Saturated 5-Membered Ring Conformations

2[†]—¹H NMR Study of Protonated N-Methylpyrrolidines

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The ¹H NMR spectra of the protonated and unprotonated forms of *cis*- and *trans*-*N*-methylhexahydroisoindoline, of 1,3,3,4,4-pentamethylpyrrolidine and of 1,3,3-trimethylpyrrolidine were analyzed. The coupling constants between the NH^{\oplus} and the CH protons α to the nitrogen allowed the study of the conformation of the cyclic systems in pseudorotation.

INTRODUCTION

Several conformational studies on saturated 5membered cyclic systems have already established that these molecules cannot be described in an unequivocal way by such forms as the 'half-chair' type, C_2 , and the 'envelope' type, C_s , due to the low potential barriers.¹ For this reason, an experimental approach involving the conformational geometry is difficult for such derivatives, particularly for pyrrolidine compounds.

Nevertheless, it is not unreasonable to assume that bicyclic derivatives with a cyclohexane ring fused to a pyrrolidine ring, i.e. *cis*- (1c) and *trans*- (1t) *N*-methylhexahydroisoindolines, will give the typical 5-membered ring 'half-chair' structure (Fig. 1). In addition, the easy protonation of nitrogen derivatives² allows the use of the ¹H NMR ³J(H, C, N⁺, H) for the interpretation of the ring conformation. It should be noted that protonation will block the nitrogen inversion and will, in some cases, result in the formation of diastereoisomers.

The ¹H parameters of the CH protons α to nitrogen in the unprotonated and protonated forms of **1c**, **1t**, 1,3,3,4,4-pentamethylpyrrolidine (2) and 1,3,3trimethylpyrrolidine (3) are discussed from the conformational point of view in this paper.



Figure 1. *cis-N*-Methylhexahydroisoindoline (1c) and *trans-N*-methylhexahydroisoindoline (1t).

ANALYSIS OF ¹H NMR SPECTRA AND DISCUSSION

trans-N-Methylhexahydroisoindoline (1t)

In the unprotonated form the pseudoaxial proton, H-A, and the pseudoequatorial proton, H-B, are iden-

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Figure 2. (a) Unprotonated and (b) protonated nitrogen ring of 1t.

tified from their coupling constants with the protons at the ring junction, which corroborate the *trans* fusion [Fig. 2(a)].

δ H-A = 2.40 ppm	${}^{3}J(\text{H-A}, \text{C}, \text{C}, \text{H}) = 10.8 \text{ Hz}$
δ H-B = 2.78 ppm	$^{3}J(\text{H-B}, \text{C}, \text{C}, \text{H}) = 6.8 \text{ Hz}$
	$^{2}J(H-A, C, H-B) = 9.3 \text{ Hz}$

The H-A and H-B protons are equivalent at room temperature because of the fast inversion of nitrogen. This equivalence disappears in the protonated form and ${}^{3}J(H, N^{+}, C, H)$ couplings were detected which, together with those due to the protons at the ring junction, allowed the assignment of H-A, H'-A, H-B and H'-B. [Fig. 2(b)].

$^{3}J(\text{H-A}, \text{C}, \text{C}, \text{H}) = 11.2 \text{ Hz}$	δ H-A = 2.6 ppm
$^{3}J(\text{H'-A}, \text{C}, \text{C}, \text{H}) = 11.6 \text{ Hz}$	δ H'-A = 3.35 ppm
${}^{3}J(\text{H-B}, \text{C}, \text{C}, \text{H}) = 6.2 \text{ Hz}$	δ H-B = 3.9 ppm
${}^{3}J(\text{H'-B}, \text{C}, \text{C}, \text{H}) = 6.8 \text{ Hz}$	$\delta \mathbf{H'} - \mathbf{B} = 3.25 \text{ ppm}$

A correlation could then be established between the ${}^{3}J(H, C, N, H)$ coupling constants after protonation and the dihedral angles of this pathway.

$^{3}J(\text{H-A, C, N^{+}, H}) = 7 \text{ Hz}$	135° dihedral angle
${}^{3}J(\mathrm{H'-A, C, N^{+}, H}) = 7.2 \mathrm{Hz}$	-15° dihedral angle
${}^{3}J(\text{H-B}, \text{C}, \text{N}^{+}, \text{H}) = 6.2 \text{ Hz}$	15° dihedral angle
$^{3}J(H'-B, C, N^{+}, H) = 3 Hz$	105° dihedral angle

The variations observed in the coupling constants between the α -CH protons and the ring junction protons in the unprotonated and protonated forms

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probably result from a modification of the ring angles on protonation, which changes the hybridization of nitrogen.

The variations in chemical shifts between the protonated and unprotonated derivatives are as follows.

$\Delta \delta H - A = +0.20 \text{ ppm}$	$\Delta \delta H' - A = +0.95 \text{ ppm}$
$\Delta \delta H$ -B = +1.12 ppm	$\Delta \delta H' - B = +0.47 \text{ ppm}$

The $\Delta\delta H$ values indicate that since the positive charge of a nitrogen atom results in a significant downfield shift (about 1 ppm), the presence of a methyl group in *cis* position shifts the signal of the appropriate proton back upfield.

cis-N-Methylhexahydroisoindoline (1c)

The NMR parameters of the interconverting unprotonated derivative (Fig. 3) are as follows.

$$δ$$
H-A = 2.48 ppm ³J(H-A, C, C, H) = 5.7 Hz
 $δ$ H-B = 2.72 ³J(H-B, C, C, H) = 7.2 Hz

Two isomers, each undergoing interconversion, were formed on protonation (Fig. 4).

The calculated chemical shift values determined from the increments observed in the *trans* derivative (above) are (taking into account the exchange described):

> δ H-A = 2.48 + (0.47 + 0.2)/2 = 2.82 ppm δ H'-A = 2.48 + (1.12 + 0.95)/2 = 3.52 ppm δ H-B = 2.72 + (1.12 + 0.95)/2 = 3.76 ppm δ H'-B = 2.72 + (0.47 + 0.2)/2 = 3.06 ppm

The observed signals were at 2.9, 3.1, 3.72 and 3.88 ppm, and were therefore assigned to H-A, H'-B, H'-A and H-B, respectively. These assignments were corroborated by the values of the measured coupling constants:

 $^{3}J(H'-A, C, C, H) = 5.2 \text{ Hz} (5.7 \text{ Hz in the} unprotonated$ *cis*compound)

 ${}^{3}J(\text{H'-A, C, N^{+}, H)} = 6.9 \text{ Hz} [6.7 \text{ Hz deduced from}$ the *trans* derivative: $1/2(J_{-15}+J_{+15})]$

 ${}^{3}J(H-B, C, C, H) = 6.7 \text{ Hz} (7.2 \text{ Hz in the})$

unprotonated cis compound)

 ${}^{3}J(\text{H-B, C, N}^{+}, \text{H}) = 6.7 \text{ Hz} [6.7 \text{ Hz deduced from the}$ trans derivative: $1/2(J_{-15}+J_{+15})]$



Figure 3. Conformational equilibrium of unprotonated 1c.



Figure 4. Conformational equilibrium of protonated 1c.

 ${}^{3}J(H'-B, C, C, H) = 7 Hz$ (7.2 Hz in the unprotonated *cis* derivative

 ${}^{3}J(H'-B, C, N^{+}, H) = 5.4 \text{ Hz}$ [5 Hz deduced from the

trans compound: $1/2(J_{105}+J_{135})$]

The multiplicity of the H-A signal, masked by the $N-CH_3$ resonance, could not be exploited.

The slight differences between the observed and estimated values (either starting from the unprotonated *cis* derivative for the coupling constants with the ring junction proton, or starting from the *trans* derivative for the ${}^{3}J(H, C, N^{+}, H)$ coupling constants) are no doubt due to a slight deformation of the half-chair pyrrolidine ring, resulting from the existence of a steric interaction between the N—CH₃ and the 6membered ring which was absent in the *trans* derivative.

1,3,3,4,4-Pentamethylpyrrolidine (2)

The unprotorated derivative shows a single signal at 2.64 ppm for the four protons on the α -carbon. This equivalence is due both to the pseudorotation, which favours equally populated C₂ half-chair forms, and to the rapid inversion of nitrogen.

In the protonated derivative (Fig. 5) where the nitrogen inversion is slow, the average chemical shifts of H- α and H- β can be calculated using the increments derived for the *trans* derivative, taking into account the following exchange:

$$\delta$$
H-α = 2.64 + (0.47 + 0.2)/2 = 2.98 ppm
 δ H-β = 2.64 + (1.12 + 0.95)/2 = 3.68 ppm



Figure 5. Conformational equilibrium of protonated 2.



Figure 6. Possible 'envelope' form of protonated 2.

The observed parameters are a signal at 3.05 ppm with a coupling constant of 6.1 Hz and a signal at 3.75 ppm with a coupling constant of 6.7 Hz. It thus follows that

³J(H-α, C, N⁺, H) = 6.1 Hz [5 Hz deduced from the *trans* derivative: $1/2(J_{105} + J_{135})$] ³J(H-β, C, N⁺, H) = 6.7 Hz [6.7 Hz deduced from the *trans* derivative: $1/2(J_{-15} + J_{+15})$]

In this case we cannot exclude *a priori* the participation of neighbouring 'envelope' forms along the pseudorotation circuit, since the interaction between the N—CH₃ and the axial methyl groups would in this way be minimized. For the closest 'envelope' form, for example (Fig. 6), the value of ${}^{3}J(H-\alpha, C, N^{+}, H)$ becomes equal to $1/2(J_{120}+J_{148.6})$ which, according to a Karplus-type curve, will be higher than the value $1/2(J_{105}+J_{135})$ corresponding to the half-chair form; the value of ${}^{3}J(H-\beta, C, N^{+}, H)$ becomes equal to $1/2(J_{0}+J_{28.6})$ which is practically equal to the $1/2(J_{-15}+J_{+15})$ of the half-chair form, the indicated dihedral angles being Pitzer's angles.³ This type of variation could certainly conform to the observed coupling constants.

1,3,3-Trimethylpyrrolidine (3)

The 2-protons are equivalent in the unprotonated derivative ($\delta = 2.26 \text{ ppm}$). The protonated derivative shows two distinct signals, one at $\delta = 2.8 \text{ ppm} [^3J(\text{H}-\alpha, \text{C}, \text{N}^+, \text{H}) = 7.5 \text{ Hz}]$ and the other at $\delta = 3.55 \text{ ppm} [^3J(\text{H}-\beta, \text{C}, \text{N}^+, \text{H}) = 5.8 \text{ Hz}]$. A 50–50 exchange between the two half-chair forms, normally the most stable, would lead to the following chemical shifts (Fig. 7).

 δ H- α = 2.26 + (0.47 + 0.2)/2 = 2.60 ppm

 δ H- β = 2.26 + (1.12 + 0.95)/2 = 3.30 ppm

It is not certain, however, that the exchange is 50-50, the A form being less favoured because of a diaxial type interaction between methyl groups, which does not exist in the B form. This, however, cannot constitute a justification for the values of the coupling



Figure 7. Conformational equilibrium of protonated 3.

constants, because the average observed between the half-chair forms is not consistent with theory. In fact, the value

 ${}^{3}J(\text{H-}\alpha, \text{C}, \text{N}^{+}, \text{H}) = p_{\text{A}}J_{105} + (1 - p_{\text{A}})J_{135} = 7.5 \text{ Hz}$

is not included between the two extreme values of $J_{105} = 3$ Hz and $J_{135} = 7$ Hz. The same is true for ${}^{3}J(H-\beta, C, N^{+}, H) = p_{A}J_{-15} + (1-p_{A})J_{+15} = 5.8$ Hz, which is lower than $J_{-15} = 7.2$ Hz and $J_{+15} = 6.2$ Hz.

It should be noted that in this derivative, where there is no eclipsing energy between the vicinal 3- and 4-methyl groups, the participation of other forms of the pseudorotation circuit will be much greater, which would even further accentuate the differences observed for 2.

CONCLUSIONS

Protonation of N-methyl 5-membered nitrogen heterocycles gave rise to vicinal coupling constants between the proton on nitrogen and the α -CH protons; these could be used to investigate the conformation of the ring during pseudorotation. Except for derivatives with a high potential barrier—*cis*- and *trans*-N-methylhexahydroisoindolines—conformations other than the half-chair forms, generally considered to be the most stable, seem to play a noteworthy role.

EXPERIMENTAL

Spectra

Protonation was achieved in the NMR tube starting with 10% weight samples in CDCl₃; CF₃COOH was then added to obtain 50% CF₃COOH-50% CDCl₃ solutions. The detection of the $J(CH_3, N^+, H)$ coupling showed that protonation had been effected. Couplings between NH and the CH protons α to nitrogen were also observed, as well as significant changes in the chemical shifts of these protons. All the coupling constants disappeared or decreased considerably on the addition of D₂O, due to NH \rightleftharpoons ND exchange; the chemical shifts did not change.

The ¹H NMR spectra were recorded at a 1 Hz s^{-1} sweep rate for different frequencies: 60 and 100 MHz in the CW mode on Varian A-60 and Varian XL-100 spectrometers and, for some samples, at 250 MHz in the FT mode on a Cameca -250 spectrometer. These conditions made it possible to interpret spectra as first order for all the derivatives. Spectral calibration was controlled by the usual side-band modulation procedure and the readings for the chemical shifts and coupling constants were, therefore, direct; chemical shifts are in ppm downfield from internal TMS. Coupling constants are in hertz (Hz).

Products

cis-N-Methylhexahydroisoindoline (1c). Compound 1c was prepared according to the literature;⁴ b.p. 92–94°/60 mm; $n_{\rm D}^{25} = 1.4710$; yield 43% (lit.⁴ b.p. 70–72°/14 mm).

trans-N-Methylhexahydroisoindoline (1t). trans-Hexahydrophthalan was treated with gaseous HBr to produce the trans-1,2-bisbromomethylcyclohexane according to Ref. 5. The dibromide (7.7g) was then reacted with anhydrous methylamine (30 cc.) at -20 to -12 °C for 80 min. The resultant mixture was treated with commercial NaOH (6 ml), diluted with water (20 ml) and the product was extracted with ether and distilled, b.p. $61-63^{\circ}/14$ mm; $n_{\rm D}^{25} = 1.4650$; yield 45.5%. Anal. calcd for $C_9H_{17}N$:mol.wt, 139. Found (mass spectroscopy):mol.wt, 139.

1,3,3,4,4-pentamethylpyrrolidine (2). Compound 2 was prepared according to the method previously described by us; b.p. 125°; yield 50%.

1,3,3-trimethylpyrrolidine (3). Compound **3** was obtained by LiAlH₄ reduction in diethyl ether solution of 1,3,3-trimethylsuccinimide according to Ref. 6; b.p. $108-110^{\circ}$ (lit.⁷ b.p. $110-111^{\circ}$).

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