

# Reaction characterization by flow NMR: quantitation and monitoring of dissolved H<sub>2</sub> via flow NMR at high pressure

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**This communication describes an *in situ* method for direct observation and quantitation of dissolved H<sub>2</sub> at high pressure with concurrent monitoring and characterization of organic reactions. This capability also allows for direct measurement of  $k_{1a}$  values and provides insight into reactions that was not previously attainable.**

Measurement of the concentration of dissolved gases in liquids is often crucial to understanding a variety of chemical phenomena and processes for several scientific disciplines. Many techniques already exist for measuring dissolved gas concentrations under atmospheric conditions as well as for systems under pressure with reasonable accuracy.<sup>1–3</sup> These techniques often have limitations with respect to solvent compatibility, pressure limits, and matrix interactions that interfere with the ability to accurately quantify dissolved gases. In addition, these techniques are often designed for detection of a single component and, therefore, do not provide simultaneous detection of other components in the system, such as the organic substrates that are reacting with the dissolved gases. The ability to quantitate and monitor H<sub>2</sub> levels in solution is particularly advantageous for catalytic reactions that make use of pressurized H<sub>2</sub> or syngas (H<sub>2</sub>/CO), which are often difficult to monitor or characterize *in situ* without perturbing the reaction. For example, pressure relief and exposure to atmospheric conditions to allow for sampling introduces the possibility of poisoning the reaction with oxygen or moisture, altering the kinetics, and loss of volatiles. This can ultimately skew the interpretation of what was actually present in the reaction at the time of sampling.

This communication describes an *in situ* method for direct observation and quantitation of dissolved H<sub>2</sub> that also enables concurrent monitoring of catalytic reactions under pressure, where the reaction mixture is heterogeneous or homogeneous. The approach utilizes <sup>1</sup>H nuclear magnetic resonance (NMR) for monitoring and quantifying dissolved H<sub>2</sub> in a wide variety of organic solvents at pressures ranging from 0 to 1000 psig. Pumping a reaction solution in a closed loop system through a NMR probe at pressure allows for

the reaction to be monitored while avoiding the potentially detrimental perturbations described earlier.<sup>4</sup> NMR is inherently quantitative, offers very good sensitivity and specificity for organic species, and provides structural information about organic and inorganic compounds in solution (*via* sequential multi-nuclear 1D and 2D acquisitions). Implementation of NMR in this fashion permits the real-time observation and characterization of reaction kinetics, reaction intermediates, catalytic species, undesired side reactions, atmospherically unstable reaction species, short-lived reaction species, and, as described herein, dissolved H<sub>2</sub> concentrations. This method also allows for direct determination of  $k_{1a}$  (the gas-liquid volumetric mass transfer coefficient), which varies based on reactor configuration, temperature, and agitation conditions. Furthermore, this approach is superior to NMR analysis of reactions in sealed, high pressure sample tubes<sup>5,6</sup> because it allows for a constant head pressure to be maintained throughout the reaction in addition to maintaining agitation of the reaction. In short, reaction monitoring of pressurized reactions *via* a flow NMR approach affords the ability to obtain a holistic view of the reaction without introducing significant sampling biases. Application of this technique for accurate quantitation does require consideration of several factors described in previous reports of flow NMR analysis.<sup>7,8</sup> Recent published examples of quantitative flow NMR do not specifically describe these factors, which may significantly impact accuracy if not addressed or compensated for in the experimental design.<sup>9</sup>

An illustration of the instrumental configuration used for this work is shown in Fig. 1. A 100 mL Parr reactor was modified to accommodate outlet and inlet transfer lines which allow for reaction solution to be continuously circulated, bubble-free, through the NMR using a high-pressure HPLC pump. The majority of the transfer lines were stainless steel; however, short sections of PTFE tubing were used to transfer reaction solution in to and out of a custom flow tube located within the NMR magnet. Five organic solvents widely used for catalytic hydrogenations were selected to evaluate H<sub>2</sub> solubility at pressures ranging from 50 to 1000 psig. An internal standard was used for the quantitative determinations reported in this work, however, alternate methods for quantitation using NMR could be utilized.

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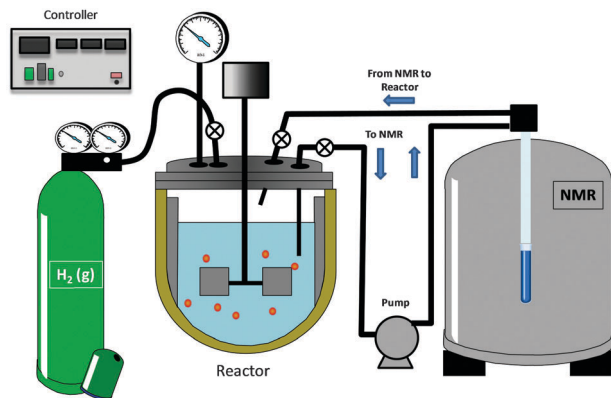


Fig. 1 Illustration of experimental setup used. Individual components are not drawn to scale.

For each solvent, a solution containing a known concentration of an internal standard (either trimethoxybenzene or *p*-toluic acid) was prepared and subsequently charged to the Parr reactor at ambient temperature. All solvents used for the analysis were fully protonated (*i.e.*, this approach does not require the deuterated solvents typically used in traditional NMR spectroscopy) and degassed *via* nitrogen sparging. The flow rate for continuous circulation through the NMR was set to 2.0 mL min<sup>-1</sup>, however, the actual flow rate may slightly differ from this value because the pump was calibrated for use with aqueous solutions (flow rate does affect the accuracy of quantitation by NMR, *vide infra*). The Parr reactor was supplied with a pressure-regulated hydrogen gas feed. The reactor was stirred at 650 rpm and allowed to stir for at least 10 minutes prior to <sup>1</sup>H spectral acquisition to ensure saturation was achieved. Saturation was indicated when the measured area of the H<sub>2</sub> resonance no longer changed between consecutive spectral acquisitions. Hydrogen pressures of 50, 100, 200, 400, and 1000 psig were evaluated for each of the five solvents studied.

Factors affecting the NMR quantitation were carefully considered and conditions were optimized in order to promote the quantitative accuracy of this approach. Significant literature precedent exists for quantitative NMR (qNMR) and associated strategies for minimizing potential errors. Important factors include, but are not limited to, accurate pulse width calibration, tuning/matching of the probe, internal standard potency, use of quantitative acquisition parameters, and relaxation differences between different nuclei.<sup>10–12</sup> Single scans (*i.e.*, no co-adding of consecutive FIDs) were collected to eliminate inter-pulse *T*<sub>1</sub> relaxation effects and long delays between replicate acquisitions were employed to ensure complete turnover of solution in the NMR flow tube. Additionally, the impact of flow rate on quantitation was carefully evaluated and was determined to be the most significant factor influencing the quantitative accuracy for this experimental setup. For each solvent–pressure combination, ten consecutive <sup>1</sup>H spectra were collected with at least a one minute delay between acquisitions while solution was being circulated at 2.0 mL min<sup>-1</sup>. Spectra were also collected at different flow rates and while circulation was temporarily paused in order to evaluate the impact on the measurement. Spectral data were processed with the Reaction Monitoring plug-in of the MestReNova software suite. Peak area integrations obtained using MestReNova for both the internal

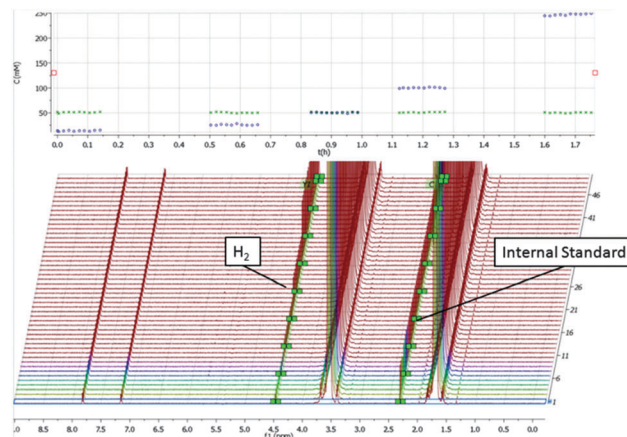


Fig. 2 Example image of MestReNova Reaction Monitoring Software that was used to extract H<sub>2</sub> concentrations.

standard and dissolved H<sub>2</sub> were used for all subsequent calculations. Fig. 2 shows an example of how this software can be used to visualize data sets for extraction of pertinent characterization information.

Calculation of the H<sub>2</sub> concentration for each pressure–solvent combination required the use of the known concentration of the internal standard concentration, accounting for the number of protons that each <sup>1</sup>H resonance represented (*e.g.*, two protons for dissolved H<sub>2</sub>), a flow rate compensation factor to be applied if spectra were acquired while flowing, and compensation for the fact that only *ortho*-H<sub>2</sub> (75% of the total H<sub>2</sub> present) is observable by NMR. The resulting dissolved H<sub>2</sub> concentrations for each pressure–solvent combination were used to generate the solubility plots shown in Fig. 3.

If an internal standard is used, a flow rate compensation factor should be used in order to obtain accurate dissolved H<sub>2</sub> concentrations. A compensation factor was obtained by first collecting a single NMR spectrum with flow stopped. This spectrum then served as a reference for determining the percentage area attenuation of the internal standard and dissolved H<sub>2</sub> resonances at a specified flow rate. Each <sup>1</sup>H resonance exhibits a unique flow rate compensation factor, as this value is directly related to the *T*<sub>1</sub> of the resonance. This relationship is a consequence of the nuclear magnetization in the

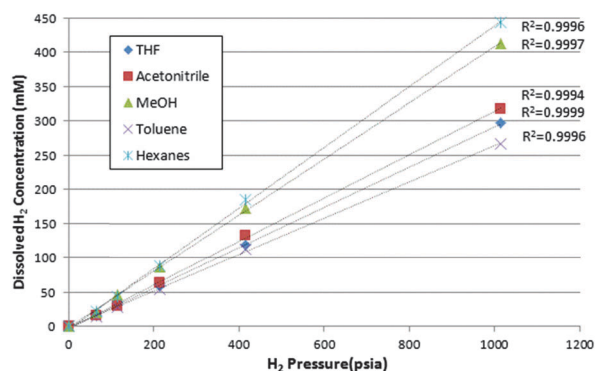


Fig. 3 Resulting solvent comparison of dissolved H<sub>2</sub> concentrations (mM) at pressures ranging from 0–1014.6 psia at ambient temperature (nominally 23 °C).

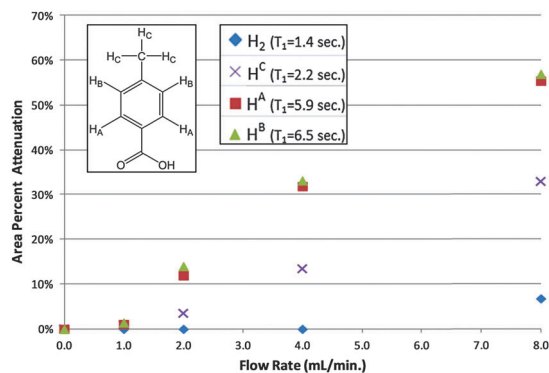


Fig. 4 Area percent attenuation of internal standard (*p*-toluic acid) and dissolved H<sub>2</sub> resonances as a function of flow rate in THF at 200 psig. Experimentally measured  $T_1$  values for each resonance (H<sup>A</sup>, H<sup>B</sup>, H<sup>C</sup>, and H<sub>2</sub>) correlate with the observed area percent attenuation.

instrument probe volume constantly being in a non-equilibrium state during flow. Fig. 4 illustrates the signal attenuation dependence on flow rate for *p*-toluic acid (50 mM) and H<sub>2</sub> (200 psig) in THF. In cases where the primary objective is measurement of dissolved H<sub>2</sub>, the use of external standard calibration or electronic signal introduction techniques may eliminate the need to employ a compensation factor because the measured  $T_1$  of dissolved H<sub>2</sub> is relatively short ( $T_1 = 1.4$  seconds in THF at 200 psig) and signal attenuation was considered to be negligible for flow rates  $\leq 4.0$  mL min<sup>-1</sup> with the equipment used in this work. The measured  $T_1$  of dissolved H<sub>2</sub> agreed well with previously reported values.<sup>13</sup>

The general method described can be repeated with different temperatures, solvents, pH, and matrix composition to characterize the impact of these variables on the solubility of dissolved H<sub>2</sub>. Table 1 provides the Henry's Law constants obtained *via* this approach. As described by Brunner,<sup>14</sup> reported solubility values of H<sub>2</sub> in organic solvents are highly variable and often exhibit poor reproducibility for a given technique. The repeatability of the NMR measurement is evident from the data in Fig. 2 and its precision can be inferred from the high  $R^2$  values in Table 1.

Much of the variation from this method can be accounted for and ultimately reduced if desired or required. Sources of variation include error in the potency and concentration of the internal standard(s) used, diffusion of H<sub>2</sub> out of the PTFE tubing region ( $\sim 2$  meters), variations in reactor temperature (temperature of the reactor was not regulated for the data

**Table 1** Resulting Henry's Law constants at room temperature obtained experimentally with this method. Measurements were performed using a range of 0–1014.6 psia H<sub>2</sub>. Constants are in units of psi L mol<sup>-1</sup> and Pa m<sup>3</sup> mol<sup>-1</sup>. Corresponding linearity values are also provided to demonstrate the precision of this method

Solvent	Flow NMR: H (psi L mol <sup>-1</sup> )	Flow NMR: H (Pa m <sup>3</sup> mol <sup>-1</sup> )	Linearity ( $R^2$ )
THF	3434	23 677	0.9999
Acetonitrile	3194	22 026	0.9994
MeOH	2452	16 910	0.9997
Toluene	3788	26 119	0.9996
<i>n</i> -Hexane	2293	15 776	0.9996

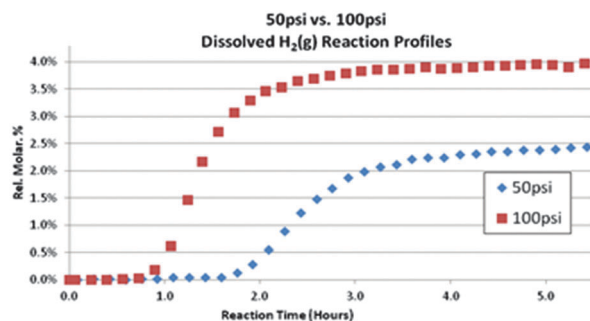


Fig. 5 H<sub>2</sub> profiles obtained from *in situ* <sup>1</sup>H NMR reaction monitoring for a reaction which was performed twice using different pressures.

reported), accuracy of pressure regulation, and accuracy of the flow compensation factor.

The ability to qualitatively and/or quantitatively monitor dissolved H<sub>2</sub> concentrations *in situ* provides valuable insight for characterizing catalytic reductions as well as other reactions that make use of H<sub>2</sub> (*e.g.*, hydroformylations). Fig. 5 shows the dissolved H<sub>2</sub> profiles for a catalytic reduction performed twice under identical conditions except for differences in H<sub>2</sub> pressure.

These H<sub>2</sub> concentration profiles reveal that each reaction is mass transfer limited for a significant duration at the beginning of the experiment (*i.e.*, no dissolved H<sub>2</sub> is observed by <sup>1</sup>H NMR because it is rapidly consumed in the reaction). The  $k_1a$  is the major factor dictating the observed reaction kinetics. Identification of this mass transfer limitation greatly facilitates process scale-up as it highlights the importance of examining variables that affect the H<sub>2</sub> uptake (*e.g.*, agitation efficiency).

In a separate experiment, direct measurement of  $k_1a$  for a lab reactor setup was performed by monitoring the H<sub>2</sub> saturation dynamics. The reactor contents and conditions were identical to that used for an actual reaction except that catalyst was not added to the solution. Fig. 6 shows a comparison of two H<sub>2</sub> saturation profiles where the only difference between the two reaction matrices was the viscosity differences due to the presence and absence of insoluble salts. Future communications will detail the approach for obtaining  $k_1a$  values *via* this direct measurement of H<sub>2</sub> quantitation method.

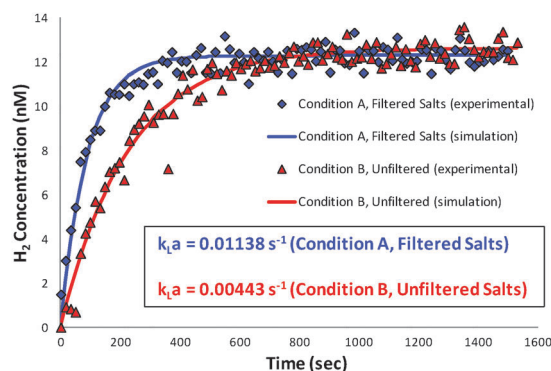


Fig. 6 H<sub>2</sub> saturation profiles where Condition A did not filter salts and Condition B was a filtered solution. Viscosity differences solely accounted for the variation in saturation rate differences and hence  $k_1a$  values.

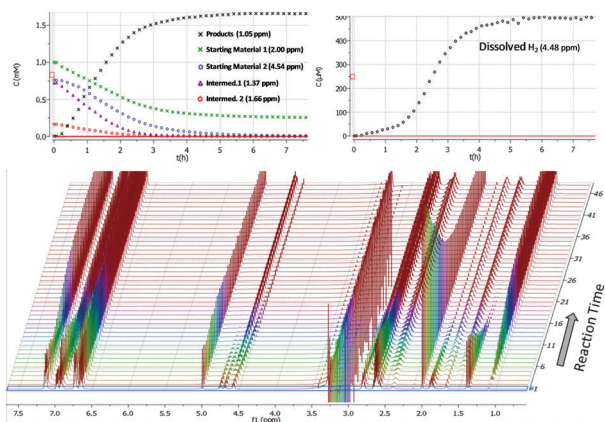


Fig. 7 Example of a reaction monitoring using  $^1\text{H}$  NMR (with solvent suppression of methanol resonances) spectral overlay illustrating resulting trends of relevant reaction components including dissolved  $\text{H}_2$ . Reaction utilized a 5 mole percent loading of Pd/C.

In addition to quantitatively monitoring dissolved  $\text{H}_2$ , this method allows for the simultaneous quantitation of various dissolved reaction components. This method affords a holistic view of the reaction that is not possible *via* other traditional means of analytical reaction monitoring. A combination of *in situ* 1D and 2D NMR analysis allows for the elucidation of reaction species that are short lived, atmospherically unstable, and challenging to otherwise elucidate. Fig. 7 shows an example of a reaction profile that includes trends for starting materials, intermediates, products, and dissolved  $\text{H}_2$ .

The capability to quantitatively monitor dissolved  $\text{H}_2$  concentration by  $^1\text{H}$  NMR at high pressure with continuous circulation provides valuable insight for the characterization of reactions, provided that the necessary precautions are taken to ensure accurate measurements. The general approach described can be extended to other NMR-active nuclei as well (*e.g.*,  $^{13}\text{C}$ ,  $^{15}\text{N}$ ,  $^{19}\text{F}$ ,  $^{31}\text{P}$ , *etc.*). In cases where the enantioselectivity of a catalytic reaction varies based on the concentration of dissolved gases,<sup>15</sup> this technique provides both a means of identifying this behaviour and optimizing conditions for a favourable yield of the desired product. Additional on-line analytical tools like HPLC may be required for enantiomer identification and monitoring in these situations. In general, the use of flow NMR analysis is a powerful tool for *in situ* reaction monitoring because it provides exquisitely

specific and quantitative information without perturbing the chemical system being studied.

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