THE "A" VALUE FOR THE METHYL GROUP IN 2-METHYLPIPERIDINES

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The difference in free energy between the axial and equatorial conformers of monosubstituted cyclohexanes (A value) has been determined for a wide variety of cyclohexanes[1]. Surprisingly perhaps, the most common heterocycle, piperidine, has received little attention[2]. In connection with our studies on the stereochemical course of reactions of nitrosamino carbanions[3], it has become important to determine the amount of steric strain in the conformer having an axial methyl group in the 2-position of a piperidine ring (i.e., the A value for 2-methylpiperidine). The classical solution to such a problem requires either direct determination of K_{eq} by spectroscopic methods or equilibration of a suitably anchored piperidine derivative. Since the system can be anticipated to be strongly anancomeric, direct measurement of K_{eq} would likely be difficult and the alternative, equilibration, lacks an available chemical method.

We have therefore chosen to determine this A value indirectly using a method of conformational analysis previously employed by Chow, Colon and Tam[4] to determine the magnitude of the 1,3 syn-diaxial methyl-methyl interaction in N-acetyl and N-nitroso 2,6-dimethylpiperidine. For our purpose, we have measured the barrier to rotation about the amide bond in N-acetyl-2-methyl-piperidine, 1, a piperidine in which the methyl group occupies the axial orientation[4,5] exclusively. For comparison, we determined the amide barrier in a model compound lacking only the ground state destabilization caused by the axial methyl group in 1. This model is N-acetyl-4-phenyl-piperidine, 2, which has been deuterated stereospecifically in both α-axial positions[6]. The difference in barriers to rotation in 1 and 2 will represent the difference in steric interactions in the ground states provided that steric interactions in the two transition states are
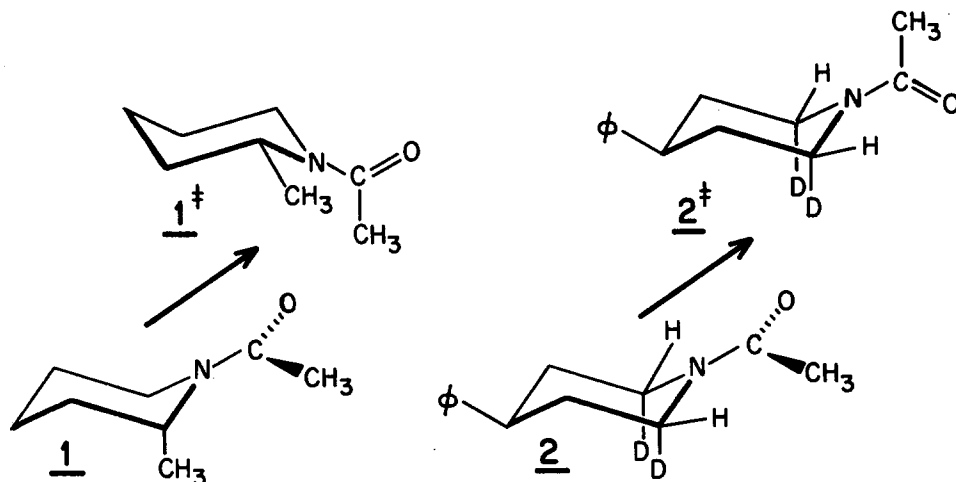
equal (see Scheme 1). Such will be the case if (a) the steric interaction between the CH_3 and NCOCH$_3$ group in the transition state $\underline{1}^{\ddagger}$ is equal to analogous H/NCOCH$_3$ interaction in $\underline{2}^{\ddagger}$ and (b) the steric interactions other than 1,3-diaxial interactions are negligible. In support of (a), a Dreiding model of $\underline{1}^{\ddagger}$ shows that the hydrogens of the equatorial methyl group are more than 2.6 Å from all atoms of the acetyl group. The calculations of <u>Allinger et al.</u>[8] on methyl-cyclohexane support the validity of (b). Thus, $\Delta\Delta G^{\ddagger}$ will represent the energy difference, $\underline{2} - \underline{1}$, i.e., two axial CH_3/H versus two axial H/H interactions. Since the two $\Delta G^{\ddagger}$'s have been determined at temperatures differing by over seventy degrees, they must not be temperature dependent if a comparison is to be valid. The recent accurate work of Neuman and Jonas[9], who found $\Delta S^{\ddagger}$ for the barrier in dimethylacetamide to be 0 ±1 eu, validates this comparison.

The most probable source of error in barrier determinations is the temperature measurement. As the table indicates, we have minimized the error by obtaining a precision in the measured temperature of ±0.5°C. Systematic errors could be equally large, but should tend to cancel out, being similar for $\underline{1}$ and $\underline{2}$. Our conservative estimate of the uncertainty in $\Delta\Delta G^{\ddagger}$ is ±0.3 kcal/mol though it is probably less than ±0.2 kcal/mole. Similar uncertainties in A values exist for data obtained by equilibration studies of anancomeric systems[1].

As the table shows, the difference in barriers to rotation in $\underline{1}$ and $\underline{2}$ is 1.9 kcal/mole. We therefore conclude that the difference between two axial CH_3/H interactions (in $\underline{1}$) and two axial H/H interactions (in $\underline{2}$) is 1.9 kcal/mole. This value represents a 2-methylpiperidine in which the nitrogen is essentially sp^2 hybridized. It seems probable that the "A" value for 2-methyl-

piperidine itself would not be too divergent in view of the observed similarity between the "A"

values found for 2-methylcyclohexanone and 2-methylcyclohexane[10]. It is interesting to note that

the magnitude of this energy difference agrees well with the "A" value for N-methylpiperidine as

determined by Eliel (1.65 kcal/mole), a value much higher than a number of previous estimates[2].

Rotational Barriers (kcal/mole) from T_c Measurements[a]				
Compound	Signal	T_c(°C)	$\Delta\nu$(Hz)	$\Delta G^{\neq}$(kcal/mole)
$\underline{1}$[e,f]	2-CH_3	17.5	12.8	15.0_9
	N-acetyl	6.0	4.5	15.0_3
$\underline{2}$	H_2[e]	84	150	16.9_6
			$\Delta\Delta G^{\neq}$	1.9

[a] Measurement made on an HA-100 instrument using 0.5 M solutions in toluene-d_8.

[b] Temperatures were determined using a copper-constantin thermocouple immersed

   in a non-spinning tube containing toluene-d_8. Using a "methanol" thermometer,

   it was found that the temperature difference between a spinning and non-spinning

   sample was less than 0.3°C.

[c] $\Delta\nu$ values at T_c were obtained by extrapolation of the values observed over a

   range of 50° below T_c.

[d] Calculated from equation,[11] $\Delta G^{\neq} = 4.58 T_c (10.32 + \log \dfrac{T_c}{2.22\Delta\nu})$.

[e] This compound was shown by integration to have equal amounts of the two amide

   rotational isomers (±1%) over the range -50 to 0°C.

[f] The barrier to rotation for $\underline{1}$ has been determined previously on a neat sample.

   H. Paulsen and K. Todt reported $\Delta G^{\neq} = 15.3$ kcal/mole[12].

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[5] Evidence regarding the exclusive axial orientation of the methyl group in 1 is cited in reference 4. We have obtained corroborative evidence from the 100 MHz spectrum of 1 in CCl_4, which shows methine absorption (position 2) for the syn and anti conformers which both have half-band widths of < 16 Hz, indicative of a predominant equatorial orientation. That this predominance is pronounced is indicated by vicinal splittings for the equatorial protons at C-4 of both syn and anti conformers. The sum of J_{ae} and J_{ee} is < 5 Hz.

[6] As anticipated from earlier work[3], treatment of N-nitroso-4-phenylpiperidine with lithium diisopropylamide in THF, followed by addition of D_2O and two repetitions of the procedure, gave a sample in which the signals for the two axial protons[7] were absent. Denitrosation and acetylation gave 2 in which the equatorial protons appeared as two singlets, broadened by vicinal coupling.

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