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# The Conformational Equilibrium in *N*,*N*'-Dimethylpiperazine

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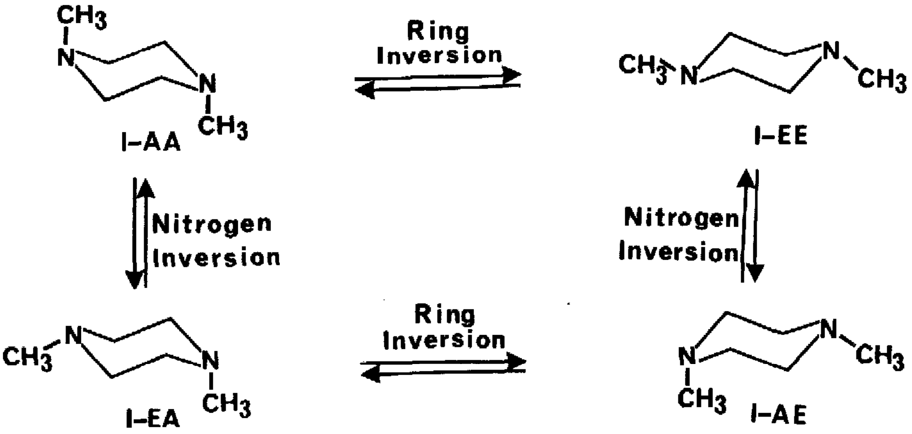
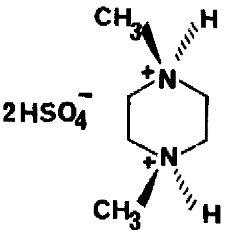
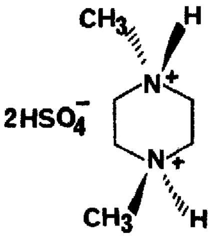
Recent investigations of a variety of *substituted* *N*-methylpiperidines indicate that the *N*-methyl group of *N*-methylpiperidine prefers the equatorial over the axial orientation by about 2.5 to 3.0 kcal/mol,[1-5] a value considerably higher than that found in methylcyclohexane.[6,7] We now report on the axial-equatorial energy difference in *N*,*N*'-dimethylpiperazine (**I**), a compound that is well suited for a conformational equilibrium study by the kinetically controlled protonation technique.[2,3,4,8]

The kinetically controlled protonation of **I-AA** and **I-EE** should give rise to the *trans*-isomer of the dimethylpiperazinium ion, **II-T**, while **I-AE** and **I-EA** should give the *cis* isomer, **II-C**.





II-C



II-T

For the protonation method to be valid, it is clearly necessary that nitrogen inversion in both I and I-$H^+$ be very slow processes compared to the protonation reactions, I → $IH^+$ → $IH_2^{2+}$ (Criterion 1). Also, II-C and II-T must not undergo equilibration in the time required for the analysis of the mixture of these salts (Criterion 2). In order to satisfy both Criteria 1 and 2, we have used 98% $H_2SO_4$ at room temperature (22°) as the trapping agent, as follows: a solution of I (1.5g) in pentane (50 ml) was added dropwise over a period of 1 hr to a vigorously stirred mixture of 98% $H_2SO_4$ (10 ml) and pentane (150 ml). Natural-abundance $^{13}C$ NMR spectra of the acid layer were measured with tetramethylsilane as an external reference and $C_6F_6$ as an external lock (Fig. 1).

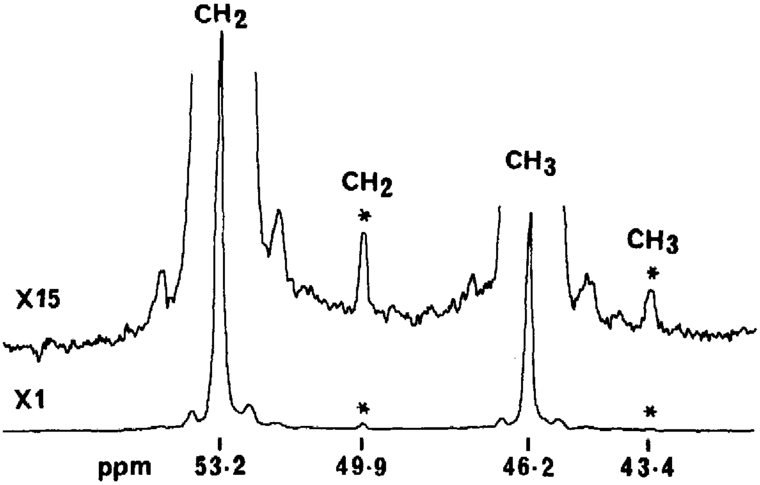


Fig. 1. 63.1 MHz $^{13}C$ NMR spectrum at 10°C of I quenched in 98% $H_2SO_4$. Protons are noise decoupled and the spectrum is the Fourier transform of the sum of 20,000 free induction decays obtained under the following conditions: 30° pulse angle, 8K data points, 4,000 Hz spectrum width, and an exponential broadening of 4 Hz. The peaks marked with asterisks belong to II-C.

Measurements of $T_1$ for the $CH_2$ and $CH_3$ carbons in II-T under the same conditions gave values of 0.11 ± 0.01 and 0.36 ± 0.02 s respectively. The $T_1$ values for II-C were not measured but should be of the same order of magnitude as those of II-T. The peak-height ratio for the $CH_2$ and $CH_3$ peaks of II-T obtained from the spectrum in Fig. 1 is only 1.8 and is reproducibly less than 2.0. Because of the very short $T_1$'s, saturation effects are negligible under the conditions used. The $T_1$ values, however, show that the resonance of the $CH_2$ carbons must be broadened by about 3 Hz, whereas the $CH_3$ carbons are broadened by less than 1 Hz. Furthermore, the $CH_2$ carbons will give rise to somewhat less than a maximum NOE, because these nuclei are just on the borderline of the "extreme narrowing region".[9] The methyl carbons, on the other hand, should show a maximum NOE as a result of internal rotation effects. Irrespective of these complications, the peak height ratios for the $CH_2$ and for the $CH_3$ bands in II-T and II-C, should, if consistent with one another, represent a good measure of the relative concentrations of the two diasteromeric salts. These ratios are 75 ± 7 and 80 ± 15 respectively (mean 76 ± 6). The proportion of II-C very slowly increases with time when the sample is kept at 50°C. At 100°C, the ratio reaches a limiting value of about 6 after 24 hrs. It has previously been observed that the ratio of II-T to II-C in concentrated hydrochloric acid is nearly temperature independent and is equal to 8 at 44°C.[10]

Experiments with 90% $H_2SO_4$ give a distinctly lower ratio (ca 50:1) for II-T:II-C than that obtained with 98% $H_2SO_4$. Since Criterion 2 is satisfied in 90% $H_2SO_4$, as shown in separate experiments, it appears that one of the protonation steps of I is not quite fast enough with this acid concentration for the protonation to be strictly kinetically controlled. It is probably the second protonation step which is slow as the pKa of $IH_2^+$ is only 4.6.[10] Thus, the conditions for kinetic protonation of piperazines are considerably more stringent than those of piperidines.

The $^1H$ spectra of I in 98% $H_2SO_4$, even at 251 MHz are not suitable for population measurements because the bands of the diastereomeric salts are rather broad in this viscous solvent and the chemical shift differences are quite small.

The present data are in agreement with recent work[1-5] in showing a large energy difference between an axial and equatorial N-methyl group, as shown by the following analysis. Since II-T must be virtually exclusively in the EE conformation, while II-C is a 1:1 mixture of the AE and EA conformations, the measured ratio of 76 ± 6 must be multiplied by 2 to obtain the ratio of II-T(EE):II-C(AE), which is therefore 152 ± 12. If the kinetic protonation method is valid, the ratio of I(EE):I(AE) in a pentane solution at 22°C is also 152 ± 12, and this corresponds to a

ΔG° of 2.96 ± 0.05 kcal/mol for the free energy difference between an axial and an equatorial N-methyl group in I under these conditions.

During the course of this work, we learned that ultrasonic absorption and relaxation measurements on neat I apparently gives an enthalpy difference of only 0.3 kcal/mol for the axial-equatorial N-methyl equilibrium.[11] Since entropy effects should be small,[11] ΔG° for this equilibrium should have the same value as ΔH° and is thus 2.6 kcal/mol lower than the value we now report. The phase difference between neat I and a pentane solution of I is highly unlikely to lead to a difference in ΔG°'s of this magnitude.[12] Ultrasonic measurements also lead to very small axial-equatorial energy differences in N-methylpiperidines[11], in disagreement with all other recent data, which includes kinetically controlled protonation,[2,3,4,8] direct dynamic NMR,[4] and kinetically controlled imidation.[5]

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(12) Although I-AE, unlike I-EE, has a dipole moment, the dielectric constant of neat I should be quite low and only slightly higher than that of pentane; thus dipole moment effects should be small.