Applied quantum chemistry to design antibiotics

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Abstract

The comparison of the PBPs and β-lactamases serine active sites clearly displays their common geometric similarities which could be involved in the acylation mechanism. Nevertheless, recent apo and acylated X-ray structures on one hand and *ab initio* reaction path models on the other point out the incidence of conformational adaptability of both partners during the process of the reaction.

Summary

Penicillin-binding proteins (PBPs) are membrane proteins involved in the final steps of peptidoglycan synthesis and are the targets of β-lactam antibiotics. PBPs fall into two major groups: the low-molecular-mass ones are monofunctional enzymes mainly acting as DD-peptidases while the high-molecular mass PBPs are multimodular enzymes also working as DD-peptidases sometimes associated with a transglycosylase activity. The serine β-lactamases also break the C-N bond of the β-lactam ring but the generated acylenzyme is hydrolysed very quickly thus inactivating the antibiotic.High resolution X-ray experiments allow to compare the 3D structure of the serine PBPs belonging to mono/bifunctional classes and PBPs with low affinity for β-lactams as PBP5fm in *Enteroccocus faecium* and PBP2a of *Staphylococcus aureus.* Superimposition of the active sites could lead to a nice hypothesis involving a common acylation mechanism. Nevertheless, the comparison between apo and acylated enzymes reveals the incidence of some relative conformational changes which could clearly be related to the accessibility of the active site. *Ab initio* reaction paths have been computed for models involving several active residues. They reveal the incidence of the conformational changes of penicillin and the ancillary role of the fused thiazolidine ring on the geometry along the path and the barrier height. This feature has been used in the design of new "conformationally adaptable" molecules.

References

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