

Simple Calibration Concept of an Online NMR Module Demonstrated in a Modularised Production Plant

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Motivation

Within the CONSENS Project [1], the challenge to adapt a commercially available benchtop NMR spectrometer to the full requirements of an automated chemical production environment was tackled successfully. The developed online NMR module (Fig. 1) was provided in an explosion proof housing and involves a compact NMR spectrometer together with automated data acquisition and evaluation unit, flow control, as well as data communication.

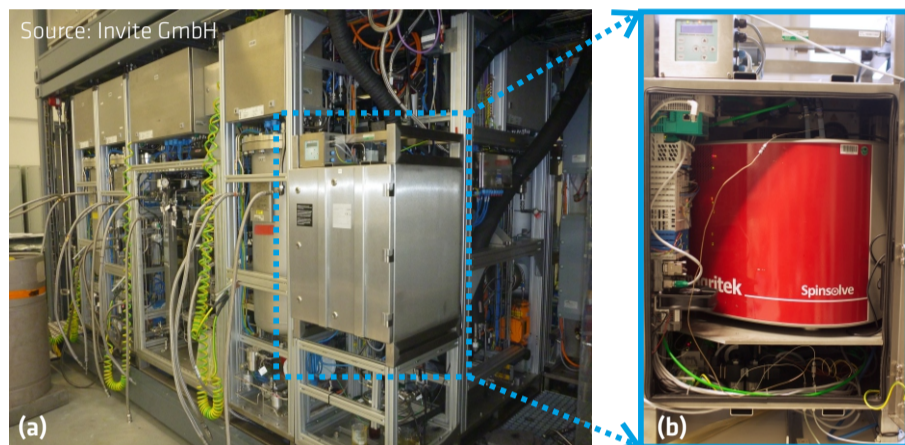
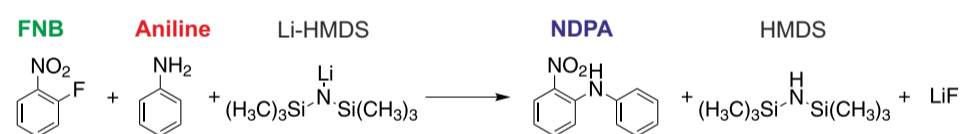


Fig. 1: Modular production plant for continuous synthesis of organic compounds (a) monitored by an online NMR module (b)

Model Reaction

In the studied model reaction two aromatic substances (Eq. 1) are coupled initiated by a lithiation step:



Eq. 1: Reaction scheme, FNB: 1-Fluoro-2-nitrobenzene, Li-HMDS: Lithium bis(trimethylsilyl)amide, NDPA: 2-Nitrodiphenylamine

Online NMR Spectra

- Reaction was investigated in semi-batch mode
- Two spectrometers (43 MHz and 500 MHz) were connected to process in by-pass via flow cells

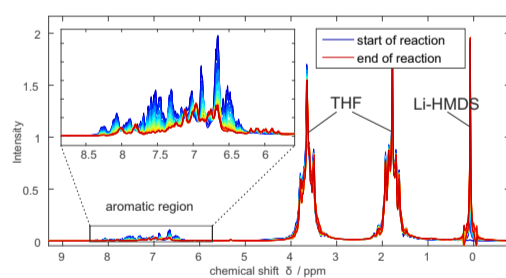


Fig. 2: Online low-field NMR spectra (43 MHz), single scan each 15s.

Quantitation and Online Validation

Relative Quantitation

Calibration free

$$x_i = \frac{A_i}{\nu_i} / \sum_{i=1}^n \frac{A_i}{\nu_i}$$

Absolute Quantitation

1-point calibration

$$c_i = CCF \cdot \frac{A_i}{\nu_i}$$

- daily check possible
- derived from neat solvent signal or raw material concentration

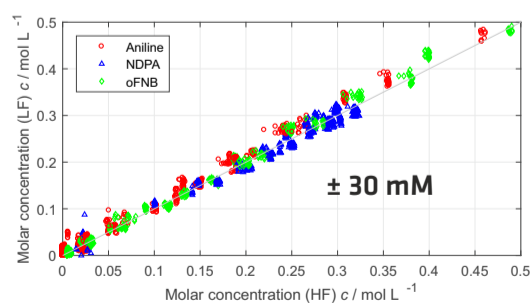


Fig. 3: Comparison of high-field (reference) and low field NMR results during steady state condition in lab environment

A = Peak area, ν = Number of nuclei, CCF = Concentration conversion factor

Flexible Peak Functions

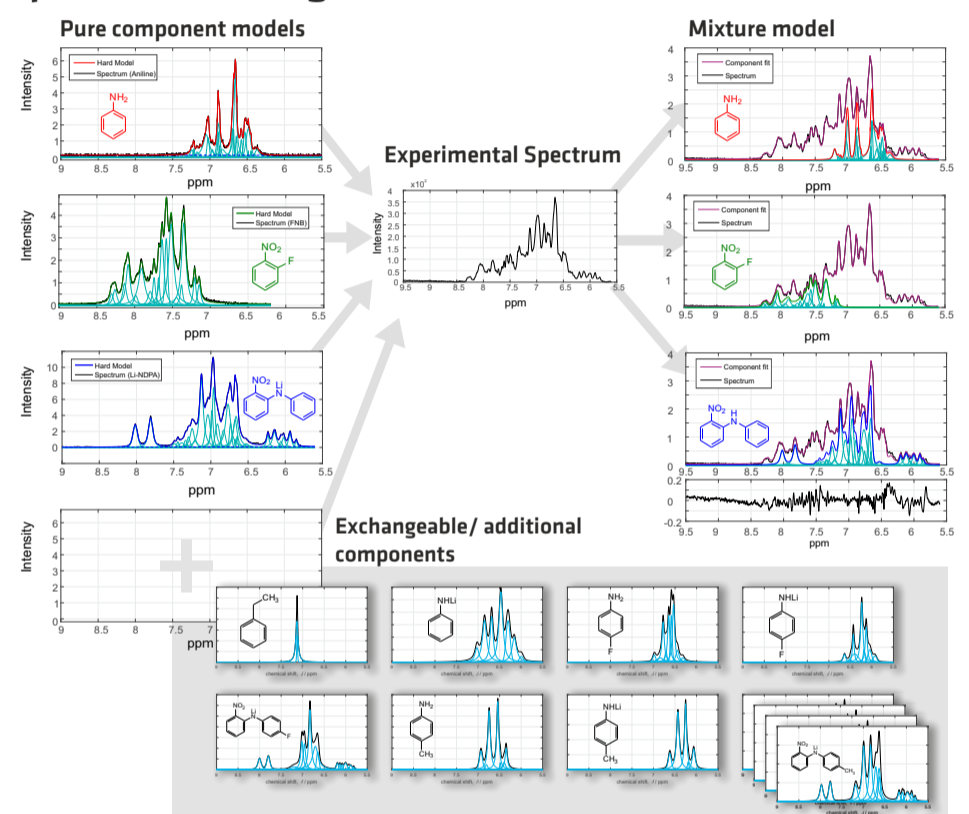
Pure component models based on Pseudo-Voigt functions (Eq. 2) can be derived via peak fitting of measured pure components [2] or by the use of spin calculations.

$$V = \alpha \left[\beta e^{-4 \ln 2 \frac{(x-\delta)^2}{\gamma^2}} + (1-\beta) \frac{\gamma^2}{(x-\delta)^2 + \gamma^2} \right]$$



Eq. 2: α = maximum, γ = width, δ = position, β = Gaussian-Lorentzian-ratio

Spectral Modeling



Step Changes of APC and Response NMR Signal

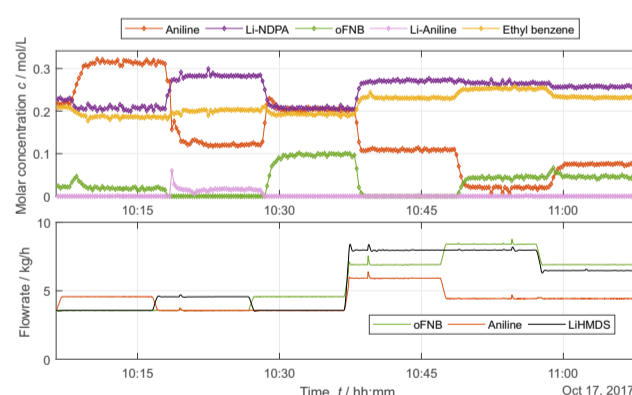


Fig. 4: Validation of fully automated online NMR module in direct loop control. The continuous synthesis of NDPA was monitored in an industrial pilot plant. The delay time between step changes of pumps and NMR signal change was in between 3-5 min.

Discussion

- Good agreement between LF and HF NMR spectrometers
- Suitable method for monitoring the model reactions
- Modeling of pure component spectra significantly reduces calibration effort compared to statistical models

References

- [1] www.consens-spire.eu
- [2] A Michalik-Onichimowska, S Kern, et al., J Magn Reson. 2017, 277, 154-161.