Poster Presentation

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High-performance, quantum mechanics-based macromolecular x-ray refinement

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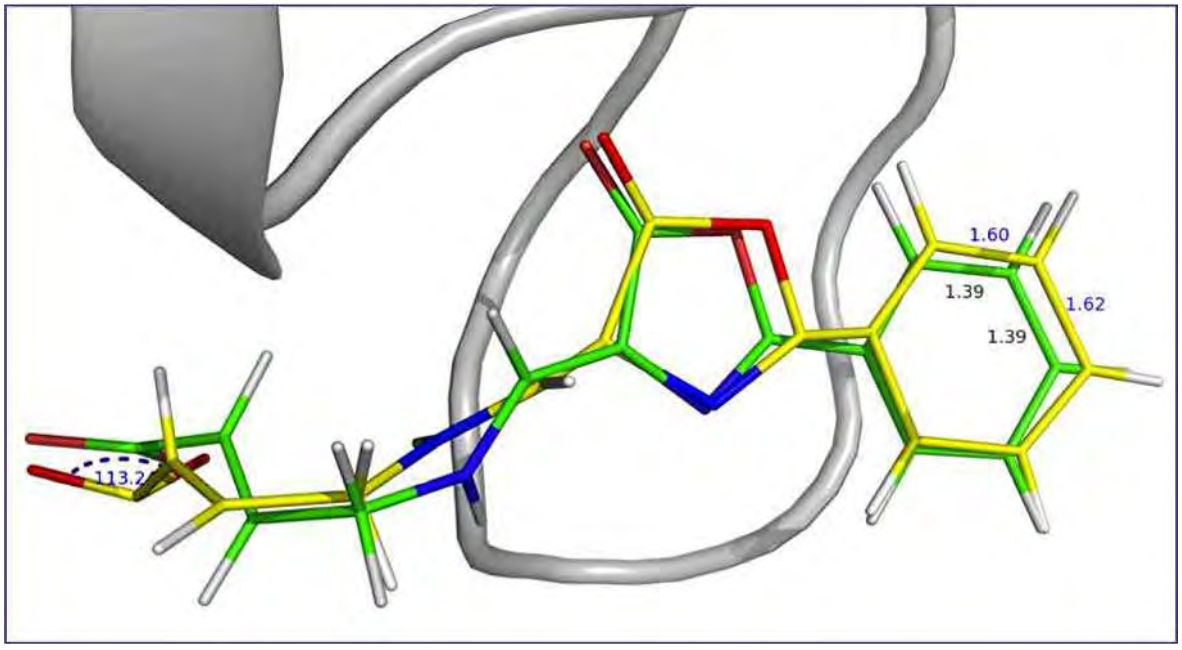
Modern, structure based drug discovery (SBDD) is dependent upon accurate protein:ligand structure determination and characterization. In conventional x-ray refinement, the geometry of the ligand within the active site is modeled according to the practitioner's beliefs as expressed in the form of stereochemical restraints provided by the ligand library or CIF file. Further, metal centers, bound species, and so on can be difficult to refine correctly without significant human intervention. Our work has addressed this problem through the integration of DivCon6 - a linear scaling, semiempirical, quantum mechanics (SE-QM) functional - with the Phenix refinement package. With Phenix/DivCon[1], SE-QM is used in "real-time" during each microcycle over the course of the refinement. With its inclusion of electrostatics, charge transfer, polarization, dispersion, hydrogen bonds, etcetera, this method is a much more rigorous, robust alternative to conventional stereochemical restraints and is better able to accurately model protein:ligand structures without "tweaking" any restraints. We report PM6 refinement results for several key examples including structures with metal coordination spheres, covalent bonds, and other exotic protein:ligand chemistry situations. When compared with the originally deposited PDB structures, we found in all cases that QM refinement leads to ligand structures with much lower strain, and in some cases, the improvement is dramatic and as much 10+ fold. At the same time, SE-QM methods are better able to capture the influence of the surrounding structure (e.g. active site) on the ligand. These interactions are particularly interesting in SBDD as they are often the targets for lead design and optimization, and examples that illustrate how these interactions are captured with SE-QM will also be discussed.

[1] *Borbulevych O. Y., Plumley J. A., Martin R. M., et al., (2014). Acta Crystallographica Section D-Biological Crystallography, in press.*



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