Jerome Karle

(1918–2013)

Chemist who pioneered mathematical methods to solve crystal structures.

Shortly after the German physicist Max von Laue discovered in 1912 that crystals diffract X-rays, the British physicist Lawrence Bragg realized that he could use the pattern of X-rays diffracted from a crystal to pinpoint the precise positions of its constituent atoms. Yet as increasingly complex materials began to be studied, ever more clever methods were needed to 'solve' the crystal structures. Jerome Karle, Jerry to those who knew him, established new ways to convert an observed diffraction pattern into a set of atomic positions. He did so in principle by deriving mathematical formulae together with Herbert Hauptman, and he did so in practice by inventing procedures for applying the formulae to real crystals together with his wife, Isabella Karle.

The mathematical approaches that Karle and Hauptman established, known as direct methods, have helped researchers to elucidate the structure of key molecules such as vitamins and hormones, and to gain insight into biochemical mechanisms. Karle and Hauptman shared the 1985 Nobel Prize in Chemistry for their work.

Karle, who died on 6 June, was born in Brooklyn in New York city. A precocious product of New York public schools, he completed high school at just 15 years old and went on to the City College of New York. He graduated in 1937 along with Hauptman and Arthur Kornberg, another of City College's many Nobel laureates. He then went to Harvard University in Cambridge, Massachusetts, where he gained a master's degree in biology. After spending about a year at the New York State Health Department in Albany, Karle pursued further graduate studies, this time in chemistry at the University of Michigan in Ann Arbor. At Michigan, Karle studied the diffraction patterns resulting from firing electrons at gases. It was also here that he met Isabella Lugoski, a fellow graduate student, whom he married in 1942 and with whom he had three daughters.

After completing his dissertation in 1943, Karle moved to the University of Chicago to work on the Manhattan Project. He returned to Michigan in 1944 to take on a research project for the US Navy, which involved studying the structure of hydrocarbon lubricants. In 1946, he and his wife moved to the US Naval Research Laboratory (NRL) in Washington DC, where they remained until their retirement in 2009.

Initially, they continued to focus on

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electron-diffraction experiments. In parallel, Karle made a theoretical analysis predicting what diffraction patterns to expect from oriented hydrocarbons, and this got him wondering about applying his theories to the analysis of crystal structures. It was around this point that Karle was joined by Hauptman.

The problem they faced was that although X-rays diffracted from crystals carry information that can produce a picture of the atomic structure, only part of that information is accessible experimentally. Only the amplitudes of the electromagnetic waves bouncing off the atoms can be observed by photon detectors; the phase offset of each periodic wave relative to the others cannot be measured. Fortunately, for typical crystals there are many more X-ray reflections than there are atoms, which implies that the reflections must be mathematically interrelated. Starting in 1950, Karle and Hauptman drew on fundamental knowledge about the nature of matter (specifically, that one cannot have negative electron density) to find mathematical relationships among the diffracted waves. Soon after, they established a probability theory, which they brashly announced in 1953 in an abstruse monograph entitled 'Solution of the Phase Problem'.

Early reception of the Karle–Hauptman work was at best muted. Quoting Karle himself, "during the early 1950s … a large number of fellow-scientists did not believe a word we said." The tide was turned by Isabella applying the work to challenging structures such as peptides. In 1966, she and Karle published a landmark paper in *Acta Crystallographica*, which laid out step by step how to determine crystal structures. Others joined the venture with computer programs, and ever increasing numbers of ever more complex structures came to be determined through direct methods.

By the time Karle and Hauptman received the Nobel prize, Karle had become prominent in crystallography circles, having served as President of the International Union of Crystallographers in the early 1980s.

As I discovered during my postdoctoral time with Karle in the early 1970s, the power of the statistical methods underlying his and Hauptman's approach is not unbounded (I tried with little success to apply his methods to protein crystals). Nevertheless, Karle's influence extends to macromolecules. He was fascinated by resonance in diffraction (whereby certain atoms behave anomalously when the energy of incident X-rays matches the energy of an electronic orbital), and he made seminal contributions to the theory underlying an approach now called multiwavelength anomalous diffraction (MAD). MAD and SAD, MAD's single-wavelength counterpart, are now commonly used to determine macromolecular structures, such as membrane proteins. Both require that the resonant atoms be located as a first step, and the Karle–Hauptman direct methods are now the approach of choice for finding them.

Karle's interests were broad, as suggested by the name he gave his unit at the NRL — the Laboratory for the Structure of Matter. The work there ranged from electron diffraction of gases to quantum chemistry of excited states, to the study of glasses and amorphous materials, and of course, crystals. Although these activities engaged several group members and were largely experimental, the Jerry I knew was a lone theoretician; he authored many papers alone and his main working interaction was with a computer programmer who tested his theories.

Ultimately, Karle's major contribution was to allow researchers to shift their focus from the intricacies and challenges of crystallography to molecules and biochemical mechanisms. He turned chemical crystallographers into crystallographic chemists. ■

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