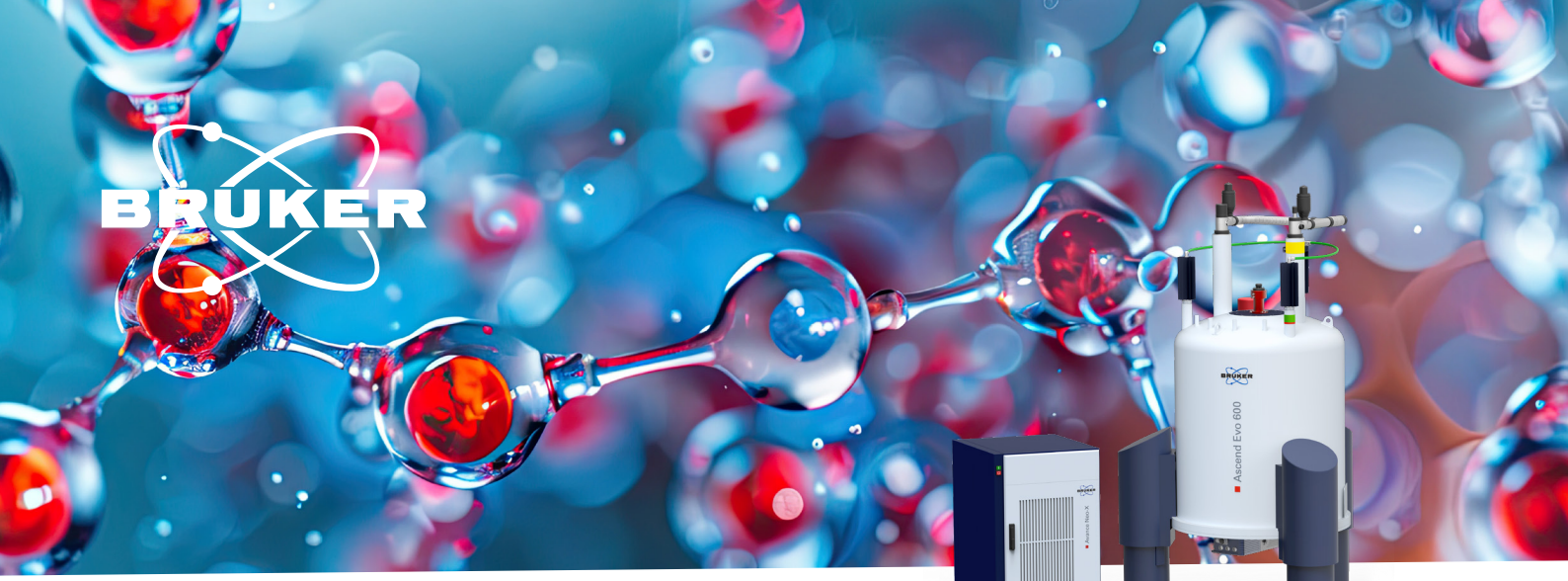


NMR

Direct NMR Analysis in Protonated Solvents: Making No-D NMR Routine Practice

Automated Lock-Free NMR Workflows Without Deuterated Solvents

Innovation with Integrity

No-D NMR and Its Importance

No-Deuterium NMR (No-D NMR) enables the direct acquisition of high-resolution ^{1}H Nuclear Magnetic Resonance (NMR) spectra in protonated solvents without requiring deuterated solvents or sample exchange. This approach allows samples to be analyzed closer to their native chemical state, helping to preserve exchangeable protons while minimizing sample handling. It also reduces solvent costs and simplifies workflows for reaction mixtures, reagent solutions, crude products, neat solvents, and sensitive materials. Recent studies have demonstrated the value of No-D NMR in a wide range of applications, including reaction monitoring, reagent analysis, organometallic titration, solvent quality assessment, water detection, peroxide and additive identification, quantitative assays, and high-throughput measurements.[1,3] Together, these capabilities establish No-D NMR as a practical and versatile approach for modern NMR spectroscopy.

Key Benefits

- **Direct analysis in protonated solvents:** No deuterated solvents or solvent exchange required
- **Faster and more cost-efficient workflows:** Reduced sample preparation time, lower solvent costs, and improved reproducibility
- **Native-state measurements:** Preserve exchangeable OH and NH signals and enable analysis of samples closer to their original chemical environment

Bruker's Advantage

- Lock-free No-D NMR workflow for direct acquisition in protonated solvents
- Automated solvent suppression and adaptive spectral referencing for robust data quality without a deuterium lock
- Fully integrated in TopSpin and IconNMR for routine, high-throughput operation

Application 1 of No-D NMR: Multi-Solvent Suppression in Wine

Wine is a complex protonated matrix containing sugars, organic acids, alcohols, esters, phenolic compounds, and numerous low-abundance metabolites. However, in conventional ^{1}H NMR spectra, the intense signals of water and ethanol dominate the spectrum and can mask signals from minor components (Figure 1a). As a result, signals from valuable low-abundance metabolites can be difficult to detect and analyze.

No-D NMR enables the direct analysis of wine in its native protonated environment without solvent exchange. When combined with multi-solvent suppression, the dominant water and ethanol signals are selectively attenuated, reducing spectral congestion and improving the visibility of minor components. The addition of ^{13}C decoupling further enhances spectral quality by eliminating ^{13}C satellite peaks, resulting in improved spectral resolution, signal-to-noise ratio, and overall spectral clarity (Figure 1b). These advantages are particularly valuable in crowded spectral regions, where satellite resonances can overlap with low-intensity signals and complicate data interpretation.

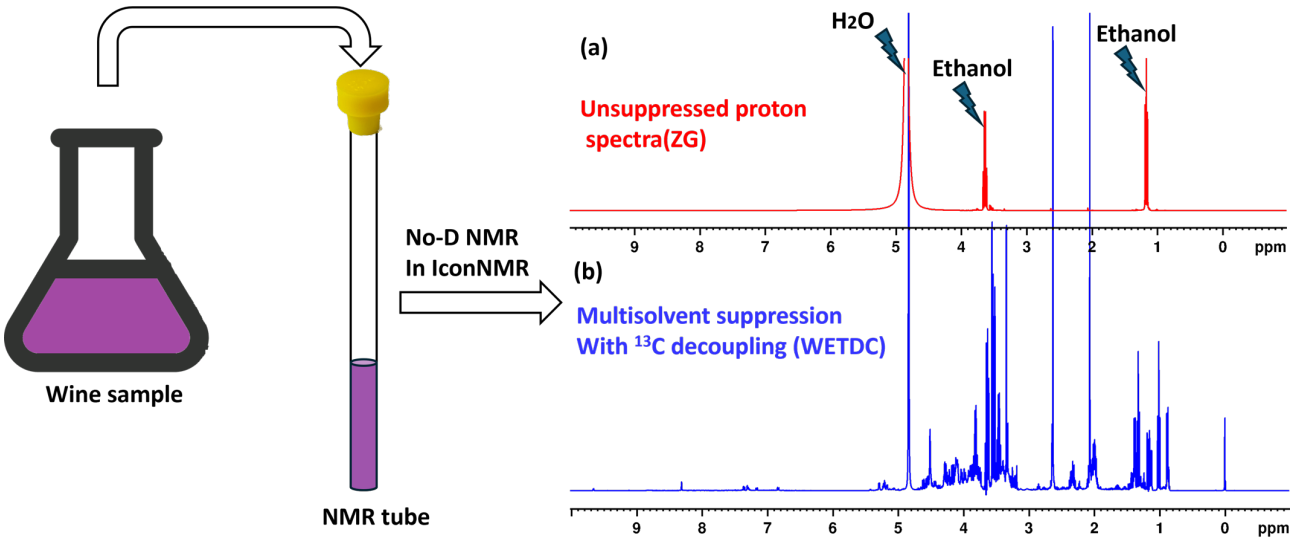


Figure 1: Comparison of conventional ^{1}H NMR and No-D NMR spectra of a wine sample. **(a)** Standard ^{1}H acquisition dominated by intense water and ethanol signals. **(b)** No-D NMR spectrum acquired with multi-solvent suppression and ^{13}C decoupling, reducing solvent and satellite signal interference while improving spectral clarity, resolution, and signal-to-noise ratio.

The combination of multi-solvent suppression and ^{13}C decoupling significantly improves spectral quality by reducing both solvent and satellite signal interference (see application note: "^{13}C Satellites in Proton NMR Spectroscopy").[4] As a result, No-D NMR reveals molecular information that would otherwise be difficult to observe in conventional ^{1}H NMR experiments, enabling more comprehensive characterization of complex wine samples.

Application 2 of No-D NMR: Observation of Exchangeable Protons

No-D NMR enables direct observation of exchangeable OH and NH proton resonances in protonated solvents. Unlike conventional deuterated-solvent workflows, in which proton-deuterium exchange can broaden or suppress these signals, No-D NMR preserves these signals and the valuable structural information they provide regarding hydrogen bonding, molecular environments, and dynamic processes. As shown in Figure 2, the exchangeable proton signals (NH) remain clearly observable, providing additional insight into molecular structure and interactions.

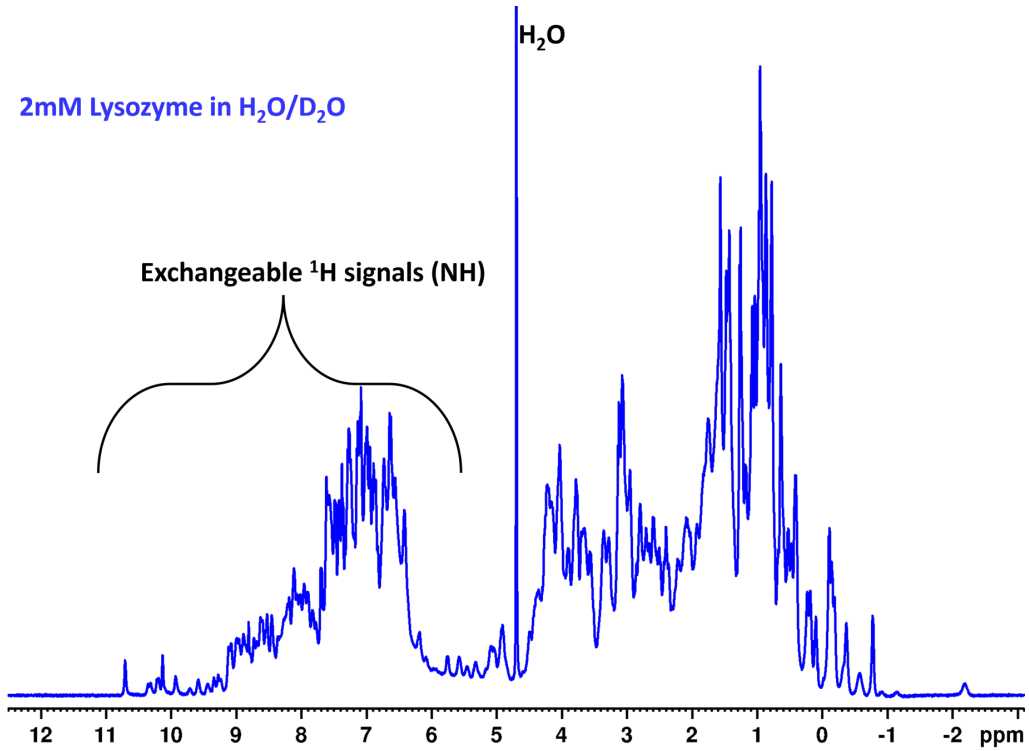
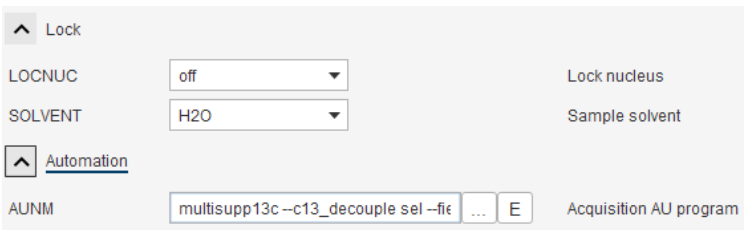


Figure 2: Preservation of exchangeable NH proton signals in a 2 mM lysozyme sample measured in H_2O/D_2O (90:10). No-D NMR enables the direct observation of NH resonances that are often weakened or lost in conventional deuterated-solvent experiments.

No-D NMR Experiment Setup in TopSpin

1. Lock-Free No-D NMR Setup with Multi-Solvent Suppression and ^{13}C Decoupling

Load the parameter set using **rpar MULTISUPPDC all** and then execute **getprosol**. As shown in the graphic below, navigate to the acquisition parameters, set **LOCNUC** to **off**, and define the appropriate protonated solvent in the **SOLVENT** field (for example, H_2O). Alternatively, enter **locnuc off** and **solvent H2O** in the TopSpin command line. Finally, execute **atma** before starting the acquisition.



The presaturation mode can be configured in the **AUNM** field. You can choose between automatic peak detection and suppression, or manual configuration.

In automatic mode, all peaks above a defined intensity threshold are automatically selected and suppressed. To use this mode, enter the following in the **AUNM** field:

multisupp13c --c13_decouple sel --field_presat 50 --threshold_pp 0.1

In manual mode, you can target specific peak frequencies by defining them in a peak list. To use this mode, enter the following in the **AUNM** field:

multisupp13c --c13_decouple sel --field_presat 50 --use_fqlist

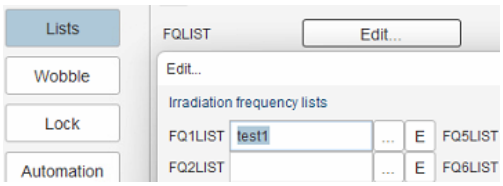
The AU program supports the following options, which may be specified in any order:

--threshold_pp 0.1 intensity threshold for peaks to be suppressed (for example 0.1)

--use_fqlist if the frequency lists in **FQ1LIST** for ^{1}H and **FQ2LIST** for ^{13}C are not empty, it uses these frequencies

for presaturation and skips the preparation experiment for automated detection of solvent peaks.

The **FQ1LIST** can be accessed through: **ACQUPARS** → **Lists** → **FQLIST** → **Edit** → **FQ1LIST**



Below is an example of an **FQ1LIST** frequency list for a 400 MHz spectrometer, configured to suppress two specific frequencies:

O 400.140000
2538.00
1427.00

You can also create the frequency list interactively via the user dialog:

--c13_decouple ".. " ^{13}C decoupling mode for satellite suppression with the following options:

"off": no ^{13}C decoupling (default)

"sel": selective ^{13}C decoupling using a shape pulse

2. Lock-Free Shimming

Perform shimming using TopShim in lock-free mode. When required, specify the solvent peak position (**o1p**) and the selective excitation width (**selwid**) to optimize shimming for the sample. For example: **topshim lockoff 1h o1p=<solvent_peak_ppm> selwid= <width_ppm>** Alternatively, automated lock-free shimming can be performed using the **lctshim** AU program.

3. Spectrum Acquisition

Execute **rga** to optimize the receiver gain, then start the experiment using **xaua**.

Important: Changes made in the No-D NMR setup become effective only when the experiment is started using **xaua**. Running **zg** bypasses the AU program and may result in the experiment being acquired with outdated settings.

4. Data Processing

Process the acquired FID using the standard 1D processing workflow **xaup** or advanced processing commands such as **ft** followed by **apbk -supp** for optimized baseline correction and solvent-suppressed spectra.

5. Chemical Shift Referencing

The **au_lc1d** AU program automatically sets the chemical shift reference based on the solvent peak. The resulting reference can be copied to other datasets, including those acquired on different nuclei, by using the **xiref** AU program. When referencing to an external standard such as **TMS or DSS**, use the **sref** command in the TopSpin command line and set the reference value to **0.0 ppm**.

Automation workflow for No-D NMR (IconNMR or SpinPilot)

Automated No-D NMR measurements in IconNMR can be performed using the following six-step workflow:

1) Select the sample position
2) Define the data storage location
3) Specify the solvent
4) Select the desired experiment
5) Define the user parameter L30, which specifies the number of solvent resonances to suppress
6) Submit the experiment

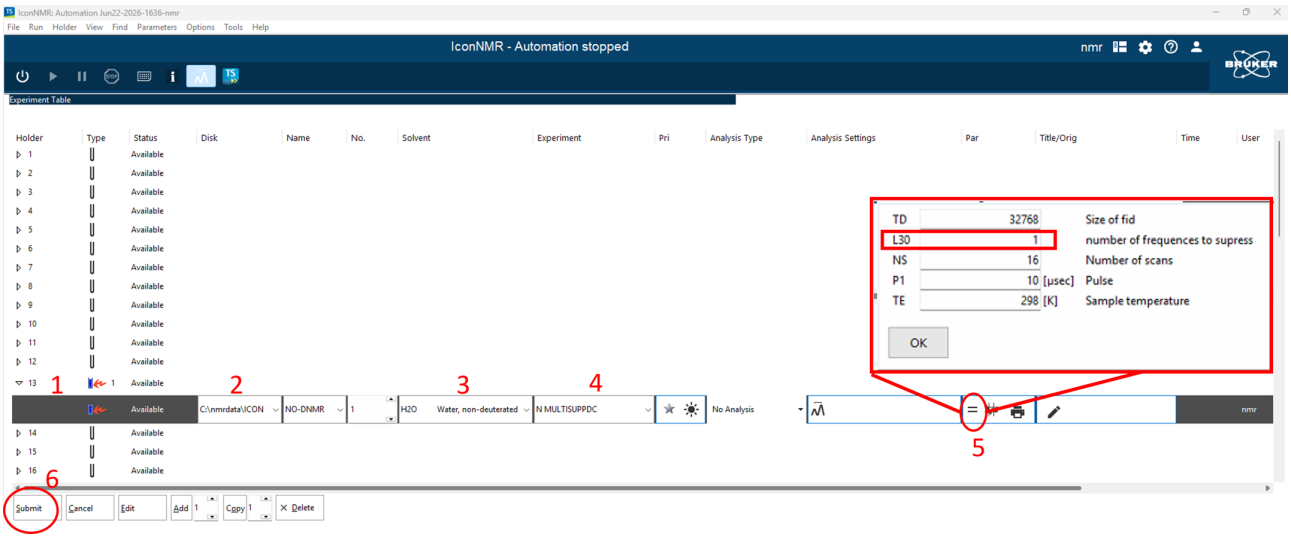


Figure 3: Simple IconNMR workflow for automated No-D NMR

The initial IconNMR configuration for No-D NMR is illustrated in Figures 4 and 5. Three configuration steps are required to enable lock-free No-D NMR measurements:

1. **Solvent configuration:**
   A predefined list of No-D NMR solvents is available in the IconNMR configuration. These settings determine how samples in protonated solvents are processed during lock-free acquisition and shimming, enabling routine No-D NMR measurements without the need for a deuterium lock.

2. **Experiment configuration:**
   As shown in Figure 5a, the optimized No-D NMR solvent-suppression experiment is added to the user-specific experiment list. The associated parameter set (wpar) should then be configured with **LOCNUC** to **OFF** to enable lock-free acquisition.

3. **User parameter configuration:**
   As shown in Figure 5b, the user parameter L30 has been added to the user-specific parameter list to define the number of solvent frequencies to be suppressed. This enables users to optimize solvent suppression by specifying the number of solvent resonances targeted during the No-D NMR experiment, thereby enhancing adaptability to diverse sample matrices and solvent compositions.

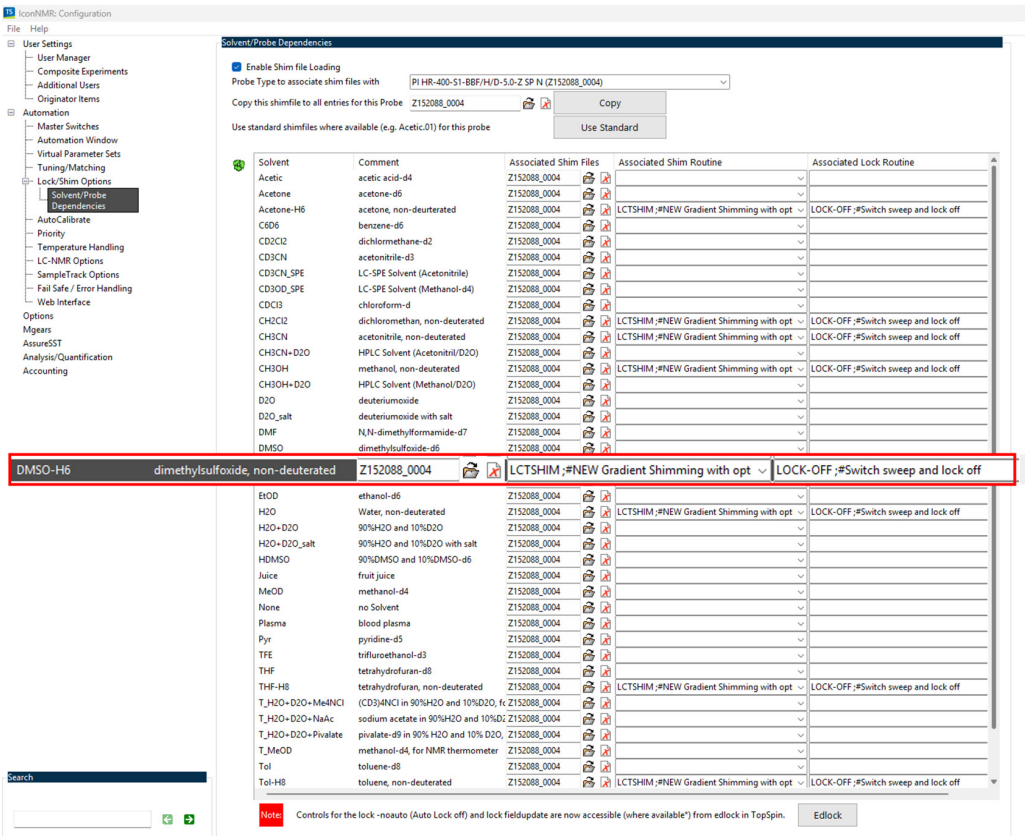


Figure 4: IconNMR configuration settings for No-D NMR lock and shimming

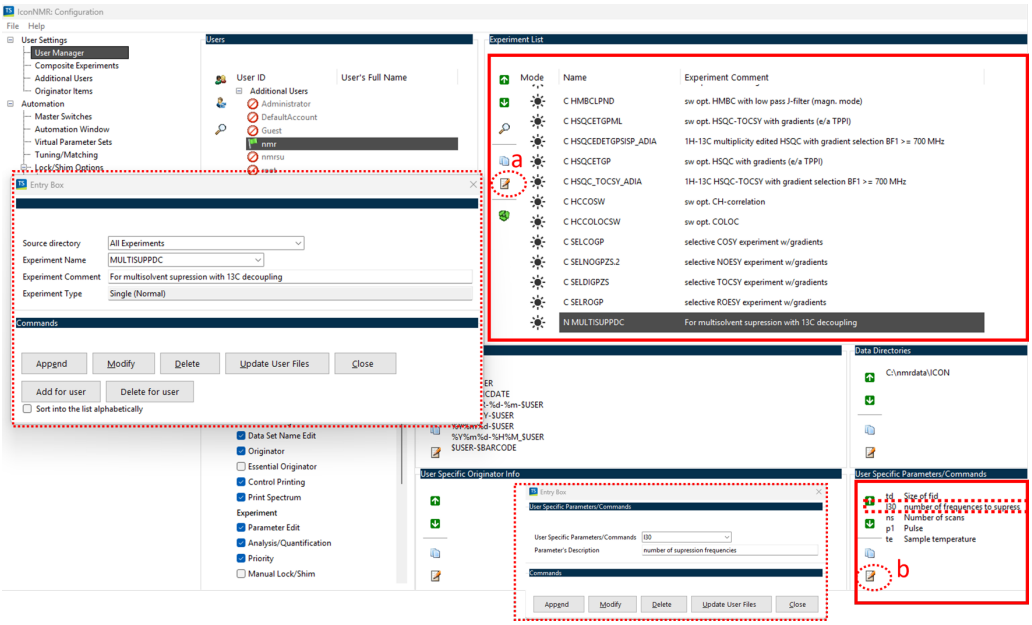


Figure 5: IconNMR configuration settings for lock-free No-D NMR. (a) Addition of the No-D NMR solvent-suppression experiment to the user-specific experiment list. (b) Addition of the user parameter L30 to define the number of solvent frequencies to be suppressed.

Summary

No-D NMR enables direct acquisition of high-quality ^{1}H NMR spectra in protonated solvents without requiring deuterated solvents or sample exchange. By preserving exchangeable proton resonances, reducing sample preparation steps, and minimizing solvent-related costs, No-D NMR offers a practical and efficient alternative to conventional workflows. Combined with automated lock-free operation, adaptive solvent suppression, and seamless integration within TopSpin, IconNMR, and SpinPilot, No-D NMR supports reliable implementation in both routine and high-throughput environments. These capabilities make No-D NMR particularly attractive for reaction monitoring, quality control, process development, and industrial analytical applications.

References

1. Hoye, T. R. et al. No-D NMR Spectroscopy: A Simple Yet Powerful Method for Analysing Reaction and Reagent Solutions. *Organic Letters, 2004.*
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