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Interaction of a C−F Bond with the π-System of a C═C Bond or “Head On” with a Proximate C−H Bond

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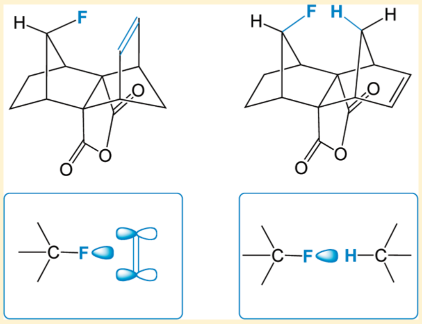
S Supporting Information

ABSTRACT: We describe the synthesis and preliminary study of two molecules, in which a fluorine atom is positioned proximately above the π-orbitals of a C═C bond or else wherein a C−F bond interacts in a “head on” fashion with a proximate C−H bond. The spectroscopic characteristics of these unusual interactions are documented, X-ray crystallographic analyses are reported, and theoretical calculations are employed to support the observed spectroscopy.

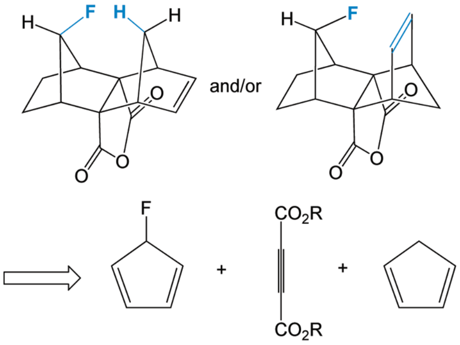


The unique properties of fluorine in organic molecules impart an unusual spectrum of reactivity and structural qualities that have intrigued chemists for decades.[1] In our eyes, one particularly outstanding problem involves the ability of fluorine to interact with the π-systems of C═C bonds;[2] a particularly close interaction[3] would also enhance the prospect of anchimeric assistance[4] by fluorine in a reaction of the double bond. Similarly, the interaction of a C−F bond with a proximate C−H bond would also be of interest.[5] Given the rising importance of organofluorine compounds in medicinal chemistry,[6] the answers to such questions may prove valuable. One good place to begin would be the design and study of systems in which a C−F bond is held directly above the π-system of a C═C bond, or else a C−F bond interacts in a “head on” fashion with a C−H bond. Such arrangements would serve as prototypical starting points for an investigation of reactivity patterns and fluorine’s potential role. In this note, we present unique systems for the investigation of the promixate interaction of F with the π-system of a double bond and its possible consequences for chemical reactivity and also report the juxtaposition of a C−F and a C−H bond.

In the design of appropriate systems, we speculated that a sequential cycloaddition of 5-fluorocyclopentadiene and cyclopentadiene (CpH) with an electron-deficient dienophile would afford products in which newly incorporated carbon atoms could be fused into close proximity to the fluorine atom (Scheme 1). Somewhat dauntingly, such a reaction could theoretically afford a mixture of eight diastereomers. Fortunately, McClinton and Sik[7] have shown that in situ generation of 5-fluorocyclopentadiene in the presence of excess dimethylacetylenedicarboxylate selectively affords diene **2**, in which the F atom is syn to a maleate moiety (Scheme 2).

Monohydrogenation of **2** followed by anhydride formation would give rise to an activated fluorinated dienophile **3** suitable for further elaboration. Still, the reaction of **3** with CpH could give rise to four different diastereomers, including the desired ones. We finally sought guidance from computation; for example, transition states for the reaction of **3** and CpH were first calculated at B3LYP/6-31G*. In all four cases, the transition states retain a plane of symmetry (C_s point group) that implies a synchronous reaction. The two desired isomers in which F interacts significantly with the *in*-C−H and C═C bonds (exo−exo and exo−endo) were found to proceed through the two lowest energy pathways in the predicted order, separated by less than 0.5 kcal/mol in free energy (Scheme 3).

Scheme 1. Synthetic Strategy



With this information in hand, the synthesis of the target molecules **1** and **4** began with the reaction of 5-fluorocyclopentadiene (generated in situ from the reaction of Selectfluor with CpTl) and excess dimethylacetylenedicarboxylate to afford bicyclic fluoride **2**. Diene **2** is monoreduced by

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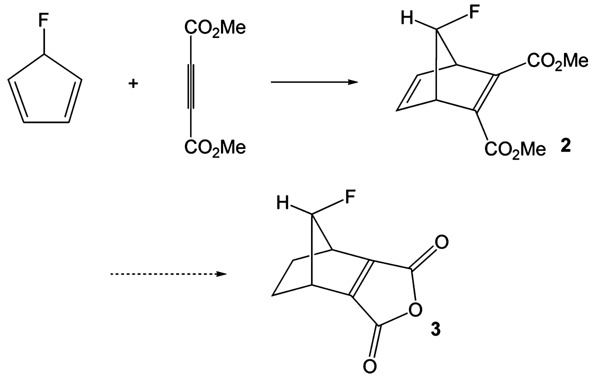
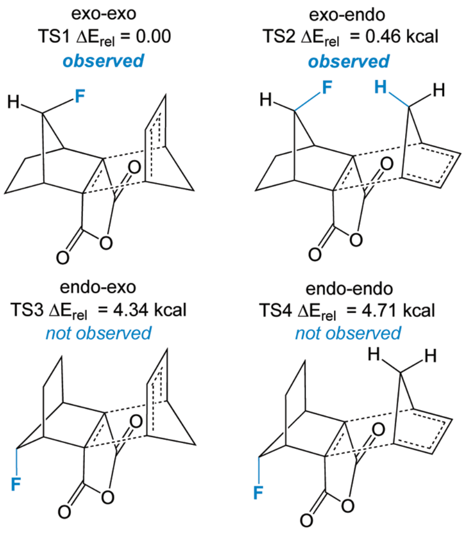
Scheme 2. Strategy for Dienophile Synthesis

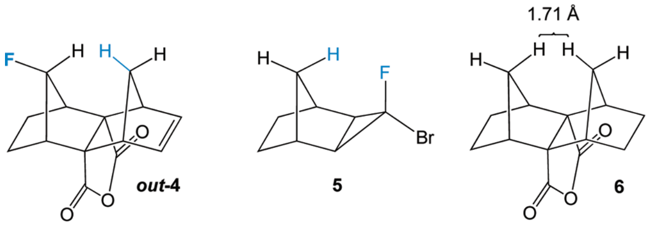


Scheme 3. Transition States for the Diels−Alder Reaction of 3 with CpH



Pd/H_2 and cyclized to anhydride **3** through treatment with ethanolic KOH followed by ring closure (trifluoroacetic anhydride [TFAA]). Diels−Alder reaction of **3** with excess CpH at 150−170 °C in a sealed tube affords a mixture of two major diastereomers (**1** and **4**) that are separable by careful column chromatography (hexanes/EtOAc eluent, Scheme 4). Diastereomer **1** (40% yield) was identified as the exo−exo isomer, whereas the structure of **4** (afforded in 30%) is consistent with the exo−endo isomer, thus confirming our theoretical prediction in a remarkably accurate fashion (see discussion below). The endo−exo and the endo−endo diastereomers, predicted to form through significantly higher energy transition states, are not observed, confirming that our theoretical investigation took place at a suitable level of theory.

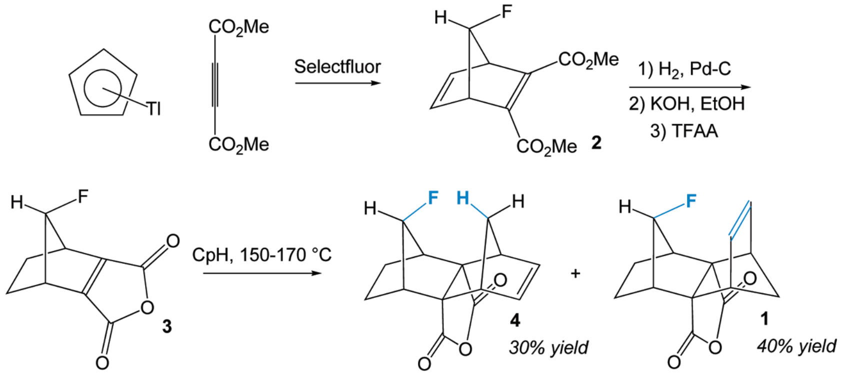
We expect the "*in*"-pointing[8] fluorine of **4** to engage in a tight interaction with the *in*-pointing hydrogen on the neighboring one-carbon bridge. For example, the optimized structure of **4** at B3LYP/6-311++G** reveals a close interaction of the *in*-fluorine and H of 1.91 Å (at HF/6-311++G**, a very similar value [1.91 Å] was obtained). The in C−H bond is abnormally compressed (1.079 Å vs >1.09 Å for all other C−H bonds). The calculated scaled ^{19}F chemical shift[9] of **4** (^{19}F $\delta = -176$, $CFCl_3$ reference) agrees very well with experiment (^{19}F $\delta = -173$), indicating that the theoretical model is consistent with observation. The primarily through-space coupling[10] ($^{1}H-^{19}F$) of the *in* atoms is 7.4 Hz (confirmed by calculation at 7.2 Hz[11]), indicating an interaction; complementarily, the coupling of F to the opposite bridgehead ^{13}C is 1.9 Hz. In analogy to **4** is cyclopropane **5**, whose *in*-H−*in*-F coupling is 3.6 Hz (calculated *in*-H−*in*-F distance 2.17 Å at B3LYP 6-311++G**).[12] Comparison of **4** to the hypothetical "*out*" fluoride, ***out*-4**, suggests that **4** is about 4 kcal/mol less stable than this configurational isomer (B3LYP/6-311++G**), a fact at least partially attributable to nonbonded interactions between H and F.



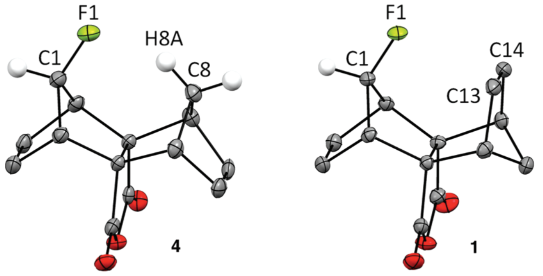
***out*-4** **5** **6**

Additionally, the structure of **4** was determined through a single crystal X-ray study (Scheme 5) in which H8A was refined freely, resulting in an F1···H8A distance of 1.96(2) Å. As hydrogen atoms are insensitive to X-ray diffraction, their location can only be approximated; in this case, 1.96 Å is almost certainly too long. Alternatively, the structure was re-refined with a more realistic C−H bond length (C8−H8A was set to 1.08 Å on the basis of the results of the DFT calculations). This refinement (F1···H8A distance of 1.88 Å) is more consistent with the optimized geometry obtained from DFT calculations; no standard uncertainty is given for the former since the H atoms attached to C8 have been placed at calculated positions.

Scheme 4. Synthesis of the Target Molecules



Scheme 5. X-ray Crystal Structures of 4 and 1 (50% Probability Thermal Ellipsoids)

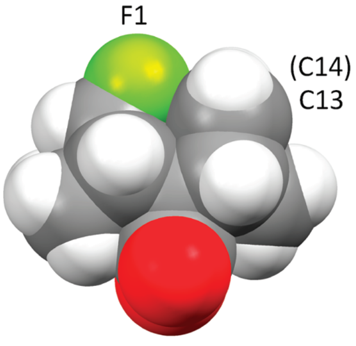


Compare this result to a similar "cage" compound synthesized by Ermer et al., in which hydrogen replaces fluorine, affording a close H−H contact of 1.71 Å (compound **6**).[5]

Turning our attention to diastereomer **1**, we found that theoretical and spectroscopic evidence is consistent with a through-space interaction between F and the *π*-orbitals of the double bond. At B3LYP/6-311++G**, fluorine is predicted to be 2.70 Å away from each alkenyl carbon (at HF/6-311++G** 2.71 Å was calculated). The empirical chemical shift of fluorine (^{19}F $\delta = -157$) is within range for a secondary alkyl fluoride and agrees well with theoretical calculations of the fluorine chemical shift at B3LYP/6-311++G** (^{19}F calcd $\delta = -156$).[13] As fluorine is generally little perturbed by ring current (anisotropic) effects, it is perhaps no surprise that a large upfield shift is not observed. A more definitive measure would be the observed coupling between the alkenyl ^{13}C and the *in*-F in **1** of 11.9 Hz, consistent with a sizable through-space interaction. It is also noted that given the geometry of the interaction, spin information is most likely transmitted through orbital overlap of F and C rather than through mediation of a C−H bond.

Similar to **4**, we were successful at determining the crystal structure of **1** (Scheme 5), which confirms that the fluorine and the double bond formed by C13 and C14 are in proximity [F1···C13 = 2.6801(19), F1···C14 = 2.7106(18) Å; both distances are consistent with those obtained from DFT calculation]. Distortions in bond angles from ideal values suggest a repulsive interaction (and resultant strain) between F and the C═C bond, as would be expected from overlap of the filled *π*-system with lone pairs on F. Not surprisingly, the distance from the alkenyl carbon to fluorine is outside the sum of the single bond covalent radii of the two elements (1.39 Å),[14a] as well as the double bond covalent radii (1.31 Å),[14b] but well within the sum of their van der Waals radii (3.17 Å, see space filling model derived from crystal structure in Scheme 6).[15] Most importantly, the X-ray data suggest that any electrophilic chemical transformation of the C═C bond may *mandatorily* involve F in some fashion through anchimeric assistance, steric hindrance, or a combination of the two. In future work, we will explore in detail the chemical reactivity of the unusual C═C bond in **1** and related molecules.

Scheme 6. X-ray Derived Space Filling Model of 1



■ EXPERIMENTAL SECTION

General Methods. Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents and reagents were dried and distilled by standard methods. ^{1}H and ^{13}C spectra were acquired on a 400 MHz NMR in $CDCl_3$; ^{19}F spectra were taken on a 300 MHz NMR in $CDCl_3$. The ^{1}H, ^{13}C, and ^{19}F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and/or $CFCl_3$ (δ 0.00 ppm). NMR data are reported in the following format: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet), integration, coupling constants [Hz]). IR data were obtained using an FT-IR with a NaCl cell. All measurements were recorded at 25 °C unless otherwise stated. Characterization of **2**[7] was consistent with the literature precedent.

Computational Methods. The Gaussian '09[16] package and Spartan '06 were used for all calculations. Transition states were calculated using Gaussian at B3LYP/6-31G* and were confirmed as proper saddle points through vibrational analyses. Chemical shifts and coupling constants were computed using Gaussian at the B3LYP/6-311++G** level of theory and scaled by 0.9614.[17] ^{19}F calculated chemical shifts were fitted to the empirical equation (at B3LYP/6-311++G**) $\delta_{calc} = -0.914\delta + 142.63$, whereas ^{13}C calculated chemical shifts were fitted to the empirical equation (at B3LYP/6-311++G**) $\delta_{calc} = -1.019\delta + 180.00$. The isotropic values ($\delta$) employed were obtained from the CS UT calculation parameter found in the results menu. Coupling constants were calculated by the Gaussian option "coupling constants" in the setup dialogue. Geometry optimizations were likewise determined using the B3LYP/6-311++G** level.

X-ray Crystallography. All reflection intensities were measured at 110(2) K using a KM4/Xcalibur (detector: Sapphire3) with enhance graphite-monochromated Mo *Kα* radiation ($\lambda = 0.71073$ Å) under the program CrysAlisPro (Versions 1.171.33.31 for **1** and 1.171.33.48 for **4**, Oxford Diffraction Ltd., 2009). The program CrysAlisPro was used to refine the cell dimensions. Data reduction was done using the program CrysAlisRED. The structure was solved with the program SHELXS (Sheldrick, 2008) and was refined on F^2 with SHELXL-97 (Sheldrick, 2008). Analytical numeric absorption corrections based on a multifaceted crystal model were applied using CrysAlisRED. The temperature of the data collection was controlled using the system Cryojet (manufactured by Oxford Instruments). The H-atoms (except when specified, see below) were placed at calculated positions using the instructions AFIX 13, AFIX 23, or AFIX 43 with isotropic displacement parameters having values 1.2 times U_{eq} of the attached C atoms. For **4**, two sets of refinement were made. In the first set, the H-atoms H8A/H8B attached to C8 were initially found from difference Fourier maps, and their atomic coordinates were allowed to refine freely without any sets of restraints/constraints. In the second refinement, the C8−H distances were set to about 1.08 Å (which is consistent from DFT calculations) using the HIMP instruction in XP (Shelxtl suite program; Sheldrick, 2008). Their atomic coordinates were then fixed so that the C8−H distances remain approximately 1.08 Å after running a few refinement cycles.

The structures of **1** and **4** are both ordered.

1, $F_w = 248.24$, colorless thick plate, 0.50 × 0.38 × 0.12 mm^3, orthorhombic, *Pbca* (No. 61), $a = 11.8147(3)$, $b = 13.0024(3)$ $c = 14.1560(3)$ Å, $V = 2174.64(9)$ Å^3, $Z = 8$, $D_x = 1.516$ g cm^{-3}, $\mu = 0.117$ mm^{-1}, abs. corr. range: 0.959−0.987. 12166 reflections were measured up to a resolution of $(\sin\theta/\lambda)_{max} = 0.62$ Å^{-1}. 2137 reflections were unique ($R_{int} = 0.0366$), of which 1694 were observed [$I > 2\sigma(I)$]. 163 parameters were refined. R_1/wR_2 [$I > 2\sigma(I)$]: 0.0393/0.0957. R_1/wR_2 [all refl.]: 0.0557/0.1012. $S = 1.063$. Residual electron density found between −0.23 and 0.32 e Å^{-3}.

4, F_w = 248.24, colorless thin rod, 0.43 × 0.13 × 0.09 mm^3, triclinic, $P\bar{1}$ (No. 2), a = 7.4987(4), b = 7.6417(5), c = 10.9956(7) Å, α = 97.190(6), β = 102.765(5), γ = 112.365(6)°, V = 552.78(6) Å^3, Z = 2, D_x = 1.491 g cm^{-3}, μ = 0.115 mm^{-1}, abs. corr. range: 0.974– 0.992. 4821 reflections were measured up to a resolution of $(\sin\theta/\lambda)_{\max}$ = 0.59 Å^{-1}. 1926 reflections were unique (R_{int} = 0.0388), of which 1491 were observed [$I > 2\sigma(I)$]. 171 (165 with atomic coordinates fixed for H8A/H8B) parameters were refined. R_1/wR_2 [$I > 2\sigma(I)$]: 0.0402/0.1025. R_1/wR_2 [all refl.]: 0.0548/0.1067. S = 1.063. Residual electron density found between −0.23 and 0.30 eÅ^{-3}.

General Procedure for Synthesis of Diels–Alder Adducts. *Anhydride* **3**. To a three-necked round-bottom flask equipped with a condenser, stopper, and glass tube was added degassed THF (100 mL), Pd/C (0.04 g), and diene **2** (4.5 g, 19.8 mmol, 1 equiv). H_2 was bubbled into the reaction for 1.5 h, after which the reaction was filtered through Celite and concentrated in vacuo to give a clear oil, which was dissolved in 30 mL of EtOH. To this solution was added KOH (3.0 g, 52.8 mmol, 2.5 equiv), and the reaction was refluxed for 1.5 h while being monitored by ^{19}F NMR. Upon completion, the reaction was quenched with H_2O, cooled in an ice bath, and acidified with concentrated H_2SO_4. The resulting precipitate was filtered and washed with EtOH. The filtrate was evaporated to dryness to yield a light brown oil. The oil was basified with 2 M NaOH, the organic entities were extracted with ether, and the aqueous layer ws acidified with concentrated H_2SO_4. Upon precipitate formation, the acidified mixture was extracted with ether and evaporated to dryness to give 3.9 g (70%) of the putative intermediate dicarboxylic acid. Without further purification, the resultant product was combined with TFAA (3.9 g, 19.4 mmol, 1.0 equiv) and refluxed overnight. The progress of the reaction was monitored by removing aliquots from the reaction mixture, concentrating them to dryness, and examining the corresponding ^{19}F NMR. Upon completion, the mixture was evaporated to dryness and was recrystallized from ether/pentane yielding a white solid as **3** (3.11 g, 60%).

Diels–Alder adducts 1 and 4. To a bomb charged with **3** (1.5 g) was added cyclopentadiene (30 mL). The resulting suspension was heated to 160 °C for 3 h, the resulting mixture was cooled, and excess cyclopentadiene and dicyclopentadiene were removed by distillation under high vacuum. The residue was dissolved in a minimal amount of $CHCl_3$ and purified by column chromatography on silica using 2% EtOAc/hexanes as eluent to give the two diastereomers **1** and **4** (0.82 g, 40% and 0.61 g, 30%).

Compound Characterization. (**3**): White solid; mp = 117 °C; ^{1}H NMR ($CDCl_3$) δ 5.0 (d, 1H, J = 75 Hz), 3.5 (s, 2H), 2.2–2.1 (m, 2H), 1.4–1.3 (m, 2H); ^{13}C NMR ($CDCl_3$) 159.9, 155.9, 108.1 (d, J = 212 Hz), 43.9 (d, J = 17 Hz), 21.3 (d, J = 5.5 Hz); ^{19}F NMR ($CDCl_3$) δ −204.5 (m, 1F); IR (CH_2Cl_2) 2998 cm^{-1}, 1782 cm^{-1}; HRMS (ESI+) calcd. for $NaC_9H_7FO_3$ calcd. 205.0277, found 205.0281.

(**4**): White solid; mp = 176 °C; ^{1}H NMR ($CDCl_3$) δ 6.5 (m, 2H), 5.1 (d, 1H, J = 62 Hz), 3.3 (s, 2H), 3.1 (m, 1H), 2.7 (s, 2H), 1.9 (d, 2H, J = 10 Hz), 1.5 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 173.1, 140.1 (d, J = 2 Hz), 102.2 (d, J = 215 Hz), 69.1, 48.6 (d, J = 40 Hz), 48.1, 42.6 (d, J = 13 Hz), 23.4 (d, J = 9 Hz); ^{19}F NMR ($CDCl_3$) δ −173.1 (m, 1F); IR (CH_2Cl_2) 2992 cm^{-1}, 1779 cm^{-1}, 1268 cm^{-1}; HRMS (ESI+) calcd. for $NaC_{14}H_{13}FO_3$ calcd. 271.0747, found 271.0743.

(**1**): White solid; mp = 103 °C ^{1}H NMR ($CDCl_3$) δ 6.2 (m, 2H), 4.7 (d, 1H, J = 60 Hz), 3.4 (m, 2H), 2.6 (s, 2H), 1.9–1.3 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.1, 136.6 (d, J = 10 Hz), 100.1 (d, J = 219 Hz), 69.1, 50.8, 49.8, 41.7 (d, J = 14 Hz), 23.5 (d, J = 10 Hz); ^{19}F NMR ($CDCl_3$) δ −157.1 (m, 1F); IR (CH_2Cl_2) 2991 cm^{-1}, 1780 cm^{-1}, 1267 cm^{-1}; HRMS (ESI+) calcd. for $NaC_{14}H_{13}FO_3$ calcd. 271.0747, found 271.0752.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR, ^{13}C NMR, ^{19}F NMR, X-ray crystallographic data, and computational coordinate files are available free of charge via the Internet at http://pubs.acs.org/.

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