Insights into the Mechanism of ATP Utilization in the Cyclodehydration of Thiazole/Oxazole-Modified Microcins

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The Thiazole/Oxazole-Modified Microcins (TOMMs) are a recently discovered class of ribosomally synthesized natural products with a diverse set of biological activities. These activities range from potent antibiotics in the case of plantazolicin and microcin B17, to cytolytic virulence factors in the case of streptolysin S and clostridiolysin S. Previous work has demonstrated that function is endowed through the posttranslational installation of azol(in)e heterocycles by an evolutionarily conserved, heterotrimeric enzyme complex. Though multiple groups have studied their biosynthesis, little is known about the mechanism of heterocycle formation. Using NMR spectroscopy, isotopic labeling, and substrate analogs, we provide evidence for a novel mechanism of heterocycle formation in this family of natural products and further refine the roles of each of the enzymes in the trimeric complex.