

CHARACTERIZATION OF SIX BOND CARBON-FLUORINE COUPLING IN 4-FLUROCHALCONES

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Abstract

Long range six bond carbon-fluorine coupling (${}^6J_{C-F}$) was observed in the ${}^{13}C$ NMR spectra of 4-fluorosubstituted chalcones. The ${}^6J_{C-F}$ coupling constants were measured to be 1.9 Hz. The magnitude of the coupling constants is consistent with ${}^6J_{C-F}$ reported in fluorinated polyaromatic hydrocarbons.

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Introduction

Chalcones are a group of 1,3-diaryl-2-propen-1-one compounds that have been found to exhibit a wide variety of biological activity including anticancer, antimicrobial, and anti-inflammatory properties.¹ This class of molecules also serves as important starting materials for the synthesis of several pharmacologically interesting types of heterocyclic compounds such as isoxazoles, pyrazolines and pyrazoles.² Chalcones which contain a fluorine substituent on one of the aromatic rings are of particular interest in pharmaceutical development since fluorine atoms in molecules often enhance the therapeutic properties of drugs.³

In our research involving the synthesis of chalcones and their derivatives, we have observed an interesting ${}^6J_{C-F}$ long range coupling between the α carbon of the alkene and a fluorine atom substituted on one of the aryl groups in the ${}^{13}C$ NMR spectra of several 4-fluorosubstituted chalcones. (Figure 1) Reports in the literature of long-range coupling between carbon and fluorine through bonds have been mostly limited to fluorinated polyaromatic hydrocarbons.⁴ Hayamizu et al documented this ${}^6J_{C-F}$ long range coupling for two 4-fluorosubstituted chalcones in their extensive compilation of NMR spectral data of 4,4'-substituted chalcones but there was no discussion as to the unique nature of this coupling.⁵ Herein we report the observation and measurement of ${}^6J_{C-F}$ coupling in six additional 4-fluorosubstituted chalcones.

EXPERIMENTAL

Materials and Methods

4-fluorobenzaldehyde (TCI America), acetophenone (Aldrich), 4-methylacetophenone (Acros), 4-methoxyacetophenone (Acros), 4-ethoxyacetophenone (TCI America), 4-fluoroacetophenone (TCI America), 4-chloroacetophenone (TCI America), 4-bromoacetophenone (TCI America), 4-iodoacetophenone (TCI America), ethanol (VWR), sodium hydroxide (VWR), dichloromethane (VWR) and hexane (VWR) were purchased from their respective suppliers and used without further purification.

All NMR spectra were collected using a JEOL 400-ECX spectrometer (400 MHz, 9.39 T, JEOL, Inc., Peabody, MA, USA) equipped with a NM40-TH5/AT/FG-B probe running Delta NMR

Software v. 4.3.6. Samples were prepared at approximately 10 mg/mL in $CDCl_3$. Proton and carbon spectra were collected at 399.78MHz and 100.52 MHz, respectively, and referenced to $CDCl_3$.

General procedure for the synthesis of chalcones (1-8)

Chalcones were synthesized by mixing 4-fluorobenzaldehyde (3 mmol) and the appropriate 4-substituted acetophenone (3 mmol) in 95% EtOH (2.5 mL). An aqueous solution of sodium hydroxide (0.3 mL, 15 mM) was added to the mixture dropwise. The mixture was allowed to stir at room temperature for 45 min. Cold dH_2O (4 mL) was added and the mixture was cooled in an ice bath before isolating the solid product by vacuum filtration. Each chalcone was purified by recrystallization with dichloromethane/hexane (4:1). Synthesis and full characterization of each chalcone has been previously reported by various authors.^{5,6}

(E)-[3-(4-fluorophenyl)-1-phenyl]prop-2-en-1-one (1).^{6a} Light yellow solid (426 mg, 63% yield), purified by recrystallization (DCM/hexane = 4:1): mp 88–91 °C; IR (ATR) ν_{max} 3067, 1660, 1602, 1574, 1494, 1158 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 8.00

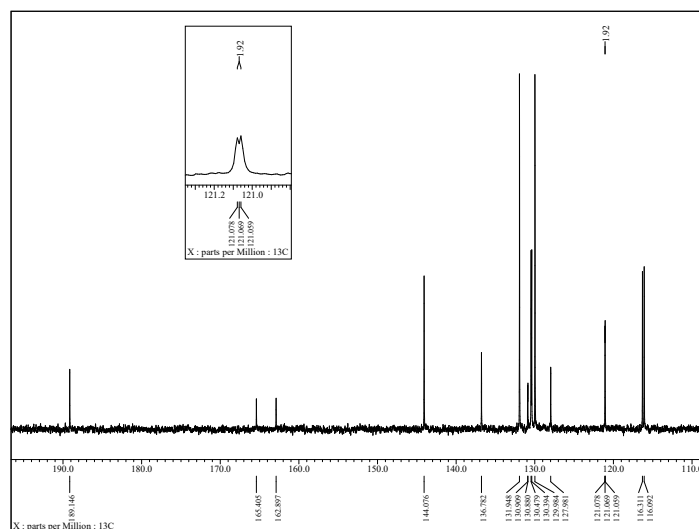


Figure 1. ${}^{13}C$ NMR spectrum of (E)-[1-(4-bromophenyl)-3-(4-fluorophenyl)]prop-2-en-1-one (7).

(d, $J = 6.9$ Hz, 2H), 7.76 (d, $J = 15.6$ Hz, 1H), 7.64–7.55 (m, 3H), 7.49 (t, $J = 7.8$ Hz, 2H), 7.45 (d, $J = 15.6$ Hz, 1H), 7.09 (t, $J = 8.9$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 190.30, 164.03 (d, $^1J_{\text{C-F}} = 252.1$ Hz), 143.48, 138.08, 132.83, 131.1 (d, $^4J_{\text{C-F}} = 3.8$ Hz), 130.32 (d, $^3J_{\text{C-F}} = 8.6$ Hz), 128.63, 128.45, 121.71 (d, $^6J_{\text{C-F}} = 1.9$ Hz), 116.11 (d, $^2J_{\text{C-F}} = 21.1$ Hz) ppm.

(E)-[3-(4-fluorophenyl)-1-(4-methylphenyl)]prop-2-en-1-one (2).^{6b} Pale yellow solid (459 mg, 64% yield), purified by recrystallization (DCM/hexane = 4:1): mp 131–135 °C; IR (ATR) ν_{max} 3048, 2916, 1655, 1596, 1588, 1505, 1161 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, $J = 8.2$ Hz, 2H), 7.71 (d, $J = 15.6$ Hz, 1H), 7.58 (dd, $J = 5.5, 8.7$ Hz, 2H), 7.41 (d, $J = 15.6$ Hz, 1H), 7.25 (d, $J = 8.7$ Hz, 2H), 7.05 (t, $J = 8.9$ Hz, 2H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 189.76, 163.96 (d, $^1J_{\text{C-F}} = 251.1$ Hz), 143.72, 143.05, 135.50, 131.18 (d, $^4J_{\text{C-F}} = 2.9$ Hz), 130.26 (d, $^3J_{\text{C-F}} = 8.6$ Hz), 129.33, 128.61, 121.74 (d, $^6J_{\text{C-F}} = 1.9$ Hz), 116.08 (d, $^2J_{\text{C-F}} = 22.0$ Hz), 21.67 ppm.

(E)-[3-(4-fluorophenyl)-1-(4-methoxyphenyl)]prop-2-en-1-one (3).⁵ White solid (597 mg, 77% yield), purified by recrystallization (DCM/hexane = 4:1): mp 119–121 °C; IR (ATR) ν_{max} 3067, 2936, 1653, 1596, 1572, 1504, 1157, 1033 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, $J = 9.2$ Hz, 2H), 7.76 (d, $J = 15.6$ Hz, 1H), 7.62 (dd, $J = 5.5, 8.7$ Hz, 2H), 7.46 (d, $J = 15.6$ Hz, 1H), 7.10 (t, $J = 8.7$ Hz, 2H), 6.79 (d, $J = 8.7$ Hz, 2H), 3.88 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 188.45, 163.90 (d, $^1J_{\text{C-F}} = 252.1$ Hz), 163.45, 142.63, 131.29 (d, $^4J_{\text{C-F}} = 2.9$ Hz), 130.97, 130.78, 130.21 (d, $^3J_{\text{C-F}} = 8.6$ Hz), 121.52 (d, $^6J_{\text{C-F}} = 1.9$ Hz), 116.05 (d, $^2J_{\text{C-F}} = 22.0$ Hz), 113.84, 55.49 ppm.

(E)-[1-(4-ethoxyphenyl)-3-(4-fluorophenyl)]prop-2-en-1-one (4).^{6c} White solid (595 mg, 73% yield), purified by recrystallization (DCM/hexane = 4:1): mp 117–119 °C; IR (ATR) ν_{max} 3077, 2979, 1655, 1597, 1572, 1507, 1154, 1049 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.01 (d, $J = 9.2$ Hz, 2H), 7.74 (d, $J = 16.0$ Hz, 1H), 7.61 (dd, $J = 5.5, 8.7$ Hz, 2H), 7.46 (d, $J = 16.0$ Hz, 1H), 7.08 (t, $J = 8.7$ Hz, 2H), 6.95 (d, $J = 9.2$ Hz, 2H), 4.10 (q, $J = 6.9$ Hz, 2H), 1.44 (t, $J = 6.9$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 188.44, 163.89 (d, $^1J_{\text{C-F}} = 251.1$ Hz), 162.90, 142.54, 131.32 (d, $^4J_{\text{C-F}} = 3.8$ Hz), 130.78, 130.19 (d, $^3J_{\text{C-F}} = 7.7$ Hz), 121.55 (d, $^6J_{\text{C-F}} = 1.9$ Hz), 116.04 (d, $^2J_{\text{C-F}} = 21.1$ Hz), 114.27, 63.76, 14.67 ppm.

(E)-[1,3-bis(4-fluorophenyl)]prop-2-en-1-one (5).⁵ Pale yellow solid (470 mg, 73% yield), purified by recrystallization (DCM/hexane = 4:1): mp 116.8–118.2 °C; IR (ATR) ν_{max} 3075.38, 1658.47, 1596.90, 1504.64 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (dd, $J = 5.50, 9.16$ Hz, 2H), 7.76 (d, $J = 15.57$ Hz, 1H), 7.62 (dd, $J = 5.50, 8.70$ Hz, 2H), 7.41 (d, $J = 15.57$ Hz, 1H), 7.16 (t, $J = 8.70$ Hz, 2H) ppm, 7.10 (t, $J = 8.70$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 188.63, 165.61 (d, $^1J_{\text{C-F}} = 255.0$ Hz), 164.09 (d, $^1J_{\text{C-F}} = 252.1$ Hz), 143.75, 134.38 (d, $^4J_{\text{C-F}} = 3.8$ Hz), 131.06 (d, $^3J_{\text{C-F}} = 9.6$ Hz), 130.96 (d, $^4J_{\text{C-F}} = 3.8$ Hz), 130.37 (d, $^3J_{\text{C-F}} = 8.6$ Hz), 121.19 (d, $^6J_{\text{C-F}} = 1.9$ Hz), 116.17 (d, $^2J_{\text{C-F}} = 21.1$ Hz), 115.77 (d, $^2J_{\text{C-F}} = 21.1$ Hz) ppm.

(E)-[1-(4-chlorophenyl)-3-(4-fluorophenyl)]prop-2-en-1-one (6).⁵ Pale yellow solid (492 mg, 70% yield), purified by recrystallization (DCM/hexane = 4:1): mp 133.2–134.2 °C; IR (ATR) ν_{max} 3062.68, 1664.46, 1598.44, 1506.69 cm^{-1} ; ^1H NMR (400 MHz,

CDCl_3) δ 7.94 (d, $J = 8.7$ Hz, 2H), 7.77 (d, $J = 15.57$ Hz, 1H), 7.62 (dd, $J = 5.50, 8.70$ Hz, 2H), 7.47 (d, $J = 8.70$ Hz, 2H), 7.40 (d, $J = 15.57$ Hz, 1H), 7.10 (t, $J = 8.70$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 189.94, 164.14 (d, $^1J_{\text{C-F}} = 252.1$ Hz), 144.00, 139.27, 136.36, 130.90 (d, $^4J_{\text{C-F}} = 3.8$ Hz), 130.42 (d, $^3J_{\text{C-F}} = 8.6$ Hz), 129.86, 128.96, 121.11 (d, $^6J_{\text{C-F}} = 1.9$ Hz), 116.19 (d, $^2J_{\text{C-F}} = 21.1$ Hz) ppm.

(E)-[1-(4-bromophenyl)-3-(4-fluorophenyl)]prop-2-en-1-one (7).⁵ Pale yellow solid (605 mg, 72% yield), purified by recrystallization (DCM/hexane = 4:1): mp 134.6–135.7 °C; IR (ATR) ν_{max} 3061.88, 1662.69, 1596.86, 1505.42 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.87 (d, $J = 8.70$ Hz, 2H), 7.77 (d, $J = 16.03$ Hz, 1H), 7.63 (m, 4H), 7.39 (d, $J = 15.57$ Hz, 1H), 7.11 (t, $J = 8.70$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 189.15, 164.15 (d, $^1J_{\text{C-F}} = 252.1$ Hz), 144.08, 136.78, 131.95, 130.90 (d, $^4J_{\text{C-F}} = 2.9$ Hz), 130.44 (d, $^3J_{\text{C-F}} = 8.6$ Hz), 129.97, 127.98, 121.06 (d, $^6J_{\text{C-F}} = 1.9$ Hz), 116.20 (d, $^2J_{\text{C-F}} = 22.0$ Hz) ppm.

(E)-[3-(4-fluorophenyl)-1-(4-iodophenyl)]prop-2-en-1-one (8).^{6d} Pale yellow solid (530 mg, 56% yield), purified by recrystallization (DCM/hexane = 4:1): mp 142.9–144.9 °C; IR (ATR) ν_{max} 3078.61, 1655.75, 1595.28, 1509.86 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J = 8.24$ Hz, 2H), 7.76 (d, $J = 15.57$ Hz, 1H), 7.70 (d, $J = 8.24$ Hz, 2H), 7.62 (dd, $J = 5.50, 8.70$ Hz, 2H), 7.37 (d, $J = 16.03$ Hz, 2H), 7.10 (t, $J = 8.70$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 189.49, 164.15 (d, $^1J_{\text{C-F}} = 254.0$ Hz), 144.11, 137.94, 137.31, 130.89 (d, $^3J_{\text{C-F}} = 3.8$ Hz), 130.44 (d, $^4J_{\text{C-F}} = 8.6$ Hz), 129.86, 121.03 (d, $^6J_{\text{C-F}} = 1.9$ Hz), 116.20 (d, $^2J_{\text{C-F}} = 22.0$ Hz), 100.83 ppm.

DISCUSSION

A representative ^{13}C NMR spectrum of 4'-bromo-4-fluorochalcone is shown in Figure 1 with an expansion of the a carbon appearing as a doublet at 121.06 ppm. The signal for the a carbon of each chalcone was attributed based on ^{13}C chemical shift assignments of 55 chalcones reported by Hayamizu et al.⁵ All of the fluorine substituted chalcones in our study exhibited a $^6J_{\text{C-F}}$ coupling with a magnitude of 1.9 Hz (Table 1). Hayamizu reported $^6J_{\text{C-F}}$ couplings for 4-fluorochalcones with $\text{R}=\text{OCH}_3$ and $\text{R}=\text{Cl}$ as 1.8 and 2.4 Hz, respectively.⁵

The observed coupling constants are similar magnitude to $^6J_{\text{C-F}}$ coupling reported for fluorinated polyaromatic hydrocarbons (F-PAHs) such as 2-fluorochrysene ($^6J_{\text{C-F}} = 0.7$ and 1.6), 3-fluorochrysene ($^6J_{\text{C-F}} = 0.4$ and 2.6) (Figure 2).⁴ Interestingly, F-PAHs also exhibit a $^5J_{\text{C-F}}$ coupling but no such coupling was observed with the b carbon in the 4-fluorochalcones. In 2-fluorochrysene and 3-fluorochrysene, the reported $^5J_{\text{C-F}}$ couplings were 1.2 Hz or less. Perhaps a $^5J_{\text{C-F}}$ coupling was

Table 1. ^{13}C - α chemical shifts (ppm) and coupling constants (Hz) between ^{13}C - α and ^{19}F in 4-fluorosubstituted chalcones.

Compound	R	^{13}C - α shift (ppm)	$^6J_{\text{C-F}}$ (Hz)
1	H	121.7	1.9
2	CH_3	121.7	1.9
3	OCH_3	121.5	1.9 ^a
4	OCH_2CH_3	121.6	1.9
5	F	121.2	1.9
6	Cl	121.1	1.9 ^b
7	Br	121.1	1.9
8	I	121.0	1.9

too small to be detected in the 4-fluorochalcones in this study but could possibly be resolved with a higher field NMR spectrometer.

Long range coupling in the NMR spectra of F-PAHs is expected due to the planarity, rigidity and extensive p systems in the molecules. Chalcones are highly conjugated but lack the structural rigidity of the fused rings in PAHs. However, a survey of the X-ray crystal structures of three of the 4-fluorochalcones analyzed here revealed torsion angles between the aryl ring and the alkene between 1.20° and 12.69°. The small torsion angles in the solid state indicate near planarity and a high degree of p orbital overlap in the aryl-alkene portion of these chalcones. These structural features can explain the observation of ${}^6J_{C,F}$ in the ${}^{13}C$ NMR spectra of these molecules.

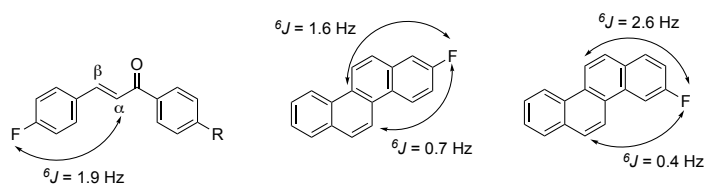


Figure 2. Comparison of ${}^6J_{C,F}$ in 4-fluoro-substituted chalcone, 2-fluorochrysene and 3-fluorochrysene.

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