Conformation of 1,4-Dineopentyl-2,5-*cis*-diphenylpiperazine and Its Diammonium Salts: Remarkable Change in Conformation Depending upon the Counter Anion

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The free base of 1,4-dineopentyl-2,5-diphenylpiperazine takes a chair conformation in CDCl$_3$, while the conformation of its diammonium salts changes depending upon the counter anion.

The conformational behavior of a piperazine moiety is rather diverse due to ring inversion and the configurational inversion of two nitrogen atoms. *cis*-Disubstitution at C-2 and C-5 makes the situation more complicated, since one of the substituents should be axial while another is equatorial in the chair conformation. Optically active *cis*-disubstituted piperazines have been used in asymmetric syntheses as chiral ligands[3] and as a chiral proton source.[4] The syntheses of several polyazamacrocycles containing 2,5-disubstituted piperazine and their binding properties to organic molecules[5] and metal ions[6] have been reported. In the course of our investigation on the synthesis and binding properties of optically active polyazamacrocycles containing (2*R*,5*R*)-diphenylpiperazine (**1**), we observed the unique conformational behavior of diammonium salts of (2*R*,5*R*)-1,4-dineopentyl-2,5-diphenylpiperazine (**2**). In this communication, we report the conformation of free base **2** and the conformational changes in diammonium salts of **2** depending upon their counter anions. This type of anion-dependent bias in conformation is unprecedented except for a molecular clip based on glycoluril.[7]

First, we examined the ^{1}H-NMR spectra of free base **2**. Part of the ^{1}H-NMR spectrum of **2** in CD$_2$Cl$_2$ is shown in Fig. 1. The pseudo C2 symmetric protons at C-2 and C-5 were observed at 3.57 ppm (dd, *J*=6.4, 3.5 Hz) as an equivalent signal at 26 °C due to rapid inversion of the nitrogen atom and fluttering of the piperazine ring on the NMR timescale (Fig. 1a). The same was true for the α protons (3.29 ppm, dd, *J*=12.3, 6.4 Hz) at C-3 and C-6 and for the β protons (2.62 ppm, dd, *J*=12.3, 3.5 Hz). All of the signals were broadened at lower temperature, and the coalescence temperature for the *tert*-Bu peaks was −62 °C. All of the signals in the region of δ 0.50—3.80 ppm were separated individually at −100 °C (Fig. 1b) due to conformational freezing. These observations clearly indicate that the free amine **2** exists in a chair conformation **3** in CD$_2$Cl$_2$. Provided that **2** is frozen in the boat conformation **4** or **5**,[8] in which the two phenyl substituents at C-2 and C-5 are equatorial, the ^{1}H-NMR signals in this region should be much simpler due to C2-symmetry.

A crystal of ditrifluoroacetate of **2** was shown to include another two molecules of trifluoroacetic acid (TFA), as confirmed by an elemental analysis[9] and its ^{1}H-NMR spectrum (Fig. 2). All of the protons of ditrifluoroacetate of **2** appeared at a lower field compared to those of free base **2** in CD$_2$Cl$_2$.[10] The behavior of the signals of the ditrifluoroacetate to kinetic equalization was totally different from that of free base **2**. Thus, no coalescence of the peaks was observed even at −110 °C in CD$_2$Cl$_2$. H–H COSY experiments established the connectivity of the three protons of the piperazine ring in the
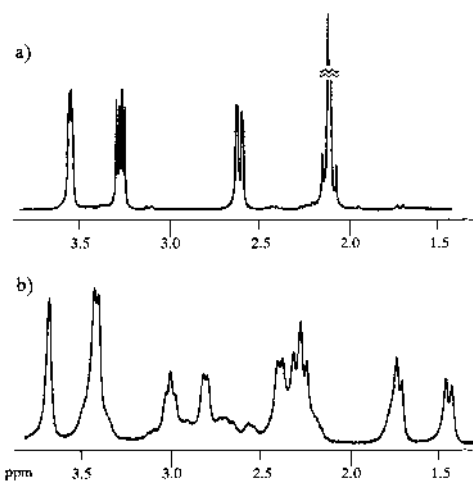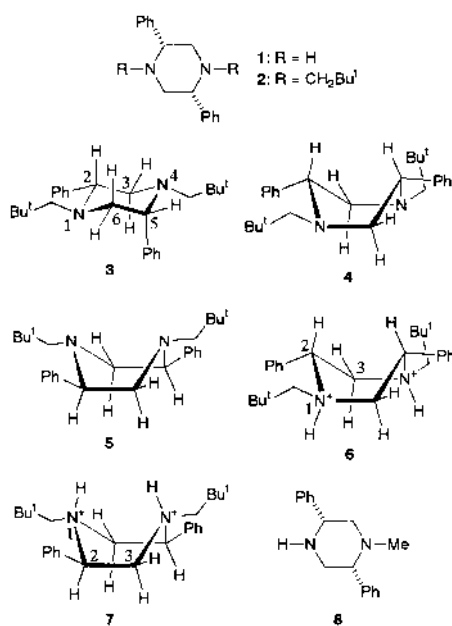

Fig. 1. ^{1}H-NMR Spectra of **2** in CD$_2$Cl$_2$
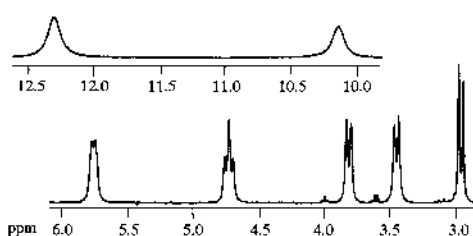*a*) At 26 °C. *b*) At −100 °C.

Fig. 2. ^{1}H-NMR Spectrum of **2**·4TFA in CDCl$_3$ at 0 °C

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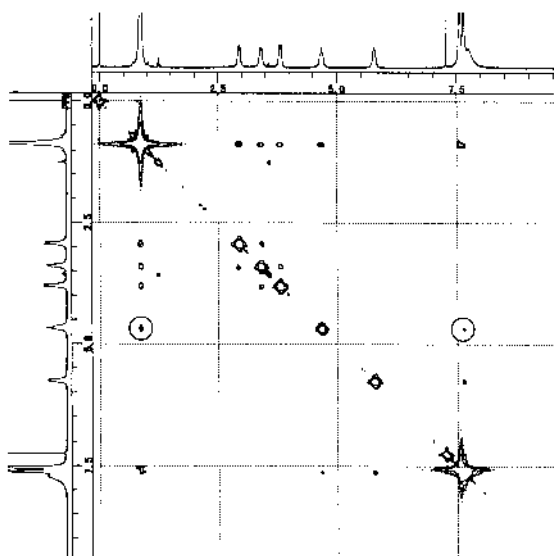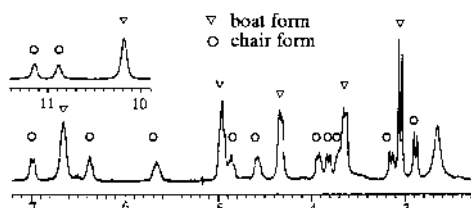
Fig. 3.   H–H NOESY Spectrum of **2**·4TFA in CDCl₃

Table 1.   Distribution of Chair/Boat Isomer of Diammonium Salts of **2** in CDCl₃

Entry	Salt	Chair : boat[a]	ΔG^0 (kJ/mol)
1	**2**·2HCl	38 : 62	1.1±0.1
2	**2**·2HBr	34 : 66	1.5±0.1
3	**2**·2HI	21 : 79	3.0±0.1
4	**2**·2MsOH	0 : 100	>10
5	**2**·2CF₃COOH[b]	0 : 100	>10
6	**2**·HOOC(CF₂)₃COOH	64 : 36[c]	−1.0±0.1

a) Determined by ¹H-NMR spectrum at 20 °C.   *b)* Additional 2 molecules of TFA were included.   *c)* Determined by ¹H-NMR spectrum at −60 °C.

Fig. 4.   ¹H-NMR Spectrum of **2**·2HCl in CDCl₃ at 27 °C

lower field. The upper two doublets at 2.96 and 3.45 ppm are those of the methylene protons of the neopentyl group. A triplet at 4.72 ppm ($J=12.9$ Hz) can be assigned to an axial proton at C-3, which indicates a boat-like conformation **6** or **7** for the ditrifluoroacetate of **2**. The axial proton at C-3 is *cis* to the phenyl group at C-2 in **6**, but *trans* in **7**. In the H–H NOESY spectrum, the signal at 4.72 ppm showed cross peaks to the protons of the phenyl ring and the *tert*-Bu group (Fig. 3). This indicates that the axial proton at C-3 must be *cis* to the phenyl group. Thus, the conformation of ditrifluoroacetate of **2** in solution was determined to be **6**, which is consistent with those of dihydrochlorides of **1** and **8** in the crystal phase.[11]

To our surprise, minor peaks appeared in addition to those of the boat conformer when the counter anion was replaced with chloride (Fig. 4). Close inspection of H–H COSY spectral data established the connectivity of these newly appearing minor peaks and indicated that the minor isomer had a chair conformation. The ratio of the two conformers in CDCl₃ at room temperature was approximately 3 : 2. The signals corresponding to the two conformers appeared in the same ratio in CDBr₃, CD₂Cl₂, DMSO-d_6, DMF-d_7 and acetone-d_6. This relationship between the conformers corresponds to the difference in the chirality of the two nitrogen atoms. In CDCl₃, the conformers slowly interconverted with

each other. Thus, "saturating transfer"[12] of the ammonium protons was observed in the NOE spectrum of dihydrochloride of **2**, which indicates that the ammonium protons of the conformers are exchangeable.

The ratio of the conformers in CDCl₃ varied with the counter anion (Table 1). ¹H-NMR showed that the major and minor conformers existed in the boat and chair forms with all halides (entries 1—3). The population of the boat conformer increased with the size of the halide anion. No signals were observed for the chair conformer when the counter anion was replaced with a bulkier one, such as methanesulfonate or trifluoroacetate (entries 4, 5). In contrast, the chair conformation slightly predominates over the boat in CDCl₃ for hexafluoroglutarate (entry 6). Although it is premature to give a conclusive explanation for this observed anion-dependent conformational bias, this property may be useful for the design of new types of allosteric molecules induced by anions.

References and Notes

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8) The conformational change in the piperazine ring is associated with nitrogen inversion. Thus, the configurations of the nitrogens are (*R,S*) in the chair form **3**, but (*R,R*) in the boat forms **4** and **5**.
9) mp, 82—83 °C (from ether). *Anal*. Calcd for C₂₆H₃₈N₂·4CF₃COOH: C, 48.92; H, 5.07; N, 3.36. Found: C, 48.86; H, 5.05; N, 3.47.
10) The ¹H-NMR spectrum in CD₂Cl₂ is essentially the same as that in CDCl₃.
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