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# 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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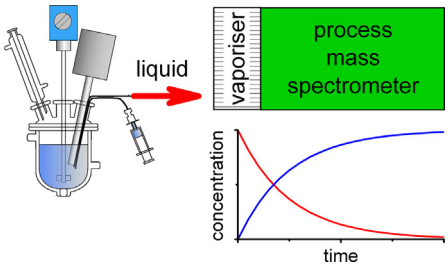
## HIGHLIGHTS

- High efficiency thermal vaporiser designed and used for on-line reaction monitoring.
- Concentration profiles of all reactants and products obtained from mass spectra.
- By-product formed from the presence of an impurity detected by MS but not MIR.
- Mass spectrometry can detect trace and bulk components unlike molecular spectrometry.

## GRAPHICAL ABSTRACT

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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

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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.



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

A number of studies have reported the use of ambient ionisation techniques for reaction monitoring. Extractive electrospray ionisation (EESI) has been used for on-line 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 reactions 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 in discovery and development. In addition, quantitative results have yet to be demonstrated with many of the techniques.

Thermal vaporisation of discrete liquid samples into a process mass spectrometer has been achieved using heated auto-injection valves [34–36], a modified GC oven [37], and a programmable temperature vaporising (PTV) GC injector and syringe pump [38]. However, these methods are not ideal for continuous sampling; when a carrier gas is used to transport the sample vapours to the mass spectrometer variations in the carrier gas flow and inefficient