NMR Spectroscopy

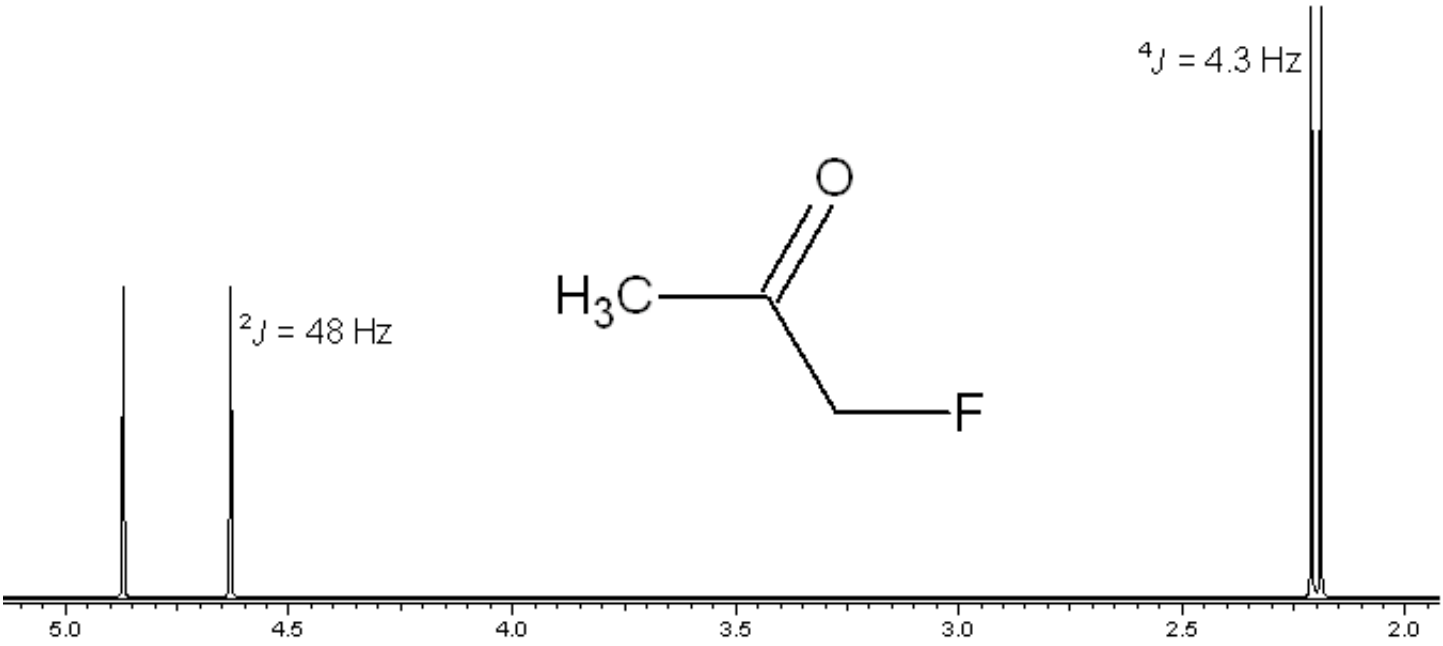
Fluorine Coupling to ^{1}H and ^{13}C

Fluorine Coupling to ^{1}H

Coupling between hydrogen and fluorine (spin 1/2) is very strong. Typical ^{2}J coupling constants are about 48 Hz. Longer range coupling is smaller. Typical ^{4}J coupling constants are about 4 Hz.

The figure below contains the NMR spectrum for fluoroacetone. The nuclear spin of fluorine is 1/2. This means that the proton signal is split into n + 1 parts.

Figure. NMR spectrum of fluoroacetone.

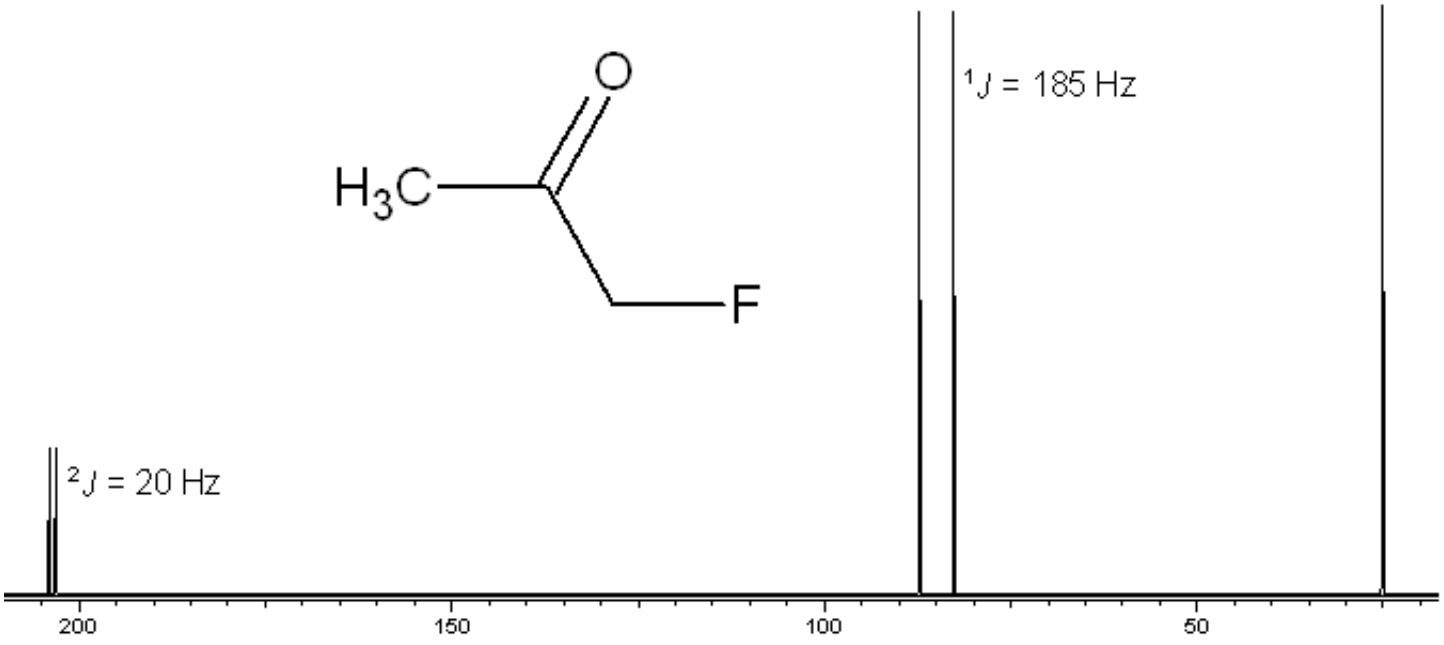


Fluorine Coupling to ^{13}C

Coupling between carbon and fluorine (spin 1/2) is very strong. Typical ^{1}J coupling constants are about 185 Hz. Longer range coupling is smaller. Typical ^{2}J coupling constants are about 20 Hz.

The figure below contains the NMR spectrum for fluoroacetone. The nuclear spin of fluorine is 1/2. This means that the carbon signals are split into n + 1 parts.

Figure. NMR spectrum of fluoroacetone.



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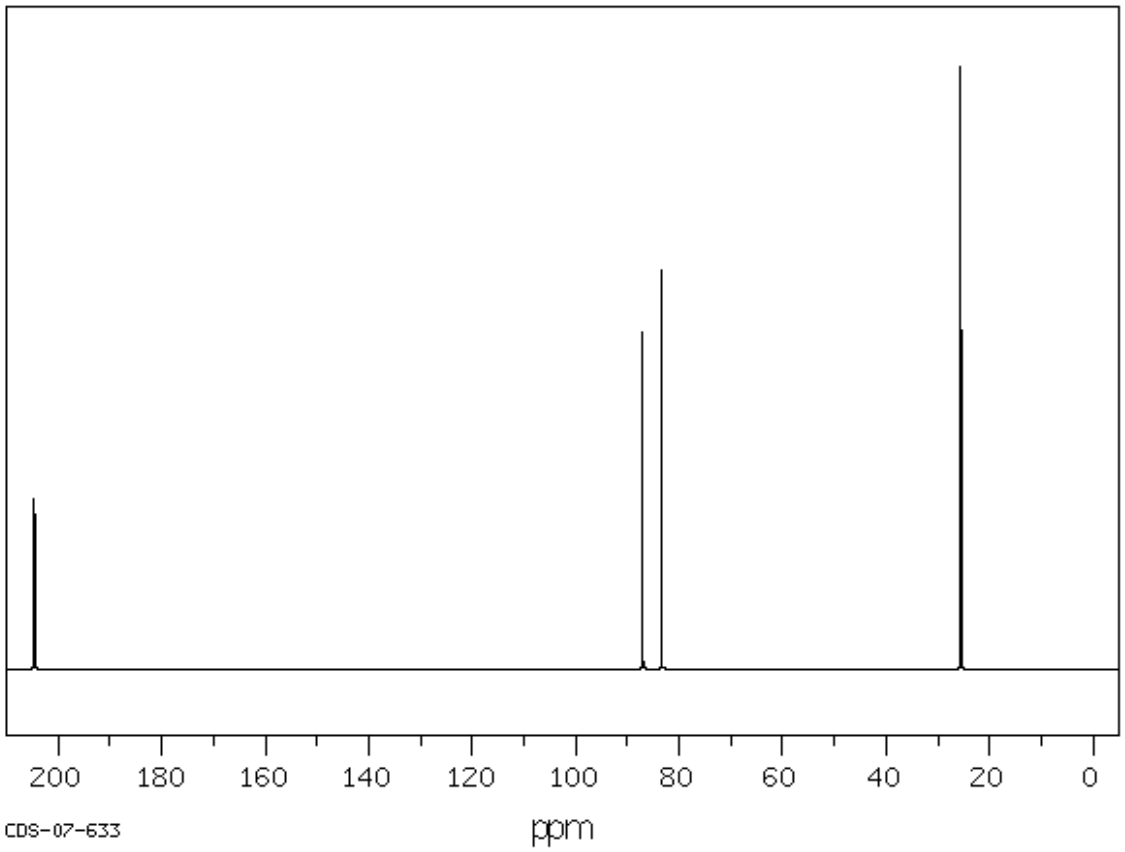
SDBS-^{13}C NMRSDBS No. 13226CDS-07-633

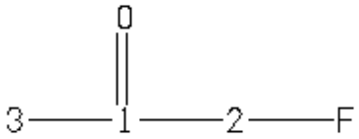
C_3 H_5 F O

fluoroacetone

50.18 MHz

0.05 ml : 0.5 ml $CDCl_3$





ppm	Int.	Assign.	
204.77	280	F	1
204.36	255	F	1
87.01	558	F	2
83.33	661	F	2
25.52	1000		3

SDBS No. 13226CDS-07-633

and hexamethylphosphoric triamide (HMPA) were purified by fractional distillation from calcium hydride. Cyclohexylamine and *tert*-butylamine were also distilled under a nitrogen atmosphere from calcium hydride before use.

A buffered acetic solution,[16a] prepared with 3.30 g of sodium acetate, 7.5 mL of glacial acetic acid, and 35 mL of distilled water, was used for hydrolyzing enolizable chiral α-fluoro ketimines. Determination of the enantiomeric excess by the use of tris[3-((heptafluoropropyl)hydroxymethylene)-(+)-camphonato]europium(III) as the chiral shift reagent was accomplished by first purifying the ketone by preparative GC or by recrystallization. The purified ketone, 3–6 mg, was diluted with 1 mL of $CDCl_3$, whereupon 100-mL increments of a standard solution of 4.6 mmol/mL of chiral shift reagent was added. After the addition of 40–46 mol % of the chiral shift reagent the diastereomeric protons were resolved and were integrated.

1-Fluoro-2-propanone (3).[18] To 250 mL of anhydrous ethylene glycol and 168 g (3.0 mol) of anhydrous potassium fluoride in a mechanically stirred 1-L flask fitted with a distillation head and a pressure-equalizing addition funnel was added dropwise at 160 °C 102 g (0.75 mol) of 1-bromo-2-propanone.[14] The crude 1-fluoro-2-propanone distilled from the reaction over a 70–120 °C boiling point range. The crude distillate was dried over anhydrous potassium carbonate and then was fractionally distilled to yield 9.00 g (20%) of fluoroacetone (**3**): bp 75–77 °C (lit.[18] bp 77 °C); ^{1}H NMR (CCl_4) δ 4.52 (d, $J_{H,F}$ = 49 Hz, 2 H, CH_2F), 2.21 (d, $J_{H,F}$ = 5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 203.50 (d, $J_{C,F}$ = 18 Hz, C=O), 84.10 (d, $J_{C,F}$ = 181 Hz, CH_2F), 23.84 (s, CH_3); ^{19}F NMR ($CDCl_3$) δ −223.5 (t, $J_{H,F}$ = 48 Hz).

Fluoroacetone Cyclohexylimine (4). To a 100-mL flask were added 7.92 g (0.08 mol) of freshly distilled cyclohexylamine, 30 mL of CCl_4, and 1 g of anhydrous magnesium sulfate. On cooling to 0 °C, 5.78 g (0.08 mol) of **3**, dissolved in 10 mL of CCl_4, was added dropwise. After warming to room temperature over 2 h, the contents were stirred an additional 12 h. Filtration, followed by removal of the solvent in vacuo and bulb-to-bulb distillation, 90–110 °C (1.5 mm), yielded 11.2 g (90%) of the α-fluoro imine: IR (neat) ν 2950 (s), 2875 (m), 1680 (m), 1460 (m), 1380 (m), 1240 (w), 1015 (s) cm^{-1}; ^{1}H NMR (CCl_4) δ 4.52 (d, $J_{H,F}$ = 48 Hz, 2 H, CH_2F), 3.41–3.10 (m, 1 H, NCH), 1.85 (d, $J_{H,F}$ = 3 Hz, 3 H, CH_3), 1.70–1.00 (m, 10 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 163.0 (d, $J_{C,F}$ = 20 Hz, C=N), 86.35 (d, $J_{C,F}$ = 178 Hz, CH_2F), 58.53 (NCH), 32.69 (CH_2), 25.08 (CH_2), 24.42 (CH_2), 12.78 (CH_3); ^{19}F NMR ($CDCl_3$) δ −223.6 ($J_{H,F}$ = 48 Hz). Anal. Calcd for $C_9H_{16}NF$: C, 68.75; H, 10.26. Found: C, 68.46; H, 10.46.

General Procedure for the Formation of 1-Fluoro-2-alkanones. To a magnetically stirred 50-mL three-necked flask containing lithium hexamethyldisilazide (LHMDS), prepared by the dropwise addition of 4.2 mL (0.007 mol) of methyllithium (1.6 M in ether) to 0.97 g (0.006 mol) of HMDS in 25 mL of THF at 0 °C, was added 1.07 g (0.006 mol) of HMPA followed by dropwise addition at −35 °C of 0.79 g (0.005 mol) of **4** in 10 mL of THF. After a half an hour, 0.005 mol of the alkyl halide in 5 mL of THF was added dropwise. After stirring another hour, the reaction mixture was poured over 10 mL of a saturated sodium bicarbonate solution and extracted with distilled hexanes (3 × 10 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed in vacuo. The crude imine, dissolved in 20 mL of pentane, was hydrolyzed by treatment with 10 mL of 5% acetic acid solution for 2 h. The phases were separated, and the organic phase was washed with saturated sodium bicarbonate solution (2 × 10 mL). After drying over anhydrous magnesium sulfate, the solvent was removed to yield the crude fluoro ketones (see Table I).

1-Fluoro-2-butanone was prepared by the addition of iodomethane (0.71 g, 0.005 mol) to **4** deprotonated with LHMDS. The reaction was worked up in the usual manner except that fluorotrichloromethane was used as solvent during the imine hydrolysis. The ketone was purified by preparative GC to yield 0.22 g (48%) of 1-fluoro-2-butanone: ^{1}H NMR (CCl_4) δ 4.68 (d, $J_{H,F}$ = 48 Hz, 2 H, CH_2F), 2.61 (dq, $J_{H,F}$ = 5 Hz, J = 7 Hz, CH_2O), 1.20 (q, J = 7 Hz, CH_3), ^{13}C NMR ($CDCl_3$) δ 84.5 (d, $J_{C,F}$ = 178 Hz, CH_2F), 31.0, (CH_2), 13.6 (CH_3); ^{19}F NMR ($CDCl_3$) δ −228.3 (t, $J_{H,F}$ = 48 Hz).

1-Fluorohex-5-en-2-one was prepared by the addition of allyl bromide (0.61 g, 0.005 mol) to **4** deprotonated with LHMDS to yield, following isolation as described, 0.35 g (60%) of 1-fluorohex-5-en-2-one: IR (neat) ν 3100 (w), 2960 (m), 1725 (s), 1640 (w), 1385 (m), 1000 (m), 720 (m) cm^{-1}; ^{1}H NMR (CCl_4) δ 5.70–5.15 (m, 1 H, CH=CH_2), 5.05–4.45 (m, 2 H, CH=CH_2), 4.54 (d, $J_{H,F}$ = 47 Hz, 2 H, CH_2F), 3.00–2.51 (m, 2 H, CH_2CH=CH_2) 2.51 (dt, $J_{H,F}$ = 5 Hz, J = 6 Hz, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 206.3 (d, $J_{C,F}$ = 19 Hz, C=O), 131.1 (CH=CH_2), 119.0 (CH=CH_2), 85.0 (d, $J_{C,F}$ = 185 Hz, CH_2F), 37.6 (CH_2), 26.6 (CH_2); ^{19}F NMR ($CDCl_3$) δ −228.3 (t, $J_{H,F}$ = 48 Hz). Anal. Calcd for C_6H_9FO: C, 62.05; H, 7.81. Found: C, 62.16; H, 7.84.

1-Fluoro-2-heptanone was prepared by the addition of 1-iodobutane (0.92 g, 0.005 mol) to **4** deprotonated with LHMDS. Workup in the normal manner yielded 0.20 g (30%) of 1-fluoro-2-heptanone. A sample for analysis was purified by preparative GC: IR (neat) ν 2960 (s), 2930 (m), 1725 (s), 1050 (m) cm^{-1}; ^{1}H NMR (CCl_4) δ 4.46 (d, $J_{H,F}$ = 48 Hz, 2 H, CH_2F), 2.50 (d, $J_{H,F}$ = 3 Hz, CH_2CO), 1.63–1.56 (m, 2 H, CH_2), 1.35–1.22 (m, 4 H, CH_2CH_2), 0.87 (t, J = 7 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 84.9 (d, $J_{C,F}$ = 185 Hz, CH_2F), 31.2 (CH_2), 26.0 (CH_2), 22.4 (CH_2), 22.3 (CH_2), 13.8 (CH_3); ^{19}F NMR ($CDCl_3$) δ −227.9 (t, $J_{H,F}$ = 49 Hz). Anal. Calcd for $C_7H_{13}FO$: C, 63.61; H, 9.91. Found: C, 63.48; H, 9.97.

1-Fluoro-4-phenyl-2-butanone was prepared by the addition of benzyl bromide (0.86 g, 0.005 mol) to **4** deprotonated with LHMDS. Workup in the normal manner yielded 0.58 g (70%) of 1-fluoro-4-phenyl-2-butanone. A sample for analysis was purified by preparative GC: IR (neat) ν 3150 (w), 3140 (w), 2950 (m), 1720 (s), 1600 (m), 1060 (s), 760 (s), 710 (m) cm^{-1}; ^{1}H NMR (CCl_4) δ 7.00 (br, 5 H, C_6H_5), 4.51 (d, $J_{H,F}$ = 49 Hz, 2 H, CH_2F), 2.82–2.50 (m, 4 H, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 134.0 (C-ipso), 129.3 (C-ortho), 128.3 (C-meta), 128.1 (C-para), 84.8 (d, $J_{C,F}$ = 184 Hz, CH_2F), 39.6 ($CH_2C_6H_5$), 26.4 (CH_2); ^{19}F NMR ($CDCl_3$) δ −227.7 (t, $J_{H,F}$ = 49 Hz). Anal. Calcd for $C_{10}H_{11}FO$: C, 72.27; H, 6.67. Found: C, 72.00; H, 6.49.

(*E*)-1-Fluoro-6-phenylhex-5-en-2-one was prepared by the addition of cinnamyl bromide (0.99 g, 0.005 mol) to **4** deprotonated with LHMDS. Workup in the normal manner yielded 0.84 g (88%) of (*E*)-1-fluoro-6-phenylhex-5-en-2-one. A sample for analysis was purified by preparative GC: IR (neat) ν 3140 (m), 3020 (m), 2950 (s), 1720 (s), 1600 (m), 1460 (w), 1340 (w), 1040 (m), 760 (s), 710 (m) cm^{-1}; ^{1}H NMR (CCl_4) δ 6.99 (br, 5 H, C_6H_5), 6.30-5.75 (m, 2 H, CH=CH), 4.48 (d, $J_{H,F}$ = 46 Hz, CH_2F), 2.80–2.15 (m, 4 H, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 205.9 (d, $J_{C,F}$ = 19 Hz, C=O), 136.9 (C-ipso), 131.1 (CH=CHC_6H_5), 128.4 (C-ortho), 127.3 (C-meta), 127.1 (C-ortho), 125.9 (CH=CHC_6H_5), 84.9 (d, $J_{C,F}$ = 184 Hz, CH_2F), 37.8 (CH_2CH=CHC_6H_5), 26.0 (CH_2); ^{19}F NMR ($CDCl_3$) δ −227.7 (t, $J_{H,F}$ = 49 Hz).

General Procedure for the Formation of 3-Fluoro-2-alkanones. To a magnetically stirred 50-mL three-necked flask under an inert atmosphere containing **4** (0.32 g, 0.002 mol) dissolved in 25 mL of dry THF was added dropwise at such a rate that the temperature did not exceed −80 °C 2.35 mL (0.004 mol) of *tert*-butyllithium (1.7 M in pentane). The solution was stirred at −85 °C for an additional 0.5 h, and then 0.002 mol of the alkyl halide dissolved in 5 mL of THF was added dropwise. After being stirred another hour, the reaction mixture was poured over 10 mL of a saturated sodium bicarbonate solution and extracted with distilled hexanes (3 × 10 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed in vacuo. A pentane solution of the imine was hydrolyzed by treatment with 10 mL of 5% acetic acid solution for 2 h. Following separation, the organic phase was washed with saturated sodium bicarbonate solution (2 × 10 mL) until neutral and was dried over anhydrous magnesium sulfate and the solvent removed to yield the crude 3-fluoro ketone.

3-Fluoro-2-butanone[20] was prepared by the addition of iodomethane (1.14 g, 0.008 mol) to **4** deprotonated with *tert*-butyllithium and by being stirred for 0.5 h. On normal workup and hydrolysis in $CFCl_3$, 0.31 g (43%) of 3-fluoro-2-butanone was isolated: ^{1}H NMR (CCl_4) δ 4.78 (dq, $J_{H,F}$ = 49 Hz, J = 7 Hz, 1 H, CHF), 2.20 (d, $J_{H,F}$ = 5 Hz, 3 H, CH_3CO), 1.41 (dq, $J_{H,F}$ = 24 Hz, J = 7 Hz, 3 H, CH_3CF); ^{13}C NMR ($CDCl_3$) δ 208.5 (d, $J_{C,F}$

(20) Griesebaum, K.; Keul, H.; Kibar, R.; Pfeffer, S.; Sprawl, M. *Chem. Ber.* **1981**, *114*, 1858–1870.