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Crystal Structure of 4-oxosebacic Acid Inhibited E.coli Porphobilinogen Synthase.

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4-Oxosebacic acid (4-OSA) and 4,7-dioxosebacic acid (4,7-DOSA) are bisubstrate reaction intermediate analogs for the porphobilinogen synthase (PBGS) family of enzymes. The PBGS enzymes catalyze the condensation of two molecules of 5-aminolevulinic acid (ALA), an essential step in tetrapyrrole biosynthesis. Here we show that 4-OSA has dramatic species-specificity as a suicide substrate for *Escherichia coli* PBGS. Human, pea, *Pseudomonas aeruginosa*, and *Bradyrhizobium japonicum* PBGS are insensitive to inhibition by 4-OSA. Some variants of human PBGS, engineered to resemble *E. coli* PBGS, have increased sensitivity to inactivation by 4-OSA, suggesting a structural basis for the specificity, some of which lies in the length and sequence of the active site lid. The specificity of 4-OSA is significantly different from that of 4,7-DOSA. High-resolution crystal structures of *E. coli* PBGS that have been inactivated by 4-OSA and by 4,7-DOSA were solved at 1.7Å and 1.9Å resolution respectively. A comparison of these structures shows significant variation in the half of the inhibitor that mimics the second substrate molecule, which is A-side ALA. There are compensatory changes in the structure of the active site lid, which suggest that similar changes normally occur to accommodate the numerous hybridization changes that must occur at C3 of A-side ALA during the PBGS-catalyzed reaction.