Crystal Structure of 4-Phenyl-piperazine-1-sulfonamide

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The structure of 4-phenyl-piperazine-1-sulfonamide was determined by X-ray crystallography. The compound crystallized in a monoclinic system and was characterized as follows: \( P2_1/c \), \( a = 24.1829(7) \), \( b = 9.5485(3) \), \( c = 9.7885(2) \), \( \beta = 92.2337(16) \), \( Z = 8 \), \( V = 2258.55(11) \). The crystal structure was solved by direct methods and refined by full-matrix least-squares on \( F^2 \) to final values of \( R1 = 0.0427 \) for 3206 reflections \( |I > 2\sigma(I)| \) and \( R1 = 0.0739 \), \( wR2 = 0.1083 \) for all the 4589 unique reflections. The crystal structure consists of layers of polar regions that enclose a sulfonamide function linked by hydrogen bonds and hydrophobic regions with \( \pi-\pi \) stacking interactions.

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The introduction of sulfonamides into clinical medicine in the 1930s marked the beginning of microbial chemotherapy.¹ Sulfonamides, an important class of pharmaceutical compounds, actually exhibit a wide spectrum of biological activities including antibacterials, diuretics, hypoglycemics and HIV protease inhibitors.² The emerging resistance of microorganisms to some synthetic antimicrobial agents makes it necessary to continue the search for new antimicrobial substances. Therefore, numerous molecules containing sulfonamide structure have been created, such as the new modified sulfonamide title compound submitted to X-ray analysis.

The vast majority of sulfonamides are prepared from the reaction of a sulfonyl chloride with ammonia, or primary or secondary amines, or via related transformations.³ More recently, a novel approach for the synthesis of alkyl and aryl sulfonamides has been reported by Shaabani et al.⁴ In our previous works, we established that chlorosulfonyl isocyanate is a suitable reagent that allows the introduction of a sulfonamide moiety in bioactive molecules.⁵ In this research 4-phenyl-piperazine-1-sulfonamide (Fig. 1) was prepared in two steps (carbamoylation-sulfamoylation) by the reaction of chlorosulfonyl isocyanate (1.62 g, 11.4 mmol) and dimethyl malate (1.84 g, 11.4 mmol) in anhydrous CH₂Cl₂ (20 mL). After 30 min, N-chlorosulfonylcarbamate was added to a solution of 4-phenyl-piperazine (1.47 g, 11.4 mmol) in the same solvent (20 mL) in the presence of triethylamine (1.1 equiv) at 0°C. The resulting mixture was stirred for less than 2 h at room temperature. The reaction mixture was washed with 0.1 M HCl and water, and the organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuum. The residue was purified by chromatography on silica gel (eluted with CH₂Cl₂) to give sulfonamide as a white solid in high yields (>80%). Single crystal suitable for X-ray structure analysis could be obtained by slow evaporation of a concentrated solution in ether at room temperature.

The crystal and structure-refinement data are summarized in Table 1. An ORTEP plot of the molecule is given in Fig. 2. All H atoms attached to C atoms were fixed geometrically and treated as riding with C-H = 0.93 Å (aromatic) or 0.97 Å (secondary CH₂ group) with Uiso(H) = 1.2 Uiso(C) or 1.5 Uiso(C),

Table 1 Crystal, experimental and refinement data

![Chemical diagram of the title compound.](image)

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respective. H atoms of amino group were located in a
difference Fourier map and included in subsequent refinement
restraints (N-H = 0.90(1)Å and H–H = 1.66(2)Å with Unw(H) =
1.2 Unw(N). In the last stage of refinement, they were treated as
riding on their parent N atom.
The asymmetric unit of the title compound is built up from 2
molecules oriented face to face in an antiparallel manner (Fig.
2). The piperazine ring has a chair conformation, the most
stable chemical conformation, with bond angles of around 109°.
The crystal structure consists of hydrophilic layers that enclose
a sulfonamide function and hydrophobic layers made of a
phenyl-piperazine structure. These layers are stacking along the
a direction (Fig. 3). In this crystal packing, the molecules are
linked via weak intermolecular N–H–O=O hydrogen bonds,
forming an infinite intermolecular hydrogen-bond network
present along the b and c directions (Table 2). This study
revealed that the π-π stacking interaction between nearby phenyl
ring is an T-shaped edge-to-face arrangement8 with a distance of
5.504 Å between the ring centers. These edge-to-face
interactions play an essential role in the cohesion of the crystal.

Table 2 Hydrogen-bonds geometry (Å and °)

<table>
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<tr>
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<th>D–H–A</th>
<th>D–H</th>
<th>H–A</th>
<th>D–A</th>
<th>DHA</th>
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<tr>
<td>N(11)-H(11A)–O(12A)</td>
<td>0.897</td>
<td>2.321</td>
<td>3.170</td>
<td>157.70</td>
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<tr>
<td>N(11)-H(11A)–O(11A)</td>
<td>0.897</td>
<td>2.621</td>
<td>3.138</td>
<td>117.53</td>
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<tr>
<td>N(11)-H(11B)–O(12A)</td>
<td>0.894</td>
<td>2.350</td>
<td>3.210</td>
<td>161.30</td>
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<tr>
<td>N(11B)-H(11C)–O(11B)</td>
<td>0.902</td>
<td>2.230</td>
<td>3.092</td>
<td>159.91</td>
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</tr>
<tr>
<td>N(11B)-H(11D)–O(11B)</td>
<td>0.899</td>
<td>2.509</td>
<td>3.348</td>
<td>155.52</td>
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<tr>
<td>N(11B)-H(11D)–O(12B)</td>
<td>0.899</td>
<td>2.515</td>
<td>3.130</td>
<td>126.07</td>
<td></td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:
(i) –x+1, –y+1, –z+1; (ii) –x+1, –y+1/2, –z+3/2; (iii) x, –y+1/2, z+1/2;
(iv) –x, y+1/2, –z+3/2; (v) –x, –y, –z+1; (vi) x, –y+1/2, z–1/2.

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