High-resolution probes for $^{19}\text{F}$ applications

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BeNeLux NMR User Meeting 2016, Brussels
25$^{th}$ of November 2016
Why $^{19}$F NMR?

- I=1/2, 100% natural abundance

\[ \frac{\gamma(^{19}F)}{\gamma(^{1}H)} = 94.09\% \]

- Large chemical shift range (+440 to -450 ppm)
  - High sensitivity of $^{19}$F on chemical environment
  - Reference substance: CCl$_3$F ($\delta_F = 0$ppm)

- Use of $^{19}$F in drugs:
  - Higher metabolic stability
  - Increased membrane permeability
  - Tune affinity to target enzyme

- $^{19}$F containing insecticides/herbicides/fungicides

- $^{19}$F containing synthetic polymers
19F NMR applications

- Probe design (inner / outer coil)
- Double resonance applications
  - BBO H&F
  - BBFO SmartProbe
- Triple resonance applications
  - TXO probe
  - TBO probe
- CryoProbes for highest 19F sensitivity
  - TCI H&F cryoprobe
  - QCIF cryoprobe
RF design & RF efficiency: $B_1 / I_{\text{coil}}$

How can the RF efficiency be improved?

- Optimize RF coil design & RF coil materials
- Reduce RF coil diameter
Probehead Type Classification

Proton inner coil: “INVERSE”

X-nucleus inner coil: “OBSERVE”

\[ ^1H \text{ (Proton)} \]

Double resonance broad-band inverse

BBI

\{ ^{109}\text{Ag} - ^{31}\text{P} \}

X-nucleus broad-band

Double resonance broad-band observe

BBO
Probehead Type Classification

Proton inner coil: “INVERSE”  X-nucleus inner coil: “OBSERVE”

Double resonance broad-band inverse BBI  Double resonance broad-band observe BBO
$^1$H sensitivity of BBI and BBO

BBI
(Proton inner coil)

BBO
(Proton outer coil)
$^{13}$C sensitivity of BBI and BBO

**BBI**
($^{13}$C outer coil)

**BBO**
($^{13}$C inner coil)
$^{19}$F NMR applications

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BBO design
Extension to $^{19}$F

BBO H&F

BBF

$\{^{109}\text{Ag} - ^{31}\text{P}\}$

$\{^{109}\text{Ag} - ^{31}\text{P}, ^{19}\text{F}\}$

BBFO SmartProbe

$\{^{109}\text{Ag} - ^{31}\text{P}, ^{19}\text{F}\}$

$^1\text{H}$ or $^{19}\text{F}$
**BBO H&F**

Tuned to $^1H$

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**1H NMR**

$^2J_{H,F}$

$^1H$ / $^{19}F$

Tuned to $^1H$

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1,1,2,3,3,3-hexafluoropropyl-ethyl-ether in CDCl$_3$
BBO H&F
Tuned to F

BB
\{^{109}\text{Ag} - ^{31}\text{P}\}

\[^1\text{H} / ^{19}\text{F}\]

Tuned to \(^{19}\text{F}\)

\(^{19}\text{F} \text{ NMR}\)

\[^2J_{\text{H,F}}\]

1,1,2,3,3,3-hexafluoropropyl-ethyl-ether in CDCl\(_3\)
BBFO SmartProbe

BBF: tuned to $^{19}$F

$^{1}$H NMR

$^{1}$H

$^{2}$J$_{H,F}$

$^{1}$H$^{({}^{19}\text{F})}$
1D $^{19}\text{F}$ NMR with $^1\text{H}$ BB decoupling
\( ^{19}\text{F} \) sensitivity - with and without \( ^1\text{H} \) decoupling

<table>
<thead>
<tr>
<th>Compound</th>
<th>SNR Ratio (decoupled/coupled)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFT</td>
<td>2.7</td>
</tr>
<tr>
<td>Hexafluoropropylethyl-ether</td>
<td>2.2</td>
</tr>
<tr>
<td>Fluoro-uracil</td>
<td>5.6</td>
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</tbody>
</table>

400MHz, \( \text{lb}=0.5\text{Hz} \), 1ppm noise range
BBFO
SmartProbe

$^{19}\text{F} - ^1\text{H}$ correlations

2D HOESY
SmartProbe

$^{19}$F background signal

- **SmartProbe** allround probe for many different applications
19F NMR applications

- Probe design (inner / outer coil)

- Double resonance applications
  - BBO H&F
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- Triple resonance applications
  - TXO probe
  - TBO probe

- CryoProbes for highest 19F sensitivity
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Triple resonance applications – simultaneous BB decoupling on two nuclei

Double Resonance:
\[ ^{19}\text{F} \{ ^1\text{H} \}, \quad ^1\text{H} \{ ^{19}\text{F} \} \]

Triple Resonance:
\[ ^{13}\text{C} \{ ^1\text{H}, ^{19}\text{F} \}, \quad ^{19}\text{F} \{ ^1\text{H}, ^{13}\text{C} \}, \quad ^1\text{H} \{ ^{19}\text{F}, ^{13}\text{C} \} \]

SmartProbe
2 RF channels
1 Proton amplifier (QNP switch)

TXO or TBO probe
3 RF channels
2 Proton amplifiers
Triple resonance $^{19}$F applications
TXO probes ($^{13}$C, $^{19}$F, $^1$H)

- $^{19}$F{$^1$H}, $^1$H{$^{19}$F} and $^{13}$C{$^1$H,$^{19}$F}, $^{19}$F{$^1$H,$^{13}$C}, $^1$H{$^{19}$F,$^{13}$C}

- TXO probes available in two «flavours»:
  - Priority on $^{19}$F (F/C/H)
  - Priority on $^{13}$C (C/F/H)

- VT range: -150 to +150° C
- $^{19}$F background reduction measures
- Full automation for all experiments with C, F & H

Priority on $^{13}$C: TXO C/F/H
400MHz TXO probe
Priority on $^{19}$F

$^{19}$F sensitivity
with $^1$H decoupling

SiNo: 827:1
(lb=0.5 Hz;
1 ppm noise region)
400MHz TXO probe
Priority on $^{19}\text{F}$

1D $^1\text{H}$ NMR
400MHz TXO probe Priority on $^{19}$F

1D $^1$H NMR with $^{19}$F and $^{13}$C decoupling
400MHz TXO probe Priority on $^{19}$F

1D $^{19}$F NMR with $^1$H BB decoupling
400MHz TXO probe Priority on $^{19}\text{F}$

1D $^{19}\text{F}$ NMR

with $^{1}\text{H}$ BB decoupling
400MHz TXO probe Priority on $^{19}\text{F}$

1D $^{19}\text{F}$ NMR

with $^{1}\text{H}$ and $^{13}\text{C}$

BB decoupling
400MHz TXO probe
Priority on $^{19}$F

$^1$H, $^{13}$C HMBC
400MHz TXO probe
Priority on $^{19}\text{F}$

$^1\text{H}$, $^{13}\text{C}$ HMBC

with $^{19}\text{F}$ decoupling in F1
Triple resonance $^{19}$F applications
TXO probes ($^{13}$C, $^{19}$F, $^{1}$H)

- $^{19}$F{$^{1}$H}, $^{1}$H{$^{19}$F} and $^{13}$C{$^{1}$H,$^{19}$F}, $^{19}$F{$^{1}$H,$^{13}$C}, $^{1}$H{$^{19}$F,$^{13}$C}

- TXO probes available in two «flavours»:
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- VT range: -150 to +150° C
- $^{19}$F background reduction measures
- Full automation for all experiments with C, F & H
400MHz TXO probe
Priority on ${}^{13}\text{C}$

1D $^{13}\text{C}$ NMR
with $^1\text{H}$ and $^{19}\text{F}$
BB decoupling

$^{19}\text{F}$ priority (F/C/H)

$^{13}\text{C}$ priority (C/F/H)
5mm TBO BB-F/H Probe

- Optimized sensitivity for X nuclei detection
- Triple resonance: X-F-H with X broadband
- BB broadband ($^{31}\text{P}-^{15}\text{N}$)
- Full automation for all experiments with X, F & H
5mm TBO BB-F/H Probe

- $^{19}\text{F}, ^{13}\text{C}$ HSQC (with $^1\text{H}$ BB decoupling)
- $ns = 1$
- 2k x 128 data points
- 2.5 min. experimental time

10 mg fluorouracil in 0.5 ml DMSO-$d_6$
19F NMR applications

• Probe design (inner / outer coil)

• Double resonance applications
  • BBO H&F
  • BBFO SmartProbe

• Triple resonance applications
  • TXO probe
  • TBO probe

• CryoProbes for highest 19F sensitivity
  • TCI H&F cryoprobe
  • QCIF cryoprobe
CryoProbe: RF coil temperature

\[
\frac{S}{N} \propto \frac{U_I}{U_N} \propto \frac{\omega \cdot M_o \cdot V \cdot \eta \cdot (B_1/I_{coil})}{\sqrt{4 \cdot k \cdot \Delta f \cdot R \cdot T}}
\]

- CryoProbe (He, ~20K)
- CryoProbe Prodigy (N\textsubscript{2}, ~85K)

S/N versus temperature (K)
Helium H&F CryoProbes
TCI

- **H&F CryoProbes with $^1$H coil tuneable to $^{19}$F**

- Probes with highest $^{19}$F sensitivity
  (without $^1$H decoupling)

- $^{19}$F{$^1$H} and $^1$H{$^{19}$F} experiments **not** possible

- Good for $^{19}$F if no alternative available

- Suitable for $^{19}$F with broad lines (PrOF NMR)
QCI HFCN CryoProbe

- H/F/C/N probe, fixed frequency for Proton, Fluor, Carbon and Nitrogen
- Probes with highest $^{19}$F sensitivity
  (with $^1$H decoupling)
- All $^{19}$F{$^1$H} and $^1$H{$^{19}$F} experiments possible
- Allow for any combination of nuclei with 4 channel spectrometer
- Useful for $^{19}$F ligand based screening
$^{19}$F labeled ligand in protein complex

PROTEIN: 18kDa, < 1mM

$^{19}$F LIGAND: 2-fold excess

1D $^{19}$F{$^{1}$H} NMR
Spin Echo CPMG

Free ligand
Linewidth = 4Hz

Bound ligand
Linewidth = 18Hz
# Summary

Probes for $^{19}$F NMR applications

<table>
<thead>
<tr>
<th>Probe</th>
<th>Field (MHz)</th>
<th>Benefits</th>
<th>Applications</th>
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</thead>
<tbody>
<tr>
<td>BBFO Smartprobe</td>
<td>400 – 600</td>
<td>$^{19}$F{$^1$H}, $^{1}$H{$^{19}$F} and $X^{1}$H, $^{1}$H{$^{19}$F}</td>
<td>Small Molecules and Polymers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VT Range -150 to +180° C</td>
<td></td>
</tr>
<tr>
<td>QCI (HFCN) Cryoprobe</td>
<td>500 – 800</td>
<td>$^{19}$F{$^1$H}, $^{1}$H{$^{19}$F} and full range of HFCN 4 channel experiments</td>
<td>Proteins, Nucleic Acids, Drug Discovery</td>
</tr>
<tr>
<td>TXO and TBO RT probes</td>
<td>400 – 800</td>
<td>$^{19}$F{$^1$H}, $^{1}$H{$^{19}$F} and $X^{1}$H,$^{19}$F, $^{1}$H{$^{19}$F,X}</td>
<td>Small Molecules, Polymers, Proteins, Drug Discovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VT Range -150 to +180° C</td>
<td></td>
</tr>
<tr>
<td>H&amp;F BBO</td>
<td>400 – 700</td>
<td>$^1$H Channel tunable to $^{19}$F (no $^1$H decoupling)*</td>
<td>Quick $^{19}$F experiments no decoupling</td>
</tr>
<tr>
<td>TCI H&amp;F Cryoprobe</td>
<td>400 - 1000</td>
<td>$^1$H Channel tunable to $^{19}$F (no $^1$H decoupling)*</td>
<td>Proteins, Nucleic Acids with broad $^{19}$F signals</td>
</tr>
<tr>
<td>Cryoprobe Prodigy</td>
<td>400 - 700</td>
<td>$^1$H Channel tunable to $^{19}$F (no $^1$H decoupling)*</td>
<td>Proteins, Nucleic Acids with broad $^{19}$F signals</td>
</tr>
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* Not available in automation with nanobay consoles
Acknowledgements

- Application colleagues Bruker Biospin
  Rainer Kümmerle, Helena Kovacs, Clemens Anklin
- R&D Bruker BioSpin

Thank you!
Innovation with Integrity