

QUANTITATIVE DETERMINATION OF ENANTIOMERIC EXCESS BY MICROWAVE THREE-WAVE MIXING

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Microwave three-wave mixing is a rotational spectroscopy technique that can measure the difference between a pair of enantiomers and quantify a ratio between them where traditional rotational spectroscopy cannot. The measurement principle was shown in 2013 by Patterson, Schnell, and Doyle using a DC field to achieve the necessary state mixing [1] and was extended by Patterson and Doyle later that year to the three-wave mixing approach most commonly used now [2]. Grabow, also in 2013, has provided a description of the measurement in the intuitive language of NMR spectroscopy [3]. Despite the introduction of the technique in 2013, there has been little work to develop the method into a quantitative analytical chemistry tool. In this talk we focus on using this method for enantiomeric excess (EE) determinations. Because the chiral signal produced in this technique is proportional to the difference in the enantiomer populations (a value that is proportional to the total amount of sample present), it is necessary to reference the amplitude of the chiral signal to a quantity proportional to the total sample concentration – available from a “normal” rotational signal measurement. Furthermore, the method requires a sample of known EE for scale calibration – a significant limitation in analytical chemistry. The results from two measurement pulse sequences that provides total population calibration will be presented. Calibration curves for samples that cover a range of EE (gravimetrically calibrated) will be presented for isopulegol and menthone. The ability to obtain accurate EE determinations in a simple mixture using the calibrated measurement scheme is tested using two commercial samples of isopulegol that contain all eight stereoisomers produced in the citronellal cyclization reaction. The three-wave mixing technique can provide EE accuracy to about 5%, and this performance, especially for high enantiopurity samples, limits its applicability in many industry applications.

[1] D. Patterson, M. Schnell, and J.M Doyle, “Enantiomer-specific detection of chiral molecules via microwave spectroscopy”, *Nature* 497, 475- 478 (2013). [2] D. Patterson and J.M. Doyle, “Sensitive Chiral Analysis via Microwave Three-Wave Mixing”, *Phys. Rev. Lett.* 111, 023008 (2013). [3] J. Grabow, “Fourier Transform Microwave Spectroscopy: Handedness Caught by Rotational Coherence”, *Angew. Chem. Int. Ed.* 52, 11698-11700 (2013).