On-the-fly reaction monitoring using correlated spectroscopies

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In situ spectroscopy is an established tool for the quantitative characterization of chemical reactions of known species. However, the analysis is usually based on characteristic spectral features of known chemicals in the mixture. Recent automated synthesis approaches can generate sufficient real-time spectroscopic data to enable instant qualitative and quantitative characterization of all chemicals in a reactor, including unknown intermediates and novel products. We use a robotic flow chemistry system equipped with in situ (near) infrared, UV-Vis, as well as online nuclear magnetic resonance spectroscopies to investigate the formation and exchange of imine compounds without intermediate workup. The spectra of the reaction mixtures are processed in real time using a mix of established and novel chemometric methods. Using the spectra of known compounds, we can extract the features of formed (intermediate) products without the typical reaction workup and compare them to theoretical spectra of likely products calculated using methods of quantum chemistry. By incorporating intermediate products in our analysis, we can optimize individual steps in multistep reactions. The ability to identify unknown compounds formed during the reaction will allow the move from in situ characterization of chemical reactions to in situ control, which leads to higher yields, fewer by-products, and accelerates closed-loop autonomous chemical experimentation.