Is there any *bona fide* example of O–H···F–C bond in solution? The cases of $HOC(CF_3)_2(4\text{-}X\text{-}2,6\text{-}C_6H_2(CF_3)_2)$ (X = Si(*i*-Pr)$_3$, CF_3)†‡

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The reinvestigation of the title compounds, which are the only examples reported to show experimentally (by NMR) O–H···F–C bonds in solution proves that the NMR data were misinterpreted and the restrictions to rotation of one CF_3 group are due to crowding, not to intramolecular O–H···F–C bond.

The ability of organic fluorine (F–C) to act as hydrogen acceptor in the formation of X–H···F–C hydrogen bonds (X = O, N), is important in order to understand the bioactivity of fluorinated molecules.[1] The interest in this question started some 20 years ago and raised with the debate around an innovative suggestion by E. T. Kool questioning the need for Watson–Crick hydrogen bonds in DNA base pair replication, at least for one specific enzyme. Kool suggested that the experimental results on a nucleoside in which thymine had been replaced by the isostere 2,4-difluorotoluene should be explained by steric effects rather than by C–F···H hydrogen bonding.[2] This proposal was questioned by K. R. Seddon, who argued that 2,4-difluorotoluene was in fact hydrogen acceptor.[3] A recent account by Kool and Sintim is available.[4]

Statistical analysis of structural data by Dunitz and others,[5] conclude that just very few examples can be regarded as unequivocal X–H···F–C bonds (X = O, N) in the solid state. There are also some reports in high vacuum gas phase.[6] However, O–H···F–C hydrogen bond in solution has been proposed only for the molecules $HOC(CF_3)_2(4\text{-}X\text{-}2,6\text{-}C_6H_2(CF_3)_2)$ (X = Si(*i*-Pr)$_3$, CF_3).[7,8] We show here that there is a misinterpretation of the spectroscopic evidence for these two molecules. This eliminates the only examples that have been taken so far as a reference for the existence of O–H···F–C hydrogen bonds in solution.

It was reported that $HOC(CF_3)_2(4\text{-Si}(i\text{-Pr})_3\text{-}2,6\text{-}C_6H_2(CF_3)_2)$ (**1**) shows, in solution in methylcyclohexane-d_{14}, chemical inequivalence of the two *ortho* CF_3 groups at 24 °C (both signals septets by coupling to the two geminal CF_3 groups in the central substituent). At −96 °C the signal of one of the *ortho* CF_3 groups decoalesced into a triplet (F^1) and a doublet (F^2 + F^3). The mononuclear structure **A** (Chart 1) was proposed, with significant intramolecular O–H···F^1–C bonding causing slow rotation of the proximal CF_3 group at −96 °C, although the expected $J(^1H–^{19}F)$ coupling to F^1 was not observed.[7] A similar behavior was found for

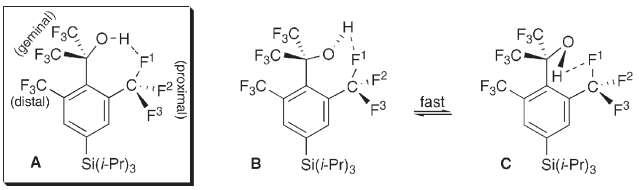

Chart 1

$HOC(CF_3)_2(2,4,6\text{-}C_6H_2(CF_3)_3)$,[8] showing that the ring substituent in *para* (Si(*i*-Pr)$_3$ or CF_3) position has no influence, whether electronic or steric, on the substituents that could be involved in H-bonding.

The literature interpretation of the NMR spectra at −96 °C leaves unanswered two main questions that make **A** unlikely: (i) why $J(H–F^1)$ is not observed?; (ii) since the seven-member ring involving the hydrogen bridge cannot be planar, why are the two geminal CF_3 groups equivalent, as are too F^2 and F^3?

Assuming initially structure **A** we considered that the reported broadness of the signals at −96 °C clearly suggests the existence of a fluxional process at −96 °C. It should create a symmetry plane in the NMR time scale producing a fast conformational exchange of the non-planar enantiomers **B** and **C**. This would not explain, however, that the coupling $J(H–F^1)$ is not observed, although it might be hidden in the broadness of the bands.

Alternatively, if cleavage of the H···F^1 bond was assumed, this would suppress the H–F^1 coupling but then the *proximal* CF_3 group should rotate rapidly rendering equivalent not only F^2 and F^3, but also F^1. We considered that the fast equilibrium depicted in Chart 2 could explain better the experimental observations. In this proposal the hydrogen bond is essentially electrostatic and is switching quickly between F^1 and F^3 at −96 °C, while a restricted swing of the CF_3 and the $C(CF_3)_2(OH)$ groups is also taking place which renders equivalent the later CF_3 groups, as well as F^1 and F^3. The time-averaged interaction making F^1 and F^3 equivalent might be represented as a time-average bifurcated electrostatic hydrogen bond (structure **F** in Chart 2).

Hartree–Fock calculations followed by a Møller–Plesset correlation energy correction (MP2),[9] carried for this scenario on the simplified model *cis*-$CH_2OH–CH{=}CH–CF_3$ (**2**), seemed to support this proposal: starting from a "staggered" geometry analogous to **F**, a local minimum was found (Chart 2) with the O–H out of the plane of the molecule, possibly interacting with F^1 (H···F^1 distance = 2.00 Å, O–H···F^1 angle = 134°). The same minimum was reached starting from an "eclipsed" geometry modelling **A**. Another local minimum must exist by symmetry with the hydrogen interacting with F^3. MP2 calculations afford

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† The HTML version of this article has been enhanced with colour images.

‡ Electronic supplementary information (ESI) available: Details of calculations including full reference 9, additional references, geometry and Cartesian coordinates of the minima and the transition states (5 pp.). See DOI: 10.1039/b710304b

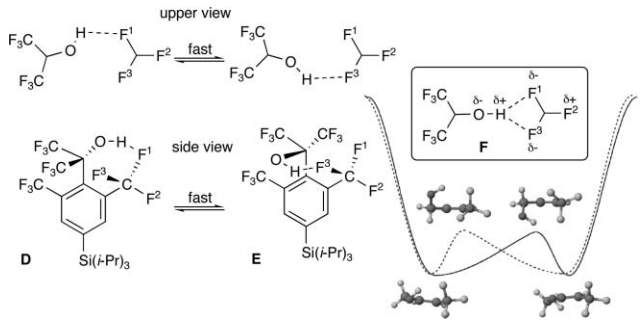

Chart 2

2.5 kcal mol^{-1} for the transition state connecting the two minima. B3LYP calculations on HOC(CF$_3$)$_2$(2-C$_6$H$_4$(CF$_3$)) (**3**), a model molecule derived from (**1**) by substituting the *distal*-CF$_3$ group and the silyl group for hydrogens, afforded a similar minimum of energy, this time with the hydroxylic hydrogen interacting with F^1, at a shorter distance (H···F^1 distance = 1.84 Å; O–H···F^1 angle = 138°).

However, when the complexity of the model was scaled up to include also the *distal*-CF$_3$ group (model compound **4**, HOC(CF$_3$)$_2$(2,6-C$_6$H$_3$(CF$_3$)$_2$, Chart 3),[10] the results changed dramatically: the minimum was a structure with the O–H bond arranged very similarly to the solid-state structure of the dimer, that is, with the O–H vector pointing outwards, away from CF$_3$. There is no intramolecular hydrogen bond! In fact the H atom gets closer to one *geminal* (yet not forming F···H bond) than to any *proximal* F atom. This result leads us to reinterpret the spectroscopic evidence as follows: (i) the reported high shift in ν(OH), from 3582 cm^{-1} (solid state) to 3616 cm^{-1} (solution in hexane), and the non-observation of J(^{1}H–^{19}F) coupling to F^1 are consistent with the molecule in solution not having any hydrogen bond. (ii) The slow rotation observed for the proximal CF$_3$ group is due to the steric hindrance associated to the high crowding produced by the bulky aryl substituents in 1,2,6, not to hydrogen bonding.

The structure of **4** (obtained by B3LYP calculation) is almost identical to half structure of the dimer **1** (solved by X-ray diffraction).[7] Both structures confirm that the considerable crowding existing in them forces a slight loss of planarity of the aromatic ring, and an alternated distribution of the aryl substituents above and below the ring plane (Charts 3 and 4). The two *geminal* and the *distal* CF$_3$ groups are scattered as much as possible. This pushes the oxygen atom towards the proximal CF$_3$, so that the oxygen is tightly incrusted in the hinge between F^1 and F^3, leaving no room left there for a hydrogen atom. In other

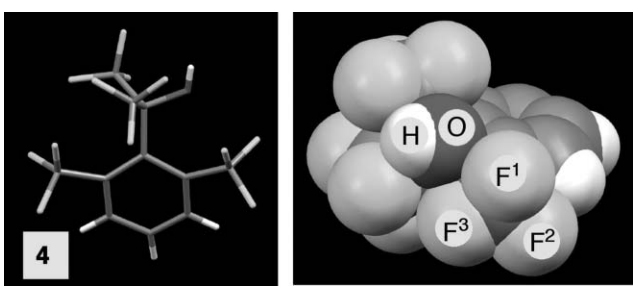

Chart 3

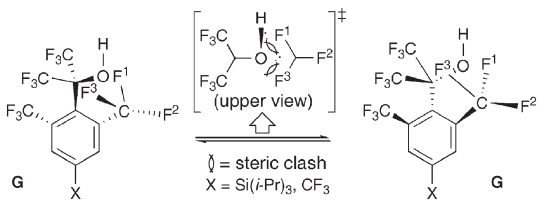

Chart 4

words, the steric hindrance impedes O–H···F hydrogen bond formation! Moreover, the rotation around the C–C(CF$_3$)$_2$OH bond is severely restricted, producing the observed inequivalence of the two *ortho*-CF$_3$ groups at room temperature.

In a rigid chiral structure **G** (having planar chirality) all the F atoms are diastereotopic. The equivalences reported for the ^{19}F NMR spectrum of **1** at −96 °C show that the racemization movement depicted in Chart 4 (a restricted swing) is fast enough at that temperature as to exchange the two *geminal* CF$_3$ groups, and F^1 with F^3, in the NMR time scale. Moreover, the two *geminal* and the distal CF$_3$ groups still manage to rotate rapidly around their C–CF$_3$ bonds, although the broadening reported for their signals, and the loss of their fine structure, suggest that they are not far from coalescence. Finally, it is the remote F^2 atom (not F^1 as suggested in the original paper) that emerges as different from the other two in the ^{19}F NMR spectrum at low temperature. Since there is no F atom involved in hydrogen bonding the restrictions to rotation are steric in nature, with higher mutual steric hindrance for the rotations around the C–C(CF$_3$)$_2$OH and C–CF$_3$-*proximal* bonds than for the C–CF$_3$-*distal* and C–CF$_3$-*geminal* pair of groups.

The results found on the less crowded species *cis*-CH$_2$OH–CH=CH–CF$_3$ (**2**) and HOC(CF$_3$)$_2$(2-C$_6$H$_4$(CF$_3$)) (**3**) might appear to suggest that there is a good opportunity for intramolecular O–H···F–C in solution in less substituted molecules, but this is deceptive. Our calculations are on "*in silico*" isolated molecules, but **2** or **3** will likely have a stronger preference to form intermolecular O–H···O–C rather than O–H···F–C bonds in the presence of other identical molecules. The steric hindrance in HOC(CF$_3$)$_2$(4-Si(*i*-Pr)$_3$-2,6-C$_6$H$_2$(CF$_3$)$_2$) (**1**) prevents the formation of alternative stronger O–H···O–C, and allows for the dimerization through O–H···F–C bonds in the solid state.

In summary, the steric crowding in compounds HOC(CF$_3$)$_2$(4-X-2,6-C$_6$H$_2$(CF$_3$)$_2$) precludes the formation of any intramolecular O–H···F–C bond in solution, while it favors the intermolecular association observed in the solid state by impeding the formation of O–H···O bonds. These results modify the present view on the likeliness of O–H···F–C in solution, as it turns out that so far there is no experimental example of such a bond.

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