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Probing Fluorine Interactions in a Polyhydroxylated Environment: Conservation of a C–F···H–C Recognition Motif in Presence of O–H···O Hydrogen Bonds

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Three conformationally locked fluorinated polycyclitols have been specially crafted on a rigid *trans*-decalin backbone, employing a surprisingly facile pyridine-poly(hydrogen fluoride)-mediated stereospecific epoxide ring opening as the key reaction. Molecular design of the three fluorinated probes under study focused on providing an efficient platform for (a) evaluating the ability of covalently bonded fluorine, vis-à-vis the isosteric hydroxy group, to act as a H-bond acceptor and (b) examining the possibility for an organic fluorine moiety, placed suitably in a spatially invariant position, to engage an 1,3-diaxial OH functionality in a purported intramolecular O–H···F hydrogen bond. The present endeavour reveals that C(sp^3)–F···H–C(sp^3) hydrogen bonds, though weak and lesser investigated, can indeed be observed and supramolecular recognition motifs, involving such interactions, can be conserved even in crystal structures laden with stronger O–H···O hydrogen bonds.

Introduction

Organofluorine compounds ("*flustrates*"), besides their utilitarian value in modern life, are also known to display intriguing structural and physico-chemical characteristics.[1] For example, in the therapeutic arena, fluorinated organic compounds are estimated to constitute ca. 20% of all pharmaceuticals.[2] Although they seldom occur in nature,[2,3] the inherent bioactivity and widespread applications of organofluorine compounds as commonly prescribed medications has been attributed to the fact that incorporation of fluorine in a drug can significantly enhance its lipophilicity, potency and in vivo stability towards cytochrome P450 enzymatic oxidation.[1b,2,4] For a rational lead optimization, however, insertion of a fluorine atom in a drug molecule would rely heavily on bioisosterism[2a,5] and an in-depth knowledge of the non-covalent interactions that organic fluorine can engage itself into.[6] Being the most electronegative element and nearly isosteric to a hydroxy group,[7] covalently bonded fluorine might appear as a successful hydroxy group mimic, capable of replacing the OH functionality as a potential hydrogen-bond acceptor. However, this ostensibly straightforward issue, which revolves around the ability of fluorine to engage itself in H-bonding, has in fact engendered one of the well-known scientific debates of recent past.[8]

While a large body of scientific evidence (almost entirely based on the behavior of aromatic C=C–F and C=C–CF_3 moieties) point towards organic fluorine being a weak H-bond acceptor, capable of engaging in C–F···H–X (X = O, N, C) interactions,[9] other studies conclude that fluorine may not involve itself in hydrogen bonding at all.[8b,8c,8e,8f] Not surprisingly, ascribing a role to organic fluorine in a supramolecular assembly as either a bystander, which merely "fits into holes" to minimize empty space, or a moiety, which stabilizes the assembly as a H-bond acceptor, still remains largely open to speculation. Given the wide ranging applications of organofluorine compounds, this ambiguity continues to stimulate search for new probe systems and approaches capable of bringing clarity to the nature of fluorine in a self-assembly. The present study, in this context, utilizes three specially designed fluorinated polycyclitols[10] **1**–**3** to investigate the role of covalently bonded fluorine in crystal structures of the lesser studied aliphatic fluorinated substrates and probe its capability to engage itself in C(sp^3)–F···H–X(sp^3) (X = O and/or C) H-bonding, in presence of its isoster, the hydroxy group.

To a large extent, the basic molecular construct of **1**–**3** followed from our previously reported studies on the solid-state supramolecular chemistry of polycyclitols, such as **4** and **5** and their siblings.[11] Conformationally locked with well defined spatial disposition of functional groups, all the fluorinated polycyclitols **1**–**3** bear a fluorohydrin moiety, embedded in a rigid *trans*-decalin framework – a functionality incidentally present in nearly all pharmaceuticals, prescribed as steroids or anti-inflammatory agents.

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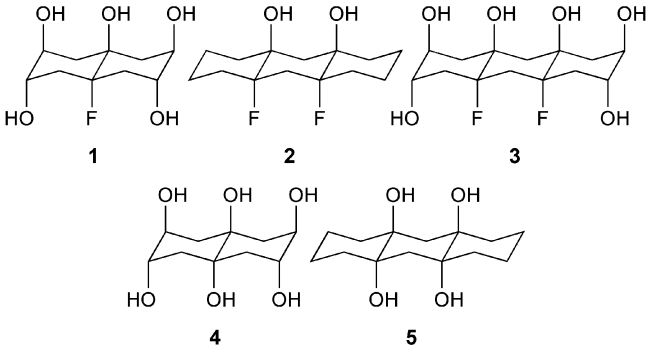
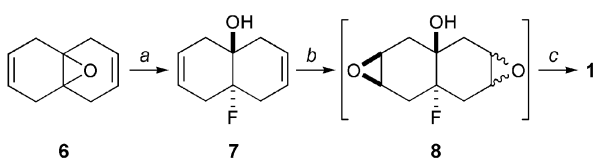


In **1** and **3**, it was conceived that the presence of a hydroxy donor in a favorable 1,3-syndiaxial relationship to a fluoro group on one side and a hydroxy group on the other would allow an unambiguous comparison between the two isosteric functionalities (C–F and C–OH) to serve as acceptors for intramolecular hydrogen bonds (O–H···F and O–H···O respectively). Though disputed, existence of O–H···F interactions, both intra- and intermolecular, has been postulated on the basis of theoretical, spectroscopic and single-crystal X-ray diffraction studies.[12] The difluorodiol **2** was sought to serve as a control to assess the change in the intermolecular C–F···H–X interactions (if any) that might be observed upon incorporating the peripheral secondary hydroxy groups in **3**.

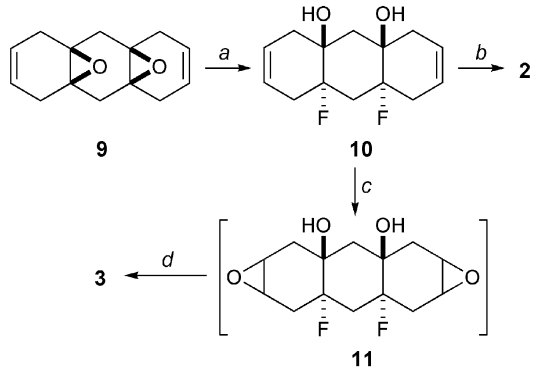
Results and Discussion

Synthesis of the Fluorinated Polycyclitols 1–3

Synthesis of the monofluoropentol **1** commenced from pyridine-poly(hydrogen fluoride)-mediated ring opening of the epoxide **6** to obtain the *trans*-fluorohydrin **7**.[13,14] *m*CPBA-mediated epoxidation in **7**, followed by mild acid hydrolysis of the resulting mixture of diepoxides **8**, yielded the desired **1** with excellent diastereoselectivity (Scheme 1). A similar synthetic stratagem was adopted to obtain the difluorohexol **3** from the *syn*-diepoxide **9**[14] via the intermediacy of the unsaturated difluorodiol **10** and the diepoxide mixture **11** (Scheme 2).[11f,15] From a synthetic perspective, it was interesting to note that the one-pot ring opening of **9** with HF/pyridine furnished the difluoride **10** with complete regio- and stereoselectivity. Catalytic hydrogenation of **10** afforded the difluorodiol **2** as a readily crystalline solid in excellent yield (Scheme 2).



Scheme 1. *Reagents and conditions.* a) pyridine poly(hydrogen fluoride) [70% HF + 30% pyridine], THF, room temp., 12 h, 97%; b) mCPBA (2.1 equiv.), CH_2Cl_2, room temp., 1 h, 78% (overall); c) 10% AcOH (aq.), THF, 50–60 °C, 3 d, 75% after recrystallization from 1:3 methanol/ethyl acetate.



Scheme 2. *Reagents and conditions.* a) pyridine poly(hydrogen fluoride) [70% HF + 30% pyridine], THF, room temp., 22 h, 78%; b) 10% Pd/C, H_2 (1 Torr), EtOAc, room temp., 2 h, 98%; c) mCPBA (2.1 equiv.), CH_2Cl_2, room temp., 12 h, 95% (overall); d) 10% AcOH (aq.), THF, 50–60 °C, 3 d, 99%.

Crystallographic Studies on the Fluorinated Polycyclitols 1–3

Single crystals of the fluorinated polyols **1** and **2** were grown from their solutions in 1:3 methanol/ethyl acetate and dichloromethane respectively. The difluorohexol **3** was however extremely polar and had to be therefore crystallized by slow evaporation from its dilute solution in deionized water alone. Details of the packing patterns in the fluorinated polycyclitols **1**–**3**, as gleaned from an analysis of their respective crystal data (see Table 4), are discussed below.

(a) Crystal Structure of the Monofluoropentol 1: Single-crystal X-ray diffraction studies revealed that the monofluoropentol **1** packed in the non-centrosymmetric orthorhombic space group $Pna2_1$ (Z = 4), with the three 1,3-syndiaxial hydroxy groups at C4, C6 and C8 participating in intramolecular O–H···O hydrogen bonding (Figure 1a, Table 1).[16,17] On the other hand, the OH functionalities at C3 and C9 did not engage themselves in intramolecular O–H···F interactions and preferred to participate in intermolecular O–H···O H-bonding instead (Table 1). Consequently, a severe electrostatic repulsion between the parallel C–F and C–O bond dipoles could be noted and was evident in the prominent increase in the C–C–C bond angles on either side of the central C–F bond in **1** [C1–C2–C3 = 114.81°; C1–C10–C9 = 114.04°]. Quite akin to that observed for any cyclitol, crystal packing in **1** was effected entirely via the agency of an intricate three-dimensional network of intermolecular O–H···O hydrogen bonds (Figure 1b). Short H···F contacts [H1O···F1 (d = 2.50 Å, θ = 129°), H3···F1 (d = 2.59 Å, θ = 106°), H1O···F1 (d = 2.39 Å, θ = 121°)] could also be discerned in the crystal structure of **1**. However, closer examination revealed that these contacts were adventitious in nature and resulted from the extensive O–H···O H-bonding, forcing the fluorines to approach nearer to the hydrogen atoms.

Table 1. Hydrogen bond geometry in the monofluoropentol **1**.[a,b]

D–H···A	D–H [Å]	H···A [Å]	D···A [Å]	D–H···A [°]
O1–H1O···O5^{i}	0.82 [*0.938*]	2.08 [*1.968*]	2.850(3)	157 [*155.90*]
O2–H2O···O1^{i}	0.82 [*0.938*]	1.96 [*1.847*]	2.759(3)	165 [*163.59*]
O3–H3O···O2^{ii}	0.82 [*0.938*]	1.96 [*1.859*]	2.682(3)	147 [*145.09*]
O4–H4O···O3^{ii}	0.82 [*0.938*]	1.98 [*1.888*]	2.685(3)	143 [*141.33*]
O5–H5O···O4^{iii}	0.82 [*0.938*]	2.00 [*1.888*]	2.803(3)	165 [*164.48*]

[a] Values in *italics* are those normalized following 1. ref.[28], 2. ref.[29] [b] Symmetry codes, i: $-x + 1/2$, $y + 1/2$, $z - 1/2$; ii: x, y, z; iii: $-x + 1$, $-y$, $z + 1/2$.

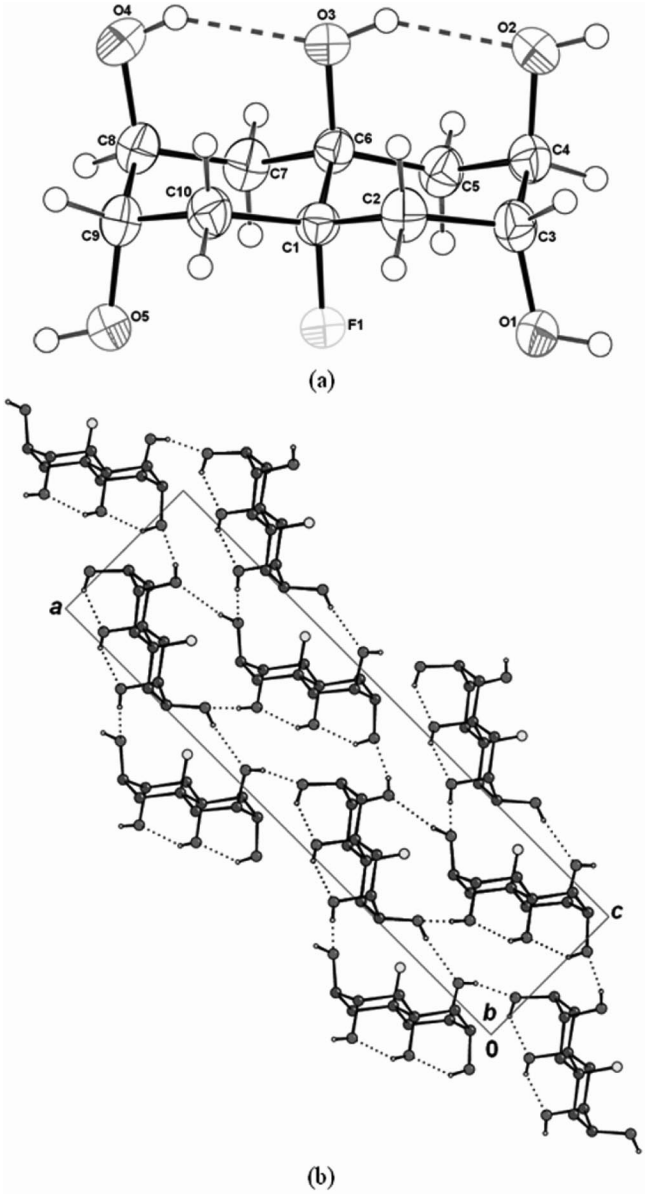


Figure 1. a) ORTEP diagram of the monofluoropentol **1**, with atom numbering scheme for the asymmetric unit. Displacement ellipsoids have been drawn at 50% probability level and H atoms are shown as small spheres of arbitary radii. The dotted lines indicate the intramolecular O–H···O hydrogen bonds; b) molecular packing in the monofluoropentol **1**. H atoms bonded to C atoms have been omitted for clarity.

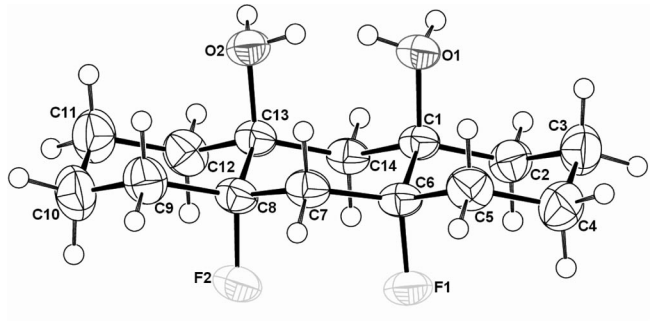


Figure 2. ORTEP diagram of the difluorodiol **2**, with atom numbering scheme for the asymmetric unit. Displacement ellipsoids have been drawn at 50% probability level and H atoms are shown as small spheres of arbitary radii. Each of the two hydroxyl H atoms is disordered over two sites (A and B) with equal occupancies, and thus represent two possible intramolecular O–H···O hydrogen bonding modes, viz. O1–H1O···O2 or O2–H2O···O2 (see Table 2).

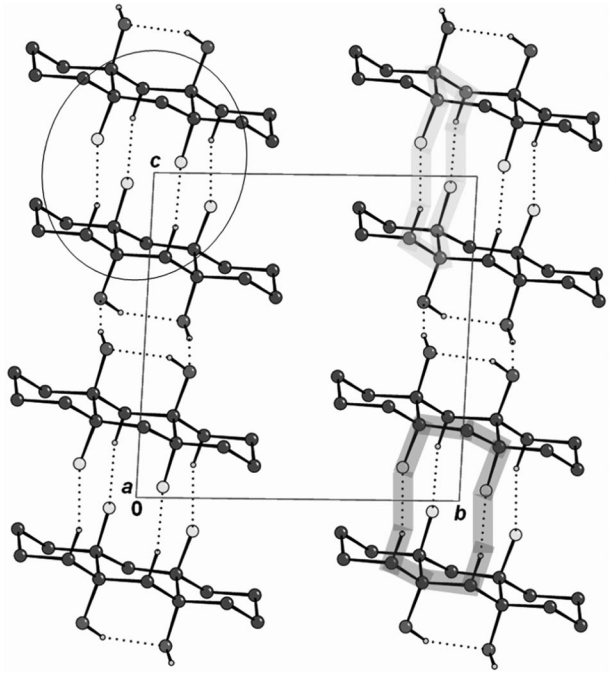


Figure 3. Molecular packing in the difluorodiol **2**, showing how each of the four intermolecular C–H···F hydrogen bonds formed a part of a $R^2_2(10)$ H-bonding motif. The centrosymmetric supramolecular recognition unit, involving the C–H···F hydrogen bonds, has been encircled. Non-interacting H atoms have been omitted for clarity.

Table 2. Hydrogen bond geometry in the difluorodiol **2**.[a,b]

D–H···A	D–H [Å]	H···A [Å]	D···A [Å]	D–H···A [°]
O1–H1OA···O2^{i}	0.81(2) [*0.938*]	2.04(2) [*1.914*]	2.834(1)	167(2) [*166.31*]
O1–H1OB···O2^{ii}	0.81(2) [*0.938*]	1.93(2) [*1.825*]	2.663(1)	149(2) [*147.19*]
O2–H2OA···O1^{i}	0.81(2) [*0.938*]	2.05(2) [*1.924*]	2.834(1)	164(2) [*162.94*]
O2–H2OB···O1^{ii}	0.81(1) [*0.938*]	1.92(2) [*1.812*]	2.663(1)	151(1) [*149.47*]
C2–H2B···F2^{iii}	0.97 [*1.080*]	2.53 [*2.431*]	3.409(1)	151 [*149.94*]
C5–H5A···F2^{iv}	0.97 [*1.080*]	2.62 [*2.521*]	3.499(1)	151 [*150.10*]
C7–H7B···F1^{iv}	0.97 [*1.080*]	2.58 [*2.483*]	3.483(1)	155 [*153.50*]
C14–H14B···F1^{iii}	0.97 [*1.080*]	2.51 [*2.409*]	3.398(1)	153 [*151.61*]

[a] Values in *italics* are those normalized following 1. ref.[28], 2. ref.[29] [b] Symmetry codes, i: –*x*, –*y*, –*z* + 1; ii: *x*, *y*, *z*; iii: –*x*, –*y*, –*z*; iv: –*x* + 1, –*y*, –*z*.

(b) Crystal Structure of the Difluorodiol 2: The crystal structure of the difluorodiol **2** was solved in the centrosymmetric triclinic space group $P\bar{1}$ (Z = 2) (Figure 2). As observed in case of the non-fluorinated tetrol **5**,[11c,11f] the hydroxy groups in **2** formed a $R^2_2(8)$ O–H···O H-bond motif to form hydrogen bonded molecular dimers.[18] These dimers are linked via four C–H···F hydrogen bonds to form zig-zag chains, growing essentially parallel to the *c* axis (Figure 3, Table 2). It was interesting to note that each of these four C–H···F hydrogen bonds formed a part of a $R^2_2(10)$ H-bonding motif[18] and thus, constituted a highly symmetric, three-dimensional centrosymmetric supramolecular recognition unit (Figure 3). Additional C–H···F interactions link the translationally related molecular chains along the *a* axis (Table 2).

(c) Crystal Structure of the Difluorohexol 3: The difluorohexol **3** crystallized as a monohydrate in the centrosymmetric triclinic space group $P\bar{1}$ (Z = 2). As observed in case of the monofluorinated **1**, all the four 1,3-syndiaxial hydroxyl groups at C4, C6, C8 and C10 in **3** participated in intramolecular hydrogen bonding (Figure 4, Table 3). No intramolecular O–H···F interactions were observed in **3** and the electrostatic repulsion between the parallel C–F and C–O bond dipoles could be discerned from the increase in the C–C–C bond angles on either side of the C–F bonds as noted in case of **1** [C1–C2–C3 = 114.36°; C1–C14–C13 = 114.19°; C11–C12–C13 = 114.26°]. Intermolecular O–H···O H-bonds linked two molecules of **3** and a pair of water molecules to form centrosymmetric molecular dimers, which were in turn connected via four C–H···F hydrogen bonds to form zig-zag chains, growing essentially parallel to the *b* axis. The translationally related molecular chains, thus formed, were linked to eachother along the *a* and *c* axis via O–H···O H-bonds (Figure 5, Table 3). Interestingly, the four C–H···F hydrogen bonds, observed in the crystal structure of **3**, defined the same centrosymmetric supramolecular recognition unit that was noted in case of **2**.

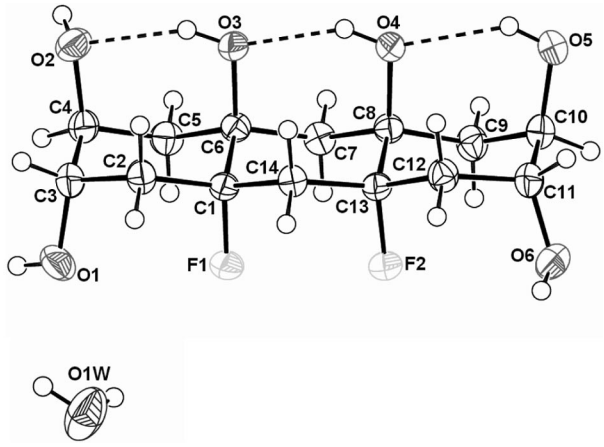


Figure 4. ORTEP diagram of the monohydrate of the difluorohexol **3**, with atom numbering scheme for the asymmetric unit. Displacement ellipsoids have been drawn at 50% probability level and H atoms are shown as small spheres of arbitary radii. The dotted lines indicate the intramolecular O–H···O hydrogen bonds.

Table 3. Hydrogen bond geometry in the difluorohexol **3**.[a,b]

D–H···A	D–H [Å]	H···A [Å]	D···A [Å]	D–H···A [°]
O1–H1O···O5^{i}	0.82 [*0.938*]	2.05 [*1.936*]	2.8614(14)	169 [*168.50*]
O2–H2O···O1W^{ii}	0.82 [*0.938*]	1.83 [*1.711*]	2.6492(18)	179 [*179.19*]
O3–H3O···O2^{iii}	0.82 [*0.938*]	1.94 [*1.834*]	2.6791(13)	150 [*148.45*]
O4–H4O···O3^{iii}	0.82 [*0.938*]	1.90 [*1.801*]	2.6232(13)	147 [*144.73*]
O5–H5O···O4^{iii}	0.82 [*0.938*]	2.02 [*1.936*]	2.6928(13)	139 [*136.28*]
O6–H6O···O1^{iv}	0.82 [*0.938*]	2.00 [*1.880*]	2.8096(17)	171 [*170.45*]
O1W–H1W···O1^{i}	0.81(2) [*0.938*]	1.96(2) [*1.834*]	2.7537(19)	167(2) [*166.13*]
O1W–H2W···O1^{i}	0.78(3) [*0.938*]	2.03(3) [*1.865*]	2.8018(18)	176(2) [*175.82*]
C7–H7B···F2^{v}	0.97 [*1.080*]	2.57 [*2.475*]	3.4726(16)	154 [*153.05*]
C9–H9B···F1^{v}	0.97 [*1.080*]	2.53 [*2.440*]	3.4055(17)	149 [*148.07*]

[a] Values in *italics* are those normalized following 1. ref.[28], 2. ref.[29] [b] Symmetry codes, i: *x*, *y*, *z* – 1; ii: *x*, *y* + 1, z; iii: *x*, *y*, *z*; iv: –*x*, –*y* + 1, –*z* + 2; v: –*x* + 1, –*y* + 1, –*z* + 2.

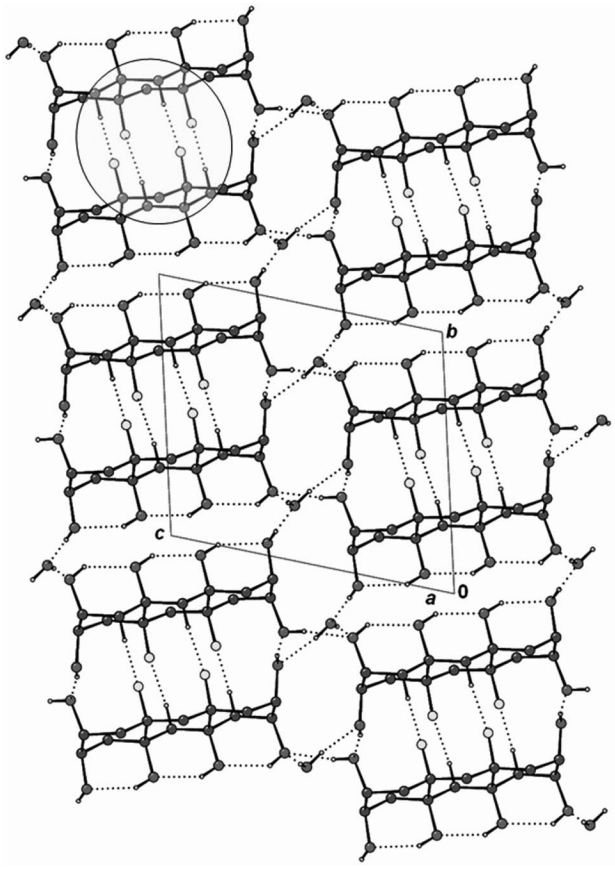


Figure 5. Molecular packing in the difluorohexol **3**. The centrosymmetric supramolecular recognition unit, involving the C–H···F hydrogen bonds, has been encircled (see Figure 3). Non-interacting H atoms have been omitted for clarity.

What Is the Role Played by Organic Fluorine in the Crystal Packing of the Fluorinated Polycyclitols 1–3?

Probing the possibility of observing the tenuous H···F interactions in crystal structures, laden with stronger O–H···O H-bonds, formed the primary objective of the present investigation. No O–H···F interactions, either intra- or inter, were observed in the crystal structures of **1**–**3**. As expected from any polyhydroxylated molecule, all the three fluorinated polycyclitols **1**–**3** strove to self-assemble in a manner that maximizes the O–H···O H-bonds possible. Indeed, the extensive O–H···O hydrogen bonding network in **1**–**3** involves all the donor oxygen atoms and might well appear to be sole interaction controlling the molecular packing in all the three fluorinated substrates under study. This premise holds true in the crystal structure of the monofluoropentol **1**, where the short H···F contacts result merely from the compressive forces induced by the intricate O–H···O H-bonding network.

In case of the difluorodiol **2**, however, a similar argument would be rendered untenable since the supramolecular assembly itself completely sequesters the fluoro and hydroxy groups from each other. By employing as many O–H···O and C–H···F H-bonds as possible, molecular packing in **2** and even in the hexahydroxylated **3** portrays an interesting adjustment to fulfil the principle of maximum hydrogen bonding.[19] Though aliphatic, the methylene hydrogens, acting as donors for the C–H···F H-bonds in **2** and **3**, are quite polarized owing to the electron withdrawing nature of the neighbouring OH and F substituents. The acidic nature of the C–H donors is particularly noticeable in the strength of the four C–H···F H-bonds that form the three-dimensional centrosymmetric supramolecular recognition unit in both **2** and **3**. It is pertinent to mention at this point that the clustering of fluoroalkyl substituents, as noted in the crystal structures of **2** and **3**, has been observed even in aggregates of fluorinated peptides and other fluorine based materials, and has been suggested to lend increased stability to the supramolecular assembly.[6b] In the self-assemblies of the difluorinated polycyclitols **2** and **3**, this enhanced stability might be contributed by the antiparallel arrangement of the C–F dipoles in the common centrosymmetric C–H···F recognition unit.

Conclusions

In conclusion, the present study reveals that covalently bonded fluorine, with appropriate substrate design, can form C(sp^3)–F···H–C(sp^3) hydrogen bonds even in the presence of stronger O–H···O H-bonds. Taken individually, C–F···H interactions are very weak. However, the cumulative stabilization provided by a multitude of co-operative C–F···H interactions would cause the self-assembling process to adjust itself to enable their inclusion, along with the stronger hydrogen bonds, in the molecular packing. This premise hold true for any weak non-covalent interaction and embodies the principle of hydrogen bond maximization.

Experimental Section

Synthesis

a) 8a-Fluoro-1,4,4a,5,8,8a-hexahydro-4a-naphthalenol (7): Pyridine-poly(hydrogen fluoride) (0.5 mL, 27.5 mmol) was added to a solution of the epoxide **6** (300 mg, 2.027 mmol) in 2 mL of dry THF at 0 °C. The reaction was allowed to proceed for 12 h at ambient temperature. The mixture was then quenched with saturated $NaHCO_3$ solution. The product was extracted with ethyl acetate (3 × 30 mL); the combined extracts were washed with brine and then dried with anhydrous sodium sulfate. Removal of solvent and subsequent column chromatography over silica gel using 15% EtOAc/petroleum ether afforded the fluorohydrin **7** (330 mg, 97%) as a pale yellow liquid. IR (thin film): $\tilde{\nu}$ = 3462, 3031, 2907, 1038, 1001, 879, 847, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 22 °C): δ = 5.71–5.63 (m, 4 H), 2.46–2.38 (m, 6 H), 2.20 (d, J = 18 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ = 124.1 (2 C), 123.8 (2 C), 92.7 (d, J = 172 Hz), 68.5 (d, J = 29 Hz), 36.3 (2 C), 34.4 (d, J = 23 Hz, 2 C) ppm. HRMS (ES) m/z calcd. for $C_{10}H_{13}FONa$ $[M + Na]^+$: 191.0848; found 191.0853.

b) 8a-Fluoroperhydro-2,3,4a,6,7-naphthalenepentaol (1): mCPBA (499 mg, 2.025 mmol, 70% purity) was added to a solution of the fluorohydrin **7** (162 mg, 0.9643 mmol) in dichloromethane (10 mL)

at 0 °C. The reaction was stirred at room temperature for 1 h and then quenched by addition of a saturated $NaHCO_3$ solution. The product was extracted with dichloromethane (3 × 20 mL); the combined extracts were washed successively with saturated $NaHCO_3$ solution and brine, and then dried with anhydrous sodium sulfate. Removal of the solvent and subsequent purification by column chromatography over silica gel with 60% EtOAc/petroleum ether furnished **8** as a diastereomeric mixture (151 mg, 78% overall).

The subsequent hydrolytic reaction was carried out with this mixture of the diepoxide **8**. Thus, a 10% solution of acetic acid in water (3 mL) was added to a solution of **8** (130 mg, 0.650 mmol) in THF (5 mL). The homogeneous mixture was kept at 50–60 °C for 3 d. The volatiles were then removed completely under vacuum; subsequent recrystallization of the crude product, thus obtained, from 1:3 methanol/ethyl acetate furnished the pure fluoropentol **1** (115 mg, 75%) as colorless crystals; m.p. 180.0–180.2 °C. IR (KBr): $\tilde{\nu}$ = 3367, 2928, 2910, 1431, 1084, 1007, 847, 832 cm^{-1}. ^1H NMR (400 MHz, D_2O, 22 °C): δ = 3.75 (brs, 4 H), 2.06 (ddd, J = 46, 16, 4 Hz, 2 H), 1.86 (td, J = 15, 3 Hz, 2 H), 1.69 (dd, J = 16, 9 Hz, 2 H), 1.52 (d, J = 15 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, D_2O, 22 °C): δ = 99.9 (d, J = 170 Hz), 75.3 (d, J = 27 Hz), 73.2 (2 C), 72.2 (2 C), 35.8 (2 C), 35.3 (d, J = 19 Hz, 2 C) ppm. ^{19}F NMR (376 MHz, D_2O): δ = –155.6 ppm. HRMS (ES) m/z calcd. for $C_{10}H_{17}FO_5Na$ $[M + Na]^+$: 259.0958; found 259.0955.

c) 8a,9a-Difluoro-1,4,4a,5,8,8a,9,9a,10,10a-decahydro-4a,10a-anthracenediol (10): The unsaturated difluorodiol **10** was obtained from **9**, following the HF/pyridine-mediated epoxide ring opening strategy adopted in the preparation of **7**. Thus, a solution of the *syn*-diepoxide **9** (30 mg, 0.139 mmol) in 1 mL of dry THF was treated with pyridine/poly(hydrogen fluoride) (0.5 mL, 27.5 mmol) at 0 °C. The reaction was allowed to proceed for 22 h at ambient temperature. The mixture was then quenched with saturated $NaHCO_3$ solution. The product was extracted with ethyl acetate (3 × 20 mL); the combined extracts were washed with brine and then dried with anhydrous sodium sulfate. Removal of solvent and subsequent column chromatography over silica gel using 30% EtOAc/petroleum ether afforded **10** (28 mg, 78%) as a colorless crystalline solid; m.p. 173.0–173.3 °C. IR (thin film): $\tilde{\nu}$ = 3238, 3031, 2916, 1644, 1442, 1225, 1073, 1064, 873, 659 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 22 °C): δ = 5.69–5.61 (m, 4 H), 3.84 (s, 2 H), 2.49–2.05 (m, 10 H), 1.73 (d, J = 15 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 22 °C): δ = 123.3 (2 C), 123.2 (2 C), 93.2 (dd, J = 182, 4 Hz, 2 C), 70.9 (dd, J = 15, 12 Hz, 2 C), 38.8, 37.2 (t, J = 20 Hz), 35.9 (2 C), 33.9 (dd, J = 13, 11 Hz, 2 C) ppm. ^{19}F NMR (376 MHz, CD_3Cl): δ = –159.9 ppm. HRMS (ES) m/z calcd. for $C_{14}H_{18}F_2O_2Na$ $[M + Na]^+$: 279.1173; found 279.1174.

d) 8a,9a-Difluoroperhydro-4a,10a-anthracenediol (2): A heterogeneous mixture of the unsaturated difluorodiol **10** (22 mg, 0.078 mmol) and Pd/C (10 mg, 10% w/w) in ethyl acetate (2 mL) was hydrogenated under 1 Torr pressure for 2 h. After the disappearance of the starting material, as indicated by TLC analysis, the reaction mixture was filtered through a small pad of Celite and washed with ethyl acetate. The combined filtrate and washings were concentrated under vacuum; the residue was purified by column chromatography over silica gel using 30% EtOAc/petroleum ether to afford **2** (22 mg, 98%) as a colorless, highly crystalline solid; m.p. 212.1–212.2 °C. IR (KBr): $\tilde{\nu}$ = 3295, 2939, 2866, 1445, 1172, 1038, 890, 824 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 22 °C): δ = 4.18 (s, 2 H), 2.21–1.25 (m, 20 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 22 °C): δ = 94.9 (dd, J = 185, 9 Hz, 2 C), 72.7 (dd appearing as a t, J = 14 Hz, 2 C), 40.7, 38.1 (t, J = 20 Hz), 33.7 (2 C), 31.4 (dd, J = 12, 11 Hz, 2 C), 19.9 (2 C), 19.3 (2 C) ppm. ^{19}F NMR (376 MHz, CD_3Cl): δ = –162.5 ppm. HRMS (ES) m/z calcd. for $C_{14}H_{22}F_2O_2Na$ $[M + Na]^+$: 283.1486; found 283.1483.

e) 8a,9a-Difluoroperhydro-2,3,4a,6,7,10a-anthracenehexaol (3): mCPBA (30 mg, 0.1228 mmol, 70% purity) was added to a solution of the difluorodiol **10** (15 mg, 0.059 mmol) in dichloromethane (1 mL) at 0 °C. The reaction was stirred at room temperature for 12 h and then quenched by addition of a saturated $NaHCO_3$ solution. The product was extracted with dichloromethane (3 × 20 mL) and the combined extracts dried with anhydrous sodium sulfate. Removal of the solvent and subsequent purification by column chromatography over silica gel with 80% EtOAc/petroleum ether furnished **11** as a diastereomeric mixture (16 mg, 95% overall).

The subsequent hydrolytic reaction was carried out with this mixture of the diepoxide **11**. Thus, a 10% solution of acetic acid in water (1 mL) was added to a solution of **11** (10 mg, 0.035 mmol) in THF (2 mL). The homogeneous mixture was kept at 50–60 °C for 3 d. The volatiles were then removed completely under vacuum to furnish the essentially pure difluorohexol **3** (11 mg, 99%) as a white powder; m.p. 262.2–262.5 °C (decomposition before melting). IR (KBr): $\tilde{\nu}$ = 3366, 2934, 1450, 1097 cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO, 22 °C): δ = 3.71 (brs, 4 H), 2.22–1.36 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO, 22 °C): δ = 96.3 (dd, J = 188, 9 Hz, 2 C), 74.8 (dd appearing as a t, J = 14 Hz, 2 C), 71.5 (2 C), 69.8 (2 C), 38.4 (t, J = 19 Hz), 34.9 (d, J = 16 Hz, 2 C), 34.9 (2 C) ppm. ^{19}F NMR (376 MHz, CD_3Cl): δ = –155.4 ppm. HRMS (ES) m/z calcd. for $C_{14}H_{22}F_2O_6Na$ $[M + Na]^+$: 347.1282; found 347.1289.

X-ray Crystallography

Single-crystal X-ray diffraction data (Table 4) was collected at 291 K on a Bruker AXS SMART APEX CCD diffractometer using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The X-ray generator was operated at 50 KV and 35 mA. The data was collected with a ω scan width of 0.3°. A total of 606 frames per set were collected using SMART[20] in three different settings of ϕ (0°, 90° and 180°), keeping the sample to detector distance of 6.03 cm and the 2θ value fixed at –28°. The data were reduced by SAINTPLUS;[20] an empirical absorption correction was applied using the package SADABS[21] and XPREP[20] was used to determine the space group. The crystal structure was solved by direct methods using SIR92[22] and refined by full-matrix least-squares method on F^2 using SHELXL97.[23] Molecular and packing diagrams were generated using ORTEP-3[24] and CAMERON[25] respectively. The geometric calculations were done by PARST[26] and PLATON.[27] All hydrogen atoms were initially located in a difference Fourier map. The methine (CH) and methylene (CH_2) H atoms were then placed in geometrically idealized positions and allowed to ride on their parent atoms with C–H distances in the range 0.97–0.98 Å and $U_{iso}(H) = 1.2U_{eq}(C)$. The OH hydrogen atoms were constrained to an ideal geometry with O–H distances fixed at 0.82 Å and $U_{iso}(H) = 1.5U_{eq}(O)$. During refinement, each hydroxy group was, however, allowed to rotate freely about its C–C or C–O bond respectively. The hydrogen atoms of the hydroxy groups in case of the diflurodiol **2** and the water molecule in case of the difluorohexol **3**, were located in a difference Fourier map and their positions were refined freely, along with an isotropic displacement parameter.

CCDC-752011 (for monofluoropentol **1**), -752012 (for difluorodiol **2**) and -752013 (for difluorohexol **3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 4. Summary of crystal data, data collection, structure solution and refinement details.

	1	2	3
Formula	$C_{10}H_{17}FO_5$	$C_{14}H_{22}F_2O_2$	$C_{14}H_{22}F_2O_6{\cdot}H_2O$
M_r	236.24	260.32	342.33
Crystal size [mm]	0.25, 0.13, 0.12	0.20, 0.14, 0.13	0.43, 0.28, 0.05
Crystal system	orthorhombic	triclinic	triclinic
Space group	$Pna2_1$	$P\bar{1}$	$P\bar{1}$
a [Å]	22.0343(19)	6.8917(2)	6.9018(5)
b [Å]	7.6562(6)	9.7719(2)	10.3898(6)
c [Å]	6.0938(4)	9.7806(2)	11.3586(7)
α [°]	90	87.394(1)	74.425(3)
β [°]	90	89.035(1)	81.758(4)
γ [°]	90	85.180(1)	77.486(3)
V [Å^3]	1028.02(14)	655.61(3)	762.81(9)
Z	4	2	2
F (000)	504	280	364
ρ_{calc} [g cm^{-3}]	1.526	1.319	1.490
μ [mm^{-1}]	0.132	0.105	0.133
Reflections collected	6338	10349	11481
Least-squares parameters	150	180	222
Unique reflections	1146	2697	2987
Observed reflections	903	2038	2390
Index range	$-27 \le h \le 27$	$-8 \le h \le 8$	$-8 \le h \le 8$
	$-9 \le k \le 8$	$-12 \le k \le 12$	$-12 \le k \le 12$
	$-7 \le l \le 6$	$-12 \le l \le 12$	$-13 \le l \le 14$
R_1 [$I > 2\sigma(I)$]	0.0348	0.0356	0.0347
wR_2 [$I > 2\sigma(I)$]	0.0789	0.1064	0.0992
Goodness of fit	1.043	1.073	1.036
$\Delta\rho_{max/min}$ [e Å^{-3}]	0.145/–0.162	0.248/–0.187	0.342/–0.177

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