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New indications for the potential involvement of C–F-bonds in hydrogen bonding

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Abstract

Solid state structures of a selection of 2-fluoro-2-phenylcyclopropane derivatives were examined by X-ray crystallography in order to identify short intermolecular contacts of C–F groups to H–X moieties (X = C, N). Particularly, several *cis*-configured fluorinated phenylcyclopropane derivatives showed extremely close intermolecular contacts. The shortest of such C–H···F–C-distances (2.17 Å, C–F–H angle 162°) was found in (1*S*,2*R*)-(2-fluoro-2-phenylcyclopropyl)methyl *N*-(4-bromophenyl)carbamate (**8**) and the closest N–H···F–C-interaction (2.01 Å, C–F–H angle 167°) was found in (±)-*cis*-2-fluoro-2-phenylcyclopropyl carboxamide (**4**). Comparison of the structures of several of the fluorinated cyclopropanes with those of the non-fluorinated counterparts revealed that close intermolecular contacts of fluorine substituents to hydrogen atoms are not solely due to crystal packing effects, but are also caused by weak X–H···F–C hydrogen bridges.

Keywords: Carboxylic acid derivatives; Enantiomers; Fluorinated cyclopropanes; Hydrogen bonding; X-ray analysis

1. Introduction

The introduction of fluorine atoms into organic molecules in general causes drastic changes of the physico-chemical properties, of the chemical reactivity and of the biological activity of these compounds in comparison to their non-fluorinated parent compounds [1–6]. Particularly, the opportunity to tune the biological activity employing fluorine substituents continues to attract much attention in bioorganic, agricultural and medicinal chemistry [7–23]. The effect of fluorine as a substituent in bioactive compounds is based on its strong electron withdrawing (−*I*) effect, but, due to the low energy lone pairs, also on an electron pair donating mesomeric (+M) effect in conjugated systems [24–26]. Moreover, intermolecular through-space interactions play an important role as well [27–29]. Consequently, this substituent is able to modify the physiological behavior of bioactive compounds [7–23].

The fluorine substituent in organic compounds is comparable in size to a hydrogen atom and in certain circumstances also to a hydroxyl group [1–6,24–26]. The van der Waals radii are 1.20 Å for H, 1.47 Å for F, and 1.57 Å for an OH group [30]. Replacement of hydrogen by a single fluorine is often regarded as an isosteric substitution [31]. Thus, a mono-fluorinated analogue of an affector molecule is geometrically very similar to its parent compound and hence meets the steric requirements at enzyme receptor sites [7–23]. But, due to its different electronic properties the original biological response can be falsified [32–35]. Moreover, the similarity of typical C–F and C–O bond lengths (1.39 vs. 1.43 Å) and the comparable electronegativity suggest that replacement of a hydroxyl group by fluorine can also be regarded as an isosteric and isopolar substitution [24–26]. The ability of fluorinated aromatics to function as substitutes for nucleobases [36] supports this assumption [37,38]. The strong electronegativity of the fluorine substituent enhances the acidity of neighboring groups by its electron withdrawing ability and leads to a different dipole moment compared to the parent compounds [3,28,39,40]. Furthermore, it was discussed that a C–F bond can function in certain cases as a weak hydrogen bond acceptor (1–3 vs. 5–10 kcal/mol for oxygen as an acceptor) [41–45]. Though these interactions are much weaker than C=O···H–X (X = O, N) interactions they do influence molecular packing in

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crystals [46–50]. In bioorganic and medicinal chemistry the formation of intermolecular O–H···F–C and N–H···F–C hydrogen bridges were assumed important in binding of fluorinated compounds to enzyme active sites [51–60]. These particular effects on the enzyme–ligand binding affinity and selectivity together with the modulation of pharmacokinetic properties by fluorine substitution resulted in a considerably large number (ca. 150) of fluorinated drugs, which are in clinical use [61,62]. Recently, in an analog of thrombin inhibitors a close intermolecular contact of an aromatic C–F bond to an H–C bond in α-position to a carbamide group as short as 2.41 Å was found in the crystal packing environment [61,62]. Similar weak intermolecular interactions of a carbonyl group to α-C–H bonds were suspected to contribute to the stabilization of protein conformation [63].

Nevertheless, the role of C–F groups as hydrogen bond acceptors is discussed controversially and it is questioned whether they have any specific role [35,41–45,64–78]. Particularly for base pair surrogates of DNA it was suggested that the nucleoside to be fitted into the growing helix is selected by different shape rather than by hydrogen bonding capacities [72–75]. In 1997 Dunitz and Taylor investigated about 6000 C–F bonds in almost 1200 crystal structures (without compounds containing metals or As, Se and Te, respectively) collected in the Cambridge Crystallographic Data File, regarding possible interactions to O–H or N–H bonds. These authors defined a distance of <2.3 Å and a bonding angle $>90°$ as the upper limits for a hydrogen bond [70]. Among the 37 out of about 6000 examined C–F bonds which formally met these criteria, only two compounds were qualified as truly hydrogen bonded. Thus, it seems extremely rare that C–F moieties can act as hydrogen bridge acceptors. At the same time, Howard et al. identified 40 monofluorinated compounds having X–H···F–C (X = O, N) contacts ≤ 2.35 Å and classified them as weakly hydrogen bonded [43]. Moreover, these authors identified more than 125 close C–H···F–C contacts ≤ 2.35 Å, which were classified as van der Waals complexes [43]. Recently, several close X–H···F–C (X = O, N) contacts below these limits have been described [79–83]. Other authors considered a distance of about the sum of the van der Waals radii (2.67 Å) or even longer for a good criteria for intermolecular hydrogen bridges between C–F and H–X moieties [64–67,84,85]. Furthermore, quite short intramolecular N–H···F–C distances have been found in crystalline state and were classified as weak hydrogen bridges stabilizing particular conformations [86–91]. Intramolecular hydrogen bonding was calculated for X–H···F–C interactions in gauche conformations of 2-fluoroethanol and 2-fluoroethylamine as well as in their protonated forms [92,93]. In general, the poor polarizability of fluorine, which is due to the energetically low-lying p-orbitals, leads to weak hydrogen bonds [94,95]. X-ray data and quantum chemical calculations reinforce the conclusion that C(sp^3)–F groups are better hydrogen bond acceptors than C(sp^2)–F moieties [43,96].

In our studies, we focused on the examination of crystal structures of monofluorinated cyclopropanes. Cyclopropane itself is known to exhibit partial double bond character [97]. A significant part of the π-character is used to form the strained C–C– and the C–H-bonds, which is reflected by the H–C–H angle of 115° [98]. Substitution of C–H bonds with C–F bonds causes destabilization of the C–C bonding and increasing ring strain [99]. These changes should also influence the acidity of C–H bonds and hence its ability to act as hydrogen bond donors. Remarkably new indications about the potential of organic fluorine to act as a hydrogen bond acceptor were found for different monofluorinated cyclopropanes. Recently, our high-level quantum chemical calculations (MP2/QZVPP) showed, that the fluorocyclopropane dimer has an intermolecular C–H···F–C distance of 2.57 Å and an interaction energy of 10 kJ/mol, about one half of that of a normal hydrogen bond of a hydroxyl group to an oxygen acceptor [96]. Herein, we report our results on a variety of monofluorinated cyclopropane derivatives, which are expected to be essential for the characterization of this biologically relevant class of compounds [100–103].

2. Experimental

Compounds **1a**, **1c**, **2a**, **5**, and **10** or **7** and **8**, respectively, were prepared as previously described in Refs. [104,105]. Synthesis of compounds **1b**, **2b**, **6a** and **6b** or **3**, **4** and **9**, is published in Ref. [100–102].

2.1. (1R,2S)-(−)-2-Fluoro-2-phenylcyclopropanecarboxylic acid ((1R,2S)-2a)

Analogous to a method described in the literature [106] (1*R*,2*S*)-(−)-(2-fluoro-2-phenylcyclopropyl)methanol (87 mg, 0.524 mmol, >98% ee), prepared as previously described [105], $KMnO_4$ (414 mg, 2.62 mmol) and Bu_4NBr (34 mg, 0.105 mmol) were dissolved in a suspension consisting of benzene (1 mL) and H_2O (4 mL) at 5 °C. After stirring the reaction mixture vigorously for 17 h at 5 °C, sat. aqueous $NaHSO_3$ solution was added until the color disappeared. The mixture was acidified with 10% H_2SO_4 and extracted with CH_2Cl_2 (4×25 mL). The combined organic layers were dried over $MgSO_4$. After purification by flash chromatography (SiO_2, cyclohexane/ethyl acetate 1:1) (1*R*,2*S*)-**2a** (65 mg, 69%) was isolated as colorless oil. Different conditions and solvent mixtures were applied to crystallize the oil. All experiments did not give crystalline material. The spectroscopic data are in good agreement with those reported in literature for the racemic compound [104].

2.2. (1R,2S)-(−)-2-Fluoro-2-phenylcyclopropanecarboxamide ((R,S)-4)

(1*R*,2*S*)-(−)-2-Fluoro-2-phenylcyclopropanecarboxylic acid ((1*R*,2*S*)-**2a**) (64 mg, 0.355 mmol, 98% ee) and $SOCl_2$ (840 mg, 7 mmol) were refluxed in benzene (4 mL) for 5 h. Benzene and excess $SOCl_2$ were removed by distillation. The crude product dissolved in 1,4-dioxane (4 mL) was treated with ice-cold NH_4OH (8 mL) and the resulting mixture was stirred for 30 min at 0 °C and 1 h at room temperature. After extraction with ethyl acetate (4×20 mL) the combined organic

layer was washed with sat. NH_4Cl (2×15 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. After recrystallization from pentane/ethyl acetate (5:1) (1*R*, 2*S*)-(**4**) (49 mg, 77%, >98% ee, determined by chiral GC) was obtained as colorless solid. $[\alpha]_D^{20}$ −91.7° (*c* 1.0, $CHCl_3$). The spectroscopic data are in good agreement with those reported in literature for the racemic compound [100].

2.3. (1S,2S)-(−)-2-Fluoro-2-phenylcyclopropanecarboxamide ((1S,2S)-3)

Enantiopure (1*S*,2*S*)-(−)-2-fluoro-2-phenylcyclopropanecarboxylic acid ((1*S*,2*S*)-**2a**) (39 mg, 0.217 mmol, >98% ee), prepared as previously described [101], and $SOCl_2$ (521 mg, 4.34 mmol) were dissolved in benzene (4 mL). The reaction mixture was refluxed for 5 h. Benzene and unconverted $SOCl_2$ were removed by distillation. The crude product dissolved in 1,4-dioxane (3 mL) was treated with ice-cold NH_4OH (6 mL) and the resulting mixture was stirred for 30 min at 0 °C and 1 h at room temperature. After extraction with CH_2Cl_2 (4×20 mL) the combined organic layers were washed with sat. NH_4Cl (2×15 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. After recrystallization from ethyl acetate at −20 °C (1*S*,2*S*)-**3** (30 mg, 77%, >98% ee, determined by chiral GC) was isolated as amorphous white solid. $[\alpha]_D^{20}$ −218.6 (*c* 0.5, $CHCl_3$). All experiments to obtain suitable crystals for X-ray structural analysis resulted in the formation of amorphous powders. The analytical data are in good agreement with those reported in literature for the racemic compound [100].

Table 1
Crystal data and experimental details for compounds **1a**–**4a**

Compound	(±)-**1a**	(1*S*,2*S*)-**1a**	(±)-**1b**	(±)-**1c**	(±)-**2a**	(±)-**2b**	(±)-**3**	(±)-**4**	(1*R*,2*S*)-**4a**
Formula	$C_{10}H_9FO_2$	$C_{10}H_9FO_2$	$C_{10}H_8F_2O_2$	$C_{11}H_{11}FO_2$	$C_{10}H_9FO_2$	$C_{10}H_8F_2O_2$	$C_{10}H_{10}FNO$	$C_{10}H_{10}FNO$	$C_{10}H_{10}FNO$
F.W.	180.17	180.17	198.16	194.20	180.17	198.16	179.19	179.19	179.19
T (K)	293(2)	223(2)	223(2)	223(2)	223(2)	223(2)	223(2)	198(2)	223(2)
Wavelength (Å)	0.71073	1.54178	1.54178	1.54178	1.54178	1.54178	1.54178	0.71073	1.54178
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Trigonal
Space group	$P2_1/c$	$P2_1$	$P2_1/n$	$P2_1/n$	$C2/c$	$P2_1/c$	$P2_1/c$	$P-1$	$R3$
A (Å)	5.4921(6)	12.054(1)	5.853(1)	8.0833(4)	24.124(3)	13.617(4)	17.620(3)	9.241(1)	21.178(2)
B (Å)	7.5687(16)	5.609(1)	7.167(1)	5.6117(4)	5.543(1)	5.591(2)	5.251(1)	9.859(2)	21.178(2)
C (Å)	20.451(2)	12.994(1)	21.175(3)	21.5716(15)	40.282(6)	12.418(2)	9.720(1)	15.262(3)	5.189(1)
α (°)	90	90	90	90	5331.4(14)	90	90	78.06(1)	90
β (°)	93.780(9)	94.56(1)	94.04(1)	91.013(5)	90	109.78(2)	93.68(1)	80.61(1)	90
γ (°)	90	90	90	90	98.20(1)	90	90	78.47(1)	120
V (Å^3)	848.3(2)	875.8(2)	886.1(2)	978.4(1)	90	889.6(4)	897.5(2)	1322.1(4)	2015.5(5)
Z	4	4	4	4	24	4	4	6	9
D_{calc} (mg/m^3)	1.411	1.367	1.486	1.318	1.347	1.480	1.326	1.350	1.329
M (mm^{-1})	0.112	0.918	1.132	0.859	0.905	1.128	0.838	0.102	0.840
F(000)	376	376	408	408	2256	408	376	564	846
Crystal size (mm^3)	0.40×0.20×0.20	0.35×0.35×0.15	0.25×0.20×0.10	0.30×0.25×0.15	0.50×0.05×0.05	0.50×0.10×0.05	0.70×0.50×0.03	0.35×0.05×0.03	0.70×0.07×0.07
θ Range (°)	2.87–24.97	3.41–74.33	4.19–74.08	4.10–74.27	2.22–60.00	3.45–74.33	5.03–74.13	2.14–22.50	4.17–69.02
Reflections collected	1654	3932	1849	2038	4032	3585	1944	8389	2184
Independent reflections	1489	1969	1803	1986	3961	1795	1825	3429	1281
R(int)	0.009	0.024	0.028	0.017	0.141	0.051	0.021	0.165	0.063
Data /restr./param.	1489/0/120	1969/1/238	1803/0/129	1986/0/130	3961/0/355	1795/0/128	1825/2/124	3429/6/370	1281/3/126
Goodness-of-fit on F^2	1.054	1.090	1.033	1.062	1.097	0.930	1.004	1.055	1.057
R [$I>2\sigma(I)$], $R1/wR2$	0.033/0.090	0.038/0.101	0.040/0.120	0.049/0.143	0.070/0.168	0.046/0.110	0.052/0.119	0.090/0.150	0.051/0.116
R (all data), $R1/wR2$	0.053/0.095	0.040/0.104	0.045/0.125	0.076/0.155	0.184/0.210	0.113/0.133	0.144/0.156	0.195/0.187	0.056/0.122
Abs. Struct. parameter	–	0.08(17)	–	–	–	–	–	–	0.3(4)
Extinction coefficient	0.026(4)	0.012(2)	0.011(1)	0.008(2)	–	–	–	–	0.0027(3)
Max. Δ peak/hole (e/Å^3)	0.18/−0.21	0.24/−0.31	0.20/−0.24	0.23/0.27	0.37/−0.34	0.17/−0.22	0.16/−0.18	0.24/−0.27	0.17/−0.18
CCDC depos. No.	245,916	280,349	245,910	245,911	245,917	245,912	280,350	280,351	245,908

Suitable single crystals for X-ray analysis of the other compounds were obtained by slow evaporation of the respective solvent or diffusion for solvent mixtures. The data were collected with Nonius CAD4 or KappaCCD diffractometers, the crystal data are presented in Tables 1 and 2. The CCD data were processed with Denzo-SMN [107] and all structures were solved by direct methods (SHELXS-97) [108] and refined on $F2$ by full-matrix least-squares techniques (SHELXL-97) [109]. The hydrogen atoms were calculated to their idealized positions with isotropic temperature factors (1.2 or 1.5 times the carbon temperature factor) and the C–H, O–H and N–H distances have been normalized to their neutron diffraction distances during the refinements, viz. C–H to 1.08 Å, O–H and N–H to 1.00 Å (done using the SHELXL command AFIX in the final refinements). The figures have been drawn using the SCHAKAL software [110].

Crystal data and experimental details for compounds **1a**–**4a** is given in Table 1 and for compounds **5**–**10** in Table 2.

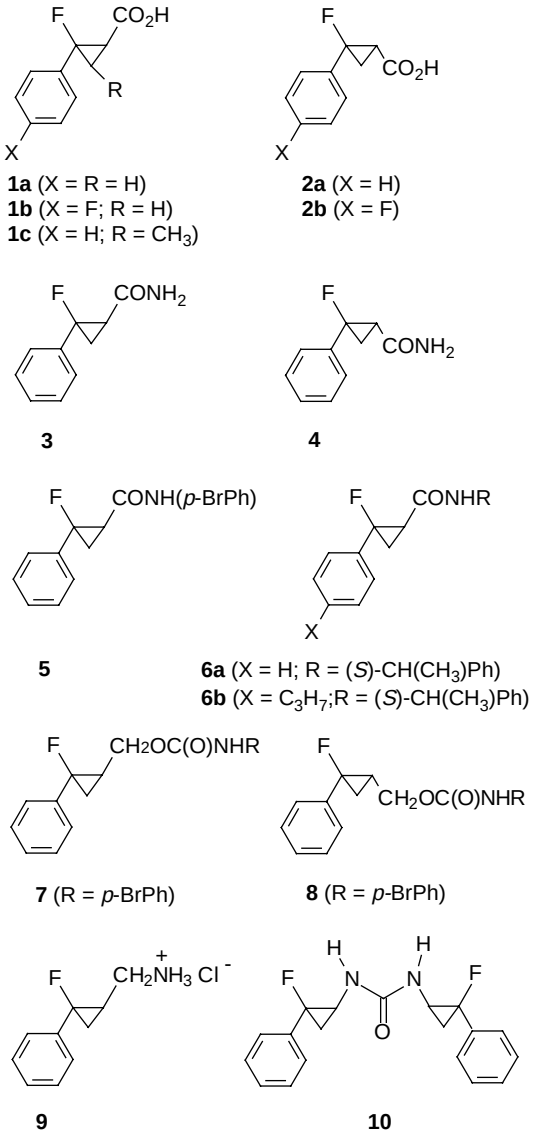
CCDC 245908-245914, 245916-245918, and 280349-280354 contain the supplementary crystallographic data (excluding structure factors) for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/const/retrieving.html (from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033).

3. Results

In particular, X-ray structures of several 2-fluoro-2-phenylcyclopropane derivatives (Scheme 1) synthesized from corresponding α-fluorostyrenes by copper catalyzed cyclopropanation with ethyl diazoacetate (Scheme 2) and subsequent further functionalization [104,105,111] were examined with respect to short X–H···F–C contacts. C–H···π interactions were not taken into account. The structures of the compounds ((±)-**1b**, (±)-**1c**, (±)-**2b**, (1*R*,2*S*)-**4**, (1*S*,2*S*)-**6a**, (1*R*,2*R*)-**6b**,

Table 2
Crystal data and experimental details for compounds **5**–**10**

Compound	(1*S*,2*S*)-**5**	(1*S*,2*S*)-**6a**	(1*R*,2*R*)-**6b**	(1*R*,2*R*)-**7**	(1*S*,2*R*)-**8**	(±)-**9**	(±)-**10**
Formula	$C_{16}H_{13}BrFNO$	$C_{18}H_{18}FNO$	$C_{21}H_{24}FNO$	$C_{17}H_{15}BrFNO_2$	$C_{17}H_{15}BrFNO_2$	$C_{10}H_{13}ClFN$	$C_{19}H_{18}F_2N_2O$
FW	334.18	283.33	325.41	364.21	364.21	201.66	328.35
T (K)	198(2)	223.0(1)	223(2)	198(2)	198(2)	198(2)	223(2)
Wavelengths (Å)	0.71073	1.5478	1.54178	0.71073	0.71073	0.71073	1.54178
Crystal system	Triclinic	Orthorhombic	Monoclinic	Orthorhombic	Monoclinic	Triclinic	Orthorhombic
Space group	$P1$	$P2_12_12_1$	$P2_1$	$P2_12_12$	$P2_1$	P-1	$P2_12_12_1$
a (Å)	5.706(1)	9.762(1)	9.788(1)	8.840(1)	16.186(1)	9.598(1)	10.717(3)
b (Å)	7.890(1)	12.912(1)	12.273(1)	34.535(1)	5.348(1)	10.227(1)	14.361(2)
c (Å)	15.613(4)	24.489(1)	15.842(1)	5.054(1)	18.294(1)	21.637(2)	21.558(4)
α (°)	90.55(1)	90	90	90	90	77.32(1)	90
β (°)	94.90(1)	90	100.87(1)	90	93.91(1)	84.67(1)	90
γ (°)	91.84(2)	90	90	90	90	88.90(1)	90
V (Å^3)	699.9(2)	3086.8(4)	1868.9(3)	1542.9(4)	1579.9(3)	2063.1(4)	3317.9(12)
Z	2	8	4	4	4	8	8
D_{calc} (mg/m^3)	1.586	1.219	1.157	1.568	1.531	1.299	1.315
M mm^{-1}	2.942	0.675	0.616	2.681	2.618	0.338	0.812
F(000)	336	1200	696	736	736	848	1376
Crystal size (mm^3)	0.20×0.10×0.05	0.70×0.10×0.10	0.25×0.25×0.05	0.50×0.10×0.05	0.40×0.06×0.03	0.40×0.10×0.03	0.40×0.10×0.10
θ Range (°)	2.58–26.48	3.61–65.61	2.84–65.53	1.18–27.87	1.63–28.24	1.94–24.76	3.70–74.30
Reflections collected	4298	4056	9730	8237	9847	9895	3788
Independent reflections	3298	4056	4078	3553	7096	6728	3788
R(int)	0.041	–	0.061	0.051	0.043	0.096	–
Data /restr./param.	3298/5/367	4056/2/384	4078/7/438	3553/1/202	7096/3/403	6728/0/473	3788/4/446
Goodness-of-fit on F^2	1.057	0.995	1.153	1.049	1.0567	1.096	1.028
$R[I>2\sigma(I)]$, $R1$/$wR2$	0.051/0.132	0.071/0.192	0.064/0.178	0.047/0.086	0.062/0.091	0.093/0.199	0.057/0.142
R (all data), $R1$/$wR2$	0.059/0.139	0.112/0.220	0.125/0.218	0.082/0.098	0.126/0.111	0.161/0.233	0.094/0.166
Abs. Struct. parameter	−0.02(2)	−0.2(4)	−0.5(4)	−0.03(1)	0.00(1)	–	0.7(3)
Extinction coefficient	–	0.0013(5)	0.0035(7)	–	–	–	0.0024(4)
Max. Δ peak/hole (e/Å^3)	0.45/−0.43	0.54/−0.23	0.19/−0.17	0.37/−0.62	0.41/−0.60	0.54/−0.29	0.30/−0.30
CCDC deposit. No.	245,918	245,913	245,914	280,352	280,353	280,354	245,909



Scheme 1. Investigated compounds. Synthesis has been described in Refs. [100–105,111].

(±)-**9** and (±)-**10**) are newly presented, the other compounds ((±)-**1a**, (1*S*,2*S*)-(**1a**), (±)-**2a**, (±)-**3**, (±)-**4**, (1*S*,2*S*)-**5**, (1*R*,2*R*)-**7** and (1*S*,2*R*)-**8**) are already published, but re-refined for this study for better comparison.

First some stereoisomeric 2-fluoro-2-arylcyclopropanecarboxylic acids **1** and **2** were investigated. As expected, these compounds formed dimers in the crystalline state. In the racemic dimer of *trans*-2-fluoro-2-phenylcyclopropanecarboxylic acid (**1a**) (monoclinic, $P2_1/c$) two strong hydrogen bridges as short as

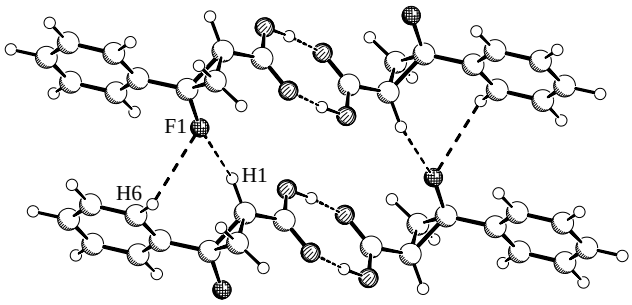


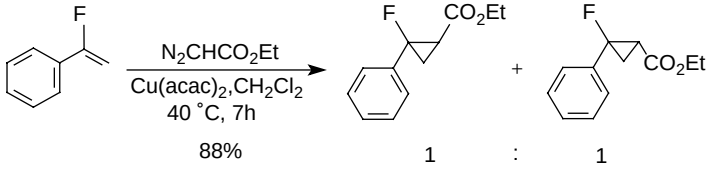
Fig. 1. Crystal structure of (±)-*trans*-2-fluoro-2-phenylcyclopropanecarboxylic acid (**1a**).

1.65 Å with a bond angle of 171° were formed between the carboxylic groups of two molecules. Additionally, there are two C–H···F–C distances, which are close to the sum of the van der Waals radii, namely 2.62 Å (C1–H1···F1 with angle of 135°) to the methine C–H in α-position to the carboxylic function and 2.65 Å to an *ortho*-hydrogen of the aryl ring (C6–H6···F1 with angle of 126°) (Fig. 1). The heavy atom close contacts [the sum of van der Waals radii of fluorine and carbon is 3.17 Å and fluorine and nitrogen it is 3.02 Å] between the fluorine and the H-bond carbon/nitrogen and the >120° angle C–F···C/N also further support the weak C–F···H interaction between the fluorine and the hydrogen atom, in **1a** these values are 3.465(2) Å (F1···C1), 3.403(2) Å (F1···C6), 170.9(1)° (C2–F1···C1), and 130.5(1)° (C2–F1···C6).

The analogous non-fluorinated (±)-*trans*-2-(4-tolyl) cyclopropanecarboxylic acid, KEMPUN [112] (data retrieved from Cambridge Crystallographic Data Base) crystallized in a centrosymmetric orthorhombic space group *Pbcn*. Beside the typical dimer formation with two strong hydrogen bonds no other short intermolecular distances were found (Fig. 2).

The enantiomerically pure (+)-(1*S*,2*S*)-2-phenylcyclopropanecarboxylic acid (*trans*-configuration) (RIWKEN) [113] crystallized in a non-centrosymmetric monoclinic space group $P2_1$. In addition to the strong dimer H-bonding a weak inter-dimer hydrogen bond, C–H···O distance 2.54 Å, C···O distance of 3.22 Å, and the C–H···O angle of 125° were found (Fig. 3).

The enantiopure fluorinated analogue (1*S*,2*S*)-**1a** crystallized also as dimers in a monoclinic crystal type ($P2_1$), but compared to the racemic compound **1a**, revealed a shorter C–H···F contact of 2.40 Å (C1A–H1A···F1A with angle of 154°) to the methine proton of the cyclopropane ring (Fig. 4). Due to the conformation, induced by the crystal packing forces, also a short intramolecular C–H···F distance (2.45 Å, 140°) to an aromatic hydrogen was found. The F···C and C–F···C values in



Scheme 2. Synthesis of diastereomeric ethyl 2-fluoro-2-phenyl-cyclopropylcarboxylates.

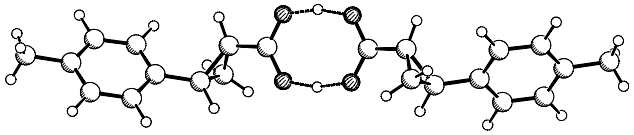


Fig. 2. Crystal structure of (±)-*trans*-2-(4-tolyl)cyclopropanecarboxylic acid (KEMPUN) [112].

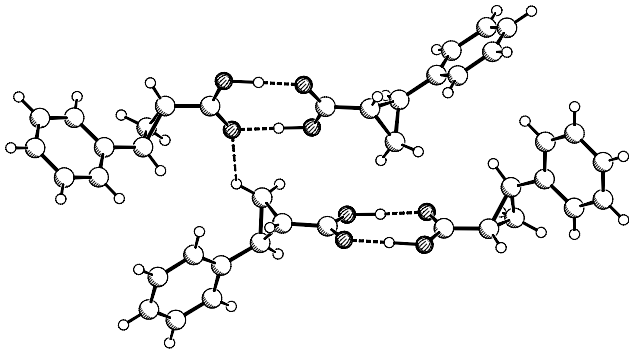


Fig. 3. Crystal structure of (+)-(1*S*,2*S*)-2-phenylcyclopropanecarboxylic acid (RIWKEN) [113].

(1*S*,2*S*)-**1a** are 3.401(3) Å (F1A···C1A), 3.350(3) (F1B···C10A), 140.6(1)° (C2A–F1A···C1A), and 128.9(1)° (C2B–F1B···C10A).

An additional methyl group in the 3-position of the cyclopropane ring *trans*-orientated relative to both the fluorine and to the carboxylic function (compound **1c**) did not disturb the formation of dimers. The acid **1c** crystallized in a centrosymmetric monoclinic space group $P2_1/n$ like racemic **1a** and shows two quite short intermolecular contacts slightly shorter than the sum of the van der Waals radii of the fluorine atom to the α-methine proton, 2.55 Å, C1–H1···F1, with angle of 142° and to the methyl group, 2.51 Å, C11–H11C···F1 with angle of 122° (Fig. 5). The F···C and C–F···C values in **1c** are 3.461(2) Å (F1···C1), 3.216(3) Å (F1···C11), 177.6(1)° (C2–F1···C1), and 132.8(1)° (C2–F1···C11).

The introduction of an additional fluorine atom into the *para*-position of the aromatic ring in the racemic compound **1b** led to a slightly different packing, nonetheless the space group is the same: monoclinic $P2_1/n$. Again two very strong hydrogen

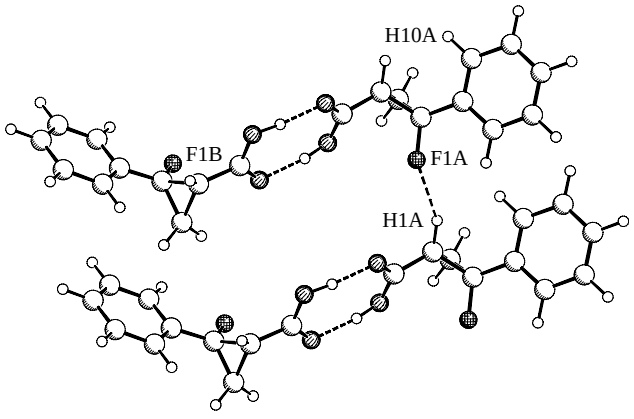


Fig. 4. Crystal structure of (1*S*,2*S*)-(−)-2-fluoro-2-phenyl-cyclopropanecarboxylic acid ((1*S*,2*S*)-**1a**).

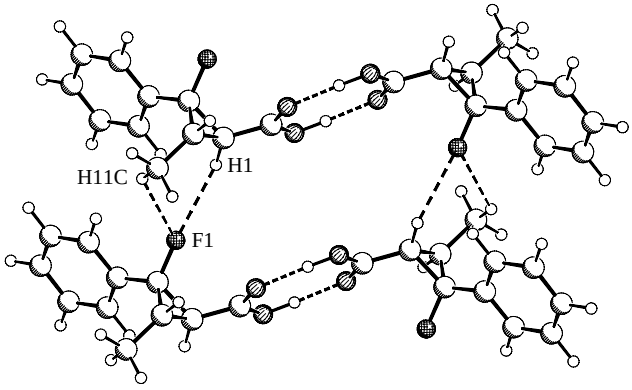


Fig. 5. Crystal structure of (±)-2-fluoro-*t*-3-methyl-*t*-2-phenylcyclopropyl-*r*-carboxylic acid (**1c**).

bridges (1.64 Å, 176°) led to the formation of dimers, but no short contacts of a fluorine of the cyclopropane ring to any of the C–H groups in the three-membered ring were found. In contrast, this fluorine atom interacts with the *ortho*-hydrogen of the next molecule, 2.49 Å, C1–H1···F2, with angle of 148°. Moreover, the *para*-fluorine atom has a short distance of 2.51 Å, C6–H6···F1, with angle of 120° to the methine C–H in α-position to the carboxylic function (Fig. 6). The F···C and C–F···C values in **1b** are 3.456(2) Å (F2···C1), 3.189(2) Å (F1···C6), 146.1(1)° (C2–F1···C6), and 125.5(1)° (C8–F2···C1). The *para*-fluorine might increase the acidity of the aromatic protons and has also some effect on the cyclopropyl fluorine lowering its electron density and hence its acceptor abilities for hydrogen bridges.

Also the racemate of the *cis*-isomer **2a** (a diastereomer of **1a**) crystallized with three molecular dimers in the asymmetric unit in a *C*-centered centrosymmetric monoclinic space group *C*2/*c* and forms dimers via strong hydrogen bridging (1.64, 1.67, and 1.67 Å with angles of 176, 173, and 161°, respectively). Three different very short intermolecular C–H···F–C contacts of 2.41 Å (C3C–H3CB···F1C) with angle of 171°, 2.32 Å (C3B–H3BB···F1B) with angle of 154° and even 2.28 Å (C3A–H3AA···F1A) with angle of 172° were formed to the cyclopropane methylene group of the adjacent molecules (Fig. 7). The F···C and C–F···C values in **2a** are 3.356(6) Å (F1A···C3A), 3.326(7) Å (F1B···C3B), 3.482(7) Å (F3C···C3C), 151.9(3)° (C2A–F1A···C3A), 142.6(3)° (C2B–F1B···C3B), and 147.1(3)° (C2C–F1C···C3C).

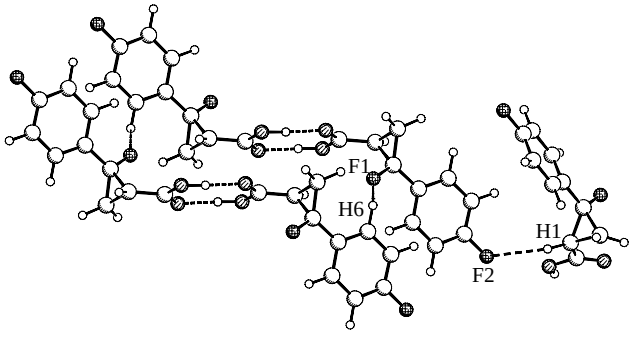


Fig. 6. Crystal structure of (±)-*trans*-2-fluoro-2-(*p*-fluorophenyl)cyclopropanecarboxylic acid (**1b**).

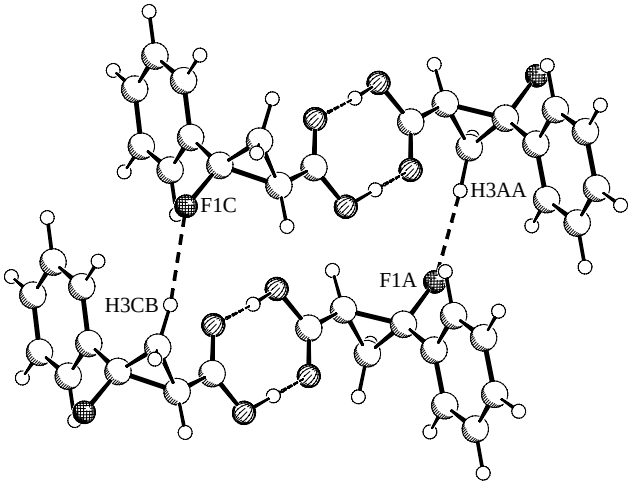


Fig. 7. A-C-Dimer of the (±)-*cis*-2-fluoro-2-phenylcyclopropanecarboxylic acid (**2a**).

Unfortunately, the (1*S*,2*R*)-enantiomer of the *cis*-configured acid **2a**, did not crystallize, but remained an oil. The corresponding non-fluorinated racemic (±)-*cis*-2-phenylcyclopropanecarboxylic acid (RUWKOJ) [114] crystallized in a centrosymmetric monoclinic space group $P2_1/n$. In addition to the strong inter-dimer hydrogen bond, also a very weak inter-dimer hydrogen bond with C–H···O distance 2.68 Å, C···O distance of 3.61 Å, and the C–H···O angle of 157° were found (Fig. 8).

The attachment of a *para*-fluorine atom at the aromatic ring (racemic compound **2b**, monoclinic $P2_1/c$), in this case led to two different short C–H···F–C-distances of the strongly hydrogen bonded dimers (1.65 Å, 174°). Between the cyclopropyl fluorine and one hydrogen atom of the methylene group of the next molecule's three-membered ring a close contact of 2.39 Å (C3–H3B···F1), 178° was found, while 2.45 Å (C9–H9···F2), 127° was observed between the *para*-

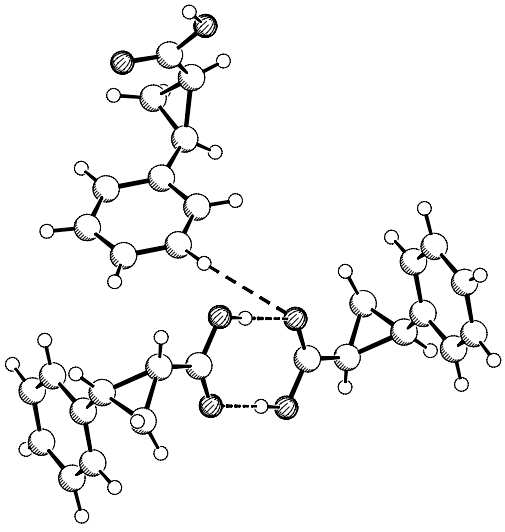


Fig. 8. Crystal structure of (±)-*cis*-2-phenylcyclopropanecarboxylic acid (RUWKOJ) [114].

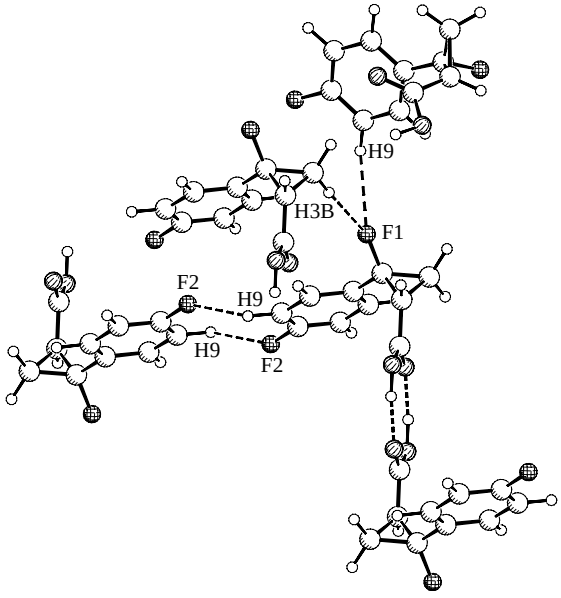


Fig. 9. Crystal structure of (±)-*cis*-2-fluoro-2-(*p*-fluorophenyl)cyclopropanecarboxylic acid (**2b**).

fluorine atom and a *meta*-hydrogen atom of the neighbored molecule (cf. the above-mentioned influences of *p*-fluorine). In addition a longer intermolecular contact of 2.68 Å (C9–H9···F1) with angle of 137° exists (Fig. 9). The F···C and C–F···C values in **2b** are 3.219(3) Å (F2···C9), 3.470(4) Å (F1···C3), 3.551(3) Å (F1···C9), 143.5(2)° (C8–F2···C9), 151.9(2)° (C2–F1···C3), and 150.3(2)° (C2–F1···C9).

Thus, all investigated cyclopropanecarboxylic acids in the crystalline state did form hydrogen bonded dimers. Additionally, the fluorinated compounds exhibited close C–H···F–C-contacts, which in general were shorter than the sum of the van der Waals radii. The *cis*-configurated compounds **2** had the shorter distances compared to the corresponding *trans*-compounds **1a** and **1b** and do approach each other as close as 2.28 Å (**2a**) or 2.39 Å (**2b**). Crystal structures of fluorinated compounds differed significantly from corresponding unfluorinated counterparts suggesting an attractive intermolecular interaction of the fluorine substituent on the crystal structure.

Next the corresponding racemic primary carboxamides **3** and **4** were investigated. The *trans*-isomer **3** crystallized in a centrosymmetric triclinic structure ($P-1$) as hydrogen bonded dimers and showed quite short N–H···O=C-contacts of 1.80 Å (N1–H1A···O1) with angle of 166° and 1.92 Å (N1–H1B···O1) and angle of 174° (Fig. 10). However, the shortest C–H···F–C-distance was found to be 2.76 Å, hence slightly above the sum of the van der Waals radii.

In contrast, the racemic *cis*-isomer **4** crystallized with three molecules in the asymmetric unit in a centrosymmetric monoclinic space group $P2_1/c$ and showed a complicated structure. Since all attempts to get crystals of better quality failed, the geometrical values with less accurancy should be discussed here. There are several quite short intermolecular N–H···O=C-contacts of 1.88 Å (N1A–H1AA···O1C) with angle of 171°, 1.89 Å (N1B–H1BA···O1A) with angle of 174°, and 1.93 Å (N1C–H1CA···O1B) with angle of 167°. Most

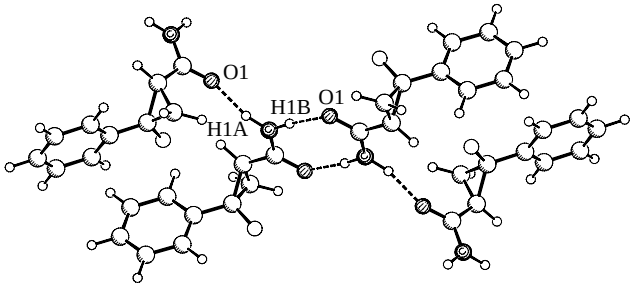


Fig. 10. Crystal structure of (±)-*trans*-2-fluoro-2-phenylcyclopropanecarboxamide (**3**).

surprisingly, there are also three extremely short intermolecular N–H···F–C distances of 2.09 Å (N1B–H1BB···F1A) with angle of 158°, 2.01 Å (N1C–H1CB···F1B), angle of 167°, and 2.03 Å (N1A–H1AB···F1C), angle of 169°. There also exists a longer C–H···F–C distance of 2.64 Å (C9B–H9B···F1C) with angle of 129° (Fig. 11). The F···C/N distances and C–F···C/N angles in **4** are 3.043(6) Å (F1A···N1B), 2.995(6) Å (F1B···N1C), 3.022(7) Å (F1C···N1A), 3.422(7) (F1C···C9B) and 167.3(4)° (C2A–F1A···N1B), 169.6(4)° (C2B–F1B···N1C), 155.8(4)° (C2C–F1C···N1A), and 125.0(4)° (C2C–F1C···C9B), respectively. The extremely short N–H···F distances in **4**, to the best of our knowledge, belong to the shortest intermolecular contacts ever observed for monofluorinated compounds.

These short distances forced us to synthesize also the corresponding enantiopure compounds. Unfortunately, the (1*S*,2*S*)-isomer of compound **3** could not be crystallized, but gave an amorphous powder. Its diastereomer, (1*R*,2*S*)-**4** crystallized in a non-centrosymmetric trigonal space group *R*3, showing normal N–H···O=C-contacts of 1.96 Å with angle of 168° and 2.19 Å with angle of 165°. Surprisingly, no short N–H···F–C-distances were found. But, in contrast to the racemic

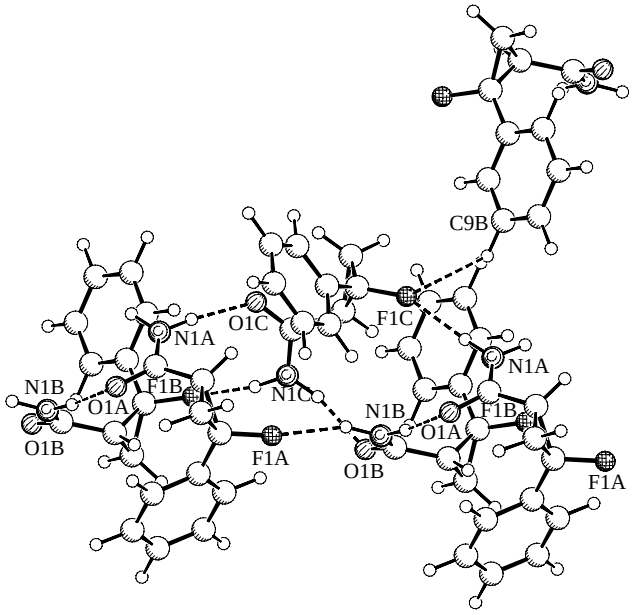


Fig. 11. Crystal structure of (±)-*cis*-2-fluoro-2-phenylcyclopropanecarboxamide (**4**).

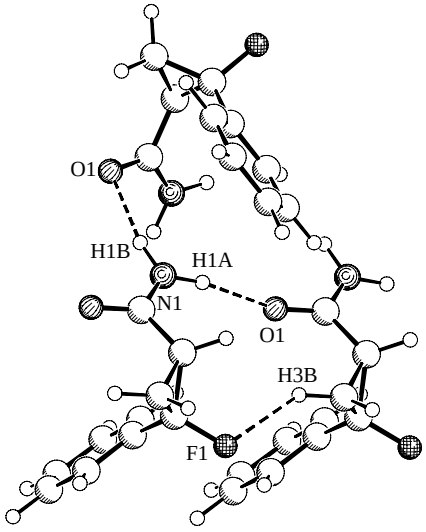


Fig. 12. Crystal structure of (1*R*,2*S*)-(−)-2-fluoro-2-phenylcyclopropanecarboxamide ((1*R*,2*S*)-**4a**).

compound, a quite short C–H···F–C-contact of 2.41 Å with angle of 142° was identified (Fig. 12). The F···C and C–F···C values in (1*R*,2*S*)-**4** are 3.326(6) Å (F1···C3) and 124.6(2)° (C2–F1···C3).

The (1*S*,2*S*)-2-fluoro-2-phenylcyclopropanecarbox-(4-bromophenyl)amide (1*S*,1*S*)-(**5**) (*trans*-configuration of phenyl group and carboxamide function) crystallized with two molecules in the asymmetric unit in a non-centrosymmetric triclinic space group *P*1. Two short N–H···O=C-distances of 1.86 Å (N1B–H1BA···O1A), angle of 151° and 1.89 Å (N1A–H1AA···OO1B), 162° were identified. Additionally, also three quite short C–H···F–C-contacts of 2.39 Å, (C3A–H3AB···F1A) with angle of 154°, 2.47 Å (C1B–H1B···F1A), 128° and 2.35 Å (C1A–H1A···F1B), 157° were found (Fig. 13). The F···C and C–F···C values in **5** are 3.392(9) Å (F1A···C3A), 3.253(8) Å (F1A···C1B), 3.375(8) Å (F1B···C1A), 148.9(4)° (C2A–F1A···C3A), 139.0(4)° (C2A–F1A···C1B), and 113.2(4)° (C2B–F2B···C1A).

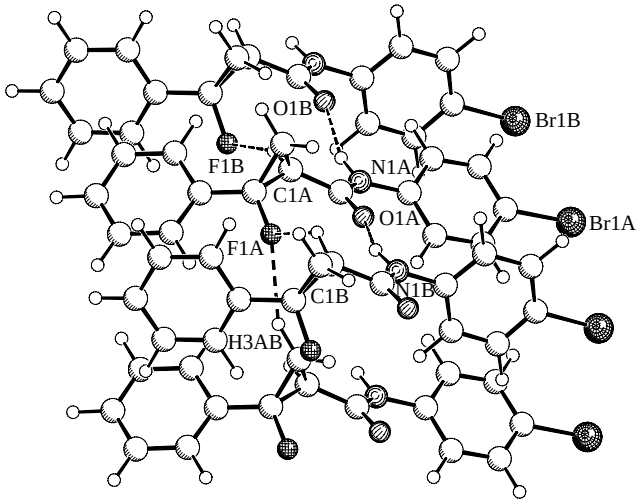


Fig. 13. Crystal structure of (1*S*,2*S*)-2-fluoro-2-phenylcyclopropanecarbox-(4-bromophenyl)amide ((1*S*,2*S*)-**5**).

Moreover, (1*S*,2*S*)-(−)-2-fluoro-2-phenylcyclopropyl-*N*-[(*S*)-1-phenylethyl)]carboxamide (**6a**) [101], crystallized in a non-centrosymmetric orthorhombic space group $P2_12_12_1$. The structure shows six short intermolecular interactions of which two are N–H···O=C interactions of 1.96 Å (N1B–H1BA···O1A) with angle of 168° and 2.04 Å (N1A–H1AA···O1B), angle 160°. The four remaining interactions are C–H···F–C and N–H···F–C of 2.23 Å (C10B–H10B···F1A) with angle of 148°, 2.49 Å (C1B–H1B···F1A), angle 162°, 2.57 (C8B–H8B···F1B), angle 128°, and 2.69 Å (N1A–H1AA···F1B) with angle 120° (Fig. 14). The F···C/N and C–F···C/N values in **6a** are 3.531(5) Å (F1A···C1b), 3.198(8) Å (F1A···C10B), 3.345(10) Å (F1B···C8B), 3.301(6) Å (F1B···N1A), 131.3(3)° (C2A–F1A···C1B), 162.0(4)° (C2A–F1A···C10B), 142.2(4)° (C2B–F1B···C8B), and 145.9(4)° (C2B–F1B···N1A).

Furthermore, (1*R*,2*R*)-2-fluoro-2-(4-propylphenyl)cyclopropyl-*N*-[(*S*)-1-phenylethyl)]carboxamide (**6b**) [101] crystallized with two molecules in the asymmetric unit in a non-centrosymmetric monoclinic space group $P2_1$ showing normal N–H···O=C hydrogen bonding distances of 1.89 Å (N1A–H1AA···O1B) with angle of 158° and 1.83 Å (N1B–H1BA···O1A) with angle of 157°. In addition there are three C–H···F–C-contacts of 2.40 Å (C1B–H1B···F1A) with angle of 165°, 2.54 Å (C7B–H7B···F1A) with angle of 159°, and 2.61 Å (C17A–H17A···F1B) with angle of 126°, (Fig. 15). The F···C and C–F···C values in **6** are 3.452(8) Å (F1A···C1B), 143.1(4)° (C2A–F1A···C1B), 3.575(10) Å (F1A···C7B), 88.0(4)° (C2A–F1A···C7B), and 3.356(10) Å (F1B···C17A), 151.0(5)° (C2B–F1B···C17A).

Two more diastereomeric enantiopure carbamates were synthesized [105] and their crystal structures were analyzed. The *N*-(4-bromophenyl)carbamate of the *trans*-configured (1*R*,2*R*)-(2-fluoro-2-phenylcyclopropyl)methanol (1*R*,2*R*)-**7** crystallized in a non-centrosymmetric orthorhombic space group $P2_12_12$. Besides the N–H···O=C-contact of 2.02 Å (N1–H1A···O2) with angle of 171°, the structure showed two relatively short intermolecular C–H···F–C-distances of 2.48 Å (C17–H17···F1) with angle of 161° towards the *ortho*-hydrogen of the phenyl ring and 2.55 Å (C4–H4A···F1) with a narrow angle of 112° to the exocyclic methylene group

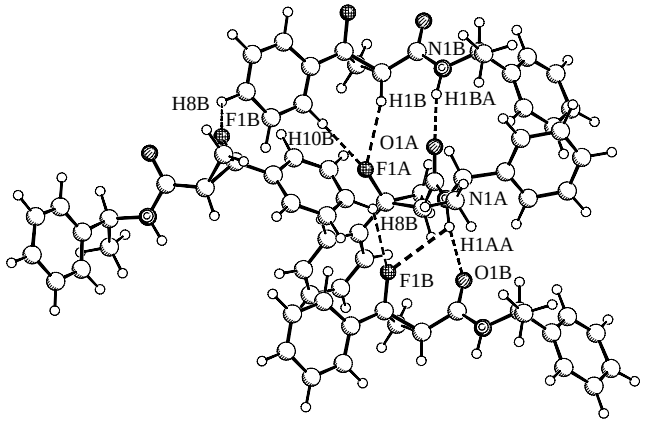


Fig. 14. Crystal structure of (1*S*,2*S*)-(−)-2-fluoro-2-phenylcyclopropyl-*N*-[(*S*)-1-phenylethyl)]carboxamide (**6a**).

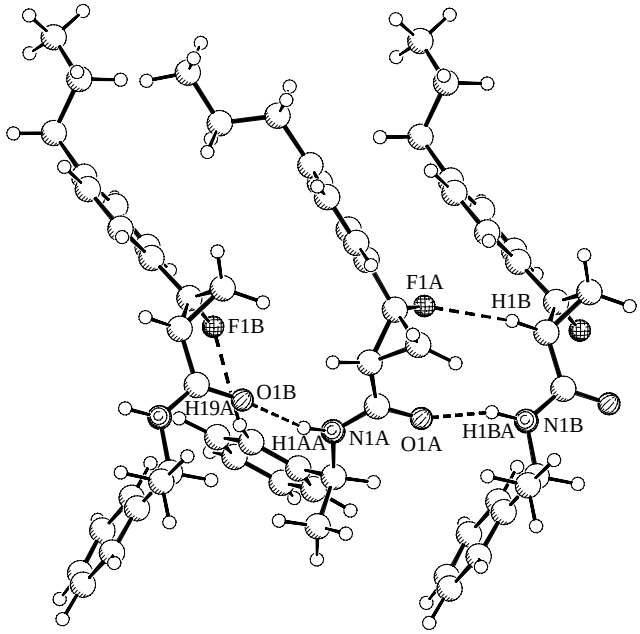


Fig. 15. Crystal structure of (1*R*,2*R*)-2-fluoro-2-(4-propylphenyl)cyclopropyl-*N*-[(*S*)-1-phenylethyl)]carboxamide (**6b**).

(Fig. 16). The F···C and C–F···C values in **7** are 3.115(4) Å (F1···C4), 3.517(5) Å (F1···C17), 125.3(2)° (C2–F1···C4) and 90.1(2)° (C2–F1···C17).

However, the *cis*-isomer (1*S*,2*R*)-(**8**) crystallized with two molecules in the asymmetric unit in a non-centrosymmetric monoclinic space group $P2_1$. The structure showed rather long N–H···O=C-distances of 2.23 Å (N1A–H1AA···O2A) with angle of 157° and 2.20 Å (N1B–H1BA···O2B), angle of 157°. Additionally, two very short intermolecular C–H···F–C-contacts were identified. There is a very close distance of 2.17 Å (C3B–H3BA···F1B) with angle of 162° of a fluorine atom to a hydrogen atom of the cyclopropane ring and another similar one in the second molecule of 2.19 Å (C3A–H3AA···F1A) with angle of 170° (Fig. 17). The F···C and C–F···C values in (1*S*,2*R*)-**8** are 3.262(6) Å (F1A···C3A), 3.215(6) Å (F1B···C3B), 144.3(3)° (C2A–F1A···C3A) and 141.0(3)° (C2B–F1B···C3B). The increased acidity of cyclopropyl hydrogens and its ability to form intermolecular

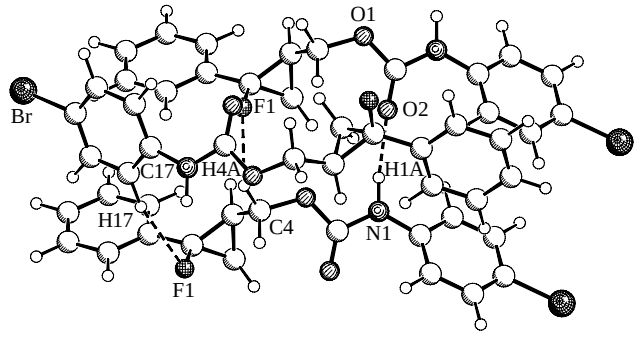


Fig. 16. Crystal structure of (1*R*,2*R*)-(2-fluoro-2-phenylcyclopropyl)methyl *N*-(4-bromophenyl)carbamate (**7**).

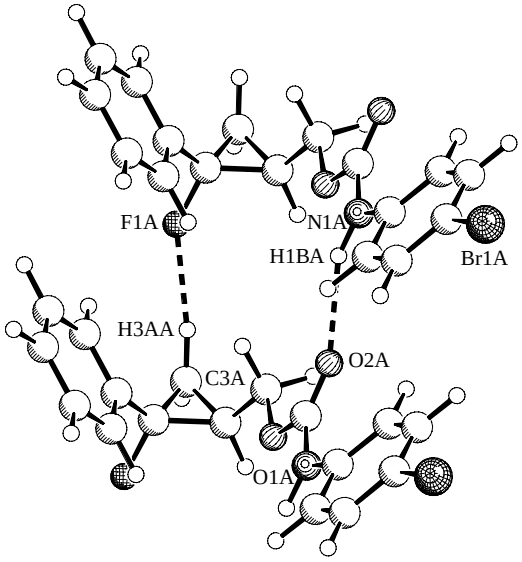


Fig. 17. Crystal structure of (1*S*,2*R*)-(2-fluoro-2-phenylcyclopropyl)methyl *N*-(4-bromophenyl)carbamate (**8**) (molecule A).

hydrogen bridges to carbonyl groups in solid state has been described already [115].

Such very close intermolecular C–H···F–C contacts, to the best of our knowledge, were not found in other non-aromatic monofluorinated compounds to date.

The racemic fluorinated aminomethylcyclopropane hydrochloride **9**, with *trans*-configuration of the phenyl and the aminomethyl groups, crystallized in a centrosymmetric triclinic space group *P*-1 with four molecules in the asymmetric unit. In this case the crystals were of poor quality leading to less accurate data. Beside twelve N–H···Cl interactions (2.11–2.31 Å, 147–178°) the structure shows three different intermolecular C–H···F–C-contacts. A short contact of 2.39 Å (C1A–H1A···F1D) with angle of 143° was found, while the two others of 2.51 Å (C1D–H1D···F1A), angle of 154° and 2.53 Å (C1C–H1C···F1B), angle 136° are only slightly shorter than the sum of the van der Waals radii (Fig. 18). The F···C and C–F···C values in **9** were 3.512(7) Å (F1A···C1D), 3.388(7) Å (F1B···C1C), 3.320(7) Å (F1D···C1A), 132.9(3)° (C2A–F1A···C1D), 131.2(3)° (C2B–F1B···C1C), and 139.2(3)° (C2D–F1D···C1A). Surprisingly, one of the fluorines (F1C) is not involved in this type of bonding, the

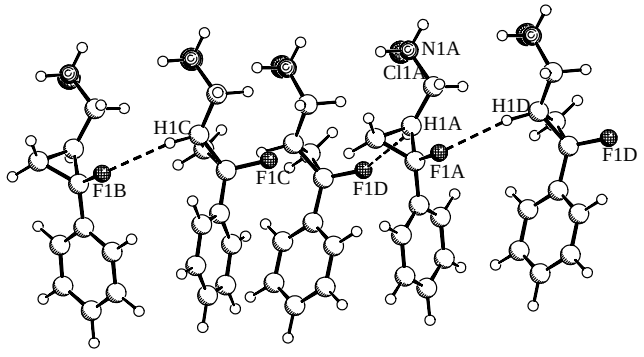


Fig. 18. Crystal structure of (±)-*trans*-1-aminomethyl-2-fluoro-2-phenylcyclopropane hydrochloride (**9**).

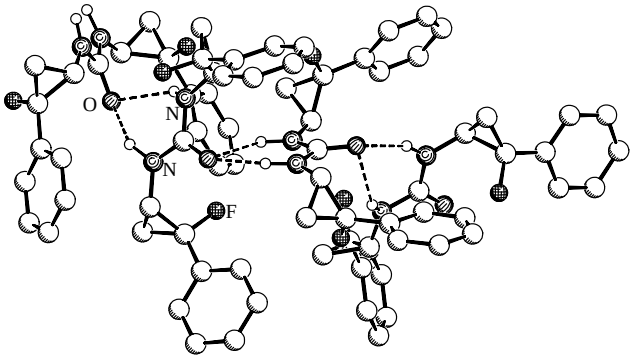


Fig. 19. Crystal structure of *N,N′*-di(2-fluoro-2-phenylcyclopropyl)urea (**10**) (only N–H···O contacts are shown, all other hydrogen atoms omitted for clarity).

closest contacts to hydrogen atoms in the neighbourhood are 2.58 Å (H6B) and 2.65 Å (H3AB).

Finally, the di(fluorocyclopropyl)urea **10** [116], isolated as a side product of the Curtius degradation of compound **1a**, crystallized in a non-centrosymmetric orthorhombic space group $P2_12_12_1$. The structure is extremely complex and showed a multitude of short intermolecular interactions. Two short and two longer N–H···O=C-distances of 1.88 Å (N1A–H1AA···O1C) with angle of 167°, 1.91 Å (N1D–H1DA···O1A), angle 149°, 2.33 Å (N1B–H1BA···O1C), angle 139° and 2.28 Å (N1C–H1CA···O1A), angle 137° were found (Fig. 19). Also two weak C–H···O=C hydrogen bonds were observed: 2.34 Å (C7D–H7D···O1A) with angle of 172° and 2.43 Å (C9A–H9A···OO1C) with angle of 133°. Moreover, in addition to the six short intermolecular C–H···F–C contacts also one short N–H···F–C contacts were identified (Table 3).

4. Discussion

The X-ray structures of the 2-fluoro-2-arylcyclopropane derivatives demonstrate that an over-all correlation between the short N/C–H···F–C-distances and angles and close to van der Waals contact of the corresponding N/C···F–C-distances and angles indeed exists. Controversy has been raised in literature with the question, whether close X–H···F–C distances (<sum of the van der Waals radii) and angles > 90°, can be regarded as true but weak hydrogen bonds [35,41–46,64–78]. The data presented here for particular 2-fluoro-2-arylcyclopropane derivatives clearly show the 'attractive' hydrogen bonding type of interaction. However, the overall 3-D structure, conformation and other types of positive interactions (e.g. 'classical' or weak hydrogen bonds) of the compounds containing the F–C moieties will have a great impact on the intermolecular 'interaction' distances. This can be seen here as most of the *trans*-configured compounds reveal longer C–H···F–C distances than the corresponding *cis*-configured analogs. Moreover, the intermolecular C–H···F–C contacts are shorter in enantiopure compounds as compared to their racemates. If additional attractive forces are present, e.g.

Table 3
Short intermolecular C–H···F–C, N–H···F–C, F···C and C–F···C contact distances and angles for compound **10**

X	H	F	H···F (Å)	X···F (Å)	X–H···F (°)	CF···X (°)
N1C	H1CA	F1A	2.56	3.416(5)	144	150.4(2)
C9D	H9D	F1A	2.57	3.348(7)	128	116.4(3)
C3B	H3BB	F1A	2.58	3.447(6)	137	114.4(2)
C1C	H1C	F1B	2.39	3.366(5)	150	117.2(2)
C1B	H1B	F1C	2.62	3.605(6)	152	121.6(3)
C7A	H7A	F1D	2.46	3.319(6)	136	130.8(3)
C8B	H8B	F1D	2.62	3.663(6)	162	84.3(2)

N–H···O=C, this will further decrease the interaction distances.

This effect for C–H···F–C distances and angles is visible for the enantiomers **7** and **8**. The *trans*-configured compound **7** (asymmetric unit contains one molecule) shows a weak N–H···O=C contact and has two intermolecular C–H···F–C contacts. The Δd (2.48–2.67 and 2.55–2.67 Å, respectively) are thus only −0.2 and −0.1 Å shorter than the sum of the van der Waals radii. However, the corresponding *cis*-configured **8** (two molecules in the asymmetric unit) has long N–H···O=C-distances too. The Δd values are −0.50 and −0.48 Å (2.17–2.67 and 2.19–2.67 Å, respectively), also the F···C and C–F···C values in **8** manifest the stronger interaction by showing much shorter values.

Extremely short N–H···F–C-interactions were found for (±)-*cis*-2-fluoro-2-phenylcyclopropane carboxamide (**4**). The crystal structure of **4** is very complex (three molecules in the asymmetric unit). As **4** is a carboxamide, intermolecular N–H···O=C-contacts represent the classical hydrogen bonding. The above N–H···O=C interactions will further enhance the weaker N–H···F–C interactions and the three extremely short intermolecular N–H···F–C distances are, to the best of our knowledge, among the shortest intermolecular contacts ever observed for organic monofluorinated compounds. The simultaneous N–H···O=C and N–H···F–C interactions correlate very well with the very short F···C/N and C–F···C/N, the three of the being in the same order than the sum of van der Waals radii of fluorine and carbon or fluorine and nitrogen, (3.17 and 3.02 Å, respectively). In contrast, enantiopure (1*R*, 2*S*)-**4a** crystallizing in a non-centrosymmetric trigonal space group *R*3, showed normal N–H···O=C-contacts. Surprisingly, no short N–H···F–C-distances were found, but, in contrast to the racemic compound, a quite short C–H···F–C-distance.

Comparison of the structures of fluorinated cyclopropanes with those of the non-fluorinated counterparts revealed that close intermolecular contacts of fluorine substituents to hydrogen atoms are not solely due to crystal packing effects, but are also caused by weak X–H···F–C hydrogen bridges.

In order to compare our results with similar structures with short C–F···H–C or C–F···H–N contacts a search from the Cambridge Structural Data Base (CSD, ConQuest 1.5, July 2003 version, 278172 X-ray structures) was performed with the following close non-covalently bonded contact distance constraints presented in Scheme 3.

The shortest C–F···H–C distance was found for CCDC structure CEKJIL [117] (2′-deoxy-2′-fluoroadenosine), this

Scheme 3. Structure fragments used, the minimum F···H search distance was 1.8 Å and the maximum 2.3 Å. Dotted line showing the H···F interaction, X and Y being any atom.

contact being 2.07 Å with angle of 166°, but simultaneously shows also an N–H···O=C contact of 2.03 Å with angle of 161°, forming a carboxylic acid type of dimer structure. The situation slightly changes with fluorine and hydrogen of an amino group. Thus, the shortest C–F···H–N distance found in catena-(bis(μ^2-thiourea-*S*,*S*-)-(2-fluorobenzoato-*O*,*O*)-lead(II) 2-fluorobenzoate monohydrate, NUMVIA [118], is only 1.95 Å with angle of 141°. However, this very short contact is between an aromatic fluorine and amino hydrogen. This is by far the shortest found organic fluorine to hydrogen interaction distance, Δd (1.95–2.67 Å) being −0.72 Å, manifesting a strong interaction between fluorine and hydrogen.

Moreover, our high level calculations (MP2/QZVPP) on the structure of cyclopropane–fluorocyclopropane adduct and of the dimer of monofluorocyclopropane in the gas phase in the first case show a C–H···F–C distance of 2.60 Å and an interaction energy of −6 kJ/mol. In the latter case a distance of 2.57 Å and about −10 kJ/mol a single C–H···F–C interaction (about 40% electrostatic and 60% dispersion forces) was calculated [96]. For 'classical' hydrogen bonds of the O–H···O-type about −20 kJ/mol involving 60–80% electrostatic forces are usual. Thus, in agreement with earlier results [46], we find it justified to characterize the close contacts found in the presented X-ray structures as weak hydrogen bonds.

The ability to form weak hydrogen bonds sems to influence the binding characteristics of monofluorinated cyclopropanes to biological targets such as enzyme receptor sites. Results for the interaction of fluorinated cyclopropylamines with monoamine oxidases indicated specific alterations of the inhibition activity induced by the fluorine substituent [23].

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