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Note

Can the $-CF_3$ Group Act as a Tight, Well-Defined Hydrogen Bond Acceptor? A Clear Crystallographic $CF_2-F\cdots H-N^+$ Interaction Says Yes

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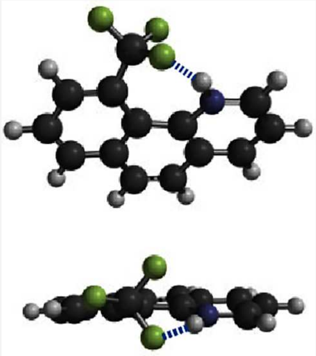
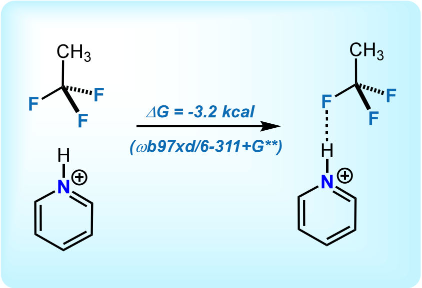
ABSTRACT: The CF_3 group is well noted for being noninteractive with other functional groups. In this Note, we present a highly rigid model system containing a significant hydrogen bonding interaction between a charged N−H donor and a CF_3 acceptor that challenges this accepted wisdom. Spectroscopic and single crystal X-ray crystallography data characterize this interaction, consistent with a weak to moderate hydrogen bond that would be difficult to observe in an intermolecular system.



The trifluoromethyl group is such a commonly occurring substituent in newly approved drugs that it is easily taken for granted.[1−4] A strongly deactivating substituent, it can inhibit metabolic degradation and extend the *in vivo* lifetime of pharmaceuticals.[5] Although useful in principle, this property renders $-CF_3$-containing compounds potential environmental contaminants. Consequently, the CF_3 group is well noted for being relatively noninteractive with other functional groups.[6] A cursory consideration would suggest little to no H-bond-accepting character from this highly electrophilic deactivating group. Nevertheless, several theoretical and experimental studies on the trifluoromethyl group as a hydrogen bond acceptor have been reported.[7−11] In general, these $C-F_2-F\cdots H-X$ (X = C, N, O) interactions were found in relatively flexible or complicated systems and, absent crystallographic evidence, their nature remains elusive.[7,8] We thought it would be worthwhile to contribute an especially well-defined example of such an interaction in which all bonding alternatives are strictly foreclosed. In this Note, we present a highly rigid model system containing a significant hydrogen bonding interaction between a charged N−H donor and a CF_3 acceptor that contravenes accepted wisdom. Spectroscopic and single crystal X-ray crystallography data characterize this interaction, consistent with a weak (perhaps moderate) hydrogen bond that would be difficult to observe in an intermolecular system

Our study began with a preliminary DFT calculation that pointed us toward an attractive interaction for a basic system (Scheme 1). Bringing together 1,1,1-trifluoroethane with a pyridinium N−H lowers the calculated free energy of the assembly by ∼3.2 kcal (ωB97XD/6-311+G**) in the gas phase. A simple survey within the CSD[12] and PDB[13] databases also demonstrates the potential existence of this interaction in crystal structures of small molecules. Figure 1 shows an array of close contacts in crystal structures deposited in the CSD as of 2024. The results included reveal a spectrum of weak interactions between trifluoromethyl groups and various H-

Scheme 1. $N^+-H\cdots F-CF_2R$ Interaction[a]



[a] Calculated at ωB97XD/6-311+G**.

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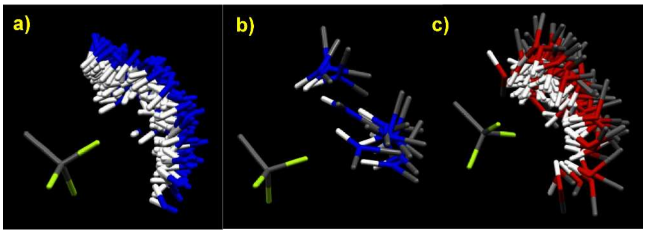


Figure 1. Through-space interactions between trifluoromethyl groups and hydrogen bond donors from crystal structures in the CCBD restricted to less than −0.2 vdW corrected distance range. Generated using IsoStar 2023.2.0 (Build 382240), pulling from the CSD version 5.44 (updated September 2023). (a) aliphatic NH^+, (b) aromatic NH^+, and (c) alcohol OH.[14]

bond donors, specifically aliphatic cationic N−H, aromatic cationic N−H, and neutral O−H substituents. The aliphatic N−H examples are particularly illustrative due to the discontinuous geometric distribution that emerges, which can be attributed to the presence of carboxylate anions in the sampled structures. In addition to a population of relatively nonuniform interactions oriented toward fluorine, there exists another population clearly aligned toward the R group of $R-CF_3$. These R-oriented groups include the carboxylates as well as other charged species or ionic interactions that fall outside the scope of this Note. To focus on the closest interactions falling below the 2.5 Å threshold at which dispersive interactions become more probable, we restricted the search to distances less than or equal to −0.2 vdW radii of the trifluoromethyl group. In any event, although the resulting interactions are not incredibly common, examples do exist, all of which are fairly weak and display an expected loose variety of directional characteristics.

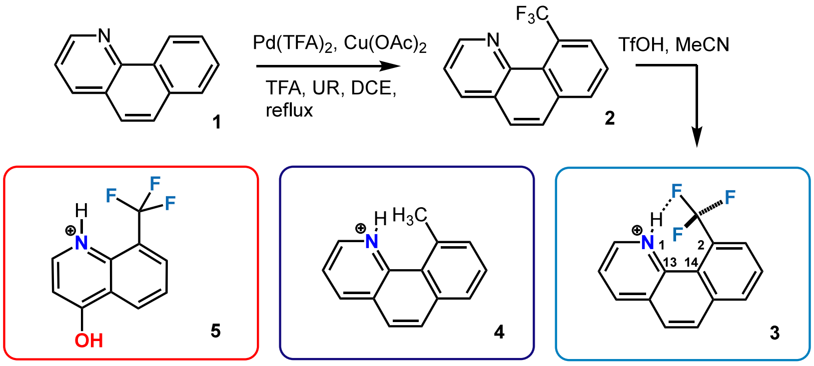
Thus, the question becomes, how can we strengthen (and thereby better define) the interaction? Recently, we reported a series of very close contacts between fluorine and various functional groups on 4,5-disubstituted phenanthrene systems whose "crossed-sword" substituents cannot escape proximity on account of the fairly rigid phenanthrene scaffold.[15−17] These earlier results caused us to consider that a hydrogen bond interaction involving a CF_3 donor would potentially occur on 10-(trifluoromethyl)benzo[*h*]quinolin-1-ium (compound **3**) because of the extreme forced polycompatibility between the N−H proton and one or more fluorine atoms. Our hypothesis was bolstered by calculations (ωB97XD/6-311+G**) that show a close $N^+H\cdots F$ contact of 1.83 Å.

In pursuit of direct evidence, our synthesis of the model system began with a palladium-catalyzed aromatic trifluoromethylation of benzo[*h*]quinoline **1** to afford **2**.[18,19] The product was then protonated by triflic acid in MeCN (or other solvents) to afford target system **3** (Scheme 2). The control compound 10-methylbenzo[*h*]quinolin-1-ium triflate (compound **4**) was also synthesized using a similar strategy.[20] With the intermediates in hand, we conducted NMR studies of compounds **3** and **4**. The N−H protons of both species display broad peaks in CD_3CN at −30 °C, suggesting dynamic activity.

Although compound **3** is more electron deficient, the N−H proton in **3** is observed at 12.85 ppm in CD_3CN, which is 0.35 ppm more shielded than its methylated analogue. In both model and control systems, a small water peak can be observed that stands in slow exchange with the pyridinium ions on the NMR time scale. A through-space spin−spin coupling of 7.5 Hz between the pyridinium hydrogen and the CF_3 group is observed as well. Correspondingly, a quartet with the same coupling constant is expected in the proton NMR spectrum, yet the N−H peak is too broad for observation, even at −80 °C in CD_2Cl_2. DFT calculations predict that the fluorine atoms of static compound **3** would split the N−H proton by 25, 3.5, and 1.7 Hz or an average of 10 Hz, fairly close to what we observe. This average takes into account that the low barrier of rotation about the $C-CF_3$ bond prevents the accurate measurement of individual spin−spin couplings in solution.

Next, we turned to single crystal X-ray crystallography as the best way to characterize the interaction. First, after some effort, a single crystal of **2** was grown by the slow evaporation of a MeCN solution. In the crystal structure of compound **2**, we first noted the structure's overall C_s symmetry (Figure 2). The molecule is characterized by an evident $n \rightarrow \sigma^*$ interaction between the lone pair of nitrogen and the *anti*-C−F bond, indicated by a lengthening of the antipositioned C−F bond observed for the two crystallographically independent molecules in the asymmetric unit (1.3546(18) and 1.3564(17) Å) relative to the other two C−F bonds (1.3305(19)/1.3460(18) and 1.3308(18)/1.3407(18) Å). This $n \rightarrow \sigma^*$ interaction is replaced by an N−H···F−C H-bond in a similarly grown crystal of cation **3**, wherein we observe a N−H···F−C distance of 1.927(12) Å; the discrepancy between the theoretical calculation and the observation in this case is best explained by the influence of the counterion, which engages in a long,

Scheme 2. Synthesis of 3 and Structures to Be Studied[a]



[a](Pd(TFA)$_2$: palladium trifluoroacetate. TFA: trifluoroacetic acid. UR: Umemoto's reagent.

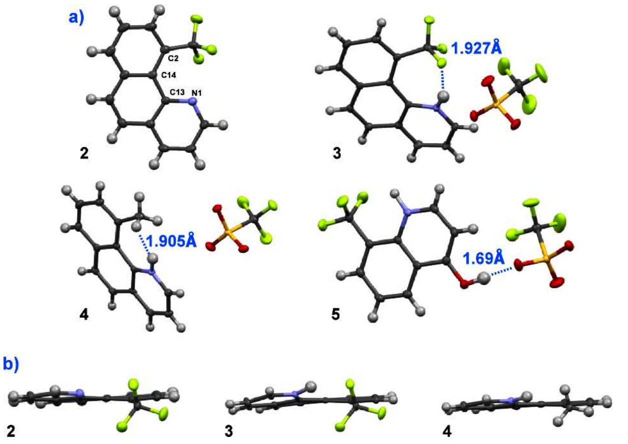


Figure 2. (a) X-ray crystal structures of the unprotonated compound **2**, the triflate salts **3** and **4**, and quinoline-based compound **5** (50% thermal ellipsoids). (b) In compound **3**, the twist in the trifluoromethyl group illustrates the distortion arising from the F-to-H interaction absent from the unprotonated compound **2**. Twist was measured through (N1−C13−C14−C2) dihedral angles, yielding 5.7(2)° and 9.38(18)° for compounds **2** and **4**, respectively, with a value of 14.7(2)° in compound **3**.

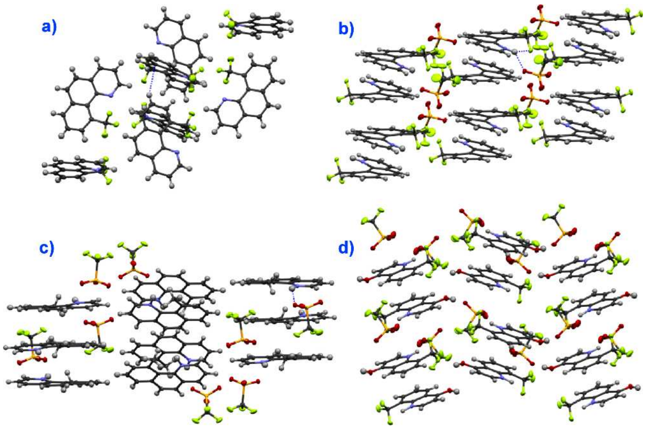


Figure 3. Packing structures of the compounds (a) **2**, (b) **3**, (c) **4**, and (d) **5** (50% probability level). (a) The dashed blue line indicates the relatively close (2.08 Å) interaction between the N−H proton and the triflate oxygen. (b) The line indicates a bifurcated interaction between the N−H proton and the CF_3 (1.93 Å) as well as the triflate oxygen (2.20 Å). (c) Edge-to-face distance of 2.98 Å is indicated by a dashed blue line.

bifurcated interaction with the pyridinium proton. In addition to the short N−H···F−C distance, the N−H···F angle is 150.0(19)°, which fulfills a basic directionality requirement for hydrogen bonding.[21,22] It is worth mentioning that the orientations of the substituents in compounds **3** and **4** are very different; in the crystal of protonated compound **4**, the two hydrogens of the methyl group spread almost symmetrically around the N−H proton with N−H···H-C distances at 1.91, 1.96, and 3.14 Å; in compound **3**, one fluorine forms the favorable H-bond interaction, whereas the other two fluorine atoms are located *away* from the proton with N−H···F−C distances at 2.41 and 3.68 Å. Furthermore, the presence of substituents distorts the conformation of the entire molecule in curious ways. For example, the torsional aromatic distortions (N1−C13−C14−C2) for compounds **4** and **3** are 9.38(18)° and a much larger 14.7(2)°. To examine the importance of benzo[*h*]quinolinium's forced geometry to the formation of the hydrogen bond interaction, the crystal structure of compound **5** was also obtained. Surprisingly, the primary hydrogen bond interactions were from $O-H\cdots O-SO_2CF_3$ (1.689(4) Å) and $N^+-H\cdots O-SO_2CF_3$ (1.897(11) Å), and only very weak interactions were observed between the N^+-H and CF_3 groups (>2.35 Å).

Examination of the extended diagrams provides illuminating indications of the way that protonation and hydrogen bond formation dictate crystal packing (Figure 3). For example, the phenanthrene-derived structures (Figure 3a−c) adopt some form of π-stacking conformation, with the compounds alternating in orientation. On the other hand, the arrangement of each intervening stack differs drastically. The unprotonated trifluoromethyl substituted compound **2** has an almost perpendicular edge-to-face "T" arrangement, whereas the protonated methyl compound **4** adopts a bent "V" arrangement intermediate between a parallel offset and a T-form. Compound **3**, in contrast, maintains a perfectly parallel and slightly offset arrangement. The perpendicular organization of compound **2** introduces a relatively close edge-to-face distance of 2.98 Å, but the most interesting difference concerns its interaction with the triflate counterion, which may play a major role in dictating the packing. In compound **4**, the positively charged N−H forms a tight interaction with the triflate counterion, resulting in an H···O distance of only 2.084(13) Å. In compound **3** that distance stretches to 2.20(2) Å as the N−H proton becomes less available because of the interaction with the CF_3 fluorines. By contrast, hydroxylated quinoline **5** adopts an arrangement best described as alternating stacks of offset pairs. Unlike the three previously discussed structures, π-stacking interactions are restricted to flipped pairs of molecules with each stack of pairs twisted 64° relative to the next and each sequential pair offset by 4.0 Å horizontally from the next pair in the stack. The arrangement puts triflate sulfonates directly between the hydroxyl group (1.69 Å) of the stack and the N−H (1.90 Å) of the next.

The $F_2C-F\cdots H-N$ hydrogen bond of **3** was further characterized through a series of computational experiments, including NBO and AIM analyses, that collectively bolster evidence for a typical electrostatic interaction. AIM analysis reveals a bond critical point[23] between one of the trifluoromethyl fluorines and the N−H proton with ρ = 0.0288, consistent with a hydrogen bond of weak to moderate strength. We also performed NBO calculations, which are visualized in Figures 4 and 5. The electrostatic potential surface map shown in Figure 6 illustrates the tight gradient between the electropositive N−H atom and a relatively electronegative trifluoromethyl fluorine atom. The electrostatic nature of the interaction is further highlighted in Figure 6 where the presence of a raised saddle-point indicates an anomalous electron density between the fluorine and proton. That shared electron density, clearly visible in both the bisecting and orthogonal planes, suggests an electrostatic interaction.[24]

A solid-state IR study performed on compound **3** indicates the H-bond interaction is blue-shifted relative to salt **4**.[25] The free N−H stretch in compound **2** was found at 3289 cm^{-1}, whereas the N−H stretch in **4** resides at 3278 cm^{-1}. The isodesmic relation depicted in Figure 6 (ωB97XD/6-311++G**, −6.74 kcal/mol) provides an indication of the stabilizing nature of the interaction in carefully designed analogues intended to minimize electronic differences. Note that this energy does not represent a true hydrogen bond

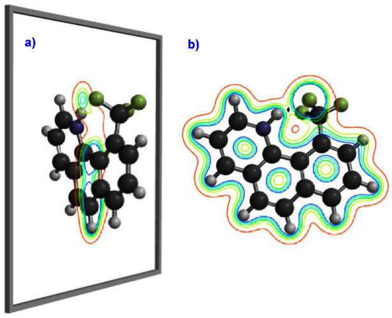


Figure 4. (a) Bisecting and (b) orthogonal contour slices from NBO-derived electron density calculations on compound **3** performed using the Spartan program at M062*X*/6-311++G** (0.04 isovalue). The saddle points (indicated in (b) with a black diamond), visible in both the bisecting and orthogonal planes, indicate an electrostatic interaction between the trifluoromethyl group and the N−H proton.

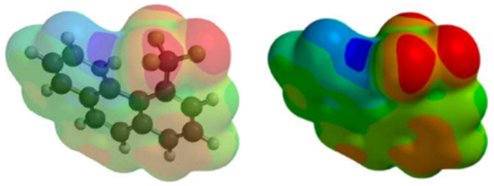


Figure 5. Electrostatic potential surface maps of compound **3**, calculated using the Spartan program at M062*X*/6-311++G** (0.002 e/au^{-3}; property range 201−572 kJ): red, negative; blue, positive.

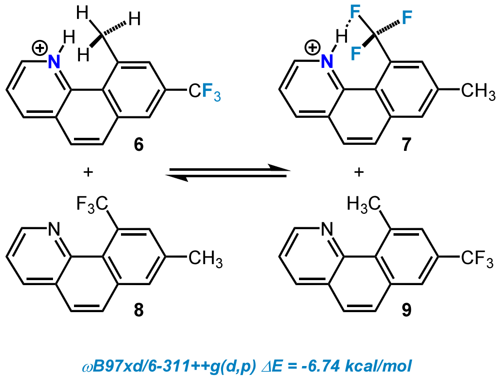


Figure 6. Isodesmic calculations of stabilization energies contrasting protonated and unprotonated groups with proximal and distal CF_3 groups.

"strength", as confounding factors within each molecule are not taken into account, for example, the fact the probe H-bond distorts the planarity of the aromatic system.

In conclusion, the "crossed-sword" system reported in this Note contains a tight, well-defined hydrogen bond interaction between the pyridinium proton and the trifluoromethyl group. The structure of the probe molecule was extensively characterized using crystallographic, spectroscopic, and computational methods. This study provides further context for the unusual bonding properties often associated with fluorinated compounds and suggests multiple avenues for future inquiry. Considering the profound significance of trifluoromethyl groups in pharmaceuticals, this study should provide deeper insight into its properties in both organic and medicinal chemistry.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c00873.

Experimental procedures, spectra, single crystal X-ray crystallography data, and computational data (PDF)

Accession Codes

CCDC 2347045−2347048 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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