

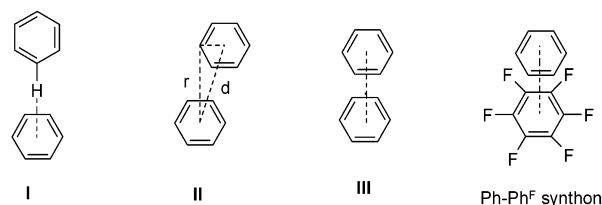
Phenyl-Perfluorophenyl Synthons Mediated
Cocrystallization of Carboxylic Acids and AmidesL. Sreenivas Reddy,[†] Ashwini Nangia,^{*,†} and Vincent M. Lynch[‡]*School of Chemistry, University of Hyderabad, Hyderabad 500 046, India, and
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ABSTRACT: The significance of face-to-face π – π stacking of phenyl and perfluorophenyl rings (Ph–Ph^F), a robust supramolecular synthon in aromatic and perfluoroaromatic crystal structures, is studied in the cocrystallization of simple aromatic carboxylic acids and amides. X-ray crystal structures of C₆H₅COOH·C₆F₅COOH **1**, C₆H₅CONH₂·C₆F₅CONH₂ **2**, and C₆H₅CONH₂·C₆F₅COOH **3** are analyzed to understand the role of Ph–Ph^F synthon in directing self-assembly and hydrogen bonding in these cocrystals. The strong hydrogen bond donor acidity of C₆F₅COOH and C₆F₅CONH₂ together with mixed stacks of phenyl and perfluorophenyl rings steer acid···acid and amide···amide hydrogen bonding in cocrystals **1** and **2**. Acid···amide hydrogen bonding is sufficiently strengthened by donor acidity and acceptor basicity in **3** that the role of the Ph–Ph^F synthon is weaker because the aromatic rings stack with lateral offset. The complex C₆H₅COOH·C₆F₅CONH₂ **4** could not be obtained under similar crystallization conditions. The crystal structure of C₆F₅CONH₂ is determined to compare molecular conformation and hydrogen bonding with motifs in the cocrystals. This study shows the viability of the Ph–Ph^F synthon in the presence of strong hydrogen bonding COOH and CONH₂ groups for crystal engineering.

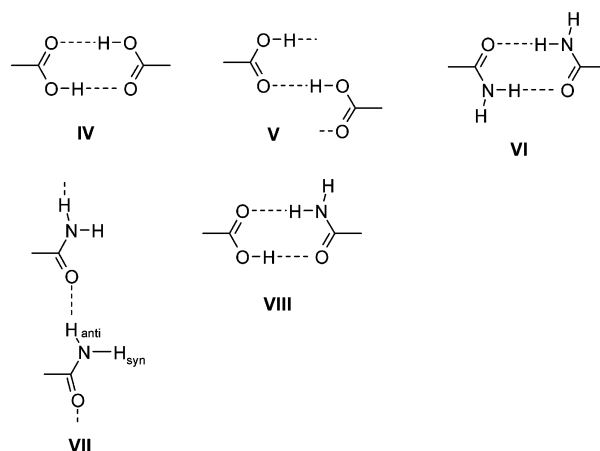
Introduction

Aromatic–aromatic interactions are important in crystal engineering, supramolecular chemistry, biological recognition, and most recently highlighted for their significance in drug design.¹ Recognition between phenyl rings adopts low energy dimers of the edge-to-face geometry or herringbone T-motif **I**, parallel-displaced geometry with lateral offset **II**, and face-to-face or π -stacked sandwich geometry **III** (Scheme 1).² Unperturbed phenyl rings generally adopt the herringbone motif **I** with major stabilization to the T-geometry arising from dipole–quadrupole interaction between the positively polarized hydrogen and the negatively charged π -cloud of the benzene ring. Electron-deficient and electron-rich aromatic rings (e.g., C₆F₅ and C₆H₅) have an overwhelming preference for the stacked geometry **III** because favorable quadrupole–quadrupole interaction between aromatic rings with – and + quadrupole moment is maximized and unfavorable electrostatic repulsion in the T-geometry is minimized. The most remarkable example of phenyl–perfluorophenyl stacking (hereafter Ph–Ph^F synthon) is the crystal structure of the 1:1 complex of benzene–hexafluorobenzene³ with an interplanar distance (*r*) of 3.4 Å and an intercentroid distance (*d*) of 3.7 Å. Noncovalent interactions in the molecular complex are so strong that melting point of the cocrystal (23.7 °C) is about 19 °C higher than the individual components. Several research groups have used the Ph–Ph^F synthon to steer supramolecular organization in the crystal⁴ and to prealign molecules for solid-state photopolymerization.⁵

Cocrystallization is a current theme in several research groups to study hydrogen bonding by X-ray diffraction, for the synthesis of supramolecular archi-

Scheme 1. Edge-to-Face and Face-to-Face Interactions between Phenyl Rings^a

^a Center-to-center distance (*d*) and interplanar distance (*r*) are defined in synthon II.

Scheme 2. Hydrogen Bond Synthons of COOH and CONH₂ Groups

tectures and interpenetrated networks, and in pharmaceutical development.⁶ Carboxylic acids and carboxamides are reliable functional groups in crystal engineering⁷ because they form robust aggregates as dimers and catemers (synthons **IV**–**VII**) via strong O–H···O and N–H···O hydrogen bonds (8–10 kcal mol^{–1}). The energy

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Table 1. Crystallographic Data and Structure Refinement Parameters^a

	1	2	3	C ₆ F ₅ CONH ₂
chemical formula	(C ₇ H ₆ O ₂)·(C ₇ HF ₅ O ₂)	(C ₇ H ₇ NO)·(C ₇ H ₂ F ₅ NO)	(C ₇ H ₇ NO)·(C ₇ HF ₅ O ₂)	C ₇ H ₂ F ₅ NO
formula weight	334.20	332.23	333.21	211.10
crystal system	monoclinic	monoclinic	monoclinic	monoclinic
space group	Cc	P2 ₁	P2 ₁ /n	P2 ₁ /c
a/Å	24.7320(4)	7.3546(3)	11.290(2)	12.749(3)
b/Å	7.7420(1)	6.0207(2)	6.7326(13)	6.1977(12)
c/Å	14.3430(3)	14.7507(5)	18.085(4)	9.5974(19)
α/°	90.00	90.00	90.00	90.00
β/°	108.4210(10)	90.568(2)	105.04(3)	99.94(3)
γ/°	90.00	90.00	90.00	90.00
Z	8	2	4	4
V/Å ³	2605.61(8)	653.13(4)	1327.5(5)	747.0(3)
T/K	153(2)	153(2)	293(2)	293(2)
D _{calc} /g cm ⁻³	1.704	1.689	1.667	1.877
μ/mm ⁻¹	0.170	0.162	0.163	0.210
reflns collected	6107	4261	5535	2784
unique reflns	6103	2706	3018	1672
obsd reflns	4307	2243	1966	718
R ₁ [I > 2σ(I)]	0.0474	0.0412	0.0421	0.0678
wR ₂ [all]	0.1221	0.0987	0.1165	0.1764
goodness-of-fit	1.047	1.099	1.032	0.982

^a CCDC deposit nos. 216156–216159.

of the C₆H₆–C₆F₆ dimer in the eclipsed face-to-face arrangement is 4–5 kcal mol⁻¹ ($r = 3.6$ – 3.7 Å) by ab initio, semiempirical, and DFT calculations.⁸ Furthermore, the heterodimer is calculated to be more stable than the homodimer in all cases. Given that the energy of Ph–Ph^F synthon is about half that of a strong O–H···O or N–H···O hydrogen bond we examined cocrystallization of aryl and perfluoroaryl carboxylic acids and amides. There are other favorable considerations in exploiting the Ph–Ph^F synthon to mediate cocrystallization. The pentafluorophenyl group activates the COOH and CONH₂ donor groups for hydrogen bonding because of the high electronegativity of fluorine (F 4.0, H 2.1, C 2.5; Pauling scale), while the similar van der Waals radius of H and F (1.20 Å, 1.47 Å; Bondi radius) means that the aryl/perfluoroaryl rings are nearly isosteric. Furthermore, organic fluorine has little hydrogen-bond acceptor ability,⁹ and hence phenyl–perfluorophenyl stacking was expected to prevail in the presence of other strong hydrogen bonding groups, e.g., COOH, CONH₂. X-ray crystal structures of benzoic acid·pentafluorobenzoic acid **1**, benzamide·pentafluorobenzamide **2**, and benzamide·pentafluorobenzoic acid **3** are reported and discussed in this paper to highlight the role of the Ph–Ph^F synthon in cocrystallization. While the crystal structure of C₆F₅COOH is known,¹⁰ the structure of C₆F₅CONH₂ was determined as part of this study to compare the conformation and hydrogen bonding of the fluorinated molecule with that in the molecular complex.

Experimental Section

In all cocrystallization experiments, the components were finely ground using mortar-and-pestle and dissolved in EtOAc/hexane (1:1). The molecular complex was characterized by its difference in melting point from the pure components and the structure confirmed by X-ray diffraction. Melting point of benzoic acid is 122 °C, benzamide is 129 °C, pentafluorobenzoic acid is 101 °C, and pentafluorobenzamide is 145 °C. Melting point is determined on Fisher-Johns apparatus (visual inspection) and confirmed by the onset temperature of endotherm measured on Perkin-Elmer DSC4 instrument (scan rate 10° min⁻¹). Crystals of pentafluorobenzamide were obtained from CH₂Cl₂ at ambient temperature. Although single crystals of

C₆F₅CONH₂ are of good quality they are soft and do not cut easily. The mosaicity factor is about 2 compared to typical values of 0.5–1.0.

Cocrystallization

(Benzoic Acid)·(Pentafluorobenzoic Acid) 1. A 1:1 mixture of benzoic acid (0.030 g, 0.25 mmol) and pentafluorobenzoic acid (0.053 g, 0.25 mmol) was dissolved in hot EtOAc/hexane (1:1). Plate-shaped colorless crystals were obtained after few days at room temperature. m.p. 85–87 °C.

(Benzamide)·(Pentafluorobenzamide) 2. A 1:1 mixture of benzamide (0.030 g, 0.25 mmol) and pentafluorobenzamide (0.052 g, 0.25 mmol) was dissolved in hot EtOAc/hexane (1:1). Needle-shaped colorless crystals were obtained after few days at room temperature. m.p. 103–105 °C.

(Benzamide)·(Pentafluorobenzoic Acid) 3. A 1:1 mixture of benzamide (0.030 g, 0.25 mmol) and pentafluorobenzoic acid (0.053 g, 0.25 mmol) was dissolved in hot EtOAc/hexane (1:1). Needle-shaped colorless crystals were obtained after few days at room temperature. m.p. 85 °C.

Cocrystallization of benzoic acid and pentafluorobenzamide using the above conditions did not afford the expected molecular complex **4**. Crystals of benzoic acid precipitated after a few days.

X-ray Diffraction. Reflections were collected on Nonius Kappa CCD diffractometer using incident X-ray radiation Mo- α ($\lambda = 0.71073$ Å). Crystals were cooled with an Oxford Cryosystem device attached to a CCD machine. Data reductions were performed using DENZO–SMN.¹¹ Structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares refinement on F² with anisotropic displacement parameters for non-H atoms using SHELXL-97.¹² In complex **1** H1A, H6A, and H3A atoms are fixed. Geometrical analysis was carried out in PLATON.¹³ Details of cell parameters, data collection, and structure refinement are summarized in Table 1, hydrogen bond metrics are given in Table 2, and selected torsion angles are listed in Table 3.

CCDC reference numbers are 216156–216159.

Results and Discussion

PhCO₂H·C₆F₅CO₂H **1** crystallizes in the monoclinic space group Cc with two residues of each component in the asymmetric unit. The molecules adopt different conformations about the C_{aryl}–C_{COOH} bond (Table 3): twisted conformation (designated A) and near-planar conformation B.¹⁴ C₆H₅CO₂H and C₆F₅CO₂H of both A

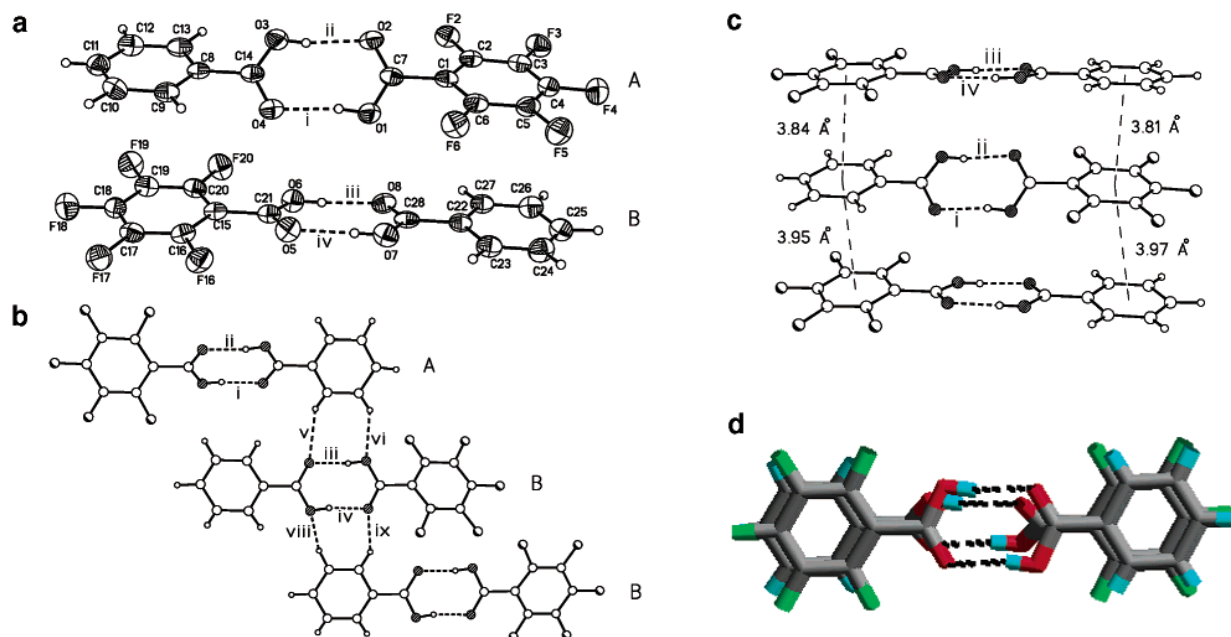


Figure 1. (a) ORTEP plot of $C_6H_5COOH \cdot C_6F_5COOH$ **1** drawn at 50% probability level for non-H atoms. Symmetry-independent carboxylic acid dimers are labeled A and B. Hydrogen bonds are shown as dotted lines and listed in Table 2. (b) C—H...O interactions between acid dimers. (c) Phenyl—perfluorophenyl stacking along the *b*-axis. (d) View down [010] to show the excellent π — π stacking in Ph—Ph^F synthon with no offset. H atoms are shown as small circles (or blue) and F atoms are shown as large circles (or green).

Table 2. Geometrical Parameters of Hydrogen Bonds

crystal		H-bond ^a	<i>d</i> /Å	<i>D</i> /Å	θ /°
1	i	O—H...O	1.67	2.647(3)	169.4
	ii	O—H...O	1.68	2.653(3)	168.7
	iii	O—H...O	1.63	2.605(3)	171.2
	iv	O—H...O	1.65	2.624(3)	170.2
	v	C—H...O	2.50	3.478(4)	149.1
	vi	C—H...O	2.50	3.437(4)	143.7
	vii	C—H...O	2.68	3.479(4)	130.6
	viii	C—H...O	2.56	3.503(4)	144.7
	ix	C—H...O	2.46	3.318(4)	135.2
	x	C—H...F	2.49	3.220(5)	123.7
2	i	N—H...O	2.16	3.118(3)	159.0
	ii	N—H...O	2.15	3.088(3)	152.9
	iii	N—H...O	2.03	2.997(3)	159.5
	iv	N—H...O	1.94	2.936(3)	169.7
	v	C—H...O	2.35	3.415(3)	167.7
3	i	N—H...O	2.02	3.003(2)	164.4
	ii	N—H...O	2.02	2.983(2)	157.3
	iii	O—H...O	1.51 (1.39) ^b	2.4873(18)	170.8
	iv	C—H...O	2.37	3.429(2)	164.1
	v	N—H...F	2.53	3.1589(19)	120.0
C₆F₅CONH₂	i	N—H...O	1.90	2.902(5)	168.6
	ii	N—H...O	1.96	2.906(5)	154.2

^a O—H, N—H, C—H bonds are neutron-normalized. ^b Experimental X-ray distance in very short hydrogen bond.

and B type molecules engage in symmetry-independent dimer **IV** (Figure 1a). The O—H...O hydrogen bond¹⁵ from $C_6F_5CO_2H$ to $C_6H_5CO_2H$ is shorter (iii, O...O 2.605(3) Å, electron-deficient donor to electron-rich acceptor) than the other hydrogen bond in **IV** from $C_6H_5CO_2H$ to $C_6F_5CO_2H$ (iv, O...O 2.624(3) Å, electron-rich donor to electron-deficient acceptor, difference $> 3\sigma$) for B molecule, but the difference is not significant for A molecule. The hydrogen bonds in synthon **IV** of twisted A molecules are longer (i, ii, O...O 2.647(3) Å, 2.653(3) Å) than iii, iv because conjugation between phenyl ring and carboxylic acid group in planar B molecules strengthens hydrogen bonding (O—H...O: i 1.67 Å, 169.4°; ii 1.68 Å, 168.7°; iii 1.63 Å, 171.2°; iv 1.65 Å, 170.2°; neutron-

Table 3. Selected Torsion Angles

crystal	atoms	θ /°
1	C2—C1—C7—O2	32.6
	C9—C8—C14—O4	27.2
	C16—C15—C21—O5	11.3
	C27—C22—C28—O8	5.0
2	C2—C1—C7—O8	42.9
	C6A—C1A—C7A—O8A	21.6
	N9A—C7A—O8A—N9	47.9
	N9—C7—O8—N9A	44.9
3	C2—C1—C7—O1	22.8
	C9—C8—C14—O3	22.5
	C6—C1—C7—O1	41.0

normalized geometry is reported). Such dimers are connected via C—H...O interactions listed in Table 2 and shown in Figure 1b. The structure has an overall van der Waals close packing such that the phenyl and perfluorophenyl groups are in proximity. The phenyl and perfluorophenyl rings of dimer aggregates A and B have excellent π -stacking with little offset (Ph—Ph^F synthon, Scheme 1) at an intercentroid distance (*d*) of 3.81, 3.84, 3.95, 3.97 Å (Figure 1c,d) and an interplanar distance (*r*) of ca. 3.5 Å. (3.53, 3.49, 3.47, 3.55 Å).

The crystal structure of binary component **1** may be compared with the structure of 1-pentafluorophenyl-4-phenylbutadiyne **5**.^{4a} Molecules of **5** are stacked in a head-to-tail fashion at interlayer distance (*r*) of ca. 3.7 Å. The diyne covalent spacer in **5** and hydrogen bond synthon **IV** in **1** are interchangeable, and, moreover, the C_{aryl} — C_{aryl} distance between Ph and Ph^F rings is very similar in the two structures (6.64 Å in **5**, 6.80 and 6.78 Å for A and B molecules of **1**). The identical packing in **1** and **5** strengthens the idea stated in the introduction that the hydrogen bonding and aromatic stacking domains in these structures are insulated from one another. We have noted the equivalence between molecular and supramolecular connectors in a family of wheel-and-axle host—guest structures.¹⁶

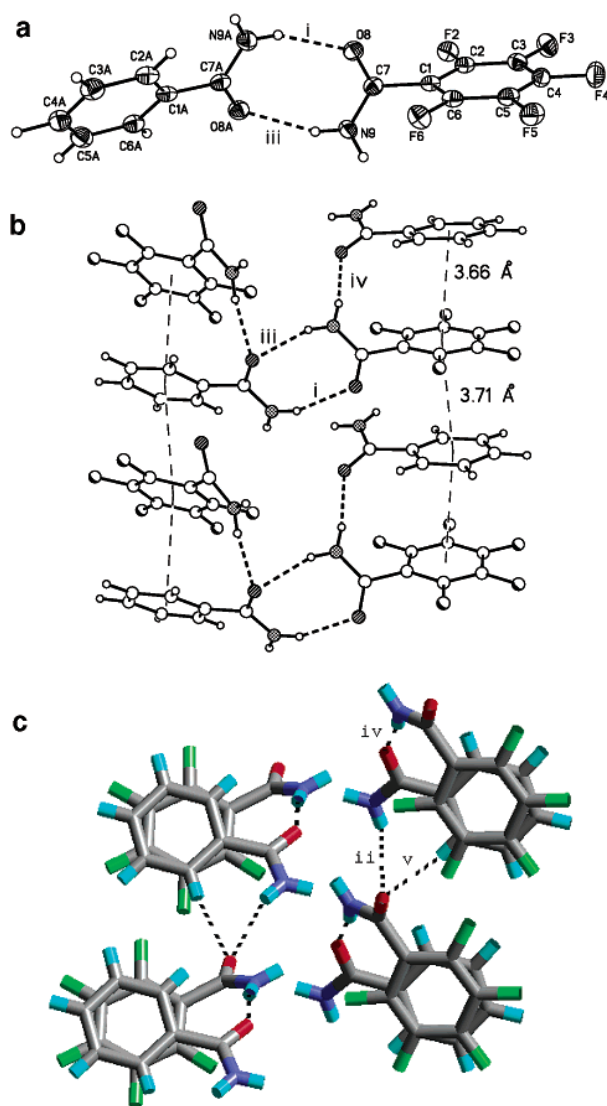


Figure 2. (a) ORTEP plot of $\text{C}_6\text{H}_5\text{CONH}_2 \cdot \text{C}_6\text{F}_5\text{CONH}_2$ **2**. (b) Ph-Ph^F stacking and $\text{N}_{\text{anti}}\text{-H}\cdots\text{O}$ bond iv along the *a*-axis. (c) View down [100] to show the excellent overlap of phenyl and perfluorophenyl rings. The $\text{N}_{\text{syn}}\text{-H}\cdots\text{O}$ hydrogen bond is not shown for clarity.

The assignment of *Cc* space group is fraught with the possibility that there might be true higher symmetry that is overlooked,¹⁷ and this error is even more likely when there are two symmetry-independent molecules ($Z' = 2$) as in **1**. We have verified that the assignment of *Cc* space group is correct in this case. There is an approximate, noncrystallographic inversion center at 0.4, 0.25, 0.2, which explains the centrosymmetric intensity statistics observed in data collection. However, from examination of the molecular conformations of PhCO_2H and $\text{C}_6\text{F}_5\text{CO}_2\text{H}$ and the two hydrogen-bonded dimers **IV** it is obvious that they are different. A check of the cif file in Platon for MISSYM also agrees with our assignment and the higher symmetry *C2/c* space group is ruled out for **1**.

$\text{C}_6\text{H}_5\text{CONH}_2 \cdot \text{C}_6\text{F}_5\text{CONH}_2$ **2** crystallizes in the polar space group *P2₁* with one molecule of each residue in the asymmetric unit. The CONH_2 group in $\text{C}_6\text{F}_5\text{CONH}_2$ is twisted with respect to the aromatic ring when compared with $\text{C}_6\text{H}_5\text{CONH}_2$ (Figure 2a, see torsion

angles in Table 3). $\text{C}_6\text{F}_5\text{CONH}_2$ and $\text{C}_6\text{H}_5\text{CONH}_2$ are connected via $\text{N-H}_{\text{anti}}\cdots\text{O}$ hydrogen bonds as catemer **VII** that run parallel to [1 1 0] and $[-1 -1 0]$ directions. The $\text{N}_{\text{anti}}\text{-H}\cdots\text{O}$ hydrogen bond iv from $\text{C}_6\text{F}_5\text{CONH}_2$ to $\text{C}_6\text{H}_5\text{CONH}_2$ is significantly shorter than the bond from $\text{C}_6\text{H}_5\text{CONH}_2$ to $\text{C}_6\text{F}_5\text{CONH}_2$ (Figure 2b, iv 1.94 Å, 169.7°; ii 2.15 Å, 152.9°, interaction ii to *b*-translated mixed stack is not shown). The syn NH groups form a twisted noncentrosymmetric dimer **VI** (iii 2.03 Å, 159.5°; i 2.16 Å, 159.0°) with N-C-O-N torsion angles of 47.9° and 44.9° (Table 3). Hydrogen bond iv is shorter than the other three N-H...O bonds in the same structure because the donor and acceptor groups are activated and it is simultaneously stabilized by the attractive Ph-Ph^F synthon (Figure 2b, *d* = 3.66 Å). The π -cloud of phenyl and pentafluorophenyl rings have excellent quadrupole-quadrupole interactions because they stack with little offset (Figure 2c). The shortness of $\text{N}_{\text{anti}}\text{-H}\cdots\text{O}$ compared to $\text{N}_{\text{syn}}\text{-H}\cdots\text{O}$ is significant because syn NH is generally assumed to be the stronger hydrogen bond donor than anti NH in primary amide.¹⁸ Weak C-H...O, C-H...F, and F...F interactions are present in the crystal. Thus, cocrystals of simple aromatic carboxylic acids and amides may be synthesized with perfluoroaromatic acids/amides keeping aryl group size considerations in mind. Crystallization of **1** and **2** in noncentrosymmetric space groups is an interesting observation but generally difficult to rationalize. That the carboxylic acid and amide dimers in structures with isomorphous substitution are devoid of center of symmetry could be a contributing factor insofar as the crystallographic inversion center is coincident with the centrosymmetric dimer.

$\text{C}_6\text{F}_5\text{CONH}_2$ crystallizes in the monoclinic space group *P2₁/c*. The amide group is highly twisted with respect to the C_6F_5 ring (Table 3). Molecules are hydrogen bonded via the centrosymmetric amide dimer **VI** (i 1.90 Å, 168.6°) and such dimers are connected to the glide-related O atom via $\text{N}_{\text{anti}}\text{-H}\cdots\text{O}$ bond (ii 1.96 Å, 154.2°, Figure 3). The shallow glide motif is adopted by some primary amides with *c*-axis of 9.8 ± 0.3 Å.¹⁹

Both dimer and catemer synthons **VI** and **VII** are present in $\text{C}_6\text{F}_5\text{CONH}_2$ and its cocrystal **2**. The question arises: which is the primary motif and which is the secondary one? We believe that the 0D dimer **VI** is the primary synthon in the structure of $\text{C}_6\text{F}_5\text{CONH}_2$ because the space group is centrosymmetric. On the other hand, the $\text{N}_{\text{anti}}\text{-H}\cdots\text{O}$ bond from $\text{C}_6\text{F}_5\text{CONH}_2$ donor to $\text{C}_6\text{H}_5\text{CONH}_2$ acceptor, strengthened by the Ph-Ph^F synthon, is the primary structural motif in cocrystal **2**. The weak amide dimer synthon and noncentrosymmetric packing of **2** argue in favor of a catemer as the main recognition motif. This hints toward the structure-directing role of the Ph-Ph^F synthon in cocrystallization of **1** and **2**.

Crystallization of benzamide and pentafluorobenzamide was attempted next. Crystals of 1:1 complex **3** were obtained from EtOAc/hexane at ambient temperature that solved in the *P2₁/n* space group. The twist in molecular conformation of acid and amide molecules is listed in Table 3. The crystal structure is stabilized by acid...amide heterodimer **VIII** (Figure 4a, O-H...O iii 1.51 Å, 170.8°; N-H...O i 2.02 Å, 164.4°). O-H...O bond iii is in the range of a very short (strong) hydrogen

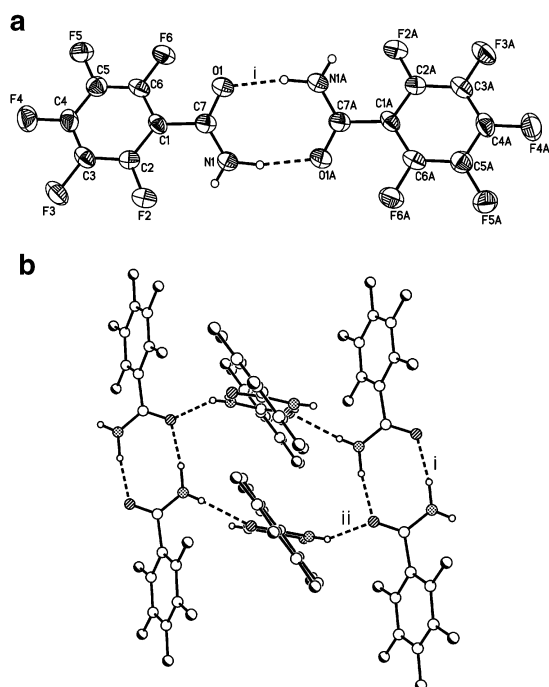


Figure 3. (a) ORTEP plot of $C_6F_5CONH_2$ to show the amide dimer synthon. (b) $N_{anti}-H\cdots O$ bond to glide-related molecule.

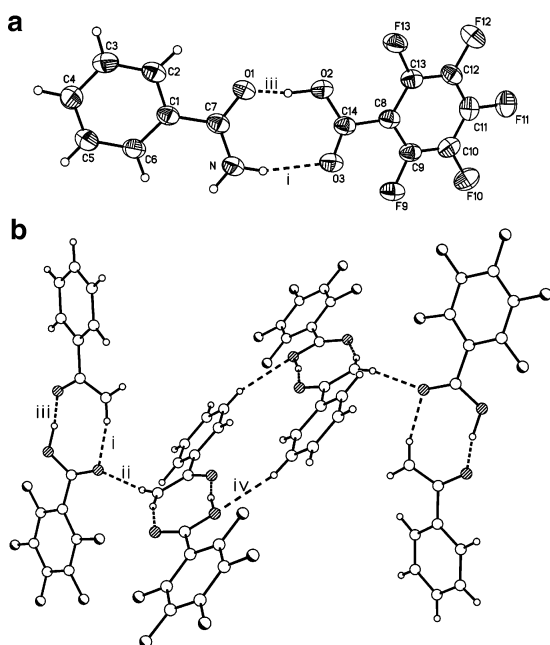


Figure 4. (a) ORTEP plot of $C_6H_5CONH_2 \cdot C_6F_5COOH$ **3** to show acid...amide heterodimer **VIII**. (b) $N_{anti}-H\cdots O$ bond and $C-H\cdots O$ interaction with C_6F_5COOH of glide- and inversion-related aggregate.

bond²⁰ ($O\cdots O$ 2.4873(18) Å) with an $H\cdots O$ distance of 1.39 Å (X-ray). The shortness of $O-H\cdots O$ is due to the very strong donor ($C_6F_5CO_2H$) and highly basic acceptor group ($PhCONH_2$). Short $O-H\cdots O$ hydrogen bonds have been noted in acid–amide cocrystals, e.g., oxalic acid·*trans*-cinamamide ($O\cdots O$ 2.489 Å, $O-H\cdots O$ 174.3°).²¹ The heterodimers are connected to the $COOH$ group of a glide-related aggregate by $N-H\cdots O$ bond (ii 2.02 Å, 157.3°), and such inversion-related dimers are connected by $C-H\cdots O$ interaction (iv 2.37 Å, 164.1°; Figure 4b).

The hydrogen bond acceptor in ii is the carbonyl group of C_6F_5COOH because of auxiliary contribution from bifurcated $N-H\cdots F$ interaction v (Table 2). Weak $C-H\cdots F$ and $F\cdots F$ interactions (distance $\geq \Sigma r_{vdW}$) can be identified in the structure. While the sandwich stack $Ph-Ph^F$ geometry **III** stabilizes structures **1** and **2**, the interaction is weaker in **3** via lateral offset motif **II** ($d = 3.93$ Å, $r = 3.47$ Å). Phenyl–perfluorophenyl mediation during cocrystallization of **3** is weaker because acid...amide heterodimer **VIII** is stronger than homodimers **IV** and **VI**. It appears that the role of the $Ph-Ph^F$ synthon toward cocrystallization is based on need, akin to anchimeric assistance in S_N2 displacement reaction.²²

The higher strength of acid...amide heterodimer **VIII** compared to acid...acid and amide...amide homodimer **IV** and **VI** is explained by the best hydrogen bond donor ($COOH$) approaching the best acceptor (amide $C=O$) and the second-best donor ($CONH$) bonding with the next acceptor (acid $C=O$) in $CO_2H\cdots CONH_2$.²³ Another reason for the formation of heterodimer is to avoid lone-pair repulsion between hydroxyl and carbonyl O atoms that occurs in hydrogen-bonded chains built from homodimers and connected via $N-H\cdots O$ hydrogen bonds. In the heterodimer arrangement, the distance between neighboring $N-H$ groups hydrogen bonded to the same O atom increases and so the lone-pair repulsion is minimized.¹⁹ Database survey shows that heterodimer **VIII** is formed in 4:1 preference compared to dimer **IV** and catemer **V** motifs between CO_2H groups.²⁴ Despite these factors, several attempts to cocrystallize pentafluorobenzamide and benzoic acid did not yield any adduct crystal $C_6F_5CONH_2 \cdot C_6H_5CO_2H$ **4** presumably because both the CO_2H donor and the amide $C=O$ acceptor are weaker hydrogen bonding groups compared to **3**.

Last we note that while the melting point of phenyl–perfluorophenyl adduct crystals is generally higher than the pure components,⁴ both **1** and **2** melt at a temperature significantly lower than the pure acids and amides. Thus, despite the attractive $Ph-Ph^F$ synthon and the stronger hydrogen bonding in these cocrystals there are possibly other factors contributing to crystal lattice forces that are not additive. Apart from enthalpy, entropy is equally important in explaining melting point lowering, though much more difficult to quantify. Factors such as the different number of residues, symmetry-independent molecules, and their conformation in the component and adduct crystals are likely to complicate a lattice energy-based approach to calculate enthalpy. This interesting observation prompts further thinking about correlation between melting point, crystal packing, and lattice energies.

There are several advantages in studying X-ray crystal structures of closely related molecules. (1) Correlation between molecular structure and crystal packing may be established because changes occur in a graded manner and these may be attributed to steric and/or electronic effects. (2) The criticism that carefully selected crystal structures from a large diverse pool of unpublished structures are presented to give the impression of “high fidelity crystal engineering”²⁵ is rebutted. (3) A strategy developed with model compounds

guides the study of complex systems to test hydrogen bond hierarchy and interplay during crystallization.

Conclusions

Although carboxylic acids and carboxamides are the two most popular functional groups in crystal engineering, very few general methods are available to synthesize their cocrystals. Molecular complexes have been prepared from electron-deficient and electron-rich aromatic carboxylic acids²⁶ (e.g., 3,5-dinitrobenzoic acid, 3,5-dinitrocinnamic acid, 4-dimethylaminobenzoic acid, 4-dimethylaminocinnamic acid, etc.). Earlier studies on the Ph-Ph^F synthon have dealt with molecules in which strong hydrogen bonding groups were generally absent.^{4,5} We demonstrate that the phenyl-perfluorophenyl stacking synthon is a viable recognition motif for the cocrystallization of strong hydrogen bonding carboxylic acids and carboxamides. Further scope of the Ph-Ph^F synthon as a facilitating group for the directed synthesis of acid/amide cocrystals and their topochemical reactions is an ongoing theme in our research.

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Supporting Information Available: X-ray crystallographic files (CIF) are available free of charge via the Internet at <http://pubs.acs.org>.

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