Features in selected area continuous rotation electron diffraction measurements that may be sensitive to molecular handedness of 3D crystals

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Considering that biological and synthetic reactivity of small molecule compounds differs between enantiomers, the confident determination of a chiral molecule's absolute configuration is of much importance to pharmaceutical and synthetic chemistry. By virtue of resonant scattering phenomena, which break Friedel symmetry in a diffraction pattern, X-ray crystallography remains the most well-established method for determining the absolute structure of a chiral, enantiopure molecular crystal. As 3D electron diffraction (3D ED) now enables atomic structure determination from crystals on the order of nanometers in size, circumventing the traditional X-ray crystallography bottleneck of growing macroscopic crystals, it is pertinent to study the extent to which information about molecular handedness might be extracted from electron diffraction. In this work, we quantify features in X-ray and electron diffraction intensities that might predict the confident resolution of a chiral crystal's absolute structure. Considering X-ray diffraction as a well-understood model to identify such qualities, we focus both on the magnitudes of intensity differences between Bijvoet pairs for diffraction data collected on a single crystal, and how these measured differences for commonly observed pairs of reflections correlate between diffraction collected on different crystals of either like or opposite hand. Our substrate scope includes crystals with a range of expected anomalous scattering. We assess the degree to which dynamical scattering might impact intensity differences between Bijvoet pairs in measured data at 200 and 300 keV. We also investigate the influence of parameters that may influence the degree of multiple elastic scattering, such as the thickness of the crystal, the scattering mean free path, and the incident wavelength of irradiation, on measured Bijvoet differences. To do so, we collect 3D electron diffraction data on large populations of nanocrystals of chiral, enantiopure substrates and separate data by enantiomer. For each crystal sampled, following diffraction data collection, we also obtain tilt series images to yield intermediate resolution tomograms from which crystal thickness can be estimated, in terms of the number of its elastic mean free path. We are sampling crystalline molecular substrates that vary in atomic composition and scattering cross-section, and collect data at a series of accelerating voltages across different TEMs. Ultimately, we aim to understand the relationship between experimental conditions or substrates and diffraction metrics that might predict accurate absolute structure prediction. If successful, we might understand when scattering differences observed for chiral crystals are meaningful and predictive of crystal chirality.