

Poster 7

“Click” analytics for “click” chemistry – a simple method for calibration-free evaluation of online NMR spectra

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Currently research in chemical manufacturing moves towards flexible plug-and-play approaches focusing on modular plants, capable of producing small scales on-demand with short down-times between individual campaigns. This approach allows for efficient use of hardware, a faster optimization of the process conditions, and thus, an accelerated introduction of new products to the market [1]. Driven mostly by the search for chemical syntheses under biocompatible conditions, so-called “click” chemistry rapidly became a growing field of research. The resulting simple one-pot reactions are so far only scarcely accompanied by an adequate optimization via comparably straightforward and robust analysis techniques. Here we report on a fast and reliable calibration-free online high field NMR monitoring approach for technical mixtures. It combines a versatile fluidic system, continuous-flow measurement with a time interval of 20 s per spectrum, and a robust, automated algorithm to interpret the obtained data. All spectra were acquired using a 500 MHz NMR spectrometer (Varian) with a dual band flow probe having a 1/16 inch polymer tubing working as a flow cell. Single scan ¹H spectra were recorded with an acquisition time of 5 s, relaxation delay of 15 s.

As a proof-of-concept, the thiol-ene coupling between N-boc cysteine methyl ester (A) and allyl alcohol (B) was conducted (Fig. 1) in non-deuterated solvents while its time-resolved behaviour was characterised with step tracer experiments.

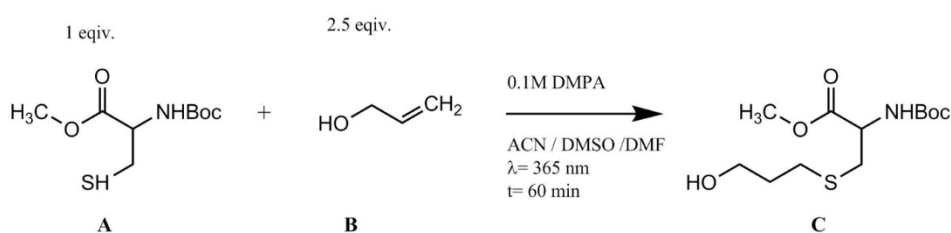


Fig. 1: Reaction mechanism of the thio-ene coupling – A: N-Boc cysteine methyl ester, B: allyl alcohol, C: thioether product.

For the conducted thiol-ene coupling online NMR spectra were processed by automated algorithms according to Fig. 2 and 3.

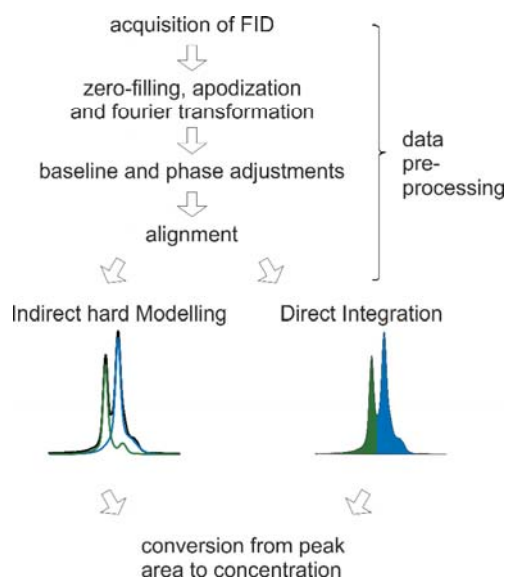


Fig. 1: Data processing scheme for online NMR data

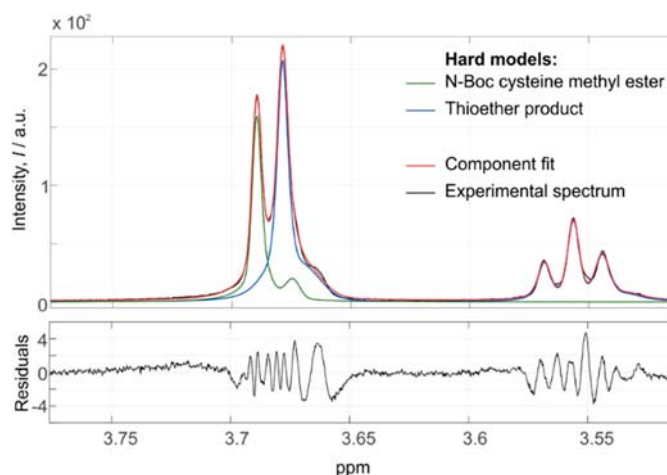


Fig. 2: Representative result for the component fitting for a reaction mixture

Due to the high linearity between absolute signal area and sample concentration in NMR spectra in most cases no need for a linear calibration model is needed. Thus, a different approach for spectral evaluation was chosen with the benefit of reducing the calibration effort aiming at reducing the set-up times for implementation of the NMR analyzer. Instead of a linear calibration model, the concentrations were directly calculated out of the peak areas of a fitted spectral model.

Overlapping signals in online spectra during thiol-ene coupling could be deconvoluted with a spectral model using calibration free indirect hard modelling (IHM) and were subsequently converted to absolute concentrations. To monitor the reaction propagation, IHM was chosen as the favourable model since it allows for a separation of overlapping peaks providing better distinction between shifts of reactants and product laying in the close vicinity. This method benefits in comparison to classical chemometric methods like partial least squares regression (PLS-R) from quantitative insight in signal areas of pure components in overlapping signals and thus yields a significantly reduced calibration effort. The obtained results were compared with direct integration (DI) of non-overlapping signals and showed good agreement with the implemented mass balance.

Through the application of IHM the signal area for each reactant can be deconvoluted in the spectrum and thus converted to the respective concentrations or molar ratios (Fig. 4 and 5). The signals which were suitable for direct integration were used herein for comparison purposes of both methods.

The sensitivity of the presented approach allows to identify minor changes in the reaction kinetics when different solvents are applied. Moreover, depicted negligible deviations in concentration during several experiments indicate high repeatability between the measurements. A direct comparison of the two methods, IHM and DI, reveal their analogous performance. IHM considers additional peaks, which cannot be resolved utilizing DI, providing more flexibility to characterize chemical systems and a more robust analysis. The ultimate advantage of IHM can be anticipated to lie in a quantitative analysis of non baseline-resolved spectra as they are typical for even more complex reaction mixtures or data obtained on lower field NMR instruments. Thus, the work presented here could eventually pave the road towards a reliable evaluation with low field NMR instruments using permanent magnets in an industrial environment. The extracted data would be beneficial for on-site kinetic studies, screening of novel reactions and optimization of reaction conditions run in small batches.

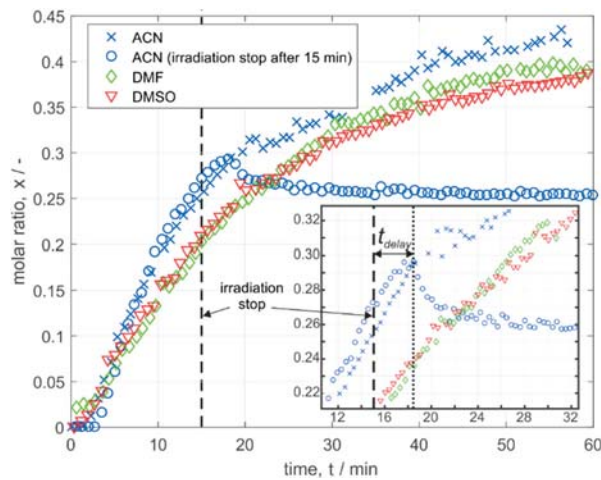


Fig. 3: Time courses of the molar ratio for the thioether product during photoreaction using various solvents. The light source was removed in one experiment after 15 min to study the time behavior of the system and the analyzer.

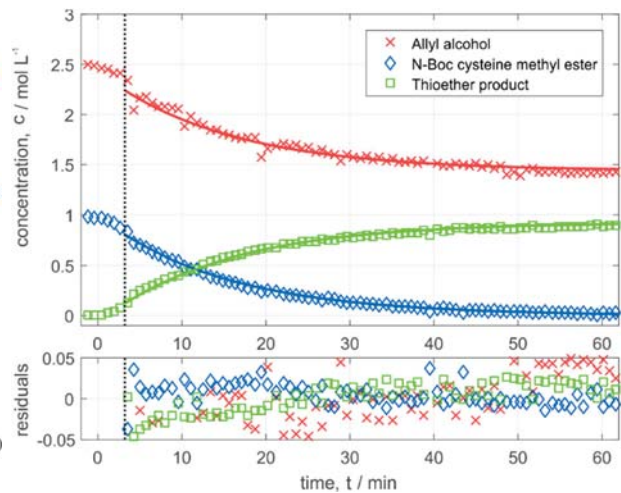


Fig. 4: Comparison of time courses for the photoreaction using DMSO as solvent calculated with IHM (symbols) and fitting results to first order reaction kinetics (lines), residuals of NMR results compared to mass balance of kinetic model

Literature:

- [1] CONSENS – Integrated Control and Sensing for Sustainable Operation of Flexible Intensified Processes, funded by the European Union's Horizon 2020 research and innovation programme under grant agreement N° 636942; www.consens-spire.eu; 30.09.2016
- [2] Meyer, K., Kern, S., Zientek, N., Guthausen, G., Maiwald, M.: Trends in Analytical Chemistry 83 (2016), S. 39–52.