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TITLE:

Characterizing Lewis Pairs Using Titration Coupled with In Situ Infrared Spectroscopy

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chemistry, infrared spectroscopy, Lewis acid, Lewis base, carbonyl, titration

SUMMARY:

Here, we present a method for the observation of solution interactions between Lewis acids and bases by employing in situ infrared spectroscopy as a detector for titration under synthetically relevant conditions. By examining solution interactions, this method represents a complement to X-ray crystallography, and provides an alternative to NMR spectroscopy.

ABSTRACT:

Lewis acid-activation of carbonyl-containing substrates is a fundamental basis for facilitating transformations in organic chemistry. Historically, characterization of these interactions has been limited to models equivalent to stoichiometric reactions. Here, we report a method utilizing in situ infrared spectroscopy to probe the solution interactions between Lewis acids and carbonyls under synthetically relevant conditions. Using this method, we were able to identify 1:1 complexation between $GaCl_3$ and acetone and a highly ligated complex for $FeCl_3$ and acetone. The impact of this technique on mechanistic understanding is illustrated by application to the mechanism of Lewis acid-mediated carbonyl-olefin metathesis in which we were able to observe competitive binding interactions between substrate carbonyl and product carbonyl with the catalyst.

INTRODUCTION:

The utilization of Lewis acids to activate substrates containing carbonyls is ubiquitous in organic synthetic methods[1–4]. The study of these interactions has relied on solid state X-ray crystallography, as well as in situ NMR spectroscopy[2]. Limitations of these techniques manifest from artifacts that arise from crystallization, or the inability to probe paramagnetic Lewis acids via NMR analysis. To overcome these issues, chemists have employed infrared (IR) spectroscopy to determine the exact structure of Lewis pairs. Further, IR has been utilized to determine Lewis acidity[4–9]. The Susz lab studied the solid-state interactions of Lewis acids and carbonyls in the stoichiometric regime. Utilizing IR in conjunction with elemental analysis, the Susz group was able to elucidate the structures of neat, 1:1 mixtures of Lewis pairs. This analysis provided a great deal of insight into structural ramifications of the interactions of simple carbonyl compounds with commonly utilized Lewis acids in the solid state, and of particular interest to our lab: $FeCl_3$[10,11]. We posited that we could add to the existing understanding of the interactions of these ou

important Lewis pairs via an in situ method that examines synthetically relevant conditions.

In situ IR enables chemists to perform real-time measurements of functional group conversions in situ. These data supply key insights into reaction rates to support hypotheses about the operating mechanisms of a process and to influence of reaction performance. Real-time observations allow chemists to directly track the interconversion of reaction components over the course of the reaction, and the information gleaned can be employed by the synthetic chemist in the development of new compounds and the optimization of synthetic routes and new chemical processes.

Employing in situ IR spectroscopy as a detection method, we probed the substrates and intermediates that participate in the catalytic cycle of metal-mediated carbonyl-olefin metathesis[12]. The Fe(III)-catalyzed carbonyl-olefin metathesis process, developed by the Schindler lab, exemplifies a powerful method for the production of C=C bonds from functional groups utilized ubiquitously in the construction of complex molecules[13–15]. Since the original report, this process has inspired a plethora of synthetic developments beyond the utilization of Fe(III)[16–25]. Importantly, this reaction requires that the Lewis acid catalyst differentiate between a substrate carbonyl and a product carbonyl for successful reactivity. To observe this competitive interaction under synthetically relevant conditions, we combined titration with the continuous observation provided by in situ IR.

We believe this method is of general importance to chemists studying carbonyl-centered reactions catalyzed by Lewis acids. This detailed demonstration aims to help chemists apply this technique to their system of study.

PROTOCOL:

1. Open-air reference spectrum

1.1. Open the data acquisition software. Click **Instrument**. Under the **Configure** tab, click **Collect Background**. Click **Continue**. Set scans to **256** and click **OK** to collect a background.

NOTE: Make sure the probe is in the same position in which data collection will take place. Position changes of the probe may impact spectra.

2. Solvent reference spectrum

2.1. In the data acquisition software, click **File**. Click **New**. Click **Quick Start**.

2.2. Set **Duration** to 15 min and **Sample Interval** to 15 s. Click **Create** to create experiment.

NOTE: At this point, the chemical system must be attached to the in situ IR probe to proceed. The following steps are for the preparation of the chemical system to be studied.

2.3. Under inert atmosphere, add Lewis acid to a flame-dried 25 mL 2-neck round bottom flask charged with a stir bar (**Figure 1B**). Seal the flask with rubber septa and attach an Ar-filled balloon to the flask. Add desired volume of anhydrous solvent via syringe (minimum 3 mL) (**Figure 1C**).

NOTE: $FeCl_3$ is not soluble in dichloroethane (DCE). $GaCl_3$ is soluble in DCE.

2.4. Remove one septum and attach the flask to the in situ IR probe (**Figure 1D**). Place the flask in a temperature-controlled bath set to desired temperature (**Figure 1E**).

2.5. Start the experiment in the data acquisition software by clicking the ▷ button to begin collecting data, and stop collecting data after 2 min.

NOTE: The name of this file is the solvent reference spectrum that you will use in step 3.1.3.

3. Titration software setup

3.1. Creating new titration experiment

3.1.1. In the data acquisition software, click **File | New | Quick Start**. Set **Duration** to 8 h and **Sample Interval** to 15 s.

NOTE: The data acquisition has the ability to set experiment duration between 15 min and 2 d and sample interval between 15 s and 1 h.

3.1.2. Click **Create** to create experiment. In the data acquisition software, go to **Spectra** tab and click **Add Spectra**. Click **From File** and open appropriate solvent reference spectrum obtained in step 2. Check the box with the time signature. Click **OK**.

3.1.3. Start experiment in the data acquisition software by clicking the ▷ button to begin collecting data.

3.2. Click **Solvent Subtraction** and select appropriate reference spectrum added in step 3.1.3. Stir for 15 min to reach temperature. Use the in situ IR probe to determine temperature.

4. Titration procedure

4.1. Add 10 µL of carbonyl analyte via syringe (**Figure 1F**).

4.2. Observe signal response on the data acquisition (**Figure 2**). System will shift from equilibrium and change with time.

4.3. When the IR signal stabilizes and remains constant, collect IR spectrum.

NOTE: The data acquisition collects spectra at a set frequency. Data in our lab are collected every

15 s. We note the time at which the system reaches equilibrium and use the spectrum collected at the time for analysis.

4.4. Repeat steps 4.1-4.3 until desired amount of analyte is added.

NOTE: $FeCl_3$ mixture becomes homogeneous once 1 equiv **1** is added and $GaCl_3$ mixture remains homogeneous regardless of amount of **1** added.

5. Analysis of IR spectra

5.1. Export data for the data acquisition software.

5.1.1. Click **File | Export | Multi-spectrum file**.

5.1.2. Under **Format**, check **CSV** and under **Data**, check **Raw**. Click **Export** to export IR data to spreadsheet or mathematical processing software.

5.2. Plot desired region of IR spectrum, as shown in **Figure 3A,D**.

5.3. Examine the spectrum for transitions and/or isosbestic points.

5.4. Separate spectra by progression, as shown in **Figures 3B,C** for $GaCl_3$ and **Figure 3E,F** for $FeCl_3$.

6. Component analysis

6.1. Identify λ_{max} of each species of interest, as shown in **Figure 4A** for $GaCl_3$ and **1** and **Figure 4D** for $FeCl_3$ and **1**, to generate a table of Absorbance vs. equivalent of analyte added, as shown in **Figure 4B** for $GaCl_3$ and **Figure 4E** for $FeCl_3$.

6.2. To account for dilution, multiply the absorbance by the total volume of the solution for each spectrum, as shown in **Figure 4B** for $GaCl_3$ and **Figure 4E** for $FeCl_3$.

6.3. Plot product of absorbance*volume as a function of equivalents of analyte, as shown in **Figure 4C** for $GaCl_3$ and **Figure 4F** for $FeCl_3$.

7. Analysis of consumption of species

7.1. For in situ-generated species that can be identified, plot a Beer-Lambert relationship, as shown in **Figure 5A**.

7.2. For known species, measure the impact of concentration on Absorbance at the desired λ_{max} and plot a Beer-Lambert relationship.

7.3. Using the two Beer-Lambert relationships, determine the observed in situ amounts of the species of interest, as shown in **Figure 5B**.

NOTE: C_{MAX} = 2 mmol as defined by the amount of $FeCl_3$ present. C_{ADD} is the moles of acetone (**1**) added. C_{COORD} is the moles of $FeCl_3$-acetone complex (**3**). C_{OBS} is the moles of unbound **1**. C_{ND} is the moles of **1** not detected. $C_{MAX} – C_{COORD}$ is the moles of **3** that have been consumed.

7.4. Plot C_{ND} vs. ($C_{MAX} – C_{COORD}$) to determine if there is a correlation, as shown in **Figure 5C**.

NOTE: The slope of this line will be in moles of species **1** per moles of species **3**.

REPRESENTATIVE RESULTS:

In this study, in situ IR-monitored titration was used to observe the interactions of **1** and $GaCl_3$ as well as **1** and $FeCl_3$ (**Figure 6**)[12]. Using this collection of protocols, we were able to determine that $GaCl_3$ and **1** form 1:1 complex **2** in solution. Alternatively, when $FeCl_3$ and **1** are combined, more complex behavior is observed. **Figure 6** displays the equilibria we were examining. **Figure 1** displays the physical setup of the titration of $FeCl_3$ with **1**. **Figure 2** displays the raw feed of data obtained by the in situ IR using the data acquisition software for the titration of $FeCl_3$ with **1**. **Figure 3** displays the process of extracting the transitions that result from this titration method applied to $GaCl_3$ and $FeCl_3$. **Figure 4** displays the extraction of λ_{max} data of the titration of $GaCl_3$ with **1** and the titration of $FeCl_3$ with **1**. **Figure 5** displays the extraction of complex coordination behavior from the titration of $FeCl_3$ with **1**. **Figure 7** displays an application of these protocols for the examination of competitive access to a Lewis acid. **Figure 8** shows the application of these protocols to revising the mechanism of metal catalyzed carbonyl-olefin metathesis.

FIGURE AND TABLE LEGENDS:

Figure 1. Visual guide to system setup. Necessary components for performing the titration (**A**). Assembled components prior to attachment to the in situ IR (**B**). Flask with Ar and ready for solvent addition (**C**). Flask attached to the in situ IR with solvent (**D**). Flask under temperature control (**E**). Ready for addition of analyte (**F**).

Figure 2. Analyte signal response in the data acquisition interface at 1636 cm^{-1} for titration of 2 mmol $FeCl_3$ in 12 mL of DCE with 1. The spectrum is collected when the system is at equilibrium, after analyte addition.

Figure 3. Analysis of IR spectra. Spectra collected for the titrations $GaCl_3$ with 0-4 equiv **1** (**A**) and $FeCl_3$ with 0-4 equiv **1** (**D**). Breakdown of titration of $GaCl_3$ with 0-1 equiv **1** showing the formation of **2** (**B**) and with 1-4 equiv **1** showing the presence of **1** (**C**). Breakdown of titration of $FeCl_3$ with 0-1 equiv **1** showing the formation of **3** (**E**) and with 1-4 equiv **1** showing the presence of **1**, the consumption of **3**, and the formation of a new species (**F**). Reprinted (adapted) with permission from Hanson, C. S., et al[12]. Copyright 2019 American Chemical Society.

Figure 4. Extraction of λ_{max} data from IR for Component Analysis. Spectra collected for the

titrations $GaCl_3$ with 0-4 equiv **1** with the λ_{max} for **1** and **2** indicated (**A**) and $FeCl_3$ with 0-4 equiv **1** with the λ_{max} for **1** and **3** indicated (**D**). Table showing representative data normalized to account for dilution for $GaCl_3$ (**B**) and for $FeCl_3$ (**E**). Data from (**B**) plotted for component analysis of titration of $GaCl_3$ with **1** (**C**) and for component analysis of titration of $FeCl_3$ with **1** (**F**). Reprinted (adapted) with permission from Hanson, C. S., et al[12]. Copyright 2019 American Chemical Society.

Figure 5. Consumption analysis of titration of $FeCl_3$ with 1. Segment of IR data used to generate a Beer-Lambert relationship for [**3**] and the segment of IR data used to determine the consumption of **3** (**A**). Moles of each **1**-containing species measured from IR (**B**). Plot of moles of **1** not detected vs. moles of **3** consumed (**C**). Reprinted (adapted) with permission from Hanson, C. S., et al[12]. Copyright 2019 American Chemical Society.

Figure 6. Lewis acid/base equilibria probed in this study. Titrations of $GaCl_3$ with **1** to form **2** and $FeCl_3$ with **1** to form **3** and **4** are reported.

Figure 7. Competitive binding experiment. Carbonyl region of IR spectrum of **3** (**A**) and of IR spectrum of **5** (**B**). Equilibrium probed in titration of **3** with **6** (**C**). IR data of titration of **3** with 1 equiv **6** (**D**). Reprinted (adapted) with permission from Hanson, C. S., et al[12]. Copyright 2019 American Chemical Society.

Figure 8. Application of in situ IR data in mechanistic proposal. Carbonyl-olefin metathesis reaction of **7** (**A**). The revised mechanistic proposal of carbonyl-olefin metathesis facilitated by titration coupled with in situ IR spectroscopy (**B**). Reprinted (adapted) with permission from Hanson, C. S., et al[12]. Copyright 2019 American Chemical Society.

DISCUSSION:

Under anhydrous conditions, Lewis acids can have a range of solubilities. The two examples we have presented are $GaCl_3$ and $FeCl_3$ in DCE. $GaCl_3$ is homogeneous at the onset of the titration, while $FeCl_3$ is largely insoluble. Beginning with the homogeneous solution of $GaCl_3$, we completed a titration from 0-4 equiv **1** in 10 μL increments and extracted the IR spectra (**Figure 3A**). Examination of the transitions that occur over the course of the titrations shows a formation of a single species in the carbonyl region at 1630 cm^{-1}, which grows from 0-1 equiv **1** (**Figure 3B**) [26,27]. When greater than 1 equiv **1** is added to the solution, no change in the peak at 1630 cm^{-1} occurs and unbound **1** is observed at 1714 cm^{-1} (**Figure 3C**). These results are consistent with the formation of **2**. When the same titration is performed with $FeCl_3$ (**Figure 3D**), a peak at 1636 cm^{-1} forms from 0-1 equiv **1**, which is consistent with **3** (**Figure 3E**). Importantly, the mixture becomes homogenous once 1 equiv **1** is achieved. When the titration proceeds beyond 1 equiv **1**, unbound **1** is observed at 1714 cm^{-1}, **3** decreases in intensity, an isosbestic point resolves at 1648 cm^{-1}, and a new peak at 1663 cm^{-1} forms.

Using the titration IR data, the equivalents of analyte used can be employed to perform Component Analysis of the solution interactions (**Figure 4**). To account for dilution, we can employ a normalization with respect to volume of the Beer-Lambert equation (eq. 1):

$$AV = \varepsilon l n \quad (1)$$

where 1) both absorbance (A) and volume (V) are measurable terms; 2) molar absorptivity (ε) and pathlength (l) are constant, allowing 3) number of moles (n) to be examined. The normalized absorbance can easily be computed in a spreadsheet (**Figure 4B,D**), and then this term can be plotted against equivalents of analyte. In **Figure 4C**, we can see that the signal for **2** increases linearly with respect to **1** until 1 equiv, at which point the signal for **1** increases linearly and **2** is unchanged. In **Figure 4F**, we see a similar linear increase in the signal of **3** to 1 equiv **1**, followed by the presence of **1** beyond 1 equiv added. However, we also observe a linear decrease in the intensity of **3,** and we observe less **1** than we should, assuming similar behavior to $GaCl_3$.

Yet more information is available from the IR data for the titration of $FeCl_3$ with **1**. The maximum amount of **3** that can form is defined by the amount of $FeCl_3$ added (C_{MAX} = 2 mmol $FeCl_3$ in the example titration). We know the amount of **1** we add to the flask (C_{ADD}), and we can measure the amount of unbound **1** we observe at 1714 cm^{-1} (C_{OBS}) and the amount of **3** we observe at 1636 cm^{-1} (C_{COORD}) using Beer-Lambert relationships. Lastly, we know we cannot account for all of the **1** added to the flask as free **1** or **3**, indicating that some **1** is not detected (C_{ND}). We can combine these terms for **1** in the following mass balance (eq. 2):

$$C_{ADD} = C_{OBS} + C_{COORD} + C_{ND} \quad (2)$$

We can use the titration data to calculate the values of these terms in each IR spectrum generated during the titration (**Figure 5B**). With these values, we can plot the amount of **1** missing (C_{ND}) as a function of the amount **3** consumed (C_{MAX}-C_{COORD}) to determine if there is a correlation (**Figure 5C**). This correlation is consistent with 3 equiv **1** consuming 1 equiv **3**, which may form a complex similar to **4**. We have obtained further support for this number of attached ketones via examination of solution conductivity, which is consistent with one or more of the chlorides being displaced to the outer sphere of Fe(III), and X-ray crystallography of an analogous structure with benzaldehyde[12]. However, it is likely that there is a mixture of different types of highly-ligated structures that are formed in solution, as is indicated by our non-whole number slopes in our consumption analysis in **Figure 5**, and the crystal structure we observe may simply be the one complex that precipitates.

In addition to the interactions between two species, this method can be used to probe competitive interactions (**Figure 7**). By establishing the formation and spectral properties of **3** (**Figure 7A**) and **5** (**Figure 7B**), the competition of carbonyls for access to the Lewis acid can be observed. By preforming **3** in solution, we can examine how **6** displaces **1** (**Figure 7C**). When we probe this system, we see that as we add **6** to **3**, not all **6** binds to $FeCl_3$. However, we do observe the consumption of **3** with concomitant presence of **1**, as well as the formation of **5**.

Using this type of competition experiment, we have been able to simulate the state of $FeCl_3$ as a catalyst in carbonyl-olefin metathesis (**Figure 8**). We previously demonstrated that at low turnovers, carbonyl-olefin metathesis operates via the primary cycle in **Figure 8B**[28]. Substrate **7** interacts with $FeCl_3$ to form complex **9** as the resting state of the cycle. Complex **9** then undergoes turnover-limiting [2+2]-cycloaddition to form oxetane complex **10**. Retro-[2+2] yields cycloalkene product **8** and **3**, which in turn must have the molecule of **1** displaced by a molecule of **7**. However, as the [**1**] increases, **3** is converted to complex **4**. Coordinatively saturated **4** then either

sequesters $FeCl_3$ or is catalytically competent, resulting in a parallel cycle via ketone complex **11** and oxetane complex **12**.

In conclusion, the utilization of in situ IR to monitor the titration of Lewis acids with carbonyl compounds allows chemists to gain insight into Lewis acid/base solution interactions under synthetically relevant conditions. Not only can this technique be employed to identify discrete structures, but it can be employed to observe the transition of one discrete species into another, as well. Findings from this method have been utilized to propose the mechanism of other metathesis reactions[29]. We are currently using data gathered via this method to facilitate the reactivity of recalcitrant substrates in carbonyl-olefin metathesis, as well as to develop new forms of metathesis reactions. Lastly, the competitive interactions between substrate carbonyls and product carbonyls likely impact other Lewis acid-catalyzed reactions. We are employing this method to examine these other catalytic regimes.

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Figure

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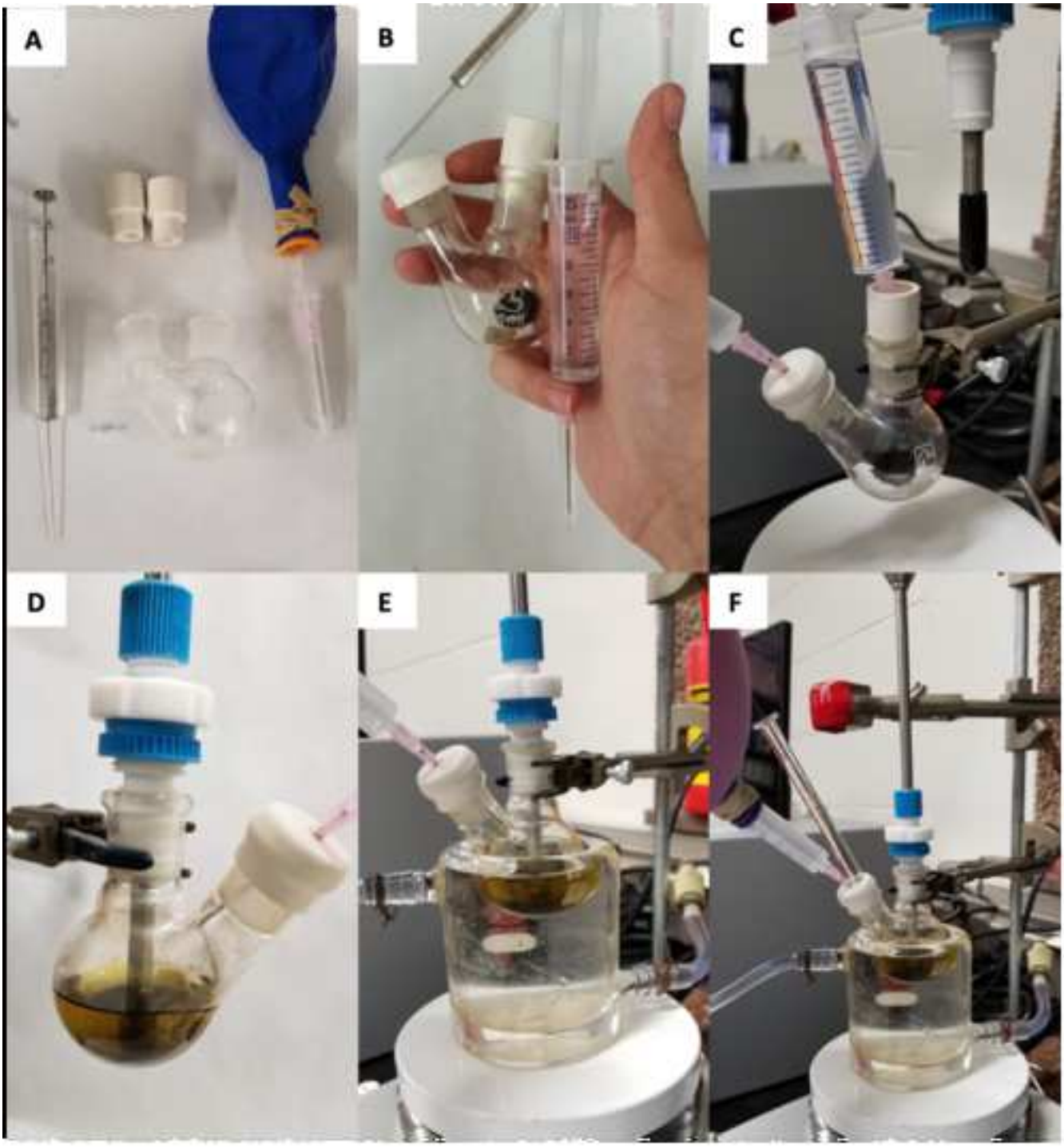

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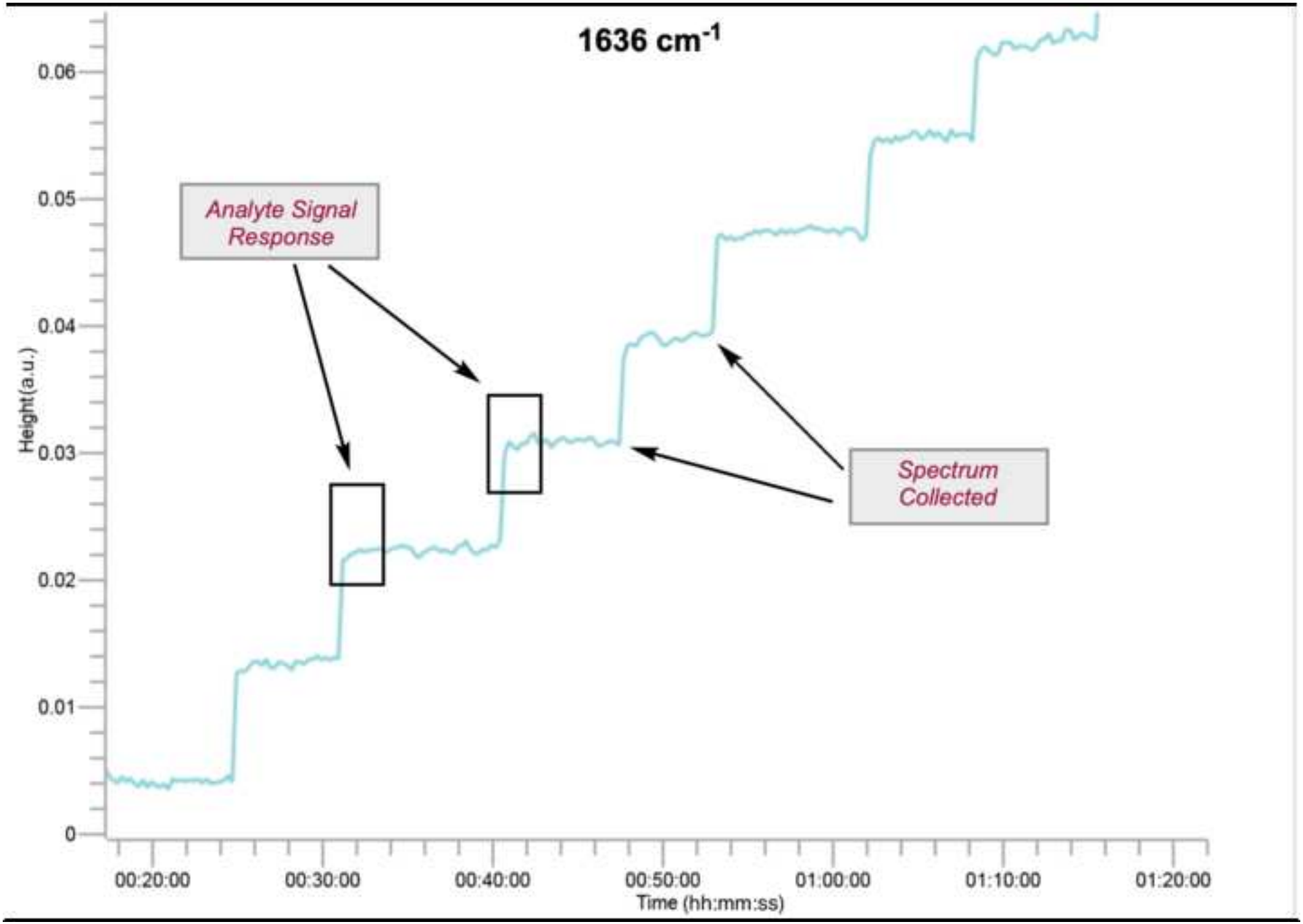

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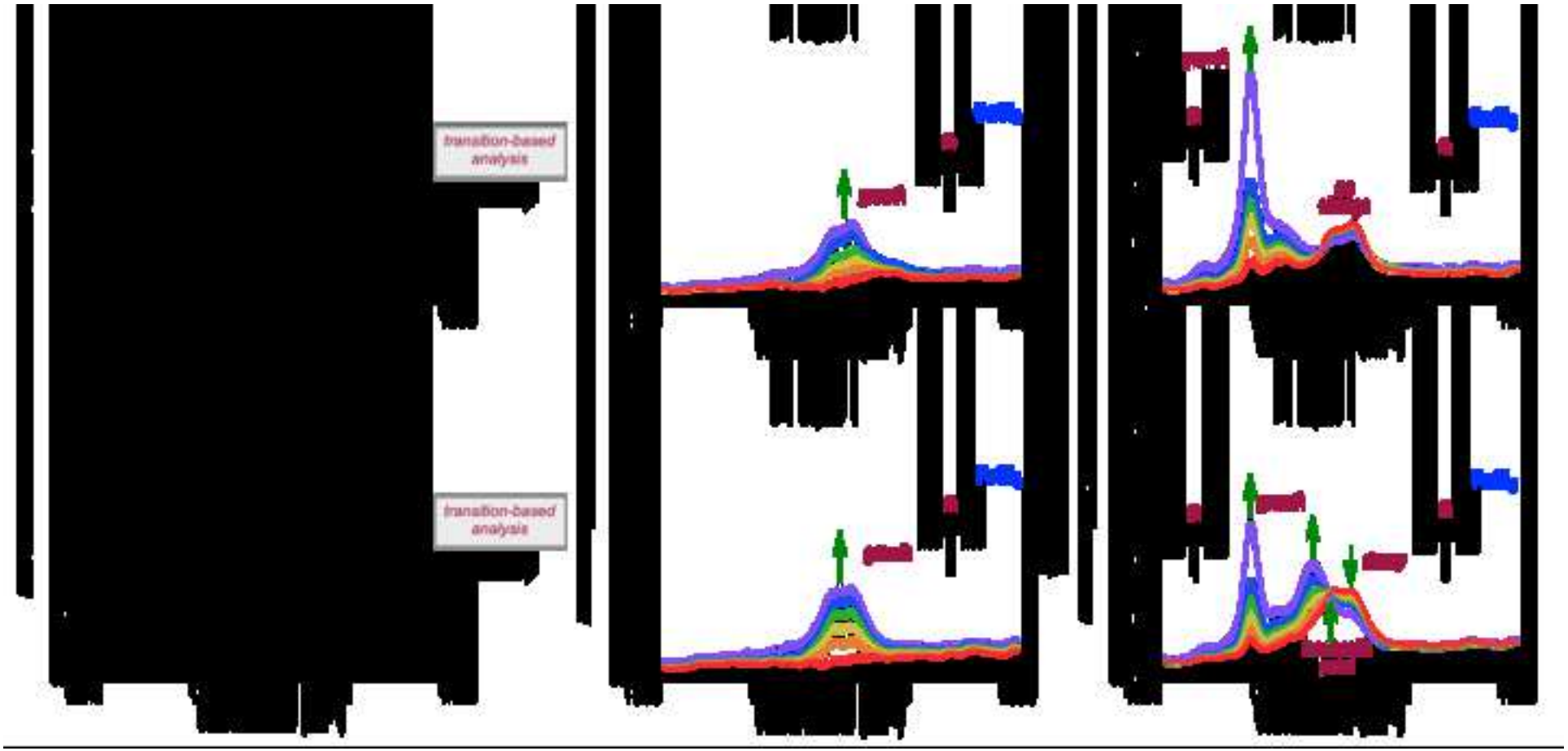

Figure

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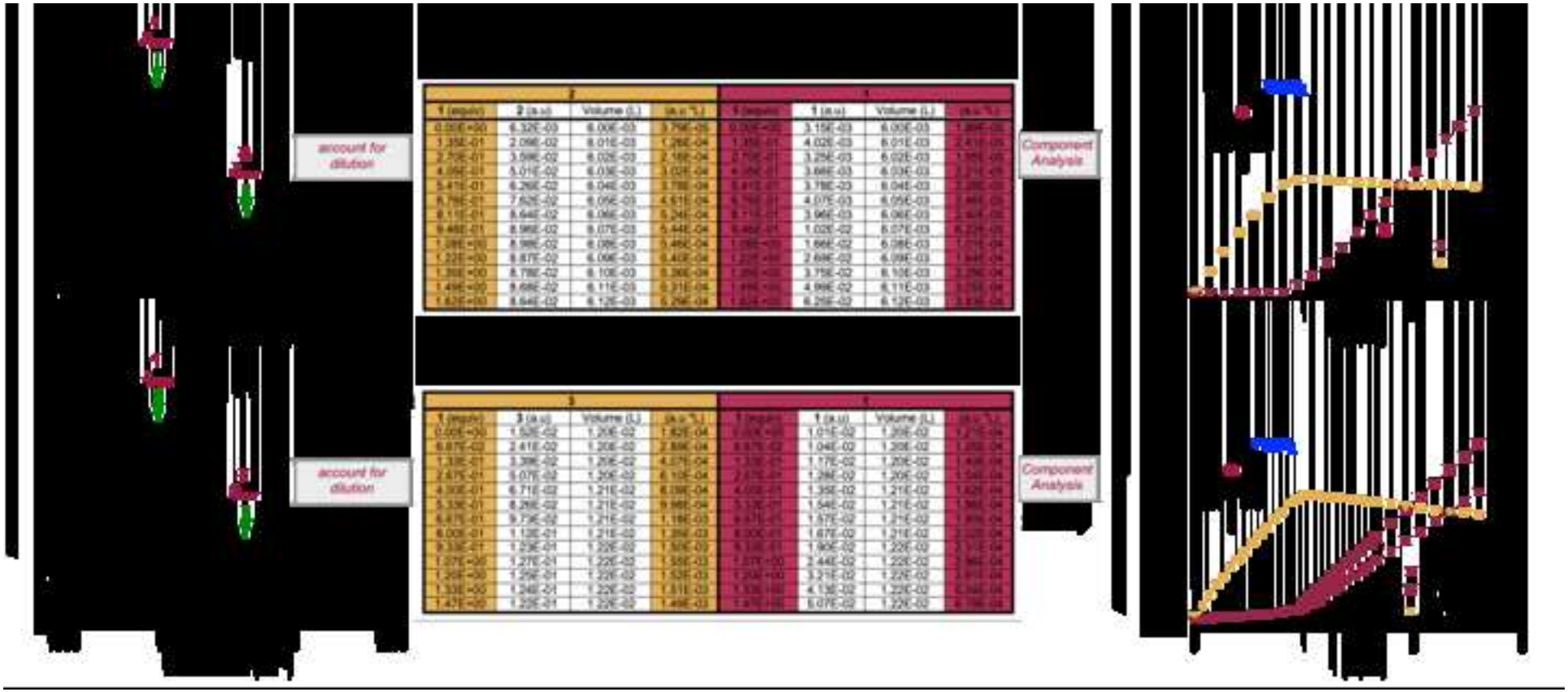
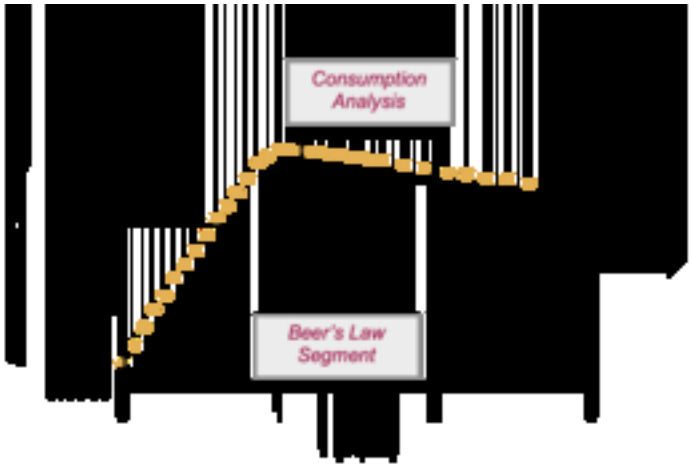
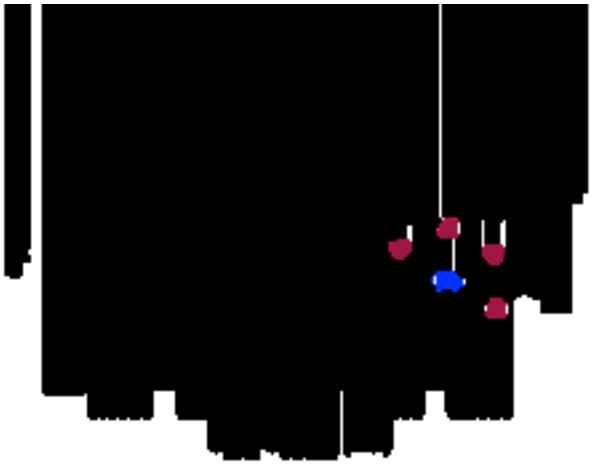


Figure

Click here to access/download;Figure;Figure5.psd



C_{COORD} (moles)	$C_{MAX} - C_{COORD}$ (moles)	C_{ADD} (moles)	C_{OBS} (moles)	C_{MD} (moles)
0.00176	**0.00024**	0.00243	0.00027	**0.00040**
0.00176	**0.00024**	0.00256	0.00037	**0.00043**
0.00175	**0.00025**	0.00270	0.00047	**0.00048**
0.00174	**0.00026**	0.00282	0.00058	**0.00050**
0.00172	**0.00028**	0.00296	0.00068	**0.00057**
0.00171	**0.00029**	0.00310	0.00077	**0.00062**
0.00169	**0.00031**	0.00325	0.00088	**0.00068**
0.00169	**0.00031**	0.00338	0.00100	**0.00069**
0.00166	**0.00034**	0.00365	0.00119	**0.00080**
0.00162	**0.00038**	0.00392	0.00139	**0.00091**
0.00159	**0.00041**	0.00419	0.00159	**0.00101**
0.00157	**0.00043**	0.00448	0.00179	**0.00112**
0.00154	**0.00046**	0.00472	0.00200	**0.00118**
0.00153	**0.00047**	0.00503	0.00222	**0.00128**
0.00149	**0.00051**	0.00523	0.00241	**0.00133**
0.00147	**0.00053**	0.00557	0.00260	**0.00150**
0.00145	**0.00055**	0.00585	0.00280	**0.00160**
0.00142	**0.00058**	0.00609	0.00299	**0.00168**



Figure

Click here to access/download;Figure;Figure6.psd

Figure 7

Click here to access/download;Figure;Figure 7.psd

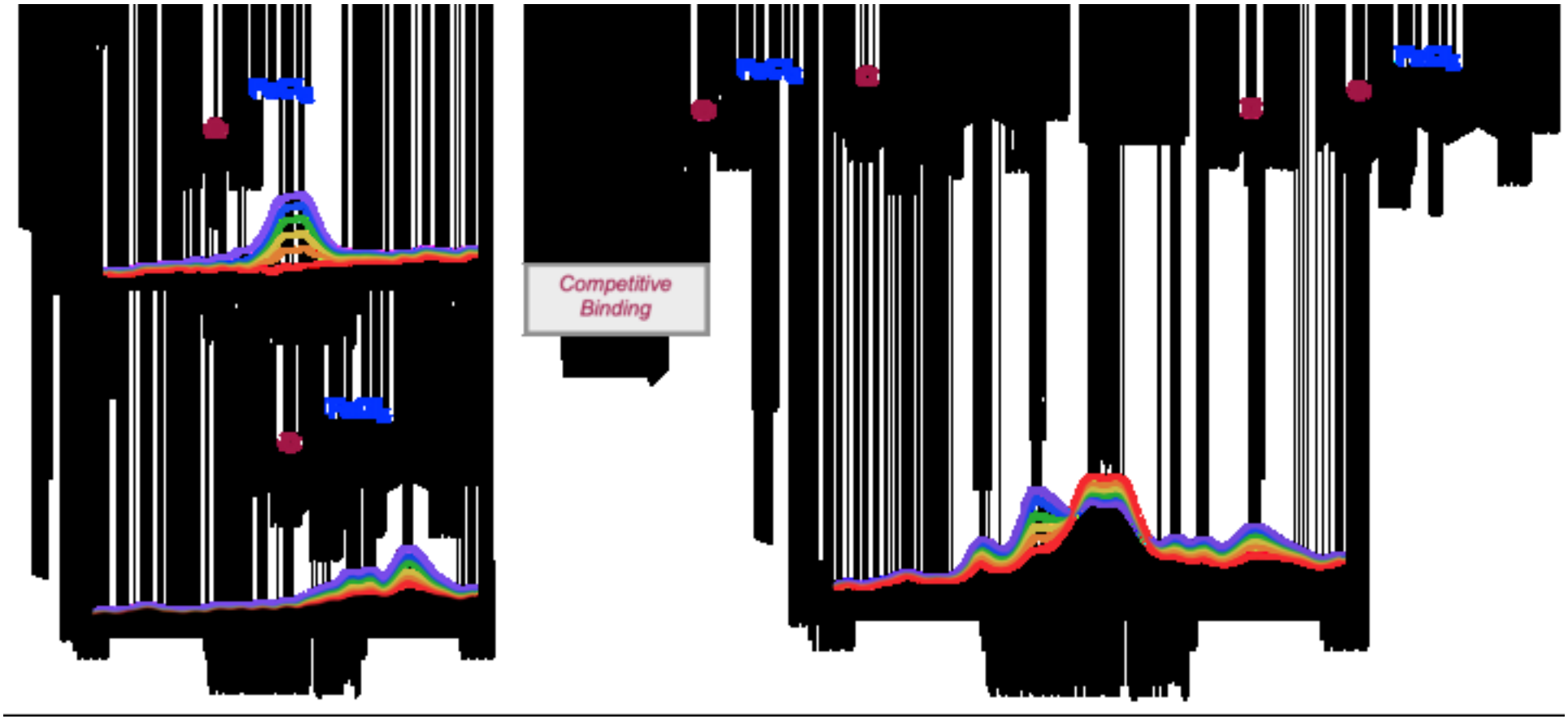
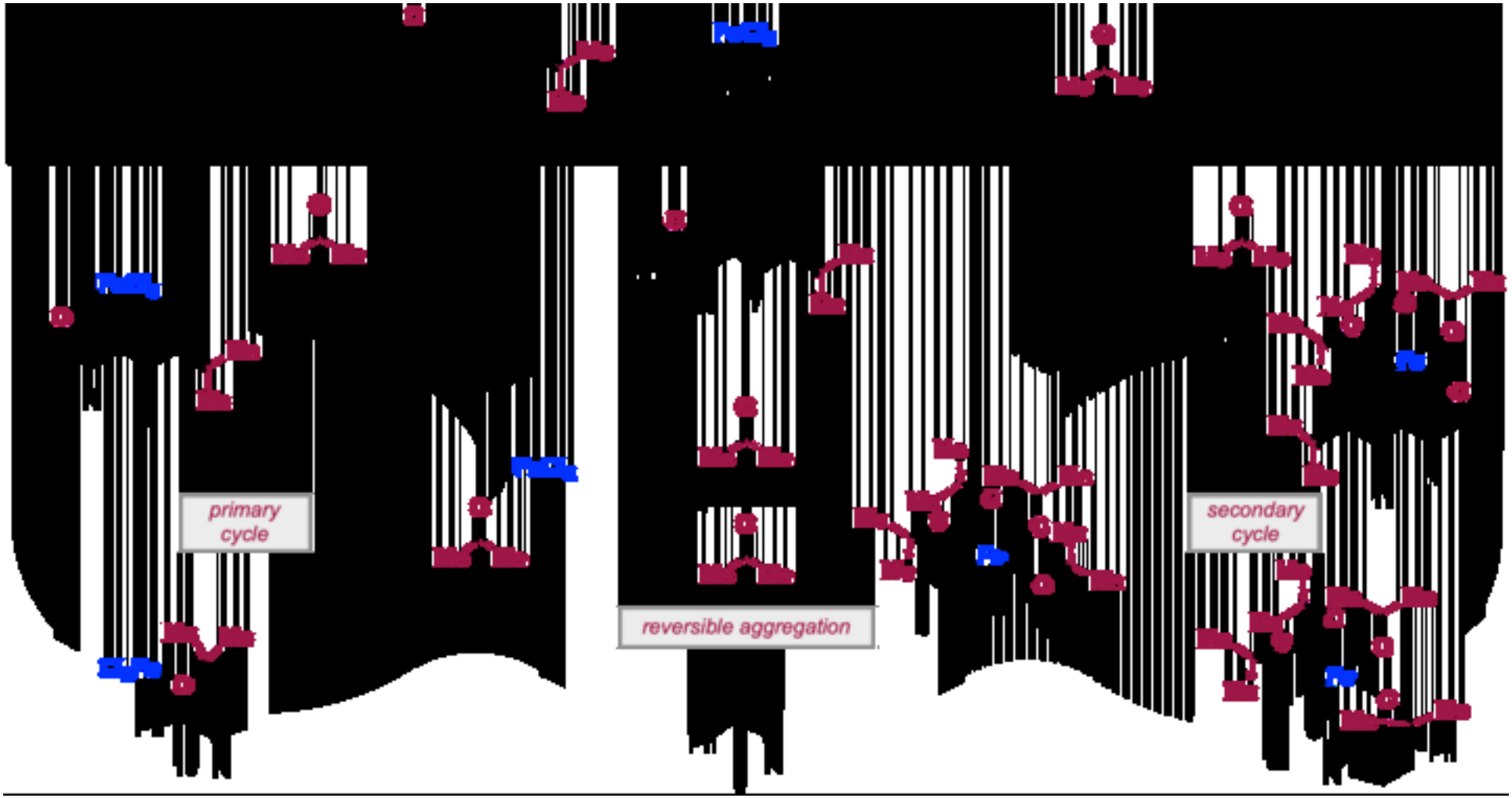


Figure 8

Click here to access/download;Figure;Figure 8.psd



Name of Material/ Equipment	Company	Catalog Number	Comments/Description
Acetone	BDH	BDH1101-19L	Dried over potassium carbonate
Balloon	VWR	470003-408	Round Balloons, Assorted Colors, 9" dia.
Detector LN2 RiR15	Mettler Toledo	14474603	
1,2 Dichloroethane	Beantown	223375-2.5L	Dried over 3Å molecular sieves
Gallium (III) Chloride	Beantown	127270-100G	anhydrous ≥99.999% (trace metals basis)
25 µL glass syringe	Hamilton	80285	
Inert Argon Gas	Airgas		Ultra High Purity
Iron (III) Chloride	Sigma Aldrich	157740-100G	Reagent Grade, 97%
100-mL Jacketed Beaker	AceGlass	5340-03	
3Å Molecular Sieves	Alfa Aesar	L05335	
25-mL 2 neck flask	CTechGlass	FL-0143-003	
18G Needle	BD Biosciences	305196	Needles with Regular Bevel, 38.1 mm (11/2'')
Potassium Carbonate	Sigma Aldrich	60109-1KG-F	Anhydrous
Prism 8	GraphPad		Mathematical Processing Software
Probe DST 6.35 x 1.5m X 203 DiComp	Mettler Toledo	14474510	*in situ* IR probe
Rice Stir Bar	Dynalon	303495	Diameter: 3 mm (1/8 "), Length: 10 mm (3/8'')
14/20 Rubbber Septa	VWR	89097-554	
5-mL Syringe	AIR-TITE	53548-005	HSW Norm-Ject Sterile Luer-Slip Syringes, Air-Tite
10-mL Syringe	AIR-TITE	53548-006	HSW Norm-Ject Sterile Luer-Slip Syringes, Air-Tite
System ReactIR 15	Mettler Toledo	1400003	*in situ* IR system
Thermostatic Bath	Haake		Haake A82

James J. Devery, III
Assistant Professor
Department of Chemistry and Biochemistry
1068 West Sheridan Road
Chicago, IL 60660

Bing Wu, Peer Review Editor
Journal of Visualized Experiments
1 Alewife Center #200
Cambridge, MA 02140

October 7th, 2019

Dear Dr. Wu,

I am pleased to submit the attached revisions to our manuscript entitled "Characterizing Lewis Pairs Using Titration Coupled with ReactIR Spectroscopy" under consideration for publication as an article in the *Journal of Visualized Experiments*. Thank you very much for the opportunity to address the comments from the expert reviewers. We feel that we have been able to adequately address their concerns. Further, the resulting changes have improved the discussion in the manuscript. I have attached to this letter the reviewer comments as well as our response to them.

Submitted materials include the revised manuscript (in MS Word format), the revised manuscript with changes tracked (in MS Word format), this cover letter, along with eight Figures (in PSD format), the Table of Materials (in xls format), and the Author License Agreement. All authors have reviewed the contents of this revision and approved of its submission.

If you require any further information, I would be happy to provide it.

Best wishes,

James J. Devery, III, Ph.D.

Editorial comments:

1. Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues.

Response: We believe we have caught all errors at this time with the revised submission.

2. Please obtain explicit copyright permission to reuse any figures from a previous publication. Explicit permission can be expressed in the form of a letter from the editor or a link to the editorial policy that allows re-prints. Please upload this information as a .doc or .docx file to your Editorial Manager account. The Figure must be cited appropriately in the Figure Legend, i.e. "This figure has been modified from [citation]."

Response: We have cited the corresponding figures accordingly and have attached the appropriate explicit copyright permission.

3. Unfortunately, there are a few sections of the manuscript that show significant overlap with previously published work. Though there may be a limited number of ways to describe a technique, please use original language throughout the manuscript. Please check the iThenticateReport attached to this email.

Response: We have updated the corresponding sections that contained significant overlap with our previously published worked and have made the following changes:

INTRODUCTION:

The utilization of Lewis acids to activate substrates containing carbonyls is ubiquitous in organic synthetic methods[1–4]. The study of these interactions has relied on solid state X-ray crystallography, as well as *in situ* NMR spectroscopy[2]. Limitations of these techniques manifest from artifacts that arise from crystallization, or the inability to probe paramagnetic Lewis acids via NMR analysis. To overcome these issues, chemists have employed infrared (IR) spectroscopy to determine the exact structure of Lewis pairs. Further, IR has been utilized to determine Lewis acidity[4–9]. The Susz lab studied the solid-state interactions of Lewis acids and carbonyls in the stoichiometric regime. Utilizing IR in conjunction with elemental analysis, the Susz group was able to elucidate the structures of neat, 1:1 mixtures of Lewis pairs. This analysis provided a great deal of insight into structural ramifications of the interactions of simple carbonyl compounds with commonly utilized Lewis acids in the solid state, and of particular interest to our lab: $FeCl_3$[10,11]. We posited that we could add to the existing understanding of the interactions of these important Lewis pairs via an *in situ* method that examines synthetically relevant conditions.

ReactIR spectroscopy enables chemists to measure functional group specific reaction trends and profiles in real-time *in situ*, providing highly specific information about kinetics, mechanism, pathways, and the influence of reaction variables on performance. Using ReactIR spectroscopy, chemists can directly track reactants, reagents, intermediates, products and byproducts as their structures change over the course of the reaction. This tool provides critical information to chemists that facilitates the development of new compounds and the optimization of synthetic routes and new chemical processes.

Employing ReactIR spectroscopy as a detection method, we probed the substrates and intermediates that participate in the catalytic cycle of metal-mediated carbonyl-olefin metathesis[12]. The Fe(III)-catalyzed carbonyl-olefin metathesis process, developed by the Schindler lab, exemplifies a powerful method for the production of C=C bonds from functional groups utilized ubiquitously in the construction of complex molecules[13–15]. Since the original report, this

process has inspired a plethora of synthetic developments beyond the utilization of Fe(III)[16–25]. Importantly, this reaction requires that the Lewis acid catalyst differentiate between a substrate carbonyl and a product carbonyl for successful reactivity. To observe this competitive interaction under synthetically relevant conditions, we combined titration with the continuous observation provided by ReactIR.

We believe this method is of general importance to chemists studying carbonyl-centered reactions catalyzed by Lewis acids. This detailed video aims to help chemists apply this technique to their system of study.

4. For in-text referencing, please insert the superscripted text number before a comma or a period.
Response: We have corrected this error.

5. Please combine some short steps so that each step contains 2-3 actions.
Response: We have corrected this error.

6. The highlighted protocol steps are over the 2.75 page limit (including headings and spacing). Please highlight fewer steps for filming.
Response: **We have corrected this error.**

7. Please do not abbreviate journal titles for references.
Response: We have corrected this error.

8. Please sort the items in alphabetical order according to the name of material/equipment.
Response: We have corrected this error.

Reviewers' comments:
Reviewer #1:
Manuscript Summary:
This manuscript must be revised and added more information before publication.

Major Concerns:
1. Reviewer can not find the useful of this manuscript. Author needs to add the discussion about the real application, for instance author should try other kinds of Lewis acids more than these.
Response: We have studied two Lewis acids that have been employed to catalyze carbonyl-olefin metathesis reactions: both ring-closing, and ring-opening metathesis. The $GaCl_3$ system offers an example of simple complexation (i.e. 1:1 complexation); whereas, the $FeCl_3$ system offers an example of more complicated complexation (i.e. highly-ligated complexes like complex 4). These examples provide a foundation for the types of interactions that could be observed for other Lewis acid/carbonyl systems. The extension of this analysis method to other Lewis acids would merely provide additional examples of the same displayed phenomena. Additionally, the findings from this method have been utilized to propose the mechanism of other metathesis reactions (*Org. Lett.* **2019**, *21*, 8132). **This citation was published while our manuscript was under review. We believe it is appropriate to include it in the conclusion, so we have added the following sentence to the last paragraph: "Findings from this method have been utilized to propose the mechanism of other metathesis reactions."**

2. Why author select only both Lewis acid. I think author needs to try strong Lewis acid as well if possible.

Response: We focused on $GaCl_3$ and $FeCl_3$ due to their ability to catalyze the carbonyl-olefin metathesis reaction that is of interest to our group, as stated in the introduction. Furthermore, $FeCl_3$ is one of the strongest Lewis acids routinely used, with only $AlCl_3$ being stronger (*JACS,* **2017**, *139*, 10832; *Chem. Rev.* **1969**, *69*, 251; *Chem. Rev.* **1978**, *78*, 1)**. We have also previously reported that when a stronger Lewis acid, $AlCl_3$, is employed, it does not facilitate the carbonyl-olefin metathesis reaction.**

3. Did author consider about the reduction of FeCl3 to FeCl2? Please explain on this reason
Response: **We did consider this electron transfer a possibility. We previously reported electron paramagnetic resonance spectroscopy studies that show no change in the oxidation state of Fe(III) either during the metathesis reaction, or when simply complexed with acetone.** (*JACS*, **2017,** *139*, 10832).

4. Ketone or Carbonyl groups have several types. Here, because wavenumber of carbonyl groups have several positions, author should consider more than these 2 types.
Response: We have shown interactions of a simple aliphatic ketone, a simple aromatic aldehyde, and a complex aromatic ketone with two different Lewis acids. We have also previously studied the interactions of a simple aromatic ketone with $GaCl_3$ and $FeCl_3$. (*JACS*, **2019**, *141,* 11870). **These precedents showcase a simple interaction between the carbonyl of the titrant and $GaCl_3$ as well as a complicated interaction between the simple titrants and $FeCl_3$. We have also included a competition study between a simple aliphatic ketone and a complex aromatic ketone to illustrate the competitive interactions between Lewis bases. Additional ketones, aldehydes, and esters would provide analogous data, and not provide additional insight. We believe that these examples showcase the capability of this analysis to identify the solution interactions between simple carbonyls and Lewis acids, and as these examples are relevant to carbonyl-olefin metathesis, we have shown its extension to aid in mechanistic investigations.**

5. If the real analysis has many functional groups (in the case of Complicated), how your research can apply it? Please discuss on this.
Response: We have included competition studies between two different carbonyl-containing compounds to elucidate their respective binding affinities with these Lewis acids. This analysis involves fairly complicated IR spectra (Figure 7), where we observed at least 4-5 different carbonyl-containing species in solution, including native carbonyl compounds, Lewis acid/carbonyl pairs, and highly ligated compounds with both same ligand, and mixed ligand structures. We believe that additional complexity would obfuscate the fundamental observations that are possible via this method and make the work less accessible to the general audience of *JoVE*.

6. Author needs to explain on chemical mechanism such as electron density on carbonyl group and moving of electron.
Response: It is not clear what the reviewer is asking, as the electronic interactions of carbonyls and Lewis acids have been well-characterized in the literature. Further, as we have previously reported, the oxidation state of $FeCl_3$ is not changing. As a result, there is no electron movement in these systems. The Susz lab dedicated more than a decade of work measuring and calculating the interactions of a significant number of Lewis acids and bases. We have cited the relevant literature that corresponds to the examples presented.

However, this manuscript provided new technique and many interesting idea but it needs to be provided more details based on above comments. I also suggested author give more information about application, why have to use your research to solve problems.
Response: The application is to provide insight into the ground state structures that are possible in solution during catalytic mechanisms facilitated by the interactions of Lewis acids and bases, which

we state in the introduction. We show the direct application of these data in determining the operating mechanism of an important new reaction (*JACS*, 2019, *141,* 11870). Further, this work has been used as the basis of mechanistic proposals by other labs (*Org. Lett.* 2019, *21*, 8132). Because of the wide range of Lewis acid-catalyzed reactions that exist in the literature (References 1-4), we believe that this method can be widely applied to a broad range of mechanisms to support proposals.

Reviewer #2:
Manuscript Summary:
The activation of chemical functionalities with Lewis acids is a crucial process in organic chemistry and the quantitative measurements of the association of carbonyl compounds with Lewis acids is very useful tool for understanding the nature (structure, reactivity...) of the reactive intermediates and complexes involved in a catalytic cycle.

Major Concerns:
- I would be surprised that there are no UV-Vis studies on the association of carbonyl compounds with Lewis acids? The second line of the introduction should be certainly revised.
Response: We agree with the Reviewer that it is surprising that there are no UV/Vis studies on the interactions between carbonyls and Lewis acids. We have performed exhaustive searches through the literature and have been unable to find UV/Vis analyses on these types of interactions. The interactions between carbonyls and Lewis acids have been primarily observed through IR and/or NMR spectroscopy, as we have cited.

- In figure 3, the starting absorbance is -0.01 whereas the maximum is 0.04. Does this mean that the background was not performed correctly?
Response: We agree with the reviewer. Our original intent for Figure 3 was to show a live feed of raw data collection and only show the first 5 additions of acetone. An entire titration typically includes 39 or more additions. We apply a baseline correction after data collection across the entire spectra as is apparent in Figure 4, 5, and 7. However, we agree with the reviewer that this presentation could be confusing to a general reader and have updated Figure 3.

- The Job plot method is often used for determining the stoichiometry of donor-acceptor complexes, would that possible to use this method to confirm the stoichiometry in complex 4?
Response: **Unfortunately, the Job plot method cannot be applied to this system because $FeCl_3$ is moisture sensitive and therefore cannot be added incrementally to a reaction flask with our described setup. Additionally, $FeCl_3$ is insoluble in DCE as we have previously mentioned, which does not allow for a solution of $FeCl_3$ to be added incrementally. Lastly, the Job method requires all components to be homogeneous at all times.**

This question is linked to the fact that the authors mentioned on page 6/6 that the FeCl3 is largely insoluble in DCE, and I do not see in the protocol if this solution become homogeneous when acetone is added.
Response: We agree with the reviewer and apologize that we did not address this observation in the protocol initially. $FeCl_3$ becomes homogenous in DCE once 1 equiv acetone has been added. We have included these observations in the protocol as well as in the discussion and have highlighted below where these changes were made.

> 2.3 Under inert atmosphere, add Lewis acid to a flame-dried 25 mL 2-neck round bottom flask charged with a stir bar (Figure 2B). Seal the flask with rubber septa and attach an Ar-filled balloon to the flask. Add desired volume of anhydrous solvent via syringe (minimum 3 mL) (Figure 2C).
>
> Note: $FeCl_3$ is not soluble in DCE. $GaCl_3$ is soluble in DCE.

4.4 Repeat steps 4.1-4.3 until desired amount of analyte is added.

Note: $FeCl_3$ mixture becomes homogeneous once 1 equiv **1** is added and $GaCl_3$ mixture remains homogeneous regardless of amount of **1** added.

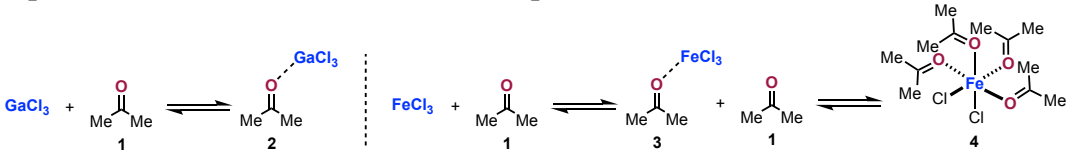
The updated Discussion is below:

DISCUSSION:

Under anhydrous conditions, Lewis acids can have a range of solubilities. The two examples we have presented are $GaCl_3$ and $FeCl_3$ in DCE. $GaCl_3$ is homogeneous at the onset of the titration, while $FeCl_3$ is largely insoluble. Beginning with the homogeneous solution of $GaCl_3$, we completed a titration from 0-4 equiv **1** in 10 μL increments and extracted the IR spectra (Figure 4A). Examination of the transitions that occur over the course of the titrations shows a formation of a single species in the carbonyl region at 1630 cm^{-1}, which grows from 0-1 equiv **1** (Figure 4B) [26,27]. When greater than 1 equiv **1** is added to the solution, no change in the peak at 1630 cm^{-1} occurs and unbound **1** is observed at 1714 cm^{-1} (Figure 4C). These results are consistent with the formation of **2**. When the same titration is performed with $FeCl_3$ (Figure 4D), a peak at 1636 cm^{-1} forms from 0-1 equiv **1**, which is consistent with **3** (Figure 4E). Importantly, the mixture becomes homogenous once 1 equiv **1** is achieved. When the titration proceeds beyond 1 equiv **1**, unbound **1** is observed at 1714 cm^{-1}, **3** decreases in intensity, an isosbestic point resolves at 1648 cm^{-1}, and a new peak at 1663 cm^{-1} forms.

- I do not understand why the association constants K of the equilibria shown in Figure 1 have not been determined. The manuscript and video will gain in interest if these equilibrium constants are determined. As the titration experiments are already done, and that the data are available, it is expected that the values of the equilibrium constant between 1 and GaCl3 and between 1 and FeCl3 should be calculated and given in the discussion section.

Response: We agree with the Reviewer that the determination of the equilibrium constants between acetone and $GaCl_3$ and between acetone and $FeCl_3$ would be beneficial. However, in the case of the equilibrium between 1 and $GaCl_3$, we observe no 1 in solution, so the equilibrium concentration of acetone is a small number and effectively 0 between 0-1 equiv acetone added. Once we get beyond 1 equiv acetone added, the concentration of the $GaCl_3$ is also a small number and effectively 0; therefore, the most we can say about the equilibrium constant is that it is a large value. In the case of the $FeCl_3$ system, we observe a similar issue with respect to 1, which is compounded by the insolubility of $FeCl_3$, having a concentration near 0. Alternatively, once we get beyond 1 equiv acetone added, we have proposed complex 4 as one possible structure that is found in solution (*JACS*, 2019, *141*, 11870); however, it is likely that there is a mixture of different types of highly-ligated structures that are formed in solution as is indicated by our non-whole number slope in our consumption analysis in Figure 6. Therefore, we cannot assume that the signal we observe around 1650 cm^{-1} is solely representative of the concentration of complex 4.



To address this comment, we have added the following language to the Discussion: "However, it is likely that there is a mixture of different types of highly-ligated structures that are formed in solution

as is indicated by our non-whole number slopes in our consumption analysis in Figure 6, and the crystal structure we observe may simply be the one complex that precipitates."

The manuscript is overall of very good technical quality and shows that IR methods and ReactIR spectroscopy can be used for performing quantitative evaluations of Lewis base interactions in the context of organic catalysis.

Interesting aspect such as competition experiments, investigations of catalytic cycles and determination of the structures of reactive Lewis acid-base adducts are investigated. This will attract the attention of organic chemistry, but also chemists interested in physical organic chemistry, catalysis, mechanistic and structural investigations and I would recommend to accept this manuscript and to proceed with the experimental part.

From: Veronica.Bracken@mt.com
Subject: RE: JoVE Language
Date: August 30, 2019 at 11:04 AM
To: jdevery@luc.edu

Jim
Please add yellow highlights as shown in excerpt below.

Also, we have some customers that use the term "ReactIR spectroscopy" if wanted to incorporate it into the script.

Everything else ok.

ReactIR enables chemists to measure functional group specific reaction trends and profiles real-time *in-situ*, providing highly specific information about kinetics, mechanism, pathways, a the influence of reaction variables on performance. Using ReactIR, chemists can directly tra reactants, reagents, intermediates, products and byproducts as their structures change over t course of the reaction. This tool provides critical information to chemists that facilitates t development of new compounds and the optimization of synthetic routes and new chemi processes.

-----Original Message-----
From: Devery, Jim <jdevery@luc.edu>
Sent: Friday, August 30, 2019 10:35 AM
To: Bracken Veronica AUTOCHEM <Veronica.Bracken@mt.com>
Subject: JoVE Language

Highlighted in yellow.

— —
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Author: Carly S. Hanson, Mary C. Psaltakis, Janiel J. Cortes, et al

Publication: Journal of the American Chemical Society

Publisher: American Chemical Society

Date: Jul 1, 2019

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Author(s):	Carly S. Hanson and James J. Devery, III

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