Crystal structure Determination of Small Molecules by 3D ED/MicroED

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Three-dimensional electron diffraction (3D ED), also known as micro-crystal electron diffraction (MicroED) has recently emerged as a promising method for crystal structure determination of small molecules[1,2]. The method complements existing methods by providing the opportunity to study crystals of small molecules too small for conventional single crystal X-ray diffraction, and too complex for powder X-ray diffraction. Recently, we have shown that 3D ED/MicroED is capable of (i) rapid structure determination at atomic resolution[1,3], (ii) discovering new polymorphs[4,5,10], (iii) studying polymorphism evolution[6,7], and (vi) performing phase analysis by high-throughput 3D ED/MicroED[8]. However, comparing to X-ray diffraction, 3D ED/MicroED is still in its infancy. Further optimization in experimental protocol and innovations in new software and hardware are required to make the method more robust and more accessible to structural chemists. At ACA 2023, I would like to present our latest developments in 3D ED/MicroED specimen preparation, data collection and data processing, as well as providing a future perspective of the method.

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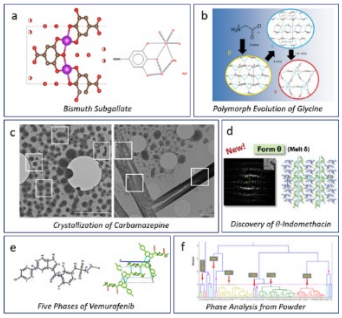

Figure 1

A summary of 3D ED/MicroED development and application in studying crystal structures of small molecules in our lab. a) structure determination of API bismuth Subgallate[9], b) Polymorphism evolution of glycine[6], c) Crystallization of carbamazepine[7], d) Discovery of indomethacin form θ, correcting a 47-year-old misunderstanding[5], e) Structure determination of five phases of vemurafenib directly from spherulites[10], and f) Phase analysis by high throughput 3D ED/MicroED[8].