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Electron diffraction in structural chemistry

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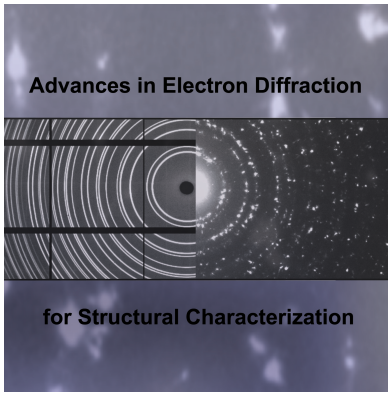
This article is part of the collection *Advances in Electron Diffraction for Structural Determination* and is gratefully dedicated to the memories of Arnold L. Rheingold (1940–2024) and George M. Sheldrick (1942–2025). Much like the particle-wave duality of electrons, they were twin epitomes of the theory and practice of crystallography and are deeply missed.

Keywords: electron diffraction; structural determination.



In 1925, de Broglie proposed that electrons have wave properties ('l'onde de phase qui, selon nous, doit être considérée comme une partie constitutive de l'électron') and proceeded to prove that the Bohr law for electrons in atoms proceeds naturally ('Ce beau résultat dont la démonstration est si immédiate quand on a admis les idées') from treating the atomic orbitals as standing waves (de Broglie *et al.*, 1925). In the same year, citing de Broglie's conclusions and preliminary scattering experiments by Davisson and Kunsman reported in 1923, Elsasser proposed, therefore, that electrons of certain energies ('slow' electrons) could then be diffracted by 'balls of the same radius as atoms' obeying the laws for photons (*i.e.* Bragg's law): 'Es sieht danach so aus, als ob die langsamen Elektronen an den Atomen nach Gesetzen gestreut würden, wie sie für Licht der berechneten WelIenlänge bei Streuung an Kugeln vom Radius der Atome gelten würden' (Elsasser, 1925). Two years later, Davisson and Germer experimentally displayed unequivocally that X-rays and electrons diffracted by a crystal of nickel obey Bragg's law: 'at sufficiently high voltages (short wavelengths) there is no difference between the occurrence of X-ray and electron diffraction beams' (Davisson & Germer, 1927).

Since electrons are charged, they can be manipulated and lensed using magnetic fields; thus, direct imaging by electron microscopes is possible. While macromolecular X-ray diffraction provided a useful tool for structural biologists, electron microscopy also became popular since the technique didn't require crystallization of proteins, many of which were notoriously difficult to crystallize. As an ancillary effect of proximity and access to electron microscopes, electron diffraction for the elucidation of structures also received broad interest by structural biologists who are often X-ray protein crystallographers as well (Aragon *et al.*, 2024; Gruene, 2024). Recently, there has been growing interest in developing electron diffraction for small molecule elucidation. The somewhat slow adoption by small molecule crystallographers of the technique was a multifaceted challenge, part of which was the practical difficulty in obtaining electron diffraction data because of the relatively higher costs of purchasing, operating, and maintaining electron microscopes *versus* X-ray diffractometers. Some are advocating regional or national centers for electron diffraction similar to existing national synchrotron beamlines (Aragon *et al.*, 2024). Although the effective wavelength of electron beams used for diffraction is usually very much shorter than Mo $K\alpha$, there can still be some difficulty in getting good diffraction data coverage because of small oscillation angles *versus* X-ray diffractometers that have φ and χ orientation angles in addition to the rotation axis, ω. Perhaps these two issues are changing with the current introduction of dedicated electron diffractometers designed for home laboratories.

Data coverage can be ameliorated by merging data from several crystals; however, this could prove difficult if there is a preferred orientation or non-uniform crystal quality. In some cases, the sample may contain several polymorphic phases or be otherwise heterogeneous (Khakurel & Mamoudi, 2025). Sample preparation, mounting, and data collection are, of course, different than for a typical X-ray diffraction experiment but not necessarily insurmountable. Typical electron diffraction workflows have been described (Aragon *et al.*, 2024; Unge *et al.*, 2025) and they share similarities to X-ray diffraction workflows. Solving the structure is often similar to solving an X-ray structure, for example, using the *SHELX* suite of programs (Sheldrick, 2015) and *OLEX2* (Dolomanov *et al.*, 2009), of course with the necessary changes to accommodate the change in wavelength, but then the next hurdle becomes apparent. Diffraction by X-rays can be treated as a kinematic phenomenon but electron diffraction has significant multiple scattering interactions and is therefore dynamical. In some cases, one could ignore the

dynamical contributions and produce a reasonable depiction of the structure without the common accompaniment of poor precision and high residuals if kinematic refinement is coupled with transferable aspherical atom model refinement (Kumar *et al.*, 2024). Currently available software for dynamic treatment includes *PETS2* (Palatinus *et al.*, 2019) and *DIALS* (Vypritskaia *et al.*, 2025) for processing, and *JANA2020* (Petříček *et al.*, 2023) for refinement.

The technique is quite attractive since it uses crystals that are far smaller than those required for X-ray diffraction; thus, in practice, electron diffraction is recommended precisely in situations wherein one could not grow X-ray-quality crystals (Aragon *et al.*, 2024). In the case of rare natural products, it is sometimes not practicable to have the quantities of material commonly used during crystal growth for X-ray diffraction or synthesizing derivatives for chiral determination (Decato *et al.*, 2024; Gurung *et al.*, 2024). In other cases, some compounds, sometimes inexplicably, adamantly refuse to yield crystals large enough or single enough (Duran *et al.*, 2024; Pham *et al.*, 2024; Rahimisheikh *et al.*, 2025). In short, electron diffraction opens opportunities in samples traditionally rejected by X-ray diffraction for insufficient crystal size. Although these are indeed exciting times in electron diffraction for structural determination with the introduction of electron diffractometers, new software, and new methods, such as Fast Event-based Electron Counting (EBEC) (Vlahakis *et al.*, 2025), the enthusiasm, however, must always be coupled with best practices and standards (Aragon *et al.*, 2024; Unge *et al.*, 2025; Gruene, 2024).

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