First steps towards field integration of benchtop NMR spectroscopy for online monitoring and process control

Simon Kern[1], Patrick Gräßer[1,3], Nicolai Zientek[1,2], Michael Maiwald[1]

[1]Bundesanstalt für Materialforschung und -prüfung (BAM), Richard-Willstätter-Str. 11, D-12489 Berlin, Germany
[2]Technische Universität Berlin, Department of Chemical Engineering, Straße des 17. Juni 136, MA 5-7, 10623 D-Berlin, Germany
[3]Humboldt-Universität zu Berlin, Institut für Chemie, Brook-Taylor-Str. 2, 12489 D-Berlin, Germany

BAM
Bundesanstalt für Materialforschung und -prüfung

Motivation

The F^3 Factory focuses on new "plug and produce" modular and standardized chemical production for low to medium scale production, in order to demonstrate cleaner and more efficient manufacturing technologies. By introducing novel online sensors & closed-loop control methods flexible intensified continuous processes can be advanced. **Online NMR spectroscopy has an enormous potential to become an important analytical tool for reaction monitoring**, when flow probes are directly coupled to reactors.

Fig. 1: Containerized modular plant from F^3 Factory project (www.f3factory.com)

Specific challenges are

- Small dimensions: fast sensors & closed-loop control
- Higher quality levels: more accurate sensors
- Innovative products: fast design, engineering and optimization
- Fouling and clogging

Methods

The intended work flow for the process integration of a benchtop 43 MHz NMR spectrometer including acquisition of NMR signal (FID), automated data correction and evaluation by univariate and multivariate models is proposed according to Fig. 2.

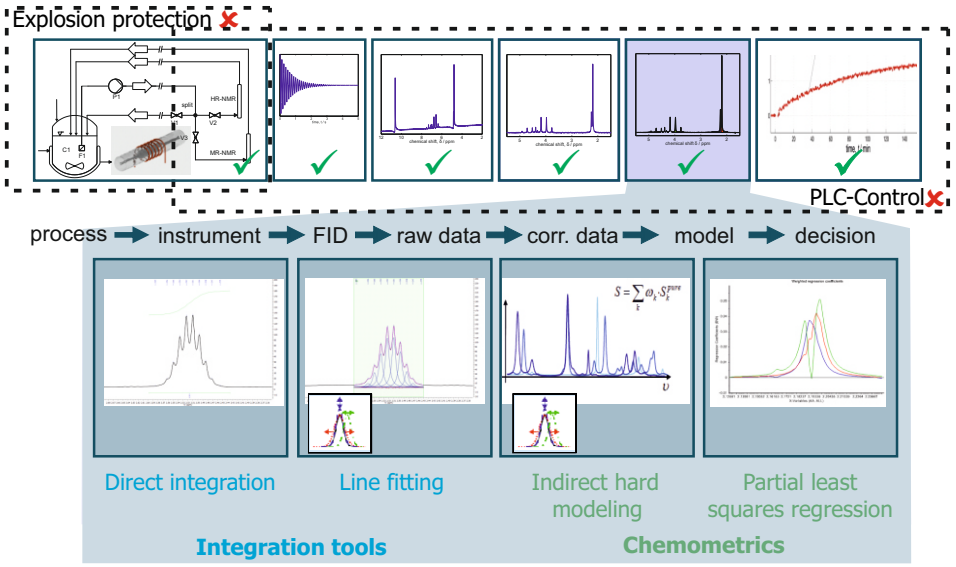


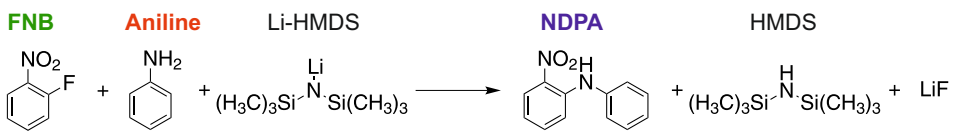
Fig. 2: Workflow for process integration of NMR sensor

Recent work proofed the following principles

- Online acquisition of quasi-simultaneous ^{1}H and ^{19}F spectra[1]
- Automated data pretreatment and evaluation methods
- Comparison to quantitative 500 MHz HR NMR spectroscopy
- Indirect hard modeling works well to compensate overlapping peaks and non-linear effects (line broadening, peak shifts)[2]
- Prediction of IHM can be improved by combined models (^{1}H and ^{19}F)[3]

Model Reaction

The first step of a pharmaceutical model reaction (Eq. 1) is focused[4]:



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

Experimental

The reaction was performed in a 25 mL glass reactor with thermal jackets for temperature control of the reaction mixture (Fig. 3). The Li-HMDS was dosed stepwise by using a glass syringe.

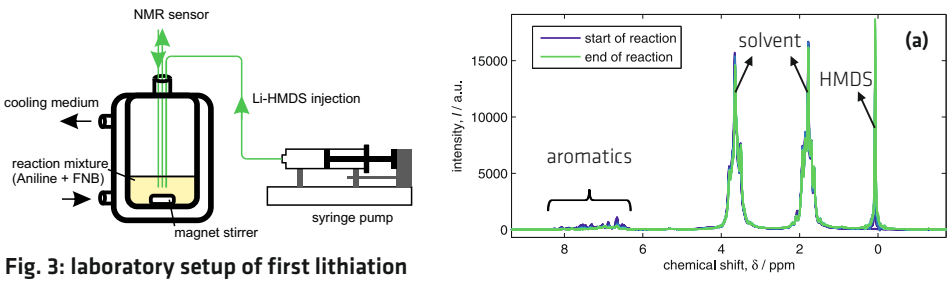


Fig. 3: laboratory setup of first lithiation

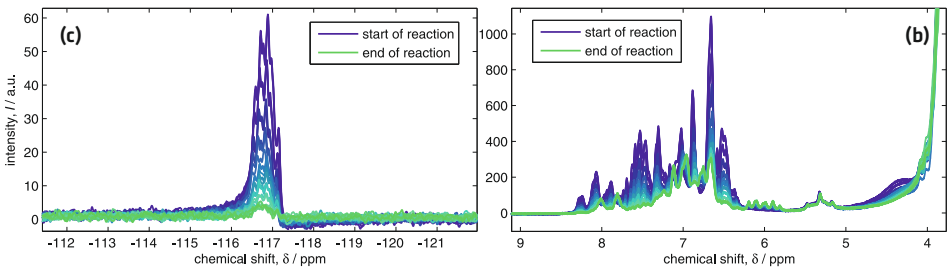


Fig. 4: ^{1}H spectra (4 scans) along reaction path (a) complete spectrum with dominat solvent signals; (b) aromatic region; (c) ^{19}F spectra (4 scans) along reaction path

First spectra in the proton and fluorine domain were recorded online using a flowrate of 3.5 mL min^{-1} and a simple 5 mm polytetrafluoroethylene tube (PTFE) as a flow cell.

Outlook

Construction of a “field” demonstrator (Fig. 5) for industrial applications

- Explosion proof housing for spectrometer, electronics and peripheral equipment
- Model based spectra evaluation by embedded PC
- Automation: programmable logic controller (PLC)
- Feedback to process control system

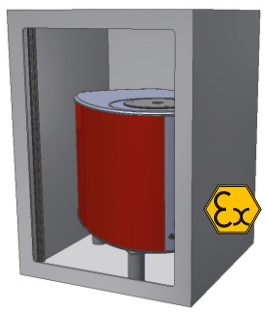


Fig. 5: ATEX housing

References and Acknowledgements

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