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Structure and Catalytic Mechanism of S-adenosylmethionine Synthetase. Fusao Takusagawa, Junichi Komoto, Taro Yamada, George Markham, Molecular Biosciences, Univ. of Kansas, 1200 Sunnyside Ave., Lawrence, KS 66045 USA.

S-Adenosylmethionine synthetase (MAT) catalyzes formation of *S*-adenosylmethionine (SAM) from ATP and L-methionine (Met) and hydrolysis of tripolyphosphate to PP_i and P_i. *E. coli* MAT (eMAT) has been crystallized with the ATP analogue AMPPNP and Met, and the crystal structure has been determined at 2.5 Å resolution. eMAT is a dimer of dimers and has a 222 symmetry. Each active site contains the products (SAM and PPNP). A modeling study indicates that the substrates (AMPPNP and Met) can bind at the same sites of the products and only a small conformation change of the ribose ring is needed in conversion of the substrates to the products. On the basis of the ternary complex structure and a modeling study, a novel catalytic mechanism of the SAM formation is proposed. In the mechanism, neutral His14 acts as an acid to cleave the C5'-O5' bond of ATP while simultaneously a change in the ribose ring conformation from C4'-*exo* to C3'-*endo* occurs, and the S of Met makes a nucleophilic attack on the C5' to form SAM. All essential amino acid residues for substrate binding found in eMAT are conserved in the rat liver enzyme, indicating that the bacterial and mammalian enzymes have the same catalytic mechanism. However, a catalytic mechanism proposed recently by González *et al.* based on the structures of three ternary complexes of rat liver MAT (*J. Mol. Biol.* **331**, 407 (2003)) is substantially different from our mechanism.