COMPUTATIONAL STUDIES OF MO OXO-TRANSFER ENZYMES

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Molybdenum (Mo) and tungsten (W) are the only known second- and third-row transition metals that occur in proteins.[1] Both metals favour high oxidation states, high coordination numbers, and hard ligands, preferably negatively charged O and S ligands. Although Mo is rather uncommon in the earth crust, it is actually the transition-metal ion that has the highest concentration in seawater. Therefore, it is quite natural that it has been employed in several biological systems. The great majority of the Mo/W enzymes belong to the mononuclear oxidases and hydroxylases. In all these enzymes, the metal is bound to a special molecule, molybdopterin (MPT). They are divided into three families, depending on the construction of the active site. The dimethylsulfoxide reductase (DMSOR) family has an active site with two MPT ligands, one protein ligand (typically Ser), and an oxo group. The sulfite oxidase (SO) family has only one MPT ligand, but two oxo groups and a Cys ligand. Finally, the xanthine oxidase (XO) family has one MPT ligand, one oxo, one sulfido, and one hydroxide ligand.

In a series of articles we have studied various Mo and W enzymes with QM methods.[2] First, we studied DMSOR and showed that this system is unusually sensitive to details in the calculations, especially the size of the basis set and the DFT methods.[3] In fact, most previous studies have given the correct barrier for the wrong reason, using a too small basis set or a DFT functional that gives a too low barrier, compensating the lack of dispersion effects. By employing LCCSD(T) we showed that not a single DFT method gives the best energies for all states of the reaction. Later, we have studied also the corresponding reaction with W and considered also the effects of optimizing the geometries with various DFT functionals.[4]

We have also studied the SO reaction, comparing all three suggested mechanisms.[5] We showed that this reaction is even more sensitive to the theoretical method and that a S→OMo mechanism gives the lowest activation barriers. However, the barrier is still too large, compared to experiments, owing to a large Coulombic barrier between the negatively charged substrate and the negatively charged active-site model. Therefore, we have studied the enzyme also with QM/MM methods, giving a more reasonable barrier.[6]

We have compared models of the three families of Mo enzymes, trying to explain the differences in the active sites.[7] We showed that the active sites are not designed to give as exothermic reactions as possible. Instead, they seem to give reactions that are only marginally exothermic, in order to make the re-reduction or re-oxidation of the active site possible. We also showed that DMSOR and SO reactions are facile and can be performed by all three types of active sites. However, the XO reaction is more complicated and can only be performed by the native site. Currently, we study several other Mo oxo-transfer enzymes with QM/MM methods, e.g. nitrate reductase[8] and formate dehydrogenase. Some of these studies will be described in this talk.

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