Conformational Difference between Mono- and Diprotonated
cis-2,5-Diphenylpiperazinium Salts in the Solid State

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Monohydrochlorides of cis-2,5-diphenylpiperazine assume a chair conformation, while the corresponding
dihydrochlorides assume a boat form regardless of the substituent(s) at the nitrogen atom.

Key words  piperazine; conformation; X-ray analysis; 1 H-NMR

The conformation of saturated six-membered azacycles has been the subject of considerable interest,3,1 since they exhibit different types of characteristic motion, such as pyramidal nitrogen inversion, ring inversion, and rotation around single bonds of the ring substituents. Several molecules containing a piperazine moiety have recently attracted attention from the viewpoint of organic reactions,4,1 coordination chemistry5, and medicinal chemistry.6,7 Previously, we reported that protonation of the lithium enolate of 2-benzylec
clohexanone with (2R,5R)-diphenylpiperazinium mono-hydrochloride (1·HCl) resulted in the formation of the corresponding (S)-ketone with up to 70% ee.8,9 Most of the reactions were carried out under heterogeneous conditions. An important conclusion drawn from this study was that variation of a substituent on the nitrogen atom did not play a significant role in asymmetric protonation, while the piperazine ring itself did. Thus, elucidation of the crystal structure of the piperazinium salts is needed to understand the reaction mechanism. This paper describes the solid-state structure of (2R,5R)-diphenylpiperazinium salts.

Single crystals of monohydrochlorides and dihydrochlorides of 1 and 2 were obtained from ethanol–water solution by slow evaporation of the solvent. Their crystal structures are given in Fig. 1.7, 10 Interestingly, monohydrochlorides of 1

\[
\begin{align*}
\text{R}^1 & = \text{R}^2 = \text{H} \\
\text{R}^1 & = \text{Me}, \text{R}^2 = \text{H} \\
\text{R}^1 & = \text{R}^2 = \text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_3
\end{align*}
\]

Fig. 1. Crystal Structures of 1·HCl (a), 1·2HCl (b), 2·HCl (c), and 2·2HCl (d)
Chlorine atoms are omitted for clarity.

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Table 1. Ring Torsion Angles (°) of 1 · HCl, 1 · 2HCl, 2 · HCl, and 2 · 2HCl

<table>
<thead>
<tr>
<th>Torsion angle</th>
<th>1 · HCl</th>
<th>1 · 2HCl</th>
<th>2 · HCl</th>
<th>2 · 2HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(6)–N(1)–C(2)–C(3)</td>
<td>70.2</td>
<td>49.6</td>
<td>61.2</td>
<td>51.9</td>
</tr>
<tr>
<td>N(1)–C(2)–C(3)–N(4)</td>
<td>−60.2</td>
<td>−58.7</td>
<td>−57.5</td>
<td>−52.2</td>
</tr>
<tr>
<td>C(2)–C(3)–N(4)–C(5)</td>
<td>58.6</td>
<td>9.0</td>
<td>55.6</td>
<td>−3.0</td>
</tr>
<tr>
<td>C(3)–N(4)–C(5)–C(6)</td>
<td>−54.7</td>
<td>48.3</td>
<td>−53.7</td>
<td>56.9</td>
</tr>
<tr>
<td>N(4)–C(5)–C(6)–N(1)</td>
<td>51.4</td>
<td>−57.3</td>
<td>57.7</td>
<td>−56.6</td>
</tr>
<tr>
<td>C(5)–C(6)–N(1)–C(2)</td>
<td>−67.7</td>
<td>8.0</td>
<td>−63.7</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Fig. 2. Solid-State 15N-NMR Spectra of 3 (a), 3 · HCl (b) and 3 · 2HCl (c). Chemical shifts are expressed in ppm from NH4Cl as an external standard.

and 2 exist in the chair conformation, while the corresponding dichlorides adopt a boat conformation, although each conformation is slightly distorted (Table 1). The position of the ammonium proton in mono-hydrochlorides of 1 and 2 was determined by assuming that the chlorine anion is located in the neighborhood of the positively charged atom due to electrostatic interaction. The distances from Cl(1) to N(4) and N(1) are 3.154 and 4.407 Å for 1 · HCl and 3.082 and 4.482 Å for 2 · HCl, respectively. Another interesting feature of monohydrochlorides of 1 and 2 is that protonation occurs at the nitrogen atom next to the carbon bearing the axial phenyl substituent. (2R,5R)-1,4-Di-neo-hexyl-2,5-diphenylpiperezine 3 and its hydrochloride salts, 3 · HCl and 2 · HCl, were prepared from 1. Solid-state 15N-NMR spectra of 3, 3 · HCl, and 2 · 2HCl were measured by using the cross polarization magic angle spinning (CPMAS) method. Two nitrogens of 3 were observed at δ 28.9 and 24.4 ppm (Fig. 2a). On the other hand, only one signal was detected for 3 · 2HCl at δ 36.7 ppm (Fig. 2c). These results indicate that the two nitrogen atoms of 3 were exposed to different environments, while the nitrogens of 3 · 2HCl were equivalent; i.e., 3 assumes a chair conformation while 3 · 2HCl exists as a boat conformer in the solid state, which is consistent with the crystal structures of 1 · 2HCl and 2 · 2HCl. 15N signals of 3 · HCl appeared at δ 37.8 for the protonated nitrogen atom and at 23.9 ppm for the free nitrogen atom (Fig. 2b). Although it is difficult to determine the ring structure from the chemical shifts, we conjecture a chair conformation for 3 · HCl by analogy with 1 · HCl and 2 · HCl.

In conclusion, conformational studies of cis-2,5-dipheny1piperazinum salts revealed that the piperazine rings of mono- and dihydrochlorides adopt different conformations in the solid state; the former has a chair conformation, while the latter has a boat form. It is possible that monoprotonated cis-2,5-disubstituted piperazines generally exist in a chair conformation while diprotonated cis-2,5-disubstituted piperazines have a boat conformation, although more examples should be collected before we generalize the present conclusion.

Experimental

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Specific rotations were obtained at a Horiba SEPA-200 polarimeter. 1H-NMR spectra were recorded on a Varian Gemini 200 (200 MHz) spectrometer and chemical shifts are given in δ (ppm) values with trimethylsilane as an internal standard. Solid state 13C-NMR spectra were recorded on a JEOL JNM-CMX 400 (400 MHz) spectrometer and chemical shifts are given in δ (ppm) values with ammonium chloride as an external standard. IR spectra were determined with a JASCO FT/IR-300. (2R,5R)-1,4-Di-neo-hexyl-2,5-diphenylpiperezine (3) To a solution of 1 (0.06 g, 2.4 mmol) and NEt3 (0.5 ml, 16 mmol) in CH2Cl2 (20 ml) was added tert-butyllacetylenechloride (2.0 g, 15 mmol) dropwise at room temperature, and the mixture was stirred for 4 h. After addition of 1x HCl, the mixture was extracted with AcOEt. The organic layer was washed successively with saturated K2CO3 and brine, dried over MgSO4, and concentrated. Column chromatography of the residue on silica gel (hexane:AcOEt=1:2 w/v) gave the corresponding diamide (1.3 g, 75%) as white amorphous. To a solution of 0.1 of the above amide (0.5 mmol) and NaBH4 (0.58 g, 15 mmol) in THF (30 ml) was slowly added BF3·Et2O (0.03 ml, 20 mmol) at 0-°C, and then refluxed for 2 h. After being cooled to room temperature, the mixture was carefully quenched by water (3 ml), and concentrated under reduced pressure. The residue was added 15% HCl (12 ml), and the mixture was refluxed for 2 h. After the neutralization by 28% NH2OH, the reaction mixture was extracted with AcOEt, which was washed with brine, dried over Na2SO4, and concentrated. The resulting residue was purified by recrystallization from hexane to give 3 (0.98 g, 96%) as colorless plates. mp 64–66-°C; 1H-NMR (CDCl3) δ: 0.76 (18H, s), 1.29 (2H, dt, J=12.1, 4.9 Hz), 1.46 (2H, dt, J=12.1, 4.9 Hz), 2.13 (2H, dt, J=11.8, 4.9 Hz), 2.31 (2H, dt, J=11.8, 4.9 Hz), 2.65 (2H, dd, J=11.8, 3.5 Hz), 2.98 (2H, dd, J=11.8, 6.3 Hz), 3.71 (2H, dd, J=6.3, 3.5 Hz), 7.52–7.40 (6H, 7.09 (4H, J=7.4 Hz). 13C-NMR (solid) δ: 24.4, 28.9, IR (KBr cm−1): 2960–2800, 2940, 1475, 1365, 1290, 790, <540 (w=1, CH2). Anal. Caled for C25H31N2: C, 82.70; H, 10.11; N, 6.89. Found: C, 82.42; H, 10.51; N, 6.94.

(2R,5R)-1,4-Di-neo-hexyl-2,5-diphenylpiperezine Monohydrochloride (3 · HCl) Obtained by the same procedure as described for the preparation of 2 · HCl. White solids; mp 87–88-°C (dec.) (from EtOH·H2O); 15N-NMR (solid) δ: 23.9, 37.8 IR (KBr cm−1): 3450, 2960, 2400, 1680, 1475, 1365, 1290, 790, 760, [ε]233 −75.4° (c=1.1, CHCl3). This compound was too hygroscopic to get the correct analytical data.

(2R,5R)-1,4-Di-neo-hexyl-2,5-diphenylpiperezine Dihydrochloride (3 · 2HCl) Obtained by the same procedure as described for the preparation of 2 · 2HCl. White solids; mp 136–137 °C (dec.) (from EtOH·H2O); 15N-NMR (solid) δ: 36.7, 19 (KBr cm−1): 2960, 2240, 1675, 1465, 1360, 1200, 760, 700, [ε]233 −92.5° (c=0.32, CHCl3). Anal. Caled for C25H31N2Cl2·2C, 70.12; H, 9.25; N, 5.84. Found: C, 70.12; H, 9.34; N, 5.75.

X-Ray Crystallographic Data. (2R,5R)-Diphenylpiperezine Monohydrochloride (1 · HCl) C25H25ClN2·H2O at 2(0,Cl,N2)-2HCl·2H2O,14
FW = 585.62, colorless, prismatic, orthorhombic, space group C222₁, a = 10.07(1) Å, b = 23.02(2) Å, c = 28.73(1) Å, V = 6658 Å³, Z = 16, Dₐ = 1.168 g/cm³. The structure was refined to R = 0.116, R₁ = 0.164.

(28,5R)-Diphenylpiperazine Dihydrochloride ¹⁰ (1·2HCl) C₂₂H₂₂Cl₂N₄, FW = 311.12, colorless, prismatic, orthorhombic, space group P2₁2₁2₁, a = 19.681(6) Å, b = 11.201(2) Å, c = 7.299(2) Å, V = 1583.2 Å³, Z = 4, Dₐ = 1.306 g/cm³. The structure was refined to R = 0.038, R₁ = 0.050.

(28,5R)-1-Methyl-2,5-diphenylpiperazine Monohydrochloride ¹⁰ (2·HCl) C₂₂H₂₂Cl₂N₄, FW = 328.80, colorless, prismatic, monoclinic, space group P2₁, a = 11.985(3) Å, b = 6.261(1) Å, c = 11.124(3) Å, β = 107.19°, V = 797.5 Å³, Z = 2, Dₐ = 1.203 g/cm³. The structure was refined to R = 0.035, R₁ = 0.047.

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7) A crystalline lattice for l-HCl has two molecules of l-HCl and two molecules of H₂O. Because the both conformations of l-HCl in the same lattice are quite similar each other, one structure of them is illustrated in Fig. 1.