

Spinsolve

Long-Range ^1H - ^{31}P HSQC for selecting one bond and multiple bond correlations

Since its introduction in the 1980s, heteronuclear two-dimensional (2D) correlation NMR spectroscopy has become an indispensable tool for organic chemists, serving as a cornerstone technique for the structural elucidation of a wide range of compounds [1]. Most 2D heteronuclear correlation experiments are based on ^1H - ^{13}C spin pairs [1-2]; however, ^1H - ^{31}P spin pairs can offer equally valuable structural information [2-4]. ^{31}P is an NMR-active nucleus with 100% natural abundance and is present in many classes of organic compounds, ranging from ligands in organometallic catalysts to the backbone of oligonucleotides therapeutics [2-4]. Given the broad prevalence of ^{31}P -containing compounds, it is therefore essential to employ 2D heteronuclear correlation experiments that directly probe ^1H - ^{31}P spin pairs to achieve reliable structural determination and confirmation [2-4].

In contrast to ^1H - ^{13}C spin pairs, the scalar couplings between directly bonded ^1H - ^{31}P nuclei can be exceptionally large, reaching values of up to 600 Hz [3]. Such large $^1J_{\text{HP}}$ couplings pose practical challenges for heteronuclear correlation experiments that rely on INEPT-based magnetization transfer. For example, a $^1J_{\text{HP}}$ coupling of 600 Hz corresponds to an optimal INEPT delay of approximately 400 μs , which can be too short when a pulsed field gradient (PFG) is employed for coherence pathway selection since this limits the length and the strength of the gradient that can be applied. However, longer delays corresponding to multiples of $^1J_{\text{HP}}$, can in principle be used; yet this approach generally results in reduced sensitivity due to relaxation losses [2-4]. Moreover, at extended delay times, longer-range couplings—such as $^2J_{\text{HP}}$, $^3J_{\text{HP}}$, and even $^4J_{\text{HP}}$ —may contribute to the observed correlations. Consequently, careful optimization of the INEPT delay is essential to selectively observe specific ^1H - ^{31}P correlations while minimizing undesired long-range coupling artifacts [2-5].

To illustrate the application of Long-Range (LR) Heteronuclear Single Quantum Coherence (HSQC) for the detection of both directly bonded and long-range coupled ^1H - ^{31}P spin pairs, a sample of 250 mM of tricyclohexylphosphine tetrafluoroborate in protonated DMSO (Figure 1) is used as a proof of concept. This compound exhibits a range of scalar couplings spanning from one-bond to four-bond interactions, making it an ideal system for demonstrating the utility and selectivity of the approach.

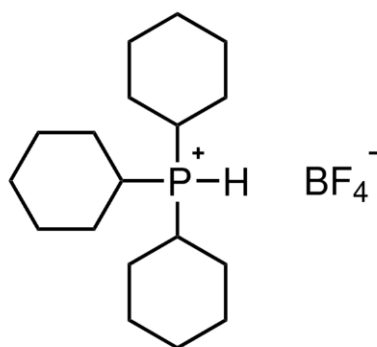


Figure 1. Molecular structure of tricyclohexylphosphine tetrafluoroborate.

NMR Results & Discussion

Two 1D ^{31}P NMR spectra were acquired with and without ^1H decoupling (Figure 2). In the absence of ^1H decoupling, a broad doublet was observed with a one-bond ^1H - ^{31}P coupling constant ($^1J_{\text{HP}}$) of approximately 400 Hz.

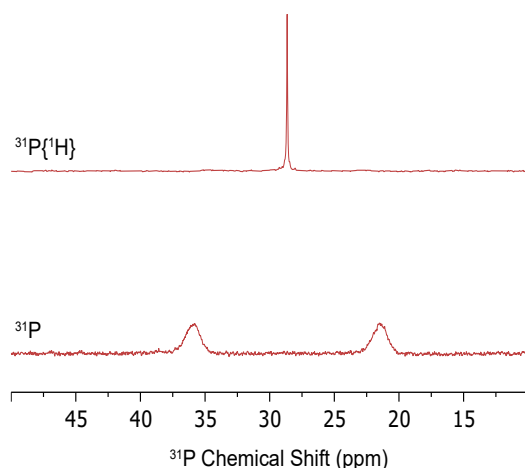


Figure 2. 1D ^{31}P NMR spectra of tricyclohexylphosphine tetrafluoroborate (Top) with ^1H decoupling and (Bottom) without ^1H decoupling.

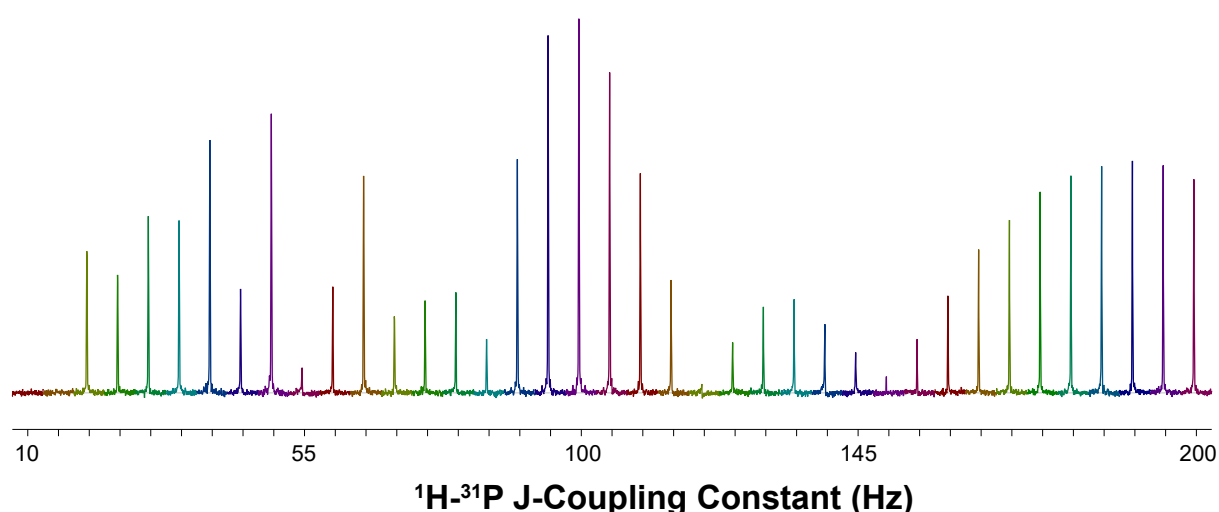


Figure 3. A series of 1D ^{31}P refocused INEPT NMR spectra acquired with delays corresponding to different ^1H - ^{31}P J -coupling constants.

To optimize the J_{HP} coupling values for the LR-HSQC experiment, a series of 1D $^{31}\text{P}\{^1\text{H}\}$ refocused INEPT spectra, shown in Figure 3, were recorded using different INEPT delays corresponding to increasing ^1H - ^{31}P J -coupling constants. The signal intensity oscillated as a function of the selected ^1H - ^{31}P J -coupling values. Maximum signal intensity was achieved when the ^1H - ^{31}P J -coupling constant was set to approximately 100 Hz. This optimized coupling constant reflects not only directly bonded ^1H - ^{31}P spin pairs but also contributions from longer-range ^1H - ^{31}P couplings. Using this value, a ^1H - ^{31}P LR-HSQC spectrum was collected (Figure 4A). For comparison, a second ^1H - ^{31}P LR-HSQC spectrum was acquired using a $1/4J$ ($^nJ_{\text{HP}} = 30\text{Hz}$) INEPT delay period of 8.3 ms, which is representative of multiple-bond correlations.

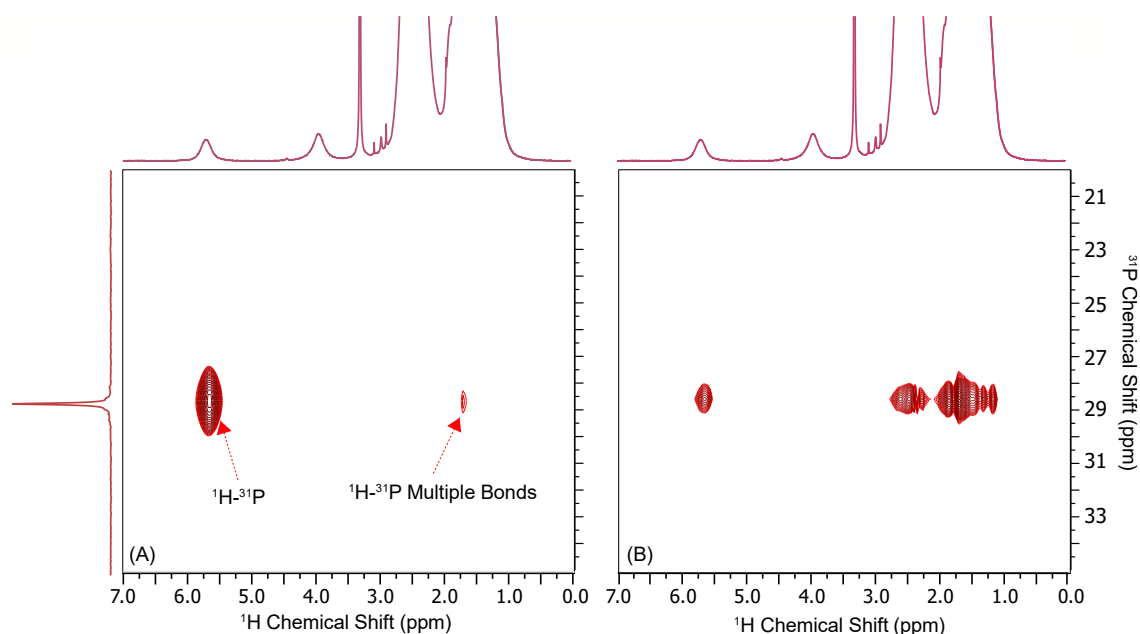


Figure 4. ^1H - ^{31}P HSQC NMR spectra of tricyclohexylphosphine tetrafluoroborate in protonated DMSO acquired using a ^1H - ^{31}P J -coupling constant of 100 Hz (A) and 30 Hz (B). Frequency Discrimination in the indirect dimension was achieved using an Echo/Anti-echo protocol. Both spectra were acquired using 4 scans and 128 complex points with a 1s repetition delay. The horizontal trace is a 1D $^1\text{H}\{^{31}\text{P}\}$ NMR spectrum showing the ^1H chemical shifts of the directly bonding ^1H - ^{31}P spin pair.

Comparing the two spectra, the resonance from the one bond ^1H - ^{31}P correlations and multiple bond ^1H - ^{31}P correlations can be distinguished based on signal intensity: the signal from the one bond correlation is higher compared to that of multiple-bond correlations for larger ^1H - ^{31}P coupling values.

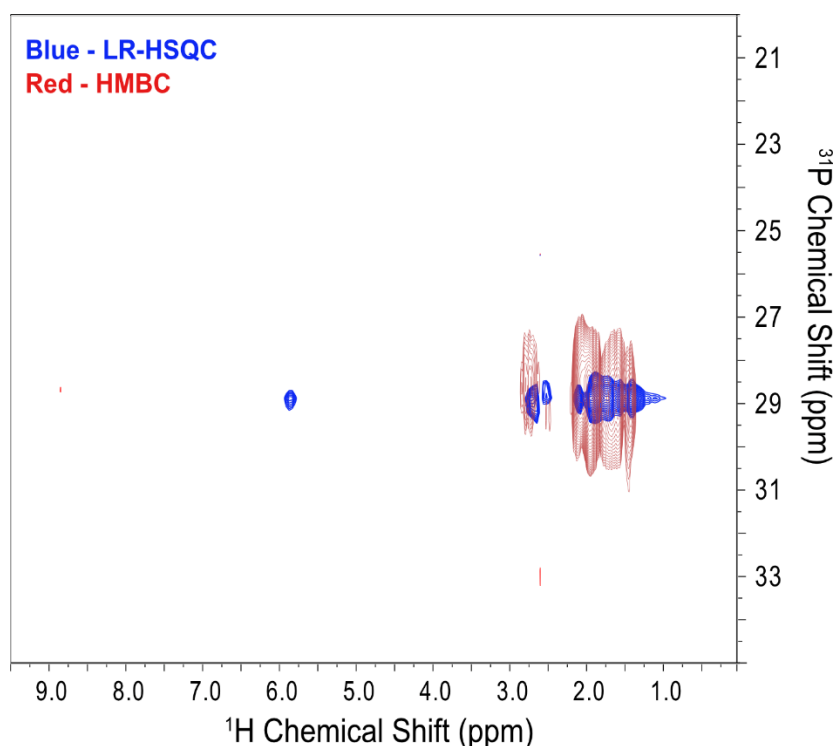


Figure 5. An overlay of ^1H - ^{31}P LR-HSQC (blue) and ^1H - ^{31}P HMBC (red) of 250 mM of tricyclohexylphosphine tetrafluoroborate in protonated DMSO using a 30 Hz ^1H - ^{31}P J -coupling constant. Frequency discrimination in the indirect dimension for LR-HSQC was achieved using Echo/Anti-echo protocol. Both spectra were acquired in 8 minutes.

Furthermore, when compared to a standard ^1H - ^{31}P HMBC (Figure 5), the LR-HSQC offers significantly improved spectral resolution with identical experimental time and increments. In addition, LR-HSQC can resolve a one bond ^1H - ^{31}P correlation without doubling the number of resonances in the ^1H dimension compared to that of HMBC when the ^1H dimension was acquired without ^{31}P decoupling. Therefore, this approach allows for the unequivocal assignment of ^1H chemical shifts for directly bonded ^1H - ^{31}P spin pairs, offering additional structural information for ^{31}P containing compounds.

Conclusion

^1H - ^{31}P LR-HSQC provides enhanced spectral resolution for the detection of both one-bond and multiple-bond correlations, making it a valuable complement to the standard ^1H - ^{31}P HMBC experiments when increased resolution is required for reliable spectral assignment. Given the structural diversity of ^{31}P -containing compounds, ^1H - ^{31}P LR-HSQC represents a powerful tool for structure determination and compound identification [2-6]. The data presented in this application note further highlights the capability of the Spinsolve spectrometers. Together with automated heteronuclear switching that enables the sequential acquisition of ^1H - ^{13}C and ^1H - ^{31}P 2D experiments, the Spinsolve constitutes a flexible and high-performance NMR solution for accurate spectral assignment, structural confirmation, and detailed molecular characterization.

References

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