In Situ Refinement Restraints from Quantum Mechanical Methods

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In macromolecular crystallographic structure refinement, the presence of ligands presents challenges for the generation of geometric restraints due to their large chemical variability, possible novel nature and their specific interaction with the protein binding pocket.

Quantum mechanical approaches are useful for providing accurate ligand geometries but can be plagued by the number of minima in flexible molecules. We have developed the Quantum Mechanical Restraints (QMR) procedure that optimises the ligand geometry in situ, thus accounting for the influence of the macromolecule on the local energy minima of the ligand. The optimised ligand geometry is used to generate target values for geometric restraints during the crystallographic refinement. As shown for protein-ligand models, QMR restraints generally result in lower deviations from ideal stereochemistry compared to conventionally generated restraints. In particular, the QMR approach provides accurate torsion restraints for ligands and other entities.