

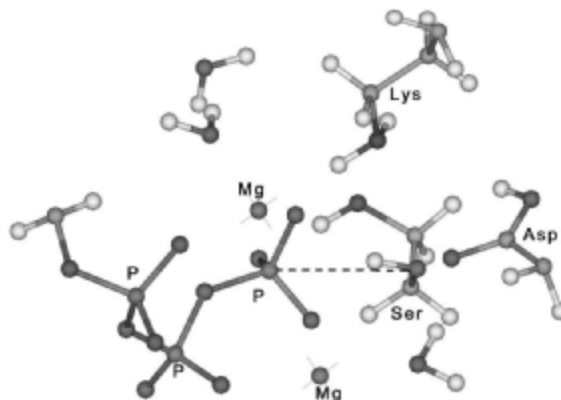
**SCC DFT-TB ENERGY CALCULATIONS OF THE PHOSPHORYL TRANSFER REACTION IN THE PKA ACTIVE SITE**

**FRANCISZEK RAKOWSKI<sup>1,2</sup>, PAWEŁ GROCHOWSKI<sup>1</sup>  
and BOGDAN LESYNG<sup>1,3</sup>**

<sup>1</sup>Interdisciplinary Centre for Mathematical and Computational Modelling (ICM), Warsaw University, Pawinskiego 5A, 02-106 Warsaw, Poland, <sup>2</sup>Institute of Physics, Warsaw University of Technology, Warsaw, Poland, <sup>1,3</sup>Department of Biophysics, Faculty of Physics, Żwirki i Wigury 93, 02-089 Warsaw, Poland

A self-consistent charge density-functional based tight binding method (SCC DFT TB) [1] is applied to study the phosphoryl-transfer reaction in the active site of protein kinase A (cAMP-dependent protein kinase). Test SCC-DFTB calculations for a model phosphoester system were compared with more advanced DFT B3LYP/6-31D+(d,p) calculations. It appeared that the much faster SCC-DFTB method provides satisfactory results for phosphate-transfer reactions. Therefore this method was chosen for further calculations.

The 3D structure of the active site domain was taken from PDB [2]. It consists of about 390 atoms. 40 atoms form a flexible subdomain, the rest form a rigid scaffold. The flexible subdomain is presented below. Protonation states of all residues have been taken from a virtual titration study [3], based on a Poisson-Boltzmann model.



The reaction path is denoted by the dotted line. The phosphate group and the serine hydroxyl group of the substrate molecule were forced to approach each other with a restrained potential. Other degrees of freedom of the flexible domain were optimized in the course of the reaction. This procedure simulates the nucleophilic attack resulting in the phosphoryl transfer process. Results of the calculations, including dissociative and associative mechanisms, will be discussed.

**REFERENCES**

1. Frauenheim, T., Seifert, G., Elstner, M., Hajnal, Z., Jungnickel, G., Porezag, D., Suhai, S. and Scholz, R.A Self-consistent charge density-functional based tight-binding method for predictive materials simulations in physics, chemistry and biology. **Physica Status Solidi B - Basic Research** 217 (2000) 41-62.
2. Knighton J.M., Bell S.M., Zheng J., Eyck L.F.T., Xuong N., Taylor S.S. and Sowadski J.M. Crystal structure of the catalytic subunit of cAMP-dependent protein kinase. **Science** 253 (1991) 407-420.
3. Błachut-Okraśńska, E., Lesyng, B., Briggs, J.M., McCammon, J.A. and Antosiewicz, J.M. Poisson-Boltzmann model studies of molecular electrostatic properties of the cAMP-dependent protein kinase. **Eur. Biophys. J.** 28 (1999) 457-467.