Small Molecules and Macromolecules make Contact: Messages from Protein Structures to Atomic Resolution

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Atomic and ultra-high resolution macromolecular crystal structure determination and *ab initio* quantum chemical calculations have become indispensable tools for comprehensive structure interpretation, as they permit acquiring snapshots along the reaction pathway and the assignment of function to the residues involved in catalysis. Fine electronic detail can be visualised and yield valuable information on protein function. The assessment and description of intra- and intermolecular contacts reaches a degree of accuracy which in the past was considered impossible for macromolecules.

The release of geometric restraints and the low coordinate error in atomic resolution protein structures allow the identification of deviations from standard stereochemistry which, at lower resolution, might not have been accounted for. These deviations may occur in intramolecular interactions as well as in intermolecular (protein-ligand) contacts. Quantum chemical calculations, or direct multipole refinement, on these accurate model templates complement the structural data with information beyond the analysis of contact distances. The charge distribution which one can obtain determines the chemical properties and hence characteristics such as substrate specificity and binding energies.

The availability of atomic resolution X-ray data allows refinement of anisotropic displacement parameters (ADPs) that complement the 3D coordinates. The information extracted from the ADPs gives insight into the mobility and the presence of ligand induced directional motion in the protein. Together with the change of contact distances and the occurrence of multiple conformers they reflect spatial rearrangement or steric strain. Thus, the analysis of the ADPs complements the time-averaged structural picture with dynamics, revealing subtleties of protein function which may not be attainable if a structure is analyzed only on the basis of the atomic coordinates.

A thorough analysis in terms of accessible conformational states deduced from the directional motion, may provide insight into the energetics of complex formation and the driving forces for allosteric mechanisms.

Examples for application of these analysis methods and their implication for protein structure interpretation will be given.

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