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Numbering-up of micro devices: a first liquid-flow splitting unit

Rainer Schenk*, Volker Hessel, Christian Hofmann, Janos Kiss,
Holger Löwe, Athanassios Ziogas

Institut für Mikrotechnik Mainz GmbH, Chemical Process Engineering, Carl-Zeiss-Str. 18-20, 55129 Mainz, Germany

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Abstract

The first reported numbering-up tool, a liquid-flow splitting unit, with three dampening tanks and six interdigital separation-layer micro mixers was recently developed [1]. A minimum/maximum deviation of the 2-propanol/water distribution below 5% and a standard deviation below 2% was achieved. In this article, such an optimised liquid-flow splitting unit was for the first time successfully applied in the field of organic synthesis which in turn weakens flow splitting. As a result, the *n*-butyl acetamide reaction is a sensitive and very selective test for the quality of flow splitting. *n*-Butyl acetamide was synthesised from the acid chloride in six parallel (numbered-up) micro reactors with an overall yield of 88% and a purity in a range from 88 to 99%. This reaction is strongly accompanied by fast precipitation. Deviations of ideal flow splitting should thus result for this reaction not only in altered reactant concentrations, but can further change the sensitive flow patterns in the separation-layer mixers, thereby leading to fouling. As most relevant result, the average and min/max deviations in the individual product masses (8%) were larger (as to be expected) than the same quantities for liquid-flow distribution using the non-reacting, model solution 2-propanol/water, albeit not totally out of reach of this benchmark.

Keywords: Numbering-up; Liquid-flow splitting unit; Separation-layer mixer

1. Introduction: the numbering-up concept

The proposed concept of numbering-up or scaling-out, i.e. the multiple, parallel repetitions of micro-channel processing units to achieve throughputs up to the production range, has attracted from the very beginning researchers to consider using micro reactor technology for their chemical processing. Numbering-up was among the major predictions on micro reactor's benefits made in pioneering, first-hour works [2], and was later a topic of in-depth industrial analyses on process intensification [3]. Recently, numbering-up has encouraged derived conceptions of generic plant construction and process control [4,5], and still fills an own section as an outlook of any of today's micro reactor reviews [5–7] or of essays on the future shape of chemical industries [8,9]. Outside the micro reactor community and in the public perception, numbering-up is also one of the most prominently recognised features of chemical micro processing (see exemplarily the recent mentioning in a cover story of a chemical-engineering journal in [10] and by financial trade press in [11]).

However, it is the same idea that virtually splits the whole micro reactor community and potential users worldwide into supporters and opponents of the concept. The latter group raises objections about the ability of economically manufacturing large number of parallel micro-flow processing units, constructing them, achieving process control, and having reliable operation. Hence many expert opinions say that production with micro reactors will be rather the exception than the rule [12]; some even go further and doubt in any of such use. The best way to solve the debate in the micro reactor community on the validity of the numbering-up concept is to build numbered-up micro reactor plants, to test them and, thus, to provide a knowledge base and, subsequently, a rational validation can be given.

Numbering-up can be performed in two ways. *External numbering-up* is referred to as the connection of many devices in a parallel fashion [13–15] (see Fig. 1). Connecting devices thus is achieved via their outer connections which most often follow commercial standards. Accordingly, conventional tubing with standard process-control equipment may be used here. External numbering-up is numbering-up in the truest sense, because virtually the complete fluid path

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* Corresponding author. Tel.: +49-6131-990-376;
fax: +49-6131-990-205.
E-mail address: schenk@imm-mainz.de (R. Schenk).

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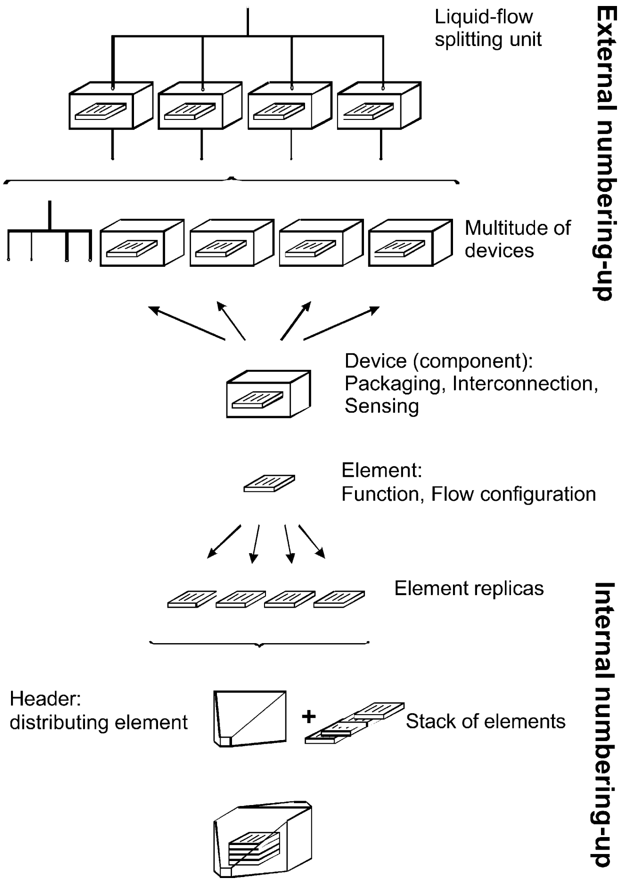

Fig. 1. Schematic representation of the generic conceptions of external and internal numbering-up.

is repeated. This resembles as well the real meaning of scaling-out. However, there are reports which claim external numbering-up to suffer from fluid equipartition. In addition, the connection of multiple micro devices with conventional non-standardised tubing does neither present a real elegant, compact engineering solution nor is economic from the view of fabrication and material costs [15].

Therefore, *internal numbering-up* has been chosen as an alternative concept already in the early investigations (see multiple, parallel arrangement of micro-channels in FZK's micro heat exchangers [16–18]). Internal numbering-up means the parallel connection of the functional elements only, rather than of the complete devices. These elements are grouped in a new way, usually as a stack, and are encompassed in a new housing, thereby providing a much more compact engineering design. This housing typically contains one flow manifold and one collection zone, most often having a simple design like a header of diffuser. Although often overlooked, internal numbering-up actually is state of the art. To name only a few realised examples, a mixer array with 10 parallel interdigital units [19], a gas/liquid contactor array with 10 packed beds [20], a micro mixer–micro heat exchanger integrated system [21] or a stack with hundreds of parallel stainless steel platelets [17,22] were realised. The internal numbering-up of the latter device type, for instance, enables a throughput of up to 7 t/h water flow [22]. Hence one device, of a size of a shoebox up to a computer, may be sufficient for a complete production.

Obviously, internal numbering-up has more arguments in favour than external numbering-up. Hence why proposing a liquid-splitting tool for external numbering-up? There are still good reasons to do so. Firstly, not all micro reactor processes may principally be amenable to internal numbering-up, e.g. for fluid dynamic reasons. In addition, safety precautions may require single-device operation rather than allowing one to choose internally numbered-up devices with large-volume distribution chambers (see e.g. [23]).

Third and possibly most valid, external numbering-up may be chosen for simple, practical reasons, if the degree of parallelism does involve only low numbers, e.g. not exceeding 10 devices. Developing an internally numbered-up device will demand for development cost and time and, therefore, may be inefficient at low degree of parallelism.

Finally, external numbering-up is a known and practised concept for specialty industrial developments with conventional non-micro devices concerning precious or specialty powder generation. In highly non-linear systems as, i.e. it is given in precipitation reactors, scale-up is better ensured when all critical parts of the process are exactly the same at all scales [24] (see also [25] for effects of mixing on crystallisation). Additionally, industrial crystallisers provide extremely unequal flow conditions, with local velocities, shear rates, and energy dissipation rates varying by orders of magnitude throughout the vessel [26]. Therefore, the concept of scaling by replication instead of the conventional scaling by dimensional changes was several times assumed as best method for powder production purposes (e.g. [27], see also “scaleable reactor” in [24], producing silver halide salts for the photographic industry).

Since one main disadvantage of existing external numbering-up solutions is the need for a sophisticated monitoring and control system to achieve fluid distribution, interfacing devices need to be developed, so-called liquid-flow splitting tools which passively guarantee flow equidistribution.

The first liquid-flow splitting unit was recently proposed, realised and tested. This device does not need active flow regulation, but achieves flow equipartition by building up a pressure barrier (see Fig. 2) [1]. It was equipped with three dampening elements and six docking stations for the same number of micro devices. Separation-layer mixers were chosen as micro devices, since the carrying out of fouling-sensitive reactions was considered as one major application of the flow splitting unit.

After hardware and process optimisation, the standard deviation between the various liquid volume flows in the splitting unit could be reduced at best below 1.5% when considering the centre stream only; considering the two outer streams, a standard deviation of about 2% is achieved, the min/max deviation being about 5%. This article is the suc-

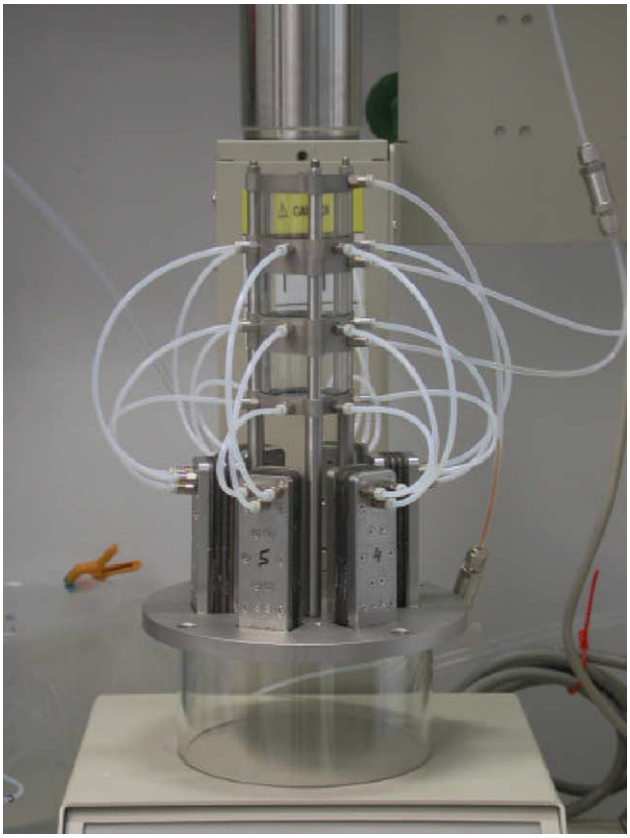

Fig. 2. Photograph of the liquid-flow splitting unit for liquid/liquid processing with three tanks and six separation-layer micro mixers.

cessor of the first scientific documentation with the focus on flow distribution [1]. Now a first example of the use of this liquid-flow splitting unit in the field of organic synthesis is described, i.e. under realistic reacting processing conditions instead of using pure inert liquids only. The reaction chosen here is further challenging in the sense that it involves fast and heavy precipitation which can tend to destabilise an existing deviation in flow splitting. Thus, it can be considered as some kind of “worst-case” scenario testing.

2. Experimental section

2.1. Fabrication

The fabrication of the liquid-flow splitting unit and of the interdigital separation-layer micro mixer with a small channel of high precision (pressure drop channel) (see Fig. 3) as well as details of their dimensions and internal structures are described in detail elsewhere [1].

2.2. Synthesis of *n*-butyl acetamide

Acetyl chloride (puriss. p.a., Fluka, order no. 00990), *n*-butylamine (>99.5%, Acros, order no. 10780), triethylamine (puriss. p.a., Fluka, order no. 90340), and tetrahydrofuran, THF (dried, Riedel-de Haen, order no. 34946) were used without further purification. Acetyl chloride

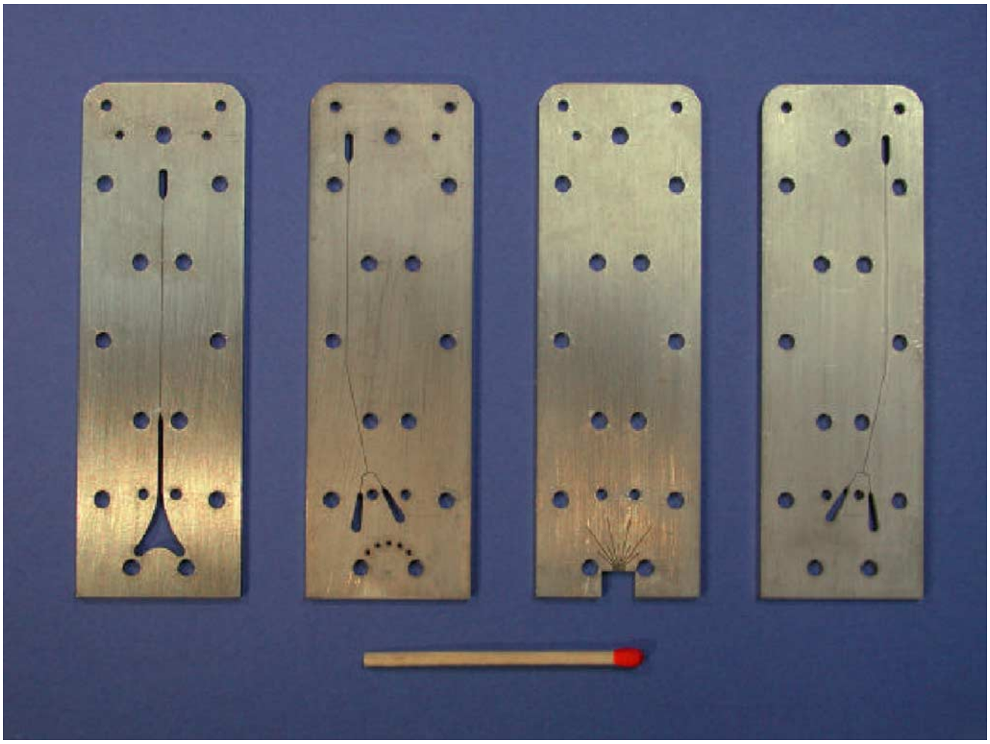

Fig. 3. Photograph of the platelet nos. 2, 4, 6, and 8 of the separation-layer micro mixer. The solvent for separation is guided through platelet 2 and the reaction solutions through the platelets 4 and 8. Platelet 6 contains the interdigital micro structure which is required for high quality mixing.

(c = 0.2 mol/l) as well as *n*-butylamine (c = 0.22 mol/l) and triethylamine (c = 0.22 mol/l) were solved in tetrahydrofuran. The flow rates of these reaction solutions were set to 800 ml/h each and the flow rate of the pure solvent THF to 2400 ml/h, respectively. Each tank of the liquid-flow splitting unit was filled with the liquid to 50–80% for dampening purposes. At room temperature, the reaction solutions were mixed in the interdigital separation-layer micro mixers, forming droplets at the outlet of the mixers, and subsequently were collected in a reaction vessel without any additional cooling. Hydrolysis of the acid chloride and hence stopping of the reaction was achieved by adding 0.1 ml of water. Subsequently, the ammonium salt was removed by filtration and the aqueous THF solvent was evaporated at 200 mbar. The purity of the obtained *n*-butyl acetamide was characterised by GC-MS.

2.3. Equipment

Pumps: a piston pump KP2000 (Desaga Company, Wiesloch, D) and a syringe pump Model 1000 D (Isco Inc., Lincoln, USA) were used.

GC-MS: a 5973 MS unit combined with 6890 N GC unit (Agilent Technologies Deutschland GmbH) with EI-ionisation source and NIST 98 MS spectra library was employed. Capillary: DB-5 ms, 29.5 m long, inner diameter: 250 μm, stationary phase: 0.25 μm. Flow rate = 1 ml/min. Oven program: 60 °C for 5 min, increasing ramp: 30 °C/min to 250 °C and then 10 min at 250 °C.

3. Results and discussion

3.1. Choice of organic test reaction

As an example of use to proof the applicability of the splitting under practical conditions, a fast organic reaction was chosen. The synthesis of butyl acetamide from butylamine and acetyl chloride in THF using triethylamine as auxiliary base (see Fig. 4) was investigated. A relatively high concentration of the reactant solutions of 0.2 mol/l was used which commonly is applied in laboratory research and chemical production. In advance to the numbering-up experiments, it was proven that this reaction cannot be carried out using standard micro mixers [28], such as the IMM interdigital micro mixers, but rather need the specialty separation-layer mixers. With standard devices, clogging occurs within a few seconds or less, depending on the experimental conditions.

3.2. Delayed mixing of precipitating solutions by separation-layer technique

The amidation reaction requires advanced micro-chemical processing solutions, as the auxiliary base is protonated during the reaction and precipitates immediately. A normal micro-channel processing is hence prohibited. Instead, a delay-type mixing is demanded, comprising a delicate feed of three liquid streams (two reactant layers and one separation layer) into a droplet at the outlet of the mixer. By special control over flow ratios a defined mixing pattern is achieved which results in precipitation only in the droplet end cap [29,30].

Therefore, the butyl acetamide formation comprises a numbering-up issue which is particularly sensitive to flow maldistribution. Besides the “normal” effect on product yield due to deviations from ideal reactant stoichiometry, any deviation in volume flow of a stream will change the mixing pattern in the droplet. This is an extremely sensitive parameter, since it relies on the interplay of three streams, one of which has much larger flow rate than the two others. Small deviations already result in a circulation flow of reactants which is redirected to the mixer outlet, i.e. the function of separating the layers is overridden. As a result, clogging will be unavoidable. In turn, proven applicability of particle-generating reactions would extend the operational range of numbered-up devices from simple organic synthesis towards functional chemicals’ manufacture.

In addition, the butyl acetamide formation allows benchmarking of the performance of the splitting tool by comparison of the six-fold number-up operation with previous studies using single-device operation [28].

3.3. Confirmation of synthesis of target product

Solutions of acetyl chloride (c = 0.2 mol/l) in THF, *n*-butylamine (c = 0.22 mol/l) and triethylamine (c = 0.22 mol/l) in THF, as well as pure THF were divided into six sub-streams each in the liquid-flow splitting unit.

At first, it was confirmed that the desired product actually was obtained in each of these streams. Using mass spectrometry (MS), it could be shown that the MS spectrum of *n*-butyl acetamide (Fig. 5, top) has a high match factor above 900 (on a scale of 1000) compared with the spectrum of *n*-butyl acetamide (Fig. 5, bottom) form the MS library. The high accordance of the measured spectrum and the spectrum of the library can easily be seen from the calculated difference spectrum shown in Fig. 5 (middle). Match factors with other compounds in the MS library are well beyond 800. Hence the

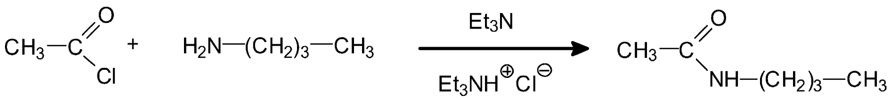

Fig. 4. Reaction scheme of the synthesis of *n*-butyl acetamide.

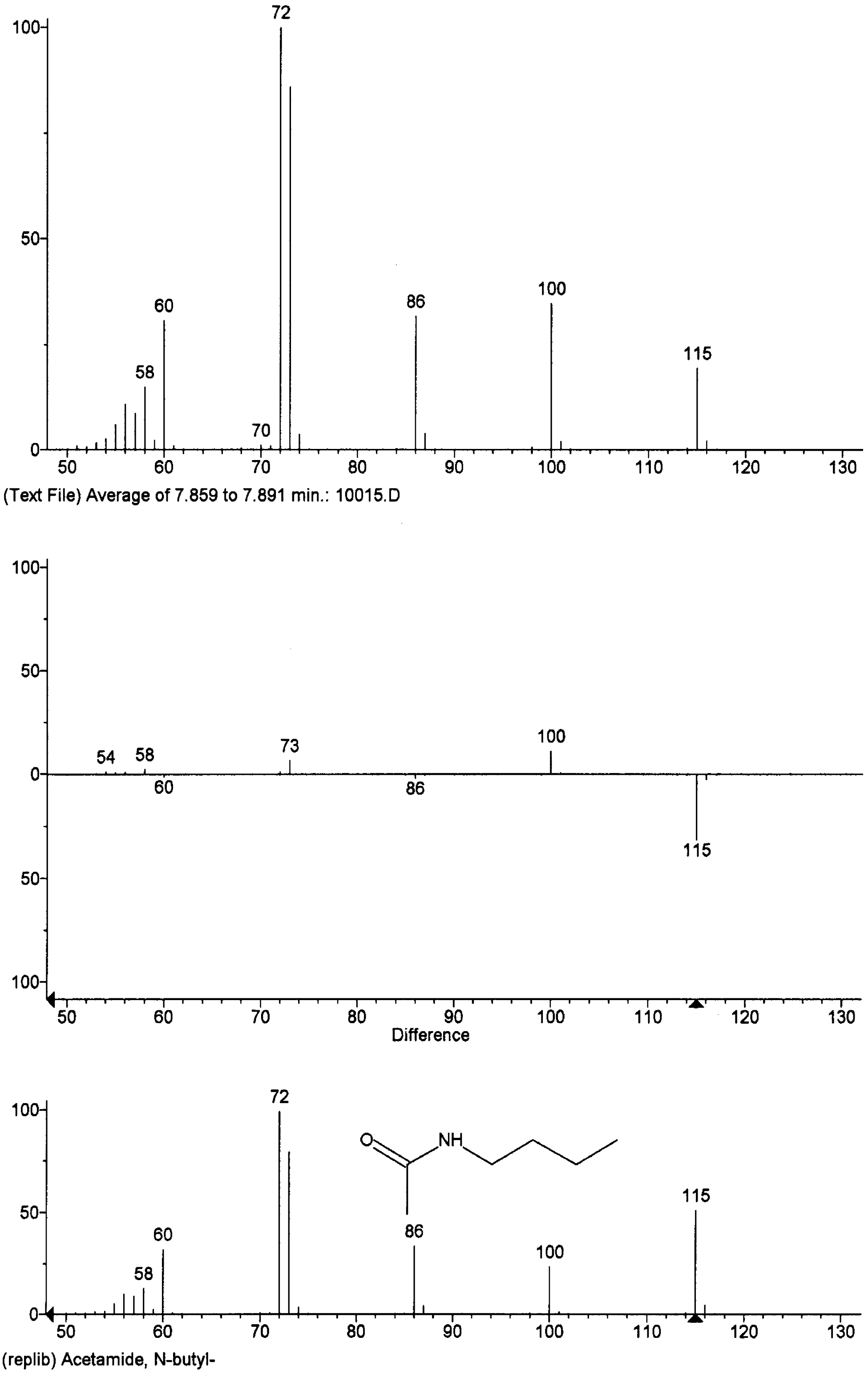

Fig. 5. MS spectrum of *n*-butyl acetamide obtained from reaction vessel no. 1 (top) compared to the MS spectrum of butyl acetamide stored in the MS library (bottom), and the difference of both spectra (middle).

Table 1
Amount of *n*-butyl acetamide and purity given for all six reaction vessels individually

	Reaction vessel no.					
	1	2	3	4	5	6
Weight raw product (mg)	355	325	333	341	362	234
Purity (%)	91	91	88	99	99	93
Calculated amount of *n*-butyl acetamide (mg)	323	296	293	338	358	218

product was independently identified by MS. The chemical structures of the different impurities are not clear at all from the MS analysis. The match factors with spectra out of the library are always clear beyond 800 and, even more important, several compounds have similar match factors. Furthermore, common chemical-mechanistic considerations do also not help, as the generation process of these by-products cannot be easily explained from the applied reaction conditions.

3.4. Determination of product purity

In a second step, the purity of the *n*-butyl acetamide was estimated by GC-MS analysis for all six reaction vessels separately (see Table 1). Purity of the product was estimated to 88% (Fig. 6, bottom, lowest purity) for reaction vessel no. 3 and to 99% (Fig. 6, top, highest purity) for the reaction vessel nos. 4 and 5 using the integration function of the GC-MS. A more reliable quantitative analysis of the purity needs concentration standards for each by-product to correct the area of the peaks individually because the same concentration of different compounds can result in different intensities of their corresponding GC/MS peaks. Since the chemical nature of the by-products was not known (see above), hence this correction could not be done.

3.5. Reaction characterisation

In Table 1 the amounts of precipitated crude product, the purity, and the thus determined amounts of clean product for each of the six docking stations, respectively, for each of the six micro mixers, are given.

When analysing the results of Table 1, it has to be considered that during the operation of the system small, but varying amounts of the triethyl ammonium salt precipitated at the outlet of the micro mixers. Especially, one of the reaction solutions running through mixer no. 6 was blocked resulting in a smaller quantity of the product *n*-butyl acetamide (see Table 1). Hence the flow rate ratio of the different solutions was not optimal at this docking station.

3.6. Deviation of product mass formed in the split streams

As the most important information in this article, the standard deviation of the product formation in the split streams was judged. This parameter was 16 or 8% for the amount of the formed product, when considering all six or only the five best mixers, respectively. The standard deviations of the flow distribution of the two reactant streams amount to 2.2 and 1.9%, respectively; the separation layer deviates by 5%. Accordingly, the results of Table 1 demonstrate that the deviation in the amounts of the products made via each docking station/mixer is larger than for the non-reacting model case, albeit not totally out of reach to the known standard deviation of the flow distribution. The reasons for this difference are firstly that profound optimisation was done for non-reacting flow splitting, whilst the results on reaction are initially aiming to show feasibility. Secondly, it stands to reason that the performance scenario of any organic reaction is more complex and, in particular, that of a precipitation. Fouling leads to an increase of pressure at the outlet and decreases the performance of the splitting. Here, much more detailed reaction optimisation studies are required.

3.7. Average product yield

The average yield was calculated by summing up the measured weights of the products of the various mixers, which were corrected by the purity obtained by GC-MS, and dividing this value by the number of the samples. Not considered in the calculation of the yield was the small amount of *n*-butyl acetamide found in the distillate.

In this way, an overall yield of 88% *n*-butyl acetamide was obtained for the six-fold numbered-up operation. This is in good agreement to yields obtained for single-device operation, which amounted to 87–100% for various sets of flow rates, ranging from 5:25:5 to 300:1000:300 (each value in ml/h) [28]. The lower yields were obtained at high total flow rates.

This confirms that in a real-case application experiments under precipitating conditions similar performance can be achieved as when using aqueous, non-reacting model solutions. Furthermore, it is indicative of completeness of reaction and thus of proper chemical processing downstream to the flow splitting tool, i.e. sufficient heat and mass transfer and residence time was provided. It, however, is admitted here that the amidation reaction of acetyl chloride and *n*-butylamine is a rather straightforward, fast organic reaction, except for the fouling constraints. More challenging organic reactions certainly may initially exhibit reduced performance and will need more technical efforts to come close to single-device performance.

3.8. Fouling and plugging

Concerning fouling and plugging sensitivity, no in-depth analysis and benchmarking to single-device operation was performed. Stable operation was achieved for 10 min, with the exception of one micro mixer which was plugged. Until then, already a vast amount of THF solution (∼1 l) and thus reactants were consumed so that the experiments were

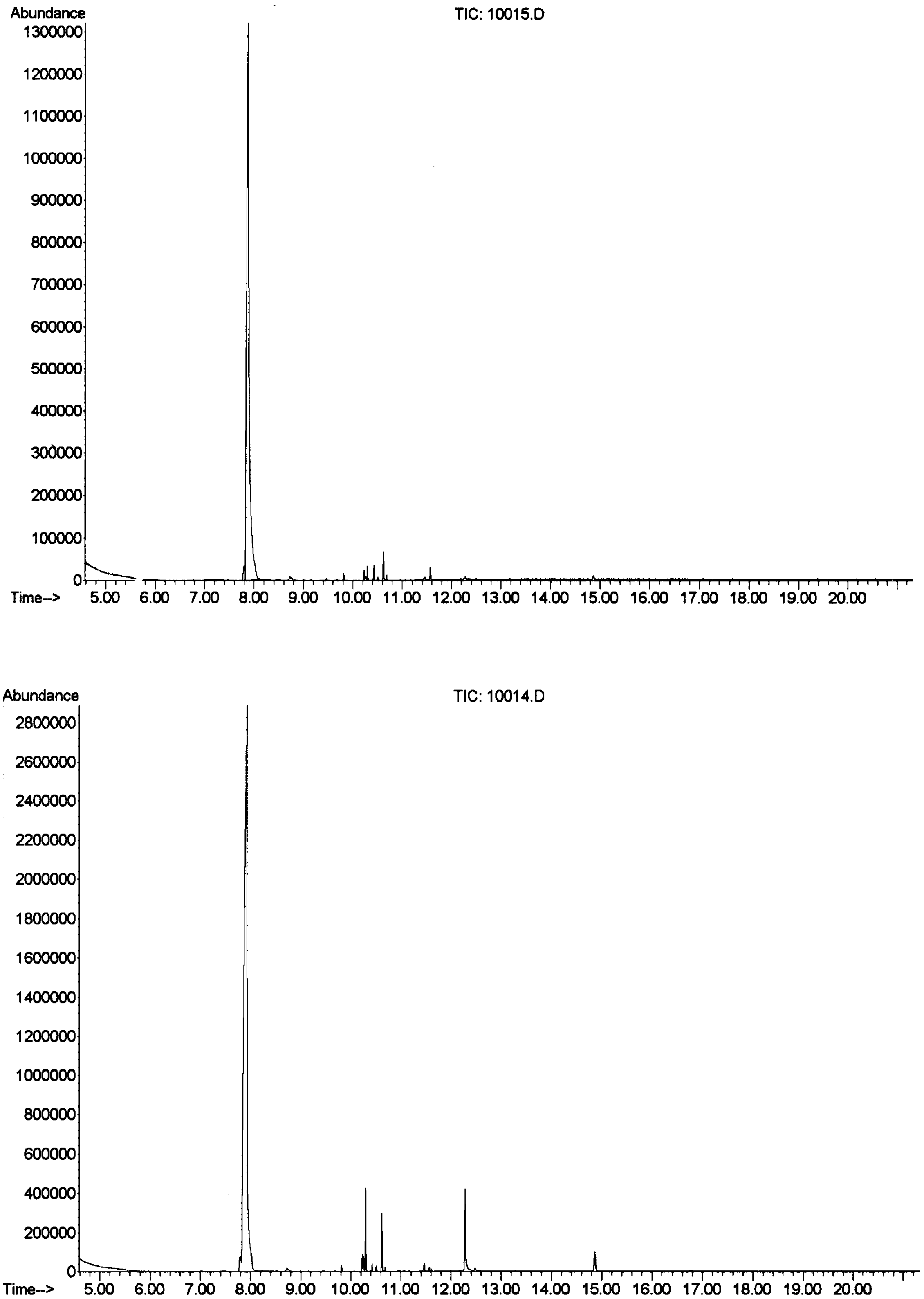

Fig. 6. Two exemplary GC-MS spectra of the *n*-butyl acetamide synthesis obtained using the mixer no. 4 (high purity, top) and no. 3 (low purity, bottom).

stopped. For single-device operation, a stable operation of at least 1 h could be achieved for a set of flow rate variations, ranging from 5:25:5 to 300:1000:300 (each value in ml/h) [28]. In particular advantageous was the setting of the flow rates to 5:250:5. Here, the reaction could be operated for 3 h.

4. Summary and outlook

It was demonstrated that liquid-flow distribution between various parallel micro devices by using an external liquid-flow splitting unit is not governed by the fluidic guidance in the unit (symmetry etc.) solely, but rather by the device's precision of micro fabrication, determining pressure loss variations. This pressure loss variation was minimised by the variation of the annealing temperature of the platelets with the pressure drop channel. A minimum/maximum deviation of the 2-propanol/water distribution below 5% and a standard deviation below 2% was achieved. For the first time, such a liquid-flow splitting unit was successfully applied in the field of organic synthesis. Long term operations need a further optimisation of the operation conditions.

At the moment, the use of the described liquid-flow splitting unit is linked to the interdigital separation-layer micro mixer. Improved future versions of the liquid-flow splitting unit aim at the use of this device with different kinds of micro devices. Additionally, experience concerning the design obtained with the current liquid-flow splitting unit will be taken into account for these future versions of the liquid-flow splitting unit.

Acknowledgements

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