CRYSTAL GROWTH & DESIGN

Article

pubs.acs.org/crystal

Crystal Engineering of *N*,*N*′-Diphenylurea Compounds Featuring Phenyl–Perfluorophenyl Interaction

Ryu Yamasaki,*[†] Mana Iida,[†] Ai Ito,[†] Kazuo Fukuda,[†] Aya Tanatani,[‡] Hiroyuki Kagechika,[§] Hyuma Masu,[‖] and Iwao Okamoto[†]

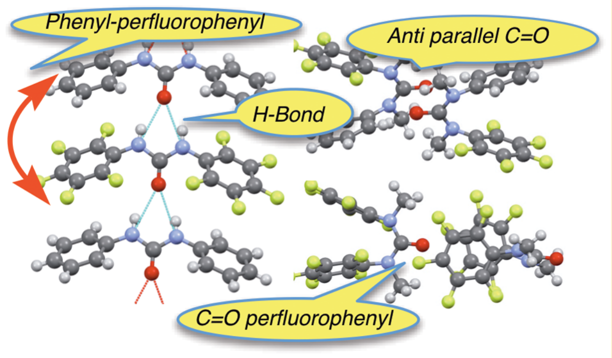
[†]Showa Pharmaceutical University, 3-3165 Higashi-Tamagawagakuen, Machida, Tokyo 194-8543, Japan

[‡]Department of Chemistry, Faculty of Science, Ochanomizu University, 2-1-1 Otsuka, Bunkyo-ku, Tokyo 112-8610, Japan

[§]Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan

[‖]Center for Analytical Instrumentation, Chiba University, 1-33 Yayoicho, Inage-ku, Chiba 263-8522, Japan

Supporting Information



ABSTRACT: Here, aiming to adopt the phenyl–perfluorophenyl interaction to regulate molecular alignment and arrangement for crystal engineering, we examined and compared in detail the crystal structures of *N*,*N*′-diphenylurea compounds **1**–**6**. We found that phenyl–perfluorophenyl interaction greatly influenced the intermolecular arrangement in the crystal, and we were able to prepare a cocrystal of **1** and **2**, in which the molecules were alternately arranged under the control of the phenyl–perfluorophenyl interaction. This arrangement was driven by the asymmetric geometry of the hydrogen bonds in the cocrystal (**1**·**2**), in which **2**, bearing two perfluorophenyl groups, worked as a better hydrogen bond donor. In contrast, NH connected to the phenyl group in **3** proved to be a better hydrogen bond donor due to the intramolecular resonance effect. *N*,*N*′-Dimethylated derivatives, **4**–**6**, existed in *cis*-*cis* form in the crystal. Antiparallel carbonyl–carbonyl arrangements were observed in **4** and **6**, while an unexpected carbonyl–perfluorophenyl interaction was observed in the crystal of **5**. These findings will be helpful in the design of diphenylurea-based functional molecules, especially for solid-state application.

INTRODUCTION

Phenyl–perfluorophenyl interaction is a useful design tool in crystal engineering and related applications, such as topochemical polymerization.[1−17] In the 1960s, benzene and hexafluorobenzene were found to form a stable complex and could be cocrystallized in an alternating stacking manner,[18] as confirmed by a high-resolution powder X-ray diffraction study.[19] This interaction is not due to donor–acceptor interaction, but is mainly due to electrostatic or quadrupole moment interaction,[20] although theoretical calculation indicated that the dispersion energy also contributed.[21,22] The magnitude of interaction was dependent on the substitution of the phenyl ring, and introduction of electron-donating substituents on the phenyl ring favored the interaction.[23]

Compounds containing urea group(s) are important as gelators,[24−28] anion sensors,[29−32] catalysts,[33] and biologically active compounds.[34−37] Among them, *N*,*N*′-diphenylurea forms a characteristic hydrogen-bond network in the crystal, which was extensively studied by Etter et al.[38−40] and other groups.[41−43] In addition, the *N*,*N*′-diphenylurea skeleton has a unique structural feature, in that *N*,*N*′-dimethylation leads to dramatic conformational switching from *trans*-*trans* to *cis*-*cis* conformation.[44−46] This structural feature has been employed to design and create various new functional molecules.[47,48]

Supramolecular polymers have recently attracted enormous interest as an emerging class of polymer materials for application to electronic and biomedical devices.[49−51] A supramolecular polymer is defined as "polymeric arrays of monomeric units that are brought together by reversible and highly directional secondary interactions, resulting in polymeric properties in dilute and concentrated solution as well as in the bulk."[49] A number of compounds have been developed as monomers for supramolecular polymers, and bis-urea compounds form supramolecular polymers linked by hydrogen bonds.[52−56] However, supramolecular polymers consisting of an alternating sequence of two different monomers have not yet received much attention.

In this study, we aimed to investigate the utility of the phenyl–perfluorophenyl interaction for crystal engineering, to regulate molecular alignment and arrangement in crystals of a

Received: July 8, 2017
Revised: September 20, 2017
Published: September 25, 2017

DOI: 10.1021/acs.cgd.7b00951
Cryst. Growth Des. XXXX, XXX, XXX−XXX

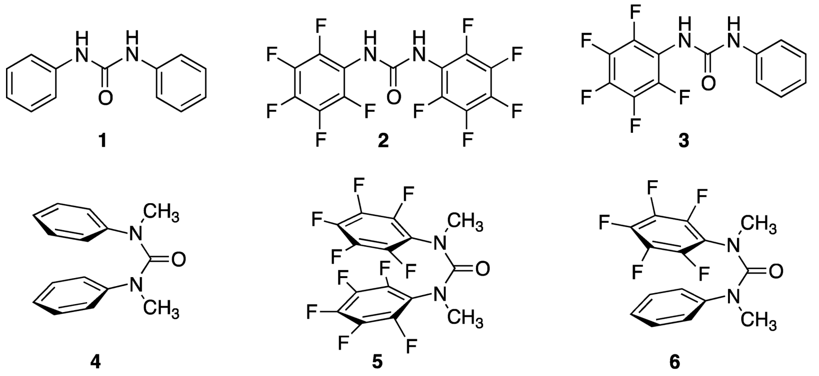
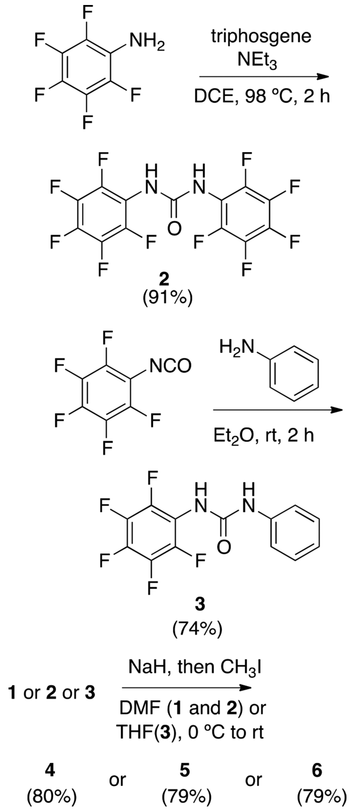


Figure 1. Structures of *N*,*N*′-diarylurea compounds used in this study.

series of compounds with an *N*,*N*′-diphenylurea skeleton (Figure 1). There has been some previous work on the crystal structure of compounds bearing phenyl–perfluorophenyl groups and hydrogen-bonding groups,[57−60] but this did not include compounds with a *N*,*N*′-diphenylurea skeleton. In single crystals of *N*,*N*′-diphenylurea compounds, the molecular arrangement and orientation are controlled by various interactions. Here, we succeeded in cocrystallizing two different *N*,*N*′-diphenylurea compounds, **1** and **2**, with the aid of hydrogen bonding and phenyl–perfluorophenyl interactions. We show that phenyl–perfluorophenyl interaction enabled alternating stacking in cocrystals of **1** and **2**, although other interactions, such as carbonyl–carbonyl and carbonyl–perfluorophenyl interactions, also played a role.

Scheme 1. Synthesis of 2–6



RESULTS AND DISCUSSION

N,*N*′-Diphenylurea (**1**) was purchased, and compounds **2–6** were synthesized as shown in Scheme 1. Reaction of 2,3,4,5,6-pentafluoroaniline with triphosgene afforded *N*,*N*′-bis(pentafluorophenyl)urea **2** in 91% yield. Unsymmetrical urea compound, **3**, with one phenyl group and one perfluorophenyl group on the urea nitrogens, was synthesized by reaction of 2,3,4,5,6-pentafluorophenyl isocyanate and aniline. *N*,*N*′-Dimethylation of **1–3** gave compounds **4–6**, respectively, in good yields.

The single-component crystal structures of **1** (CCDC 838624)[61,62] and polymorphs of **2** (**2a** (CCDC 128559)[63] and **2b** (CCDC 935702)[64]), have been previously reported, and the reported structures were used for comparison in this work. Recrystallization of **3** afforded a suitable crystal for X-ray crystallographic analysis, and the crystallographic parameters and solved crystal structure are shown in Table S1 and Figure 2 (thermal ellipsoids in Figure S1). In the crystal structures of **1–3**, all clearly showed the typical 1D chain structure formed by intermolecular hydrogen bonds between two NH proton donors and the C=O proton acceptor of the adjacent molecule. The phenyl or perfluorophenyl groups were distorted from the urea plane with dihedral angles of 27.7–61.8°, and the two phenyl groups of adjacent molecules were also nonplanar (Table 1 and Figure 3). Introduction of an *N*-perfluorophenyl group, as in **2** (**2a** and **2b**) and **3**, resulted in larger dihedral angles between the aromatic and urea planes (47.4–56.4°) than those of **1** (27.7° and 41.9°) (Table 1). In particular, intramolecular aromatic interaction was not apparent in the crystal structures of **1–3** because of the *trans*-*trans* conformation of the compounds. In the crystal structure of **1**, a T-shaped alignment of intermolecular phenyl groups (edge to face) was observed with dihedral angles of 74.7° and 66.5° (Table 2, see Figure 4 for the explanation of values shown in Table 2). In contrast, the intermolecular interactions of the two perfluorophenyl groups of **2** were different in the two types of crystals; in the structure of **2a**, one pair of perfluorophenyl groups was in a face-to-face relationship (2.3°) with very close contact (3.97 Å), while the groups of the other pair were directed differently. However, in the structure of **2b**, both pairs of intermolecular perfluorophenyl groups were in parallel relationships (0.0°) (Figure 3 and Table 2). It is noteworthy that intermolecular phenyl and perfluorophenyl stacked alternately and face-to-face (4.9 and 6.8°) at a moderate centroid distance (4.52 and 4.54 Å) in the crystal of **3** (Figures 2 and 3). Although two independent molecules existed in the asymmetric unit of the crystal of **3**, the structures of the two molecules are similar in terms of the dihedral angles between urea and the aromatic planes. Overall, it appears that

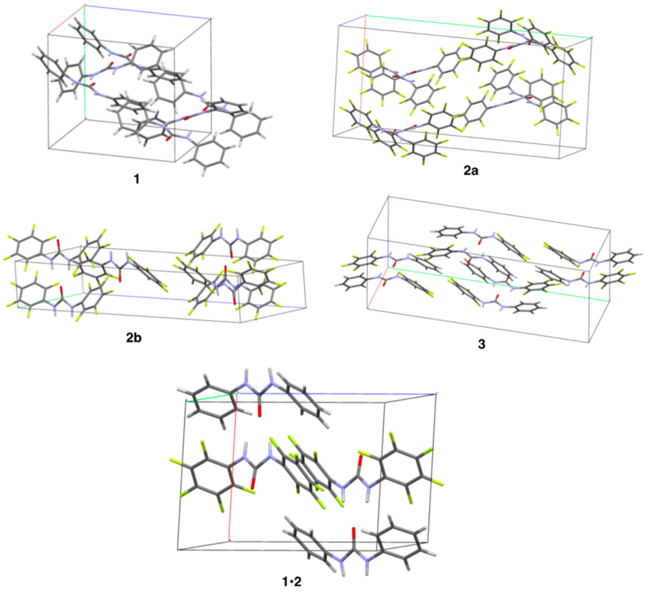


Figure 2. Views of the structures in crystals **1**, **2**, **3**, and cocrystal (**1**·**2**). Two polymorphs, **2a** (CCDC 128559)[63] and **2b** (CCDC 935702),[64] of **2** are shown.

Table 1. Dihedral Angle (deg) of Urea Plane and Phenyl (or Perfluorophenyl) Group Observed in Crystals of 1−3[a]

	1	2a	2b	3[b]		1(1·2)	2(1•2)
Ar^H−urea	41.9			54.6	56.4	47.8	
	27.7					33.5	
Ar^F−urea		61.8	50.5	56.2	55.8		56.5
		47.4	54.8				58.2
Ar−Ar[c]	35.5	37.0	30.1	43.9	38.8	51.6	39.0

[a] Ar^H = phenyl (C_6H_5), Ar^F = perfluorophenyl (C_6F_5). [b] Two asymmetric molecules exist in a single unit. [c] Dihedral angle of two closely located intramolecular phenyl groups.

introduction of the perfluorophenyl group favored intermolecular aromatic−aromatic interaction, which resulted in twisting of the urea plane and aromatic ring (*vide supra*) to optimize the geometry of the aromatic moiety.

To our delight, cocrystallization of **1** and **2** was successful by slow evaporation from a 1:1 molar ratio in DMF solution, and the molecular alignment in this cocrystal, denoted as **1**·**2**, was as expected from the phenyl−perfluorophenyl interaction;[1−23] molecules **1** and **2** in **1**·**2** were aligned alternately via hydrogen bonds and phenyl−perfluorophenyl interaction (Figure 2). The intermolecular phenyl−perfluorophenyl dihedral angle was in the range of 7.1−7.6°, and the centroid distance was 4.51−4.60 Å, similar to that of **3**. These values were close to those of a benzanilide derivative bearing phenyl and perfluorophenyl groups in the same molecule (4.54 and 4.78 Å),[57] but larger than those of a cocrystal of C_6H_5COOH and C_6F_5COOH (3.81−3.97 Å).[58] The presence of linker moieties (amide or urea) between the two aromatic groups (phenyl or perfluorophenyl) and hydrogen bonds would prevent close contact of the aromatic groups. In fact, phenyl and perfluorophenyl were displaced by 2.91−3.31 Å for **3** and 2.74−3.44 Å for **1**·**2**, evaluated by the value of *r*, respectively, and those values were close to twice that of cocrystal of C_6F_6−C_6D_6 (1.49−1.71 Å) (see Table 2).[19] It is noteworthy that in all phenyl−perfluorophenyl interaction observed **3** and **1**·**2**, the distance from perfluorophenyl centroid (*D*) was larger than that from phenyl moiety, which means perfluorophenyl group was tilted toward the phenyl moiety so that the F atoms are directed to the phenyl plane. In addition, 3D assemblies in the crystal of **3** and **1**·**2** were characteristic in that phenyl and perfluorophenyl was separated along other axes, which might be an interesting feature for further crystal design and engineering (Figure S6).

The effect of hydrogen bonding and phenyl−perfluorophenyl interaction was examined in detail by comparing bond lengths and atom−atom distances related to intermolecular hydrogen bonds (Table 3 and 4). The C═O bond of **1** was lengthened by hydrogen bond acceptance as a result of cocrystallization with **2** (from 1.223 to1.239 Å, Table 3). This indicates that **1** in **1**·**2** is a better hydrogen bond acceptor than **1** in the crystal of **1** alone. Superior hydrogen-bonding ability of **1** in **1**·**2** is further supported by the intermolecular hydrogen bond distance; the distance of $N(Ar^F(C_6F_5))−H\cdots O(Ar^H(C_6H_5))$ (2.760 and 2.770 Å) was shorter than that of $N(Ar^H)−H\cdots O(Ar^F)$ (2.822 and 2.923 Å), suggesting that the former pair forms a stronger hydrogen bond (Table 4). It is reasonable to think that the urea compound **2** with the strongly electron-withdrawing perfluorophenyl group would be more acidic and would be the better hydrogen bond donor. On the other hand, the bonds in **3**, especially the $N(Ar^H)−C(═O)$ bond, were unsymmetrical; $N(Ar^H)−C(═O)$ (1.349 or 1.350 Å) was clearly shorter than $N(Ar^F)−C(═O)$ (1.374 or 1.375 Å) or even than the corresponding bond of **1** (1.369 or 1.365 Å) (Table 3). This might be due to the unsymmetrical resonance structure of **3**, as depicted in Scheme 2; namely, the nitrogen atom attached to C_6H_5 makes a larger contribution to the resonance structure (**III**). Consequently, the NH proton attached to the phenyl group seems to be a better hydrogen bond donor than that on the perfluorophenyl group, and this was supported by the shorter and more linear hydrogen bond of $N(Ar^H)−H\cdots O(Ar)$ (156.2 and 157.1°), compared with $N(Ar^F)−H\cdots O(Ar)$ (154.0 and 149.5°) (Table 4). The Ar^H−N bond length was longer than the Ar^F−N bond length, which implies the existence of electron transfer from the nitrogen atom to the electron-deficient perfluorophenyl group, reducing the contribution of the resonance structure **I** in Scheme 2.

Infrared (IR) spectra and melting points of crystal **1**, **2**, and **1**·**2** were also measured, and no marked difference was found between the individual components (**1** and **2**) and the cocrystal (**1**·**2**). The cocrystal **1**·**2** exhibited a morphological change at 240 °C (mp of **1**) and melted at 270.5 °C (mp of **2**). The IR spectrum (KBr tablet) of **1**·**2** was not distinguishable from the superposition of those of the two components (**1** and **2**). Overall, the hydrogen bonds governed structure and molecular coordination, but alignment and bond length were affected by the introduction of the phenyl−perfluorophenyl pair.

The structures of *N*,*N*′-dimethylated *N*,*N*′-diphenyl urea derivatives, compounds **4**−**6**, were also analyzed by crystallography and views of the crystal packing are shown in Figure 5. In the crystal structures of those compounds, the *cis*-*cis* conformer, with two intramolecular aromatic groups located at the face-to-face position, was observed even for compounds **5** and **6** bearing perfluorophenyl group(s) with two unsymmetrical molecules in a single unit. Unfortunately, attempts to cocrystallize **4** and **5** have not been successful to date, indicating a key role of hydrogen bonding in cocrystallization of urea compounds. The dihedral angles of the urea plane N−C(═O)−N and the phenyl or perfluorophenyl moiety of **4**−**6** lay in a narrow range, 67.8−73.1°, but were larger than those of

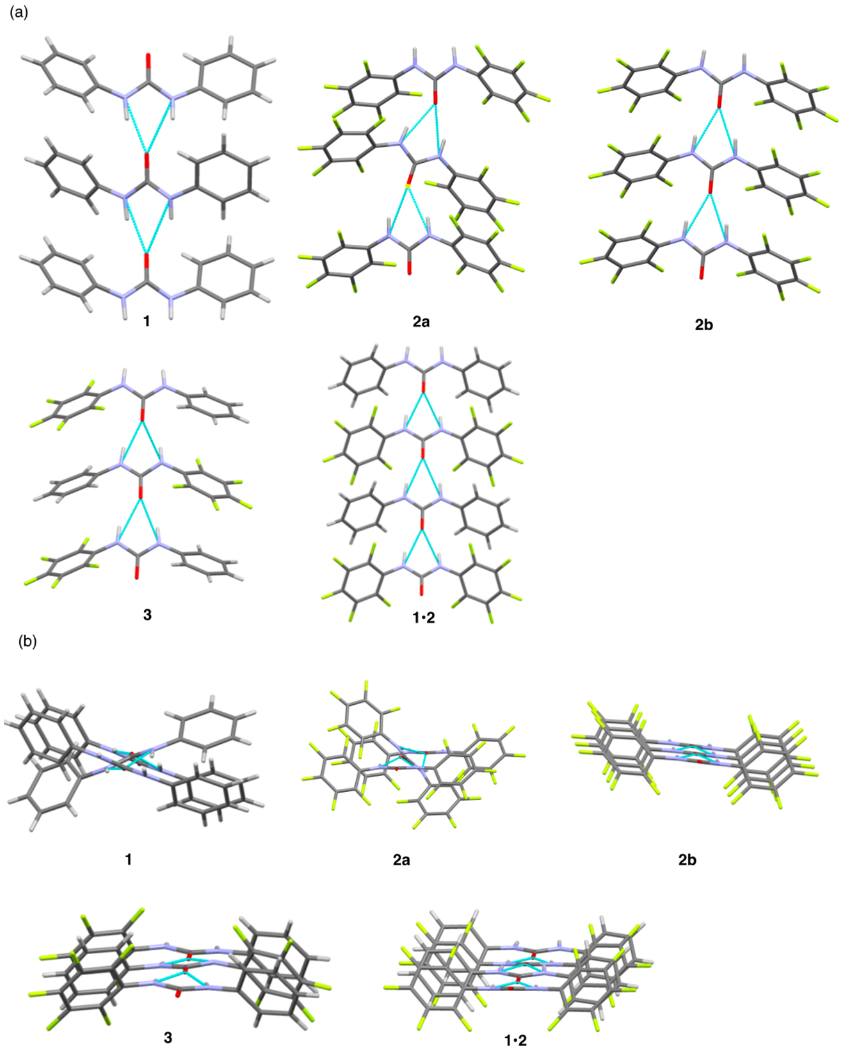


Figure 3. Views of hydrogen-bond networks in the crystal structures of **1**, **2**, **3**, and **1·2**. (a) Front views. (b) Vertical views.

1−**3** (Table 5). Introduction of the methyl groups on urea nitrogen would tend to tilt the phenyl moiety from the urea plane. Dihedral angles and centroid distances of the intramolecular aromatic group pairs in **4**−**6** were similar, though a small decrease in the dihedral angle of **6** was observed, due to the intramolecular phenyl−perfluorophenyl interaction. It is noteworthy that intermolecular phenyl−perfluorophenyl stacking was observed in the crystal structure of **6**, and the intermolecular centroid distance of **6** (3.79 and 3.85 Å) was smaller than that of **3** (4.52 and 4.56 Å) (Figure 6). Absence of hydrogen bonds in **6** manifested the intermolecular phenyl−perfluorophenyl interaction, and displacement of phenyl−perfluorophenyl (*r*, 0.53−1.67 Å) was close to that of C_6F_6−C_6D_6 rather than that of **3** (Figure 6 and Table 2). In addition, the phenyl and perfluorophenyl group of **6** in the crystal assembled separately in 3D images, similarly to that of **3** and **1·2** (Figure S6). The bond lengths in the crystal structures of **4**−**6** are summarized in Table 6. The C═O bond was shortened in **4**−**6** compared to **1**−**3** as a result of the lack of hydrogen bonding. The unsymmetrical resonance effect of the urea bond observed in **3** was retained in **6**, albeit to a lesser extent.

The crystal structures of **4**−**6** showed characteristic arrangements of the carbonyl group. In the crystal structures of **4** and **6**, the carbonyl group of the urea moiety formed an *anti*-parallel type dimer. Raines et al. recently suggested that carbonyl-carbonyl $n-\pi^*$ interaction serves to stabilize protein secondary structures, such as helix and turn, and protein−ligand interactions.[65−67] The orthogonal geometry that would enable the $n-\pi^*$ interaction seen in amide or peptide compounds was not observed in the crystal structures of **4** and **6**. The geometry observed in the crystal structures of ureas **4** and **6** showed values typical of antiparallel dimers, as judged from a database study (Figure 7);[68] the intermolecular O···C distance was around 3.5−3.6 Å, and the angle (∠C−O−C) was around 90°. The carbonyl−carbonyl interaction is weak (ca. ∼5 kcal/mol based on the calculation),[68] and may have been masked in the crystal structures of **1**−**3** due to the existence of the dominant hydrogen bonds. Carbonyl−carbonyl interaction was also not observed in the crystal structure of **5**, which has two perfluorophenyl groups. On the other hand, an interesting feature that the carbonyl group was sandwiched by the two perfluorophenyl groups connected by *cis*−*cis* urea architecture was observed (Figure 8). The feature might manifest the existence of carbonyl−perfluorophenyl interaction, presumably derived from the electrostatic interaction similar to $n-\pi^*$ interaction between hexafluorobenzene and water which was estimated to stabilize the complex ca. 2−3 kcal/mol based on the calculation.[69−72]

Table 2. Dihedral Angles and Distances of Intermolecular Aromatic–Aromatic Stacking Observed in Crystals 1–3 and Cocrystal 1·2

	planar angle (deg)	centroid distance (D) (Å)	d (Å)[b]	r (Å)[b]
1	74.7	5.38		
	66.5	5.12		
2a	2.3	3.97		
	2.3	6.84		
2b	0.0	4.58		
	0.0	4.58		
3[c]	4.9	4.52	3.46, 3.21	2.91, 3.19
	6.8	4.54	3.45, 3.14	2.95, 3.28
	4.9	4.57	3.45, 3.19	2.99, 3.27
	6.8	4.55	3.43, 3.12	2.99, 3.31
1·2	7.6	4.59	3.52, 3.11	2.95, 3.38
	7.1	4.51	3.53, 3.19	2.85, 3.19
	7.6	4.52	3.59, 3.21	2.74, 3.18
	7.1	4.60	3.43, 3.05	3.07, 3.44
C_6F_6–C_6D_6[a]	4.7	3.76	3.45, 3.35	1.49, 1.71

[a] Calculated with the structure reported in ref 19 (CCDC 1110270). [b] D, d, and r indicate the distance as in the Figure 4. Two values were shown for distances from the centroid of C_6F_5 and C_6H_5, in this order. [c] Two asymmetric molecules exist in a single unit.

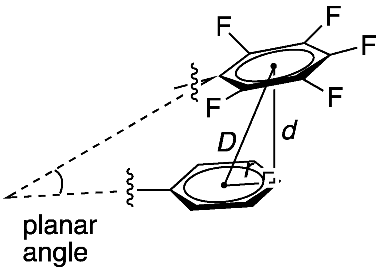


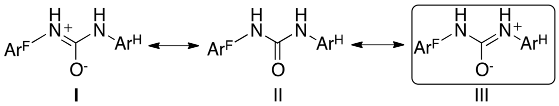
Figure 4. Schematic presentation of planar angle, centroid distance (D), and d.

Table 4. Distance and Angles Relevant to Hydrogen Bonds in crystals 1–3 and Cocrystal 1·2

crystal	H-bond	D/Å[a]	θ/°[b]
1	N(Ar^{H})–H···O(Ar^{H})	2.772	155.4
		2.896	145.3
2a	N(Ar^{F})–H···O(Ar^{F})	2.798	154.0
		2.929	146.8
2b	N(Ar^{F})–H···O(Ar^{F})	2.850	152.2
		2.825	154.1
3	N(Ar^{H})–H···O(Ar)	2.811	156.2
		2.813	157.1
	N(Ar^{F})–H···O(Ar)	2.829	154.0
		2.833	149.5
1·2	N(Ar^{H})–H···O(Ar^{F})	2.822	156.5
		2.923	148.5
	N(Ar^{F})–H···O(Ar^{H})	2.760	152.3
		2.770	153.8

[a] Distance between N–O. [b] θ = ∠N–H–O.

Scheme 2. Resonance Structures of Urea Bond in 3

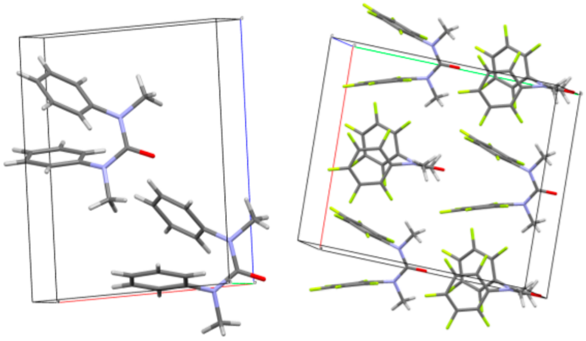


CONCLUSION

We examined and compared the crystal structures of *N,N′*-diphenylurea compounds **1**–**6** in detail in order to acquire insight into the relative importance of the various interactions, such as hydrogen bonding, phenyl–perfluorophenyl, carbonyl–carbonyl, and carbonyl–perfluorophenyl interactions. Phenyl–perfluorophenyl interaction was particularly important for the control of the molecular arrangement of these diphenylurea derivatives. However, the stronger intermolecular interaction, hydrogen bonds, played the major role to decide the geometry of the urea compounds. The hydrogen bonds of cocrystal of **1** and **2** (**1·2**) were characteristic: urea worked as a hydrogen bond donor with perfluorophenyl compound **2**, but as a hydrogen bond acceptor with phenyl compound **1**. In contrast, the NH proton attached phenyl nitrogen seemed to be a stronger hydrogen bond donor than the NH proton attached to perfluorophenyl, due to the unsymmetrical resonance structure. In the crystal structures of **4**–**6**, where no hydrogen bond is involved and *cis*-*cis* conformation of the urea skeleton is observed, antiparallel type carbonyl-carbonyl interaction was seen in **4** and **6**, and carbonyl–perfluorophenyl interaction in **5**. This new type of carbonyl–perfluorophenyl interaction resembles the anion–π interaction in catalytic systems,[73,74] and might be applicable for the design of novel catalysts for asymmetrical reactions as a new oxyanion hole motif. Even though, these interactions, phenyl–perfluorophenyl, carbonyl-carbonyl, and carbonyl–perfluorophenyl interactions, contrib-

Table 3. Bond Lengths (Å) Observed in Crystals 1–3 and Cocrystal 1·2

	1	2a	2b	3		1(1·2)	2(1·2)
Ar^{H}–N	1.419(6)			1.426(2)	1.429(2)	1.421(2)	
Ar^{F}–N		1.405(3)	1.406(2)				1.401(2)
N(Ar^{H})–C(=O)	1.369(5)			1.349(2)	1.350(2)	1.358(2)	
N(Ar^{F})–C(=O)		1.359(3)	1.365(2)				1.365(2)
C=O	1.223(4)	1.225(3)	1.232(3)	1.237(2)	1.236(2)	1.239(2)	1.225(2)
N(Ar^{F})–C(=O)		1.357(3)	1.368(3)	1.374(2)	1.375(2)		1.371(2)
N(Ar^{H})–C(=O)	1.365(6)					1.357(2)	
Ar^{F}–N		1.390(3)	1.406(2)	1.404(2)	1.405(2)		1.407(2)
Ar^{H}–N	1.418(6)					1.424(2)	



4 5 6

Figure 5. Views of the crystal structures of **4**–**6**.

Table 5. Dihedral Angle (deg) of Urea Plane (N–C(=O)–N) and Phenyl (or Perfluorophenyl) Group and Intramolecular Phenyl–Phenyl (or Perfluorophenyl) Centroid Distance (Å) Observed in Crystals of 4–6

	4	5a	5b	6a	6b
Ar^H–Urea	71.6			67.3	67.8
	67.5				
Ar^F–Urea		70.3	73.1	71.7	70.7
		70.3	73.1		
Ar–Ar					
angle (deg)	34.6	35.9	36.0	26.7	31.4
distance (Å)	3.87	3.52	3.74	3.69	3.76

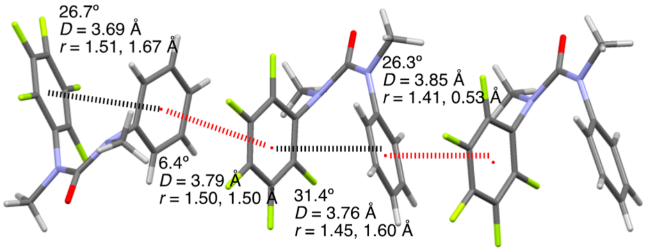
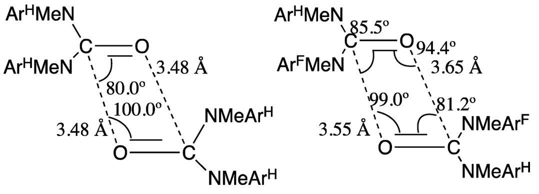


Figure 6. Views of intermolecular stacking structures of phenyl–perfluorophenyl rings in the crystal structure of **6**. Dihedral angle and centroid distance are shown. Hydrogen atoms are omitted for clarity. For explanation of D and r values (Å), see Figure 4.

ute subtly in energy, it would be nonnegligible to predict molecular arraignment in crystalline state.



4 6

Figure 7. Carbonyl–carbonyl interactions observed in the crystal structures of **4** and **6**.

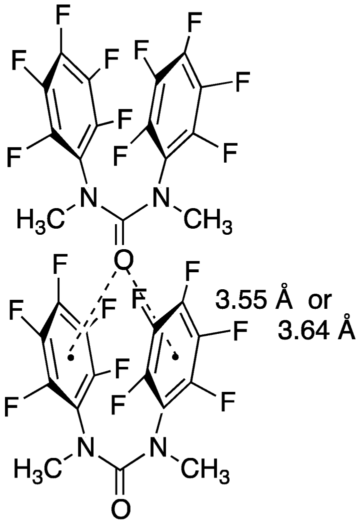


Figure 8. Carbonyl–perfluorophenyl interactions observed in the crystal structure of **5**.

Table 6. Bond Length (Å) Observed in Crystals of 4–6

	4	5a	5b	6a	6b
Ar^H–N	1.431(2)			1.435(2)	1.436(2)
Ar^F–N		1.418(2)	1.415(2)		
N–CH_3	1.466(2)	1.474(2)	1.474(2)	1.463(2)	1.467(2)
N(Ar^H)–C(=O)	1.376(2)			1.372(2)	1.380(2)
N(Ar^F)–C(=O)		1.379(2)	1.383(2)		
C=O	1.227(1)	1.220(2)	1.219(2)	1.219(2)	1.219(2)
N(Ar^F)–C(=O)		1.379(2)	1.383(2)	1.392(2)	1.385(2)
N(Ar^H)–C(=O)	1.383(1)				
N–CH_3	1.464(2)	1.474(2)	1.474(2)	1.466(2)	1.465(2)
Ar^F–N		1.418(2)	1.415(2)	1.413(2)	1.410(2)
Ar^H–N	1.433(1)				

DOI: 10.1021/acs.cgd.7b00951

Our findings here should be helpful to predict and control the molecular arrangement of urea compounds, and to create new functional molecules in the context of supramolecular polymers consisting of alternating sequences of two different monomers.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were obtained from commercial suppliers and were used as received. Melting points were determined by using a Yanaco melting point apparatus MP-S3 and are uncorrected. FT-IR spectra were recorded on a Horiba FT-710. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a JEOL AL-300 or BRUKER AV-300, or AV-600, and chemical shifts are expressed in parts per million relative to benzotrifluoride ($C_6H_5CF_3$ at −63.72 ppm for ^{19}F) or residual solvent peak (2.49 ppm (^{1}H), 39.5 ppm (^{13}C) for DMSO-d_6 and 7.26 ppm (^{1}H), 77.0 ppm (^{13}C) for $CDCl_3$). Mass spectra were measured on a JEOL MS700 V or HX110. Silica gel [silica gel 40−50 μm neutral (Kanto Chemical Co., Inc.)] was used for all chromatographic procedures.

Single Crystal X-ray Diffraction. Variable-temperature single-crystal X-ray diffraction experiments were carried out on an Rigaku R-AXIS Rapid II (graphite-monochromated Cu Kα radiation, λ = 1.541 Å). Crystals were mounted on MiTeGen dual-thickness MicroMounts using parabar oil. Data collections were carried out at low temperature (93−102 K) using liquid nitrogen. The crystal structures were solved by direct methods using SHELXS-2013[75] (for crystals of **3**, **5**, and **1·2**) or SIR2011[76] (for crystals of **4** and **6**). All non-hydrogen atoms were refined with anisotropic displacement parameters. Some hydrogen atoms of urea groups (in crystals of **3** and **1·2**) were refined isotropically. Other hydrogen atoms were included at their calculated positions. Crystallographic refinement details are summarized in Table S1 (CCDC 1560994−1560998). Structure analysis was performed with Mercury ver. 3.9 (CCDC) programs.

Synthesis of 1,3-Bis(pentafluorophenyl)urea (2). To 2,3,4,5,6-pentafluoroaniline (1.83 g, 10.0 mmol) in a 100 mL two-necked flask filled with argon was added triphosgene (0.53 g, 1.7 mmol) in 1,2-dichloroethane (20 mL) and triethylamine (2.8 mL, 20 mmol). The mixture was refluxed for 2 h at 98 °C, then cooled to rt, diluted with CH_2Cl_2 (130 mL), and washed with 10% HCl (60 mL) and brine. A colorless precipitate formed on standing for 12 h, and was collected by suction. The crude product was recrystallized from CH_3OH afforded a colorless powder (1.79 g, 91%). mp 270.0−270.5 °C; IR (KBr) 3342, 3022, 2924, 1648, 1587, 1533, 1498, 1466, 1329, 1273, 1236, 1190, 1155, 1076, 1030, 976, 739, 710 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.04 (2H, brs, -NH); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.0, 143.1 (m), 138.8 (m), 137.2 (m), 113.6; ^{19}F NMR (282 MHz, DMSO-d_6) δ −148.9, −161.2, −166.4; HRMS (EI$^+$) m/z: [M]$^+$ Calcd for $C_{13}H_2F_{10}N_2O$ 392.0002; Found 391.9997.

Synthesis of *N*-(Pentafluorophenyl)-*N′*-phenylurea (3). To a solution of aniline (300 μL, 3.29 mmol) in diethyl ether (3 mL) was added pentafluorophenyl isocyanate (0.43 mL, 3.29 mmol) in diethyl ether in an ice bath. The reaction mixture was warmed to room temperature and stirred for 2 h. The resulting colorless precipitate was collected by suction to afford the title compound (741 mg, 74%). This compound was purified by recrystallization from CH_3OH to afford colorless needles. mp 225.0−230.0 °C; IR (KBr) 3293, 1645, 1595, 1570, 1525, 1502, 1327, 1292, 1265, 1228, 1059, 1012, 978, 858, 825, 756, 694, 551 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.07 (1H, brs, -NH), 8.48 (1H, brs, -NH), 7.43 (2H, dd, J = 8.1, 1.2 Hz), 7.28 (2H, t, J = 8.1 Hz), 6.99 (2H, tt, J = 8.1, 1.2 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.9, 142.9 (m), 139.2, 138.6 (m), 137.2 (m), 128.8, 122.4, 118.4, 114.0 (m); ^{19}F NMR (282 MHz, DMSO-d_6) δ −149.0, −162.3, −166.7; HRMS (EI$^+$) m/z: [M]$^+$ Calcd for $C_{13}H_7F_5N_2O$ 302.0473; Found 302.0476.

Cocrystallization of 1 and 2. A solution of **1** in DMF was added to a solution of **2** in DMF to give a 1:1 molar ratio. The precipitate after slow evaporation was collected by suction to afford the cocrystals as colorless needles.

General Procedure for *N*-Methylation of Ureas 1−3 to Afford *N,N′*-Dimethylated Ureas (4−6). To a suspension of NaH (60% oil suspension, 450 mg, 11.3 mmol; washed twice with n-hexane and dried) in DMF (5 mL) was added **1** (955 mg, 4.50 mmol) in DMF (6 mL) in an ice bath. The reaction mixture was stirred for 15 min, then CH_3I (0.84 mL, 13.5 mmol) was added on the ice bath. After additional stirring for 24 h, the mixture was diluted with diethyl ether (250 mL), washed with sat. NH_4Cl aq. (700 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and evaporated in vacuo to afford a colorless powder (867 mg, 80%). The crude product was further purified by recrystallization from diethyl ether to afford colorless prisms. Analytical data were in good accordance with reported values.[77]

***N,N′*-Dimethyl-*N,N′*-bis(pentafluorophenyl)urea (5).** Synthesized according to the general procedure. mp 107.5−108.0 °C; IR (KBr) 2952, 1672, 1529, 1495, 1439, 1352, 1227, 1147, 1107, 1053, 1014, 989, 930, 837, 783, 739, 707, 660, 548 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.5, 143.3 (m), 140.3 (m), 137.6 (m), 119.1 (m), 38.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −147.3, −155.5, −161.9; HRMS (EI$^+$) m/z: [M]$^+$ Calcd for $C_{15}H_6F_{10}N_2O$ 420.0315; Found 420.0312.

***N,N′*-Dimethyl-*N*-(pentafluorophenyl)-*N′*-phenylurea (6).** Synthesized according to the general procedure, except that THF was used as the reaction solvent instead of DMF. Recrystallization from diethyl ether afforded colorless prisms. mp 94.5−95.0 °C; IR (KBr) 2941, 1678, 1595, 1518, 1498, 1429, 1352, 1302, 1209, 1117, 1078, 1049, 989, 891, 773, 748, 700, 658, 579 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (2H, t, J = 7.5 Hz), 7.06 (1H, t, J = 7.5 Hz), 6.89 (2H, d, J = 7.5 Hz), 3.26 (3H, s), 3.14 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.9, 143.5 (m), 139.6 (m), 137.4 (m), 129.2, 126.0, 124.9, 120.1 (m), 39.7, 37.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −146.9, −158.3, −164.7; HRMS (EI$^+$) m/z: [M]$^+$ Calcd for $C_{15}H_{11}F_5N_2O$ 330.0786; Found 330.0768.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.7b00951.

ORTEP drawing images of 3D assemblies; copies of ^{1}H, ^{13}C and ^{19}F NMR spectra of the compounds (PDF)

Accession Codes

CCDC 1560994−1560998 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

*Tel: (+81)-42-721-1570. Fax: (+81)-42-721-1570. E-mail: yamaryu@ac.shoyaku.ac.jp.

ORCID

Ryu Yamasaki: 0000-0002-8976-2962

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Mr. Chiba (Showa Pharmaceutical University) for HR-MS measurement.

REFERENCES

(1) Pace, C. J.; Gao, J. *Acc. Chem. Res.* **2013**, *46*, 907−915.
(2) Reichenbächer, K.; Süss, H. I.; Hulliger, J. *Chem. Soc. Rev.* **2005**, *34*, 22−30.

(3) Sharber, S. A.; Baral, R. N.; Frausto, F.; Haas, T. E.; Müller, P.; Thomas, S. W., III *J. Am. Chem. Soc.* **2017**, *139*, 5164−5174.

(4) Pawle, R. H.; Haas, T. E.; Müller, P.; Thomas, S. W., III *Chem. Sci.* **2014**, *5*, 4184−4188.

(5) Hsu, S.-M.; Lin, Y.-C.; Chang, J.-W.; Liu, Y.-H.; Lin, H.-C. *Angew. Chem., Int. Ed.* **2014**, *53*, 1921−1927.

(6) Ryan, D. M.; Doran, T. M.; Nilsson, B. L. *Langmuir* **2011**, *27*, 11145−11156.

(7) Xu, R.; Schweizer, W. B.; Frauenrath, H. *Chem. - Eur. J.* **2009**, *15*, 9105−9116.

(8) Xu, R.; Schweizer, W. B.; Frauenrath, H. *J. Am. Chem. Soc.* **2008**, *130*, 11437−11445.

(9) Rasmusson, T.; Martyn, L. J. P.; Chen, G.; Lough, A.; Oh, M.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7009−7012.

(10) Mu, Z.; Shu, L.; Fuchs, H.; Mayor, M.; Chi, L. *J. Am. Chem. Soc.* **2008**, *130*, 10840−10841.

(11) Kishikawa, K.; Oda, K.; Aikyo, S.; Kohmoto, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 764−768.

(12) Shu, L.; Mu, Z.; Fuchs, H.; Chi, L.; Mayor, M. *Chem. Commun.* **2006**, 1862−1863.

(13) Watt, S. W.; Dai, C.; Scott, A. J.; Burke, J. M.; Thomas, R. L.; Collings, J. C.; Viney, C.; Clegg, W.; Marder, T. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3061−3063.

(14) Vangala, V. R.; Nangia, A.; Lynch, V. M. *Chem. Commun.* **2002**, 1304−1305.

(15) Ponzini, F.; Zagha, R.; Hardcastle, K.; Siegel, J. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2323−2325.

(16) Blanchard, M. D.; Hughes, R. P.; Concolino, T. E.; Rheingold, A. L. *Chem. Mater.* **2000**, *12*, 1604−1610.

(17) Coates, G. W.; Dunn, A. R.; Henling, L. M.; Ziller, J. W.; Lobkovsky, E. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 3641−3649.

(18) Patrick, C. R.; Prosser, G. S. *Nature* **1960**, *187*, 1021.

(19) Williams, J. H.; Cockcroft, J. K.; Fitch, A. N. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1655−1657.

(20) Williams, J. H. *Acc. Chem. Res.* **1993**, *26*, 593−598.

(21) Ehrlich, S.; Moellmann, J.; Grimme, S. *Acc. Chem. Res.* **2013**, *46*, 916−926.

(22) Tsuzuki, S.; Uchimaru, T.; Mikami, M. *J. Phys. Chem. A* **2006**, *110*, 2027−2033.

(23) Adams, H.; Jimenez Blanco, J.-L.; Chessari, G.; Hunter, C. A.; Low, C. M. R.; Sanderson, J. M.; Vinter, J. G. *Chem. - Eur. J.* **2001**, *7*, 3494−3503.

(24) Yamanaka, M.; Fujii, H. *J. Org. Chem.* **2009**, *74*, 5390−5394.

(25) Schoonbeek, F. S.; van Esch, J. H.; Hulst, R.; Kellogg, R. M.; Feringa, B. L. *Chem. - Eur. J.* **2000**, *6*, 2633−2643.

(26) van Gorp, J. J.; Vekemans, J. A. J. M.; Meijer, E. W. *J. Am. Chem. Soc.* **2002**, *124*, 14759−14769.

(27) Schoonbeek, F. S.; van Esch, J. H.; Wegewijs, B.; Rep, D. B. A.; de Haas, M. P.; Klapwijk, T. M.; Kellogg, R. M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1393−1397.

(28) van Esch, J.; De Feyter, S.; Kellogg, R. M.; De Schryver, F.; Feringa, B. L. *Chem. - Eur. J.* **1997**, *3*, 1238−1243.

(29) Diemer, V.; Fischer, L.; Kauffmann, B.; Guichard, G. *Chem. - Eur. J.* **2016**, *22*, 15684−15692.

(30) Custelcean, R.; Jiang, D.; Hay, B. P.; Luo, W.; Gu, B. *Cryst. Growth Des.* **2008**, *8*, 1909−1915.

(31) Caltagirone, C.; Hiscock, J. R.; Hursthouse, M. B.; Light, M. E.; Gale, P. A. *Chem. - Eur. J.* **2008**, *14*, 10236−10243.

(32) Boiocchi, M.; Del Boca, L.; Gómez, D. E.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507−16514.

(33) Connon, S. J. *Synlett* **2009**, *2009*, 354−376.

(34) Solinas, A.; Faure, H.; Roudaut, H.; Traiffort, E.; Schoenfelder, A.; Mann, A.; Manetti, F.; Taddei, M.; Ruat, M. *J. Med. Chem.* **2012**, *55*, 1559−1571.

(35) Müller, S.; Pantoş, G. D.; Rodriguez, R.; Balasubramanian, S. *Chem. Commun.* **2009**, 80−82.

(36) Drewe, W. C.; Nanjunda, R.; Gunaratnam, M.; Beltran, M.; Parkinson, G. N.; Reszka, A. P.; Wilson, W. D.; Neidle, S. *J. Med. Chem.* **2008**, *51*, 7751−7767.

(37) Shantz, E. M.; Steward, F. C. *J. Am. Chem. Soc.* **1955**, *77*, 6351−6353.

(38) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120−126.

(39) Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415−8426.

(40) Etter, M. C.; Panunto, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5896−5897.

(41) Politzer, P.; Murray, J. S. *Cryst. Growth Des.* **2015**, *15*, 3767−3774.

(42) Custelcean, R. *Chem. Commun.* **2008**, 295−307.

(43) Chang, Y.-L.; West, M.-A.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 5991−6000.

(44) Galan, J. F.; Germany, E.; Pawlowski, A.; Strickland, L.; Galinato, M. G. *J. Phys. Chem. A* **2014**, *118*, 5304−5315.

(45) Clayden, J.; Hennecke, U.; Vincent, M. A.; Hillier, I. H.; Helliwell, M. *Phys. Chem. Chem. Phys.* **2010**, *12*, 15056−15064.

(46) Yamaguchi, K.; Matsumura, G.; Kagechika, H.; Azumaya, I.; Ito, Y.; Itai, A.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 5474−5475.

(47) Kagechika, H.; Azumaya, I.; Tanatani, A.; Yamaguchi, K.; Shudo, K. *Tetrahedron Lett.* **1999**, *40*, 3423−3426.

(48) Fukutomi, R.; Tanatani, A.; Kakuta, H.; Tomioka, N.; Itai, A.; Hashimoto, Y.; Shudo, K.; Kagechika, H. *Tetrahedron Lett.* **1998**, *39*, 6475−6478.

(49) Yang, L.; Tan, X.; Wang, Z.; Zhang, X. *Chem. Rev.* **2015**, *115*, 7196−7239.

(50) Aida, T.; Meijer, E. W.; Stupp, S. I. *Science* **2012**, *335*, 813−817.

(51) De Greef, T. F. A.; Smulders, M. M. J.; Wolffs, M.; Schenning, A. P. H. J.; Sijbesma, R. P.; Meijer, E. W. *Chem. Rev.* **2009**, *109*, 5687−5754.

(52) Brocorens, P.; Linares, M.; Guyard-Duhayon, C.; Guillot, R.; Andrioletti, B.; Suhr, D.; Isare, B.; Lazzaroni, R.; Bouteiller, L. *J. Phys. Chem. B* **2013**, *117*, 5379−5386.

(53) Isare, B.; Pembouong, G.; Boué, F.; Bouteiller, L. *Langmuir* **2012**, *28*, 7535−7541.

(54) Simic, V.; Bouteiller, L.; Jalabert, M. *J. Am. Chem. Soc.* **2003**, *125*, 13148−13154.

(55) Lortie, F.; Boileau, S.; Bouteiller, L. *Chem. - Eur. J.* **2003**, *9*, 3008−3014.

(56) Boileau, S.; Bouteiller, L.; Lauprêtre, F.; Lortie, F. *New J. Chem.* **2000**, *24*, 845−848.

(57) Wang, J. L.; Xu, J. S.; Wang, D. Y.; Wang, H.; Li, Z. T.; Zhang, D.-W. *CrystEngComm* **2014**, *16*, 2078−2084.

(58) Reddy, L. S.; Nangia, A.; Lynch, V. M. *Cryst. Growth Des.* **2004**, *4*, 89−94.

(59) Meejoo, S.; Kariuki, B. M.; Harris, K. D. M. *ChemPhysChem* **2003**, *4*, 766−769.

(60) Gdaniec, M.; Jankowski, W.; Milewska, M. J.; Połoński, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3903−3906.

(61) Uehara, K.; Mizuno, N. *J. Am. Chem. Soc.* **2011**, *133*, 1622−1625.

(62) Dinesh, R.; Deshmukh, M. B.; Kamni; Rajnikant. *Bull. Mater. Sci.* **2006**, *29*, 239−242.

(63) Jai-nhuknan, J.; Karipides, A. G.; Hughes, J. M.; Cantrell, J. S. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1997**, *53*, 455−457.

(64) Okuno, T. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2013**, *69*, o608.

(65) Bartlett, G. J.; Choudhary, A.; Raines, R. T.; Woolfson, D. N. *Nat. Chem. Biol.* **2010**, *6*, 615−620.

(66) Choudhary, A.; Gandla, D.; Krow, G. R.; Raines, R. T. *J. Am. Chem. Soc.* **2009**, *131*, 7244−7246.

(67) Bretscher, L. E.; Jenkins, C. L.; Taylor, K. M.; DeRider, M. L.; Raines, R. T. *J. Am. Chem. Soc.* **2001**, *123*, 777−778.

(68) Allen, F. H.; Baalham, C. A.; Lommerse, J. P. M.; Raithby, P. R. *Acta Crystallogr., Sect. B: Struct. Sci.* **1998**, *54*, 320−329.

(69) Singh, S. K.; Das, A. *Phys. Chem. Chem. Phys.* **2015**, *17*, 9596−9612.

(70) Egli, M.; Sarkhel, S. *Acc. Chem. Res.* **2007**, *40*, 197−205.
(71) Jain, A.; Purohit, C. S.; Verma, S.; Sankararamakrishnan, R. *J. Phys. Chem. B* **2007**, *111*, 8680−8683.
(72) Gallivan, J. P.; Dougherty, D. A. *Org. Lett.* **1999**, *1*, 103−105.
(73) Zhao, Y.; Cotelle, Y.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2016**, *138*, 4270−4277.
(74) Zhao, Y.; Cotelle, Y.; Avestro, A.-J.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2015**, *137*, 11582−11585.
(75) Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112−122.
(76) Camalli, M.; Carrozzini, B.; Cascarano, G. L.; Giacovazzo, C. *J. Appl. Crystallogr.* **2012**, *45*, 351−356.
(77) Wakita, Y.; Kobayashi, Y.; Maeda, M.; Kojima, M. *Chem. Pharm. Bull.* **1982**, *30*, 3395−3398.

DOI: 10.1021/acs.cgd.7b00951
Cryst. Growth Des. XXXX, XXX, XXX−XXX