Monitoring of an esterification reaction by on-line direct liquid sampling mass spectrometry and in-line mid infrared spectrometry with an attenuated total reflectance probe

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Abstract

A specially designed thermal vaporiser was used with a process mass spectrometer designed for gas analysis to monitor the esterification of butan-1-ol and acetic anhydride. The reaction was conducted at two scales: in a 150 mL flask and a 1 L jacketed batch reactor, with liquid delivery flow rates to the vaporiser of 0.1 and 1.0 mL min^{-1}, respectively. Mass spectrometry measurements were made at selected ion masses, and classical least squares multivariate linear regression was used to produce concentration profiles for the reactants, products and catalyst. The extent of reaction was obtained from the butyl acetate profile and found to be 83% and 76% at 40 °C and 20 °C, respectively, at the 1 L scale. Reactions in the 1 L reactor were also monitored by in-line mid-infrared (MIR) spectrometry; off-line gas chromatography (GC) was used as a reference technique when building partial least squares (PLS) multivariate calibration models for prediction of butyl acetate concentrations from the MIR spectra. In validation experiments, good agreement was achieved between the concentration of butyl acetate obtained from in-line MIR spectra and off-line GC. In the initial few minutes of the reaction the profiles for butyl acetate derived from on-line direct liquid sampling mass spectrometry (DLSMS) differed from those of in-line MIR spectrometry owing to the 2 min transfer time between the reactor and mass spectrometer. As the reaction proceeded, however, the difference between the concentration profiles became less noticeable. DLSMS had advantages over in-line MIR spectrometry as it was easier to generate concentration profiles for all the components in the reaction. Also, it was possible to detect the presence of a simulated impurity of ethanol (at levels of 2.6 and 9.1% mol/mol) in butan-1-ol, and the resulting production of ethyl acetate, by DLSMS, but not by in-line MIR spectrometry.

45 ## Keywords

46 On-line direct liquid sampling mass spectrometry; Thermal vaporiser; Quantitative reaction
47 monitoring; Trace analysis; Process analysis; In-line mid infrared spectrometry.

48

1. Introduction

Process mass spectrometry (PMS) [1, 2] has been applied to the analysis of gaseous systems in a wide range of industries. Applications include on-line monitoring of gases in the iron and steel industries [3-6] and petrochemical processes [4, 6, 7], reaction monitoring [8] and the analysis of high purity gases in the electronics industry [9, 10], the determination of trace components in complex biological systems [11], measurement of O_2, CO_2, and Ar in fermentation gases [12], and control of ethylene oxide production [4]. In contrast, on-line monitoring of liquid phase chemical reactions by PMS is less common owing to challenges in interfacing the analyser with the process stream.

Membrane inlet mass spectrometry (MIMS) [13] can allow direct analysis of volatile molecules in gases and liquids or even solid matrices [2, 14, 15]. The majority of MIMS techniques involve use of a polymer membrane to transfer the analyte from the sample into a gaseous acceptor phase (e.g. helium carrier gas or the high vacuum environment of the spectrometer) for introduction to the ion source of the spectrometer. The detection limits for MIMS can be as low as parts-per-trillion [16, 17] or even parts-per-quadrillion [18]. Such low detection limits are possible due to the preferential permeability of the analyte compounds through the membrane material relative to the matrix. MIMS has been used for on-line monitoring of various analytes such as ethanol, acetic acid and lactic acid in fermentation broths [19], nitrogen-containing compounds in a bioreactor [20], methanol and ethanol in chloroform [21], and aromatic halides in ethanol-water [22]. For samples where the analytes are chemically similar to the matrix, e.g. small polar molecules in polar matrices, MIMS is not a viable option for sample introduction.

Over recent years, there has been increasing interest in the use of atmospheric pressure ionisation (API) techniques such as electrospray ionisation (ESI) and atmospheric pressure chemical ionisation (APCI) for on-line analysis of liquids. Dell'Orco *et al.* [23]

74 employed nebulizer assisted ESI for on-line reaction monitoring. The experimental set-up
75 employed a series of HPLC pumps to dilute the reaction mixture by a factor of 3000 prior to
76 analysis. Identification of reaction components was successful and kinetic information could
77 be derived. The ion response was, however, affected by the analyte pKa due to proton
78 competition arising from the electrospray process. More recently, use of an autosampling
79 flow injection analysis (FIA) system in conjunction with APCI mass spectrometry was
80 demonstrated for real-time monitoring of a Michael addition reaction [24]. The reaction was
81 carried out in a syringe, in an infusion syringe pump, and quantitative results were obtained at
82 the molar concentration level. It is anticipated that this approach could be applied to a wide
83 range of reaction types and the infusion syringe pump could be replaced to enable sampling
84 from a reaction vessel. MIMS systems with liquid acceptor phases have been used in
85 conjunction with API techniques for the analysis of large, polar molecules [25, 26]. So called
86 condensed-phase MIMS has been used for *in situ* monitoring of the chlorination of phenol in
87 an aqueous solution [26]. Creaser *et al.* connected a membrane interface to the APCI source
88 of a quadrupole mass spectrometer for the off-line monitoring of a Michael addition reaction
89 [25]. A hydrophobic polyvinylidene fluoride membrane was used with an acetonitrile/water
90 acceptor phase to dilute the concentrated reaction mixture to a suitable level for direct
91 analysis. Hence, it was possible to introduce samples, which were manually extracted from
92 the reaction vessel, directly into the membrane interface for analysis without the need for any
93 sample pre-treatment. However, the approach was extremely susceptible to changes in
94 pressure and flow on both sides of the membrane and a feed loop would need to be developed
95 for on-line analysis.

96 A number of studies have reported the use of ambient ionisation techniques for
97 reaction monitoring. Extractive electrospray ionisation (EESI) has been used for on-line
98 analysis of organic reactions [27, 28]. In one example, a stream of nitrogen was used to

transfer the gas phase above the reaction mixture in the vessel to the ESI source [28], this assumes that the composition of the headspace is representative of the bulk. In another study, a secondary, grounded nebuliser was used to produce an analyte aerosol, and a Venturi pump was used to transfer a sample of the aerosol to the electrospray source for ionisation [27]. A low-temperature plasma (LTP) probe has been used for *in situ* monitoring of acetylation, esterification and Schiff base formation reactions [29]. The probe was positioned about 1 cm from the surface of the reaction mixture, and the LTP enabled desorption and ionisation of the reaction mixture without the need for any sample pre-treatment. Again, this approach assumes that the surface composition is representative of the bulk reaction mixture. A transesterification reaction was monitored on-line by ultrasonication-assisted spray ionisation mass spectrometry [30]. However, ultrasonication can also affect the reaction, which is not desirable from a monitoring perspective. One of the most simple interfaces employed for on-line analysis was a capillary, which functioned as both a sampling tip and spray emitter for contactless API mass spectrometry [31]. However, variations in the pressure above the sample affected the signal intensity. Recently, use of inductive ESI mass spectrometry was reported for direct and continuous monitoring of organic reaction in situ [32]. A pulsed positive potential was used to produce transient strong electric fields in the spray solution; the reaction solution was transferred to the emitter-spray tip by a capillary under positive gas pressure and ionised inductively. Direct analysis in real time (DART) mass spectrometry has been used for analysis of a model batch slurry reaction [33]. Semi-quantitative analysis of the slurry samples was achievable using a combination of manual sample deposition and automatic sample introduction across the helium beam. While ambient ionisation techniques permit direct analysis of liquid samples with minimal or no sample preparation, most currently lack the robustness for use in a process environment although they offer considerable promise for use

123 in discovery and development. In addition, quantitative results have yet to be demonstrated
124 with many of the techniques.

125 Thermal vaporisation of discrete liquid samples into a process mass spectrometer has
126 been achieved using heated auto-injection valves [34-36], a modified GC oven [37], and a
127 programmable temperature vaporizing (PTV) GC injector and syringe pump [38]. However,
128 these methods are not ideal for continuous sampling; when a carrier gas is used to transport
129 the sample vapours to the mass spectrometer variations in the carrier gas flow and inefficient
130 mixing with the sample vapour can cause signal instability. In a previous study, a thermal
131 vaporiser for direct liquid sampling mass spectrometry (DLSMS) was reported that can be
132 used for continuous analysis of liquid streams [39]. Benzene, toluene and o-xylene in the
133 range 0 – 110 mg kg^{-1} were determined in ethanol and the vaporiser could be used to generate
134 stable mass spectrometric responses for the analytes over several hours. In this report, the
135 suitability of the vaporiser and DLSMS has been assessed for rapid, on-line quantitative
136 monitoring of the reaction of butan-1-ol and acetic anhydride in a 1 L reactor, with pyridine as
137 a catalyst. Off-line gas chromatography was used as the reference technique for determination
138 of butyl acetate. The performance of the DLSMS procedure was also compared to that of in-
139 line mid-IR spectrometry [40] which used an insertion probe that has an attenuated total
140 reflectance (ATR) crystal at one end, coupled by chalcogenide fibres to a miniature mid-IR
141 spectrometer at the other end of the probe.
142

2. Experimental

2.1. Experimental set-up and procedure

Preliminary reactions were conducted in a 150 mL conical flask on a magnetic stirrer hotplate. A volume of 26 mL (0.275 moles) of acetic anhydride (>99%; Sigma-Aldrich, Dorset, UK) was pipetted in to the conical flask and heated to 40 °C. Over 10 minutes, 1 mL was sampled through 50 cm of 0.5 mm i.d. PTFE tubing into the thermal vaporiser using a milliGAT pump (VICI AG Valco International, Switzerland) set at 0.1 mL min^{-1}; 2 mL (0.025 moles) of pyridine (>99%; Sigma-Aldrich) was then added to the flask and the mixture was equilibrated for 5 min before 23 mL (0.251 moles) of butan-1-ol (>99%; Sigma-Aldrich) was added to begin the reaction.

Most of the experiments involved reactions in a 1 L oil jacketed glass reactor (VWR International, Dorset, UK) connected to a Haake C25 heater/chiller with F6 circulator. A schematic diagram of the experimental apparatus is given in Figure 1. A stainless steel PT100 temperature probe was connected to the F6 circulator and was used to measure the temperature of the reaction liquid every 5 s; the F6 controller used the temperature readings to control the reactor temperature. The reactor lid was fitted with a condenser and an IKA Eurostar digital stirrer (VWR International) with a glass stirrer rod and paddle operated at a stir rate of 150 rpm. A CM4000 HPLC pump (Milton Roy, Ivyland, Pennsylvania, USA) was used to continuously transfer liquid at 1 mL min^{-1} from the reactor to the vaporiser for analysis by mass spectrometry. The reactor and pump were connected by PTFE tubing (30 cm length, 0.5 mm i.d.) and the pump and the vaporiser by stainless steel 316 HPLC tubing (30 cm length, 0.5 mm i.d.). The tubing was flushed with acetic anhydride to prime the pump and remove traces of the cleaning solvent (water/methanol). The reactor was loaded with 500 mL (5.289 moles) of acetic anhydride over approximately 1 minute using a

dropping funnel and the temperature allowed to equilibrate to the set temperature (20 or 40 °C). The HPLC pump was then started. After 5 minutes, 40 mL (0.49 moles) of pyridine was added as the catalyst and the system equilibrated for a further 5 minutes before addition of 484 mL (5.289 moles) of butan-1-ol. For some experiments, ethanol (>99%; Sigma-Aldrich) was added to butan-1-ol (2.6 or 9.1% mol/mol) to simulate the presence of an impurity in one of the reagents. The contents of the reactor were analysed continuously by on-line mass spectrometry and in-line mid-infrared spectrometry from the initial addition of acetic anhydride. The transfer time from the reactor to the mass spectrometer was found experimentally to be 2 min. For off-line analysis by GC, 1 mL aliquots of the reaction mixture were drawn through Teflon tubing using a glass syringe. Usually, 15 samples were collected for GC analysis.

2.2. On-line mass spectrometry with thermal vaporiser

The process mass spectrometer was a Thermo Electron Prima 600S (Thermo Fisher Scientific Cheshire, UK). This is a magnetic sector instrument that has two detectors: an electron multiplier detector for low intensity ions and a Faraday cup for high intensity and matrix ions. The analyte gas was transported to the ion source via a molecular leak and bypass through a capillary inlet heated to 180 °C. The ion dwell time was set to 1 s ion^{-1}. The custom designed thermal vaporiser is shown in Figure 2 and has been described previously [39]. Glass lined tubing (SGE Analytical Science, UK) was wrapped around a metal block that was heated by a 350 W cartridge heater. A thermocouple was inserted into the heater block and connected to a temperature control unit which controlled the power supply to the cartridge heater. The temperature controller was set to 180.0 ± 0.2 °C. The heated transfer capillary of the mass spectrometer was connected to one end of the tubing via a tee which allowed excess vapour to vent. The advantage of this approach is that stable analysis was achieved because any fluctuations in fluid flow did not affect the composition of the gas. Furthermore, as the

composition of the gas entering the mass spectrometer was 100% vaporised sample without dilution by a carrier gas, the maximum possible sensitivity was achieved. However, use of the thermal vaporiser is limited to volatile samples that are thermally stable at the operating temperature of the vaporiser and transfer capillary.

Data were acquired from the mass spectrometer using GasWorks (Build 217, Thermo Fisher Scientific) with ion intensities saved as comma separated variable files.

2.2.1. Ion selection

Process magnetic sector instruments with flat-topped peaks are more stable to ion overlap by analytes compared to laboratory quadrupole instruments [6]. This means that noise on the ions signals did not have to be taken into account when selecting the best ions to use, as has been done elsewhere [41, 42]. Mass spectra for each of the reaction components were downloaded from the NIST spectral library [43]. For reactions conducted in the 150 mL conical flask, the m/z values of the ions selected (from visual inspection of the overlaid spectra) and their percent abundance are shown in Table 1. For reactions conducted on the 1 L scale, ions were selected based upon their multivariate leverage. The m/z values for the ions selected and their percentage abundance are listed in Table 2.

2.2.2. Calibration

Before any reactions were carried out the pure component spectra, **S**, of acetic anhydride, butan-1-ol, acetic acid, butyl acetate, pyridine and the simulated impurities, ethanol and ethyl acetate (all reagents >99%; Sigma-Aldrich), were obtained by pumping liquid straight from vials, which contained the pure component being analysed or a binary mixture of the pure component in butan-1-ol. The pure component spectra were the average of 5 scans at the selected m/z values.

The concentration profiles (**C**) of the analytes during the reaction were calculated from the reaction data (**X**) using a classical least squares multivariate linear regression model:

$$\mathbf{C} = \mathbf{X}\,\mathbf{S}^{+}$$

where $\mathbf{S}^{+}$ denotes the pseudo-inverse of the pure component spectra, **S**, of the reactants (butan-1-ol and acetic anhydride), products (butyl actetate and acetic acid) and catalyst (pyridine). For experiments where ethanol was added to butan-1-ol to simulate the presence of an impurity, **S** also contained the pure component spectra for ethanol and ethyl acetate. The concentration profiles, **C**, were then normalised to their sum giving relative concentrations to correct for flow fluctuations and sampling variations due to stirring. The mean of the concentrations determined for the last 10 scans for each reaction component were used to obtain the extent of reaction. This simple calibration procedure is only possible due to the linearity of the system, the unbiased response of the Faraday detector and the fact that the identity of all reaction components is known.

2.3. In-line mid-infrared spectrometry

A SpectraProbe Linx 5-10 (SpectraProbe, Hayes, UK) instrument was used [40]. The spectrometer (105 mm × 120 mm × 195 mm) was connected to an in-line hastelloy probe (375 mm long, 12 mm outside diameter). Chalcogenide fibres in the hastelloy probe transmitted the light from the spectrometer source to the ATR crystal and back. The crystal was made of amorphous material that transmits in the infrared region. A fixed diffraction grating dispersed the signal onto the 128-element pyroelectric array detector covering the range 1000 – 2000 cm^{-1}.

Data were acquired using a computer with the SpectraProbe user interface that outputs the data to Microsoft Excel (Microsoft Corporation, Redmond, USA). An air background was collected initially, and the instrument set to collect data for 50 s every minute during the reaction.

A multivariate partial least squares (PLS) calibration model was built based on the MIR spectra and concentrations of butyl acetate obtained from analysis of samples by GC as

a reference technique. The optimum calibration model was chosen using a design of experiments approach [44], which revealed that a PLS model with 2 latent variables was the best, and the optimal pre-processing conditions were Savitzky-Golay derivatisation (1st derivative calculated using a 5 point filter-width and a 2nd order polynomial) and mean centring. The model was assessed using the root mean square error of calibration (RMSEC) and root mean square error of prediction (RMSEP).

2.4. Off-line gas chromatography

The gas chromatograph was an HP 5890 Series II, equipped with a polydimethylsiloxane stationary phase capillary column, CP-SIL 19, 25 m × 0.22 mm internal diameter (Chrompack, London, UK). The column temperature was set at 50 °C, and the flame ionisation detector and injector port temperature were maintained at 250 °C. The flow rate of the nitrogen carrier gas was 5.82 mL min^{-1} and a split ratio of 40:1 was used; the analysis time was about 2 min.

Approximately 1 mL of sample was removed from the reactor into a glass vial and a 200 µL aliquot was then transferred into a 10 mL flask and the reaction quenched by addition of 8 mL methanol (HPLC grade; >99.9%; Sigma-Aldrich) and 200 µL 4-methyl-2-pentanone (MIBK) (HPLC grade; >99.5%; Sigma-Aldrich) as the internal standard; the volume was then made up with methanol. The calibration standards were also prepared in methanol in 10 mL flasks and contained 0, 1.86×10^{-2}, 3.73×10^{-2}, 5.60×10^{-2}, 7.46×10^{-2} and 9.33×10^{-2} mol L^{-1} butyl acetate and 200 µL of MIBK. 1 µL of each calibration or sample solution was injected into the column to produce a chromatogram. For experiments where ethanol was added as a simulated impurity to butan-1-ol, a standard was prepared containing both butyl acetate and ethyl acetate (>99%; Sigma-Aldrich) to confirm the presence of ethyl acetate in the sample solution. The retention times for ethyl acetate and butyl acetate were 0.5 and 1.1 min, respectively.

2.5. Data analysis

All data analysis was performed in the Matlab environment (Version 6.5; Mathworks, Natick, USA) using PLS_Toolbox 3.0 (Eigenvector Research Inc., Washington, USA).

3. Results and discussion

An example of the concentration profiles of the reactants and products of the esterification reaction in the 150 mL flask is shown in Figure 3, derived from the mass spectrometry measurements. The time when butan-1-ol was added was set as 0 min, as this was the start of the reaction. Initially, only acetic anhydride was pumped to the vaporiser; at approximately -5 min the catalyst was added and the concentration of acetic anhydride decreased as a result. A small signal for acetic acid was detected at this point, which was due to an impurity of about 1% in the acetic anhydride used for this experiment. The profile of butan-1-ol initially increased when the alcohol was added to the flask, but as it reacted rapidly with the acetic anhydride (causing an increase in the temperature to 80 °C) the concentration decreased after about 2 min. The profiles of the products, butyl acetate and acetic acid, confirmed that the rate of reaction was rapid in the first 2 min after addition of butan-1-ol, but then slowed reaching completion at around 40 min (concentrations of about 43% mol/mol).

Concentration profiles similar to those in Figure 3 were obtained by DLSMS for the reactions in the 1 L jacketed reactor. The larger vessel enabled simultaneous *in situ* monitoring of the reaction by MIR spectrometry using an ATR probe. Also, small samples of the reactor contents were removed periodically for analysis by gas chromatography (GC) as an off-line reference technique. As mentioned in the experimental section, the concentrations of butyl acetate obtained by GC were used along with corresponding MIR spectra to build a PLS calibration model with 2 latent variables (LV). The results of the MIR modelling are shown in Figure 4. Two reactions were carried out at 20 and 40 °C to provide a different reaction profile; the GC derived concentrations and MIR spectra for the first reaction were used to generate the calibration model and the data from the second reaction were used to validate the model. Figure 4 shows that there was good agreement between the concentrations of butyl acetate predicted from MIR measurements and analysis by GC. Although the

296 reactions used for calibration and validation were performed at different temperatures, the
297 calibration data set contained spectra acquired over a range of temperatures as the reaction is
298 exothermic. Hence, the model gave accurate predictions of butyl acetate concentration for
299 reactions conducted at both 20 and 40 °C. Figure 5 shows a comparison of the concentration
300 profiles obtained for butyl acetate when a reaction initiated at 20 °C in the 1 L reactor was
301 monitored by all three techniques. The exothermic nature of the reaction causes the
302 temperature to rise to 65 °C and the set temperature is not re-established until about 40 min,
303 by which time the reaction is almost complete. In the initial period of the reaction, the
304 concentration profile obtained by DLSMS is less than those obtained from MIR spectrometry
305 and GC; as the reaction nears completion, there is a much better agreement between the
306 profiles. A number of factors contributed to the differences in the profiles obtained between 0
307 and 10 min. When the reaction was initiated by addition of butan-1-ol, although butyl acetate
308 was generated in the reactor (as detected by *in situ* MIR measurements), there was no butyl
309 acetate in the liquid delivered to the vaporiser until about 2 min after the start of the reaction
310 (the transfer time between reactor and mass spectrometer). Comparison of results in the initial
311 period was also complicated by the fact that the reaction was still continuing during transfer
312 of liquid to the vaporiser, albeit at a lower rate as the transfer line was not heated. The net
313 effect is that the concentration profile obtained by DLSMS is offset and increases more
314 quickly at the start of the reaction compared to the profiles obtained by GC and MIR
315 spectrometry. As the reaction proceeded, however, the difference in the concentration of
316 butyl acetate in the reactor at a certain time and the concentration delivered to the mass
317 spectrometer decreased, as exemplified by the better comparison between the butyl acetate
318 profiles after 10 min. When the percentage conversion of reactions at 20 and 40 °C were
319 calculated from the results obtained by GC, DLSMS and MIR, respectively, the values
320 obtained were 77, 76 and 77% for 20 °C and 84, 83 and 85% for 40 °C.

Two reactions were carried out at 20 °C in the 1 L reactor with addition of 2.6 or 9.1% mol/mol ethanol as an impurity in butan-1-ol. It was not possible to detect the presence of ethanol and ethyl acetate by MIR spectrometry owing to the similarity of their spectra to those of butan-1-ol and butyl acetate, respectively. However, as indicated by the profiles in Figure 6, it was possible to detect ethanol and production of ethyl acetate by DLSMS with a corresponding reduction in the amount of butyl acetate formed.

4. Conclusions

The thermal vaporiser used in this study was shown to be an effective device for continuous vaporisation of the liquid stream from an esterification reaction at flow rates of 0.1 or 1.0 mL min^{-1}. When operated with a process mass spectrometer normally configured for gaseous process stream analysis it was possible to generate concentration profiles for the reactants and products of the esterification of butan-1-ol and acetic anhydride. An integrated MIR spectrometer and insertion probe with ATR crystal was found to give good estimations of butyl acetate concentrations throughout the reaction when compared to the results of a reference off-line GC procedure. The transfer time of about 2 min required to pump liquid from the 1 L reactor to mass spectrometer caused a mismatch in the concentrations obtained by DLSMS and the other two techniques in the initial period of the reaction, but as the reaction proceeded to completion these differences became less significant. The concentrations of butyl acetate at the end of the reaction and the percentage conversion rates derived from each of the techniques were similar.

DLSMS had advantages over ATR-MIR spectrometry as the calibration procedure was simpler, it was easier to track the concentration changes of all the components during the reaction and the presence of a simulated by-product (ethyl acetate) formed through the presence of small amounts of ethanol impurity in butan-1-ol could be detected. However, it was only possible to use classical least squares multivariate linear regression here as the identity of all reaction components was known. In situations where this is not the case, methods such as multivariate curve resolution or partial least squares could be used to quantify the components of interest. The main disadvantage of DLSMS compared to the in situ MIR method was the sample transfer time, an issue faced in all on-line extractive procedures.

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Tables

Table 1. The percent abundance (ions normalised to the most intense peak of the pure component spectra) for the reaction components monitored at the 150 mL scale.

m/z	Butanol	Acetic anhydride	Acetic acid	Butyl acetate	Pyridine
15	10.4	5.5	17.0	7.5	0.0
43	68.4	99.9	99.9	99.9	0.0
56	99.9	0.0	0.0	37.1	0.0
60	0.0	0.2	74.7	0.4	0.0
61	0.0	0.0	1.9	14.6	0.0
73	1.5	0.0	0.0	18.1	0.0
79	0.0	0.0	0.0	0.0	99.9
115	0.0	0.0	0.0	0.1	0.0

488 Table 2. The percent abundance (ions normalised to the most intense peak of the pure
489 component spectra) for the reaction components monitored at the 1 L scale.
490

m/z	Butanol	Acetic anhydride	Acetic acid	Butyl acetate	Pyridine	Ethyl acetate	Ethanol
31	98.1	0.1	2.5	2.0	0.0	0.9	99.9
41	87.6	2.1	3.5	18.9	0.0	0.3	1.3
43	68.4	99.9	99.9	99.9	0.0	99.9	11.4
45	7.7	2.0	90.3	1.2	0.0	14.6	51.4
56	99.9	0.0	0.0	37.1	0.0	0.1	0.0
60	0.0	0.2	74.7	0.4	0.0	0.9	0.0
70	0.1	0.0	0.0	0.1	0.0	11.8	0.0
73	1.5	0.0	0.0	18.1	0.0	4.9	0.0
79	0.0	0.0	0.0	0.0	99.9	0.0	0.0

491

Figure captions

Figure 1. Schematic diagram of experiment set-up for 1 L reactor.

Figure 2. The vaporising device. Reproduced from Ref. [39] by permission of The Royal Society of Chemistry.

Figure 3. The concentration profiles of butan-1-ol, acetic anhydride, acetic acid, butyl acetate and pyridine derived from direct liquid sampling mass spectrometry; reaction at 40 ^{o}C in a 150 mL flask.

Figure 4. Concentrations of butyl acetate predicted from in-line MIR spectrometry (solid line) compared to the concentrations derived by GC (X) for a) calibration and b) validation reactions, conducted at 20 and 40 °C, respectively.

Figure 5. Concentration profile of butyl acetate obtained by DLSMS (green solid line) for the esterification reaction in a 1 L jacketed reactor at 20 °C. Also shown are the butyl acetate concentrations obtained by *in situ* MIR spectrometry (blue diamonds) and off-line gas chromatography (red crosses), and the temperature of reactor contents (black solid line).

Figure 6. Concentration profiles of acetic acid, butyl acetate, ethyl acetate and ethanol obtained by DLSMS when butan-1-ol contained 9.1% mol/mol ethanol (left) and 2.6% mol/mol ethanol (right) as a simulated impurity.

510 **Figures**

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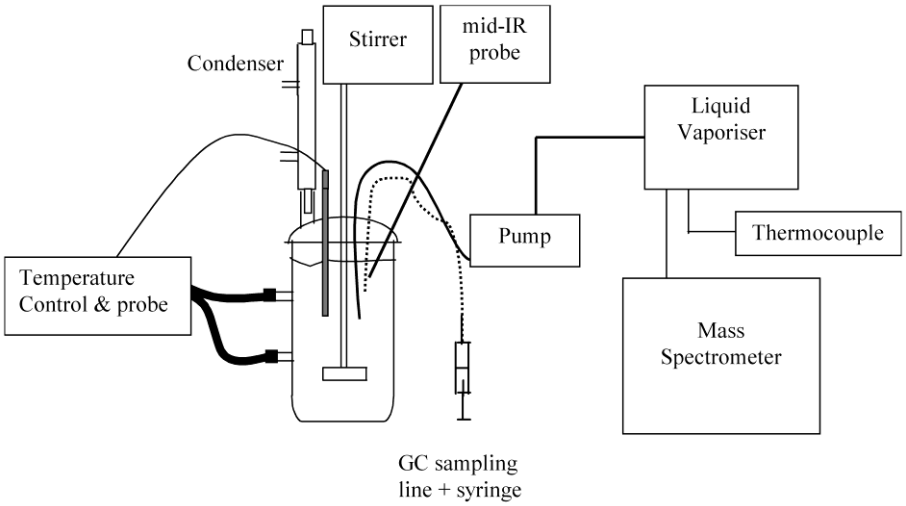

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515 Figure 1

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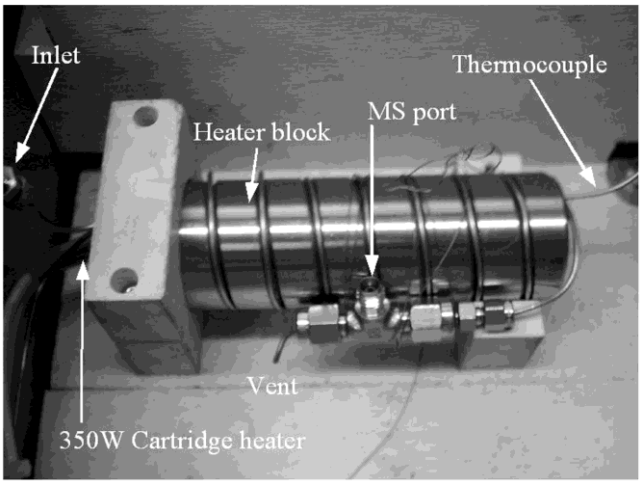
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Heater block
Vent
350W Cartridge heater

Figure 2

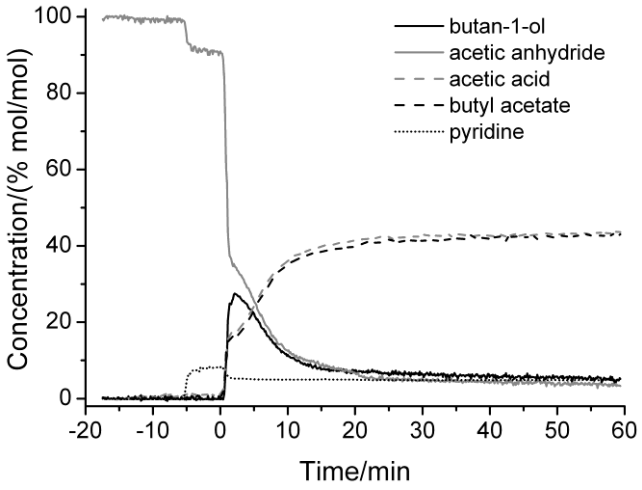

Figure 3

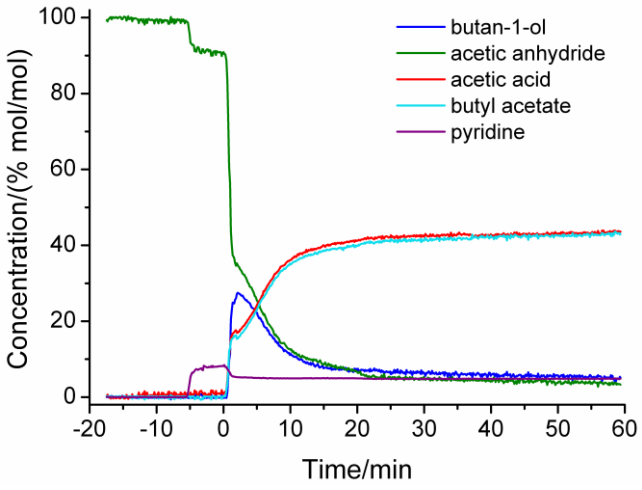

Figure 3 (colour version – web only)

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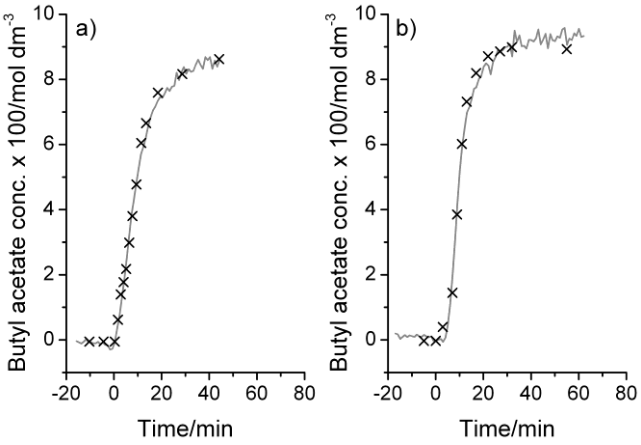

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539 Figure 4

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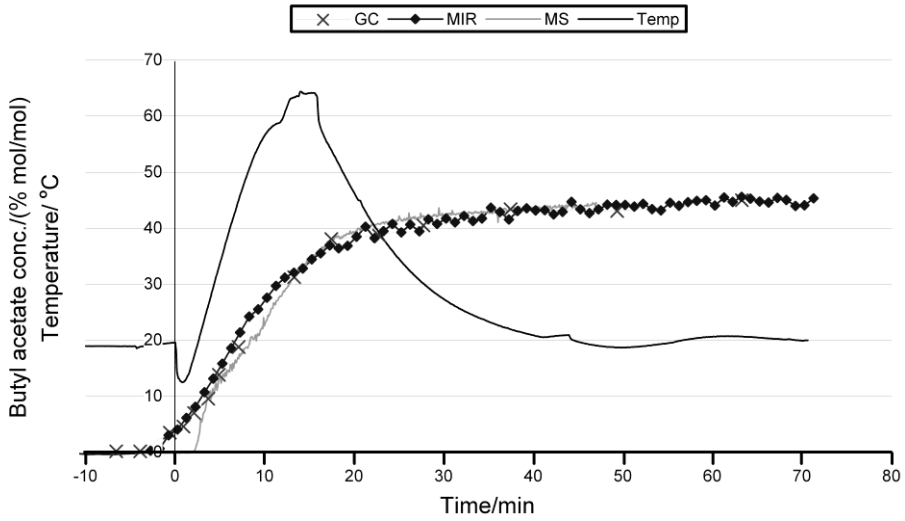
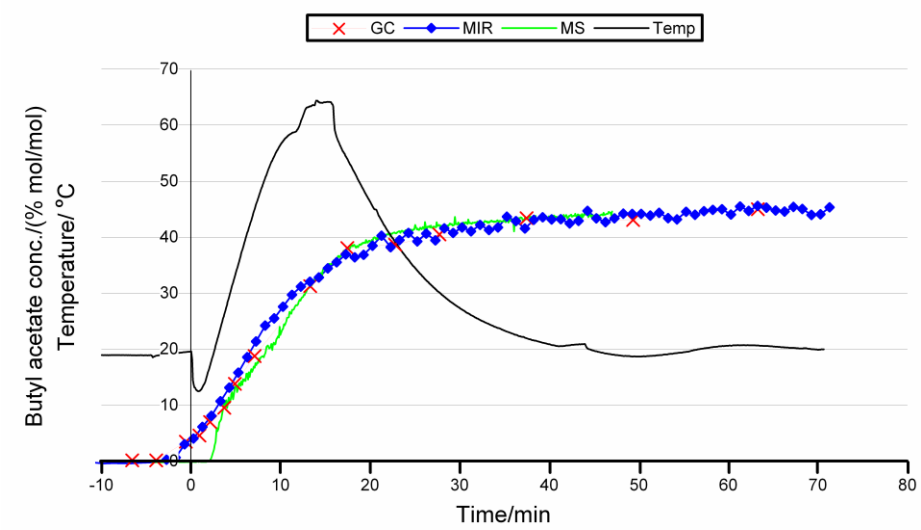


Figure 5



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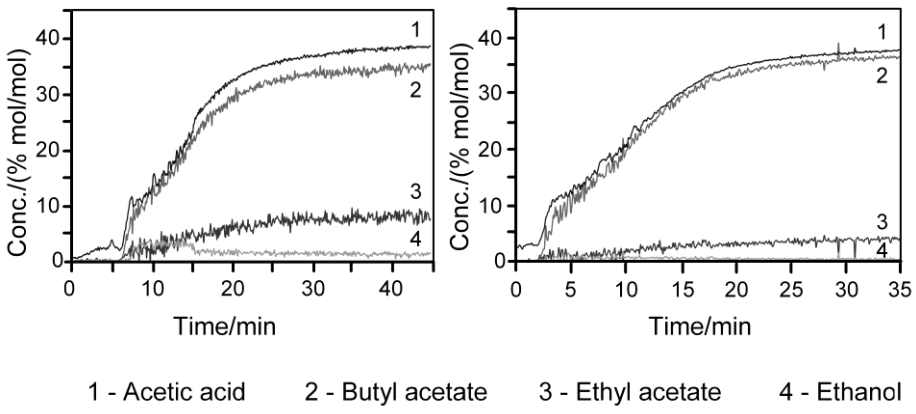

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557 Figure 6

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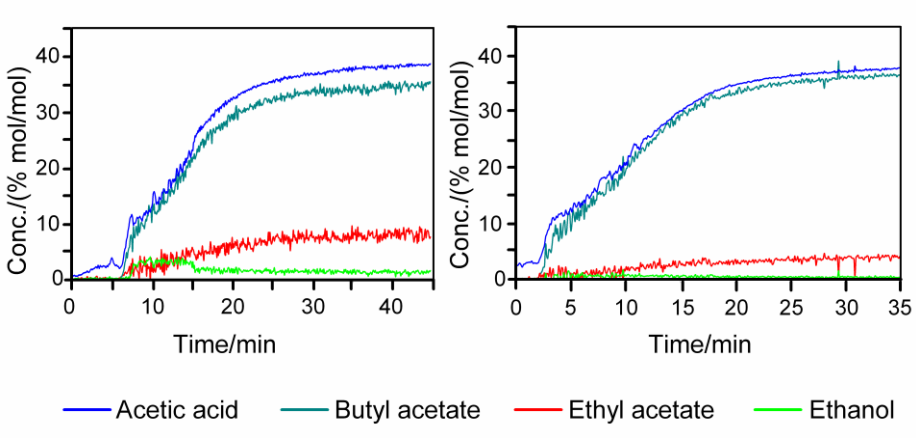

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560 Figure 6 (colour version – web only)

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