Hydrogen Bonding

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Intramolecular OH···FC Hydrogen Bonding in Fluorinated Carbohydrates: CHF is a Better Hydrogen Bond Acceptor than CF_2**

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Hydrogen bonds (H-bonds) are well-appreciated key interactions, playing a major role in stabilizing tertiary structures of peptides and nucleic acids, and being involved in molecular recognition. Still, an official definition of the hydrogen bond was only recently published by the IUPAC.[1] Fluoroorganic compounds are widely used in materials, pharmaceuticals, and agrochemicals, but the extent to which organofluorines can act as hydrogen bond acceptor and how the proximal substituents affect this interaction is still actively researched and debated. A recent review of Schneider summarizes the current knowledge about X–H···F–C H-bonds (X = O, N, S, and C) and describes the methods used to experimentally identify factors influencing this weak interactions.[2] X–H···F–C H-bonds are best assigned by X-ray diffraction in the solid state, by computational methods in the gas phase, and by IR and NMR spectroscopy in the liquid phase. They prefer to be linear, with the bending of intramolecular H-bonds leading to a decrease of the stabilization (e.g. 14 kJ mol^{-1} for a linear[3] and 5 kJ mol^{-1} for a bent O–H···F H-bond in a five-membered ring[4]). The strong interest on XH···F H-bonds is evidenced by a recent IR investigation of the intramolecular OH···F H-bonding in fluorinated anancomeric cyclohexanols[5] and by the detection of intermolecular XH···F (X = O or N) H-bonds by ^{19}F NMR spectroscopy in complexes of fluorinated agents with enzymes.[6]

Dunitz and Taylor with their paper titled "Organic Fluorine Hardly Ever Makes Hydrogen Bonds" initiated an ongoing debate about X–H···F–C H-bonds.[7] This statement is correct for the solid state where alcohols prefer to form bands of co-operative intermolecular OH···OH H-bonds.[8] Examination of the Cambridge Structural Database revealed that only 0.6% of all CF groups are engaged as H-bond acceptors of X–H (X = N or O).[7,9] A Protein Database search, however, suggests that approximately 10% of all CF groups may be involved in intermolecular H-bonding,[10] an observation reflecting the high importance of H-bonding in protein–ligand interactions. The two classes of compounds that form X–H···F–C H-bonds in the solid state are fluorinated sterically crowded tertiary alcohols and fluorinated polyols. The bulky substituents of the former class prevent the formation of co-operative intermolecular OH···OH H-bonds and favor the formation of dimers through O–H···F–C H-bonds[11] or of monomers possessing an isolated intramolecular O–H···F–C H-bond.[12] Fluorinated polyols have the capacity to form both co-operative intermolecular OH···OH H-bonds and bifurcated or tetravalent H-bonds with O- and F-substituents as H-bond acceptors.[13]

Understanding the structure and properties of the increasing number of newly designed fluorinated agents requests a detailed investigation of the intra- and intermolecular interactions of organofluoro compounds. In solution, X–H···F–C H-bonds are formed in apolar environments in the absence of stronger competing H-bond acceptors. Intramolecular X–H···F H-bonds are observed in apolar solvents (like $CDCl_3$ and C_6D_6) and are replaced in polar solvents by intermolecular H-bonds to the solvent.[14,15]

Scalar coupling between XH and F (^{1h}J(XH,F[16])) in the ^{1}H NMR spectra is useful for the detection of X–H···F–C H-bonds. The size of this coupling roughly reflects the strength of the H···F H-bond. It decreases from 530 Hz for gaseous HF to < 4 Hz for C–H···F–C H-bonds and close contacts between C–H and F as observed for example in 2-fluorotoluene.[14] Most X–H···F–C H-bonds (X = O,[17,18] N,[19,20] or S[18a]) show ^{1h}J(XH,F) couplings of 5–12 Hz. The precise orientation of X–H of primary and secondary XH groups may be deduced from the vicinal ^3J(H,XH) couplings. Cyclic carbohydrates, especially rigid pyranosides, are ideal for the investigation of O–H···F H-bonds; they allow access to epimers with the desired orientation of the F and the secondary OH substituents. Since OH groups of carbohydrates show maximal ^3J(H,OH) couplings to antiperiplanar CH of 12–12.5 Hz,[15a] the Karplus equation of Fraser et al.[21] (J_{180} = 12.1 Hz) is considered in preference to the more recent equation of Serianni and co-workers[22] (J_{180} = 14.6 Hz). Vasella, Bernet, and co-workers investigated the intramolecular O–H···F–C H-bonds of fluorinated *myo*-inositols (**1**[23] and **2**[24]) and levoglucosans (**3**–**6**)[14] in $CDCl_3$ (Figure 1). The combined analysis of the ^{1h}J(OH,F) and ^3J(H,OH) couplings evidenced divalent H-bonds in **1**, **2**, and **6** and trivalent (so-called bifurcated) H-bonds in **3**–**5**. Bifurcated H-bonds were also observed in α-L-talopyranoside **7** (R = daunomycinon-7-yl)[25] and in β-L-ribopyranoside **8.**[26]

Herein, we investigate the intramolecular H-bonding of pyranosides possessing 1,3-diaxial fluoro and hydroxy substituents and evaluate the influence of the nature and the

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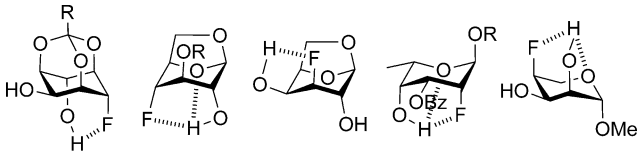
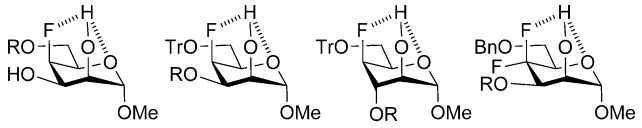


1 R = H
2 R = *n*Bu
3 R = H
4 R = Si(*i*Pr)$_3$
5 R = Ac
6
7
8

Figure 1. Intramolecular O–H···F–C H-bonds of carbohydrates in $CDCl_3$ solution.

orientation of the vicinal O-substituent. Replacement of the CHF group by a CF_2 group served to probe the different H-accepting properties of these two moieties.

The 4,4-difluoro-α-D/L-*lyxo*-hexopyranosides D/L-**15** and D/L-**16**[27] are well-suited to investigate OH···F H-bonds (Figure 2). For studying the effect of the O-substituent at C3, the 4-monofluorinated analogs, the 4-fluoro-α-D-talopyranosides **9**–**12**, and the 4-fluoro-α-D-idopyranosides **13** and **14** were prepared.[28] Here, we describe the results of the H-bonding analysis of these fluorinated compounds by ^1H and ^{19}F NMR spectroscopy.



9 R = Piv
10 R = Tr
11 R = Ac
12 R = Tf
13 R = H
14 R = Ac
D/L-**15** R = H
D/L-**16** R = Tf

Figure 2. Intramolecular bifurcated H-bonds of HO-2 to F and O5 in 4-fluoro- and 4,4-difluorohexopyranosides.

In apolar solvents, HO-2 of the monofluorinated **9**–**14** and of the difluorinated D/L-**15** and D/L-**16** forms a bifurcated H-bond to the axial F atom and to O5 (Figure 3). The torsion angle H-C2-O-H may vary from 210° (OH···F H-bond) to 150° (OH···O5 H-bond). Whereas ^{1h}J(OH,F) decreases upon decrease of torsion angle, ^3J(H,OH) increases from both extreme conformations and reaches the maximal value at H-C2-O-H torsion angle of 180° when a symmetric bifurcated H-bond is formed.

Solutions (about 0.025 M) of the monofluoro compounds **9**–**14** and the difluoro compounds D/L-**15** and D/L-**16** in a range of polar and apolar solvents were analyzed by measuring F-coupled and F-decoupled ^1H NMR spectra and ^{19}F NMR spectra to assign ^{1h}J(OH,F), ^3J(2,OH), and ^3J(3,OH)

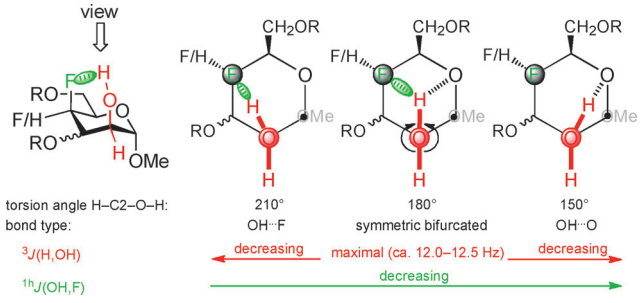
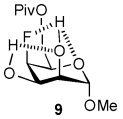
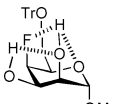
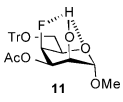
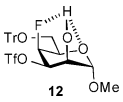
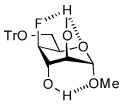
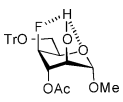
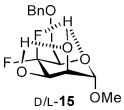
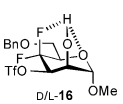


Figure 3. The range of bifurcated H-bond of HO-2 to F and O5 in 4-fluoro- and 4,4-difluorohexopyranosides.

couplings unambiguously (Table 1). The large ^3J(2,OH) values of all compounds (> 10.8 Hz for **9**–**13**; 9.2–10.5 Hz for **14** and D/L-**15**–**16** in [D_8]toluene and $CDCl_3$ evidence intramolecular H-bonds of HO-2. In [D_6]DMSO, the intramolecular H-bond is mostly replaced by an intermolecular H-bond to the solvent as evidenced by ^3J(2,OH) = 4.5–5.6 Hz (typical for a completely solvated OH group[15]) and ^{1h}J(OH,F) ≤ 1.1 Hz. Intermediate ^3J(2,OH) values in CD_3CN, [D_8]THF, and [D_6]acetone reveal the existence of intra- and intermolecularly H-bonded species. Noteworthy is the strong H-bond of HO-3 to HO-2 of the diols **9**, **10**, and D/L-**15**

Table 1: ^1H NMR ^{1h}J(2-OH,F), ^3J(2,OH), and ^3J(3,OH) coupling constants [Hz] of **9**–D/L-**16**. The pictures reflect the intramolecular H-bonds in apolar solvents.

Structure	Solvent	^{1h}J(2-OH,F)[a]	^3J(2,OH)	^3J(3,OH)
 **9**	[D_8]toluene	8.4 (8.4)	12.2	11.3
	$CDCl_3$	8.1 (8.0)	12.0	10.8
	CD_3CN	4.3	8.0	9.2
	[D_8]THF	4.6 (4.6)	8.6	10.0
	[D_6]DMSO	1.0	4.8	7.8
 **10**	[D_8]toluene	9.1 (9.2)	12.1	10.9
	$CDCl_3$	9.1 (8.7)	12.1	11.2
	[D_8]THF	5.6 (5.8)	9.3	10.0
	[D_6]acetone	5.2 (5.0)	8.1	9.3
	[D_6]DMSO	0.9 (0)	4.8	7.8
 **11**	[D_8]toluene	11.4 (11.4)	11.4	
	$CDCl_3$	10.8 (10.8)	10.8	
	CD_3CN	5.3 (5.1)	8.0	
	[D_8]THF	5.3 (5.5)	9.2	
	[D_6]DMSO	0 (0)	5.4	
 **12**	[D_8]toluene	10.0 (10.1)	11.8	
	$CDCl_3$	10.5 (10.4)	11.6	
	CD_3CN	3.1	8.4	
	[D_8]THF	3.3 (3.0)	9.1	
	[D_6]DMSO	< 1.5 (br. s)	br. s	
 **13**	[D_8]toluene	9.3 (8.1)	11.4	9.7
	$CDCl_3$	9.8 (9.6)	11.7	10.0
	CD_3CN	br.	6.2	[b]
	[D_8]THF	1.0	6.2	5.1
	[D_6]DMSO	0 (0)	5.0	5.0
 **14**	[D_8]toluene	4.7 (4.7)	10.2	
	$CDCl_3$	5.7 (5.6)	10.5	
	CD_3CN	0 (0)	6.2	
	[D_8]THF	0.8	6.9	
	[D_6]DMSO	0 (0)	5.6	
 D/L-**15**	[D_8]toluene	< 1.5 (0)	9.2	10.4
	$CDCl_3$	< 1.5 (0)	9.7	10.4
	[D_8]THF	0 (0)	6.2	9.2
	[D_6]DMSO	0 (0)	4.7	7.9
 D/L-**16**	[D_8]toluene	3.2	9.6	
	$CDCl_3$	4.2	10.2	
	CD_3CN	0 (0)	6.7	
	[D_8]THF	0 (0)	6.7	
	[D_6]acetone	0 (0)	6.3	
	[D_6]DMSO	0 (0)	5.5	

[a] Values from ^{19}F NMR spectra in parenthesis. [b] Not assigned.

persisting to about 50% even in [D$_6$]DMSO (^3J(3,OH) = 7.8–7.9 Hz) and revealing co-operative intra- and intermolecular O(3)–H···O(2)–H···O = SMe$_2$ H-bonds.

All three coupling constants of **10** in $CDCl_3$ are slightly larger than those of the parent compound **8** (Δ^3J(H,OH) = 0.6–0.7 Hz, $\Delta^{1h}J$(OH,F) = 1.6 Hz) probably because of the stabilization of the $^4C_1$ conformation imposed by the trityloxymethyl substituent. The data assembled for **9** and **10** indicate that the protecting group of HO-6 has no influence on ^3J(2,OH) and very little impact on ^{1h}J(OH,F) (ca. 0.8 Hz reduction with the more polar pivaloyl group). The large ^3J(2,OH) values (12.0–12.2 Hz) of **9** and **10** in [D$_8$]toluene and $CDCl_3$ are consistent with an antiperiplanar arrangement of the C2–H and O–H bonds and therefore with a symmetric bifurcated H-bond ($\theta_{H\text{-}C2\text{-}O\text{-}H} \approx 180°$). Protection of HO-3 by an acetyl (**11**) or a triflyl group (**12**) led to a slight reduction of ^3J(2,OH) (10.8–11.8 Hz) and an increase of ^{1h}J(OH,F) (10.0–11.4 Hz, ΔJ = 0.9–2.3 Hz). This reveals an asymmetric bifurcated H-bond with a shorter OH···F distance ($\theta_{H\text{-}C2\text{-}O\text{-}H}$ = 190–200°). As anticipated, the different protection of HO-3 has a negligible influence on the H-accepting capacity of F-4, since RO-3 and F-4 are synclinal causing a poor overlap of the $\sigma_{C\text{-}O}$ and $\sigma^*_{C\text{-}F}$ orbitals. The difference in the intramolecular H-bonding of the diols **9** and **10** and the monoalcohols **11** and **12** in aprotic solvents is rationalized by the formation of a co-operative intramolecular O(3)–H···O(2)–H···F-4/O-5 H-bond (^3J(3,OH) = 11.0–11.3 Hz, $\theta_{H\text{-}C3\text{-}O\text{-}H}$ = 160–165°) in the diols. This O(3)–H···O(2) H-bond entails a restriction of the rotational freedom of HO-2. Modeling of **9** suggests a highly unlikely H···O2–H bond angle of 64° with F acting as the sole H-bond acceptor, and a more likely bond angle of 94° correlating well with the experimentally preferred symmetric bifurcated H-bond.

In their H-bond analysis of levoglucosans **3**–**5**, Bernet and Vasella observed that the electron-withdrawing nature of an antiperiplanar OR substituent affects the H-accepting properties of the F atom.[14] Thus, the antiperiplanar orientation of the C–F and C3–OR bonds in the α-D-idopyranosides **13** and **14** should allow an optimal overlap of the $\sigma_{C\text{-}O}$ and $\sigma^*_{C\text{–}F}$ bonds; hence, F of these idopyranosides, especially of diol **13** with an electron-rich O-substituent (partial deprotonation because of the intramolecular H-bond to the methoxy group), should be a good H-bond acceptor.[29]

The intramolecular H-bonds of **13** and **14** in [D$_8$]toluene and $CDCl_3$ are mostly replaced in CD_3CN and [D$_8$]THF by intermolecular H-bonds to the solvent and completely so in [D$_6$]DMSO. In the absence of intramolecular H-bonds, **13** and **14** adopt an $^OS_2$ skew boat conformation which is characteristic for protected idopyranosides.[30] The intramolecular H-bond is responsible for the $^4C_1$ conformation of **13** and **14** in apolar solvents. The ^3J(2,OH) values of **13** in [D$_8$]toluene and $CDCl_3$ (11.4 and 11.7 Hz) correspond to a torsion angle $\theta_{H\text{-}C2\text{-}O\text{-}H} \approx \pm 167°$. The slightly larger ^{1h}J(OH,F) of **13** versus epimer **10** (ΔJ = 0.2–0.7 Hz) reveals that F of **13** is a stronger H-bond acceptor than O5 ($\theta_{H\text{-}C2\text{-}OH.} \approx 193°$). The ^3J(3,OH) values of **13** (9.7 and 10.0 Hz) correspond to a torsion angle $\theta_{H\text{-}C3\text{-}O\text{-}H}$ = 150° evidencing an intramolecular O(3)–H···OMe H-bond. The strongly reduced ^{1h}J(OH,F) values of the acetate **14** in [D$_8$]toluene and $CDCl_3$ (4.9 and 5.7 Hz) inform that F is the weaker H-acceptor of the bifurcated H-bond. However, ^3J(2,OH) of 10.3 and 10.5 Hz corresponds to a torsion angle $\theta_{H\text{-}C2\text{-}O\text{-}H} \approx 157°$ suggesting a H-bond exclusively to O5; this highlights the limits of the Karplus equation of Fraser et al.[21]

Recently, a significant shielding of ^{19}F of organofluoro compounds engaged in intermolecular H-bonding interactions with enzymes has been postulated.[6] However, we could not detect any influence on the chemical shift of ^{19}F of the talopyranosides **9**–**12** and the *lyxo*-hexopyranosides D/L-**15** and D/L-**16** upon replacement of the bifurcated intramolecular H-bond observed in [D$_8$]toluene and $CDCl_3$ by an intermolecular H-bond to the solvent in [D$_6$]DMSO ($\Delta\delta \leq 1.4$ ppm). The larger $\Delta\delta$ values (2.2–3.9 ppm) for the idopyranosides **13** and **14** are attributed to the change of the conformation from $^4C_1$ in the apolar solvents to $^OS_2$ in [D$_6$]DMSO.

A comparison of the 4,4-difluorohexosides D/L-**15** and D/L-**16** with the corresponding 4-fluorotalosides **10** and **12** in [D$_8$]toluene and $CDCl_3$ shows a significant decrease of ^3J(2,OH) (9.2–10.2 Hz, ΔJ = 1.4–2.9 Hz) and a strong decrease of ^{1h}J(OH,F) (< 1.5 for D/L-**15** and 3.2–4.2 of D/L-**16**, $\Delta J \geq 6.3$ Hz). The values of D/L-**15** and D/L-**16** are consistent with an asymmetric bifurcated H-bond of HO-2 with O5 as the dominant H-bond acceptor. These results provide experimental evidences that CF_2 is a weaker H-bond acceptor than CHF as already postulated by calculation (CH_2F_2 is a 0.8 kJ mol^{-1} weaker H-bond acceptor than CH_3F[2]).

The H-bonding of **10**–D/L-**16** was investigated by DFT calculations (B3LYP function, and 6-31-G* basis set) using the program Spartan 08 on Macintosh.[31] These calculations were carried out on the parent *gt*-configured O6-benzyl ethers **10B**, **11B**, **12B**, **13B**, and **14B**, and on D-**15** and D-**16**. Energy profiles were calculated by varying the torsion angle $\theta_{H\text{-}C2\text{-}O\text{-}H}$ from 150 to 210° in 10° steps (Figure 4). As anticipated, the different protection of the acetate **11B** (minimum at 190°) and the triflate **12B** (minimum at 188°; graph not shown in Figure 4) only had a negligible influence upon the energy profile. To determine the limiting torsion angle $\theta_{H\text{-}C2\text{-}O\text{-}H}$, the

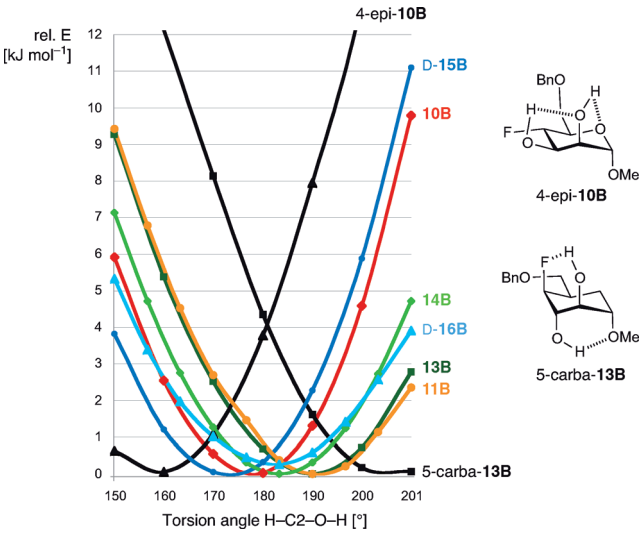


Figure 4. DFT calculated energy profiles for the intramolecular H-bonding of HO-2 of 4-fluoro- and 4,4-difluoro-α-D-hexopyranosides.

energy profiles of 5-carba-**13B** and 4-epi-**10B**, which exclusively form an intramolecular 2-OH···F-4 ($\theta_{H\text{-}C2\text{-}O\text{-}H} = 206°$) and 2-OH···O-5 H-bond ($\theta_{H\text{-}C2\text{-}O\text{-}H} = 158°$), were also calculated. The energy profiles corroborate with the experimental results: firstly, F of the monofluorinated **10B**, **11B**, and **12B** is a better H-acceptor than F of the difluorinated D-**15** and D-**16**, respectively; secondly, F of the 3-O-protected and D-*talo*-configured **11B**, **12B**, and D-**16** is a better H-acceptor than F of the corresponding diols **10B** and D-**15**, respectively; finally, F of the D-*ido*-configured diol **13B** is a better H-acceptor than F of the corresponding acetate **14B**.

The lowest-energy structures of the above energy profiles were further optimized and the calculated torsion angles $\theta_{H\text{-}C2\text{-}O\text{-}H}$ determined from the resulting minimum structures and compared with the corresponding experimental torsion angles calculated from ^3J(2,OH) in $CDCl_3$ solutions using the Karplus equation of Fraser et al.[21] (Table 2). The experimental and calculated data coincide well for diols **10** and **13**. The experimental $\theta_{H\text{-}C2\text{-}O\text{-}H}$ values suggest the F atom as the only H-acceptor for the acetate **11** and the triflate D-**16**, and O5 for the acetate **14** and the difluoride D-**15**. In contrast, the calculated $\theta_{H\text{-}C2\text{-}O\text{-}H}$ values hint at bifurcated H-bonds in the θ range of 173–190°. Proximal polar substituents lead to the reduction of geminal and vicinal coupling constants.[32] The reduction due to OH groups is already included in Fraser's Karplus equation, but the electron-withdrawing AcO and TfO, and the additional equatorial fluoro substituent of the above compounds should lead to an additional reduction of ^3J(2,OH). This prevents the applicability of Fraser's Karplus equation to **11**, **14**, D-**15**, and D-**16**; an analogous generalization as done in Altona's generalized Karplus equation for $^3J_{HCCH}$[33] would be required. Corrected $\theta_{H\text{-}C2\text{-}O\text{-}H}$ values (Table 2) were obtained by assuming a bona fide reduction of 1 Hz for each additional polar substituent (one in **11**, **14** and D/L-**15**; two in D/L-**16**). These corrected values fit well with the calculated values suggesting that the DFT calculations correctly predict the H-accepting properties of these 4-fluorinated hexopyranosides.

Table 2: Comparison of the experimental $\theta_{H\text{-}C2\text{-}O\text{-}H}$ values from $CDCl_3$ solution with the calculated ones from modeling.

Structure	**10**	**11**	**13**	**14**	D/L-**15**	D/L-**16**
^3J(2,OH) [Hz]	12.1	10.8	11.7	10.5	10.6	10.1
Exp. $\theta_{H\text{-}C2\text{-}O\text{-}H}$ [°]	180	200	191	158	159	205
Corr. $\theta_{H\text{-}C2\text{-}O\text{-}H}$ [°][a]		189		193	168	180
Structure	**10B**	**11B**	**13B**	**14B**	D-**15**	D-**16**
Calc. $\theta_{H\text{-}C2\text{-}O\text{-}H}$ [°]	178	190[b]	190	184	173	183

[a] Assuming a reduction of ^3J(2,OH) by 1.0 Hz for each additional polar substituent. [b] 188° for **12B**.

The 2,4-difluoro-α-D-talopyranoside **17**[28] and the 2,4,4-trifluoro-α-D/L-*lyxo*-hexopyranoside D/L-**18**[27] are interesting as HO-3 of these 2,4-difluorohexosides should form a bifurcated H-bond to two F atoms (Figure 5). Analogous bifurcated H-bonds of an equatorial OH to two vicinal axial O-substituents have been described, for example, for HO-2 of *myo*-inositols **1** and **2** in $CDCl_3$ and were evidenced by large ^3J(H,OH) couplings of 11.8–12 Hz.[23,24] Furthermore, asymmetric bifurcated H-bonds of NH of benzanilides to two

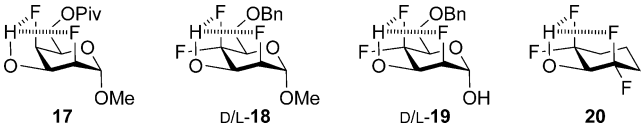
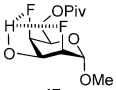
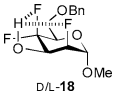


Figure 5. Intramolecular bifurcated H-bonds of HO-3 to two F in 4-fluoro-, 4,4-difluorohexopyranosides, and in 2,2,6,6-tetrafluorocyclohexanol.

different F atoms have been assigned by scalar ^{1h}J(NH,F) couplings of 17.7 and 3.7 Hz[34] and by X-ray crystallography.[35]

The large ^3J(3,OH) values of 11.5–12.2 Hz for **17** and D/L-**18** in [D_8]toluene and $CDCl_3$ reveal symmetric bifurcated H-bonds, although F-2 of D/L-**18** should be a better H-acceptor than F_{ax}-4 (Table 3). These H-bonds persist to about 70% in

Table 3: ^{1}H NMR ^{1h}J(OH,4-F), ^{1h}J(OH,2-F), and ^3J(3,OH) coupling constants [Hz] of **17** and D/L-**18**. The pictures reflect the intramolecular H-bonds in apolar solvents.

Structure	Solvent	^{1h}J(OH,4-F)[a]	^{1h}J(OH,2-F)[a]	^3J(3,OH)
	[D_8]toluene	< 1.5 (0)	< 1.5 (0)	12.2
	$CDCl_3$	< 1.5 (0)	< 1.5 (0)	12.1
	[D_8]THF	< 1.5 (0)	< 1.5 (0)	10.2
17	[D_6]DMSO	0	0	7.0
	[D_8]toluene	1.8 (2.0)	1.6 (2.0)	11.8
	$CDCl_3$	2.3 (2.5)	2.3 (2.5)	11.5
	[D_8]THF	< 1.5 (0)	< 1.5 (0)	10.0
D/L-**18**	CD_3CN	0	0	7.9
	[D_6]DMSO	0	0	7.5

[a] Values from ^{19}F NMR spectra in parenthesis.

[D_8]THF and to 35–40% in [D_6]DMSO. These data evidence for **17** and D/L-**18** in polar solvents a tetravalent H-bond with two F as intra- and a solvent molecule as intermolecular H-bond acceptor. Such a tetravalent H-bond is also present in the solid state of D/L-**19**[27] (see X-ray structure in the Supporting Information). Despite the strong persistence of the bifurcated H-bond, the ^{1h}J(OH,F) couplings of **17** (only line broadening) and D/L-**18** are small ($\leq$ 2.5 Hz), probably because of a strong reduction by the two axial F atoms. The ^{1h}J(OH,F) couplings of the pivaloylate **17** are about 0.8 Hz smaller than those of the benzyl ether D/L-**18** as already stated for the pivaloylate **9** as compared to the trityl ether **10**. The ^{1}H NMR spectrum of the 2,2,6,6-tetrafluorocyclohexanol **20** was published without discussion of the H-bonding.[36] The data however inform that the two equatorial F atoms lead to reduction of ^3J(1,OH) to 6.6 Hz and to the complete disappearance of the ^{1h}J(OH,F) coupling.

In conclusion, the ^{1}H and ^{19}F NMR studies and DFT calculations reported here confirm that intramolecular OH···FC H-bonding is an important interaction of fluorinated carbohydrates in apolar solvents. Our data provide further evidence that 1) the F atom competes favorably as H-acceptor with the endocyclic O5 of hexopyranosides; 2) the bifurcated H-bond to F and O5 is remarkably persistent in acetone, acetonitrile, and THF, and almost completely disrupted in DMSO; 3) the strength of the OH···FC bond is modulated by the nature of a vicinal O-substituent disposed antiperiplanar

to the F-substituent. In addition, a series of new conclusions can be drawn from the present study: 4) we found that the strength of the OH···FC H-bond is also modulated by vicinal O-substituent that are synperiplanar with respect to the F-substituent; 5) we provide the first experimental evidence demonstrating unambiguously that CHF is a better H-bond acceptor than CF_2; 6) we demonstrate that bifurcated H-bonds of an equatorial OH group to two axial F atoms are highly persistent in polar solvents; 7) the reduction of ^{1h}J(OH,F) and ^{3}J(H,OH) couplings by polar substituents is an additional important output in this study; this observation suggests that caution is necessary in the qualitative and quantitative interpretation of the size of these couplings. These advances are of fundamental interest and may help with the design of high-performance materials or pharmaceuticals.

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