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Reaction monitoring via ^{19}F NMR spectroscopy

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1.855.NMReady

INTRODUCTION

Nuclear magnetic resonance (NMR) spectroscopy has developed into one of the most valuable tools a chemist has due to its extraordinary ability for structural elucidation and quantification. This ability gives NMR spectroscopy the capacity to monitor and analyze reactions in an effective manner. Recent advances in flow chemistry have allowed NMR to be used for in-line and on-line flow analysis. This transition allows for chemical processes to move from "batch mode" to "continuous flow mode" and can eventually lead to automation. Automating processes improves safety, enables chemists to maximize efficiency as well as focus on more technical work such as planning experiments, interpreting data, and developing new projects.[1]

An important benefit of flow chemistry is that it allows chemists to have real-time access to the state of chemical reactions, which helps one to control the kinetics, yield, scalability, and efficiency of the reaction. Currently, chemists employ analytical techniques such as gas chromatography (GC), high-performance liquid chromatography (HPLC), ultraviolet-visible spectroscopy (UV-vis), and high-resolution NMR spectroscopy to gain insight into on-line flow reactions.[2]

Despite its superiority over other techniques for structural elucidation and its accuracy for quantification, NMR is still oftentimes underrepresented.

In industry, the implementation of a high field NMR spectrometer is not always feasible due to the large size and expensive nature of the instrument (significant initial cost, maintenance, cryogens, and knowledgeable full-time staff to keep the instrument operational and in good working condition). However, due to advances in low field benchtop NMR spectroscopy, having in-line or on-line analysis with NMR spectroscopy is possible for a fraction of the cost and a much smaller footprint than with a high field system. For this analytical technique to be utilized for flow chemistry, some conditions must be met before undertaking reaction monitoring:

1. The chemical species of interest must be soluble in the desired solvent
2. The chemical species of interest must contain an NMR active nucleus (e.g. ^{1}H)
3. The signals of interest must be distinguishable from other signals

The terms "in-line" and "on-line" specify the ability to analyze chemical species without any manual manipulation of the sample. Both processes require the reaction mixture and the NMR probe to be connected in some form. "On-line" analysis refers to when an aliquot of the reaction mixture is periodically diverted from the manufacturing process. "In-line" analysis occurs when the sample is not removed from the process stream, and the flow is continuously analyzed.[3]

The NMReady-60 can be easily modified for on-line reaction monitoring using our NMReady-flow kit. This kit consists of:

1. A customized borosilicate glass flow cell designed to span the length of the NMReady-60
2. The necessary joints required to connect the glass flow cell with the chromatography tubing

Once fully assembled, the on-line reaction system (reaction mixture, necessary connections, pump, and NMReady-60) resembles the illustration in **Figure 1**.

Due to the non-destructive nature of NMR spectroscopy, reaction monitoring with NMR can be hyphenated with other analytical techniques in series, allowing for more information to be gathered.

In this experiment, the esterification of 4-fluorobenzoic acid with 2,2,2-trifluoroethanol is monitored via on-line ^{19}F NMR spectroscopy with the NMReady-60, following a slightly modified procedure by Zell *et al*.[4] The data obtained from this reaction can then be used to calculate the percentage of each fluorinated species present at each stage semi-quantitively.

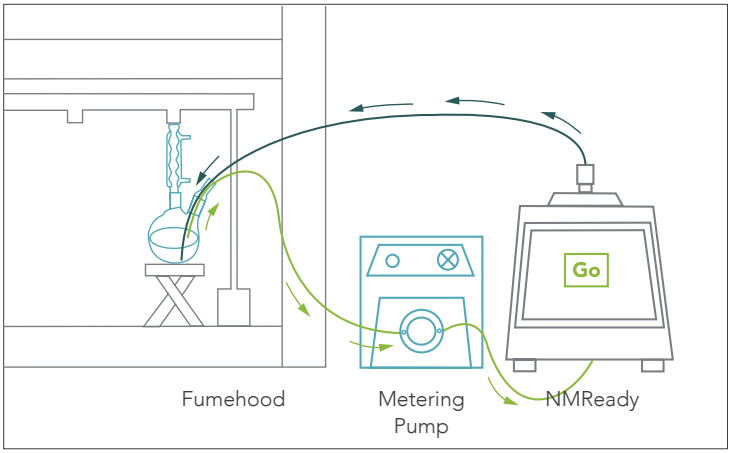

Figure 1. Illustrative schematic of on-line flow loop and reaction monitoring system using the NMReady-60.

PROCEDURE

Preparing the solution

2,2,2-trifluoroethanol (0.25 g, 2.5 mmol) and 4-fluorobenzoic acid (0.35 g, 2.5 mmol) were dissolved in 5 mL of acetone (non-deuterated). This reaction mixture was then circulated at a rate of 1 mL min^{-1}. Carbonyldiimidazole (70 mg, 0.43 mmol per addition; 840 mg, 5.18 mmol in total) was added in regular intervals (every 4 minutes for 48 minutes) in between acquisitions as the reaction progressed.

Monitoring the reaction

Before the addition of carbonyldiimidazole (CDI), a ^{19}F NMR spectrum is obtained (spectral width = 100 ppm, spectral center = -100 ppm, number of scans = 16, delay = 0 sec, number of points = 8192). The reaction is initiated by adding CDI into the reaction mixture. A ^{19}F NMR spectrum is recorded every 4 minutes for the duration of the experiment using the kinetics module on the NMReady (wait type = linear, number of clusters = 12, wait units = seconds, wait time (tau) = 240). To monitor the progress of the reaction, the trifluoromethyl resonances (-CF_3) were measured for the reactant (**2**, -77.7 ppm), the major product (**3**, -74.5 ppm), and the minor product (**4**, -75 ppm).

The reaction progress can be monitored using the following equation.

$$\%_x = \frac{\left(\frac{I_x}{3}\right) * Mm_x}{\left(\left(\frac{I_R}{3}\right) * Mm_R\right) + \left(\left(\frac{I_{P1}}{3}\right) * Mm_{P1}\right) + \left(\left(\frac{I_{P2}}{3}\right) * Mm_{P2}\right)} * 100\%$$

Where $\%_x$ = percent of compound x in the reaction mixture (x = I_R, I_{P1}, I_{P2})
I_x = Integral of compound x (I_x = I_R, I_{P1}, I_{P2})
Mm_x = molar mass of compound x (Mm_x = Mm_R, Mm_{P1}, Mm_{P2})
$I_{R, P1, P2}$ = integral of reactant, major product, and minor product
$Mm_{R, P1, P2}$ = molar mass of reactant, major product, and minor product

RESULTS/DISCUSSION

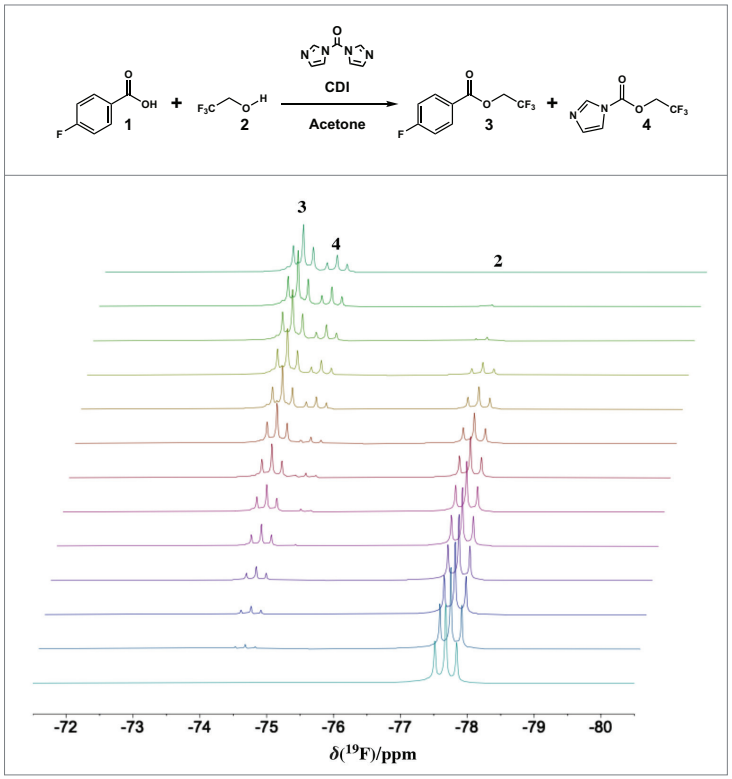

Figure 2. Reaction scheme (top) and stacked plot of ^{19}F NMR spectra (bottom) for the esterification reaction between 2,2,2-trifluoroethanol, 4-fluorobenzoic acid, and CDI over time.

As seen in **Figure 2**, the magnified ^{19}F NMR spectra of the reaction mixture displays three triplets. The signal at -77.7 ppm is the reactant (2,2,2–trifluoroethanol, **2**), the signal at -74.5 ppm is the major product (2,2,2-trifluoroethyl 4-fluorobenzoate, **3**), and the signal at -75 ppm is the minor product (*N*-(2,2,2-trifluoroethoxycarbonyl) imidazole, **4**). It is readily apparent that the signal for compound **2** decreases over time, as the reaction progresses with the concomitant increase of signals for compounds **3** and **4**. **Figure 3** shows the relative integration areas of each species over time. It is evident that the reactant is fully consumed in the reaction with a steady formation of the major and minor products. The total integration area of all species was included to show mass balance between reactants and products. In **Figure 4**, three different time points of the reaction mixture with the relative integrations of the fluorinated species are shown. From these relative integrations, it is possible to determine the progression of the reaction and the amount of reactant and products present. By using **equation 1**, the amount of each reactant and product of interest can be calculated. **Table 1** shows that at time point **a**, only compound **2** is present. At time point **b**, approximately 31.4% of compound **2** has not yet reacted, and at time point **c** it is seen that all of compound **2** has been consumed in the reaction mixture.

Time point	Compound 2	Compound 3	Compound 4
a	100	0	0
b	32	59	9
c	0	79	21

Table 1. Reaction progression (%) based on integration areas of fluorinated reactant and products in ^{19}F NMR spectra.

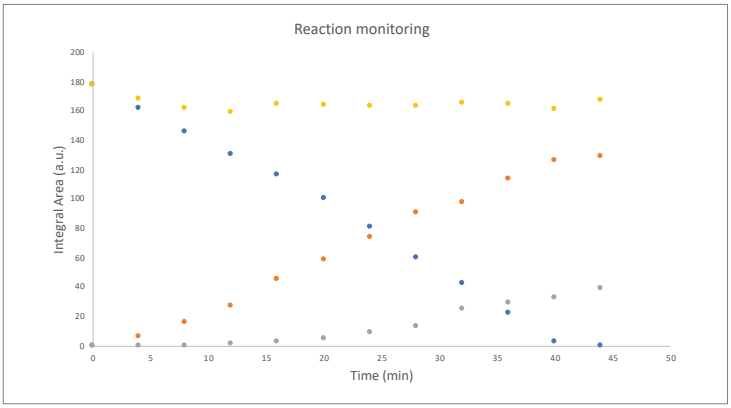

Figure 3. Integration area vs. time (minutes) plot for the amount of each reactant, major product, and minor product at varying time points by tracking their respective -CF_3 groups. The sum of integrals was included to show mass balance between reactants and products.

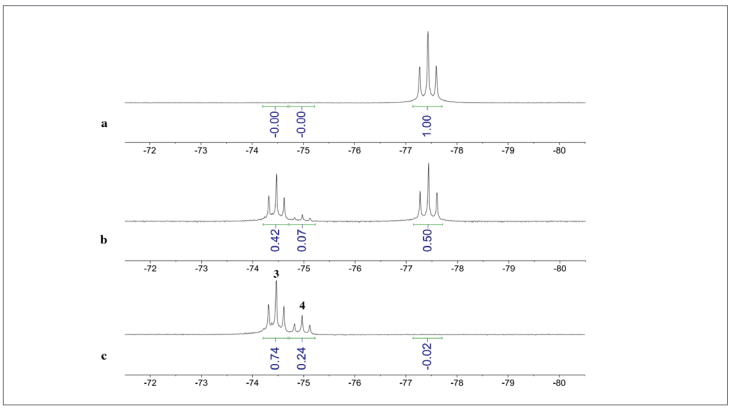

Figure 4. Three different time points of the reaction mixture: a) beginning, b) middle, and c) end of the reaction with the relative integrations of each fluorinated species of interest in solution.

CONCLUSION

In this experiment, an esterification reaction was monitored using fluorine NMR spectroscopy. Due to the differences in chemical shifts between the -CF_3 groups of the reactant and products, ^{19}F NMR spectroscopy can be used to monitor the progress of the reaction using the NMReady-60. Furthermore, semi-quantitative data was obtained from the spectra where the amounts of compounds **2**, **3**, and **4** (reactants and products) could be determined in solution.

References

[1] Gomez, M.; de la Hoz, A. *Beilstein J.Org.Chem.* **2017**, *13*, 285-300.

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[3] Browne, D.; Wright, S.; Deadman, B.; Dunnage, S.; Baxendale, I.; Turner, R.; Ley, S. *Rapid Commun. Mass Spectrom.* **2012**, *26* (17), 1999-2010.

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