CRYSTAL GROWTH & DESIGN

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Polymorphism of Aromatic Sulfonamides with Fluorine Groups

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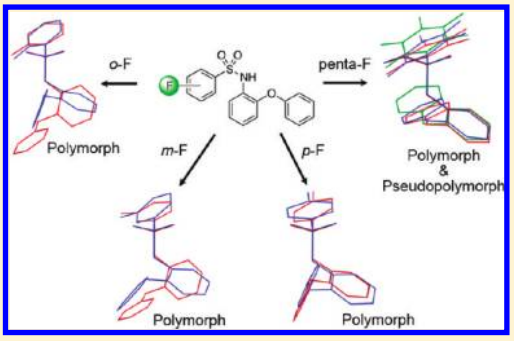
Supporting Information

ABSTRACT: *N*-(2-Phenoxyphenyl)benzenesulfonamide (**1**) and fluorine-substituted *N*-(2-phenoxyphenyl)benzene sulfonamides (**2**–**5**) were designed to examine the effect of a fluorine group in the polymorphism of aromatic sulfonamides. Single-crystal X-ray analysis revealed that those with a fluorine (**2**–**5**) afforded polymorphs or pseudopolymorphs while the sulfonamide without fluorine (**1**) did not. From the differential scanning calorimetry measurements, stable (**2a**–**5a**) and metastable (**2b**–**5b**) crystalline forms were identified. The sulfonamide **1** formed a dimer through hydrogen bonds (H-bonds), which were aligned into two-dimensional (2D) layers via π/π and CH/π interactions. In **2b**, **3b**, and **4a**, the sulfonamide constructed a dimer through H-bonds, which formed 2D layers via CH/F interactions. The sulfonamides **4** formed a one-dimensional (1D) straight chain via H-bonds, which were arranged into 2D layers via CH/F, CH/O, and CH/π interactions in **4b**. The sulfonamide **5** either formed a dimer through H-bonds, which formed 2D layers via CH/O and π/π interactions in **5a**, or formed a 1D straight chain via CH/O and π/π interactions, which were arranged into 2D layers via F/F and CH/F interactions in **5b**. In the pseudopolymorph **5c**, the sulfonamide **5** formed a 1D zigzag chain via CH/F interactions and was assembled into 2D layers via π/π interactions.



INTRODUCTION

Polymorphism and pseudopolymorphism of organic compounds have attracted significant attention in medicinal chemistry and materials science because compounds exhibit various types of physical and chemical properties due to the different packing types of the component molecules.[1] Generally, most polymorphisms and pseudopolymorphisms occur for organic molecules and are derived from multiple intermolecular weak noncovalent interactions such as hydrogen bonds,[2] CH/π interactions,[3] aromatic–aromatic interactions,[4] and others,[5] where solvent,[6] temperature,[7] and other factors[8] are involved in the crystal-growth process. Especially, polymorphism of organic molecules bearing a fluorine group are important because a large number of drugs contain fluorine groups on their organic skeleton, and they are important for the drugs' specific pharmacological activities. Thus, comparisons between polymorphs offer fundamental and valuable information on the relation between the alignment of individual molecules and their properties in the solid state. In addition, the fluorine group shows unique and specific chemical properties including F/π, F/F, and donor–acceptor intermolecular interactions.[9] Thus when fluorine groups are introduced into organic molecules that previously did not show polymorphism, we expect that these unique interactions may result in the fluorine-substituted compounds having a higher probability of demonstrating polymorphism.

Previously, we reported polymorphism and pseudopolymorphism of aromatic bis-phenyl and macrocyclic molecules containing sulfonamide parts.[10] Recently, Nangia et al. also reported that several substituted aromatic sulfonamides yield polymorphism of two or more crystal systems.[11] These polymorphs and pseudopolymorphs are comprised of various types of molecular network structures through noncovalent interactions. However, the effects of fluorine groups on polymorphs and pseudopolymorphs of aromatic sulfonamides are rarely reported. Here, we describe the syntheses and characterization of the crystal structures of a series of aromatic sulfonamides that have fluorine groups: *N*-(2-phenoxyphenyl)-benzenesulfonamide (**1**), 2-fluoro-*N*-(2-phenoxyphenyl)benzene-sulfonamide (**2**), 3-fluoro-*N*-(2-phenoxyphenyl)benzenesulfonamide (**3**), 4-fluoro-*N*-(2-phenoxyphenyl)benzenesulfonamide (**4**), and 2,3,4,5,6-pentafluoro-*N*-(2-phenoxyphenyl)benzene-sulfonamide (**5**). All of these aromatic sulfonamides with fluorine groups exhibited polymorphism in contrast to a compound that did not have fluorine groups. The crystal arrangements were constructed by intermolecular hydrogen bonds, CH/F, CH/O, and CH/π interactions, and π/π interactions between the component units.

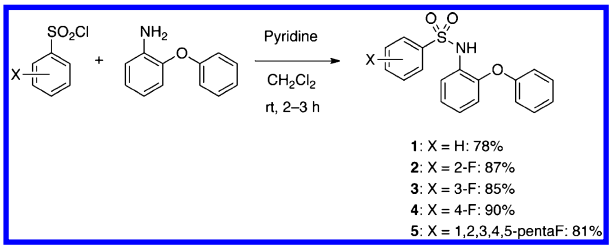
EXPERIMENTAL SECTION

General. Benzenesulfonyl or fluorobenzenesulfonyl chloride (2.0 mmol) was added dropwise to a solution of 2-phenoxyaniline (2.2 mmol) in pyridine (50 mL) with stirring under an Ar atmosphere. After being stirred at room temperature for 3 h, the reaction mixture was poured into ice and extracted with chloroform. The organic layer was successively washed with 2 M HCl (30 mL), saturated aqueous

Received: January 23, 2012
Revised: April 11, 2012

   dx.doi.org/10.1021/cg300098q | *Cryst. Growth Des.* XXXX, XXX, XXX–XXX

Scheme 1. Synthetic Procedure for the Preparation of Sulfonamides 1−5



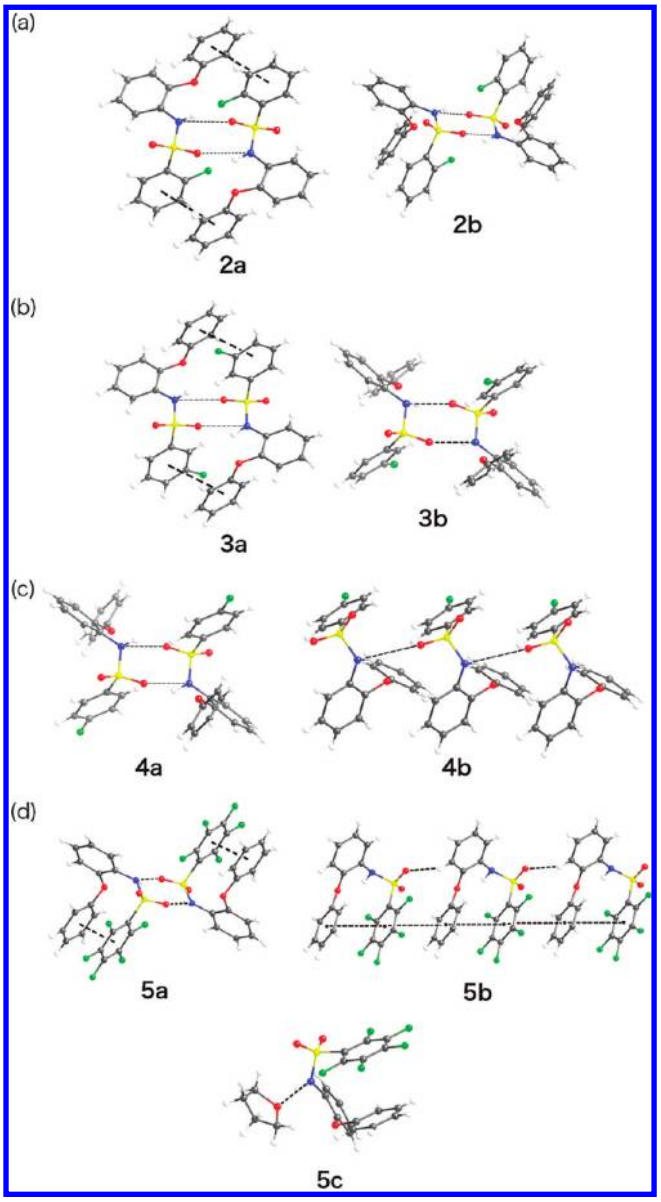


Figure 1. Comparison between polymorphs and pseudopolymorph of the crystals (a) **2**, (b) **3**, (c) **4** and (d) **5**. Black dotted lines show H-bonds, CH/O interactions, and aromatic−aromatic interactions.

$NaHCO_3$ (30 mL), and brine (30 mL) and dried over Na_2SO_4. The solvent was evaporated, and the crude product was recrystallized from 20 different types of mixed solvents to give a pure product.

N-(2-Phenoxyphenyl)benzenesulfonamide, ***1****.* Yield 0.60 g, 87%. Mp 110−111 °C. IR (KBr) ν 1149, 3242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.83 (dt, J = 2.0, 8.0 Hz, 1H), 7.63 (dd, J = 2.4, 8.0 Hz, 1H), 7.49 (m, 1H), 7.38 (s, 1H), 7.27 (m, 3H), 7.17 (dt, J = 0.8,

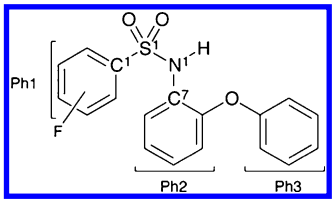
Table 1. Crystallographic Data for Sulfonamides 1−5

	1	2a	2b	3a	3b	4a	4b	5a	5b	5c
formula	$C_{18}H_{15}NO_3S$	$C_{18}H_{14}FNO_3S$	$C_{18}H_{14}FNO_3S$	$C_{18}H_{14}FNO_3SS$	$C_{18}H_{14}FNO_3SS$	$C_{18}H_{14}FNO_3S$	$C_{18}H_{14}FNO_3SS$	$C_{18}H_{10}F_5NO_3S$	$C_{18}H_{10}F_5NO_3S$	$C_{18}H_{10}F_5NO_3S{\cdot}C_4H_8O$
cryst. syst.	monoclinic	monoclinic	triclinic	monoclinic	monoclinic	triclinic	monoclinic	monoclinic	monoclinic	monoclinic
space group	$P2_1/n$	$P2_1/n$	$P\bar{1}$	$P2_1/n$	$P2_1/n$	$P\bar{1}$	$P2_1/c$	$P2_1/n$	$P2_1$	$P2_1/n$
a (Å), α (deg)	9.376(3), 90	9.446(2), 90	8.196(3), 101.227(3)	9.489(2), 90	8.665(8), 90	8.250(3), 102.597(4)	9.667(2), 90	8.865(3), 90	7.887(3), 90	9.363(3), 90
b (Å), β (deg)	12.139(4), 90.636(5)	12.131(2), 90.798(2)	9.587(3), 108.692(3)	12.364(3), 91.139(2)	16.09(2), 101.46(1)	9.528(3), 107.235(4)	15.535(1), 97.790(2)	19.508(6), 98.662(3)	5.836(2), 93.745(4)	24.015(8), 101.286(4)
c (Å), γ (deg)	13.585(4), 90	13.454(3), 90	11.428(4), 103.611(4)	13.435(3), 90	12.12(1), 90	11.468(4), 104.579(3)	28.746(6), 90	9.849(3), 90	17.557(6), 90	9.747(3), 90
V (Å^3)	1546.1(8)	1541.4(5)	790.4(4)	1574.8(5)	1656(3)	790.3(4)	1524.1(6)	1683.9(8)	806.4(5)	2149(1)
D_{calcd} (Mgm^{-3})	1.398	1.480	1.443	1.448	1.377	1.443	1.496	1.638	1.480	1.506
Z	4	4	2	4	4	2	4	4	2	4
T (K)	150	120	120	150	296	120	120	120	100	120
R_1, wR_2 (all data)	0.0369, 0.0880	0.0396, 0.0903	0.0402, 0.0915	0.0395, 0.0875	0.0997, 02273	0.0837, 0.1433	0.0600, 0.1052	0.0364, 0.0850	0.0384, 0.0782	0.0846, 0.1900
recryst. from	$CHCl_3$/hexane[a]	$CHCl_3$/hexane[a]	$CHCl_3$/THF[a]	THF/hexane[a]	$CHCl_3$/hexane[a]	$CHCl_3$/hexane[a]	$CHCl_3$/THF[a]	$CHCl_3$/hexane[a]	$CHCl_3$/cyclohexane[a]	$CHCl_3$/THF
H-bond motif	dimer (type A)	dimer (type A)	dimer (type B)	dimer (type A)	dimer (type B)	dimer (type B)	straight (type C)	dimer (type B)	straight (type D)	pseudopolymorph (type E)
CCDC number	860537	860538	860539	860540	860541	860542	860543	860544	860545	860546

[a]Solvent molecules are not included in the crystals.

dx.doi.org/10.1021/cg300098q | *Cryst. Growth Des.* XXXX, XXX, XXX−XXX

Table 2. Conformational Parameters of Sulfonamides 1−5



crystal	torsion angle C1−S1−N1−C7 (deg)	dihedral angle Ph1−Ph2 (deg)
1	66.9(1)	82.9(7)
2a	66.9(2)	83.5(8)
2b	69.9(1)	72.1(9)
3a	66.4(1)	86.8(8)
3b	62.1(3)	75.9(2)
4a	67.9(2)	68.4(2)
4b	72.4(2)	62.7(1)
5a	71.0(1)	68.7(1)
5b	71.6(2)	71.1(1)
5c	74.6(7)	78.8(6)

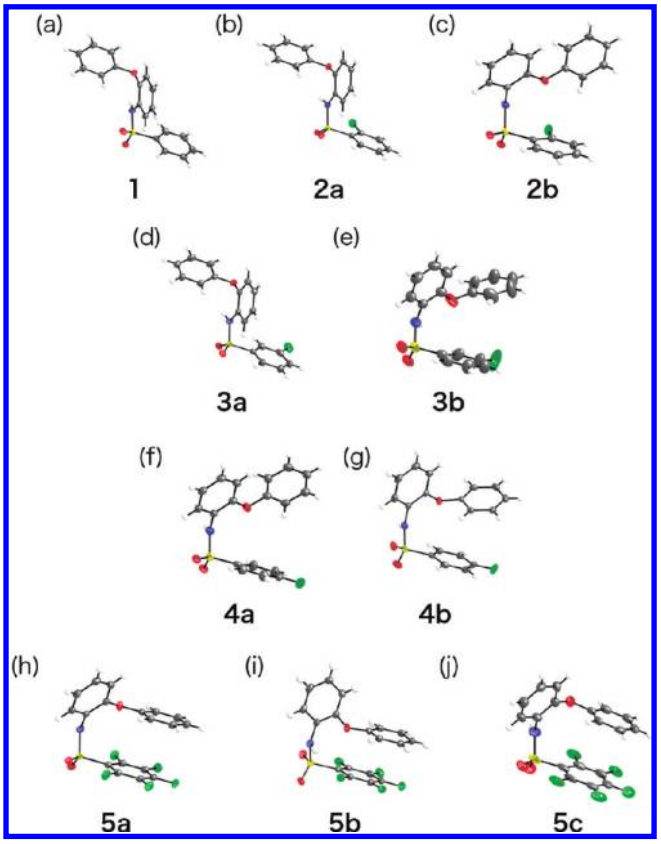


Figure 2. Thermal ellipsoid models of the crystal structures of sulfonamides (a) **1**, (b) **2a**, (c) **2b**, (d) **3a**, (e) **3b**, (f) **4a**, (g) **4b**, (h) **5a**, (i) **5b**, and (j) **5c**. Ellipsoids of all non-hydrogen atoms are drawn at the 50% probability.

7.6 Hz, 1H), 7.12 (dt, J = 1.2, 8.4 Hz, 1H), 7.0 (m, 3H), 6.75 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.91, 117.11, 117.78, 118.47, 122.46, 123.81, 124.00, 124.15, 124.19, 125.78, 127.31, 129.86, 130.78, 135.28, 135.36, 147.53, 155.97, 160.26 ppm. MS (FAB): m/z = 343.0 $[M]^+$. Elemental Anal. Calcd for $C_{18}H_{15}O_3NS$: C, 62.96; H, 4.11; N, 4.08. Found: C, 62.83; H, 3.84; N, 4.17.

2-Fluoro-N-(2-phenoxyphenyl)benzenesulfonamide, 2. Yield 0.60 g, 87%. Mp 110−111 °C. IR (KBr) ν 1149, 3242 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.83 (dt, J = 2.0, 8.0 Hz, 1H), 7.63 (dd,

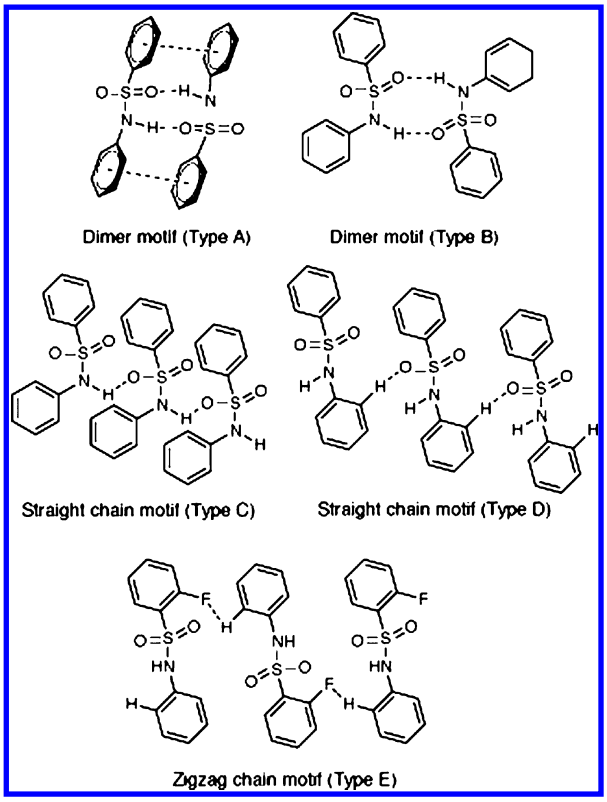


Figure 3. Hydrogen bond motifs of the sulfonamides.

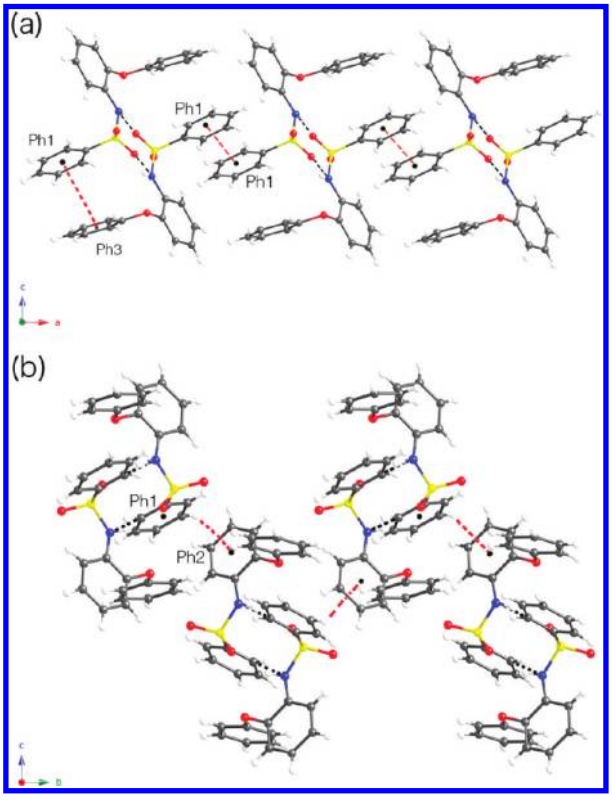


Figure 4. Crystal structure of the sulfonamide **1** in a ball and stick model: (a) arrangement of dimeric units through intermolecular π/π interactions; (b) arrangement of dimeric units through CH/π interactions. Black dotted lines and red dotted lines show H-bonds and aromatic−aromatic interactions, respectively.

dx.doi.org/10.1021/cg300098q | *Cryst. Growth Des.* XXXX, XXX, XXX−XXX

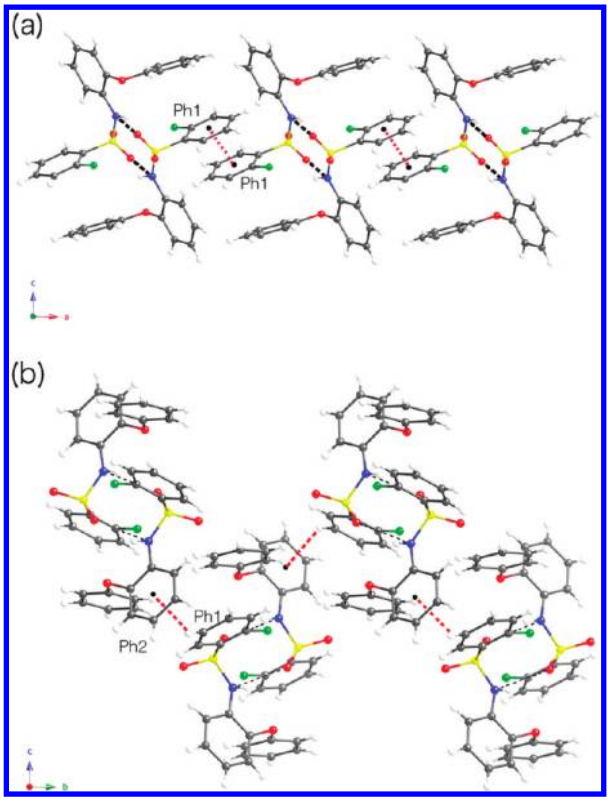


Figure 5. Crystal structure of the sulfonamide **2a** as a ball and stick model: (a) arrangement of the dimeric units through intermolecular π/π interactions; (b) arrangement of dimeric units through CH/π interactions. Black dotted lines and red dotted lines show H-bonds and aromatic−aromatic interactions, respectively.

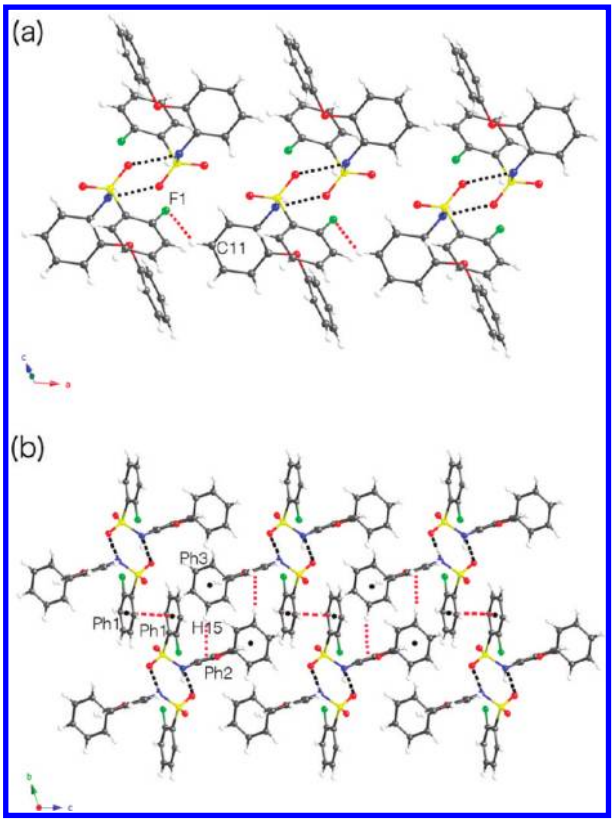


Figure 6. Crystal structure of the sulfonamide **2b** as a ball and stick model: (a) arrangement of the dimeric units through intermolecular CH/F and CH/π interactions; (b) arrangement of dimeric units through π/π and CH/π interactions. Black dotted lines and red dotted lines show H-bonds and aromatic−aromatic interactions, respectively.

J = 2.4, 8.0 Hz, 1H), 7.49 (m, 1H), 7.38 (s, 1H), 7.27 (m, 3H), 7.17 (dt, J = 0.8, 7.6 Hz, 1H), 7.12 (dt, J = 1.2, 8.4 Hz, 1H), 7.0 (m, 3H), 6.75 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.91, 117.11, 117.78, 118.47, 122.46, 123.81, 124.00, 124.15, 124.19, 125.78, 127.31, 129.86, 130.78, 135.28, 135.36, 147.53, 155.97, 160.26 ppm. MS (FAB): m/z = 343.0 $[M]^+$. Elemental Anal. Calcd for $C_{18}H_{14}O_3NSF$: C, 62.96; H4.11; N, 4.08. Found: C, 62.83; H, 3.84; N, 4.17.

*3-Fluoro-N-(2-phenoxyphenyl)benzenesulfonamide, **3***. Yield 0.58 g, 85%. Mp 109−110 °C. IR (KBr) ν 1152, 3242 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (dt, J = 2.0, 8.0 Hz, 1H), 7.53 (m, 1H), 7.44 (m, 1H), 7.36 (m, 1H), 7.25 (t, J = 16.0 Hz, 3H), 7.07 (m, 4H), 6.70 (dd, J = 2.4, 8.0 Hz, 1H), 6.62 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 114.58, 114.83, 117.87, 118.40, 120.10, 120.31, 122.67, 123.08, 123.12, 124.01, 124.18, 126.12, 127.33, 129.95, 130.66, 130.74 ppm. MS (FAB): m/z = 343.0 M^+. Elemental Anal. Calcd for $C_{18}H_{14}O_3NSF$: C, 62.96; H, 4.11; N, 4.08. Found: C, 62.63; H, 4.06; N, 4.08.

*4-Fluoro-N-(2-phenoxyphenyl)benzenesulfonamide, **4***. Yield 0.61 g, 90%. Mp 114−115 °C. IR (KBr) ν 1142, 3240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (m, 3H), 7.25 (t, J = 16.0, 2H), 7.05 (m, 6H), 6.70 (dd, J = 2.0, 8.0 Hz, 1H), 6.62 (dd, J = 2.2, 8.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.02, 116.07, 118.02, 118.28, 122.81, 124.04, 124.09, 126.04, 127.58, 129.92, 129.96, 130.05, 147.56, 155.77 ppm. MS (FAB): m/z = 343.0 M^+. Elemental Anal. Calcd for $C_{18}H_{14}O_3NSF$: C, 62.96; H, 4.11; N, 4.08. Found: C, 62.92; H, 3.78; N, 4.32.

*2,3,4,5,6-Pentafluoro-N-(2-phenoxyphenyl)benzenesulfonamide, **5***. Yield 0.67 g, 81%. Mp 122−123 °C. IR (KBr) ν 1145, 3250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71−7.67 (m, 1H), 7.49 (brs, 1H), 7.31 (t, J = 8.4 Hz, 2H), 7.18−7.12 (m, 3H), 6.88−6.84 (m, 1H), 6.78 (d, J = 8.0 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.97, 147.73, 129.98, 127.38, 126.08, 124.53, 124.13, 124.06, 118.72, 117.51 ppm. MS (FAB): m/z = 416.3 $[M+H]^+$. Elemental Anal. Calcd for $C_{18}H_{10}O_3NSF_5$: C, 52.05; H, 2.43; N, 3.37. Found: C, 52.30; H, 2.44; N, 3.24.

Crystallization. The sulfonamides were dissolved with chloroform, ethyl acetate, or tetrahydrofuran as good solvents. Each solution was put into microtubes that included chloroform, ethyl acetate, toluene, hexane, methanol, acetone, acetonitrile, and tetrahydrofuran as poor solvents. (See Supporting Information).

Measurement. X-ray data of the crystals were collected on a CCD diffractometer with graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation. Data collection for crystals of **3b** was carried out at room temperature. For other crystals, data collections were carried out at low temperature (150−100 K) using liquid nitrogen. The crystal structures were solved by the direct method SHELXS-97 and refined by full-matrix least-squares SHELXL-97.[12] All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included at their calculated positions.

Differential scanning calorimetry (DSC) was measured at a heating rate of 10 K/min. Samples weighing 2−3 mg were heated in open aluminum pans under a nitrogen gas flow of 20 mL/min.

Thermogravimetric analysis (TGA) experiment was measured at a heating rate of 10 °C/min. Sample of **5c** (4.591 mg) was heated in open aluminum pan from 30 to 500 °C.

■ RESULTS AND DISCUSSION

Aromatic sulfonamides (**1**−**5**) were prepared by the reaction of the substituted sulfonyl chloride with 2-phenoxyaniline (Scheme 1). After confirmation of their purities by ^{1}H NMR, ^{13}C NMR, and mass spectrometry (FAB), they were crystallized from 24 combinations of solvents (Table S3, Supporting Information). Two types of solvent-free polymorphs of the crystal for compounds **2**−**5** and a pseudopolymorph of **5** were

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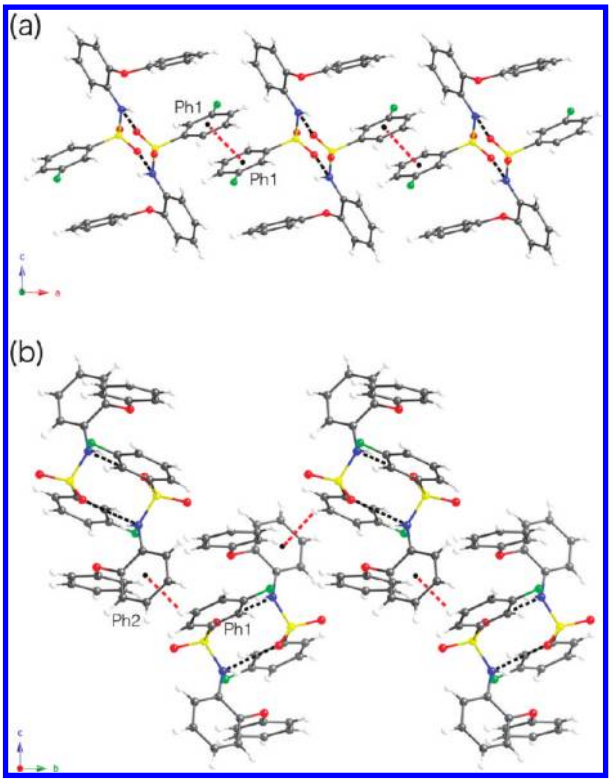

Figure 7. Crystal structure of the sulfonamide **3a** as a ball and stick model: (a) arrangement of the dimeric units through intermolecular π/π interactions; (b) arrangement of dimeric units through tilted CH/π interactions. Black dotted lines and red dotted lines show H-bonds and aromatic−aromatic interactions, respectively.

obtained (Figure 1). Crystal data and conformational parameters of **1**−**5** are shown in Tables 1 and 2. In the all crystal structures, the sulfonamide bonds of all compounds exist in *synclinal* conformation (Figure 2). The torsion angles of the sulfonamide moiety [$C^1-S^1-N^1-C^7$] ranged from 62.1(3)° to 74.6(7)°, and the dihedral angles of Ph1 and Ph2 ranged from 62.7(1)° to 86.8(8)° (Table 2). The intermolecular H-bond motifs of the sulfonamide in the crystal structure were classified as dimer, straight chain, and zigzag chain (Figure 3). Furthermore, the dimer motif was subdivided into type A or type B depending on whether the dimeric structure was stabilized by aromatic−aromatic interactions. A straight chain motif via H-bonds between the sulfonyl oxygen and amide nitrogen was classified as type C, a straight chain motif via CH/O interactions between the sulfonyl oxygen and phenyl carbon was classified as type D, and a zigzag chain motif via CH/F interactions was classified as type E.

Compound **1** crystallized in a monoclinic system, space group $P2_1/n$, and included four molecules in the unit cell. This crystal is classified as Type A and has the sulfonamide dimer motif (N1−H1···O2, 2.933(2) Å, 163.2°, Table S1, Supporting Information) together with an offset π/π stacking interaction. The ring center−ring center distance of two phenyl groups (Ph1 and Ph3) is 3.979(2) Å (Table S2, Supporting Information). As shown in Figure 4a, the dimeric units extend along the *a* axis through π/π stacking interactions to form 1D polymers (Ph1−Ph1 = 3.768(2) Å). Furthermore, the 1D polymers associate along the *b* axis through the tilted T-shaped aromatic−aromatic (CH/π) interaction (Figure 4b). The ring center−ring center distance of the two phenyl groups (Ph1 and Ph2) is 4.909(2) Å, and the angle between two phenyl groups (Ph1 and Ph2) is 72.53°.

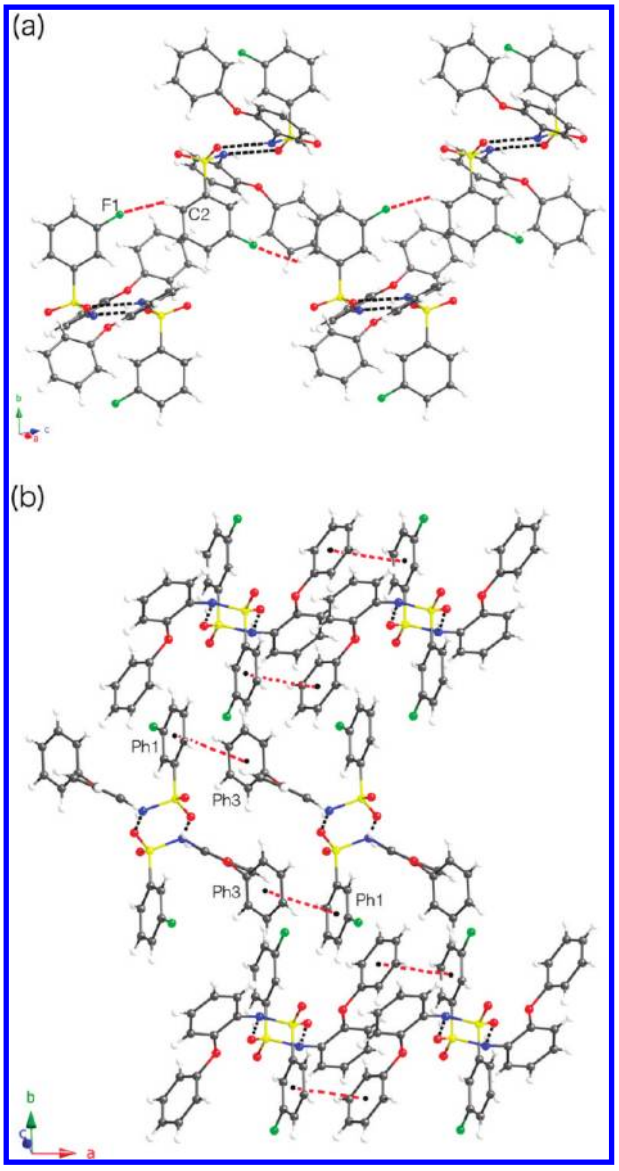

Figure 8. Crystal structure of the sulfonamide **3b** as a ball and stick model: (a) arrangement of the dimeric units through CH/F interactions; (b) arrangement of the dimeric units through π/π interactions. Black dotted lines and red dotted lines show H-bonds and aromatic−aromatic interactions, respectively.

The sulfonamide **2** crystallized as two different polymorphs, **2a** and **2b**, by slow evaporation of $CHCl_3$/hexane or $CHCl_3$/THF solution, respectively (Figure 1a). Crystal **2a** crystallized in a monoclinic system, space group $P2_1/n$, and included four molecules in the unit cell. The sulfonamide **2** forms an NH/O dimer motif with a π/π interaction. The ring center−ring center distance of the two phenyl groups (Ph1 and Ph3) is 4.012(1) Å (Table S2, Supporting Information). The molecular packing of this molecule is similar to that of **1**, which is classified as type A (Figure 5). As shown in Figure 5a, the dimeric units extend along the *a* axis through aromatic−aromatic interactions to form the 1D network (Ph1−Ph1 = 3.805(1) Å). Furthermore, the sulfonamide **2** associates along the *b* axis through the CH/π interaction (Figure 5b). The ring center−ring center distance of the two phenyl groups (Ph1 and Ph2) is 4.828(2) Å, and both

dx.doi.org/10.1021/cg300098q | *Cryst. Growth Des.* XXXX, XXX, XXX−XXX

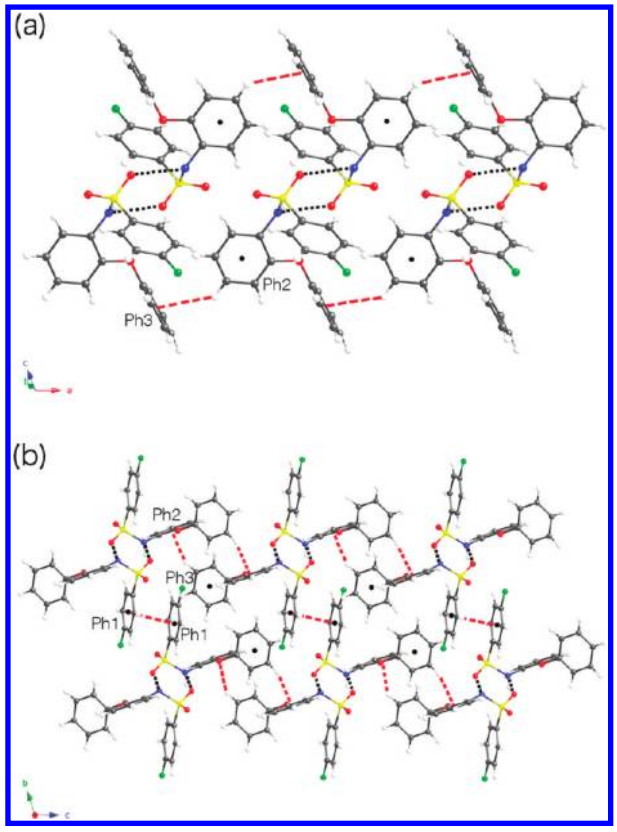

Figure 9. Crystal structure of the sulfonamide **4a** as a ball and stick model: (a) arrangement of the dimeric units through CH/π interactions; (b) arrangement of the dimeric units through π/π and CH/π interactions. Black dotted lines and red dotted lines show H-bonds and aromatic−aromatic interactions, respectively.

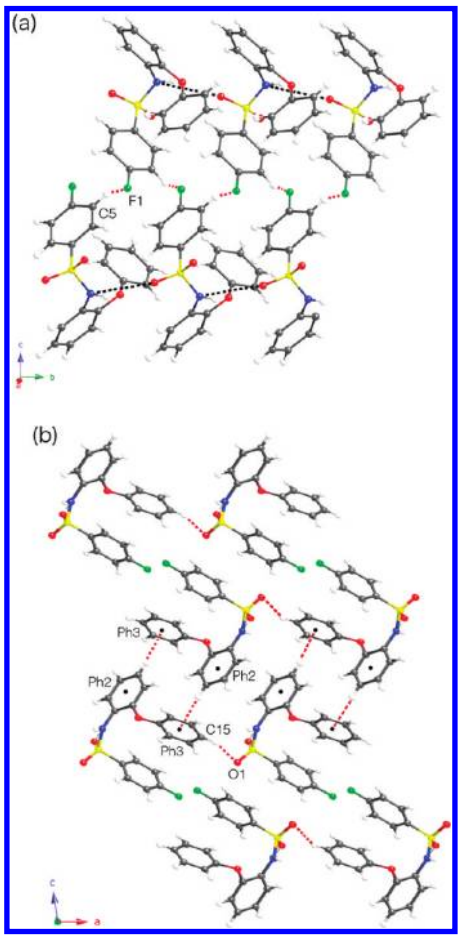

Figure 10. Crystal structure of the sulfonamide **4b** as a ball and stick model: (a) arrangement of the straight chain units through CH/F interactions; (b) arrangement of the straight chain units through CH/O and CH/π interactions. Black dotted lines show H-bonds. Red dotted lines show CH/O and CH/π interactions.

angles between the two phenyl groups (Ph1 and Ph2) are 73.31° (Table S2, Supporting Information). Crystal **2b** forms a dimer motif without π/π interactions in the $P\bar{1}$ space group. As shown in Figure 6a, the sulfonamide **2** associates along the *a* axis through CH/F interactions (C(11)−F(1) = 3.216(2) Å, Table S1, Supporting Information). Furthermore, the dimeric units extend along the *c* axis through π/π and CH/π interactions (Ph1−Ph1 = 3.670(2) Å, Ph2−Ph3 = 4.851(2) Å, Figure 6b).

The sulfonamide **3** crystallized as two different polymorphs, **3a** and **3b**, by slow evaporation of THF/*n*-hexane or $CHCl_3$/*n*-hexane, respectively (Figure 1b). Crystal **3a** crystallized in a monoclinic system, space group $P2_1/n$, and included four molecules in the unit cell. The sulfonamide **3a** forms a dimer motif with π/π stacking. The ring center−ring center distance of the two phenyl groups (Ph1 and Ph3) is 3.919(1) Å (Table S2, Supporting Information). The molecular packing of this molecule is similar to that of **1** and **2a**, which is classified as type A. As shown in Figure 7a, the dimeric units extend along the *a* axis through π/π interactions to form the 1D network (Ph1−Ph1 = 3.943(1) Å). Furthermore, the sulfonamide **3** associates along the *b* axis through the CH/π interactions (Figure 7b). The ring center−ring center distance of Ph1 and Ph2 is 4.928(2) Å, and the angle between Ph1 and Ph2 is 74.05° (Table S2, Supporting Information). In contrast, **3b** forms a dimer motif without π/π interactions in the $P2_1/n$ space group. Type B dimeric units extend in the *ac* plane through CH/F interactions (C(2)−F(1) = 3.236(6) Å, Figure 8a). Furthermore, the sulfonamide **3** extends in the *bc* plane through π/π interactions (Ph1−Ph3 = 4.176(5) Å, Figure 8b).

The sulfonamide **4** crystallized as two different polymorphs, **4a** and **4b**, by slow evaporation of $CHCl_3$/*n*-hexane or $CHCl_3$/THF, respectively (Figure 1c). Crystal **4a** forms a dimer motif without π/π interactions in the $P\bar{1}$ space group. The molecular packing of sulfonamide **4a** is similar to that of **2b**, which is classified as type B. As shown in Figure 9a, the sulfonamide **4** associates along the *a* axis through CH/π interactions (the ring center−ring center distance of Ph2 and Ph3 is 5.035(3) Å, and the angle between Ph2 and Ph3 is 88.25°, Table S2, Supporting Information). Furthermore, the dimeric units extend along the *c* axis through π/π and CH/π interactions (Figure 9b). The ring center−ring center distances of the two phenyl groups (Ph1−Ph1, Ph2−Ph3) are 3.897(2) and 4.857(2) Å, respectively. On the other hand, the sulfonamide **4b** forms a straight chain motif via H-bonds, which is classified as type C. Crystal **4b** crystallized in a monoclinic system, space group $P2_1/c$, and included four molecules in the unit cell. The straight chain units are bridged by CH/F interactions (C(5)−F(1) = 3.409(3) Å, Figure 10a). Furthermore, the straight chain units extend along the *a* axis through CH/O interactions and along the *c* axis through CH/π interactions (O(1)−C(15) = 3.365(3) Å, Ph2−Ph3 = 4.989(2) Å, Figure 10b).

The sulfonamide **5** crystallized as two different polymorphs and a pseudopolymorph, **5a**, **5b**, and **5c** by slow evaporation of

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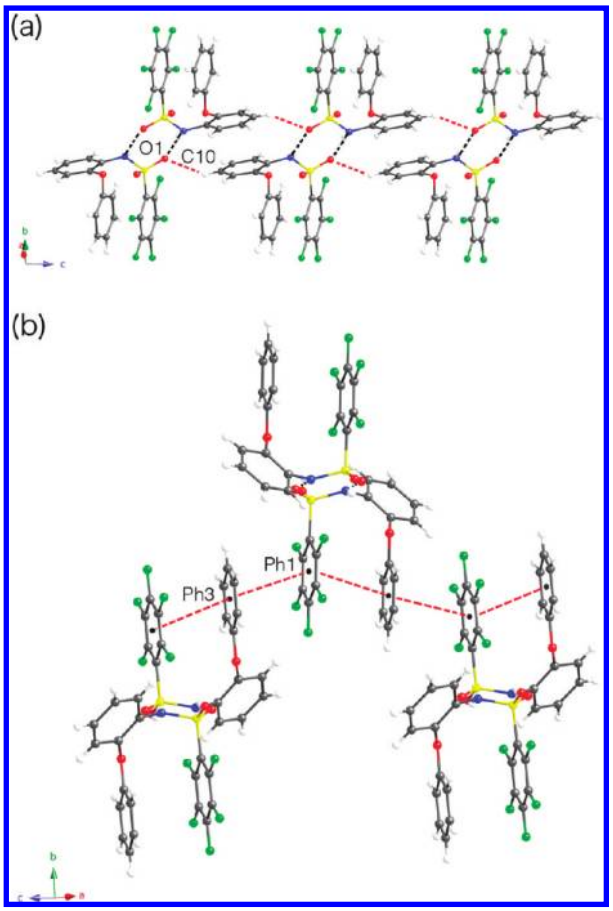

Figure 11. Crystal structure of the sulfonamide **5a** as a ball and stick model: (a) arrangement of the dimeric units through CH/O interactions; (b) arrangement of the dimeric units through π/π interactions. Black dotted lines show H-bonds. Red dotted lines show CH/O and π/π interactions.

$CHCl_3$/*n*-hexane, toluene/MeOH, or $CHCl_3$/THF, respectively (Figure 1d). Crystal **5a** forms a dimer motif without π/π interactions in the $P2_1/n$ space group. As shown in Figure 11a, the sulfonamide **5** associates along the *c* axis through CH/O interactions (O(1)−C(10) = 3.416(2) Å, Figure 11a). Furthermore, the dimeric units extend along the *a* axis through π/π interactions (Ph1−Ph3 = 3.749(2) Å, Figure 11b). The sulfonamide **5b** crystallized in a monoclinic system, space group $P2_1$, and included two molecules in the unit cell. Crystal **5b** forms a straight chain motif via CH/O and π/π interactions, which is classified as type D (C(9)−O(1) = 3.134(3) Å, Ph1−Ph3 = 4.026(2) Å, Figure 12a). The straight chain units associate along the *b* axis through F/F interactions (F(1)−F(5) = 2.888(3) Å, F(2)−F(4) = 2.874(3) Å, Figure 12b). Furthermore, the straight chain units extend along the *c* axis through CH/F interactions (C(15)−F(3) = 3.356(4) Å, Figure S28, Supporting Information). In contrast, the solvent-included pseudopolymorph was obtained from THF by slow evaporation. The sulfonamide **5c** crystallized in a monoclinic system and space group $P2_1/n$. The unit cell contained four molecules of **5** and four molecules of THF. Crystal **5c** forms a zigzag chain motif via CH/F interactions, which is classified as type E (C(18)−F(2) = 3.269(8) Å, Figure 13a). Furthermore, the sulfonamide **5** associates along the *a* axis through π/π interactions (Ph1−Ph3 = 3.701(4) Å, Figure 13b).

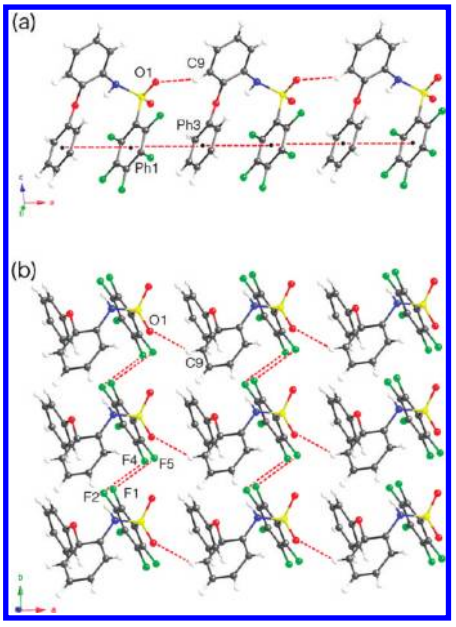

Figure 12. Crystal structure of the sulfonamide **5b** as a ball and stick model: (a) straight chain units via CH/O and π/π interactions; (b) arrangement of the straight chain units through F/F interactions. Black dotted lines show H-bonds. Red dotted lines show CH/O, π/π, and F/F interactions.

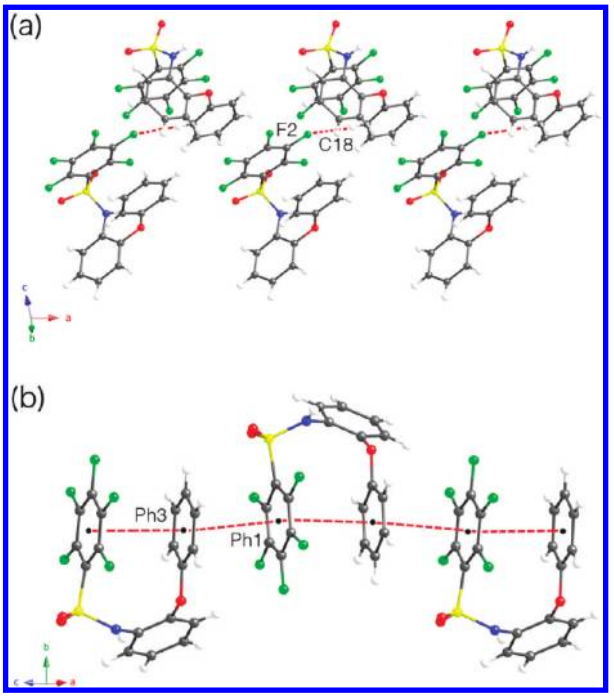

Figure 13. Crystal structure of the sulfonamide **5c** as a ball and stick model: (a) zigzag chain units via CH/F interactions; (b) arrangement of sulfonamide units through π/π interactions. THF molecules are omitted for clarity. Red dotted lines show CH/F and π/π interactions.

Using differential scanning calorimetry (DSC) measurements, we examined the melting points and enthalpies of fusion for all crystals (Table 3 and Supporting Information). The crystals **2a**, **3a**, and **5a** have higher melting points and larger enthalpies than those of **2b**, **3b**, and **5b**, respectively. In the case of the sulfonamide **4**, the crystal packing of **4a** is similar to that of the metastable forms (**2b** and **3b**), and **4b** has higher density than that of **4a**; nevertheless, the crystallization reproducibility of **4b** was not observed.

dx.doi.org/10.1021/cg300098q | *Cryst. Growth Des.* XXXX, XXX, XXX−XXX

Table 3. Thermodynamic Parameters of Crystals 1, 2a, 2b, 3a, 3b, 4a, 5a, and 5b

	melting point (°C)	ΔH_{fus} (kJ mol^{-1})
1	102.0	30.84
2a	108.9	33.38
2b	88.59	28.60
3a	87.27	30.75
3b	86.42	21.30
4a	113.7	31.16
5a	109.5	29.36
5b	98.09	24.30

The molecules in the two polymorphs are conformationally similar, and an overlay diagram of the polymorphs shows that the conformers of the sulfonamides differ only in the diphenyl ether moiety but not the benzenesulfonyl moiety (Figure S31, Supporting Information). In contrast, both exist with different crystal packing depending on the intermolecular behavior of the fluorine group. The introduction of fluorine groups into the aromatic sulfonamides gave rise to the polymorphism due to additional intermolecular CH/F interactions.

CONCLUSION

We demonstrated that the aromatic sulfonamides containing a fluorine group on the benzenesulfonyl moieties showed polymorphs and pseudopolymorphs by crystallization from usual solvents. In crystal **1** without the fluorine group, the sulfonamide formed a dimer through H-bonds, which are assembled into 2D layers through aromatic−aromatic and CH/π interactions. Sulfonamide **1** did not afford a different crystalline form. In the crystals **2a** and **3a**, the molecular packing was similar to that of **1**. In contrast, the sulfonamide constructed dimers through H-bonds, which are assembled into 2D layers via CH/F interactions in the polymorphs **2b** and **3b**. In the crystals **4a** and **4b**, the sulfonamide constructed dimers through H-bonds, which are assembled into 2D layers via CH/F interactions and formed 1D straight chains via H-bonds, which are arranged into 2D layers via CH/F, CH/O, and CH/π interactions. Furthermore, the sulfonamide **5** formed dimers through H-bonds, which are assembled into 2D layers via CH/O and π/π interactions in the crystal **5a**. The sulfonamide **5** formed 1D straight chains via CH/O and π/π interactions, which are arranged into 2D layers via F/F and CH/F interactions in the crystal **5b**. In the pseudopolymorph **5c**, the sulfonamide **5** formed 1D zigzag chains via CH/F interactions, which are assembled into 2D layers via π/π interactions. We believe that the introduction of a fluorine atom into crystalline compounds will affect the appearance of the polymorphs, and the results obtained from these investigations will lead to the development of methodology for controlling the potential for polymorphism of pharmaceutical compounds.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectroscopic data, the DSC charts of **1**, **2a**, **2b**, **3a**, **3b**, **4a**, **5a**, and **5b**, and all crystallographic data and crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of Houansha foundation (I.A.) and Tokushima Bunri University Research Grant for Collaborative Research.

REFERENCES

(1) (a) McCrone, W. C. *Physics and Chemistry of the Organic Solid State*; Fox, D., Labes, M. M., Weissberger, A., Eds.; Wiley Interscience: New York, 1965; Vol. 2, pp 725−767. (b) Bernstein, J. *Organic Solid State Chemistry*; Desiraju, G. R., Ed.; Elsevier: Amsterdam, 1987; pp 471−518. (c) Dunitz, J. D.; Bernstein, J. *Acc. Chem. Res.* **1995**, *28*, 193−200. (d) Bilton, C.; Howard, J. A. K.; Madhavi, N. N. L.; Nangia, A.; Desiraju, G. R.; Allen, F. H.; Wilson, C. C. *Chem. Commun.* **1999**, 1675−1676. (d) Bernstein, J. *Polymorphism in Molecular Crystals*; Clarendon: Oxford, 2002. (e) Kumar, V. S. S.; Addlagatta, A.; Nangia, A.; Robinson, W. T.; Broder, C. K.; Mondal, R.; Evans, I. R.; Howard, J. A. K.; Allen, F. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3848−3851. (f) Dyker, G.; Mastalerz, M.; Müller, I. M.; Merz, K.; Koppe, K. *Eur. J. Org. Chem.* **2005**, 4963−4966. (g) Brittain, H. G. *Polymorphism in Pharmaceutical Solids*; Marcel Dekker, Inc.: New York, 1999. (h) Desiraju, G. R. *Cryst. Growth Des.* **2008**, *8*, 3−5. (i) Brillante, A.; Bilotti, I.; Guido, R.; Valle, D.; Venuti, E.; Girlando, A. *CrystEngComm* **2008**, *10*, 937−946. (j) Bernstein, J.; Dunitz, J. D.; Gavezzotti, A. *Cryst. Growth Des.* **2008**, *8*, 2011−2018. (k) Tian, J.; Dalgarno, S. J.; Atwood, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 1399−1404.

(2) (a) Blagden, N.; Davey, R. J. *Cryst. Growth Des.* **2003**, *3*, 873−885. (b) Vishweshwar, P.; Nangia, A.; Lynch, V. M. *Cryst. Growth Des.* **2003**, *3*, 783−790. (c) Yu, L. *CrystEngComm* **2007**, *9*, 847−851. (d) Bond, A. D.; Boese, R.; Desiraju, G. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 615−617. (e) Porter, W. W., III; Elie, S. C.; Matzger, A. J. *Cryst. Growth Des.* **2008**, *8*, 14−16. (f) Baburin, I. A.; Blatov, V. A.; Carlucci, L.; Ciani, G.; Proserpio, D. M. *Cryst. Growth Des.* **2008**, *8*, 519−539. (g) Nangia, A. *Acc. Chem. Res.* **2008**, *41*, 595−604. (h) Chandran, S. K.; Nath, N. K.; Roy, S.; Nangia, A. *Cryst. Growth Des.* **2008**, *8*, 140−154. (i) Price, S. *Acc. Chem. Res.* **2009**, *42*, 117−126. (j) Babu, N. J.; Cherukuvada, S.; Thakuria, R.; Nangia, A. *Cryst. Growth Des.* **2010**, *10*, 1979−1989. (k) Clarke, H. D.; Arora, K. K.; Wojtas, L.; Zaworotko, M. J. *Cryst. Growth Des.* **2011**, *11*, 964−966. (l) Pindelska, E.; Dobrzycki, L.; Wozniak, K.; Kolodziejski, W. *Cryst. Growth Des.* **2011**, *11*, 2074−2083.

(3) (a) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063−5070. (b) Desiraju, G. R. *Acc. Chem. Res.* **1991**, *24*, 290−296. (c) Steiner, T. *Crystallogr. Rev.* **1996**, *6*, 1−51. (d) Nishio, M.; Hirota, M.; Umezawa, Y. *The CH/π Interaction, Evidence Nature, and Consequences*; Wiley-VCH: New York, 1998. (e) Steiner, T. *New J. Chem.* **1998**, *22*, 1099−1103. (f) Desiraju, G.; Steiner, T.; *The Weak Hydrogen Bond: In Structural Chemistry and Biology*; Oxford University Press: Oxford, U.K., 2001. (g) Nishio, M. *CrystEngComm* **2004**, *6*, 130−158. (h) Chopra, D.; Nagarajan, K.; Row, T. N. G. *Cryst. Growth Des.* **2005**, *5*, 1035−1039. (i) Dey, A.; Pati, N. N.; Desiraju, G. D. *CrystEngComm* **2006**, *8*, 751−755. (j) Gao, Y.-H.; Zhou, W.; Li, L.; Wu, J.-Y.; Zhou, H.-P.; Yang, J.-X.; Tian, Y.-P. *Cryst. Growth Des.* **2009**, *9*, 253−257.

(4) (a) Hobza, P.; Selzle, H. L.; Schlag, E. W. *J. Am. Chem. Soc.* **1994**, *116*, 3500−3506. (b) Williams, V. E.; Lemieux, R. P.; Thatcher, G. R. J. *J. Org. Chem.* **1996**, *61*, 1927−1933. (c) Tsuzuki, S.; Honda, K.; Uchimura, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 104−112. (d) Rashkin, M. J.; Waters, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 1860−1861. (e) Tsuzuki, S.; Honda, K.; Azumi, R. *J. Am. Chem. Soc.* **2002**, *124*, 12200−12209. (f) Dunitz, J. D.; Gavezzotti, A. *Cryst. Growth Des.* **2005**, *5*, 2180−2189.

(5) (a) Vrcelj, R. M.; Sherwood, J. N.; Kennedy, A. R.; Gallagher, H. G.; Gelbrich, T. *Cryst. Growth Des.* **2003**, *3*, 1027−1032. (b) Wolf, A. K.; Glinnemann, J.; Schmidt, M. U. *CrystEngComm* **2008**, *10*, 1364−1371. (c) Suzuki, M.; Kobayashi, K. *Cryst. Growth Des.* **2011**, *11*, 1814−1820.

(6) (a) Bernstein, J. *Chem. Commun.* **2005**, *41*, 5007−5012. (b) Kitamura, M.; Hara, T.; Takimoto-Kamimura, M. *Cryst. Growth Des.* **2006**, *6*, 1945−1950. (c) Planas, J. G.; Viñas, C.; Teixidor, F.; Light, M. E.; Hurthouse, M. B. *CrystEngComm* **2007**, *9*, 888−894. (d) Cheng, H.-L.; Lin, J.-W. *Cryst. Growth Des.* **2010**, *10*, 4501−4508.

(7) (a) Sonoda, T.; Takata, Y.; Ueno, S.; Sato, K. *Cryst. Growth Des.* **2006**, *6*, 306−312. (b) Tsekova, D. S.; Escuder, B.; Miravet, J. F. *Cryst. Growth Des.* **2008**, *8*, 11−13. (c) Roy, S.; Nangia, A. *Cryst. Growth Des.* **2010**, *10*, 2047−2058.

(8) (a) Allen, Kimberley, Davey, R. J.; Ferrari, E.; Towler, C.; Tiddy, G. J. *Cryst. Growth Des.* **2002**, *2*, 523−527. (b) Kálmán, A.; Fábián, L.; Argay, G.; Bernáth, G.; Gyarmati, Z. *J. Am. Chem. Soc.* **2003**, *125*, 34−35. (c) Price, C. P.; Grzesiak, A. L.; Matzger, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5512−5517. (d) David, W. I. F.; Shankland, K.; Pulham, C. R.; Blagden, N.; Davey, R. J.; Song, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7032−7035. (e) Erdemir, D.; Lee, A. Y.; Myerson, A. S. *Acc. Chem. Res.* **2009**, *42*, 621−629. (f) Li, T.; Ayers, P. W.; Liu, S.; Swadley, M. J.; Aubrey-Medendrop, C. *Chem.—Eur. J.* **2009**, *15*, 361−371. (g) Sarma, B.; Sanphui, P.; Nangia, A. *Cryst. Growth Des.* **2010**, *10*, 2388−2399. (h) Salzmann, I.; Nabok, D.; Oehzelt, M.; Duhm, S.; Moser, A.; Heimel, G.; Puschnig, P.; Ambrosch-Draxl, C.; Rabe, J. P.; Koch, N. *Cryst. Growth Des.* **2011**, *11*, 600−606.

(9) (a) Davey, R. J.; Blagden, N.; Potts, G. D.; Docherty, R. *J. Am. Chem. Soc.* **1997**, *119*, 1767−1772. (b) Coates, G. W.; Dunn, A. R.; Henling, l. M.; Dougherty, D. A.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1997**, *36*, 248−251. (c) Vishnumurthy, K.; Guru Row, T. N.; Venkatesan, K. *Photochem. Photobiol. Sci.* **2002**, *1*, 427−430. (d) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210−1250. (e) Kitamura, M. *Cryst. Growth Des.* **2004**, *4*, 1153−1159. (f) Barga, D.; Brammer, L.; Champness, N. R. *CrystEngComm* **2005**, *7*, 1−19. (g) Reichenbächer, K.; Süss, H. I.; Hulliger, J. *Chem. Soc. Rev.* **2005**, *34*, 22−30. (h) Dolbier, W. R., Jr. *J. Fluorine Chem.* **2005**, *126*, 157−163. (i) Torbeev, V.; Shavit, E.; Weissbuch, I.; Leiserowitz, L.; Lahav, M. *Cryst. Growth Des.* **2005**, *5*, 2190−2196. (j) Chopra, D.; Guru Row, T. N. *Cryst. Growth Des.* **2005**, *5*, 1679−1681. (k) Kitamura, M.; Hara, T.; Takimoto-Kamimura, M. *Cryst. Growth Des.* **2006**, *6*, 1945−1950. (l) Reichenbächer, K.; Neels, A.; Stoeckli-evans, H.; Balasubramaniyan, P.; Müller, K.; Matsuo, Y.; Nakamura, E.; Weber, E.; Hulliger, J. *Cryst. Growth Des.* **2007**, *7*, 1399−1405. (m) Schwarzer, A.; Weber, E. *Cryst. Growth Des.* **2008**, *8*, 2862−2874. (n) Kirchner, M. T.; Blaser, D.; Boese, R.; Desiraju, G. D. *CrystEngComm* **2009**, *11*, 229−231. (o) Kitamura, M. *CrystEngComm* **2009**, *11*, 949−964. (p) Nayak, S. K.; Reddy, M. K.; Chopra, D.; Row, T. N. G. *CrystEngComm* **2012**, *14*, 200−210. (q) Akpinar, H.; Mague, J. T.; Novak, M. A.; Friedman, J. R.; Lahti, P. M. *CrystEngComm* **2012**, DOI: 10.1039/c1ce06096a.

(10) (a) Azumaya, I.; Takako, K.; l Okamoto, I.; Yamasaki, R.; Tanatani, A.; Yamaguchi, K.; Kagechika, H.; Takayanagi, H. *Org. Lett.* **2003**, *5*, 3939−3942. (b) Katagiri, K.; Kato, T.; Masu, H.; Tominaga, M.; Azumaya, I. *Cryst. Growth Des.* **2009**, *9*, 1519−1524.

(11) Sanphui, P.; Sarma, B.; Nangia, A. *Cryst. Growth Des.* **2010**, *10*, 4550−4564.

(12) A short history of SHELX. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112−122.