Caractérisations par RMN solide de biomatériaux inorganiques et hybrides

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Examples of materials studied by NMR

(1) Formulations of organoboron drugs

(2) Biomaterials based on calcium pyrophosphates
Benzoxaborole-based drugs

Antifungal
Tavaborole (AN2690)
FDA-approved (2014)

Anti-inflammatory
Crisaborole (AN2728)
(Phase 3 completed)

Antitrypanosomal agent
SCYX-7158 (AN5568)
(Phase 1 in progress)

Antiviral
(Laboratory stage)

Privileged scaffold
Benzoxaborole formulations

- **Topical**: 5% in solution (propylene glycol, ethanol)
- **Topical ointment**
- **Oral/parenteral solution**: (PEG, ethanol, carboxymethylcellulose...)

**Development of novel materials formulations** for benzoxaboroles.

→ Need to characterize benzoxaborole(s) within these formulations: local environment? stability?

→ Multinuclear ($^{11}$B, $^{13}$C, $^1$H) solid-state NMR
1- Benzoxaborole formulations

**Topical**
- 5% in solution (propylene glycol, éthanol)

**Oral/parenteral**
- Solution (PEG, ethanol, carboxymethylcellulose...)

**Crystalline phases**

**Disordered phases**
1- Crystalline materials involving benzoxaborol(at)es

**Benzoxaborole**

- Mainly H-bonding & $\pi$-stacking interactions between the benzoxaboroles

**Benzoxaborolate**

- Benzoxaborolates coordinated or not to Mg$^{2+}$
1- NMR characterization of the crystalline materials

11B MAS NMR

- Solid state 11B NMR signatures of benzoxaborola(ates)
- Distinction between B_{planar} and B_{tetrahedral}
- Resolution of different 11B sites by 2D NMR studies

11B MQMAS NMR

- 400 MHz 18.5 kHz MAS
NMR characterization of the crystalline materials

**11B MAS NMR**
- 600 MHz
- 20 kHz MAS

**13C CPMAS NMR**
- 600 MHz
- 20 kHz MAS

**11B MQMAS NMR**
- 400 MHz
- 18.5 kHz MAS

Materials:
- MgBBzx·7H₂O
- MgBBzx·10H₂O
- CaBBzx·3H₂O

Chemical shifts:
- $\delta$ (ppm)
- $\delta_1$ (ppm)
- $\delta_2$ (ppm)
Disordered materials involving benzoxaborolates

Benzoxaborolates

Layered Double Hydroxides (LDH)

\[ [M^{2+}_{1-x}M^{3+}_{x}(OH)_{2}]^{p+}(A^{n-}_{p/n}H_{2}O) \]

Specificities:
- Possible intercalation of various anionic species (including drugs)
- **Mg-Al** LDH approved by the pharmaceutical industry
Intercalation of benzoxaborolates in LDH: NMR

\[ \text{NO}_3^- \rightarrow \text{NO}_3^- \rightarrow \text{NO}_3^- \rightarrow \text{NO}_3^- \]

H₂O - 50 °C - 16 h Ar atm.

\[ \delta \text{(ppm)} \]

![Graphs showing NMR measurements for 27Al MAS and 25Mg MAS.](image)
Intercalation of benzoxaborolates in LDH: $^{11}$B NMR

Drying/Storage conditions must be optimized to avoid any benzoxaborol(at)e degradation.
1- Intercalation of benzoxaborolates in LDH: $^{11}$B NMR

The benzoxaborole and benzoxaborolate species are in close proximity between the LDH layers.
NMR studies of materials containing organoboron species

(1) Formulations of organoboron drugs

Multinuclear solid state NMR well-suited and necessary to analyze the structure of novel formulations for organoboron molecules

- Structure?
- Stability?
(& Polymorphism?)

\[ ^1H, ^{13}C, ^{11}B, ^{19}F \]
and also
\[ ^{25}Mg, ^{27}Al... \]

*CrystEngComm, 2014, 16, 4999*

*Chem Mater, 2015, 27, 1242*

*J Mater Chem B, 2016, 4, 257*
Examples of materials studied by NMR

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<tr>
<td><img src="image1.png" alt="Organoboron Drug Structure" /></td>
<td><img src="image2.png" alt="Calcium Pyrophosphate Structure" /></td>
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Crystallization of Ca$_2$P$_2$O$_7$.2H$_2$O in the fluids around the joints (pseudo-gout)

http://www.nationalinstituteofarthritis.com/images/services_image/06.jpg
2- Structure of Ca-((pyro)phosphate) biominerals

→ Multinuclear solid state NMR
   ($^{31}$P, $^1$H and $^{43}$Ca)

→ XRD & PDF analyses

→ Computational modelling
   (MD & DFT)

Synthetic models

Amorphous Ca-pyrophosphate
($\sim$Ca$_2$P$_2$O$_7$.4H$_2$O)

a-CPP

m-Ca$_2$P$_2$O$_7$.4H$_2$O
m-CPP.4H$_2$O

m-Ca$_2$P$_2$O$_7$.2H$_2$O
m-CPP.2H$_2$O

t-Ca$_2$P$_2$O$_7$.2H$_2$O

10 µm
31P and 43Ca MAS NMR studies of Ca-pyrophosphates

- Multinuclear solid state NMR (31P, 1H and 43Ca)
- XRD & PDF analyses
- Computational modelling (MD & DFT)

31P MAS NMR
14.1 T, 10 kHz MAS, 10°C
(1 pulse, spinal-64 1H decoupling)
31P and 43Ca MAS NMR studies of Ca-pyrophosphates

**43Ca MAS NMR**
20 T, 5 kHz MAS  
(DFS-1pulse)

~6 h
~5 h
~6 h
~14 h

δ(43Ca) / ppm

**31P MAS NMR**
14.1 T, 10 kHz MAS, 10°C  
(1pulse, spinal-64 1H decoupling)

a-CPP
m-CPP.4H2O
m-CPP.2H2O
t-CPP.2H2O

δ(31P) / ppm
31P and 43Ca MAS NMR studies of Ca-pyrophosphates

**43Ca MAS NMR**
20 T, 5 kHz MAS  
(DFS-1pulse)

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**31P MAS NMR**
14.1 T, 10 kHz MAS, 10°C  
(1pulse, spinal-64 1H decoupling)

δ(31P) /ppm
NMR studies of Ca-pyrophosphate based materials

Multinuclear solid state NMR well-suited to analyze the structure of crystalline and amorphous Ca-(pyro)phosphate based materials

- Structure?
- Reactivity?

\[^{31}\text{P}, \text{H}, \text{Ca}\]

*J Mater Chem, 2011, 21, 18783*

*Acta Biomater. 2016, 31, 348*
Acknowledgements

(1) Formulations of organoboron drugs

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(2) Materials based on calcium pyrophosphates

Christian BONHOMME & Christel GERVAIS (UPMC)

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