FAST CHIRAL MONITORING IN A CONTINUOUS PHARMACEUTICAL SYNTHESIS BY MOLECULAR ROTATIONAL RESONANCE SPECTROSCOPY

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We present the successful application of MRR spectroscopy in the microwave region to monitor the output of a continuous pharmaceutical synthesis. Microwave spectroscopy has an excellent capability to distinguish isomers and other structurally similar compounds, and techniques have been developed recently that are also sensitive to enantiomeric excess. A Balle-Flygare-style Fourier transform microwave spectrometer was employed as the detector in this study, along with a new solutions sampling interface that injects crude product solution directly from the reactor, bakes off the solvent, and volatilizes the analyte mixture for analysis. The reaction under study was the catalytic asymmetric hydrogenation of artemisinic acid to produce a stable intermediate in the synthesis of artemisinin, an important antimalarial.

The instrument is fully automated and consumes less than 1 mg of analyte in order to analyze the composition of 4 species with a detection limit of approximately 75 ppmw in the solution: the starting material, desired product, epimer of the product, and an overreduction byproduct that is not readily detectable by HPLC or NMR. This talk will describe the results of this study and prospects for future application in pharmaceutical process development.