Aggregation Feature of Fluorine-Substituted Benzene Rings and Intermolecular C–H···F Interaction: Crystal Structure Analyses of Mono- and Trifluoro-L-phenylalanines

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X-Ray crystal structures of four different fluorine-substituted phenylalanines (two mono- and two tri-substitutions) were analyzed to investigate the effect of fluorine atom on the association pattern of benzene rings. Although respective structures showed similar molecular packing in such a way that the layers of hydrophobic benzene rings and hydrophilic amino/carboxyl groups were alternately running along a crystallographic axis, the association patterns of benzene rings were different depending on the substitution position and number of fluorine atoms. The general features could be that the partially displaced face-to-face interactions are increased with increase in the number of fluorine atoms, whereas the edge-to-face interactions are decreased. The C–H bond next to a fluorine-substituted carbon atom could serve as a donor of an intermolecular C–H···F hydrogen bond.

Key words fluorophenylalanine; crystal structure; benzene–benzene interaction; C–H···F interaction

It is well documented that noncovalent aromatic–aromatic interactions are important in determining the molecular conformation, stability and activity of biological macromolecules.[1,2] In globular proteins, the close interactions between the aromatic amino acids Phe, Tyr and Trp often form a part of a hydrophobic pocket to bind an aromatic substrate.[3—5] As for the aromatic interaction of phenylalanine (Phe) residues in proteins, either an off-center displaced face-to-face or a T-shaped edge-to-face structure has been considered as the preferred orientation since it is nearly isoenergetic.[6] In the latter structure, the acidic C–H group on the benzene ring acts as a weak hydrogen-bonding donor and the π-electron on the ring acts as an acceptor. This means that the benzene ring can serve as a pocket accepting the cationic molecule through the cation$\cdots\pi$ interaction.[2,7] On the other hand, the benzene ring in which H atoms are substituted by fluorine atoms could serve as an anion-acceptor through the anion$\cdots\pi$ interaction,[2,8] based on the crystal structure of $C_6H_6\cdot C_6F_6$ complex at 30 K.[9] Thus, the benzene ring can be said to form different noncovalent interactions by replacing the hydrogen atoms with other atoms, information on the association pattern of heteroatom-substituted benzene rings in the crystal structure is useful for designing an acceptor molecule to recognize a specified aromatic molecule.

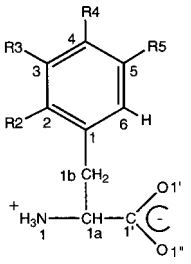
Herein, we report the crystal structures of four kinds of fluorophenylalanines (3-fluoro-, 4-fluoro-, 2,4,5-trifluoro-, and 3,4,5-trifluoroPhes). The observed structural features make it clear how the noncovalent interaction of benzene rings is affected by the substituted position and number of fluorine atoms. Especially, we focus on (i) how the acidity of benzene C–H proton is activated by the substitution of fluorine atom, and (ii) which donor group (benzene C–H or amino N–H) participates preferentially in the interaction with the electronegative fluorine atom. The present results are of interest to learn why thrombin receptor-derived peptide SFLLRNP (Ser-Phe-Leu-Leu-Arg-Asn-Pro) is able to activate the activity several fold by the substitution of *para*-fluoroPhe for Phe-2.[10] The atomic numbering of the four kinds of fluorophenyl-alanines used in this work is given in Fig. 1.

Experimental

Material Three kinds of monofluoro-L-Phe were purchased from Wako Pure Chemical (Tokyo). Di- and trifluoroPhes were prepared according to the previously reports.[11,12] The purities were verified by analytical RP-HPLC.

X-Ray Crystal Analysis Among various attempts to crystallize a series of mono-, di-, and tri-fluoroPhes, single crystals of 3- and 4-monofluoro and 2,4,5- and 3,4,5-trifluoroPhes were obtained from the slow evaporation of aqueous ethanol or methanol solution at room temperature in the form of transparent needles. The X-ray measurements were made on a Rigaku AFC-5 diffractometer with graphite-monochromated Cu$K\alpha$ radiation (λ= 1.5418 Å) using a ω–2θ scan mode for 3-fluoroPhe and a Brucker SMART APEX CCD diffractometer with graphite-monochromated Mo$K\alpha$ radiation (λ=0.71073 Å) using ϕ and ω scans for the others. Empirical absorption corrections were applied for all crystals. A summary of the crystallographic data and structure refinements is given in Table 1.

The crystal structures were solved by the direct method using the SHELXS97 program.[13] For the structural refinement, reflections with $I>2\sigma(I)$ were used, and the atomic scattering factors and terms of anom-



(a) R3=F, R2=R4=R5=H

(b) R4=F, R2=R3=R5=H

(c) R2=R4=R5=F, R3=H

(d) R3=R4=R5=F, R2=H

Fig. 1. Chemical Structures of Four Kinds of Fluorophenylalanines ((a) 3-Fluoro-, (b) 4-Fluoro-, (c) 2,4,5-Trifluoro-, (d) 3,4,5-TrifluoroPhes) and Atomic Numbering Used in This Study

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Table 1. Summary of Crystal Data Collections and Structure Refinement

	3-FluoroPhe	4-FluoroPhe	2,4,5-TrifluoroPhe	3,4,5-TrifluoroPhe
Crystallographic data				
Radiation	Cu$K\alpha$	Mo$K\alpha$	Mo$K\alpha$	Mo$K\alpha$
Empirical formula	$C_9H_{10}FNO_2\cdot H_2O$	$C_9H_{10}FNO_2$	$C_9H_8F_3NO_2\cdot H_2O$	$C_9H_8F_3NO_2$
Molecular weight	201.28	183.18	237.18	219.16
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$	$C2$	$P2_1$
Unit cell dimensions				
a (Å)	13.051 (4)	8.813 (1)	29.771 (4)	12.239 (2)
b (Å)	5.455 (2)	5.9830 (7)	5.3706 (7)	5.3956 (8)
c (Å)	14.144 (5)	16.046 (2)	13.281 (2)	14.684 (2)
β (°)	101.43 (3)	91.349 (2)	103.066 (2)	98.179 (3)
Volume (Å^3)	986.9 (6)	845.9 (2)	2068.5 (5)	959.8 (3)
Z	4	4	8	4
F(000)	424	384	976	448
Crystal size (mm^3)	0.05×0.1×1.0	0.2×0.5×0.8	0.1×0.15×0.8	0.05×0.1×0.7
Density (calculated) (g·cm^{-3})	1.354	1.438	1.523	1.517
Absorption coefficient (mm^{-1})	0.973	0.116	0.147	0.145
Data collection				
Max/min. transmission	0.9530/0.4429	0.9127/0.9771	0.9854/0.8911	0.9928/0.9054
Index ranges	$-15\leqq h\leqq 15$	$-11\leqq h\leqq 11$	$-39\leqq h\leqq 33$	$-13\leqq \eta\leqq 16$
	$-6\leqq k\leqq 0$	$-7\leqq k\leqq 7$	$-7\leqq k\leqq 7$	$-7\leqq k\leqq 6$
	$-16\leqq l\leqq 16$	$-21\leqq l\leqq 14$	$-13\leqq l\leqq 17$	$-19\leqq l\leqq 19$
θ_{max} (°)	67.53	28.26	28.30	28.29
No. of all reflection data measd.	3911	5251	6567	5540
No. of unique data measd.	1967	3497	4296	3494
Completeness of unique data (%)		93.0	93.0	89.3
No. of reflections with $I>2\sigma(I)$	1679	2737	3935	2308
Structure refinement				
Refinement on	F^2	F^2	F^2	F^2
Coefficients a and b for weighting scheme	0.0376 0.5764	0.0803 0.0	0.0658 0.9552	0.0632 5.9513
No. of variables refined	253	234	288	270
R (Rw) (for $I>2\sigma(I)$)	0.042 (0.109)	0.040 (0.105)	0.058 (0.143)	0.108 (0.299)
R (Rw) (for all data)	0.056 (0.119)	0.051 (0.105)	0.063 (0.146)	0.164 (0.326)
Goodness-of-fit on F^2	1.143	0.968	1.106	1.326
Extinction coefficient	0.037 (2)	—	—	—
Largest diff. peak and hole (e Å^{-3})	0.171 and −0.188	0.381 and −0.180	0.269 and −0.205	0.750 and −0.457
Max and mean shift/esd	0.000 and 0.000	0.000 and 0.000	0.001 and 0.000	0.003 and 0.000

alous dispersion corrections were taken from the literature.[14] The refinements of non-H atoms were carried out by the full-matrix least-squares calculations on F_O^2 intensities with anisotropic thermal parameters using the program SHELXL97.[15] The positions of H atoms participating in hydrogen bonds were determined from the difference Fourier maps, and the others were geometrically located. These were treated as riding with fixed isotropic displacement parameters ($U_{iso}=1.2U_{eq}$ for the associated C or N atoms, or $U_{iso}=1.5U_{eq}$ for methyl C or O atoms); their atomic positions were not included as variables for the refinements. The function of $\Sigma w(F_O^2-F_C^2)^2$ was minimized by using the weighting scheme of $w=1/[\sigma^2(F_O^2)+(aP)^2+bP]$, where $P=(F_O^2+2F_C^2)/3$ and the values of a and b are given in Table 1. Final R [$=\Sigma(|F_O|-|F_C|)/\Sigma|F_O|$]], Rw [$=(\Sigma w(|F_O|-|F_C|)^2/\Sigma w|F_O|^2)^{1/2}$] and S (goodness of fit) [$=(\Sigma w(|F_O|-|F_C|)^2/(M-N))^{1/2}$, where M=no. of reflections and N=no. of variables used for the refinement] are also given in Table 1. The final atomic and bonding parameters were deposited in the Cambridge Crystallographic Data Centre (CCDC), Cambridge University Chemical Laboratory, Cambridge CB21EW, UK (CCDC 210164 for 3-fluoroPhe, CCDC 210165 for 4-fluoroPhe, CCDC 210166 for 2,4,5-trifluoroPhe, and CCDC 210167 for 3,4,5-trifluoroPhe). The averaged estimated standard deviations for the bond lengths and angles of non-H atoms at the final stage were 0.006 Å and 0.4° for 3-fluoroPhe, 0.003 Å and 0.2° for 4-fluoroPhe, 0.005 Å and 0.4° for 2,4,5-trifluoroPhe, and 0.01 Å and 1° for 3,4,5-trifluoroPhe. The crystal structure of 3,4,5-trifluoroPhe was not satisfactorily refined to the acceptable accuracy because of relatively high mosaic and small size crystal. All numerical calculations were carried out at the Computer Center, Osaka University of Pharmaceutical Sciences.

Results and Discussion

Molecular Structure Characteristically, respective molecules were crystallized as neutral zwitterionic forms. This is in contrast to the case of Phe, because the crystal structure has not yet been analyzed for the neutral Phe, but only for the cationic Phe, in which the amino and carboxyl groups take the cationic and neutral forms, respectively, by forming a salt bridge with acid such as HCl. It is also characteristic that respective crystals consist of two crystallographically independent molecules (hereafter termed conformers A and B). Their conformations are shown in Fig. 2. Some selected torsion angles, together with those of Phe in its HCl crystal,[16] are given in Table 2.

3-FluoroPhe, 2,4,5- and 3,4,5-trifluoroPhe: Some notable conformational/structural similarities could be observed in these crystal structures. As is obvious from Fig. 2 and Table 2, respective A and B conformers, although they are different from each other at the χ_1 torsion angle, take similar conformations among these crystal structures, irrespective of the substituted number and position of fluoride atoms. Another similarity could be observed in the interaction mode between conformers A and B. The two conformers are linked to each other by cyclic N–H···O hydrogen bond pairing (Table 3). In the 3-fluoroPhe and 2,4,5-trifluoroPhe crystals, there are two water molecules per asymmetric unit which occupy the space created by the molecular packing, in order to keep this cyclic N–H···O hydrogen-bonded linkage between the two con-

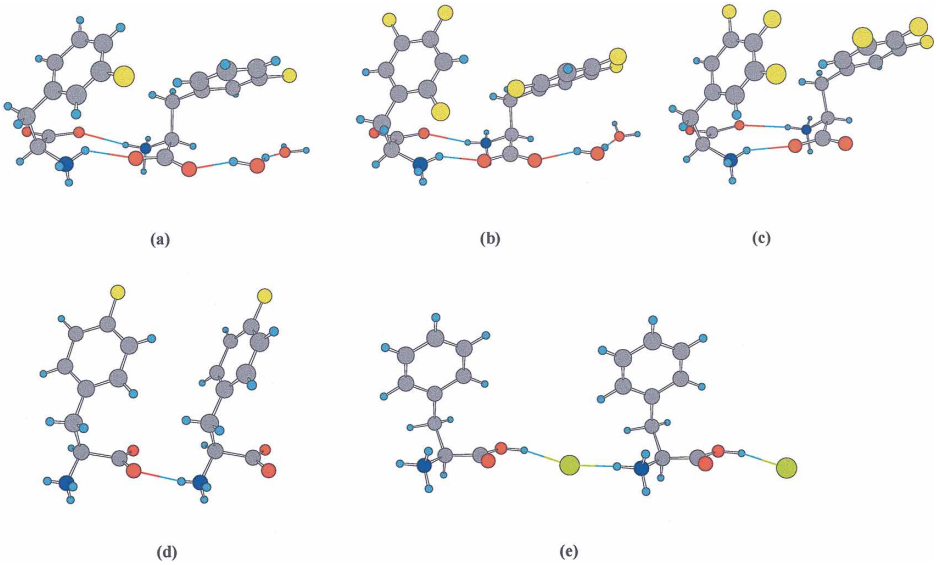

Fig. 2. Molecular Conformations of Two Crystallographically Independent FluoroPhes

(a) 3-FluoroPhe, (b) 2,4,5-trifluoroPhe, (c) 3,4,5-trifluoroPhe, (d) 4-fluoroPhe, and (e) Phe for comparison. In (e), two of the same conformers, which are linked by hydrogen bonds *via* chloride anion, are shown. The respective atoms are indicated by different colors: Cl^- (green), F (yellow), O (red), N (purple), H (blue). Thin lines represent intermolecular hydrogen bonds between amino and carboxyl groups. FluoroPhes of left and right sides correspond to conformer A and B, respectively.

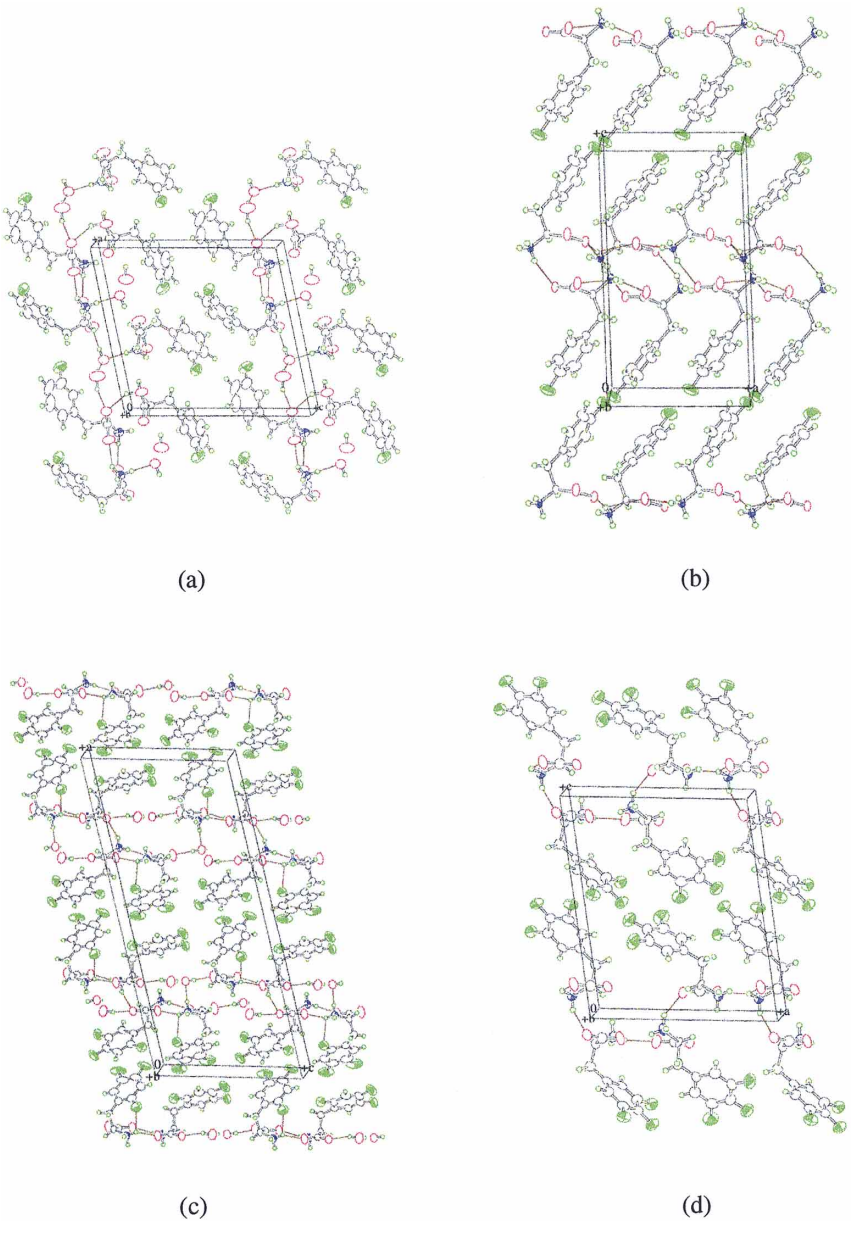

Fig. 3. Perspective Molecular Packing of 3-FluoroPhe (a), 4-FluoroPhe (b), 2,4,5-TrifluoroPhe (c), and 3,4,5-TrifluoroPhe (d) Crystals, Viewed from *b*-Axis

The hydrophilic and hydrophobic layers are alternately running along the *a*- or *c*-axis. The fluoride and nitrogen atoms are shown by the green and purple-colored ellipsoids with 50% probability, respectively. Thin lines represent intermolecular hydrogen bonds formed within one unit cell.

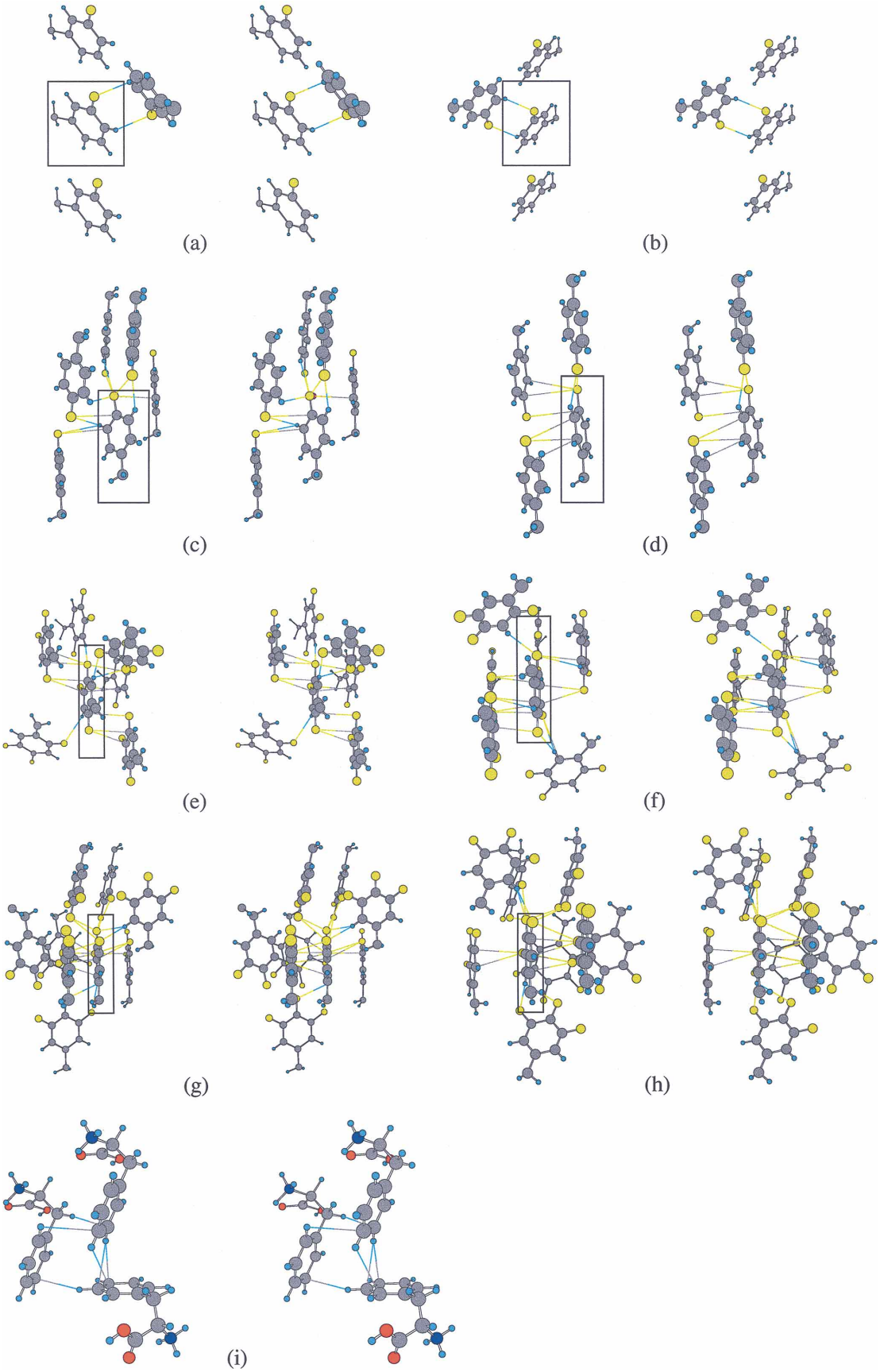

Fig. 4. Stereoscopic View of the Interaction of the Central Fluorobenzene Ring (Marked with a Box) with the Nearest Neighboring Ones

3-FluoroPhe conformer A (a) and B (b), 4-fluoroPhe conformer A (c) and B (d), 2,4,5-trifluoroPhe conformer A (e) and B (f), 3,4,5-trifluoroPhe conformer A (g) and B (h). The association mode of Phe molecules in the crystal of its HCl salt is shown in (i) for comparison. Thin lines show the interatomic short contacts less than 3.5 Å. The respective atoms are indicated by the same color as in Fig. 2.

Table 2. Selected Torsion Angles (°) of FluoroPhes, Together with Angles of Phe (HCl salt) for Comparison[a)]

	φ[b)]	χ_1[c)]	χ_2[d)]
3-FluoroPhe			
Conformer A	156.3 (4)	59.9 (4)	98.2 (4)/−80.8 (4)
Conformer B	139.4 (4)	−170.2 (4)	−101.2 (5)/78.1 (4)
4-FluoroPhe			
Conformer A	134.4 (2)	−179.6 (2)	96.3 (2)/−88.0 (2)
Conformer B	130.2 (2)	177.5 (2)	56.3 (2)/−125.8 (2)
245-TrifluoroPhe			
Conformer A	160.0 (4)	79.1 (3)	99.9 (4)/−78.8 (4)
Conformer B	148.8 (3)	−168.3 (3)	78.6 (3)/−101.2 (3)
3,4,5-TrifluoroPhe			
Conformer A	152 (1)	59 (1)	−81 (1)/101 (1)
Conformer B	145 (1)	−165 (1)	73 (1)/−106 (1)
Phe (HCl salt)	177.5	62.1	83.6/−97.6

a) The estimated standard deviations for the present X-ray analyses are given in parentheses. *b*) N1–C1a–C1′–O1′(O1″). *c*) N1–C1a–C1b–C1. *d*) C1a–C1b–C1–C6/C2.

Table 3. Hydrogen Bonds with Their Estimated Standard Deviations in Parentheses

Donor (D) at x,y,z	Acceptor (A)	Sym. code of A	Distance (Å) D···A	Distance (Å) H···A	Angle (°) D–H···A
3-FuoroPhe					
N(1)A[a)]	O(1″)B	x,y,z	2.831 (5)	2.07	136
N(1)B	O(1′)A	x,y,z	2.780 (5)	1.95	164
O(1)W	O(1′)B	x,y,z	2.748 (6)	1.82	157
O(1)W	O(2)W	x,y,z	2.982 (7)	1.96	167
4-FluoroPhe					
N(1)B	O(1′)A	x,y,z	2.706 (3)	1.96	171
2,4,5-TrifluoroPhe					
N(1)A	O(1′)B	x,y,z	2.807 (4)	1.98	151
N(1)B	O(1″)A	x,y,z	2.800 (4)	1.99	169
O(2)W	O(1″)B	x,y,z	2.761 (4)	1.92	158
O(2)W	O(1)W	x,y,z	2.911 (5)	1.99	176
3,4,5-TrifluoroPhe					
N(1)A	O(1″)B	x,y,z	2.83 (1)	2.1	147
N(1)B	O(1′)A	x,y,z	2.88 (1)	2.1	159

a) The suffix letters A, B, and W represent conformers A and B, and water molecule, respectively.

formers. This means that such a cyclic N–H···O hydrogen-bonded arrangement is preferable for the molecular packing of perfluoroPhe crystals. Also, a similar spatial arrangement between the fluorine-substituted benzene rings of conformers A and B suggests the importance of an intermolecular C–H···F interaction for the molecular packing, *i.e.*, *ortho*C–H (conformerB)···F (molecule A)=2.56 Å for 3-fluoroPhe, *meta*C–H (conformer A)···*ortho*F (conformer B)= 2.63 Å for 2,4,5-trifluoroPhe, and *ortho*C–H (conformer B)···*meta*F (conformer A)=2.4 Å for 3,4,5-trifluoroPhe. Although these values are not shorter than the sum of respective van der Waals radii (2.55 Å), this electrostatic interaction appears to be strong enough to form two different conformers, consequently leading to the energetically stable cyclic N–H···O hydrogen-bonded linkage between them.

4-FluoroPhe: It is notable that only 4-fluoroPhe shows a different molecular packing from the others in the intermolecular linkage, although the crystal commonly consists of two different conformers. Conformers A and B, which are linked by a single N–H···O(=C) hydrogen bond, are most significantly different at the χ_2 torsion angle. Generally, the most frequently observed value of this torsion angle is near ±90°, but that of conformer B deviates considerably. This is probably the result of the interaction between the benzene rings of conformers A and B. The *meta*H atom of conformer A forms a kind of C–H···π interaction with the benzene ring of conformer B, because the H atom is located almost on the benzene C2 atom near 3.2 Å.

Comparison with Phe: As compared with the molecular packing of Phe in the HCl crystal,[16] the most notable feature of fluoroPhes is that their crystals consist of two different conformers. This could be due to the additive intermolecular nonbonded interactions in which fluorine atoms participate. By the fluorine substitution of benzene H atom, the remaining H atoms would increase their acidity, leading to the C–H···F interaction with the negatively charged fluorine atom, as was observed in the present fluoroPhe crystals, and this is in contrast to the crystal packing of Phe, in which the benzene ring does not participate in any distinguishable interaction, except for the usual van der Waals contacts (see Fig. 4i).

Crystal Packing Intermolecular hydrogen bonds are summarized in Table 3 and short contacts between the fluorine atoms and between fluorine and carbon atoms of neighboring benzene rings in Table 4. Perspective views of respective crystal structures are shown in Fig. 3. Characteristically, the molecular packing patterns in respective crystal structures are very similar in such a way that the hydrophobic double layers consisting of fluorobenzene moieties and the hydrophilic ones of amino and carboxyl groups are alternately arranged parallel to one of three crystallographic axes, and these layers themselves are stabilized by van der Waals interactions including the C–H···F interactions (Table 4) and by N–H···O or O–H···O hydrogen bonds among the amino and carboxyl groups and water molecules, respectively.

Effect of Fluorine Atom for Self-Association of Benzene Rings To investigate the effect of fluorine atom on the self-association of benzene rings, the interaction mode of the ring with the nearest neighboring fragments was extracted from the respective fluoroPhe crystals and compared with that observed in the crystal structure of Phe hydrochloride.[16] The interaction patterns are shown in Fig. 4.

In the crystal structure of Phe hydrochloride (Fig. 4i), three benzene rings are associated with one another by two kinds of interactions, *i.e.*, the edge-to-face and displaced face-to-face interactions. Such C–H···π and π···π types of nonbonded interactions have been observed in the molecular association of many aromatic compounds. In contrast, the present structure analyses clarified that the substitution of fluoride atom affects the self-association of benzene rings in such way that the partially displaced face-to-face interactions are increased with the incremental substitution, while the edge-to-face interactions are conversely decreased. This is due to the increase of the vertical electrostatic interactions between the fluorine atom and the C–H group of neighboring benzene rings, together with the linear C–H···F interactions, because the acidity of C–H proton could be increased by the substitution of fluorine atom. On the other hand, it has been reported[17,18] that the addition of fluorine atom in the interaction between the aromatic and perfluoroaromatic compounds decreases the repulsion in the stacked ground state upon removal of electron density from the ring. Also, the interplay

Table 4. Short Contacts of F···C and F···F Atomic Pairs of Neighboring Benzene Rings (<3.54 Å) with Their Estimated Standard Deviations in Parentheses, Together with F···H–C Angles

Fluorine atom at x,y,z	Atom 2	Translated by sym. code of Atom 2	Distance (Å) F···C	F···H	Angle (°) F···H–C
3-FluoroPhe					
F(3)A[a)]	C(5)A	$x,y+1,z$	3.288 (6)	2.91	105
F(3)A	C(4)B	$2-x,y+1/2,1-z$	3.319 (9)	2.62	131
F(3)A	C(6)B	x,y,z	3.531 (6)	2.56	169
F(3)B	C(4)A	$2-x,y-1/2,1-z$	3.501 (7)	2.67	145
4-FluoroPhe					
F(4)A	C(2)B	$x,y+1,z$	3.263 (3)	3.03	96
F(4)A	C(3)A	$1-x,y+1/2,-z$	3.395 (3)	2.56	144
F(4)B	C(4)A	$1-x,y-1/2,-z$	3.371 (4)		
F(4)B	C(5)A	$1-x,y-1/2,-z$	3.316 (4)	3.44	75
F(4)A	C(4)B	$1-x,y+1/2,-z$	3.360 (3)		
F(4)B	C(3)B	$-x,y+1/2,-z$	3.308 (4)	2.51	141
F(4)A	F(4)A	$1-x,y+1/2,-z$	3.363 (2)		
F(4)B	F(4)B	$-x,y+1/2,-z$	3.244 (3)		
2,4,5-TrifluoroPhe					
F(2)B	C(3)A	x,y,z	3.420 (6)	2.63	140
F(5)A	C(1)A	$x,y-1,z$	3.417 (6)		
F(5)A	C(2)A	$x,y-1,z$	3.297 (6)		
F(2)A	C(4)A	$x,y+1,z$	3.360 (7)		
F(2)A	C(5)A	$x,y+1,z$	3.266 (6)		
F(4)B	C(6)A	$x,y,z-1$	3.362 (6)	2.77	121
F(5)A	C(3)B	$-x,y-1,-z$	3.304 (6)	2.38	164
F(4)A	C(1)B	$-x,y,-z$	3.367 (6)		
F(4)A	C(2)B	$-x,y,-z$	3.212 (6)		
F(5)A	C(4)B	$-x,y,-z$	3.453 (6)		
F(2)A	F(2)B	x,y,z	3.468 (3)		
F(2)A	F(5)A	$x,y+1,z$	3.468 (4)		
F(4)A	F(2)B	$-x,y-1,-z$	3.448 (5)		
F(4)B	F(4)B	$-x,y,-z-1$	2.989 (5)		
F(4)A	F(4)A	$-x,y,-z$	3.167 (6)		
3,4,5-TrifluoroPhe					
F(5)A	C(2)B	x,y,z	3.42 (2)	2.4	173
F(4)B	C(2)A	$x-1,y,z$	3.29 (2)	2.8	110
F(3)A	C(5)A	$x,y-1,z$	3.05 (1)		
F(3)A	C(6)A	$x,y-1,z$	3.26 (1)	3.3	78
F(5)A	C(3)A	$x,y+1,z$	3.38 (2)		
F(3)B	C(5)B	$x,y+1,z$	3.37 (2)		
F(3)B	C(6)B	$x,y+1,z$	3.43 (2)	3.5	76
F(3)B	C(3)B	$1-x,y+1/2,1-z$	3.40 (2)		
F(4)A	C(4)B	$1-x,y+1/2,1-z$	3.42 (2)		
F(3)A	C(2)A	$2-x,y-1/2,1-z$	3.25 (1)	3.6	63
F(3)A	C(3)A	$2-x,y-1/2,1-z$	3.04 (1)		
F(3)A	C(4)A	$2-x,y-1/2,1-z$	3.40 (1)		
F(3)A	F(5)A	$x,y-1,z$	2.99 (1)		
F(3)A	F(4)B	$1-x,y-1/2,1-z$	3.06 (1)		
F(3)A	F(3)A	$2-x,y-1/2,1-z$	3.351 (7)		
F(4)A	F(3)B	$1-x,y-1/2,1-z$	3.00 (1)		
F(4)A	F(4)B	$1-x,y-1/2,1-z$	3.18 (1)		
F(4)A	F(4)B	$1-x,y+1/2,1-z$	2.99 (1)		
F(4)A	F(5)B	$1-x,y+1/2,1-z$	3.21 (1)		
F(5)A	F(4)B	$1-x,y+1/2,1-z$	3.10 (1)		

a) The suffix letters A and B represent the conformers A and B, respectively.

among the phenyl–perfluorophenyl stacking, C–H···F, C–F···π and F···F interactions has been shown in the crystalline aromatic azines.[19)] These are consistent with the present results, meaning that the so-defined "polar/π" interactions that feature significant electrostatic contributions to π–π stacking between the heterogeneous aromatic and fluoroaromatic rings are also applicable for the interaction between the homogeneous fluoroaromatic rings.

In the present crystal structures, the (amino)N–H···F and (benzene)C–H···O (carboxyl group) interactions were not observed. This indicates that the negative charge of fluorine atom or the positive charge of C–H proton is not strong enough to overcome the hydrophobic interactions between the neighboring benzene rings or the hydrophilic ones between the polar amino and carboxyl groups. Instead, the fluorine atom and the C–H group participated in the C–H···F interaction, although this interaction was not formed for all possible combinations, but only for the selected pair. Judging from the H···F distances and C–H···F angles (Table 4), one or two C–H···F short contacts in each crystal could be assigned as hydrogen bonds, although the remainder are due to the electrostatic interactions. Characteristically, the C–H bond adjoining the C–F bond serves as a hydrogen-bonding donor. As was already stated, this characteristic is a main reason why the present fluoroPhe crystals consist of two different conformers.

In conclusion, it was shown to be a common feature of mono- and trifluoroPhe crystals that fluorine substitution of the benzene ring increases the off-center displaced parallel stacking ring association by virtue of the interplay of the polarized $\pi\cdots\pi$, C–H···F, C–F···π, and F···F interactions. It is characteristic, however, that only 4-fluoroPhe was different from the others in the interaction mode between neighboring molecules. This difference may be related to the high potency of 4-fluoroPhe in SFLLRNP against thrombin receptor activation,[10)] as compared with the lower potency of the other fluorine atom substitutions.[20,21)]

References

1) Burley S. K., Petsko G. A., *Science*, **229**, 23—28 (1985).
2) Meyer E. A., Castellano R. K., Diederich F., *Angew. Chem. Int. Ed.*, **42**, 1210—1250 (2003).
3) Hangauer D. G., Monzingo A. F., Matthews B. W., *Biochemistry*, **23**, 5730—5741 (1984).
4) Obst U., Banner D. W., Weber L., Diederich F., *Chem. Biol.*, **4**, 287—295 (1997).
5) Brejc K., Van Dijk W. J., Klaassen R. V., Schuurmans M., Van der Oost J., Smit A. B., Sixma T. K., *Nature* (London), **411**, 269—276 (2001).
6) Singh J., Thornton J. M., *FEBS Lett.*, **191**, 1—6 (1985).
7) Mecozzi S., West A. P., Jr., Dougherty D. A., *Proc. Natl. Acad. Sci. U.S.A.*, **93**, 10566—10571 (1996).
8) Quinonero D., Garau C., Rotger C., Frontera A., Ballester P., Costa A., Deya P. M., *Angew. Chem. Int. Ed.*, **41**, 3389—3392 (2002).
9) Williams J. H., Cockcroft J. K., Fitch A. N., *Angew. Chem. Int. Ed. Engl.*, **31**, 1655—1657 (1992).
10) Nose T., Shimohigashi Y., Ohno M., Costa T., Shimizu N., Ogino Y., *Biochem. Biophys. Res. Commun.*, **193**, 694—699 (1993).
11) Fujita T., Nose T., Matsushima A., Okada K., Asai D., Yamauchi Y., Shirasu N., Honda T., Shigehiro D., Shimohigashi Y., *Tetrahedron Lett.*, **41**, 923—927 (2000).
12) Matsushima A., Fujita T., Okada K., Shirasu N., Nose T., Shimohigashi Y., *Bull. Chem. Soc. Jpn.*, **73**, 2531—2538 (2000).
13) Sheldrick G. M., *SHELXS97*. Program for the Solution of Crystal Structure, University of Gottingen, Germany, 1997.
14) "International Tables for X-Ray Crystallography," Vol. C, Kluwer Academic Publishers, Dordrecht, 1992, pp. 219—222.
15) Sheldrick G. M., *SHELXL97*. Program for the Refinement of Crystal Structures, University of Gottingen, Germany, 1997.
16) Al-Karaghouli A. R., Koetzle T. F., *Acta Cryst.*, **B31**, 2461—2465 (1975).
17) Cozzi F., Siegel J. S., *Pure Appl. Chem.*, **67**, 683—689 (1995).
18) Cozzi F., Ponzini F., Annunziata R., Cinquini M., Siegel J. S., *Angew. Chem. Int. Ed. Engl.*, **34**, 1019—1020 (1995).
19) Vangala V. R., Nangia A., Lynch V. M., *Chem. Commun.*, **2002**, 1304—1305 (2002).
20) Nose T., Fujita T., Nakajima M., Inoue Y., Costa T., Shimohigashi Y., *J. Biochem.* (Tokyo), **124**, 354—358 (1998).
21) Matsushima A., Fujita T., Nose T., Shimohigashi Y., *J. Biochem.* (Tokyo), **128**, 225—232 (2000).