# In-Situ Reaction Monitoring: Tracking an Intermediate

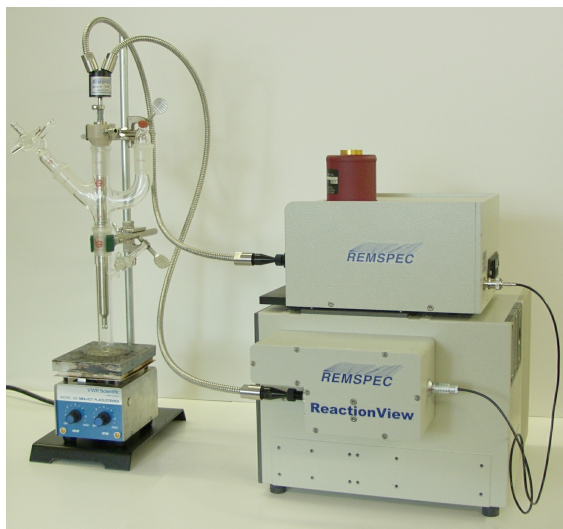**REMSPEC CORPORATION**

## *Mary Thomson*



Figure 1  Single-channel ReactionView System



**Compound A**

*DMF*          *[base in DMF]*

**Anion**

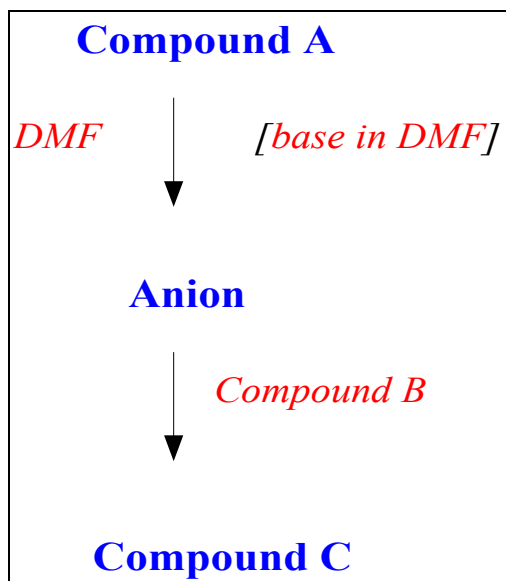*Compound B*

**Compound C**

Figure 2: Reaction outline (details proprietary)

A major advantage of real-time, *in-situ* reaction monitoring with a powerful spectroscopic technique like FTIR is the ability to detect and characterize reaction intermediates without the need to isolate them—something that may not be possible, in many cases.  Flexible IR-transmitting fiber bundles and a variety of sampling heads mean that this system is suitable for a wide range of reactor types and conditions.

### Monitoring a 2-Step Organic Synthesis:
### Anion formation and reaction in DMF

The reaction outlined in Fig. 2 was carried out at a customer's facility and involves research compounds, and some reaction conditions, that are not identified for proprietary reasons. The key reaction steps are the formation of an anionic intermediate which is subsequently converted into the desired product. Although the intermediate is relatively stable under the reaction conditions, it cannot be isolated without interrupting the overall reaction. Hence, direct spectroscopic monitoring is very useful in this case.

*Experimental*

A stirred glass reactor (250 mL capacity) was charged with dimethyl formamide (DMF, approx. 100 mL). A ReactionView mid-IR probe fitted with a high-temperature ATR head (zinc sulfide ATR crystal, overall probe diameter 15 mm) was fitted into one of the unused 24/40 ground glass fittings in the top of the reactor using a Teflon adapter. A background spectrum was obtained in air, then a solution of Compound A (starting material) in DMF (100 mL) was added. Data collection at 4 cm$^{-1}$ resolution, one spectrum every 30 sec, was begun. After 5 minutes, a solution of base in DMF (approx. 25 mL) was added. Data collection as continued for a total of 2 h.

*Results*
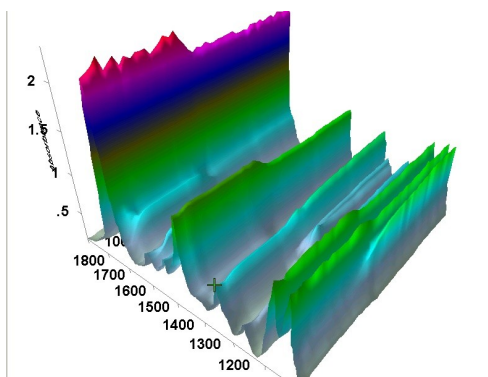


VizIR™ is the reaction-monitoring software used by ReactionView®. This screen shot, taken towards the end of the reaction, shows a 3D plot of the spectra collected during experiment. It is clear by visual inspection that the spectra are dominated by the solvent, but that several features in the spectrum grow, then diminish, while additional features develop more slowly.

When the range of the 3D display is changed, the time-based changes become easier to see. Absorbance/time trendlines can be added in real time for individual peaks that exhibit interesting behavior, either by using a visual "peak-picking" tool or by fitting peak models against complex spectral features. (All of these trendlines can be saved as text files for import into a spreadsheet.)
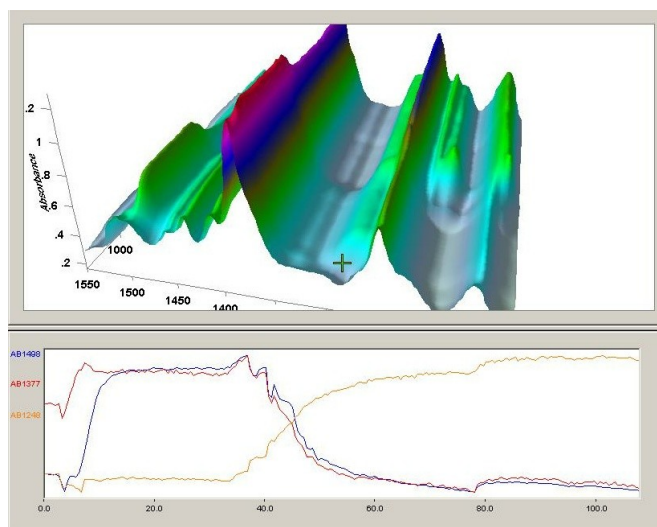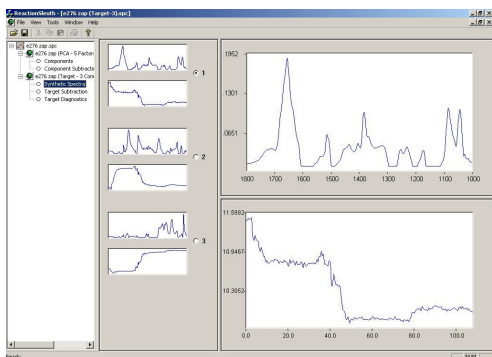
A PCA/Target Transform technique can be used to calculate "synthetic spectra" once the dataset is complete. A set of three spectra is shown, with the "loading" curve for each, showing changes in the contribution of each spectrum to the dataset over time. The highlighted spectrum is the solvent, showing dilution effects in the loading.

The upper, blue, trace is a spectrum of liquid DMF, the solvent in this reaction. The lower, red, trace is one of the synthetic spectra calculated from the reaction data set. The spectra are not identical, but there is sufficient similarity to conclude that the solvent spectrum has been identified in the reaction data.
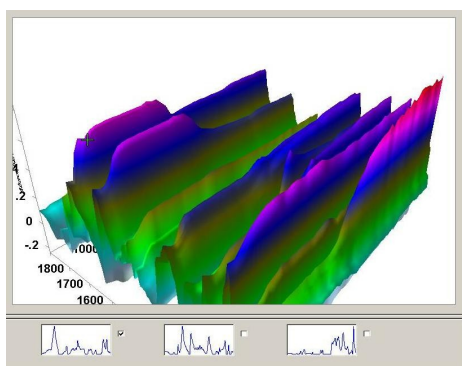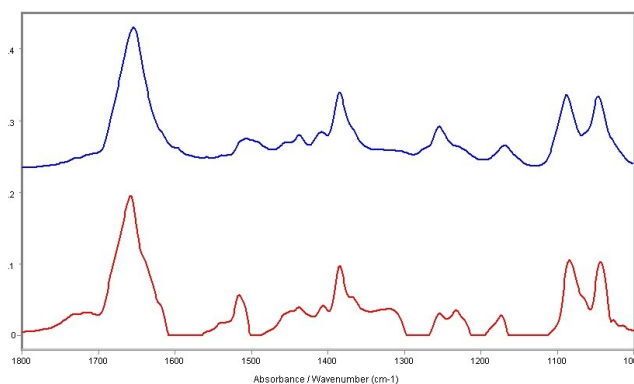




When the synthetic spectrum that corresponds to the solvent is subtracted from the dataset, the behavior of the intermediate and the product becomes clearer.

The result is a subtracted data set in which the contribution of the solvent to each individual spectrum is based on the calculated loading. This is usually more useful than a real-time subtraction based on the actual solvent spectrum, which often results in large negative features in the dataset.

The blue and cyan lines in this graph represent the absorbance at 1224 cm$^{-1}$ (blue) and 1500 cm$^{-1}$ (cyan).

The red and magenta lines represent the loading, or proportional contribution over time, of the synthetic spectra shown below. It is clear that trendlines based on simple absorbances are very similar to those calculated by the PCA/ITTR method.



♦ AB1224   ▼ Loading2   ▲ Loading3   ► AB1500



Synthetic spectrum 2

Synthetic spectrum 3
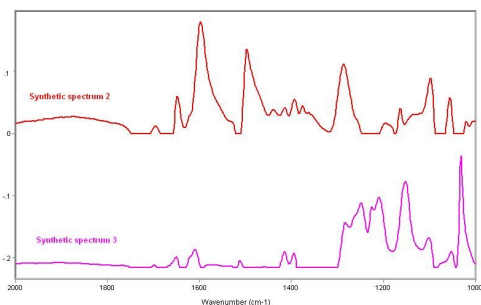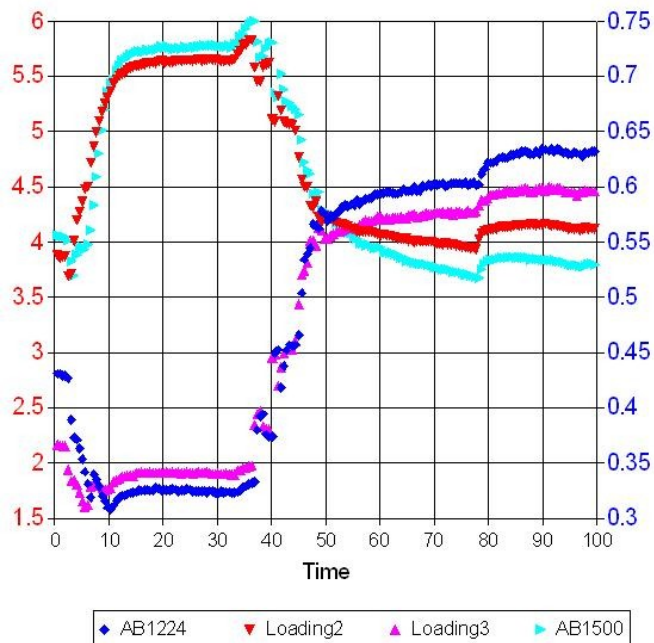
Based on the calculated loadings, these two synthetic spectra represent the transient intermediate (red trace) and the product of the reaction (magenta trace). Comparison with spectra of the pure compounds would be required to confirm the correctness of the calculated spectra.

*Discussion*

In-situ mid-IR spectroscopy with ReactionView® opens up a chemical "eye" inside a reactor to measure changes in chemical composition directly and in real time. The method is particularly useful for studying transient intermediates, as in this case, and for reactions that require a controlled atmosphere. Simple absorbance-versus-time trendlines can be generated in real time and compare very well with calculated loadings for synthetic spectra calculated from the complete data set.

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