X-Nuclei NMR Spectroscopy

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Nuclear magnetic resonance (NMR) spectroscopy isn't all about protons although people often primarily think that due to the excellent sensitivity of the nucleus and its wide-ranging uses in organic chemistry. In fact, many more nuclei are NMR active and can be used to build a better picture of your chemistry. Fluorine-19 NMR is incredibly useful in applications involving pharmaceuticals to Li-ion batteries and has been available on benchtop NMR instruments for many years. A broadband channel, capable of collecting spectra from a variety of different nuclei (so called X-Nuclei), has until now been restricted to high field NMR applications. X-Pulse however, delivers a true tuneable broadband channel to the benchtop for the first time, enabling investigations of systems not easily analysed with just protons. This article gives an overview of many of the nuclei which can be investigated by the Oxford Instruments X-Pulse Broadband Benchtop NMR Spectrometer and provides examples of applications.

When the first commercial NMR instruments were introduced in the early 1950s, they analysed a single nucleus: hydrogen-1 (^{1}H, proton). Only many years later would commercial multinuclear spectrometers be introduced. These soon became a mainstay of analysis in both academia and industry, fuelling discoveries in fields including chemistry, biotechnology, pharmaceuticals, polymers, and energy. Benchtop NMR instruments, which offer NMR capabilities in a more compact, low-maintenance form factor, have followed a similar, if faster, development path. The introduction of the first, singlenucleus spectrometers in 2009 was followed swiftly by two- and three-nucleus models. Just a decade later in 2019, the X-Pulse, the first true broadband multinuclear benchtop NMR spectrometer launched, significantly expanding the benchtop applications into academic and industrial arenas, previously reserved for traditional high-field spectrometers.

Modern NMR spectrometers usually incorporate three different nuclei channels: one for a lock signal, traditionally optimised for deuterium (^{2}H, hydrogen-2); a second for proton and fluorine-19 (^{19}F) signals; and the third, X-channel, for another nuclei, often referred to by NMR spectroscopists as an X-nuclei. The introduction of the X-Pulse broadband instrument uniquely allowed operators to quickly tune between many different X-nuclei. For the first time in a single benchtop platform, operators could select a nuclei of their choice from a broad frequency range at any time. No longer were the range of applications restricted to those enabled by just the one or two additional nuclei that had to be pre-selected before an instrument was purchased. Furthermore, the structure and properties of chemicals containing many different nuclei could now be comprehensively characterised.

X-Nuclei

Many elements are observable by NMR, but not every atom of each element is. Chemical elements differ by the number of protons in their nucleus (their atomic number); each atom of an element has the same number of protons. However, atoms of the same element can have different numbers of neutrons in the nucleus, producing multiple isotopes each with a unique atomic mass. This varying composition of atomic nuclei alters their physical properties, affecting their suitability for NMR spectroscopy. Some of the properties relevant to NMR spectroscopy of selected isotopes are summarised in *Table 1*.

Nuclear spin is one such physical property. In principle, all nuclei with a non-zero nuclear spin may be observed by NMR spectroscopy. In practice, other considerations, such as the abundance of the isotope, its sensitivity, and its typical linewidth, make some nuclei easier to analyse than others.

In nature, most chemical elements are found as a mixture of isotopes. The NMR signal is directly proportional to the number of nuclei in the sample producing that signal, therefore the abundance of an NMR active isotope greatly influences the ease of analysis. For isotopes with low natural abundance, isotopic enrichment can increase sensitivity; doubling the percentage of a low abundance isotope in the sample would double the signal. One everyday example is the use of deuterated solvents, in which the percentage of deuterium (^{2}H) is routinely increased from its natural abundance of 0.0115% to 99% or higher to provide a strong deuterium lock signal.

Another consideration is that each NMR active isotope has a different level of sensitivity, which is related to the frequency of the signal it produces. In a fixed magnetic field, each isotope resonates at a characteristic frequency (called the Larmor frequency). Although the term 'Larmor frequency' may be unfamiliar to casual NMR users, they probably use it every day, as magnet strengths are commonly expressed as the ^{1}H Larmor frequency (for example, 60 MHz for the X-Pulse 1.4 tesla magnet). All other considerations being equal, in a fixed magnetic field, an isotope that produces a signal at a higher frequency will be more sensitive. Other than the low abundance, radioactive tritium (^{3}H) isotope, the high-abundance proton (^{1}H) has the highest sensitivity, which is a major reason for its popularity in NMR.

The receptivity of an isotope quantifies the overall ease of observation by NMR spectroscopy, including both natural abundance and physical properties. Receptivity is usually reported either relative to proton or to carbon-13 (as done in *Table 1*). Comparing values of the different isotopes shows that observation of ^{1}H is almost six thousand times "easier" than that of ^{13}C. Low receptivity in NMR spectroscopy can be overcome by increasing sample concentration, running longer experiments (increasing the number of scans), and choosing specific experiments designed to enhance sensitivity.

In addition to the properties of a nucleus, the capabilities of the NMR spectrometer are also a critical consideration. To analyse a nucleus, the NMR spectrometer hardware must be designed to operate at its Larmor frequency. Different nuclei can have very different Larmor frequencies; for example, a proton will resonate at 60 MHz on a 1.4 tesla magnet, but ^{13}C will resonate at just 15 MHz. As an example of the scope of an NMR spectrometer, the broadband channel on the X-Pulse can analyse nuclei with Larmor frequencies between 11 - 25 MHz at 1.4 tesla; a few of the nuclei in this range include, ^{13}C, ^{31}P, ^{7}Li, ^{11}B, ^{23}Na, ^{27}Al, and ^{29}Si.

Table 1: NMR properties of selected isotopes. Data from: Pure Appl. Chem., 2001, 73, 1795-1818.

Isotope	Nuclear Spin, I	Natural Abundance (%)	Larmor Frequency @ 1.4 T (MHz)	Relative Receptivity versus ^{13}C
Hydrogen-1 (proton)	1/2	99.99	59.70	5870
Hydrogen-2 (deuterium)	1	0.0115	9.16	<0.01
Lithium-7	3/2	92.41	23.20	1590
Boron-11	3/2	80.10	19.15	777
Carbon-13	1/2	1.07	15.01	1
Nitrogen-14	1	99.63	4.31	5.90
Fluorine-19	1/2	100	56.17	4900
Sodium-23	3/2	100	15.79	545
Aluminium-27	5/2	100	15.56	1220
Silicon-29	1/2	4.68	11.86	2.16
Phosphorus-31	1/2	100	24.17	391
Cobalt-59	7/2	100	14.17	1640
Tin-119	1/2	8.59	22.26	26.6
Platinum-195	1/2	33.83	12.83	20.7

Carbon-13 NMR Spectroscopy

Carbon-13 (^{13}C) is likely the second most studied nucleus by NMR spectroscopy, after protons, due to the importance of carbon in organic chemistry and the life sciences. However, due to its low natural abundance and gyromagnetic ratio, it has one of the lowest receptivity values of any NMR active nuclei. Indeed, if not for its ubiquitous nature, ^{13}C NMR would likely be an uncommonly studied nucleus by NMR spectroscopy, rather than one of the driving forces in its development. Instead, NMR spectroscopists have developed many useful techniques to examine this crucial element, such as two-dimensional proton-carbon correlation experiments.

^{13}C NMR spectra are usually obtained using a technique known as decoupling, to remove the proton-carbon couplings, which greatly simplifies the spectrum and enhances the signal-to-noise ratio. Most small organic molecules typically produce proton-decoupled ^{13}C (commonly denoted: ^{13}C{^{1}H}) NMR spectra made up of a series of sharp singlets over the chemical shift range of δ_C 0 to +200 ppm. Unlike in ^{1}H and ^{19}F NMR spectra, the peak area of a signal in a standard ^{13}C NMR spectrum will not typically correlate with the number of carbon atoms in the sample, making the spectra more useful for qualitative, rather than quantitative, applications.

A ^{13}C NMR spectrum of ethyl crotonate (*Figure 1*), for example, clearly distinguishes the different carbon environments. The spectrum shows the carbonyl carbon at δ_C 166 ppm, the alkene carbons in the range δ_C 120 - 145 ppm, the ether-adjacent carbon at δ_C 60 ppm, and the methyl carbons between δ_C 10 - 20 ppm.
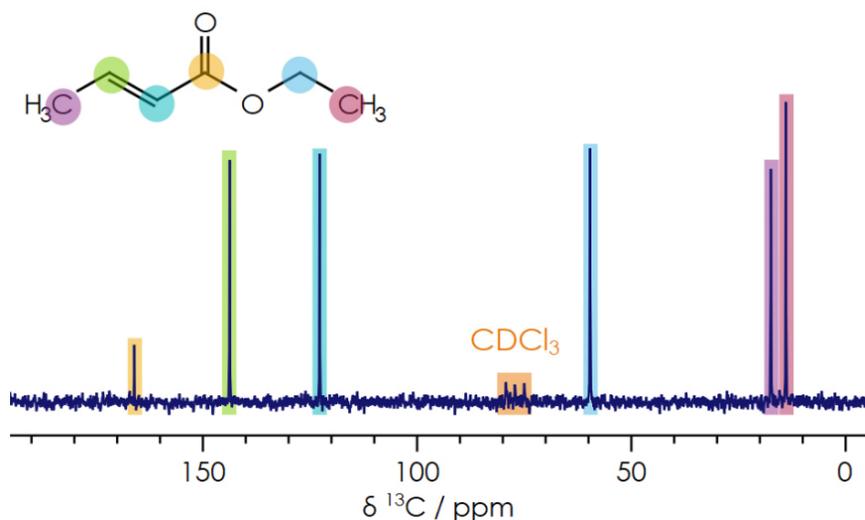
Figure 1: ^{13}C{^{1}H} NMR spectrum of ethyl crotonate in CDCl3.

Phosphorus-31 NMR Spectroscopy

Phosphorus-31 (^{31}P) NMR spectroscopy is commonly used in coordination chemistry, and hence catalysis, where phosphorus containing ligands are often employed (for example those shown in *Figure 2a*). Also, due to the importance of phosphate (PO$_4$ $^{3-}$) in many biochemical pathways, phosphorous containing compounds are found in pharmaceuticals and dietary supplements which are amenable to study by NMR. Additionally, there are many phosphorus containing anions, for example hexafluorophosphate (*Figure 2b*), which is commonly used in lithium-ion batteries. As with ^{13}C NMR spectra, ^{31}P spectra are commonly proton decoupled, giving generally sharp signals over a wide range of δ_P −180 to +250 ppm.

Due both to the wide chemical shift range and the fact that most phosphorus containing compounds have only a few phosphorus atoms, ^{31}P NMR spectroscopy is ideal for distinguishing them. For example, triphenylphosphine {PPh$_3$}, triphenylphosphine oxide {OPPh$_3$}, triphenylphosphite {P(OPh)$_3$}, and triphenylphosphate {OP(OPh)$_3$}, have effectively identical ^{1}H and ^{13}C NMR spectra arising from the phenyl rings, yet can be readily distinguished by their ^{31}P{^{1}H} NMR spectra (*Figure 2a*).
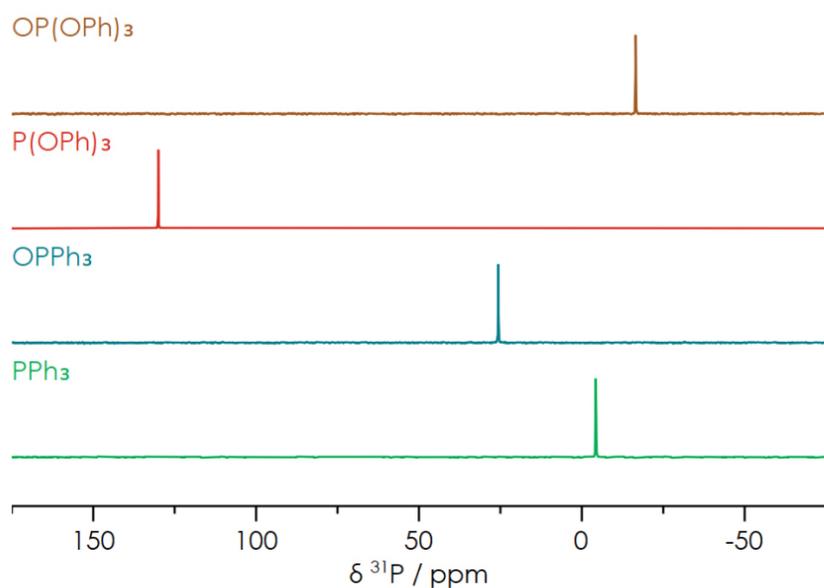
Figure 2a: ^{31}P{^{1}H} NMR spectra of triphenylphosphine, triphenylphosphine oxide, triphenylphosphite, and triphenylphosphate.
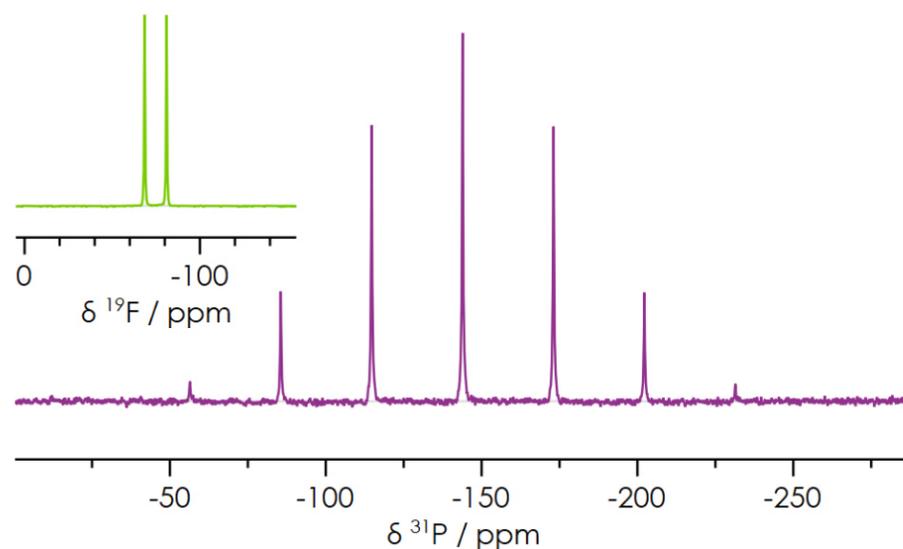
Figure 2b: ^{31}P NMR spectrum of the hexafluorophosphate anion; insert of the corresponding ^{19}F NMR spectrum; $^1J_{PF}$ = 706 Hz.

Boron-11 NMR Spectroscopy

Unlike ^{1}H, ^{13}C and ^{31}P, boron-11 (^{11}B) is a quadrupolar nucleus (which means that it has a nuclear spin greater than 1/2), causing it to have different NMR properties. The ^{11}B spin of 3/2 leads to generally broader signals than spin 1/2 nuclei, which are observed over a range of δ_B −120 to +90 ppm. Boron containing compounds have a range of applications, including as Lewis acid catalysts and in Suzuki cross-coupling reactions (Nobel Prize in Chemistry 2010); hence, they are commonly used as intermediates in the synthesis of fine chemicals and pharmaceuticals.

One complication with ^{11}B NMR spectroscopy is that the glass commonly used to make NMR tubes and indeed components of the NMR spectrometer contains boron, often leading to a background signal in the NMR spectrum. This background signal can be minimised and even eliminated by appropriate hardware and experimental design. As demonstrated in *Figure 3a*, while a background signal (causing a wide, flat hump in the baseline) is present in the spectrum obtained on a high-field instrument, none is visible in the spectrum collected on the X-Pulse.

Since ^{11}B is a quadrupolar nucleus, the linewidths of its NMR signals are strongly dependent on the size of the molecule and symmetry around the boron centre. For example, the four-coordinate tetrahedral tetra(aryl)borane shown in *Figure 3a* has a peak width of 20 Hz; while the three-coordinate trigonalplanar boronic acid derivative shown in *Figure 3b*, has a peak width greater than 200 Hz; and the small tetrahedral tetrafluoroborate anion in *Figure 3c* has peak widths of less than 1 Hz. As a result, simple linewidth measurements of a boron spectrum can be a probe of structure and symmetry.

The spectra of the tetrafluoroborate anion in *Figure 3c* demonstrate an important feature of quadrupolar nuclei in NMR spectroscopy. Basic NMR courses teach the 'n+1 rule' for the number of peaks in a multiplet: if a nucleus has n equivalent nearest neighbours, they will split the signal into a multiplet consisting of n+1 peaks, with the peak intensity predicted using Pascal's triangle. However, this rule is valid only for spin 1/2 nuclei such as ^{1}H, ^{13}C, and ^{19}F. As a result, while the ^{11}B spectrum shows a 1:4:6:4:1 pentet arising from coupling to four equivalent spin 1/2 ^{19}F nuclei, the corresponding ^{19}F spectrum (inset, *Figure 3c*) shows a 1:1:1:1 quartet, due to coupling to a single spin 3/2 ^{11}B nucleus. In contrast, coupling to a single spin 1/2 nucleus would produce a 1:1 doublet (see for [PF$_6$]$^-$, *Figure 2b*, insert).
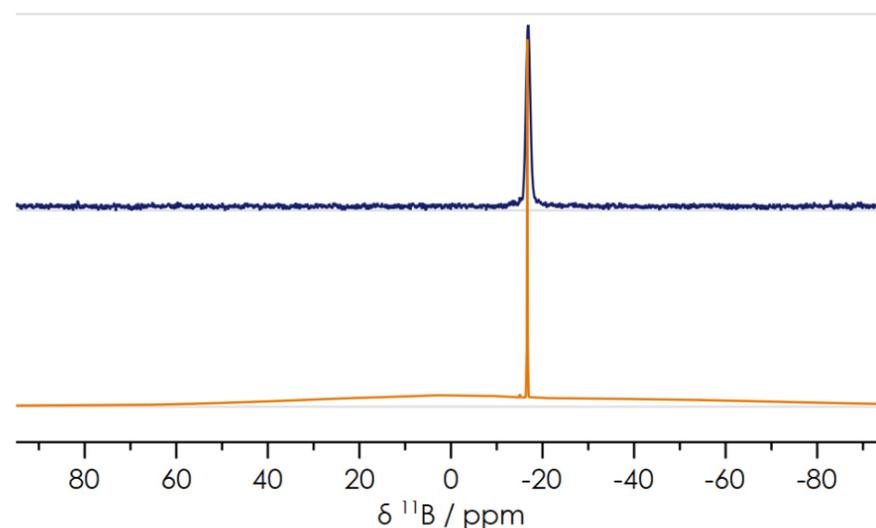
Figure 3a: ^{11}B NMR spectra of a tetra(aryl)borane recorded on X-Pulse (blue, top) and a high-field instrument (orange, bottom); peak widths at half height are 20 Hz.
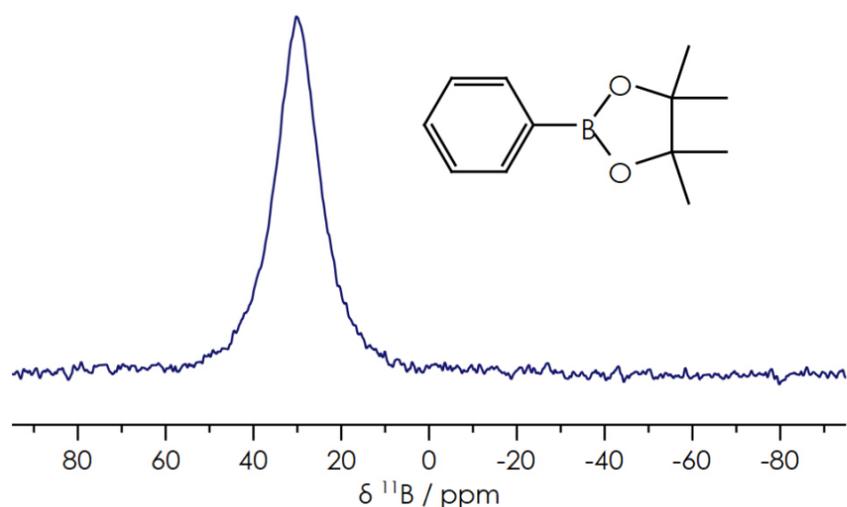
Figure 3b: $^{11}B\{^1H\}$ NMR spectrum of a phenylboronic acid pinacol ester; peak width at half height is > 200 Hz.
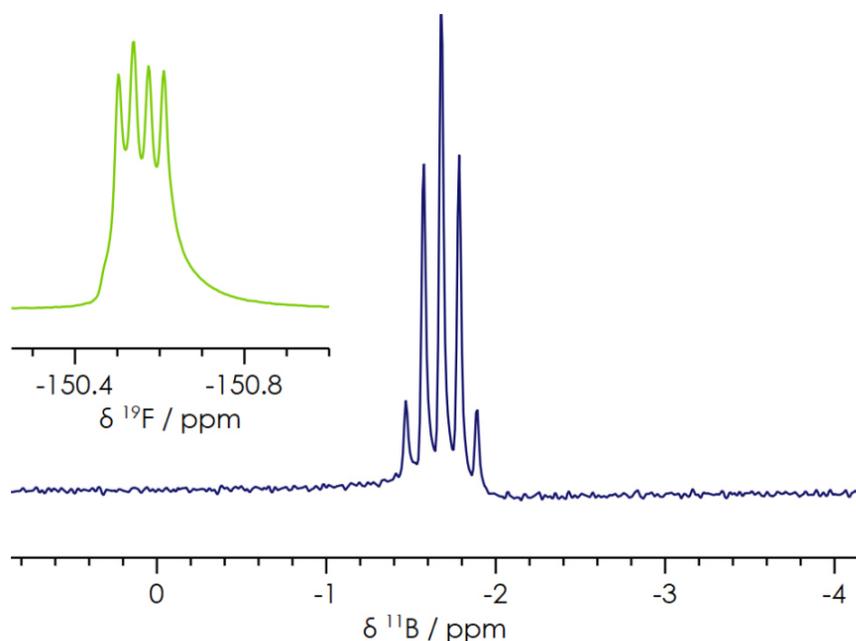
Figure 3c: ^{11}B NMR spectrum of tetrafluoroborate in aqueous solution; the inset shows the corresponding ^{19}F NMR spectrum; peak widths at half height are < 1 Hz; $^1J_{BF}$ = 2 Hz.

Sodium-23 NMR Spectroscopy

Sodium is the sixth most abundant element on earth and is ubiquitous in living organisms. In addition, sodium containing compounds are valuable reagents in organometallic chemistry. Moreover, sodium is a component of an extremely wide range of substances from food and drink to pharmaceuticals, petroleum additives, and polymers, just to name a few.

As with ^{11}B, sodium-23 (^{23}Na) is a quadrupolar nucleus, with a linewidth strongly dependent on the local symmetry and the size of the molecule. ^{23}Na signals can be observed over the range of δ_{Na} +10 to −60 ppm. Sodium cations in aqueous solutions give sharp signals close to 0 ppm (*Figure 4*).

Lithium-7 NMR Spectroscopy

As with sodium, lithium containing compounds are valuable reagents in organometallic chemistry. Unlike sodium, lithium does not have a known biological role, although it is used in pharmaceuticals. One of the rapidly growing applications of lithium is in energy storage systems, and solutions containing Li+ cations, such as those used in batteries, which are amenable for study by NMR spectroscopy.
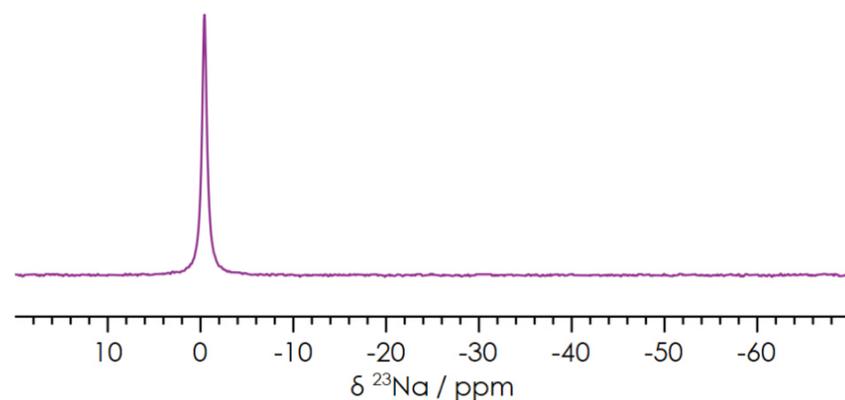
Figure 4: ^{23}Na NMR spectrum of Na+ in aqueous solution; peak width at half height is 9 Hz.

As with ^{11}B and ^{23}Na, lithium-7 (^7Li) is a quadrupolar nucleus with linewidths strongly dependent on molecular symmetry and size. ^7Li signals appear over a range from δ_{Li} +15 to −20 ppm. Like sodium, lithium cations in aqueous solutions give sharp signals near 0 ppm.

Figure 5 shows a series of Pulsed Field Gradient Spin-Echo (PGSE) NMR spectra of the lithium cation in a dialkyl carbonate, as is commonly used in lithium-ion batteries. By obtaining these spectra at varying gradient strengths (between 0 and 0.26 T.m$^{−1}$), the diffusion coefficient of Li+ may be directly measured. The knowledge of diffusion coefficients is valuable for the analysis of electrochemical data, and hence in the development of batteries and super-capacitors.
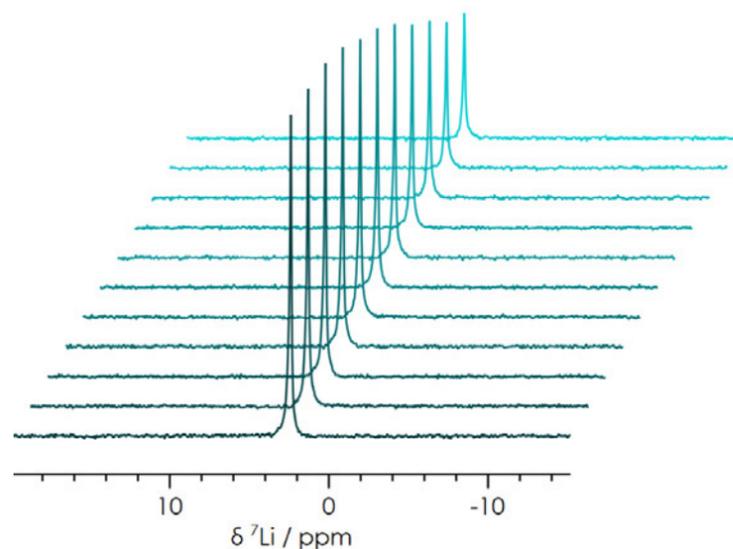
Figure 5: series of ^7Li PGSE NMR spectra of Li+ in a dialkyl carbonate for measuring diffusion coefficients in battery electrolytes.

Silicon-29 NMR Spectroscopy

Silicon is another extremely abundant element with many industrial uses, including being a major component of computers and electronics, and as a major constituent of glass. While some of silicon's most familiar applications are in a solid form, silicon-29 (^{29}Si) benchtop NMR spectroscopy is useful for other applications, such as the analysis of polysiloxanes (silicones) and their monomer precursors, which have a range of applications including as adhesives, lubricants, and sealants, along with uses in medicine and in the home.

Like ^{13}C, ^{29}Si has a low receptivity due to both its low natural abundance and gyromagnetic ratio. Spectra are usually obtained using inverse-gated proton decoupling, giving rise to sharp signals while minimising reduction of the ^{29}Si signal that can occur from other decoupling methods. Signals appear over the very wide range from δ_{Si} −350 to +175 ppm. Some of the methods for sensitivity enhancement used in ^{13}C NMR are also applicable to ^{29}Si NMR. Examples include the use of spin-lock polarisation (*Figure 6a*), and two-dimensional HMBC (*Figure 6b*) pulse sequences, where the higher receptivity protons, rather than the X-nuclei, are excited.

Figure 6a shows two signals, one for each of the two silicon environments, while the HMBC two dimensional correlation spectrum in Figure 6b shows cross-peaks at ^{29}Si and ^{1}H frequencies that clearly correlate those silicon signals with the hydrogens on the attached methyl groups. This HMBC spectrum was optimised for two-bond couplings (Si–C–H), so the Si–H bonds do not appear on the spectrum.
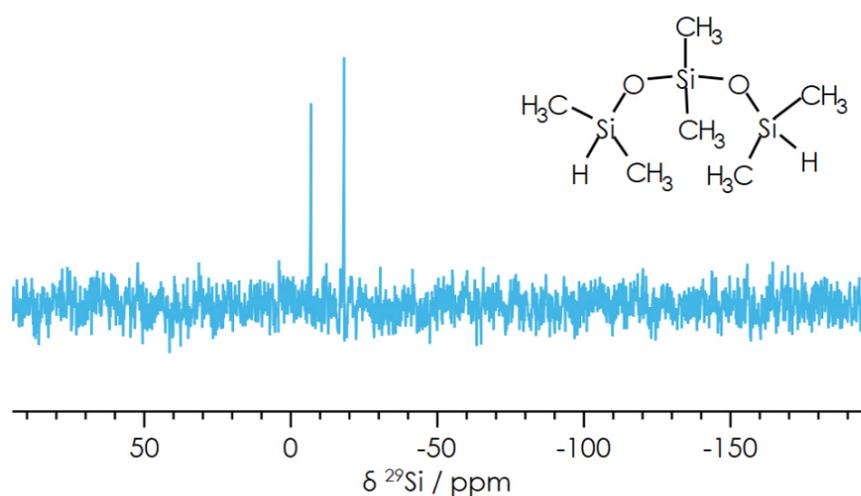
Figure 6a: ^{29}Si-^{1}H Spin-Lock Polarised NMR spectrum of 1,1,3,3,5,5-hexamethyltrisiloxane.
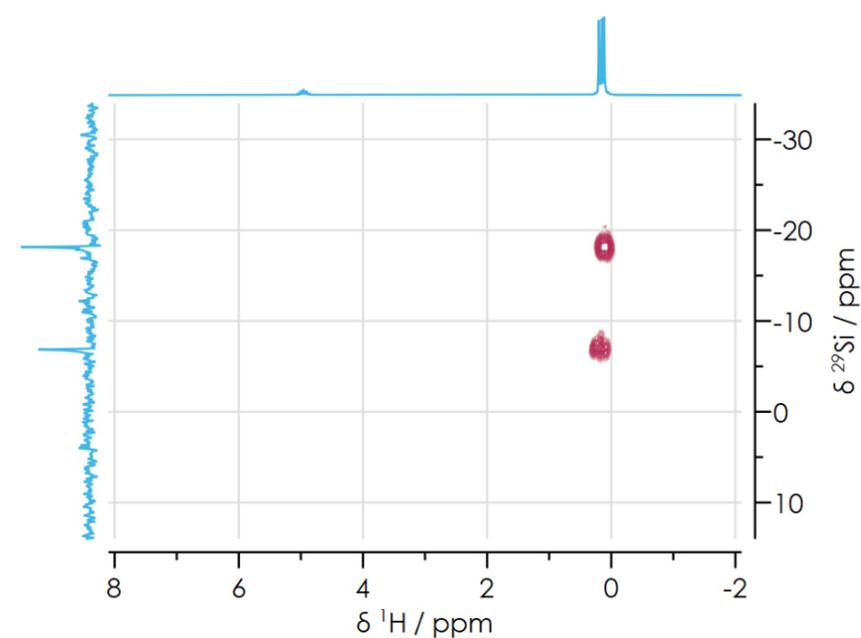
Figure 6b: ^{1}H-^{29}Si HMBC NMR spectrum of 1,1,3,3,5,5-hexamethyltrisiloxane.

Cobalt-59 NMR Spectroscopy

Cobalt-59 (^{59}Co) played an important role in the development of NMR spectroscopy, as the first nucleus for which the variation in chemical shift for different compounds was observed. Since many cobalt compounds are paramagnetic, ^{59}Co NMR spectroscopy is generally limited to lowspin cobalt(I) and cobalt(III) complexes, which are observed over the largest chemical shift range of any nucleus, δ_{Co} –4,000 to +14,000 ppm, making ^{59}Co an interesting nucleus for educational purposes. ^{59}Co NMR spectroscopy also has applications for research and development in organometallic and coordination chemistry, along with studies of cobalt containing metalloenzymes. In this example (Figure 7), chemical shifts of the cobalt(III) complexes [Co(CN)$_6$]$^{3-}$ and [Co(en)$_3$]$^{3+}$ (en = ethylenediamine) are observed to be separated by 7093 ppm.
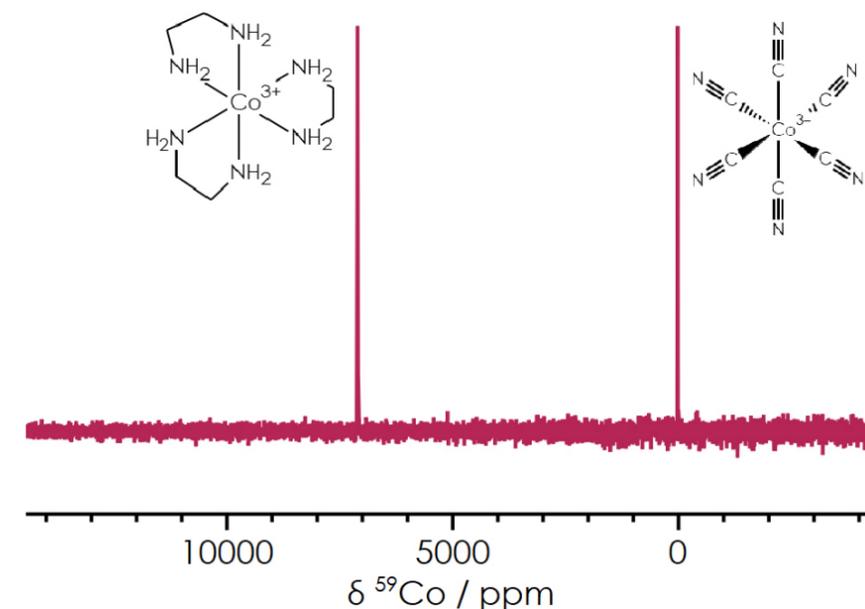
Figure 7: ^{59}Co NMR Spectra of [Co(en)$_3$]$^{3+}$ and [Co(CN)$_6$]$^{3-}$ in aqueous solution.

Summary

This article demonstrates some highlights of the X-nuclei NMR spectra which can be readily obtained using a single X-Pulse broadband benchtop NMR spectrometer, together with some of their potential applications.

Switching between nuclei on the X-Pulse probe is rapid and convenient, requiring only the selection of the new nucleus in the software and optimising the probe for the new frequency. The entire process usually takes less than two minutes to switch between different X-nuclei.

Standard one-dimensional spectra are shown, along with examples of two-dimensional correlation spectroscopy and diffusion measurements using the standard included X-Pulse gradients. The X-Pulse broadband NMR spectrometer opens the door to many new applications involving the analysis of multiple nuclei for education, research, and quality control on a single benchtop instrument. More applications notes and case studies can be downloaded at https://nmr.oxinst.com.

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Mass Spectrometry Structural Analysis of Fluoroelastomers

BioChromato Inc has published a report describing how their ionRocket sample preparation device, used in combination with Direct Analysis in Real Time Mass Spectrometry (DART-MS) and Kendrick Mass Defect (KMD) analysis, provides a valuable new tool for chain analysis of fluoroelastomers.

Due to their excellent heat, chemical and abrasion resistance, fluoropolymers are widely used in automotive parts and many other industrial products. Since copolymerization and chain end modification are used to achieve high polymer functionality, structural analysis is important for product development and to understand how a fluoropolymer might degrade.

However, using traditional techniques such as Pyrolysis GC/MS only information on the constituent monomers can be obtained. Similarly, it has been found to be very difficult to obtain MALDI-MS spectra from fluoropolymers. Fluoropolymers are one class of materials that, to date, have proven difficult to structurally analyse.

The ionRocket is a temperature-heating device for direct thermal desorption and pyrolysis of samples, prior to ionisation and analysis by mass spectrometry. Using ionRocket a temperature gradient from ambient up to 600ºC can be achieved in just a few minutes. This enables fluoropolymers to be pyrolysed and then introduced into the DART-MS gas stream.

The report shows how the ion-Rocket DART-MS technique can be used to detect the pyrolysis products of fluoroelastomers from low to high molecular weight. This unique capability allows the technique to be applied to the chain analysis of fluoroelastomers. In addition, by using KMD analysis, the detected pyrolysis components can be understood relatively easily.

Read the application report in full: ilmt.co/PL/ZG2v

More information online: ilmt.co/PL/Q62J

For More Info, email: **55755pr@reply-direct.com**