

NMR SPECTROSCOPY: A BRIEF INTRODUCTION

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| Nucleus | Gyromagnetic ratio, $\text{rad s}^{-1} \text{T}^{-1}$, $\times 10^{-7}$ | NMR Frequency (MHz) at 11.75 T | Natural Abundance, % | Relative Sensitivity (constant number of nuclei) | Shift parameter range, ppm |
|-----------------|---|-----------------------------------|----------------------|---|----------------------------|
| ^3H | 28.535 | 533. | 0 | 1.2 | 13 |
| ^1H | 26.7519 | 500. | 99.98 | 1.0 | 13 |
| ^{19}F | 25.181 | 470.4 | 100. | 0.83 | 400 |
| ^{31}P | 10.841 | 200.2 | 100 | 0.066 | 530 |
| ^{13}C | 6.7283 | 125.7 | 1.108 | 0.0159 | 250 |
| ^{15}N | -2.712 | 50.7 | 0.37 | 0.00134 | 1700 |

Fluorine-19 nuclear magnetic resonance

- ❖ Fluorine-19 nuclear magnetic resonance is an analytical technique used to identify fluorine-containing compounds. ^{19}F is one of the most important nuclei for NMR spectroscopy
- ❖ ^{19}F has a nuclear spin of $1/2$ and a high magnetogyric ratio, which means that this isotope is highly responsive to NMR measurements.
- ❖ Furthermore, ^{19}F comprises 100% of naturally-occurring fluorine.
- ❖ Because of its favorable nuclear properties and high abundance, ^{19}F NMR measurements are very fast, comparable with ^1H NMR spectroscopy.
- ❖ ^{19}F is an important nucleus for NMR spectroscopy because of its receptivity and large chemical shift dispersion, which is greater than that for proton NMR spectroscopy
- ❖ The reference compound for ^{19}F is CFCl_3 .
- ❖ ^{19}F NMR chemical shifts are more difficult to predict than ^1H NMR shifts. Specifically, ^{19}F NMR shifts are strongly affected by contributions from electronic excited states whereas ^1H NMR shifts are dominated by diamagnetic contributions.

Fluorine-19 nuclear magnetic resonance

- ❖ ^{19}F has a nuclear spin of $\frac{1}{2}$, a high magnetogyric ratio, is 100% naturally abundant in fluorine and hence it is very similar to ^1H NMR and very compatible for NMR analysis.
- ❖ It also has a very large chemical shift range.
- ❖ ^{19}F NMR is interesting for two main reasons, one is the significance of fluorine containing compounds and another is the compatibility of the ^{19}F nucleus for NMR.
- ❖ Fluorine is a constituent in many organic compounds and can give organic compounds special properties. Hence scientists who need to analyze organic compounds containing fluorine would find ^{19}F NMR useful.
- ❖ For ^{19}F NMR, the frequency of the radiation is adjusted to the small range in which ^{19}F nuclei absorb the energy and undergo nuclear spin transitions.

Differences between ^1H and ^{19}F NMR

- Unlike ^1H spectra which is referenced to tetramethylsilane $[\text{Si}(\text{CH}_3)_4]$, the prevalent and established internal reference for fluorine NMR is fluorotrichloromethane (CFCl_3), which is given a chemical shift of zero.
- Like ^1H -NMR, negative chemical shifts correlate to upfield shifts of the reference.
- **Some other references**
 - $\text{CF}_3\text{CO}_2\text{H}$ (δ -76.2ppm); hexafluorobenzene (δ -162.2ppm)
 - trifluoromethylbenzene (δ -63.2ppm); ethyl trifluoroacetate (δ -75.8 ppm).
- Nonetheless, fluorotrichloromethane is superior as it will not influence the sample's chemical shifts. Also, its detected signal is usually far downfield from that of most fluorine atoms in organofluorine compounds, hence most of the chemical shifts in ^{19}F spectra are negative.

Fluorine-19 nuclear magnetic resonance

^{19}F has a very large chemical shift range of around δ 500 ppm as compared to that of ^1H of around 1-10 ppm, causing interferences and overlapping of signals to be less likely in ^{19}F NMR.

For ^1H NMR, most solvents contain hydrogen, hence special solvents are required for ^1H NMR. Unlike ^1H NMR, deuterated solvents are not required for ^{19}F NMR, since most solvents do not contain fluorine and hence does not affect the ^{19}F NMR signal. Hence ^{19}F is very compatible for NMR analysis of compounds containing fluorine.

For anticipating the chemical shifts due to shielding effects for fluorine substituents, the usual logic that applies to ^1H NMR spectra does not work for ^{19}F NMR spectra.

The three most frequently used solvents in F-19 NMR are CDCl_3 , DMSO-d_6 and acetone- d_6 . The deviation in chemical shift between these solvents when they are used is generally 1 ppm or less.

Fluorine-19 nuclear magnetic resonance

This is explained below.

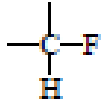
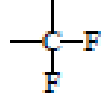


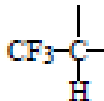

The resonance frequency of nuclei detected by NMR depends on the magnetic environment of the nuclei. The effective magnetic field strength (B_{eff}) on a nucleus is affected by the applied magnetic field (B_0) and shielding constant (σ) as seen in Equation.

$$B_{\text{eff}} = B_0 - \sigma \cdot B_0$$

The shielding constant is affected by Equation, where the σ_{dia} term is the diamagnetic term, which represents the opposing magnetic field that comes from the effect of the applied magnetic field on the electrons directly surrounding the nucleus (s-orbitals). The shielding effect provided by the s-orbital electrons. While the paramagnetic term, σ_{para} , comes from p-orbital electrons when they are affected by the applied magnetic field. The shielding effect provided by the p-orbital electrons. The paramagnetic term, σ_{para} , affects the shielding effect in the fluorine nucleus more significantly, while, only the σ_{dia} term is required for ^1H NMR as hydrogen does not have p-orbital electrons.

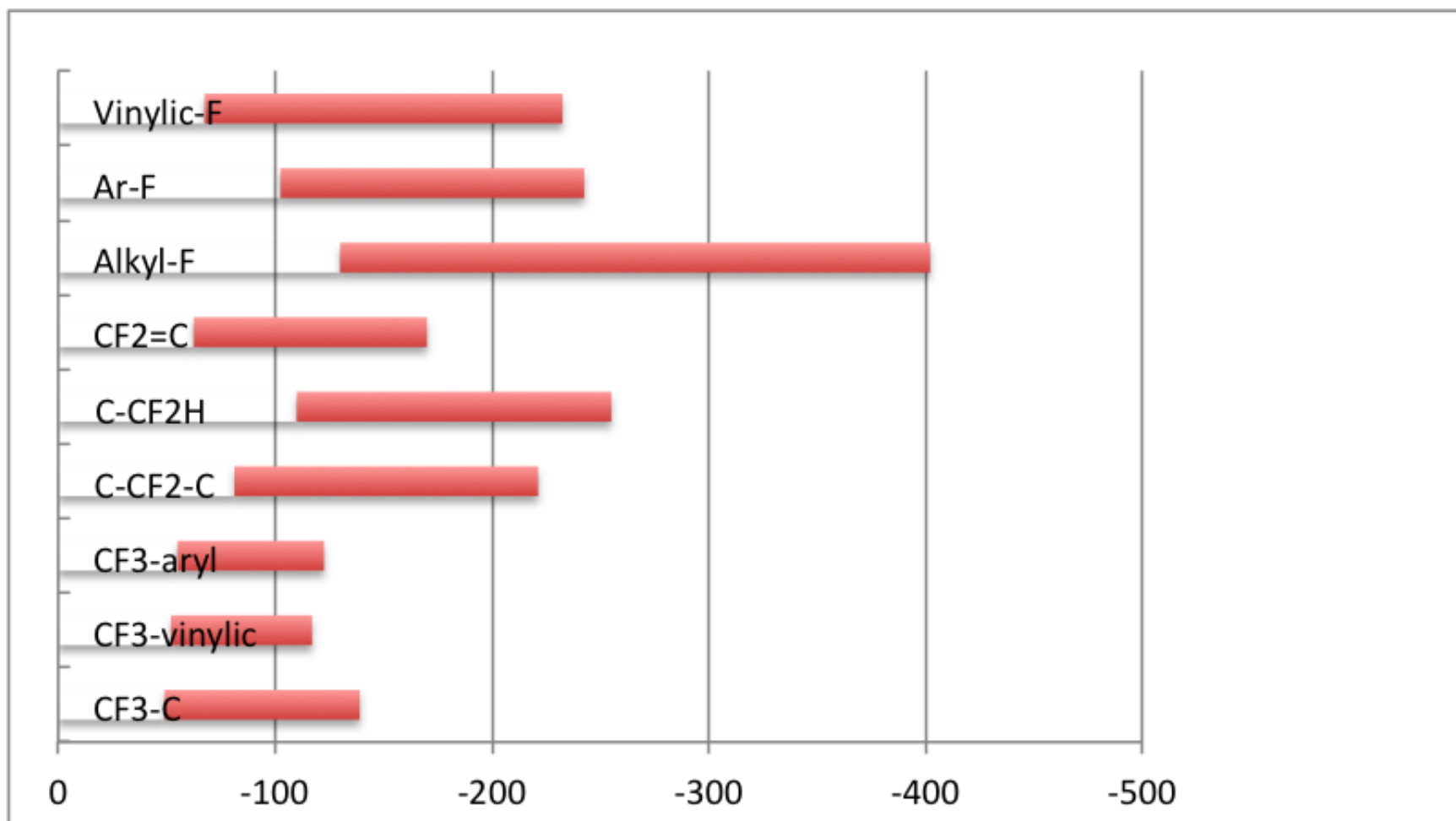
$$\sigma = \sigma_{\text{dia}} + \sigma_{\text{para}} + \sigma_{\text{i}}$$

Overview of ^{19}F NMR spectra chemical shift ranges

| Chemical group | σ relative to CFCl_3 , ppm | σ relative to CF_3COOH , ppm | σ relative to $\text{C}_6\text{H}_5\text{F}$, ppm |
|---|--|---|---|
|  | -210 | -131 | -96 |
|  | -140 | -69 | -26 |
|  | -140 | -60 | -26 |
|  | -125 | -46 | -11 |
|  | -75 | 4 | 39 |
|  | -81 | -2 | 33 |
| $\text{—SO}_2\text{F}$ | 50 | 129 | 164 |

Overview of ^{19}F NMR spectra chemical shift ranges

Similar to ^1H NMR, fluorine chemical shifts are dependent on their local chemical environments. The table below shows the chemical shifts ranges for the fluorine atoms of some F, CF_2 and CF_3 branches and some representative chemical shifts for F-19 NMR referenced to CFCl_3 .

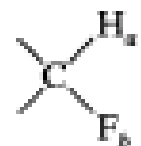

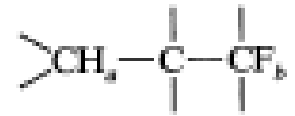

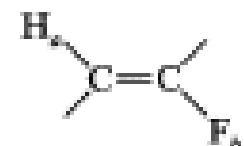
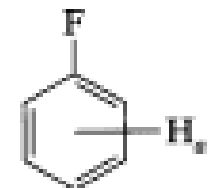



Overview of ^{19}F NMR spectra chemical shift ranges

| Compound | δ (ppm) | Compound | δ (ppm) | Compound | δ (ppm) |
|-----------------------------------|----------------|----------------------------------|----------------|----------------------------------|----------------|
| MeF | -271.9 | FCH=CH ₂ | -114 | CBr ₃ | 7.4 |
| EtF | -213 | F ₂ C=CH ₂ | -81.3 | CF ₂ Br ₂ | 7 |
| CF ₂ H ₂ | -1436 | F ₂ C=CF ₂ | -135 | CFH ₂ Ph | -207 |
| CF ₃ R | -60 to -70 | C ₆ F ₆ | -163 | CF ₂ Cl ₂ | -8 |
| AsF ₅ | -66 | [BeF ₄] ⁻ | -163 | [AsF ₆] ⁻ | -69.5 |
| BF ₃ | -131 | ClF ₅ | 247, 412 | ClF ₃ | 116, -4 |
| IF ₇ | 170 | ReF ₇ | 345 | MoF ₆ | -278 |
| SeF ₆ | 55 | Sb ₅ | -108 | [SbF ₆] ⁻ | -109 |
| [SiF ₆] ²⁻ | -127 | WF ₆ | 166 | TeF ₆ | -57 |
| XeF ₂ | 258 | XeF ₆ | 550 | XeF ₄ | 438 |

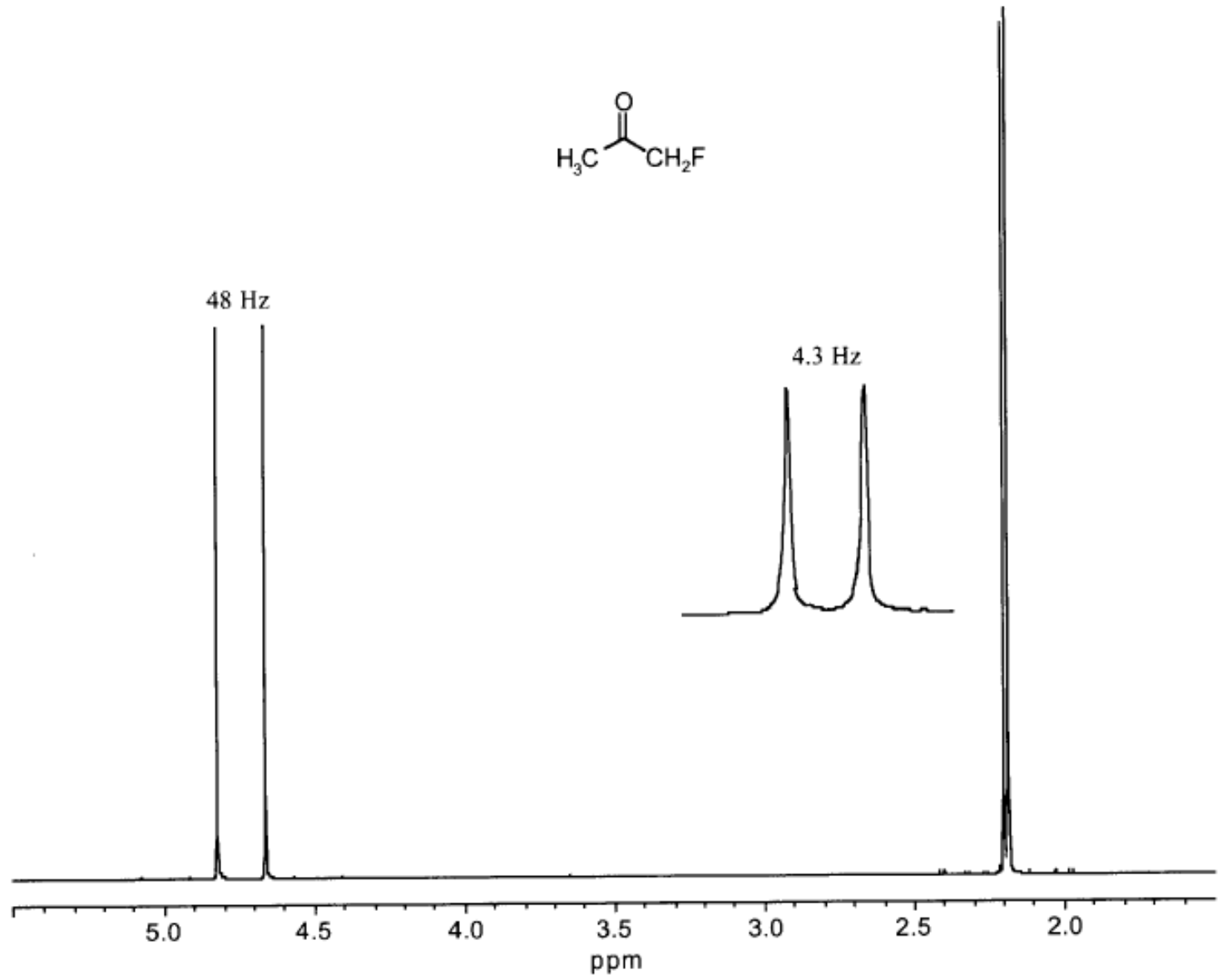
Fluorine-19 nuclear magnetic resonance

- ^{19}F - ^{19}F coupling constants are generally larger than ^1H - ^1H coupling constants.
- Long range ^{19}F - ^{19}F coupling, (^2J , ^3J , ^4J or even ^5J) are commonly observed. Generally, the longer range the coupling, the smaller the value.
- Hydrogen couples with fluorine, which is very typical to see in ^{19}F spectrum. With a geminal hydrogen, the coupling constants can be as large as 50 Hz.
- Other nuclei can couple with fluorine, however, this can be prevented by running decoupled experiments. It is common to run fluorine NMRs with both carbon and proton decoupled.
- Fluorine atoms can also couple with each other. Between fluorine atoms, homonuclear coupling constants are much larger than with hydrogen atoms. Geminal fluorines usually have a J-value of 250-300 Hz.

| Proton-Fluorine | |
|---|---|
|  | 44-81 |
|  | 3-25 |
|  | 0-4 |
|  | 1-8 |
|  | 12-40 |
|  | <i>o</i> 6-10 <i>m</i> 5-6 <i>p</i> 2 |
|  | $\alpha\gamma$ 4.3 $\beta\gamma$ 48 |

Fluorine-19 nuclear magnetic resonance

It shows the effect of fluorine on ^1H spectra. In this both the methylene and methyl group were split by ^{19}F atom, each in to doublets with different coupling constants.



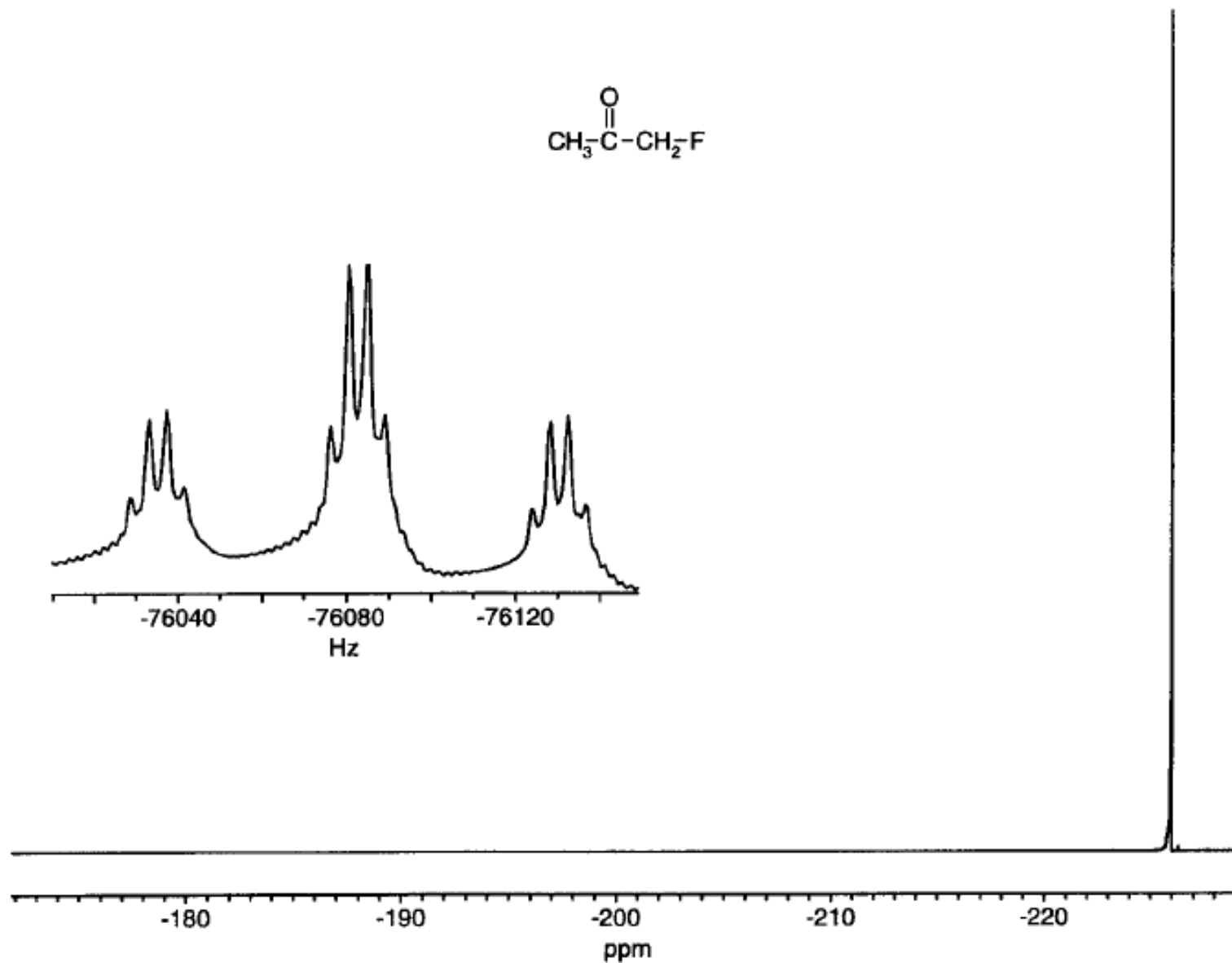
Fluorine-19 nuclear magnetic resonance

In this figure, we see the reciprocal effect of the protons on the fluorine atom.

In this proton decoupled spectra, we see only a singlet for the fluorine atom.

In the proton coupled spectrum, however we see that the fluorine is coupled to two sets of hydrogens, producing triplet with a large coupling constant.

The triplet is further split in to three quartets by a four bond coupling with the methyl group.

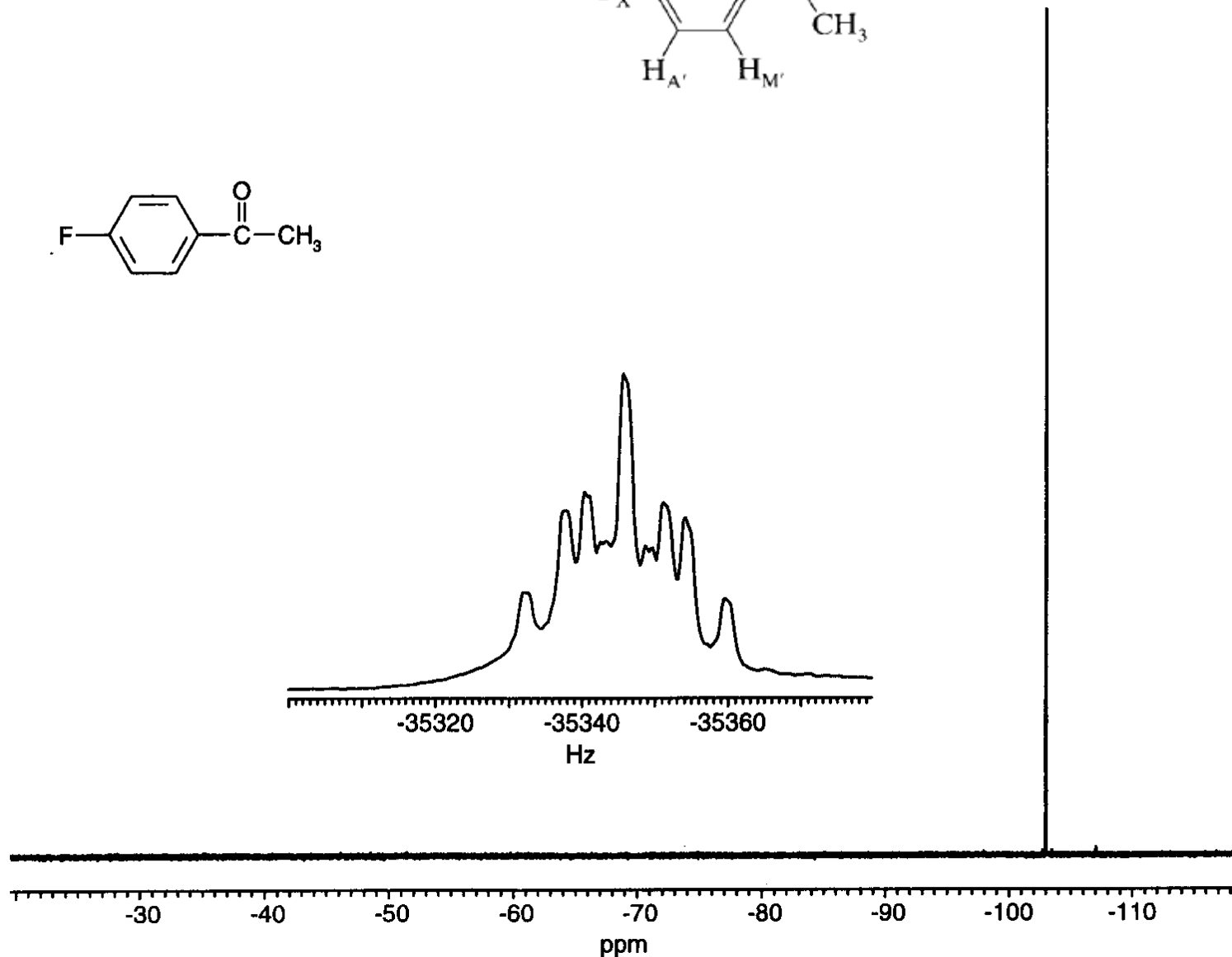
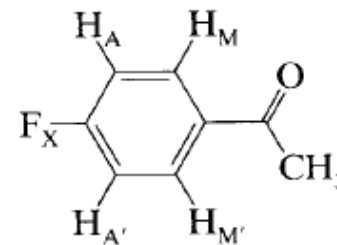
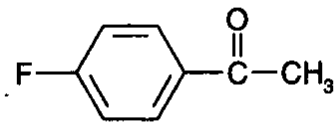


Fluorine-19 nuclear magnetic resonance

This is an example of an aromatic fluorine containing compound of p-fluoroacetophenone.

In proton decoupled spectra we find a singlet for the fluorine atom while in a proton coupled spectrum we find a complex multiplet.

The fluorine atom is coupled differently to the ortho and meta protons in this para-substituted compound.



Fluorine-19 nuclear magnetic resonance

Drug analysis

There is an increasing demand for techniques to analyze and conduct quality control for pharmaceuticals containing fluorine. Drugs that contain fluorine in their structure make up around one-third of top-selling drugs in the market.

However, ^{19}F NMR is very sensitive to its local chemical environment and hence the structure of the molecule; it also gives an exceptional amount of analytical information as it has large chemical shift ranges. Hence, drugs can be analyzed quantitatively by ^{19}F NMR if fluorinated compounds are in sufficient concentrations and by using an appropriate time scale.

Monitoring reactions

^{19}F NMR can be used as a diagnostic tool for the monitoring of reactions when fluorine substituents are involved. This is because the ^{19}F NMR spectra of most reactants and products are different. For example, the polymerization of PFCP aryl amine polymers from perfluorocyclopentene monomers with biphenols can be monitored, as the monomers have a different ^{19}F NMR spectra from the polymer.

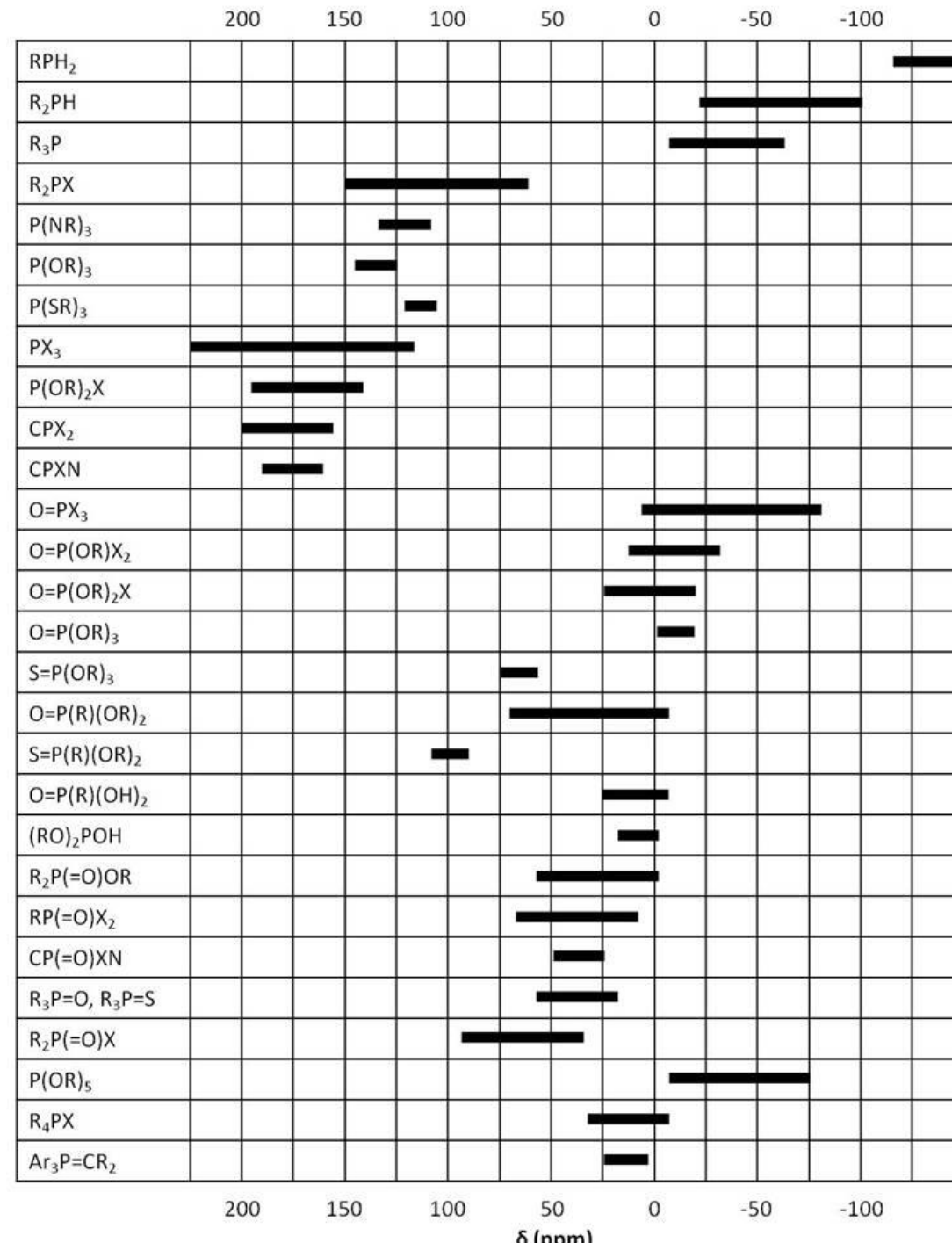
- **Phosphorus-31 nuclear magnetic resonance (^{31}P NMR) is conceptually the same as proton (^1H) NMR.**
- **The ^{31}P nucleus is useful in NMR spectroscopy due to its relatively high gyromagnetic ratio (17.235 MHzT⁻¹).**
- **For comparison, the gyromagnetic ratios of ^1H and ^{13}C are (42.576 MHz T⁻¹) and (10.705 MHz T⁻¹), respectively.**
- **Furthermore, ^{31}P has a 100% natural isotopic abundance.**
- **Like the ^1H nucleus, the ^{31}P nucleus has a nuclear spin of $1/2$ which makes spectra relatively easy to interpret.**
- **^{31}P NMR is an excellent technique for studying phosphorus containing compounds, such as organic compounds and metal coordination complexes.**

Differences between ^1H and ^{31}P NMR

- While ^1H NMR spectra is referenced to tetramethylsilane [$\text{Si}(\text{CH}_3)_4$], the chemical shifts in ^{31}P NMR are typically reported relative to 85% phosphoric acid ($\delta = 0$ ppm), which is used as an external standard due to its reactivity. However, trimethyl phosphite, $\text{P}(\text{OCH}_3)_3$, is also used since unlike phosphoric acid its shift ($\delta = 140$ ppm) is not dependent on concentration or pH.
- As in ^1H NMR, positive chemical shifts correspond to a downfield shift from the standard. Chemical shifts in ^{31}P NMR commonly depend on the concentration of the sample, the solvent used, and the presence of other compounds. This is because the external standard does not take into account the bulk properties of the sample. As a result, reported chemical shifts for the same compound could vary by 1 ppm or more, especially for phosphate groups ($\text{P}=\text{O}$).
- ^{31}P NMR spectra are often recorded with all proton signals decoupled, i.e., $^{31}\text{P}\{-^1\text{H}\}$, as is done with ^{13}C NMR. This gives rise to single, sharp signals per unique ^{31}P nucleus.
- Herein, we will consider both coupled and decoupled spectra.

Interpreting spectra

- As in ^1H NMR, phosphorus signals occur at different frequencies depending on the electron environment of each phosphorus nucleus. In this section we will study a few examples of phosphorus compounds with varying chemical shifts and coupling to other nuclei.



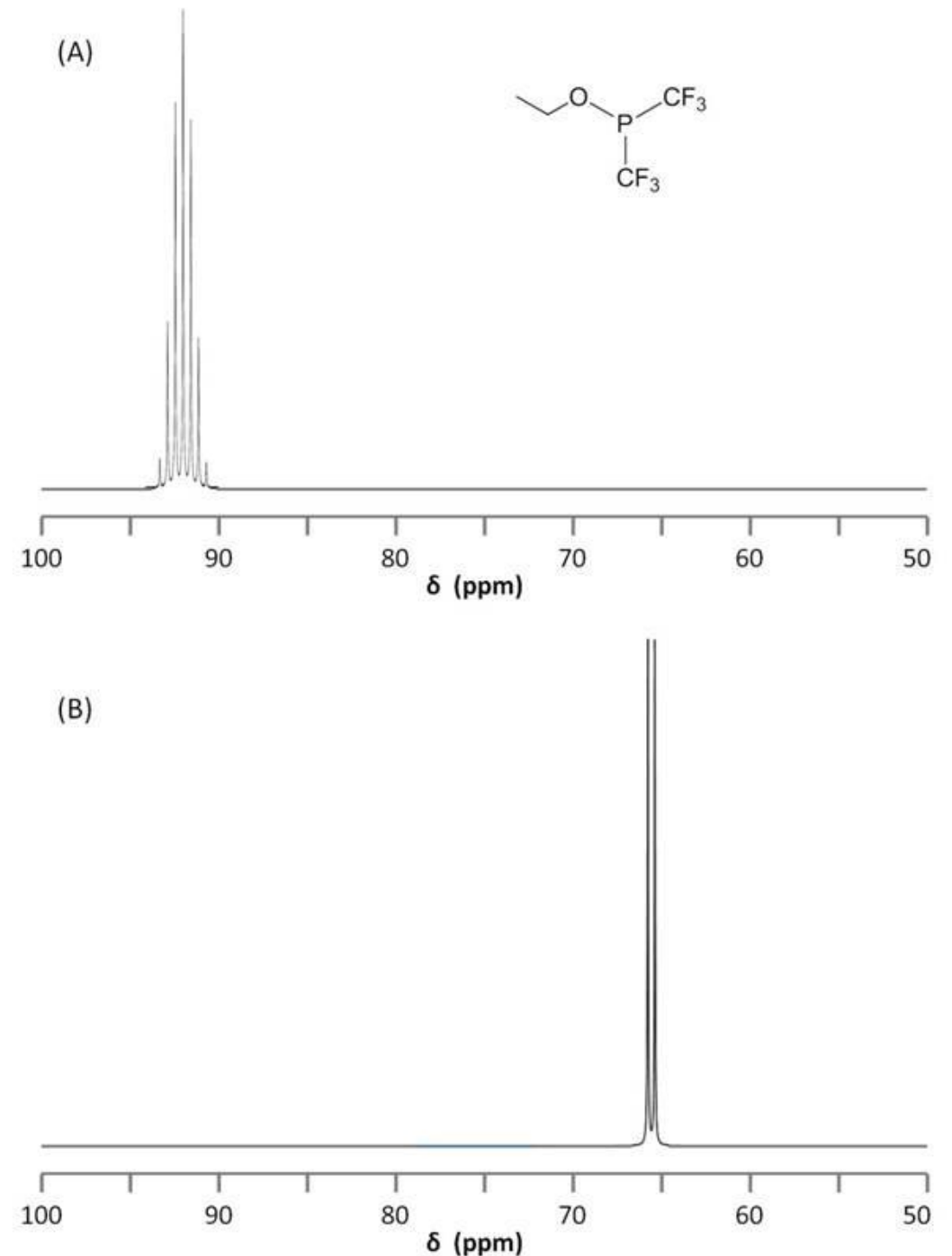
- The range of ^{31}P chemical shifts in diamagnetic compounds covers some 2000 ppm, and is thus one order of magnitude larger than that of carbon, and two orders of magnitude larger than proton.
- The upfield end in ^{31}P -NMR is due to white phosphorus P_4 at $\delta\text{P} = -527$ to -488 ppm, depending on solvent and water content of the sample.
- Chemical shift values of Phosphorus resonance also dependence upon the bond angle, electronegativity of the substituent's and the p-bonding character of the substituent's .
- From ^{13}C -NMR, we know that an olefin resonates downfield from an alkane, and an acetylene is found in between, but closer to the alkane. This is explained by diamagnetic anisotropy and the behavior of P-C , $\text{P}=\text{C}$, and $\text{P}\equiv\text{C}$ bonds also same

Coupling constant

| Proton-Phosphorus | | |
|--|-------------|------------|
| $\begin{array}{c} \text{O} \\ \\ \text{>P} \\ \text{H} \end{array}$ | 630–707 | |
| $(\text{CH}_3)_3\text{P}$ | 2.7 | |
| $(\text{CH}_3)_3\text{P}=\text{O}$ | 13.4 | |
| $(\text{CH}_3\text{CH}_2)_3\text{P}$ | 0.5 (HCCP) | 13.7 (HCP) |
| $(\text{CH}_3\text{CH}_2)_3\text{P}=\text{O}$ | 11.9 (HCCP) | 16.3 (HCP) |
| $\begin{array}{c} \text{O} \\ \\ \text{CH}_3\text{P}(\text{OR})_2 \end{array}$ | 10–13 | |
| $\begin{array}{c} \text{O} \\ \\ \text{CH}_3\text{C} \text{---} \text{P}(\text{OR})_2 \\ \end{array}$ | 15–20 | |
| $\text{CH}_3\text{OP}(\text{OR})_2$ | 10.5–12 | |
| $\text{P}[\text{N}(\text{CH}_3)_2]_3$ | 8.8 | |
| $\text{O}=\text{P}[\text{N}(\text{CH}_3)_2]_3$ | 9.5 | |

Coupling to fluorine

➤ ^{19}F NMR is very similar to ^{31}P NMR in that ^{19}F has spin 1/2 and is a 100% abundant isotope. As a result, ^{19}F NMR is a great technique for fluorine-containing compounds and allows observance of P-F coupling. The coupled ^{31}P and ^{19}F NMR spectra of ethoxybis(trifluoromethyl)phosphine, $\text{P}(\text{CF}_3)_2(\text{OCH}_2\text{CH}_3)$, are shown in Figure. It is worth noting the splitting due to $J_{\text{PCF}} = 86.6$ Hz.

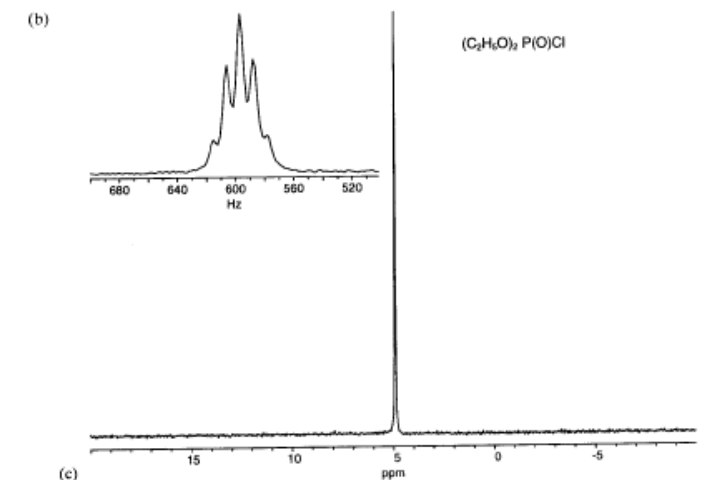
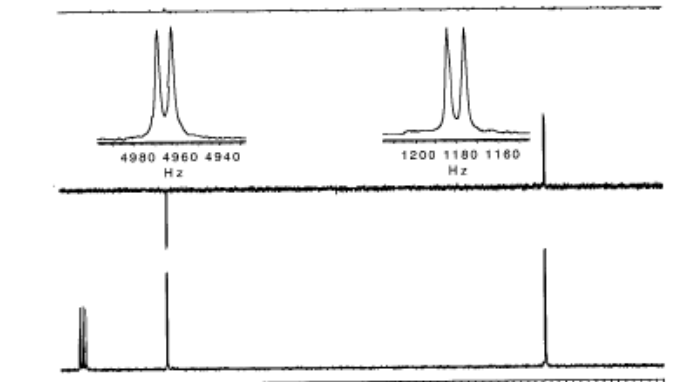
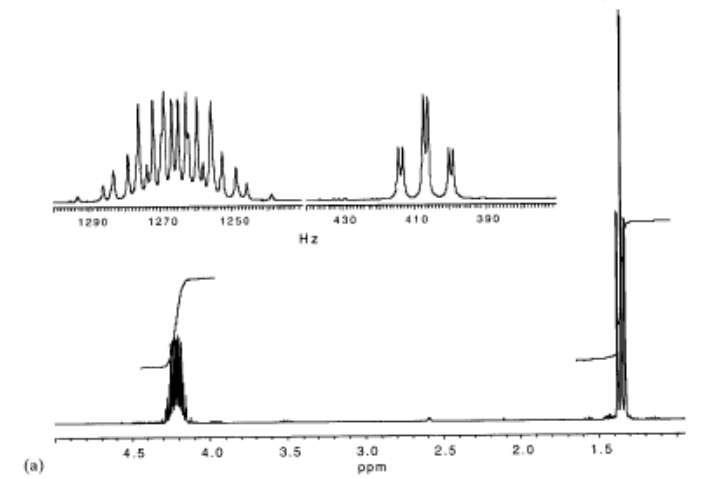


Structure, ^{31}P - $\{^1\text{H}\}$ spectrum (A), and ^{19}F - $\{^1\text{H}\}$ spectrum (B) for $\text{P}(\text{CF}_3)_2(\text{OCH}_2\text{CH}_3)$.

(a) The proton decoupled ^{31}P NMR spectrum of diethyl chlorophosphite reveals that the methyl groups are actually a triplet of doublets with the four bond ^{31}P - ^1H coupling constant of 1 Hz.

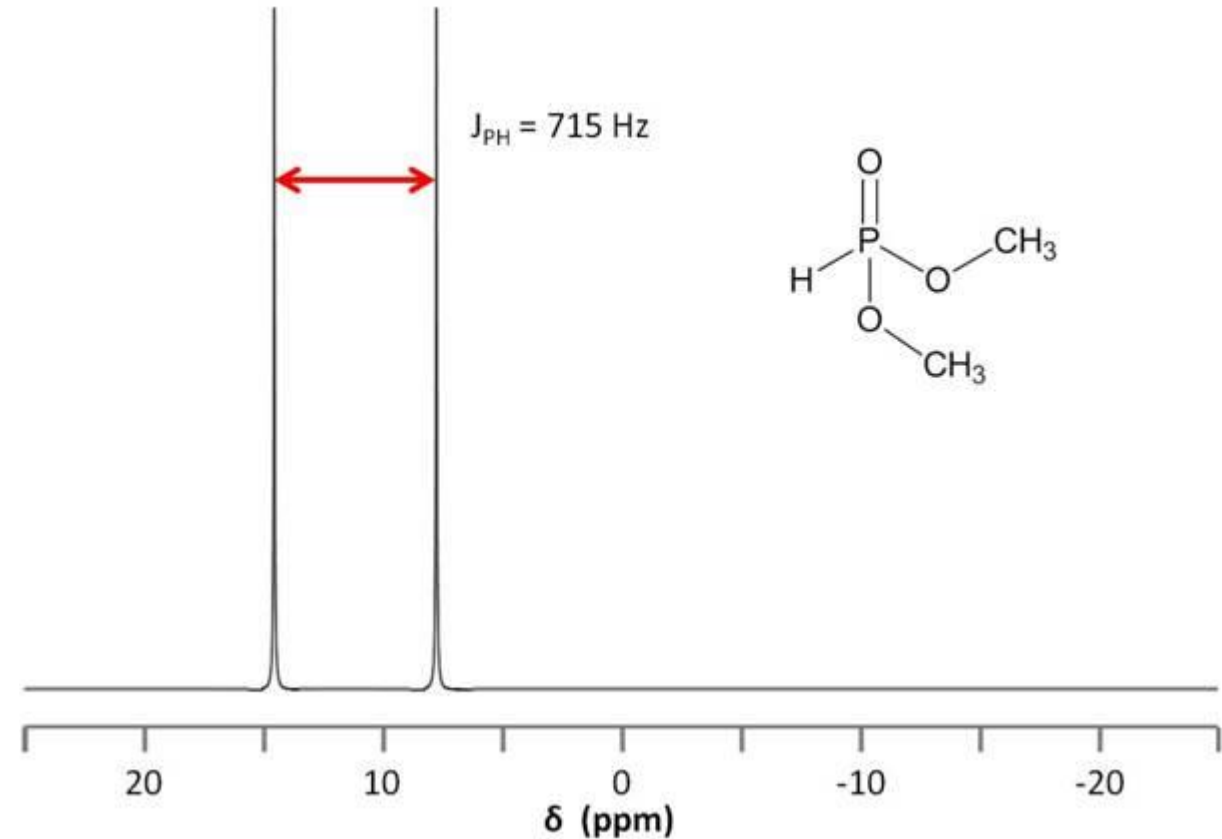
(b) ^{13}C and DEPT spectra

(c) The proton coupled ^{31}P NMR spectrum of diethyl chlorophosphite shows an apparent quintet, means that there is no appreciable coupling of the phosphorous atom to the methyl protons of the methyl groups.



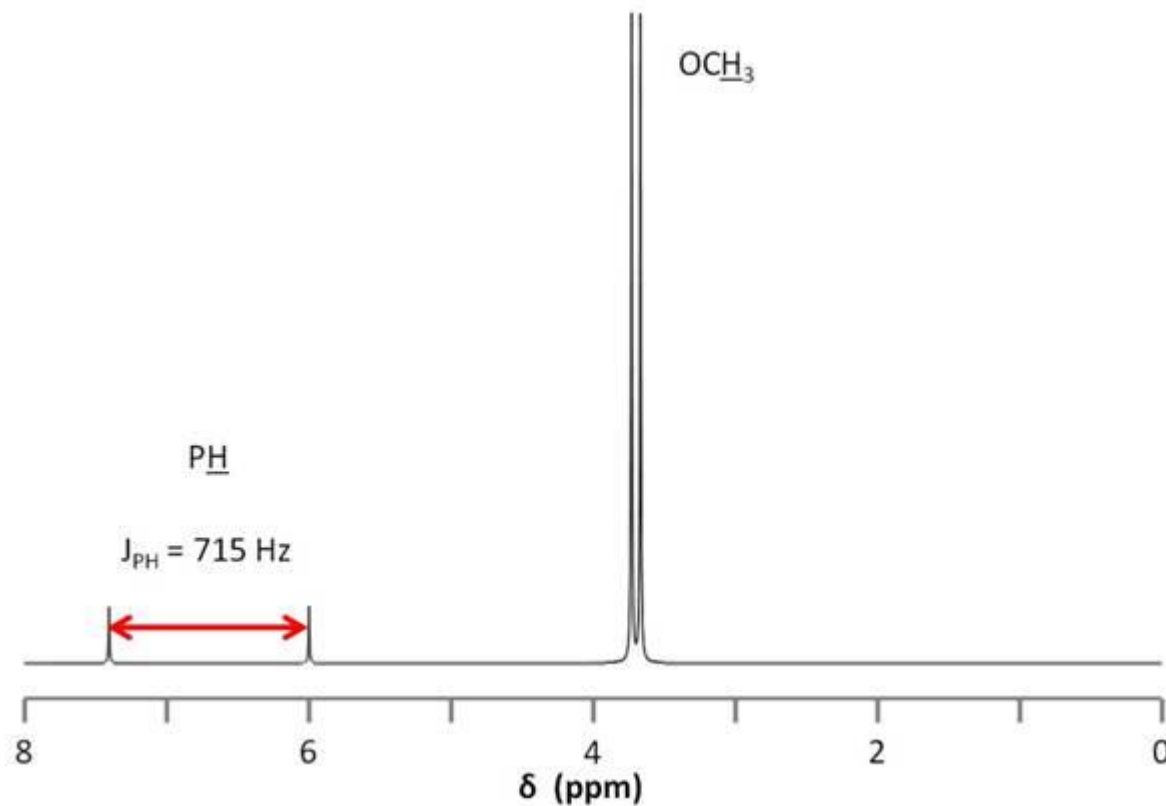
31P-1H coupling

➤ Consider the structure of dimethyl phosphonate, $\text{OPH}(\text{OCH}_3)_2$, shown in Figure. As the phosphorus nucleus is coupled to a hydrogen nucleus bound directly to it, that is, a coupling separated by a single bond, we expect J_{PH} to be very high. Indeed, the separation is so large (715 Hz) that one could easily mistake the split peak for two peaks corresponding to two different phosphorus nuclei.



Structure and ^{31}P NMR spectrum of $\text{OPH}(\text{OCH}_3)_2$ with only the OCH_3 protons decoupled.

- This strong coupling could also lead us astray when we consider the ^1H NMR spectrum of dimethyl phosphonate (Figure). Here we observe two very small peaks corresponding to the phosphine proton. The peaks are separated by such a large distance and are so small relative to the methoxy doublet (ratio of 1:1:12), that it would be easy to confuse them for an impurity. To assign the small doublet, we could decouple the phosphorus signal at 11 ppm, which will cause this peak to collapse into a singlet.



^1H spectrum of $\text{OPH}(\text{OCH}_3)_2$.

- **^{31}P NMR spectroscopy is a simple technique that can be used alongside ^1H NMR to characterize phosphorus-containing compounds. When used on its own, the biggest difference from ^1H NMR is that there is no need to utilize deuterated solvents. This advantage leads to many different applications of ^{31}P NMR, such as assaying purity and monitoring reactions.**
- **Phosphorus-31 nuclear magnetic resonance is an analytical technique used to identify phosphorus-containing compounds, such as organic compounds and metal complexes.**