

## P17

## Process Monitoring of an Intensified Continuous Production Unit with Compact NMR Spectroscopy

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Monitoring chemical reactions is the key to chemical process control. Today, mainly optical online methods are applied. NMR spectroscopy has a high potential for direct loop process control [1, 2]. Compact NMR instruments based on permanent magnets are robust and relatively inexpensive analyzers, which feature advantages like low cost, low maintenance, ease of use, and cryogen-free operation. Instruments for online NMR measurements equipped with a flow-through cell, possessing a good signal-to-noise-ratio, sufficient robustness, and meeting the requirements for integration into industrial plants (i.e., explosion safety and fully automated data analysis) are currently not available off the rack. Recently, promising benchtop NMR instruments with acceptable performance came to market and process integrated sensors developed on basis of such laboratory instruments are on their way [2].

Intensified continuous processes are in focus of current research. Compared to traditional batch processes, these are giving admittance to new and difficult to produce compounds, leading to better product uniformity, and drastically reducing the consumption of raw materials and energy. Flexible (modular) chemical plants can produce different products using the same equipment with short down-times between campaigns, and quick introduction of new products to the market. Typically, such plants have smaller scale than big size facilities for production of basic chemicals but are still capable to produce kilograms to tons of specialty products each day. Such flexible (modular) plants can be provided in the size of 20 ft freight containers and represent a promising approach by their ability of easy transfer to production sites as well as the possibility of increasing production capacity by a simple numbering-up-approach.

However, full automation is a prerequisite to realize such benefits of intensified continuous production. In continuous flow processes steady automated measurements and tight closed-loop control of the product quality are mandatory. If these are not available, there is a huge risk of producing large amounts of out-of-spec (OOS) products. This is addressed in the European Union's Research Project CONSENS (Integrated Control and Sensing [3]) by development and integration of smart sensor modules for process monitoring and control within such modular plant setups.

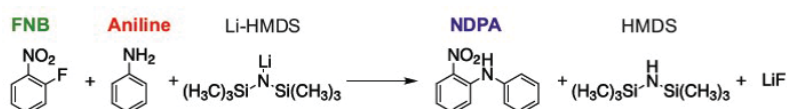
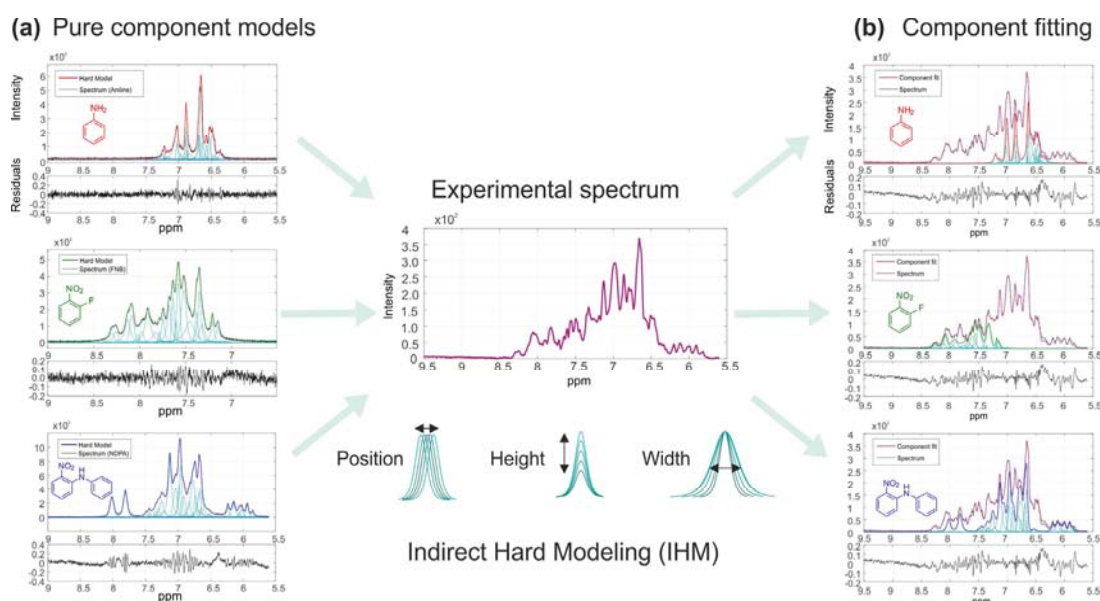


Fig. 1: Reaction scheme [4]: FNB: 1-Fluoro-2-nitrobenzene, Li-HMDS: Lithiumbis(trimethylsilyl)amide, NDPA: 2-Nitrodiphenylamine.

Figure 1 represents a given example of a pharmaceutical reaction step [4], within two aromats are coupled using the lithium base Li-HMDS. The reaction takes place in a 5 wt-% solution in THF. Deviations from unknown starting material and reactand concentrations together with the precipitation of LiF will lead to severe fouling and blocking of the modules. Typically, metal organic reactands are difficult to analyse due to the sensitivity to

air and moisture. Thus, this example reaction was chosen in CONSENS to develop and validate a compact NMR sensor to maintain an optimal stoichiometry during the full course of the continuous production [3, 5].

The NMR analyzer is provided in an explosion proof housing of 57 x 57 x 85 cm modul size and involves a compact 43.5 MHz NMR spectrometer together with an acquisition unit and a programmable logic controller for automated data preparation (phasing, baseline correction) and evaluation. Indirect Hard Modeling (IHM) was selected for data analysis of the low-field NMR spectra. Therefore, the aromatic region of the NMR spectra had to be chosen; representing higher order NMR spectra (cf. Figure 4a). A couple of semi batch reactions were performed for development of IHM models. Within these studies Li-HMDS was dosed stepwise to the reactands aniline and FNB along the reaction coordinate using 500 MHz high-field NMR spectroscopy as reference method.



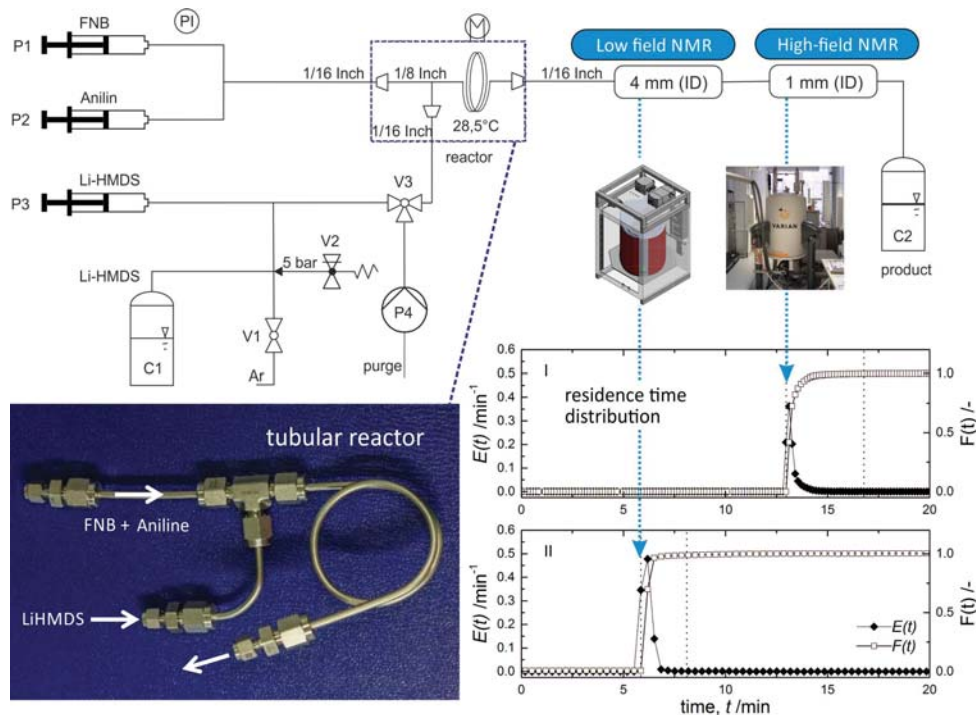
**Fig. 2:** Data analysis scheme for Indirect Hard Modeling (IHM) of the aromatic region (see Figure 4a) of the NMR spectrum: **a** pure component models are built upon NMR spectra of the reactands and products; **b** experimental spectrum; **c** representation of the experimental spectrum by adjustment of the three pure component models. Selected parameters of Lorentzian-Gaussian functions such as position, height, or width can be optimized to account for line shifts or other non-linear effects along the course of the reaction.

IHM model development consists of three steps as represented in Figure 2: Firstly, pure component models are built upon NMR spectra of the reactands and products (Fig. 2.a). Each pure component model (“Hard Model”) consists of a number of Lorentzian-Gaussian functions, representing the spectral peaks. Within that Hard Model, the peak areas are fixed against each other. Secondly, an experimental NMR spectrum is acquired and prepared by phasing and baseline correction (Fig. 2b). Finally, this experimental spectrum is represented by the given pure component models from the beginning step by iterative fit routines aiming at minimized residues (Fig. 2c). Within this step, selected parameters of Lorentzian-Gaussian functions such as position, height, or width can be optimized. This allows for slight line shifts or other non-linear effects along the course of the reaction, which likely occur in NMR spectra of technical mixtures and make IHM the method of choice.

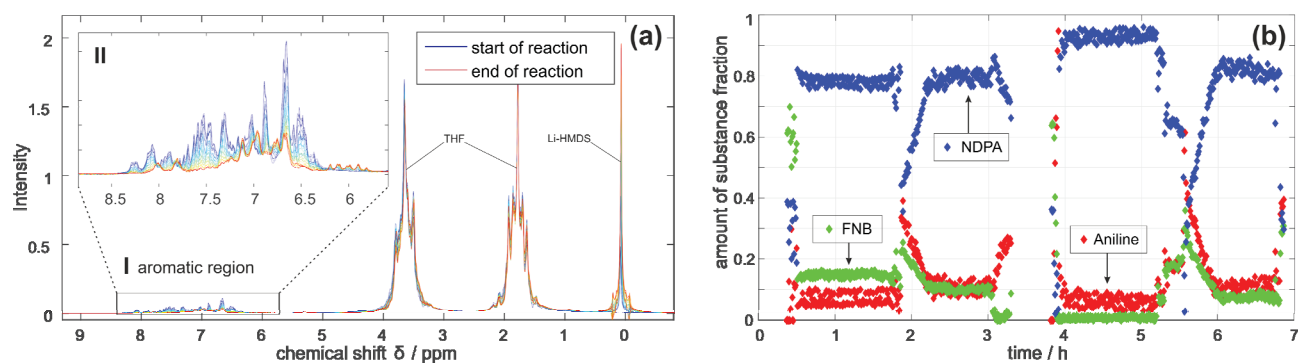
A set-up for monitoring of the continuous lithiation reaction in a thermostated 1/8” tubular reactor using syringe pumps was used to validate the IHM models according to the scheme in Figure 3 again using high-field NMR spectroscopy for comparison.

A considerable number of continuous experiments were performed for validation taking account for various reaction conditions by individually adjusting the flow rates of the reagents aniline, FNB, and Li-HMDS. Figure 4b depicts amount of substance fractions observed with the NMR sensor and the IHM methods over an observation period of 6.5 hours. The largest prediction uncertainties were found for aniline to be 5–7 % relative, i.e.,

0.25–0.35 % absolute. As can be seen in Figure 2a and 2c, the signals of aniline totally overlap with the further reagents giving reason for model deviations. IHM overestimates aniline in the low concentration range during equivalent adjustments of the three pure component models. These overestimates lead to systematic underestimates of the product FNB due to application of a 100 % approach hence exhibiting comparable scatter.



**Fig. 3:** Schematic representation of the validation set-up for monitoring of the continuous reaction unit with the compact NMR sensor. The lithiation reaction (Figure 1) is continuously carried out in a thermostated 1/8" tubular reactor using syringe pumps. A 500 MHz online high-field NMR spectrometer provided reference data, which were time corrected according to the residence time distribution.



**Fig. 4a:** 43.5 MHz  $^1\text{H}$  NMR spectra along the course of the lithiation reaction (from calibration experiments). The aromatic region i represents higher order NMR spectra and signals are weak due to the concentration level of about 5 wt-% in THF; ii enlargement of the aromatic region. **b** Amount of substance fractions observed with the NMR sensor of the reagents aniline and FNB and the product NDPA along an observation period of 6.5 hours.

#### Literature

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