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Taking compact NMR to monitoring real reactions in large-scale chemical industries – general considerations and learnings from a lab-scale test case

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/mrc.5061

Abstract:

The considerations for use of compact NMR in a large-scale industrial environment clearly differ from those in academic and educational settings and even from those in smaller companies. In the first part of this article, these differences will be discussed along with the additional requirements that need to be fulfilled for successful applicability in different use cases. In the second part of the article, outcomes from different research activities aiming to fulfill these requirements will be presented with a focus on an online reaction-monitoring study on a lab-scale nucleophilic chlorination reaction.

Introduction:

Over the last ten years, compact NMR spectroscopy equipment has made great progress from educational demonstrator systems to a serious analytical lab tool [1]. These instruments are based on well-homogenized permanent magnet setups and usually operate at proton NMR frequencies between 40 and 90 MHz.

Progress has been made especially in signal-to-noise ratio and sensitivity as well as in the development of adapted data processing routines. Nevertheless, limitations with respect to the different ratio between couplings and natural line widths and sensitivity will always persist compared to high-field NMR.

While these differences are only of minor importance in educational applications, they will need some more detailed consideration in the corporate world. In most large chemical companies, some internal high-field NMR capabilities are available, usually at some central research sites. For samples from these sites, transfer times tend to be short (minutes to half hour). Like that, the use case for compact NMR equipment will

mainly be limited to cases like reaction monitoring or high-throughput screening in which a large number of samples requiring analysis with minimal transfer time are produced.

For samples from sites with no NMR, longer transfer times and cost from safety requirements for shipping will have an influence on the overall assessment of economic viability: even a few samples per day may already provide a viable case for installation of a compact NMR system on site. The increased workload for operating and maintaining the compact NMR should be balanced against the time spent on packaging samples for shipping and the documentation required to do so.

In all cases, a careful alignment of the spectra from compact NMR with those from classical high-field NMR is needed and the persons involved in interpretation of the compact NMR data need to be especially trained in recognizing spectra with possible peculiarities that suggest the need for a second tier measurement by high-field NMR. In order to avoid possible ageing effects of the samples during transfer, the alignment of high-field and compact NMR spectra should be done by simultaneous measurements wherever possible.

Of the different use scenarios for compact NMR, reaction monitoring is the most challenging as measurement conditions as close as possible to the actual reaction are desirable. In many cases, this corresponds to measurements at elevated pressure and temperature in order to avoid:

- physical changes to the sample, such as evaporation and foaming or precipitation of certain components due to temperature-induced solubility changes
- chemical changes, such as shifts in chemical equilibria or the reaction of intermediates along different pathways.

If those challenges are mastered, the information from NMR measurements can be used for automated adjustment of process parameters to increase product yield and asset utilization [2]. In addition to measuring at reaction conditions, NMR instrumentation for process analytics needs to come with a sufficiently rugged and possibly explosion-proofed housing in order to be usable under process site conditions. Like this, the compact NMR with no need for cryogenic magnets and with a compact footprint comes with unique advantages over classical NMR in this field of application.

Furthermore, the NMR instrument needs to be capable of automatic operation and data processing with minimal human user involvement. On the hardware side, this requires a flow-through sample cell. Historically, NMR flow-cells have mainly been used in the context of hyphenated analytical methods, such as HPLC-NMR [3,4] and electrophoretic separation NMR [5,6]. More recently, some reaction monitoring was performed on high-field NMR systems with dedicated model process setups installed in the immediate vicinity of high-field NMR systems [7], often with a focus on pharmaceutical products [8,9]. Flow cells in these studies range from flow-through systems for use in a conventional NMR probe head [8] to dedicated probe heads with sophisticated temperature control systems [10].

With the availability of compact NMR setups with better and better spectral performance, an increasing number of publications on reaction monitoring on lab setups using compact NMR have been published over the last decades [11, 12]. In many of these studies, the degree of automation remained rather low and the focus was on a proof of principle. Such studies may only be considered as intermediate steps towards NMR systems for 24/7 reaction control in process industry. Later work includes the optimization of lab-scale organic syntheses [13, 14] and the determination

of chemical engineering parameters, such as distribution coefficients [15]. Newer work includes the applicability of compact NMR systems to study phase equilibria and reactions [16] and to monitor dynamic processes, such as batch distillation [17]. Kern et al. demonstrated that compact NMR facilitates the optimization [18] and control [19] of complex chemical processes that are relevant for technical or pharmaceutical applications.

In the present work, a fully automated NMR system based on a prototype compact NMR spectrometer has been developed which fulfills three of the above-mentioned requirements (the fourth, explosion protection, has also been fulfilled by building an Ex p II T4 rated inert-gas flushed box with a flexible barrier around the sample flow line even allowing measurements on combustible samples together with a local specialized company, but that development is out of scope of the present article). Its applicability in real life syntheses and especially the proper collaboration of parts from many different vendors is shown by online monitoring of the chlorination reaction path of an alcohol into its alkyl chloride using both NMR's structural and quantitative information. The chosen test reaction is a good example for an industrially relevant synthesis. The results demonstrate that the developed automated NMR system is a very useful and versatile tool with a broad fiel d of application in industries among others screening studies (e.g. catalysts, solvents, process parameters) in an early stage of process development or for fast quality control in production plants.

System design and component validation

In order to use a compact NMR system in process analytics, several changes compared to a lab instrument need to be made. Some involve the actual NMR instrument which needs to be equipped with a flow- cell suitable for operation at

elevated temperatures and pressures without negative impact on the probe and magnet of the instrument. The remaining challenges involve the integration of the NMR instrument with appropriate sampling hardware and the development of an automation platform able to control sampling and measurement as well as an evaluation of the NMR signals without a need for human intervention.

The automatic control was implemented in the standard modular lab automation platform of BASF running on an industrial PC obtained from Beckhoff (Verl, Germany). The different sampling and analytical modules are connected via RS-232 to this setup. The sampling system consists of a membrane pump from Fink ChemTech (Leinfelden-Echterdingen, Germany), a actively-automated 4-way-valve from VICI (Schenkon, Switzerland), Julabo heating jackets (Julabo, Seelbach, Germany) and PEEK and Teflon tubings of 2.0 mm ID and 4 mm from IDEX (Oak Harbor, WA, USA). As a compact NMR spectrometer, a prototype NMReady 60 compact NMR spectrometer from Nanalysis Inc. (CalgaryAB, Canada) with a 1.4 T Halbach magnet, equipped with a Dewar with 5.3 mm internal bore diameter and 60 MHz proton resonance frequency was used. The specially constructed probe with the removable Dewar is sketched in figure 1. Control of this instrument via the industrial PC was performed using the NMReady Control interface API provided by Nanalysis.

For the process analytical measurements, the instrument was equipped with a 5 mm coaxial flowcell purchased from Bruker Biospin (Rheinstetten, Germany) [20,21] in combination with the InSightMR package. This package consists of a combination of three software tools from Bruker:Dynamic Center for integration and evaluation of integration results, TopSpin for automated processing of NMR spectra and IconNMR for automated conduction of NMR experiments. The software package was adapted by Bruker to the special needs of this project, c.f. raw data were stored in a special

watch-dog folder, NMR signals were automatically processed and data were saved in a general Excel format. Additionally, the length of the glass tube of the flow cell was adapted to reach the active volume of the Nanalysis NMR spectrometer. Further details of the InsightMR package can be found on the Bruker homepage [22]. The modified software package only consists of standard commercial products and is now available on the market as option in standard InsightMR. For visualization of processed data and spectra, some further standard software packages, such as MNova (Mestrelab, Santiago de Compostela, Spain) and Origin (Originlab, Northampton MA USA) were used.

In order to validate that the modified prototype NMR system is actually capable of serving the needs of reaction monitoring, several sets of additional experiments were performed. A range of different tests was conducted to explore the impact of the sample temperature on the stability of the NMR measurements. In a first set of tests, both an NMReady with a standard probe and the prototype instrument with the Dewar were subjected to a mock at-line study with a sample tube filled with n-octanol preheated to 100 °C. This sample was inserted into the instrument for about 1 min to conduct a standard measurement. After that, the hot sample was removed and a water-filled standard shimming sample was inserted and the line width as determined by the shimming routine was recorded as a function of time. In both cases, two runs of this experiment were performed. The results are given in figure 2.

As can be seen from the figure, there is thermally introduced magnet inhomogeneity in both systems but the impact of the exposure to the hot sample is much more pronounced in the spectrometer with the standard probe. After about 15 min, the impact of the heat exposure is compensated for both systems and line widths very

close to the original ones reached. (I.e. no long-term damage on the magnet is inflicted.) Furthermore, it is interesting to note that there is sufficient thermal inertia in the system to record a single good-quality spectrum on a hot sample every 30 min (provided the temperature change in the sample during the measurement has no detrimental impact on the quality of the spectrum).

In a further experiment, the sensitivity of the line width of DMSO circulating at various temperatures through the flow cell was studied in stopped flow measurements with different inlet temperatures for the DMSO flow through the cell. The results are shown in figure 3. As one can see from the figure, there is a pronounced impact even of moderate temperature differences between magnet (constantly kept at 32°C for optimal performance) and flowing medium on the line width. Like that, a sample temperature of 45°C was chosen for the continuous reaction monitoring experiments shown in the next section of this paper as a compromise between ensuring no precipitation and achieving as sharp lines as possible.

For experiments at higher sample temperatures, it would be necessary to combine the Dewar with an air or liquid flow at magnet temperature between the magnet and the Dewar. While the prototype spectrometer offers this possibility, it was not implemented yet as it would be costly in terms of instrument footprint and heat load when it comes to explosion proof housing of the instrument.

The spectrometer settings were unless otherwise noted: single scan mode, 90° pulse angle, 15 s polarization time before each measurement set by control unit, 12 ppm spectral width, 8k data points, internal proton lock. The internal proton lock is a

software based lock system which uses the highest signal in the spectrum, which normally is represented by the used solvent, and sets it to a fixed value. In the present case the highest signal is that of the alkyl chains which was set to 4.8 ppm in the raw spectra. During processing, it was recalibrated to 1.4 ppm to get chemically reasonable spectra.

The complete setup is shown in figure 4. The reaction mixture is sampled from the vessel via a Teflon tube of 2 mm internal diameter into the membrane pump. All transfer lines to the NMR were heated or isolated to avoid TPPO precipation. The membrane pump is fully made of Teflon to avoid corrosion of sample contacting parts. The volumetric flow of the sample transfer was set to 8 ml/min. This leads to a delay time of roughly 45 s since the dead volume between sampling point and active volume inside the NMR is about 5.5 ml. All measurements were done in stopped-flow mode by bypassing the flowcell with the 4-port valve. After flushing the flowcell of about 1 min with new sample, the control unit switches the valve to bypass and sets a waiting period of 15 s for polarization. Then it starts the NMR experiment and afterwards transfers the raw spectra to the watch-dog folder. NMR spectra processing and integration is then done automatically by the InsightMR process control package. Quantification results were transferred to the Excel file which then can be read by the control unit for further processing.

Experimental

The practical application was tested with a standard reaction of process chemistry, the chlorination of alcohols into the respective alkyl chlorides. While the large-scale chlorination uses phosgene as chlorination agent, in the present study thionyl chloride

was used instead. Thionyl chloride is less harmful, requires less safety precautions and the reaction is well documented by BASF patents [23]. The reaction scheme according to standard text books of organic chemistry [24] is shown in figure 5.

1-octanol, 1-chlorooctane, triphenylphosphinoxide (TPPO) and thionyl chloride were purchased from Sigma-Aldrich (Germany), glassware was standard material from in-house stock supply. A motor stirrer on top of the reaction vessel was used (IKA Eurostar 20, Germany).

The chlorination reaction was executed at 100°C reaction temperature. 0.69 mol (about 108 ml) of 1-octanol and either 0.014 mol of TPPO catalyst or not were placed in the reaction vessel, stirred, and heated up to 100°C. Then, the process-NMR setup was started with a data acquisition rate of 40 spectra per hour. After an initial period of about 10 min, 0.69 mol of thionyl chloride were added dropwise at about 1 ml/min (without catalyst) or at about 0.4 ml/min (with catalyst). All spectra were automatically processed and integrated directly after their individual acquisition without human interaction. Peak tracking of the strongly shifting hydroxyl proton worked without malfunctions

The hydroxyl group is substituted by a chlorine atom and equimolar amounts of sulfur dioxide and hydrochloric acid will be released. TPPO can be used as a catalyst to speed up the reaction strongly [23]. HCl and SO_2 generation rises the practical requirements to the system setup in a way that all sample contacting parts have to be chemically stable. TPPO as a catalyst introduces another obstacle: during reaction the polarity of the solvent changes and TPPO might precipitate at room temperature and block the flow cell. Thus, all sampling lines were heated and the temperature of the

incoming liquid into the flow probe was 45°C, therefore above the precipitation limit of roughly 35°C.

Prior to conducting the online reaction monitoring a test of the system with non-reactive mixtures of 1-octanol and 1-chlorooctane reference materials was performed. The molar fraction of reactant and product was shifted between 0 (not present) and 1 (neat material) and the quantification was done via calculation of the signal area ratio of the hydroxyl proton of 1-octanol versus the adjacent methylene group protons of 1-octanol and 1-chlorooctane. The results are given in figure 6. The regression data show a very good concordance between theoretical and experimental values, the slope is nearly one and the y-intercept close to zero. Additionally, the hydroxyl proton signal was proven to be suitable for quantification. The reaction is conducted without any organic solvent and therefore coming close to industrial conditions. Thus, under the present conditions the hydroxyl protons lack partners for exchanging protons and their signals can be used for quantification as any other proton signal. Repeatability was tested by consecutive analysis of one sample of mean concentration and it revealed a relative standard deviation of about 1.5 % for integration results.

The NMR spectra of the reaction are shown in figure 7, their quantitative evaluation in figure 8. Again, the molar ratio is given for each substance. 1-Octanol is quantified via the hydroxyl proton signal area, the other compounds by the signal area of the adjacent methylene group protons. All data were weighed by the number of protons. Reaction time starts upon addition of the first drop of thionyl chloride.

Discussion

Online NMR data reveal that the reaction path appears to be more complicated than described in the standard text books. Literature study of former work on this type of reaction offers deep insight into the reaction path. It goes via different steps with two intermediates, the octyl chlorosulfinate and dioctyl sulfite [25, 26, 27].

The combination of historic literature data, chemical knowledge and present online NMR information indicates a reaction mechanism following the path as described in figure 9: in a first reaction step, one molecule of 1-octanol **1** reacts with one molecule thionyl chloride **2** by loss of one molecule HCl to octyl chlorosulfinate **3**. This compound is described as highly reactive [25] and directly reacts in presence of another molecule of **1** to the first stable intermediate dioctyl sulfite **4**. Intermediate **3** is therefore at that point in the reaction path not accessible by present NMR spectroscopy. Intermediate **4** is quite stable and has a high activation energy for further conversion with **2** into octyl chlorosulfinate **3** again. This conversion starts at degrees above 80°C without catalyst and above 60°C with TPPO catalyst [23].

Present online NMR data support these assumptions. In both experiments, with and without TPPO catalyst, a formation of octyl chlorosulfinate **3** can only be seen at concentrations of free 1-octanol approaching zero. In figure 8 a), without TPPO, reaction progress is only observed after full addition of thionyl chloride **2** and nearly complete conversion into dioctyl sulfite. Only the excess of **2** and absence of **1** lead to the formation of **3**. The same holds for the reaction with catalyst added.

A similar behavior is found for the final SO_2 elimination reaction which converts the octyl chlorosulfinate **3** into the final product 1-chlorooctane **5**. Without catalyst this reaction step's kinetics is quite slow leading to significant amount of free octyl

chlorosulfinate in solution and a slow product generation. An opposite behavior is found when TPPO is added: the last reaction step is strongly accelerated and nearly no free **3** is found in the reaction solution (see figure 8 b).

The NMR data indicate the benefit of the catalyst TPPO [23]. It strongly accelerates the cleaving and elimination reactions in the present reaction scheme. The addition of TPPO might decrease this offset temperature [23] or strongly increases the overall reaction kinetics when operating at constant temperature. In the reaction without catalyst, the product formation takes hours and finally ends at 50 % conversion, maybe due to thionyl chloride undergoing side reactions (figure 8 a) while significant amounts of both intermediates remain in solution. However, when having TPPO catalyst added, the cleavage reaction and the elimination of SO_2 are highly accelerated and, as consequence, the practical concentration of octyl chlorosulfinate remains quite low due to the strong enhancement of the elimination reaction's kinetics. Fast kinetics accompanied by much less side reactions let the product yield approach nearly 100 % in a reasonable amount of time of about 5 hours. The results show that the presented NMR analysis method enables deep insights into the reaction mechanism (among others the selectivity to target products, formation of undesired side products) and the effect of a catalyst on the reaction. Thereby, essential information for the optimization of the process e.g. by choosing suitable catalysts, solvents or process conditions can be obtained faster.

Conclusion

Lab-based compact NMR spectroscopy has been successfully converted into a fully automated spectroscopic system for reaction monitoring. Former tedious work by hand in NMR spectroscopy like parameter setting from default, data handling between different software and computer systems as well as spectra processing has been automated and can now be run with highly reduced human interaction. The use of flow cells with improved thermal insulation in combination with the compact NMR spectrometers' characteristics allow the investigation of reactions in their neat solutions without the need of deuterated solvents and without initial calibration. The results show that even with this comparatively simple set-up valuable information on a complex reaction network with several intermediates and with the formation of gaseous species in the liquid phase can be gained. The reduced complexity of the set-up and the analysis allows their use in standard research laboratories or even in laboratories of production plants. The method facilitates fast insights into important key parameters of a complex reaction network, such as information on yield and selectivity of target components, the occurrence of unwanted side products and estimation of time constants of reagents. Thus, the method is especially suited for fast screening studies (e.g. catalysts, solvents, process parameters) in an early stage of process development or for fast quality control in production plants. If desired the accuracy of the method used to gain quantitative information of the acquired NMR spectra can be further improved for example by employing chemometrics or other advanced analysis methods. In this case, the presented method can be applied for development and validation of for example kinetic or thermodynamic models (see e.g. [15,16]).

Thus, compact NMR spectroscopy opens the way for NMR to be used in various laboratories and process environments in which NMR with high-field instruments is inherently prohibited. Compact NMR spectroscopy offers manifold possible applications in process and chemical industries as it enables to get swiftly valuable information on complex syntheses.

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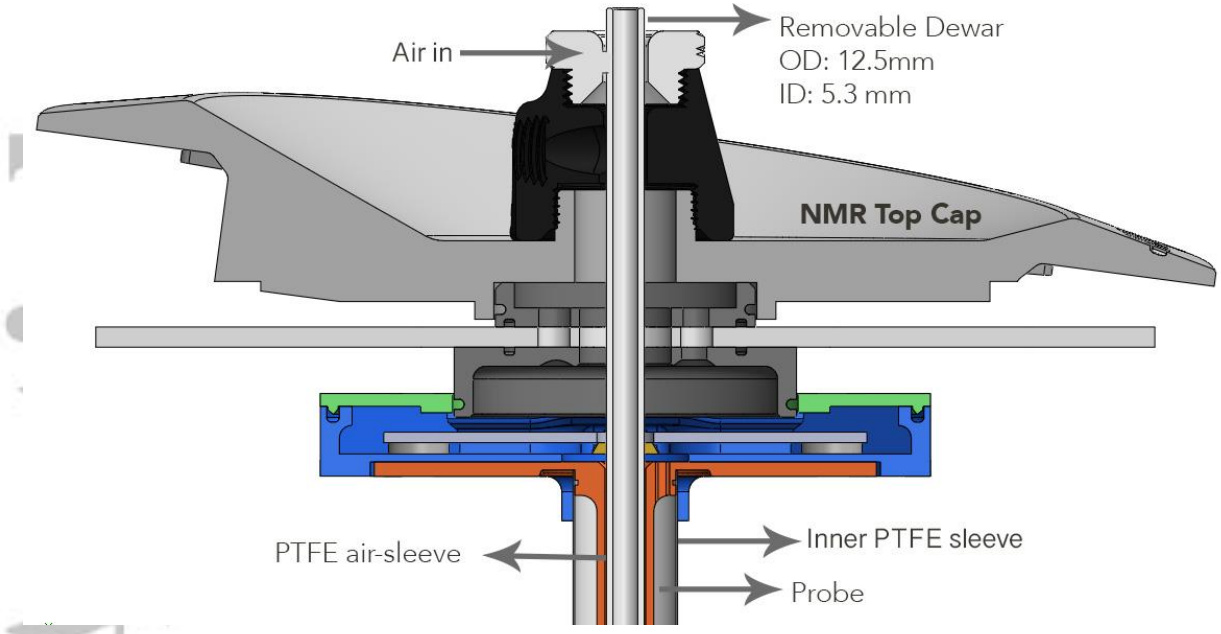


Figure 1 Sketch of the upper part of the prototype NMReady with air sleeve and removable Dewar

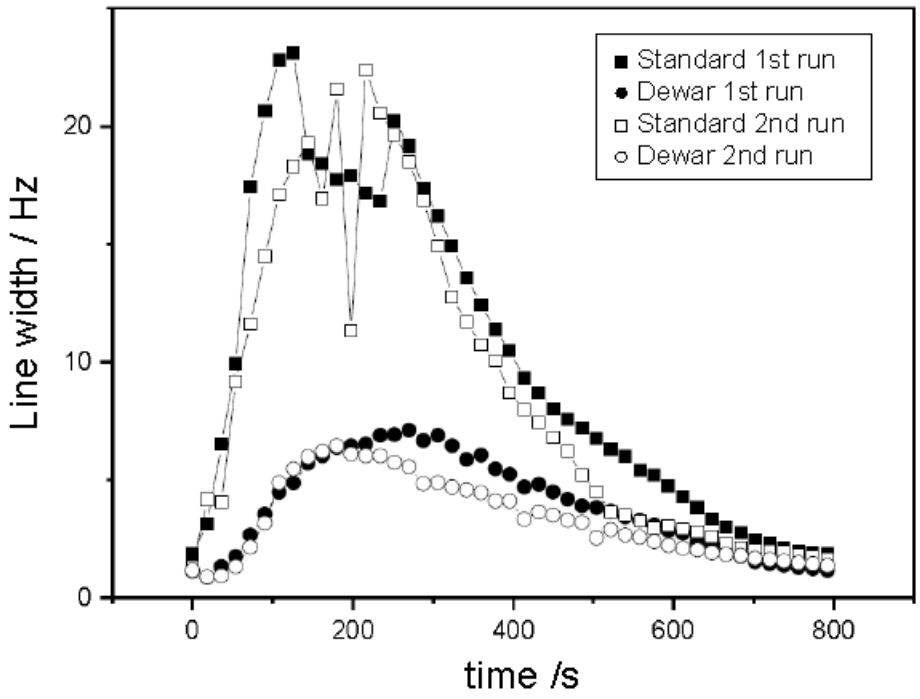


Figure 2 Water line width as determined by the by internal shimming of the NMR instruments as a function of time after 1 min exposure to an octanol sample preheated to 100°C. Square symbols: standard instrument, round symbols: prototype with Dewar

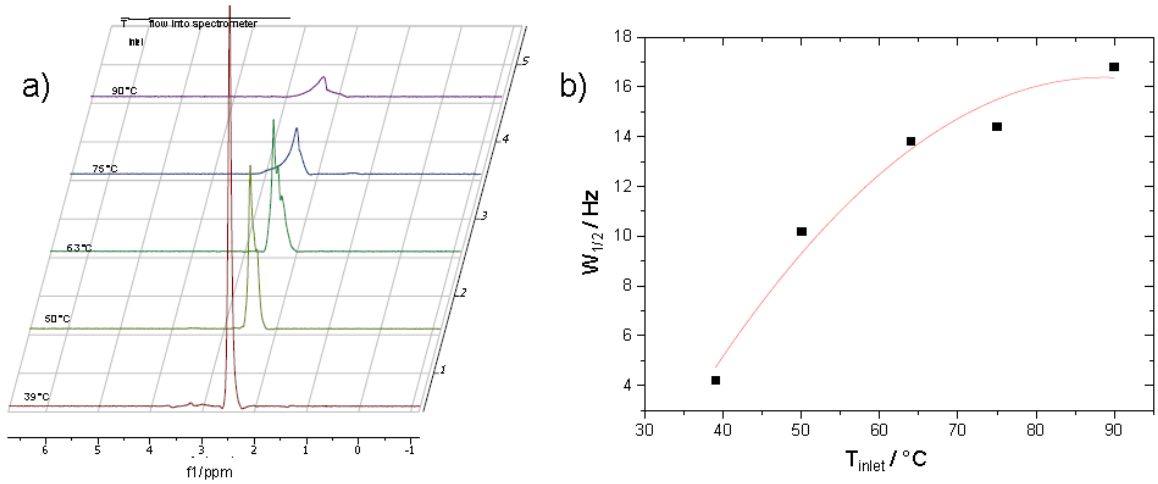


Figure 3 a) Stacked spectra of DMSO at different continuous flow temperature and b) line width of DMSO peak at different continuous flow temperature

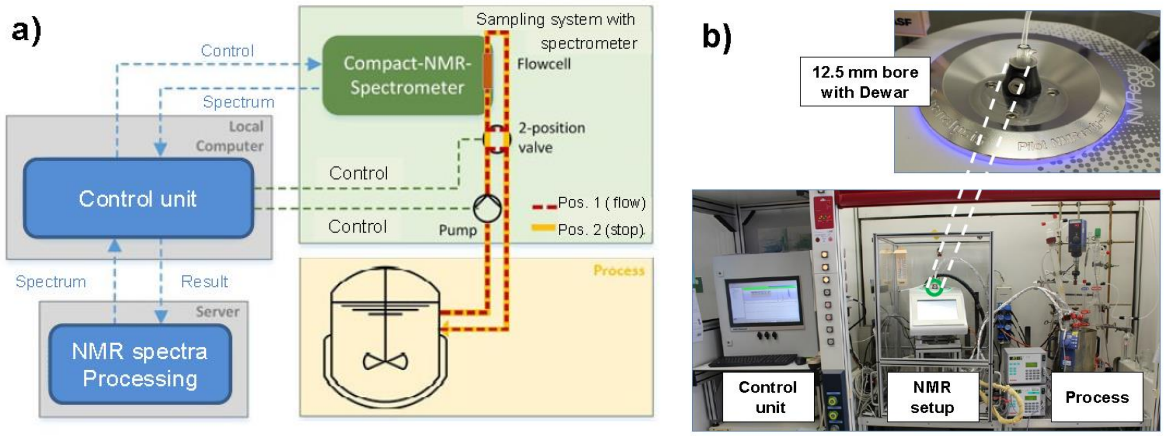


Figure 4 a) Schematic drawing of the process NMR system. Sampling system and the NMR spectrometer must be installed in vicinity to the respective process, control and spectra processing computers are connected via Ethernet and are stored in a watchdog folder. b) Photograph of the test assembly in a hood and photograph of the prototype NMR probe with Dewar for heated samples.

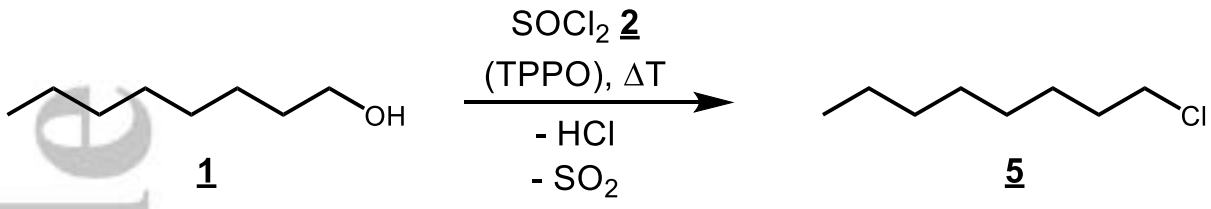


Figure 5 Reaction scheme for the model reaction studied in this paper

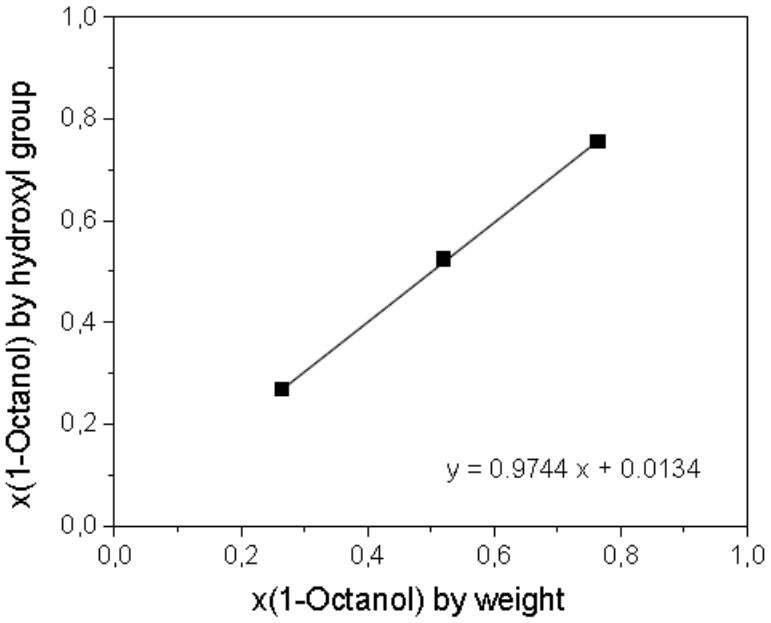
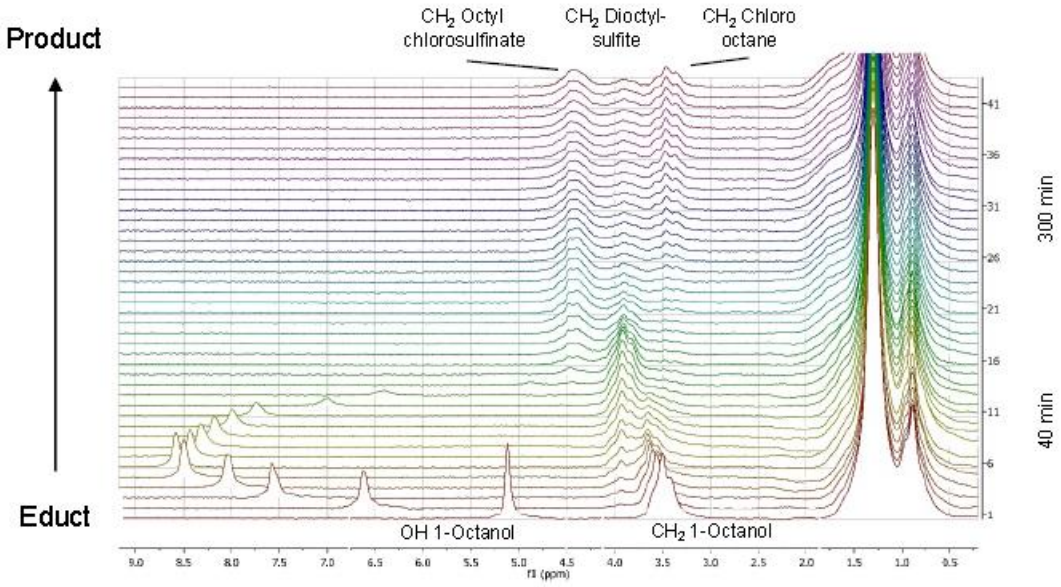
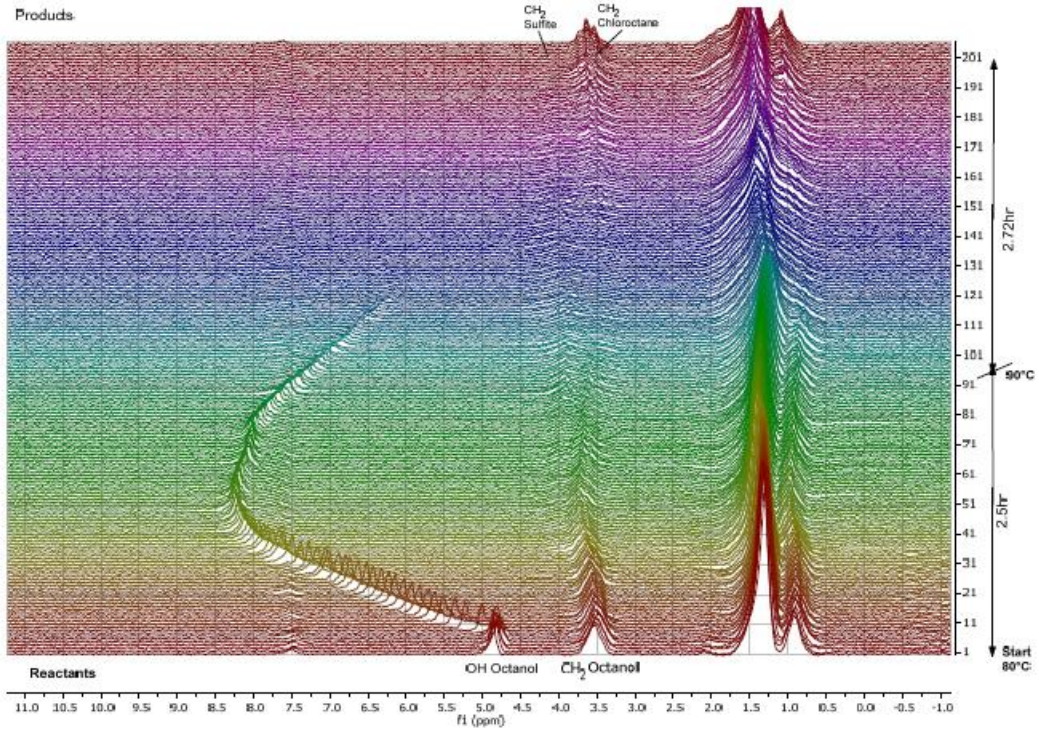


Figure 6 Quantitative evaluation of unreactive mixtures of reagent (1-octanol) and product (1-chlorooctane) of the chlorination reaction. The molar fraction of 1-octanol by found amount versus weighed in amount is given. Hydroxyl proton and CH_2-Cl or CH_2-O protons are used for quantification.



a)



b)

Figure 7 ^{1}H-NMR spectra plot at 60 MHz of the nucleophilic chlorination reaction at 100°C reaction temperature a) without TPPO catalyst and b) with 2 mol-% TPPO catalyst added. The NMR signal attribution was done on basis of the pure spectra and based on the reaction mechanism (3.5 ppm: CH_2-X methylene group of 1-octanol and 1-chlorooctane, 4.0 ppm: CH_2-O methylene group of octyl disulfite, 4.5: CH_2-O methylene group of octyl chlorosulfinate, 7.5 ppm: TPPO).

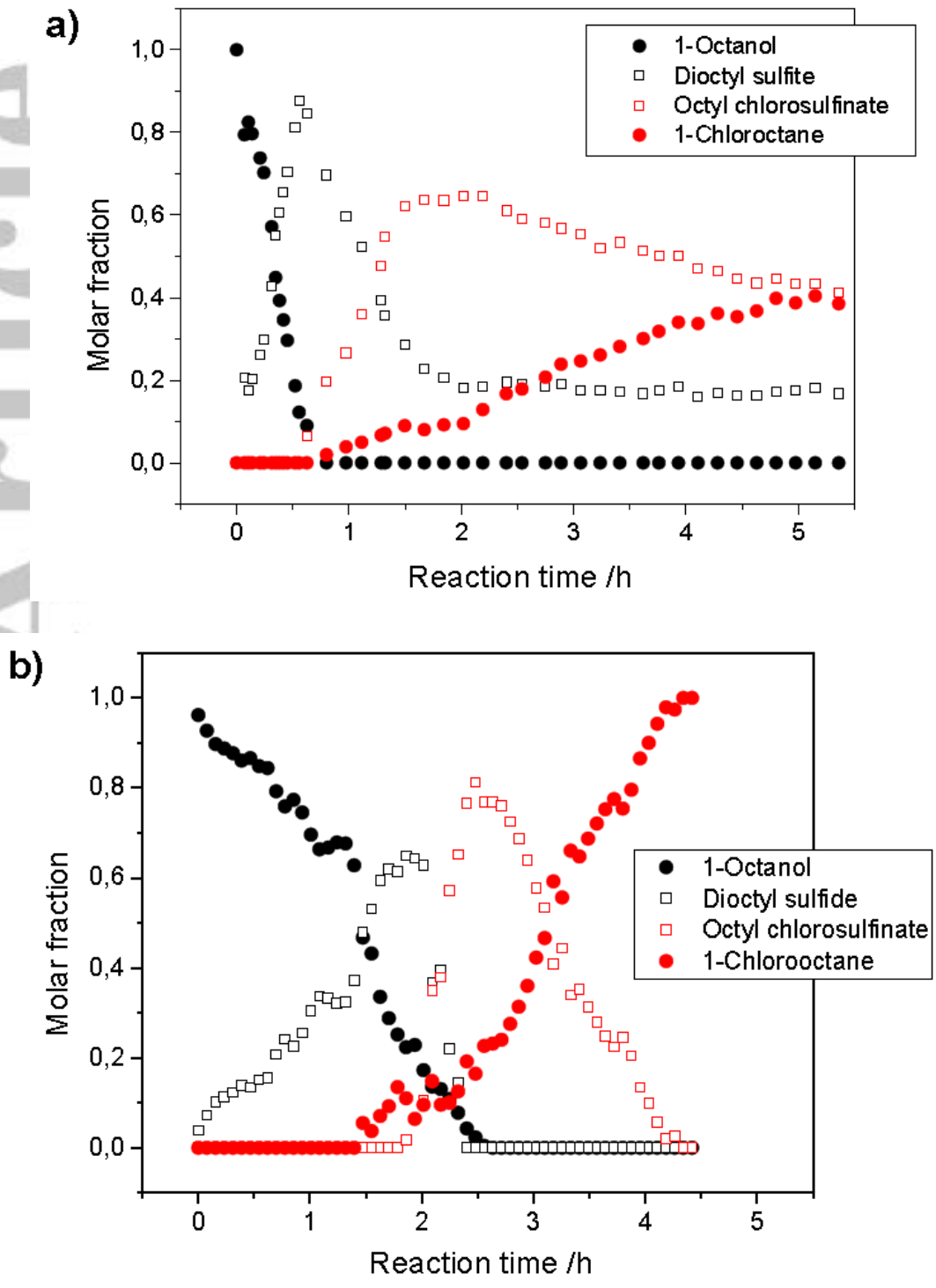


Figure 8 Quantitative NMR data by plotting the molar fraction of each compound against reaction time at 100°C reaction temperature a) without TPPO catalyst and b) with 2 mole-% TPPO catalyst added.

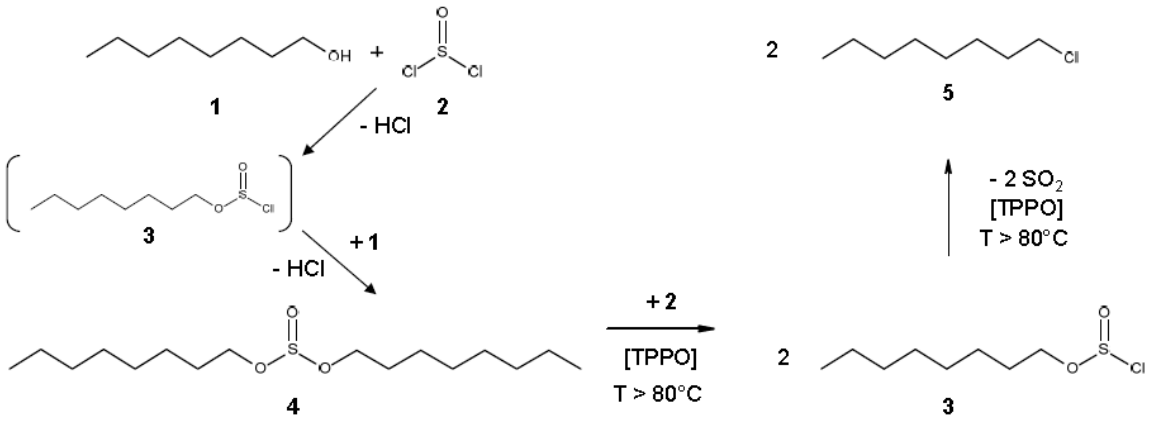
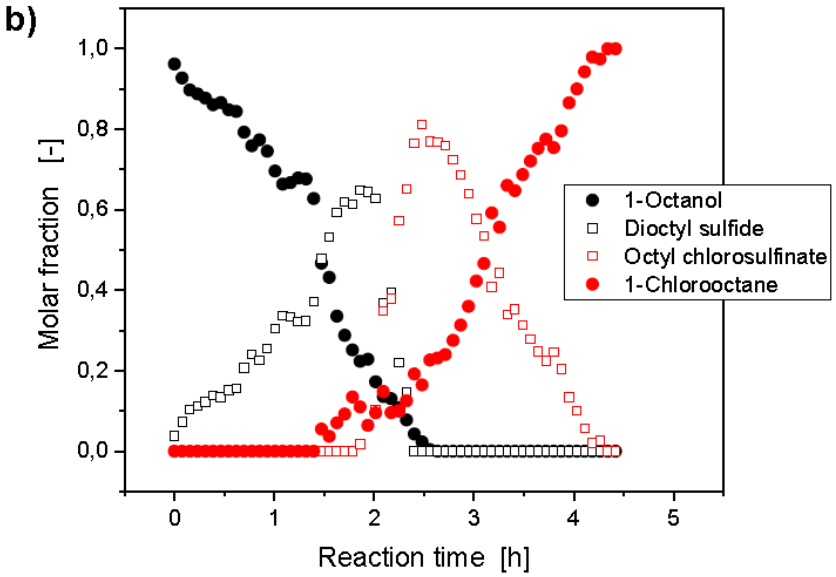


Figure 9 Full reaction scheme of the nucleophilic substitution reaction as suggested by the NMR results in this work

A prototype compact NMR spectrometer equiped with a Dewar for long-time measurements on samples with elevated temperature and a flow cell was validated for application in reaction monitoring and a nucleophilic chlorination reaction was studied as an example. Furthermore, some general considerations on the possible future role of compact NMR in chemical industry are made.



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