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**Large-scale Motion of the Ligand Binding Domain of Nikkomycin Synthase.** Christopher J. Carrell, David Venci, Robert Bruckner, Marilyn S. Jorns, F. Scott Mathews, Dept. of Biochemistry & Molecular Biophysics,, Washington Univ. School of Medicine, St. Louis, MO 63110.

Nikkomycins are a class of antifungal compounds that inhibit chitin synthase. NikD is a 389-residue flavoenzyme in the nikkomycin biosynthesis pathway of *Streptomyces tendae Tü901* that is postulated to catalyze the four-electron oxidation of piperidine-2-carboxylic acid to picolinic acid, as well as a substrate isomerization step.<sup>1</sup> NikD is a member of the family of flavoenzymes that includes monomeric sarcosine oxidase (MSOX),<sup>2</sup> with nikD having approximately 25% sequence identity with MSOX. We have determined the crystal structure of Se-Met nikD to 1.75 Å resolution, as well as the native nikD to 1.9 Å. Both Se-Met and native nikD bind a ligand that is structurally consistent with picolinate. NikD contains two domains and, like MSOX, the flavin is covalently bound to the enzyme by a thioether linkage from the C8 methyl group of flavin to a cysteine side chain. In SeMet nikD, the carboxylic acid moiety of the putative picolinate ligand is bound in a manner similar to MSOX, while the remainder of the active site differs radically in spatial orientation and the placement of active site side chains. Furthermore, in native nikD, the face of the aromatic ring of the ligand has been rotated by approximately 90° with respect to the ligand as found in Se-Met nikD. Native nikD also appears to have an open conformation while Se-Met nikD has a closed conformation, with a movement of the ligand-binding domain by approximately 7 Å between the open and closed forms. This large scale motion may be related to a decrease in pH from 6.5 in the Se-Met enzyme to 6 in the native nikD.

<sup>1</sup> D. Venci, G. Zhao, and M.S. Jorns. (2002) *Biochemistry*. 41:15795-15802.

<sup>2</sup> P. Trickey, M.A. Wagner, M.S. Jorns, and F.S. Mathews (1999) *Structure*. 7:331-345.