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Direct Methods and Macromolecular Neutron Diffraction. Herbert A. Hauptman, David A. Langa, Hauptman-Woodward Medical Research Inst., Buffalo, NY, Dept. of Structural Biology, SUNY, Buffalo, NY.

For many years most crystallographers believed that it was much more difficult to solve crystal structures using neutron data as compared to X-ray data due to the significant neutron scattering of hydrogen atoms which could be either negative (${}_1\text{H}^1$) or positive (${}_1\text{H}^2$). Structures having as many as 1300 non-hydrogen light atoms have been solved by direct methods using X-ray data, but few structures having more than 50 non-hydrogen atoms have ever been reported to have been solved from neutron data by these methods. We recently reported a new SnB protocol which solved cyclosporin A ($\text{C}_{62}\text{H}_{113}\text{N}_{11}\text{O}_{113}$) from experimental neutron data alone (88% complete at 0.916 Å). Paradoxically, it was shown that the native structure with negative ${}_1\text{H}^1$ scatterers was much easier to solve than the ${}_1\text{H}^2$ isomorph for which all atoms should appear as positive peaks in the electron density map. This led us to believe that much larger ${}_1\text{H}^1$ structures, even proteins, could be solved from neutron data sets using these methods if atomic resolution data were available.

To this end we generated error-free neutron data for hen egg white lysozyme, a triclinic structure containing 1270 non-hydrogen as well as ~1600 negatively scattering hydrogen atoms. We first showed that a stable solution could be obtained using the triples phase invariants generated from the neutron data if the error in the starting phases was less than $\sim 75^\circ$. Although no solutions were detected in the first 2000 *ab initio* random trials that were examined, we were able to identify a small percentage of convergent solutions from a much larger list of random 3-atom starting sets. Thus, as preposterous as it seems, three atoms, fortuitously placed, are sufficient to solve this 2800 atom structure if sufficiently accurate high-resolution data can be measured! Research supported by NIH GM46733.