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Incorporation of the quantum chemical package DivCon into the PHENIX suite

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X-ray crystallography is the primarily technique used to reveal the three-dimensional structure of protein complexes that play a critical role in Structure Based Drug Design. Because of the low ratio of observed data to refined parameters, macromolecular crystallographic refinement at moderate and low resolution relies heavily on the set of known amino acid geometric parameters that ensures the correct stereochemistry of the model. Available programs for macromolecular refinement such as REFMAC, PHENIX or SHELX use simple harmonic oscillator functions to introduce stereochemistry restraints and commonly do not account for electrostatic interactions in the system. This approach inevitably masks important structural details that are often crucial to the understanding of ligand binding within the active site of the protein. To overcome these limitations and achieve a much more realistic description of the protein-ligand geometry, we replaced these stereochemistry restraints with the energy functional derived from quantum-mechanical (QM) treatment. This treatment has been demonstrated with the successful integration of the commercial DivCon ToolKit developed by QuantumBio with the popular Python-based crystallographic package PHENIX. DivCon employs semiempirical QM methods such as AM1, PM3 or PM6 and is based on the divide-and-conquer approach to evaluate the density matrix allowing linear-scaling of the QM problem. As a result, DivCon dramatically decreases the computation costs traditionally associated with QM-based methods, making the application of quantum chemistry for large protein systems feasible.

We proposed a novel protocol to incorporate QM gradients and energy targets into individual ("XYZ") coordinate refinement step in PHENIX without altering the other refinement stages such as the bulk solvent correction or temperature factor refinement. Furthermore, a user has a choice to use DivCon methods either for the whole structure or a selected region - a ligand and protein active site residues, for example. Based on five test protein structures downloaded from Protein Data Bank (PDB) we report the detailed comparison of the conventional and QM driven refinements. Our preliminary results indicate that incorporation of the QM function not only improves the local geometry but also reduce the R/Rfree factors. For example, the re-refinement of a 17-residue short protein at 2 Å resolution (PDB ID 1S9Z) using the PHENIX/DivCon package indicates a number of significant structural improvements as compared to the conventional PHENIX refinement. Notably, PHENIX/DivCon compared to PHENIX alone improved the peptide bond geometry for the non-standard N terminus residue of that protein and the DivCon driven refinement accurately represents the stereochemistry in this region. Furthermore, the QM approach results in more reasonable H-bond network throughout the protein molecule.

Keywords: DivCon, phenix, refinement

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Olex2 – A complete package for molecular crystallography

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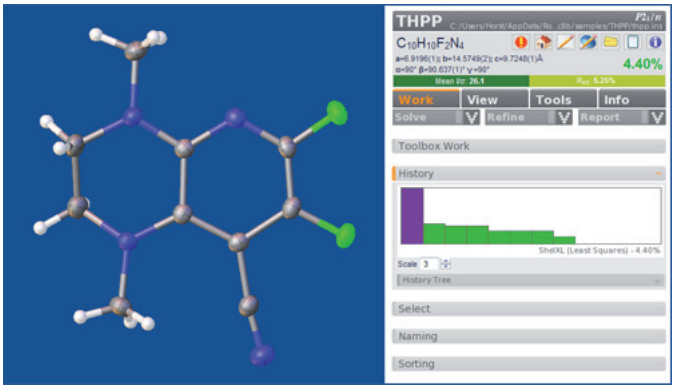
Olex2 [1] has become established in the community of small-molecule crystallographers as an easy-to-use unified package that provides tools needed for day-to-day analyses of small molecule structures. There is a rapidly growing number of installations of the software world-wide and our core paper [2] has attracted a significant number of citations since 2009.



Structure Solution is achieved by our own charge-flipping implementation, ***olex2.solve***, based on E^2.

Structure Refinement can be carried out with ***olex2.refine***. The refinement engine is based on the cctbx and provides all the functionality required for a meaningful structure refinement. A general system allows the implementation of any constraints, which has been used to provide all ShelXL constraints.

The solution and refinement programs are based on the small-molecule toolbox (*smtbx*), that our group has contributed to the family of tools available in the *cctbx* [3].

Structure Analysis tools covering most requirements are an integral part – growing, packing, geometric measurements, void, molecular and solvent accessible volume calculation, π–π analysis and many more.

Structure Publication is made easy. Complete and correct CIFs result automatically, the generation of reports is easy and images – bitmaps or ORTEP-style drawings – can be generated with minimum effort.

Olex2 is Open Source under the BSD Licence and available free of charge from [1] for academic users for Windows, Linux and MaxOSX.

[1] www.olex2.org [2] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard, H. Puschmann, Olex2, *J. Appl. Cryst.* **2009,** *42*, 339-341. [3] R.W. Grosse-Kunstleve et al, http://cctbx.sourceforge.net/

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Full matrix refinement with the small molecule toolbox

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The Computational Crystallography Toolbox (cctbx) [1] opened a new era in crystallographic computing by providing a free, open and