

P020 An internal reaction chamber in dimethylglycine oxidase provides efficient protection from exposure to toxic formaldehyde: Part II

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The catabolism of dimethylglycine through methyl group oxidation can potentially liberate toxic formaldehyde, a problem common to many amine oxidases and dehydrogenases. In Dimethylglycine Oxidase (DMGO), the formation of formaldehyde is prevented by coupling the oxidation of dimethylglycine with the synthesis of 5,10-methylenetetrahydrofolate. Surprisingly, x-ray structure of DMGO revealed that this coupling should take place through the channeling of a reactive intermediate between the two active sites (40 Å apart).

Using Brownian Dynamics and Molecular Dynamics simulations, we show that this channeling occurs by non-biased diffusion of the labile intermediate through a large solvent cavity connecting both active sites. This central “reaction chamber” is created by a modular protein architecture that appears primitive when compared to the sophisticated design of other paradigm substrate channeling enzymes. The evolutionary origins of the latter were likely similar to DMGO. This work points to novel channeling mechanisms that protect the cell milieu from potentially toxic reaction products.