CATALYTIC MECHANISM OF PEPTIDE BOND HYDROLYSIS BY METAL CYCLEN COMPLEXES. Tingting Zhang and Rajeev Prabhakar, Department of chemistry, University of Miami, 1301 Memorial Drive, Coral Gables, FL 33146.

Reaction mechanisms of a target-selective peptide cleaving catalyst, Cu(II) cyclen (Cu(II) aqua complex of 1,4,7,10-tetraazacyclododecane) complex and its analogue Cu(II) oxacyclen (1-oxa-4,7,10-triazacyclodedecane) have been investigated. The Cu(II) cyclen complex recognizes the target protein and selectively hydrolyzes the Phe20-Ala21 peptide bond of Alzheimer amyloid beta (Aβ) peptide. Our DFT calculations show that the Cu(II) ion of the complex polarizes the amide bond by binding to the carbonyl oxygen atom and created the hydroxide ion nucleophile. Of the four conformations (anti-anti, syn-syn, syn-anti and syn-anti-II) of the Cu(II) cyclen complex, the syn-syn conformation is found to be the energetically most favorable. The energy barrier in this conformation is computed to be 37.6 kcal/mol. The role of the metal ion in the functioning of this catalyst was investigated by substituting Cu(II) with Ni(II), Zn(II), Pd(II) and Cd(II).