# SUPPLIMENTARY INFORMATION

## Practical Aspects of Real-time Reaction Monitoring using

## Multi-nuclear High Resolution FlowNMR Spectroscopy

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## Reynolds Number calculation

The Reynolds number for the FlowNMR apparatus was calculated using the equation for Reynolds number in a circular cross-section pipe:

$$R_e = \frac{QD_h}{\nu A}$$

$R_e$ = Reynolds Number, Q = Volumetric Flowrate (m³s⁻¹), $D_h$ = Pipe Diameter (m), ν = Kinematic Viscosity (m²s⁻¹), A = Cross-sectional area (m²).

For the 1/16" PEEK tubing (I.D. 0.75 mm) with a flowrate of 4 mLmin⁻¹ water (ν = 1x10⁻⁶ m²s⁻¹) the Reynolds number is calculated as follows:

$$R_e = \frac{6.67 \times 10^{-8}\, m^3 s^{-1} \cdot 7.5 \times 10^{-4}\, m}{1.00 \times 10^{-6}\, m^2 s^{-1} \cdot 4.42 \times 10^{-7}\, m^2} = 112.7$$

Systems with $R_e$ < 2300 are usually considered to be in the laminar flow regime.[1]

## Diagrams
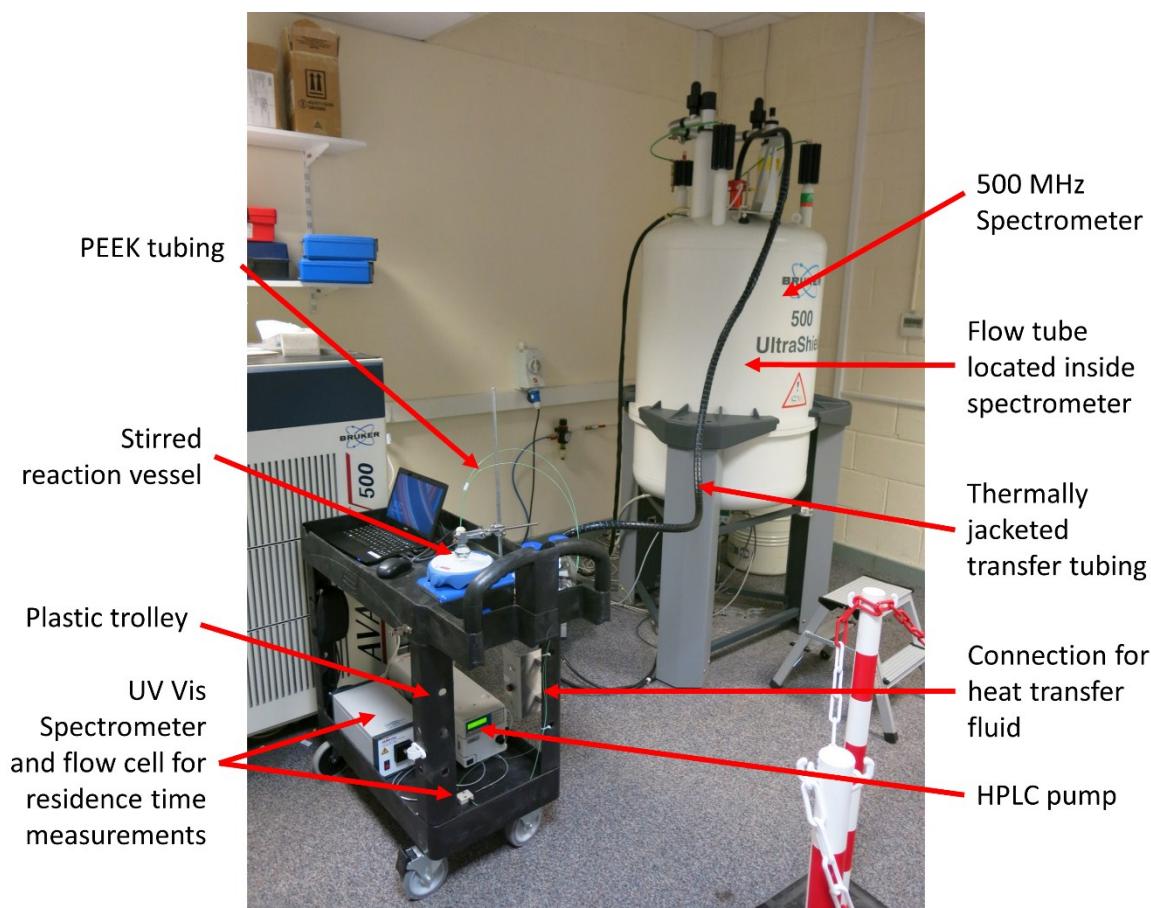


**Figure S1:** FlowNMR experimental setup, showing location of apparatus on trolley next to NMR spectrometer.
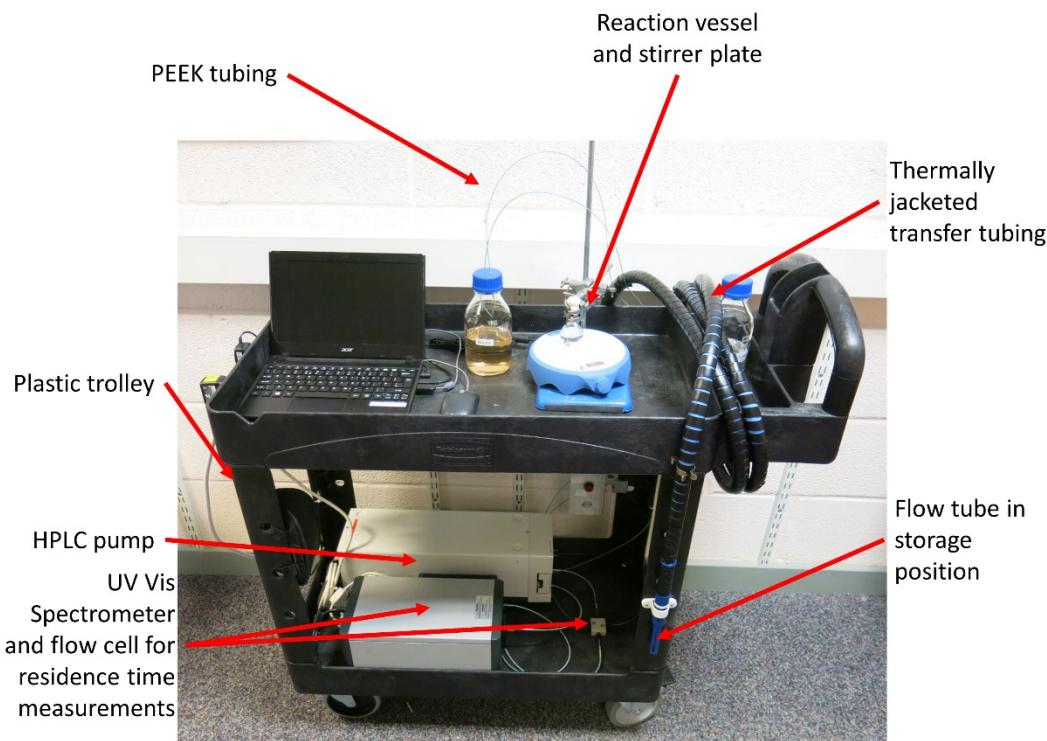
**Figure S2:** FlowNMR experimental setup, showing apparatus in storage position.
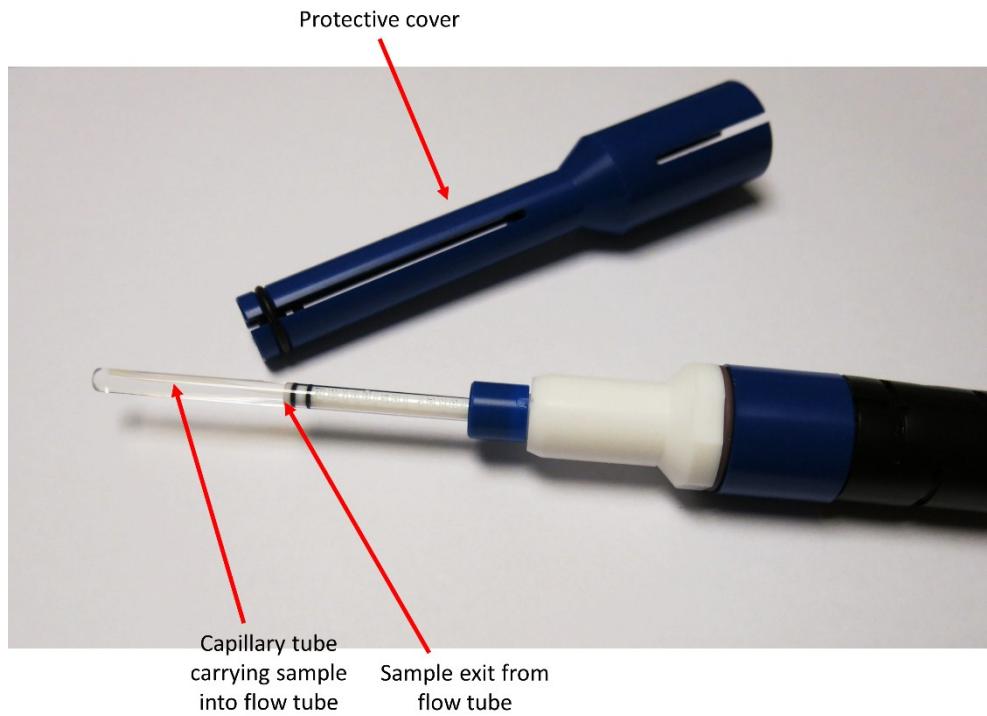


**Figure S3:** FlowNMR flow tube.
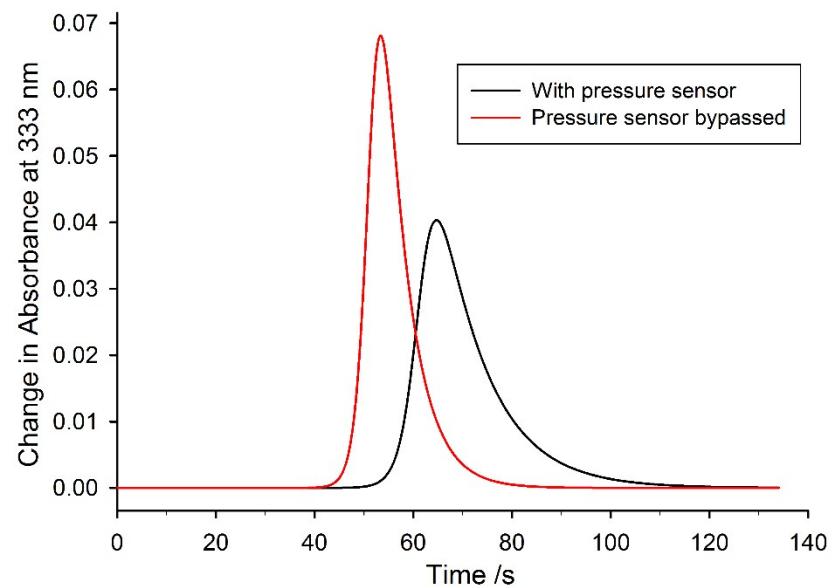
**Figure S4:** Residence time distribution profiles for the apparatus described in Figure 1 at a flowrate of 4 mLmin$^{-1}$ (acetone, 25˚C), comparing the effects on residence time distribution with and without the pump pressure sensor (flow tube connected; cf. Figure 2).
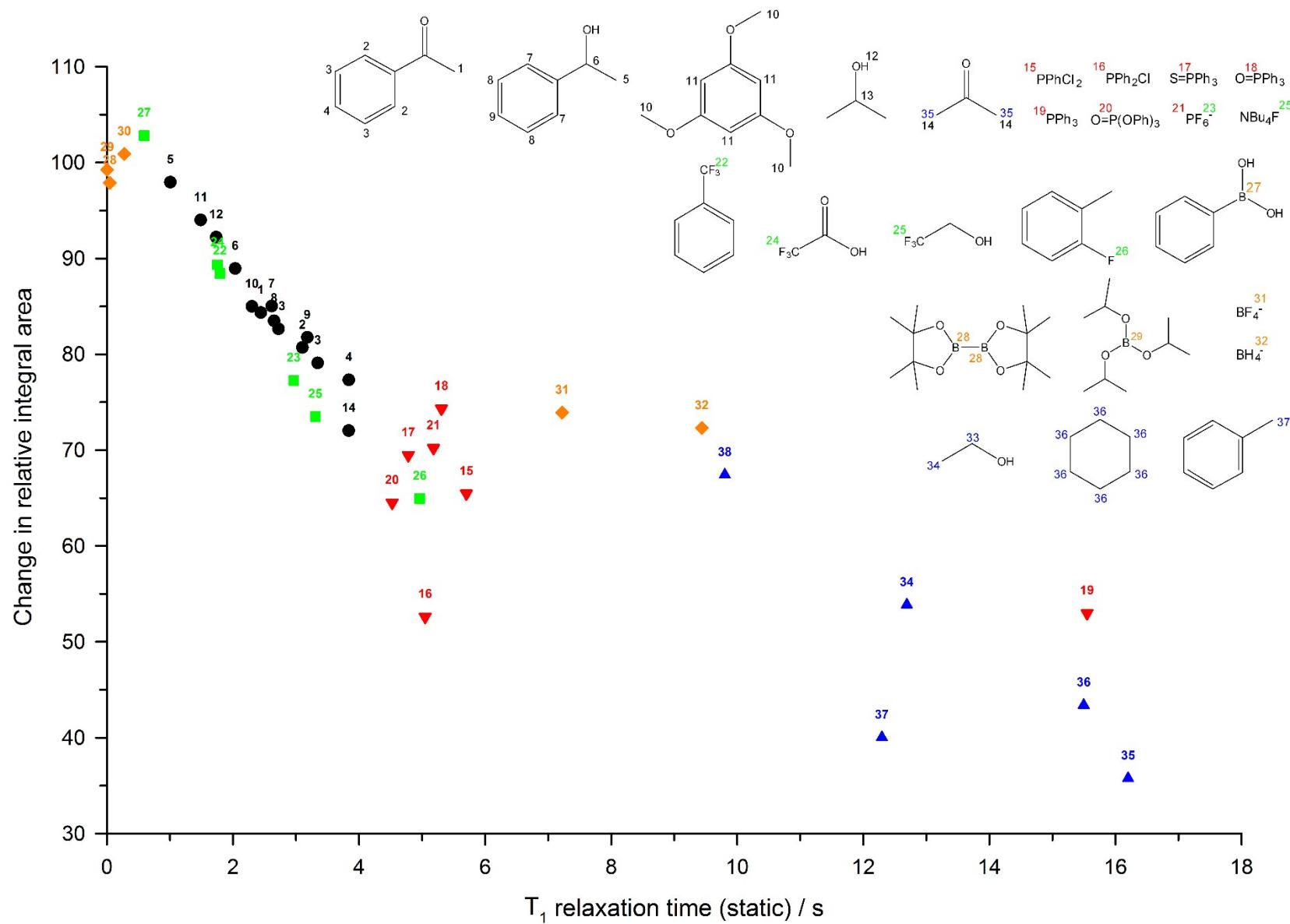
**Figure S5:** Correlation between the decrease in integral area at a flow rate of 4 mLmin⁻¹ and the T₁ relaxation time at a flow rate of 0 mLmin⁻¹ for a variety of commonly used NMR nuclei, with structural assignment (25°C, 30° pulse, inverse gated decoupling for ³¹P and ¹³C, various delay and acquisition times – see experimental section for details).
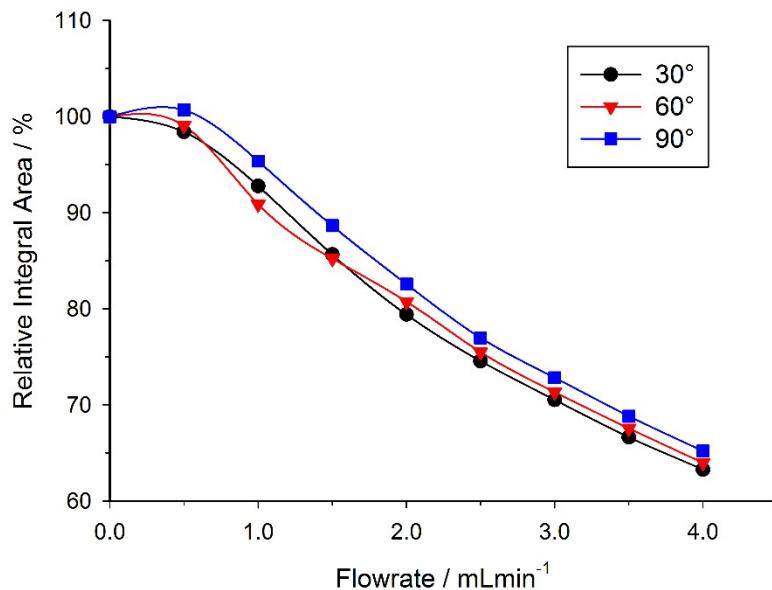
**Figure S6:** Variation in integral area of acetone $^1$H peak with increase in flowrate for different flip angles, showing increase in integral areas due to relaxation delay time effects for flip angles greater than 30°. (25°C, 3.17 sec acquisition time, 15 sec relaxation delay).
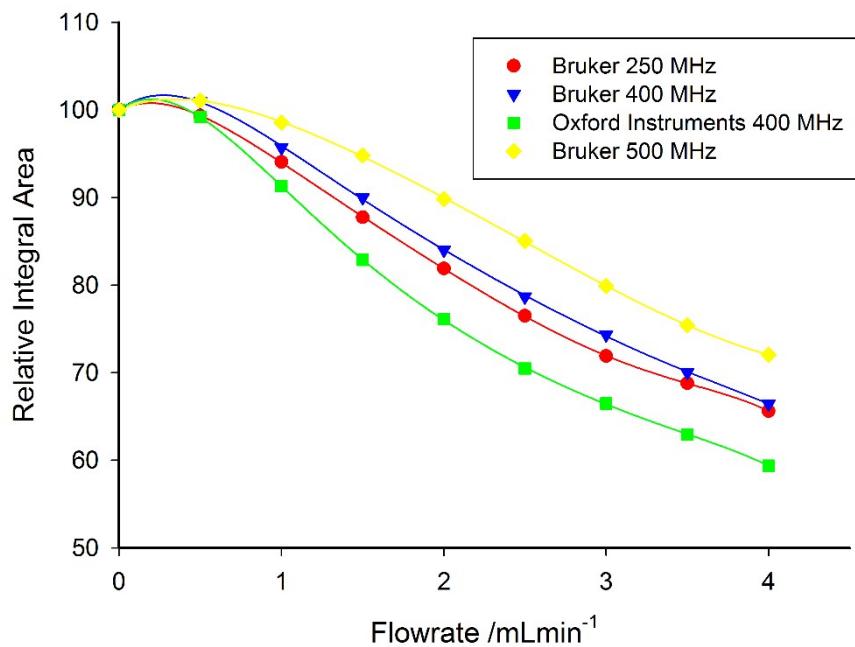


**Figure S7:** Comparison of in-flow effects on relative integral area of the acetone $^1$H resonance using the same flow tube setup with different spectrometers (25°C, 30° flip angle, 4 sec acquisition time, 15 sec relaxation delay).
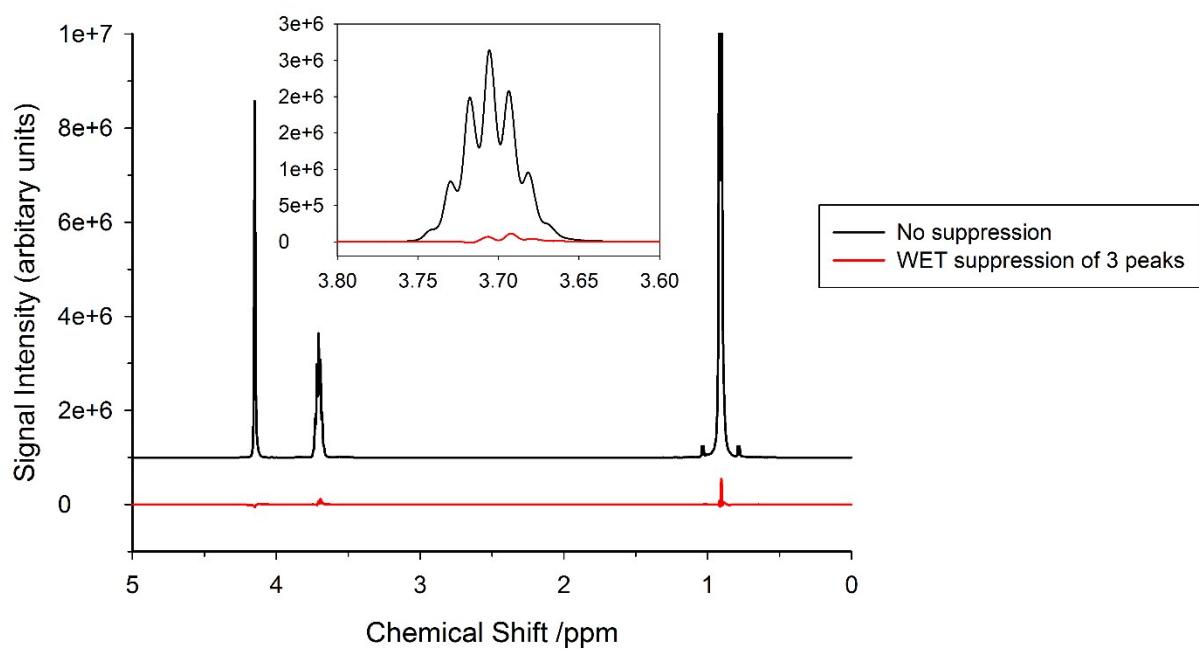
**Figure S8:** Triple solvent suppression of all isopropanol ^{1}H resonances using WET pulse sequence with automated peak detection and suppression including ^{13}C decoupling, leading to an approximately 100-fold reduction in peak intensity (500 MHz, 25°C, 2 sec acquisition time, 4 sec relaxation delay, 0 mLmin$^{-1}$ flow rate).

## Additional Experimental Details

Comparison between different spectrometers was performed using a mixture of acetophenone, 1-phenylethanol, acetone and 1,3,5-trimethoxybenzene in isopropanol with a standard 30° pulse sequence (15 sec delay, 4 sec acquisition time, 8 scans) at flowrates between 0-4 mLmin$^{-1}$. Tests were performed using a Bruker 500 MHz Avance II+ Ultrashield spectrometer (broadband BBO probe), a Bruker 400 MHz Avance Ultrashield Spectrometer (broadband BBO probe), a Bruker 250 MHz Avance Spectrometer ($^{13}$C/$^{1}$H dual probe) with an Oxford/Spectrospin unshielded magnet, and a Bruker Avance III 400 MHz spectrometer (broadband BBO probe) with an Oxford Instruments unshielded magnet.

Triple solvent suppression using WET was carried out with the Bruker pulse program "wetdc", using a standard LC-NMR automated acquisition program, "au_lc1d" that first acquires a scout scan to identify and subsequently suppress the desired number of solvent peaks.

## Example Methodology for FlowNMR reaction:

In the case of air sensitive reactions, the flow tube and apparatus were purged with a flow of dry nitrogen for at least 30 minutes before use to remove any traces of air or moisture in the system. The system was then purged with fresh, inert solvent for a minimum of 5 minutes at 4 mLmin$^{-1}$ before connecting to the reaction vessel containing the reagents and solvent under an atmosphere of dry nitrogen. The solution volume in the flask was adjusted considering the volume of solvent already in the apparatus; typically an overall liquid volume of 10 mL was used. Where possible the final reagent or catalyst was not added to the reaction mixture until ready to start the reaction. The reaction mixture was circulated around the apparatus for several residence times to ensure the sample was uniformly mixed throughout the apparatus.

The flow tube was then inserted into the spectrometer and automated shimming and tuning routines were performed. Best results were obtained if automated shimming and tuning was performed on static samples, however acceptable results were still obtained in flow. Frequency lock was switched off when using non-deuterated solvents, and shimming performed on proton peaks. Manual fine tuning of X and Y shims was often required to get a good peak line width. Spectra of the reagents were recorded without flow and again at the flowrate desired for the reaction. Comparison of the integral area of the peaks in each spectrum was used to calculate a correction factor for each reagent peak. (I = peak integral, CF = correction factor).

$$I_{Corrected} = CF \times I$$

$$CF = \frac{I_{Static}}{I_{Flow}}$$

With the sample flowing, data acquisition was started using an automated kinetic routine or dedicated reaction monitoring software, with spectra recorded at specified time intervals. The reaction was then started by the addition of the final reagent or catalyst to the stirred flask using a syringe.

At the end of the reaction, or if intermediates of interest were observed, additional spectra were recorded with and without flow, and correction factors were calculated for the intermediate or product peaks, which were applied to each spectrum to give the final peak areas for calculation of species concentration and plotting of kinetic data.

## References

1.     O. Levenspiel, *Chemical Reaction Engineering*, Wiley, New York ; Chichester, 3rd ed. edn., 1999.