A Computational Analysis of Metal Interactions in C-Terminal Src Kinase[1]

Chris Furey and Glênisson de Oliveira

Rhode Island College
Physical Sciences Department
600 Mt. Pleasant Ave.
Providence, RI 02908

C-terminal src kinase (csk), is a protein that participates in controlling cell growth, and is a promising target for the development of new anti-cancer drugs. The protein includes two Mg^{2+} binding sites which are integral to the normal function of the protein, and is has been shown experimentally that other dications can substitute for Mg^{2+}, leading to altered protein activity. Although the effects of substitution have been well documented, the structure and mechanisms of the active protein have not been resolved at the molecular level. As a result the current conclusions about Csk are based on proposed metal binding sites. The goal of this project is to computationally examine these proposed binding sites, which are based on the inactive structure of Csk, and the active structure of a homologous kinase protein, Insulin Receptor Kinase (irk).

Initially methods were selected by testing a variety of Density Functional Theory approaches against High Level ab initio calculations using small, representative systems. This testing indicated that the mPW1PW91 functional, paired with the 6-31g* basis set would offer a reasonable compromise of accuracy and efficiency when dealing with larger calculations.

Next, potential energy scans were performed to map the surface of the various dication-phosphate systems an interaction that is integral in the proposed binding sites, and a correlation between computational results and experimental results would help support the proposed sites. These scans suggest not only the overall affinity for the dications for phosphate, but the barriers associated with changes in orientation as the protein and substrate "flex" during the reaction.

The results of these scans had a strong correlation with known substitution effects on Csk, a correlation that not only supports the proposed binding sites but may help explain the mechanism behind the effect of substitution on the activity of Csk.

[1] This work was partly supported by RI-BRIN/NIH grant P20 RR16457-03, NSF grant CHE 0116435, as part of the MERCURY supercomputer consortium, and the Rhode Island College Faculty Research Funds.