Proteolysis mechanism in matrix metalloproteinases suggested by molecular modeling

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The matrix metalloproteinases (MMPs) comprise a family of zinc-dependent endopeptidases which play key roles in tumour growth of metastasis. Their proteolytic activities in living organisms are regulated by tissue inhibitors of metalloproteinases (TIMPs) and disruption of this balance results in different diseases. Numerous of resent studies are devoted to the rational design of the artificial inhibitors of the MMPs based on the results of molecular docking. We suppose that a complex analysis of this problem involving modeling of the mechanism of proteolysis in the active site of the MMPs by means of combined quantum mechanics/molecular mechanics (QM/MM) approaches considerably expands the current knowledge. Application of quantum based approaches allows one to overcome shortcomings in using conventional force field parameters in molecular mechanics modeling and to proceed to simulations of chemical reactions in the enzyme active sites. Combined quantum mechanics/molecular mechanics (QM/MM) approach was applied to calculate energy profiles for the rate limiting step of the proteolysis of the native oligopeptide substrate Ace-Gln-Gly-Ile-Ala-Gly-Nme by MMP-2. The QM calculations were carried out in density functional theory (DFT) approximation with hybrid functional BB1K and the double-ζ 6-31G** basis set for all atom except Zn and 6-31G* for Zn. MM region was treated with the AMBER force field. According to our calculations, the first step, corresponding to the nucleophilic addition of OH- to the carbonyl carbon atom of the substrate coupled to proton transfer from the water molecule to the carboxyl group of the glutamate is rate limiting and has activation barrier 12 kcal/mol.

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