Modeling and Characterization of Bioactive Glasses: New Insights by Solid State NMR and DNP (Dynamic Nuclear Polarization)

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S2: Glasses in Healthcare - Fundamentals and Application

Fundamentals of Bioactive Glass I: Atomic and Molecular Structure
Solid state NMR: a pertinent tool of investigation

Bioactive glasses

Polymorphs, Proteins

Biomaterials

Nanomaterials

Structure
Dynamics
Imaging
QM predictions

Hybrid materials
Outline

■ NMR of quadrupolar nuclei in glasses.

■ NMR crystallography and modeling.

■ Sr-doped bioactive glasses:
  • $^{87}$Sr NMR at very high field.
  • modeling of glass structures.

■ DNP applied to substituted HAp.

■ Future trends in $^{43}$Ca NMR spectroscopy.
NMR and quadrupolar nuclei

the quadrupolar tensor: $C_Q$ (in MHz!) and $\eta_Q$

$\text{Si}^{29}$ $I = 1/2$

$\text{O}^{17}$ $I = 5/2$

$\text{Ca}^{43}$ $I = 7/2$

$\text{Sr}^{87}$ $I = 9/2$

76.9SiO$_2$ – 17.6CaO – 5.5SrO

NMR methodology for: $^{43}\text{Ca}$, $I = 7/2$ ("small" Q broadening)

- **Magic Angle Spinning** at *moderate* spinning frequency (5 kHz)

- **Very high magnetic field** (20 T): reduction of *second-order* Q broadening; sensitivity

- **Large volume rotor** (7mm): low $\gamma$ nucleus, NA: 0.14 % (!)

**Multifield experiments:** $C_Q$ and $\eta_Q$
NMR methodology for: $^{87}\text{Sr}$, $I = 9/2$ ("very large" Q broadening)

- Static mode only
- Very high magnetic field (20 T): reduction of second-order Q broadening; sensitivity
- Large volume rotor (7mm): low $\gamma$ nucleus, NA: 7%
- + (smart) tricks

Iuga et al., J. Magn. Reson., 2000 and Bräuniger

Variable Offset Cumulative Spectra

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First principles calculations of NMR parameters


DFT periodic systems all-electron hamiltonians
evaluation of $j^{(1)}(r')$ using pseudopotentials

$$B_{in}^{(1)}(r) = \frac{1}{c} \int d^3r' j^{(1)}(r') \times \frac{r-r'}{|r-r'|^3}$$

**CSA**

**GIPAW**

**EFG**

**J**

**IDRIS**

- structure / assignment of spectra
- dynamics
- amorphous slabs
- distributions

$\delta, C_Q, J$


$^{43}\text{Ca} (I = 7/2)$ NMR parameters (NA 0.14 %, low $\gamma$)


see also: Charpentier, Pedone et al.
NMR crystallography approach: $^{43}$Ca as an example

hydrated Ca oxalate: cf kidney stones

$\text{CaC}_2\text{O}_4\cdot\text{H}_2\text{O}$

$^{43}\text{Ca}$

CaC$_2$O$_4$·H$_2$O

variable field experiments (2 sites)

$\delta_{\text{iso}}(^{43}\text{Ca})$

C$_Q$(43Ca)

H. Colas, C. Bonhomme et al.,
Applications of GIPAW to glasses

- T. Charpentier, M.C. Menziani, A. Pedone: MD, DFT, GIPAW


- MD–GIPAW methodology for NMR glass studies
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Sr–derivatives and Sr–doped bioactive glasses

The Effects of Strontium Ranelate on the Risk of Vertebral Fracture in Women with Postmenopausal Osteoporosis
Pierre J. Meunier, M.D., Christian Roux, M.D., Ph.D., Ego Seeman, M.D., Sergio Ortolani, M.D., Janusz E. Badurski, M.D., Tim D. Spector, M.D., Jorge Cannata, M.D., Adam Balogh, M.D., Ernst-Martin Lemmel, M.D., Stig Pors-Nielsen, M.D., René Rizzoli, M.D., Harry K. Genant, M.D., and Jean-Yves Reginster, M.D.

Effects of Sr–derivatives and Sr–doped bioactive glasses.

Original Article

Journal of Materials Chemistry
Cite this: J. Mater. Chem., 2012, 22, 7395
www.rsc.org/materials

PAPER

Influence of strontium substitution on structure and crystallisation of Bioglass® 4555
K. Fujikura, N. Karpukhina, T. Kasuga, D. S. Brauer, R. G. Hill and R. V. Law

Synthesis and dissolution behaviour of CaO/SrO-containing sol–gel-derived 58S glasses
Anthony L. B. Maçon, Sungho Lee, Gowsihan Pugongasundarampilli, Toshihiro Kasuga, and Julian R. Jones


New Strontium-based Bioactive Glasses:
Physicochemical Reactivity and Delivering Capability of Biologically Active Dissolution Products
Jonathan Lao, Edouard Jallot, and Jean-Marie Nedelec

Effects of boron oxide substitution on the structure and bioactivity of SrO-containing bioactive glasses
Xiaonan Lu, Lu Deng, Po-Hsuen Kuo, Mengguo Ren, Ian Buterbaugh, and Jincheng Du
$^{87}$Sr solid state NMR methodology (NA: 7%, low $\gamma$, "very large" Q broadening)

1. very high field (20 T)
2. 7mm rotors
3. $^{87}$Sr isotopic labeling
4. VOCS – DFS – WURST – QCPMG

Glass modeling
GIPAW calculations of $^{87}$Sr parameters
NMR crystallography

$^{87}$Sr isotopic labeling

SrCO$_3$
$C_Q \sim 9$ MHz

Sr(NO$_3$)$_2$
$C_Q \sim 15$ MHz

SrSO$_4$
$C_Q \sim 28$ MHz

very few data in the literature...


87Sr NMR GIPAW calculations

... the need for GIPAW calculations...

CASTEP

... C_Q is relevant, not δ_iso.

Bonhomme, Gervais, Laurencin et al.,

**87Sr NMR in bioactive glasses**

- **Composition:**
  6.9 SiO₂−17.6 CaO−5.5 SrO, mol %
  ⇒ ~ 9 wt % in SrO

- **Protocol:**
  - sol–gel process
  - *SrCO₃ (90 % in ⁸⁷Sr) in 2N HCl
  - Ca(NO₃)₂ / EtOH / H₂O / TEOS

2 sites for SrSiO₃

C_Q = 18.5 MHz, C_Q = 46.0 MHz
Modeling Sr–doped bioactive glasses

Effect of Strontium Substitution on the Structure of 45S5 Bioglasses

Ye Xiang and Jincheng Du*
Department of Materials Science and Engineering, Center for Advanced Scientific Computing and Modeling (CASCaM) University of North Texas, Denton, Texas 76203, United States

- SiO$_2$ – CaO – SrO
- SiO$_2$ – SrO
- MD in DL-Poly (Buckingham)
- extraction of ~ 200 atoms
- DFT relaxation in VASP
- GIPAW calculations of C$_O$(87Sr)

Interpretation of the $^{87}$Sr QCPMG spectra

- a realistic description of the spectra

- a deeper insight:
  - increase the "size" of the cells
  - "inversion" of the spectra starting from $C_Q$ (?)

"small" $C_Q^{(87}\text{Sr)}$

"large" $C_Q^{(87}\text{Sr)}$
Influence of SBF (Simulated Body Fluid)

- *in vitro* interaction with SBF, acellular (Kokubo, Bohner)
- 20 mg of glass in 20 mL
- 25 times replication
- acetone rinsing
- air–dried (RT)

from: A. Stein’s group, University of Minnesota… and others (C. Rey…)!
Influence of SBF: $^{87}\text{Sr}$ NMR experiments

ICP-AES / analysis of final SBF

20 % of Sr ions remains in the glass

B75-*Sr10 before immersion in SBF
exp. time: ~ 1 h

B75-*Sr10 after immersion in SBF
exp. time: ~ 16 h
Influence of SBF: $^{87}$Sr NMR experiments

assumption:

- a minority of Sr$^{2+}$ cations in the "core"
- a majority of Sr$^{2+}$ cations at the surface (not detectable due to OH$^-$ groups)

$^{1}$H, $^{31}$P NMR characterization of the HAp layer

- high field (850 MHz)
- fast MAS
- 2D {$^1$H–$^{31}$P} correlations

very sensitive experiments! ... but rather limited!
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Context: biological hydroxyapatites (HAp)

\[ \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 + \text{substitutions (C}^+\text{ and A}^-) \]

\[ \text{Na}^+, \text{K}^+, \text{Mg}^{2+}, \text{Zn}^{2+}, \text{Sr}^{2+} \ldots \]

\[ \text{F}^-, \text{Cl}^-, \text{CO}_3^{2-}, \text{SiO}_4^{4-} \ldots \]

\[ ^{43}\text{Ca}: \text{low } \gamma \text{ and N.A. } \sim 0.14\% \]

\[ \text{low wt}\% \text{ for all C}^+\text{ and A}^- \]
Intrinsically distributed materials

FTIR ("too local")

PXRD ("average")
Dynamic Nuclear Polarization (DNP) MAS

- **SENSITIVITY**
  - "impossible experiments"

- **LOW TEMPERATURE & MAS**
  - (~ 100 K or lower…)
  - depending on the sample…
    - enhanced spin locking during CP
    - better homonuclear decoupling
    - …

- **but: questions …**

- **solvant + AMUPOL**
  - huge gain in nuclear polarization!!

- **DNP juice**
  - $^1\text{H, } ^{29}\text{Si, } ^{13}\text{C…}$

- **bulk**

- **spin diffusion**
The HAp structure (hexagonal)

channels of OH⁻ groups

$D_{H-H,\text{inter}} \ll D_{H-H,\text{intra}}$

A site substitutions (▲)

orientation of OH⁻

\[
\frac{\partial P}{\partial t} = D \frac{\partial^2 P}{\partial z^2} - \frac{P}{T_{1n}}
\]

\[
D = \Omega a^2
\]

\[
\varepsilon = \varepsilon_{1H}^0 \frac{2\sqrt{D T_{1n}}}{L} \tanh\left(\frac{L}{2\sqrt{D T_{1n}}}\right)
\]

C. Bonhomme et al., Analytical Chem., 2017

see also:

Synthetic carbonated nanosized HAp

- synthetic HAp, ~ 1 wt % in C
- 1D, 2D, double- and triple resonance CP, SQ-DQ experiments

C. Bonhomme et al., Analytical Chem., 2017
Towards structural models

δ_{iso}^{(13C)} = δ_{m} (m: 1 → 8)

C_{1} \rightarrow C_{1}
C_{1} \rightarrow C_{2}
C_{1} \rightarrow C_{3}
C_{1} \rightarrow C_{4}

C. Bonhomme et al., Analytical Chem., 2017
From NMR … to "DNP crystallography" @ 100 K  
(Coll.: Y. Petit, F. Tielens, UPMC)

[Diagram of molecular structures and plots showing chemical shifts vs. P-C distance]
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Options for $^{43}\text{Ca}$ solid state NMR

**natural abundance**: large volume rotor, highest magnetic field, moderate MAS

$^{43}\text{Ca} \text{ MAS}$

7mm, 850 MHz, 5 kHz, ~ 10 hours
No 2D

**labeled samples**: 60% labeled $^{*}\text{CaCO}_3$ (calcite)

fast… and 2D
but costs !!
Natural abundance $^{43}$Ca DNP spectroscopy

$v_0(^{43}$Ca) = 26.94 MHz, 100 K, **DNP juice**: glycerol-d$_8$/D$_2$O/H$_2$O (60/30/10; v/v/v) + AMUPol, sample: ~ 20 mg

**N.A. 2D $^{1}$H–$^{43}$Ca HETCOR CP MAS DNP**

<table>
<thead>
<tr>
<th>Duration</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1h</td>
<td>$^{1}$H–$^{43}$Ca CP MAS DNP for synthetic HAp</td>
</tr>
<tr>
<td>6h</td>
<td>DFS $^{43}$Ca MAS for synthetic HAp</td>
</tr>
<tr>
<td>0 ppm</td>
<td>Core sites, Surface Ca$^{2+}$, synthetic HAp at 0 ppm</td>
</tr>
<tr>
<td>4h</td>
<td>$^{1}$H–$^{43}$Ca CP MAS DNP for mice teeth</td>
</tr>
<tr>
<td>&lt; 1h</td>
<td>$^{1}$H–$^{43}$Ca CP MAS DNP for synthetic HAp</td>
</tr>
</tbody>
</table>

Nature Commun., 2017 and Coll.: S. L-Dalicieux
$^{43}$Ca: pushing the limits of sensitivity & resolution at 1.5 GHz, 35.2 T

C. Wang, J. Paulino, I. Hung, Z. Gan

- series-connected hybrid magnet
- from 0 to 35.2 T in 30 minutes
- 20 kA
- very efficient lock
- from 7:00 AM to 3:30 PM
- no "overnight" experiment
- 3.2 mm X MAS probe, 18 kHz
43Ca MAS and MQ-MAS experiments

(Coll.: D. Laurencin, Montpellier)

unpublished results
(April-May, 2018)

*a/CaHPO₄*

MAS

20 T

35.3 T

b/ 50 min.

3Q MAS

Ca pyrophosphates and oxalate (NA)

Ca₂P₂O₇.4H₂O

4 hours

Ca₂P₂O₇.2H₂O

GIPAW (2 sites)

CaC₂O₄·H₂O

COM (850 MHz, 7mm, 10h)

m-DFS-MAS

COM (1.5 GHz, 3.2mm, 4h)


Bonhomme, Laurencin et al., CrystEngComm., 2013
Modeling of hydrated amorphous calcium pyrophosphates (a-CPP)

▶ osteoarthritis, pseudogout
▶ potential role of amorphous precursor? (biomineralization)

presence of water, no melt-and-quench approach
MC → AIMD → "hydration" → relaxation → GIPAW ($^{43}$Ca)

a-CPP models
(Ca$_2$P$_2$O$_7$.nH$_2$O, n = 2 to 6)

Coll.: J. Rimsza, J. Du (UNT, USA)

manuscript under preparation
Conclusions

► NMR crystallography applied to Sr-doped bio-active glasses
► New insights in substituted HAp structures by DNP
► DNP crystallography
► Future trends in low $\gamma$ nuclei Q NMR @ *ultra-high magnetic field* (1.5 GHz)

... 

► Perspectives:

**$^{23}\text{Na}$**

**Physiological Review B 92, 144310 (2015)**

*Phonon effects on x-ray absorption and nuclear magnetic resonance spectroscopies*

Rudy Nemausat,1,2,* Delphine Cabaré,1 Christel Gervais,2 Christian Brouder, Nicolas Tricera,3 Amélie Bordage for Erra,5,6 and Francesca Mauri1

**$^{23}\text{Na}$ MAS variable $\nu_{\text{rot}}$**

**$\nu_{\text{rot}}$**

quantum thermal fluctuations
description of the effects of T

GIPAW

see also: MD, *ab initio* MD, Path

Integral MD (J. N. Dumez, C. Pickard, J. Yates, P. Hodgkinson...)


2016

**NaHC$_2$O$_4$. H$_2$O**
Aknowledgments

► Y. Petit, F. Tielens (Paris, France)
► F. Aussenac (Bruker Biospin, Wissembourg, France)
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► D. Laurencin (Montpellier, France)

►► J.V. Hanna, M.E. Smith (Warwick, UK)

►►► C. Wang, J. Paulino, I. Hung, Z. Gan
Perspectives: pathological calcifications (kidney stones)

$^{13}$C DNP CP MAS approach (400 MHz & 100 K)

- Sapphire rotor + CaF$_2^*$
- One plaque + {AMUpol in D$_2$O/H$_2$O (9:1)}


"Unfortunately, it is challenging to collect sufficient Randall’s plaque material in the mg to tens of mg quantities necessary for $^{13}$C$^{31}$P REDOR".

Unpublished results

400 MHz DNP → ~ 3 hours
700 MHz & RT → ~ 43 hours!

$S/N$ per unit $t^{1/2}$
~ 25
625 in time
Strontium malonate

starting material: *SrCO₃, strontianite

87Sr*: 90 %, 200 mg ~ 5000 $