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Short Communication

Synthesis and X-Ray crystallography of a substituted trityl fluoride: Ordering power of a C-F bond

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A B S T R A C T

Herein we report the synthesis and X-ray crystallographic study of a per(meta-t-butyl) substituted trityl fluoride in order to explore possible intermolecular F—F interactions, as inspired by the recent work of Schreiner et al. on close H contacts. Instead of proximate F atoms, we uncovered an unusual ordering effect caused by an interaction between the polar fluorine and nearby C—H bonds, a result that may carry some interest in regards to fluorinated compounds' interactions with enzymes.

1. Introduction

Recently, Schreiner et al. reported the crystal structure of a remarkable per(meta-t-butyl) substituted trityl derivative in which an astonishingly close intermolecular contact (1.566 Å) between hydrogen atoms exists. [1]. What would otherwise be an unfavorable steric interaction in the crystal structure is more than counterbalanced by favorable London dispersion interactions between tert-butyl groups that serve to enforce the close contact. It made us consider the effect that fluorine substitution of the tertiary hydrogen could have on the structure - would a similar close contact result, or would fluorine's increased size and electron density dictate another packing regime?

Regardless of the outcome, we thought it an interesting problem to address, as fluorine is sometimes touted as an "isostere" for hydrogen, [2,3] especially for medical chemistry purposes [4–7]. In our minds, this supposition is simplistic if not naïve, and is always worth further exploration given the prominence of fluorine in agricultural [8–10] and pharmacological [4,5,7,11–13] chemistry. We therefore synthesized a per(meta-t-butyl) substituted trityl fluoride analogue **2** to Schreiner's molecule, and crystallized it for an X-ray analysis.

2. Results

The synthesis of the target molecule began with the lithiation of 3,5-t-butylbromobenzene (t-butyllithium in THF) followed by reaction with ethyl carbonate to yield tertiary alcohol **3**. Fluorination of **1** was accomplished with excess diethylaminosulfurtrifluoride (DAST) in MeCN. The resulting tertiary fluoride **2** proved to be very highly moisture sensitive, and was only isolable in our hands through direct crystallization from the reaction mixture that only then afforded fine needles suitable for X-ray structure determination. [14] The instability of **2** made spectroscopic characterization difficult, although ^{19}F, ^{1}H, and proton-decoupled ^{13}C NMR turned out to be feasible to obtain with proper solvent choice and preparation (see supporting information) (Scheme 1).

The single crystal X-ray analysis revealed that the introduction of fluorine results in an entirely different crystal packing regime than the one observed for Schreiner's molecule. Although certain t-butyl groups do interact closely with one another as noted by Schreiner, there is none of the characteristic alkyl group interweaving observed in Schreiner's molecule. Nor was a head-to-head orientation of the tertiary F-substituent observed; the molecules in the unit cell adopt an off-center, head-to-tail arrangement instead, with alternating lines of cells arranged antiparallel to one another (Scheme 2).

In the crystal of **2**, fluorine exhibits relatively fewer interactions with the atoms around it. In fact, it occupies a somewhat "open pocket" in the observed structure - surrounded by t-butyl groups, but with only two close contacts of ca. 2.57 Å and 2.62 Å to hydrogen atoms residing on a t-butyl group of a neighboring molecule. Surprisingly, this weak dipolar interaction had the effect of "locking down" the affected t-butyl group in the crystal packing regime. Many other t-butyl groups within the structure had a degree of rotational freedom - observed as disorder - within the crystal structure; the t-butyl groups in contact with fluorine maintain a single orientation, presumably due to a favorable dispersion interaction between the oppositely polarized atoms that rigidly anchors the group. Similar polar/nonpolar contacts have been noted in previous studies of the interactions of fluorinated drugs bound to enzymes [15], but to our knowledge this represents a rare instance in which the resulting ordering effect has been acknowledged. Although the van der Waals radii of hydrogen and fluorine are not that far apart (1.46 Å for

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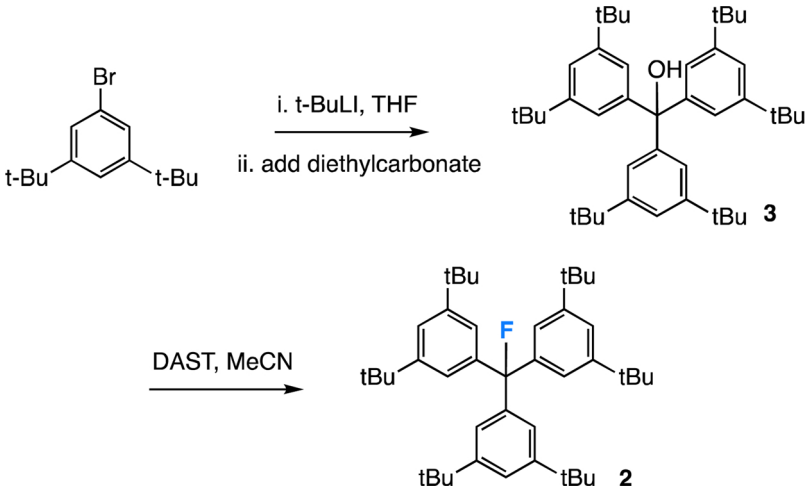
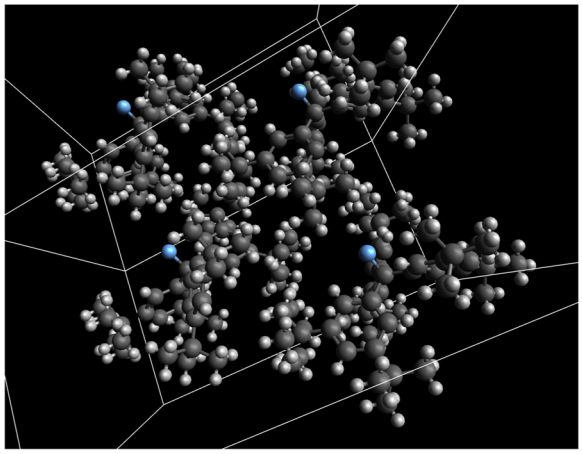


Scheme 1. Synthesis of **2**.



Scheme 2. Packing diagram of the crystal of **2**.

fluorine and 1.20 Å for hydrogen) [3], the similarities don't go much further. Fluorine is highly electronegative; hydrogen is not. Fluorine possesses three lone pairs of electrons whereas hydrogen possesses none. Of course, although one cannot rule out alternative crystal morphologies obtained through different crystallization regimens, in several crystallization attempts we obtained only the form described above.

To shed more light on the t-butyl group "locking" mechanism, we carved out a minimalist motif of atoms from the crystal structure that isolates the C—F—H interactions and subjected it to calculation. Several of the atoms in the crystal structure had to be replaced with hydrogen atoms (ideal, optimized bond lengths) in order to simply the motif. For example, the dissociation energy of motif **4** is calculated to be 0.88 kcal (ωB97xd/6-311 + + G**). No doubt, the dipolar interaction between the C—F bond and the proximate hydrogen atoms is weak, but ca. one kcal seems to be enough to achieve "anchoring" in the crystal (Scheme 3).

As a point of reference, the X-ray structure of alcohol **3**, first synthesized by Rösel et al. [16], was contrasted with **2**. In **3,** one set of hydroxyl groups interacts through a key hydrogen bond (approximate OH—O distance = 2.33 Å), whereas the others, in analogy to fluorine, interact with proximate t-butyl groups.

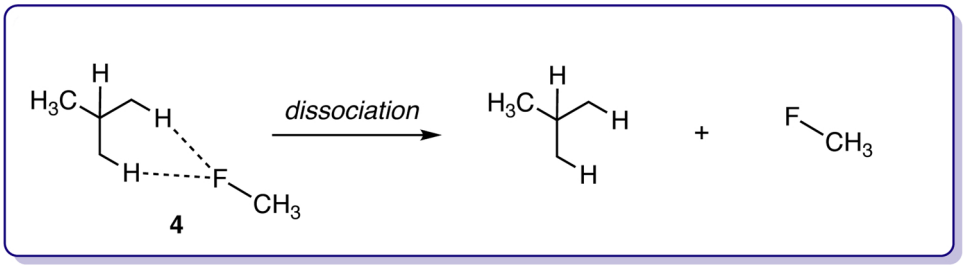
3. Conclusion

We have shown that trityl fluoride **2** crystallizes in a fundamentally different way than the corresponding trityl hydride **1** of Schreiner et al. Rather than in close contact, the F atoms orient themselves in order to interact instead with proximate t-butyl groups. In each instance in which a fluorine atom interacts with a proximate t-butyl group, that group is ordered, whereas certain others in the crystal are not. One could imagine that this "locking" phenomenon could manifest as rigidifying differences that we envision as having some effect on the biochemical machinery of an enzyme– substrate complex [4,17,18], for example. Given the prominence of fluorine in current high-impact medicinal chemistry [19,20], it is our hope that such possibilities will be explored further.

4. Experimental

4.1. Synthesis of tris(3,5-di-tert-butylphenyl)methanol (3)

3,5-Di-tert-butylbromobenzene (3.8 g, (14.0 mmol, 3.0 eq.) was added to a flame-dried three-neck flask equipped with a stir-bar under an inert atmosphere. Freshly distilled THF (60 mL) was added, and the mixture was stirred until the bromide was completely dissolved. The reaction mixture was then cooled to −78 °C, and 25 mL of 1.7 M t-butyllithium in pentanes (42.0 mmol, 6.0 eq) were added dropwise by cannulation under



Scheme 3. Dipolar interaction of a C–F bond with proximate methyl groups.

continuous stirring. The reaction mixture was allowed to warm to room temperature, at which point 0.150 mL (1.23 mmol, 1.0 eq) of diethyl carbonate was added dropwise to the stirring solution. The reaction was allowed to proceed for 1 h before quenching with water. The aqueous layer was extracted with Et_2O (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude product as a white solid. Crystallization from acetonitrile afforded **3** as clear prisms. IR (solid ν/cm^{-1}): 2962, 2903, 2866, 1595, 1476, 1392, 1361, 1248, 1202, 1173, 897, 880, 826, 737, 728, 718. ^1H NMR (400 MHz, CD_3CN, 25 °C, TMS): δ 7.33 (t, 3 H, J_{HH} = 1.8 Hz, arom. H), δ 7.11 (d, 6 H, J = 1.8 Hz, arom. H), δ 4.16 (s, 1H, COH), δ 1.22 (s, 54 H, CH_3). ^{13}C NMR (400 MHz, CD_3CN): δ 31.82, δ 35.62, δ 118.36, δ 121.31, 123.41, δ 148.39, δ 150.79. EIMS, 200 °C, *m/z* (rel. int.): 592.9633 (5.59), 595.4906 (18.55), 596.4973 (100) $[M^+]$, 597.5003 (46.95), 598.5049 (10.93); HRMS (EI), *m/z* calcd. for $C_{43}H_{64}O$ 596.4957 $[M]^+$; found 596.4973.

4.2. Synthesis of tris(3,5-di-tert-butylphenyl)methylfluoride (2)

To a flame-dried three-neck flask equipped with a stir bar and under an inert atmosphere were added 0.1 g (0.167 mmol, 1.0 eq) of alcohol **3** and 10 mL of freshly distilled MeCN. The mixture was stirred under gentle heating until **2** had dissolved completely, then cooled to 0 °C. 0.16 mL (0.20 mmol, 1.2 eq) of diethylaminosulfurtrifluoride (DAST) was then added dropwise while continuing to stir. Once all of the DAST had been added the stir bar was removed, the reaction was allowed to come to room temperature, and dry nitrogen was forced over the reaction to remove solvent and produce fine needle crystals of **2**. The crystals were washed with freshly distilled MeCN while still under N_2 to remove any remaining DAST. A sample was taken and dried for NMR, IR, and mass analysis before submitting for X-ray analysis [19]. IR (solid, ν/cm^{-1}): 2964, 2905, 2866, 1598, 1477, 1459, 1433, 1361, 1248, 1220, 1206, 984, 897, 880, 861, 829, 728, 715, 645, 604. NMR data: ^1H NMR (400 MHz, CD_3CN, 25 °C, TMS): δ 7.44 (dt, 3 H, J_{HH} = 1.8 Hz, J_{HF} = 0.9 Hz, arom. H), δ 7.05 (dd, 6 H, J_{HH} = 1.8 Hz, J_{HF} = 1.0 Hz, arom. H), δ 1.23 (s, 54 H, CH_3). ^{13}C NMR (400 MHz, CD_3CN): δ 31.81, δ 35.73, δ 118.33, δ 122.81 (d, J_{CF} = 2.2 Hz), δ 123.22 (d, J_{CF} = 5.9 Hz), δ 144.23 (d, J_{CF} = 23.59 Hz), δ 151.50. ^{19}F NMR (300 MHz, CD_3CN); δ -127.0 (m, 1 F, CF). EIMS, 200 °C, *m/z* (rel. int.): 598.4923 (61) $[M]^+$, 583.4693 (100) $[M-CH_3]^+$; HRMS (EI), *m/z* calcd. for $C_{43}H_{63}F^+$ 598.4914 $[M]^+$; found 598.4923.

Declaration of Competing Interest

The authors declare no competing interests/no conflicts of interests.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jfluchem.2019.109377.

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