A simple method for the direct determination of phases from experimentally measured intensities obtained from the x-ray diffraction of a single crystal was described. This method was applied to the structure determination of a cyclic hexapeptide that has played a basic role in experimental and theoretical investigations of conformational and other structural properties of oligopeptide. [The SCI® indicates that this paper has been cited over 280 times since 1963.]

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"Starting in 1950, J. Karle and H. Hauptman published a number of theoretical papers in which simple formulas and procedures were presented for the determination of the phases of the rays diffracted by a single crystal. Unexpectedly, the phases could be determined by use of the measured intensities. The basis for this development was the non-negativity of the electron density in a crystal and associated probabilistic considerations. The potential value of this development lay in the fact that if the phases are known, the electron density of the crystal can be computed by means of a Fourier series, thus readily revealing the atomic positions. Despite the potential usefulness of the proposed procedures, there was little positive response from colleagues in this field of research.

"By the late 1950s, it was decided that it would be worthwhile to develop an experimental program in crystal structure analysis in our laboratory to complement the theoretical studies and facilitate their application. I. L. Karle thus diverted her activities from the field of electron diffraction of molecules in the vapor state to apply the phase determining formulas to crystal structure problems. She taught herself the techniques of collecting x-ray diffraction data, borrowed apparatus, and found a modus operandi for applying the theoretical formulas to experimental data. The 'symbolic addition procedure' for phase determination, as described in this paper, resulted. It became a broadly used procedure and, as time passed, phase determination was adapted to automatic processing. Although very large numbers of structures can now be solved automatically, there still remain a significant number of occasions in which the talents of a professional crystallographer are indispensable.

"The solution of structures is only one of many parts to the science of crystallography. Of very great importance are the insights into chemical and physical properties that such studies provide in their applications. It follows, therefore, that there are a number of reasons why this publication has been highly cited. Not only had a simple and rapid procedure for phase determination been established but it was applied to a crystal of a substance with unusual features. The chemistry and biology of small peptides was just gaining impetus and the crystal structure of cyclic hexaglycyl contributed many insights into the conformations of these very flexible molecules. This paper contained the first example of the folding of the backbone in a cyclic peptide (except for the special case of a dipeptide which was published earlier). It presented the first example of the coexistence of four very different stable conformers in the same unit cell, and gave the first good experimental parameters for the 4!1 hydrogen bond in chain reversal. This paper has also provided the structural data used in numerous theoretical conformational analyses and minimum energy calculations. It is of interest to note that the structure determination was not facilitated by the presence of any heavy atoms. It consists entirely of light atoms, i.e., 98 independent C, N, and O atoms in an asymmetric unit of the unit cell."