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NITROGEN INVERSION IN *N*-CHLOROPIPERIDINE

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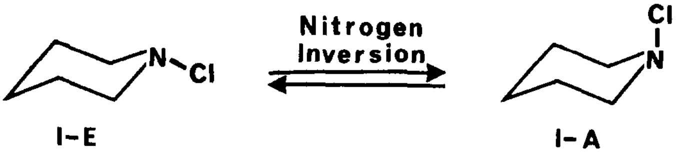
Definite experimental data on the conformational equilibrium and the barrier to nitrogen inversion in *N*-chloropiperidine (**I**) have been lacking, despite much work on the effect of *N*-chloro and other *N*-substituents on the conformational properties of amines.[1-13] On the other hand, the barrier to ring inversion in **I**-3,3,5,5-d_4 has been studied in detail by dynamic ^{1}H NMR and has a $\Delta G^{\ddagger}$ of 13.5 kcal/mol at -1°C.[10] We now show that the ^{13}C NMR spectrum of **I** at low temperatures provides conformational information that is unavailable from the ^{1}H NMR spectrum.

Measurements of the ^{13}C NMR spectrum of **I** from +5 to -120°C (Figure 1) reveal that the C-2,6 and C-3,5 resonances are quite broad at about -32°C, while the C-4 resonance remains sharp.[14] The broad lines sharpen at lower temperatures and new weak resonances for C-2,6 and C-3,5 appear. These new lines are sharp at -98°C, but they are broad at about -70°C and are not visible at -60°C. We ascribe the weak lines to the axial conformer of **I**. The C-4 resonance of this conformer could not be definitely located; it is expected to be close to the resonance of the equatorial conformer since the C-4 resonance broadens very little at intermediate temperatures. From relative peak heights in several different spectra at -98°C, the population of the axial conformer is estimated to be 0.95 ± 0.10% corresponding to $\Delta G°$ of 1.5 ± 0.1 kcal/mol for the equatorial to axial process.

The maximum exchange broadening at half peak height ($\nu_{\frac{1}{2}\text{max.}}$) of the C-3,5 resonance is 25 ± 2 Hz and this occurs at -32°C. Since the $\nu_{\frac{1}{2}\text{max.}}$ for a two site system with very unequal populations is given by $P_B(|\nu_A - \nu_B|)$,[7,15] where P_B



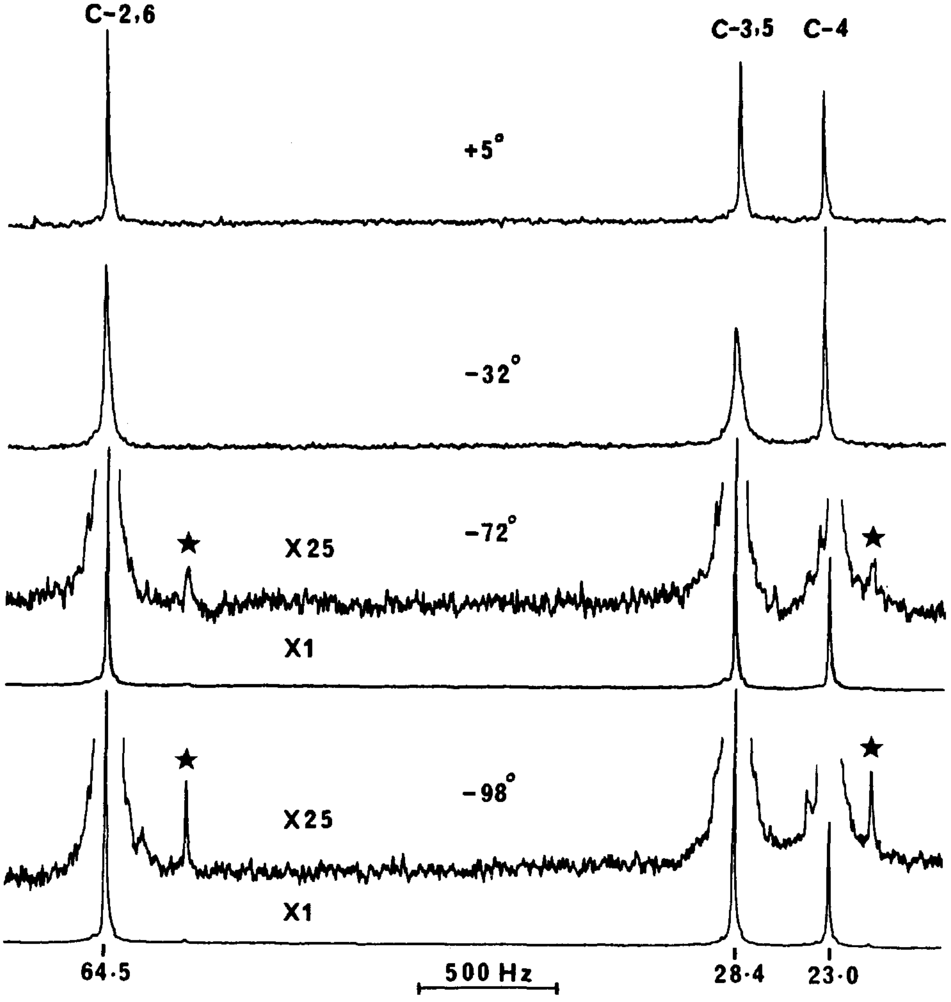


Figure 1. The 63.1 MHz ^{13}C NMR spectra of N-chloropiperidine in $CHFCl_2$ (20% v:v solution), with protons noise decoupled. The peaks marked with stars are assigned to the axial conformer.

is the fractional population of the minor conformer, the axial conformation is calculated to be populated to the extent of 4% at this temperature. A line-shape calculation carried out with $P_{axial} = 0.04$, $k_{equatorial \rightarrow axial} = 150 \pm 20\ s^{-1}$, and with the chemical shift differences for C-2,6 and C-3,5 determined at -98°C, reproduces well the observed spectrum at -32°C. The free-energy of activation ($\Delta G^{\ddagger}$) for nitrogen inversion is then 10.2 ± 0.2 kcal/mol (axial to equatorial) or 11.7 ± 0.2 kcal/mol (equatorial to axial), and $\Delta G°$ is 1.5 ± 0.1 kcal/mol. Thus, $\Delta G°$ is temperature independent and therefore $\Delta S° \simeq 0$ and $\Delta H° \simeq \Delta G°$. From these data the population of the axial conformer is calculated to be 7% at room temperature. The high value for $\Delta G°$ in **I** is consistent with ir,[13] Raman,[13] and ^{1}H NMR data.[10]

There is a substantial difference in the conformational equilibria of *N*-chloropiperidine ($\Delta G°$ = 1.5 kcal/mol) and chlorocyclohexane ($\Delta G°$ = *A* value = 0.5 kcal/mol).[16] Somewhat similar differences occur in the case of *N*-methylpiperidine ($\Delta G°$ = 2.7 kcal/mol)[7,11] and *N*,*N*'-dimethylpiperazine (**II**) ($\Delta G°$ = 2.96 kcal/mol)[12,17] *versus* methylcyclohexane ($\Delta G°$ = 1.7 kcal/mol).[18] The free energy difference between the equatorial and axial conformers of piperidine is only 0.4 kcal/mol[3,8] and cannot account for the highly one-sided conformational equilibria in *N*-substituted piperidines. The axial conformers of *N*-chloro- and *N*-methylpiperidine may be more strained than their cyclohexane analogs because of ring puckering effects.[2]

The value of $\Delta G^{\ddagger}$ for nitrogen inversion in *N*-chloropiperidine is very close to that predicted[9] for **I** (10.1 kcal/mol) on the basis of additivity effects, and to the $\Delta G^{\ddagger}$ for nitrogen inversion in *N*-benzyl *N*-methylchloramine (10.3 kcal/mol).[4]

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