Flexibility of a biotinylated ligand in artificial metalloenzymes based on streptavidin—an insight from molecular dynamics simulations with classical and ab initio force fields

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In the field of enzymatic catalysis, creatingactivity from a non catalytic scaffold is a dauntingtask. Introduction of a catalytically active moiety within aprotein scaffold offers an attractive means for the creationof artificial metalloenzymes. With this goal in mind,introduction of a biotinylated d6-piano-stool complexwithin streptavidin (SAV) affords enantioselective artificialtransfer-hydrogenases for the reduction of prochiralketones. Based on an X-ray crystal structure of a highlyselective hybrid catalyst, displaying significant disorderaround the biotinylated catalyst [g6-(p-cymene)Ru(Biot-p-L)Cl], we report on molecular dynamics simulations toshed light on the protein–cofactor interactions and contacts.The results of these simulations with classical force fieldindicate that the SAV-biotin and SAV-catalyst complexesare more stable than ligand-free SAV. The point mutationsintroduced did not affect significantly the overall behaviorof SAV and, unexpectedly, the P64G substitution did notprovide additional flexibility to the protein scaffold. Themetal-cofactor proved to be conformationally flexible, and the S112K or P64G mutants proved to enhance this effectin the most pronounced way. The network of intermolec-ular hydrogen bonds is efficient at stabilizing the positionof biotin, but much less at fixing the conformation of anextended biotinylated ligand. This leads to a relative con-formational freedom of the metal-cofactor, and a poorlylocalized catalytic metal moiety. MD calculations withab initio potential function suggest that the hydrogen bondsalone are not sufficient factors for full stabilization of thebiotin. The hydrophobic biotin-binding pocket (and gen-erally protein scaffold) maintains the hydrogen bondsbetween biotin and protein.

Słowa kluczowe

(Strept)avidin, Biotinylation, Enantioselectivity, DFT, Classical and ab initio force field molecular dynamics

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