

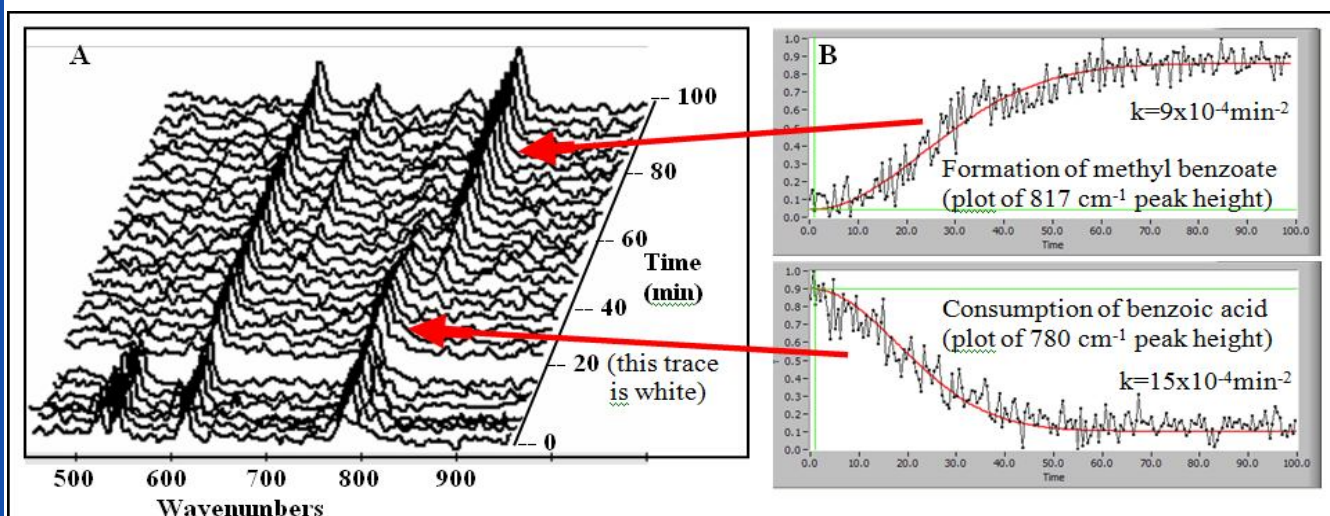
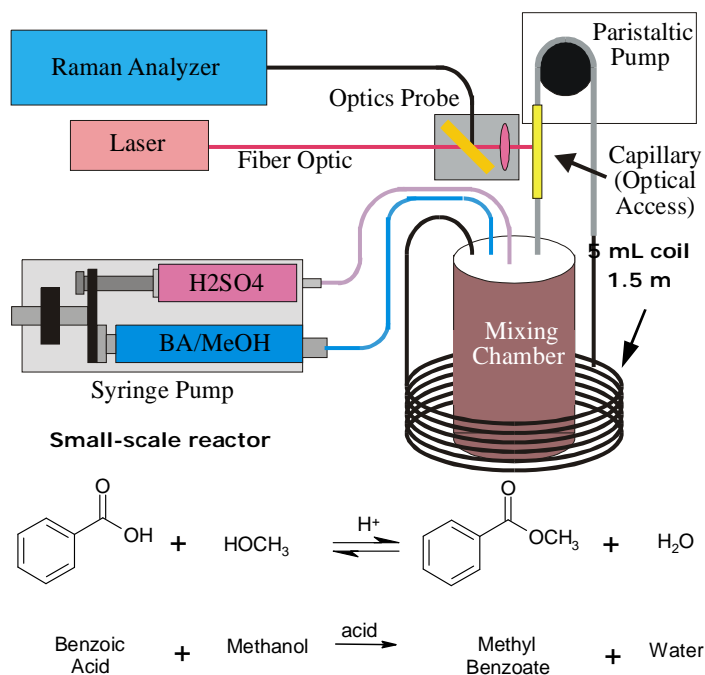
Analytical Control of Micro-Reactors

RTA Application Note # 06b

Small-scale reactors (microliter to milliliter) are being developed to: 1) create new chemical reaction processes, 2) increase yields of existing processes, and 3) replace scaling-up by numbering-up production. Rapid optimization AND successful process operation of these reactors requires analytical measurements to identify and quantify ($\pm 1\%$) all reactants and products in real-time (e.g. 1 min), preferably without requiring sample preparation. The Industrial Raman Analyzer with a fiber optic connected in-line sample probe is ideal for this application.

To demonstrate this capability, we constructed a simple 5 milliliter batch-reactor and used RTA's Industrial Raman Analyzer to monitor the esterification of benzoic acid to form methyl benzoate. This reaction, protecting carboxylic acid groups by esterification, represents one of the most often used reaction steps during the synthesis of pharmaceuticals.

As shown in the figures below, quality Raman spectra were easily obtained continuously throughout the reaction. A spectrum was generated every 30 seconds using 325 mW of 785 nm laser excitation. This allowed monitoring the disappearance of the reactant, benzoic acid (780 cm^{-1}), and the appearance of the product methyl benzoate (817 cm^{-1}). By modifying the reactor temperature, and varying the catalyst type, it was found that greater than 90% yield could be obtained at $60\text{ }^\circ\text{C}$ and in 1 hour.



A) 3-D plot of Raman spectra as a function of time for the esterification reaction performed at $60\text{ }^\circ\text{C}$ in the 5 mL small-scale reactor. Only every 10th spectrum is shown for clarity. B) Plots of the methyl benzoate product peak (817 cm^{-1}) and the benzoic acid reactant peak (780 cm^{-1}). Differences in rate constants determined from the rate equations (curve fits) suggest the possible formation of a complex intermediate.

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