CRYSTAL GROWTH & DESIGN
2004
VOL. 4, NO. 6
1403−1409

Characterization of Pseudopolymorphs of a Hydroxybenzoic Acid Derivative

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Received September 9, 2004

ABSTRACT: Hydroxybenzoic acid is used in many applications, including medicine and polymer synthesis. The synthesis, self-assembly, and characterization of three pseudopolymorphs of a derivative of a widely used 4-hydroxybenzoic acid (**1**) are described in detail. In this investigation, we have incorporated hydrophobic (biphenyl groups) and hydrophilic (-OH and -CO_2H) groups on an aromatic ring to influence the self-assembly in the solid lattice. Compound **1** crystallizes into three crystalline forms: (i) monoclinic from a solution of DMSO (**1A**), (ii) triclinic from a 1:1 solution of DMSO/hot ethyl acetate (**1B**), and (iii) triclinic from pyridine solution (**1C**). The formation of these pseudopolymorphs and the structural similarities in their packing motifs can be rationalized through a few multipoint solute−solvent interactions. In all three structures, the crystallographic aspects pertaining to the influence of solvent molecules towards the formation of hydrogen bonded network structures are described. In addition to the strong hydrogen bonds, intermolecular C−H···O, C−H···π, and π···π interactions were found to stabilize the crystal structures.

Introduction

Polymorphism is the existence of two or more different crystal structures of a compound, and pseudopolymorphism refers to the existence of one or more solvated crystalline forms of the same compound.[1] Pseudopolymorphism is a common phenomenon in drug targets and biological molecules.[2] Recently, the existence of pseudopolymorphism in a number of organic compounds has been reported.[3−7] Multipoint recognitions involving strong (e.g., O···H−O, N···H−O) and weak (e.g., C−H···O) hydrogen bonds exists between the solvent and the solute molecules; therefore, solvent molecules are retained and integrated in the crystal lattice.[3]

Hydroxybenzoic acids and their derivatives represent a class of highly useful compounds[8] in which the presence of hydroxyl and carboxylic acid groups renders various hydrogen bonding motifs leading to the formation of polymorphs in the crystal lattice. Two polymorphs of *p*-hydroxybenzoic acid are reported.[9] We are interested in exploring the self-assembly of functionalized 4-hydroxybenzoic acid to understand the interplay of intermolecular interactions and packing forces in the crystal lattice. In this paper, we report the existence of pseudopolymorphism observed in the crystal lattice of compound **1**. Bulky and nonpolar biphenyl groups are incorporated to introduce aromatic interactions and to study the interplay of electrostatic and van der Waals interactions.

Experimental Section

General. All reagents were purchased from commercial sources and were used without further purification unless mentioned otherwise. Tetrahydrofuran (THF) was distilled under N_2 over sodium/benzophenone prior to use. Purifications by flash column chromatography were performed using silica gel 60 (0.040−0.063 mm) purchased from commercial sources. ^{1}H and ^{13}C NMR spectra were recorded on Bruker ACF 300 spectrometer at 300 K with tetramethylsilane as internal standard at 300 and 75.4 MHz, respectively. FT-IR spectra were recorded on a Perkin-Elmer 1710 Infrared Fourier Transform spectrometer. Mass spectra (MS-ESI) were determined using a Finnigan MAT LCQ or Finnigan TSQ 7000 mass spectrometer at an ion spray voltage of 4.5 kV, and a capillary temperature of 270 or 350 °C. The elemental analyses were performed at the Elemental Analysis Laboratory at the Department of Chemistry, National University of Singapore.

Single-Crystal X-ray Diffraction Studies. Good quality single crystals of forms **1**(**A**−**C**) were carefully chosen and glued onto a thin glass fiber. X-ray diffraction data on single crystals were collected on a Bruker AXS SMART CCD 3-circle diffractometer with a Mo−Kα radiation (λ = 0.71073 Å). The software used was SMART[10] for collecting frames of data, indexing reflections and determining lattice parameters; SAINT[10] for integration of intensity of reflections and scaling; SADABS[11] for absorption correction; and SHELX-TL[12] for space group determination, structure solution, and least-squares refinements on F^2. Structures were solved by direct methods and non-hydrogen atoms were refined anisotropically. Hydrogen atoms were introduced at fixed distances from carbon atoms and assigned fixed thermal parameters. All calculations were performed on a Silicon Graphics workstation, using programs provided by Siemens Pvt. Ltd. Some crystal data and structural refinement parameters of pseudopolymorphs **1**(**A**−**C**) are given in Table 1.

Synthesis. 4-Acetoxy-3,5-dibromo Benzoic Acid Methyl Ester (3). Acetyl chloride (5.06 g, 0.065 mol) in 20 mL of dry THF was added dropwise to a solution of 3,5-dibromo 4-hydroxy benzoic acid methyl ester, **2** (10 g, 0.032 mol) and triethylamine (59.7 g, 0.096 mol) dissolved in 100 mL of THF at 0 °C. The reaction mixture was allowed to stir for 6 h at room temperature, concentrated, and extracted with dichloromethane (3 × 150 mL). The organic layer was washed with 2 N Na_2CO_3 solution followed by water, dried over anhydrous Na_2SO_4, and concentrated. The crude compound was purified using column chromatography over silica gel (hexane/dichloromethane) to give a colorless solid. (Yield, 72%). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.41(s, 3H, −COC**H**$_3$), 3.92(s, 3H, −COOC**H**$_3$), 8.22(s, 2H, Ar−**H**). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): 20.3, 52.6, 117.8, 130, 133.4, 149.8 (Ar-**C**), 163.9(⟩C═O),

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10.1021/cg0496890 CCC: $27.50
Published on Web 10/19/2004

Table 1. Selected Crystal Data and Structural Refinements for Pseudopolymorhs 1(A−C)

form	1A	1B	1C
empirical formula	$C_{31}H_{22}O_3 \cdot \{C_2H_6SO\}$	$C_{31}H_{22}O_3 \cdot \{C_2H_6SO\}$	$C_{31}H_{22}O_3 \cdot C_5H_5N$
crystal system	monoclinic	triclinic	triclinic
space group	$P2_1/n$	$P\bar{1}$	$P\bar{1}$
a/Å	5.9262(6)	15.2949(8)	6.4563(3)
b/Å	22.095(2)	16.3926(8)	14.5436(7)
c/Å	19.9471(19)	18.4924(10)	16.4454(8)
α/°	90	102.875(10)	66.106(10)
β/°	91.57(2)	101.539(10)	85.282(10)
γ/°	90	109.65(10)	77.955(10)
Z	4	6	2
V/Å^3	2610.9(4)	4061.3(4)	1380.76(11)
D_{calc}/g cm^3	1.324	1.277	1.255
absorption coefficient (mm^{-1})	0.162	0.156	0.079
F(000)	1096	1644	548
crystal size mm^3	0.40 × 0.34 × 0.14	0.46 × 0.28 × 0.26	0.40 × 0.28 × 0.20
index ranges	$-7 \le h \le 7$	$-19 \le h \le 19$	$-8 \le h \le 8$
	$-28 \le k \le 26$	$-21 \le k \le 21$	$-18 \le k \le 18$
	$-25 \le l \le 14$	$-24 \le l \le 24$	$-21 \le l \le 21$
R(int)	0.0470	0.0480	0.0202
max/min transmission	0.9776/0.9379	0.9605/0.9315	0.9843/0.9689
data/restraints/parameters	5992/0/347	18636/23/1059	6339/0/366
R_1	0.0642	0.0753	0.0592
wR_2	0.1339	0.1895	0.1650
GOF	1.048	1.046	1.046
θ range/°	1.38−27.50	1.18−27.50	1.35−27.50
reflns collected	17892	53697	18365
independent reflns	5992	18636	6339
solvent	DMSO	DMSO/ethyl acetate	pyridine
color/crystal shape	colorless/rod	yellow/block	colorless/rod

166.5(⟩C═O, ester). FT-IR (KBr, cm^{-1}): 2955, 1782, 1727, 1554, 1441, 1373, 1282, 1115, 1007, 964, 905, 733 598. MS-ESI: *m/z*, 349(M$^+$) Elemental Anal. Calcd $C_{10}H_8Br_2O_4$ (349.88): C, 34.12; H, 2.29, Br, 45.40. Found: C, 34.21; H, 2.13, Br, 45.02.

Synthesis of Methyl-3,5-bis(biphenyl)-4-acetoylbenzoate (4). To a vertical three neck RB flask equipped with a condenser was added **3** (5 g, 0.014 mol), biphenyl boronic acid (7.01 g 0.036 mol), toluene (75 mL), and 2 N aqueous potassium carbonate solution (75 mL). The flask was degassed three times before the catalyst, tetrakispalladium triphenylphosphine (10 mol %) was added in the absence of light under argon atmosphere and the contents were refluxed under argon atmosphere for 48 h. The reaction mixture was cooled, filtered, concentrated, and extracted with diethyl ether. The resulting crude compound was purified using column chromatography with hexane/dichloromethane as eluent to afford **4** as a white solid in 50% yield. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.55(s, 3H, −COC**H**$_3$), 3.95(s, 3H, −COOC**H**$_3$), 7.35−7.69(m, 18H, Ar−H), 8.15(s, 2H, Ar−H). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): 20.5, 52.2, 126.9, 127, 127.4, 128.4, 128.7, 129.2, 131.3, 135.8, 140.4, 140.6, 148.7 (Ar-**C**), 166.1 (⟩C═O), 168.4(⟩C═O, ester). FT-IR (KBr, cm^{-1}): 2933, 1762, 1726, 1594, 1433, 1346, 1237, 1184, 1008, 910, 842, 763, 692. MS-ESI: *m/z*, 498.1 (M$^+$) Elemental Anal. Calcd $C_{34}H_{26}O_4 \cdot (H_2O)_{0.1}$ (499.98): C, 81.60; H, 5.22. Found: C, 81.20; H, 5.43.

Synthesis of 3,5-bis(biphenyl)-4-hydroxybenzoic Acid (1). A mixture of compound **4** (2 g, 0.004 mol) and sodium hydroxide (0.01 mol, 0.4 g) in ethanol−water mixture (2:1, 50 mL in volume) was refluxed for 8 h. The solution was then acidified with 5 N hydrochloric acid, concentrated, and extracted with diethyl ether. The ether extract was washed with water and dried over sodium sulfate. The solvent was evaporated to give a white solid which was recrystallized from methanol and characterized. Yield 95%. ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 7.36−7.79 (m, 18H, Ar−**H**), 7.85 (s, 2H). ^{13}C NMR (75.4 MHz, DMSO-d_6, δ ppm): 122.6, 126.5, 127.4, 128.9, 129.8, 130, 131, 136.8, 139, 139.7, 154.9 (Ar−**C**), 166.9-(⟩C═O). FT-IR (KBr, cm^{-1}): 3539, 2882, 1682, 1595, 1484, 1425, 1327, 1257, 1236, 1117, 919, 846, 759, 690. MS-ESI: *m/z*, 442.1(M$^+$) Elemental Anal. Calcd $C_{31}H_{22}O_3 \cdot (H_2O)_{0.2}$ (443.96): C, 83.45; H, 5.03. Found: C, 83.09; H, 5.09.

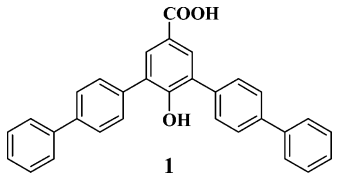

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Figure 1. Molecular structure of acid **1**.

Results and Discussion

Self-Assembly of Pseudopolymorphs 1(A−C). The three solvated crystals of compound **1** were obtained from DMSO (**1A**), DMSO/hot ethyl acetate (**1B**) and pyridine (**1C**) via slow evaporation technique with various morphologies such as colorless rods (**1A**, **1C)** and yellow blocks (**1B**). Solvated crystal structure of acid **1B** was obtained serendipitously when attempts to cocrystallize **1** with 4,4′-bipyridine were made.

Solid State Self-Assembly of 1A. The crystal structure of form **1A** was found to be monoclinic with the space group of $P2_1/n$. ORTEP representation with atom labeling scheme of form **1A** is shown in Figure 3a.

The crystal packing with DMSO molecules incorporated into the crystal lattice is shown in Figure 3b. Investigations of the crystal structure revealed strong and weak intermolecular interactions responsible for the observed self-assembly in the lattice. Each molecule in **1A** forms acid dimer with its neighbor through O−H···O hydrogen bonding (O1−H1···O2: O···O: 2.65(2) Å, ∠O−H···O: 178° at x, $y - 1$, $z + 1$, Figure 3b). The host molecules are stacked in layers along the c-axis with the interlayer distance of 4.7 Å. The solvent molecules are held in approximately wedge-shaped cavities with dimensions of ca. 7 × 4 Å^2 (Figure 3b). The DMSO molecules inside the cavities form a continuous chain and the stacked layers of compound **1** are held between the chains of interconnected solvent molecules along the c-axis (Figure 4a). The crystal packing of the solvent

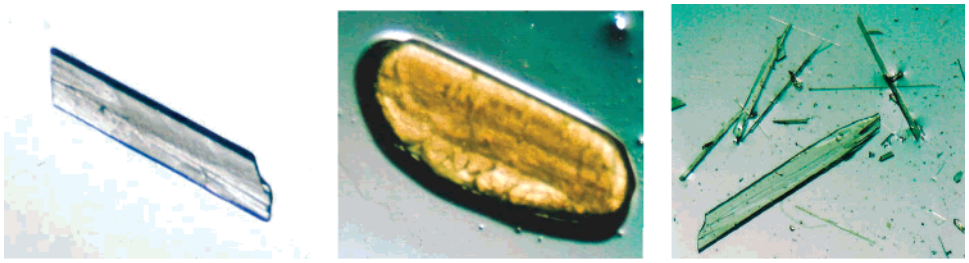


Figure 2. Morphologies of crystals **1**·DMSO (A), **1**·DMSO (B), and **1**·pyridine (C).

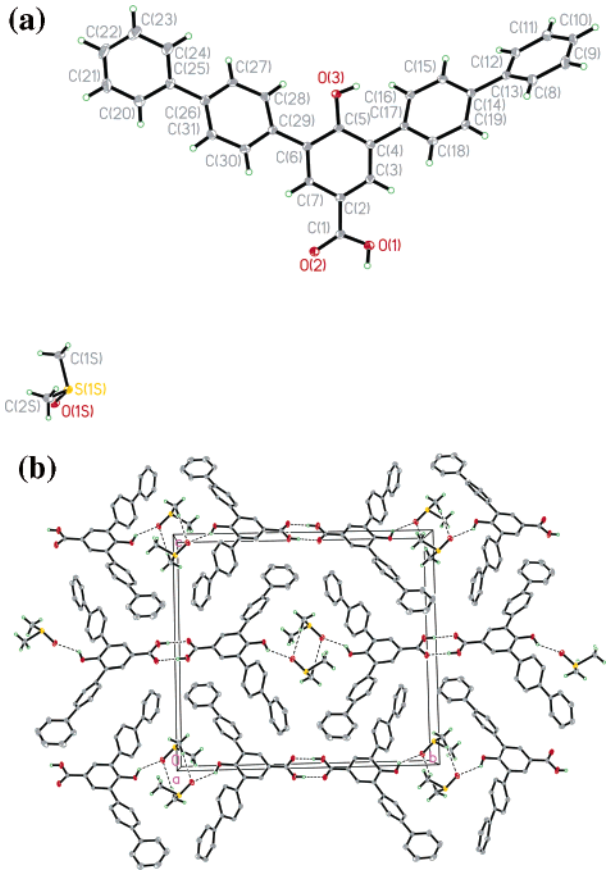


Figure 3. (a) ORTEP diagram showing labeling scheme for form **1A** and thermal ellipsoids are drawn at 30% probability level. (b) 3D packing along the *a*-axis showing DMSO molecules occupying the cavities. Intermolecular O1−H1···O2 hydrogen bonding between the carboxylic acid moieties (at x, $y-1$, $z+1$) are shown as dotted lines. Color codes: O red; C grey; H green; S yellow.

molecules indicate the characteristic double acceptor motif of DMSO.[13] The DMSO forms cyclic dimers with a pseudo-chairlike conformation as the S=O interacts with the O−H of **1** and with the C−H of the neighboring DMSO molecules (Figure 4b). The metrics of the C−H···O interactions are C1S···O1S = 3.494(3) Å, $\theta = 166°$ at [$1-x$, $2-y$, $1-z$]; C2S−H2S···O1S: C2S···O1S = 3.487(3) Å, $\theta = 161°$ at [$1-x$, $3-y$, $-1-z$].

This unique and atypical pseudo-chairlike conformation of the DMSO dimer extends into an interconnected undulating tube and is additionally stabilized by the O−H···O interactions with the host molecule, O3−H3···O1S at [x, $-1+y$, $1+z$]; O3···O1S = 2.721(2) Å, $\theta = 128°$. Neighboring phenyl units are stabilized by multiple C−H···π interactions (2.8−3.1) Å (Figure 4c).

Table 2. X−H···Cg (π-ring) Hydrogen Bond Parameters for 1A (Å, °)[a]

X−H···C_g	H···C_g	X···C_g	X−H···C_g
C1S−H1B···C_ga^{i}	2.85	3.803(3)	169
C19−H19···C_ga^{ii}	2.94	3.735(3)	143
C20−H20···C_gb^{iii}	3.16	3.895(3)	137
C27−H27···C_gc^{i}	3.10	3.834(3)	136

[a] Symmetry codes are (i) $1-x$, $2-y$, $-z$; (ii) $1/2+x$, $1/2-y$, $-1/2+z$; (iii) $3/2+x$, $3/2-y$, $1/2+z$ [Cga: $C_{26}-C_{31}$; Cgb: $C_{14}-C_{19}$; Cgc: $C_{20}-C_{25}$] Cg refers to the ring center of gravity and the letters refer to the ring involved in the interaction.

The hydrogen atoms of the phenyl ring interact with the π cloud of the neighboring phenyl unit. Here, the π electron-rich aromatic ring serves as the acceptor and the hydrogen on the ring behaves as the donor. Weak C−H···π interactions also exist between the solvent and the host molecules (Figure 4d). Table 2 shows the interacting hydrogen atoms from the nearest π-bonded carbon atoms.

Solid State Self-Assembly of 1B. In form **1B**, each asymmetric unit consists of three molecules of the acid and three molecules of DMSO and exists in the space group $P\bar{1}$. The ORTEP representation of **1B** with atom numbering is shown in Figure 5a. The sulfur atoms are disordered and the angle between the O−H vectors ∠C5−O3−H3O, ∠C36−O6−H6O, and ∠C67−O9−H9O are 107°, 115°, and 109°, respectively. The acid group interacts with its neighbor through dimerization. The wedge-shaped voids in the lattice are occupied by DMSO molecules bonded to the phenolic -OH group through S=O···H−O hydrogen bonds [O−H···O, d(O···O) = 2.59−2.69 Å]. Apart from the strong O−H···O, weak C−H···O interactions exist between one of the solvent molecules and the host, C1S−H1SC···O6, d(C···O) = 3.533(11) Å, ∠C−H···O 165°). The important hydrogen bonding parameters are given in Table 3. The cavities are occupied by disconnected chains of DMSO molecules running infinitely through the crystal lattice. The striking difference between **1A** and **1B** is the lack of significant hydrogen bonded interactions among the DMSO molecules in the lattice of **1B** but are linked through the C−H···O interactions from the host (Figure 5b).

The crystal structure is constituted by layers (wave-type pattern) of the acid, and the coordinated solvent molecules are stacked in a head-to-head fashion with an interlayer distance of *ca*. 4.8 Å (Figure 5c). The void spaces between the layers are translated into channels containing the solvent molecules in the 3D arrangement (Figure 5b). There appears to be no direct hydrogen bonding involved between the stacked layers but nevertheless are stabilized by a weak edge to face C−H···π

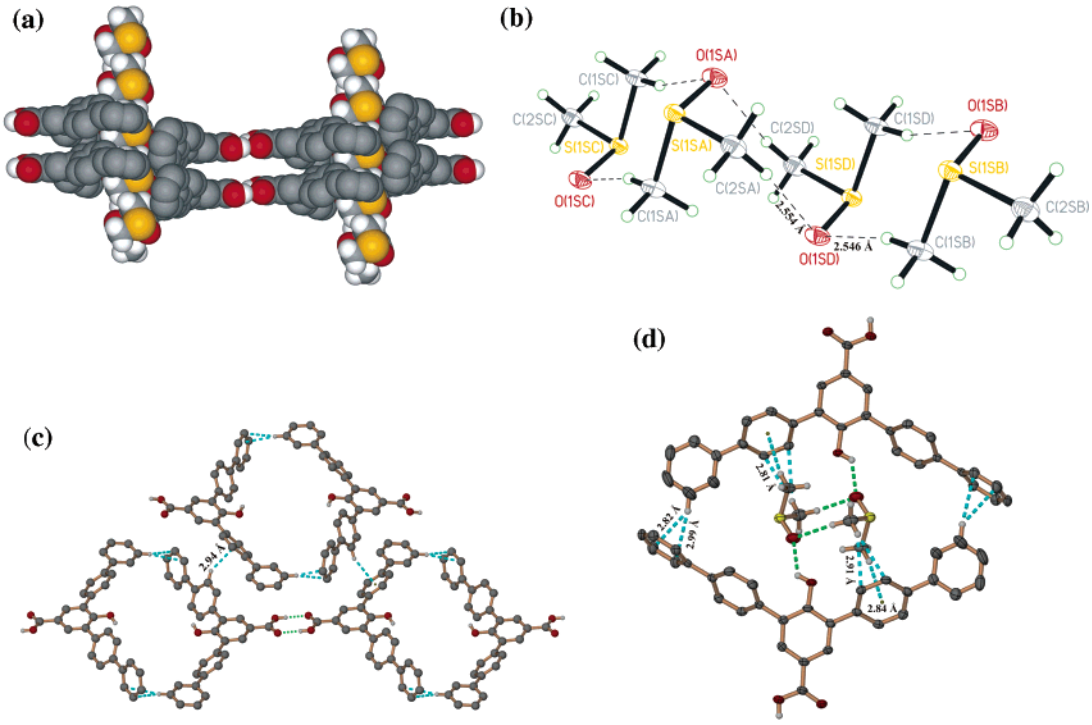


Figure 4. (a) Layers of acid dimers are held between linear chains of DMSO molecules along the *c*-axis. (b) DMSO self-associates into pseudo-chairlike conformation through weak C−H···O hydrogen bonding; (c) representation of C−H···π interactions (blue dotted lines) between adjacent phenyl units. Solvent molecules have been removed for clarity C19−H19···C_ga: 2.94 Å, 143° (Table 2) at [1/2 + *x*, 1/2 − *y*, −1/2 + *z*]. (d) C−H···π interactions (blue dotted lines) between DMSO molecules and the aromatic hydrogens C2S−H2SB···C27: 2.81 Å, 151°; C2S−H2SB···C28: 2.91 Å, 141° at [1 − *x*, 1 − *y*, 1 − *z*]; C23−H23···C8: 2.99 Å, 164°; C23−H23···C9: 2.83 Å, 142° at [1 − *x*, 1 − *y*, 1 − *z*]. Strong hydrogen bonds are shown by green dotted lines. Color codes: C − grey; O − red; H − white; S − yellow.

Table 3. Hydrogen Bond Parameters for 1B [Å and °][a]

D−H···A	d(D−H)	d(H···A)	d(D···A)	∠DHA
O1−H1O···O2^{i}	0.85(5)	1.78(6)	2.614(4)	168(7)
O3−H3O···O1S^{ii}	0.85(4)	1.83(4)	2.590(5)	148(3)
O4−H4O···O8^{iii}	0.85(3)	1.76(3)	2.605(3)	178(4)
O6−H6O···O2S	0.85(3)	1.95(3)	2.693(3)	143(6)
O7−H7O···O5^{iv}	0.84(3)	1.80(3)	2.630(3)	170(4)
O9−H9O···O3S^{vi}	0.83	1.85	2.656(5)	163

[a] Symmetry transformations used to generate equivalent atoms: (i) −*x* + 2, −*y* + 1, −*z* + 1; (ii) −*x* + 2, −*y*, −*z* + 1; (iii) *x*, *y*, *z* + 1; (iv) *x*, *y*, *z* − 1.

Table 4. X−H···Cg (π-Ring) Hydrogen Bond Parameters for 1B (Å, °)[a]

X−H···C_g	H···C_g	X−H···C_g	X···C_g
C2S−H2SB···C_gd^{i}	2.81	139	3.6(6)
C4S−H4SA···C_ge^{ii}	3.23	153	4.084
C40−H40S···C_gf^{iii}	2.78	149	3.61(4)
C47−H47S···C_gb^{iv}	3.17	151	4.020
C73−H73S···C_gc^{v}	2.93	145	3.731
C86−H86S··· C_ga^{vi}	2.75	150	3.593

[a] Symmetry codes are (i) *x*, *y*, *z*; (ii) 1 + *x*, *y*, *z*; (iii) *x*, 1 + *y*, *z* (iv) −1 + *x*, *y*, *z* (v) *x*, −1 + *y*, *z* (vi) 1 − *x*, −*y*, 1 − *z* [Cga: C_2−C_7; Cgb: C_{14}−C_{19}; Cgc: C_{51}−C_{56}; Cgd: C_{57}−C_{62}; Cge: C_{70}−C_{75}; Cgf: C_{82}−C_{87}]. Cg refers to the ring center of gravity and the letters refer to the ring involved in the interaction.

(2.7−3.2) Å and π···π stacking (3.8 Å) interactions. As in **1A**, C−H···π interactions were also observed between the DMSO and the phenyl rings of **1B** (Table 4).

Solid State Self-Assembly of 1C. Surprisingly, compound **1** did not form molecular assemblies with basic compounds such as 4,4′-bipyridine, pyrazine, and 1,10-phenanthroline. Hence, attempts were made to overcome the higher affinity of the carboxylic acid groups to form dimers by crystallizing **1** from a solvent capable of forming N···H−O/C−H···N bonds, e.g., pyridine. Single-crystal analysis of **1C** revealed a triclinic crystal system with $P\bar{1}$ space group. The ORTEP perspective is shown in Figure 6a. The adjacent molecules are held together via acid dimer through a relatively strong O−H···O hydrogen bonding [O3−H3A···O2: d(O···O): 2.590(2) Å, ∠O−H···O: 175(3)° at (2 − *x*, −*y*, 1 − *z*)]. The pyridine molecules occupy the voids between X-shaped dimers as seen in Figure 6b. The fact that the pyridine is hydrogen bonded with the phenolic O−H group through strong O−H···N interactions indicates the specificity of phenol−pyridine hydrogen bonds in the presence of carboxylic acid group.[14] The metrics of the O−H···N bonds are [O1−H1A···N1 at [−1 + *x*, *y*, *z*]: O···N: 2.689(3) Å, ∠O−H···N: 147(3)°]. Hence, it is conceivable that the formation of a strong carboxylic acid dimer of higher dimensionality prevents the coupling of **1** with aza compounds. Similar to **1A** and **1B**, a layered arrangement is observed in the 2D arrangement in which the molecules are held together by strong and weak interactions in the lattice of **1C** (Figure 6c). The interlayer distances are found to be ∼6.5 Å. The 3D packing of the molecules in the crystal lattice is shown in Figure 6b. Interplay of extensive interconnected network of weak interactions was found to stabilize the crystal structure of **1C** (Figure 6 c,d). Edge-to-face C−H···π interactions propagate from the aryl hydrogen atoms of the pyridine to the phenyl ring of the adjacent molecules of compound **1** (Table 5).

The π···π interactions between the phenyl rings connect the molecules of **1** in a parallel stepwise fashion

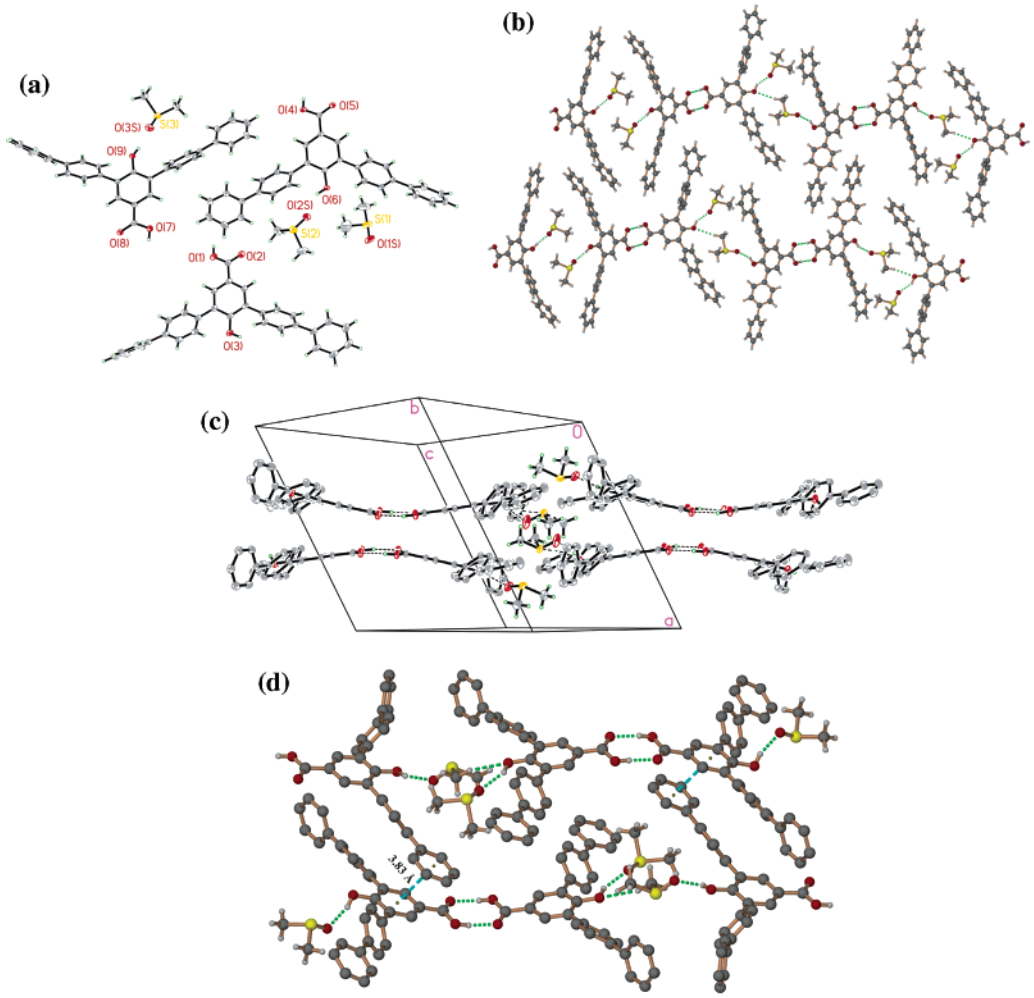


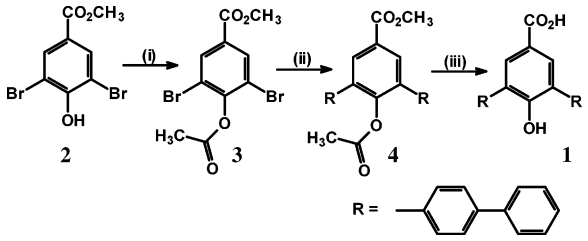
Figure 5. (a) ORTEP diagram showing labeling scheme for form **1B** and thermal ellipsoids are drawn at 30% probability level; (b) 3D packing arrangement showing O−H···O hydrogen bonds (O1−H1O···O2, O4−H4O···O8, O7−H7O···O5) between carboxylic acid dimers. Symmetry operators are $-x+2, -y+1, -z+1$; $x, y, z+1$; $x, y, z-1$; (c) 2D layer arrangement along the *b*-axis. Hydrogen bonds between the DMSO molecules and the phenolic − OH moieties are also shown in dotted lines. (d) Representations of $\pi-\pi$ interactions between neighboring phenyl units (blue dotted lines). Color codes: C − grey; O − red; H − green; S − yellow.

Table 5. X-H···Cg (π-Ring) Hydrogen Bond Parameters for 1C (Å, °)[a]

X−H···C_g	H···C_g	X−H···C_g	X···C_g
C23−H23···C_ga^{i}	2.808	132	3.50(2)
C32−H32···C_gb^{ii}	3.104	123	3.70
C36−H36···C_gc^{iii}	3.105	118	3.63(2)

[a] Symmetry codes are (i) $1+x, y, z$; (ii) x, y, z; (iii) $-1+x, y, z$ [Cga: N_1-C_{36}; Cgb: $C_{20}-C_{25}$; Cgc: C_8-C_{13}]. Cg refers to the ring center of gravity and the letters refer to the ring involved in the interaction.

Scheme 1. Synthesis of the Target Molecule 1[a]



[a] Reagents and conditions: (i) CH_3COCl, triethylamine/ THF, 0 °C−RT, 6 h; (ii) 4-biphenyl boronic acid, 2 N Na_2CO_3, toluene, $Pd(PPh_3)_4$, reflux, 48 h; (iii) 2 N NaOH/EtOH, H^+, 8 h.

[d(Cg···Cg): 4.2 Å, Figure 6d]. The pyridine molecules are also stabilized in the same manner through $\pi\cdots\pi$ interactions at a intermolecular distance of 4.02 Å (Figure 6c). Weak C−H···O interactions are observed between the acid groups of one layer with the aromatic hydrogen atoms of the adjacent layer [C9−H9···O3 at $[-1+x, y, z]$: d(C···O): 3.235(2) Å, ∠C−H···O: 143°; C21−H21···O2: at $[-1+x, y, z]$: d(C···O): 3.264(2) Å, ∠C−H···O: 149°].

Comparisons of the Pseudopolymorphs. The supramolecular assemblies formed in the crystal lattice of **1** with various solvents are described. A schematic representation of the packing motifs in the pseudopolymorphs of **1** (**A**, **B**, and **C**) is shown in Scheme 2. In all the crystal lattices, a layered organization of molecules was observed in 2D and a combination of strong and weak interactions were found to stabilize the crystal structure. In **1A**, the DMSO molecules are held in wedge-shaped cavities. The solvent molecules form a continuous chain and interact with the stacked layers of **1**. In the process, DMSO adopts a unique pseudo-chairlike conformation and thus stabilizes the structure through strong O−H···O and weak C−H···O interactions with the host. The packing in **1B** is similar to that of **1A**; however, no significant hydrogen bonded interactions among the DMSO molecules were observed inside

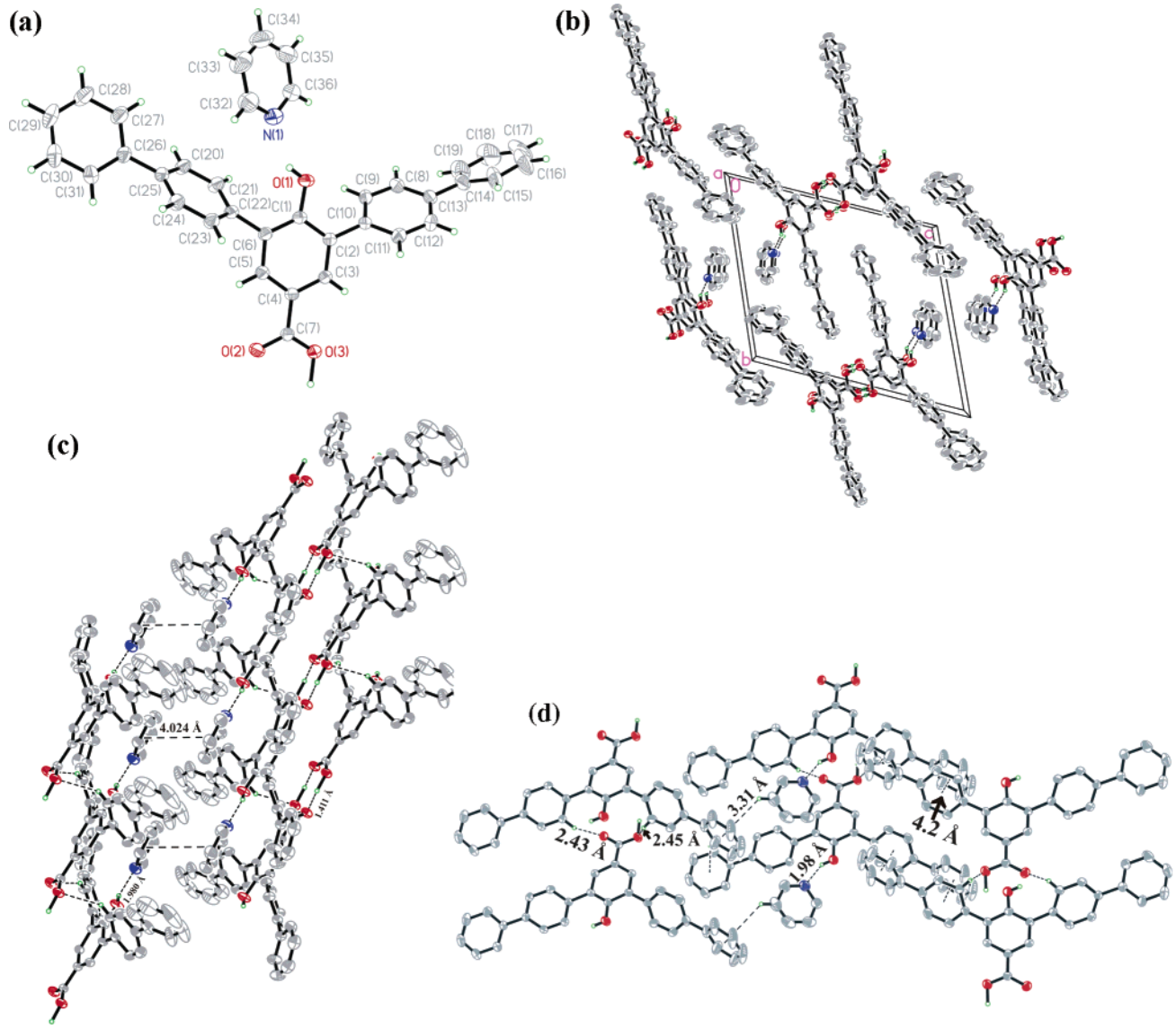
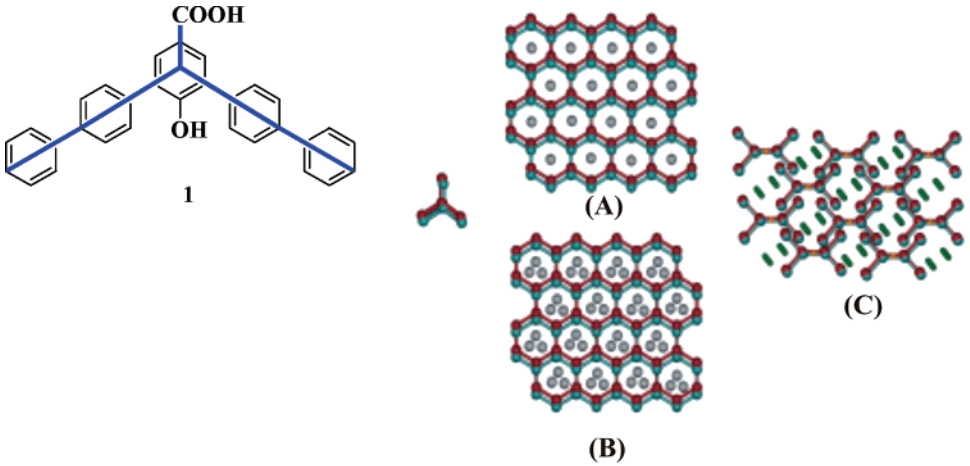


Figure 6. (a) ORTEP diagram showing labeling scheme for form **1C** and thermal ellipsoids are drawn at 30% probability level; (b) 3D layered arrangement along the *b*-axis showing hydrogen bonding between the carboxylic acid groups (O3−H3A···O2) and phenolic −OH with pyridine (O1−H1A···N1). Symmetry operators: [2 − *x*, −*y*, 1 − *z*, −1 + *x*, *y*, *z*]; (c, d) interconnected pattern of weak C−H···O, C−H···π (aryl) and π···π interactions. (Side view and top view respectively). H-bonds are represented by dotted lines. Color codes: O, red; C, grey, H green, N, blue.

Scheme 2. Schematic Representation of the 3D Crystal Lattices of Pseudopolymorphs of 1[a]



[a]DMSO molecules interact with each other to form a chain in the lattice of **1A** (A). Crystal lattice of **1B** with entrapped DMSO molecules (B) and organization of pyridine molecules in **1C** (C). Grey circle represents DMSO (A, B), and green lines represent pyridine molecules held in voids (C).

the lattice. The calculated densities of **1A** and **1B** are 1.324 and 1.277 mg/m^3, respectively. In **1C**, the solvent pyridine is hydrogen bonded to the phenolic O−H via O−H···N interactions. The pyridine molecules are confined in the voids between X-shaped dimers as shown in Scheme 2C. The pyridine molecules are stabilized via $\pi-\pi$ and C−H···π interactions among themselves and also with the molecules of **1**.

Thus, the formation of a number of pseudopolymorphs of compound **1** signifies the importance of structure regulating interactions and enthalpic factors.[15] Moreover, the absence of acid−base interactions between compound **1** and the added aromatic bases suggests strong packing forces and recognition of identical functional groups.

Conclusions

Compound **1** shows pseudopolymorphism in the crystal lattice and did not form molecular complexes with basic compounds such as pyrazine, 4,4′-bipyridine, or 1,10-phenanthroline; instead it crystallized with solvent molecules. This is an interesting case of hydrogen bonds (O−H···O) among the reactant molecules being stronger than those in the supramolecular assembly of acid and bases in which formation of N···H−O bonds is expected.[16] In all the three crystal structures, a layered lattice is formed with a combination of strong and weak interactions. In the lattice of pseudopolymorph **1A**, the DMSO molecules interact to form a linear chain, whereas in **1B**, discrete DMSO molecules were observed. In the lattice of **1C**, the pyridine molecules form hydrogen bonds with phenolic -OH groups and organize in a parallel fashion.

Since 4-hydroxybenzoic acids are known to be applicable in many areas (e.g., medicine, food stabilizers, etc.) it would be interesting to explore the activity of our target compound in these fields. However, the presence of two large biphenyl groups ortho- to the hydroxyl group is expected to show significant differences from the parent compound. Results from such studies will be published soon.

Acknowledgment. We thank Prof. Koh Lip Lin and Ms. Tan Geok Kheng at the X-ray Diffraction Laboratory for their assistance in data collection and structure refinement. S.V. and J.A. thank the National University of Singapore for research funding and a scholarship. All technical support from various laboratories at the Department of Chemistry, National University of Singapore, is acknowledged.

Supporting Information Available: Details of crystal coordinates and torsion angles for pseudopolymorphs **1**(**A**−**C**) as a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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CG0496890