Observation of Piperidine Conformational Equilibria at Room Temperature Using a Cobalt(III) Porphyrin Shift Reagent

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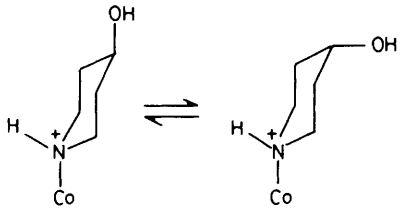
meso-Tetraphenylporphyrincobalt(III) chloride is used as a novel n.m.r. shift reagent to allow the observation of axial and equatorial conformations of monosubstituted piperidines at room temperature.

The differing chemical properties of axial and equatorial substituents on the cyclohexane ring were first described by Barton[1] in 1950. Since that time, n.m.r. spectroscopy has proved an invaluable tool in the determination of activation parameters and axial–equatorial conformational energy differences.[2] However, the technique has not been without problems, such as complex proton spectra and small chemical shift separations of axial and equatorial protons.[2] Thus, the direct low temperature n.m.r. determination of conformational energy differences in substituted piperidines has mainly been performed by ^{13}C n.m.r. spectroscopy,[3,4] with the attendant problems of quantitative measurement, sensitivity, *etc.*

As an alternative to variable temperature n.m.r. spectroscopy, we present the use of readily prepared *meso*-tetraphenylporphyrincobalt(III) chloride, Co(tpp) Cl, as an n.m.r. shift reagent which allows direct measurement of conformational equilibria from the proton spectrum at room temperature. Addition of excess of the porphyrin to the piperidine in deuteriochloroform results in selective complexation at the piperidine nitrogen atom. Ligand exchange is slow on the n.m.r. time-scale, allowing the observation of axial and equatorial conformations. Furthermore, the ligand protons experience large changes in chemical shift due to the porphyrin ring current, such that most resonances are in a clear spectral region upfield of $SiMe_4$. Unlike lanthanide-induced shifts, this dispersion does not lead to excessive line broadening.



A typical 250 MHz ^1H spectrum is shown in Figure 1. The resonances at δ −7.5 are unusual, in that they arise from amine protons in slow exchange. High sensitivity means that only small amounts of sample are required, typically only 2—4 mg of amine, with total acquisition times of only a few minutes. Enhanced dispersion and zero-filling ensure that accurate integration ratios are obtained.

Conformational energy differences (kJ mol^{-1}) obtained for 4-substituted piperidines are 0.9 ± 0.2 (X = Br), 1.5 ± 0.4 (X

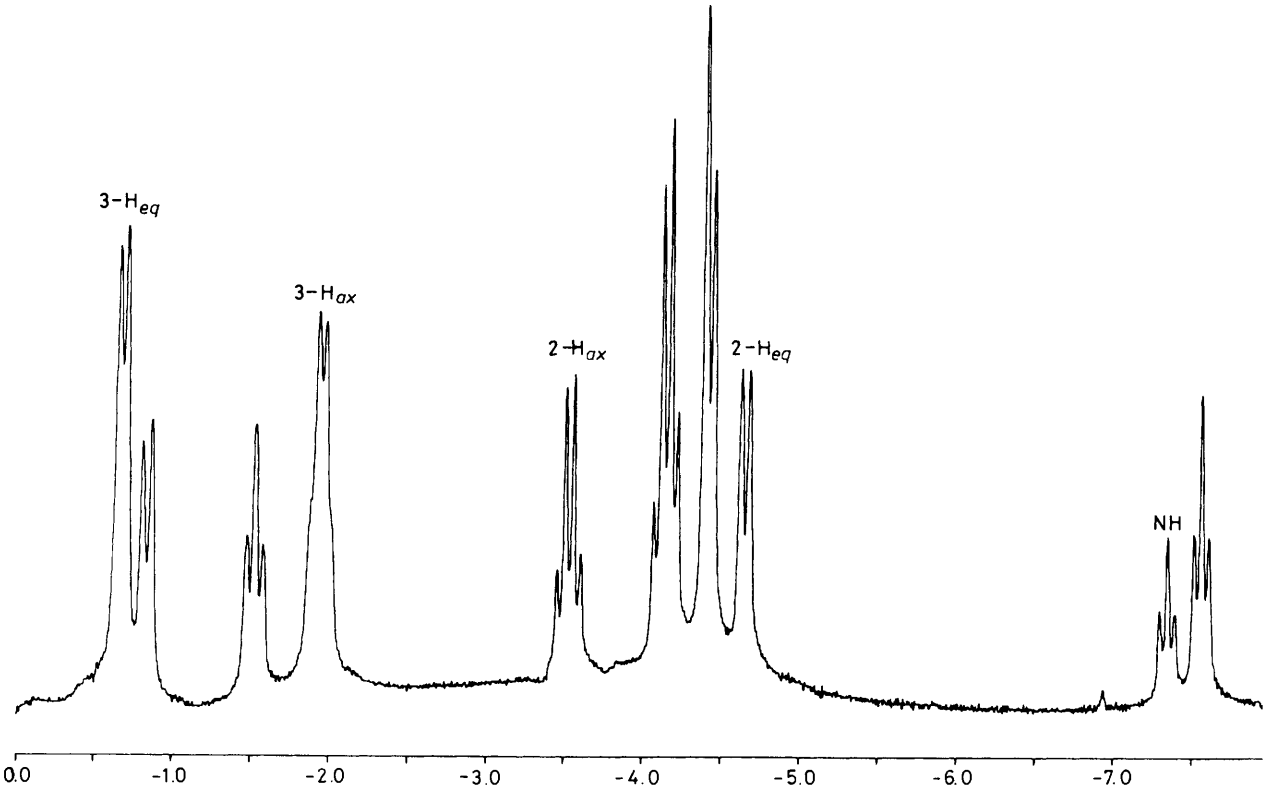


Figure 1. The 250 MHz n.m.r. spectrum of 4-hydroxypiperidine complexed to Co(tpp)Cl.

= OH), and 6.0 ± 0.8 (X = Me), which compare well with literature values (*N*-methylpiperidines) of 0.7 (X = Br),[4] 1.8 (X = OMe),[4] and 7.6 (X = Me)[3] obtained by low-temperature ^{13}C n.m.r. studies. We could not detect any axial phenylpiperidine (<2%; >10 kJ mol^{-1}), in agreement with data reported for phenylcyclohexane (11.0 kJ mol^{-1}).[5]

Co(tpp)Cl may also be used as a locking group when conformers cannot be resolved by low-temperature n.m.r. experiments, *e.g.* pyrrolidines, hexamethyleneimines. For example, 3-hydroxypyrrolidine complexes to Co(tpp)Cl in two conformations which can be deduced from their vicinal coupling constants, with a free energy difference of 4 kJ mol^{-1} being reproduced by theoretical (MNDO) calculations on the protonated amine.[6]

We are currently examining a range of piperidines in order to understand how complexation affects the observed conformational energy differences. This may open the way for an examination of the spatial requirements of tetravalent *versus* trivalent nitrogen, a long-standing problem in piperidine chemistry.[7]

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