Reaction monitoring by Benchtop NMR spectroscopy using a novel stationary flow reactor setup

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Abstract

A flow reactor setup for non-invasive monitoring of reactions using a compact Benchtop nuclear magnetic resonance (NMR) spectrometer is presented, in which a tubular flow reactor is inserted into the bore of the NMR spectrometer and operated at stationary conditions. To monitor the composition change of reaction mixture in the flow reactor, the entire reactor is moved to different longitudinal positions in the bore. As the flow is stationary, the composition of the reaction mixture does not change with time at a fixed reactor position. Thus, also time-consuming 2D NMR techniques can be applied to elucidate unknown products. As quantitative information is obtained directly from the NMR spectrum without calibration, the method is also appropriate for quantifying substances that are unstable as pure components. As test cases, two esterification reactions, the formation of methyl formate (MF) and the formation of methyl acetate (MA) from the pure alcohols and acids, were investigated using this technique. In addition, three 2D NMR pulse sequences (H-H-COSY, HETCOR, and HMBC) were applied in flow. The comparison of the results of the present work to literature data shows that the new method gives reliable results.

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Introduction

Nuclear magnetic resonance (NMR) spectroscopy is widely used for online monitoring and elucidation of reactions.^{1,2} It is a non-invasive method. Thus, analysis of complex fluid mixtures is possible in-situ without sampling. Contrarily to other spectroscopic methods, no previous calibration is needed for quantitative analysis by NMR spectroscopy.³ Two different types of NMR spectrometers are used for reaction monitoring: high field NMR spectrometers with cryogenically cooled super-conducting magnets and Benchtop NMR spectrometers with permanent magnets. Benchtop NMR spectroscopy is easy to apply as no cryogenic media and no special requirements are needed, e.g. regarding climatisation or a vibrational-free location. The instrument can be operated in a standard laboratory, e.g. next to a reactor.^{4,5} The lower magnetic field strength and field homogeneity, however, entail lower chemical resolution and sensitivity compared to high field NMR spectrometers.⁶ Nevertheless, quantitative spectra can be obtained⁷ and enhanced evaluation methods have been applied to further improve the quality of spectra.^{8,9}

NMR spectroscopy has been applied in the field of reaction monitoring in many different ways: in the simplest case, samples are withdrawn from a reactor and are analyzed by NMR spectroscopy. In more advanced settings, a batch reactor is coupled to a NMR spectrometer that is equipped with a flow cell and the reacting mixture is pumped from the reactor to the spectrometer.^{5,10–15} Such setups can be operated either in a flow mode (stationary measurement) or in a stopped flow mode, in which after transferring the sample the flow is stopped and the reaction is monitored inside the NMR cell, which then acts as batch reactor (instationary measurement). Also special micro-mixer NMR probe heads have been developed that enable the monitoring of fast reactions either in flow or stopped flow mode.^{16–21}

In a stationary flow reactor the extent of reaction depends only on the residence time in the reactor. At a certain position in the reactor the extent of reaction does not change with time and time-consuming NMR experiments (e.g. 2D measurements or 1D measurements with a large number of scans to increase the signal to noise ratio) can be carried out that take longer than the lifetime of the intermediate or even the time constant of the reaction. Using an instationary measurement

(e.g. a batch reactor coupled via a sample loop to the spectrometer) only short NMR sequences are feasible so that the change of the extent of reaction during the NMR measurement is negligible. In all previous applications, in which stationary NMR measurements were used, the monitoring of the progress of the reaction required either a variation of the flow rate or a variation of the hold-up volume in the system.^{22–26} However, there are limits to both of these approaches. The maximal flow rate is restricted by the T_1 relaxation time of the nuclei that are monitored, as problems with purging of the active volume and premagnetization may arise; changing the hold-up volume must usually be done mechanically and is tedious. Hence, better solutions for the application on stationary NMR measurements in reaction monitoring are desired. In the present work, a new method for achieving this is introduced, which is easy to apply.

The idea is to use a capillary as a tubular reactor and pass it through the bore of the NMR spectrometer. By changing the longitudinal position of the capillary, the progress of the reaction can be monitored without changing the flow rate or the hold-up volume. In the experiments of the present work, a Benchtop spectrometer was used, as for these instruments inserting a capillary in the bore is particularly simple. The volume flow rate was kept constant and was optimized to achieve a sufficient mixing of reactants at the entry of the reactor and to ensure a complete premagnetization of the flowing reactive mixture in the spectrometer. The method could also be adapted for application in high field NMR spectrometers.

A limitation of the Benchtop NMR spectrometers that are presently commercially available is the lacking temperature control. The magnets are thermostated to ensure field stability and that temperature also prevails in the bore. Several workarounds have been suggested, like using a dewar in the bore to insulate the sample and the magnet thermally,¹² but no fully satisfactory solution is presently available. Hence, the experiments in this work are conducted at the magnet temperature which was 302 K. This limitation does not exist for high field instruments and it can be expected that solutions for Benchtop instruments will become available in the next years.

In this work, two esterification reactions were chosen to test the new method: 1) the formation of methyl formate (MF) from methanol (MeOH) and formic acid (FA) and 2) the formation of

methyl acetate (MA) from methanol and acetic acid (AA). For comparison, these reactions were also examined in batch experiments in conventional NMR sample tubes. The experimental data of this work were furthermore compared to data from literature: Brächer et al.²⁷ obtained data for the formation of methyl formate using a micro-mixer high field NMR probe head in stopped flow mode. Dörrhöfer et al.²⁸ presented an activity based reaction kinetic model for the formation of methyl acetate which was parametrized based on experiments in a stirred tank reactor with conventional GC analysis. In the experiments temperature and amount of catalyst were varied. Details on the parametrization of the model is given in the Supporting Information.

Besides the main issue of the new experimental setup for studying reaction kinetics with NMR spectroscopy, also the important question of choosing an appropriate reactor model for the evaluation of experimental reaction kinetic data is revisited in the present work.^{29,30} For a given set of reaction kinetic data, different models of the reactor that was used for the study, can lead to significantly different results for the rate constants. A suitable model for the evaluation of the data from the present setup is identified based on measurements of the residence time distribution (RTD).

Furthermore, 2D Benchtop NMR experiments (homonuclear: H-H-COSY, heteronuclear: HETCOR and HMBC) were carried out in stationary flow measurements.

Reaction systems and kinetic model

In the present work, two homogeneously catalyzed esterification reactions were investigated: the formation of methyl formate (Eq. (1)) and the formation of methyl acetate (Eq. (2)). Sulfuric acid was used as catalyst.

A second order type model was used to describe the reaction kinetics in both cases, see Eq. (3):

$$r = \frac{1}{x_W} \cdot [k_f(T, x_{H_2SO_4})a_{MeOH}a_{acid} - k_b(T, x_{H_2SO_4})a_{ester}a_W] \quad (3)$$

where 'acid' refers to FA or AA and 'ester' refers to MF or MA, r is the rate of reaction related to the total amount of substance, x_i the mole fraction, a_i the activity of the component i , and k_f and k_b are the rate constants of the forward and backward reaction, respectively. The term $1/x_W$ on the right hand side of Eq. (3) is introduced to account for the dependence of catalyst activity on the mole fraction of water following a suggestion of Liu et al.³¹ Activities were used to ensure thermodynamic consistency. The activity coefficients γ_i were calculated using the UNIQUAC model with parameters from Pöppken et al.³² The rate constants of the forward and backward reaction (k_f and k_b) are connected by the thermodynamic equilibrium constant K_a .

$$K_a = \frac{k_f}{k_b} \quad (4)$$

Reactor models

For the evaluation of reaction kinetic experiments the kinetic model (see previous section) has to be coupled with a reactor model. The reactor that was used in the present experiments was a simple capillary (see next section). It is described here using a tanks-in-series (TSR) model where N ideally mixed tanks with the same volume V_k are connected in series. The extent of reaction in the TSR model $\xi_k^{\text{mod,TSR}}$ is described for a constant molar density of the mixture by Eq. (5):

$$\xi_k^{\text{mod,TSR}} = \xi_{k-1}^{\text{mod,TSR}} + \frac{V_k}{\dot{V}} \cdot r \quad (5)$$

$$\forall k = 1 \dots N; \xi_0 = 0$$

where $\dot{V}$ is the invariant flow rate and r the rate of reaction. The index *mod* is used to distinguish between modeling and experimental results for the extent of reaction. The parametrization of the

TSR model (number of tanks N and volume of one tank V_k) and the determination of the reaction time τ , which is the mean residence time in the reactor at a given position z , is done based on RTD measurements, which are described below.

The instationary kinetic measurement in the NMR sample tubes were evaluated using a stirred tank batch reactor model. The derivative of the extent of reaction $\xi^{\text{mod, batch}}$ with respect to the reaction time τ is linked to the rate of reaction r as follows:

$$\frac{d\xi^{\text{mod, batch}}}{d\tau} = r \quad (6)$$

Experiments

Chemicals

Table 1 lists the chemicals, the suppliers and the purities according to the supplier's specifications. All chemicals were used without further purification. Ultrapure water was produced using a Milli-Q integral water purification system from Merck Millipore (Merck). No significant amounts of side components were detected in the analysis of the sample.

Experimental setup and procedure

Kinetic ^1H NMR measurements and 2D NMR measurements were carried out in a stationary flow reactor setup. For comparison, also instationary kinetic ^1H NMR measurements were carried out in NMR sample tubes.

Figure 1 shows the stationary flow reactor setup. The setup consists of two feed vessels (reactant A: acid, reactant B: methanol+sulfuric acid) that were fed to a high-pressure mixer (Upchurch) using high-pressure dosage pumps (Wadose Plus, Wagner MSR). The flows in both lines were measured with Coriolis flow sensors (Mini Cori-Flow, Bronkhorst, accuracy: ± 0.01 ml/min). The feed lines were PEEK capillaries with an inner diameter of 1 mm. The same type of capillary was connected to the outlet of the mixer and was used as flow reactor, which had a total length of

11 m. Only for the heteronuclear 2D NMR measurements, a capillary with a larger inner diameter of 3.2 mm was used to increase the active volume (i.e. the volume of sample inside the NMR detection region). The capillary was passed through the bore of the NMR spectrometer in such a way that the position z of the active volume within the capillary could be varied. A back pressure regulator was used to achieve a pressure of about 7 bar in the flow reactor. The feed vessels, the feed lines and the reactor capillary were thermostated in a water bath which was regulated to a temperature of 302 K by a heating thermostat (Julabo) and which was positioned under the NMR spectrometer.

All chemicals were degassed before the experiment. To ensure steady-state in the reactor, the pumps were operated for 60 min before the experiment was started. The flow rates of the reactants were chosen such that an equimolar feed ratio of the reactants was achieved and the total flow rate in the reactor was 0.1 ml/min for the methyl formate formation and 0.2 ml/min for the methyl acetate formation, respectively. At these conditions the mixer ensures a good mixing of the reactants. This was checked in a preliminary test with pure water and pure acetonitrile as feed components. By varying the flow rates in both pumps the concentration of the obtained mixture was changed but the overall flow rate was kept constant. The composition measured spectroscopically fulfilled the mass balance induced by the adjusted flow rates. No flow artifacts were observed in the NMR spectrum indicating a homogeneous mixture. The smallest distance between the mixer and the active volume was $z_1 = 26$ cm (mixer position at the entry of the spectrometer bore), the largest distance was $z_{10} = 1004$ cm. Information on the 8 intermediate positions $z_2 - z_9$ is given below. The mean residence time for each position was determined by RTD measurements, as discussed in the Supporting Information. For each position ten quantitative ^1H NMR measurements were performed and their results were averaged. The positions for the 2D NMR experiments were $z_{10} = 1004$ cm (homonuclear) and $z_3 = 121$ cm (heteronuclear).

The NMR sample tube experiments were carried out in standard 5 mm Wilmad NMR glass tubes. The degassed reactants and sulfuric acid were weighed in the NMR tube such that an equimolar ratio of reactants was achieved. After intensive shaking for 30 s the NMR tube was

inserted in the NMR spectrometer and a series of ^1H NMR measurement was started for 120 min.

NMR instrument and methods

All NMR measurements were carried out with a Magritek Spinsolve[®] Carbon NMR spectrometer with a field strength of 1 T, corresponding to a Larmor frequency of 42.5 MHz for ^1H . The optimization of the magnetic field homogeneity (shimming) was performed with water in the reactor capillary using the automatic routines provided by the manufacturer.

In the studies in the stationary flow mode, the ^1H NMR spectra were measured with an acquisition time of 6.4 s, a dwell time of 200 μs , 32k data points, a 90° pulse and one scan per spectrum. The following 2D NMR measurements were performed: 2D homo nuclear pulse sequence H-H-COSY (number of scans: 4, repetition time: 2 s) and the 2D hetero nuclear pulse sequences HETCOR and HMBC (both number of scans: 16, repetition time: 5 s). The instationary kinetic experiments in sample tubes were performed with ^1H NMR measurements with intervals of 60 s between the spectra (acquisition time: 6.4 s, 32k data points, 90° pulse, one scan per spectrum).

Integration and post processing of the NMR spectra were carried out with the MNova software 9.1 (MestReLabs). For baseline correction, a Whittaker smoother algorithm was used. The phase correction was done manually. For the evaluation of the ^1H NMR spectra, the ^{13}C satellites were left outside the integration range. All peaks were integrated directly without using deconvolution as the evaluated peaks were well-separated.

Premagnetization in flow

NMR measurements on continuously flowing liquids are quantitative only if all components that have different T_1 relaxation times are fully premagnetized before the measurement. This is only achieved if the flow rate does not exceed a certain threshold, which depends on the instrument and setup.^{5,33} The maximal flow rate was determined here in preliminary experiments in which signal intensities were measured as a function of the flow rate. The procedure is described in the Supporting Information. From the results, the relative magnetization M_{rel} was calculated as

the ratio of signal intensity at a given flow rate $\dot{V}$ to signal intensity at equilibrium magnetization at $\dot{V} = 0$. Furthermore, the T_1 relaxation time was measured for each pure component with an inversion recovery pulse sequence (number of scans: 2, acquisition time: 6.4 s, dwell time: 200 μ s, 32k data points, repetition time: 30 s, max. inversion: 10 s, number of steps: 41) in standard 5 mm Wilmad NMR glass tubes at 302 K.

The results of these preliminary measurements are summarized here in a graph in which the relative magnetization is shown as a function of the product of the flow velocity and the T_1 relaxation time. The resulting premagnetization curve is characteristic for the present NMR instrument when it is used in flow experiments with the flow direction from bottom to top, see Figure 2. With increasing flow rate the relative magnetization decreases. The extent to which the relative magnetization decreases depends on the T_1 relaxation time of the studied nucleus. The T_1 relaxation times that were measured in the present work are reported in Table 2. For the esterification of formic acid the maximum volume flow rate is 0.1 ml/min, for the esterification of acetic acid the maximum volume flow rate is 0.2 ml/min.

RTD measurements

To parametrize the TSR model (number of tanks N and volume of one tank V_k) and to determine the reaction time τ in the reactor at a given position z , the RTD in the reactor capillary and the mean residence time $\bar{t}$ was measured at four positions ($z_2 = 71$ cm, $z_4 = 177$ cm, $z_7 = 415$ cm, $z_9 = 709$ cm) in preliminary experiments. A tracer step response experiment was performed and the results were monitored with the NMR spectrometer. The procedure is described in the Supporting Information. The normalized molar ratio of the tracer F was calculated from NMR data and was plotted as a function of dimensionless time θ , which is the ratio of absolute time t to mean residence time $\bar{t}$ for a given reactor position. The resulting setup response curves $F(\theta)$ were evaluated using Eq. (7):

$$F = 1 - e^{-N\theta} \left[1 + N\theta + \frac{(N\theta)^2}{2!} + \dots + \frac{(N\theta)^{N-1}}{(N-1)!} \right] \quad (7)$$

Figure 3 shows the step response curves $F(\theta)$ for both flow rates. All response curves are close to a symmetrical shape and show no tailing. This indicates an undisturbed laminar flow profile.²⁹ The response curves deviate from the ideal plug flow (PFR) model but are well described by the laminar dispersive TSR model. The calculated number of tanks N as well as the mean residence time $\bar{t}$ of each investigated reactor position z are linearly dependent on the position z . This results in a total number of tanks for the reaction capillary (at position z_{10}) of $N = 1137$ for 0.1 ml/min and $N = 658$ for 0.2 ml/min. The mean residence times for all ten reactor positions are interpolated from the RTD measurements. See Supporting Information for detailed description. The volume of one tank V_k is calculated from Eq. (8):

$$V_k = \frac{A_i \cdot z_{10}}{N} \quad (8)$$

where A_i is the inner cross section of the reactor capillary. As the number of tanks is large for the present reactor capillary, the TSR model only slightly deviates from the ideal PFR model. In a preliminary investigation, which is described in more detail in the Supporting Information, reaction rate constants were determined from the same kinetic data sets using the TSR and the PFR model, respectively. The deviations were found to be below 8%.

Peak assignment and data analysis

Figure 4 shows the structures of all components and the peak assignment. Figure 5 shows typical spectra of both reaction mixtures. The integrals of the methanol educt peak H2 and of the ester product peak H4 or H7, respectively, were used for quantifying the molar ratio of ester to the sum of methanol and ester ζ . In a preliminary test with binary mixtures of methanol and ester the absolute deviation between the molar ratio determined gravimetrically and the molar ratio determined from NMR spectroscopy was below 0.007 mol/mol.

For a given reaction time τ (corresponding to a given position z in the reactor), the molar ratio

ζ was determined from the ratio of peak areas A_i of ester and methanol using Eq. (9):

$$\zeta(\tau) = \frac{A_{\text{ester}}(\tau)}{A_{\text{ester}}(\tau) + A_{\text{methanol}}(\tau)} \quad (9)$$

Using the initial mole fractions $x_{i,0}$ of the components methanol and ester, the experimental extent of reaction ξ^{exp} was calculated from:

$$\xi^{\text{exp}}(\tau) = \zeta(\tau)(x_{\text{ester},0} + x_{\text{methanol},0}) - x_{\text{ester},0} \quad (10)$$

In order to obtain the rate constants from the measured NMR spectra, the following minimization procedure with the sum of squared errors (SSE) as objective function was applied.

$$\sum_{j=1}^{M_{\text{obs}}} \left(\xi_j^{\text{exp}}(\tau_j, x_0) - \xi_j^{\text{mod}}(\tau_j, x_0, k_f, k_b) \right)^2 \stackrel{!}{=} \min \quad (11)$$

M_{obs} is the total number of spectra and τ_j the corresponding reaction time. ξ^{exp} is the experimental extent of reaction (Eq. (10)). ξ^{mod} is the predicted extent of reaction. It was obtained by solving the set of equations of TSR model (Eq. (5)) or the ordinary differential equation of batch model (Eq. (6)) with Matlab. The experimental data was fitted individually for each kinetic experiment at isothermal conditions.

Results and discussion

In the following section, the results of the reaction kinetic measurements (Figure 6 and Figure 7) and the 2D NMR measurements (Figure 8) are shown. Table 3 lists the reaction conditions and the initial molar ratio of the reactants. The experimental values of ξ as a function of the reaction time τ are reported in the Supporting Information. The rate of reaction was fitted to the experimental data by means of the TSR model for stationary flow experiments and by means of the stirred tank model for the instationary batch experiments (see Eq. (11)). The resulting rate constants k_f and the

equilibrium constants K_a are listed in Table 4.

Kinetic measurements

Figure 6 shows the results of the reaction kinetic measurements of the formation of methyl formate from the present work. Results from the flow experiments are compared to those from the batch experiments from the present work. Also data from literature that were taken at the same conditions as those studied here are shown for comparison. The literature data were obtained by Brächer et al.²⁷ A micro-mixer high field NMR probe head in stopped flow mode was used.

Two cases are shown: results from uncatalyzed experiments and results from experiments in which sulfuric acid was added. Temperature and feed ratio are the same in both cases. For both cases, the three data sets agree very well, cf. Figure 7. The model describes the experimental data well - including the equilibrium composition.

Figure 7 shows the results of the reaction kinetic measurements of the formation of methyl acetate. The presentation is similar to that in Figure 6. Two catalyzed cases are studied, the equilibrium is not reached in the investigated time interval. No experimental literature data is available for a direct comparison. Therefore, instead of experimental data from the literature, results from a reaction kinetic model of the studied system from the literature are shown (Dörrhöfer et al.²⁸). Again, the data from the flow and the batch experiments from the present work agree well, and the reaction kinetic model of Eq. (3) describes the data well. The results from the present work agree well with those from the model of Dörrhöfer et al. They determined their model based on experiments in a batch reactor apparatus.²⁸

The rate constants (see Table 4) obtained in the flow experiments are in good agreement with those from the batch experiments. Brächer et al.²⁷ used the same kinetic model and reactor model for the evaluation of the kinetic measurements. For the esterification of formic acid with 2 ma% catalyst a rate constant of $k_f = 5.6 \cdot 10^{-3}$ mol/(mol s) was reported by Brächer et al.²⁷ It slightly differs from the k_f obtained in the present work. This deviation can be explained by the differences in the data that were used for the fit. The experimental setup of Brächer et al.²⁷ was designed to

study fast reactions, the first data point was recorded after seconds in their studies. In the stationary flow setup of the present work the reactants are mixed outside the spectrometer and the first data point is recorded only after minutes. The differences in the data sets lead to differences in k_f . For studying fast reactions, the delay time between the mixing and the radio frequency coil would have to be reduced. This can be achieved by positioning the mixer inside the NMR bore, following the ideas described by Brächer et al.²⁷ for high field NMR instruments.

For the esterification of acetic acid, no rate constants are available in literature for the temperature that was studied in the present work. Therefore k_f that was obtained by Brächer et al.²⁷ at 313 K was extrapolated using the Arrhenius equation. The activation energy was published by Liu et al.³¹ The resulting rate constants k_f are $1.3 \cdot 10^{-4}$ mol/(mol s) (for $w_{\text{H}_2\text{SO}_4} = 1.3$ ma%) and $3.3 \cdot 10^{-4}$ mol/(mol s) (for $w_{\text{H}_2\text{SO}_4} = 3.5$ ma%). These results are in good agreement with the values from Table 4. These comparisons show that the new setup gives reliable results.

2D NMR measurements

Figure 8 shows the results of the 2D NMR experiments. The figures on the left side refer to the formation of methyl formate, the ones on the right side to the formation of methyl acetate. The following experiments are presented: first row: H-H-COSY, second row: HETCOR, third row: HMBC.

The results demonstrate that all relevant information of a 2D NMR spectrum can be obtained with the present setup in flow. Hence, the time-consuming 2D NMR sequences can also be used for reaction monitoring as well as for elucidation of intermediate products during course of reaction.

Conclusions

In the present work, a novel setup for reaction monitoring with NMR spectroscopy was developed and successfully tested. A slidable capillary was used as a flow reactor and passed through the bore of a Benchtop NMR spectrometer. The reactor was operated stationary. The progress of the

reaction was monitored by shifting the position of the capillary. The setup was tested using two esterification reactions. The reaction kinetic results obtained with the new setup were found to agree well with literature data as well as with results from dynamic batch experiments that were carried out in the present work for comparison. As the conditions are stationary, also time consuming NMR experiments can be carried out to investigate the reaction at any point of its progress. The new setup is suited for studying reaction kinetics with rate constants between about 10^{-4} s^{-1} and 10^{-2} s^{-1} . Unfortunately, the Benchtop NMR spectrometers that are presently available, can be operated only at a single temperature near room temperature. This is no systematic problem of the new method that was developed here. It is expected that Benchtop NMR spectrometers with thermostatzation will become available in the foreseeable future. When this is the case, the new method can also be used for reaction kinetic studies at different temperatures. Furthermore, the new method can be applied using high field instruments, under the condition that a probe head is available that can accommodate the slidable capillary. The new method is simple and robust and extends the tool box of NMR techniques for reaction monitoring.

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Supporting Information Available

Kinetic model of Dörrhöfer, Premagnetization in flow - procedure, RTD measurements - procedure, parametrization of TSR model, sensitivity study - reactor model PFR, default parameters of pulse sequences, experimental data: kinetic data.

This material is available free of charge via the Internet at <http://pubs.acs.org/>.

Table 1: List of chemicals used for the investigations.

Chemical name	Source	Grade	Purity
Acetic acid	Carl Roth	Rotipuran	≥ 0.998 g/g
Formic acid	Sigma Aldrich	ACS reagent	≥ 0.980 g/g
Methanol	Carl Roth	Anhydrous	≥ 0.998 g/g
Sulfuric acid	JT Baker	Analyse	≥ 0.960 g/g

Table 2: Longitudinal relaxation times of protons in different groups of the studied pure components at 302 K.

	Water OH	Methanol CH ₃ OH	Formic acid CH OH	Acetic acid CH ₃ OH	Methyl formate OCH ₃ CH	Methyl acetate OCH ₃ CH ₃
T_1 / s	2.99	2.97 2.87	3.97 3.86	1.91 2.72	6.38 7.58	3.52 3.49

Table 3: Initial molar fractions of reactants for all kinetic experiments. Water content is induced by impurities in the acids. All kinetic experiments were performed at 302 K. The initial mixture contains no esters for all kinetic experiments.

Formation methyl formate								
	$w_{\text{H}_2\text{SO}_4} = 0 \text{ ma}\%$				$w_{\text{H}_2\text{SO}_4} = 2 \text{ ma}\%$			
	x_{MeOH}	x_{FA}	x_{W}	$x_{\text{H}_2\text{SO}_4}$	x_{MeOH}	x_{FA}	x_{W}	$x_{\text{H}_2\text{SO}_4}$
	mol/mol				mol/mol			
NMR sample tube	0.4942	0.4931	0.0127	0.0000	0.4889	0.4893	0.0143	0.0075
Stationary Flow	0.4936	0.4936	0.0127	0.0000	0.4888	0.4888	0.0144	0.0080
Formation methyl acetate								
	$w_{\text{H}_2\text{SO}_4} = 1.3 \text{ ma}\%$				$w_{\text{H}_2\text{SO}_4} = 3.5 \text{ ma}\%$			
	x_{MeOH}	x_{FA}	x_{W}	$x_{\text{H}_2\text{SO}_4}$	x_{MeOH}	x_{FA}	x_{W}	$x_{\text{H}_2\text{SO}_4}$
	mol/mol				mol/mol			
NMR sample tube	0.4850	0.4910	0.0179	0.0061	0.4757	0.4848	0.0206	0.0189
Stationary Flow	0.4881	0.4881	0.0178	0.0061	0.4817	0.4817	0.0200	0.0165

Table 4: Rate constants and equilibrium constants of the methyl formate and methyl acetate formation at 302 K.

Formation methyl formate				
	$w_{\text{H}_2\text{SO}_4} = 0 \text{ ma}\%$		$w_{\text{H}_2\text{SO}_4} = 2 \text{ ma}\%$	
	k_f	K_a	k_f	K_a
	mol/(mol s)		mol/(mol s)	
NMR sample tube	$1.02 \cdot 10^{-4}$	36.5	$4.41 \cdot 10^{-3}$	36.7
Stationary flow	$1.10 \cdot 10^{-4}$	32.5	$4.16 \cdot 10^{-3}$	32.9
Formation methyl acetate				
	$w_{\text{H}_2\text{SO}_4} = 1.3 \text{ ma}\%$		$w_{\text{H}_2\text{SO}_4} = 3.5 \text{ ma}\%$	
	k_f	K_a	k_f	K_a
	mol/(mol s)		mol/(mol s)	
NMR sample tube	$8.71 \cdot 10^{-5}$	32.1	$3.31 \cdot 10^{-4}$	32.8
Stationary flow	$8.60 \cdot 10^{-5}$	32.1	$3.39 \cdot 10^{-4}$	32.8

Figure 1: Experimental setup that was used in this work for the stationary flow reaction kinetic studies and the 2D NMR experiments in flow.

Figure 2: Relative ^1H NMR magnetization of pure components as a function of the product of mean velocity and longitudinal relaxation time. Experimental data from the present work: MeOH (CH_3 ■), W (OH □), FA (CH ▲), FA (OH △), MF (OCH_3 ▼), MF (CH ▽), AA (OH ◆), AA (CH_3 ◇), MA (OCH_3 ►), MA (CH_3 ▷).

Figure 3: Step response curves obtained at four axial reactor positions. a) Flow rate of 0.1 ml/min: experimental RTD data: ($\square$) R2 ($N=38$), ($\triangle$) R4 ($N=203$), ($\circ$) R7 ($N=461$), (∇) R9 ($N=807$), b) Flow rate of 0.2 ml/min: experimental RTD data: ($\square$) R2 ($N=28$), ($\triangle$) R4 ($N=123$), ($\circ$) R7 ($N=263$), (∇) R9 ($N=469$). Reactor model: (—) TSR, (---) PFR.

Figure 4: Chemical structures of the components. The labels refer to the ^1H and ^{13}C peak assignment.

Figure 5: Typical Benchtop ^1H NMR spectra of both studied reaction mixtures.

Figure 6: Extent of reaction as a function of reaction time for the formation of methyl formate. Experimental data from the present work: (■) Stationary flow, (Δ) Batch reactor, both at 302 K. Literature data: ($\square$) Brächer et al.²⁷ at 303 K. Lines: TSR model at 302 K, parameters see Table 4. Feed ratio see Table 3.

Figure 7: Extent of reaction as a function of reaction time for the formation of methyl acetate. Experimental data from the present work: (■) Stationary flow, (△) Batch reactor, both at 302 K. Lines: (—) TSR model at 302 K, parameters see Table 4, (---) Model of Dörrhöfer.²⁸ Feed ratio see Table 3.

Figure 8: 2D NMR measurements of the formation of methyl formate: (a) COSY, (c) HETCOR, and (e) HMBC and the formation of methyl acetate: (b) COSY, (d) HETCOR, and (f) HMBC, all in stationary flow mode. All correlations are indicated with dashed lines for better visualization.

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