The Kinetic Assessment of N-Methyl-2-Methoxy-Pyridinium Species as Phosphonate Anion Methylating Agents

Supporting Information

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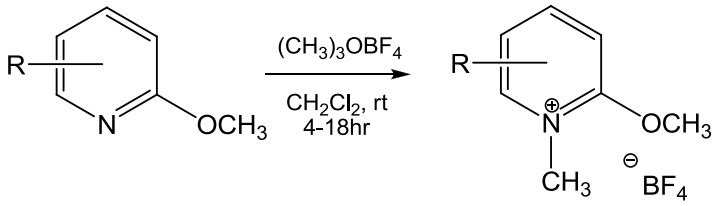
Methods and Reagents. All chemicals and reagents were obtained from commercial vendors and used without purification. Dry tetrahydrofuran, toluene, methylene chloride and diethyl ether were obtained from commercial vendors (Aldrich, STREM, Acros, Combi-Blocks, or Alfa) in a septum sealed container, which was kept under inert gas. Thin-layer chromatography (TLC) was routinely used to monitor the progress of the reactions. TLC was performed using pre-coated plastic plates with 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm, Sorbent Technologies). Visualization was achieved using a standard 245 nm UV visualization light, potassium permanganate (1% solution in acetone), or phosphomolybdic acid (1% solution in ethanol). Organic solutions were concentrated by rotary evaporation at or below 50 ^{o}C at 25 torr. Flash chromatography was performed on a Teledyne Isco CombiFlash Rf system utilizing normal phase pre-column cartridges and gold high performance columns eluting with a gradient of ethyl acetate and hexanes (Fischer scientific) unless noted otherwise.

Instrumentation. All proton (^{1}H) nuclear magnetic resonance spectra were recorded on a 500 MHz Bruker spectrometer. All carbon (^{13}C) nuclear magnetic resonance spectra were

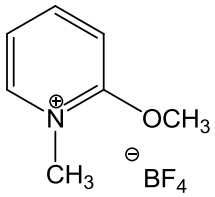
recorded on 125 MHz NMR spectrometer. All fluorine (^{19}F) nuclear magnetic resonance spectra were recorded on a 470 MHz NMR spectrometer with proton decoupling. Chemical shifts are expressed in parts per million (scale) and are referenced to residual ^{1}H in the NMR solvent ($CDCl_3$: 7.26 ppm, acetone: 2.05, DMSO: 2.50), to the central carbon in the NMR solvent ($CDCl_3$: 77.0 ppm, acetone: 30.0, DMSO: 39.5) or to trifluorotoluene as an internal standard ($PhCF_3$: -63 ppm). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and bs = broad singlet), integrated intensity, and coupling constant in Hertz (Hz). Infrared (IR) spectral data were collected on a JASCO FT/IR 4100 instrument and are reported in cm^{-1}. High resolution mass spectrometry (Waters GCT – 30 meeter DB5-MS) utilizing electrospray ionization or electron impact ionization in positive mode was performed to confirm the identity of the compounds.

General Procedure for the Synthesis N-Methylpyridinium Tetrafluoroborates (Scheme 1)



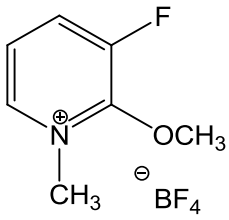
The following procedure for synthesis of 2-methoxy-5-trifluoromethyl-*N*-methylpyridinium tetrafluoroborate is typical of the procedures used for all compounds. A 3 mL glass vial was equipped with a rubber septum and magnetic stir bar. The vial was brought into a glove box and charged with trimethyloxonium tetrafluoroborate (101 mg, 0.68 mmol). The vial was sealed and removed from the glove box. A separate 3 mL vial was charged with 2-methoxy-5-trifluoromethylpyridine (122 mg, 0.69 mmol) and was dissolved in CH_2Cl_2 (1 mL). The solution of pyridine was added via syringe onto the solid trimethoxonium tetrafluoroborate at

room temperature. The vial which contained the pyridine was rinsed with CH_2Cl_2 (1 mL) and the rinse solution was injected into the reaction vial. The reaction vial was kept at room temperature and stirring was maintained at ca. 400-600 rpm. Over the course of the reaction (4-20 hr), the solid trimethoxonium tetrafluoroborate gradually dissolved, the solution clarified, and a new precipitate gradually formed. At the end of the reaction, hexanes (2 mL) was added after which stirring was stopped. Any solid or oil was allowed to settle and the solvent was removed by glass pipette. The solid or oil was then rinsed with several portions of hexanes, diethyl ether, ethyl acetate or diethyl ether/isopropyl alcohol to remove any unreacted starting materials, again removing the solvent by pipette. Residual solvent was then removed *in vacuo* to provide the N-ethylpyridinium tetrafluoroborate.

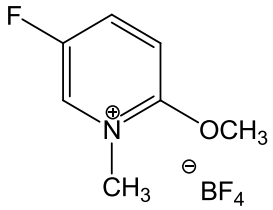


2-Methoxy-*N*-methylpyridinium tetrafluoroborate (1a): This compound has been previously synthesized and characterized.[1] The data given here are in accordance with that report and are provided for convenience. Reaction time: 4 hr, Isolated Yield: 79%

^{1}H NMR (DMSO, 500 MHz): δ = 8.65 (d, *J* = 6.5 Hz, 1H), 5.50 (dd, *J* = 8.9, 7.3 Hz, 1H), 7.72 (d, *J* = 6.6 Hz, 1H), 7.55 (t, *J* = 6.8 Hz, 1H), 4.25 (s, 3H), 3.98 (s, 3H). **^{13}C NMR (DMSO, 125 MHz):** δ = 160.8, 148.1, 144.1, 118.8, 117.5, 111.6, 59.8, 41.7. **IR (film, cm^{-1}):** ν = 1640, 1588, 1524, 1438, 1295, 1054, 1012.

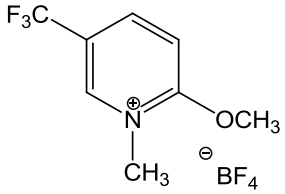


3-Fluoro-2-methoxy-*N*-methylpyridinium tetrafluoroborate (1b): Reaction time: 4 hr, Isolated Yield: 78% **^{1}H NMR (acetone, 500 MHz):** δ = 8.47 (d, *J* = 6.4 Hz, 1H), 8.43 (m, 1H), 7.60 (m, 1H), 4.61 (d, *J* = 5.6 Hz, 3H), 4.18 (s, 3H). **^{1}H NMR (D_2O, 500 MHz):** δ = 8.23 – 8.18 (m, 2H), 7.42 – 7.38 (m, 1H), 4.48 (d, *J* = 6.0 Hz, 3H), 4.00 (s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 8.56 – 8.52 (m, 2H), 7.65 – 7.62 (m, 1H), 4.48 (d, *J* = 5.5 Hz, 3H), 4.02 (s, 3H). **^{13}C NMR (acetone, 125 MHz):** δ = 153.6 (d, $J_{C\text{-}F}$ = 19.9 Hz), 151.3 (d, $J_{C\text{-}F}$ = 251 Hz), 141.0 (d, $J_{C\text{-}F}$ = 4.2 Hz), 134.6 (d, $J_{C\text{-}F}$ = 18.2 Hz), 120.4 (d, $J_{C\text{-}F}$ = 6.7 Hz), 64.6 (d, $J_{C\text{-}F}$ = 11.6 Hz), 43.2. **^{19}F NMR (acetone, 470 MHz):** δ = -132.0 (1F), -152.0 (4F). **IR (film, cm^{-1}):** ν = 1697, 1644, 1530, 1431, 1278, 1257, 1031, 982. **HRMS (TOF EI+)**: calc. for C_7H_9OFN $(M)^+$: 142.0668; found: 142.0671.

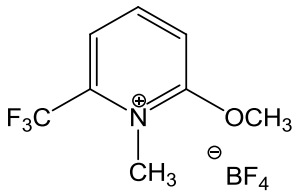


5-Fluoro-2-methoxy-*N*-methylpyridinium tetrafluoroborate (1c): Reaction time: 4 hr, Isolated Yield: 68%. **^{1}H NMR (acetone, 500 MHz):** δ = 8.76 (t, *J* = 3.3 Hz, 1H), 8.48 (m, 1H), 7.81 (dd, *J* = 9.8, 4.5 Hz, 1H), 4.37 (s, 3H), 4.14 (s, 3H). **^{1}H NMR (D_2O, 500 MHz):** δ = 8.56 (t, *J* = 2.7 Hz, 1H), 8.41 – 8.37 (m, 1H), 7.65 (dd, *J* = 10.0, 4.7 Hz, 1H), 4.31 (s, 3H), 4.07 (s, 3H). 4.26 (s, 3H), 3.97 (s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 9.10 (t, *J* = 3.5 Hz, 1H), 8.68 – 8.64 (m, 1H), 7.83 (dd, *J* = 9.8, 4.3 Hz, 1H). **^{13}C NMR (acetone, 125 MHz):** δ = 159.7, 155.7 (d, $J_{C\text{-}F}$ = 245 Hz), 137.2 (d, $J_{C\text{-}F}$ = 21.4 Hz), 132.8 (d, $J_{C\text{-}F}$ = 39.5 Hz), 113.3 (d, $J_{C\text{-}F}$ = 7.7 Hz), 60.6, 42.9.

^{19}F NMR (acetone, 470 MHz): δ = -133.6 (1F), 151.8 (4F). **IR (film, cm^{-1}):** ν = 3093, 1698, 1536, 1436, 1299, 1259, 1048, 1010, 890, 831. **HRMS (TOF ESI+)**: calc. for C_7H_9OFN $(M)^+$: 142.0668; found: 142.0667.

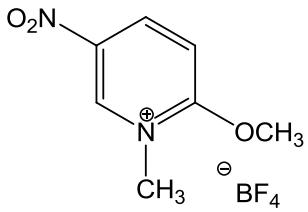


2-Methoxy-5-trifluoromethyl-*N*-methylpyridinium tetrafluoroborate (1d): Reaction time: 4 hr, Isolated Yield: 86%. **^{1}H NMR (acetone, 500 MHz):** δ = 9.21 (bs, 1H), 8.85 (dd, *J* = 9.3, 2.2 Hz, 1H), 8.04 (d, *J* = 9.3 Hz, 1H), 4.52 (s, 3H), 4.27 (s, 3H). **^{1}H NMR (D_2O, 500 MHz):** δ = 9.03 (s, 1H), 8.77 (dd, *J* = 9.5, 2.1 Hz, 1H), 7.81 (d, *J* = 9.3 Hz, 1H), 4.42 (s, 3H), 4.13 (s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 9.41 (s, 1H), 8.95 (dd, *J* = 9.5, 2.3 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 4.37 (s, 3H), 4.03 (s, 3H). **^{13}C NMR (acetone, 125 MHz):** δ = 164.4, 145.2 (q, $J_{C\text{-}F}$ = 2.9 Hz), 143.8 (q, $J_{C\text{-}F}$ = 5.0 Hz), 123.1 (q, $J_{C\text{-}F}$ = 272 Hz), 121.8 (q, $J_{C\text{-}F}$ = 36.5 Hz), 113.7, 61.3, 43.5. **^{19}F NMR (acetone, 470 MHz):** δ = -62.8 (3F), -152.0 (4F). **IR (film, cm^{-1}):** ν = 3100, 1666, 1594, 1547, 1338, 1298, 1114, 1036, 896, 835. **HRMS (TOF EI+)**: calc. for $C_8H_9OF_3N$ $(M)^+$: 192.0636; found: 192.0625.

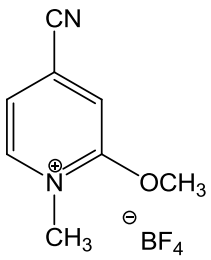


2-Methoxy-6-trifluoromethyl-*N*-methylpyridinium tetrafluoroborate (1e): Reaction time: 23 hr, Isolated Yield: 58%. **^{1}H NMR (acetone, 500 MHz):** δ = 8.76 (t, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 9.0 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 4.54 (s, 3H), 4.22 (s, 3H). **^{1}H NMR (D_2O, 500 MHz):** δ = 8.51 (t, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 9.2 Hz, 1H), 4.33 (s, 3H), 4.03

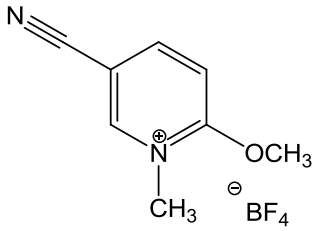
(s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 8.70 (t, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 4.39 (s, 3H), 3.97 (s, 3H). **^{13}C NMR (acetone, 125 MHz):** δ = 164.6, 149.2, 138.4 (q, $J_{C\text{-}F}$ = 35 Hz), 120.4 (q, $J_{C\text{-}F}$ = 275 Hz), 119.6 (q, $J_{C\text{-}F}$ = 5.4 Hz), 117.8, 61.6, 38.4 (q, $J_{C\text{-}F}$ = 4.2 Hz). **^{19}F NMR (acetone, 470 MHz):** δ = -63.5, -152.4. **IR (film, cm^{-1}):** ν = 1643, 1519, 1361, 1308, 1239, 1200, 1145, 1038, 816. **HRMS (TOF EI+)**: calc. for $C_8H_9OF_3N$ $(M)^+$: 192.0636; found: 192.0648.



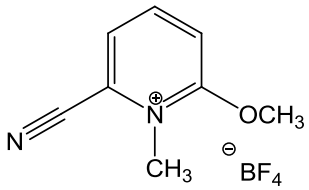
2-Methoxy-5-nitro-*N*-methylpyridinium tetrafluoroborate (1f): Reaction time: 23 hr, Isolated Yield: 64%. **^{1}H NMR (acetone, 500 MHz):** δ = 9.72 (d, *J* = 2.7 Hz, 1H), 9.21 (dd, *J* = 9.7, 2.6 Hz, 1H), 9.8 (d, *J* = 9.8 Hz, 1H), 4.56 (s, 3H), 4.32 (s, 3H). **^{1}H NMR (D_2O, 500 MHz):** δ = 9.67 (d, *J* = 2.6 Hz, 1H), 9.21 (dd, *J* = 9.8, 2.6 Hz, 1H), 7.85 (d, *J* = 9.9 Hz, 1H), 4.49 (s, 3H), 4.19 (s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 9.92 (d, *J* = 2.4 Hz, 1H), 9.23 (dd, *J* = 9.7, 2.7 Hz, 1H), 7.92 (d, *J* = 9.7 Hz, 1H), 4.42 (s, 3H), 4.09 (s, 3H). **^{13}C NMR (acetone, 125 MHz):** δ = 165.1, 143.2, 142.4, 140.3, 112.8, 61.9, 43.5. **IR (film, cm^{-1}):** ν = 3096, 1654, 1593, 1531, 1358, 1329, 1032, 1000, 929, 807. **HRMS (TOF EI+)**: calc. for $C_7H_9O_3N_2$ $(M)^+$: 169.0601; found: 169.0613.



4-Cyano-2-methoxy-*N*-methylpyridinium tetrafluoroborate (1g): Reaction time: 20 hr, Isolated Yield: 85%. **^{1}H NMR (acetone, 500 MHz):** δ = 8.91 (d, *J* = 6.6 Hz, 1H), 8.35 (d, *J* = 1.6 Hz, 1H), 7.97 (dd, *J* = 6.7, 1.6 Hz), 4.52 (s, 3H), 4.25 (s, 3H). **^{1}H NMR (D_2O, 500 MHz):** δ = 8.68 (d, *J* = 6.6 Hz, 1H), 8.18 (d, *J* = 1.0 Hz, 1H), 7.83 (dd, *J* = 6.8, 1.6 Hz, 1H), 4.39 (s, 3H), 4.13 (s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 8.96 (d, *J* = 6.8 Hz, 1H), 8.48 (d, *J* = 1.3 Hz, 1H), 8.05 (dd, *J* = 6.6, 1.6 Hz, 1H), 4.32 (s, 3H), 4.02 (s, 3H). **^{13}C NMR (acetone, 125 MHz):** δ = 162.7, 146.5, 130.5, 121.0, 116.7, 115.3, 61.1, 43.2. **IR (film, cm^{-1}):** ν = 3116, 1650, 1578, 1509, 1488, 1421, 1327, 1271, 1046, 1019, 927. **HRMS (TOF EI+)**: calc. for $C_8H_9ON_2$ $(M)^+$: 149.0715; found: 149.0711.

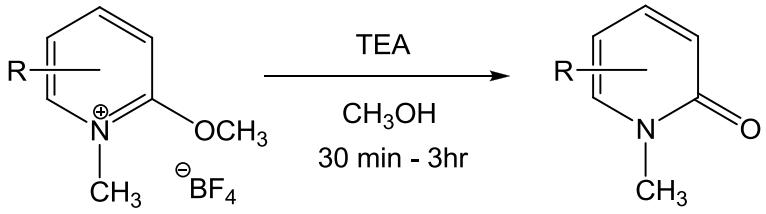


5-Cyano-2-methoxy-*N*-methylpyridinium tetrafluoroborate (1h): Reaction time: 20 hr, Isolated Yield: 50%. **^{1}H NMR (Acetone, 500 MHz):** δ = 9.30 (d, *J* = 2.1 Hz, 1H), 8.89 (dd, *J* = 9.3, 2.2 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 4.54 (s, 3H), 4.25 (s, 3H). **^{1}H NMR (D_2O, 500 MHz):** δ = 9.10 (d, *J* = 2.0 Hz, 1H), 8.76 (dd, *J* = 9.4, 2.4 Hz, 1H), 7.80 (d, *J* = 9.2 Hz, 1H), 4.43 (s, 3H), 4.12 (s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 9.50 (d, *J* = 2.0 Hz, 1H), 8.94 (dd, *J* = 9.2, 2.2 Hz, 1H), 7.95 (d, *J* = 9.3 Hz, 1H), 4.35 (s, 3H), 3.97 (s, 3H). **^{13}C NMR (Acetone, 125 MHz):** δ = 164.1, 150.4, 149.8, 114.4, 113.6, 105.0, 61.4, 43.2. **IR (film, cm^{-1}):** ν = 3084, 2248, 1646, 1646, 1580, 1540, 1333, 1034, 1005, 928, 837. **HRMS (TOF EI+)**: calc. for $C_8H_9ON_2$ $(M)^+$: 149.0715; found: 149.0709.

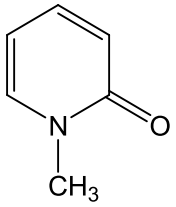


6-Cyano-2-methoxy-*N*-methylpyridinium tetrafluoroborate (1i): Reaction time: 18 hr, Isolated Yield: 62%. **^{1}H NMR (DMSO, 500 MHz):** δ = 8.66 (t, *J* = 8.1 Hz, 1H), 8.33 (d, *J* = 7.1 Hz, 1H), 8.11 (d, *J* = 9.0 Hz, 1H), 4.38 (s, 3H), 4.07 (s, 3H). **^{1}H NMR (D_2O, 500 MHz):** δ = 8.59 (t, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 4.44 (s, 3H), 4.24 (s, 3H). **^{13}C NMR (DMSO, 125 MHz):** δ = 161.6, 147.2, 125.6, 124.6, 117.0, 111.4, 60.7, 39.9. **IR (film, cm^{-1}):** ν = 3122, 1625, 1587, 1506, 1306, 1169, 1098, 1028, 885, 807. **HRMS (TOF EI+)**: calc. for $C_8H_9ON_2$ $(M)^+$: 149.0715; found: 149.0711.

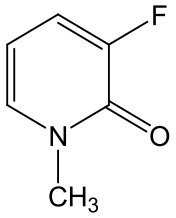
General Procedure for the Independent Synthesis of *N*-Methylpyridones (2a – 2i)



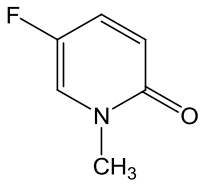
The following procedure for synthesis of 5-trifluoromethyl-*N*-methylpyridone is typical of the procedures used for all compounds. A vial was charged with a stir bar and solid 2-methoxy-5-trifluoromethyl-*N*-methylpyridinium tetrafluoroborate (32 mg, 0.12 mmol). To this vial, methanol (0.8 mL) and triethylamine (TEA, 0.1 mL) were sequentially added. The vial was caped and allowed to stir at room temperature. After 90 minutes, the solvent was removed under vacuum and the residue was purified by column chromatography (0% - 100% of ethyl acetate or isopropyl alcohol in hexanes). This afforded 5-trifluoromethyl-*N*-methylpyridone (17 mg, 82%) as a colorless wax.



N-Methyl-2-Pyridone (2a): This compound is commercially available and was used as received.

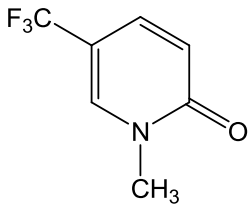


3-Fluoro-*N*-methylpyridone (2b): Yield: 92%. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ = 7.23 – 7.07 (m, 2H), 6.11 – 6.07 (m, 1H), 3.60 (s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 7.50 (dt, *J* = 6.8, 1.6 Hz, 1H), 7.39 – 7.35 (m, 1H), 6.19 – 6.15 (m, 1H), 3.49 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ = 156.7 (d, $J_{C\text{-}F}$ = 24.3 Hz), 152.4 (d, $J_{C\text{-}F}$ = 249 Hz), 133.5 (d, $J_{C\text{-}F}$ = 5.3 Hz), 120.2 (d, $J_{C\text{-}F}$ = 16.7 Hz), 103.7 (d, $J_{C\text{-}F}$ = 5.8 Hz), 37.5. **IR (film, cm^{-1}):** ν = 1661, 1604, 1561, 1458, 1240, 1240, 1058, 970. **HRMS (TOF EI+)**: calc. for C_6H_6ONF $(M)^+$: 127.0433; found: 127.0434.

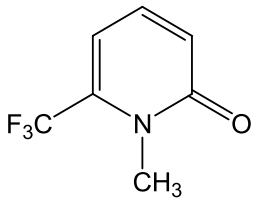


5-Fluoro-*N*-methylpyridone (2c): Yield: 40%. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ = 7.28 (ddd, *J* = 10.1, 6.9, 3.3 Hz, 1H), 7.21 (t, *J* = 3.8 Hz, 1H), 6.55 (dd, *J* = 10.0, 5.3 Hz, 1H), 3.52 (s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 7.92 (dd, *J* = 4.6, 3.5 Hz, 1H), 7.56 – 7.53 (m, 1H), 6.39 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.38 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ = 161.1, 147.1 (d, $J_{C\text{-}F}$ = 230 Hz), 131.2 (d, $J_{C\text{-}F}$ = 23.9 Hz), 123.6 (d, $J_{C\text{-}F}$ = 19.9 Hz), 121.3 (d, $J_{C\text{-}F}$ = 36.7 Hz), 37.8. **IR**

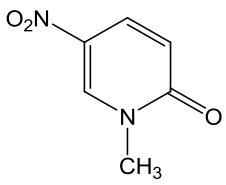
(film, cm^{-1}): ν = 2923, 1678, 1582, 1423, 1247, 1145, 1057. **HRMS (TOF EI+)**: calc. for C_6H_6OFN $(M)^+$: 127.0441; found: 127.0433.



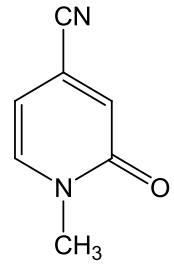
5-Trifluoromethyl-*N*-methylpyridone (2d): Yield: 82%. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ = 7.69 (bs, 1H), 7.45 (dd, *J* = 9.5, 2.3 Hz, 1H), 6.62 (d, *J* = 9.6 Hz, 1H), 3.58 (s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 8.34 (s, 1H), 7.65 (dd, *J* = 9.5, 2.6 Hz, 1H), 6.51 (d, *J* = 9.4 Hz, 1H), 3.48 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ = 162.3, 137.8 (q, $J_{C\text{-}F}$ = 5.8 Hz), 135.2 (q, $J_{C\text{-}F}$ = 2.4 Hz), 123.3 (q, $J_{C\text{-}F}$ = 271 Hz), 121.2, 109.5 (q, $J_{C\text{-}F}$ = 35.2 Hz), 38.1. **IR (film, cm^{-1}):** ν = 3046, 1662, 1611, 1547, 1449, 1433, 1328, 1161, 1100, 1031, 910, 832. **HRMS (TOF EI+)**: calc. for $C_7H_6OF_3N$ $(M)^+$: 177.0401; found: 177.0418.



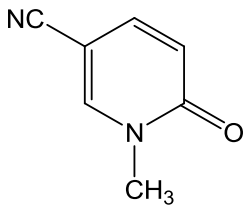
6-Trifluoromethyl-*N*-methylpyridone (2e): Yield: 64% **^{1}H NMR (acetone, 500 MHz):** δ = 7.52 – 7.48 (m, 1H), 6.77 (d, *J* = 6.6 Hz, 1H), 6.68 (d, *J* = 9.4 Hz, 1H), 3.55 (q, *J* = 1.4 Hz, 1H). **^{1}H NMR (DMSO, 500 MHz):** δ = 7.54 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 6.8 Hz, 1H), 6.75 (d, *J* = 9.0 Hz, 1H), 3.49 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ = 162.6, 155 (m), 138.4, 125.7, 121.4 (q, $J_{C\text{-}F}$ = 271 Hz), 107.0 (q, $J_{C\text{-}F}$ = 6.4 Hz), 31.8 (q, $J_{C\text{-}F}$ = 3.6 Hz). **^{19}F NMR ($CDCl_3$, 125 MHz):** δ = -65.0. **IR (film, cm^{-1}):** ν = 1678, 1611, 1394, 1305, 1188, 1136, 1069, 810. **HRMS (TOF EI+)**: calc. for $C_7H_6ONF_3$ $(M)^+$: 177.0401; found: 177.0400.



5-Nitro-*N*-methylpyridone (2f): Yield: 64%. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ = 8.63 (d, *J* = 3.1 Hz, 1H), 8.09 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.55 (d, *J* = 10.1 Hz, 1H), 3.65 (s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 9.19 (d, *J* = 3.2 Hz, 1H), 8.13 (dd, *J* = 10.0, 3.2, Hz, 1H), 6.47 (d, *J* = 10.0 Hz, 1H), 3.55 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ = 161.9, 140.0, 133.3, 119.3, 38.8. **IR (film, cm^{-1}):** ν = 3069, 1671, 1606, 1560, 1344, 1304, 1109, 837. **HRMS (TOF EI+)**: calc. for $C_6H_6O_3N_2$ $(M)^+$: 154.0378; found: 154.0387.

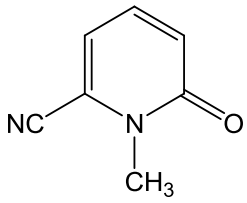


4-Cyano-*N*-methylpyridone (2g): Yield: 45%. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ = 7.41 (bd, *J* = 6.9 Hz, 1H), 6.79 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.27 (dd, *J* = 7.0, 1.9 Hz), 3.57 (s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 7.93 (d, *J* = 7.0 Hz, 1H), 7.00 (d, *J* = 1.9 Hz, 1H), 6.52 (dd, *J* = 7.0, 1.9 Hz, 1H), 3.46 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ = 160.9, 140.1, 126.3, 123.8, 115.7, 105.1, 38.1. **IR (film, cm^{-1}):** ν = 3089, 2230, 1662, 1594, 1524. **HRMS (TOF EI+)**: calc. for $C_7H_6ON_2$ $(M)^+$: 134.0480; found: 134.0494.



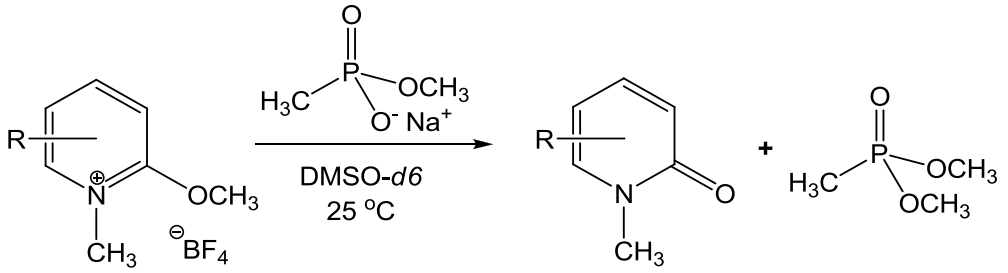
5-Cyano-*N*-methylpyridone (2h): Yield: 88%. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ = 7.85 (d, *J* = 2.5 Hz, 1H), 7.40 (dd, *J* = 9.5, 2.5 Hz, 1H), 6.57 (d, *J* = 9.6 Hz, 1H), 3.57 (s, 3H). **^{1}H NMR (DMSO, 500 MHz):** δ = 8.59 (d, *J* = 2.6 Hz, 1H), 7.67 (dd, *J* = 9.5, 2.6 Hz, 1H), 6.47 (d, *J* = 9.5 Hz, 1H), 3.44 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ = 161.3, 145.6, 138.9, 121.3, 116.1, 91.2, 38.2.

IR (film, cm^{-1}): ν = 3045, 2223, 1682, 1617, 1533, 1439, 1251, 856. **HRMS (TOF EI+)**: calc. for $C_7H_6ON_2$ $(M)^+$: 134.0480; found: 134.0491.



6-Cyano-*N*-methylpyridone (2i): Exposure of the 6-cyano compound to general conditions for pyridone formation resulted in decomposition. The ^{1}H NMR data reported here were obtained from the methylation reaction in DMSO (see next paragraph). **^{1}H NMR (DMSO, 500 MHz):** δ = 7.49 (dd, *J* = 9.4, 6.9 Hz, 1H), 7.07 (dd, *J* = 7.0, 1.5 Hz, 1H), 6.77 (dd, *J* = 9.5, 1.5 Hz, 1H), 3.53 (s, 3H).

General Procedure for Kinetic Measurements of Phosphonate Methylation (Table 1)

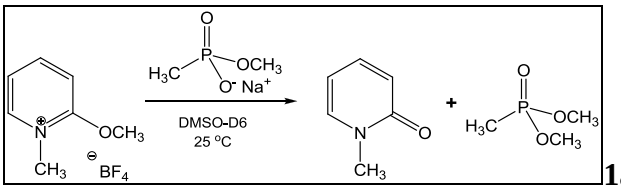


Solution Preparation. Sodium methyl methanephosphonate was prepared from sodium iodide and dimethylmethylphosphonate via a literature procedure.[2] A saturated DMSO-d_6 solution of sodium methyl methanephosphonate was prepared by adding 100 mg solid sodium methyl methanephosphonate to 10 mL of DMSO-d_6, slightly heating to ca. 45 ^{o}C, stirring thoroughly, and letting the solution cool to room temperature. To keep the solution as free as possible from adventitious water, 3A molecular sieves were added (ca 10% w/w) to the cooled solution. A DMSO solution prepared in this manner had a concentration of 27 mM ($\pm$ 2 mM) sodium methyl methanephosphonate, determined by the relative ^{1}H NMR integration of known masses of the various substituted N-methylpyridinium species that were subjected to the methyl transfer reaction. A solution prepared in this manner was used for all methyl transfer reactions and kinetics measurements described below.

Reaction Preparation. A vial was charged with R-substituted *N*-methyl-2-methoxypyridinium tetrafluoroborate (3-5 mg), sealed and brought into the NMR lab. The NMR spectrometer was pre-locked and shimmed onto a DMSO-d_6 solution. A volume of saturated sodium methyl methanephosphonate in DMSO-d_6 (using 27 mM in phosphonate anion) was calculated so that the ratio of the pyridinium species and the phosphorous species would be close to unity at time = 0 (0.5-0.75 mL). The DMSO-d_6 solution was added to solid *N*-methyl-2-methoxypyridinium tetrafluoroborate, the solution was mixed, drawn up by glass pipette, injected into an NMR tube, caped, and loaded into the NMR. The time from mixing to the time

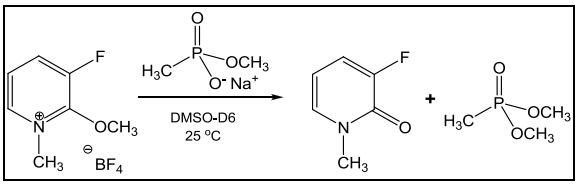
at which a spectrum was obtained was between 45 and 90 seconds. For simplicity, the first ^{1}H NMR obtained was set to time = 1 min for all kinetics calculations. The time for subsequent data points was determined to the min by difference using the FID time stamps. For early time points or for rapid reactions, 16 ^{1}H NMR spectral scans were obtained for every time point. For latter time points, after 10 min, or for slower reactions 32 ^{1}H NMR scans were obtained for every data point. A new time point was obtained at periodic intervals which vary by R substituent. Between each data acquisition, the tube was maintained at 25.0 $^{o}C \pm 0.5\ ^{o}C$ either within the NMR instrument (for fast reactions), or in a heated water bath (for slow reactions).

The quantity of each species present was obtained from integration of the ^{1}H NMR spectrum at every time point and was used in subsequent kinetics calculations. The peaks integrated were chosen from ^{1}H NMR spectra taken in dilute DMSO-d_6 of authentic independent samples of the pyridinium ion reactant and the pyridone product. For the pyridinium/pyridone pair, two well resolved peaks which were either a singlet or a narrow doublet were chosen for each species. For the phosphorous species, the P-CH_3 methyl doublet was utilized: 1.42 ppm for dimethylmethylphosphonate; 0.9 ppm – 1.1 ppm for sodium methyl methanephosphonate (this methyl peak drifted downfield and broadened as the reaction progressed). The integration of residual DMSO-d_5 was used as an internal standard by which the integrations were normalized. A sample ^{1}H NMR spectrum, taken at an intermittent time point, has been included in the spectra portion of the Supplemental Information for each reaction. The final reaction mixture was subjected to GC-HRMS analysis, using authentic samples as retention time standards, which confirmed the presence of the pyridone and dimethylmethylphosphonate. Additionally, ^{31}P NMR analysis of the final mixture confirmed the presence of dimethylmethylphosphonate.



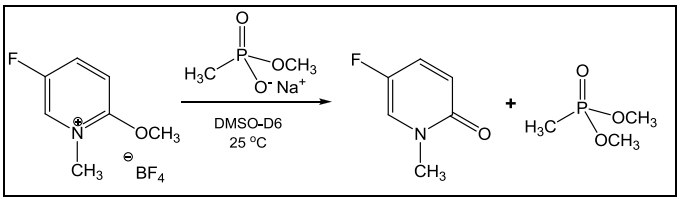
1a → 2a

GC-HRMS (TOF EI+) retention time (RT) for pyridone 9.66 min: calc. for C_6H_7ON $(M)^+$: 109.0528; found: 109.0544. GC-HRMS (TOF EI+) RT for dimethylmethylphosphonate 3.43: calc. for $C_3H_9O_3P$ $(M)^+$: 124.0289; found: 124.0316.



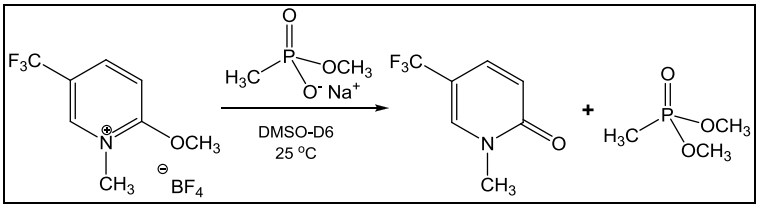
1b → 2b

GC-HRMS (TOF EI+) retention time (RT) for pyridone, 8.73 min: calc. for $C_6H_7O_2NF$ $(M)^+$: 127.0433; found: 127.0440. GC-HRMS (TOF EI+) RT for dimethylmethylphosphonate 4.97 min: calc. for $C_3H_9O_3P$ $(M)^+$: 124.0289; found: 124.0291.



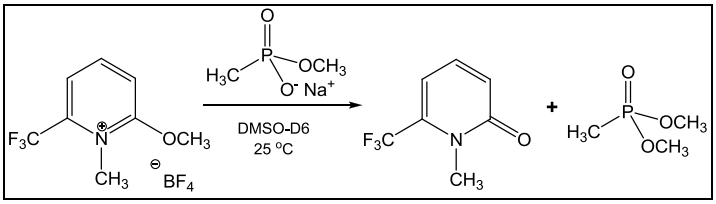
1c → 2c

GC-HRMS (TOF EI+) RT for pyridone 9.12 min: calc. for C_6H_6ONF $(M)^+$: 127.0433; found: 127.0434. GC-HRMS (TOF EI+) RT for dimethylmethylphosphonate 3.63 min: calc. for $C_3H_9O_3P$ $(M)^+$: 124.0289; found: 124.0318.



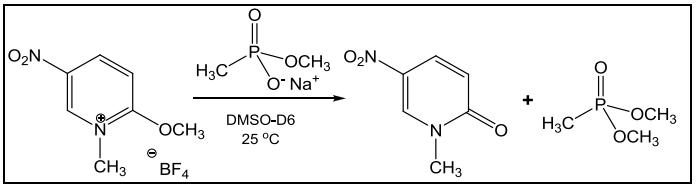
1d → 2d

GC-HRMS (TOF EI+) RT for pyridone 7.55 min: calc. for $C_7H_6ONF_3$ $(M)^+$: 177.0401; found: 177.0396. GC-HRMS (TOF EI+) RT for dimethylmethylphosphonate 5.00 min: calc. for $C_3H_9O_3P$ $(M)^+$: 124.0289; found: 124.0291.



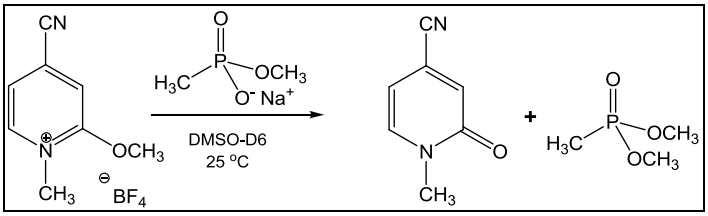
1e → 2e

GC-HRMS (TOF EI+) RT for pyridone 6.76 min: calc. for $C_7H_6ONF_3$ $(M)^+$: 177.0401; found: 177.0405. GC-HRMS (TOF EI+) RT for dimethylmethylphosphonate 5.02 min: calc. for $C_3H_9O_3P$ $(M)^+$: 124.0289; found: 124.0291.



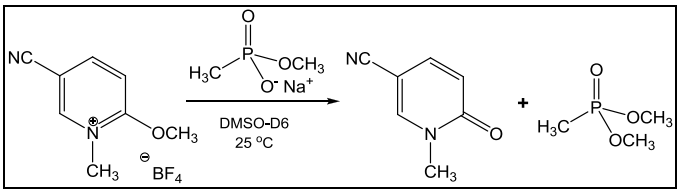
1f → 2f

GC-HRMS (TOF EI+) RT for pyridone 18.16 min: calc. for $C_6H_6O_3N_2$ $(M)^+$: 154.0378; found: 154.0385. GC-HRMS (TOF EI+) RT for dimethylmethylphosphonate 6.95 min: calc. for $C_3H_9O_3P$ $(M)^+$: 124.0289; found: 124.0299.



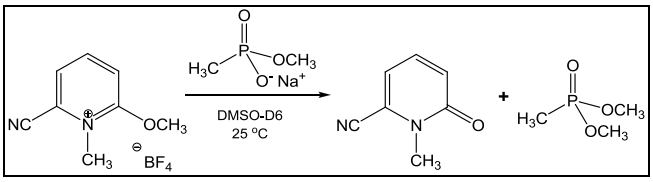
1g → 2g

GC-HRMS (TOF EI+) RT for pyridone 13.22 min: calc. for $C_7H_6ON_2$ $(M)^+$: 134.0480; found: 134.0461. GC-HRMS (TOF EI+) RT for dimethylmethylphosphonate 3.61 min: calc. for $C_3H_9O_3P$ $(M)^+$: 124.0289; found: 124.0292.



1h → 2h

GC-HRMS (TOF EI+) RT for pyridone 13.86 min: calc. for $C_7H_6ON_2$ $(M)^+$: 134.0480; found: 134.0501. GC-HRMS (TOF EI+) RT for dimethylmethylphosphonate 3.64 min: calc. for $C_3H_9O_3P$ $(M)^+$: 124.0289; found: 124.0317.



1i → 2i

GC-HRMS (TOF EI+) RT for pyridone 9.41 min: calc. for $C_7H_6ON_2$ $(M)^+$: 134.0480; found: 134.0486. GC-HRMS (TOF EI+) RT for dimethylmethylphosphonate 4.95 min: calc. for $C_3H_9O_3P$ $(M)^+$: 124.0289; found: 124.0290.

Second-Order Kinetics of Methyl Transfer and Hydrolysis in DMSO

The following differential equations describe the kinetics of methyl transfer from the various substituted N-methyl-2-methoxypyridiniums with methyl methanephosphonate anion and H_2O:

$$-d[B]/d = k_{Me}[A][B] \quad (1)$$

$$d[Q]/dt = k_{Me}[A][B] \quad (2)$$

$$-d[A]/dt = k_{Me}[A][B] + k_{hyd}[H_2O][A] \quad (3)$$

$$d[P]/dt = k_{Me}[A][B] + k_{hyd}[H_2O][A] \quad (4)$$

In these equations the respective reactants A and B are substituted N-methyl-2-methoxypyridinium and methyl methanephosphonate anion, and the respective products P and Q are substituted N-methylpyridone and dimethyl methanephosphonate. These differential equations were integrated numerically to simultaneously provide best fits of the time courses for all four species by utilizing fourth-order Runge-Kutta integration, as outlined by Carpenter.[3] According to this method, the species concentrations at time j along the methyl transfer time courses are given by equations 5-8:

$$[B]_j = [B]_{j-1} + (b_{1j} + 2b_{2j} + 2b_{3j} + b_{4j})/6 \quad (5)$$

$$[Q]_j = [Q]_{j-1} + (q_{1j} + 2q_{2j} + 2q_{3j} + q_{4j})/6 \quad (6)$$

$$[A]_j = [A]_{j-1} + (a_{1j} + 2a_{2j} + 2a_{3j} + a_{4j})/6 \quad (7)$$

$$[P]_j = [P]_{j-1} + (p_{1j} + 2p_{2j} + 2p_{3j} + p_{4j})/6 \quad (8)$$

The concentration increments, b_{ij}, in equation 5 are defined in equations 9-12:

$$b_{1j} = \{-k_{Me}[A]_{j-1}[B]_{j-1}\}\theta_t \quad (9)$$

$$b_{2j} = \{-k_{Me}([A]_{j-1} + a_{1j}/2)([B]_{j-1} + b_{1j}/2)\}\theta_t \quad (10)$$

$$b_{3j} = \{-k_{Me}([A]_{j-1} + a_{2j}/2)([B]_{j-1} + b_{2j}/2)\}\theta_t \quad (11)$$

$$b_{4j} = \{-k_{Me}([A]_{j-1} + a_{3j})([B]_{j-1} + b_{3j})\}\theta_t \quad (12)$$

Equation 9 is a finite difference analog of differential equation 1, in which the finite time step is defined as θ_t; equations 10-12 are similar in form, except that the concentration increments are increased by using concentration increments in the respective preceding equations. Similar sets of equations are written for q_{ij}, a_{ij} and p_{ij} by considering differential equations 2-4, respectively. For the reactions of all N-methyl-2-methoxypyridiniums except that with R = H, θ_t = 0.5 min; for R = H θ_t = 25 min.

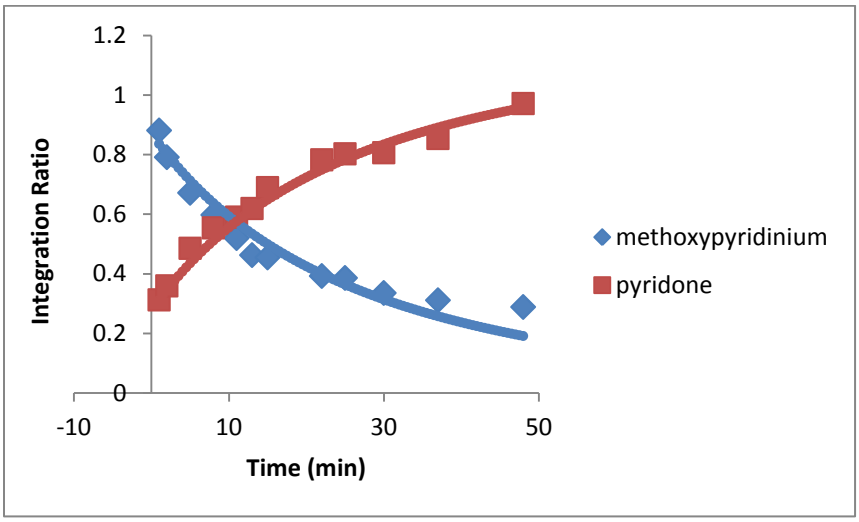
In equation 5 the concentration of B (= methyl methanephosphonate) at time j is the sum of the concentration at time j-1 (one time step θ_t earlier) and a weighted average of concentration increments b_{ij}. Concentrations of Q, A, and P are calculated in a similar manner in equations 6-8. The respective species concentrations *per se* were not used in this kinetics analysis. Rather, the ratios of integrated intensities for the respective species to that of residual ^{1}H intensity in the solvent DMSO-d_6 were used, as outlined earlier in this document. The integration ratios at t = 1 min, the time of the first NMR spectrum acquisition, were used as initial values for B, Q, A and P, and integration ratios were then calculated one time step θ_t later by using equations 5-8. The computation was repeated until the end of the time courses for the respective species. The calculation was carried out by using an initial set of guesses of the rate constants k_{Me} and k_{hyd} and is continued over a grid of pairs of these rate constants. For each rate constant pair of the grid, the value of χ^2 was calculated according to equation 13:

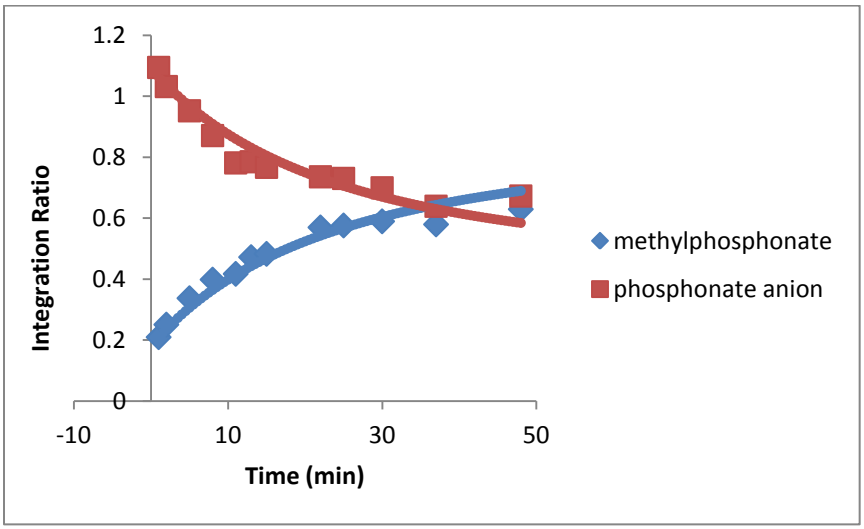
$$\chi^2 = \frac{([B]_{cal}-[B]_{ob})^2}{[B]_{ob}} + \frac{([Q]_{cal}-[Q]_{ob})^2}{[Q]_{ob}} + \frac{([A]_{cal}-[A]_{ob})^2}{[A]_{ob}} + \frac{([P]_{cal}-[P]_{ob})^2}{[P]_{ob}} \qquad (13)$$

The subscripts cal and ob denote the respective calculated and observed values of the various species in the reactions. The rate constant pair of the grid search that gave the minimum value of χ^2 was taken as the set of best estimates. For the best fit pair, the uncertainties of the rate constants were estimated by assuming that the variation of χ^2 with respect to each rate constant is independent of the value of the other rate constant. In this case the following expression applies for the jth rate constant k_j:[4]

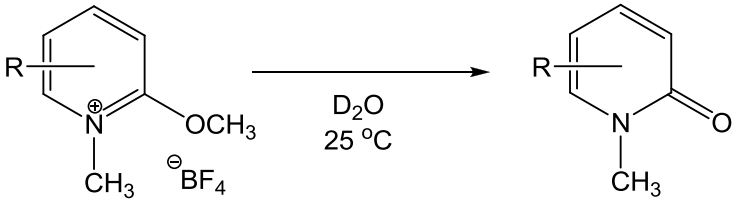
$$\sigma_{k_j}^2 = \frac{2}{\partial^2 x^2 / \partial k_j^2} \qquad (14)$$

The following figures show the fits generated by these procedures for the time courses of the various species when the methyl donor is 3-fluoro-N-methyl-2-methoxypyidinium tetrafluoroborate.

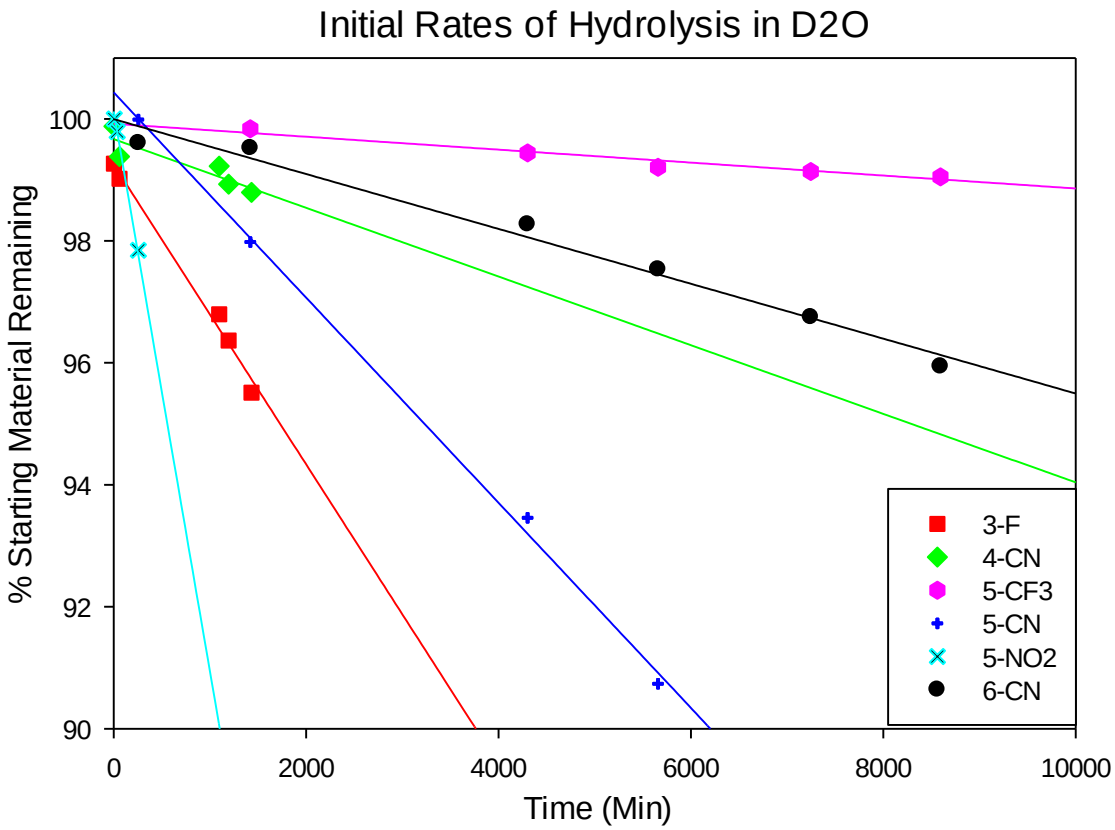




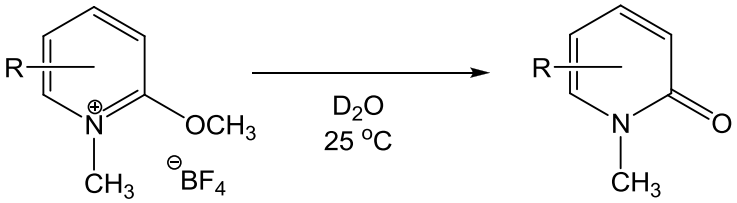
General Procedure for Hydrolysis Kinetics in D_2O (Table 2)



Reaction Preparation. A vial was charged with R-substituted *N*-methylpyridinium tetrafluoroborate (3-9 mg), sealed and brought into the NMR lab. The NMR spectrometer was pre-locked and shimmed onto a D_2O solution. D_2O (0.6 mL) was added to the *N*-methyl-pyridinium tetrafluoroborate, the solution was mixed, drawn up by glass pipette, injected into an NMR tube, caped, and loaded into the spectrometer. The time from contact to the time at which a spectrum was obtained was between 45 and 90 seconds. For simplicity, the first ^{1}H NMR spectrum obtained was set to t = 1 min for all kinetics calculations. The time for subsequent data points was determined to the minute by difference using the FID time stamps. Thirty-two ^{1}H NMR scans were obtained for every time point. A new time point was obtained at periodic intervals that varied by R-substituent over 7 days. Reaction progress was measured by integration of the pyridone and pyridinium *N*-methyl singlets. The formula: pyridinium/(pyridinium+pyridone) was used to calculate reaction progress at each point. The initial rate was determined by a linear fit of the initial data points (below). For the R = H, 5-F, and 6-CF_3 compounds, no degradation was observed over the 7 day experiment. The rate constant of hydrolysis was not determined for these compounds.

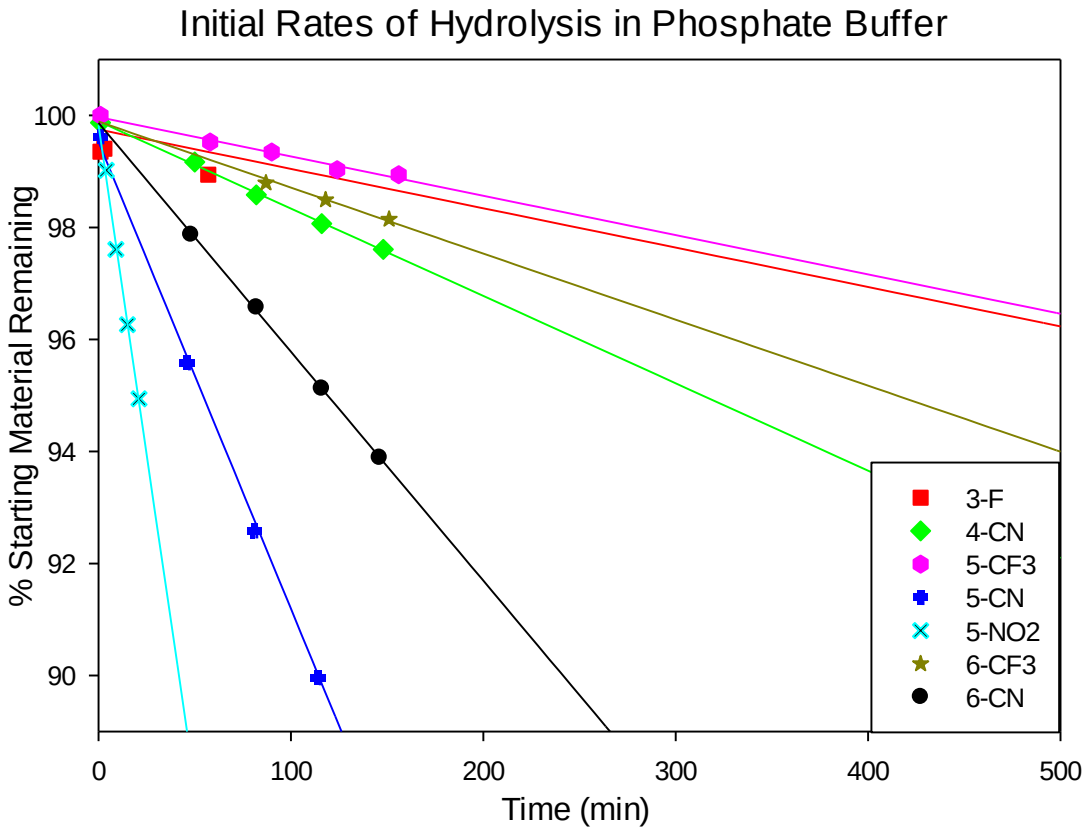


General Procedure for Hydrolysis Kinetics in Phosphate Buffer (Table 2)



Solution Preparation. Sodium hydrogen phosphate monobasic monohydrate ($NaH_2PO_4 \cdot H_2O$, 30.4 mg) and sodium phosphate dibasic (Na_2HPO_4, 39.5 mg) were weighed in to a glass vial and dissolved in D_2O (10 mL). A portion of the resulting solution (0.5 mL) was diluted with water (4.5 mL) and the pH was determined to be 7.23 on an ISE pH meter (Fisher accumet basic AB15).

Reaction Preparation. A vial was charged with R-substituted *N*-methylpyridinium tetrafluoroborate (3-5 mg), sealed and brought into the NMR lab. The NMR spectrometer was pre-locked and shimmed onto a D_2O solution. The D_2O solution of phosphate buffer (0.6 mL) described in the preceding paragraph was added to the *N*-methylpyridinium tetrafluoroborate, the solution was mixed, drawn up by glass pipette, injected into an NMR tube, caped, and loaded into the spectrometer. The time from contact to the time at which a spectrum was obtained was between 45 and 90 seconds. For simplicity, the first ^{1}H NMR spectrum obtained was set to t = 1 min for all kinetic calculations. The time for subsequent data points was determined to the minute by difference using the FID time stamps. 32 ^{1}H NMR scans were obtained for every data point. A new time point was obtained at periodic intervals which varied by R-substituted compound over several days. Reaction progress was measured by integration of the pyridone and pyridinium *N*-methyl singlets. The formula: pyridinium/(pyridinium+pyridone)*100 was used to calculate reaction progress at each point. The initial rate was determined by a linear fit of the initial data points. For the R = H, and 5-F, compounds, no degradation was observed over the 7 day experiment. The rate constant of hydrolysis was not determined for these two compounds.



References

1). Beak, P.; Bonham, J.; Lee, J. T. Jr. *J. Am. Chem. Soc.* **1968**, *90*, 1569-1582.

2) Boutevin, B.; Hervaud, Y.; Jeanmaire, T.; Boulahna, A.; Elasri, M. *Phosphorus, Sulfur and Silicon and the Related Elements* **2001**, *174*, 1-14.

3) Carpenter, B. K. *Determination of Organic Reaction Mechanisms*, 1st ed.; John Wiley & Sons: New York, **1984**; pp 76-82.

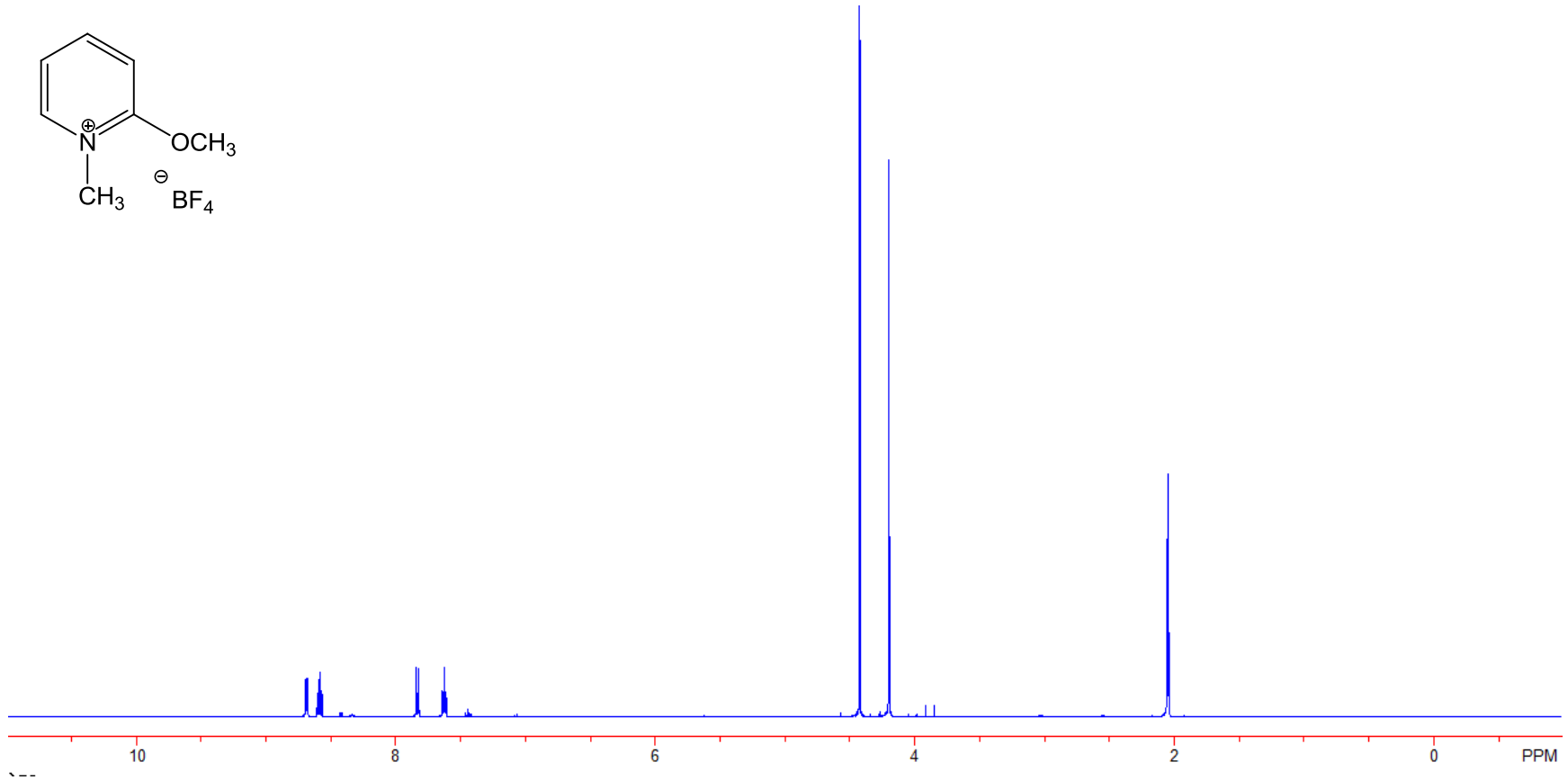
4) Bevington, P. R. *Data Reduction and Error Analysis for the Physical Sciences*, McGraw-Hill: New York, **1969**; pp 242-245.

The Kinetic Assessment of N-Methyl-2-Methoxy-Pyridinium Species as Phosphonate Anion Methylating Agents

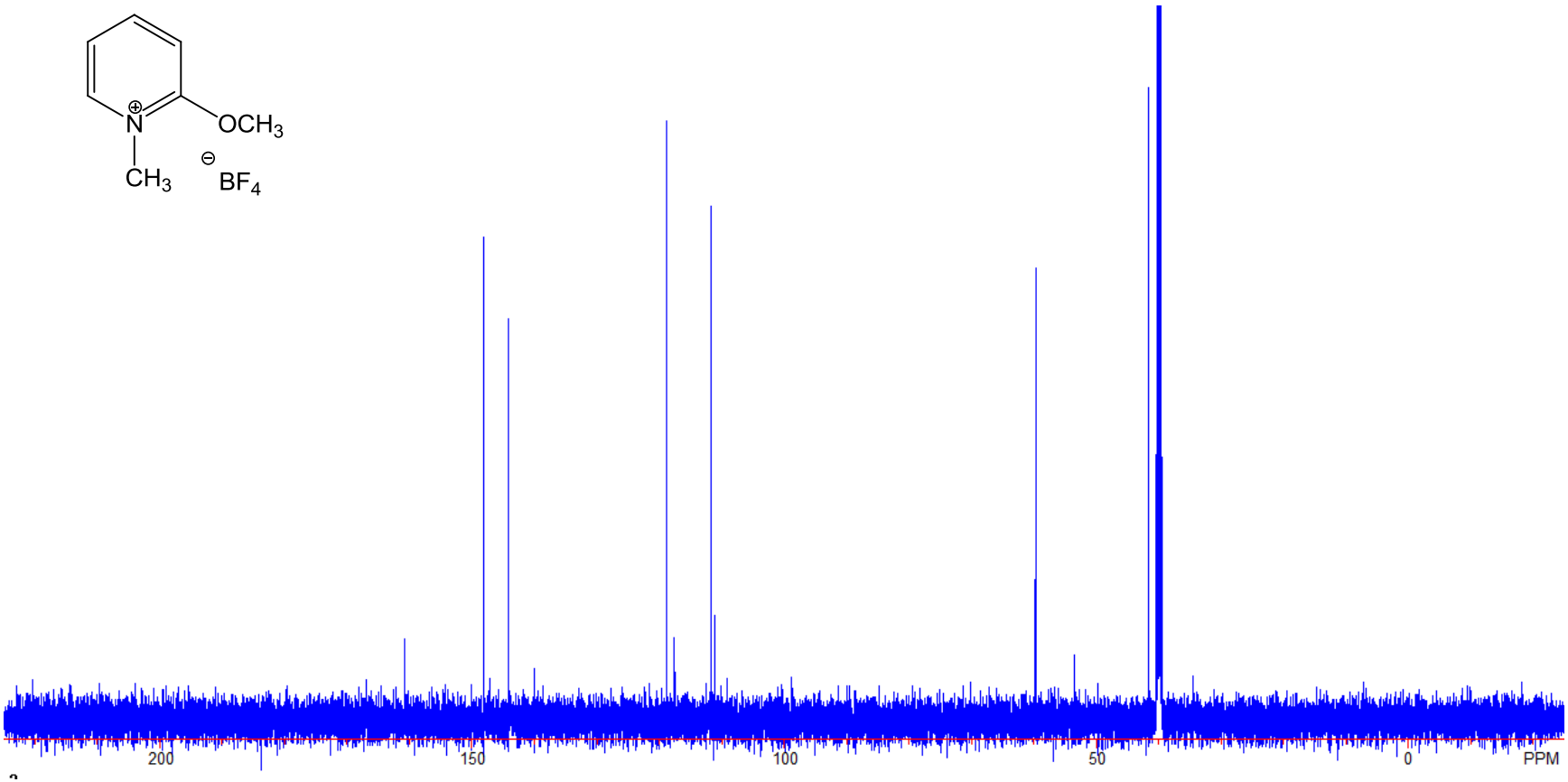
Joseph J. Topczewski and Daniel M. Quinn*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, United States

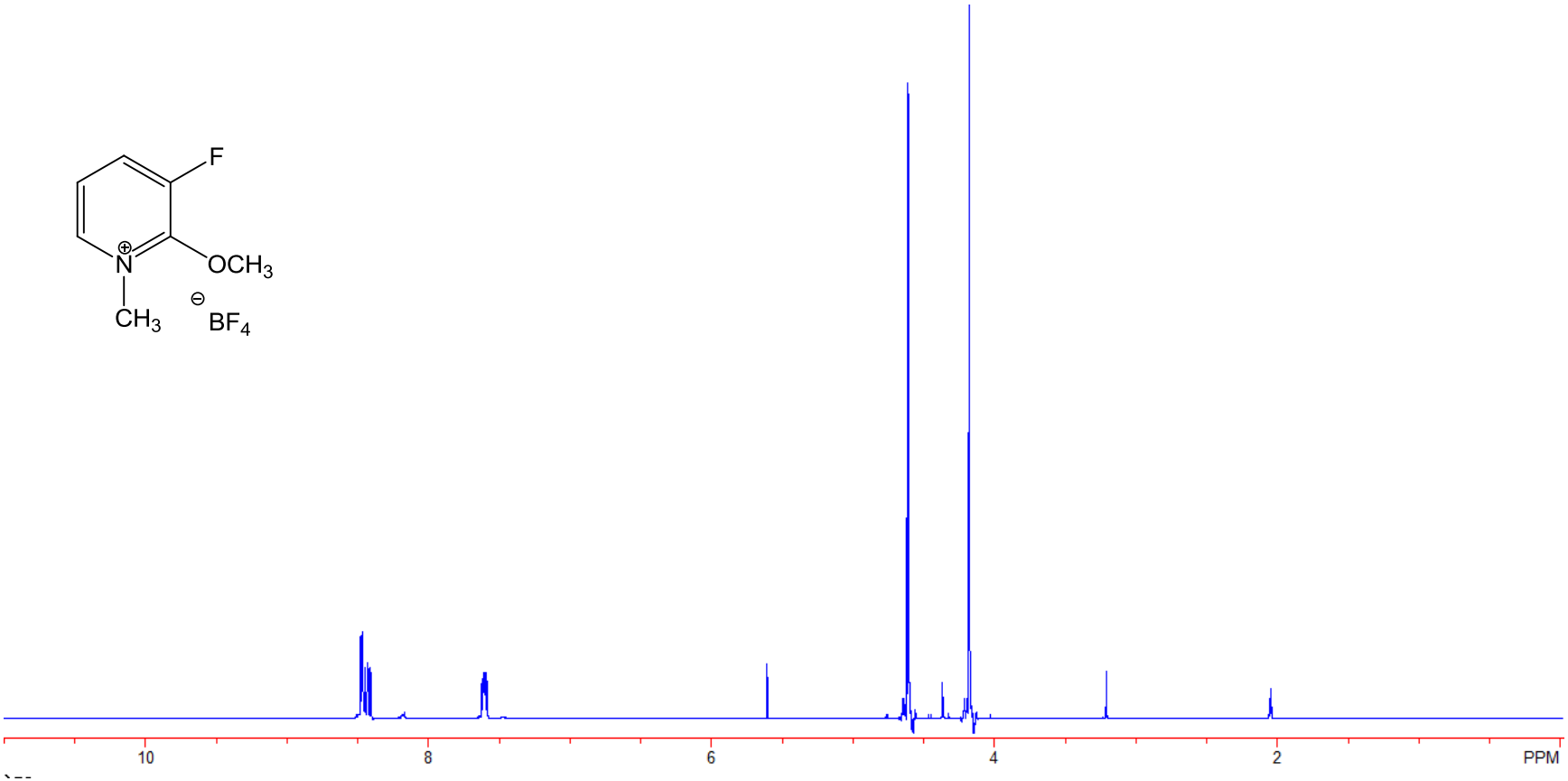
Spectral Data



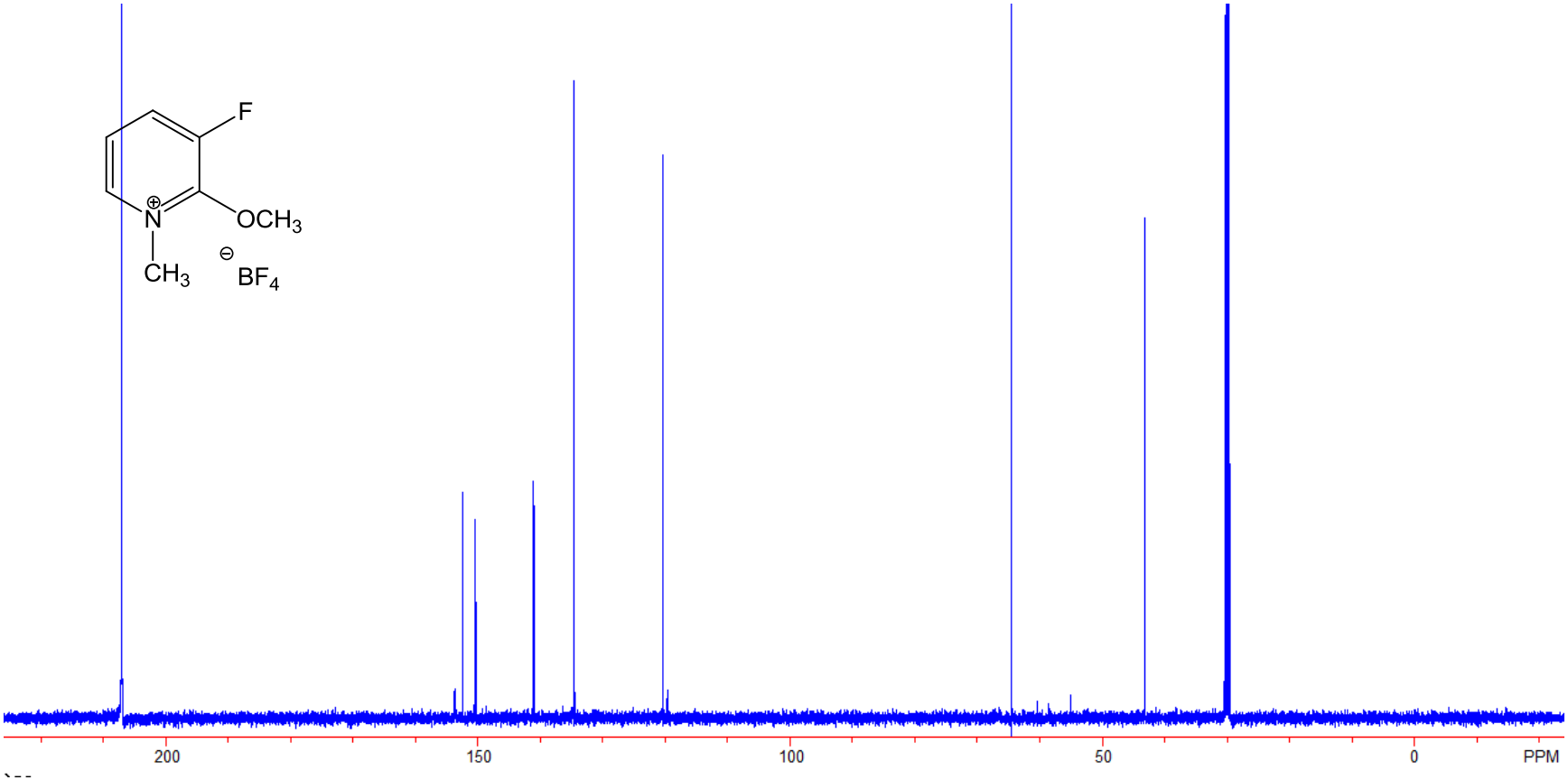
500 MHz ^{1}H NMR Spectrum in acetone (1a)



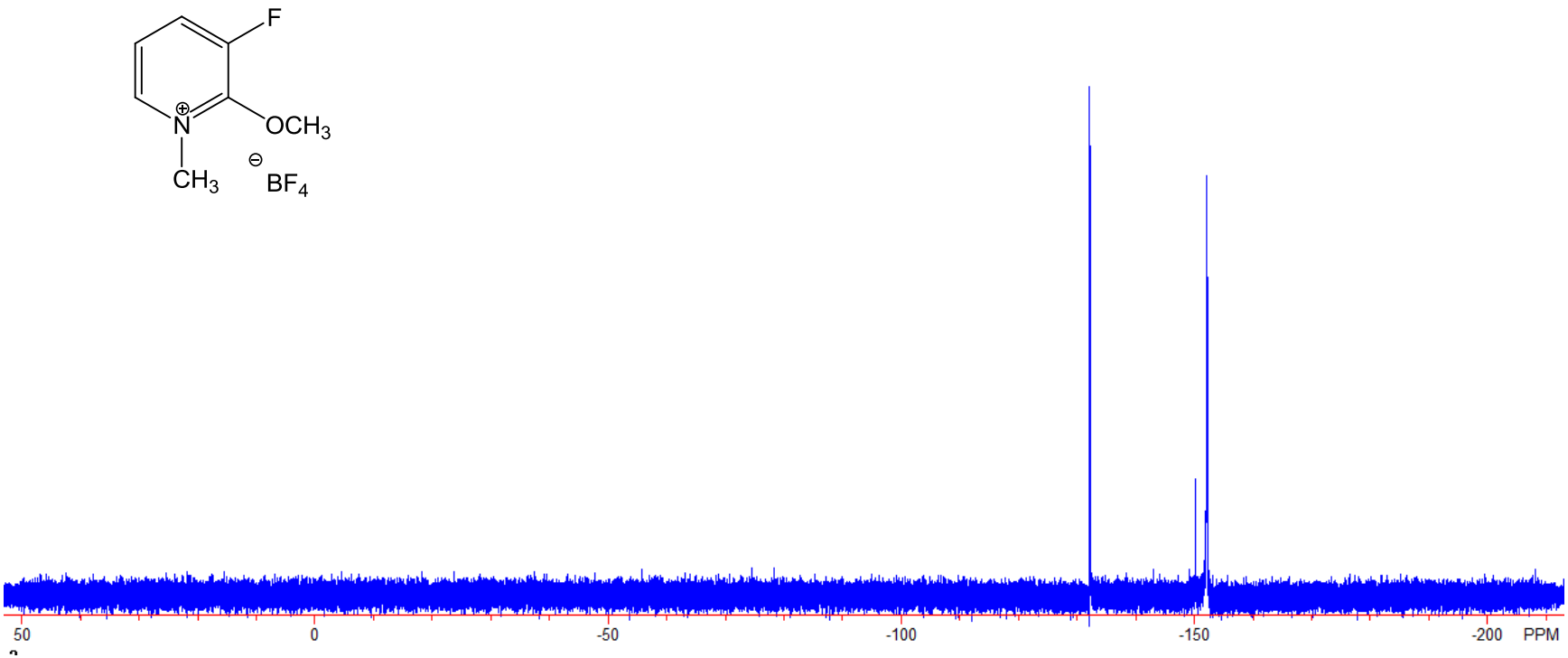
100 MHz ^{13}C NMR Spectrum in MeOD (1a)



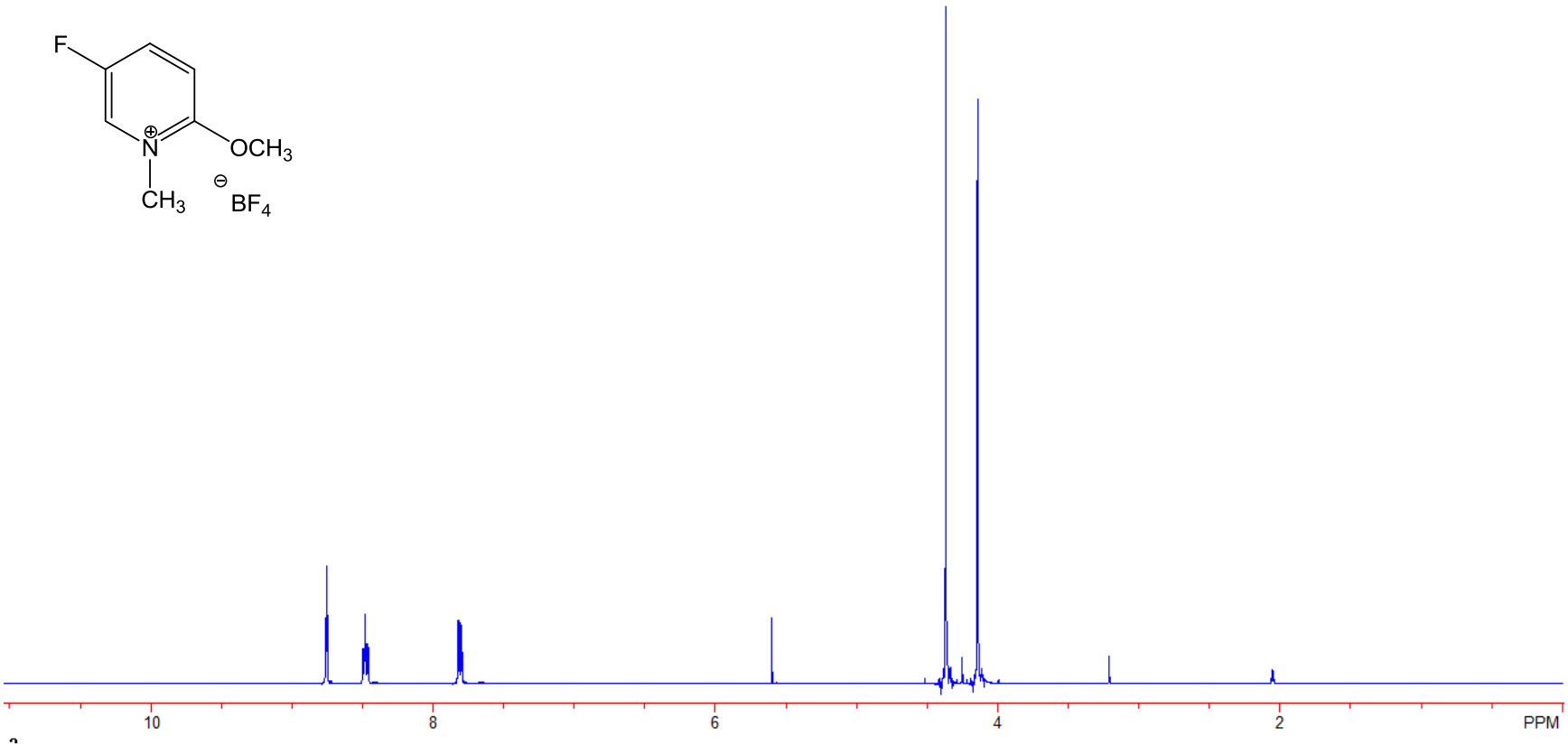
500 MHz ^{1}H NMR Spectrum in acetone (1b)



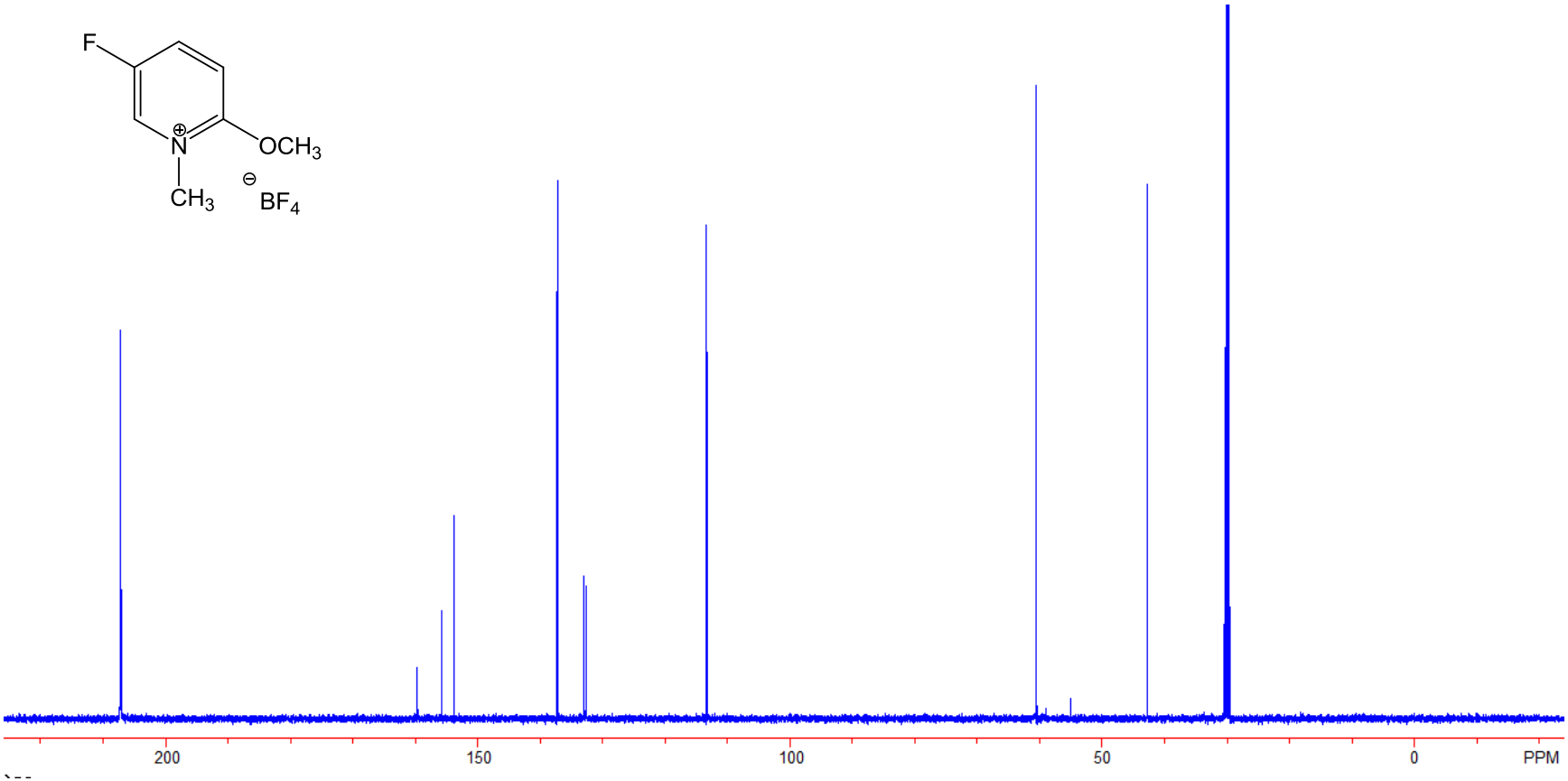
125 MHz ^{13}C NMR Spectrum in acetone (1b)



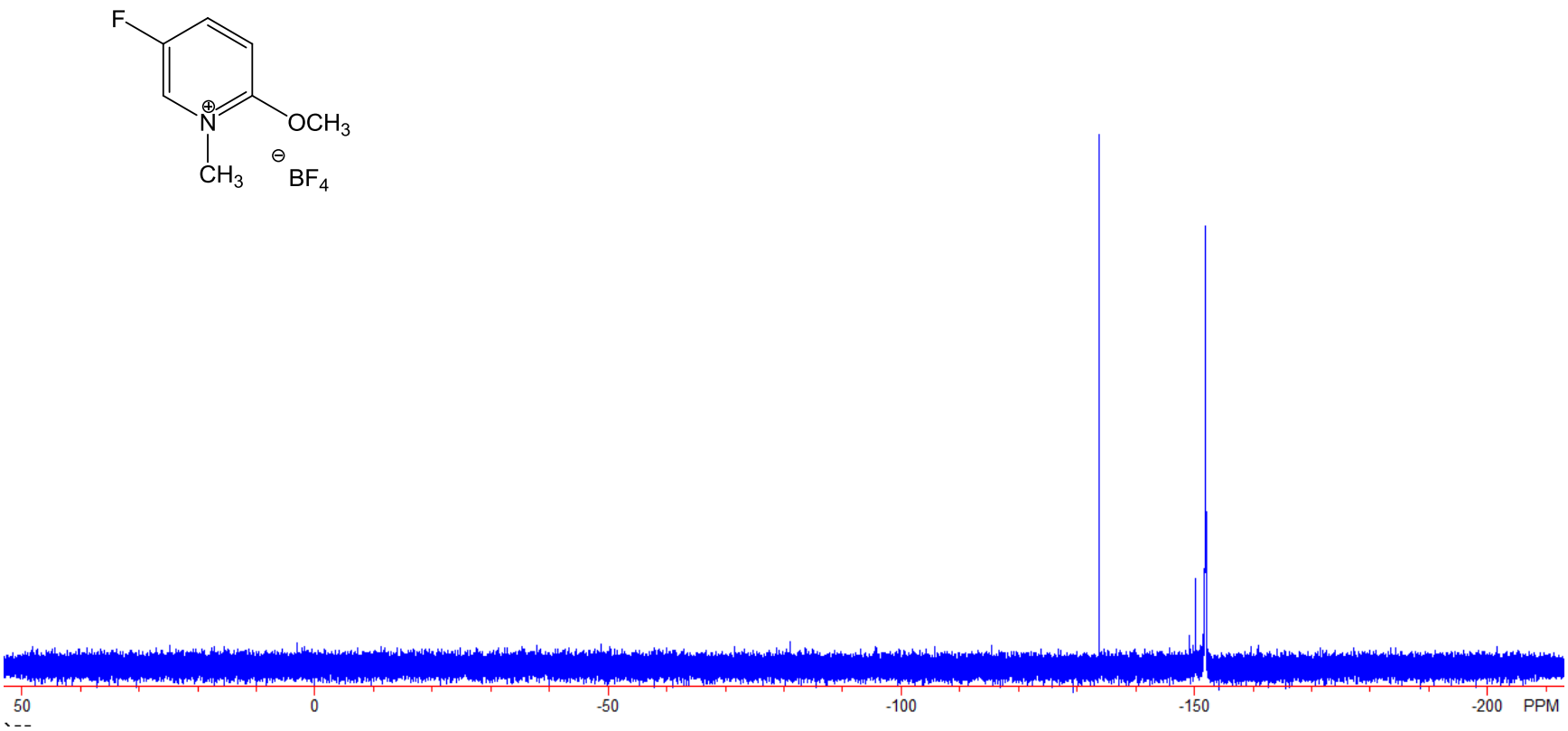
477 MHz ^{19}F NMR Spectrum in acetone **(1b)**



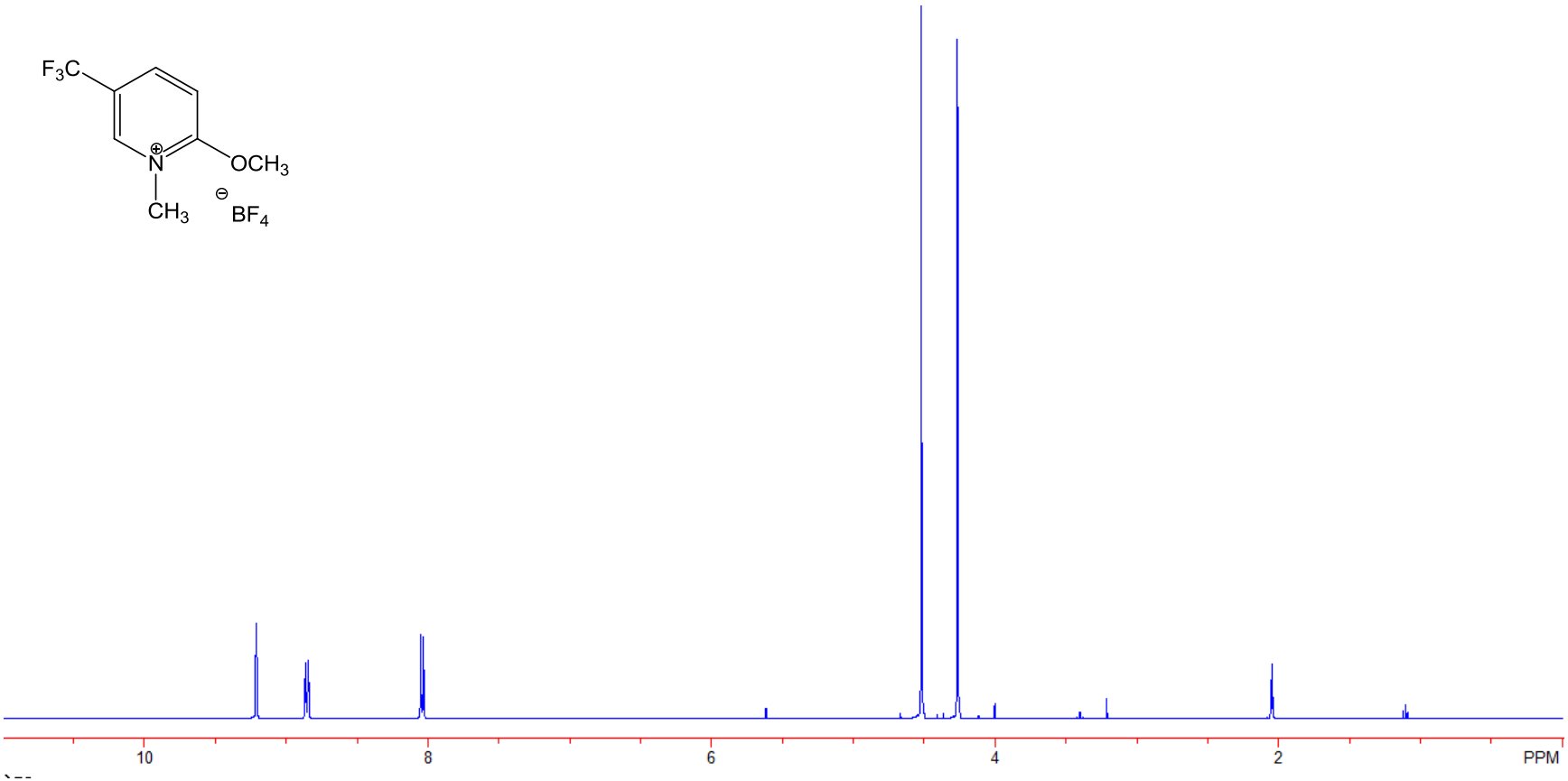
500 MHz ^{1}H NMR Spectrum in acetone (1c)



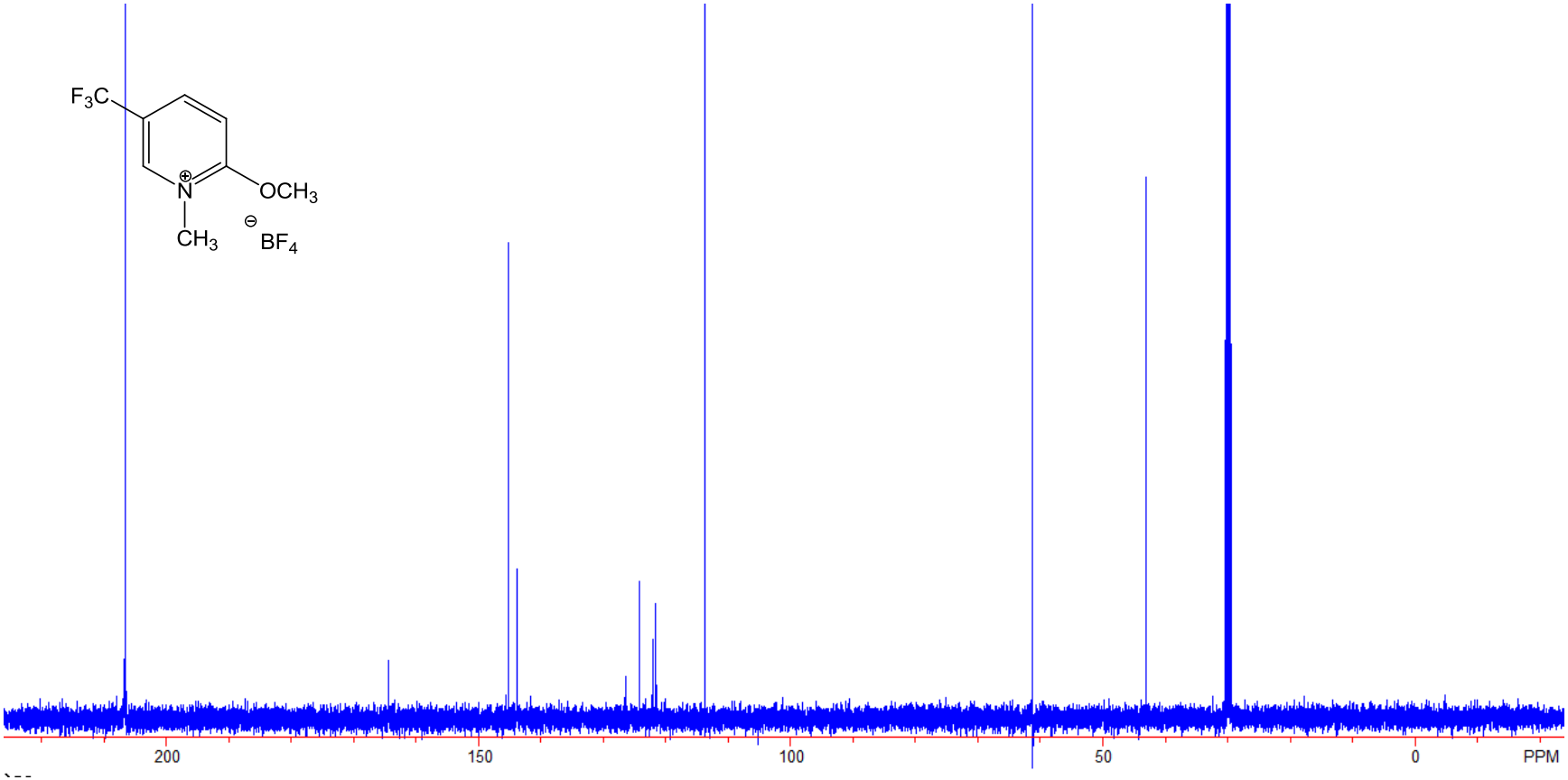
125 MHz ^{13}C NMR Spectrum in acetone (1c)



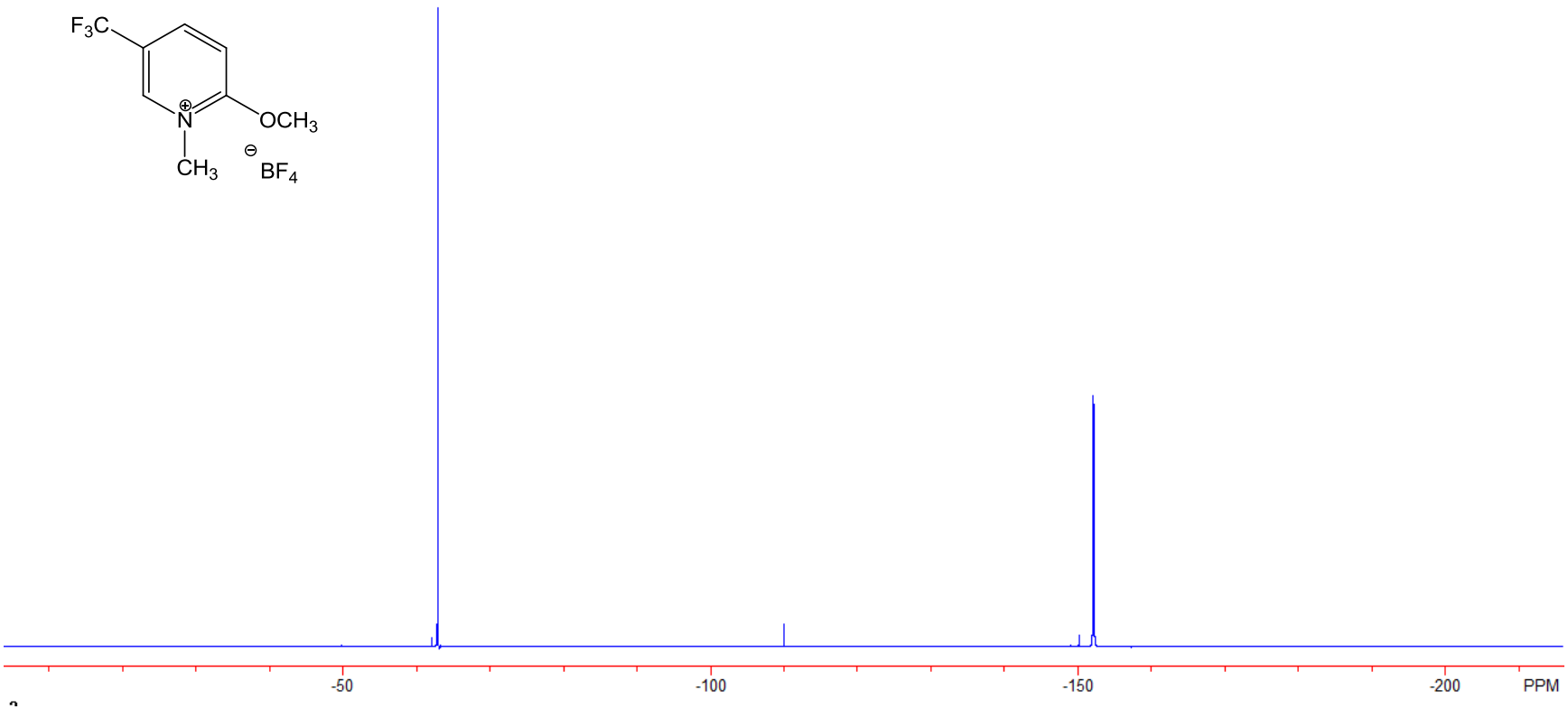
477 MHz ^{19}F NMR Spectrum in acetone **(1c)**



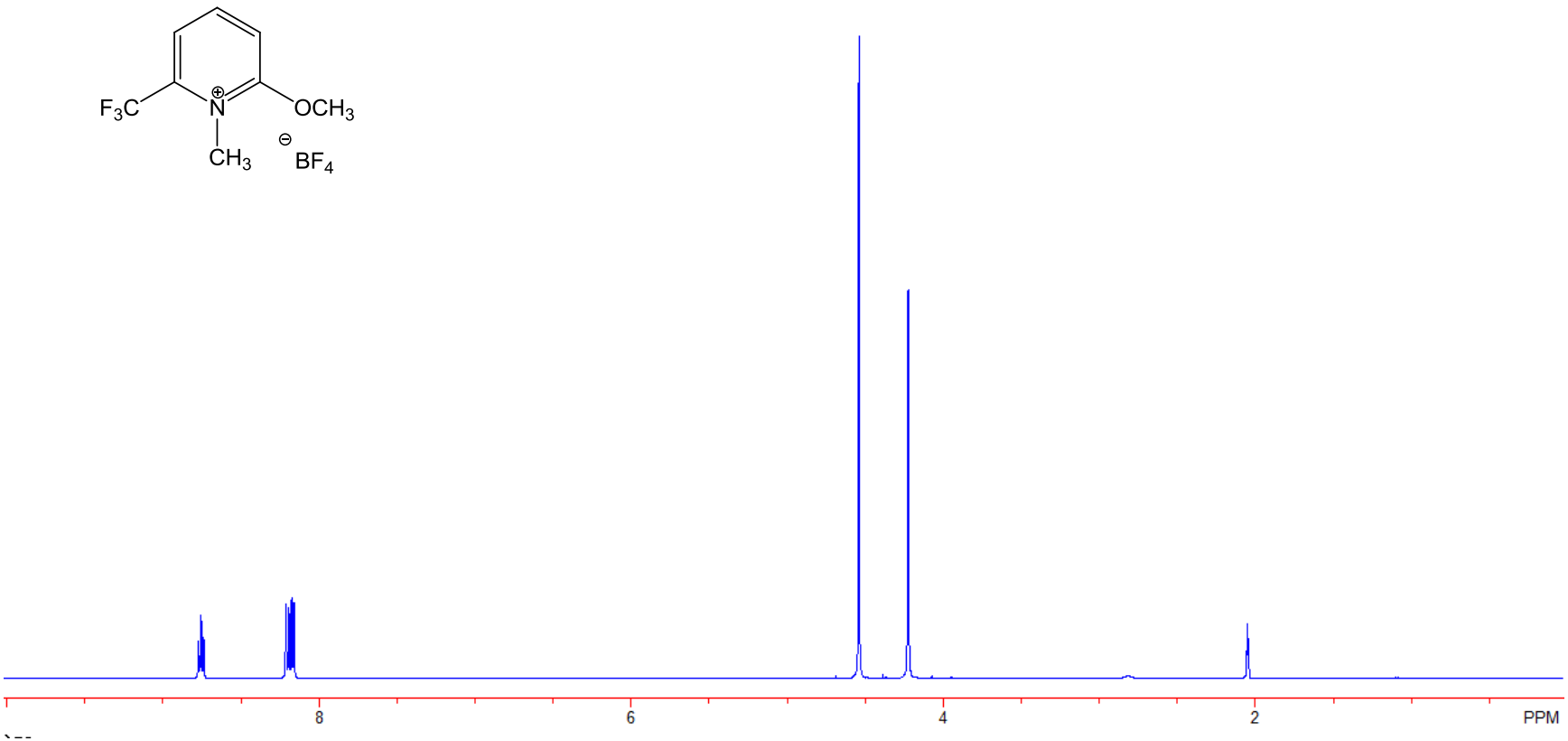
500 MHz ^{1}H NMR Spectrum in acetone (1d)



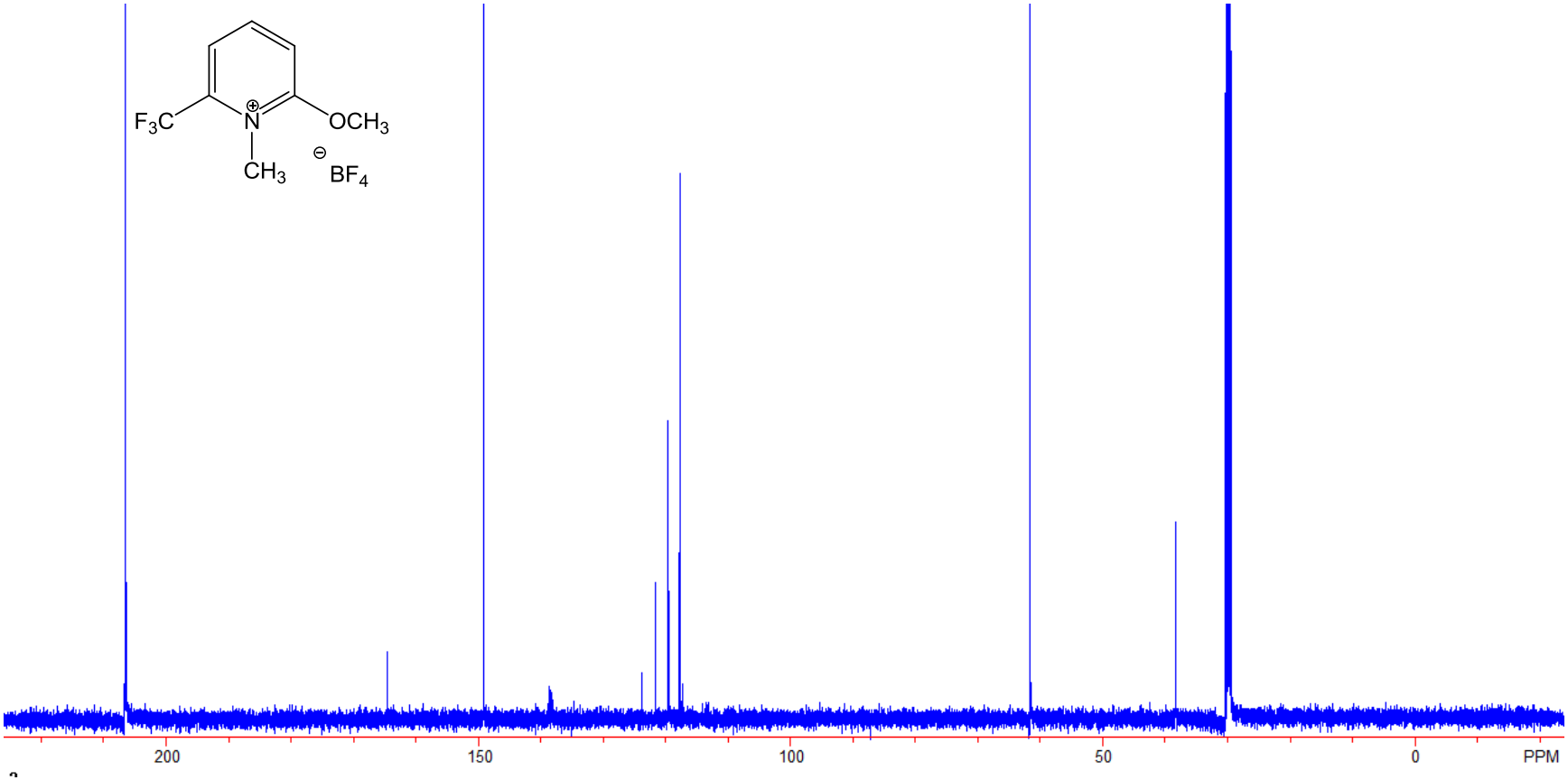
125 MHz ^{13}C NMR Spectrum in acetone (1d)



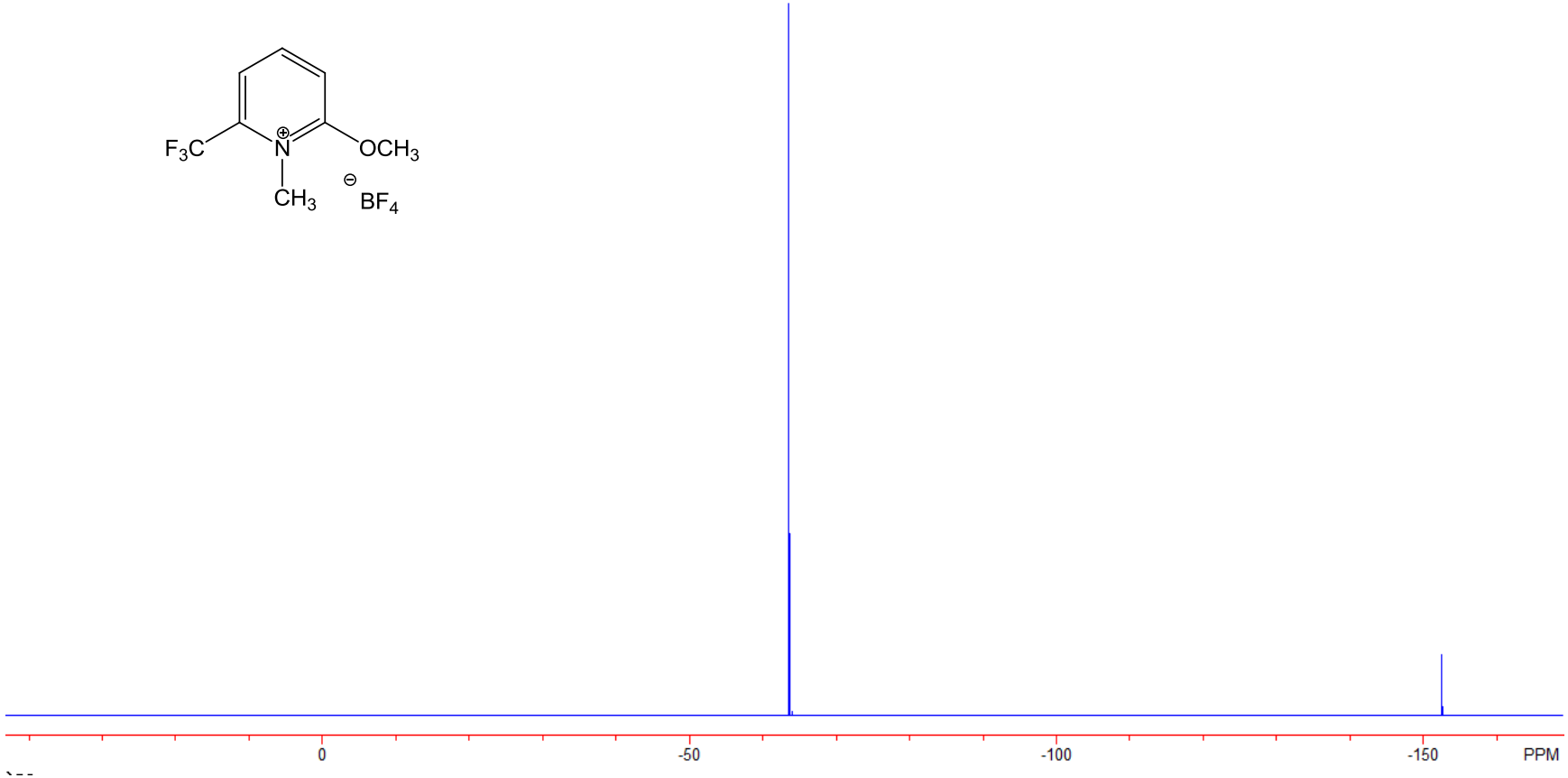
477 MHz ^{19}F NMR Spectrum in acetone (1d)



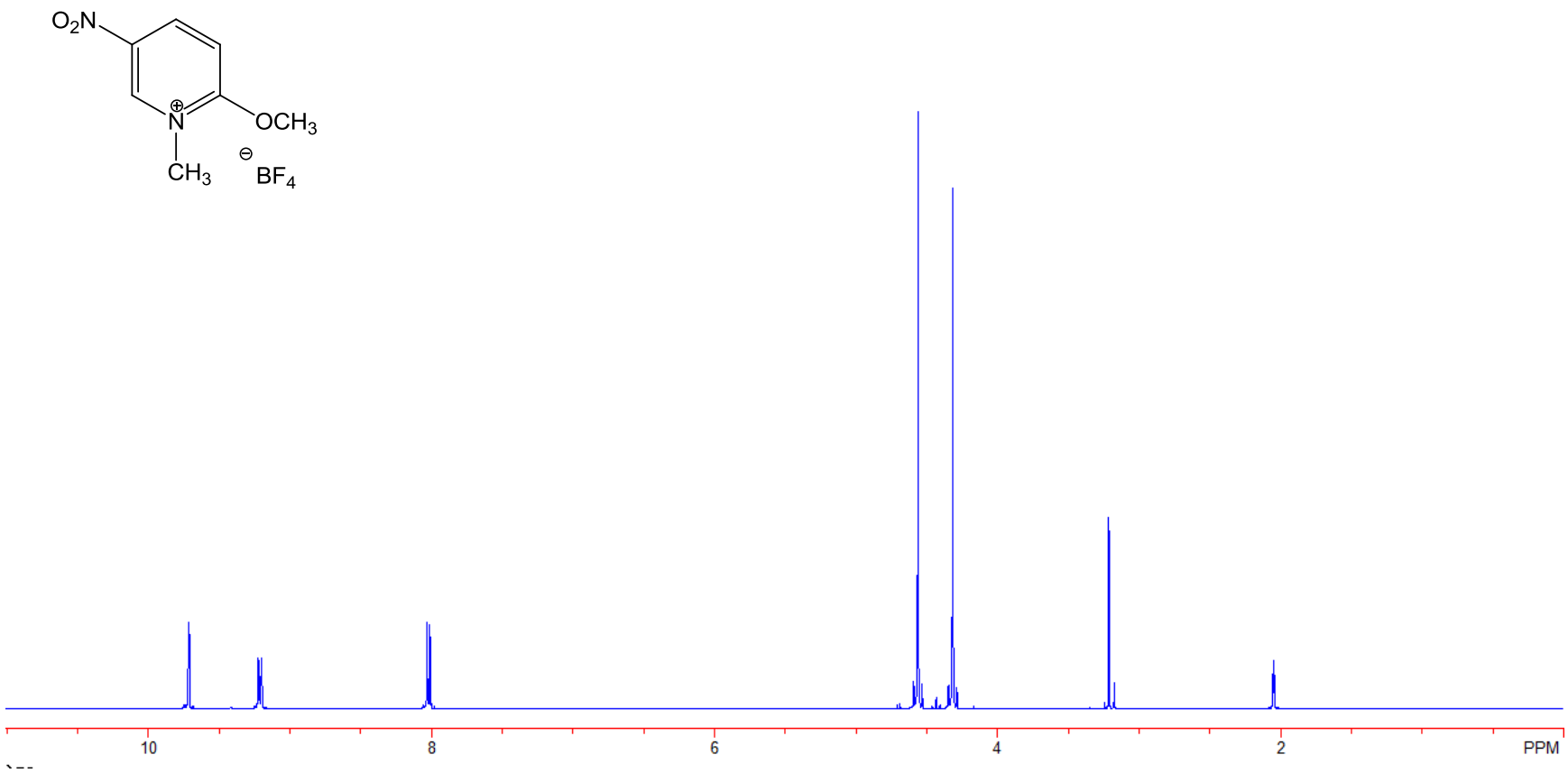
500 MHz ^{1}H NMR Spectrum in acetone (1e)



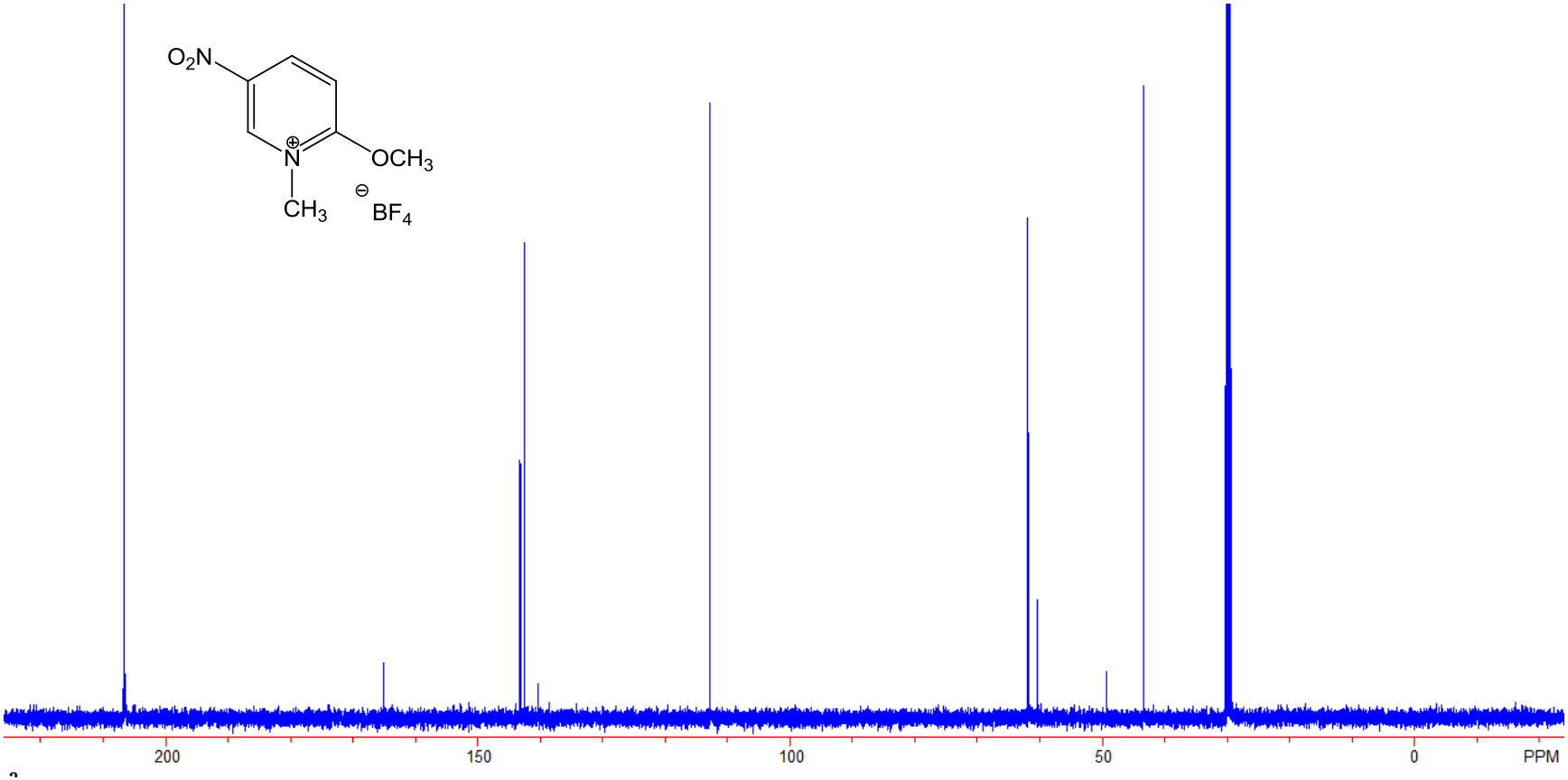
125 MHz ^{13}C NMR Spectrum in acetone (1e)



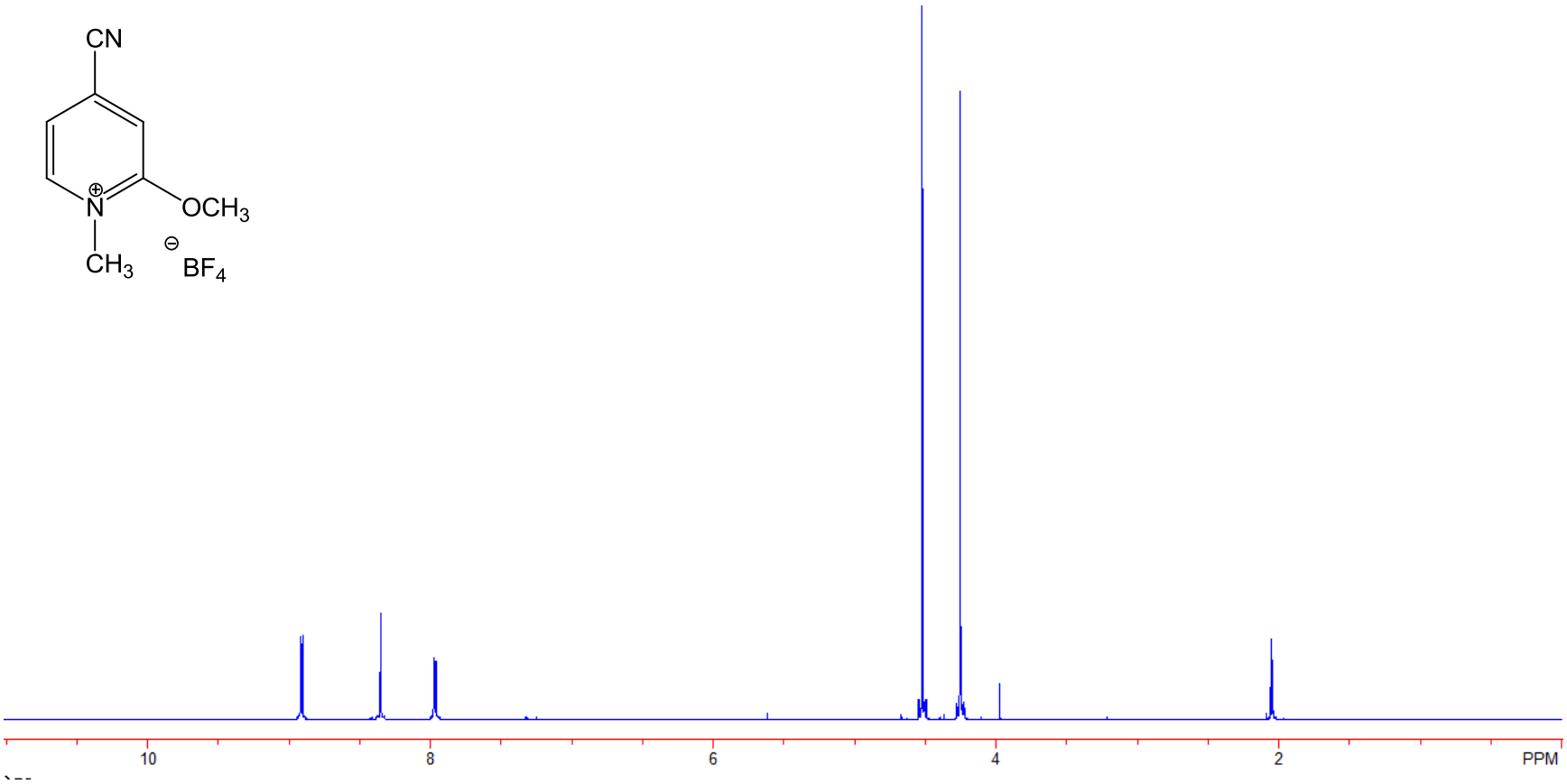
477 MHz ^{19}F NMR Spectrum in acetone (1e)



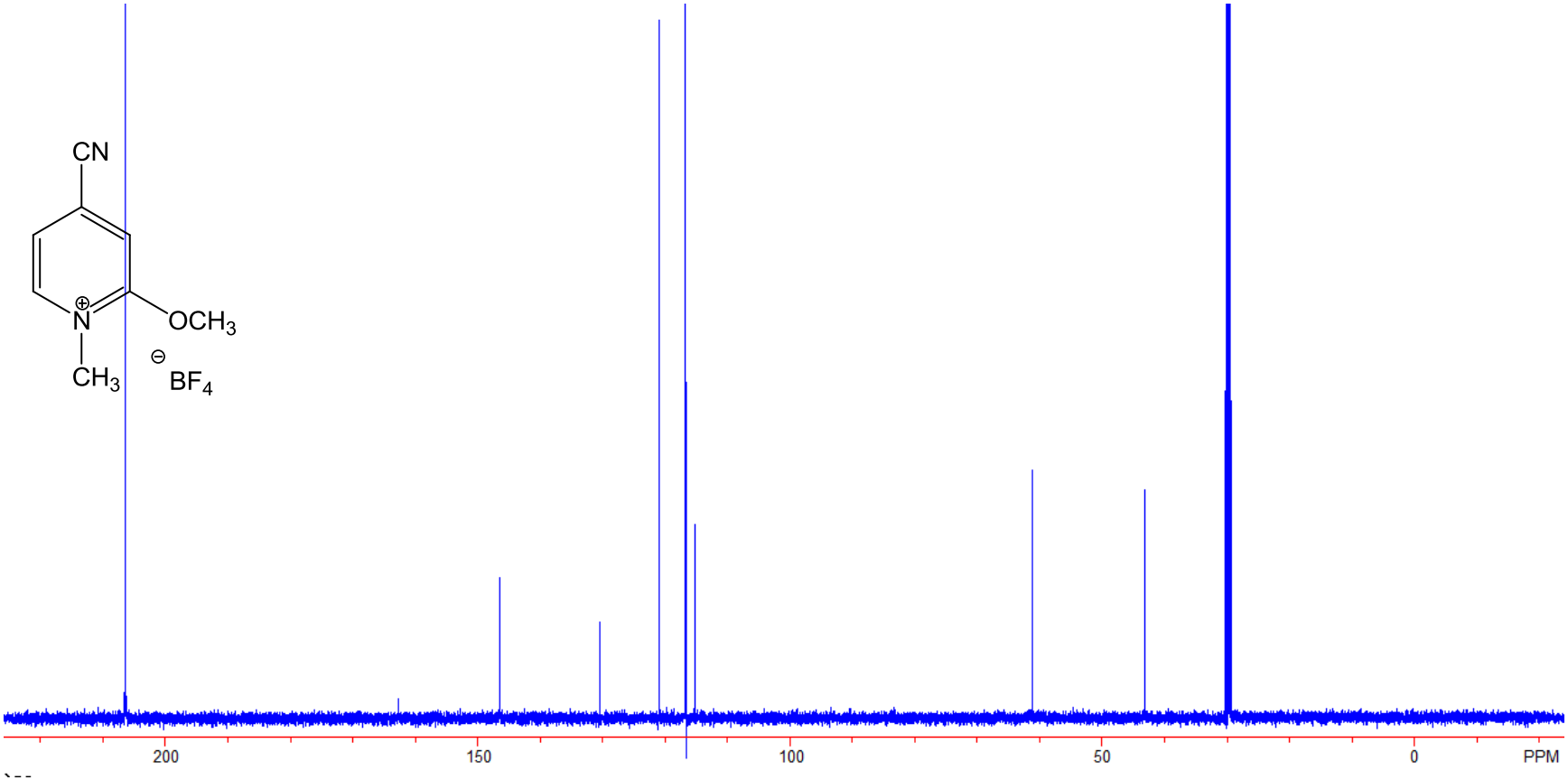
500 MHz ^{1}H NMR Spectrum in acetone (1f)



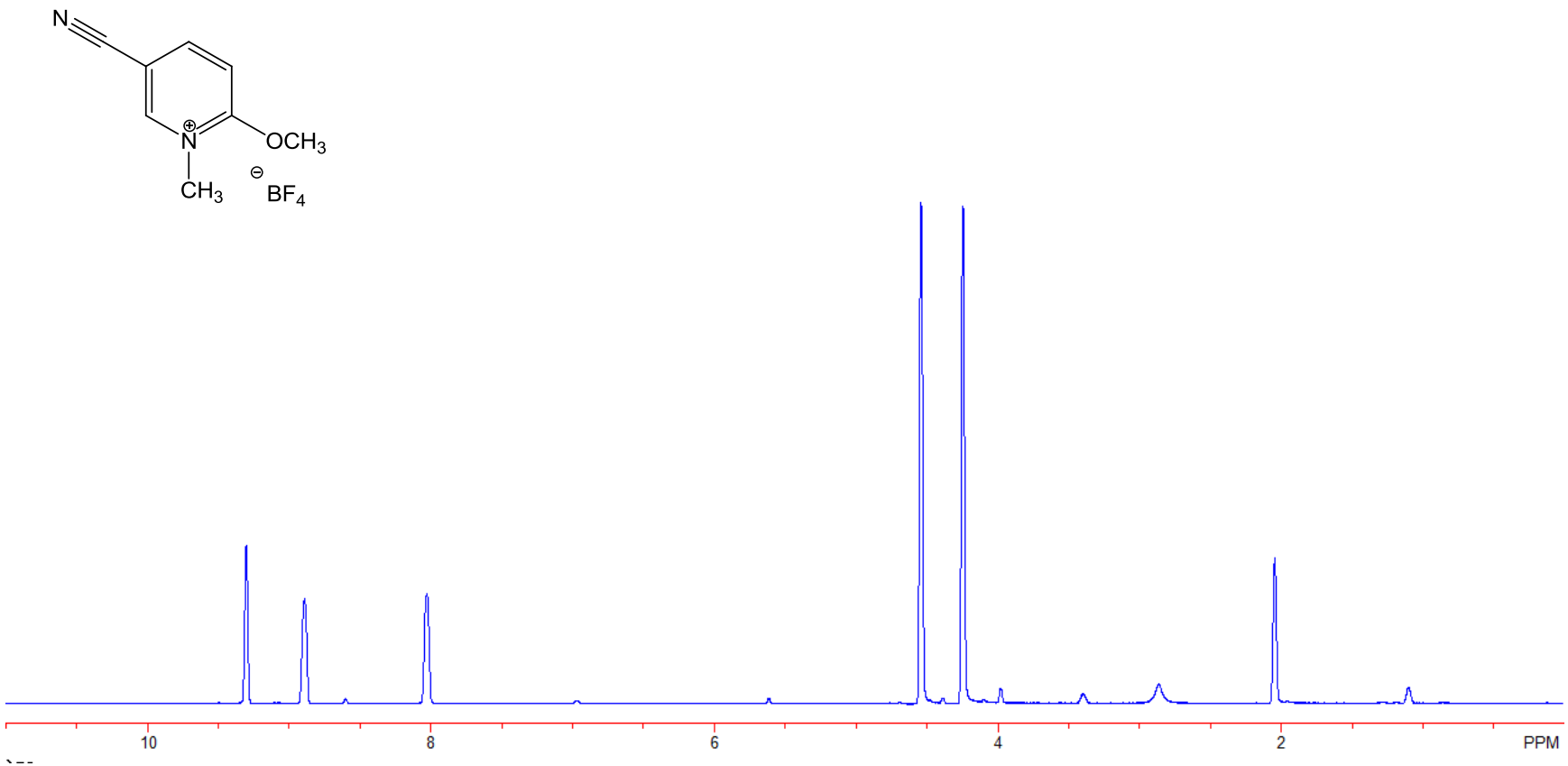
125 MHz ^{13}C NMR Spectrum in acetone (1f)



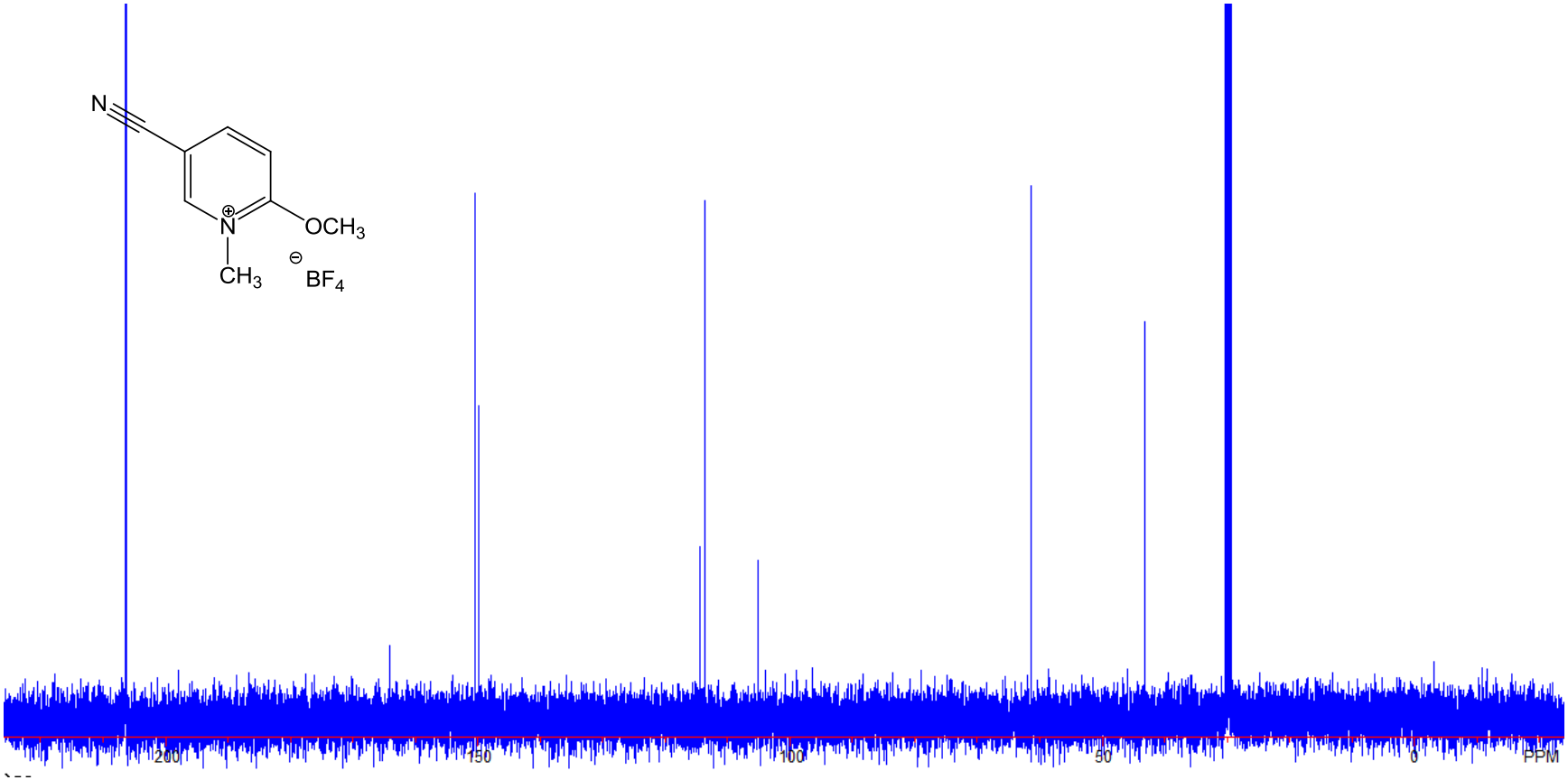
500 MHz ^{1}H NMR Spectrum in acetone (1g)



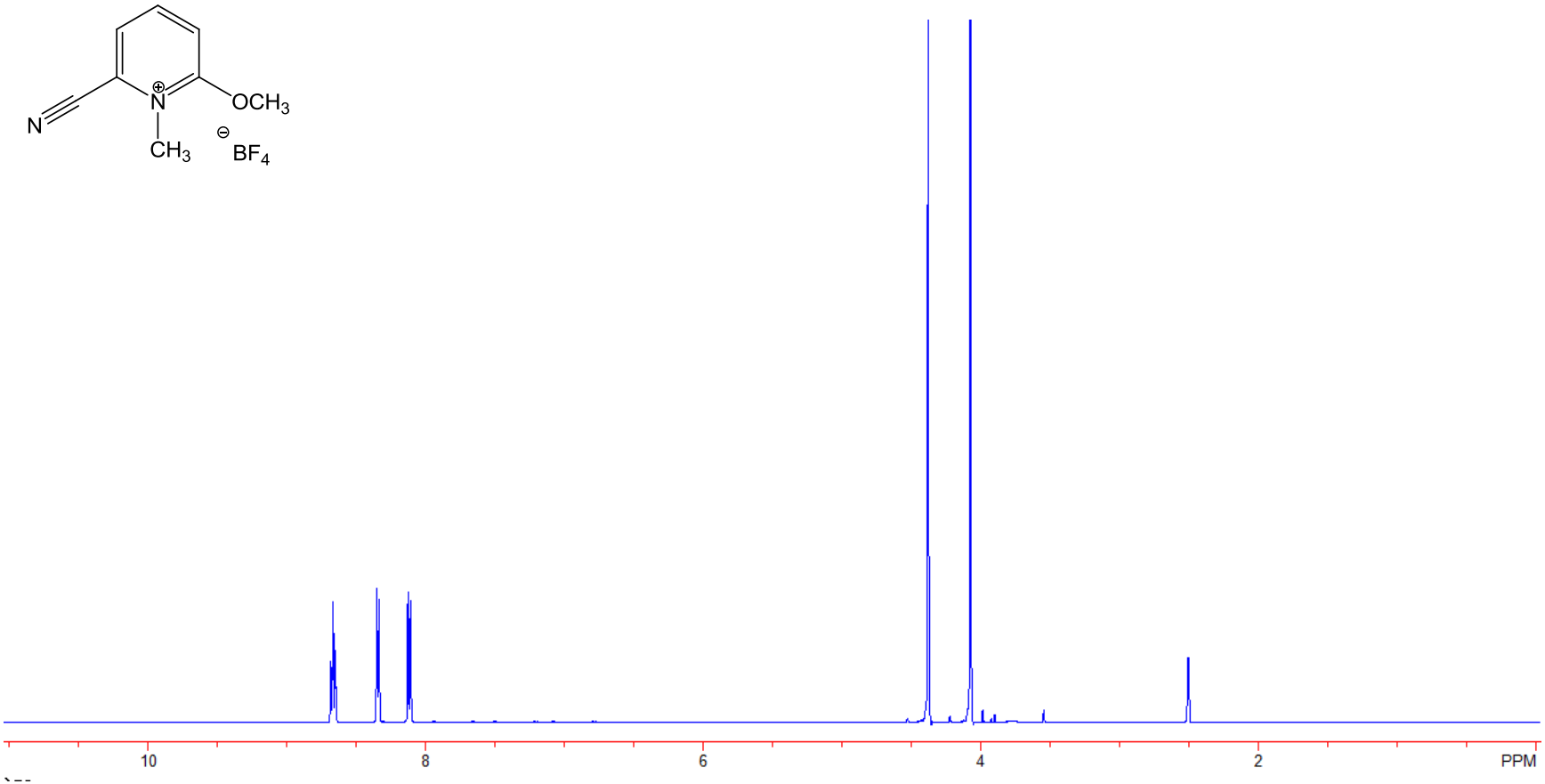
125 MHz ^{13}C NMR Spectrum in acetone (1g)



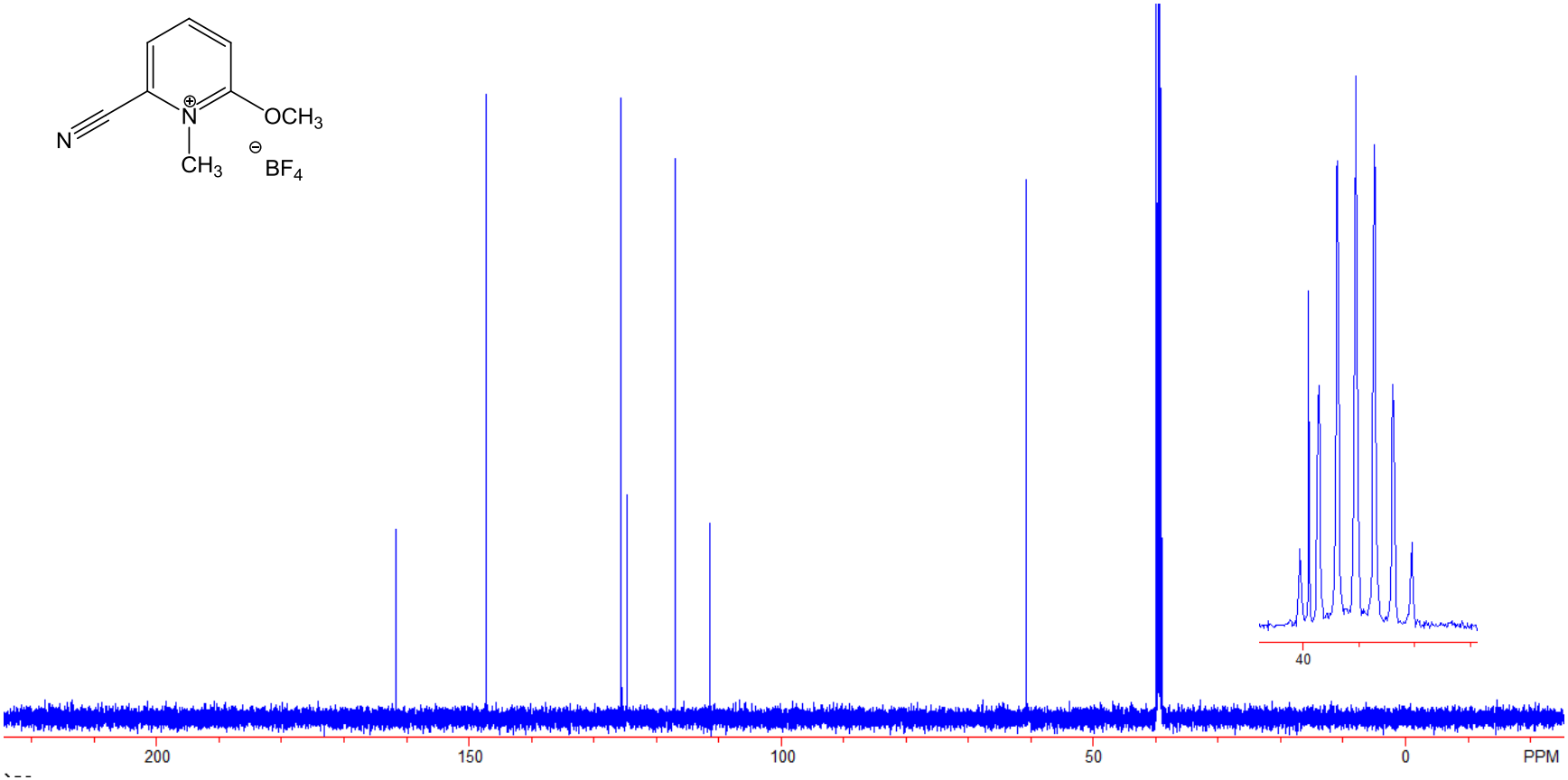
500 MHz ^{1}H NMR Spectrum in acetone (1h)



125 MHz ^{13}C NMR Spectrum in acetone (1h)

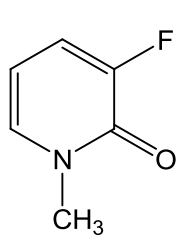


500 MHz ^{1}H NMR Spectrum in DMSO (1i)

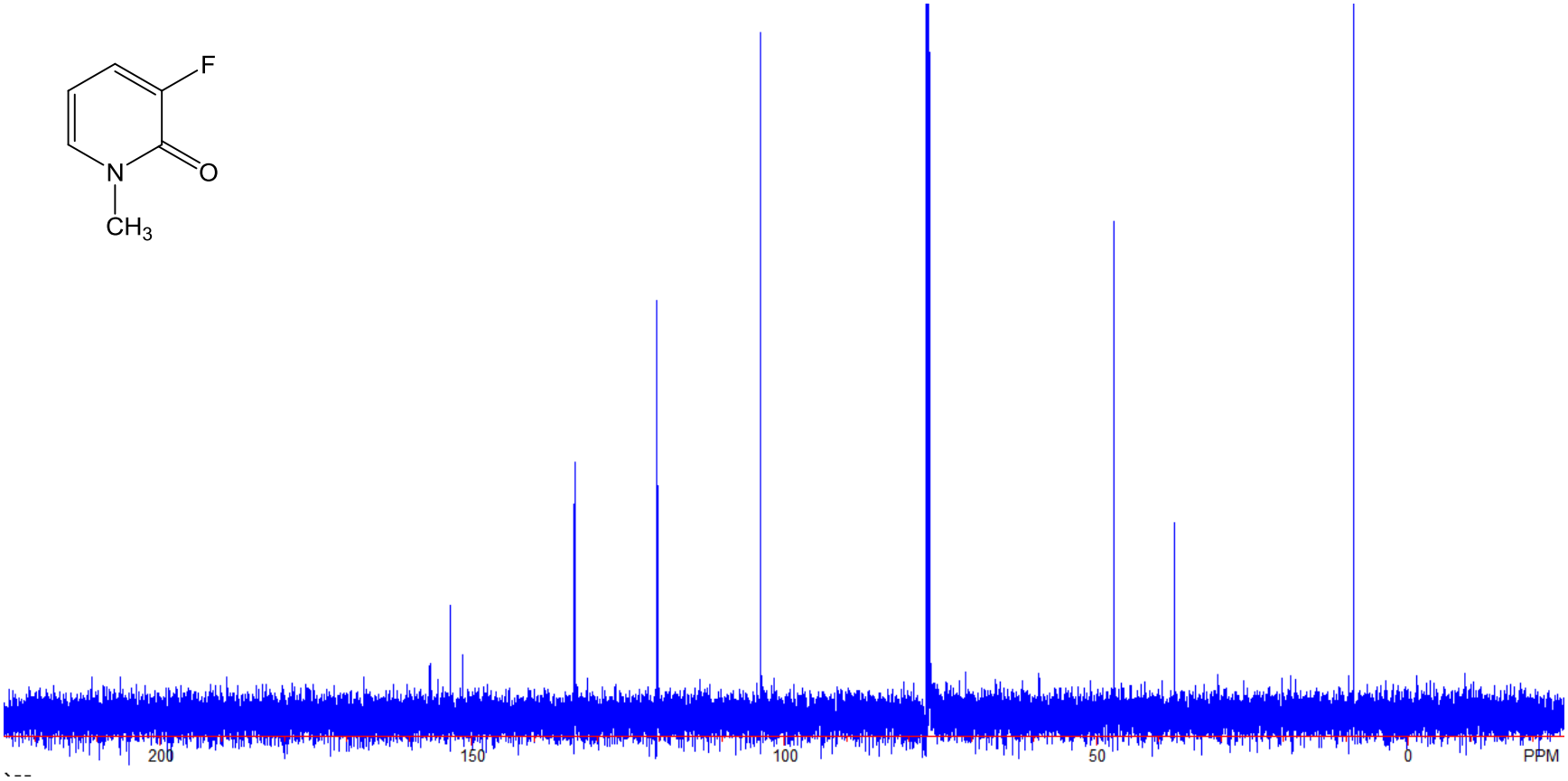


125 MHz ^{13}C NMR Spectrum in DMSO (1i)

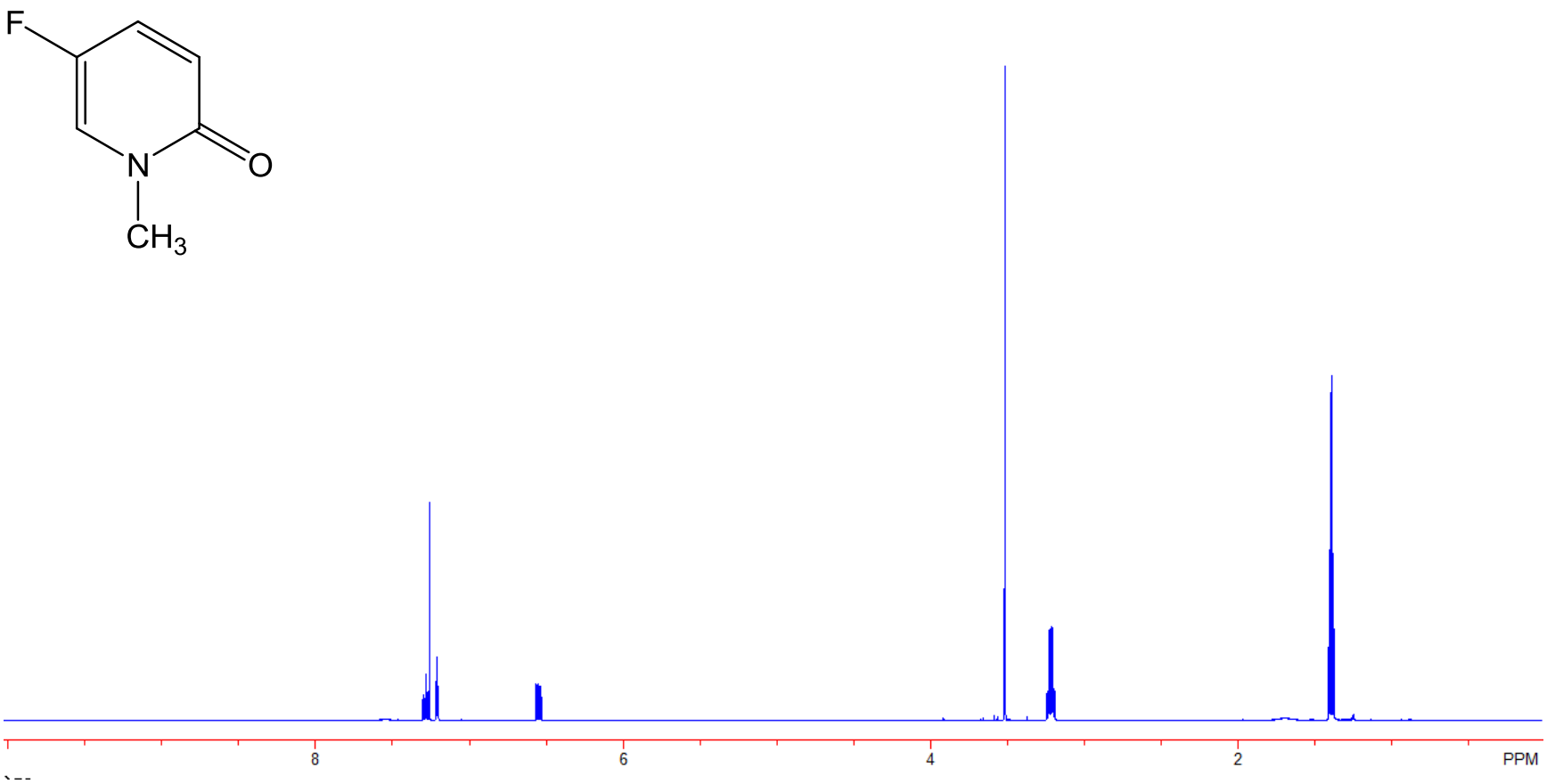
Pyridone 1a is commercially available.



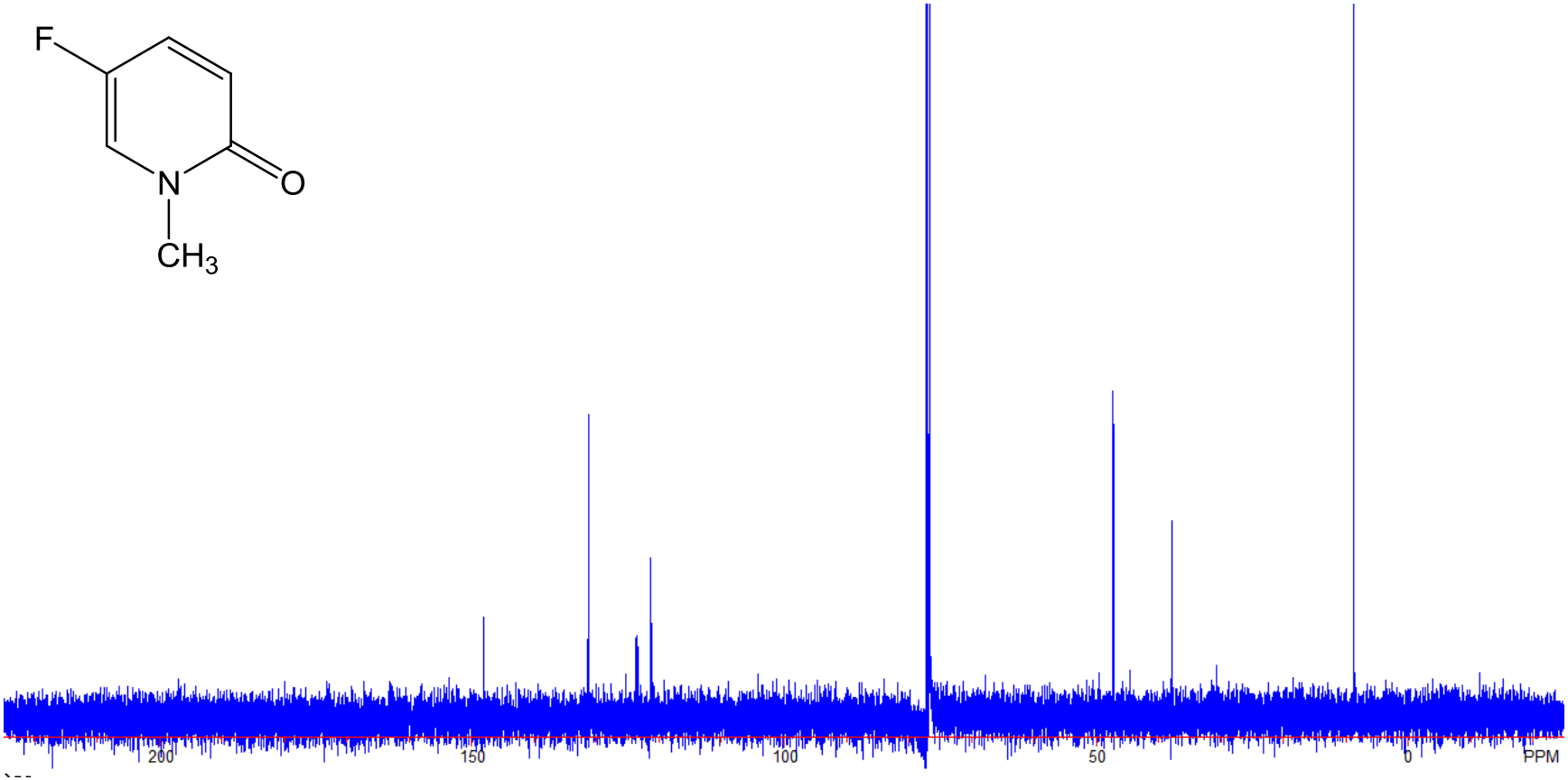
500 MHz ^{1}H NMR Spectrum in $CDCl_3$ (2b)



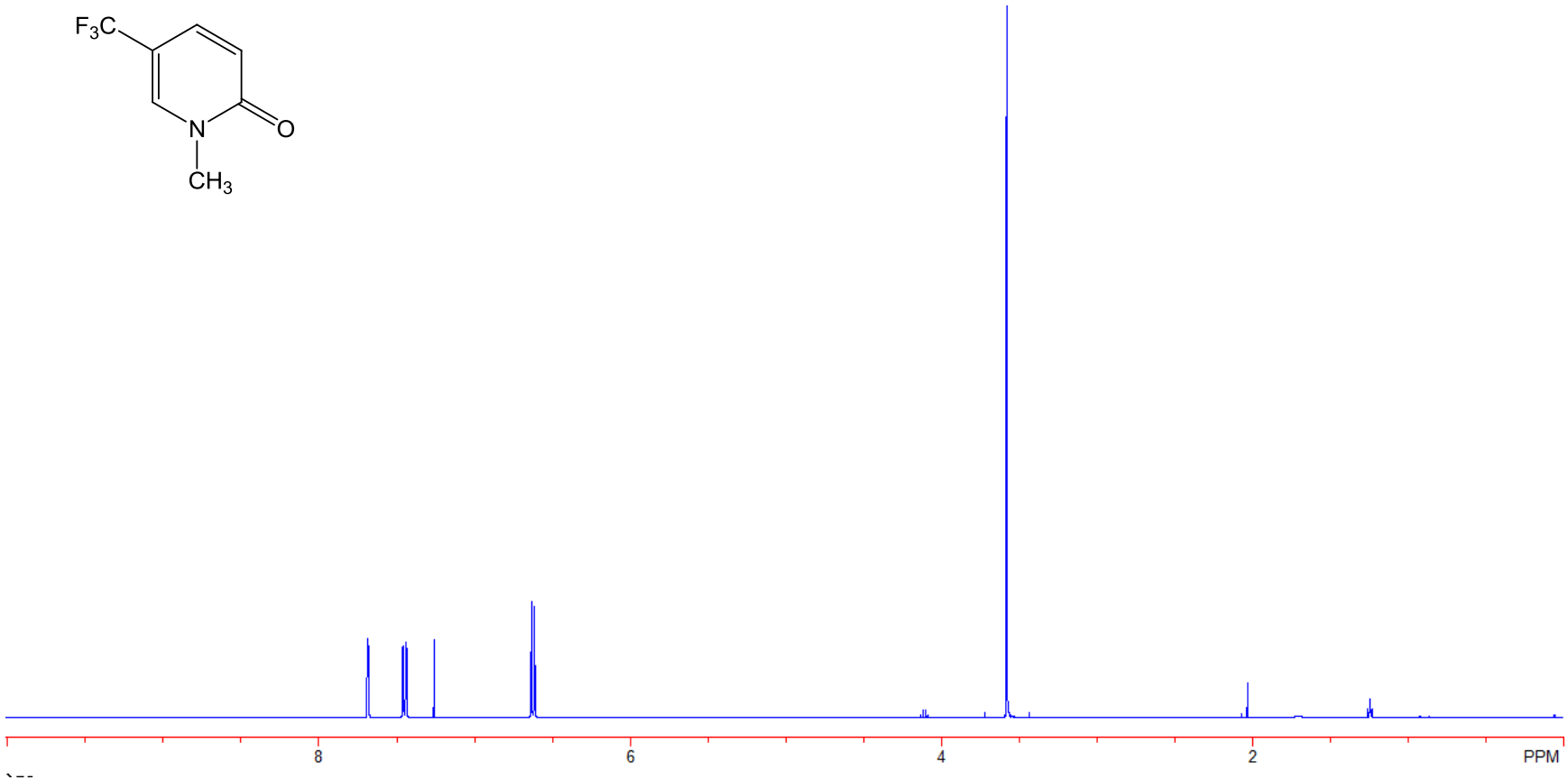
125 MHz ^{13}C NMR Spectrum in $CDCl_3$ (2b)



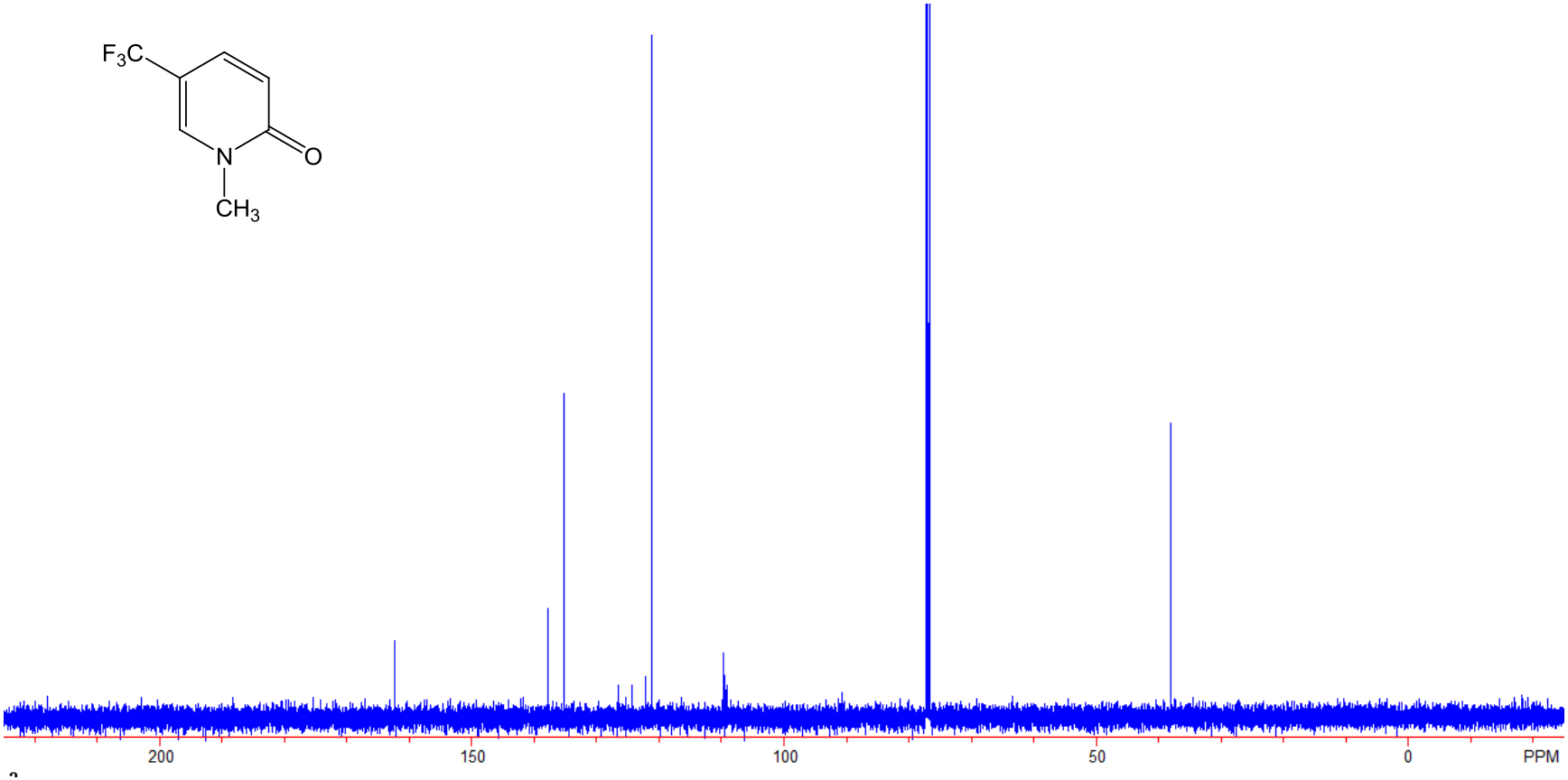
500 MHz ^{1}H NMR Spectrum in $CDCl_3$ (2c)



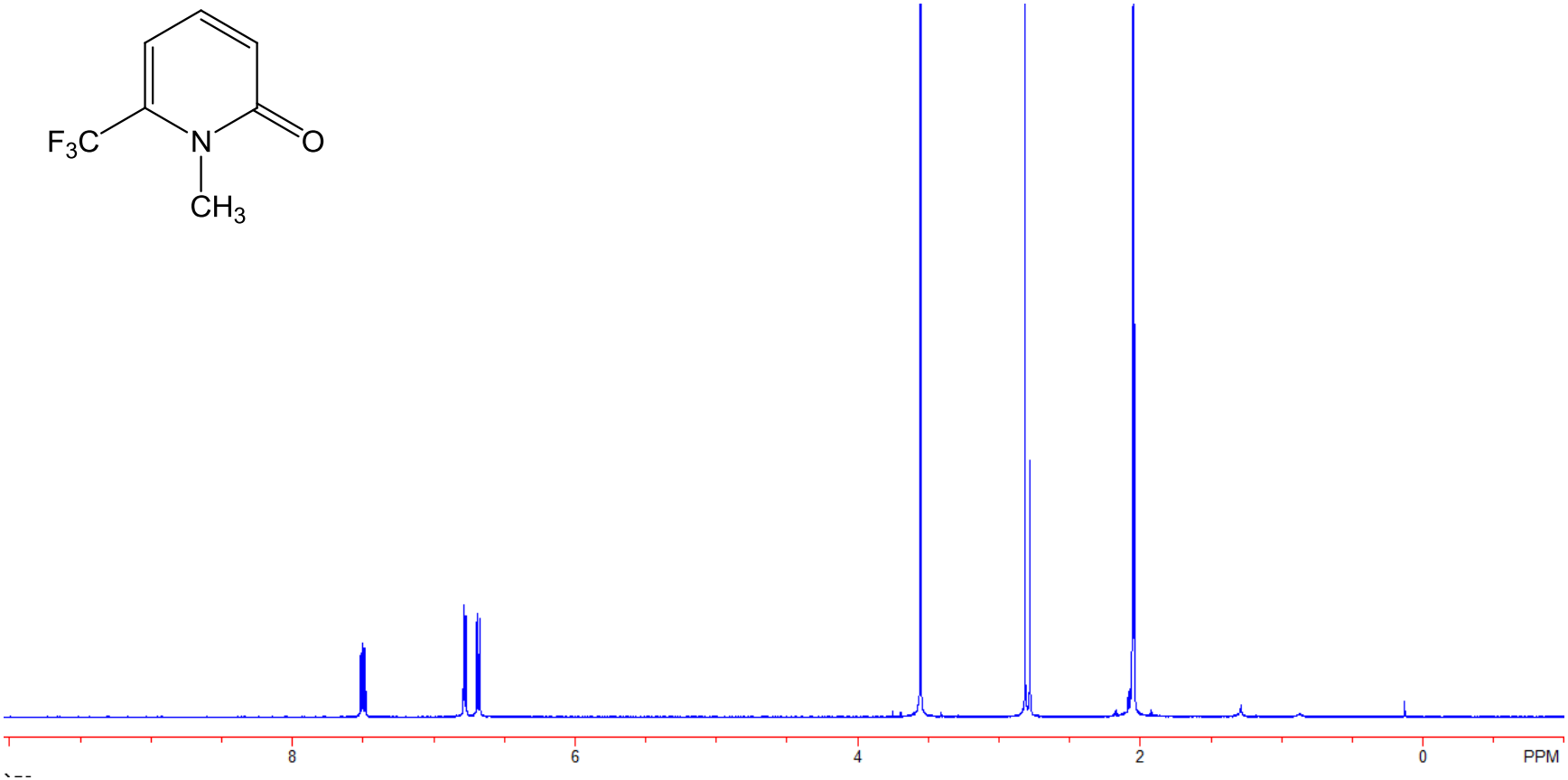
125 MHz ^{13}C NMR Spectrum in $CDCl_3$ (2c)



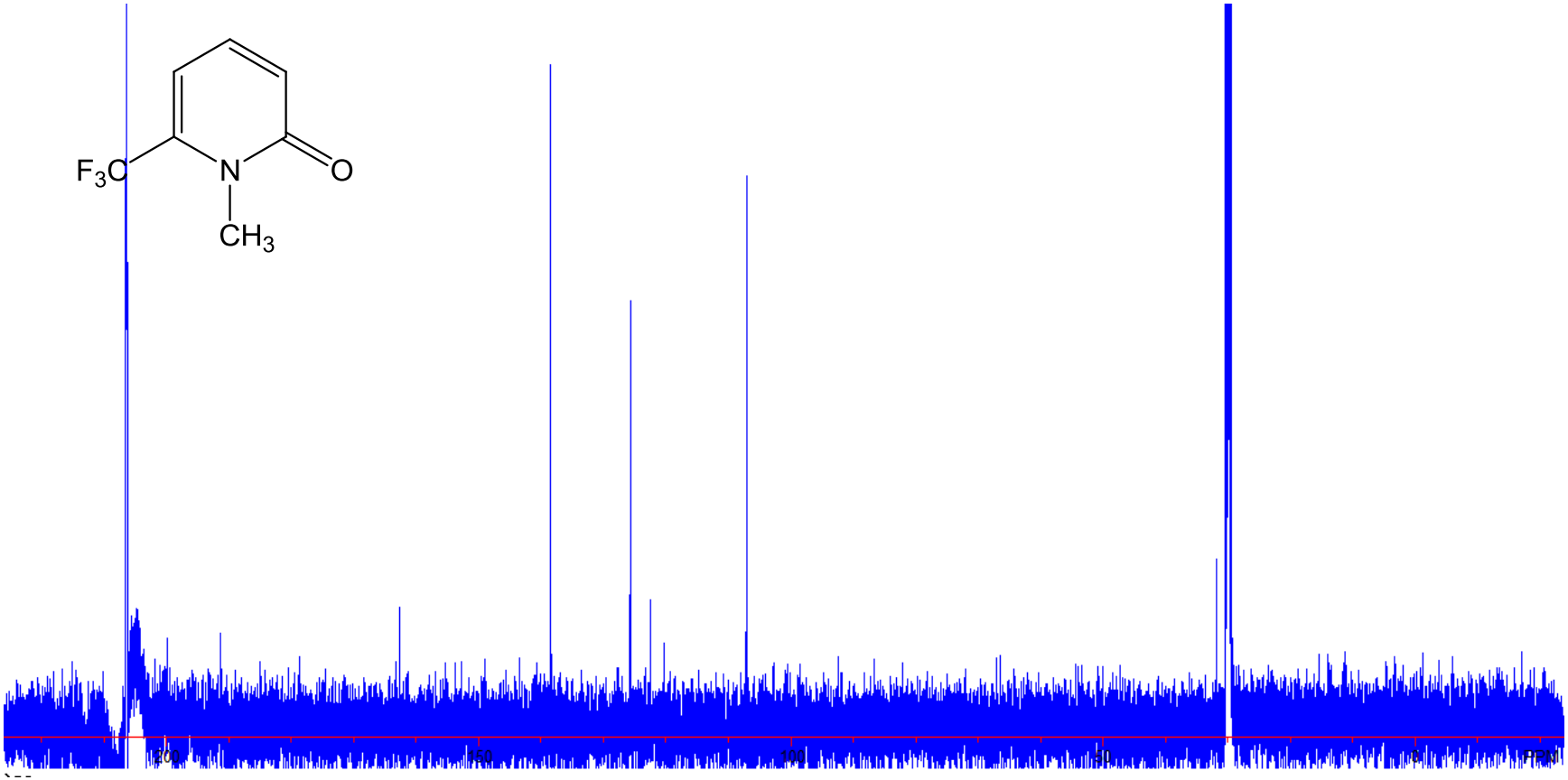
500 MHz ^{1}H NMR Spectrum in $CDCl_3$ (2d)



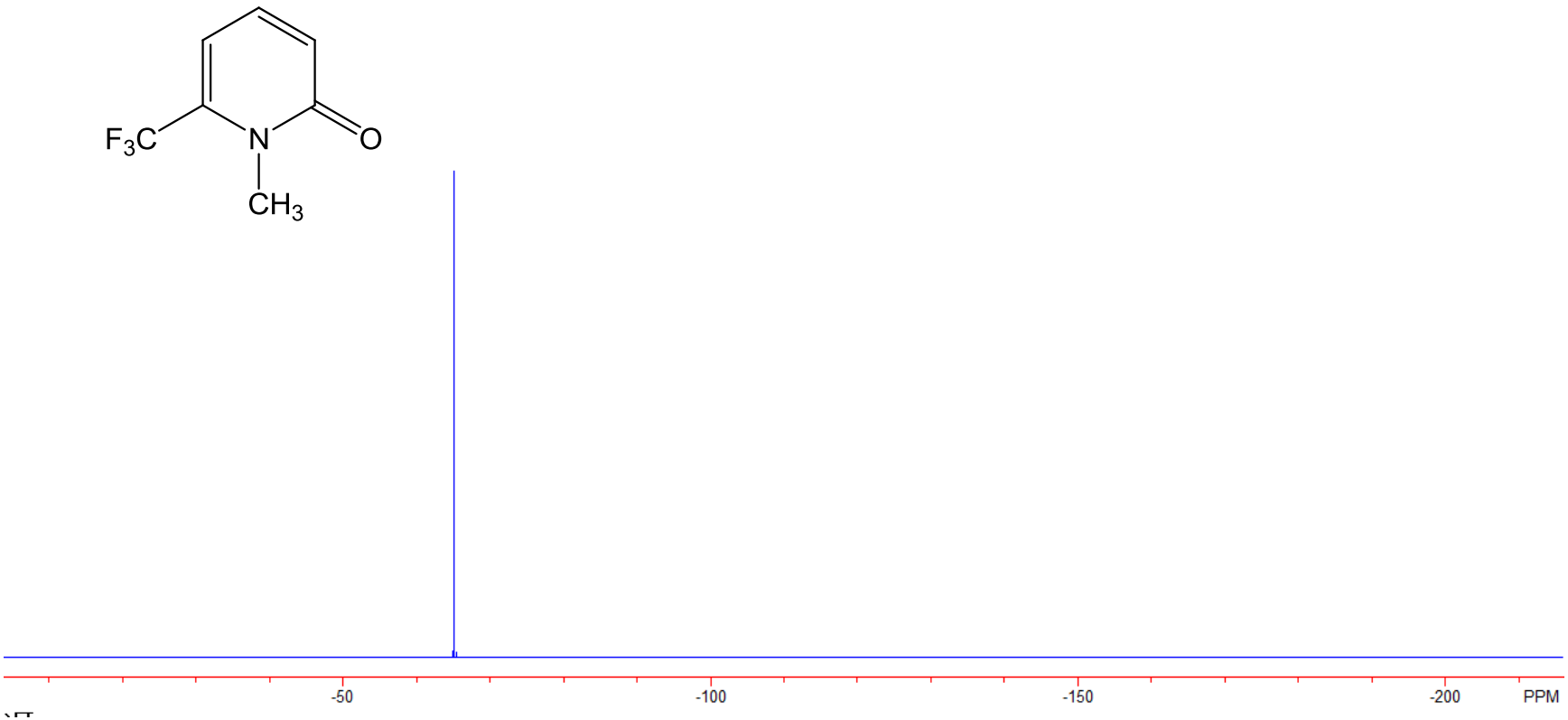
125 MHz ^{13}C NMR Spectrum in $CDCl_3$ (2d)



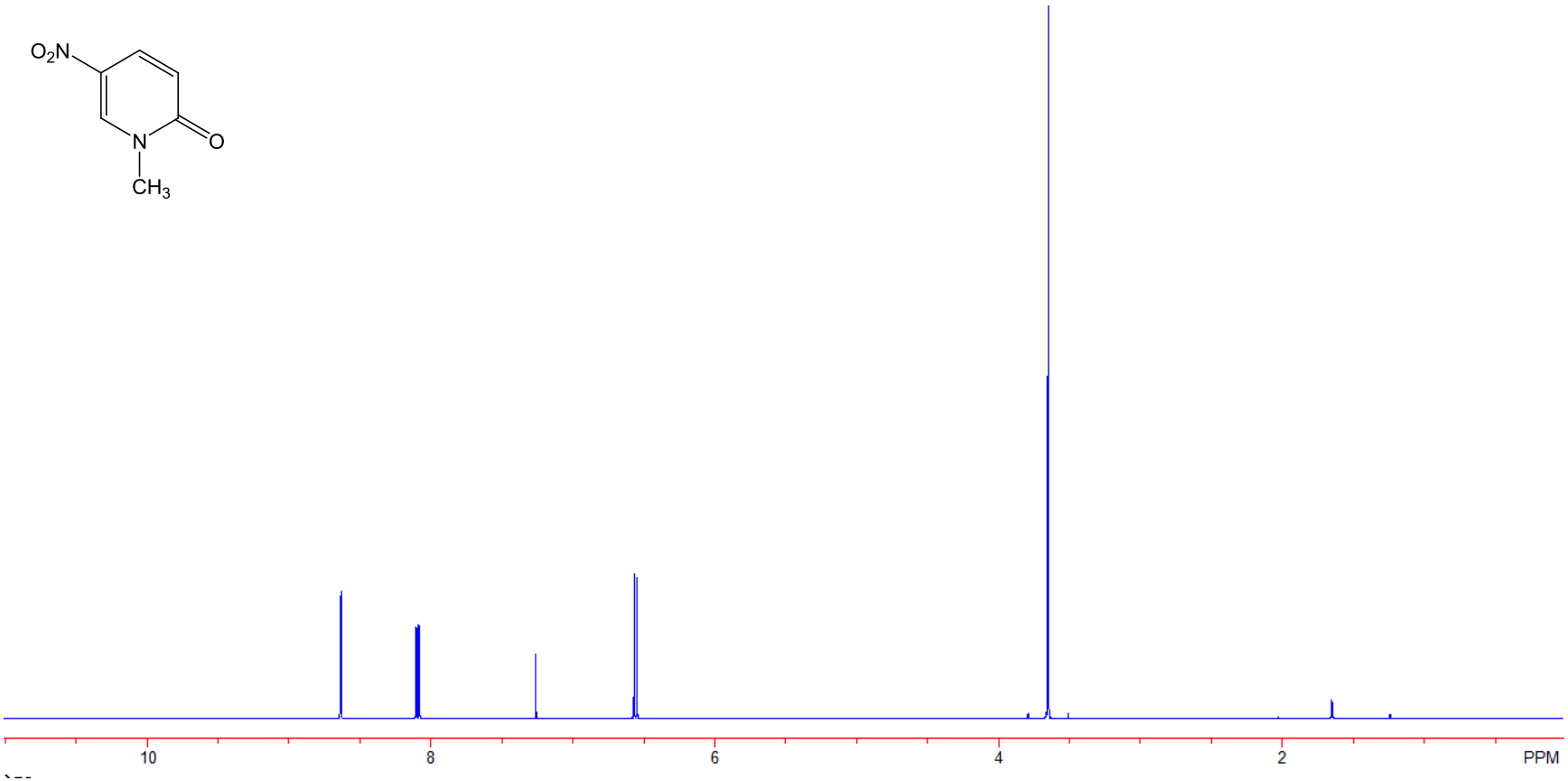
500 MHz ^{1}H NMR Spectrum in acetone (2e)



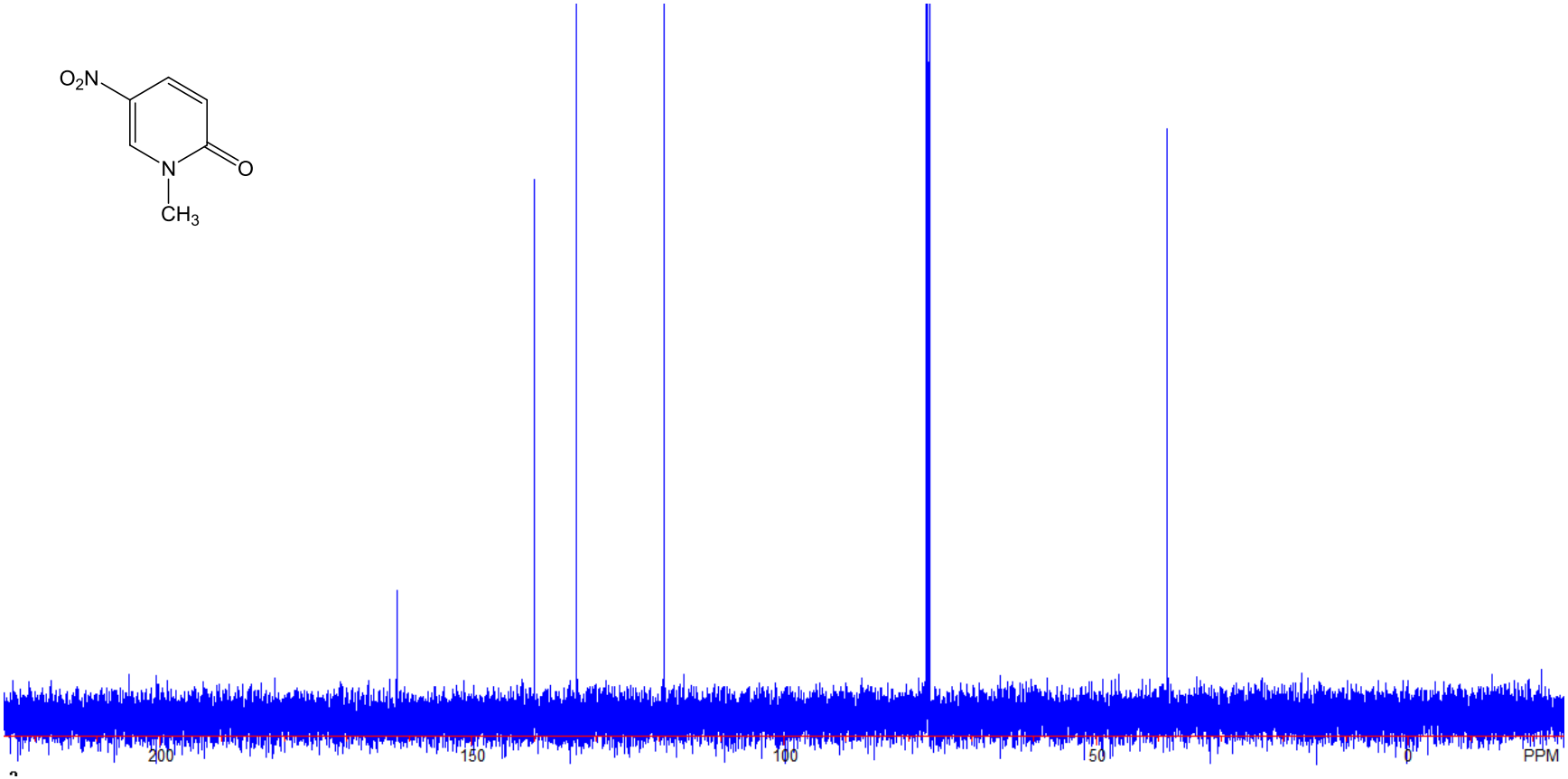
125 MHz ^{13}C NMR Spectrum in acetone (2e)



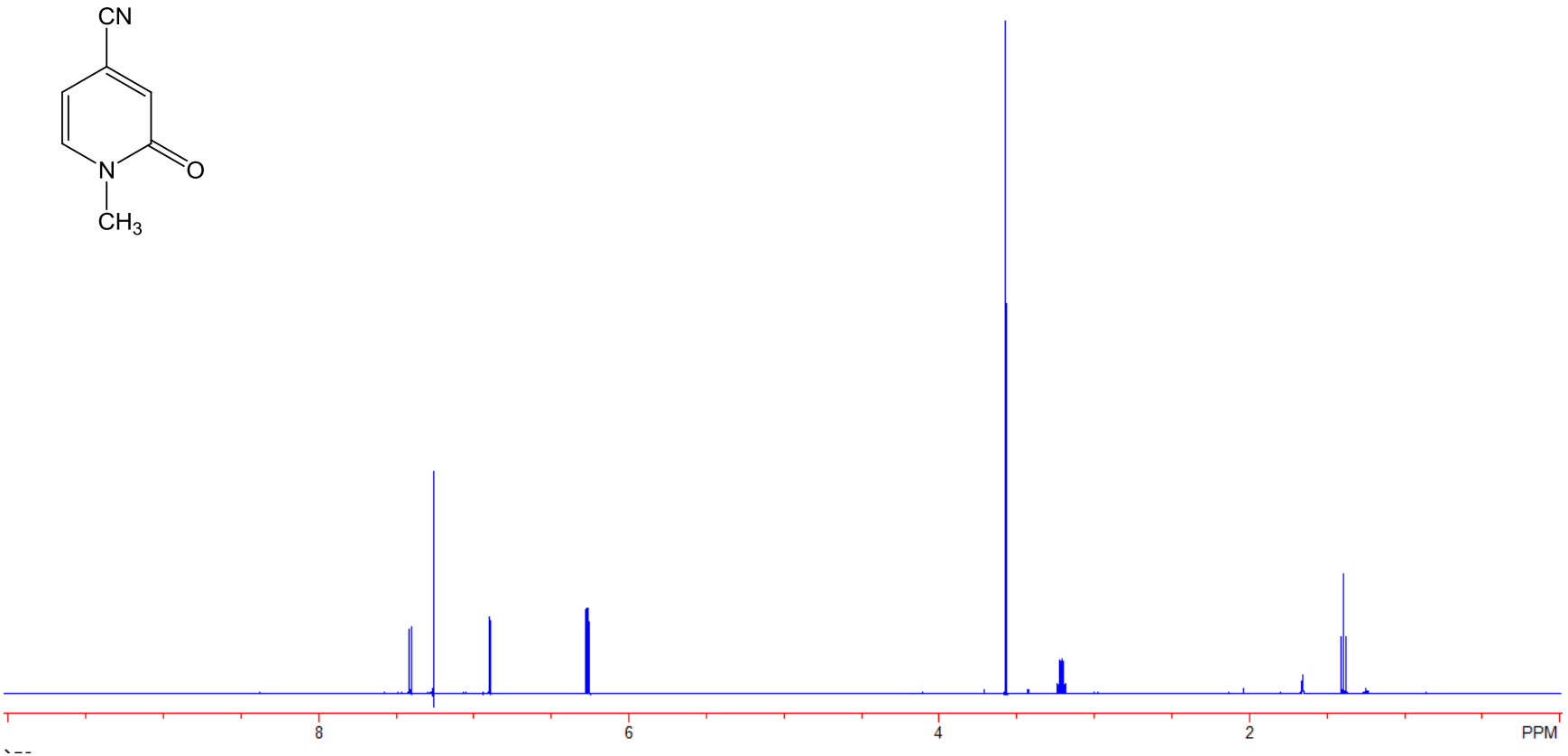
477 MHz ^{19}F NMR Spectrum in acetone (2e)



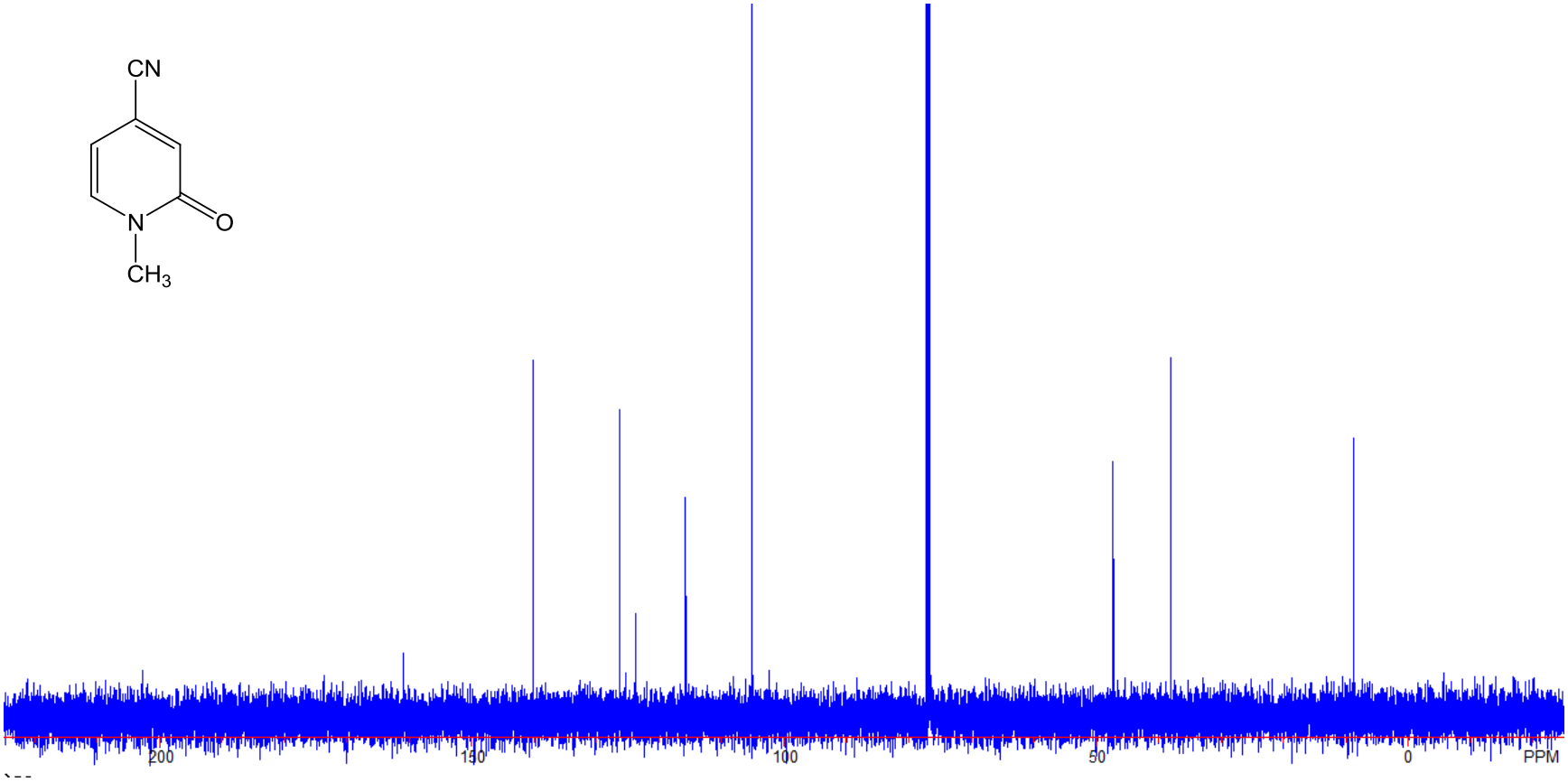
500 MHz ^{1}H NMR Spectrum in $CDCl_3$ (2f)



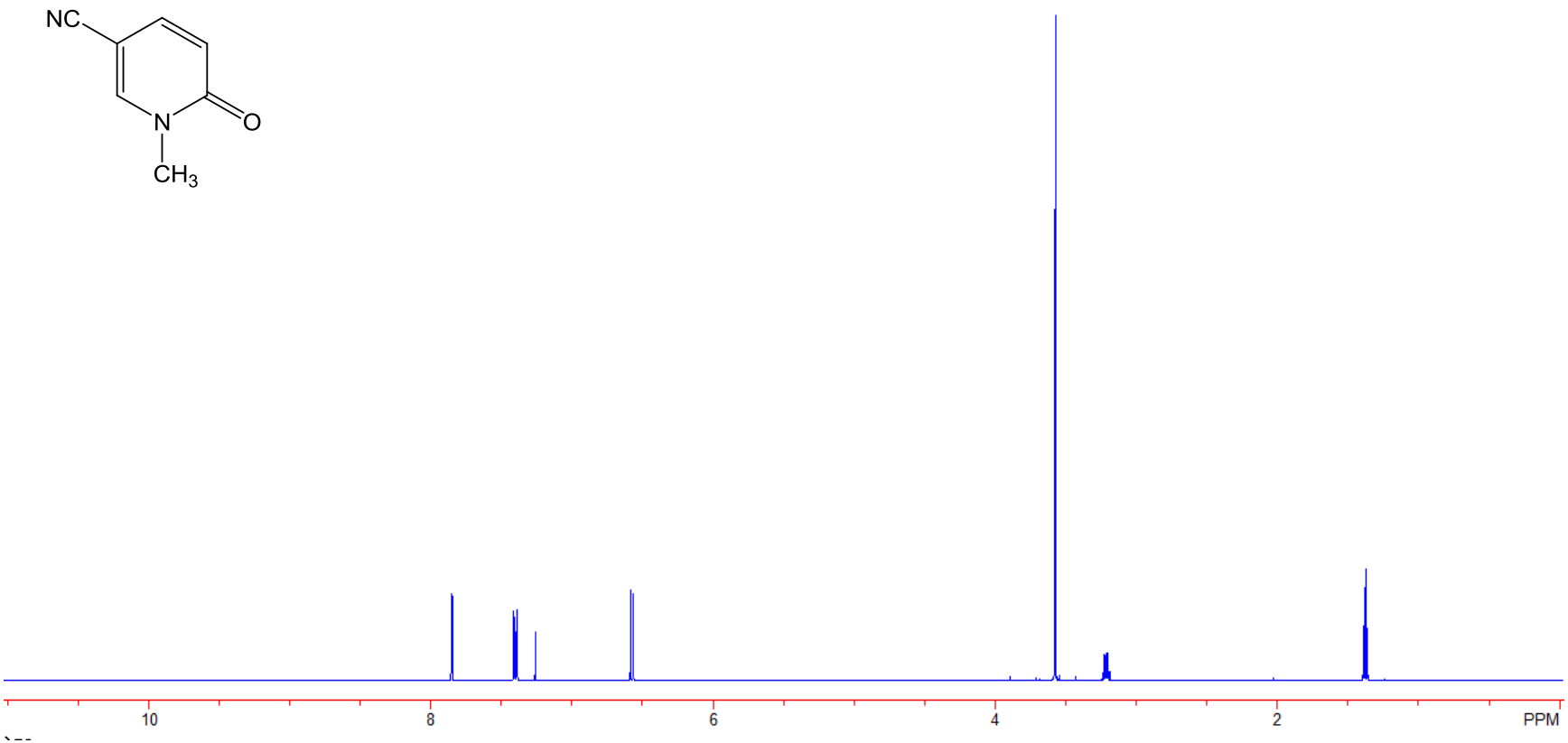
125 MHz ^{13}C NMR Spectrum in $CDCl_3$ (2f)



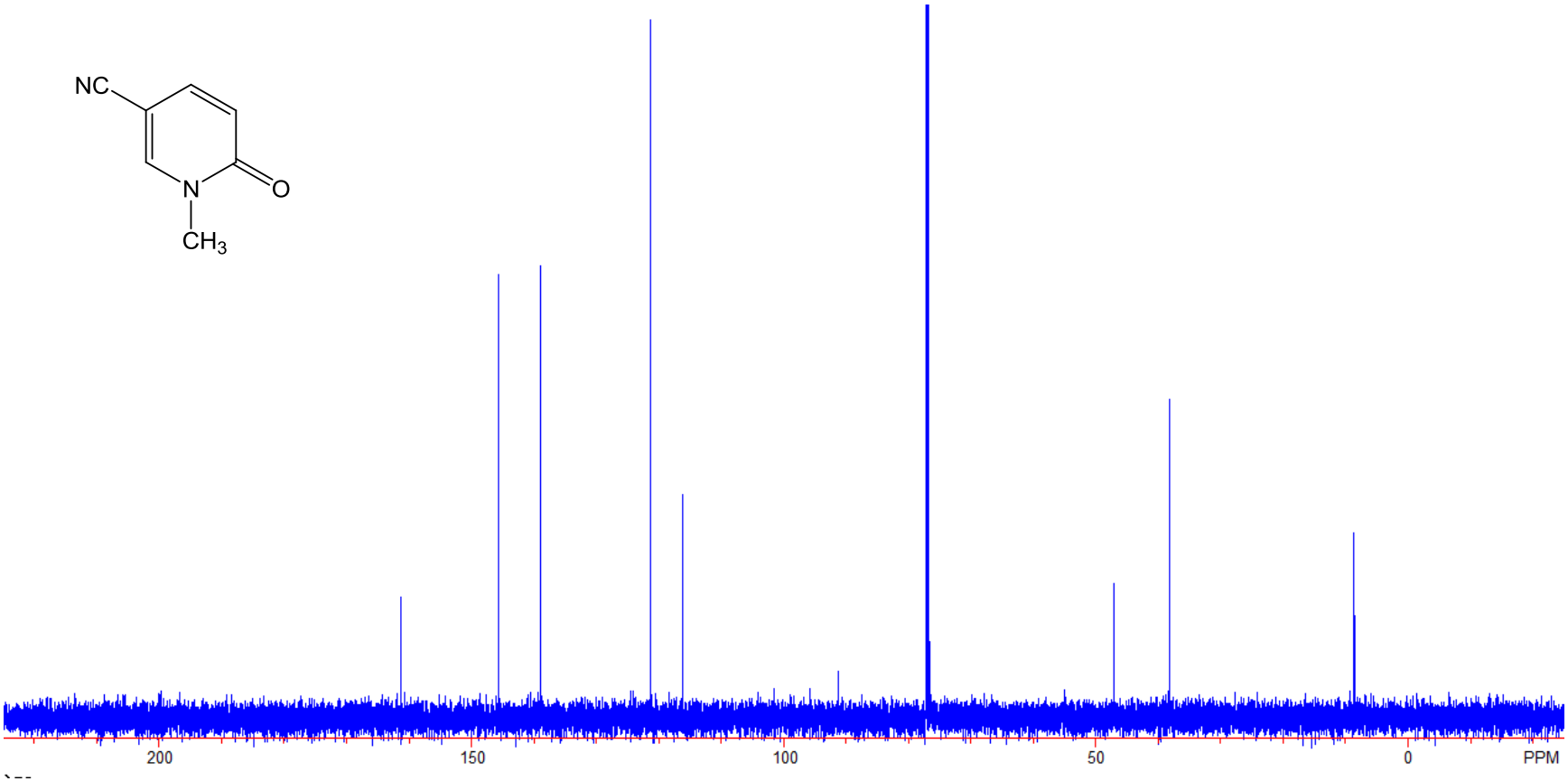
500 MHz ^{1}H NMR Spectrum in $CDCl_3$ (2g)



125 MHz ^{13}C NMR Spectrum in $CDCl_3$ (2g)

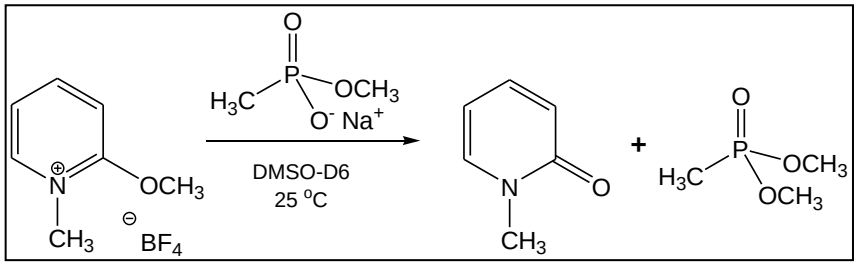


500 MHz ^{1}H NMR Spectrum in $CDCl_3$ (2h)

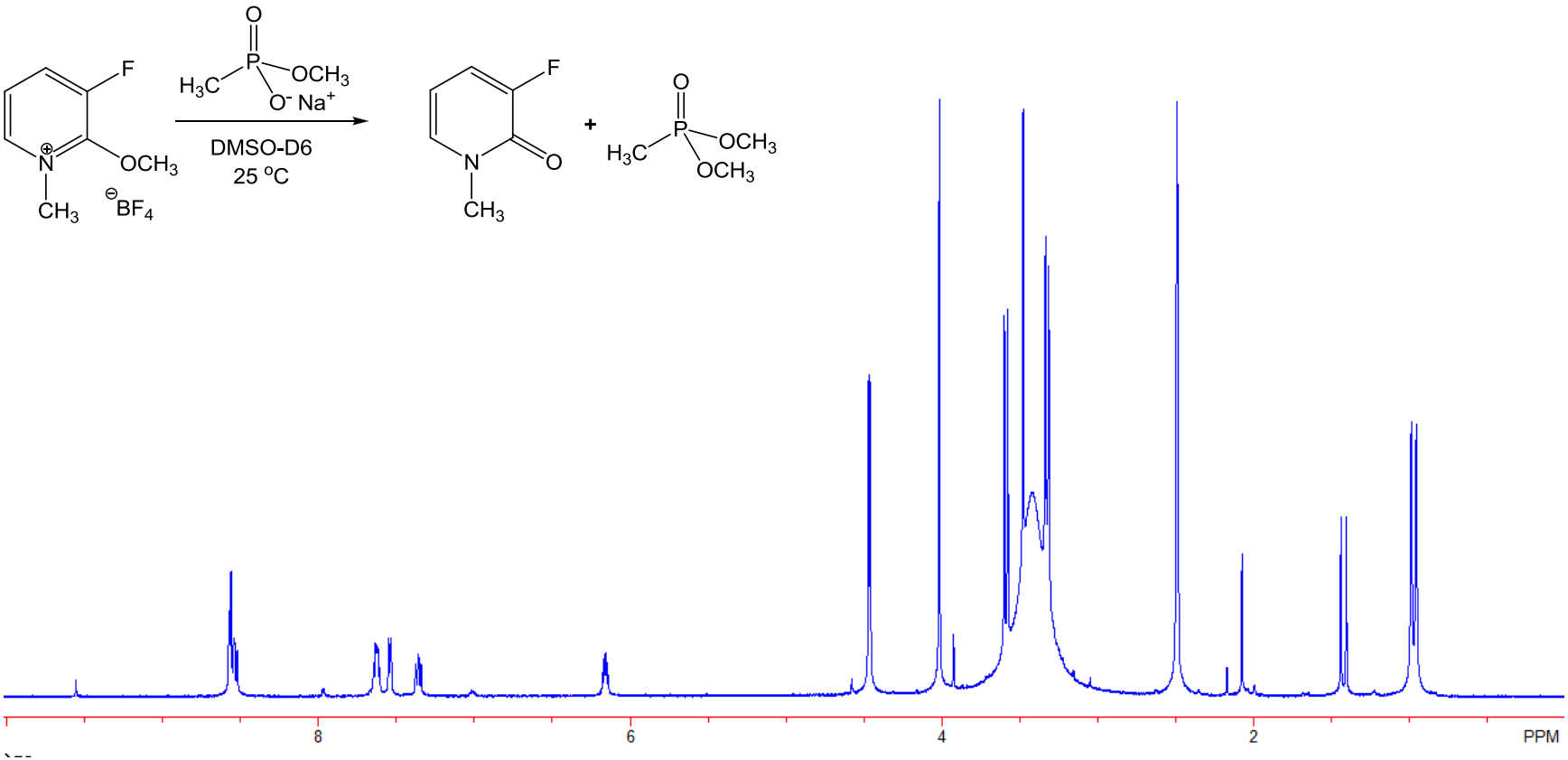


125 MHz ^{13}C NMR Spectrum in $CDCl_3$ (2h)

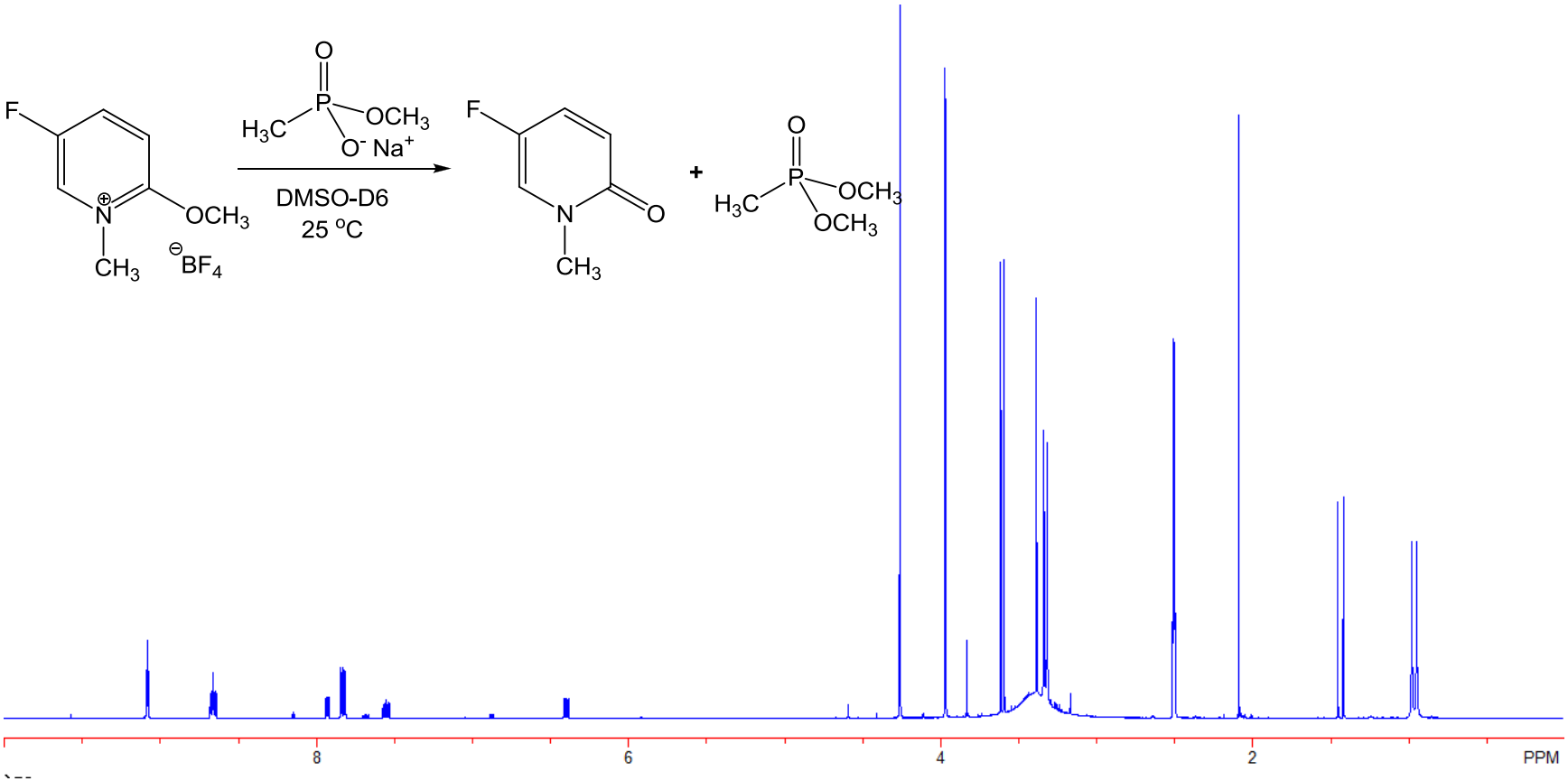
Compound 2i was prepaired only in the reaction displayed below. See 1i → 2i and note in experimental section.



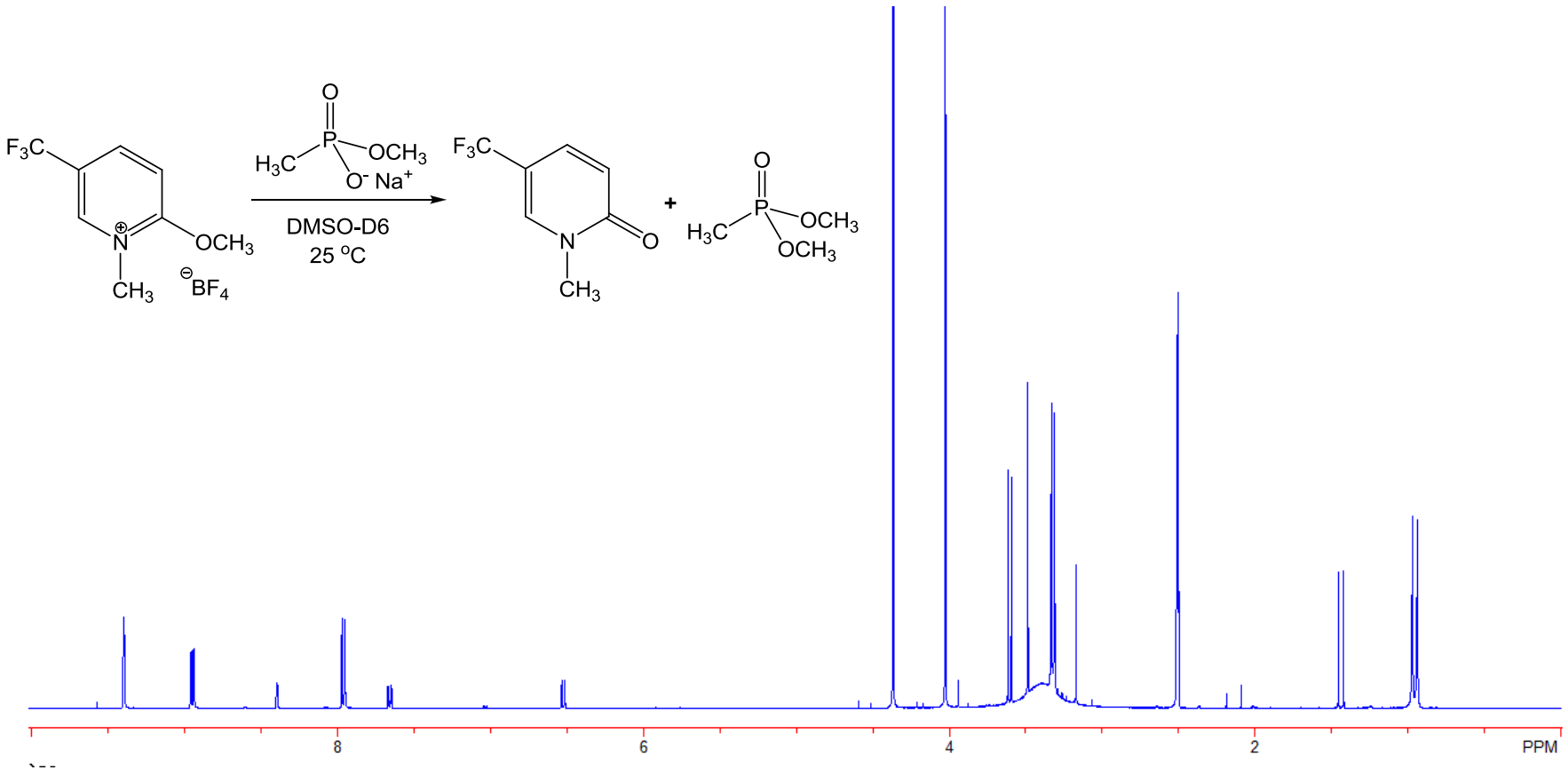
500 MHz ^{1}H NMR Spectrum in DMSO (Table 2: 1a → 2a)



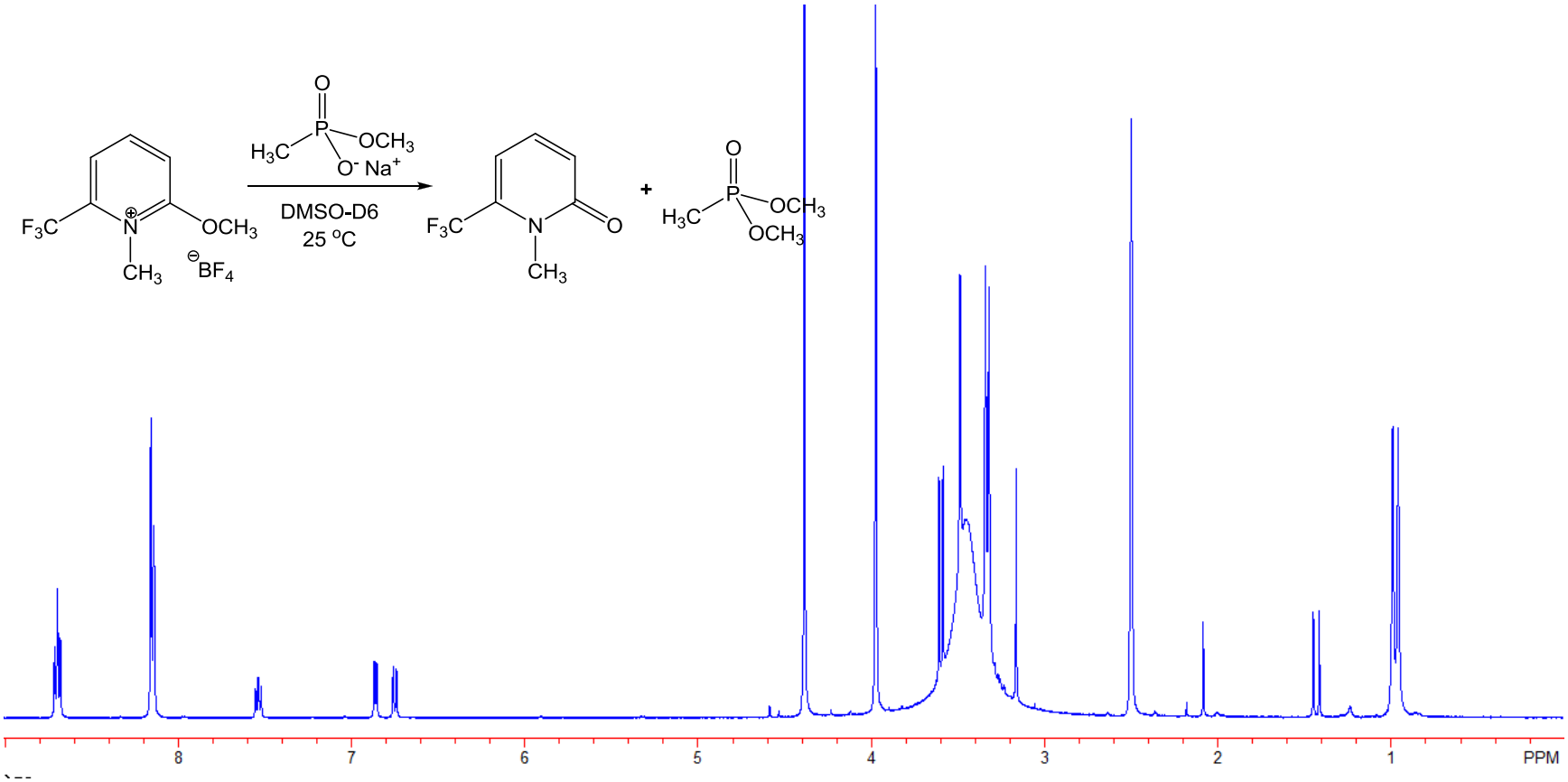
500 MHz ^{1}H NMR Spectrum in DMSO (Table 2: 1b → 2b)



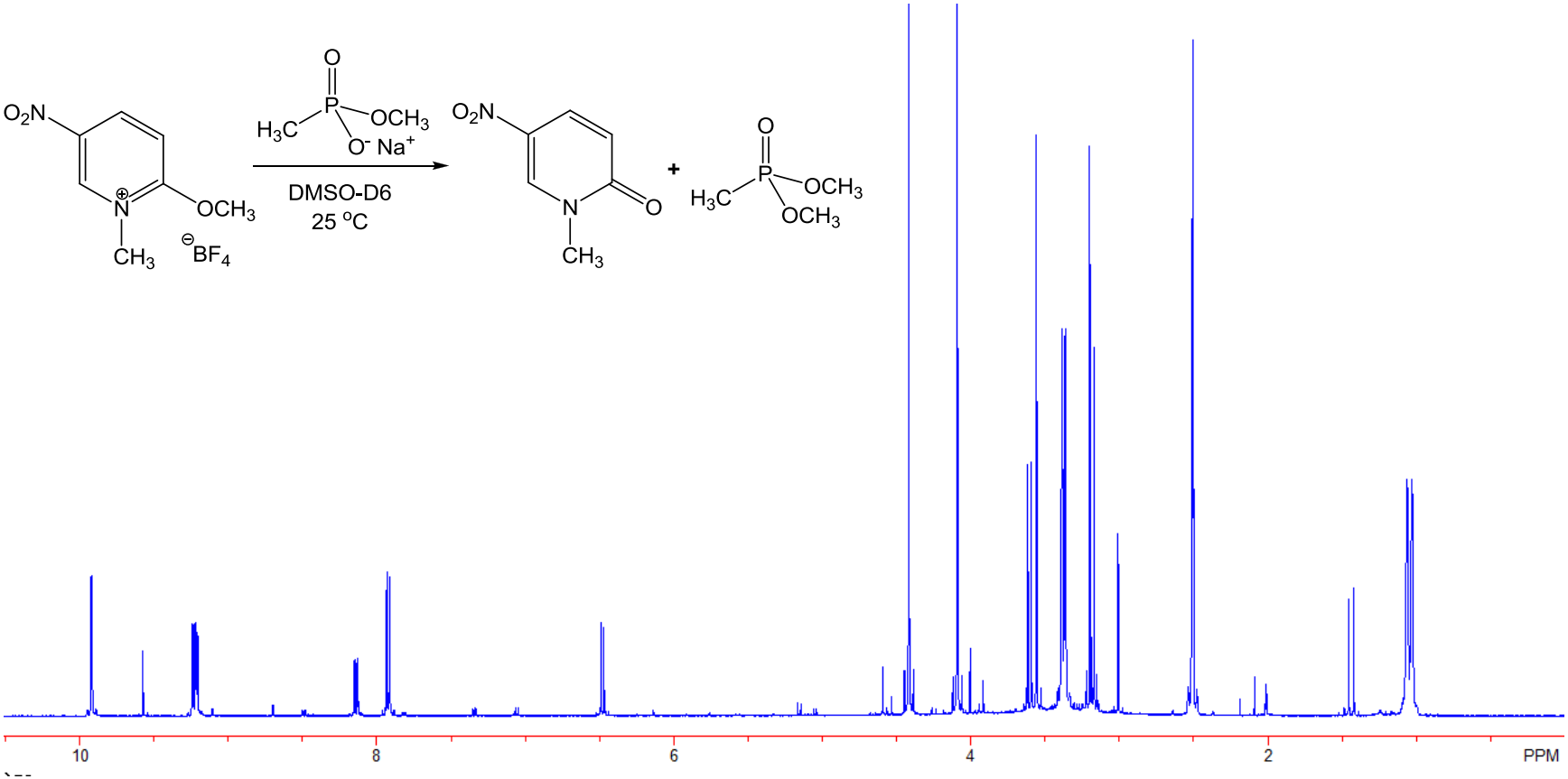
500 MHz ^{1}H NMR Spectrum in DMSO (Table 2: 1c → 2c)



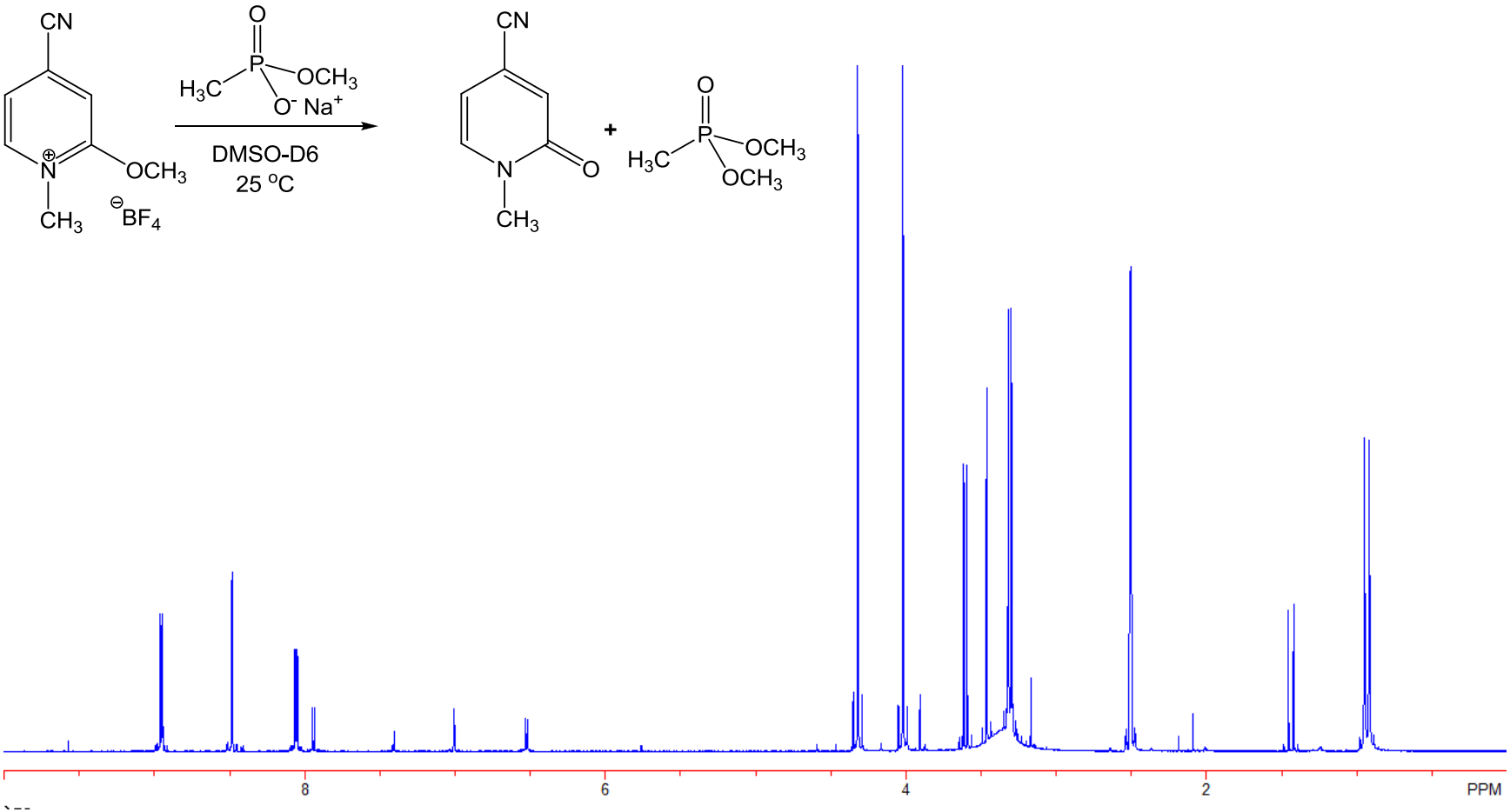
500 MHz ^{1}H NMR Spectrum in DMSO (Table 2: 1d → 2d)



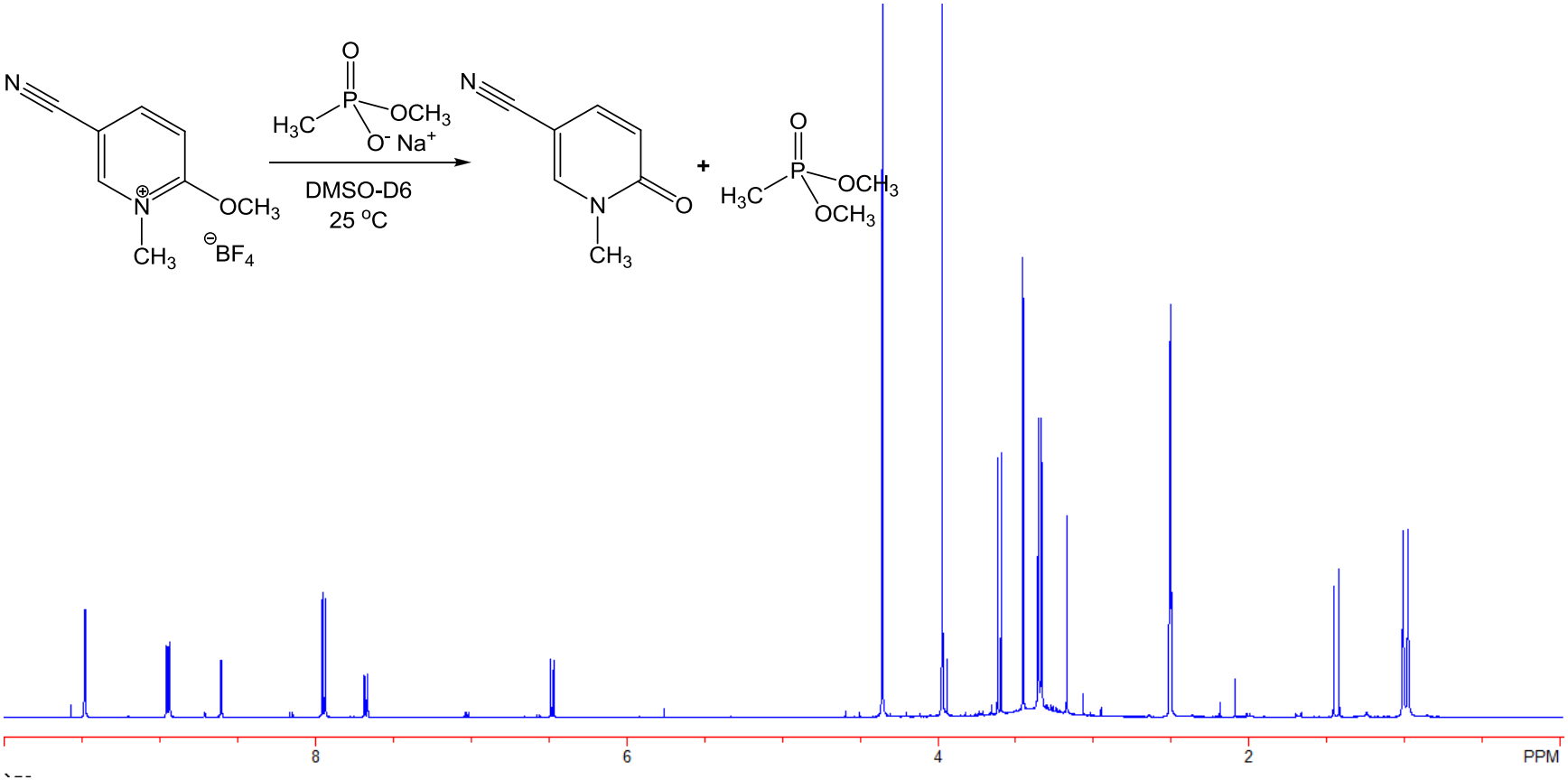
500 MHz ^{1}H NMR Spectrum in DMSO (Table 2: 1e → 2e)



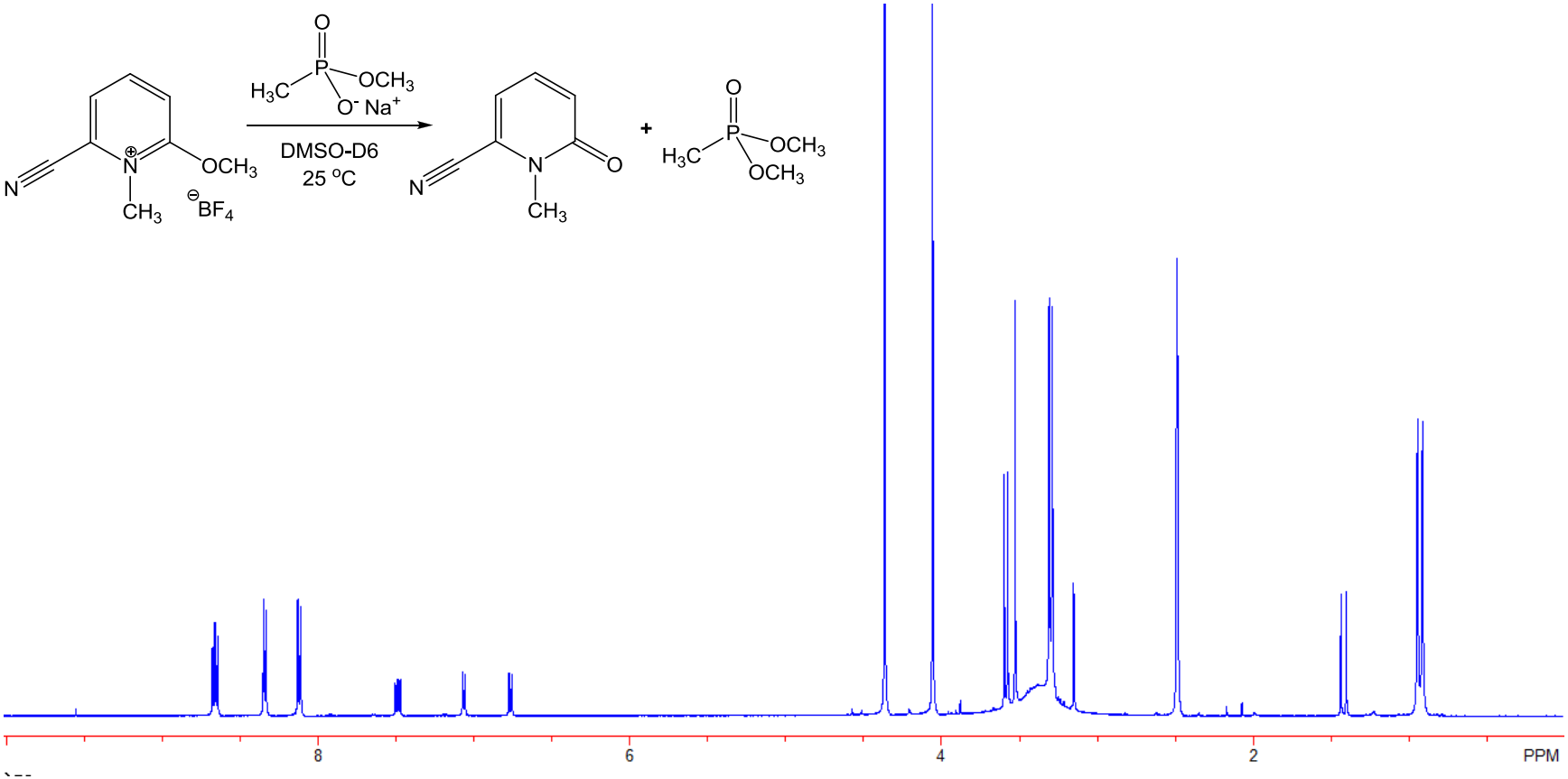
500 MHz ^{1}H NMR Spectrum in DMSO (Table 2: 1f → 2f)



500 MHz ^{1}H NMR Spectrum in DMSO (Table 2: 1g → 2g)



500 MHz ^{1}H NMR Spectrum in DMSO (Table 2: 1h → 2h)



500 MHz ^{1}H NMR Spectrum in DMSO (Table 2: 1i → 2i)