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Enzyme Flexibility is the Key to Cyclizing a Linear Tetrapyrrole. Heidi L. Schubert, John D. Phillips, Christopher P. Hill, Dept. of Biochemistry, Univ. of Utah, Salt Lake City, 84112, USA.

Uroporphyrinogen III synthase, U3S, the fourth enzyme in the porphyrin biosynthetic pathway, catalyzes cyclization of the linear tetrapyrrole, hydroxymethylbilane, to the macrocyclic uroporphyrinogen III, which is used in several different pathways to form heme, siroheme, chlorophyll, F_{430}, and vitamin B_{12}. U3S activity is essential in all organisms, and decreased activity in humans leads to the autosomal recessive disorder congenital erythropoetic porphyria. We have solved nine unique apo-structures and two product-bound complexes of U3S (two human structures and nine from the *Thermus thermophilus* HB8 sequence) at 1.6-2.4 Å resolutions. The proteins' two domains are connected by a non-conserved β-ladder which enables a large degree of conformational flexibility. The highly complex catalytic mechanism requires multiple nucleophilic attacks to initiate hydroxyl loss, C-C bond formation followed by an additional C-C bond breakage and subsequent formation. Very few conserved amino acids flank the active site, and the two invariant residues are distant from the uroporphyrinogen III product suggesting that the linear tetrapyrrole substrate may be recognized by an alternate region of the active site prior to cyclization.