

Already producing or still calibrating? – Advances of model-based data evaluation concepts for quantitative online NMR spectroscopy

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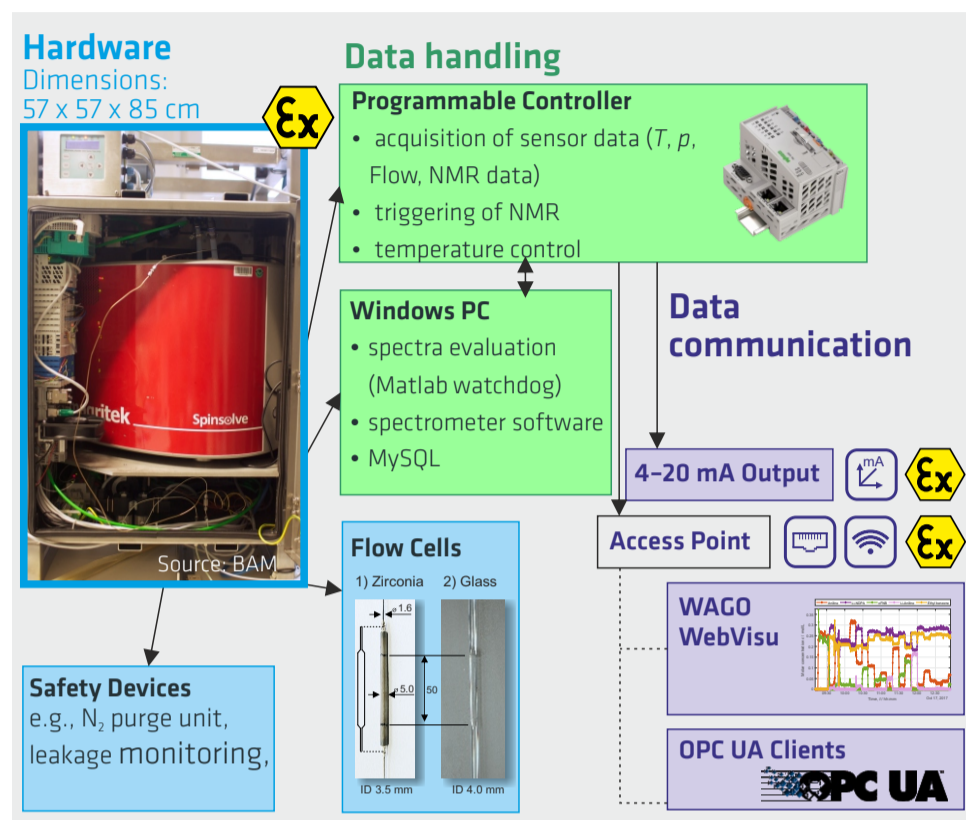


Figure 1:

Overview of the online NMR module: Reacting mixtures were pumped through a NMR flow cell within the module. For data evaluation of the low-field NMR spectra, a spectral modeling procedure based on Indirect Hard Modeling (IHM) was developed and validated (Fig. 2). Online concentration profiles were shared with process control systems via an integrated OPC UA server over intrinsically safe Ethernet cable and/or Wi-Fi connection.

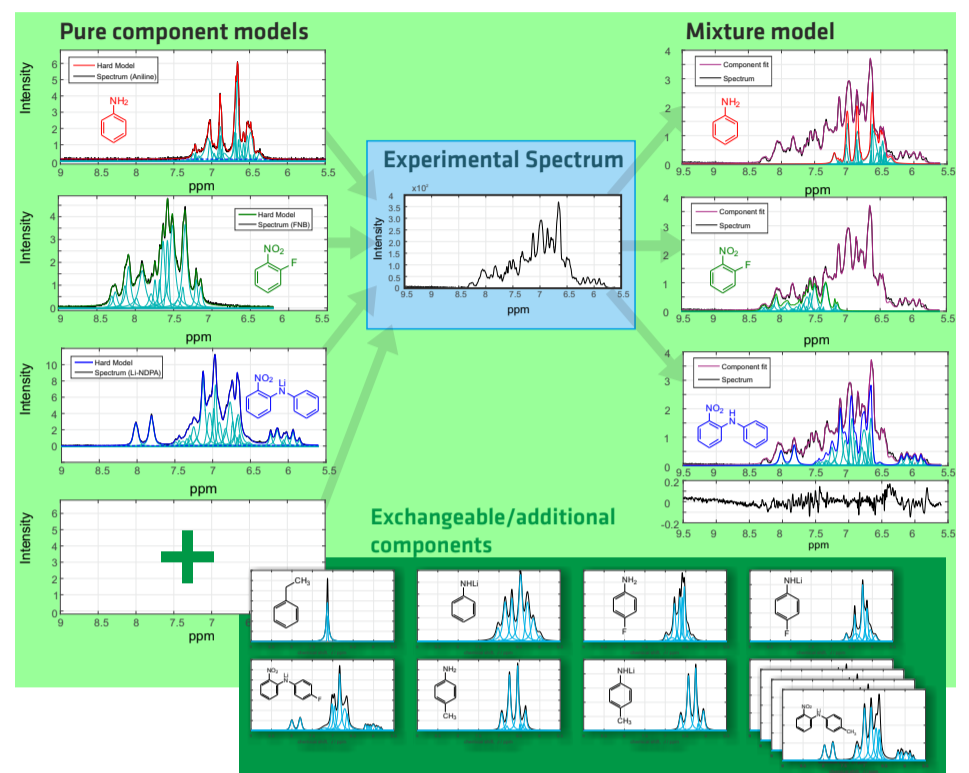


Figure 2:

Automated Data analysis using IHM in two steps: (1) Pure component models are built upon NMR spectra of the reactants and products; (2) Experimental spectra are represented by the given pure component models.

Integrated Process Design using Modular Plants

Compared to traditional batch processes, intensified continuous production gives admittance to new and difficult to produce compounds, leads to better product uniformity, and drastically reduces the consumption of raw materials and energy. Consequently, full automation – ideally in a modular configuration – is a prerequisite to realize such benefits of intensified continuous plants [1, 2].

From Lab Bench to Industrial Scale

Within the CONSENS Project [1], the challenge was to adapt a commercially available benchtop NMR spectrometer to the full requirements of an automated chemical production environment including ATEX certification (Fig. 1, 3).

As a typical pharmaceutical reaction, the coupling of two aromats in THF (5–10 wt-% level) using a lithium base was chosen as an example (Fig. 4).

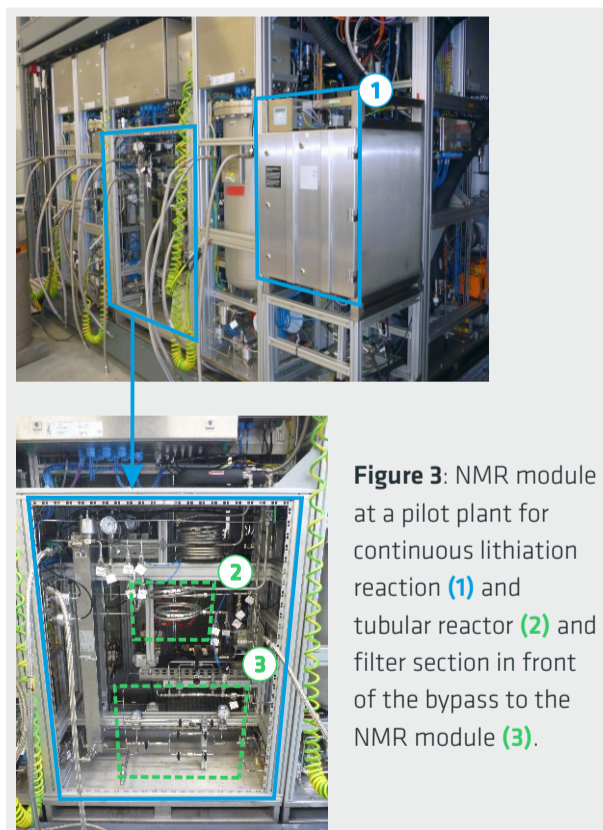


Figure 3: NMR module at a pilot plant for continuous lithiation reaction (1) and tubular reactor (2) and filter section in front of the bypass to the NMR module (3).

Automated Data Preparation and Analysis

For the automated spectra analysis we moved away from conventional multivariate statistical approach, (i.e., PLS-R) to physically motivated spectral models (i.e., Indirect Hard Modelling, IHM), which can meet the demands of low calibration effort or even be calibration free (Fig. 2).

Results: Test Runs in the Modular Plant

Several test runs served as validation experiments lasting from 6 to 11 hours each. The NMR module was used in combination with advanced process control, sensor failure detection, as well as performance monitoring algorithms to control and optimise the given lithiation reaction process (Fig. 5).

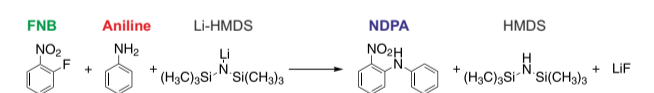


Figure 4: FNB: 1-Fluoro-2-nitrobenzene, LiHMDS: Lithium bis(trimethylsilyl)amide, NDPA: 2-Nitrodiphenylamine

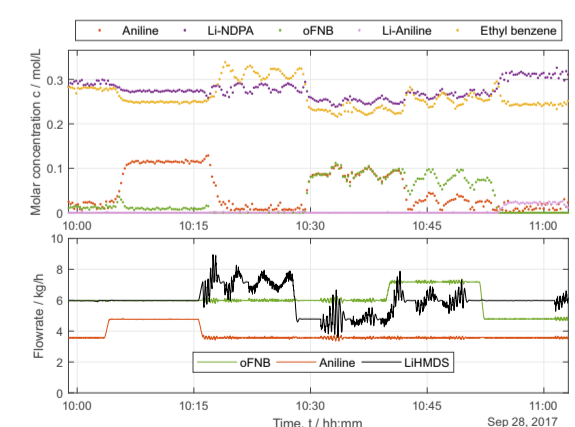


Figure 5: Representative NMR module results during an 11 hours continuous run of the production plant at INVITE (detail with feed pump oscillations). Molar concentrations of five different species, i.e., the reactants of Fig. 4 plus lithiated aniline (pink) and the “stabilizer” ethylbenzene (orange). Below: mass flows of the starting materials at reactor inlet.

References

- [1] www.consens-spire.eu
- [2] Klas Meyer, et al. "Process control with compact NMR." *Trends in Analytical Chemistry* 83 (2016): 39–52.
- [3] Simon Kern, et al. "Online Low-Field NMR Spectroscopy for Process Control of an Industrial Lithiation Reaction – Automated Data Analysis, ABC (2018), submitted