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Pi Stacking

Stacking of Sterically Congested Trifluoromethylated Aromatics in their Crystals – The Role of Weak F···π or F···F Contacts

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Abstract: Five electron-deficient aromatic compounds bearing 3,5-bis(trifluoromethyl)benzyl moieties were investigated by X-ray diffraction. In the crystals, the stacking of π systems between non-planar electron-deficient aromatics leads to an assembly with weak F···π and/or F···F interactions as the controlling factor.

"π–π Stacking" has been identified as a weak but significant supramolecular interaction, which is widely found in chemical and biological systems.[1–3] It is important to control the formation of well-defined crystalline materials.[4,5] In principle, there are three basic stacking geometries between two aromatic rings: cofacial, parallel-displaced and edge-to-face.[6] Recently, investigation of the crystal packing involving fluorinated organic compounds confirmed that the molecular packing mode could be controlled or tuned via the formation of weak H···F, F···F and F···π contacts.[7–11] It is well known that the trifluoromethyl group possesses a strong electron-withdrawing character. Therefore, this moiety is a very important unit in medicinal chemistry and material science, as it can dramatically change the solubility, lipophilicity, surface and optical properties of organic compounds.[12–14]

Most of the π–π stacking investigations focus on the interactions of coplanar aromatic rings such as hexafluorobenzene, pentafluorophenyl, 8-sulfonyl-quinoline, perylene-monoimides, naphthalene diimide, pyrenes etc.[15–19] Only rare studies on π–π stacking involve trifluoromethylated aromatic rings, although CF_3 is a significant unit with promising potential applications in chemistry, material and crystal engineering.[20–24] Moreover, trifluoromethylated aromatic rings cannot be coplanar because of the steric demand of the peripheral CF_3 group. Therefore it is of high interest to study π–π stacking between CF_3 substituted aromatics.

Generally, π–π stacking in the solid-state was rationally designed previously to take place between electron-deficient and -rich aromatic groups by "electronic complementarity".[25] In the present study, non-classical π–π stacking between electron-deficient aromatic rings is shown. The symmetric CF_3 aromatics (**1**, **2**, and **5**), dissymmetric amide **3**, and charged quinoline derivative **4** were studied in the solid-state to investigate this kind of π–π stacking between electron-deficient aromatics in the single-crystal structures (Figure 1). Compounds **1**, **3**–**5** are novel structures firstly synthesized here, while compound **2** has already been reported in our previous work which was focused on anion–π interactions. The neutral compounds **1**, **2**, **3**, and **5**

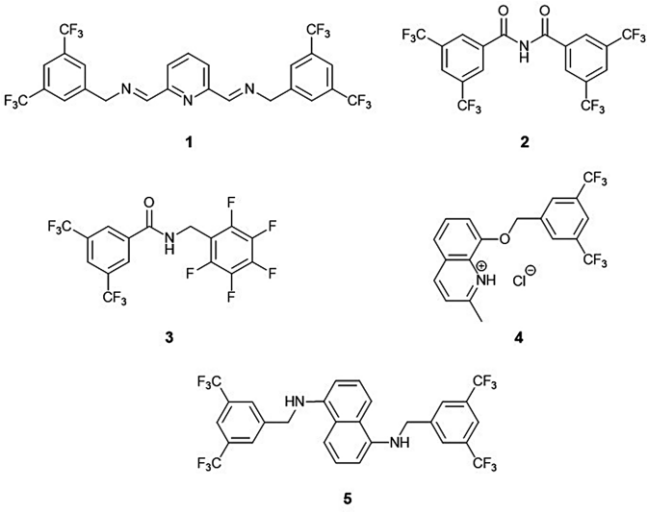

Figure 1. Aromatic compounds prepared for the investigation of π–π stacking involving CF_3 substituted aromatics.

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bear two electron-deficient moieties at both ends of the molecules connected through 2,6-bis(azaneylidene)pyridine, imide, amide, and 1,5-diamino naphthalene as spacer units, respectively.

Lone pair- or anion–π interactions with electron-deficient aromatics are important forces not only in the crystal but also in solution.[26,27] In a systematic study, compounds **1**–**5** were structurally studied in order to evaluate the influence of CF_3···π interactions. The crystal structure analyses of **1**–**5** show some parallel-displacement of the aromatic units resulting in three types of stacking motifs enforcing some weak F···π and/or F···F interactions (Figure 2). Due to the high Van-der-Waals volume of the CF_3 group as very weak lone-pair electron···π donor, longer center to center distances are observed between neighboring electron-deficient aromatics. These kinds of stacking motifs were not observed in the non-fluorine similar structures (CCDC 1874147, 1577926, see SI).

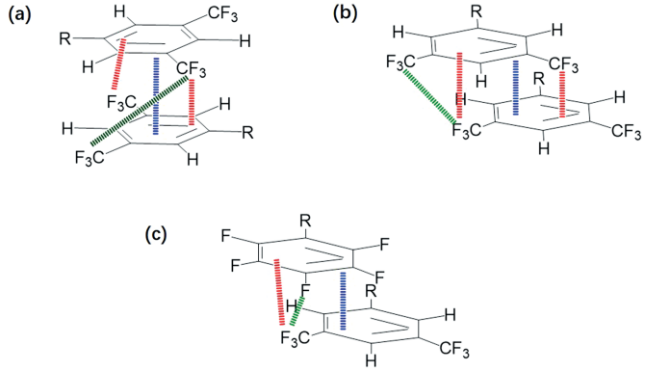

Figure 2. Different motifs of π–π (blue dotted line) stacking controlled by F···π (red dotted line) and/or F···F (green dotted line) interaction (a) with opposite orientation of the CF_3 substituents; (b) with parallel orientation of the CF_3 substituents; (c) between C_6F_5 and CF_3-arenes.

Compound **1** was synthesized via condensation reaction of pyridine-2,6-dicarbaldehyde with two equivalents of [3,5-bis(trifluoromethyl)phenyl]methanamine (see SI). It crystallized out from MeOH/Et_2O in the space group $P2_1/n$. The molecular structure in the crystal is shown in Figure 3. The planes of both 3,5-bis(trifluoromethyl)phenyl units are not exactly parallel. A very small angle is observed between those two planes as well as interplanar angles of 32.04° and 32.83° are found with the pyridine unit, respectively (Figure 3a). In the crystal, the molecules are located in different layers and the orientations of H-(C=N) units of two molecules in adjacent layers are arranged oppositely resulting in unequal center-to-center distances (3.71, 3.79, and 4.18 Å) between the stacking electron-deficient aromatics (Figure 3b). Moreover, H···F (2.63 Å) and F···F (2.93 Å) contacts are observed in adjacent molecules, which might be the significant factors for the stacking motif (Figure 3c). The CF_3 substituents force the adjacent aromatic units to orientate parallel-displaced instead of "face-center stacked" as shown in Figure 2b.

Compound **2** was synthesized via the substitution reaction of trifluoromethylated benzamide with the corresponding benzoyl chloride in anhydrous THF (see SI). A crystal was obtained from

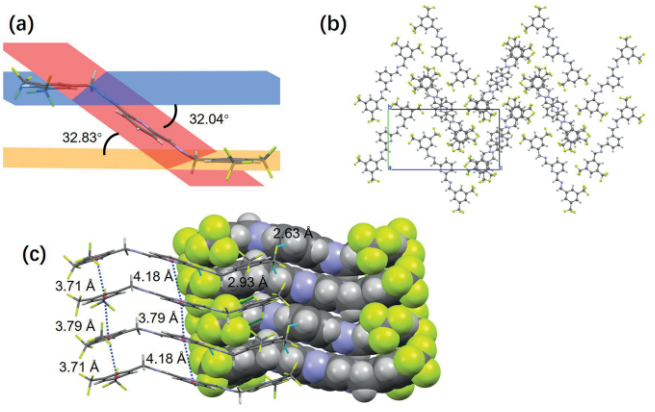

Figure 3. (a) molecular structure of **1** shown with capped sticks. (b) The stacking of molecules in part of the crystal lattice of **1**; (c) H···F and F···F contact and π–π stacking between different layers. Atoms shown in Spacefill mode highlight the π–π stacking of neighboring CF_3-substituted aromatic units in the crystal. C: grey, H: white, N: blue, F: yellow. (CCDC 1995532).

DMSO/Et_2O containing one co-crystallized solvent molecule. The single-molecule of **2** adopts a conformation with a planar C(=O)–NH–C(=O) unit, whereas the aromatic rings are tilted towards this plane with interplanar angles of 7.95° and 46.94°, respectively. The co-crystallized DMSO undergoes hydrogen binding of 1.95 Å N–O distance with an N–H unit of molecule **2** (Figure 4a). Viewing down the *b* axis, π–π stacking is observed between CF_3-aromatics in each of the three molecules, which form different layers in the crystal (Figure 4b). Besides the hydrogen binding between the oxygen atom of DMSO and the N–H unit, C–F···π interaction can also be observed in the crystal lattice with (C)F···C distances of 3.05 (F···C7), 3.17 (F···C7) or 3.14 (F···C3) Å. Those contribute to an off-center stacking (showing with Figure 2a) between CF_3 aromatics of neighboring molecules with aryl–aryl distances of 3.94 or 3.75 Å (Figure 4c).

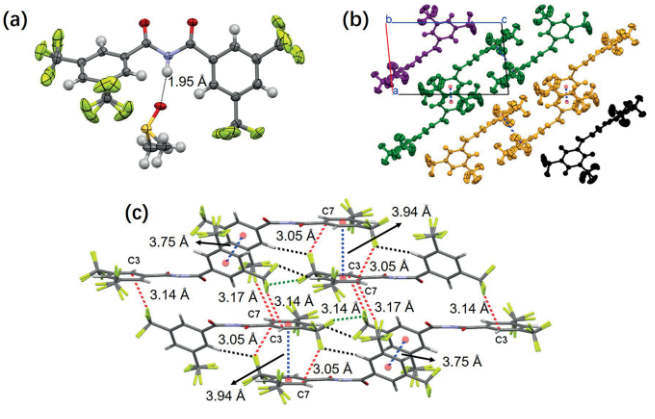

Figure 4. (a) Molecular structure of **2** shown with ellipsoid at 50 % probability, showing a DMSO co-crystallized by hydrogen binding with N–H unit. (b) Tripolymers formed by intermolecular interactions reveal π–π stacking of the adjacent electron-deficient aromatics. (c) The capped sticks mode of crystal structure **2** showing F···π (red dotted line), F···F (green dotted line), H···F (black dotted line) contact and π–π stacking (blue dotted line). The co-crystallized DMSO molecules are omitted for clarity in b and c. The fluorine atoms are disordered. C: grey, H: white, O: red, N: blue, S: gold, F: yellow. (CCDC 1995533).

By contrast, the non-fluorinated reference N-benzoylbenzamide can only generate T-shape π stacking motifs driven by CH···π and hydrogen bond contacts in the crystal structure (CCDC 1874147).[28]

Compound **3** which was obtained from the reaction of pentafluorobenzyl bromide with trifluoromethylated benzamide (see SI). It crystallized in the space group *Cc* by diffusing Et_2O into a methanol solution of the sample. The two aromatic units of **3** in the solid-state are tilted forming an interplanar angle of 107.6°. Molecules gather into different columns in the solid-state (Figure 5a) and in each column one pentafluorophenyl unit stacks with the two adjacent CF_3-aromatics leading to a "zigzag" arrangement (Figure 5b). Two molecules nearby form a dimer by hydrogen bonds between N–H and the carbonyl with a distance of 1.97 Å as well as a non-classical C=O···H–C hydrogen bond (2.41 Å). The other pentafluorophenyl/CF_3-aromatic unit adopts a somewhat offset parallel conformation with a center to center distance of 3.71 Å, due to a C–F···F–C interaction with a distance of 2.91 Å. A somewhat longer central distance of 5.78 Å between pentafluorophenyl and CF_3-aromatic unit is found in the stacked form with a distance of F···π is 3.17 Å. Obviously, F···F interactions are ubiquitous in this crystal. Specifically, two neighbouring C_6F_5-aromatics are formed as T-shaped stack between two adjacent columns by both F···π (3.03 or 3.17 Å) and F···F (2.89 Å) interactions. In addition, the fluorine atoms of two CF_3 and two C_6F_5-aromatics of different columns could also form F···F contacts with distances of 2.64 or 2.74 Å, which may also intervene this packing motif (Figure 5c). Moreover, there are two conformations of molecule **3** in the crystal-"C_6F_5-upwards" and "C_6F_5-downwards", which lead to the CF_3-aromatic/pentafluorophenyl/CF_3-aromatic stacking motif (Figure 5d). On the other hand, analyzing the corresponding crystal structure of N-benzylbenzamide (CCDC 1577926),[29] the T-shape π stacking was observed, generated by both CH···π and hydrogen bond interactions, instead of the face-to-face stacking found in the crystal structure of compound **3**.

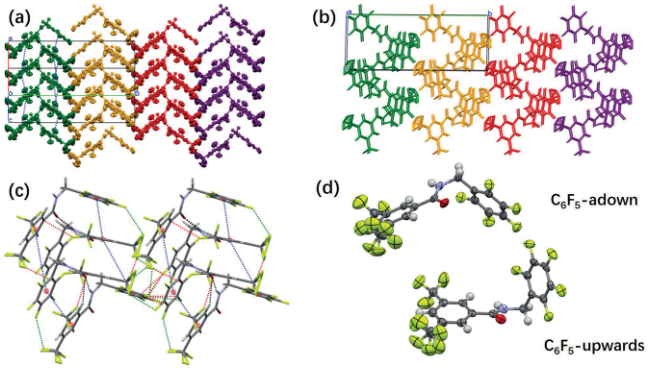

Figure 5. (a) Viewing down perpendicular to ab plane of the crystal lattice of **3**. (b) Viewing down crystallographic *a* axis of the crystal lattice of **3**; (c) F···π (red dotted line, 3.17, 3.14, 3.03 Å), F···F (green dotted line, 2.91, 2.74, 2.89, 2.64 Å), H···F (black dotted line, 1.97, 2.41 Å) contacts and π–π stacking (blue dotted line, 3.71, 5.78 Å) shown in this crystal. (d) Two different conformations of molecule **3** in the crystals. The fluorine atoms are disordered. C: grey, H: white, O: red, N: blue, F: yellow. (CCDC 1995534).

Compound **4** was obtained from an ethanolic HCl solution as the hydrochloride adduct of the product which was synthesized from trifluoromethylated benzyl bromide and 2-methylquinolin-8-ol (see SI). In the triclinic crystals obtained from DMF/Et_2O the plane of methylquinoline is nearly perpendicular to that of the CF_3-aromatic unit with the interplanar angle of 88.68°. Water molecules are co-crystallized, which form hydrogen bridges between chloride and the molecular frame with the distances of 1.86 Å (N–H···O–H) and 2.36 or 2.43 Å (O–H···Cl) (Figure 6a). The 8-{[3,5-bis(trifluoromethyl)benzyl]-oxy}-2-methylquinoline-1-iums assemble like "Tetris-blocks", so that the CF_3-aromatics are stuck in the middle of the methylquinoline layers, which form square columns in the crystal and water, as well as chloride anions, fill in the space between the columns (Figure 6b).

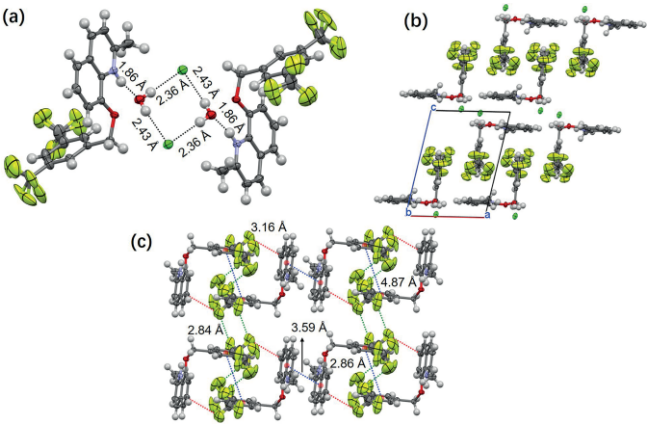

Figure 6. (a) The molecular structure of chloride **4** shown with ellipsoid at 50 % probability revealing water molecules co-crystallized forming hydrogen bridges in the crystal. (b) Viewing down crystallographic *b* axis of the crystal lattice of **4**. (c) The stacking motifs of the electron-deficient aromatics with a longer center to center distances indicating the F···π and F···F interaction in the crystal. The co-crystallized water and Cl^- are omitted for clarity. The fluorine atoms are disordered. C: grey, H: white, O: red, N: blue, F: yellow, Cl: green. (CCDC 1995536).

The solid-state structure reveals not only a parallel-displaced conformation of CF_3-aromatic rings with a longer center to center distances (4.87 Å) and stacking of methylquinolines (3.59 Å) but also a T-shaped stacking of CF_3 rings and the methylquinolines with partial positive charge induced by F···π (3.16 Å) and F···F (2.84, 2.86 Å) contacts (Figure 6c). The structure of **4** was also obtained in monoclinic crystal with similar features. This alternative structure **4a** (CCDC 1995535) is found in the ESI material.

Di-substituted derivative **5** was synthesized from the reaction of naphthalene-1,5-diamine with 3,5-bis(trifluoromethyl)benzyl bromide. Figure 7a shows the "*trans*" conformation of the structure **5** crystallized from ethyl acetate/hexane in the space group $P\bar{1}$ with the intramolecular angle between the plane of fluorinated ring and naphthalene of 82.5°. The stacking of the π systems can be found between the corresponding close by naphthalene units or fluorinated aromatics. Neighboring aromatics adopt a parallel arrangement with center to center dis-

tances of 4.98 Å (Figure 7b). The trifluoromethylated aromatic units adopt the off-center parallel form, which is induced by F···π interaction with a shortest distance between (C)F and the carbon atom of the adjacent aromatic of 3.22 Å as well as the F···F contacts with a distance of 3.15 Å (Figure 7c). This parallel stacked structure without hydrogen bonding can be observed in the solid-state, revealing the lone-pair F···π and F···F interaction as the prominent non-covalent effect in the crystal.

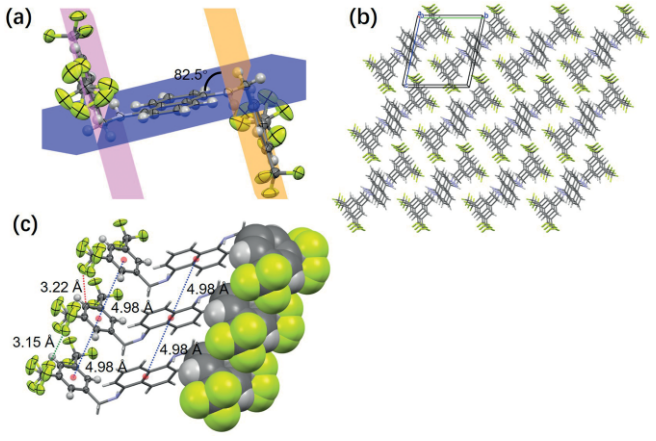

Figure 7. (a) The "zigzag" conformation of compound **5** in crystal. (b) Viewing down crystallographic *a* axis of the crystal lattice of **5**. (c) Spacefill mode of **5** showing the parallel arrangement of neighboring aromatics, which is induced by the F···π, F···F and π–π interaction between the neighboring 3,5-bis(trifluoromethyl)phenyl aromatic unit. The fluorine atoms are disordered. C: grey, H: white, N: blue, F: yellow. (CCDC 1995537).

Both 3,5-bis(trifluoromethyl)benzylated and 3,5-bis(trifluoromethyl)benzoylated compounds are frequently used organic building blocks, which comprise electron-deficient aromatic rings in their structures. In addition, two CF_3 groups play a pivotal role in the generation of F···π, F···F, and even H···F interactions. These are all principal elements in the investigation of supramolecular chemistry and crystal engineering.

The role of weak F···π, F···F contacts in stabilizing the sterically congested crystal structures of small organic molecules to assemble these kinds of face-to-face stacking of π systems has been analyzed with the described trifluoromethylated aromatics. Especially, F···π interactions are induced by attractive electrostatic interaction between an electronegative fluorine atom and either electron-deficient or positive charge aromatic moieties, which play a substantial role in determining the stacking motifs in fluorine-rich structures.

In conclusion, the non-classical π–π stacking interactions of several trifluoromethylated aromatics have been studied in crystals. Despite the bulkiness of the CF_3 group, the stacking motif is still observed between electron-deficient units. The motifs of intermolecular parallel-displaced stacking between neighboring electron-deficient units are due to the prominent formation of lone-pair F···π and/or F···F interactions, which support the special molecular assembly accompanied with or without hydrogen bonding. As one form of the stacking motifs, these fluorinated units could be utilized as candidates to form supramolecular architectures with electron-deficient aromatics.

Deposition Numbers 1577926, 1874147, and 1995532–1995537 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Keywords: Crystals · Fluorinated compounds · Solid-state structures · Stacking interactions · Trifluoromethyl substituents

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