

## Significant Inter- and Intramolecular O–H···FC Hydrogen Bonding

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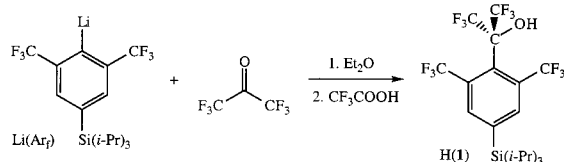
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The incorporation of one or more fluorine atoms into biologically active compounds continues to be an active endeavor.<sup>1</sup> Many bioorganic chemists and biochemists believe that the formation of intermolecular O–H···FC and N–H···FC hydrogen bonds may be important in the binding of fluorinated substrates to enzyme active sites.<sup>2</sup> Nevertheless, the role of organic fluorine atoms as hydrogen bond acceptors in at least some systems remains controversial,<sup>3,4</sup> in part because there are few detailed studies of “unconstrained” intermolecular O–H···FC and N–H···FC hydrogen bonds that are formed in the absence of other, stronger intermolecular interactions. We now report the synthesis and characterization of the first member of a new class of fluorinated alcohols, a class that may allow inter- and intramolecular O–H···FC hydrogen bonding to be systematically studied in great detail.

The new compound HOC(CF<sub>3</sub>)<sub>2</sub>(4-Si(*i*-Pr)<sub>3</sub>-2,6-C<sub>6</sub>H<sub>2</sub>(CF<sub>3</sub>)<sub>2</sub>), H(1), was prepared by adding trifluoroacetic acid to a reaction mixture of Li(Ar)<sub>7</sub><sup>5,6</sup> and hexafluoroacetone<sup>7</sup>



Colorless crystals of the volatile alcohol H(1) were grown by cooling a saturated hexane solution. Its solid-state structure was determined by X-ray crystallography and is shown in Figure 1.<sup>8</sup> The C–C, C–F, C–O, and C–Si bond distances are normal.

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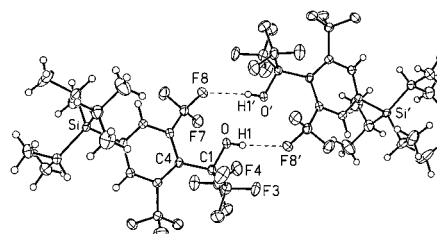
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(7) Synthesis of H(1). A –78 °C solution of 1-Si(*i*-Pr)<sub>3</sub>-3,5-C<sub>6</sub>H<sub>2</sub>(CF<sub>3</sub>)<sub>2</sub> (0.580 g, 1.57 mmol) in diethyl ether (40 mL) was treated with *n*-BuLi (1.58 mmol). After stirring for 15 min, the reaction mixture was warmed to 24 °C and stirred for an additional 5 h. The orange solution was frozen to –196 °C, and CF<sub>3</sub>COCF<sub>3</sub> (1.94 mmol) was added. The yellow solution was stirred for 12 h at 24 °C, after which an excess of CF<sub>3</sub>COOH (1 mL) was added. After removing ether and any other volatiles under vacuum, the product was extracted into hexane. Removal of hexane under vacuum afforded a yellow crystalline solid consisting of H(1) and some impurities (0.598 g, 67% yield based on 1-Si(*i*-Pr)<sub>3</sub>-3,5-C<sub>6</sub>H<sub>2</sub>(CF<sub>3</sub>)<sub>2</sub>). Repeated recrystallizations from hexane afforded crystals of H(1) (~10% overall yield) that contained less than 2% of an impurity that may be HOC(CF<sub>3</sub>)<sub>2</sub>(2-Si(*i*-Pr)<sub>3</sub>-4,6-C<sub>6</sub>H<sub>2</sub>(CF<sub>3</sub>)<sub>2</sub>).



**Figure 1.** Structure of H(1) (50% probability ellipsoids; H atoms omitted for clarity except for H1 and H1'). Selected distances (Å) and angles (deg) (distances and angles calculated with a fixed H1–O distance of 0.967 Å listed in square brackets): H1–O, 0.783(19) [0.967]; H1···F8', 2.19(2) [2.01]; H1···F3, 2.35(2) [2.32]; H1···F4, 2.20(2) [2.16]; H1···O', 2.60(2) [2.53]; O–H1···F8', 173(2) [171]; O–H1···F3, 100(2) [96]; O–H1···F4, 105(2) [100]; O–H1···O', 110(2) [107]; O···F8', 2.971(1); O···F3, 2.600(1); O···F4, 2.520(1); O···O', 2.960(1); O···F7, 2.546(1); O···F8, 2.588(1); C1–O···F8', 113.8(1); C1–O···F3, 64.1(1); C1–O···F4, 68.5(1); C1–O···F7, 93.4(1).

The aromatic ring is distorted from planarity, a feature commonly observed in the related 2,4,6-tris(trifluoromethyl)phenyl substituent.<sup>9</sup> The two aromatic hydrogen atoms and the isopropyl hydrogen atoms were placed in calculated positions. The hydroxyl hydrogen atom, H1, was located in a difference Fourier map and was refined. The O–H1 distance, at 0.783(19) Å, is considerably shorter than the value of 0.967 Å typically found for alcohols by neutron diffraction.<sup>10</sup> For this reason, inter- and intramolecular contacts involving H1 were normalized by fixing the O–H1 distance at 0.967 Å along the original refined O–H1 vector, a procedure commonly used when evaluating X-ray-derived results involving hydrogen atoms.<sup>10,11</sup> All distances and angles involving H1 given below were calculated by using this normalized position.

The most interesting feature of the centrosymmetric dimeric structure is the presence of two intermolecular, nearly linear O–H···FC hydrogen bonds: H1···F8' = 2.01 Å; O···F8' = 2.971(1) Å; O–H1···F8' = 171°. This is the shortest intermolecular O–H···FC hydrogen bond yet observed.<sup>11</sup> There are also two relatively short intramolecular OH···FC distances involving one fluorine atom from each of the geminal CF<sub>3</sub> groups: H1···F3 = 2.32 Å; O–H1···F3 = 96°; H1···F4 = 2.16 Å; O–H1···F4 = 100°. Finally, there is a relatively weak intermolecular OH···O' contact: H1···O' = 2.53 Å; O–H1···O' = 107°. It is significant that the solid-state dimerization of H(1) appears to be driven by the formation of the intermolecular O–H···FC hydrogen bonds. We believe that the [H(1)]<sub>2</sub> dimer contains only the second example of intermolecular O–H···FC hydrogen bonds that are unequivocally not the consequence of additional, stronger intermolecular contacts such as OH···O, OH···N, etc.<sup>11</sup> the other example is 2-fluoro-1,1,2-triphenylethanol, which forms a dimer in the solid state via a pair of O–H···FC hydrogen bonds (H···F' = 2.04 Å; O···F' = 2.924(5) Å; O–H···F' = 153°).<sup>12</sup>

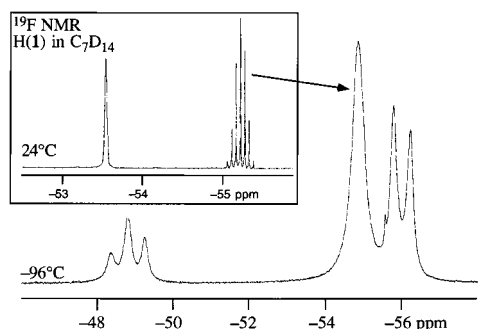
(8) Crystals of H(1) were grown by cooling a saturated hexane solution: monoclinic, *P*2<sub>1</sub>/*c*, *a* = 8.7214(1) Å, *b* = 22.6672(1) Å, *c* = 12.2598(2) Å, β = 101.245(1)°, *V* = 2377.11(5) Å<sup>3</sup>, *Z* = 4. Data were collected at –115(2) °C on a Siemens SMART System with Mo *K*<sub>α</sub> radiation to a maximum 2θ = 56.64°, giving 15822 unique reflections; the structure was solved by direct methods (Sheldrick, G. M. SHELXTL, vers. 5.03, 1994) with full-matrix least-squares refinement on *I*<sup>2</sup>, yielding *R*<sub>1</sub> = 0.031 (*I* > 2σ(*I*)), *wR*<sub>2</sub> = 0.078 (all data).

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**Figure 2.** 282.4 MHz  $^{19}\text{F}$  NMR spectra of H(1) dissolved in methylcyclohexane- $d_{14}$ . Only the *ortho*- $\text{CF}_3$  region is shown in both spectra.

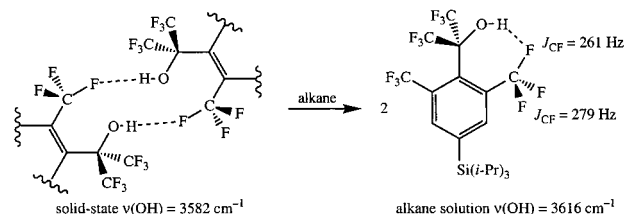
The exceptionally rare nature of the hydrogen bonding in H(1) is further revealed by examination of the Cambridge Structural Database (CSD). In a 1997 study, Dunitz and Taylor concluded that “organic fluorine hardly ever accepts hydrogen bonds.”<sup>11d</sup> In a 1996 study, Howard and co-workers found only 12 compounds in the CSD containing  $\text{OH}\cdots\text{FC}$  interactions of 2.35 Å or less (compounds containing  $\text{CF}_2$  or  $\text{CF}_3$  groups were excluded from their study);<sup>11c</sup> H(1) contains three such interactions. In a 1994 study, Shimoni and Glusker found that the mean  $\text{XH}\cdots\text{FC}$  distance ( $\text{X} = \text{N}, \text{O}$ ) for all relevant compounds in the CSD was 2.5 Å whether the acceptor fluorine atom was part of a  $\text{CF}_3$  group or not (the median distance was also 2.5 Å).<sup>11b</sup>

The IR spectrum of crystalline H(1) exhibited a  $\nu(\text{OH})$  band at  $3582\text{ cm}^{-1}$ , which shifted to  $3616\text{ cm}^{-1}$  when the compound was dissolved in hexane (30 mM). Since it is unlikely that H(1) is dimeric in dilute hydrocarbon solution, we attribute the  $+34\text{ cm}^{-1}$  shift to the replacement of the linear intermolecular  $\text{O}-\text{H1}\cdots\text{F8}'$  hydrogen bond in the solid state with one or more weaker, bent, intramolecular  $\text{O}-\text{H1}\cdots\text{FC}$  hydrogen bonds in hexane solution. The shift is nearly twice as large as the difference in  $\nu(\text{OH})$  values for the intramolecular  $\text{O}-\text{H}\cdots\text{FC}$  hydrogen-bonded conformer and non-hydrogen-bonded conformer of 2-fluoroethanol ( $\Delta\nu(\text{OH}) = +17\text{ cm}^{-1}$ )<sup>13</sup> and of 2,2,2-trifluoroethanol ( $\Delta\nu(\text{OH}) = +19\text{ cm}^{-1}$ ).<sup>14</sup> These data suggest that a linear  $\text{O}-\text{H}\cdots\text{FC}$  hydrogen bond may be significantly stronger than bent varieties,<sup>15</sup> although the energies involved are probably rather small: a recent theoretical study predicted that the  $\text{HOH}\cdots\text{FCH}_3$  complex is bound by only  $2.4\text{ kcal mol}^{-1}$  (a linear  $\text{O}-\text{H}\cdots\text{F}$  framework was assumed; the optimized  $\text{H}\cdots\text{F}$  distance was 1.9 Å),<sup>11c</sup> a value consistent with theoretical results for related systems.<sup>13b,16</sup>

The intramolecular  $\text{O}-\text{H1}\cdots\text{FC}$  hydrogen bonding in H(1) dissolved in hexane probably involves one of the *ortho*- $\text{CF}_3$  groups rather than one or both of the geminal  $\text{CF}_3$  groups. This is a sensible prediction based on the solid-state structure of H(1). The  $\text{O}\cdots\text{F3}$ ,  $\text{O}\cdots\text{F4}$ ,  $\text{O}\cdots\text{F7}$ , and  $\text{O}\cdots\text{F8}$  distances are very similar (2.600(1), 2.520(1), 2.546(1), and 2.588(1) Å, respectively). However, if one assumes an optimum  $\text{C1}-\text{O}-\text{H1}$  bond angle of  $\sim 109^\circ$ , the  $\text{C1}-\text{O}\cdots\text{F3}$  and  $\text{C1}-\text{O}\cdots\text{F4}$  angles of  $64.1(1)$  and  $68.5(1)^\circ$ , respectively, would be much less conducive to effective hydrogen bonding than the  $\text{C1}-\text{O}\cdots\text{F7}$  and  $\text{C1}-\text{O}\cdots\text{F8}$  angles of  $93.4(1)$  and  $125.2(1)^\circ$ , respectively. For comparison, the  $\text{C1}-\text{O}\cdots\text{F8}'$  angle is  $113.8(1)^\circ$ . Variable temperature  $^{19}\text{F}$  NMR spectra of H(1) dissolved in methylcyclohexane- $d_{14}$  support this prediction. The *ortho*- $\text{CF}_3$  region of spectra recorded at  $24^\circ\text{C}$  and  $-96^\circ\text{C}$  are shown in Figure 2. As expected, there is slow rotation about the  $\text{C1}-\text{C4}$  bond at all temperatures, rendering the two

*ortho*- $\text{CF}_3$  groups ( $\delta(^{19}\text{F}) -53.5, -55.2$ ) and the two aromatic hydrogen atoms ( $\delta(^1\text{H}) 7.99, 7.90$ ) inequivalent. The  $^{19}\text{F}$  spectral assignments are based on integrated intensities and magnitudes of the long-range  $^{19}\text{F}-^{19}\text{F}$  coupling (confirmed by homonuclear decoupling experiments) between the *ortho*- $\text{CF}_3$  groups and the two equivalent geminal  $\text{CF}_3$  groups ( $\delta(^{19}\text{F}) -70.6$ ). Each *ortho*- $\text{CF}_3$  group multiplet is a septet, with the larger long-range  $^{19}\text{F}-^{19}\text{F}$  coupling (15 Hz) assigned to the *ortho*- $\text{CF}_3$  group distal to the hydroxyl group and the smaller coupling ( $\leq 2$  Hz) assigned to the proximal *ortho*- $\text{CF}_3$  group. As the temperature was lowered to  $-96^\circ\text{C}$ , the  $^{19}\text{F}$  multiplet at  $\delta -53.5$  decoalesced into two multiplets with equal  $J(^{19}\text{F}^{19}\text{F})$  spacings of 124 Hz, a triplet with intensity 1 ( $\delta -48.8$ ) and a doublet with intensity 2 ( $\delta -56.0$ ), a pattern indicative of slow rotation of this  $\text{CF}_3$  group about its  $\text{C}-\text{C}$  bond.<sup>17</sup> We suggest that significant intramolecular hydrogen bonding between the OH group and the proximal *ortho*- $\text{CF}_3$  group causes the slow rotation of this  $\text{CF}_3$  group on the NMR time scale at  $-96^\circ\text{C}$ .

Although we did not observe  $J(^1\text{H}^{19}\text{F})$  coupling directly or by NOE experiments, we observed changes in  $J(^{13}\text{C}^{19}\text{F})$  by  $^{19}\text{F}$ -detected heteronuclear multiple quantum coherence spectroscopy.<sup>18</sup> At  $24^\circ\text{C}$ ,  $J(^{13}\text{C}^{19}\text{F})$  was 274(1) Hz for both *ortho*- $\text{CF}_3$  groups; at  $-96^\circ\text{C}$ ,  $J(^{13}\text{C}^{19}\text{F})$  was unchanged for the distal *ortho*- $\text{CF}_3$  group but was 261(1) Hz for the triplet and 279(1) Hz for the doublet (weighted average = 274 Hz). These results suggest that the OH group is hydrogen-bonded to only one of the F atoms in the proximal *ortho*- $\text{CF}_3$  group (the alternative would have been a bifurcated hydrogen bond involving two of the  $\text{CF}_3$  group's F atoms); the hydrogen bond slightly weakens the unique  $\text{C}-\text{F}$  bond that interacts with the hydroxyl-group proton and slightly strengthens the other two  $\text{C}-\text{F}$  bonds that do not interact with the proton, as shown below



To our knowledge, H(1) is the first example of a compound with an  $\text{O}-\text{H}\cdots\text{FC}$  hydrogen bond for which (i) the effects of linearity of the  $\text{O}-\text{H}\cdots\text{F}$  linkage on  $\nu(\text{OH})$  and (ii)  $\text{C}-\text{F}$  bond-weakening, as measured indirectly by  $J(^{13}\text{C}^{19}\text{F})$  values, have been experimentally observed. Many questions about the nature and strength of  $\text{O}-\text{H}\cdots\text{FC}$  and  $\text{N}-\text{H}\cdots\text{FC}$  hydrogen bonds remain unanswered. The synthesis of a variety of compounds similar in structure to H(1) (e.g., substituting one or more of the  $\text{CF}_3$  groups with  $\text{CH}_3\text{-}_n\text{F}_n$  groups or other substituents), along with complete X-ray and neutron diffraction and spectroscopic investigations of them, should lead to a better understanding of the biological importance of these weak dipole-dipole interactions.

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**Supporting Information Available:** Figures S-1–S-5,  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectra of H(1) and related fluoro alcohols; Figure S-6, numbering scheme for H(1); and Tables S-1–S-5, listing crystallographic parameters, atomic coordinates, bond distances and angles, thermal parameters, and hydrogen atom positions for H(1) (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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