

A Radical Solution for C(sp³)–C(sp³) Bond Formation during the Biosynthesis of Macrocyclic Membrane Lipids

Archaea synthesize isoprenoid-based ether-linked membrane lipids, which enable them to withstand extreme environmental conditions, such as high temperatures, high salinity, and low or high pH values. In some archaea, such as *Methanocaldococcus jannaschii*, these lipids are further modified by forming carbon–carbon bonds between the termini of two lipid tails within one glycerophospholipid to generate the macrocyclic archaeol or forming two carbon–carbon bonds between the termini of two lipid tails from two glycerophospholipids to generate the macrocycle glycerol dibiphytanyl glycerol tetraether (GDGT). GDGT contains two 40-carbon lipid chains (biphytanyl chains) that span both leaflets of the membrane, providing enhanced stability to extreme conditions. How these specialized lipids are formed has puzzled scientists for decades. The reaction necessitates coupling two completely inert sp³-hybridized carbon centers, which has not been observed in nature. Here we use X-ray crystallography, high-resolution mass spectrometry, chemical synthesis, and biochemical analyses to show that the gene product of *mj0619* from *M. jannaschii*, which encodes a radical S-adenosylmethionine enzyme, is responsible for biphytanyl chain formation during synthesis of both the macrocyclic archaeol and GDGT membrane lipids.