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THE AMBIGUITY OF RING AND ATOMIC INVERSION IN N-CHLOROPIPERIDINE

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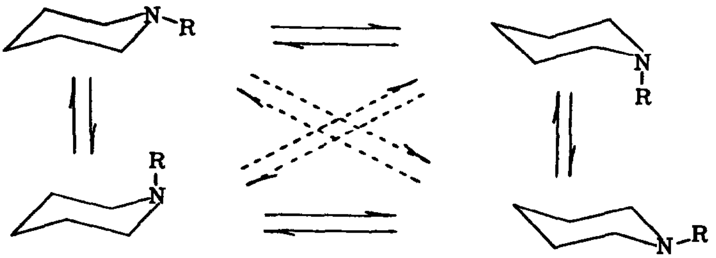
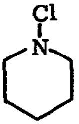
Early studies of nitrogen inversion and ring flip were confined to unambiguous examples.[1] Nitrogen-containing six-membered rings, however, can engage in either or both processes[2] (Scheme 1). Many authors have attempted, with some success, to observe the two processes independently, although not in a single system.[2-4] We wish to report experiments with N-chloropiperidine (I), which do not admit of an unambiguous interpretation. The usually faster nitrogen inversion has been slowed by the chlorine atom to a point that it is indifferentiable, if not synchronous, with ring flip. Model systems used in this study, N-chloro- and N-methylpyrrolidine (II, III), also furnish the first examples of slow nitrogen inversion in simple five-membered heterocycles.

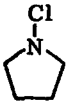


Scheme 1

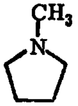
I



II



III



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The α protons of N-chloropiperidine-3,3,5,5-d_4 present a singlet resonance at 40° in CH_2Cl_2. As the temperature is lowered, reversible broadening of the resonance occurs (T_c = -1°). Below -40°, the spectrum of the α protons consists of a single AB pattern (δ_{ae} = 37.2 Hz at 60 MHz). No further changes occur down to -100°. The γ protons follow a similar program. A complete line-shape analysis yielded an Arrhenius activation energy of 15.9 ± 0.7 kcal/mole and a pre-exponential factor of $10^{14.9 \pm 0.7}$ sec^{-1}. The observations are nearly identical to those made previously by us with piperidine (IV) and its N-methyl and N-t-butyl derivatives (E_a = 14.5, 14.4, and 14.0, respectively) and attributed to ring inversion.[2]

For the sake of comparison with a system incapable of ring inversion, we examined N-chloropyrrolidine in CF_2Cl_2, with double irradiation of the β proton resonances. A similar conversion of the α singlet at room temperature into an AB spectrum below -80° was observed (T_c = -64°, $\Delta\nu_{AB}$ = 26.3 Hz at 100 MHz). The complete line-shape analysis gave an Arrhenius activation energy of 13.9 ± 0.7 kcal/mole and a pre-exponential factor of $10^{16.9 \pm 0.7}$ sec^{-1}. This process may unambiguously be designated as nitrogen inversion.

Our models for nitrogen inversion in a cyclic chloramine (II) and for ring flip in a piperidine (IV) thus have almost identical spectral changes and E_a's. A traditional differentiation by models cannot therefore be made for N-chloropiperidine (I), which combines these structural components. There are in fact at least four mechanisms consistent with the spectral observations for this heterocycle. (1) Ring flip is slow with respect to n.m.r. criteria below -40°, but nitrogen inversion is fast at all temperatures. (2) Nitrogen inversion is slow below -40°, but ring flip is fast at all temperatures. (3) The rate process involves a synchronous ring-flip-nitrogen-inversion (dotted lines in Scheme 1). (4) Both ring flip and nitrogen inversion are slow below -40°, but the separate AB patterns expected[4,5] from the chlorine-axial and chlorine-equatorial isomers did not materialize, either because they are superimposed or because one is in an unobservably low proportion (this provision is also applicable to mechanism 3). Present evidence does not fully exclude any of these mechanisms since the observable is a methylene singlet transformed into only one AB at low temperatures.

If the reaction is not synchronous, the rate-determining process may be nitrogen inversion, because of the relatively high activation energy, but a clear distinction cannot be made. Furthermore, since unsubstituted pyrrolidine and its N-methyl derivative (III) did not undergo spectral changes down to -90°, the previously reported rate process in the corresponding piperidines[2] is confirmed to be the ring flip. Below -90°, however, the ring-proton resonances of N-methylpyrrolidine broaden in response to the onset of effects presumably due to slowing of nitrogen inversion. Although the activation energy in this case must be lower than that in II, these observations show that slow inversion is not exclusively associated with N-substituents bearing lone pairs.*

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*Solvent effects have been used to distinguish between ring flip and nitrogen inversion, but the situation is controversial and has yet to be resolved. Compare the following references: D. L. Griffith and J. D. Roberts, J. Am. Chem. Soc., **87**, 4089 (1965), with A. H. Cowley, M. J. S. Dewar, and W. R. Jackson, ibid., **90**, 4185 (1968); and J.-M. Lehn, F. G. Riddell, B. J. Price, and I. O. Sutherland, J. Chem. Soc. (B), 387 (1967), with H. S. Gutowsky and P. A. Temussi, J. Am. Chem. Soc., **89**, 4358 (1967). Should further experimentation prove the method to be valid, it shall certainly be applied to the present case. Experiments along this line are in progress.

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