LA-UR-20-28887

Approved for public release; distribution is unlimited.

Title: Earth's Field NMR for Detection of Chemical Warfare Agents

Author(s): Kaseman, Derrick

Intended for: Seminar at Ohio State

Issued: 2020-11-02

Disclaimer:

Los Alamos National Laboratory, an affirmative action/equal opportunity employer, is operated by Triad National Security, LLC for the National Nuclear Security Administration of U.S. Department of Energy under contract 89233218CNA000001. By approving this article, the publisher recognizes that the U.S. Government retains nonexclusive, royalty-free license to publish or reproduce the published form of this contribution, or to allow others to do so, for U.S. Government purposes. Los Alamos National Laboratory requests that the publisher identify this article as work performed under the auspices of the U.S. Department of Energy. Los Alamos National Laboratory strongly supports academic freedom and a researcher's right to publish; as an institution, however, the Laboratory does not endorse the viewpoint of a publication or guarantee its technical correctness.

Earth's Field NMR for Detection of Chemical Warfare Agents

Derrick C. Kaseman
Scientist

Bioenergy and Biome Sciences Division

11/10/20

Managed by Triad National Security, LLC for the U.S. Department of Energy's NNSA

Introduction to Nerve Agents

- Chemical warfare agents (CWAs) have become more lethal and easier to obtain
- 10,000+ potential organophosphorus nerve agents but only 1152 agents[†] measured by any analytical technique

G-Agents

V-Agents

Novichok Agents

Critical need to be able to quickly and accurately identify CWAs

[†]from OPCW Analytical Database (OCAD)

Recent Examples of Nerve Agent Use

- Navalny
- Skirpal
- Kim Jong-Nam

Nerve Agent Detector

Nerve Agent Attack

Detector

- ✓ Identify agent class
- ✓ Identify the molecule
- ✓ Quantify
- ✓ Portable
- ✓ Affordable

G-Agents

NMR for Nerve Agent Detection

High Field
Superconducting(T)

- ✓ Identify agent class
- ✓ Identify the molecule
- ✓ Quantify
- X Portable
- X Affordable

Low Field
Permanent (mT)

- ? Identify the agent class
- ? Identify the molecule
- ✓ Quantify
- ✓ Portable
- ✓ Affordable

There seems to be a trade-off between portability and resolution

Microtesla (μT) NMR

Heteronuclear J-Couplings

Additional Heteronuclear J-Couplings

The μT regime provides high resolution “J-coupled” spectra and additional information not present at high field!

J-Coupled Spectroscopy Theory

N+1
splitting

Strong
Heteronuclear
Coupling Limit

$$B_2^{\text{up}} = \frac{J^2}{2\Delta\nu(\gamma_I - \gamma_S)}$$

J=J-Coupling
 $\Delta\nu$ =linewidth
 γ =gyromagnetic ratio
I= ^1H
S= ^{13}C

$$B_C^{\text{up}} = \frac{(1 + \frac{1}{\sqrt{2}})J}{(\gamma_I - \gamma_S)}$$

$$B_3^{\text{up}} = \frac{3J^2}{4\Delta\nu(\gamma_I - \gamma_S)^2}$$

As the magnetic field is decreased, more heteronuclear peaks are observable

Achieving J-Coupled Spectra (JCS)

- In order to have a JCS $J < \nu_{H,F} - \nu_{F,P} < 100J$ must be satisfied
- $\nu_{H,F,P} \propto$ Magnetic field
- J-Couplings are field independent
- Larmor frequencies remain, but chemical shifts usually disappear

30-70 μT is an optimal magnetic field to obtain JCS of CWAs

Historical Overview of J-coupled Spectroscopy

- Only 22 molecules JCS ever recorded (only 3 contain P)
- Resolution issues in laboratory settings and at room temp
- 2 orders of magnitude from detecting a lethal dose of sarin

JCS requires large spin volumes and spectral investigations are lacking

Simulating JCS: G-Agents

- JCS may be simulated using previously measured J-couplings
- For clarity, only certain regions are shown

^{19}F Region

^1H Region

JCS of G-agents have distinct spectral features in the ^{19}F and ^1H regions for each molecule

Spectrometer Designs

J-cOUpled SpecTromEteR (JOUSTER)

Flow J-coupled Spectrometer (FLOWSTER)

Benchmarking the Spectrometers

- Reduces spin density by 10 - 10^5 and reduces volume by 10 - 10^3
- 29 unique JCS (previously 22)
- 17 new P-containing JCS (previously 3)

JOUSTER

FLOWSTER and JOUSTER are the most sensitive J-coupled spectrometers ever reported

Samples Investigated

Most samples are CWA precursors, surrogates, and decomposition products

JCS of CWA Surrogates

Diisopropyl methylphosphonate
Sarin surrogate

Dipinacolyl methylphosphonate
Soman surrogate

Dicyclohexyl methylphosphonate
Cyclosarin surrogate

Acephate
V-Agent Surrogate

Malathion
V-Agent Surrogate

Dimefox
Novichok Surrogate

Surrogate compounds have unique JCS that allow for identification

JCS of Structurally Similar Organophosphates

JCS is very sensitive to relatively small structure changes and are unique to the molecules

Structure Back-Prediction

- The idealized detector would be able to identify a signature without resorting to a lookup table
- Using the Organization for the Prohibition of Chemical Weapons analytical database, the J-couplings for 28 G-agents were obtained and the JCS were simulated
- The spectra were then analyzed holding either an R_1 or R_2 group constant, letting the R_2 or R_1 group vary and identifying peaks common in all of the other spectra

Structure Back-Prediction

- R_1 groups typically have characteristic peaks >5 Hz
- R_2 groups typically have characteristic peaks <5 Hz

JCS have common structural motifs and spectrum is summation of individual R group's JCS

Identification of CWAs by Hydrolysis Pathways

Case Study: Operation in a Complex Environment

- Potting mix (peat, bark, soil, sand, and mushroom compost) is mixed with 200 μL of ethanol
- Sample makes dirt moist, not a solution
- JCS signature is still present!
 - Lower signal intensity is due to detector volume constraints

Even in a complex environment, the JCS is unique and background free!

Detecting P-F Couplings

^{19}F

^1H

^{19}F

^{19}F

^1H

^{19}F

The P-F J-coupling is unique, characteristic of G-agents and can be detected in JCS

Impact on the Relative J-Coupling Sign

Positive $^3J_{\text{HF}}$

Negative $^3J_{\text{HF}}$

Experimental

$\text{H}_\text{A}\text{H}_\text{B}\text{F}$ (ABX) spin system
3 unique J-couplings J_{AX} , J_{BX} , and J_{AB}

JCS provides relative sign of J-couplings in coupled spin systems with >2 spins

Difluor Case Study: Detecting H, F, and P

- Difluor is a synthetic precursor for G-agents

- 9 detectable regions in the spectrum

- 1 H
- 4 F
- 4 P

- Able to detect 6 of the 9 regions, but all of the observable nuclei

All 3 NMR active nuclei are detectable in JCS

Multinuclear Excitation and Detection

- All NMR active nuclei are contained in a spectra region of a few kHz
- Therefore, all NMR active nuclei may all be acquired in a single experiment

Multinuclear excitation and detection offers a means simultaneously obtaining information from all NMR active nuclei.

JCS of Fluorobenzenes

Hydrogen

Fluorine

Unique spectra were obtained using simultaneous excitation and detection

^{19}F Chemical Shifts

- Chemical shift scales with magnetic field and usually not considered at these magnetic fields
- Benzene+hexafluorobenzene mixture demonstrates chemical shift information is available for heteronuclei
- All fluorobenzene spectra needed chemical shift correction

First ^{19}F chemical shift information obtained at μT fields

Chemical and Magnetic Equivalence

- Magnetic equivalence (ME) between nuclei means the nuclei have same chemical shift and equivalent coupling to a shared nucleus
- Chemical equivalence (CE) between nuclei means the nuclei have same chemical shift but different couplings between a shared nucleus

JCS can provide better structural insights than high field NMR

Heteronuclear Quantitation from JCS

- Simultaneous excitation and detection provides a means for direct quantitation and determining pseudo-empirical formulas
- Receptivity (Ξ) must be accounted for with the heteronuclei and homonuclei

$$\Xi_{local} = \chi I(I + 1) \gamma \omega_{eff}^2$$

χ =natural abundance

I = spin of nucleus

γ =gyromagnetic ratio

ω_{eff}^2 =peak resonant frequency

Compound	^1H - ^{19}F Stoichiometric	Experimental	Ξ - Experimental	Ξ - Simulated
Benzene + Hexafluorobenzene	1.00	1.16	0.963	1.00
Monofluorobenzene	5.00	7.04	5.86	5.00
1,2-Difluorobenzene	2.00	2.26	1.88	2.00
1,3-Difluorobenzene	2.00	2.20	1.84	2.00
1,4-Difluorobenzene	2.00	2.37	1.98	2.00
1,2,4-Trifluorobenzene	1.00	0.979	0.815	1.00
1,2,4,5-Tetrafluorobenzene	0.500	0.687	0.572	1.00
Pentafluorobenzene	0.200	0.292	0.243	1.00

JCS are fully quantitative, which has never been demonstrated

Receptivity at Earth's Magnetic Field

High Field Receptivity

$$\Xi = \chi I(I + 1) \gamma^3$$

Low Field Receptivity

$$\Xi_{local} = \chi I(I + 1) \gamma \omega_{eff}^2$$

¹⁹F:¹H Ratio (4:1 Stoichiometry)

	Experimental	Simulation
Raw	6.62 (65.4%)	5.40 (35.1%)
Ξ	5.51 (37.8%)	4.50 (12.6%)
Ξ_{local}	4.41 (10.35%)	4.19 (4.87%)

If $J \sim$ Larmor frequency then Ξ_{local} must be used

Other Quantitative Aspects

Mixture Analysis

Homonuclear Group Quantitation

1.88:1

The quantitative aspects are afforded by the detection method

Multidimensional NMR (Heteronuclear COSY)

Experiment

SPINACH

Structure elucidation remains an open question

Conclusions

- 2 portable J-coupled spectrometers were developed that identified CWA surrogates, precursors and decomposition products
- JCS is capable of simultaneously detecting 3 nuclei (^1H , ^{19}F , and ^{31}P) common to CWAs.
- JCS is able to differentiate between the different molecular groups that are appended to the P atom
- JCS is quantitative allowing for pseudo-empirical formulas to be measured
- In many cases the JCS provides MORE information than conventional high field NMR

Nerve Agent
Detector

- ✓ Identify agent class
- ✓ Identify the molecule
- ✓ Quantify
- ✓ Portable
- ✓ Affordable

Acknowledgments

- Robert Williams, Michelle Epsy, Michael Janicke, Per Magnelind, Jacob Yoder, Scarlett Widgeon Paisner, Al Urbaitis, Marc Alvarez, Rami Beatrice, Pulak Nath, Michael Malone
- LANL Laboratory Directed Research and Development Project #20170048DR
- LANL Director's Postdoc Fellowship Project #20190641PRD3