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APPLICATION NOTE AN52995

Evaluation of fluoroorganic compounds with benchtop ^{19}F NMR

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Application benefits

With a dedicated Thermo Scientific™ picoSpin™ 80 ^{19}F nuclear magnetic resonance (NMR) spectrometer, spectral acquisition is as easy as proton NMR. Due to the unique attributes of fluorine nuclei, the ^{19}F NMR spectra are easy to interpret, and provide a wealth of molecular structure information as well as its associated chemical environment.

Keywords

Fluoroorganic compounds, ^{19}F NMR, fluorotelomer, hydrofluorocarbon, *J* coupling, multiplicity

Abstract

Fluorine-19 NMR adds a new dimension in the analysis portfolio of fluorine containing compounds. The broader chemical shift range in ^{19}F NMR helps resolve individual fluorine containing functional groups, while the often large variable magnitude of ^{19}F-^{19}F and ^{1}H-^{19}F coupling provides additional insight into structural effects. Furthermore, first-order coupling and highly resolved resonance lines simplify analysis.

Introduction

Fluorine (^{19}F) plays an important role in pharmaceutical, agrochemical, and medicinal chemistry because the judicious placement of fluorine atoms in a molecule can have a significant influence on its chemical and physical properties. While the steric impact of replacing a hydrogen (^{1}H) atom with fluorine is minimal, the electron withdrawing and inductive field effects from a single fluorine nucleus are profound, affecting such properties as acidity, lipophilicity, and polarity. Examples of fluoroorganic compounds, with varying degree of structural complexity and fluorination, are shown in Figure 1. Biologically active pharmaceutical and agrochemical compounds incorporating fluorine are typically “lightly” fluorinated, containing one or only a few fluorine-containing substituents. Electronic liquids, on the other hand, are oligo perfluorocarbon compounds. They are chemically inert and are often used as lubricants and in low temperature heat transfer applications.

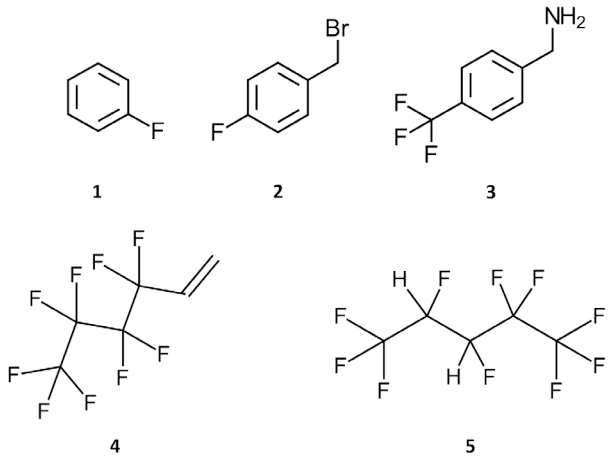

Figure 1: Chemical structures of the fluoroorganic compounds used in this study. (1) Fluorobenzene; (2) 4-fluorobenzyl bromide; (3) [4-(trifluoromethyl)phenyl]methanamine; (4) perfluoro-n-butyl ethylene, trade name Zonyl® PFBE; and (5) 2H,3H-decafluoropentane, trade name Vertrel® XF.

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^{19}F is one of the most studied nuclides after ^{1}H and ^{13}C in NMR spectroscopy. The advantages of ^{19}F NMR are multifold:

1. For lightly fluorinated bioactive molecules, the relatively small number of fluorine atoms yield fewer signals for easy spectral interpretation.

2. Fluorine couples strongly to other ^{19}F nuclides as far as six bonds away, while also coupling to proximate ^{1}H nuclei and carbon atoms. The resulting ^{19}F NMR spectrum is therefore information-rich in molecular structure as well as associated chemical environment.

3. The ^{19}F NMR spectra are typically first-order in nature in that spin-spin coupling follows the n+1 rule for multiplicity.

4. Being the most electronegative element on the periodic table, ^{19}F displays large shift dispersion (from -300 ppm to 400 ppm), resulting in far larger chemical shifts in ^{19}F spectra than in ^{1}H, and a much smaller probability of peak overlapping.

To demonstrate the wealth of ^{19}F spectral information, in this application note, we present the ^{19}F NMR spectra of a series of commercially available fluoroorganic compounds, obtained using a Thermo Fisher Scientific picoSpin 80 ^{19}F NMR spectrometer.

Experimental

Spectra were acquired using a picoSpin 80 NMR spectrometer. The spectrometer is a pulsed, Fourier transform ^{19}F NMR permanent magnet instrument equipped with a capillary cartridge probe. To ensure the highest sensitivity, the spectrometer was tuned to the fluorine Larmor frequency of 77 MHz. The spectrometer's capillary cartridge was fitted with micro-fluidic inlet and outlet connectors that allow liquid sample injection into the spectrometer's RF coil. The fluid path was Teflon/Quartz capillary tubing with a total flowpath volume of 40 microliters (µL). Liquid samples were introduced by manual injection using a disposable 1 mL syringe and a 22-gauge blunt tip needle. Hexafluorobenzene (HFB, C_6F_6) was added to fluorinated samples at approximately 1% (v/v) concentration as an internal shift reference. Hexafluorobenzene is a high fluorine density compound providing a strong fluorine signal, and is assigned a chemical shift value of -164 ppm. Due to large shift dispersion and solubility requirements of fluorine compounds, other reference compounds, such as fluorotrichloromethane (0 ppm), trifluoromethylbenzene (-63.2 ppm), trifluoroacetic acid (-76.2 ppm), and ethyl trifluoroacetate (-75.8 ppm), are also used to capture the full range of possible chemical shifts.

Spectra were acquired using the following acquisition parameters: a 90° RF excitation pulse, a 1000 ms acquisition time, and a 10 second recycle delay. The spectral width was adjusted to capture the large chemical shift dispersion of the ^{19}F spectrum. All spectra were acquired with signal averaging. Spectral data were stored in a JCAMP-DX file format and imported into MestreLab Research's Mnova™ NMR analysis program for processing. Standardized data processing was applied across all spectra, specifically, by applying zero filling, applying phase correction, and filtering using exponential Apodization.

Results and discussion

Examples of lightly fluorinated compounds

The ^{19}F NMR spectra of two mono-substituted aromatic fluoroorganic compounds, and one trifluoromethyl-substituted phenylmethylamine are presented in Figure 2. Fluorine substituents on the aromatic ring generally absorb in the same region (from -200 ppm to -100 ppm) because shielding zones due to the ring currents in the benzene ring have little influence on fluorine atoms. The mono-fluorine substituted aromatic experiences $^{3}J_{FH}$ and $^{4}J_{FH}$ coupling to ring protons, resulting in complicated but well-defined multiplets. The trifluoromethyl group (CF_3) in compound 3, on the other hand, appears as a singlet.

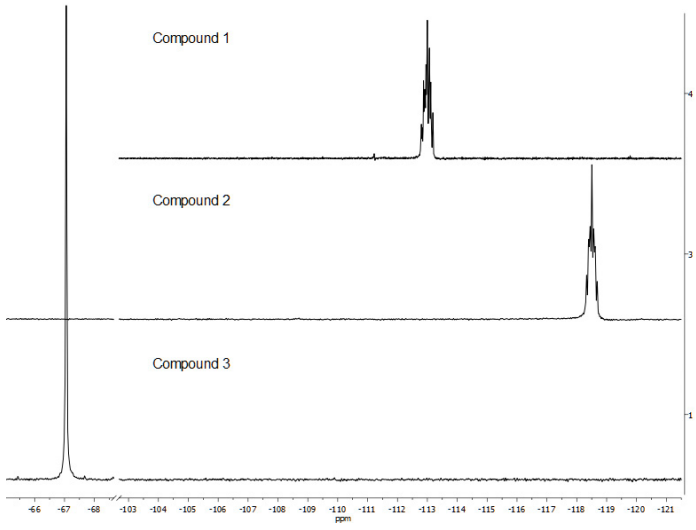

Figure 2: Full ^{19}F NMR spectra of, from top down, fluorobenzene (compound 1), 4-fluorobenzyl bromide (compound 2), and [4-(trifluoromethyl)phenyl]methanamine (compound 3).

Note that *J* coupling is indirect, through-bond scalar coupling between nuclei of like spin. The superscripts preceding the *J* term, e.g., ^{2}J, ^{3}J, or ^{4}J, indicate the number of bonds separating the coupled nuclei. ^{3}J coupling is most commonly observed in ^{1}H NMR, whereas with ^{19}F NMR, coupling 2-6 bonds away is routinely observed. The subscripts, e.g., J_{HH}, J_{FH}, or J_{FF}, indicate which nuclei are coupled. Coupling constants provide valuable information on which nuclei are close to one another. Coupled nuclei split the signal intensity of an otherwise uncoupled nuclei, resulting in a multiplet signal. The multiplicity, following the n+1 rule for first-order coupling, signifies the number of adjacent coupled nuclei, n.

An example of a fluorotelomer

Fluorotelomers are fluorocarbon-based oligomers synthesized by radical polymerization. They are used in a variety of manufacturing processes as flame retardants, and as non-conductive coatings due to their lipophobicity. Fluorotelomers are also the basis of many environmentally persistent perfluorinated carboxylic acids because of their use as surfactants.

The compound perfluoro-n-butyl ethylene is a fluorotelomer intermediate sold under the trade name Zonyl® PFBE. It has an ethylene functional group and fluorocarbon backbone. The higher spectral resolution of the fluorine peaks makes multiplet analysis and structural determination facile (Figure 3).

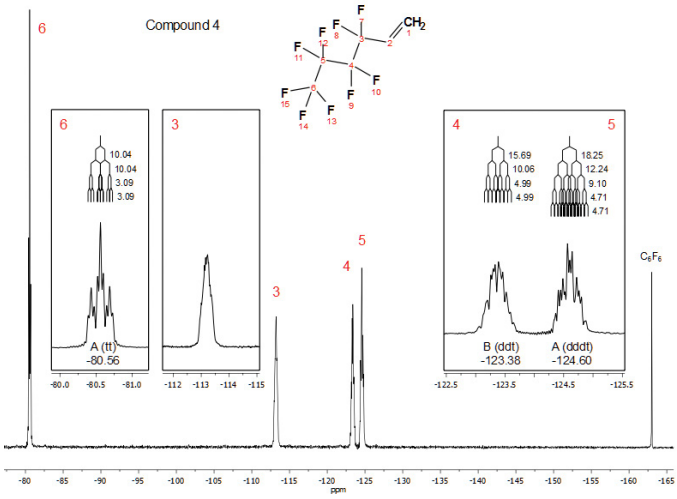

Figure 3: Full ^{19}F NMR spectrum of perfluoro-n-butyl ethylene. Inset: Multiplet analysis of the splitting pattern of individual peaks, with a *J*-coupling tree and coupling constants overlaid on the spectrum.

The insets show the *J*-coupling trees for the peaks of well-defined multiplicity (peaks 4, 5, and 6). The magnitude of the $^{3}J_{FF}$ coupling constants are of the expected size for linear, symmetric primary and secondary fluoroalkyl groups. For peak 3, the coupling of fluorine atoms to adjacent protons ($^{3}J_{FH}$) at position C_3 disrupts the symmetry at this position, causing the loss of a well-defined multiplet.

An example of a hydrofluorocarbon

Hydrofluorocarbon (HFC) electronic fluids are used in a variety of applications, such as heat transfer fluids, lubricants, and in precision and optics cleaning. Figures 4 and 5 are the ^{1}H and ^{19}F spectra, respectively of 2H,3H-decafluoropentane, a specialty fluid sold by DuPont™ under the trade name Vertrel® XF.

In the ^{1}H spectrum (Figure 4), in addition to the H-H coupling $^{3}J_{HH}$, both protons experience strong ^{1}H-^{19}F geminal coupling ($^{2}J_{FH}$; coupling of spin ½ nuclei attached to the same carbon center) to fluorine, and vicinal coupling ($^{3}J_{FH}$; coupling of spin ½ nuclei on adjacent carbon centers) to adjacent fluorine atoms, yielding a complex multiplet splitting pattern. The complexity is further compounded by the asymmetry of proton substitution at the C_2 and C_3 positions and slightly different chemical shifts for the two protons. Multiplet analysis of the splitting pattern suggests a *dddd* class, with a $^{2}J_{FH}$ coupling constant of 43.4 Hz.

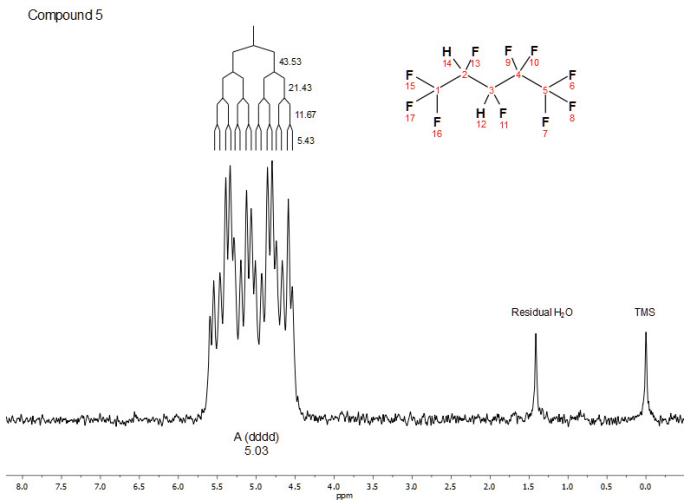

Figure 4: Full ^{1}H NMR spectrum of 2H,3H-decafluoropentane ($C_5H_2F_{10}$; neat) with TMS added as a chemical shift reference. Multiplet analysis of the splitting pattern reveals a *dddd* class; a *J*-coupling tree and coupling constants are overlaid on the spectrum.

In the ^{19}F spectrum (Figure 5), primary and secondary alkyl fluorides experience vastly different shielding along the carbon backbone, spanning a range from -220 ppm to -75 ppm, allowing for the analysis of individual fluorine groups separately. Confirmation of the strong geminal $^{2}J_{FH}$ coupling observed in the ^{1}H spectrum is in the multiplet analysis of the splitting pattern of fluorine atoms at positions C_2 and C_3 (inset for peaks 2 and 3).

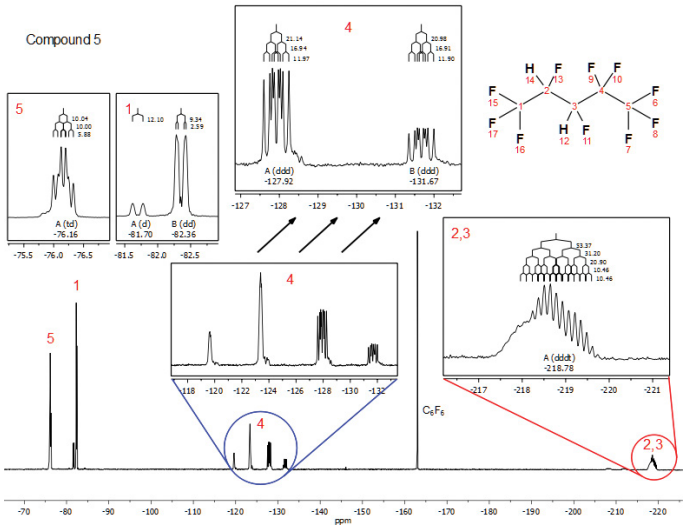

Figure 5: Full ^{19}F NMR spectrum of 2H,3H-decafluoropentane ($C_5H_2F_{10}$; neat) with C_6F_6 added as a chemical shift reference. Inset: Expanded view of chemical shift regions showing complex, multiplet splitting patterns arising from $^{2}J_{FH}$ and $^{3}J_{FH}$ coupling, and molecular asymmetry. *J*-coupling trees and coupling constants are overlaid on the spectrum.

Conclusions

Fluorine-19 NMR compliments ^{1}H and ^{13}C NMR in structure determination. The broader chemical shift range in ^{19}F NMR helps resolve individual fluorine containing functional groups, while the often-large variable magnitude of ^{19}F-^{19}F and ^{1}H-^{19}F coupling provides additional insight into structural effects. First-order coupling and highly resolved resonance lines also simplify analysis. Overall, ^{19}F NMR adds a new dimension in the analysis portfolio of fluorine containing compounds.

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