Discrimination of the Geometrical Isomers of 2,3-, 2,5-, and 2,6-Dimethylpiperazines Based on ^{1}H–Nmr Spectral Data

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^{1}H-Nmr spectra of *cis* and *trans* isomers of 2,3-, 2,5-, and 2,6-dimethylpiperazines were taken at various temperatures. The spectra of geometrical isomers bearing the ae or ea dimethyl groups showed broadening at lower temperatures. It was clarified that the measurement of the spectra at lower temperatures is useful for the discrimination of the geometrical isomers of dimethylpiperazines.

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Nmr spectroscopy has been widely used for geometrical analysis in stereochemistry (1). This method has also been employed in the piperazine field for various compounds (2). We previously reported the synthesis of 1-hydroxy-4-methylpiperazines (3), but stereochemical analysis of the products was not made at the time. In continuation of the investigation on piperazines, nmr spectra of two geometrical isomers of 2,3-, 2,5-, and 2,6-dimethylpiperazines were measured and it was found that the measurements of spectra at low temperatures is useful for geometrical analysis of the isomers.

Chart 1 shows two chair forms of each isomer of three dimethylpiperaiznes. Among them, the two forms with ae or ea dimethyl orientation may be interchangeable at room temperature. However, the forms which exist in ee dimethyl configurations may not change into the less stable forms with diaxial orientation. Therefore, at room temperature, the signals due to the ring hydrogen atoms of *trans*-2,3-dimethylpiperazine (**2**), *trans*-2,5-dimethylpiperazine (**4**), and *cis*-2,6-dimethylpiperazine (**5**) are expected to be more complex than those of *cis*-2,3-dimethylpiperazine (**1**), *cis*-2,5-dimethylpiperazine (**3**), and *trans*-2,6-dimethylpiperazine (**6**). On the other hand, the nmr spectra of **2**, **4**, and **5** would not change even at a low temperature, whereas the spectra of **1**, **3**, and **6** may indicate considerable changes upon cooling.

The nmr spectra of two isomers of 2,3-, 2,5-, and 2,6-dimethylpiperazines were taken at room temperature and in the temperature range of 0° to -80°, and are shown in Figures 1, 2, and 3. The appearance and changes of the spectra were in good agreement with the above-mentioned assumption.

Chart 1

Conformations of Dimethylpiperazines

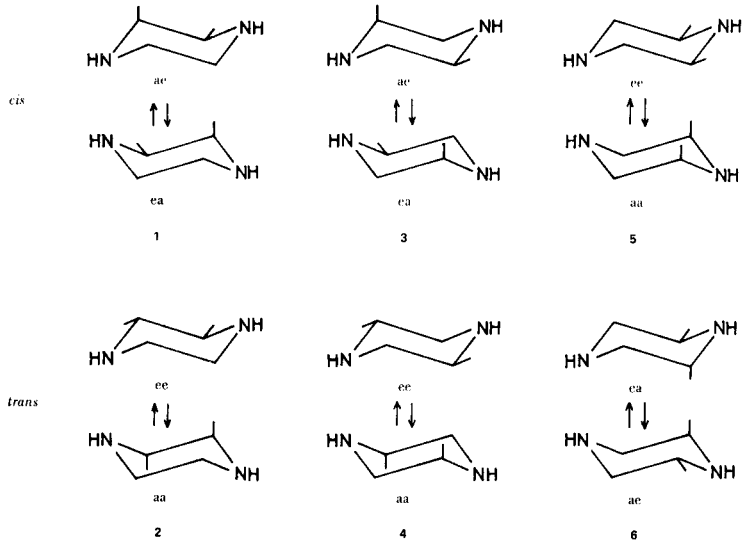

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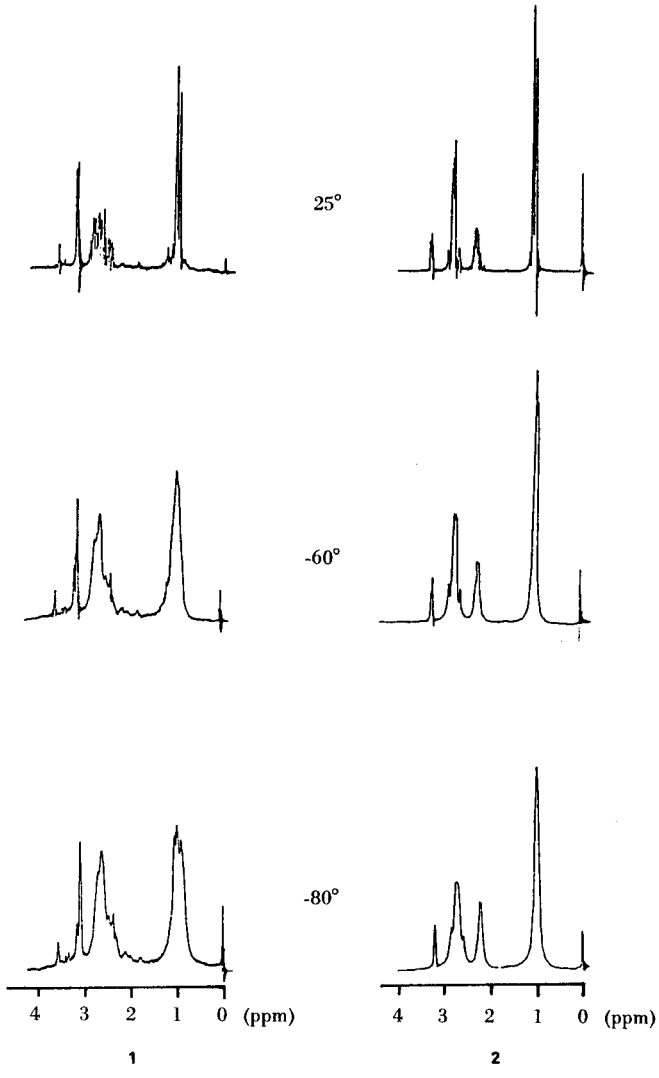
Figure 1

Nmr Spectra of the Isomers of 2,3-Dimethylpiperazine as a Function of Temperature



As shown in these Figures, in the spectra of **1**, **3**, and **6**, particularly in that of **3**, broadening of the signals due to the overlapping of axial and equatorial methyl doublets was apparent at a lower temperature. The spectra of **2**, **4**, and 5 also indicated the broadening though slightly, which may be due to lowering of the resolving power by frosting on the spinning tubes. Figure 4 shows changes in the peak width at half height of the methyl signals at various temperatures. The difference between the ae or ea and ee orientations is apparent.

Consequently, these spectral results suggested that the measurement at lower temperatures is efficient for geometrical analysis of disubstituted piperazines.

EXPERIMENTAL

Preparation of *cis*- and *trans*-2,3-dimethylpiperazines followed the method reported (4). Samples of *cis*- and *trans*-2,5-dimethylpiperazines were obtained commercially from Tokyo Chemical Industry Co., Ltd. and *cis*-2,6-dimethylpiperazine was purchased from Aldrich Chemical Co., U.S.A. *trans*-2,6-Dimethylpiperazine was prepared according to the literature (5) but debenzylation by hydrogenolysis in the last step failed and was carried out successfully by treatment with phenyl chloroformate and the successive hydrolysis in an alkaline medium (6).

Nmr spectra were obtained with a JEOL JNM-PS-100 spectrometer in methanol-d_4, using TMS as an internal standard.

Figure 2

Nmr Spectra of the Isomers of 2,5-Dimethylpiperazine as a Function of Temperature

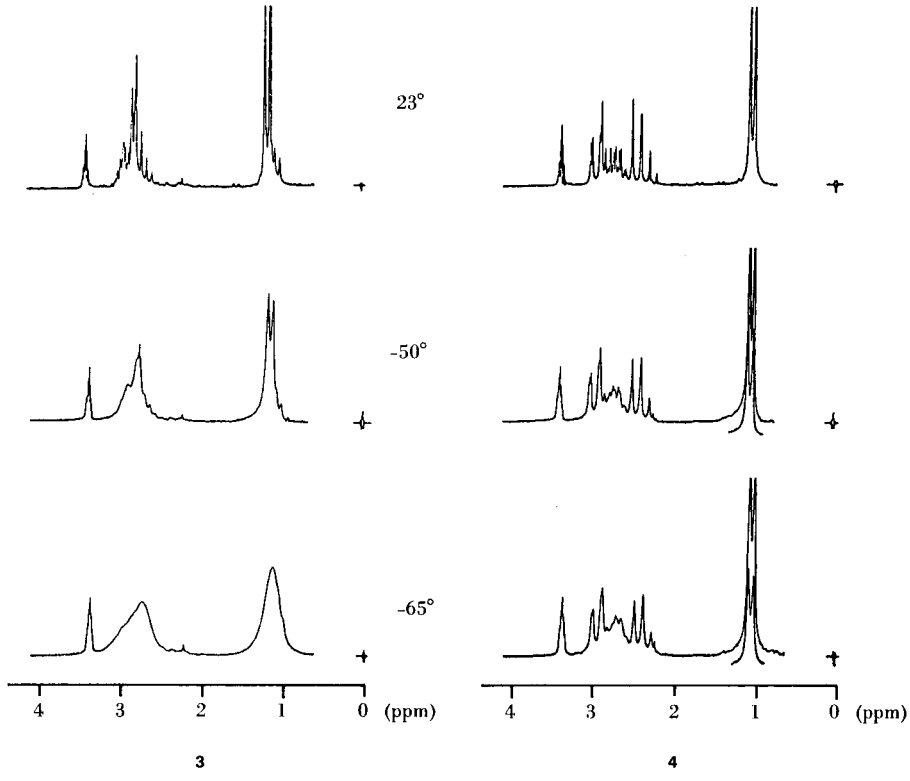


Figure 3

Nmr Spectra of the Isomers of 2,6-Dimethylpiperazine as a Function of Temperature

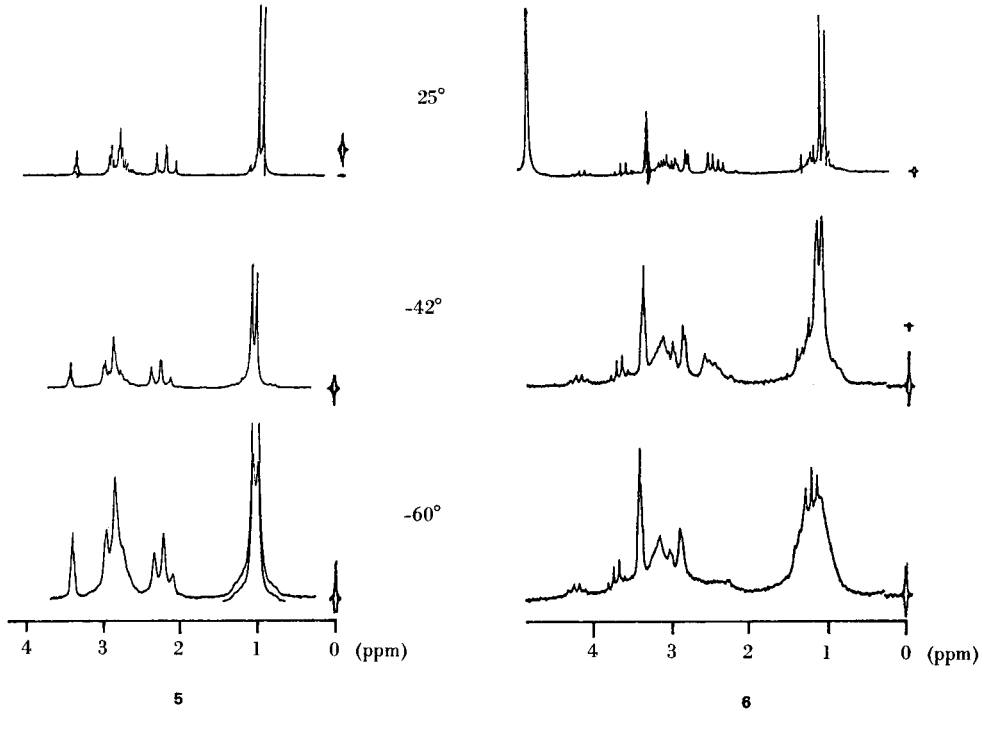
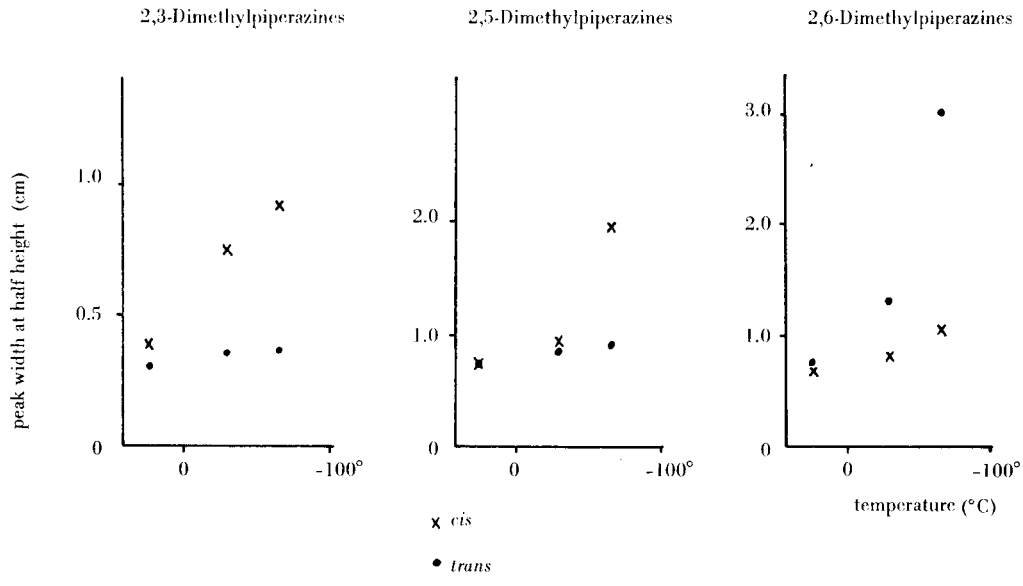


Figure 4

Changes in the Peak Width at Half Height of the Methyl Signals



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