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Combining reaction calorimetry and ATR-IR spectroscopy for the *operando* monitoring of ionic liquids synthesis

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Abstract

For the routine application of ionic liquids in organic synthesis and catalysis, high purity is a key issue. Prerequisite for this is a reproducible synthesis procedure, so a detailed knowledge of kinetics and thermodynamics is required. We combined reaction calorimetry with ATR-IR spectroscopy based on fibre optics for the *operando* monitoring in order to achieve an appropriate characterisation of the established batch processes. Based on this a continuous process utilising micro-structured equipment was realised that avoids end-of-pipe workup.

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Keywords: ATR-IR; Fiber optics; Reaction monitoring; Microreaction engineering; Reaction calorimetry

1. Introduction

The interest in the application of ionic liquids (ILs) has grown tremendously over the last decade which is reflected by several review articles [1,2] as well as by the increasing number of IL publications in general. ILs have not only been used successfully as non-volatile substitutes for organic solvents in monophasic catalysis and organic synthesis. Interesting applications also include the use in biphasic systems for homogeneous, heterogeneous and biocatalysis [3–7].

Regarding their use in transformations employing potentially sensitive or unstable compounds such as organometallic catalysts, a reproducible protocol for IL synthesis is crucial. The most common access to salts derived from both aliphatic and aromatic amines is the *N*-alkylation of an amine precursor R_3N by reacting it with an alkylating agent $R'X$ that upon alkyl transfer releases the desired anion [8]:

$$R_3N + R'X \rightarrow R_3R'N^+X^- \quad (1)$$

Anion metathesis of X^- against Y^- *via* adding a metal salt MY, adding a Brönsted acid HY, or using anion exchange materials can follow this quaternisation step. Commonly, the quaternisation reactions are carried out batch-wise. As many of those transformations are accompanied by significant heat evolution, organic solvents like toluene have often been used for an improved heat removal [8]. Solvent use leads to increased reaction times due to the dilution and requires quantitative removal in an additional process step. An ionic liquid synthesis in a tubular reactor (inner diameter: 6 mm) has recently been carried out [9], revealing the need for high heat transfer rates and a possible use of micro reaction technology.

Here we present the results of studies for a continuously operated process. The use of micro-structured equipment is advantageous in terms of high specific surfaces (some 10 000 m^2/m^3 compared to some 100 m^2/m^3 in traditional stirred tanks) and good mixing [10–15]. Numerous processes requiring high heat transfer rates have already been performed in micro plants (see Refs. [10,11]).

2. Experimental

1-Methylimidazole (MIM) and diethylsulfate (DES) were distilled under reduced pressure prior to use and stored under dry nitrogen. Fibre optical based ATR (attenuated total

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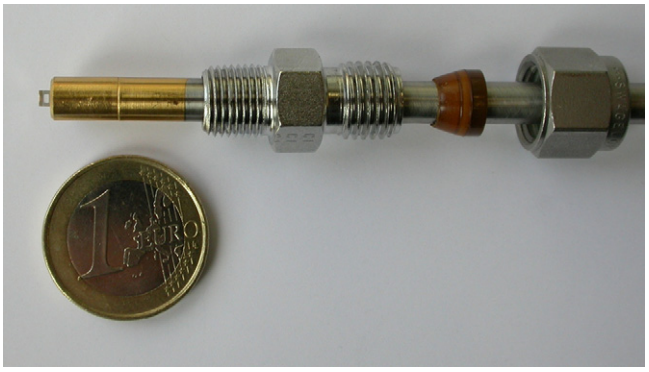

Fig. 1. Fibre probe by *ifs-Aachen* with diamond prism as internal reflection element.

reflectance) infrared spectroscopy was carried out with a newly developed diamond tip probe (infrared fiber sensors, Aachen, Germany) [16](Fig. 1) attached to a Nicolet 380 or 5700 FTIR spectrometer with a Smart Mid-IR fibre port (Thermo Inc., Waltham, MA, USA). Sampling frequency was 0.1 Hz (6 spectra/min) at a spectral resolution of 0.96 cm^{-1}. Quantification was carried out with the OMNIC Pro and TQ Analyst software. Calibration was performed with binary and ternary mixtures of the two reactants and the product at 293 K using the method of partial least squares (PLS).

Semi-batch experiments were performed in an RC1e reaction calorimeter (Mettler Toledo, Gießen, Germany) equipped with an HP 60 stainless steel stirred tank reactor (Büchi Glas Uster, Uster, Switzerland) under an atmosphere of Argon (99.995% purity) at 308 K. One reactant was charged to the reactor (typically 4–6 mol, minimum 0.4 L), while the second was thermally pre-equilibrated and injected *via* a thermostated dosing unit with slight overpressure of Argon. Consecutive injections were not carried out after constant time intervals, but rather when deviation from starting conditions was negligible ($dT/dt \leq 10^{-5}$ K/s for jacket and reactor temperature). Calibrations of the effective thermal transfer coefficient UA and the heat capacity C_{pr} of the reactor content were performed at least before and after each run. The IR fibre probe was conveniently fitted into the reactor lid with standard 1/4 in. fittings.

A flow chart of the setup for continuous flow experiments is shown in Fig. 2. Reactant streams were fed to a SIMM stainless steel micromixer (Institut für Mikrotechnik Mainz, Mainz, Germany) at flow rates between 0.6 and 200 mL/h with a continuously working syringe pump (MicroMechatronic Technologies AG, Siegen, Germany) equipped with glass syringes with Teflon pistons (ILS microsyringes, Stützerbach, Germany). Due to the corrosivity of the reactants, PTFE or PEEK connections, fittings and tubes (Upchurch Scientific, Oak Harbor, WA, USA) were chosen for the delay loop (inner diameter: 1/16 in.) attached to the outlet of the micromixer. The fibre probe was inserted into the flow path with a specifically designed low volume flow cell (port to port volume $\leq$ 20 μL) made from PEEK (Mechanical workshop, ITMC/RWTH Aachen University).

For off-line quantification, samples were taken at the reactor outlet. Excess DES was reacted with a minimum five-fold excess of *n*-propylamine (nPA). Preliminary experiments show that under these conditions DES is completely converted into ethylpropylammonium ethylsulfate [EPA]$EtSO_4$, and that excess nPA does not dealkylate [EMIM]$EtSO_4$. Quenched reaction mixtures were diluted in deuterated chloroform and analysed by ^{1}H NMR spectroscopy (Bruker DPX-300 NMR). MIM was quantified by integrating the signals of the methine protons on C-4 and C-5 ($\delta = 6.77$ and 6.88 ppm), for the $[EMIM]^+$ cation and the $EtSO_4^-$ anion the signals of the methylene groups were considered ($\delta = 4.17$ and 3.93 ppm, respectively). The discrimination between [EMIM]$EtSO_4$ and [EPA]$EtSO_4$ was achieved with the mass balance.

3. Results and discussion

Methods for a simultaneous *in situ* analysis of heterogeneous catalysts and of their performance in terms of activity and selectivity under working conditions have become known as *operando* methods [17]. The *operando* approach is similarly powerful as a tool for non-catalytic process monitoring, e.g. in microchannels where reaction volumes are in the same order of magnitude as typical volumes for external sampling (e.g. 100 μL). Thus, with in-line monitoring distortion of the process conditions by sampling can be reduced to a minimum. ATR-IR spectroscopy (attenuated total reflectance in the mid-infrared range) based on fibre optics and chemometric models for the quantification of multicomponent mixtures were established for the *operando* monitoring of the discussed process. Due to the flexibility of setups based on miniaturised fibre optical probes it was possible to use the ATR-technique in batches (e.g. 1.5 L and

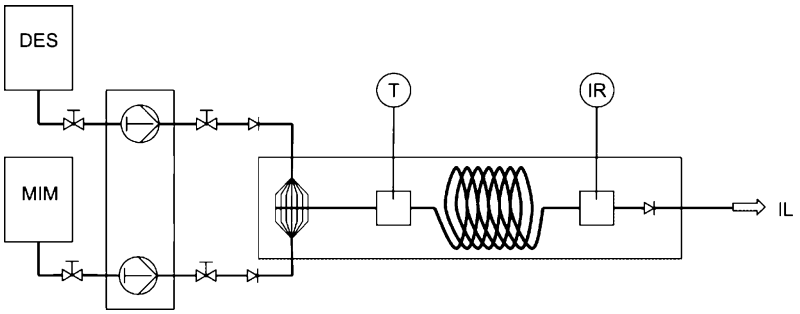

Fig. 2. Flow chart of a micro reaction setup for continuous flow experiments (DES/MIM: reservoirs for diethyl sulfate and methylimidazole; T: temperature sensor; IR: flow cell for IR spectroscopic measurements; IL: ionic liquid outlet).

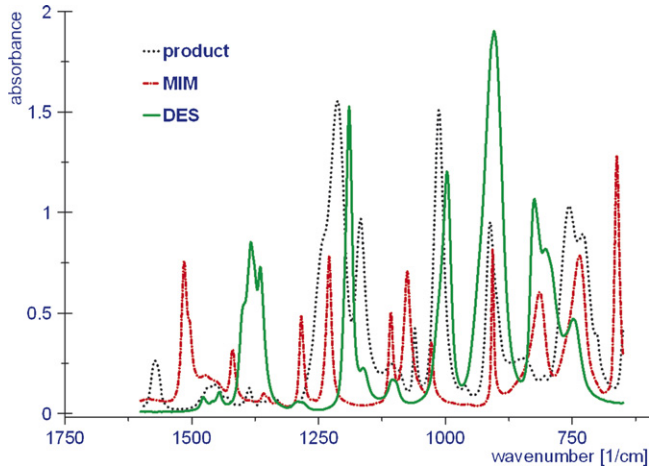

Fig. 3. IR spectra of the compounds involved in the presented synthesis.

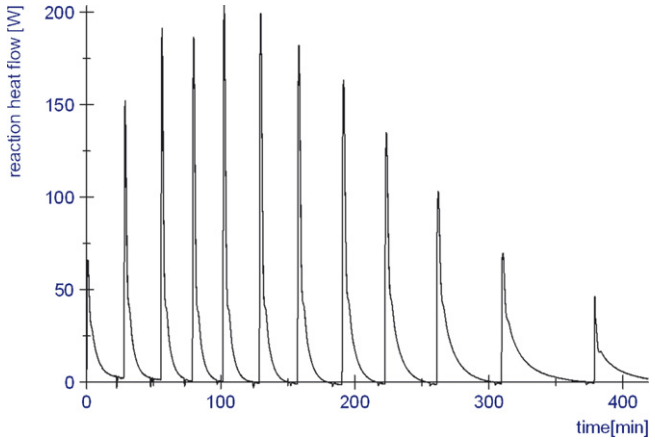

Fig. 4. Reaction heat flow in a dosing experiment with 12 injections (DES charged, MIM added).

1 mL) as well as in miniaturised flow cells for micro-structured equipments (internal volume $\leq$ 20 μL).

Pure component spectra of the involved species show that a spectral discrimination is easily available due to the intense absorption maxima in the fingerprint range (Fig. 3).

Reaction calorimetry has been employed for the simultaneous study of thermodynamics and kinetics. The primary signal from such an experiment, the time profile of the reaction heat flow $\dot{Q}_r(t)$ from a reacting mixture, can be integrated along an interval $[0, t_e]$ corresponding to the reaction time in such a way that division by the molar amount n of converted material yields the molar reaction enthalpy:

$$\Delta_r H_m = -\frac{1}{n}\int_0^{t_e} \dot{Q}_r(t)\,dt \quad (2)$$

Kinetic information can be derived from the reaction heat flow itself. In a reaction volume V_R, the overall heat flow $\dot{Q}(t)$ is directly correlated to the sum of all processes i with a non-zero enthalpy difference $\Delta_i H_m$:

$$\dot{Q}(t) = -V_R \sum_i r_i(t)\,\Delta_i H_m \quad (3)$$

The power of reaction calorimetry as a source of differential kinetic information is further increased by its rather straightforward experimental synchronisation with methods for integral kinetic information as e.g. the optical spectroscopy described above [18].

The solvent-free *N*-alkylation of 1-methylimidazole (MIM) with diethylsulfate (DES) has been performed in a semi-batch mode as it has been described for dosing experiments in reaction calorimetry [19]. The reaction heat flow for a typical reaction run is shown in Fig. 4.

Due to the need for slight pressure release before each injection, a negative heat flow peak can be observed (e.g. at $t = 22$, 48 or 73 min). The deviation of injection 4 (at $t = 80$ min) from the overall trend in maximum heat flows is not considered to be significant.

Integration of the discrete heat flow pulses yields the reaction enthalpies per injection with a low level of scattering (Fig. 5). Values are correlated with the degree of conversion that has been determined gravimetrically. Surprisingly, $\Delta_r H_m$ is not independent from conversion. The absolute values of $\Delta_r H_m$ show a systematic trend with conversion including an increase to nearly the 1.5-fold of the starting exothermicity and a decrease at conversions higher than 0.9. The error related to the assignment of a linear baseline for the integration is well below 0.5% (i.e., 0.4–0.7 kJ/mol). However, injection 12 at $t = 379$ min was excluded in further considerations due to incomplete conversion. The arithmetic mean values of reaction enthalpies are a measure for the average reaction enthalpy for full conversion and were calculated without the implementation of weighing factors since the absolute amount of reagent per injection was kept constant. Values from the experiments with MIM charged ($\Delta_r H_m = -123$ kJ/mol) and with DES charged ($\Delta_r H_m = -130$ kJ/mol) are in acceptable accordance. For the calculation individual values have been excluded (isolated points in Fig. 5).

Preliminarily assuming a pseudo-first-order kinetic model, in which DES concentration is regarded constant, the average first-order rate constant for the injections at $t = 1$, 29, 56 and 80 min is between 4 and 5×10^{-3} s^{-1}. However, a detailed

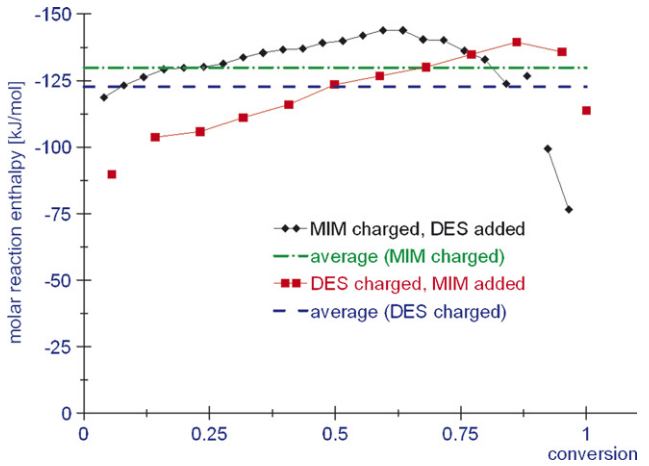

Fig. 5. Molar reaction enthalpy as a function of conversion. Isolated points have been excluded from the calculation of mean values.

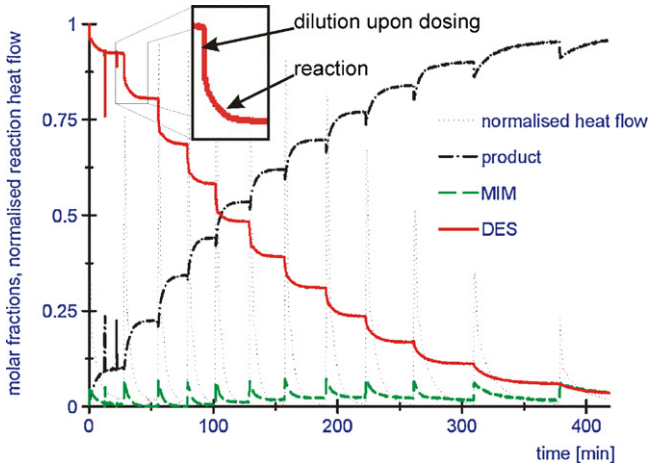

Fig. 6. Synchronisation of heat flow signal and quantifications from IR monitoring (DES charged, MIM added). Detail: two contributions to the decrease in diethyl sulfate concentration.

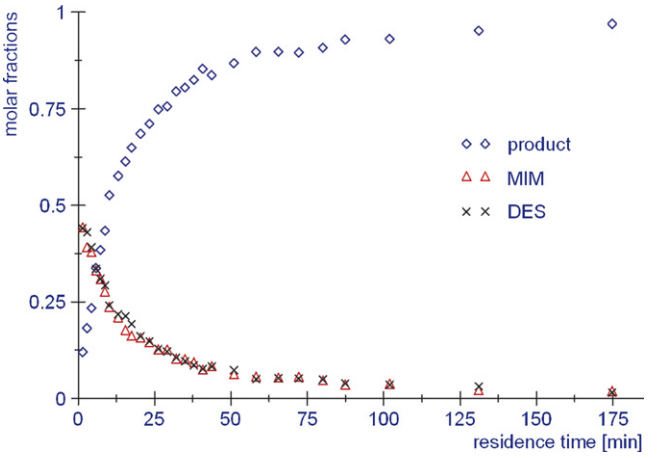

Fig. 8. Conversion and yield determined by proton NMR spectroscopy as a function of residence time in a continuous microplant.

kinetic evaluation and the search for a molecular explanation for the trends in reaction enthalpies is part of ongoing work.

With the *operando* measurement of IR spectra and the online quantification the reaction could be followed without any obstacles. The courses of molar fractions of all compounds can be synchronised with the normalised heat flow (Fig. 6).

The quantification method shows a robustness that reduces the scattering to less than 0.002 units on the molar fraction axis. However, at DES conversions above 30% a systematic offset in MIM fraction can be observed, suggesting a residual MIM content at the end of the injection interval which cannot be explained by limited equilibrium conversion. Both concentrations of DES and product undergo a sudden decrease between the acquisition of two consecutive spectra (i.e., 10 s) at the time of injection due to the dilution effect upon dosing of MIM. For the product this can clearly be seen in form of the downward spikes, for DES the sudden decrease due to the dilution is directly followed by an exponential decrease caused by the reaction (detail of Fig. 6).

In order to obtain kinetic information about the continuous flow process (correlation between conversion and temperature, residence time and linear flow rate, respectively) the alkylation reaction was transferred to a continuously operated setup with a micromixer. Composition was detected *via* IR spectroscopy at various residence times by varying the volume flow rates of the reactant streams (Fig. 7).

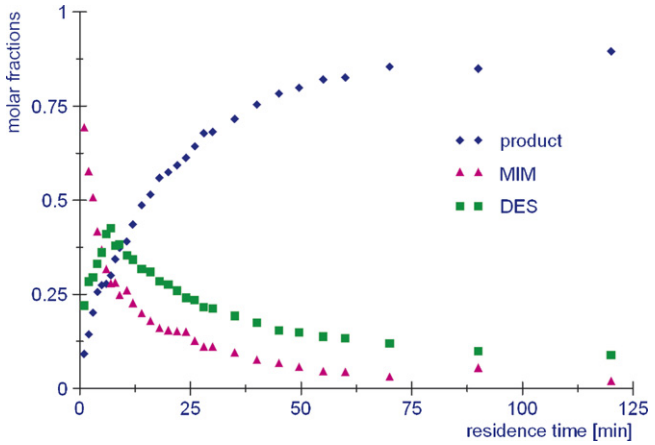

Fig. 7. Conversion and yield determined by ATR-IR spectroscopy as a function of residence time in a continuous microplant.

Concentration profiles as obtained from PLS quantification again show only little scattering and suggest an exponential decay of reactant concentrations. However, the overall trends of reactant concentrations for residence times up to 7 min cannot be explained on a molecular level so far. The existence of the trend in DES concentration has been verified by quantification of the IR spectra with a spectral modeling tool based on the algorithms presented by Marquardt and coworkers [20,21]. As an external validation method, ^{1}H NMR spectroscopy was used for the quantification of mixtures leaving the plant at the reactor outlet (Fig. 8).

The analysis of the chemically quenched samples supports the assumption of an exponential decay of reactant concentrations, but no confirmation is found for the initial increase of DES concentration as a function of residence time. It is supposed that any intermediate will react with the quenching agent and would therefore not be identifiable after the quenching procedure. In addition to the data sets for kinetic evaluation, the IL product was obtained in a quality that had improved significantly in terms of coloured by-products.

4. Conclusion

We have demonstrated the applicability of fibre optical based ATR-IR spectroscopy for the monitoring of solvent-free syntheses of Ionic Liquids. In combination with reaction calorimetry, extensive data is accessible that allows for detailed kinetic analysis. The molar reaction enthalpy of the *N*-alkylation of 1-methylimidazole with diethyl sulfate has been found to be between −123 and −130 kJ/mol. In combination with a fast reaction rate the maximum heat output generated exceeds 0.4 kW L^{-1} showing clearly the need for good heat transfer rates as provided by micro-structured reaction

channels. For the IL synthesis, micro-structured devices allowed to realise narrowly defined process conditions in a solvent-free surrounding, thus intrinsically providing constant product specifications.

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