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Article:

Real-Time Feedback Control Using Online Attenuated Total Reflection Fourier Transform Infrared (ATR FT-IR) Spectroscopy for Continuous Flow Optimization and Process Knowledge

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The use of automated continuous flow reactors is described, with real-time online Fourier transform infrared spectroscopy (FT-IR) analysis to enable rapid optimization of reaction yield using a self-optimizing feedback algorithm. This technique has been applied to the solvent-free methylation of 1-pentanol with dimethyl carbonate using a γ-alumina catalyst. Calibration of the FT-IR signal was performed using gas chromatography to enable quantification of yield over a wide variety of flow rates and temperatures. The use of FT-IR as a real-time analytical technique resulted in an order of magnitude reduction in the time and materials required compared to previous studies. This permitted a wide exploration of the parameter space to provide process understanding and validation of the optimization algorithms.

Index Headings: FT-IR spectroscopy; Flow chemistry; Process optimization; Etherification.

INTRODUCTION

There is a growing development in the use of continuous flow reactors for the manufacture of fine chemicals and pharmaceuticals.[1,2,3] Efficient rapid experimentation using flow reactors enables automated reaction screening and optimization methodologies resulting in a shift from current batch-wise chemical reaction development.[4] In particular, there is considerable interest in the development of automation of such reactors with the capability of varying the reaction parameters to achieve optimal production.[5] By combining the reactor system, process control instrumentation, and online analysis, it is possible to create an autonomous unit capable of optimization of chemical reactions without the need for any human intervention after initialization.

A number of recent publications have demonstrated this concept by combining reactor control with feedback algorithms. The optimization of nanoparticle production in a microreactor system has been reported.[6] The flow rates and temperature were controlled using an automated computer system using the Stable Noisy Optimization by Branch and Fit (SNOBFIT) algorithm with an online fluorimeter to characterize the nanoparticles. Optimization has been demonstrated for reactions such as a Heck coupling,[7] a Knoevenagel condensation reaction, and the oxidation of benzyl alcohol using the Nelder and Mead Simplex (NMSIM) algorithm[8] with microreactors and online HPLC analysis.[9]

We have demonstrated the optimization of continuous etherification using online gas-liquid chromatography (GLC) as the analytical technique and the Super Modified Simplex (SMSIM) algorithm.[10,11,12] Specifically, we investigated the optimization of the reaction of dimethyl carbonate (DMC) and 1-pentanol (**1**) in supercritical CO_2 (scCO_2) to form pentyl methyl ether (**2**); see Scheme 1.[13] We showed that the apparatus could be programmed to optimize the reaction for any one of a range of different criteria (i.e., yield, space-time yield, E factor or a weighted yield function).[14]

Although we reported that self-optimization is fast compared to manual optimization of one parameter at a time, the process is still quite lengthy (>2 days for 4 parameters) largely because of the time required for the GLC analysis. Here, using the solvent-free etherification of 1-pentanol as an example, we report how the whole process of optimization can be greatly accelerated by using Fourier transform infrared (FT-IR) spectroscopy analysis.

There are many reports of using online FT-IR spectroscopy as a rapid and non-destructive method for real-time analysis in flow chemistry.[15,16,17] Applications of FT-IR spectroscopy in continuous flow systems include monitoring the profile of continuous flow reactions, aiding more precise addition of reagents in segmented flow,[17,18] and the automation of a microfluidic system for performing self-optimization of residence time and reaction temperature.[19] In this paper, we are using online FT-IR, but as explained below, the nature of the chemical problem dictates that our approach has to be somewhat different from those in the publications above.

EXPERIMENTAL

Figure 1 shows a schematic of the automated self-optimizing reactor and the associated feedback loops. All organic solutions were pumped by HPLC pumps (Jasco PU-980). The pre-mixer and reactor were both heated using cartridge heaters within aluminum heating blocks controlled by programmable heating controllers (Eurotherm 2416). The pre-mixer and reactor were 1.8 mL 316 stainless steel tubes (156 mm × 1/4-inch outside diameter) filled with sand in the pre-mixer and the catalyst [Puralox NWA-155a γ-alumina powder (150 m^2/g surface area and containing trace impurities of SiO_2, Fe_2O_3, and Na_2O)]. The system was not pressurized because of the pressure limitations of the IR probe, and it was monitored by pressure transducers in both HPLC pumps. Analysis of reactor output was measured by an online Shimadzu GC-14B, with a Vici high-pressure sample loop (0.06 µL), using an AllTech SE-30 (30 m, 0.25 mm ID, 0.25 µm FT, hold 50 °C 1 min, ramp to 90 °C at 10 °C/min, hold 90 °C 1 min, ramp to 240 °C at 25 °C/min, hold 240 °C 1 min) and a Mettler-Toledo ReactIR with a
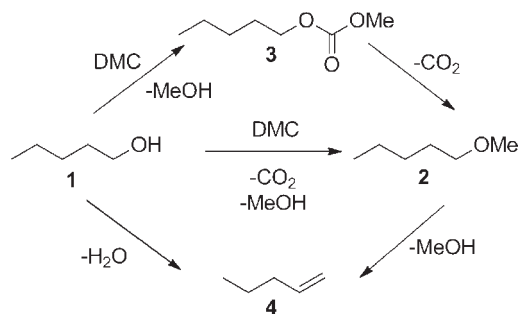
SCHEME 1. Simplified reaction scheme for the methylation of 1-pentanol (*1*) with dimethyl carbonate, DMC. The formation of pentyl methyl carbonate (*3*) is favored at lower temperatures (150–200 °C), while pentyl methyl ether (*2*) is favored 200–290 °C; above 300 °C, the decomposition of pentyl methyl ether and dehydration of 1-pentanol to pentene (*4*) become significant.[13]

flow probe attachment (Diamond ATR cell, 10 μL internal volume, 15 s sampling time).

In a typical experiment, system parameters and starting conditions are input into the custom control program, the HPLC pumps are supplied with the required organic solution, and a complete leak test is carried out. Commercially available dimethyl carbonate, DMC (Alfa Aesar, 99%) and 1-pentanol (Sigma-Aldrich, 99%) were used in all experiments without further purification.

Our system is solvent-free, unlike the recently reported reactions,[17,19] which means that the concentrations of the different components vary widely as the algorithm changes the flow rates of the reactants and as gaseous byproducts are generated in the reactor. Therefore, our apparatus combines online FT-IR with online GLC, which not only allows the FT-IR to be calibrated for varying reactant concentrations, but also provides independent validation of the FT-IR analysis. Infrared calibration is achieved by having an additional pump which adds a reference compound, ethyl acetate, downstream of the reactor at the same flow rate as the 1-pentanol (i.e., the flow rate of the ethyl acetate is automatically adjusted as the algorithm changes the flow rate of the 1-pentanol). Both the product and ethyl acetate exist in the liquid phase, which wets the diamond window of the ATR, giving spectra with a good signal-to-noise ratio.

The calibration procedure is described fully in the Supplemental Material, but briefly, a $3 \times 3 \times 3$ grid of different 1-pentanol flow rates (0.48, 0.86, 1.24 mL/min), DMC flow rates (0.48, 0.86, 1.24 mL/min) and reactor temperatures (120, 210, 300 °C) resulting in 27 different conditions was conducted. For each of these conditions, measurements were taken in duplicate using both the online GLC analysis and inline flow ATR using the Mettler-Toledo ReactIR system simultaneously. The GLC data permitted quantification of the composition of the product mixtures as well as the yield of pentyl methyl ether. The FT-IR results from the calibration procedure are shown in Fig. 2. The majority of bands could be identified from running standards. Two peaks indicated by the arrows in Fig. 2 at 850 and 1120 cm^{-1} were chosen to quantify the relative amount of pentyl methyl ether and ethyl acetate, and hence the yield (i.e., the concentration of pentyl methyl ether in relation to the original concentration of 1-pentanol). The FT-IR spectra could be correlated with the actual yield measured by GLC to generate a calibration curve with a good level of fit ($R^2 = 0.99$); this calibration was then
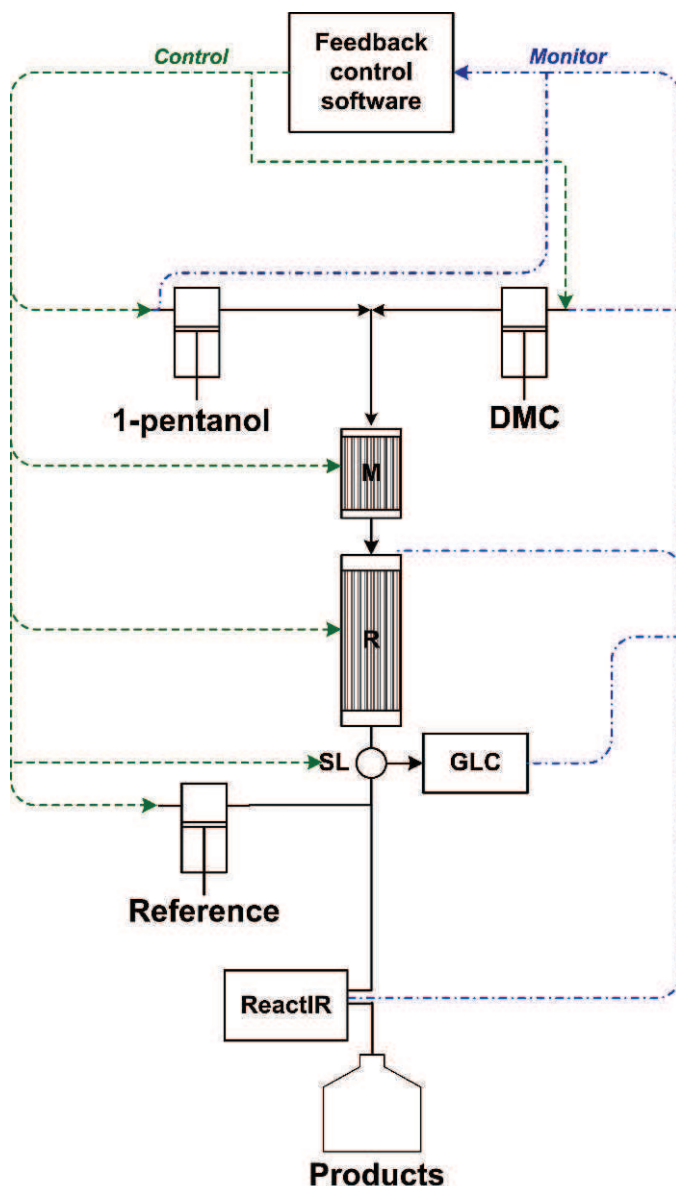

FIG. 1. Diagram of the automated self-optimization rig with the ATR installed. The fluid stream passes from the pumps through the mixer (M), packed with sand which also serves as a pre-heater, and into the reactor (R) where the catalyst was loaded. The reactor output was either sampled for GLC analysis by the sample loop (SL) or flowed directly into the ATR flow probe after being mixed with a reference material (ethyl acetate).

used to calculate the yield in real-time, solely from FT-IR spectra.

RESULTS AND DISCUSSION

Our initial investigation of the FT-IR approach involved optimization of the reaction using the SMSIM algorithm.[10] The whole optimization was completed, with >99% yield of pentyl methyl ether, in ~150 min with the average time required per data point of 3.2 min compared to the 35 min required our previous work using GLC.[11] This reduction in the optimization time was due to the increased sampling rate of the FT-IR, which not only allowed the chemical yields to be measured, but enabled us to detect precisely when the reactor had reached steady state operation (see Supplemental Material for details).
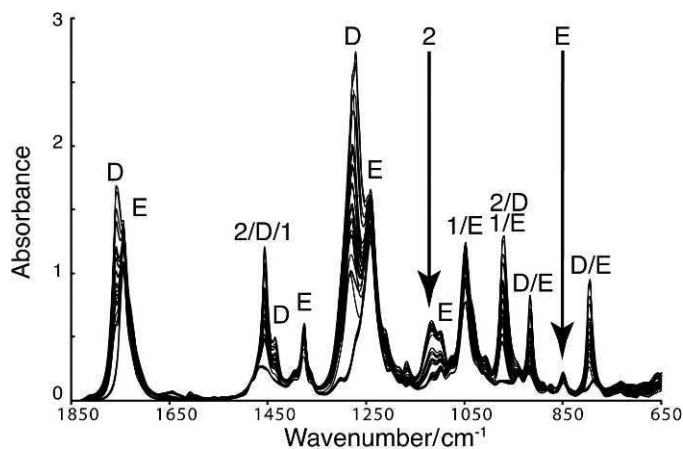
FIG. 2. Set of IR spectra taken during the calibration procedure, with different compositions and conversions. Peaks are labeled based on spectra of individual standards: (**2**) pentyl methyl ether, (**D**) dimethyl carbonate, (**1**) 1-pentanol, (**E**) ethyl acetate, (**M**) methanol. The arrowed peak at $\sim$850 cm^{-1} was used as the reference peak to overcome concentration effects and the relative height of the arrowed peak at 1120 cm^{-1} was used to determine the reaction yield of pentyl methyl ether, with respect to 1-pentanol, for the pentyl methyl ether product. (For full details of calibration, see Supplemental Material).

Since chemicals are pumped into the reactor continuously, the reduction in optimization time also represents very substantial savings in the amount of chemicals required for the optimization.

The optimization process was then repeated using the SNOBFIT algorithm, which combines both local and global search functions when searching for the optimum.[20] Unlike the SMSIM algorithm, SNOBFIT does not require the user to specify the starting conditions. Instead, the user specifies the volume of parameter space within which the program searches using a space-filling algorithm to determine the initial points of measurement. A significant advantage of SNOBFIT when compared to SMSIM is the greater confidence that the global optimum has been located, due to the global search elements of the algorithm, although generally this does require extra measurements. The result is that the SNOBFIT algorithm can

TABLE I. The optimized conditions and yields of pentyl methyl ether, with respect to 1-pentanol, identified via the SMSIM and SNOBFIT optimizations of the methylation of 1-pentanol by DMC.

Parameter	SMSIM	SNOBFIT
Temperature (°C)	200	246
1-pentanol (mL/min)	0.24	0.20
DMC (mL/min)	1.28	1.44
Yield[a] of **2** (%)	>99%	>99%

[a] Confirmed by GLC.

be slower than SMSIM, and we had previously discounted its use with GLC analysis because of the increased time needed for optimization. However, the greater number of measurements is more accessible with the FT-IR method.

Figure 3 shows the result of the SNOBFIT optimization, which required an average of 8 min rather than 3.2 min per measurement for the SMSIM. The reason why the SNOBFIT experiment takes longer per point than the SMSIM optimization is that the points are on average further apart in parameter

FIG. 4. Grid of measurements at 252 different conditions to gain a more detailed view of the methylation of 1-pentanol within the selected parameter space. (**a**) shows the variation of the yield of pentyl methyl ether, with respect to 1-pentanol; (**b**) shows the corresponding variation of the E factor. The optimal region of the E factor is located near the top face in (**b**), while the optimal region for yield is close to the front face (**a**). This validates the optimal yields identified by the SMSIM (⊕) and SNOBFIT (✕) adaptive optimization algorithms.
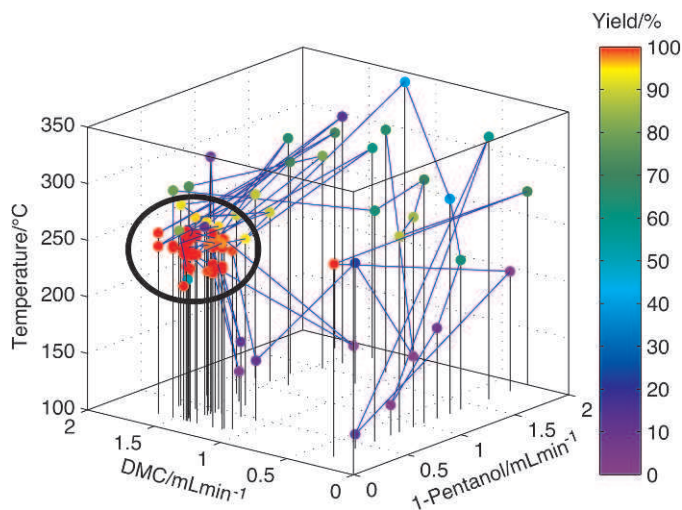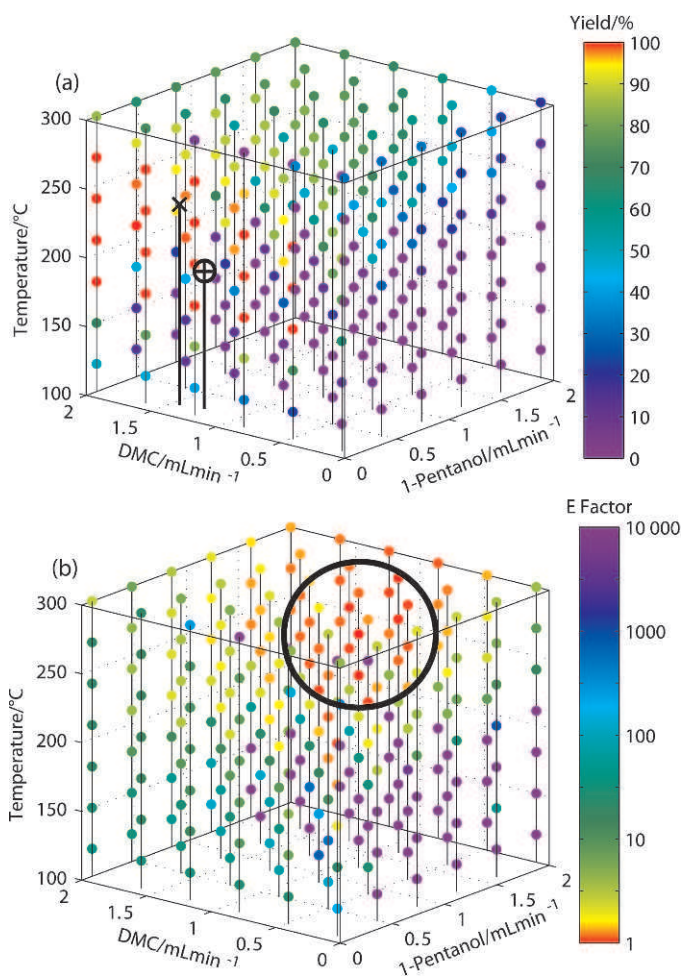

FIG. 3. SNOBFIT optimization of the yield of pentyl methyl ether, with respect to 1-pentanol, for the methylation of 1-pentanol by DMC with the optimum region circled.
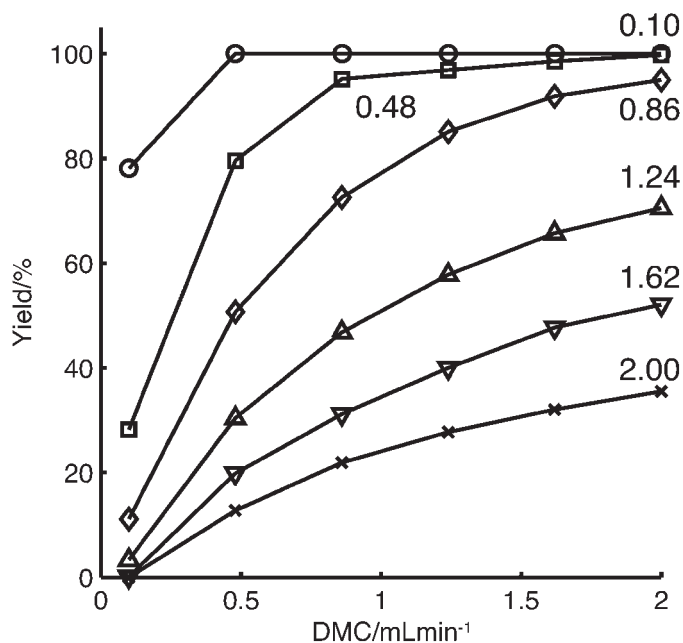
FIG. 5. Graph derived by slicing horizontally through the data at 210 °C, in Fig. 4a, showing the effect on the yield of pentyl methyl ether of varying DMC flow rates, the numbers (0.1, 0.48, etc.) indicate the different flow rates of 1-pentanol in mL/min. Note that, for a given flow rate of DMC, the yield drops monotonically with increasing flow rate of 1-pentanol.
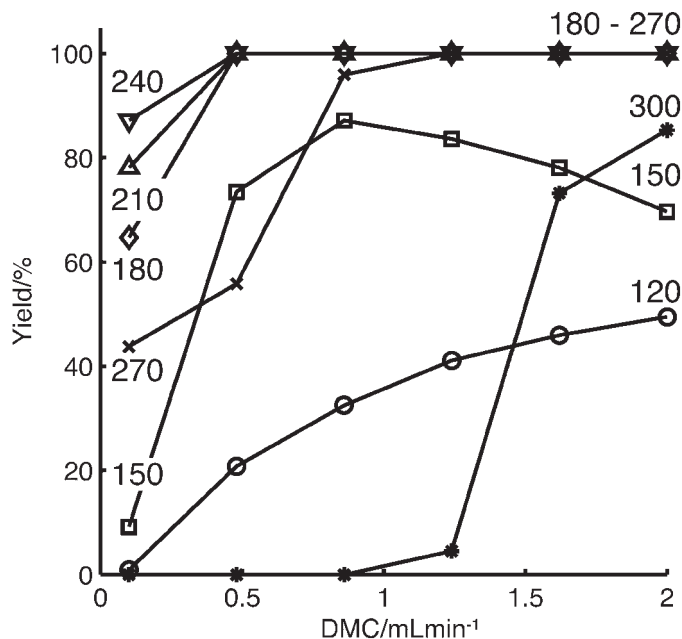

FIG. 6. Graph derived by slicing vertically through the data in Fig. 4a at a flow rate of 0.1 mL/min of 1-pentanol, illustrating the effect of increasing DMC flow rate at different temperatures, as indicated by ○ − 120 °C, □ − 150 °C, ◇ − 180 °C, △ − 210 °C, ▽ − 240 °C, × − 270 °C, ✳ − 300 °C. Note that, as discussed in the text, the variation in yield is far more complex than the example shown in Fig. 5.

space (due to global searching), and the reactor takes correspondingly longer to reach the new conditions. The optimal yields for the two optimizations were both >99% but, interestingly, the optimal conditions identified by the two algorithms were not identical (Table I). This suggests that the optimum is a region rather than a distinct peak, which both of the algorithms were able to locate. Figure 3 also demonstrates the global searching of the SNOBFIT algorithm, giving greater confidence that SNOBFIT has identified the global optimum.

The speed of the FT-IR analysis allowed us to map out the entire volume of the defined parameter space so that we could understand better how the optimum values were found by the two different algorithms. A grid of 252 measurements spaced at regular intervals within the parameter space was performed; see Fig. 4 (and Table S1 in the Supplemental Material). This experiment, which took ~24 hours, would have taken at least ten times longer and required more than 50 L of chemicals if it were performed using GLC analysis. Figure 4a provides an overall visual representation of the results, from which it is clear there is an optimum volume of parameter space, between ~180–270 °C and when DMC is in excess of 1-pentanol. This is consistent with the findings of both the SMSIM and SNOBFIT algorithms.

In addition, it is possible to calculate the value of other metrics from the data in the grid. Figure 4b shows the calculated values of the E factor (kg waste/kg product), which show a very large variation across the parameter space, with the lowest values located in a different region from the optimum yield, as indicated in Fig. 4a. The lowest and, hence, optimal E factor of 0.91 is achieved at 270 °C, 1.24 mL/min of 1-pentanol, 0.86 mL/min of DMC with a yield of 71%.

Mapping the data in this fashion means that it is possible to see the influence of reaction parameters on other metrics to enable the most effective optimization. In addition, it is

possible to visualize the effect of the various reaction parameters and their interdependence. In some cases, the observed effects are relatively simple to understand. For example, Fig. 5 is derived from the grid data at 210 °C; it shows the effect on the yield of increasing the flow rate of DMC at different flow rates of 1-pentanol. In this slice, an increase of flow rate of 1-pentanol leads to a decrease in yield, whereas increasing the flow rate of DMC increases it. These effects can be rationalized as follows. At 210 °C, all reagents are in the gas phase. Therefore, increasing the flow rates of either reactant will reduce the residence time in the reactor. However, increasing the flow rate of DMC or lowering the flow rate of 1-pentanol and, hence, the relative concentration of the methylating agent, increases the rate of reaction more than is needed to compensate for the change in residence time.

A more complex situation is shown in Fig. 6, which is a good example of the interdependence of two variables and illustrates why conventional optimization of a single parameter, followed by the optimization of the next, may not always locate the optimum correctly.

Figure 6 is derived from the data at a fixed flow rate of 0.1 mL/min of 1-pentanol. Immediately, one can see that the dependence on temperature is less straightforward because increasing the flow of DMC or increasing the temperature will decrease the residence time. At the same time, increasing temperature will increase the rate of reaction but may also increase the rate of formation of pentene from both 1-pentanol and pentyl methyl ether, thereby decreasing the yield.

CONCLUSION

In this paper, we have demonstrated that FT-IR can be used effectively as a means of providing analytical data for feedback control and reaction optimization by using data from the online

GLC for calibration of the FT-IR. Although the calibration procedure is relatively lengthy and therefore removes some of the speed advantage of FT-IR optimization, the high speed of the optimization itself provides major savings in material and permits a far wider exploration of parameter space than would be possible with GLC alone. Further examples of the effects of reaction parameters and their interdependence are given in the Supplemental Material. The important point is that the increased amount of information that can be obtained through the speed of FT-IR analysis adds a new level of understanding compared to the direct optimization.

SUPPLEMENTAL MATERIAL

All supplemental material mentioned in text, including description of the procedure, calibration of data, and full data mapping is available in the online version of the journal at http://www.s-a-s.org.

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