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^{11}B Benchtop NMR Spectroscopy No Longer BORing

A Multidimensional Approach for ^{1}H-^{11}B Correlation NMR Spectroscopy

Boron is increasingly recognized for its medicinal applications [1]. Over the past two decades, significant advancements in boron organic chemistry have led to a profound impact on drug design and development [1]. These advancements have facilitated the incorporation of boron-containing functional groups into pharmaceuticals, enhancing their accessibility and practicality. Notably, several FDA-approved boron-containing compounds have been developed, including bortezomib (Velcade), tavaborole (Kerydin), ixazomib (Ninlaro), crisaborole (Eucrisa), and vaborbactam (in combination with meropenem in Vabomere) [1]. Therefore, distinguishing between various boron chemical environments is becoming critical to the development of pharmaceuticals against emerging diseases.

There are two Boron NMR active isotopes, ^{11}B (80.1% natural abundance) has a spin of 3/2 and ^{10}B (19.9 % natural abundance) has a spin of 3. ^{11}B isotope offers higher sensitivity in NMR experiments owing to its higher natural abundance, a higher gyromagnetic ratio, and a lower quadrupole moment. Currently, most benchtop ^{11}B NMR applications are restricted to only 1D NMR spectroscopy. This poses a significant limitation on the breadth of applications and structures that benchtop NMR can discern. In this application note we present HSQC and HMBC multi-dimensional ^{11}B NMR experiments performed on a 90 MHz Spinsolve Ultra Benchtop NMR spectrometer. The results illustrate the Spinsolve's capability to investigate boron containing compounds and their potential in boron chemistry applications.

NMR Results & Discussion

NMR techniques involving **H**eteronuclear **S**ingle **Q**uantum **C**oherence (HSQC) are often applied to ^{1}H-^{13}C or ^{1}H-^{15}N spin pairs. Yet, HSQC applications outside of these spin pairs remain rare. For some ^{11}B-containing compounds, a 1D ^{11}B NMR experiment may be sufficient to discern the chemical environment around the boron center [2,3]. However, a boron cluster with overlapping boron signals may necessitate a multidimensional approach to assist in spectral assignment [2,3]. One such example is carboranes, an electron-delocalized (non-classically bonded) cluster composed of boron, carbon and hydrogen atoms [2,3]. Carboranes and their derivatives are often used in the field of antitumor research and include: boron neutron capture therapy (BNCT), BNCT/photodynamic therapy dual sensitizers, and anticancer ligands [2]. The structure of an *ortho*-carborane and its 1D ^{11}B and ^{1}H NMR spectra are shown in Figure 1.

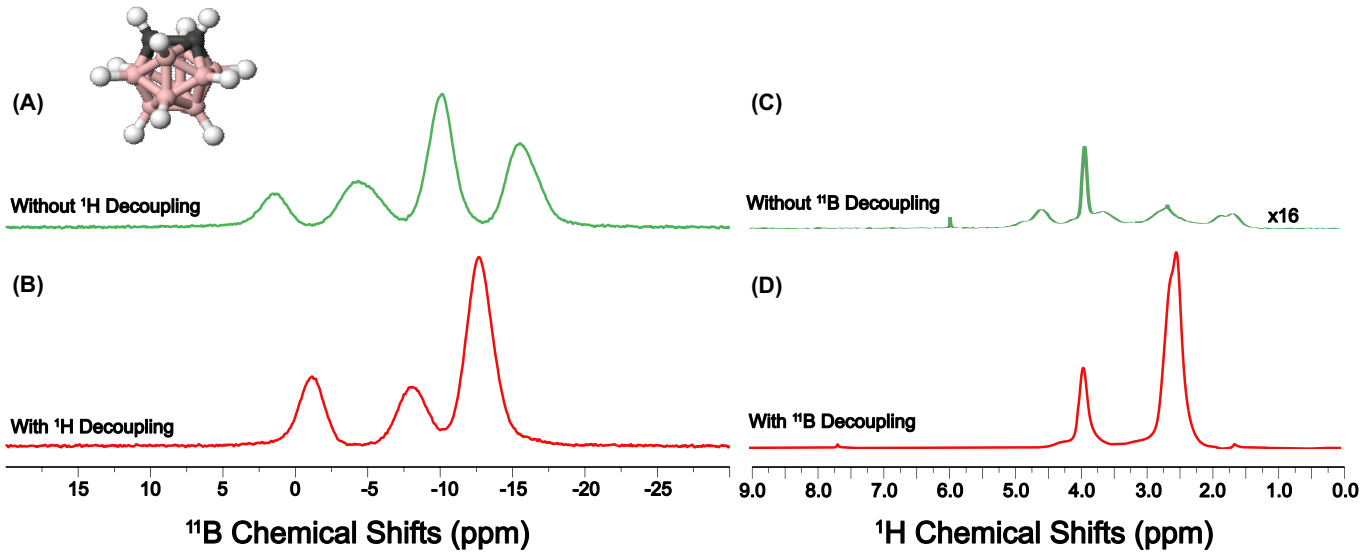

Figure 1. ^{11}B NMR spectrum (A) without ^{1}H decoupling and (B) with ^{1}H decoupling. ^{1}H NMR spectrum (C) without ^{11}B decoupling and (D) with ^{11}B decoupling.

Without ^{1}H decoupling, the 1D ^{11}B NMR spectrum shows overlapping multiplets. Similarly, for 1D ^{1}H NMR spectrum in the absence of ^{11}B decoupling, overlapping multiplet patterns are observed. Based on high-field NMR data, four ^{11}B signals and four ^{1}H NMR signals are expected when acquired under ^{1}H and ^{11}B decoupling [2,3]. However, due to the narrow chemical shifts dispersion of a benchtop NMR system, only three^{11}B signals and two ^{1}H NMR signals were observed in Figures 1B and 1C. Therefore, this illustrates a situation where a multidimensional NMR approach will prove beneficial to resolve spectral overlap. To resolve the overlap in both ^{1}H and ^{11}B 1D NMR spectra, a ^{1}H-^{11}B HSQC NMR technique is implemented and the resulting ^{1}H-^{11}B correlation NMR spectrum is shown in Figure 2. From the 2D HSQC ^{1}H-^{11}B correlation NMR spectrum, four ^{11}B NMR signals were observed and their proposed assignments are labeled on the *ortho*-carborane structure [2,3]. Since the *ortho*-carborane molecular structure contains four unique boron sites and four distinct ^{11}B peaks are indeed observed, this data illustrates the successful implementation of multidimensional ^{11}B NMR spectroscopy at the benchtop NMR frequency [2,3].

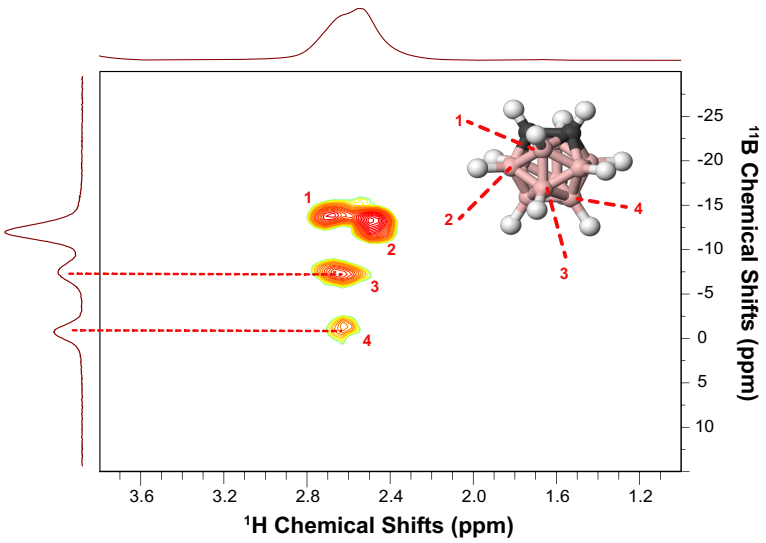

Figure 2. A 2D ^{1}H-^{11}B HSQC NMR spectrum of *ortho*-carborane was acquired in 17 minutes using 8 scans, 64 increments and a 1-second repetition delay. Echo/Anti-Echo was used for frequency discrimination in the indirect dimension.

Despite the power of the HSQC to discriminate between ^{1}H-^{11}B spin pairs, the HSQC experiment struggles to identify ^{11}B sites without a directly bonded ^{1}H. This is often the case for borate ester and other organoboron compounds. Therefore, ^{11}B sites without a directly bonded ^{1}H may require correlations that are derived from several bonds away. Hence, ^{1}H-^{11}B **H**eteronuclear **M**ultiple **B**onds **C**oherence (HMBC) will be beneficial in these situations [4]. Tetraphenyl borate (TPB) is used to illustrate the application of ^{1}H-^{11}B HMBC. The structure of TPB is shown in Figure 3. TPB offers an ideal case to illustrate the^{1}H-^{11}B HMBC sequence since the nearest ^{1}H are four bonds aways from the ^{11}B center. Also, the symmetry offered by the four identical ligands around the Boron center significantly reduces its quadrupole couplings, allowing for multidimensional NMR to be performed.

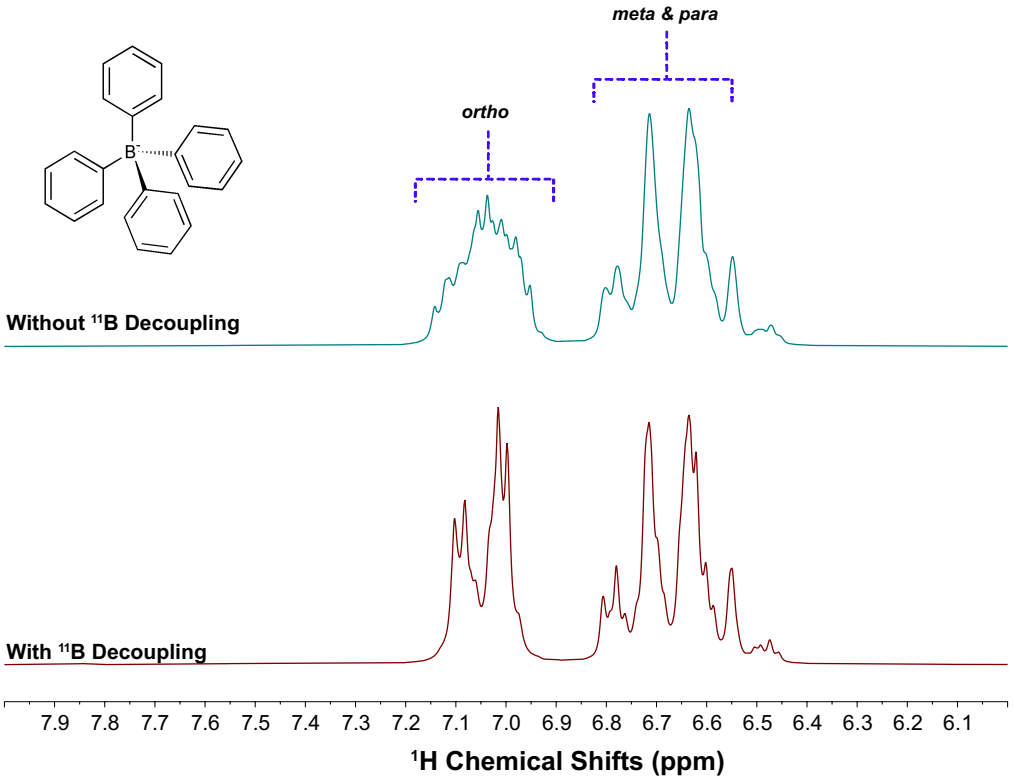

Figure 3. ^{1}H NMR spectra acquired using a Spinsolve 90 MHz with and without ^{11}B decoupling.

As a first step to analyze TBP, a 1D ^{1}H experiment was recorded with and without ^{11}B decoupling (see Fig. 3). The ^{11}B decoupling enhances the resolution of the ^{1}H NMR spectrum and the degree of enhancement is proportional to proximity of the protons to the ^{11}B metal center. For example, the proton on the *ortho* position is hugely sensitive to the degree of ^{11}B coupling compared to that of the *meta* and *para* position. To optimize the ^{1}H-^{11}B magnetization transfer for a 2D HMBC experiment, a series of HMBC experiments was acquired using different long range ^{1}H-^{11}B transfer times and the 1D traces extracted from the HMBC are illustrated in Figure 4. This series of spectra shows the modulation pattern as a function of the ^{1}H-^{11}B transfer time. Based on this series of spectra, an optimized transfer time (determine by the ^{1}H-^{11}B J coupling) is found and used to acquire the 2D ^{1}H-^{11}B HMBC NMR spectrum shown in Figure 5. This spectrum successfully provides long range correlations between ^{11}B and ^{1}H that are several bonds away, providing a potential avenue for spectral assignments for organoboron compounds without a directly bonded ^{1}H-^{11}B spin pairs.

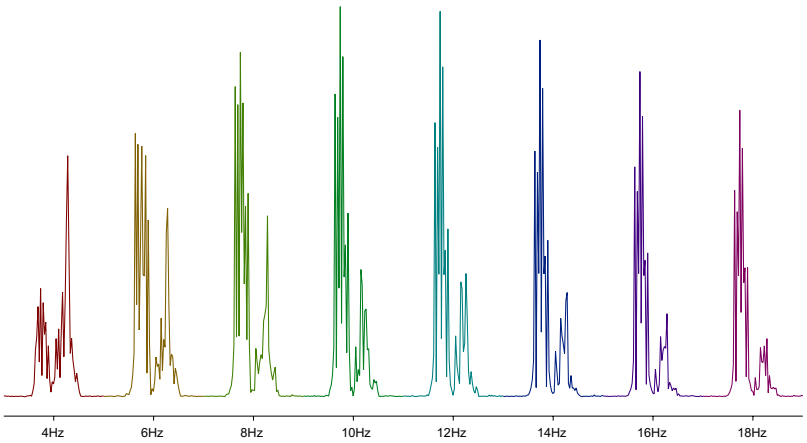

Figure 4. ^{1}H trace projections extracted from a series of ^{1}H-^{11}B HMBC NMR spectra acquired for different transfer times corresponding to the long range $^{n}J_{BH}$-coupling listed under the trace. The different transfer times lead to different modulation patterns that depnd on the J coupling constant of the different groups. The optimized J-coupling was determined based on maximizing the ^{1}H signal intensity of *ortho*, *meta* and para positions on the phenyl rings.

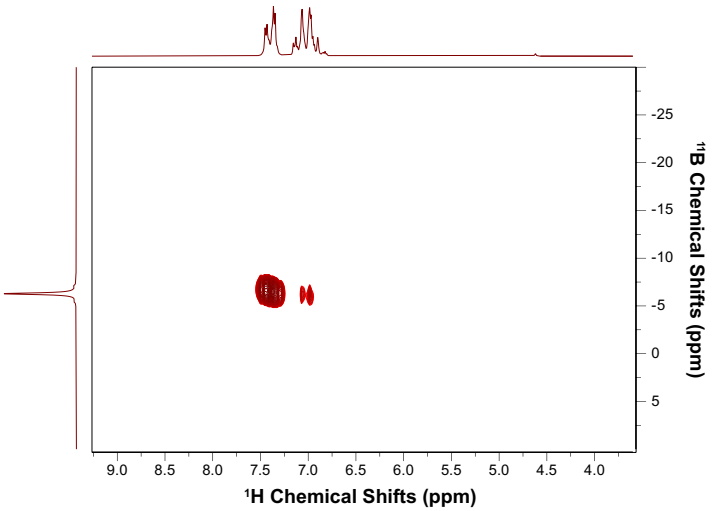

Figure 5. A 2D ^{1}H-^{11}B HMBC NMR spectrum was acquired using a long-range $^{n}J_{BH}$-coupling of 12 Hz. The spectrum was acquired in 5 minutes using 4 scans, 64 increments and a 1-second repetition delay.

Conclusion

This application note highlights the capability of Spinsolve spectrometers to conduct multidimensional ^{1}H-^{11}B NMR experiments. These 2D ^{1}H-^{11}B experiments, HSQC and HMBC, yielded more information than 1D experiments alone. However, these 2D experiments require a symmetric arrangement of ligands around the ^{11}B center to reduce the quadrupolar coupling. Therefore, not all ^{11}B compounds will benefit from these 2D experimental approaches. Nevertheless, with excellent sensitivity and the ability to automatically switch between heteronuclei for routine 2D experiments, the Spinsolve NMR instrument is equipped to deliver high-quality assignments, structural verification, and analysis of boron-containing compounds.

References

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