

Hydrogen Bonding Patterns in Sulfonylureas: Pattern Dependence on the Nature of Amine Substituent

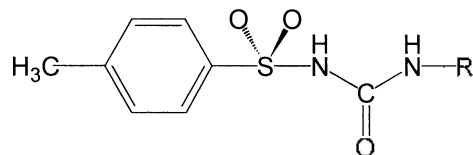
Byeang Hyeon Kim,* Mi Kyoung Ahn, and Gil Tae Hwang

Department of Chemistry, Center for Biofunctional Molecules, Pohang University of Science and Technology, Pohang 790-784, Korea

Received December 14, 1998

Sulfonylureas have constituted an important class of therapeutic agents in medicinal chemistry since the discovery of their hypoglycemic activity and weed-growth inhibiting properties.¹ Sulfonylurea hypoglycemic tolbutamide² and sulfonylurea herbicides³ are among most representative examples. Even though their synthetic, pharmacological studies, and structure-activity relationship studies are reported frequently,⁴ their studies for hydrogen bonding self-assemblies are relatively rare. Recently, sulfonylurea motif was extensively used for the generation of calixarene capsules.⁵ Calix[4]arene tetrasulfonylurea derivatives dimerize to the capsules with certain cavities through hydrogen bonds in a cyclic "head-to-tail" arrangement. To investigate the hydrogen bonding patterns of simple and acyclic sulfonylurea homodimers we synthesized two types (diaryl, and alkyl aryl) of sulfonylureas. We report here the hydrogen bonding patterns, x-ray crystal structures, and crystal packing diagrams of these sulfonylureas.

In order to find out structure-pattern relationship in the hydrogen bonding array of sulfonylurea, we prepared sulfonylureas **1** and **2** by using the reactions of *p*-toluenesulfonyl isocyanate with methylamine and aniline in 88% and 96% yield, respectively. After purification, x-ray diffraction-grade single crystals of the compounds **1**⁶ and **2**⁷ were grown by slow solvent evaporation of an acetonitrile solution and vapor diffusion technique (chloroform:solvent, hexane:non-solvent), respectively. The x-ray crystal structures of these sulfonylureas are shown in Figure 1.



1; R=CH₃

2; R=Ph

Sulfonylureas **1** and **2** are readily self-assembled to homodimers **1·1** and **2·2**, respectively. Hydrogen bonding patterns and distances in the homodimers of these sulfonylureas are shown in Figure 2. In the case of alkyl aryl sulfonylurea homodimer **1·1**, the usual "head-to-tail" hydrogen bonding pattern, which is typically observed in the crystal structures of urea derivatives, is the normal mode of hydrogen bonding.⁸ However, the diaryl sulfonylurea **2** shows a rare "head-to-head" hydrogen bonding pattern which may attribute to

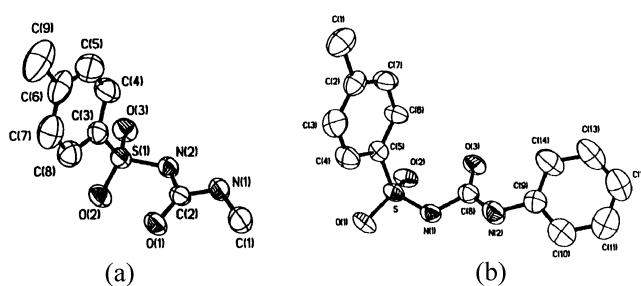


Figure 1. ORTEP (50% probability thermal ellipsoids) views of (a) compound **1**, and (b) compound **2**. Solvent acetonitrile in the crystal structure of **1** is omitted for clarity.

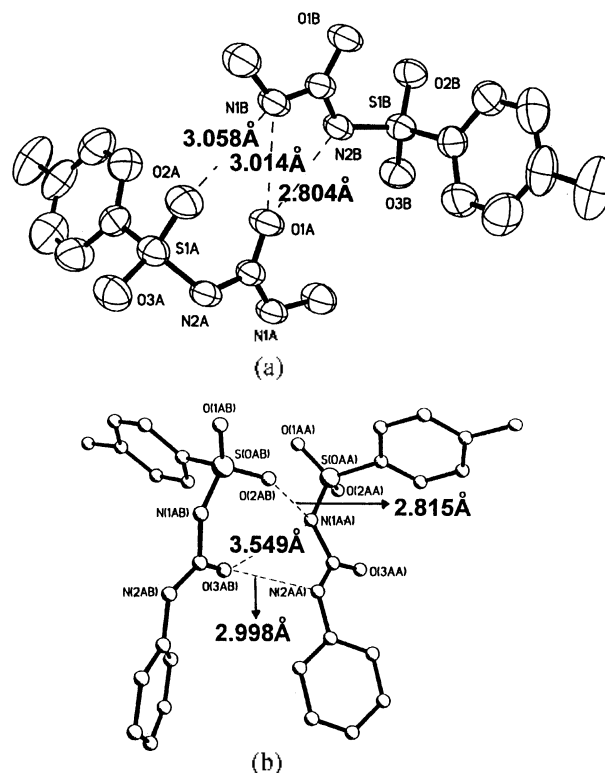


Figure 2. Views of the H-bonded dimers of (a) **1·1** and (b) **2·2**. Dashed lines are indicative of H-bonding interaction. The numbers in boldface represent the H-bonding distances.

the combination of aromatic-aromatic interactions and steric effects. This rationale is further supported by the comparison of packing diagrams between **1** and **2** (Figure 3). In crystal packing, hydrogen bonding and aromatic-aromatic interac-

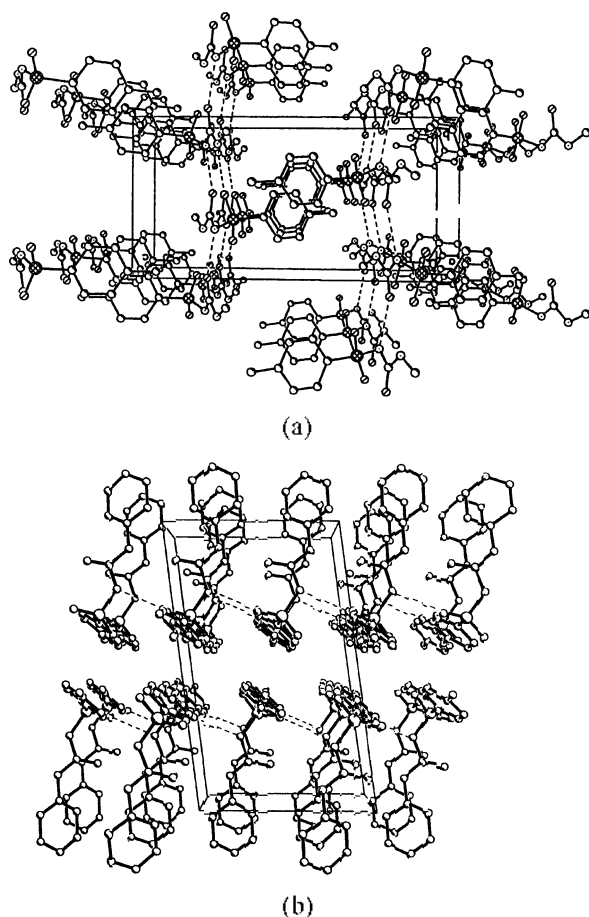


Figure 3. Crystal packing diagrams of (a) compound **1** viewed down the crystallographic *a* axis, and (b) compound **2** viewed down the crystallographic *b* axis.

tions play important roles. In the cases of alkyl aryl and diaryl sulfonylureas, aromatic-aromatic interactions as well as hydrogen bonding might be expected to influence crystal packing. However, aromatic-aromatic interactions are complicated by the spatially anisotropic nature of aromatic rings.⁹ In the crystal packing of **1** and **2**, the major stabilizing interactions are hydrogen bonds and additional stabilization comes from aromatic-aromatic interactions. Both "head-to-head" and "head-to-tail" bonding patterns possess three hydrogen bonds per homodimer. To get enough additional stabilization in the multiple hydrogen bonding arrays of **1** and **2**, these arrays need the favorable aromatic-aromatic interactions as many as possible. In the case of sulfonylurea **1**, "head-to-tail" arrangement provides maximum numbers of aromatic-aromatic interactions. On the other hand, "head-to-head" pattern of sulfonylurea **2** afford a better crystal packing from the viewpoint of aromatic-aromatic interactions and steric effects. Due to the general tendency for better accommodation of aromatic-aromatic interactions in crystal packing, subtle structural change from alkyl to aryl induces the switch in the hydrogen bonding pattern from "head-to-tail" to "head-to-head".

Hydrogen bonding shapes and distances in sulfonylureas are quite different from those of normal ureas because of the

participation of one of sulfonyl oxygens in hydrogen bonding. In the homodimers of normal ureas, two hydrogen bonding distances are almost identical. Because sulfonylurea has two hydrogen bonding N-H donors and two acceptors (O-S, and O-C), there are three different hydrogen bonds (two N-H...O-C and one N-H...O-S) in sulfonylurea homodimers. These hydrogen bonding distances are in the range of 2.804 Å–3.549 Å (Figure 2). The main reason for the discrepancy in hydrogen bonding distance results from the increased acidity (increased donor ability) of the sulfonylurea-NH proton.¹⁰ Therefore sulfonylurea-NH proton makes the strongest hydrogen bond in both **1-1** (SO₂N-H...O-C, N...O distance: 2.804 Å) and **2-2** (SO₂N-H...O-S, N...O distance: 2.815 Å). The distances of two remaining hydrogen bonds are similar in **1-1** (3.014, 3.058 Å) but different in **2-2** (2.998, 3.549 Å). The difficulty to obtain the heterodimer **1-2** by mixing equimolar quantity of **1** and **2** may be attributable to the difference in hydrogen bonding patterns, shapes, and distances between homodimers **1-1** and **2-2**.

In summary, we observed two different types of hydrogen bonding pattern ("head-to-head" and "head-to-tail") in pharmacologically important sulfonylureas depending on the nature of substituents (aryl and alkyl) of amine components. We analyzed the hydrogen bonding characteristics such as patterns, shapes, and distances in the sulfonylurea homodimeric units with the aid of x-ray crystal structures and packing diagrams of sulfonylureas **1** and **2**. This study clearly demonstrates that sulfonylurea is a useful hydrogen bonding motif with multiple donor and acceptor sites.

Acknowledgment. We are grateful to the Korea Science and Engineering Foundation (96-0501-04-01-3) for financial support. We thank Professor Kimoon Kim and Dr. Ki Min Park for the x-ray work.

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- Crystal data* for **1**: C₉H₁₂N₂O₃S·C₁₁H₅CN, M=269.32, crystal system: monoclinic, space group: P2(1)/n, a=8.204(5) Å, alpha=90°, b=9.196(3) Å, beta=93.85(4)°, c=18.389(8) Å, gamma=90°, V=1384.3(11) Å³, Z=4, d_{calc}=1.292 g cm⁻³, T=296(2) K, Siemens SMART diffractometer with CCD detector, Mo K_α (λ=0.71073 Å), μ=2.38

cm^{-1} . Of 2573 measured data, 1886 were independent ($R_{\text{int}}=0.0459$), $R1 [I > 2\sigma(I)]=0.0722$, $wR2$ (all data)=0.2091 and $\text{GOF}=1.078$. There is one molecule of $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$ along with one CH_3CN solvated molecule per asymmetric unit. Solvent molecules have nothing to do with the hydrogen bonding pattern of the homodimer.

7. Crystal structure for **2**: $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$, $M=290.33$, crystal system: monoclinic, space group: $P2_1/C$, $a=15.7030(17)$ Å, $\alpha=90^\circ$, $b=9.7740(10)$ Å, $\beta=97.535(2)^\circ$, $c=9.5580(10)$ Å, $\gamma=90^\circ$, $V=1454.3(3)$ Å³, $Z=4$, $d_{\text{calc}}=1.326$ g cm^{-3} , $T=293(2)$ K, Siemens SMART diffractometer with CCD detector, Mo K_α ($\lambda=0.71073$), $\mu=2.31$ cm^{-1} . Of 5613 measured data, 2265 were independent ($R_{\text{int}}=$

0.0469), $R1 [I > 2\sigma(I)]=0.0876$, $wR2$ (all data)=0.2537 and $\text{GOF}=1.162$.

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