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Quantitative high-resolution on-line NMR spectroscopy in reaction and process monitoring

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Abstract

On-line nuclear magnetic resonance spectroscopy (on-line NMR) is a powerful technique for reaction and process monitoring. Different set-ups for direct coupling of reaction and separation equipment with on-line NMR spectroscopy are described. NMR spectroscopy can be used to obtain both qualitative and quantitative information from complex reacting multicomponent mixtures for equilibrium or reaction kinetic studies. Commercial NMR probes can be used at pressures up to 35 MPa and temperatures up to 400 K. Applications are presented for studies of equilibria and kinetics of complex formaldehyde-containing mixtures as well as homogeneously and heterogeneously catalyzed esterification kinetics. Direct coupling of a thin-film evaporator is described as an example for the benefits of on-line NMR spectroscopy in process monitoring.

Keywords: On-line ^{1}H NMR spectroscopy; On-line ^{13}C NMR spectroscopy; Quantitative NMR spectroscopy; Thermodynamics; Reaction kinetics; Fluid mixtures; Flow NMR

1. Introduction

Flow nuclear magnetic resonance (NMR) spectroscopy is a fascinating tool for engineering studies to obtain both qualitative and quantitative information from complex reacting multicomponent mixtures for equilibrium or reaction kinetic studies [1–11]. On-line coupling of NMR spectrometers was primarily developed in the field of HPLC [12–14] and SFC [15] using NMR as an analytical detector with high spectral dispersion. Flow NMR probes are also used for high-throughput NMR spectroscopy [16,17]. In other applications, low field on-line NMR spectroscopy [18] is applied for process monitoring and quality control using chemometrics for evaluation.

In many technical processes, complex multicomponent mixtures have to be handled, e.g., in reaction and separation equipment. There is a need to study these mixtures and gain insight into their behavior in the processes. Once the physicochemical behavior of such mixtures is understood, predictive models for their properties can be developed which are needed to design reactors or separation equipment, like distillation, extraction, or absorption columns. For on-line studies in engineering applications under process conditions, flow NMR can be used across a wide range of temperatures and pressures nearly non-invasively, where other analytical methods suffer from insufficient resolution of different components.

Flow NMR spectroscopy allows one to investigate reaction processes almost in real time and under process conditions, in a wide range of temperatures and pressures [19–22]—commercial NMR probes presently for 0.1–35 MPa and 270–350 K (Bruker) and 0.1–3.0 MPa and 270–400 K (Varian), respectively. A further extension of this range is the focus of on-going research. The flow cells typically have an active volume of 60–120 μl and a total volume of about 120–240 μl.

For many engineering and physicochemical applications a "non-invasive" analytical technique is desirable, which does not disturb process conditions like pressure,

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temperature, or composition during sampling and analysis. On-line NMR comes close to this ideal when thermostated tubing and pieces are used. Samples can rapidly be transferred to the place of detection. The typical delay time of on-line monitoring with ^{1}H NMR spectroscopy is below one minute compared to 5–10 min using conventional 5 mm tubes (sample preparation, shimming).

Although deuterated solvents play an important role for lock, shim, and reference purposes in NMR, they are not tolerable for most process engineering applications and physicochemical studies. Even a 5–10% addition to the system is usually not acceptable due to its cost when working with considerable sample amounts. Furthermore, deuterium can cause unwanted isotope effects which may falsify the results [23]. Intense signals of non-deuterated solvents can be reduced by solvent suppression techniques [24]. Commonly used solvent presaturation techniques are not recommended for quantitative studies as they can lead to magnetization transfer between analyte protons. Alternatively, selective saturation techniques such as WET can be used [25], particularly for flow experiments. Furthermore, working with deuterium-free samples excludes field-frequency stabilization (lock). Despite this, due to the excellent B_0-stability of modern NMR magnets, acquisition times of several hours without lock can be realized without substantial line-broadening.

Field homogenization (shimming) normally relies on deuterium in the solvents. Shimming of deuterium-free samples can be accomplished by an automatic shim process with proton shim maps (^{1}H field mapping)—[26–28]. A pulsed field gradient (PFG) NMR probe and gradient amplifier are required for this method although on some spectrometers the homospoil circuit can be used. Field mapping works reliably (normally in less than 1 min), even for concentrated samples or solvent mixtures, for which solvent peaks have the same order of magnitude as analyte peaks and even under flow conditions.

In samples that are reacting, the physicochemical properties like magnetic susceptibility, pH, or electrolyte concentration may change considerably during an experiment. This can lead to solvatochromic peak shifts of analytes, reference material, and solvents. Due to a defined cell contour and design, NMR flow probes are quite insensitive to changes in magnetic susceptibility of the sample, so that shimming or tuning of the probe during a sample change or a reaction kinetical experiment is not required in almost all cases. This is a major advantage compared to NMR using sample tubes.

Few restrictions concerning the chemical nature and corrosiveness of the studied fluids arise in flow NMR spectroscopy. Solutions containing up to 20 mass% sulfuric acid or almost pure acetic acid were so far successfully investigated by NMR spectroscopy in our laboratory, mostly under elevated temperatures (up to 400 K) and pressures (up to 3.0 MPa).

Whereas most NMR experiments aim at obtaining qualitative information, additional requirements have to be fulfilled in order to acquire reliable spectra suited for quantification, cf. [29–31]. Provided that frequency independent magnetic saturation is attained, NMR peak areas can be used directly for quantification without further calibration [32–35].

For quantitative NMR experiments under flow conditions, the effect of flow can be understood as a contribution to the overall magnetic relaxation in the detection volume—assuming complete pre-magnetization of all nuclei of interest. The theory of flow NMR is well documented in reviews [36–38] and papers on special topics like signal enhancement in flowing liquids [39–41]. In order to achieve full Boltzmann distribution, a prerequisite for quantitative measurements, the sample must reside longer than 5 times the spin lattice relaxation time of the slowest relaxing nucleus $T_{1,\max}$ inside the pre-magnetization volume of the magnetic field prior to detection. This is accomplished by adjusting the flow rate $\dot{V}_{\text{flow}}$ to $T_{1,\max}$ and the pre-magnetization volume of the NMR probe to a value given by

$$\dot{V}_{\text{flow,max}} = \frac{V_{\text{premagn}}}{5 \cdot T_{1,\max}}. \quad (1)$$

With a typical proton T_1 time of 2 s at 300 K and a pre-magnetization volume of 150 μl the maximum flow rate is around 0.9 ml min^{-1}.

Compared to ^{1}H NMR, additional precautions have to be taken in quantitative ^{13}C NMR (e.g., inverse-gated decoupling)—[42]. To maximize the signal-to-noise ratio per unit time, it is common to use excitation flip angles in ^{13}C NMR spectra according to the Ernst condition [43–45]. Pulsing under the Ernst angle is generally not recommended for quantitative spectroscopy. Nevertheless, in special cases when differences in T_1 are small for the investigated nuclei, only small quantitative errors are made so that the method is applicable. In investigations of ternary formaldehyde–water–methanol mixtures reliable quantitative results were achieved despite using the Ernst angle method [46].

2. Experimental section

The majority of experiments described in the present work were carried out at the University of Stuttgart using a 400 MHz NMR spectrometer (Unity Inova 400, Varian, Palo Alto, USA) equipped with a modified ^{1}H{^{13}C,^{15}N} inversely detected, triple resonance, PFG, microflow probe with an active detection volume of 95 μl which can be used in a pressure range up to 3.0 MPa and temperatures between 253 and 403 K.

Other experiments were performed at the University of Tübingen with a 400 MHz NMR spectrometer (ARX 400, Bruker, Rheinstetten, Germany) equipped with a $^{1}H\{^{13}C\}$ inversely detected SFC flow probe with an active detection volume of 120 µl. The probe was especially designed for pressures up to 35 MPa and temperatures between 273 and 353 K.

2.1. Infra structure

The experiments in Stuttgart were carried out in vented cabins (about 4 m × 3 m × 1 m), located in the immediate vicinity of the NMR spectrometer, allowing safe handling of hazardous chemicals. The superconducting magnet (Oxford Instruments 400/54 narrow bore) used for the experiments has a static magnetic stray field of 1.0 mT at 224 cm and 0.5 mT at 280 cm from the center of the magnet. No interference was observed between the magnet and the laboratory instruments when positioned outside the 0.5 mT line. Recent developments have led to actively shielded magnets with an extremely low stray field (0.5 mT at 100 cm) [47] which can be used in cases with lack of laboratory space.

2.2. Flow scheme

Fig. 1 shows a typical on-line set-up for NMR studies of reacting systems. A dosing pump P1 (HPD Multitherm 200, Bischoff Chromatography, Leonberg, Germany, 0.1–20 ml min^{-1} flow rate, thermostated hastelloy pump head) was used to transport the sample from the reactor C1 to the NMR probe. A 10 µm filter (F1) was used to prevent dust and solid precipitate from entering the system. Before entering the NMR spectrometer, the flow was split. This allowed a quantitative flow rate in the NMR probe (0.1–1.5 ml min^{-1}) while the flow rate in the transfer line was high enough to allow a rapid sample transfer. The bypass could be adjusted by a variable back pressure regulator V4 (M420, Upchurch Scientific, Oak Harbor (WA), USA). The back pressure regulator V2 (1.72 MPa, Upchurch) was only used to give a constant resistance to the pump P1. For the measurement of pressure prior to the NMR an ultra low volume pressure transducer (PIR2, XT-190M 3.0 MPa, Kulite Semi-Conductor Products, Leonia (NJ), USA) was used.

Care has to be taken as high pressure can damage the NMR flow probe. Dust particles or precipitating solids are particularly dangerous as they can block the tubing. Filters, pressure relief valves (V5, 0.7 MPa and V6, 1.75 MPa in Fig. 1, U456, Upchurch), pressure control, automated pump switch off, were therefore used in all set-ups. Mass flow rates were determined with a balance close to the reactor. For this purpose the flow was routed (via V7 and V8 in Fig. 1) to a (pressurized) container C2 on the balance.

2.3. Hyphenation

For the connections between the reactor and the NMR only inert media like stainless steel, Hastelloy or PEEK were used. A choice of tubing with small inner diameter (ID) results in short delay times but high pressure drops. The tubes leading to the NMR were typically 0.02″ ID, while wider tubing (0.03″ ID) was used to the return to the reaction cell. PEEK material was chosen in most cases due to its good mechanical properties, chemical resistance and biocompatibility.

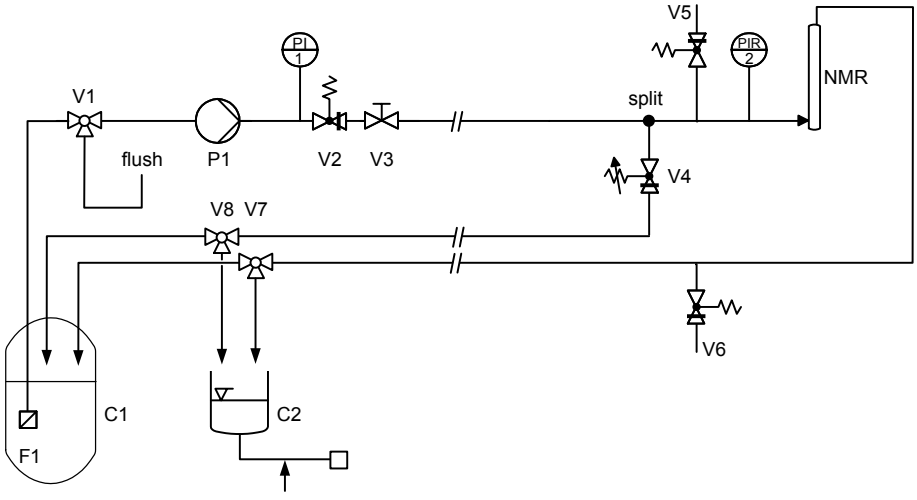

Fig. 1. Typical set-up for on-line NMR measurements. C1, laboratory reactor; F1, inlet filter; V1, (tee) purging valve; P1, thermostated dosing pump; V2, back pressure regulator; V3, shut off valve; V4, variable back pressure regulator for split adjustment; V5, V6, pressure relief valves; PI1, PIR2, pressure transducer; NMR, thermostated flow probe of NMR spectrometer; V7, V8, tee valves, C2 container on balance for mass flow control. All tubing 1/16″ OD.

All lines were thermostated. For this purpose, the lines were mounted inside insulated silicon tubing filled with heat transfer medium which was connected to the cryostat via tees. Most parts in contact to the solution were also thermostated. The total hold-up of the described system (reactor–NMR–reactor) was experimentally determined to be (4.72 ± 0.14) ml including filters, tubing, pump, valves, pressure transducer, and the NMR flow cell.

2.4. Residence times

The delay time between a change in the reactor and the according change of the NMR signal is an important parameter in online studies. Of special importance is the question of precisely when reliable data can be obtained after the initialization of a reaction. It was shown experimentally that this time is in the order of 2–4 min for the experiments carried out in the present work, which is short compared to the reaction times of the experiments.

The non-ideal flow of the sample from the reactor to the active region of the NMR probe is described by the residence time distribution (RTD) function. This describes the transfer and spreading of the sample on its way to the active detection region as a result of laminar flow in the lines, stagnant regions (pressure gauge), and back mixing (pump head). The RTD function can be obtained from pulse tracer or step tracer experiments, where either a concentration pulse or a concentration step is produced in the reactor and the NMR-signal is monitored. The desired time-dependent concentration in the reactor (analytical signal $s_{\mathrm{reactor}}(t)$) can be reconstructed from the NMR-signal $s_{\mathrm{NMR}}(t)$, if the RTD function is known. Methods for the deconvolution of $s_{\mathrm{NMR}}(t)$ to determine $s_{\mathrm{reactor}}(t)$ are described elsewhere in the literature [48].

When relatively slow processes are monitored, it is sufficient to correct the NMR time by the mean residence time $\bar{t}_{\mathrm{res}}$ of the probe in the system between the reactor and the NMR-probe according to

$$s_{\mathrm{reactor}}(t) = s_{\mathrm{NMR}}(t + \bar{t}_{\mathrm{res}}), \tag{2}$$

where $\bar{t}_{\mathrm{res}}$ is determined by a pulse tracer experiment. Alternatively, step tracer experiments also yield characteristic time segments. t_{trans} is the transfer time, which is defined as the time until the first significant change of concentration is observed in the NMR experiment. The delay time t_{delay} is found as the time after which the detected tracer concentration has risen from zero to its stationary value. The time span between t_{trans} and t_{delay} is called dwell time t_{dwell}. When only results from step tracer experiments are available, $\bar{t}_{\mathrm{res}}$ in Eq. (2) can be calculated as $t_{\mathrm{trans}} + (t_{\mathrm{dwell}}/2)$ to a first approximation as long as the monitored reaction time is long compared to any of these times.

For homogeneously reacting systems, the reaction does not only take place in the reactor, but also in the system connecting the reactor and the NMR-probe. In this case, the time of the NMR acquisition is directly the time for which the solution has reacted, and, hence the time used in the evaluation of the reaction kinetics (as long as the NMR data acquisition is started upon initialization of the reaction at $t = 0$). However, reliable NMR data can only be obtained after the delay time t_{delay}, when the solution in the NMR probe is completely replaced by sample from the reactor after the perturbation.

As an example, Fig. 2 shows original NMR data from a kinetic experiment in which chemical processes after the dilution of an aqueous formaldehyde solution were monitored. NMR data collection was started at the time of dilution. During the transfer time t_{trans}, although the reaction has already started, NMR spectra show the composition of the initial mixture, subject to some perturbations. During the dwell time t_{dwell} NMR spectra stem from poorly defined mixtures of the reacting solution and the initial solution and must not be used for evaluation. The first reliable NMR spectra are only obtained after the delay time t_{delay}. It is important to minimize the delay time t_{delay} in order to be able to monitor reactions shortly after their initialization, which usually gives the densest information on the process.

As an alternative to continuous flow, stop flow techniques can also be used to monitor homogeneous reactions. That is, the pump can be switched off after the reacting mixture was transferred to the NMR. Thus, also for those experiments the knowledge of the delay time t_{delay} is important as the flow must not be stopped before that time has elapsed. However, continuous flow has some advantages over stopped flow such as keeping a steady state of pressure and temperature in the NMR flow probe or controlling the viscosity of the studied mixture. In addition constant supply of new sample from the reactor typically provides more representative data.

It should be mentioned that the dwell time t_{dwell} as defined above is not equal to the dwell time of nuclei in the active detection region, which is commonly used to adjust the pulse repetition time. The latter is only a consequence of flow within the NMR detection cell, defined assuming a plug flow pattern and thus shorter than the above-mentioned dwell time t_{dwell}.

3. Application 1: Formaldehyde containing systems

3.1. Background

Formaldehyde (CH_2O, FA) is one of the most important chemical intermediates. It is used in aqueous, methanolic solutions where formaldehyde is almost entirely chemically bound to the solvents, forming methylene glycol ($HOCH_2OH$, MG), poly(oxymethylene)

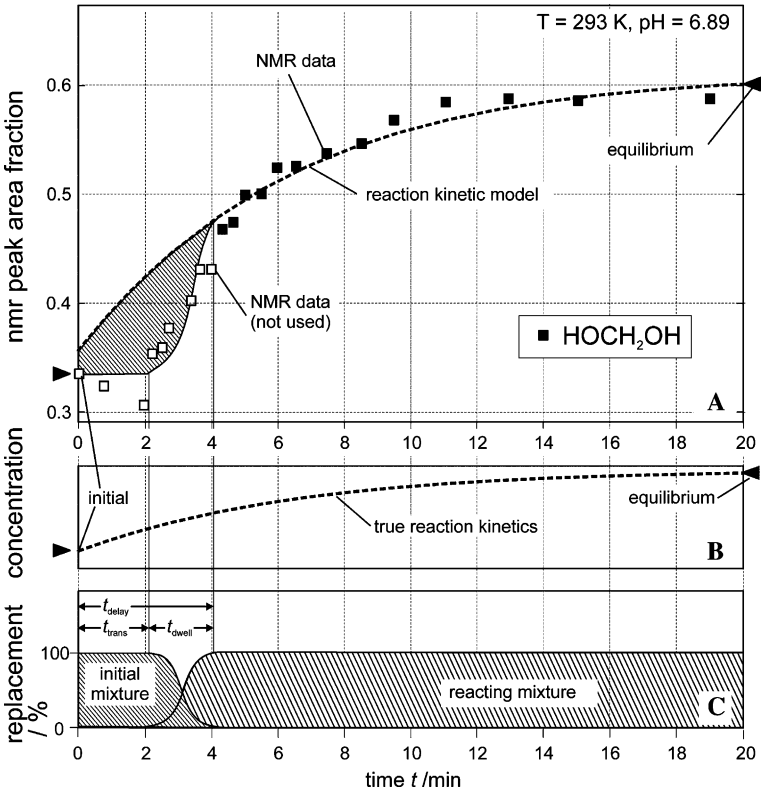

Fig. 2. NMR data from a reaction kinetic experiment and its evaluation. Dilution of a formaldehyde–water mixture (0.340 g g^{-1} FA) with water (mass ratio 1:1) at 293 K, pH 6.89 [51]. (A) Changes of NMR peak area fractions vs time (dilution at $t = 0$) and fit by a reaction kinetic model. Open symbols are not used for the fit. (B) Concentration changes during reaction in the reactor (qualitative). (C) Replacement of solution according to the RTD function measured independently. The delay time t_{delay} is the sum of the transfer time t_{trans} and the residence time t_{dwell} in the probe.

glycols ($H(OCH_2)_nOH$, MG_n, $n > 1$), hemiformal ($HOCH_2OCH_3$, HF), and poly(oxymethylene) hemiformals ($H(OCH_2)_nOCH_3$, HF_n, $n > 1$). The reactions leading to these oligomers make aqueous, methanolic formaldehyde solutions complex systems containing more than 20 components in significant amounts.

Thermodynamic and kinetic data are needed to develop predictive models of the physicochemical properties of formaldehyde containing solutions which are used in the design of reactors and separation equipment, like formaldehyde distillation and absorption columns [23,49,50]. For this purpose quantitative information on chemical equilibria and reaction kinetics of all species is needed. Due to the chemical similarity of the functional groups of individual oligomer species, formaldehyde containing systems are an excellent example for demonstrating the benefits of the extreme high spectral dispersion of NMR spectroscopy. No other analytical technique can distinguish between different components in this case. Beyond this, NMR is fast enough to obtain quantitative information required for kinetic studies in these systems.

Chemical equilibria of ternary mixtures at various temperatures have been investigated recently in our laboratory using a simple set-up for stop-flow NMR experiments at elevated pressures [51]. In addition, reaction kinetics were studied for the binary systems formaldehyde–methanol and formaldehyde–water well as recently for some ternary systems formaldehyde–water–methanol at various temperatures and under pressure [52].

3.2. Experimental

The reactions were studied by a dilution of concentrated equilibrated solutions, e.g., with pure solvent (perturbation of the system). Such reactions are readily carried out in stirred glass reactors as long as the vapor pressure at the higher temperature does not exceed normal pressure. Most of the investigations presented here were carried out in a fully thermostated 250 ml stirred flat flange glass cell equipped with thermostated pressure equalized 100 ml dropping funnel and KPG stirrer. Reactions of mixtures with boiling pressure above $p = 0.1$ MPa were carried out under a helium atmosphere at $p = 0.5$ MPa in a fully thermostated custom made stainless steel reactor with thermostated dropping funnel.

The preparation of the formaldehyde solutions and adjustment of the pH has been described elsewhere [46,51]. Approximately 100 g of formaldehyde solution was filled into the reactor. About the same amount of

pure solvent was filled into the reservoir. Care was taken to clear the tubing from remaining samples of previous experiments by rinsing. All sample amounts were determined by back weighing (±0.01 g). Both liquids were thermostated for 0.5–4 h in the reaction cell and in the dropping funnel depending on the kinetics of the system under investigation. Under fast stirring the pure solvents were poured into the stock solution (within not more than 15 s) and NMR acquisition was started at the same time.

For formaldehyde–water kinetics a pseudo 2D pulse sequence (one dimensional ^{1}H NMR vs time) was used—predominantly without solvent suppression to avoid unwanted signal suppression of formaldehyde species. Experiments yield T_1 values of 3–4 s for ^{1}H and 6–8 s for ^{13}C at 383 K resulting in flow rates in the range of 0.45 ml min^{-1} for ^{1}H and 0.22 ml min^{-1} for ^{13}C according to Eq. (1). For lower temperatures, T_1 values are significantly shorter so that the flow rates can be increased. Typically a single transient per spectrum was recorded, equal to an acquisition time of 3.8 s per spectrum. In total 40–70 spectra were obtained over 30–240 min, depending on the kinetics. The kinetics of methanolic and ternary formaldehyde mixtures were recorded in the same way.

In all cases overlapping NMR signals were quantified by peak deconvolution. For that purpose a MATLAB based tool was developed in our group. It uses a four parameter Lorentz-Gauss function for representing NMR peaks. The program is especially suited for semi-automatic studies of large sets of spectra, e.g., from reaction kinetic experiments [52].

Where solvent suppression was necessary, a WET pulse sequence with a π/2 Gaussian shaped excitation pulse was used, ensuring a narrow and monotone falling Gaussian excitation profile on each peak side without "wiggles." The smallest allowable distance of the excitation frequency to the closest analyte signal was determined before solvent suppression was used on this signal. Fig. 3 shows an example in which effective water suppression is obtained with the excitation frequency 35 Hz offset from the main solvent frequency. As can be seen in Fig. 3A, for the original spectrum, a quantitative evaluation of the spectrum is impossible due to unusual phase errors due to radiation damping of the water signal, whereas with solvent suppression a smooth baseline is obtained (Fig. 3B), allowing quantitative spectral deconvolution.

3.3. Results and discussion

^{1}H and ^{13}C assignments of the formaldehyde–water and formaldehyde–methanol species were validated with 1D and 2D NMR experiments and confirm literature data [23,53,54]. Equilibrium species distributions of various ternary mixtures of formaldehyde–water–methanol were investigated using ^{13}C NMR spectra. It was demonstrated in repeatability and reproducibility studies, that typical errors in NMR peak area fractions in those experiments are in the order of ±0.3% [46].

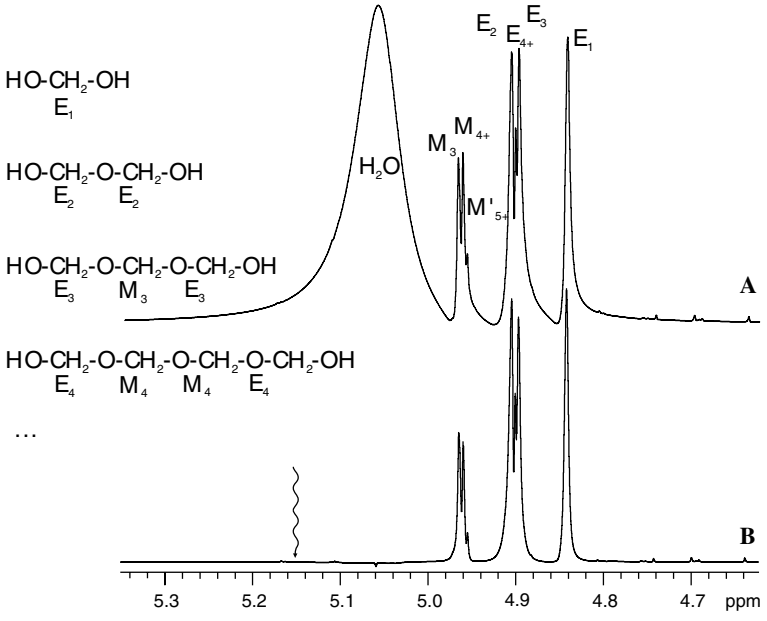

Fig. 3. 400 MHz ^{1}H NMR spectra of formaldehyde in water (0.340 g g^{-1} FA, pH 2, 293 K) with peak and structural assignment. (A) Section of the spectrum without solvent suppression. (B) Water suppression using WET with the transmitter frequency as indicated by an arrow (π/2 Gaussian shape, duration 47 ms, 40 Hz bandwidth).

3.4. Reaction kinetics

Fig. 4 shows proton NMR data taken during a typical kinetic study of a formaldehyde–methanol mixture, which was diluted with pure methanol at $T = 373$ K and $p = 0.5$ MPa. The NMR data was used to develop a thermodynamically consistent reaction kinetic model, which uses a second order model in activities for each of the oligomerization reactions [51]. To determine the reaction kinetic constants, NMR peak area fractions were calculated from the model for each time step in a kinetic run and compared to the experimental data. The numbers for the kinetic constants were adjusted to give a good fit. A typical result is shown in Fig. 4, where the concentration of methylene glycol increases after dilution, while the oligomer concentrations (higher poly(oxymethylene) hemiformals HF_2, HF_{3+}) decrease with time. More details are given elsewhere [51,52].

4. Application 2: Rapid evaporation of formaldehyde solutions

4.1. Background

The amount of formaldehyde which can be dissolved in water or methanol is limited due to precipitation of solid long chained oligomers. In order to obtain highly concentrated liquid formaldehyde solutions the species distribution has to be shifted from the equilibrium values to predominantly shorter oligomers. This can be achieved in a thin-film evaporator, which allows high evaporation rates at low residence times and moderate temperatures [55]. The evaporator was directly coupled to the NMR spectrometer in order to monitor the species distribution in the highly concentrated bottom product under various process conditions up to 80 mass% formaldehyde. The experiments serve as an example for process monitoring with NMR spectroscopy.

4.2. Experimental

The thin-film evaporator used for the experimental work (QVF, Mainz, Germany, Miniplant DN50) had an inner diameter of 50 mm and a wiped film length of 300 mm. The experimental set-up is shown in Fig. 5. The evaporator was operated at pressures of about 5–10 kPa and high evaporation rates. A controlled valve membrane pump (BF414-1002, Telab GmbH, Moers, Germany) was used to continuously withdraw the bottom product. PTFE tubing was used which offers the advantage of being transparent, allowing the observation of any clouding or solid precipitation.

Experiments for direct process monitoring of the bottom product under various process conditions (e.g., evaporator pressure, temperature, feed flow rate, or evaporation ratio) were performed in single pass flow mode represented in Fig. 5 using the valve position "normal operation" in which P3 pumps freshly withdrawn solution to the NMR. As the pump P2 was operated with slightly larger flow rate, some excess solution was discarded into container C4 via tubing T1. The reflux from P3 was collected in container C3 via tubing T3 + T4.

For kinetic measurements, to monitor the aging of the bottom product, the sample was recycled through the NMR with valves V2 and V3 in position "loop operation." In this position P3 takes out the sample from

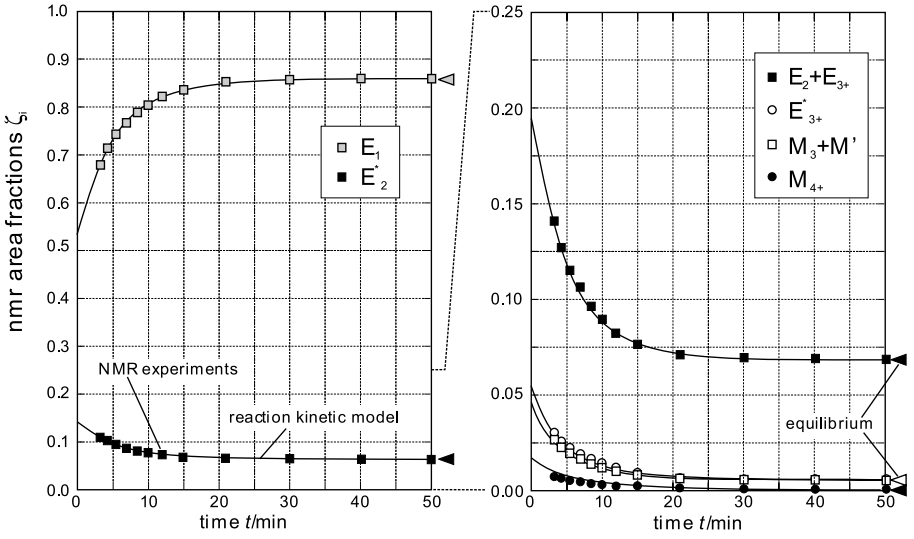

Fig. 4. Reaction monitoring in a formaldehyde–methanol solution (0.466 g g^{-1} FA, 373 K, 0.5 MPa He, pH 4) after dilution with pure methanol (mass ratio 1:1), observed by 400 MHz on-line ^{1}H NMR spectroscopy. Comparison with a thermodynamically consistent reaction kinetic model (solid lines)—[51]. Assignment of methylene groups based on existing literature [46] (The labels (E_1, etc.) are described in Fig. 3).

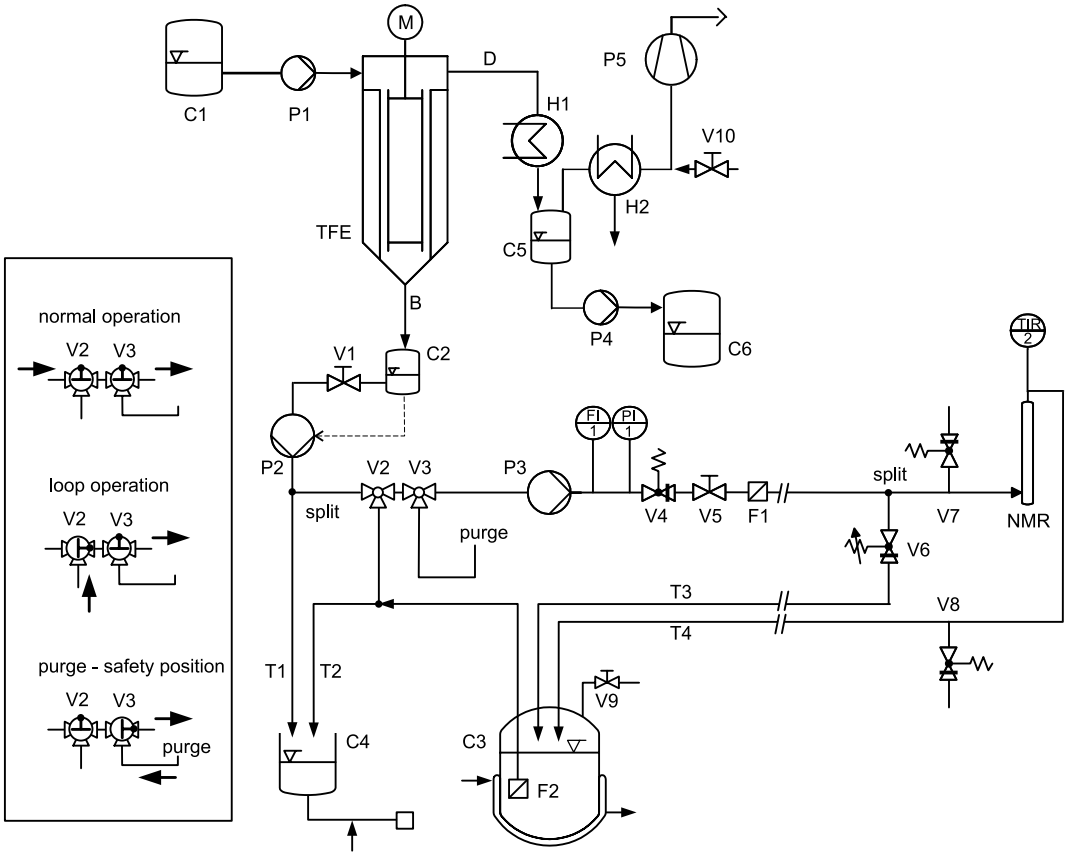

Fig. 5. Experimental set-up for NMR process monitoring of a thin-film evaporator (focus on bottom product B). C1, feed solution; P1, dosing pump; M, wiper motor; TFE, thin-film evaporator; D, distillation product; C2, low volume collector for bottom product; pump (P2) control; V1, outlet valve; P2, controlled-valve membrane pump; T1, T2, PTFE tubing; V2, three way valve for loop operation (see text); V3, three way valve for purge; P3, thermostated dosing pump; V4, back pressure regulator; V5, shut off valve; F1, filter 10 μm; V6, variable back pressure regulator; V7, V8, pressure relief valves, NMR, thermostated NMR flow cell; V9, pressure control valve; T3, T4, thermostated PEEK tubing; C3, thermostated vessel with magnetic stirrer; F2, filter 10 μm; C4, collecting container on balance. H1, condenser for distillation product; C5, low volume collector for distillation product; P4, controlled-valve membrane pump; C6, container for distillation product; H2, cooling trap; P5, membrane vacuum pump; V10, pressure control.

container C3 via F2. The solution is completely looped back to C3 via tubing T3 + T4. In case of the highly concentrated mixtures, flow NMR spectroscopy is risky due to the high viscosity of the samples and danger of rapid solid precipitation during the experiments. The sample viscosity was continuously observed via the back pressure indicated by PI1. Observation under flow is for this reason more appropriate than acquiring at stopped flow, where oligomer precipitation could not have been detected. When clouding was observed, the valves were adjusted to position "purge" and the whole system flushed with water.

Kinetics of the changes in species distribution were predominantly observed by ^{13}C NMR spectroscopy. At a total flow rate of 7.0 ml min^{-1} (due to the wider inner diameter of the tubing) and an NMR flow rate of 0.5 ml min^{-1} 16–32 transients per spectrum were recorded, equal to an acquisition time of 8–16 min per spectrum. Reaction kinetics were observed over about 2 h. Some ^{1}H NMR spectra were recorded additionally with the parameters given in Application 1.

4.3. Results and discussion

Fig. 6 shows typical results of a thin-film evaporator experiment monitored by on-line NMR spectroscopy. Fractions of CH_2O in poly(oxymethylene) glycols are plotted versus the number i of these segments in the oligomers. The evaporator was fed with equilibrated aqueous formaldehyde solution (30 mass% FA). The evaporation rate was 70 mass% in that example.

The experimentally determined species distribution of the feed is represented in Fig. 6A. The liquid bottom product had a formaldehyde content of almost 80 mass% and a species distribution depicted in Fig. 6B. After evaporation, the free solvent was nearly completely removed. The remaining water is almost entirely chemically bound in the oligomers. The hatched columns show the distribution of the formaldehyde to the various oligomers in the fresh non-equilibrium bottom product as experimentally determined by on-line NMR spectroscopy. The black columns correspond to the equilibrium state of the solution, predicted by a model

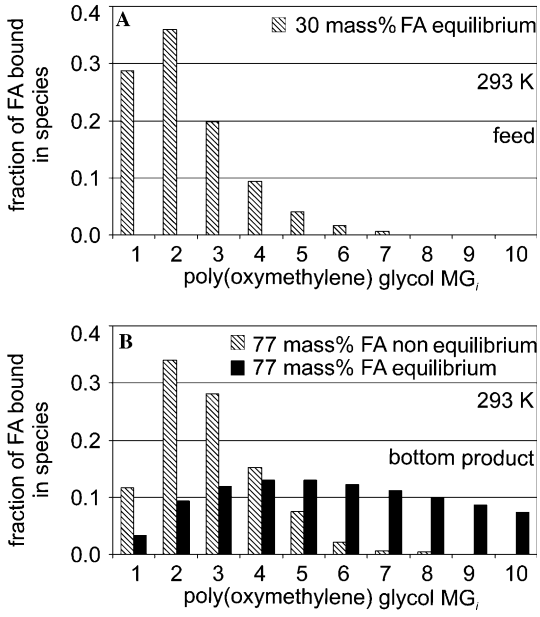

Fig. 6. NMR process monitoring of a rapid evaporation of aqueous formaldehyde solution in a thin-film evaporator leading to a non-equilibrated bottom product. (A) Feed species distribution: Fraction of CH_2O groups in poly(oxymethylene) glycols as experimentally determined by NMR. (B) Bottom product species distribution. 76.9 mass% formaldehyde in water. Hatched columns indicate non-equilibrium distribution as experimentally determined by NMR. Species distribution of equilibrated bottom product from model calculations is represented by black columns.

[46]. This distribution can not be observed by flow NMR as solid precipitation occurs before equilibrium is reached. It should be noted that the species distribution of the fresh non-equilibrium bottom product is almost the same as that of the feed solution, as can be seen by comparing Figs. 6A and B. Only the methylene glycol content is decreased by evaporation due to its high volatility. Upon storage the liquid bottom product turns slowly into colorless, solid paraformaldehyde. This process can take several hours. Reaction kinetics in the bottom product were also recently studied by means of ^{13}C NMR spectroscopy [55].

5. Application 3: Hetero- and homogeneously catalyzed ester formation

5.1. Background

Reactive distillation can be favorable both for the reaction (increased conversion) and the separation (circumventing azeotropes). The combination of reaction and distillation in one unit, however, leads to complex process behavior which is difficult to model. Reliable reaction kinetic data are the key to success in the design and scale-up of these integrated processes. Reactive distillation is also interesting for producing esters [56,57].

In the present work the butyl acetate esterification was studied.

$$C_4H_9OH + HCOOCH_3 \rightleftharpoons C_4H_9COOCH_3 + H_2O \quad (3)$$

The common quantitative analysis (gas chromatography) suffers from long analysis runs. As a result, the monitoring of rapidly changing compositions shortly after starting the kinetic experiment is difficult and valuable information is often lost. On-line ^1H NMR spectroscopy allows a fast and reliable analysis of all reaction compounds with sufficient data point densities for an accurate description of the reaction kinetics. It also provides reliable quantitative data despite extreme changes in composition during most of the experiments.

5.2. Experimental

For the investigation of homogeneous and heterogeneous acetate kinetics a small, custom made, fully thermostated glass vessel with 30 ml total volume was used. The heterogeneous catalyst was Lewatit K2621. The catalyst was freshly rinsed six times using 15–20 g solution (*n*-butanol–acetic acid at equal molar ratio) over a period of 10–15 min for each rinsing. The reaction was started in a freshly prepared solution of *n*-butanol and acetic acid by addition of catalyst (homogeneous or heterogeneous). The solution was withdrawn through a 10 μm filter. The further set-up was the same as shown in Fig. 1, except that narrow tubing was used (0.01″ ID sample supply, 0.02″ ID reflux), reducing the hold-up in the lines drastically. The total sample volume in the entire system was only 15 ml. 35–40 ^1H NMR spectra were acquired over a time of 6.5 h with single transients, $\pi/2$ excitation pulse (4.5 μs), spectral width of 4000 Hz with 64 k data points.

The ^1H NMR spectra show completely separated peaks of oxymethylene groups in *n*-butanol (3.59 ppm) and butyl acetate (4.04 ppm), which were used to monitor the concentration of these species during the reaction. The concentration of acetic acid was calculated from the peak appearing at 2.00 ppm representing the sum of the methyl peaks of acetic acid and butyl acetate. The water concentration was determined from the OH signal appearing between 9.00 and 3.80 ppm, depending on the composition of the mixture. It was possible to obtain the quantitative information from the mixtures by direct peak integration.

5.3. Results and discussion

In Fig. 7 quantitative results from NMR studies of homogeneously and heterogeneously catalyzed butyl acetate kinetics are shown. At the same proton concentration homogeneously catalyzed reactions are expected to be faster than heterogeneously catalyzed reactions due to the reduced accessibility of the active catalytic centers

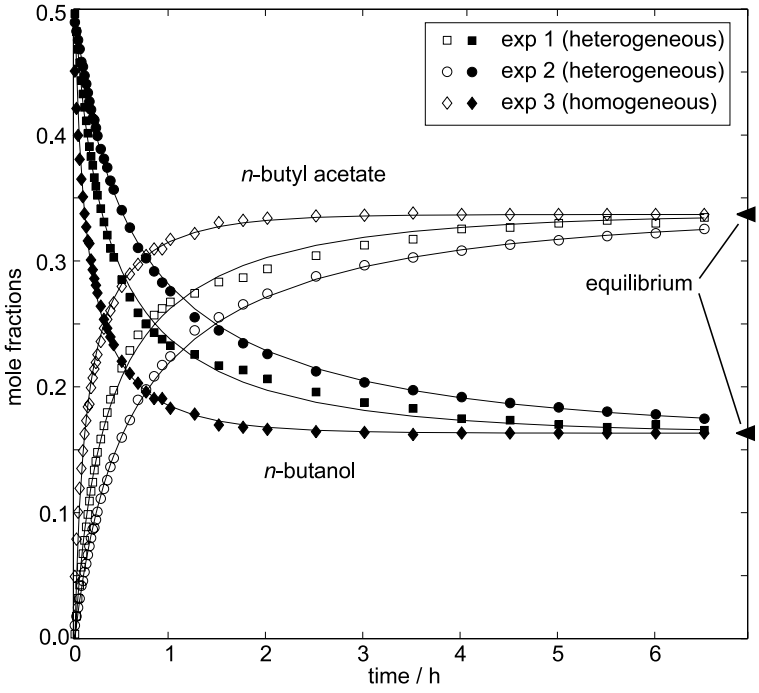

Fig. 7. Homogeneously and heterogeneously catalyzed *n*-butyl acetate formation at 363 K. Experimental mole fractions from on-line NMR for *n*-butanol (black) and *n*-butyl acetate (open) are plotted vs time over 6.5 h for three different experiments. Feed: equimolar mixture of *n*-butanol and acetic acid. Exp. 1, heterogeneous, 14.70 g feed, 4.85 g catalyst Lewatit K2621; exp. 2, heterogeneous, 14.10 g feed, 2.38 g catalyst; and exp. 3, homogeneous, 0.002 g g^{-1} conc. sulfuric acid (~10% of proton activity compared to exp. 1).

in the solid heterogeneous catalyst. The effects of decreasing the catalyst amount as well as changing from heterogeneous to homogeneous catalysis are clearly seen in the figure and found to be as expected. It was shown in test measurements that the accuracy of the NMR data is equal or even better than that of GC analysis (cf. low scatter of the data shown in Fig. 7). The major advantage over GC analysis is that NMR data can be taken 1–2 min (delay time) after initialization at short intervals of typically 3–5 s compared to about 15–20 min typically needed for a chromatogram. Also, faster kinetics than the ones shown in Fig. 7 were successfully studied, with equilibrium being reached in less than 10 min.

A thermodynamically consistent reaction kinetic model produced a good fit to the experimental data (cf. Fig. 7), providing insights into the activities of heterogeneous catalysts [58].

6. Conclusion

It has been shown that on-line NMR spectroscopy is an attractive technique for physicochemical and process engineering studies, yielding reliable quantitative information on mixtures in a fast non-invasive way. On-line NMR spectroscopy is the method of choice for investigations of chemical equilibria and reaction kinetics of complex reacting multicomponent mixtures [46,51,55].

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References

[1] P.J. Giammatteo, J.C. Edwards, Reliable refinery control using process NMR, Control 6 (1999) 71–74.
[2] P.A. Keifer, NMR tools for biotechnology, Curr. Opin. Biotechnol. 10 (1999) 34–41.
[3] H. Weber, L. Brecker, Online NMR for monitoring biocatalysed reaction, Curr. Opin. Biotechnol. 11 (2000) 572–578.
[4] J.C. Edwards, P.J. Giammatteo, On-line acid strength measurement and sulfuric acid alkylation process control using process NMR, ISA Tech/Expo Technol. Update 2 (1998) 63–67.
[5] R. Neudert, E. Ströfer, W. Bremser, On-line NMR in process engineering, Magn. Res. Chem. 24 (1986) 1089–1092.

[6] S.I. Selivanov, B.A. Ershov, The application of high resolution nuclear magnetic resonance in the study of fast non-equilibrium reactions, Russ. Chem. Rev. 55 (1986) 395–410.
[7] K. Woelk, J. Bargon, High-pressure NMR probes for the in situ investigation of gas/liquid reactions, Rev. Sci. Instrum. 63 (1992) 3307–3310.
[8] H.G. Niessen, P. Trautner, S. Wiemann, J. Bargon, K. Woelk, The toroid cavity autoclave for high-pressure and variable-temperature in situ nuclear magnetic resonance studies, Rev. Sci. Instrum. 73 (2002) 1259–1266.
[9] R. Chen, J.E. Bailey, Observations of aerobic, growing *Escherichia coli* metabolism using an on-line nuclear magnetic resonance spectroscopy system, Biotechnol. Bioeng. 42 (1993) 215–221.
[10] C. Sarazin, F. Ergan, J.-P. Séguin, G. Goethals, M.-D. Legoy, J.-N. Barbotin, NMR on-line monitoring of esterification catalyzed by cutinase, Biotechnol. Bioeng. 51 (1996) 636–644.
[11] C. Bianchini, H.M. Lee, A. Meli, F. Vizza, In situ high-pressure $^{31}P\{^{1}H\}$ NMR studies of the hydroformylation of 1-hexene by $RhH(CO)(PPh_3)_3$, Organometallics 19 (2000) 849–853.
[12] E. Bayer, K. Albert, M. Nieder, E. Grom, T. Keller, On-line coupling of high-performance liquid chromatography and nuclear magnetic resonance, J. Chromatogr. 186 (1979) 497–507.
[13] H.C. Dorn, High-performance liquid chromatography nuclear magnetic resonance, in: Encyclopedia of Nuclear Magnetic Resonance, Wiley, Chichester, NY, 1996, 12070–12085.
[14] K. Albert, Liquid chromatography–nuclear magnetic resonance spectroscopy, J. Chromatogr. A 856 (1999) 199–211.
[15] K. Albert, Supercritical fluid chromatography–proton nuclear magnetic resonance spectroscopy coupling, J. Chromatogr. A 785 (1997) 65–83.
[16] P.A. Keifer, High-resolution NMR techniques for solid-phase synthesis and combinatorial chemistry, Drug Discov. Today 2 (1997) 468–478.
[17] B.C. Hamper, D.M. Synderman, T.J. Owen, A.M. Scates, D.C. Owsley, A.S. Kesselring, R.C. Chott, High-throughput H-1 NMR and HPLC characterization of a 96-member substituted methylene malonamic acid library, J. Comb. Chem. 1 (1999) 140–150.
[18] R. McDermott, A.H. Trabesinger, M. Mück, E.L. Hahn, A. Pines, J. Clarke, Liquid-state NMR and scalar coupling in microtesla magnetic fields, Science 295 (2002) 2247–2249.
[19] R.L. Haner, W. Llanos, L. Mueller, Small volume flow probe for automated direct-injection NMR analysis: design and performance, J. Magn. Reson. 143 (2000) 69–78.
[20] R.L. Haner, J.Y. Lee, Flow-through NMR Probe Having a Replaceable NMR Flow Tube, Pat. US 6177798 (2001).
[21] K. Albert (Ed.), On-Line LC-NMR and Related Techniques, Wiley, Chichester, NY, 2002.
[22] M. Hofmann, M. Spraul, Sample Head for Flowthrough NMR Spectroscopy, Pat. US 5258712 (1993).
[23] I. Hahnenstein, M. Albert, H. Hasse, C.G. Kreiter, G. Maurer, NMR-spectroscopic and densimetric studies of reaction kinetics of formaldehyde-polymer formation in water, deuterium oxide and methanol, Ind. Eng. Chem. Res. 34 (1995) 440–450.
[24] M. Guéron, P. Plateau, M. Decorps, Solvent signal suppression in NMR, Prog. NMR Spectrosc. 23 (1991) 135–209.
[25] S.H. Smallcombe, S.L. Patt, P.A. Keifer, WET solvent suppression and its applications to LC NMR and high-resolution NMR spectroscopy, J. Magn. Reson. Ser. A 117 (1995) 295–303.
[26] S. Sukumar, M. O'Neil Johnson, R.E. Hurd, P.C.M. van Zijl, Automated shimming for deuterated solvents using field profiling, J. Magn. Reson. 125 (1997) 159–162.
[27] H. Barjat, P.B. Chilvers, B.K. Fetler, T.J. Horne, G.A. Morris, A practical method for automated shimming with normal spectrometer hardware, J. Magn. Reson. 125 (1997) 197–201.
[28] P.C.M. van Zijl, S. Skumar, M. O'Neil Johnson, P. Webb, R.E. Hurds, Optimized shimming for high-resolution NMR using three-dimensional image-based field mapping, J. Magn. Reson. A 111 (1994) 203–207.
[29] R.F. Evilia, Quantitative NMR spectroscopy, Anal. Lett. 34 (2001) 2227–2236.
[30] L. Griffiths, A. Irving, Assay by nuclear magnetic resonance spectroscopy: quantification limits, Analyst 123 (1998) 1061–1068.
[31] G. Maniara, K. Rajamoorthi, S. Rajan, G.W. Stockton, Method performance and validation for quantitative analysis by ^{1}H and ^{31}P NMR spectroscopy. Applications to analytical standards and agricultural chemicals, Anal. Chem. 70 (1998) 4921–4928.
[32] J.N. Shoolery, Quantitative measurements, in: Encyclopedia of Nuclear Magnetic Resonance, Wiley, Chichester, NY, 1996, 3907–3916.
[33] F. Malz, H. Jancke, R. Radeglia, W. Hässelbarth, Intercomparisons for quantitative ^{1}H-NMR spectroscopy, Federal Institute for Materials Research and Testing (BAM), Berlin, Germany, presented at 22th meeting of the magnetic resonance spectroscopy division of the German Chemical Society, 27–30 September 2002, Regensburg, Germany.
[34] R. Freeman, H.D.W. Hill, Phase and intensity anomalies in Fourier transform NMR, J. Magn. Reson. 4 (1971) 366–383.
[35] R.E. Hoffman, G.C. Levy, Modern methods of NMR data processing and data evaluation, Prog. NMR Spectrosc. 23 (1991) 211–258.
[36] A.I. Zhernovoi, G.D. Latyslev, Nuclear Magnetic Resonance in Flowing Liquids, Consultants Bureau, New York, 1965.
[37] D.W. Jones, T.F. Child, in: J.S. Waugh (Ed.), Advances in Magnetic Resonance, Academic Press, New York, 1976 (Chapter 3).
[38] H.C. Dorn, Flow NMR, in: Encyclopedia of Nuclear Magnetic Resonance, Wiley, Chichester, NY, 1996, 2026–2037.
[39] C.A. Fyfe, M. Cocivera, S.W.H. Damji, Flow and stopped-flow nuclear magnetic resonance investigations of intermediates in chemical reactions, Acc. Chem. Res. 11 (1978) 277–282.
[40] D.A. Laude Jr., R.W.K. Lee, C.L. Wilkins, Signal enhancement of long-relaxing ^{13}C nuclei by flow NMR, J. Magn. Reson. 60 (1984) 453–459.
[41] J.L. Sudmeier, U.L. Gunther, K. Albert, W.W. Bachovchin, Sensitivity optimization in continuous flow FT-NMR, J. Magn. Reson. A 118 (1996) 145–156.
[42] H. Günther, in: NMR-Spektroskopie, Georg Thieme, Stuttgart, NY, 1992, 355–371.
[43] R.R. Ernst, W.A. Anderson, Application of Fourier transform spectroscopy to magnetic resonance, Rev. Sci. Instr. 37 (1966) 93–102.
[44] D.E. Jones, H. Sternlicht, Fourier transform nuclear magnetic resonance, I. repetitive pulses, J. Magn. Reson. 6 (1972) 167–182.
[45] E.D. Becker, J.A. Ferretti, R.N. Gambhir, Selection of optimum parameters for pulse Fourier transform nuclear magnetic resonance, Anal. Chem. 51 (1979) 1413–1420.
[46] M. Maiwald, H.H. Fischer, M. Ott, R. Peschla, C. Kuhnert, C.G. Kreiter, G. Maurer, H. Hasse, Reaction kinetics in aqueous and methanolic formaldehyde solutions: NMR experiments up to 373 K and thermodynamically consistent model, Ind. Eng. Chem. Res. 42 (2003) 259–266.
[47] Oxford Instruments, Specifications for standard, vertical bore high-resolution NMR magnet systems (2001).
[48] O. Levenspiel, in: Chemical Reaction Engineering, Wiley, Chichester, NY, 1999, 255 ff.
[49] W. Dankelman, J.M.H. Daemen, Gas chromatographic and nuclear magnetic resonance determination of linear formaldehyde oligomers in formalin, Anal. Chem. 48 (1976) 401–404.
[50] H. Hasse, G. Maurer, Kinetics of the polyoxymethylene glycol formation in aqueous formaldehyde solutions, Ind. Eng. Chem. Res. 30 (1991) 2195–2200.

[51] M. Ott, H.H. Fischer, M. Maiwald, K. Albert, H. Hasse, Reaction kinetics in aqueous and methanolic formaldehyde solutions: NMR experiments up to 373 K and thermodynamically consistent model, Chem. Eng. Progr., to appear.
[52] M. Ott, Doctoral Dissertation, University of Stuttgart, Stuttgart 2003, in preparation.
[53] D.J. Le Botlan, B.G. Mechin, G.J. Martin, Proton and carbon-13 nuclear magnetic resonance spectrometry of formaldehyde in water, Anal. Chem. 55 (1983) 587–591.
[54] A.L. Balashov, S.M. Danov, V.L. Krasnov, A.Yu. Chernov, T.A. Ryabova, Association of formaldehyde in aqueous-alcoholic systems, Russ. J. Gen. Chem. 72 (2002) 744–747.
[55] K. Schilling. M. Sohn, E. Ströfer, H. Hasse, Reaktive verdampfung formaldehydhaltiger mischungen und process monitoring mit online NMR-spektroskopie, Chem. Ing. Tech. (2003), in press.
[56] B. Bessling, J.-M. Löning, A. Ohligschl äger, G. Schembecker, K. Sundmacher, Investigations on the synthesis of methyl acetate in a heterogeneous reactive distillation process, Chem. Eng. Technol. 21 (1998) 393–400.
[57] M.F. Doherty, G. Buzad, Reactive distillation by design, Trans IChemE 70 (1992) A448–A458.
[58] S. Grob, Doctoral Dissertation, University of Stuttgart, Stuttgart 2003, in preparation.