Unusual Population of the Axial–Equatorial Conformation in *NN'*-Dichloropiperazine

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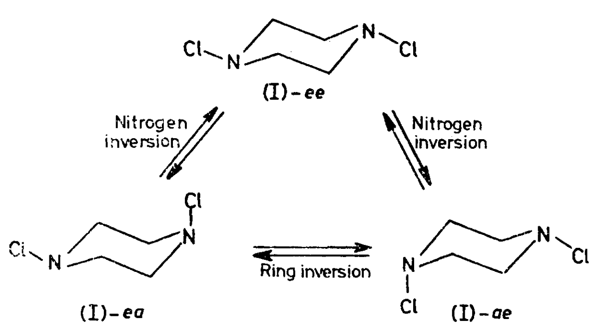
Summary The population ratio of the *ee* and *ae* + *ea* conformations in *NN'*-dichloropiperazine at −45 °C is 3 : 1 (ΔG° = 0·5 kcal mol^{-1}); this unusually low value possibly arises from a generalized anomeric effect.

The axial–equatorial free-energy difference for *N*-chloropiperidine has recently been shown to be 1·5 kcal mol^{-1}, corresponding to about 1% of the axial form at −100 °C.[1] In *NN'*-dichloropiperazine (I), however, it has been reported[2] from dynamic ^{1}H n.m.r. data that the equilibrium at −50 °C is such that either only the *ae* conformation is populated, or alternatively (and less likely) that there is a mixture of two conformations (*i.e.*, *ee–ae*, *ee–aa*, or *ae–aa*) in equal amounts. This apparent anomaly led us to measure the ^{13}C n.m.r. spectrum of (I) as a function of temperature. In either $(CD_3)_2CO$ or $CHCl_2F$, the ^{13}C n.m.r. spectrum of (I) changes from a very broad line at room temperature to a fairly sharp line at +50 °C and to three sharp lines in the ratio of 6 : 1 : 1 at −45 °C (see Table). This is best explained if (I) is a

Table. Carbon-13 resonances[a] in *NN'*-dichloropiperazine

Temp/°C	Conformation	$^{13}CH_2$
+50	*ee* and *ae*	61·9
−45	*ee*	63·7
−45	*ae*	60·7, 57·5

[a] Measured at 61·1 MHz in $(CD_3)_2CO$ solution with respect to internal Me_4Si.

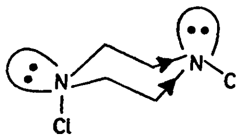


Scheme

mixture of *ee* and *ae* conformations (see Scheme) in the ratio of 3 : 1 at −45 °C. The ^{13}C chemical shifts of the *ae* conformation are expected to be at higher field than the ^{13}C chemical shift of the *ee* conformation, since the shielding effects of an *axial-N*-chloro group (compared with an *equatorial-N*-chloro group) on the α and β carbons in *N*-chloropiperidine are 4·8 and 8·0 p.p.m. respectively.[1] The published 90 MHz ^{1}H n.m.r. spectrum of (I) at −50 °C is not inconsistent with a 3 : 1 conformational ratio, in our opinion. Furthermore, the 251 MHz spectrum of (I) at −50 °C clearly shows the presence of a dominant AA′BB′ spectrum partially overlapped with a weaker complex (presumably ABCD) spectrum.

From the equilibrium constant observed at −45 °C in the ^{13}C n.m.r. spectrum, a $\Delta G°$ of 0·5 ± 0·1 kcal mol^{-1} can be calculated. The entropy of the *ee* form is 1·4 cal K^{-1} mol^{-1} lower than that of the *ae* form because the symmetry numbers of the *ee* and *ae* forms are 2 and 1 respectively, and therefore $\Delta H°$ is 0·8 ± 0·1 kcal mol^{-1}. In $CHCl_2F$ solution, $\Delta G°$ is 0·45 ± 0·05 kcal mol^{-1}, and this is not significantly different from the value in $(CD_3)_2CO$, despite pronounced differences in dielectric constants (21 for acetone at 25 °C and 5·3 for $CHCl_2F$ at 28 °C). Line-shape fitting of the broad ^{13}C resonance of (I) in $(CD_3)_2CO$ at +5 °C gives a $k(ae \rightarrow ee)$ of 150 ± 20 s^{-1}, corresponding to a $\Delta G^{\ddagger}$ of 13·5 ± 0·2 kcal mol^{-1}. This rate constant corresponds approximately to the largest line-width at half height of the coalesced resonances. At this point the calculated line shape is virtually independent of the rate of ring inversion in the *ae* conformation. At lower temperatures the line shape should depend significantly on the rate constant for ring inversion, and a detailed investigation of the ^{13}C dynamic n.m.r. spectrum in a ^{13}C-labelled (I) is planned.

On the basis of the *N*-chloropiperidine data, (I) would have been expected to be a mixture of *ee* and *ae* forms in the ratio of about 15 : 1 at −45 °C, whereas the observed ratio is only 3 : 1. The peculiar conformational equilibrium in (I) may arise from a stabilization of the *ae* form by the generalized anomeric effect. The CH_2–N(Cl*e*)–CH_2 group is considered to remove electron density from the C–C bonds, which are parallel to the equatorial lone pair on the nitrogen atom bearing the axial chlorine (see Figure). There could also be contributions from dipole moment differences between the two conformers; however, the lack of a strong solvent dependence on the equilibrium constant shows that such effects are probably not very important. The effects observed in (I) appear to be different from those occurring in the *ee* to *aa* equilibrium in *trans*-1,4-dichlorocyclohexane.[4] Unlike the *N*-chloro-substituent, the *N*-methyl substituent appears to behave quantitatively in the same conformational manner in both the piperidine and piperazine series, with $\Delta G°$'s (*e* to *a*) of 2·7—3·0 kcal mol^{-1} (corrected for entropy in the case of *NN′*-dimethylpiperazine).[1,5]



Figure

We thank the National Foundation for financial support.

(*Received*, 6*th October* 1977; *Com.* 1049.)

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