

Reading Between the Lines – Automated Data Analysis for Low-Field NMR Spectra

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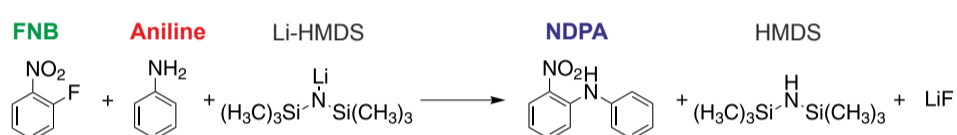
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Motivation

For reaction monitoring using NMR instruments, in particular, after acquisition of the FID the data needs to be corrected in real-time for common effects using automated methods. When it comes to NMR data evaluation under industrial process conditions, the shape of signals can change drastically due to nonlinear effects. However, the structural and quantitative information is still present but needs to be extracted by applying predictive models.

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

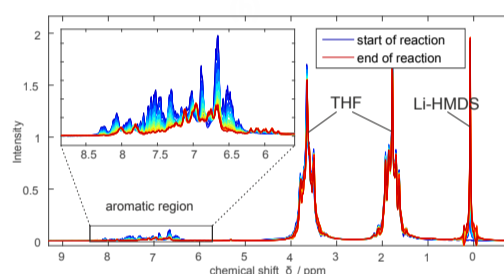
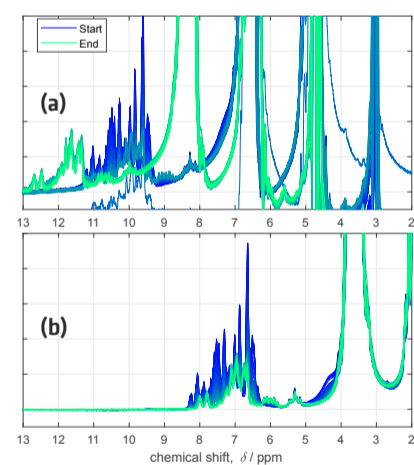


Fig. 1: Online low-field NMR spectra (43 MHz), single scan each 15 s

Automated Data Processing



Acquired raw spectra were processed with the following tools:

- Phase correction (Entropy minimization method, [1])
- Baseline correction (Low-order Polynomial fit, [2])
- Alignment (icoshift, [3])

Fig. 2: Online low-field NMR spectra (43 MHz), (a) raw spectra, (b) processed spectra

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

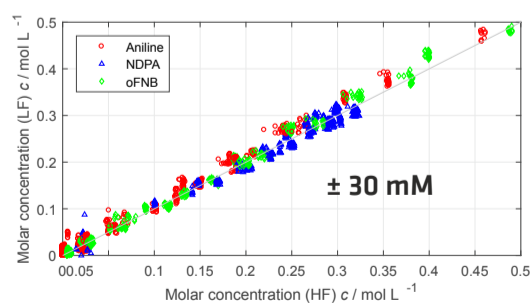
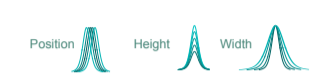


Fig. 3: Comparison of high-field (reference) and low-field NMR results during steady state condition in lab environment

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

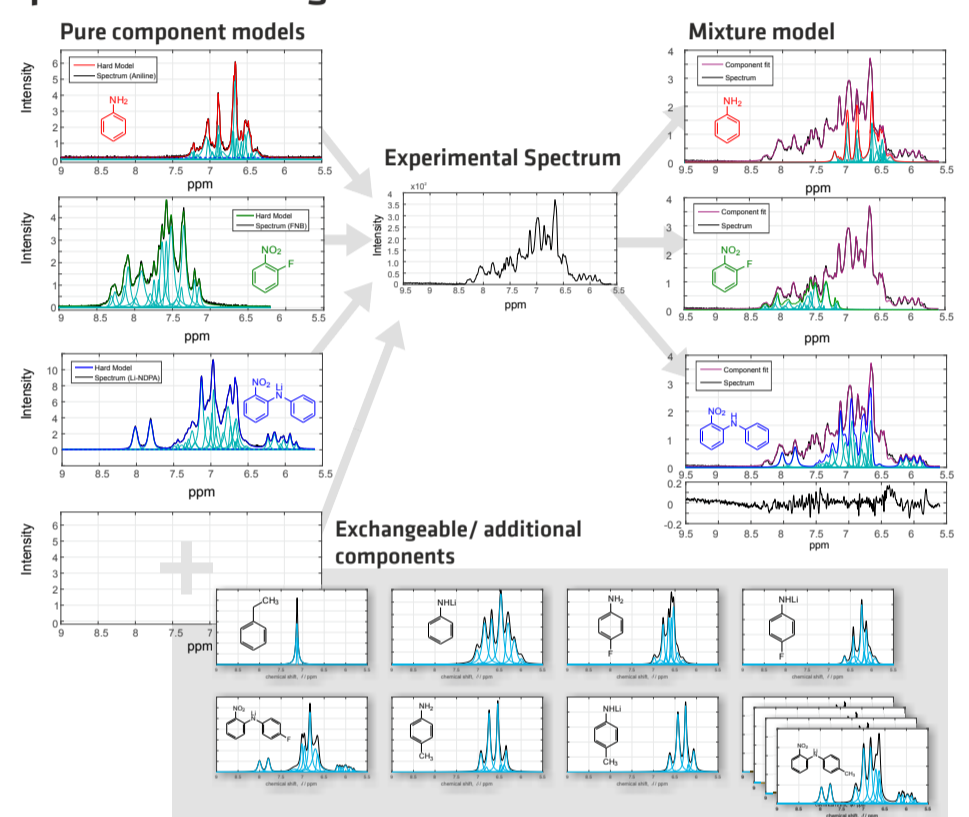
Flexible Peak Functions

Pure component models based on Pseudo-Voigt functions (Eq. 2) can be derived via peak fitting of measured pure components [4] 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

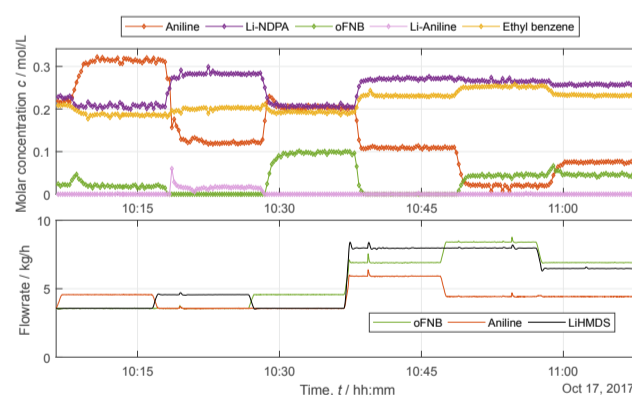


Fig. 4: Validation of fully automated online NMR module in direct loop control. The continuous synthesis of NDPA was monitored in an industrial pilot plant. The delay time between step changes of pumps and NMR signal change was in between 3-5 min.

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] Chen et al., J Magn Reson. 2002, 158, 164-168.
- [2] Mazet et al., Chemometrics Intell. Lab. Sys. 2005, 76, 121-133.
- [3] Savorani et al., J Magn Reson. 2010, 2, 190-202.
- [4] A. Michalik-Onichimowska, S. Kern, et al., J. Magn. Reson. 2017, 277, 154-161.