

Recent EXAFS studies on metallo-beta-lactamases

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Metallo-beta-lactamases confer antibiotic resistance to bacteria by catalysing the hydrolysis of beta-lactam antibiotics, including carbapenems. This relatively new form of resistance is spreading and thereby escaping the effective inhibitors developed to fight the better known serine- β -lactamases. For all metallo-beta-lactamases investigated, structurally similar enzyme active sites comprising two zinc binding sites are reported. Three subclasses namely B1, B2 and B3 can be discriminated according to the amino acid composition of their active sites. As representatives for each subclass three enzymes namely BcII from *Bacillus cereus*, CphA from *Aeromonas hydrophila* and L1 from *Stenotrophomonas maltophilia* have been chosen for inhibition study.

The EXAFS-spectroscopic investigation of the binding of the inhibitor Captopril presented here is based on results obtained from enzyme kinetic and thermodynamic studies. To achieve maximum comparability with perturbed angular correlation of gamma rays (PAC) spectroscopic data zinc has been replaced by cadmium in case of BcII and CphA.

For the enzymes from *Bacillus cereus* (BcII) and *Aeromonas hydrophila* (CphA) we found that the mono-nuclear enzymes are the favoured targets for inhibition whereas the enzyme from *Stenotrophomonas maltophilia* (L1) is inhibited as the dinuclear species. Although different catalytic mechanisms for mono- and binuclear metallo-beta-lactamases have been discussed in the literature it is still not clearly understood why the enzymes have two conserved metal binding sites. The motivation for the present investigation was the demand for a better knowledge of the nature of metal ion binding in presence of bound ligands.