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An X-ray Crystallographic Analysis of UDP-N-Acetylglucosamine Enolpyruvyl Transferase from *Haemophilus influenzae* in Complex with UDP-N-Acetylglucosamine and Fosfomycin

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Peptidoglycan is an extensively cross-linked polymer essential for the integrity of the bacterial cell wall. Many antibiotics act by disruption of its biosynthesis and assembly, several are targeted against the cytoplasmic enzymes that synthesize the key intermediate UDP-N-acetylmuramyl pentapeptide. One such drug is fosfomycin, which inactivates the first enzymes in this pathway, UDP-N-acetylglucosamine enopyruvyl transferase (murZ). We determined the crystal structure of murZ from *H. influenzae* complexed with substrate UDP-N-acetylglucosamine and the inhibitor fosfomycin at 2.2 Å resolution by the molecular replacement method. The crystal of murZ is orthorhombic, belonging to the space group I222 with unit cell dimensions of a=64.5, b=126.9 and c=129.0 Å. One monomer of murZ is present in an asymmetric unit. The structure reveals the monomeric arrangement of subunits and the substrate and the drug are bound in a deep active-site cavity interacting with residues from both domains. The domains have a very similar secondary structure, and the overall protein architecture is similar to that of UDP-N-acetylglucosamine enolpyruvyl transferase from *E. coli*. The structure of murZ from *H. influenzae* provides a great deal of information on the residues involved in the substrate and the drug binding. It thus provides a template upon which novel inhibitors of this important enzyme class may be designed.