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DOI: 10.1002/ange.201403599

# Search for a Strong, Virtually "No-Shift" Hydrogen Bond: A Cage Molecule with an Exceptional OH···F Interaction**

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***Abstract:*** *Reported herein is the synthesis of a molecule containing an unusually strong hydrogen bond between an OH donor and a covalent F acceptor, a heretofore somewhat ill-defined if not controversial interaction. This unique hydrogen bond is to a large extent a product of the tight framework of the rigid caged system. Remarkably, the interaction shows little to no perceptible shift in the OH stretch of the IR spectrum relative to appropriate nonhydrogen-bound standards in fairly non-interactive solvents. This fascinating example of what has been termed a virtual "no-shift" hydrogen bond is investigated through NMR (coupling constants, isotopic chemical shift perturbations, proton exchange rates) and IR studies which all tell a consistent story.*

As every chemistry student learns in school, a key spectroscopic signature of a hydrogen bond (X–HY) is found in the IR spectrum, wherein the YH stretch is generally red-shifted.[1] However, recent studies have revealed intriguing examples of hydrogen bonds in which the YH stretch is blue-shifted—a phenomenon which has become important in its own right.[2] In a nutshell, the red-shifted examples are often attributed largely to weakening of the YH bond as a result of the overlap of lone pairs on X with σ*(YH).[3] Blue shifts, in contrast, have been ascribed to the dominant influence of rehybridization-induced YH bond strengthening (in the manner of Bent's rule).[4]

Blue shifts in the IR spectrum often involve the interactions of CH bonds with donors. In contrast, OH groups that engage in hydrogen bonding are generally red-shifted (Figure 1). A lively debate has surrounded the question of whether blue-shifted hydrogen bonds represent a fundamentally different concept than their red-shifted counterparts, but the most common belief at the moment is that there exists no basic difference between red- and blue-shifted hydrogen bonds, just a changing balance between hyperconjugative- and rehybridization-induced effects. If this is the case, what about the interesting possibility of a fairly strong hydrogen-bonding interaction in which no meaningful shift in the YH stretch can be observed in a non-interactive solvent because of canceling red- and blue-shifting tendencies?[5–6] There would be in fact no compelling rationale why such a hydrogen bond could not exist. Herein, we report a serendipitous but apparently rare example of a strong, virtually no-shift hydrogen bond. The discovery was made during the investigation of a cage molecule that was specially designed to exhibit an intense F···HO interaction, thereby helping to clarify the controversy about whether such hydrogen bonds can in fact exist in solution.[7] In our case, NMR studies (coupling constants, isotopic chemical shift perturbations, and proton exchange rates) tell the tale of a strong hydrogen bond, a story which the IR spectra cannot tell, and seem to confirm the emerging orthodoxy concerning the nature of blue- versus red-shifted hydrogen bonds.

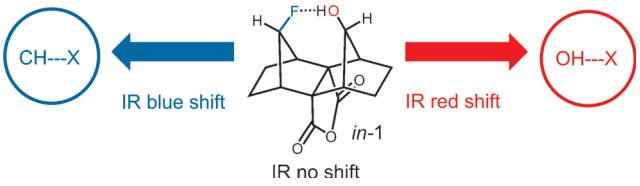


***Figure 1.*** Blue, red, and no-shift hydrogen bonds.

Hydrogen bonding to fluorine as a covalent acceptor is a fascinating subject which has gained relevance recently as fluorinated molecules become more prevalent in medicine and biology, and the precise role that fluorine plays in medicinal chemistry assumes a central, if not urgent, role.[8] Whereas it is generally accepted nowadays that fluorine, as part of a C–F bond, is a competent hydrogen-bond acceptor, several outstanding questions remain, the most important of which involves the strength of the interaction. From a biochemical standpoint, the ubiquity of hydroxy groups would indicate that the C–F···H–O interaction could be especially important.[9] In contrast, periodic screens of the Cambridge structural database indicate that significant interactions (<2.2 Å H–F distance) are uncommon.[10] Rarer still are strong interactions between covalent fluorine and relatively non-acidic aliphatic alcohols,[11] and controversy has arisen over whether such interactions qualify as hydrogen bonding at all.[12] One way to establish such an interaction beyond certitude is to place the OH group in extreme proximity to a neighboring covalently bound fluorine atom, thus making a strong hydrogen-bonding interaction literally unavoidable. Recently, we reported the synthesis of a versatile polycyclic cage system designed to examine close interactions of fluorine atoms with carbocationic centers,[13] proximate C–H bonds,[14] and C=C bonds.[15] The alcohol **1** ("*in*-**1**"; Figure 1) seemed to be an attractive candidate for a new study of extreme interactions involving fluorine. For example, at the B3LYP/

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[**] T.L. thanks the NSF (CHE 1152996) for a grant and M.D.S. thanks JHU for a Gary H. Posner Fellowship. Dr. Cathy Moore is also thanked for her NMR expertise.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201403599.

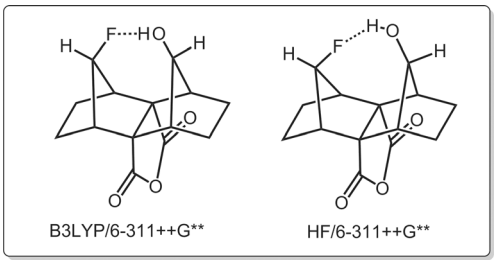
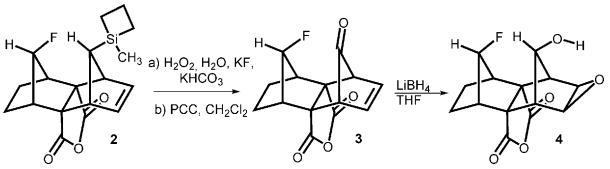



***Figure 2.*** Structures of *in*-**1** generated at the B3LYP/6-311++G** (F-H=1.58 Å) and HF/6-311++G** (F-H=2.01 Å) levels of theory.

6-311++G** level of theory, the optimized structure clearly reveals an unusually strong interaction between OH and F (Figure 2).[16] The calculated H···F distance is only 1.58 Å, and the distance between O and F is predicted to be 2.54 Å [use of a newer functional paired with a triple-ζ basis set (ωB97XD/cc-pVTZ) that is noted for an accurate account of dispersion effects yields a similar result: 1.59 Å; 2.53 Å].[17] The hydrogen bond itself is roughly linear (170°), and the system, remarkably, does not attempt to relieve strain by bending much. In contrast, at the HF/6-311++G** level of theory, the situation is quite different. The hydrogen bond is apparently much weaker. It is highly bent (OH–F bond angle = 104°), the H–F distance is 2.0 Å, and the $C_s$ symmetry of the B3LYP structure is disrupted. Evidently, the account of electron correlation taken by the hybrid DFT methods is significant to the predicted structure of *in*-**1**.

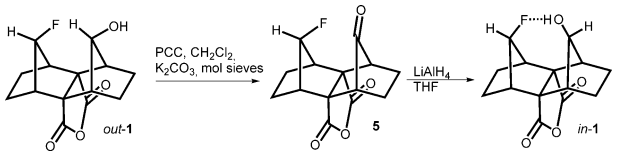
Our first attempt at the synthesis of *in*-**1** began with the known unsaturated silane **2** (Scheme 1).[13] The silyl group of **2** is cleaved by the Fleming–Tamao oxidation and subsequent




***Scheme 1.*** First attempt at synthesis of *in*-**1** leads to **4** instead. PCC = pyridinium chlorochromate, THF = tetrahydrofuran.

treatment with PCC in dichloromethane to afford the ketone **3**. We reasoned that reaction of **3** with a borohydride reducing agent (such as $LiBH_4$) would then afford the unsaturated *in*-alcohol. To our surprise, the epoxide **4** was produced instead, even after substantial measures were taken to exclude oxygen gas (presumably the source of the epoxy-O) from the reaction flask. A crystal structure of **4** shows the *out*-alcohol isomer displaying a notable intramolecular OH···O epoxy hydrogen bond.

We then turned our attention to the saturated *out*-**1** as a suitable alternative starting point for the synthesis of *in*-**1** (Scheme 2). The goal then would be to epimerize the *out*-OH group to the *in*-position. Oxidation of *out*-**1** with PCC proceeds slowly (presumably due to steric hindrance) over a 24 h period to afford the ketone **5** in 75% yield. In turn, subjecting **5** to $LiAlH_4$ for 2 hours in THF at reflux affords the




***Scheme 2.*** Synthetic pathway for the generation of *in*-**1**.

alcohol *in*-**1** in 32% yield after workup (Fieser method) and column chromatography on silica gel. The reaction requires harsh reaction conditions for a ketone reduction, as models indicate a potentially poor hydride attack angle which deviates significantly from the optimal Bürgi–Dunitz trajectory.[18]

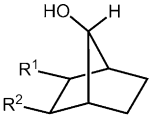
Anxious to document the hydrogen bond, one of the first things we did was to undertake an IR study. In fact, the free OH stretch of *in*-**1** was observed at 3620 $cm^{-1}$ in $CH_2Cl_2$ (concentrations ranging from $10^{-3}$ to $10^{-2}$ M). Contrast this with the alcohol *out*-**1** (employed as an appropriate intramolecular nonhydrogen-bonded reference in dilute solution) whose free OH stretch appears at 3614 $cm^{-1}$. Turning to other solvents, in benzene *out*-**1** is red-shifted from that for *in*-**1** by 45 $cm^{-1}$, presumably because of its propensity for π-cloud–OH interactions. Additionally, in MeCN, *out*-**1** is predominately hydrogen bound to solvent, whereas *in*-**1** is not.[19] In π-electron-poor benzotrifluoride, the π-cloud-induced shift is virtually gone; the absence of a significant shift is also observed in $CCl_4$. In cyclohexane, a very non-interactive solvent and about as close to the gas phase as we can get,[20] the shift also virtually disappears (Table 1). Keep in mind that OH groups are almost invariably red-shifted upon strong hydrogen bonding,[21] so these findings are quite unusual.

***Table 1:*** IR study of the OH stretches of *out*-**1** and *in*-**1**.

| Solvent | *out*-**1**[a] | *in*-**1**[a] |
|---|---|---|
| $CH_2Cl_2$ | 3614 | 3620 |
| PhH | 3591 | 3636 |
| $PhCF_3$ | 3636 | 3633 |
| $CCl_4$ | 3638 | 3639 |
| CyH | 3658 | 3659 |

[a] Values are in $cm^{-1}$. For details of solution concentrations and instrumentation see the Supporting Information.

It must be said that the choice of references can be somewhat subjective, especially when considering an intramolecular hydrogen bond. Although *in*-**1** and *out*-**1** match up spectroscopically, calculationally, several DFT methods predict a 20–30 $cm^{-1}$ red shift upon hydrogen-bond formation. Alcohols **6a–d** (Figure 3) were thus compared as alternative intermolecular references as well (imagine excising the C–F bond and its support from *in*-**1**, but leaving behind the strained norbornane motif). These controls are also predicted to show little or no shift of the OH stretch by DFT calculations. In $CCl_4$, **6a** and **6b** display free OH stretches at 3631 $cm^{-1}$




**6a**: $R^1$ = Me, $R^2$ = H
**6b**: $R^2$ = Me, $R^2$ = Me
**6c**: $R^1$ = Cy, $R^2$ = H
**6d**: $R^1$ = $R^2$ = H

***Figure 3.*** Controls for intermolecular hydrogen-bonding interactions.

(consequently a very slight blue shift separates *in*-**1** from these controls), whereas **6c** displays at 3635 $cm^{-1}$,[22] and 7-norbornanol itself (**6d**) at 3633 $cm^{-1}$. Thus, it appears that our putative strong interaction exhibits very little, if any, OH stretch perturbation in non-interactive solvents, compared with that of the relevant controls.

Compare also the large red shifts observed when the control *out*-**1** interacts through intermolecular hydrogen bonding with basic solvents and additives. In other words, chemically, the OH groups in *out*-**1** and *in*-**1** are very different. For example, titration of a solution of *in*-**1** with DMAP [4-(*N*,*N*-dimethylamino)pyridine] afforded little change in the OH stretch of the IR spectrum up to and beyond 5 equivalents. In contrast, the OH stretch of *out*-**1** shifts greatly in the presence of excess DMAP to become a broad, strong band centered around 3000 $cm^{-1}$, thus indicating classical intermolecular hydrogen bonding and a red shift of ca. 600 $cm^{-1}$.

In contrast, investigation of the structure of *in*-**1** through X-ray crystallography shows clear evidence of the strength of the hydrogen bonding interaction (Figure 4). When the *in*-hydrogen atom was fully refined (resulting in a difference

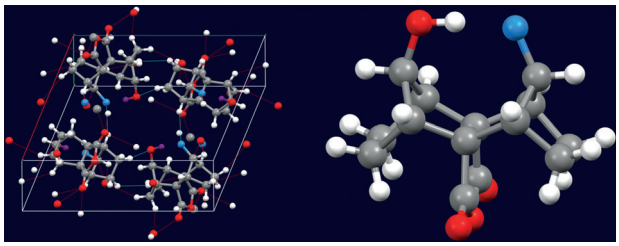


***Figure 4.*** Packing diagram of *in*-**1** (left; alcohol protons are shown in purple) and the crystal structure of *in*-**1** (right).

Fourier map which showed the position of the hydrogen clearly) the structure yielded bond lengths in fairly good agreement with the calculated values. The O–H bond in the structure is measured at 0.93 Å (calc. 0.96 Å) and the H–F distance is 1.58 Å (calc. ωB97XD/cc-pVTZ 1.59 Å), and the O–F distance is 2.51 Å (calc. 2.53 Å). The O-H-F angle is given as 171° which fits closely with the calculated value (170°) as well. Investigation of the packing diagram generated from the crystal reveals the robustness of the hydrogen-bonding interaction. The alcohol hydrogen atom is not observed to have any furcating or otherwise short contact interactions.[23] In contrast, the packing diagram of the crystal structure of *out*-**1** reveals several close, polyfurcating interactions of its alcohol hydrogen atom with neighboring oxygen atoms.

Examination of the $^1$H NMR spectrum of *in*-**1** immediately suggested some unusual features which aid in clarifying the situation. A sharp multiplet at $\delta = 4.8$ ppm (OH) encompassing strong coupling between H and F was observed (68 Hz). The one-bond coupling between F and H is calculated at 76 Hz (B3LYP/6-311++G**). Perhaps more than any factor, this value would be indicative of a strong interaction.[24] The one-bond H–F coupling of the weaker, bent alternative structure predicted at the HF/6-311++G** level of theory is only 18 Hz. Coupling to the proton vicinal to the oxygen atom was also seen, thus representing very slow exchange with the $CDCl_3$ solvent. Even in the presence of several equivalents of water, this slow exchange was maintained. Computationally, the sequential placement of water molecules in this vicinity of the O–H···F bond resulted in only very slight distortions to its geometry. On the contrary, *out*-**1** has no discernable alcohol proton visible in the NMR spectrum under identical conditions and concentrations, thus indicating fast exchange with water. In anhydrous $CDCl_3$, *out*-**1** displays its hydroxy proton signal at $\delta = 1.6$ ppm, more than 3 ppm upfield from that of *in*-**1**. Coupling to fluorine is negligible, thus suggesting a predominately through-space interaction for the hydrogen bond of *in*-**1**, and it is, surprisingly, of the same magnitude as the fluorine's strong coupling to the geminal proton.

Clearly the alcohol hydrogen atom on *in*-**1** is tightly held. This fact gave us the idea to attempt to replace it with a deuterium and observe, through NMR spectroscopy, what effects such a substitution would have. Deuteration of *in*-**1** was achieved by dissolution in MeOD with the aid of light heat under a nitrogen atmosphere. The solvent was removed in vacuo and the deuterated product was redissolved in $CD_2Cl_2$ for the NMR experiments. In keeping with our hypothesis, the deuterated *in*-**1** was found to undergo exchange in solution ($CDCl_3$ saturated with $H_2O$) at a fraction (less than 0.001 times) of the rate of *out*-**1**. The $^{19}$F NMR spectrum shows a large isotopic shift δ(F-DO)−δ(F-HO) of −0.37 ppm, which is of the same value as the isotope shift for F-H-F,[25] known as the strongest documented hydrogen bond.[26] Additionally, the $^1$H/$^2$H spectra show a large negative isotopic shift (−0.17 ppm). Together, these results, along with the large downfield shift ($\delta = 3.2$ ppm), and solvent exchange behavior are evidence of a strong, almost linear hydrogen bond.[27] Comparatively, the IR spectrum is fairly uninformative in a classical sense, thus barring a fourfold increase in the extinction coefficient of the OH stretch of *in*-**1** compared to that of *out*-**1**.[28]

Could this be an example of what Jemmis et al. term a no-shift hydrogen bond, that is, one in which OH bond-shortening and bond-lengthening factors precisely cancel?[5] Excellent overlap between a lone pair (*n*) on F and the σ* of OH should command a red shift. Nevertheless, the predicted OH bond lengths are close (0.962 Å for *in*-**1** versus 0.961 Å for *out*-**1**). The lack of elongation in the OH bond of *in*-**1** may be due in part to strain. After all, the rigid nature of the cage places the OH group in close proximity to the fluorine. It is illustrative to compare the anhydride **7** as a control in which red-shifting hydrogen-bonding tendencies have been minimized, yet a substantial proximity-based "jousting" interaction (with an attendant blue shift) remains (Figure 5). At the B3LYP/6-311++G** level of theory, the C-*in*-H bond (1.083 Å, 25.5% s character in hybrid) is shorter than the C-*out*-H (1.094 Å, 23.2% s) by 0.011 Å. The coupled vibrations of the C-*in*-H bonds are predicted to be blue-shifted by 50 $cm^{-1}$ (asym) and 93 $cm^{-1}$ (sym) from the closest CH vibrations in the molecule. To summarize, the low-energy structure of *in*-**1** seems to lie at the equilibrium distance at which blue and red shifts cancel. However, depending upon reference compounds, a very slight

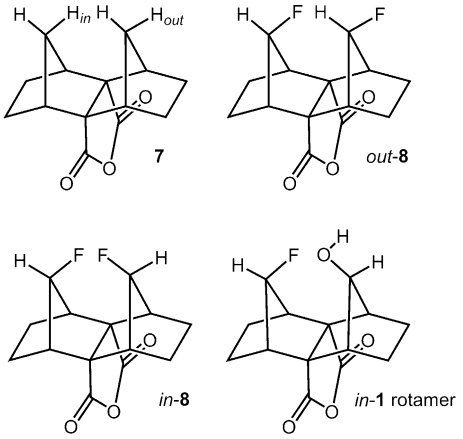



***Figure 5.*** Structures of hydrogen-bond controls used in calculations.

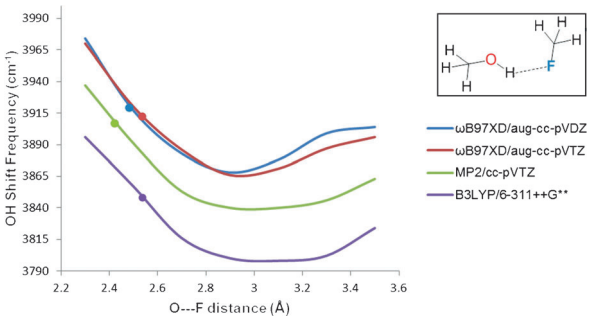



***Figure 6.*** Effect of O···F distance on the predicted OH stretch of the MeOH/MeF complex. Predicted OH stretch of free MeOH is marked with a solid dot.

blue-shift hydrogen-bond may be inferred, thus reminding us that the no-shift aspect is virtual rather than exact.

The nature of the hydrogen bond in *in*-**1** can also be evaluated by the application of QTAIM parameters (B3LYP/6-311++G**).[29] For example, the electron density ($\rho$) at the BCP is appreciable (0.052). The question of strain is germane as well, and *out*-**1** is predicted to be more stable than *in*-**1** by 3.7 kcal at B3LYP/6-311++G**. In contrast, the *in*-difluoride and *out*-difluoride isomers **8**, which contain significantly lower hydrogen-bonding capability, are separated by 13.1 kcal. These molecules can be thought of as computational controls. They are sterically fairly similar to *in*-**1** and *out*-**1**. Thus the significant attenuation in the gap between *in*-**1** and *out*-**1** is largely attributable to the hydrogen-bond. Alternatively, the $C_s$-symmetric bond rotamer of *in*-**1** may provide another semiquantitative measure[31]—it is 7.1 kcal less stable than *in*-**1** itself, and its calculated OH···F though-space coupling is only 11 Hz. Once again, these data point to *in*-**1** as possessing a significant hydrogen bond.

As a control to judge the no-shift aspect of the O-H-F interaction, we subjected the simplest model system, the complex of fluoromethane (MeF) and methanol (MeOH), to calculations at a level of theory (ωB97XD/aug-cc-pVTZ) known to handle hydrogen bonding in an exemplary fashion (Figure 6).[17] At equilibrium, the complex shows an H–F distance of 2.07 Å, and an F–O distance of 2.92 Å (bond angle 144°). Varying the F–O distance of the complex provides an illuminating insight. At large distances, the OH stretch approaches that of calculated free MeOH at 3914 $cm^{-1}$. As the distance shrinks (and the complex strengthens) a red shift occurs in the OH stretch and peaks at near the equilibrium distance of the complex (2.92 Å). As the F–O distance is further shortened, a blue-shift trend appears and rapidly increases. At around 2.5–2.6 Å, the complex reveals cancelling red and blue shifts resulting in a no-shift interaction (relative to MeOH), which not coincidentally, is close to the O–F distance in *in*-**1** as determined by both calculation and crystal structure. At 2.5 Å, the interaction is predicted to have a higher density at the BCP (0.035) than in the equilibrium structure (0.018). Repeating the process at the ωB97XD/aug-cc-pVDZ level of theory resulted in a similar result, albeit with slightly higher frequencies at larger F–O distances.

Finally, when the rigid structure of *in*-**1** is loosened (e.g. in congeners **13**–**14**), a red shift is calculated, even though the magnitude of the H–F interaction decreases (Figure 7), a result which is in line with our prediction for the MeF/MeOH system as well.

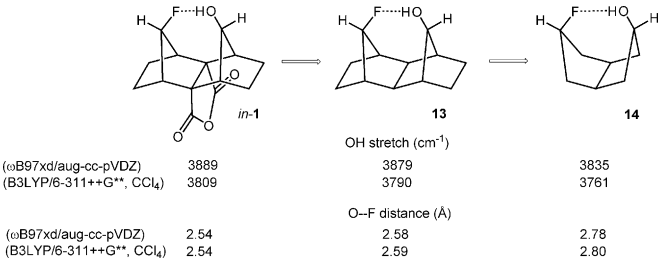



***Figure 7.*** Effect of O···F distance on the predicted OH stretches of **13**–**14**.

In conclusion, the cage system reported herein contains an unusually strong asymmetric hydrogen bond between an OH donor and a covalent F acceptor. The structure has been extensively characterized by NMR methods (coupling constants, isotopic chemical shift perturbations, proton exchange rates and calculations) and crystallographic studies, all of which are consistent with a strong interaction. In contrast, *in*-**1** shows little to no perceptible shift in the OH stretch of the IR spectrum relative to nonhydrogen-bound standards in non-interactive solvents, an example of a putative no-shift hydrogen bond, in which blue and red shifts virtually cancel relative to that of the controls.

## *Experimental Section*

General experimental procedures and characterization data can be found in the Supporting Information. CCDC 991440 (*in*-**1**), 991441 (**4**), 991442 (**5**) 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.

Received: March 22, 2014
Revised: June 2, 2014
Published online: July 2, 2014

**Keywords:** cage molecules · fluorine · hydrogen bonds · noncovalent interactions · NMR spectroscopy

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