

## Application Note 30

# Real-Time Monitoring of Small Molecule Reactions using the X-Pulse Benchtop NMR

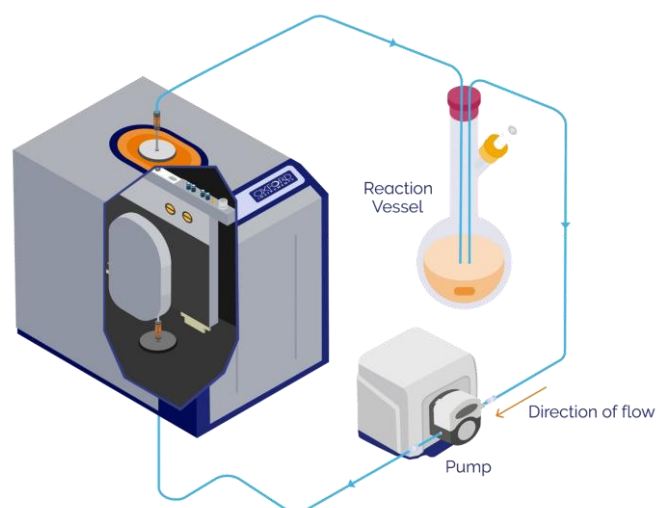
### Introduction

Flow Nuclear Magnetic Resonance (FlowNMR) spectroscopy offers a significant advancement in the real-time analysis of dynamic chemical processes. By continuously circulating a reaction mixture through an NMR spectrometer, FlowNMR provides detailed insights into reaction mechanisms, kinetics, and product formation, making it an invaluable tool across various scientific disciplines.

The **Oxford Instruments X-Pulse Broadband Benchtop** NMR Spectrometer brings high-field capabilities to a benchtop format, offering versatility and accessibility in a range of applications. Particularly well-suited for multinuclear FlowNMR spectroscopy, the X-Pulse's broadband X-channel supports the observation of a wide array of nuclei, spanning from the commonly analysed  $^1\text{H}$  &  $^{19}\text{F}$  to less receptive nuclei such as  $^{13}\text{C}$  &  $^{29}\text{Si}$ . This capability is essential for studying complex reactions, catalysis, and pharmaceutical formulations, where multiple types of nuclei must be monitored, and their interactions elucidated in real time.

This application note explores the setup, operation, and advantages of using the X-Pulse for multinuclear FlowNMR spectroscopy. We will discuss the key technical considerations involved in setting up a FlowNMR experiment, the system's capabilities

for monitoring different nuclei, and provide case studies demonstrating its application in real-world applications.



**Figure 1** FlowNMR apparatus consisting of a reaction vessel, transfer lines, pump, and Flow Cell (inserted in the probe).

Our goal is to illustrate how the X-Pulse can be utilised to gain comprehensive insights into complex chemical systems, driving the development of new materials and processes.

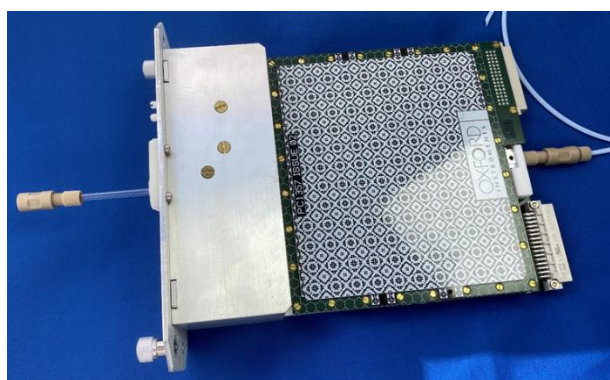
### FlowNMR with the X-Pulse

The **Oxford Instruments X-Pulse Broadband Benchtop** NMR Spectrometer is designed to support advanced FlowNMR experiments, offering a non-invasive, quantitative analysis that can monitor changes within a reaction or

process under realistic conditions without disrupting the system.

FlowNMR setups typically consist of a reaction vessel, transfer lines, a positive displacement pump, and the Flow Cell, which is inserted into the NMR probe (see Figure 1). The design of the X-Pulse accommodates a straightforward setup for experiments.

The technical setup begins with the preparation of the reaction vessel, which can vary from a simple bottle to a Schlenk flask, or a pressure reactor, depending on the experiment's requirements. These vessels are equipped to ensure a closed and secure environment, with specialised ports for the inflow and outflow of materials, thus maintaining the integrity of the reaction conditions.



**Figure 2** Flow cell installed in our user removeable probe.

FlowNMR operations are facilitated through a well-designed flow path, incorporating high-grade tubing such as FEP or PEEK. This ensures the safe and continuous transport of reaction mixture between the vessel and the NMR flow cell, avoiding any chemical interactions or contaminations that might affect the sample's integrity. The peristaltic pump used in the setup, running at different flow rates, typically 1 to 3 mL/min, depending on the experiment's requirements. The pump can also be fully automated, allowing for remote control and real-time adjustments during the experiment, enhancing the flexibility of FlowNMR operations.

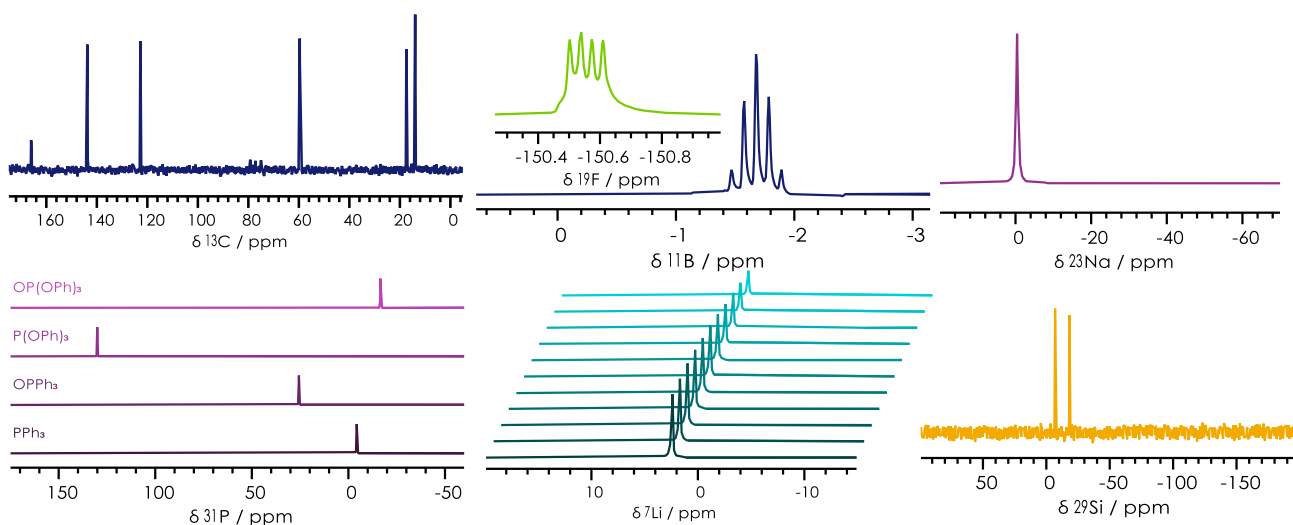
The system is designed with operational efficiency in mind. Its user-removable probe and an easy-to-install flow cell, located within the spectrometer's probe (Figure 2), allow for rapid configuration changes. This setup enables easy transition from standard to flow NMR setups in under 20 minutes which is a key consideration in fast-paced research environments. Such adaptability enhances the system's applicability across varied settings, from small-scale laboratory experiments to on-site analysis in industrial contexts.

Through this setup, the X-Pulse not only supports routine analysis, but also adapts to complex research demands, making it an invaluable tool for industries and academia alike, engaged in the cutting-edge study of chemical dynamics and material science, previously limited to larger, more cumbersome equipment.

### **Multinuclear FlowNMR**

One of the X-Pulse's most notable and unique features is its broad multinuclear capability, facilitated by a fully tuneable broadband (X-)channel. This channel can observe a wide range of nuclei with Larmor frequencies between 11.8 and 24.2 MHz at 1.4 T, including important elements such as carbon-13, phosphorus-31, boron-11, lithium-7, sodium-23, aluminum-27, and silicon-29 as well as fluorine-19 on the H-F channel. The ability to monitor this array of nuclei in real-time FlowNMR experiments provides unparalleled flexibility in studying dynamic chemical reactions.

This capability is especially valuable in fields such as organometallic chemistry, catalysis, and pharmaceutical formulation, where complex reactions often involve multiple elements. For example,  $^{31}\text{P}$  NMR can be used to study hexafluorophosphate anions,  $^{11}\text{B}$  NMR for monitoring tetrafluoroborate species, and  $^{29}\text{Si}$  NMR for distinguishing different silicon environments in siloxanes (see Figure 3 for some examples).



**Figure 3** Various examples of multinuclear NMR.

### Example reactions with FlowNMR

The versatility of the X-Pulse in monitoring a range of nuclear types is exemplified through several specific reactions.

#### Case study 1 - using $^1\text{H}$ NMR:

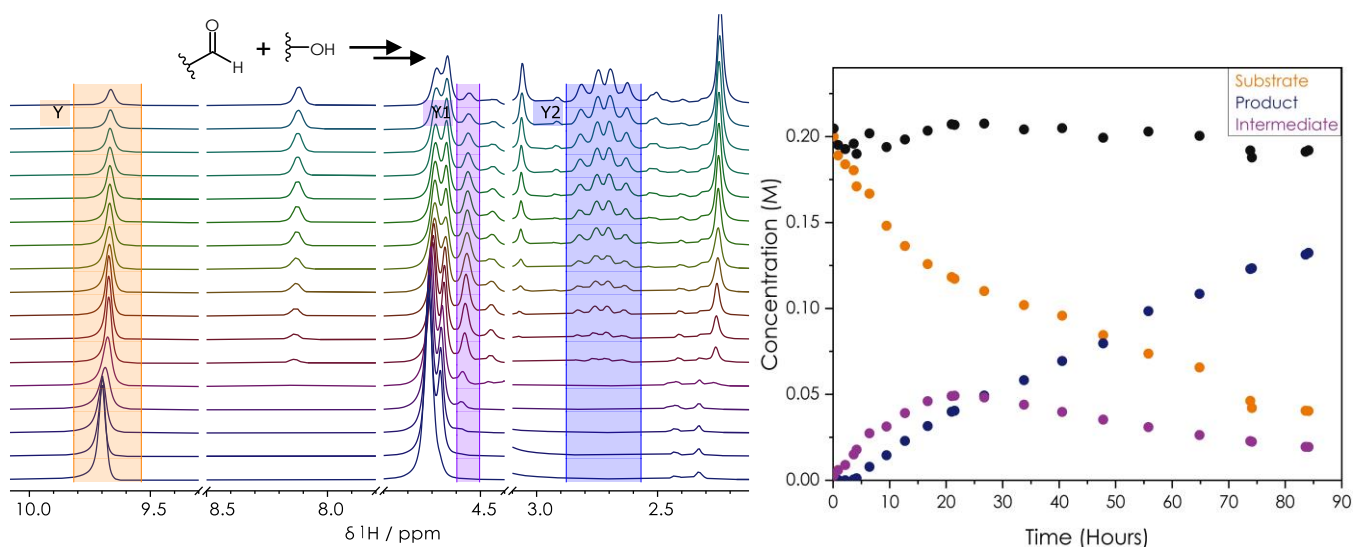
The formation of acetals, typically from aldehydes and alcohols, is an important transformation in organic synthesis. Acetals serve as protecting groups for aldehydes and are widely used in pharmaceuticals, and the fragrance and polymer industries.

Understanding the reaction mechanisms and

monitoring the formation of intermediates in real-time is useful for optimising reaction conditions and catalyst efficiency.

In this example, we monitored a catalysed acetal formation reaction for over 90 hours, with the initial concentration of the reactants at 200 mM (Figure 4).

Substrate monitoring: The aldehyde signal at  $\delta_{\text{H}} + 9.7$  ppm (orange) decreased as the starting material as the reaction progressed, indicating the consumption of the aldehyde.



**Figure 4**  $^1\text{H}$  NMR spectra and corresponding concentration profile of the catalysed acetal reaction.

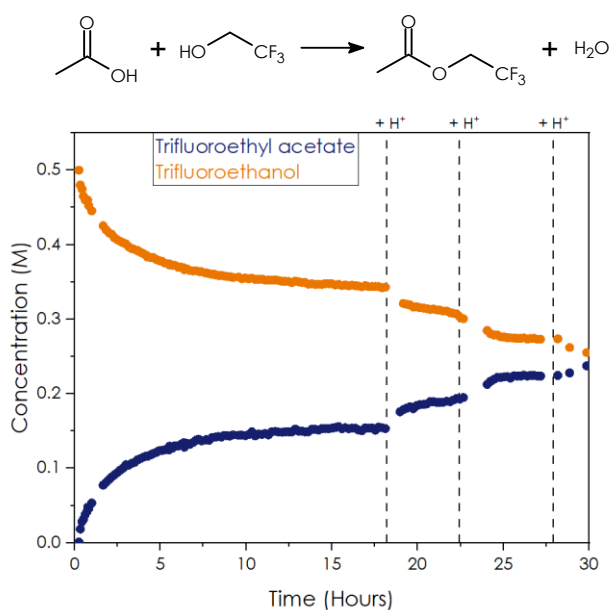
Intermediate detection: An intermediate species was detected at  $\delta_H +4.6$  ppm (purple), which remained transient in nature but was observed at concentrations as low as 20 mM within a couple minutes of acquisition.

Product identification: The formation of the acetal product was marked by the appearance of distinct signals, including singlets at  $\delta_H +8.1$  ppm and  $\delta_H +2.3$  ppm (blue), as well as a quartet at  $\delta_H +2.7$  ppm.

By integrating these species over the course of the reaction, FlowNMR allows us to quantitatively track the substrate consumption, intermediate formation, and product accumulation. The ability to track real-time changes in the reaction mixture provides valuable information about the reaction kinetics and the presence of intermediates.

#### Case study 2 - using $^{19}\text{F}$ NMR:

Esterification reactions are important for producing esters used in pharmaceuticals, fragrances, and polymers. Here, we examine the reaction of trifluoroethanol with acetic acid to form trifluoroethyl acetate, a compound with industrial relevance due to its fluorinated properties (Figure 5).



**Figure 5**  $^{19}\text{F}$  NMR concentration profile for the conversion of trifluoroethanol to trifluoroethyl acetate.

Using  $^{19}\text{F}$  FlowNMR, we monitored the reaction over 30 hours, tracking the formation of trifluoroethyl acetate in real-time. As the reaction progressed, we observed the system reaching equilibrium, allowing us to add more catalyst at specific intervals to evaluate its effect. This monitoring provided valuable information into how catalyst concentration influenced the reaction dynamics and the subsequent shifts in equilibrium. Despite low concentrations of trifluoroethanol, the X-Pulse system demonstrated high sensitivity for detecting  $^{19}\text{F}$  signals, making it ideal for studying fluorinated compounds in real-time reactions.

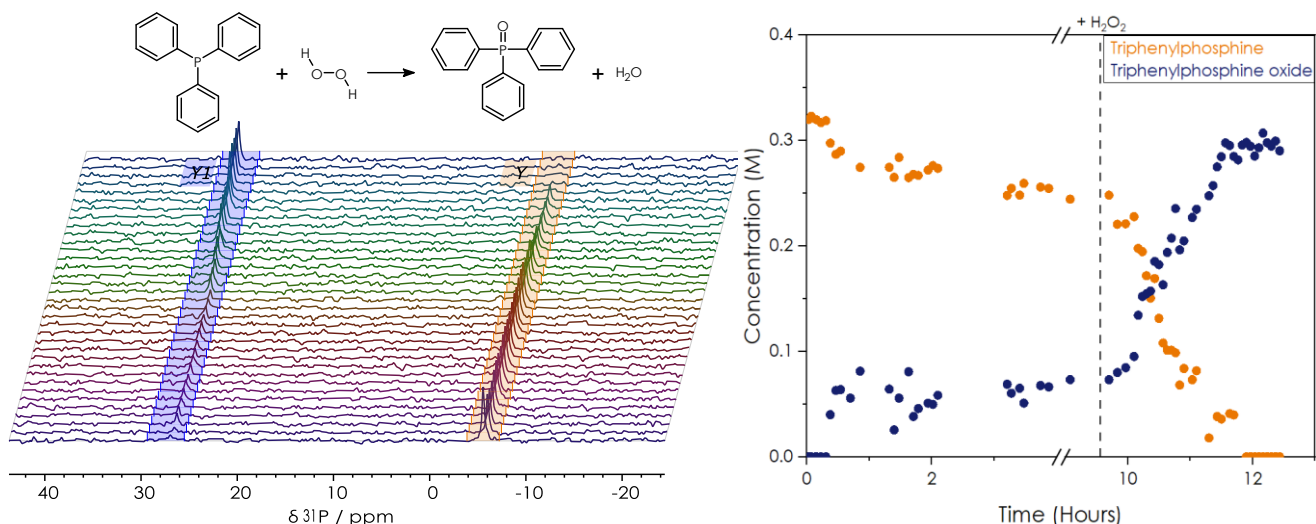
#### Case study 3 - using $^{31}\text{P}$ NMR:

Oxidation reactions are fundamental in phosphorus chemistry, playing a key role in the formation of various phosphorus oxides, which are essential in catalysis and material science. Understanding the progression of oxidation reactions, how long it can take, and amount of oxidant can help in optimising catalytic processes and improving functional material development.

In this study, we monitored the oxidation of triphenylphosphine to triphenylphosphine oxide over a 12-hour period using  $^{31}\text{P}$  NMR FlowNMR (Figure 6). The system reached equilibrium after a couple of hours, after approximately 9 hours additional oxidant was introduced to drive the reaction to completion. The X-Pulse enabled rapid data acquisition, with each spectrum acquired in under 4 minutes. Even at a concentration of around 50 mM, we were able to quantify the reaction progress.

#### Case study 4 - using $^{11}\text{B}$ NMR:

Cross-coupling reactions are essential in synthetic organic chemistry, enabling the formation of carbon-carbon bonds in complex molecules. The Suzuki-Miyaura cross-coupling in particular, is widely used for the synthesis of biaryls and other key organic compounds, playing a critical role in pharmaceuticals, materials science, and agrochemicals. It also



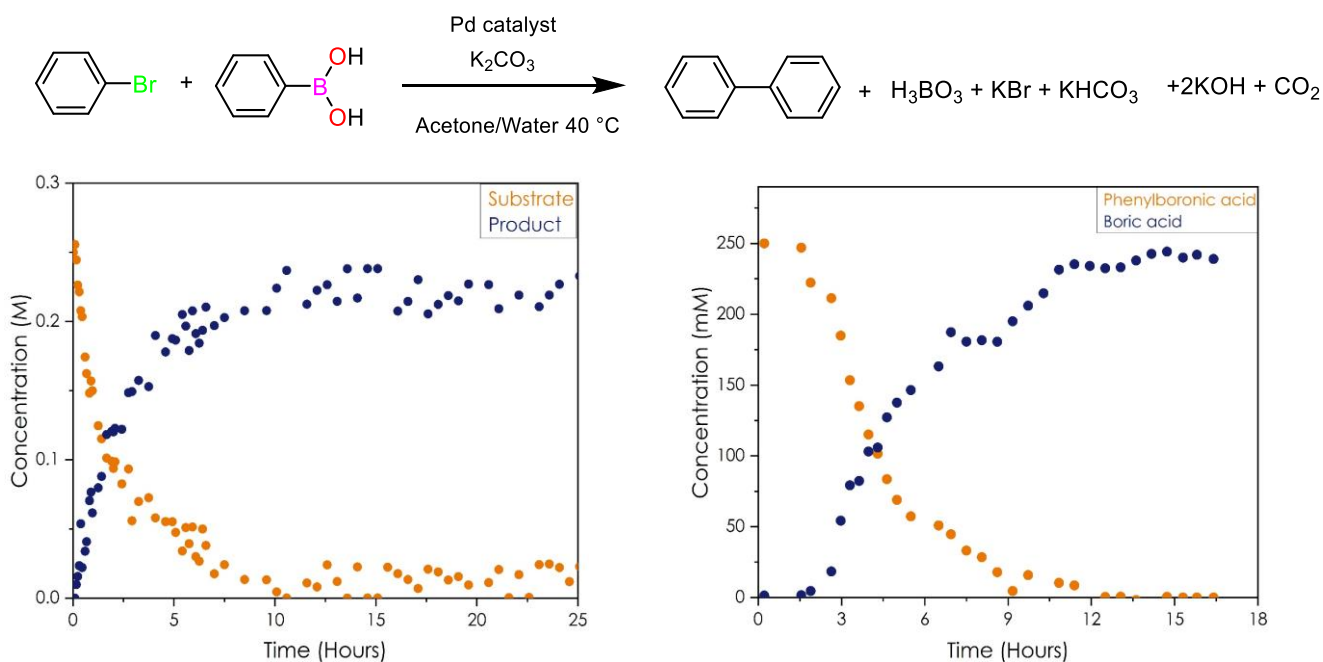
**Figure 6**  $^{31}\text{P}$  NMR spectra and corresponding concentration profile for the oxidation of triphenylphosphine.

highlights its potential to study complex organometallic reactions and catalytic cycles.

In this study, we used  $^{11}\text{B}$  NMR to track the conversion of phenylboronic acid to boric acid, alongside  $^1\text{H}$  NMR monitoring of the product formation and substrate consumption. This allowed us to correlate the changes in both boron species and the overall reaction progress (Figure 7).

The experiments were set up to interleave  $^{11}\text{B}$  and  $^1\text{H}$  NMR acquisitions, with both datasets acquired in under 6 minutes. Thanks to the

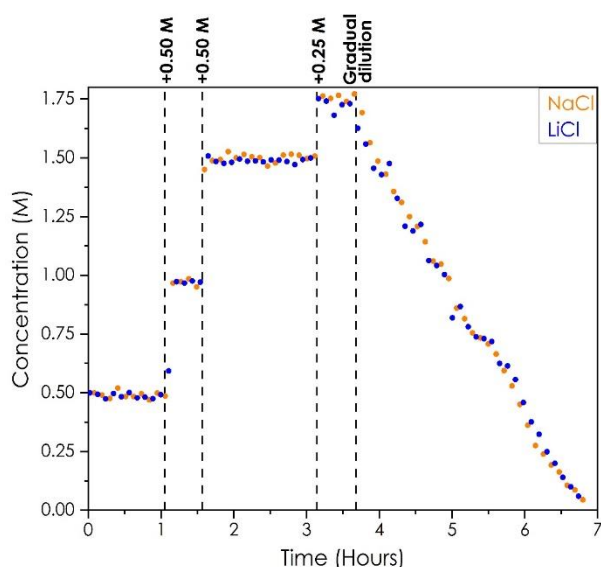
sensitivity of the X-Pulse, we were able to accurately monitor concentrations as low as 25 mM over the course of a full day. By switching between flowing and non-flowing conditions, we maximised data accuracy and obtained valuable insights into the reaction dynamics in both phases.



**Figure 7**  $^{11}\text{B}$  NMR and  $^1\text{H}$  NMR concentration profiles for the Suzuki-Miyaura cross-coupling.

### Case study 5 - using $^7\text{Li}$ and $^{23}\text{Na}$ NMR:

Monitoring lithium extraction from brine is essential for optimising processes in the energy and environmental sectors. Using FlowNMR, we continuously tracked the concentration changes of lithium and sodium (Figure 8), providing real-time feedback on extraction efficiency and kinetics. This method enables dynamic adjustments, allowing operators to maintain optimal conditions for maximum yield without interrupting the process, while also minimising waste. Additionally, for applications such as this FlowNMR helps fine-tune key parameters such as pH, temperature, and flow rates, improving lithium recovery rates and managing sodium and other impurities more effectively. For further details on this application, please refer to *Application Note 26*.



**Figure 8** Concentration profile of  $^7\text{Li}$  and  $^{23}\text{Na}$  FlowNMR monitoring of NaCl and LiCl at 2ml/min.

### Quantitative analysis

All the data presented in this application note is quantitative, ensuring precision throughout the experiments. This approach allows users to obtain results that are both reliable and representative of the real-time reaction dynamics, enabling informed decision-making based on the data.

The X-Pulse enables continuous data acquisition. By circulating the sample through the spectrometer's detection region, the system captures molecular structure and concentration changes as the reaction progresses. Data is collected at predefined intervals, recording shifts in chemical shifts, peak intensities, and multiplet structures while maintaining high sensitivity ensuring that key aspects of the reaction, such as progress and kinetic parameters, are monitored without interrupting the process.

For accurate quantification, the setup is carefully optimised, particularly with respect to the relaxation delay. Flow correction factors are obtained and applied to the flowing dataset to account for inflow and outflow effects ensuring all data is reliable and quantitative. In some cases,  $T_1$  times are calculated first to ensure that the data accurately reflects the concentrations of reactants, intermediates, and products.

By integrating these capabilities, the X-Pulse supports detailed, quantitative analysis of FlowNMR data, making it a robust tool for monitoring complex chemical reactions in real-time.

## Summary

The X-Pulse Benchtop NMR system offers significant advantages in FlowNMR, providing the ability to monitor a wide range of nuclei at low, realistic concentrations. This enables researchers to gather real-time reaction data, supporting decision-making in both academic and industrial applications. Its ability to capture essential information during key reaction stages makes it a valuable tool for optimizing processes in fields like catalysis and environmental science.

At a lower cost than high-field systems, the X-Pulse makes advanced NMR techniques more accessible. With ongoing improvements in NMR technology, the future of FlowNMR looks promising, with potential for enhanced sensitivity and faster data acquisition. The X-Pulse is well-equipped to support these advancements, driving more efficient and precise chemical analysis across a wide range of applications.



If you have any questions about this application note, please contact our experts: [magres@oxinst.com](mailto:magres@oxinst.com)

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