Structure Elucidation of Fluorinated Compounds by NMR

INTRODUCTION

- Fluorine is increasingly being used in many new drugs
  - As of 2011 there were approximately 200 fluorine containing drugs. [ref 1]
  - Fluoro-organic compounds account for 40% of the new chemical entities entering phase III trials in 2012 and 2013. [ref 2]
  - Fluorine is use in a wide range of drug applications including: Anesthetics, Antacids, Anti-anxiety, Antibiotics, Antidepressants, Anti-fungal antibiotics, Antihistamines, Antilipemics, Anti-malarial, Antimetabolites, Appetite suppressants, Arthritis/ anti-inflammatory agents, Psychotropic, Steroids/ anti-inflammatory agents. [ref 3]
- Fluorine is now appearing in illicit and illegal synthetic drugs:
  - These include: Cannabinoids [ref 4], and psychedelic phenethylamines [ref 5]
- Fluoro Polymers are important to everyday life, for example PTFE (Teflon™)

CHALLENGES

- The potential Fluorine chemical shift range is 500 ppm, 188 kHz at 9.4T (^{1}H 400 MHz) to 282 kHz at 14.1T (^{1}H 600 MHz).
- ^{19}F-^{1}H j coupling constants up to 60 Hz
- ^{19}F-^{13}C j coupling constants up to 280 Hz
- ^{19}F long range J coupling interactions complicate NMR spectra making interpretation difficult
- These spectral features combine to make ^{19}F difficult to excite and to decouple from other nuclei.

SOLUTIONS

- What is needed is a robust easy to use HFX NMR Probe and NMR console that can do every routine or sophisticated HFX experiment well!
- Including all HFX experiments, ^{1}H{^{19}F}, ^{19}F{^{1}H}, ^{13}C{^{1}H,^{19}F} & X{^{1}H,^{19}F}

By utilizing new published and patented probe technologies the powerful general-purpose ROYAL Probe now provides coupled with ECZ consoles unparalleled flexibility as the new JEOL ROYAL-HFX Probe.

How does the Technology Work?

- The Royal HFX probe uses for the first time in any commercial NMR probe magnetic coupling as an efficient purely "on" or "off" switch for the associated coil to be dual-tuned to ^{1}H and ^{19}F or single tuned to each. These improvements are related to the use of magnetic coupling in NMR circuits to improve the performance and function of NMR probes. [ref 6 – 8].
- Magnetic tuning allows the probe to retain the exact same highest performance for either ^{1}H or ^{19}F in single tune mode. In dual tune mode the switch can be tuned to easily balance the relative efficiencies of ^{19}F and ^{1}H. Because of the huge ^{19}F spectral window.
- JEOL ECZ NMR Spectrometer
- ECZS routine NMR spectrometers can generate simultaneous ^{1}H and ^{19}F frequencies with no additional hardware
- ECZR research NMR spectrometers with an optional 3rd channel can collect ^{1}H and ^{19}F data over wide ^{19}F frequency ranges in all dimensions.
- JEOL Royal HFX NMR Probe
- Spec's Royal Probe = Spec's Royal HFX Probe
- No Loss in RF or S/N performance relative to the standard ROYAL probe for ^{1}H, ^{19}F, ^{13}C, or X
- Includes Auto-Tune compatibility to allow easy switching between modes.

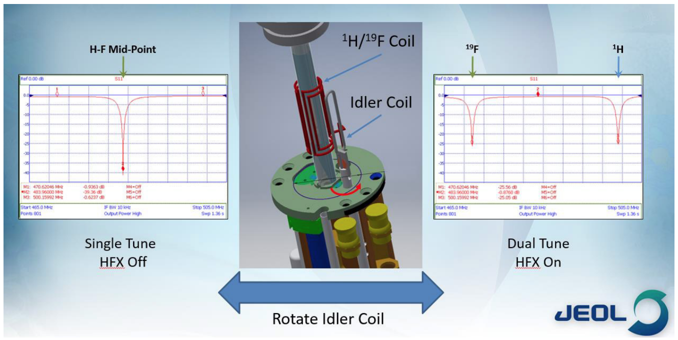


Figure 1. *Illustration of magnetic coupling technology as a perfect switch between single tune and dual tune modes in the ROYAL-HFX Probe.*

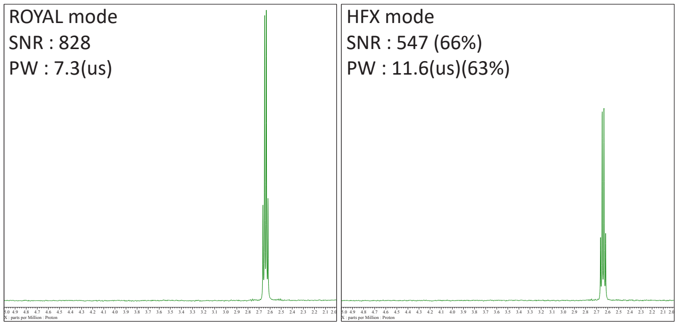


Figure 2. *¹H signal to noise and pw90 for a 500 MHz ROYAL-HFX Probe in single and dual-tune illustrating the expected changes in performance when switching modes.*

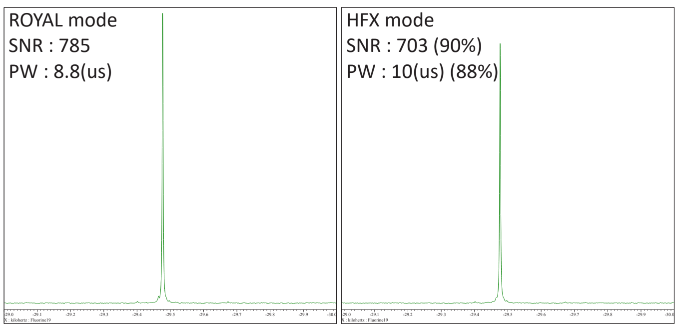


Figure 3. *¹⁹F signal to noise and pw90 for a 500 MHz ROYAL-HFX Probe in single and dual-tune modes.*

OUT OF THE BOX HFX EXPERIMENTS

Most commonly needed 1D and 2D pulse programs are provided for easy use in a fully automated environment. Because of the often dramatic requirement for very wide bandwidths associated with ¹⁹F NMR fully optimized combinations of adiabatic decoupling and 180 refocusing/inversion technologies are fully utilized in all dimensions. The Chemist can focus on Chemistry while the console worries about the complex details. Figures 5 – 8 show typical examples and the improvements resulting from HFX techniques for a couple of example molecules.

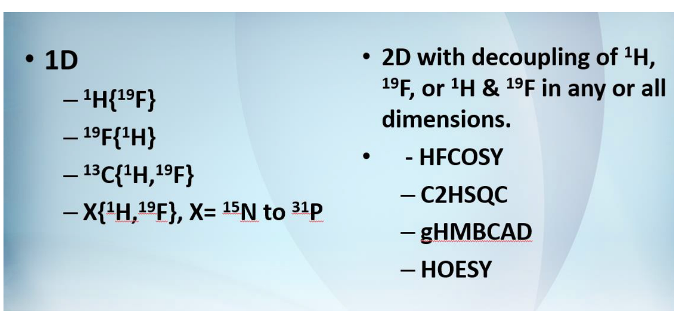


Figure 4. *Matrix of common out of the box 1D and 2D NMR techniques provided in the software.*

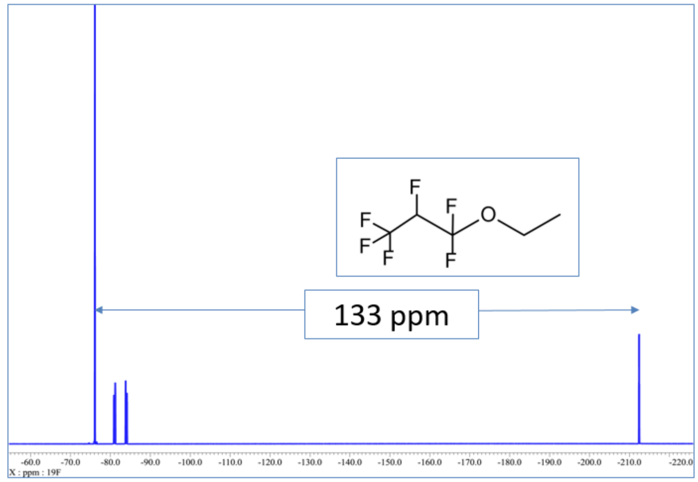


Figure 5. *¹⁹F{¹H} 1D spectrum for a fluoro-ether illustrating the potential for large ¹⁹F frequency bandwidth.*

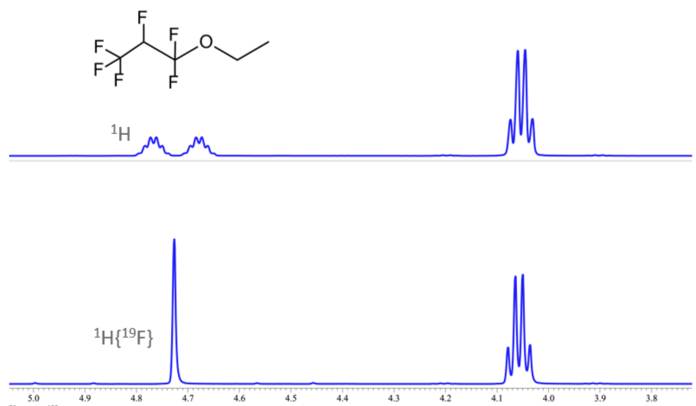


Figure 6. *¹H observe with and without {¹⁹F}.*

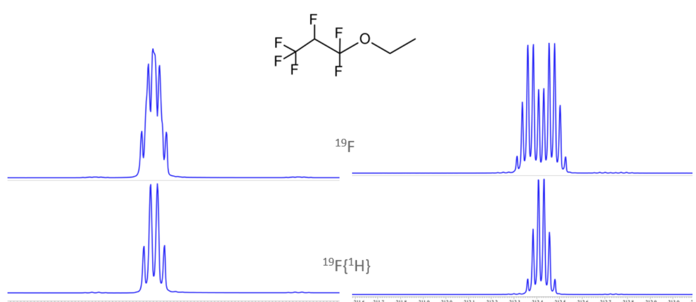


Figure 7. *Detail of ¹⁹F spectrum with and without {¹H}.*

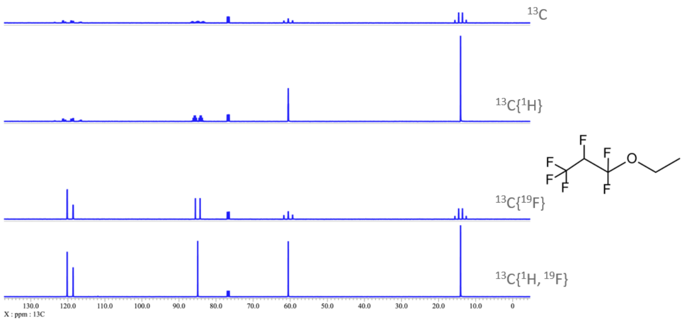


Figure 8. *Full ^{13}C spectrum for the fluoro-ether example showing all possible combinations of ^{1}H and ^{19}F decoupling. Results are shown with identical scaling to accentuate the dramatic improvement to ^{13}C spectra of fluorine containing molecules by dual {^{1}H,^{19}F}.*

It is important to remember that the low band channel of the ROYAL-HFX Probe retains full broadband capabilities. Figure 9 first illustrates another example of ^{13}C observe with {^{1}H,^{19}F} while figure 10 shows the power of {^{1}H,^{19}F} with a ^{31}P spectrum.

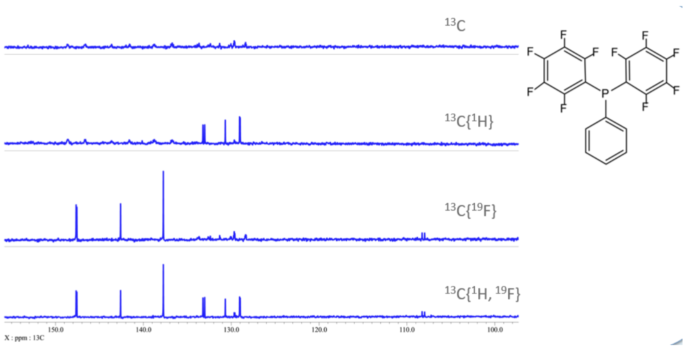


Figure 9. *Another example of the amazing improvement obtained by {^{1}H,^{19}F} for ^{13}C observe with a fluorine containing molecule.*

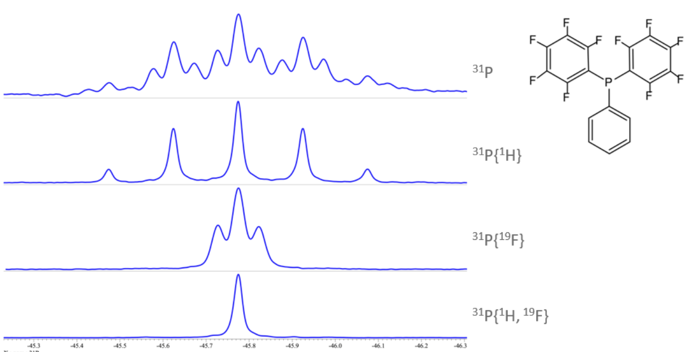


Figure 10. *Effects of all combinations of ^{1}H and ^{19}F decoupling for a ^{31}P resonance. In this figure the results for either no decoupling of single nucleus decoupling have the vertical scaling greatly increased relative to the {^{1}H,^{19}F} example.*

The simplification of spectral information in multi-dimensional experiments can be just as significant as was just shown for simple decoupling with 1D observe. This is because the J-couplings occur in all dimensions! Often it is desirable to obtain 2D information illustrating ^{1}H/^{19}F connectivity both though bonds (HFCOSY/HFHETCOR) or through space as with the HFHOESY example shown in figure 11.

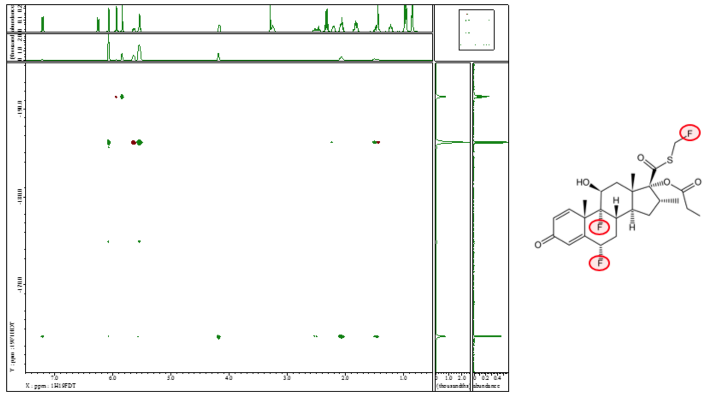
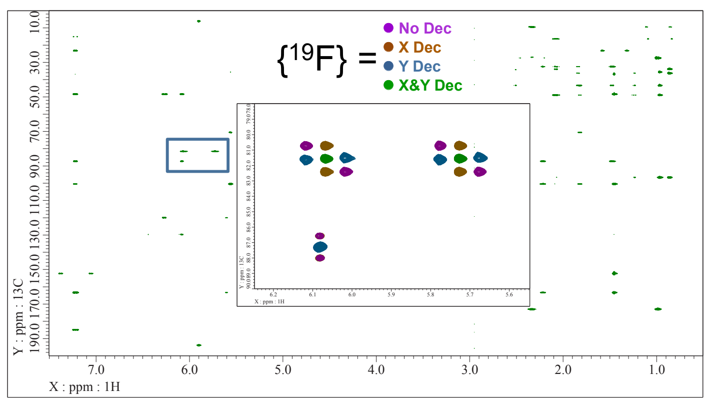


Figure 11. *HFHOESY obtained for Fluticasone propionate aka Flonase™.*

Having the ability to acquire ^{1}H/^{13}C or ^{19}F/^{13}C, or ^{1}H ^{19}F/X 2D data with decoupling as either ^{1}H or ^{19}F is particularly powerful. The following figure 12 illustrate the effects for decoupling ^{19}F in both the F1 and F2 dimensions in gHMBCAD again using Fluticasone as a simple example molecule. In general ^{19}F can introduce coupling in all dimensions in every heteronuclear 2D NMR experiment reducing sensitivity and increasing complexity.



^{1}H-^{13}C gHMBCAD, ^{19}F Decoupling Simplifies Assignments, 25% NUS, 8 Scans 10mg Fluticasone Propionate/DMSO-d6.

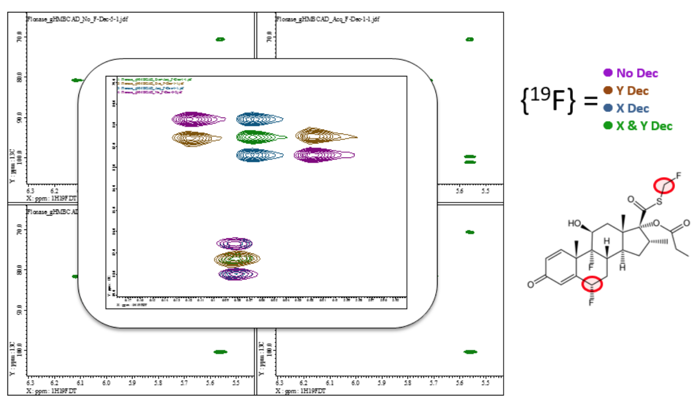


Figure 12. *gHMBCAD example illustrating the simplifying effects of F decoupling for 2D ^{1}H/^{13}C responses being applied in either, F1 (blue), F2 (brown), or both in dimensions (green). The diagonal purple re-sponses clearly show how the ^{19}F coupling exists in both dimensions.*

SUMMARY

It is hoped that this application note provides an informative introduction to the science which is easily done using the ROYAL HFX probe and a JEOL ECZ series NMR Spectrometer.

REFERENCES

1. Wang et al, *Chem. Rev.* 2014, 114, p2432−2506
2. Zhou et al, *Chem. Rev.* 2016, 116, p422−518
3. http://www.slweb.org/ftrcfluorinatedpharm.html
4. Banister et al, ACS *Chem. Neurosci.*, 2015, 6 (8), p1445–1458
5. Trachsel, D., Drug Test. Analysis, (2012) 4: p577–590
6. B. Taber and A.P. Zens, *J. Magn. Reson.*, 259, 2015, p114-120
7. P. Bowyer, J. Finnigan, B. Marsden, B. Taber, and A. Zens, *J. Magn. Reson.*, 2015, p190-1
8. V. Lim, B. Marsden, B. Taber, and A. Zens, *J. Magn. Reson.*, 2016.268

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