E	-3124	0.82	1.8		4.9		29

end of paper regarding supplementary material. Table III records values of k and also values of K_e/K_a corresponding to a range of values of x and to a range of geometric factors.

For the *N*-ethyl (4) and *N*-methyl (5) compounds, we believe that $x = 0.15$ and 0.25 , respectively;¹² some workers¹⁶ favor rather lower values of x , but for these compounds the assumption $K_e = K_a$ used in the previous treatment⁵ is clearly erroneous. Our results demonstrate that $K_e = K_a$ would require an *axial preference* of the *N*-alkyl groups.

In this situation, the fact that placing $K_e = K_a$ would likewise indicate an axial preference for the NH group in piperidine itself is clearly inadmissible as evidence for the NH orientation.

The most probable geometric factors (case C) and values of x of 0.15, 0.25, and 0.40¹² for NEt, NMe, and NH give values of K_e/K_a of 20, 11, and 2, respectively. Such values of K_e/K_a demonstrate the greater influence of steric crowding on axial approach by the cobalt species. This is consistent with kinetic results on the quaternization rates of *N*-substituted piperidines.¹⁷

While uncertainties in the exact conformation of the phenyl group and in the precise dependence of k on molecular structure preclude determination of the NH-axial/NH-equatorial equilibrium in piperidine using

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the shift reagents, the results are not inconsistent with our previous conclusion² of NH-equatorial preference. A further independent treatment¹⁸ of nmr contact shifts in piperidines recently compared the shifts induced by nickel(II) diethyldithiophosphate with INDO calculated spin densities. The inconsistent conclusion was reached that the NH proton was equatorial in the piperidine but axial in the morpholine adduct.

We emphasize that shift reagents cannot be applied to the study of equilibrating systems unless specific consideration is given to possible differences in the complexing ability between the equilibrating species.¹⁹

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Supplementary Material Available. Data supplementary to this article 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. 20036. Remit check or money order for \$3.00 for photocopy or \$2.00 for microfiche, referring to code number JACS-74-682.

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