MRR: An Emerging Tool for Online Stereoselective Analysis

OVERVIEW

In-process monitoring of stereoselective chemical reactions is a challenging task for conventional analytical techniques. Spectroscopy-based tools, such as UV-VIS, NIR, FTIR, Raman, and fluorescence are well suited for in-process analysis but fail to provide stereoselective information. Conventional stereoselective techniques, such as chiral chromatography and NMR, require skilled operators and/or frequent human interventions, which makes these techniques not practical for automated in-process monitoring.

Molecular Rotational Resonance (MRR) spectroscopy combines stereoselectivity and online capability with ease of use and reliability of quantitative results. MRR spectral features are numerous, extremely sharp, and precisely reflect molecular geometry.[1] As such, MRR enables monitoring of chiral and achiral crude reaction mixture constituents directly, and with unprecedented chemical specificity.[2] As a result of its performance metrics, MRR can likely become a valuable tool for developing next-generation quality control strategies aligned with Process Analytical Technology (PAT) and Quality-by-Design (QbD) initiatives.

MRR ANALYSIS EXAMPLE

This example demonstrates that MRR can completely fulfill the in-process reaction monitoring requirements for Ru/C catalyzed stereoselective hydrogenation of artemisinic acid (AA) to dihydroartemisinic acid (DHAA). Specifically, MRR can resolve and quantify not only the starting material (AA) and product (DHAA) but also both side-products such as DHAA's epimer and the tetrahydroartemisinic acid (THAA, overreduction byproduct) directly, without chemical separation or chemometrics.

MRR Selectivity. Figure 1 compares MRR[2] and Raman[3] spectra of the DHAA synthesis crude reaction mixtures. Even though Raman can monitor the reaction progress, this technique cannot resolve the side-products (DHAA's epimer and THAA) to fully characterize the reaction. In contrast, MRR enables direct interference-free quantitation of all four crude reaction mixture constituents including starting material, product, and both side-products.

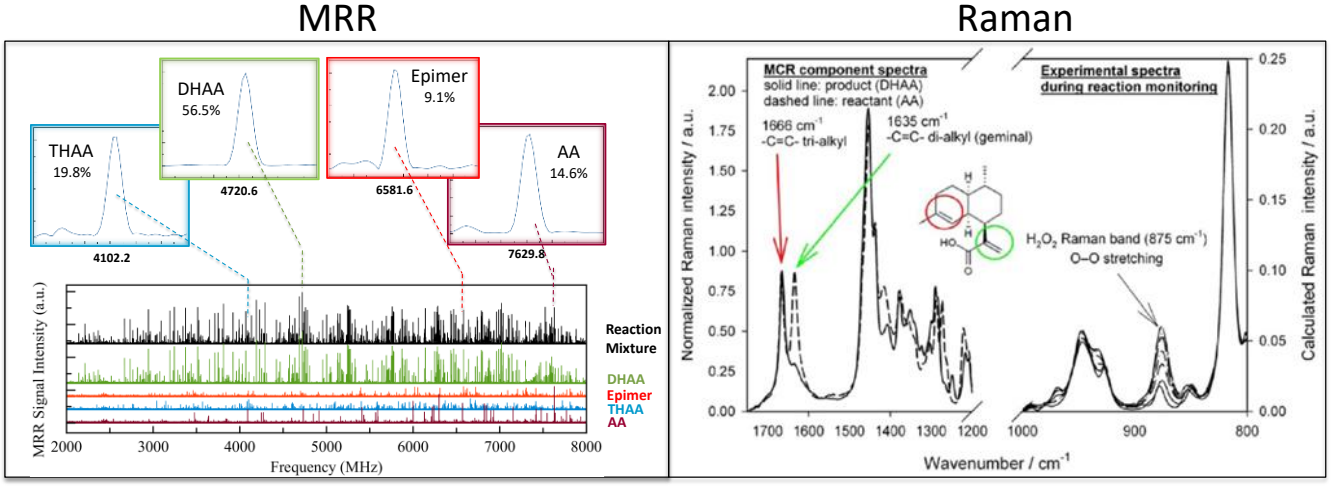

Figure 1. Left Panel. Broadband MRR spectra of individual reaction species extracted from the DHAA crude reaction mixture spectrum (black) without any use of reference standards or chemometrics.[2] As evident, MRR can analyze starting material (AA), product (DHAA, product's epimer, and the overreduction byproduct (THAA) directly.

Right Panel. Raman spectra of crude DHAA reaction mixtures.[3] Raman can monitor reaction progress but not the side-products.

In-Process MRR Measurements. Online and at-line stereoselective chemical reaction monitoring can be performed using an iso*MRR*™ instrument (Figure 2, left panel). This instrument measures narrow-band rotational spectra around pre-selected MRR transitions (Figure 2, central panel) to achieve automated operation and fast sample-to-sample cycle time (approximately 15 minutes). The targeted MRR frequencies for each analyte can be chosen either by using the BrightSpec spectral library, or by measuring the broadband spectra of pure components, or by extracting the spectra of pure components directly from a crude reaction mixture spectrum using the method demonstrated by Neill et al.[2]

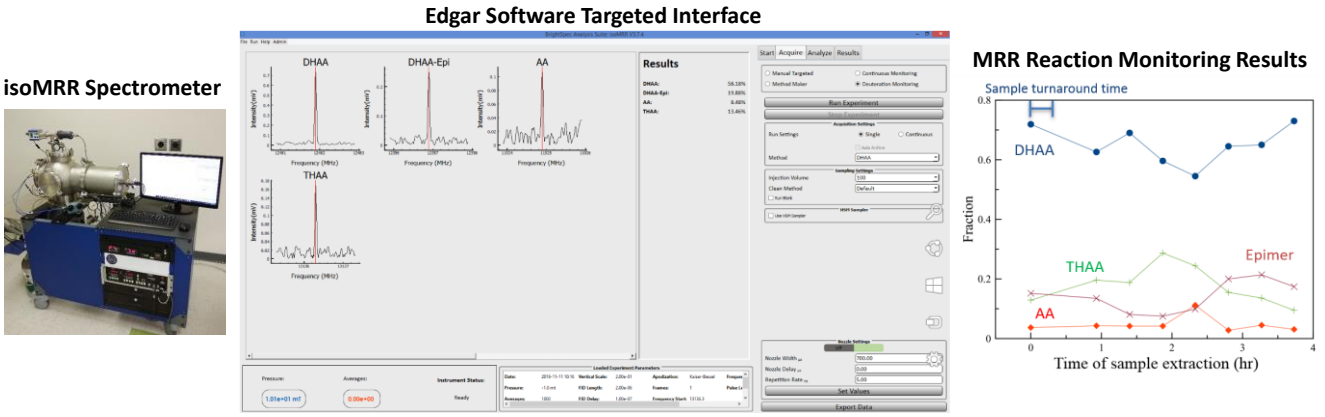

Figure 2. Left Panel: Picture of isoMRR instrument capable of online and at-line quantitative analysis of impurities in complex chemical mixtures including regioismers, diastereomers, enantiomers, dehalogenation species, isotopologues, and isotopomers.
Central Panel: Targeted MRR peaks of four constituents of DHAA crude reaction mixture measured 'as is' (8 seconds per analyte).
Right Panel: Online MRR reaction monitoring results.[2] Please see text for detail.

Figure 2 (right panel) shows DHAA synthesis reaction monitoring results obtained by online MRR. Concertation changes between the reaction constituents were deliberately initiated by changing the conditions in the reactor. MRR results are consistent with both these changes and offline ^{1}H-NMR data.[2]

In contrast to fully automated MRR analysis that requires only about 0.1 to 1 mg of analyte and takes only about 15 minutes, ^{1}H-NMR required a much larger sample and about 4 hours of labor to complete. In addition, due to a lack of characteristically-shifted proton for THAA, it was not possible to determine its concentration with ^{1}H-NMR directly. THAA analysis using HPLC with UV detector was also challenging due to THAA's saturated nature (data not shown).[2] In summary, MRR was not only the fastest and most convenient method utilized in this work but also the only method that was capable of quantifying all the reaction constituents directly.

CONCLUSION

The recently commercialized MRR technology enables direct stereoselective analysis in the online regime, thus bridging the current analysis gap that exists between other techniques. Benefits of MRR implementation include ability to easily discriminate between all types of isomers and isotopologues, ability to perform chiral and achiral analyses in one run, and no need for chemometrics or standards. As a result, MRR can likely streamline process monitoring and contribute to developing the next generation of PAT and QbD-based quality control strategies.

REFERENCES

1. G.B. Park and R.W. Field, *"Perspective: The first ten years of broadband chirped pulse Fourier transform microwave spectroscopy"*, J. Chem. Phys., **2016**, *144*, 200901.
2. J.L. Neill et al., *"Online Stereochemical Process Monitoring by Molecular Rotational Resonance Spectroscopy"*, Org. Process Res. Dev., **2019**, *23 (5)*, pp. 1046-1051.
3. M.P. Feth et al. *"Pilot Plant PAT Approach for the Diastereoselective Diimide Reduction of Artemisinic Acid"*, Org. Process Res. Dev., **2013**, *17 (2)*, pp. 282-293.

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