MOLECULAR MODELING OF MECHANISM OF ANTIBIOTICS HYDROLYSIS BY METALLO-BETA- LACTAMASES

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We present the results of studying the mechanism of the enzymatic reaction of nitrocefin hydrolysis in the active site of metallo-beta-lactamase, an enzyme responsible for the resistance of bacteria to a number of antibiotics. To study the mechanism, a combined quantum mechanics / molecular mechanics (QM/MM) approach was used. The active site of the enzyme and the substrate was described at the density functional (DFT) level of theory with the hybrid functional PBE0 and two-exponential basis sets with polarization functions on all atoms 6-31G **. To study the mechanism, a colored substrate was chosen in the work. Its absorption spectra differ in the reagents, intermediate and product states. From the point of view of experimental studies, it is possible to monitor the concentration of all participants in the reaction and determine not only the effective parameters of the whole reaction, but also the rate constants of the elementary stages. Based on the calculations performed, time-resolved absorption spectra were constructed and directly compared with the experimental data. Based on the knowledge of the reaction mechanism, the structure-property relationship was analyzed for the rates of hydrolysis of a group of related antibiotics. This work was supported by the Russian Foundation for Basic Research (Project No. 16-03-00077).