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The intramolecular C–F···HO hydrogen bond of 2-fluorophenyldiphenylmethanol†

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The intramolecular C–F···HO hydrogen bond of 2-fluorophenyldiphenylmethanol was observed by X-ray crystallographic analysis and NMR spectroscopy. The features of the spectra were compared to triphenylmethanol (a fluorine-free analog) and 2-fluorophenyldiphenylmethane.

In a previous report, we discussed the C–F···HO hydrogen bond of 9-fluoro-18-hydroxy[3.3]metacyclophane,[1] and its stabilization energy was estimated to be 0.84–3.7 kJ mol^{-1}.

C–F···HO or C–F···HN hydrogen bonds occur very rarely because they are weak,[2] and other stronger interactions predominate under typical circumstances. However, several attempts have continued in order to observe and estimate these hydrogen bonds under particular conditions (mainly in the gas phase) using various modern spectroscopic methods or *ab initio* calculations.[3] In both solution and the solid phase, there are controversies about the existence of this hydrogen bond. Shimoni and Glusker concluded that "C–F···H–X (X = C, N, O) interactions cannot be ignored in predictions of modes of molecular packing in complexes and in crystals" based on crystallographic analyses and a CSD (Cambridge Structural Database) database analysis.[4] On the contrary, Dunitz and Taylor took a negative view about the interaction after their analysis of the CSD.[5] In a recent study, Hulliger *et al.* pointed out that X–H···F contacts are caused not only by hydrogen bonds but also by crystal packing, and that the number of O–H···F and N–H···F contacts is significantly lower because O–H and N–H act rather as proton acceptors than proton donors.[6] Another group, however, support the positive role of the F atom in crystal engineering.[7] In bioorganic chemistry, the isosteric and isoelectronic nature of the F atom to the OH group were noted, and Hagan and Rzepa mentioned that the F atom is an OH mimic hydrogen bond acceptor in desolvated enzyme cavities, although rare.[8] However, there are a few observations of O–H···F and N–H···F interactions in solution. Recently, experimental O–H···F evidence by Strauss *et al.*[9] was denied by Espinet *et al.*[10] On the other hand, N–H···F hydrogen bonding-driven foldamers were found by Li *et al.*[11] Other examples have been found by our group[1] and by Vasella *et al.* (described below).[12] In such a situation, the role of the C–F···HO hydrogen bond is somewhat subtle, and thus we must accumulate examples. In our opinion, because the interaction is very weak, the C–F···HO hydrogen bond is influenced by the subtle conditions of molecular structure; in some cases being visible and in others invisible.

The aim of this study is to observe a C–F···HO interaction by some of the most common and familiar tools to organic chemists, X-ray crystallographic analysis, and NMR and IR spectroscopy. For this purpose, the molecular design of the target molecule becomes very important. Similar approaches were attempted by Vasella *et al.* using fluorinated saccharides, and they succeeded in observing the C–F···HO hydrogen bond by ^{1}H NMR and IR spectroscopy.[12] However, their X-ray crystallographic analyses revealed that the OH proton in each compound was not directed toward the F atom.

In our current approach to detect such a weak hydrogen bond, we chose 2-fluorophenyldiphenylmethanol (**1**)[13] as a touchstone because it is a simple molecule and its reference compound analogues are accessible. Furthermore, as shown in Fig. 1, the F and H(–O) atoms of **1** would form a six-membered ring through C–C bonds. This is very important and a preferable condition for the formation of a hydrogen bond. Triphenylmethanol (**2**) and 2-fluorophenyldiphenylmethane (**3**) were used as reference compounds, and were purchased or prepared according to the literature.[14,15] A single crystal of **1** suitable for an X-ray crystallographic analysis was obtained from n-hexane, and its molecular structure is shown in Fig. 2. An analysis shows that H(15) and F are adjacent to each other and that the distance between them (223 pm) is much shorter than the sum of the van der Waals radii of the two atoms (267 pm), although rotating C–OH and C(OH)–Ar bonds is very easy. In this report, the values of the van der Waals radii used are those reported by Bondi.[16] The O(1)–F distance (283 pm) is also shorter than the sum of the van der Waals radii of the F (147 pm) and O (152 pm) atoms. Accordingly, these values are definitive evidence of a C–F···HO hydrogen bond in **1**. The F···H–O angle is somewhat acute (118.7°) for a hydrogen bond, but this is due to the very nature of the molecular structure.

On the contrary, four molecules of **2** form an intermolecularly hydrogen-bonded tetrahedron with each four OH groups.[17] This is a distinct difference between **1** and **2** caused by the presence of the F atom at an appropriate position.

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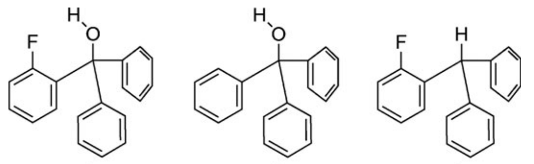

1 **2** **3**

Fig. 1 The structure of **1** and its reference compounds **2** and **3**.

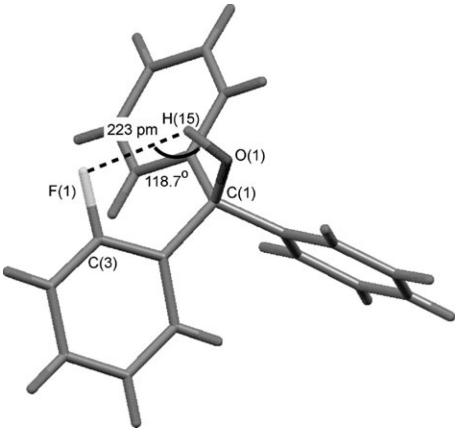

Fig. 2 The molecular structure of 2-fluorophenyldiphenylmethanol (**1**).

In addition to the crystallographic information, the hydrogen bond was also observed in solution. In the ^{1}H NMR spectra, the OH signal of **1** appeared as a doublet ($^5J_{H,F}$ = 9.2 Hz) at 3.51 ppm in CD_2Cl_2 (1×10^{-2} mol dm^{-3}). The coupling constant was too large for long-range coupling through five bonds, because the OH signal of 2-fluorobenzyl alcohol (when considered to be a partial structure of **1**) appears as a singlet at 2.8 ppm. Bernet and Vasella have described that the coupling constant is reduced in basic solvents.[12a] Also, in the case of **1**, the coupling constant was reduced to 2.2 Hz (5.50 ppm) in THF-d_8, and the OH signal appeared as a sharp singlet at 6.41 ppm in DMSO-d_6. The disappearance of the coupling is due to the strong OH···DMSO hydrogen bond, which breaks the weak C–F···HO bond. On the other hand, the OH signal of **2** appeared as a sharp singlet at 2.88 ppm in CD_2Cl_2 (2×10^{-2} mol dm^{-3}). Thus, the large difference in chemical shift ($\Delta\delta_{OH}$ = 0.71–0.63 ppm) between **1** and its reference compounds (**1**, 3.51 ppm; 2-fluorobenzyl alcohol, 2.8 ppm; **2**, 2.88 ppm), together with the spin coupling, represent a hydrogen bond between the F and HO of **1** in solution.

As a result of previous studies, high field shifts in the ^{19}F NMR signal and a reduced $^2J_{C,F}$ coupling constant in ^{13}C NMR spectra are acknowledged as specific for C–F···M$^+$ interactions.[18] Since the hydrogen bond can be considered C–F···H$^{\delta+}$O$^{\delta-}$, similar spectroscopic features are expected. However, in the ^{19}F NMR spectra, the ^{19}F signal of **1** appeared in a rather lower field region (−110.5 ppm, $CFCl_3$) than that of **3** (−116.9 ppm). Also, in the ^{13}C NMR spectra, the $^2J_{C,F}$ values of **1** and its reference compounds **3**, 2-fluorobenzylalcohol, fluorobenzene and 2-fluorotoluene, were not in such a relationship. These results show the weakness of the C–F···H$^{\delta+}$ interaction in comparison with the C–F···M$^+$ interaction. As a result, in the NMR spectra, the chemical shift and the coupling of the OH proton signal are indices of a C–F···HO hydrogen bond in this system.[19]

In the IR spectra, the ν_{HO} of **1** appeared as a sharp band at 3569 cm^{-1} in KBr and that of **2** appeared as a broad band at 3472 cm^{-1}. Because fluorine-free **2** forms an intermolecular hydrogen bond in the crystal, the broadening and red-shifting of the band is plausible. In the case of **1**, as shown in the crystallographic analysis, no intermolecular hydrogen bond in the crystal is formed, and thus the sharp band of **1** is characterized as an intramolecularly hydrogen-bonded $\nu_{C\text{–}F\cdots HO}$ band. Thus, in the solid state spectra, we cannot compare unimolecular ν_{HO} bands between **1** and **2**. The IR spectra in CCl_4 were then obtained. In solution, the intermolecular hydrogen bond of **2** was easily broken, as depicted in the ^{1}H NMR spectra (it was negligible, even at the concentration of 2×10^{-2} mol dm^{-3}). The ν_{OH} bands of **1** and **2** in CCl_4 (1×10^{-3} mol dm^{-3}) appeared at almost the same wavenumber values, 3612 and 3611 cm^{-1}, respectively, and these are within experimental error. In solution, each observed band can be considered as a unimolecular band, but the difference is very small and can be ignored. Thus, the effect of the hydrogen bond on the solution spectra is equivocal. A similar phenomenon was also observed in a previous report.[1]

In part, the interaction described here can be explained by a dipole–dipole interaction (~5.6 kJ mol^{-1}) that is *ca.* ten times larger than O–H rotation (~470 J mol^{-1}).‡ However, the spin coupling between the OH and F atoms in this strain-free system is definitive evidence of a redistribution of electrons between the OH and F orbitals. Therefore, the electrostatic term in this hydrogen bond should be evaluated too. Furthermore, the proximity of the F and H atoms is also evidence of a bond, because molecule **1** has no steric crowding and the rotation of each bond is free. If there is no interaction between F and HO, compound **1** would form an intermolecular OH···OH hydrogen bond, just as for **2**.

Therefore, the observed phenomena in this report appropriately indicate the presence of C–F···HO hydrogen bond.

In conclusion, another example of a C–F···HO hydrogen bond system has been confirmed by crystallographic analysis and ^{1}H NMR spectroscopy. As mentioned above, the C–F···HO hydrogen bond is very weak; thus, careful molecular design is very important in order to observe the interaction using the typical techniques available to organic chemists.

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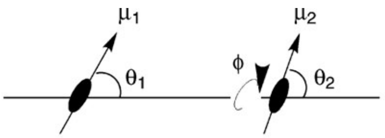

$$E = \frac{-\mu_1\mu_2(2\cos\theta_1\cos\theta_2 - \sin\theta_1\sin\theta_2\cos\phi)}{4\pi\varepsilon r^3}$$

Fig. 3 A diagram of a dipole–dipole interaction

Experimental

Melting points: Yanaco MP-500D apparatus in Ar sealed tubes; values are uncorrected.

NMR: JEOL AL-300 (300.4 MHz for ^{1}H, 75.6 MHz for ^{13}C and 283.0 MHz for ^{19}F, with TMS and $CFCl_3$ as internal references, respectively).

IR: JASCO IR-FT/IR 4200 (CCl_4, in NaCl cells (0.1 and 0.5 mm) at 25 °C).

FAB MS: JEOL JMS-SX/SX102A.

Elemental analysis: the Service Centre of the Elementary Analysis of Organic Compounds affiliated with the Faculty of Science, Kyushu University.

Chromatography was performed using the YAMAZEN YFLC-254-GRII medium-pressure liquid chromatography system.

2 was purchased from Tokyo Chemical Industry Co., Ltd. and used without purification.

2-Fluorophenyldiphenylmethanol (1)

This compound was obtained by the reaction of methyl 2-fluorobenzoate and phenyl magnesium iodide, and its physical and spectral properties were consistent with those in the literature.[13]

2-Fluorophenyldiphenylmethane (3)

This compound was prepared by the reduction of **1** by Et_3SiH in CH_3COOH.[14] Compound **1** (100.2 mg, 0.36 mmol) was dissolved in 1.8 mL of AcOH, and 0.4 mL of Et_3SiH was added. The mixture was heated under reflux for 40 h. The mixture was then evaporated *in vacuo* and the resultant brown oil was chromatographed on silica gel using hexane–CH_2Cl_2 (50 : 50 volume) as the eluent. Colorless crystals, 28.0 mg (29.6%). m.p. 84.3–84.7 °C (lit. 85–87 °C[15]). δ_H (300 MHz, $CDCl_3$, Me_4Si): 7.31–6.91 (m, 14H, ArH) and 5.83 (s, 1H, CH). δ_C (75.4 MHz, $CDCl_3$, Me_4Si): 160.7 (d, J = 246.8 Hz), 142.6 (s), 130.9 (d, J = 3.6 Hz), 129.3 (s), 128.4 (s), 128.1 (d, J = 8.2 Hz), 126.5 (s), 123.8 (d, J = 3.7 Hz), 115.3 (d, J = 21.9 Hz) and 49.4 (s). δ_F (282.2 MHz, $CDCl_3$, $CFCl_3$): −116.86 (m). HRMS (FAB) calc. for $C_{19}H_{15}F$ 262.1158, found 262.1155.

Crystallographic data for 1. $C_{19}H_{15}OF$, $M_r = 278.31$ g mol^{-1}, platelet crystal (grown from n-hexane), size 0.53 × 0.45 × 0.37 mm, monoclinic, space group $P2_1/n$ (#14), $a = 8.2379(3)$, $b = 10.9417(4)$, $c = 15.6797(4)$ Å, $V = 1411.10(8)$ Å^3, $Z = 4$, $\rho_{calc} = 1.310$ g cm^{-3}, $\mu_{Cu\text{-}K\alpha} = 0.88$ cm^{-1}, $F(000) = 584.00$, $T = 113$ K using the ω-2θ scan technique to a maximum 2θ value of 54.5°. A total of 3160 reflections were collected. The final cycle of the full-matrix least-squares refinement was based on 2749 observed reflections ($I > 2\sigma(I)$) and 194 variable parameters, and converged with unweighted and weighted agreement factors of $R = 0.0544$, $Rw = 0.1797$ and GOF = 1.409. The maximum and minimum peaks on the final difference Fourier map corresponded to 1.054 and −0.530 e$^-$ Å^{-3}, respectively.†

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‡ Based on the crystallographic analysis data, the dipole–dipole interaction energy of the O–H and C–F groups in compound **1** was roughly estimated (Fig. 3). Here, $\theta_1 = 70.3°$, $\theta_2 = 109.1°$, $\phi = 9.7°$, $\mu_1 = 4.7 \times 10^{-30}$ C m, $\mu_2 = 5.0 \times 10^{-30}$ C m, $\varepsilon_0 = 8.85 \times 10^{-12}$ C^2 J^{-1} m^{-1} and $r = 2.83 \times 10^{-10}$ m. From these data, we obtained $E \cong 5.6$ kJ mol^{-1}. The resultant energy is close to our previously reported value, and thus it is shown that the interaction is reproducible by simple estimation of the dipole–dipole interaction. Furthermore, the rotational energy of the O–H group was estimated to be 467 J ($E = h^2/8\pi 2I \times J(J + 1)$, $I = m \times r_{OH} \times \cos 14.5°$ ($\angle_{H\text{–}O\text{–}C} - 90°$)). Thus, the dipole–dipole interaction is enough to stop the OH rotation.

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