ISOTOPOMER DISTRIBUTION IN DEUTERATED ACTIVE PHARMACEUTICAL INGREDIENTS MEASURED BY MOLECULAR ROTATIONAL RESONANCE SPECTROSCOPY

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Molecular rotational resonance (MRR) spectroscopy is used to determine the distribution of deuterium isotopomers of varenicline produced in catalytic hydrogen isotope exchange of the active pharmaceutical ingredient (API) using Ni(I)-X complexes with bulky α-diimine ligands.[a] In this reaction, four hydrogen atoms on varenicline can be exchanged for deuterium, leading to 10 distinct isotopic forms of the API. The sensitivity of MRR spectra to mass distribution, via the principle moments-of-inertia, enables the spectral signatures of all 10 isotopomers to be resolved in the reaction product. The MRR spectrum of the deuterated API is measured from the crude reaction product (including the metal complex) using a 2-8 GHz chirped-pulse Fourier transform microwave spectrometer.[b] Two samples were analyzed that differed in reaction time: 8 hours (70 mg crude product) and 24 hours (40 mg crude product). The API is volatilized by direct heating to 175°C and the vapor is entrained in neon. Isotopomers are identified by comparing the experimental spectrum with MRR spectrum predictions of each isotopic species. Theoretical rotational constants of each isotopic species are calculated from a single quantum chemistry reference geometry (B3LYP D3BJ 6-311++G(d,p)) and then scaled using a comparison of the theoretical and experimental rotational constants of the normal isotopic species. For both samples, the average number of deuterium substitutions per molecule determined by MRR spectroscopy is in agreement with the mass spectrometry characterization. The relative abundances of the 10 isotopomers at 8-hour and 24-hour reaction times are modeled using a first-order kinetics model. This model indicates deuterium incorporation at the two chemically distinct reaction sites occurs at the same rate with a rate constant of 0.125/hr. The ability to rapidly monitor the isotopomer distribution is demonstrated using the BrightSpec IsoMRR instrument based on the cavity-enhanced Balle-Flygare instrument.[c]

[a] C. Zarate, et al., *J. Am. Chem. Soc.* **2019**, *141*(12), 5034-5044.

[b] C. Pérez, et al., *Chem. Phys. Lett.* **2013**, *571*, 1-15.

[c] T. J. Balle, W. H. Flygare, *Rev. Sci. Instrum.* **1981**, *52*(1), 33-45.