2024
4(2), 696

Journal of
Molecular Chemistry

Chemistry of Coenzyme F_{420} in Environment

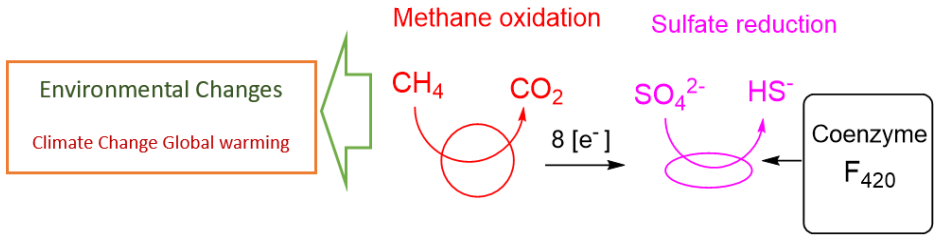
Shive Murat Singh Chauhan

Department of Chemistry, University of Delhi, New Delhi-110007, India

Submitted on: 12-Dec-2023, Accepted and Published on: 29-Apr-2024

Review

ABSTRACT



Coenzyme F_{420} is one of the ancient and rare coenzymes. The unique electrochemical properties of F_{420} are compared with the ubiquitous flavin coenzymes FMN (flavin mononucleotide), FAD (flavin adenine dinucleotide), and nicotinamide coenzyme NADP+ (nicotinamide adenine dinucleotide phosphate). The 7,8-didemethyl-8-hydroxy-5-deazaflavin core of F_{420} is structurally and biosynthetically related to FMN and FAD, but chemical reactions are similar to NADP+. The role of F_{420} and related ancient coenzymes and cofactors in methanogenesis and methanotrophic reactions in methane and short alkane oxidations is widely increasing to understand the mechanism of global warming and climate change.

Keywords: Coenzyme F_{420}, Methanogenesis, Methanotrophic archaea, Biochemical reactions, Climate change.

INTRODUCTION

Coenzymes are organic molecules that bind to the active site of selected enzymes during the catalysis of the reactions. These are small organic non-protein molecules that bind especially to proteins and participate in catalytic biotransformation. Most of them are distributed across all phylogenetic kingdoms. Coenzymes are involved in redox reactions, group activations, group transformations, and other diverse reactions.[1–3] Several ancient coenzymes and metal-based cofactors are involved in methanogenesis and they do not occur in other organisms.[3] These methanogens belong to the domain of the archaea and are capable of the biosynthesis of methane.[4,5] Methanogenesis has been widely accepted as an ancient metabolism, but the precise evolutionary trajectory remains hotly debated.[6–8] Revisiting the phylogenies of key catabolism-involved proteins further suggests that the last archaea common ancestor (LACA) was capable of versatile H_2, CO_2, and methanol-utilizing methanogenesis. Methanogenesis is not only a hallmark metabolism of archaea, but also the key to resolving the enigmatic lifestyle that ancestral archaea took and the transition that led to physiologies prominent today. Based on phylogenetic and experimental analyses indicate that methane (and other alkanes) metabolism preceded the origin of archaea and the innovation of a protein dedicated to methane production coincided with the emergence of LACA.[9] From this ancestor, downstream inheritance and loss of methane metabolism paralleled early diversification of the domain, pointing towards a key role of methanogenesis in the origin and evolution of archaea.[10] Archaea are abundant in soils, ocean sediments, and the water column. They have crucial roles in processes mediating global carbon and global warming. Moreover, they represent an important component of the human microbiome, where their role in human health and disease is well understudied.[11] The development of culture-independent sequencing techniques has provided unprecedented access to genomic data from a large number of inaccessible archaeal lineages. This is revolutionizing the diversity and metabolic potential of the archaea in a wide variety of environments, an important step toward understanding their ecological role and industrial applications.[12–14]

The ancient coenzyme F_{420} is one of the important members of the ancient coenzymes and cofactors that participate in methanogenesis, sulfate-reduction, and methanotrophic reactions in archaea.[15,16] The coenzyme F_{420} is also present in a wide range of actinomycetes, mycobacteria, and other bacteria. The coenzyme F_{420} more structurally resembles universal flavin-coenzymes FMN and FAD. Further, coenzyme F_{420} chemically more resembles nicotinamides NADH and NADPH (Figure-1).[15,16] The coenzyme F_{420} consists of three components: a) the redox active isoalloxazine head group F_0, b) a phospho-organic acid linker, and c) a ϒ-link polyglutamate tail of variable length.

*Corresponding Author: Prof. S.M.S. Chauhan, Department of Chemistry, University of Delhi, New Delhi, India.
Email: smschauhan1952@gmail.com

URN:NBN:sciencein.jmc.2024.696

Published by: ScienceIn Publishing
https://pubs.thescienceinorg/jmc

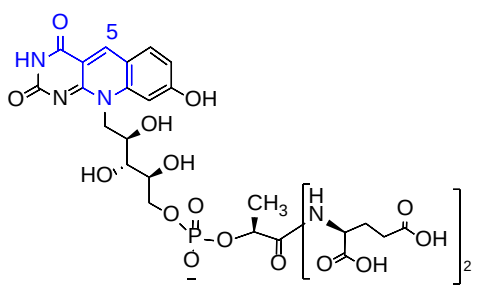
The F_0 is a 5-deazaflavin moiety that contains three chemical substituents as compared to flavin which gives F_{420} unique spectral and electrochemical properties. The important change is the substitution of the redox active N-5 atom of the isoalloxazine ring for a carbon which prevents F_{420} from forming a stable semiquinone leading to F_{420} as a hydride carrier similar to NAD^+ and $NADP^+$. The second change is that C-7 and C-8 methyl of flavin are demethylated in F_{420} and the third is a hydroxyl group which is introduced at the C-8 position. As a result of three substituents, F_{420} has a much lower standard redox potential (-340 mV) than riboflavin (-210 mV), FAD (-220 mV), and FMN (-190 mV). This leads to F_{420} being well suited to mediate the low potential reactions of anaerobic metabolism, as well as reductions that require a low potential electron donor. The reduced coenzyme F_{420} H_2 functions as cellular hydride transfer similar to $NADPH_2$ (Figure-1). The $F_{420}H_2$ is used by different $F_{420}H_2$-dependent reductases to reduce substrates in ene-reduction and enantioselective reductions.[12–14] The coenzyme F_{420} is used in the catalysis of different steps in antibiotic biosynthesis, xenobiotic biodegradation, climate change, reductive activation of prodrug nitroimidazole, and biosynthesis of natural products.[15,16] In this brief account, the isolation of F_{420}, characterization by spectroscopic techniques, chemical synthesis, biosynthesis, and applications of various reactions of coenzyme F_{420} in the environment are discussed.

Isolation, Characterization, and Chemical Synthesis of Coenzyme F_{420}

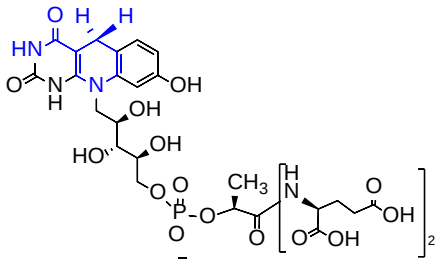
Isolation of coenzyme F_{420}

The isolation, purification, and properties of a fluorescent compound from *Methanobacterium* strain M. o. H was reported in 1972.[17] The yellow compound had a strong absorption maximum at 420 nm and blue-green fluorescence which disappeared on reduction. The results of analysis of hydrolytic fragments and periodate oxidation products of the coenzyme by infrared, UV-visible, ^1H, and ^{13}C-NMR spectroscopy, mass spectrometry, and quantitative elemental analyses indicate that coenzyme F_{420} is N-[N-O-[5-(8-hydroxy-5-deazaisoalloxazin-10-yl)-2,3,4-tryhydroxy-4-pentoxy hydroxy phosphinyl]-L-lactyl]-ϒ-L-glutamyl]-L-glutamic acid (Figure-2).[17–19] The acidic hydrolysis of cofactor F_{420} gives cofactor F_0, F_0-P and lactyl-ϒ-L-glutamyl-L-glutamic acid (Figure-2).[19] The hydrolysis product of the co-factor F_{420} is F_O-5′-phosphate (F_O-P). The structure of F_O-P is an analogue of FMN (Figure 2). Chemoenzymatic synthesis of this unnatural deazaflavin cofactor has been achieved and used as F_{420}-dependent reductase.[20,21] The high-performance liquid chromatographic analysis of aerobically grown stationary-phase cultures of three bacterial species confirmed that these bacteria-synthesized F_{420} with oligo glutamate side chains of different lengths.[22,23] The analysis of the distribution, phylogeny, and genetic organization of the Cof genes suggest that F_{420} was first synthesized in ancestral actinobacterium and F_{420} biosynthesis genes were then disseminated horizontally to archaea and other bacteria.[22,23]

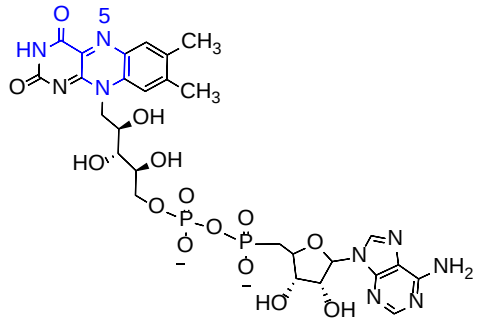
Coenzyme F_{420} has been isolated from marine sponges and its structure was characterized.[24] Analyses of the F_{420}s present in *Methanococcus jannaschii* have shown that these cells contain a series of ϒ-glutamyl-linked F_{420}s capped with a single, terminal α-linked L-glutamate. The predominant form of F_{420} was designated as α-F_{420}-3 and represented 86% of the F_{420}s in these cells. Analyses of *Methanosarcina thermophila*, *Methanosarcina barkeri*, *Methanobacterium thermoautotrophicum*, *Archaeoglobus fulgidus*, and *Mycobacterium smegmatis* showed that they contained only ϒ-glutamyl-linked F_{420}s.[25] The methanogenic archaea *Methanosarcina thermophila* and *Methanoclleus thermophilus* were cultivated on different carbon sources and their coenzyme F_{420} composition has been assayed by reversed-phase ion-pair high-performance liquid chromatography regarding both, overall cofactor F_{420} production and distribution of F_{420} glutamyl tail length.[26] Flow cytometric quantification, sorting, and sequencing of methanogenic archaea based on F_{420} autofluorescence.[27] Purification of a novel coenzyme F_{420} from *Mycobacterium smegmatis* was characterized by UV-visible spectrum.[28] Purification of a novel coenzyme F_{420}-dependent glucose-6-phosphate dehydrogenase from *Mycobacterium smegmatis* was achieved and Si-Face stereospecificity at C-5 of coenzyme F_{420} for F_{420}- dependent glucose-6-phosphate dehydrogenase was confirmed.[29–32] Production of coenzyme F_{420} and its biosynthetic precursor F_0 was examined with a variety of aerobic actinomycetes to identify an improved source for these materials. Based on fermentation costs, safety, and ease of growth, *Mycobacterium smegmatis* was the best-reported source for F_{420}-5,6. *M. smegmatis* produced 1 to 3 μmol of intracellular F_{420} per liter of culture, which was more than the 0.85 to 1.0 μmol of F_{420}-2 per liter usually obtained with *Methanobacterium thermoautotrophicum* and ~10-fold higher than the best reported aerobic actinomycetes.[33,34] Coenzyme F_{420} has been assayed by high-performance liquid chromatography with fluorimetric detection; this permits quantification of individual coenzyme F_{420} analogs, whilst avoiding the inclusion of interfering materials. The most abundant analogs in *M. barkeri* were coenzymes F_{420}-2 and F_{420}-4, whilst in *M. mazei* coenzymes F_{420}-2 and F_{420}-3 predominated. Significant changes in the relative proportions of the coenzyme F_{420} analogs were noted during batch growth, with coenzymes F_{420}-2 and F_{420}-4 showing opposite responses to each other and the same being also true for coenzymes F_{420}-3 and F_{420}-5. F_{420} degradation in *Methanobacterium thermoautotropicum* during exposure to oxygen. This suggests that an enzyme responsible for transferring pairs of glutamic acid residues may be active. The degradation fragment F_O was also detected in cells in the late exponential and stationary phase.[35] This isolation is important to know that F_0 is degradation or residual from an unreacted intermediate during the biosynthesis of F_{420}.[36] The isolation and identification of a naturally occurring 7,8-didemethyl-8-hydroxy-5-deazariboflavins with mono glutamate of coenzyme F_{420} was reported from *Mycobacterium avium*.[37] In the search for lincomycin cosynthetic factor (LCF) the Isolation and identification of 7,8-didemethyl-8-hydroxy-5-deazaribo flavin(F_0) in place of F_{420}, an unusual cosynthetic factor in streptomycetes, from *Streptomyces lincolnesis* has been reported.[38,39] Similarly, in the search for synthetic factor I, a factor



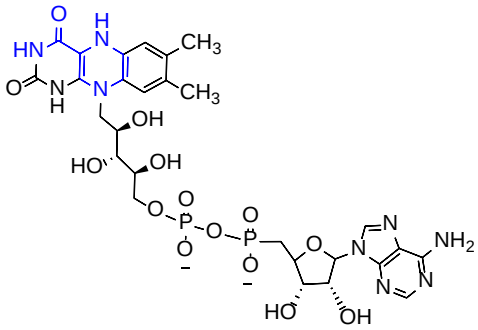
Coenzyme F_{420}



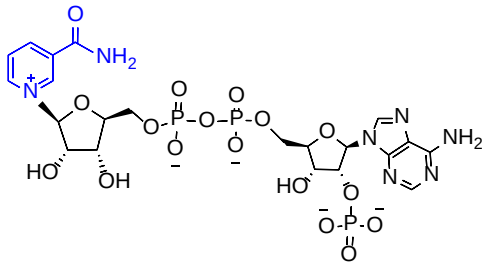
$F_{420}H_2$



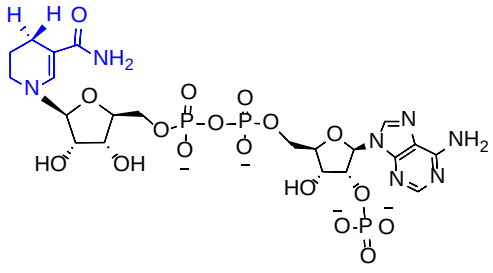
Flavin adenine dinucleotide (FAD)



$FADH_2$



Nicotinamide adenine dinucleotide phosphate ($NADP^+$)



$NADPH_2$

Figure 1: Comparison of Coenzyme F_{420} with FAD and $NADP^+$

involved in hydrogen-transfer in *Streptomyces aureofaciens*, the isolation and characterization of F_0 has been reported.[40,41] The F_0 was abundant in the culture supernatant, whereas F_{420} was restricted. Hence the fluorescence observed in bacterial cells of *P. rhizoxinica* is derived from 3PG-F_{420} and F_0. Genome sequencing revealed F_{420} biosynthetic genes in the Gram-negative, endofungal bacterium *P. rhizoxinica* a symbiont of phytopathogenic fungi. The structure elucidation by Fluorescence microscopy, high-resolution LC-MS, and high-resolution NMR demonstrated that the encoded pathway is active and yields the unexpected derivatives of a new coenzyme F_{420} (3PG-F_{420}).[42]

Synthesis of Cofactor F_0:

To confirm the chemical structure of naturally occurring 5-deazaisoalloxazine cofactors F_{420}, the synthesis of cofactor F_0, the acid hydrolysis product of cofactor F_{420}, has been undertaken by different research groups. In the first synthesis, the important intermediate N-(ribityl)-3 hydroxy aniline was prepared by reduction of N-(ribosyl)-3-hydroxyaniline with $NaBH_3CN$. The reaction of N-ribityl-3-hydroxyaniline with 6-chlorouracil formed 6-N[(ribityl)3-hydroxylanilino] uracil which on reaction with a large excess of trimethyl orthoformate in the presence of p-toluene sulfonic acid as catalyst formed cofactor F_0[43] which is identical to natural product.[19]

1-Deoxy 1-(3,4-dihydro-8-hydroxy-2,4-dioxopyrimido[4,5-b] quinolin-10-(2H)-yl)-D-ribitol (7,8-didemethyl-8-hydroxy-5-deazariboflavin), the flavin moiety of *Methanobacterium* coenzyme F_{420}, and its 7-methyl analog were prepared by acid-catalyzed reaction of appropriately substituted 6-(N-D-ribityl anilino) uracil with trimethyl or triethyl orthoformate followed by deprotection.[44]

The cofactor F_0 was prepared by method A without the use of protecting groups by condensation of 2-chloro-4-hydroxybenzaldehyde with 6-D-ribitylaminouracil in 70% yield, whereas in method B cofactor F_0[45] was formed in 92% yield by condensation of N-ribityl-3-hydroxyaniline with 6-chloro-5-formyluracil in by modifications of their earlier publications.[46,47]

The purification of natural and non-natural deazaflavins is challenging, hence the synthesis of F_0 and F_{420} is more tedious due to the presence of electron-rich and acidic 8-hydroxyl substituent in both cofactors. The anaerobic and dark conditions are required for early-stage intermediates purification by ion exchange chromatography, hence the synthesis of deazaflavin cofactor F_0 has been started by O-protection of 3-aminophenol with tert-butyl dimethyl silyl chloride in the preparation of 5-[(3-(tert-butyl dimethyl silyl)oxy)phenyl)amino]pentane which on reaction with 6-chloro-2,4-dioxohexahydropyrimidine-5-carbaldehyde gave cofactor F_0.[48]

The bis-isopropylidene D-ribose was converted to the corresponding aldehyde, then to the corresponding ribitylamine via oxime followed by reduction with $LiAlH_4$.The reaction of amine with 6-chlorouracil followed by deprotection with TFA and subsequent reaction with 6-chloro-4-hydroxybenzaldehyde gave the cofactor F_0.[49] The study of chromatographic and spectral properties indicates that the detected low molecular-weight activators and putative emitters in the luminescent reaction of Siberian enchytraeid Henlea sp. is F_0.[50] The reaction of N(ribityl)-3(silyl protected hydroxy) aniline with paraformaldehyde and barbituric acid in DMF/acetic acid followed by purification by column chromatography gives F_0 in moderate yield.[45,50]

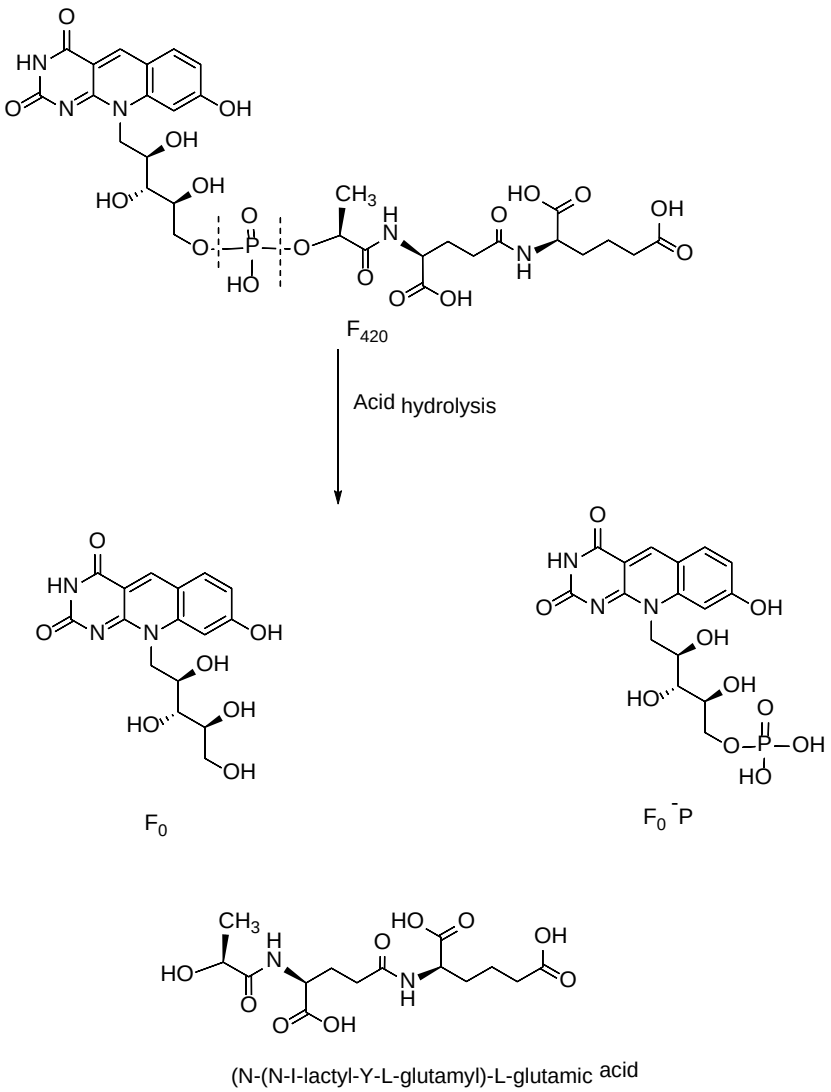


Figure-2: Acid hydrolysis products of Coenzyme F_{420}

Chemical synthesis of the selected coenzyme F_{420}:

The first total synthesis of *Methanobacterium* redox coenzyme Factor F_{420} has been achieved by the formation of a phosphotriester bond between a protected 8-hydroxy-10-D-ribityl-5- deazaisoalloxazine moiety and a peptide moiety, (L-lactoyl-Ɣ-L-glutamyl) -L-glutamic acid tribenzyl ester, by the phosphite triester approach using 2,2,2-trichloroethyl phosphorodichloridite, followed by successive deprotection.[46] The synthetic product was comparable to natural F_{420} in terms of chromatographic and spectroscopic methods.[17] A proposed isomer of redox coenzyme F_{420} having α-glutamyl bonding, has been synthesized from 8- benzoyloxy-10-D-ribityl-5-deazaflavin and α-L-glutamyl-l glutamic acid moiety, by the phosphite triester approach followed by deprotection procedure[51] which is similar to the product isolated from natural source.[25,52]

Chemoenzymatic synthesis of F_0, F_0-P and their application in enzymatic reactions:

The main challenge in the use of F_{420}-dependent enzymes is the limited availability of the coenzyme F_{420}. Many of the organisms that produce F_{420} are hard to culture or grow relatively slowly. The best organism for the isolation of coenzyme F_{420} is *Mycobacterium smegmatis*.[34] Hence the applications of F_0 and F_0-P in selected enzymatic reactions have been examined. Fo is redox-active and used in the catalysis of hydride transfer reactions with less efficiency than F_{420}.[48] F_{420} has been replaced by F_0 in the biosynthesis of tetracycline in *S. cerevisiae*. [53]

The structure of F_O-P is analogous to FMN, the cofactor that is used in enzymes that share homology with the TIM barrel fold and split β-barrel-like fold F_{420}-dependent oxidoreductases and that may be the ancestors of F_{420}-dependent oxidoreductases. The F_O core was synthesized by following the literature procedure with small modifications.[48] F_O was 5′-phosphorylated with an engineered variant of the riboflavin kinase from *C. ammoniagenes* and site-directed mutagenesis was applied to the enzyme to accommodate F_O. The enzyme activity with F_O-P as a coenzyme was tested for a representative member of each structural class of F_{420}-dependent oxidoreductases and results indicate show that F_O-P could be used as an alternative

deazaflavin cofactor in vivo.[20] Heterologous expression of the riboflavin kinase from *Schizosaccharomyces pombe* enabled in vivo phosphorylation of F_O, which was supplied by either organic synthesis ex vivo, or by a co-expressed F_O synthase in vivo, producing F_O-P in E. coli as well as in *S. cerevisiae*. The results show that bacterial and eukaryotic hosts can be engineered to produce the functional deazaflavin cofactor mimic F_O-P for the biocatalytic production of valuable compounds.[20]

Recombinant DNA technology in the production of coenzyme F_{420} and biosynthesis of secondary metabolites:

Protein production using recombinant DNA technology has had a fundamental impact on molecular biology. A combination of co-expression of the F_{420} biosynthetic proteins and fine-tuning of the culture media has encreased the production of F_{420} levels of up to 10 times higher compared to the wild-type *M. smegmatis* strain.[34,54]

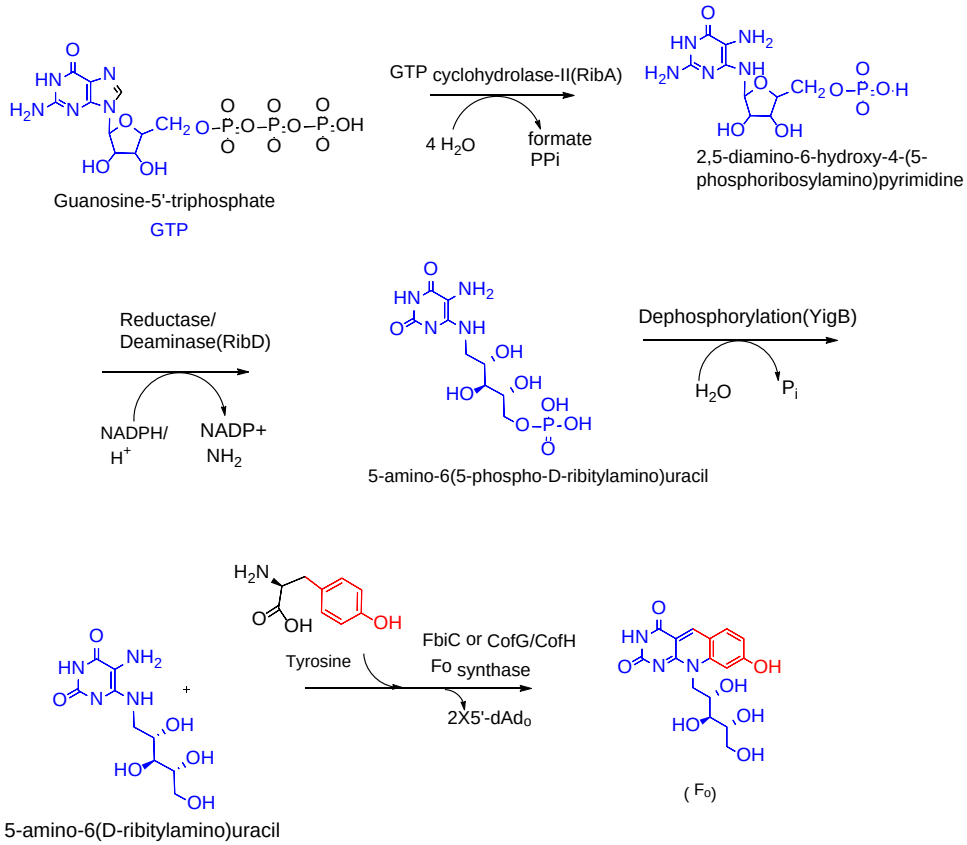
The identification of phospho-enol pyruvate (PEP) as a limiting precursor and its improvement by use of gluconeogenic carbon sources and overexpression of PEP synthase, the biosynthesis of F_{420} in E. coli has been optimized.[55] The combination of F_0 biosynthesis and variations of T7 promoter strengths and ribosome binding site activity to varying the expression ratio for the eight biosynthetic genes have been used in the high-yield production of F_{420} in E. coli.[36] The extensive and increasing availability of genomic and metagenomic data and their uses in the F_{420}-dependent transformations may lead to the discovery of novel secondary metabolites and untapped resources in various technological applications.[56]

BIOSYNTHESIS OF F_{420}

The early steps of the F_{420} biosynthesis pathway are shared with riboflavin biosynthesis[57] starting with the cleavage of the imidazole ring of GTP by enzyme GTP cyclohydrolase II (RibA), deamination/reduction by RibD and YigB-mediated dephosphorylation to 5-amino-6-(ribitylamino)-uracil.[58]

Biosynthesis of cofactor F_{420}

A key step in the biosynthesis of F_{420} is the formation of the deazaflavin fluorophore F_0 which is formed by condensation of tyrosine with 5-amino-6-ribiytylaminouracil. It is demonstrated



Scheme 1: Biosynthesis of Archaeal Cofactor F_0

that fbiC is required by *Mycobacterium bovis* BCG for coenzyme F_{420} and F_O biosynthesis.[59] Further CofG and CofH are required for Fo biosynthesis in *Methanocalducoccus jannaschii*.[60] The F_0 synthase is isolated from the thermophilic soil bacterium *Thermobifida fusca* (T. fusca) with high G+C content. The bioinformatic study predicted that the *T. fusca* genome contains genes encoding for F_{420}-dependent enzymes.[61] Further, the isolation and characterization of thermostable F_{420}: NADPH oxidoreductase confirmed the presence of an F_{420}-dependent enzyme in *T. fusca*.[62] The sequence analysis of the gene coding for the enzyme responsible for F_0 biosynthesis, F_0 synthase, suggests that it contains two subunits in archaea and cyanobacteria (CofG/CofH), whereas a single large bifunctional enzyme is present in actinobacteria. The chemically challenging step is catalyzed by the radical SAM enzyme complex CofG/H in archaea or the homologous dual-domain protein FbiC in actinobacteria.[63–66] The abstraction of the tyrosine amine hydrogen by the CofH 5' deoxyadenosyl radical undergoes fragmentation leading to the formation of the p-hydroxybenzyl radical. The addition of this radical to diamino uracil followed by oxidation gives an intermediate that diffuses to the CofG active site where a second hydrogen abstraction generates a radical which on cyclization, followed by oxidation and elimination of ammonia completes the formation of deazaflavin F_O.[67,68] No crystal structures have been reported for any F_0 synthase and would be important to obtain in the future to provide structural evidence for the mechanistic details of the two radical SAM

reactions necessary for the synthesis of the unique deazaflavin core F_0. (Scheme-1).[67,68]

The subsequent decoration of F_0 is diverged and therefore hampered the transferability to other hosts.[69] F_{420} is biosynthesized through two converging biosynthetic branches. In one branch, F_0 synthase (FbiC or CofGH pair, where Fbi and Cof refer to mycobacterial and archaeal protein respectively) catalyzes the formation of the cofactor F_0 which is the first intermediate in the biosynthetic pathway to possess a complete deazaflavin chromophore. F_0 is redox-active and capable of catalyzing hydride transfer reactions but is less efficient than F_{420}. Fo is uncharged and might easily diffuse across membranes.[54]

Diversity in the Biosynthesis of F_{420}

Biosynthesis in archaea:

The rare metabolite 2-phospho-L-lactate represents a new natural product that was chemically identified in *Methanobacterium thermoautotrophicum*, *M. thermophila*, and *M. Jannaschii*. In the biosynthetic pathway of F_{420} in archaea, the lactaldehyde is converted to L-lactate by CofA to L-lactate.[70] The biochemical route for the formation of the phosphodiester bond in coenzyme F_{420} has been studied in the *Methanoarchaea*: *Methanosarcina thermophila* and *Methanococcus jannaschii* by Graupner and White in 2001.[71] The enzyme-lactate kinase catalyzes the reaction of GTP to 2-phospho-L-lactate(2PL).[72] The enzyme 2-PL guanylyltransferase (CofC) activates 2PL by condensation with GTP to form the intermediate compound lactyl-diphospho-5'-guanosine. The CofD transfers 2PL from LPPG to F_0 to form F_{420}-0. The enzyme CofE catalyzed the reaction of F_{420}-0 with L-glutamate in the presence of GTP to form variable-length-ϒ-linked glutamate F_{420}.[52,73–76] The α-F_{420}-3 is produced by CofF from ϒ-F_{420}-2 (Scheme 2).[52]

Biosynthesis in bacteria

The analysis of purified F_{420} biosynthesis enzymes from mycobacteria indicated that the central glycolytic and gluconeogenic intermediate phosphoenolpyruvate (PEP), is a precursor for F_{420} biosynthesis.[77–80] The bacterial enzyme Mtb-FbiD[64] catalyzes the reaction of GTP with PEP to form enolpyruvyl-diphospho-5'-guanosine (EPPG) which subsequently reacts with F_0 in the presence of FbiA to form DH-F_{420}-0.[64,65] The DH-F_{420}-0 is modified to form mature F_{420} by dual-function enzyme FbiB.[77,81] The bacterial enzyme FbiB possesses an N-terminal domain homologous to archaeal enzyme CofB, which adds a variable-length ϒ-linked polyglutamate tail of residues. The C-terminal domain of FbiB reduces the enol group of DH-F_{420} converting it into mature F_{420}.[82,83] The reduction of DH-F_{420} improves the stability of the molecule by removing the high-energy phosphate bond. The methylene group of the enolpyruvyl moiety is reduced by $FMNH_2$ of FbiB/CofX. The FbiB is a two-domain protein and produces F_{420} with predominantly 5–7 L-glutamate residues in the polyglutamate tail. The N-terminal domain of FbiB is homologous to CofE with an annotated ϒ-glutamyl ligase activity, whereas the C-terminal domain has sequence similarity to an FMN-dependent family of nitroreductase.[82,83] Genomic analysis indicates that independent FbiE homologs are present in the genomes of several predicted bacterial and archaeal F_{420} producers and putative F_{420}-producing members of the archaeal phylum *Lokiarchaeota* possess a dual functional FbiB homolog suggesting that bacteria and archaea also employ a PEP dependent pathway for F_{420} biosynthesis.[82,83] (Scheme-2). A convergent pathway to the biosynthesis of the versatile coenzyme F_{420} is presented for a deeper understanding of F_{420}-dependent enzymes and metabolites across microorganisms.[69] The biosynthetic route of coenzyme F_{420} in a class of Gram-negative bacteria redefines functional subgroups of the NTR superfamily by heterologous expression and in vitro assays that stand-alone NTR enzymes from *Thermomicrobia* exhibit dehydro-F_{420} reductase activity.[84]

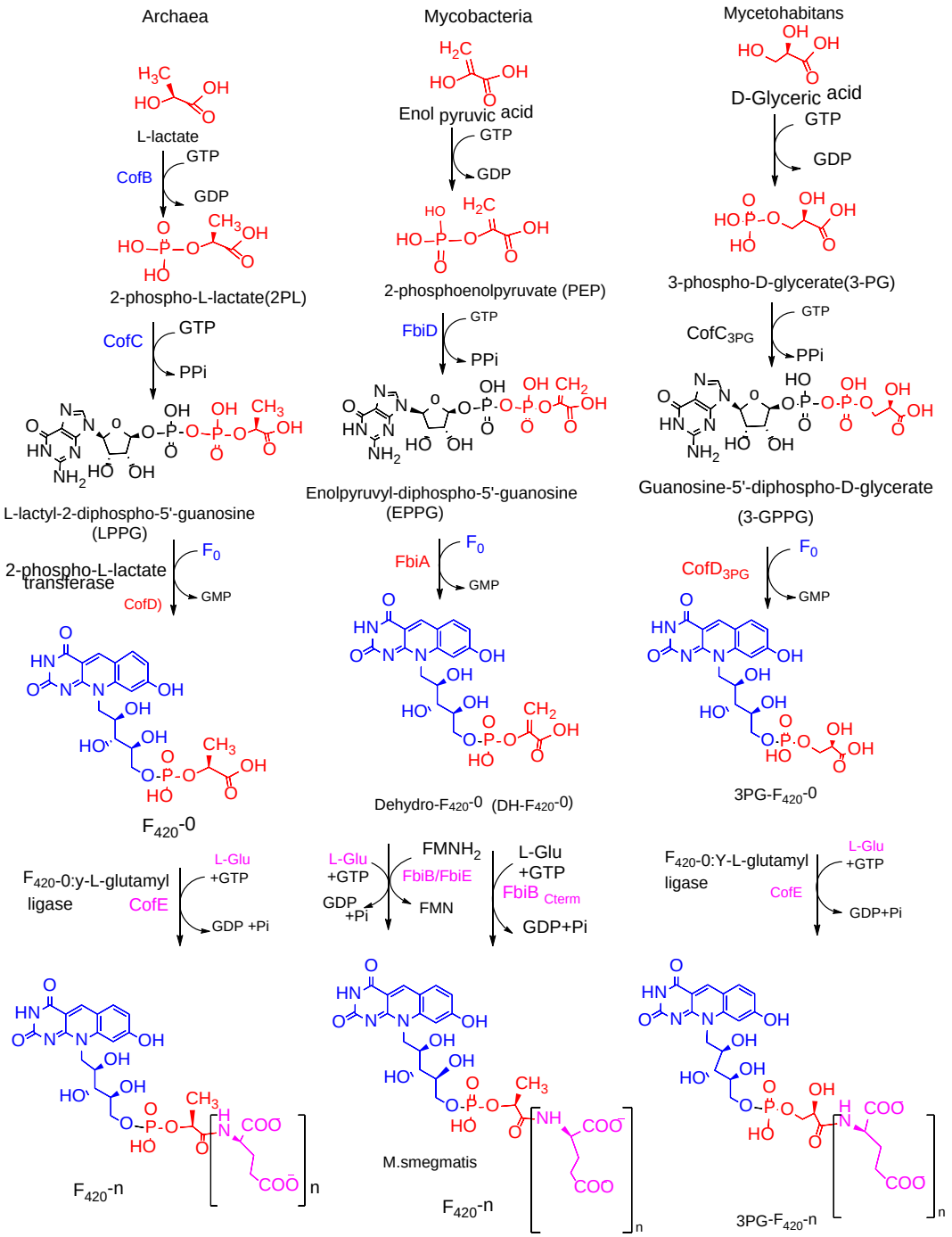
Biosynthesis in betaproteobacterium *P. rhizoxinica*

Genome sequencing, fluorescence spectroscopy, and analytical chemistry revealed that some Gram-negative bacteria have acquired F_{420} genes by horizontal transfer.[4,5,22] Gram-negative, endofungal bacterium *Paraburkholderia rhizoxinica*, a symbiont of phytopathogenic fungi.[85,86] *P. rhizoxinica* produces F_{420} derivatives(3PG-F_{420}) both in symbiosis as well as axenic culture. Heterologous expression and large-scale production in *E. coli* allowed for the elucidation of their chemical structure. Enzyme assays showed that a switch in substrate specificity of CofC is responsible for the biosynthesis of 3PG-F_{420}. The most plausible scenario is that CofC is incorporated in 3-phospho-D-glycerate(3PG) in place of 2PL or PEP for F_{420} biosynthesis. The $CofD_{3PG}$catalyzes the reaction of 3PG with GTP to form 3-guanisine-5'-diphospho-D-glycerate (GPPG) which further reacts with F_0 in the presence of $FbiA_{3PG}$ to form 3PG-F_{420}-0. A homolog of CofE catalyzes a variable-length-ϒ-linked poly glutamate tail of 1-6 residues to form mature F_{420}[42,87] (Scheme-2).

Role of coenzyme F_{420} in methanogenesis and methanotrophic reactions and their impacts on the environment:

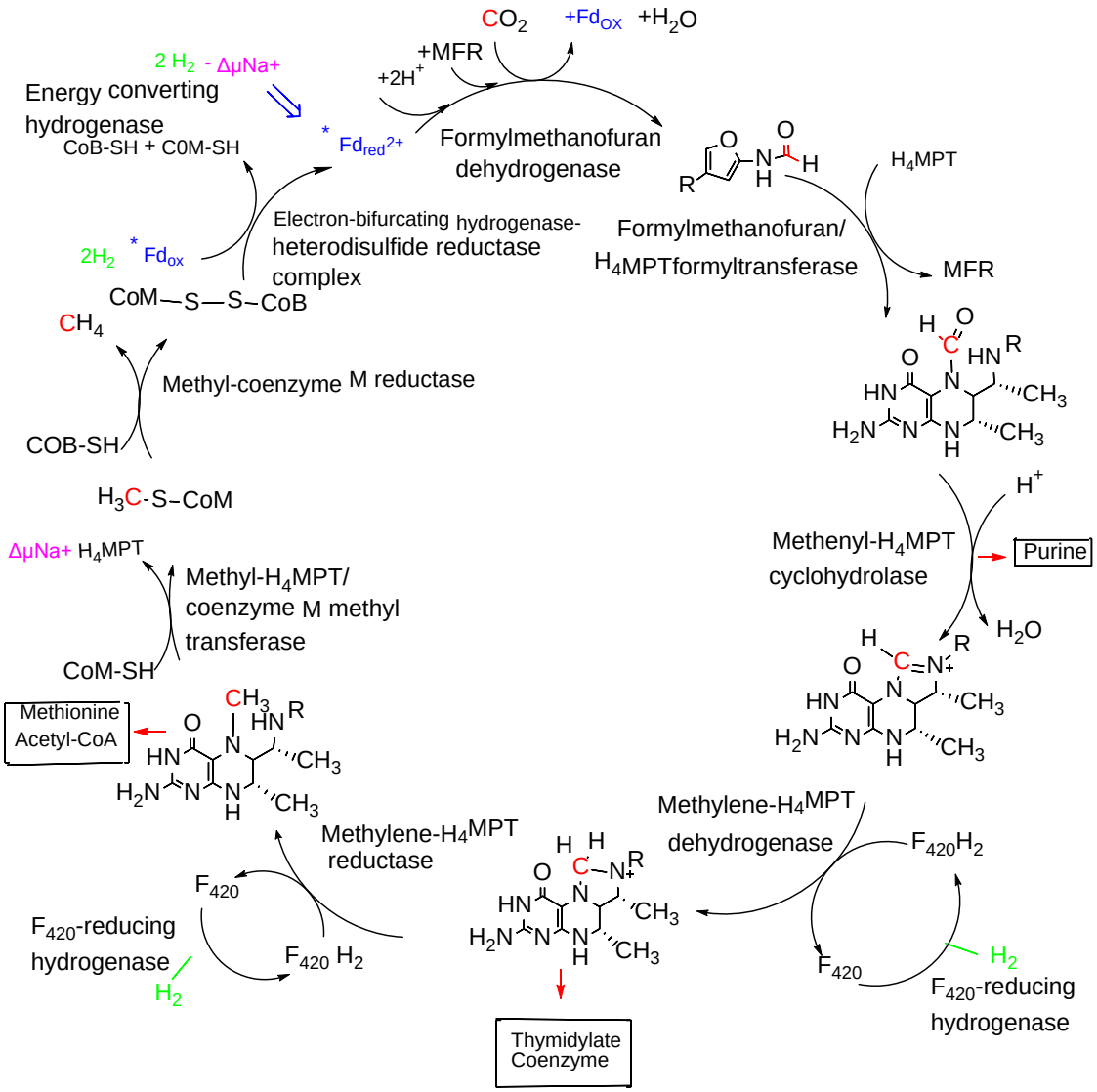
Methanogenesis:

The production of methane greatly impacts our society. The impact of methane is positive, when it is considered as renewable fuel produced in biogas generators and the impact of methane is negative, when it is considered as it is a strong greenhouse gas. Methanogenesis is first proposed in 1970s.[88,89] The majority of biological methane production is performed by methanogenic archaea, strict anaerobes that use carbon dioxide gas as a carbon source and hydrogen gas as an electron donor for methane production.[90] The methane formation from hydrogen and carbon dioxide by methanogenic archaea could be cyclic in nature.[90] Indirect evidence indicated that the first step, the reduction of CO_2 to formylmethanofuran, was somehow coupled with to last step, the reduction of the heterodisulfide (CoM-S-S-CoB) by electron-bifurcating hydrogenase-heterodisulfide reductase complex to coenzyme M (CoM-SH) and coenzyme B (CoB-SH) (Scheme 3).[91] The coupling mechanism was unraveled in 2011 via flavin-based electron bifurcation, the reduction of CoM-S-S-CoB with H_2 provides the reduction to formylmethanofuran. Sodium motive force-driven reduction of ferredoxin with hydrogen catalyzed by the energy-converting hydrogenase EhaA-T as anaplerotic reaction (Scheme 3).[92] Biological methane



Scheme 2: Biosynthesis of the coenzyme F_{420} in Archaea, Mycobacteria and Mycetohabitans

formation from H_2 and CO_2 (Wolfe cycle) is not only a quantitatively important process but possibly one of the ancient.[93] The anaerobic production of methane from CO_2 requires seven coenzymes (Coenzyme F_{420}, Methanofuran, Coenzyme M, Coenzyme B, Tetrahydromethanopterin, FeGP cofactor and Cofactor F_{430}).[94] The coenzyme F_{420} is the dominant catabolic coenzyme involved in hydrogenotrophic, formatotrophic, and methylotrophic methanogenesis.[1-3,95–97] Anaerobic oxidation of the methane route occurs in the reverse direction of CO_2 reduction to methane. Warren and co-workers elucidated the biosynthetic pathway of F_{430}, where the late stage comprises four enzymatically controlled steps in which the porphyrin-like skeleton is gradually modified including chelation, amidation, reduction by six electrons with the addition of seven protons, lactamization, and closure of a propionate side chain coupled to water extrusion.[98–100] Anaerobic oxidation of methane proceeds from CH_3-S-CoM in the same way in the reverse direction of CO_2 reduction.[101] The methane activation reaction is considered to be a reversal of methane formation during the final step of methanogenesis (Scheme 3). A radical mechanism involving the heterodisulfide made of coenzymes M and B (CoB-S-S-CoM) would react with methane, generating methyl-S-CoM and HS-CoB.[102] The structural information about the MtrA-H complex is only available for MtrA from *M. Jannaschii* and the cytoplasmic MtrA homolog from *Metbanotbermus fervidus*.[103] The reaction is assumed to be catalyzed by the methyl-coenzyme M reductase (MCR) family harbouring a nickel-containing porphinoid, the cofactor F_{430}[103] (Scheme 3). The activation of methane and reaction with heterodisulfide is involved in methanotrophic reaction. The change in the substitutions in cofactor F_{430} such as the normal cofactor is present in methanogen and ANME-2 and ANME-3, whereas the modified cofactor is present in ANME-1. [103–105]



Scheme 3: Wolfe cycle of CO_2 reduction to methane with $4H_2$ in methanogenic archaea

Sulfate-reducing archaea

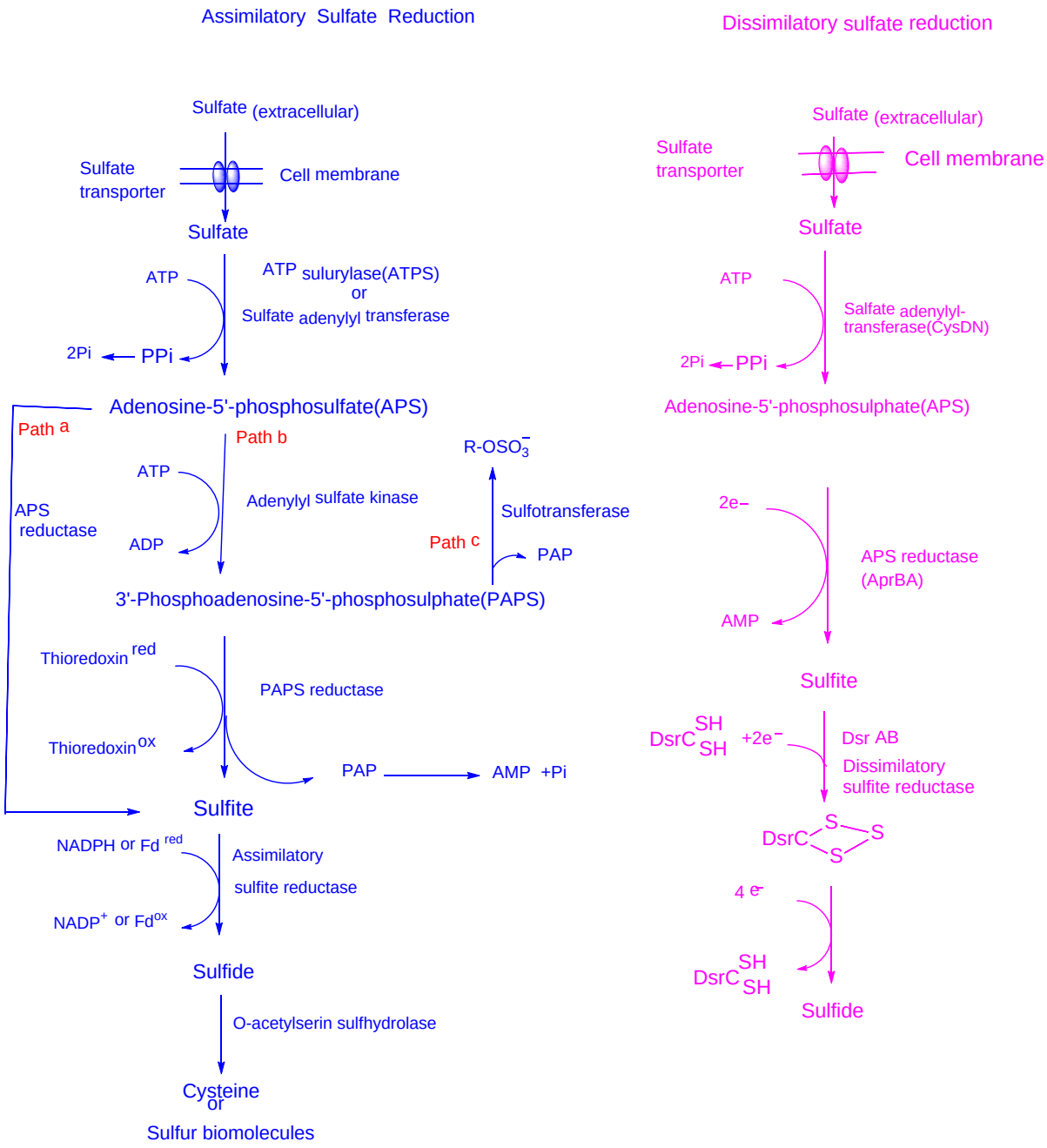
The most common methane-producing microorganisms have a high demand for sulfur due to their specific enzymes and metabolism. Most of these methanogens use sulfides (HS-), and some methanogens have been shown to metabolize higher oxidation states of sulfur or even metal sulfide (for example FeS_2) for sulfur acquisition.[106–110] However, *Methanothermococcus thermolithtrophicus* is the known methanogen capable of growing on sulfate (SO_4^{2-}) as its sole sulfur source.[111,112] The metabolism of this hydrogenotroph, isolated from geothermally heated sediments near Naples (Italy), is paradoxical, as SO_4^{2-} reduction should lead to several physiological obstacles for methane-producing microbes: (a) methanogens commonly thrive in reduced sulfidic environments where all electron acceptors other than CO_2 are depleted, including (SO_4^{2-}),[113] (b) at the interface where methanogens and SO_4^{2-} ion coexist, hydrogenotrophic methanogens must out compete with dissimilatory SO_4^{2-} reducing microorganisms for common substrate dihydrogen(H_2).[114] and (c). methanogens live thermodynamic limits of life and the adenosine triphosphate (ATP) hydrolysis coupled with sulfate reduction would be a substantial investment for such energy-limited microorganisms.[110] Finally, the SO_4^{2-} -reduction pathway generates toxic intermediates that would interfere with cellular processes. To assimilate SO_4^{2-}, the organisms would have to capture the anion and transport it into the cell using a transporter inside the cell, SO_4^{2-} is activated by an ATP sulfurylase (ATPS) to generate adenosine 5'-phosphate (APS).[115–117] Organisms can use different strategies: Path a, APS is directly reduced by an ApS reductase (APSR) to generate AMP and SO_3^{2-}. Path b, APS can further be phosphorylated to 3'-phosphoadenosine-5'-phosphate (PAPS)by APS kinase (APSK). A PAPS reductase will reduce PAPS to SO_3^{2-} and the toxic nucleotide 3'-phosphoadenosine-5'-phosphate (PAP). PAP must be quickly hydrolyzed to AMP and inorganic phosphate by PAP phosphatase (PAPP). Path c, in a different pathway, the sulfite group of PAPS is transferred to

another acceptor to build up sulfated metabolites (Scheme 4).[118–121]

Sulphite is reduced to sulfide (HS^-) by sulfite reductase and finally incorporated into cysteine by O-acetylserine-(thiol)-lyase (Scheme 4, Assimilatory sulfite reduction). The dissimilatory APsRs and dissimilatory sulfite reductases are structurally and phylogenetically distinct from their assimilatory counterparts and indirectly couple their reactions to membrane pumps allowing for energy conservation[122–126] (Scheme 4, Dissimilatory sulfite reductase). Dissimilatory sulfate reduction (DSR) is one of the oldest and most prominent microbial metabolic pathways on Earth. It is generally accompanied by zero-valent sulfur (ZVS) that is involved in several cryptic pathways in marine and terrestrial environments. The unknown DSR pathway or sulfate-to-ZVS conversion is mediated by sulfate-reducing microorganisms.[122] The simultaneous microbial production and consumption of methane appears to be an important process preventing the build-up of methane in these sediments and the emission into the water column and atmosphere.[126]

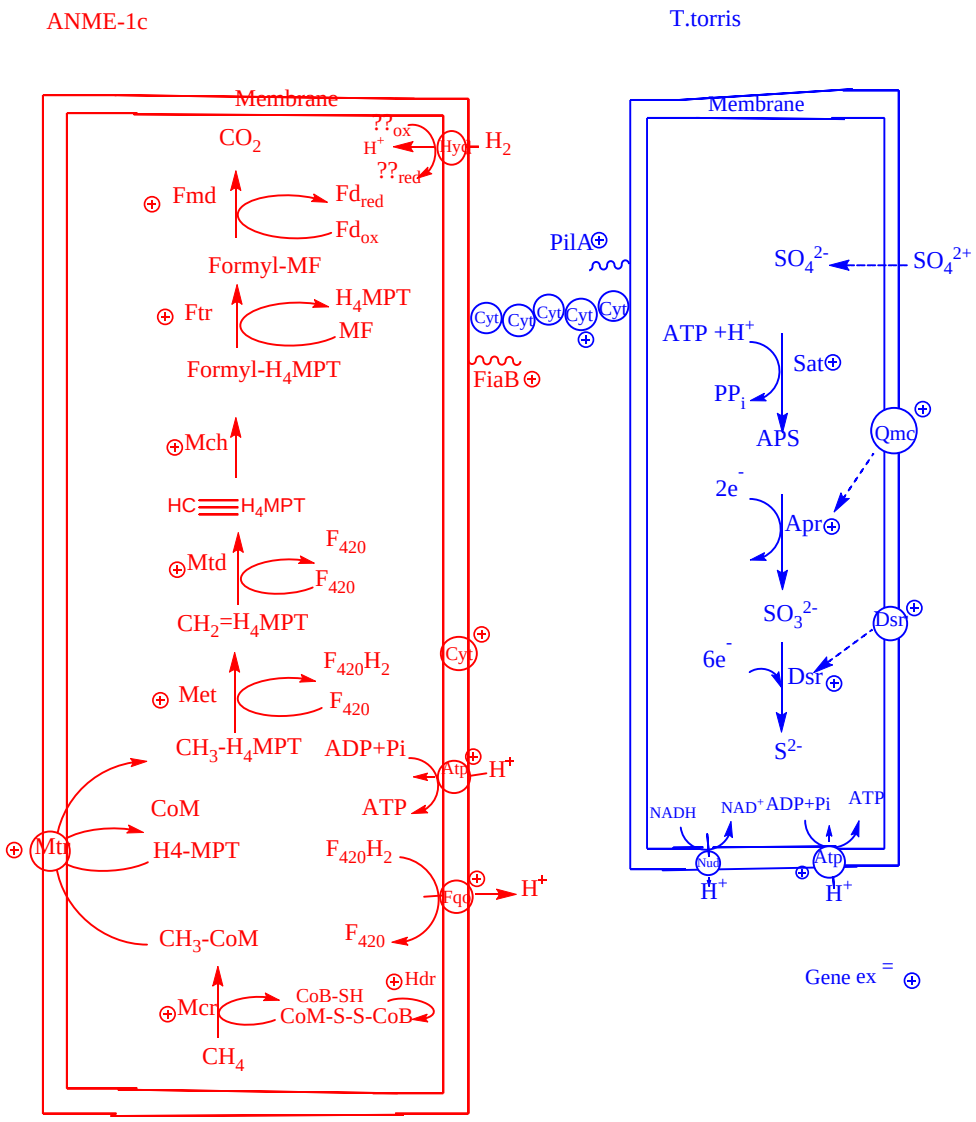
Anaerobic oxidation of methane with sulfate, iron, manganese, nitrate, and humic substances

The coenzyme F_{420} is an important coenzyme in CO_2 reduction and methylotrophic pathways of methanogenesis. Methane is a climate-active greenhouse gas that is approximately 30 times



Scheme 4: Assimilatory and Dissimilatory Sulfate Reduction

more potent than carbon dioxide.[104,127] Methane is consumed through the process of anaerobic oxidation of methane (AOM) in seep sediments. This process removes approximately 90% of the methane produced globally in marine sediments and acts as an efficient filter. Thus, the marine sediments are critical in regulating the amount of methane released into the overlying waters and atmosphere and they play a vital role in mitigating global warming. AOM is performed by anaerobic methanotrophic archaea (ANME).[128] Anaerobic methanotrophs archaea are involved in the regulation of the earth's climate and environment. In seafloor sediments, the anaerobic oxidation of methane (AOM) consumes most of the methane formed in anoxic layers, preventing this greenhouse gas from reaching the water column and finally the atmosphere. Anaerobic oxidation of methane is performed by syntrophic consortia of specific anaerobic methane-oxidizing archaea (ANME) and sulfate-reducing bacteria (SRB). Hydrothermally heated sediment of the Guaymas Basin, the cultured deep-branching ANME-1c grows in syntrophic consortia with *Thermodesulfobacterium torris* (*T. torris*) at 70°C. Both partners encode and express genes coding for extracellular appendages and multiheme cytochromes by direct interspecies electron transfer (DIET). ANME-1c might be associated specifically with *T. torris*, but their co-occurrence is so far only documented for heated sediments of the Gulf of California (Scheme 5).[129,130] Anaerobic oxidation of methane (AOM) coupled with sulfate reduction is a key microbiological process in ocean sediments that controls the amount of methane released into overlying waters and the atmosphere. However, despite the global relevance and importance of this process, there are currently no pure culture isolates available. Thus, the physiological and biochemical basis for AOM has advanced much more slowly than for many other microbially mediated biogeochemical processes.[131] Strong evidence emerged that archaea may be involved in AOM based on stable isotope measurements of archaeal lipids and small subunit ribosomal RNA (SSU or 16S rRNA) gene clone libraries from marine methane seeps and fluorescence in situ hybridization demonstrating consortia consisting of an archaeon related to known methanogens and a bacterium related to sulfate-reducing bacteria (SRB).[132–134]



Scheme 5: Anaerobic oxidation of methane with sulfate

The driving force for different microbial syntrophic interactions is important for both partners by sharing their nutrients and electrons, combining their resources, and avoiding the need for both partners to expend energy for the synthesis of common nutrients. Syntrophic interactions appear to be specific in at least some cases, with the same organisms co-associating across different ecosystems and environments.[135] A classic syntrophic partnership is at the heart of the important biogeochemical process, sulfate-coupled anaerobic oxidation of methane.[136] Anaerobic methanotrophic archaea (ANME) and sulfate-reducing bacteria (SRB) coexist in multicellular consortia, with ANME performing methane oxidation coupled with sulfate reduction by the SRB.[137–139] Direct interspecies electron transfer (DIET) from ANME to SRB is predicted to be the dominant mechanism of syntrophic coupling in many observed cases of sulfate-coupled anaerobic oxidation of methane AOM[140] though

diazotrophic nitrogen is also shared between these partners.[141] Genomic evidence indicates that multi-heme c-type cytochromes (MHCs) may facilitate the extracellular electron transfer (EET) from ANME to different electron sinks (Scheme 5).[105,141]

Anaerobic oxidation of methane (AOM) coupled with reduction of metal oxides is supposed to be a globally important bioprocess in marine sediments. High amounts of buried reactive Fe (III)/Mn (IV) minerals could be an important available electron acceptor for AOM.[142] Archaea of the order *Methanosarcinales*, related to "*Candidatus Methanoperedens nitroreducens*," couple the reduction of environmentally relevant forms of Fe^{3+} and Mn^{4+} to the oxidation of methane.[143] The iron-dependent AOM to microorganisms detected in numerous habitats worldwide enables a better understanding of the interaction between the biogeochemical cycles of iron and methane.[144] Experimental evidence supporting cytochrome-mediated EET for the reduction of metals and electrodes by '*Candidatus Methanoperedens nitroreducens*', an ANME acclimated to nitrate reduction.[145,146] Microorganisms from marine methane-seep sediment in the Eel River Basin in California are capable of using manganese (birnessite) and iron (ferrihydrite) to oxidize methane, revealing that marine AOM is coupled, either directly or indirectly, to a larger variety of oxidants than previously thought. Large amounts of manganese and iron are provided to oceans from rivers, indicating that manganese- and iron-dependent AOM have the potential to be globally important.[147–150] Nitrate-dependent AOM, in contrast, seems to be catalyzed by an archaeal methanotroph alone that was named *Methanoperedens nitroreducens* and is affiliated to the ANME-2d clade.[151–153] The environmental genome and transcriptome of a *Methanoperedens*-like archaeon that was found in an enrichment culture performing nitrate-dependent anaerobic oxidation of methane. The genomics is used to establish a putative model for nitrate-dependent anaerobic oxidation of methane. The cytoplasmic process of methane oxidation via reverse methanogenesis may be coupled to the pseudoperiplasmically located reduction of nitrate to nitrite and ammonium by Nar- and Nrf-type nitrogen cycle enzymes. Several cytoplasmic and membrane-bound enzyme complexes homologous to enzymes in methanogens were found and are combined with several metabolic traits not previously found in methanogenic or methanotrophic archaea.[154] The oxidation of methane and aromatic compounds has been studied in different environments.[155–157] Further anaerobic oxidation of methane in wetlands, cold seep sediments, and different parts of the ocean have been examined in different environments.[158–163] Humic substances are redox-active organic molecules, that play pivotal roles in several biogeochemical cycles due to their electron-transferring capacity involving multiple abiotic and microbial transformations. The redox properties of humic substances and the metabolic capabilities of microorganisms to reduce and oxidize them. Humic substances mediate the anaerobic oxidation of methane (AOM) coupled with the reduction of nitrous oxide (N_2O) in wetland sediments. The humic substances might play an important role in preventing the emission of greenhouse gases (CH_4 and N_2O) from wetland sediments.[164] Methane (CH_4) is both generated and consumed in paddy soils, where anaerobic oxidation of methane (AOM) serves as a crucial process for mitigating CH_4 emissions.[165] The application of $Fe_2(SO_4)_3$ enhanced the iron reduction synergistic quinone redox cycling and promoted the generation of free radicals during the humification of composting.[166] Anaerobic oxidation of methane (AOM) mediated by microorganisms plays an important role in the global carbon cycle and methane emission control. This study demonstrated the simultaneous multi-electron acceptor-driven AOM that existed in the electroactive constructed wetland environment of freshwater, which is crucial to global carbon, sulfur, and nitrogen cycles in the presence of manganese, iron, and humic substances.

Conclusions

Coenzyme F_{420} is one of the ancient coenzymes that are involved in the reduction of carbon dioxide to methane. Methanogenic archaea produce methane for their energy-generating metabolism. Archaea are a diverse group of single-celled organisms that are found in a variety of habitats such as deep-sea hydrothermal vents, wetlands, anaerobic digesters, agriculture fields, the rumen of cattle, and the hindgut of termites. Coenzyme F_{420} and related ancient coenzymes are also involved in the methanotrophic oxidation of methane to carbon dioxide. The emission of methane is also one of the main contributors to climate change and the environment of the earth.

Acknowledgement

I acknowledge DST, DBT, CSIR, ICMR, and UGC for their financial assistance during my stay at the University of Delhi, India. I thank my teachers and students for their support during the last fifty years.

Conflict of Interest Statement

There is no conflict of interest for this review work.

References and Notes

1. A. Kirschning. Coenzymes and Their Role in the Evolution of Life. *Angew. Chemie - Int. Ed.* **2021**, 60 (12), 6242–6269.
2. A. Kirschning. The coenzyme/protein pair and the molecular evolution of life. *Nat. Prod. Rep.* **2021**, 38 (5), 993–1010.
3. A. Kirschning. On the evolution of coenzyme biosynthesis. *Nat. Prod. Rep.* **2022**, 2175–2199.
4. A.A. DiMarco, T.A. Bobik, R.S. Wolfe. Unusual coenzymes of methanogenesis. *Annu. Rev. Biochem.* **1990**, 59 (1), 355–394.
5. J.M. Wolfe, G.P. Fournier. Horizontal gene transfer constrains the timing of methanogen evolution. *Nat. Ecol. Evol.* **2018**, 2 (5), 897–903.
6. M.C. Weiss, F.L. Sousa, N. Mrnjavac, et al. The physiology and habitat of the last universal common ancestor. *Nat. Microbiol.* **2016**, 1 (9), 16116.
7. B.J. Baker, V. De Anda, K.W. Seitz, et al. Diversity, ecology and evolution of Archaea. *Nat. Microbiol.* **2020**, 5 (7), 887–900.
8. B.A. Berghuis, F.B. Yu, F. Schulz, et al. Hydrogenotrophic methanogenesis in archaeal phylum Verstraetearchaeota reveals the shared ancestry of all methanogens. *Proc. Natl. Acad. Sci.* **2019**, 116 (11), 5037–5044.
9. P.N. Evans, J.A. Boyd, A.O. Leu, et al. An evolving view of methane metabolism in the Archaea. *Nat. Rev. Microbiol.* **2019**, 17 (4), 219–232.

10. R. Mei, M. Kaneko, H. Imachi, M.K. Nobu. The origin and evolution of methanogenesis and Archaea are intertwined. *PNAS Nexus*. 2023.
11. S.M.S. Chauhan. Chemistry and Biology of Coenzyme F420 in Tuberculosis treatment. *Chem. Biol. Lett.* **2024**, 11, Accepted.
12. S.W. Kang, J. Antoney, R.L. Frkic, et al. Asymmetric Ene-Reduction of α,β-Unsaturated Compounds by F420-Dependent Oxidoreductases A Enzymes from Mycobacterium smegmatis. *Biochemistry* **2023**, 62 (3), 873–891.
13. S. Mathew, M. Trajkovic, H. Kumar, Q.-T. Nguyen, M.W. Fraaije. Enantio- and regioselective ene -reductions using F 420 H 2 -dependent enzymes. *Chem. Commun.* **2018**, 54 (79), 11208–11211.
14. S.W. Kang, J. Antoney, D.W. Lupton, et al. Asymmetric Ene-Reduction by F 420 -Dependent Oxidoreductases B (FDOR- B) from Mycobacterium smegmatis. *ChemBioChem* **2023**, 24 (8), 0797.
15. C. Greening, F.H. Ahmed, A.E. Mohamed, et al. Physiology, biochemistry, and applications of F420- and Fo-dependent redox reactions. *Microbiol. Mol. Biol. Rev.* **2016**, 80 (1), 451–493.
16. R. Grinter, C. Greening. Cofactor F420: An expanded view of its distribution, biosynthesis and roles in bacteria and archaea. *FEMS Microbiol. Rev.* **2021**, 45 (5), 1–46.
17. P. Cheeseman, A. Toms-Wood, R.S. Wolfe. Isolation and properties of a fluorescent compound, factor 420 , from Methanobacterium strain M.o.H. *J. Bacteriol.* **1972**, 112 (1), 527–531.
18. L.D. Eirich, G.D. Vogels, R.S. Wolfe. Proposed structure for coenzyme F 420 from methanobacterium. *Biochemistry* **1978**, 17 (22), 4583–4593.
19. L.D. Eirich, G.D. Vogels, R.S. Wolfe. Distribution of coenzyme F420 and properties of its hydrolytic fragments. *J. Bacteriol.* **1979**, 140 (1), 20–27.
20. J. Drenth, M. Trajkovic, M.W. Fraaije. Chemoenzymatic synthesis of an unnatural deazaflavin cofactor that can fuel F420-dependent enzymes. *ACS Catal.* **2019**, 9 (7), 6435–6443.
21. M. Lee, J. Drenth, M. Trajkovic, R.M. de Jong, M.W. Fraaije. Introducing an Artificial Deazaflavin Cofactor in Escherichia coli and Saccharomyces cerevisiae. *ACS Synth. Biol.* **2022**, 11 (2), 938–952.
22. L.G. Gorris, C. van der Drift. Cofactor contents of methanogenic bacteria reviewed. *Biofactors* **1994**, 4 (3–4), 139–145.
23. B. Ney, F.H. Ahmed, C.R. Carere, et al. The methanogenic redox cofactor F420 is widely synthesized by aerobic soil bacteria. *ISME J.* **2017**, 11 (1), 125–137.
24. G. Lackner, E.E. Peters, E.J.N. Helfrich, J. Piel. Insights into the lifestyle of uncultured bacterial natural product factories associated with marine sponges. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, 114 (3), E347–E356.
25. M. Graupner, R.H. White. Methanococcus jannaschii coenzyme F420 analogs contain a terminal α-linked glutamate. *J. Bacteriol.* **2003**, 185 (15), 4662–4665.
26. X.L. Lin, R.H. White. Occurrence of coenzyme F420 and its γ-monoglutamyl derivative in nonmethanogenic archaebacteria. *J. Bacteriol.* **1986**, 168 (1), 444–448.
27. M. Wunderer, R. Markt, N. Lackner, A.O. Wagner. The glutamyl tail length of the cofactor F420 in the methanogenic Archaea Methanosarcina thermophila and Methanoculleus thermophilus. *Sci. Total Environ.* **2022**, 809, 151112.
28. J. Lambrecht, N. Cichocki, T. Hübschmann, et al. Flow cytometric quantification, sorting and sequencing of methanogenic archaea based on F420 autofluorescence. *Microb. Cell Fact.* **2017**, 16 (1), 180.
29. E. Purwantini, L. Daniels. Purification of a novel coenzyme F420-dependent glucose-6-phosphate dehydrogenase from Mycobacterium smegmatis. *J. Bacteriol.* **1996**, 178 (10), 2861–2866.
30. E. Purwantini, T.P. Gillis, L. Daniels. Presence of F420-dependent glucose-6-phosphate dehydrogenase in Mycobacterium and Nocardia species, but absence from Streptomyces and Corynebacterium species and methanogenic Archaea. *FEMS Microbiol. Lett.* **2006**, 146 (1), 129–134.
31. A.R. Klein, H. Berk, E. Purwantini, L. Daniels, R.K. Thauer. Si -Face Stereospecificity at C5 of Coenzyme F 420 for F 420 -Dependent Glucose-6- Phosphate Dehydrogenase from Mycobacterium smegmatis and F 420 -Dependent Alcohol Dehydrogenase from Methanoculleus thermophilicus. *Eur. J. Biochem.* **1996**, 239 (1), 93–97.
32. E. Purwantini, L. Daniels. Molecular Analysis of the Gene Encoding F 420 -Dependent Glucose-6-Phosphate Dehydrogenase from Mycobacterium smegmatis. *J. Bacteriol.* **1998**, 180 (8), 2212–2219.
33. T.B. Bair, D.W. Isabelle, L. Daniels. Structures of coenzyme F420 in Mycobacterium species. *Arch. Microbiol.* **2001**, 176 (1–2), 37–43.
34. D. Isabelle, D.R. Simpson, L. Daniels. Large-Scale Production of Coenzyme F 420 -5,6 by Using Mycobacterium smegmatis. *Appl. Environ. Microbiol.* **2002**, 68 (11), 5750–5755.
35. M.W. Peck. Changes in concentrations of coenzyme F420 analogs during batch growth of Methanosarcina barkeri and Methanosarcina mazei. *Appl. Environ. Microbiol.* **1989**, 55 (4), 940–945.
36. D. Last, M. Hasan, L. Rothenburger, D. Braga, G. Lackner. High-yield production of coenzyme F420 in Escherichia coli by fluorescence-based screening of multi-dimensional gene expression space. *Metab. Eng.* **2022**, 73, 158–167.
37. T. Naraoka, K. Momoi, K. Fukusawa, M. Goto. Isolation and identification of a naturally occurring 7, 8-didemethyl-8-hydroxy-5-deazariboflavin derivative from Mycobacterium avium. *Biochim. Biophys. Acta - Gen. Subj.* **1984**, 797 (3), 377–380.
38. M.-S.T. Kuo, D.A. Yurek, J.H. Coats, G.P. Li. Isolation and identification of 7,8-didemethyl-8-hydroxy-5-deazariboflavin, an unusual cosynthetic factor in streptomycetes, from Streptomyces lincolnensis. *J. Antibiot. (Tokyo).* **1989**, 42 (3), 475–478.
39. J.H. Coats, G.P. Li, M.-S.T. Kuo, D.A. Yurek. Discovery, production, and biological assay of an unusual flavenoid cofactor involved in lincomycin biosynthesis. *J. Antibiot. (Tokyo).* **1989**, 42 (3), 472–474.
40. J.R.D. McCormick, G.O. Morton. Identity of Cosynthetic Factor 1 of Streptomyces aureofaciens and Fragment FO from Coenzyme F420 of Methanobacterium Species. *J. Am. Chem. Soc.* **1982**, 104 (14), 4014–4015.
41. L. Daniels, N. Bakhiet, K. Harmon. Widespread Distribution of a 5-deazaflavin Cofactor in Actinomyces and Related Bacteria. *Syst. Appl. Microbiol.* **1985**, 6 (1), 12–17.
42. D. Braga, D. Last, M. Hasan, et al. Metabolic Pathway Rerouting in Paraburkholderia rhizoxinica Evolved Long-Overlooked Derivatives of Coenzyme F420. *ACS Chem. Biol.* **2019**, 14 (9), 2088–2094.
43. W.T. Ashton, R.D. Brown, F. Jacobson, C. Walsh. Synthesis of 7,8-didemethyl-8-hydroxy-5-deazariboflavin and confirmation of its identity with the deazaisoalloxazine chromophore of Methanobacterium redox coenzyme F420. *J. Am. Chem. Soc.* **1979**, 101 (15), 4419–4420.
44. W.T. Ashton, R.D. Brown. Synthesis of 8-demethyl- 8- hydroxy-5-deazariboflavins. *J. Heterocycl. Chem.* **1980**, 17 (8), 1709–1712.
45. V.N. Petushkov, M. V. Vavilov, I.A. Ivanov, et al. Deazaflavin cofactor boosts earthworms Henlea bioluminescence. *Org. Biomol. Chem.* **2022**, 21 (2), 415–427.
46. T. Kimachi, M. Kawase, S. Matsuki, K. Tanaka, F. Yoneda. First total synthesis of coenzyme factor 420. *J. Chem. Soc. Perkin Trans. 1* **1990**, No. 2, 253–256.
47. F. Yoneda, Y. Sakuma, S. Mizumoto, R. Ito. Syntheses of 5-deazaflavins. *J. Chem. Soc. Perkin Trans. 1* **1976**, No. 16, 1805.
48. M.S. Hossain, C.Q. Le, E. Joseph, et al. Convenient synthesis of deazaflavin cofactor FO and its activity in F420-dependent NADP reductase. *Org. Biomol. Chem.* **2015**, 13 (18), 5082–5085.
49. M. Bender, H. Mouritsen, J. Christoffers. A robust synthesis of 7,8-didemethyl-8-hydroxy-5-deazariboflavin. *Beilstein J. Org. Chem.* **2016**, 12, 912–917.
50. V.N. Petushkov, N.S. Rodionova. Low-Molecular-Weight Components of Luminescent Reaction of the Siberian Enchytraeid Henlea sp. *Dokl. Biochem. Biophys.* **2018**, 481 (1), 212–216.
51. T. Kimachi, K. Tanaka, F. Yoneda. Synthesis of a proposed isomer of F420 having α-glutamyl bonding. *J. Heterocycl. Chem.* **1991**, 28 (2), 439–443.

52. H. Li, H. Xu, D.E. Graham, R.H. White. Glutathione synthetase homologs encode α-L-glutamate ligases for methanogenic coenzyme F420 and tetrahydrosarcinapterin biosyntheses. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, 100 (17), 9785–9790.
53. E. Herbst, A. Lee, Y. Tang, S.A. Snyder, V.W. Cornish. Heterologous Catalysis of the Final Steps of Tetracycline Biosynthesis by Saccharomyces cerevisiae. *ACS Chem. Biol.* **2021**, 16 (8), 1425–1434.
54. G. Bashiri, A.M. Rehan, D.R. Greenwood, J.M.J. Dickson, E.N. Baker. Metabolic engineering of cofactor F420 production in mycobacterium smegmatis. *PLoS One* **2010**, 5 (12), 15803.
55. M. V. Shah, H. Nazem-Bokaee, J. Antoney, et al. Improved production of the non-native cofactor F420 in Escherichia coli. *Sci. Rep.* **2021**, 11 (1), 21774.
56. G. Bashiri. Cofactor F420, an emerging redox power in biosynthesis of secondary metabolites. *Biochem. Soc. Trans.* **2022**, 50 (1), 253–267.
57. C.A. Abbas, A.A. Sibirny. Genetic Control of Biosynthesis and Transport of Riboflavin and Flavin Nucleotides and Construction of Robust Biotechnological Producers. *Microbiol. Mol. Biol. Rev.* **2011**, 75 (2), 321–360.
58. I. Haase, S. Sarge, B. Illarionov, et al. Enzymes from the Haloacid Dehalogenase (HAD) Superfamily Catalyse the Elusive Dephosphorylation Step of Riboflavin Biosynthesis. *ChemBioChem* **2013**, 14 (17), 2272–2275.
59. K.-P. Choi, N. Kendrick, L. Daniels. Demonstration that fbiC Is Required by Mycobacterium bovis BCG for Coenzyme F 420 and FO Biosynthesis. *J. Bacteriol.* **2002**, 184 (9), 2420–2428.
60. D.E. Graham, H. Xu, R.H. White. Identification of the 7,8-didemethyl-8-hydroxy-5-deazariboflavin synthase required for coenzyme F 420 biosynthesis. *Arch. Microbiol.* **2003**, 180 (6), 455–464.
61. J.D. Selengut, D.H. Haft. Unexpected abundance of coenzyme F420-dependent enzymes in Mycobacterium tuberculosis and other actinobacteria. *J. Bacteriol.* **2010**, 192 (21), 5788–5798.
62. H. Kumar, Q.T. Nguyen, C. Binda, A. Mattevi, M.W. Fraaije. Isolation and characterization of a thermostable F420:NADPH oxidoreductase from Thermobifida fusca. *J. Biol. Chem.* **2017**, 292 (24), 10123–10130.
63. J.B. Broderick, B.R. Duffus, K.S. Duschene, E.M. Shepard. Radical S -Adenosylmethionine Enzymes. *Chem. Rev.* **2014**, 114 (8), 4229–4317.
64. A.P. Mehta, S.H. Abdelwahed, N. Mahanta, et al. Radical S-adenosylmethionine (SAM) enzymes in cofactor biosynthesis: A treasure trove of complex organic radical rearrangement reactions. *J. Biol. Chem.* **2015**, 290 (7), 3980–3986.
65. Y. Nicolet. Structure–function relationships of radical SAM enzymes. *Nat. Catal.* **2020**, 3 (4), 337–350.
66. Y. Nicolet, M. V. Cherrier, P. Amara. Radical SAM Enzymes and Metallocofactor Assembly: A Structural Point of View. *ACS Bio Med Chem Au* **2022**, 2 (1), 36–52.
67. L. Decamps, B. Philmus, A. Benjdia, et al. Biosynthesis of F 0, precursor of the F 420 cofactor, requires a unique two radical-SAM domain enzyme and tyrosine as substrate. *J. Am. Chem. Soc.* **2012**, 134 (44), 18173–18176.
68. B. Philmus, L. Decamps, O. Berteau, T.P. Begley. Biosynthetic versatility and coordinated action of 5′-deoxyadenosyl radicals in deazaflavin biosynthesis. *J. Am. Chem. Soc.* **2015**, 137 (16), 5406–5413.
69. G. Bashiri, E.N. Baker. Convergent pathways to biosynthesis of the versatile cofactor F420. *Curr. Opin. Struct. Biol.* **2020**, 65, 9–16.
70. L.L. Grochowski, H. Xu, R.H. White. Identification of lactaldehyde dehydrogenase in Methanocaldococcus jannaschii and its involvement in production of lactate for F420 biosynthesis. *J. Bacteriol.* **2006**, 188 (8), 2836–2844.
71. M. Graupner, R.H. White. Biosynthesis of the phosphodiester bond in coenzyme F420 in the methanoarchaea. *Biochemistry* **2001**, 40 (36), 10859–10872.
72. M. Graupner, H. Xu, R.H. White. Characterization of the 2-Phospho-<scp>l</scp> -lactate Transferase Enzyme Involved in Coenzyme F $_{420}$ Biosynthesis in *Methanococcus jannaschii*. *Biochemistry* **2002**, 41 (11), 3754–3761.
73. L.L. Grochowski, H. Xu, R.H. White. Identification and Characterization of the 2-Phospho- <scp>l</scp> -lactate Guanylyltransferase Involved in Coenzyme F $_{420}$ Biosynthesis. *Biochemistry* **2008**, 47 (9), 3033–3037.
74. H. Li, M. Graupner, H. Xu, R.H. White. CofE Catalyzes the Addition of Two Glutamates to F 420 -0 in F 420 Coenzyme Biosynthesis in Methanococcus jannaschii. *Biochemistry* **2003**, 42 (32), 9771–9778.
75. F. Forouhar, M. Abashidze, H. Xu, et al. Molecular insights into the biosynthesis of the F420 coenzyme. *J. Biol. Chem.* **2008**, 283 (17), 11832–11840.
76. B. Nocek, E. Evdokimova, M. Proudfoot, et al. Structure of an Amide Bond Forming F420:γγ-glutamyl Ligase from Archaeoglobus Fulgidus - A Member of a New Family of Non-ribosomal Peptide Synthases. *J. Mol. Biol.* **2007**, 372 (2), 456–469.
77. G. Bashiri, J. Antoney, E.N.M. Jirgis, et al. A revised biosynthetic pathway for the cofactor F 420 in prokaryotes. *Nat. Commun.* **2019**, 10 (1).
78. J. Snášel, I. Pichová. Allosteric regulation of pyruvate kinase from Mycobacterium tuberculosis by metabolites. *Biochim. Biophys. Acta - Proteins Proteomics* **2019**, 1867 (2), 125–139.
79. I. Machová, J. Snášel, M. Zimmermann, et al. Mycobacterium tuberculosis phosphoenolpyruvate carboxykinase is regulated by redox mechanisms and interaction with thioredoxin. *J. Biol. Chem.* **2014**, 289 (19), 13066–13078.
80. J. Lim, J.J. Lee, S.K. Lee, et al. Phosphoenolpyruvate depletion mediates both growth arrest and drug tolerance of Mycobacterium tuberculosis in hypoxia. *Proc. Natl. Acad. Sci. U. S. A.* **2021**, 118 (35), 2105800118.
81. R. Grinter, B. Ney, R. Brammananth, et al. Cellular and Structural Basis of Synthesis of the Unique Intermediate Dehydro-F 420 -0 in Mycobacteria. *mSystems* **2020**, 5 (3), 0389.
82. G. Bashiri, A.M. Rehan, S. Sreebhavan, et al. Elongation of the Poly-γ-glutamate Tail of F420 Requires Both Domains of the F420:γ-Glutamyl Ligase (FbiB) of Mycobacterium tuberculosis. *J. Biol. Chem.* **2016**, 291 (13), 6882–6894.
83. G. Bashiri, E.M.M. Bulloch, W.R. Bramley, et al. Poly-γ-glutamylation of biomolecules. *Nat. Commun.* **2024**, 15 (1), 1310.
84. D. Braga, M. Hasan, T. Kröber, D. Last, G. Lackner. Redox coenzyme F420 biosynthesis in thermomicrobia involves reduction by stand-alone nitroreductase superfamily enzymes. *Appl. Environ. Microbiol.* **2020**, 86 (12), 00457–20.
85. G. Lackner, N. Moebius, L.P. Partida-Martinez, S. Boland, C. Hertweck. Evolution of an endofungal Lifestyle: Deductions from the Burkholderia rhizoxinica Genome. *BMC Genomics* **2011**, 12 (mics,2011,12:210. (b)G).
86. G. Lackner, C. Hertweck. Impact of Endofungal Bacteria on Infection Biology, Food Safety, and Drug Development. *PLoS Pathog.* **2011**, 7 (6), e1002096.
87. M. Hasan, S. Schulze, L. Berndt, et al. Diversification by CofC and Control by CofD Govern Biosynthesis and Evolution of Coenzyme F 420 and Its Derivative 3PG-F 420. *MBio* **2022**, 13 (1), 2022,13 1 03501–21.
88. K. Decker, K. Jungermann, R.K. Thauer. Energy Production in Anaerobic Organisms. *Angew. Chemie Int. Ed. English* **1970**, 9 (2), 138–158.
89. C.R. Woese, L.J. Magrum, G.E. Fox. Archaebacteria. *J. Mol. Evol.* **1978**, 11 (3), 245–252.
90. P.E. Rouviere, R.S. Wolfe. Novel biochemistry of methanogenesis. *J. Biol. Chem.* **1988**, 263 (17), 7913–7916.
91. A.K. Kaster, J. Moll, K. Parey, R.K. Thauer. Coupling of ferredoxin and heterodisulfide reduction via electron bifurcation in hydrogenotrophic methanogenic archaea. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, 108 (7), 2981–2986.
92. T.J. Lie, K.C. Costa, B. Lupa, et al. Essential anaplerotic role for the energy-converting hydrogenase Eha in hydrogenotrophic

methanogenesis. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, 109 (38), 15473–15478.
93. R.K. Thauer. The Wolfe cycle comes full circle. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, 109 (38), 15084–15085.
94. D.E. Graham, R.H. White. Elucidation of methanogenic coenzyme biosyntheses: From spectroscopy to genomics. *Nat. Prod. Rep.* **2002**, 19 (2), 133–147.
95. P.S. Adam, G. Borrel, C. Brochier-Armanet, S. Gribaldo. The growing tree of Archaea: new perspectives on their diversity, evolution and ecology. *ISME J.* **2017**, 11 (11), 2407–2425.
96. G. Huang, T. Wagner, U. Ermler, S. Shima. Methanogenesis involves direct hydride transfer from H2 to an organic substrate. *Nat. Rev. Chem.* **2020**, 4 (4), 213–221.
97. S. Shima, G. Huang, T. Wagner, U. Ermler. Structural Basis of Hydrogenotrophic Methanogenesis. *Annu. Rev. Microbiol.* **2020**, 74 (1), 713–733.
98. S.J. Moore, S.T. Sowa, C. Schuchardt, et al. Elucidation of the biosynthesis of the methane catalyst coenzyme F430. *Nature* **2017**, 543 (7643), 78–82.
99. D.A. Bryant, C.N. Hunter, M.J. Warren. Biosynthesis of the modified tetrapyrroles—the pigments of life. *J. Biol. Chem.* **2020**, 295 (20), 6888–6925.
100. K.D. Allen, G. Wegener, R.H. White. Discovery of multiple modified F430 coenzymes in methanogens and anaerobic methanotrophic archaea suggests possible new roles for F430 in nature. *Appl. Environ. Microbiol.* **2014**, 80 (20), 6403–6412.
101. P. Bharadwaz, M. Maldonado-Domínguez, J. Chalupský, M. Srnec. Reactivity Factors in Catalytic Methanogenesis and Their Tuning upon Coenzyme F430 Biosynthesis. *J. Am. Chem. Soc.* **2023**, 145 (16), 9039–9051.
102. O.N. Lemaire, T. Wagner. A Structural View of Alkyl-Coenzyme M Reductases, the First Step of Alkane Anaerobic Oxidation Catalyzed by Archaea. *Biochemistry* **2022**, 61 (10), 805–821.
103. R.K. Thauer. Methyl (Alkyl)-Coenzyme M Reductases: Nickel F-430-Containing Enzymes Involved in Anaerobic Methane Formation and in Anaerobic Oxidation of Methane or of Short Chain Alkanes. *Biochemistry* **2019**, 58 (52), 5198–5220.
104. M. Saunois, R.B. Jackson, P. Bousquet, B. Poulter, J.G. Canadell. The growing role of methane in anthropogenic climate change. *Environ. Res. Lett.* **2016**, 11 (12), 120207.
105. F. Beulig, H. Røy, S.E. McGlynn, B.B. Jørgensen. Cryptic CH 4 cycling in the sulfate–methane transition of marine sediments apparently mediated by ANME-1 archaea. *ISME J.* **2019**, 13 (2), 250–262.
106. G. Muyzer, A.J.M. Stams. The ecology and biotechnology of sulphate-reducing bacteria. *Nat. Rev. Microbiol.* **2008**, 6 (6), 441–454.
107. L.G. Gorris, A.C. Voet, C. van der Drift. Structural characteristics of methanogenic cofactors in the non-methanogenic archaebacterium Archaeoglobus fulgidus. *Biofactors* **1991**, 3 (1), 29–35.
108. Y. Liu, L.L. Beer, W.B. Whitman. Methanogens: a window into ancient sulfur metabolism. *Trends Microbiol.* **2012**, 20 (5), 251–258.
109. L. Daniels, N. Belay, B.S. Rajagopal. Assimilatory reduction of sulfate and sulfite by methanogenic bacteria. *Appl. Environ. Microbiol.* **1986**, 51 (4), 703–709.
110. D. Payne, R.L. Spietz, E.S. Boyd. Reductive dissolution of pyrite by methanogenic archaea. *ISME J.* **2021**, 15 (12), 3498–3507.
111. O. Nercessian, N. Bienvenu, D. Moreira, D. Prieur, C. Jeanthon. Diversity of functional genes of methanogens, methanotrophs and sulfate reducers in deep-sea hydrothermal environments. *Environ. Microbiol.* **2005**, 7 (1), 118–132.
112. K.O. Stetter, G. Lauerer, M. Thomm, A. Neuner. Isolation of Extremely Thermophilic Sulfate Reducers: Evidence for a Novel Branch of Archaebacteria. *Science (80-.).* **1987**, 236 (4803), 822–824.
113. R.K. Thauer, A.K. Kaster, H. Seedorf, W. Buckel, R. Hedderich. Methanogenic archaea: Ecologically relevant differences in energy conservation. *Nat. Rev. Microbiol.* **2008**, 6 (8), 579–591.
114. J.K. Kristjansson, P. Schnheit. Why do sulfate-reducing bacteria outcompete methanogenic bacteria for substrates? *Oecologia* **1983**, 60 (2), 264–266.
115. W.P. Hocking, R. Stokke, I. Roalkvam, I.H. Steen. Identification of key components in the energy metabolism of the hyperthermophilic sulfate-reducing archaeon Archaeoglobus fulgidus by transcriptome analyses. *Front. Microbiol.* **2014**, 5 (MAR).
116. H. Yu, D. Susanti, S.E. McGlynn, et al. Comparative Genomics and Proteomic Analysis of Assimilatory Sulfate Reduction Pathways in Anaerobic Methanotrophic Archaea. *Front. Microbiol.* **2018**, 9, 2917.
117. M. Diao, S. Dyksma, E. Koeksoy, et al. Global diversity and inferred ecophysiology of microorganisms with the potential for dissimilatory sulfate/sulfite reduction. *FEMS Microbiol. Rev.* **2023**, 47 (5), 1–18.
118. M. Jespersen, T. Wagner. Assimilatory sulfate reduction in the marine methanogen Methanothermococcus thermolithotrophicus. *Nat. Microbiol.* **2023**, 8 (7), 1227–1239.
119. M. Jespersen, A.J. Pierik, T. Wagner. Structures of the sulfite detoxifying F420-dependent enzyme from Methanococcales. *Nat. Chem. Biol.* **2023**, 19 (6), 695–702.
120. C. Heryakusuma, E.F. Johnson, E. Purwantini, B. Mukhopadhyay. Nitrite reductase activity in F420-dependent sulphite reductase (Fsr) from Methanocaldococcus jannaschii. *Access Microbiol.* **2023**, 5 (4).
121. J.H. Gwak, S.I. Awala, N.L. Nguyen, et al. Sulfur and methane oxidation by a single microorganism. *Proc. Natl. Acad. Sci. U. S. A.* **2022**, 119 (32), 2114799119.
122. S. Wang, Q. Lu, Z. Liang, et al. Generation of zero-valent sulfur from dissimilatory sulfate reduction in sulfate-reducing microorganisms. *Proc. Natl. Acad. Sci.* **2023**, 120 (20).
123. S. Neukirchen, I.A.C. Pereira, F.L. Sousa. Stepwise pathway for early evolutionary assembly of dissimilatory sulfite and sulfate reduction. *ISME J.* **2023**, 17 (10), 1680–1692.
124. R.A. Schmitz, S.H. Peeters, S.S. Mohammadi, et al. Simultaneous sulfide and methane oxidation by an extremophile. *Nat. Commun.* **2023**, 14 (1), 2974.
125. C. Rückert. Sulfate reduction in microorganisms — recent advances and biotechnological applications. *Curr. Opin. Microbiol.* **2016**, 33, 140–146.
126. S.J.E. Krause, J. Liu, D.J. Yousavich, et al. Evidence of cryptic methane cycling and non-methanogenic methylamine consumption in the sulfate-reducing zone of sediment in the Santa Barbara Basin, California. *Biogeosciences* **2023**, 20 (20), 4377–4390.
127. A.J. Wallenius, P. Dalcin Martins, C.P. Slomp, M.S.M. Jetten. Anthropogenic and Environmental Constraints on the Microbial Methane Cycle in Coastal Sediments. *Front. Microbiol.* **2021**, 12, 631621.
128. Y. Han, C. Zhang, Z. Zhao, et al. A comprehensive genomic catalog from global cold seeps. *Sci. Data* **2023**, 10 (1), 596.
129. D. Benito Merino, H. Zehnle, A. Teske, G. Wegener. Deep-branching ANME-1c archaea grow at the upper temperature limit of anaerobic oxidation of methane. *Front. Microbiol.* **2022**, 13 (988871).
130. I. Nashier Gahlawat, P. Lakra, J. Singh, B.S. Chhikara. Developmental and histochemical studies on carposporophyte of Solieria robusta (Greville) Kylin Solieriaceae, Gigartinales) from Port Okha, India. *J. Integr. Sci. Technol.* **2020**, 8 (2), 12–20.
131. A.O. Leu, S.J. McIlroy, J. Ye, et al. Lateral Gene Transfer Drives Metabolic Flexibility in the Anaerobic Methane-Oxidizing Archaeal Family Methanoperedenaceae. *MBio* **2020**, 11 (3), 1–16.
132. D.L. Valentine, W.S. Reeburgh. New perspectives on anaerobic methane oxidation. *Environ. Microbiol.* **2000**, 2 (5), 477–484.
133. V.J. Orphan, C.H. House, K.-U. Hinrichs, K.D. McKeegan, E.F. DeLong. Methane-Consuming Archaea Revealed by Directly Coupled Isotopic and Phylogenetic Analysis. *Science (80-.).* **2001**, 293 (5529), 484–487.
134. R.K. Thauer. Anaerobic oxidation of methane with sulfate: on the reversibility of the reactions that are catalyzed by enzymes also involved in methanogenesis from CO2. *Curr. Opin. Microbiol.* **2011**, 14 (3), 292–299.

135. P.H.A. Timmers, C.U. Welte, J.J. Koehorst, et al. Reverse Methanogenesis and Respiration in Methanotrophic Archaea. *Archaea* **2017**, 2017, 1–22.
136. S. Bhattarai, C. Cassarini, P.N.L. Lens. Physiology and Distribution of Archaeal Methanotrophs That Couple Anaerobic Oxidation of Methane with Sulfate Reduction. *Microbiol. Mol. Biol. Rev.* **2019**, 83 (3), 00074–18.
137. S. Scheller, H. Yu, G.L. Chadwick, S.E. McGlynn, V.J. Orphan. Artificial electron acceptors decouple archaeal methane oxidation from sulfate reduction. *Science (80-.).* **2016**, 351 (6274), 703–707.
138. G.L. Chadwick, C.T. Skennerton, R. Laso-Pérez, et al. Comparative genomics reveals electron transfer and syntrophic mechanisms differentiating methanotrophic and methanogenic archaea. *PLOS Biol.* **2022**, 20 (1), e3001508.
139. R. Murali, H. Yu, D.R. Speth, et al. Physiological potential and evolutionary trajectories of syntrophic sulfate-reducing bacterial partners of anaerobic methanotrophic archaea. *PLoS Biol.* **2023**, 21 (9 September).
140. Z. Yan, K. Du, Y. Yan, et al. Respiration-driven methanotrophic growth of diverse marine methanogens. *Proc. Natl. Acad. Sci.* **2023**, 120 (39).
141. J. Wang, Y.-N. Qu, P.N. Evans, et al. Evidence for nontraditional mcr -containing archaea contributing to biological methanogenesis in geothermal springs. *Sci. Adv.* **2023**, 9 (26).
142. X. Xiao, M. Luo, C. Zhang, et al. Metal-Driven Anaerobic Oxidation of Methane as an Important Methane Sink in Methanic Cold Seep Sediments. *Microbiol. Spectr.* **2023**, 11 (2), 05337–22.
143. K.F. Ettwig, B. Zhu, D. Speth, et al. Archaea catalyze iron-dependent anaerobic oxidation of methane. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, 113 (45), 12792–12796.
144. C. Cai, A.O. Leu, G.J. Xie, et al. A methanotrophic archaeon couples anaerobic oxidation of methane to Fe(III) reduction. *ISME J.* **2018**, 12 (8), 1929–1939.
145. X. Zhang, G.H. Joyce, A.O. Leu, et al. Multi-heme cytochrome-mediated extracellular electron transfer by the anaerobic methanotroph 'Candidatus Methanoperedens nitroreducens.' *Nat. Commun.* **2023**, 14 (1), 6118.
146. D. Gupta, K.E. Shalvarjian, D.D. Nayak. An Archaea-specific c-type cytochrome maturation machinery is crucial for methanogenesis in Methanosarcina acetivorans. *Elife* **2022**, 11, 76970.
147. G. Giangeri, P. Tsapekos, M. Gaspari, et al. Magnetite Alters the Metabolic Interaction between Methanogens and Sulfate-Reducing Bacteria. *Environ. Sci. Technol.* **2023**, 57 (43), 16399–16413.
148. W. Liu, S. Xu, H. Ma, et al. Anaerobic consortia mediate Mn(IV)-dependent anaerobic oxidation of methane. *Chem. Eng. J.* **2023**, 468.
149. W. Liu, H. Xiao, H. Ma, et al. Reduction of methane emissions from manganese-rich constructed wetlands: Role of manganese-dependent anaerobic methane oxidation. *Chem. Eng. J.* **2020**, 387, 123402.
150. A.O. Leu, C. Cai, S.J. McIlroy, et al. Anaerobic methane oxidation coupled to manganese reduction by members of the Methanoperedenaceae. *ISME J.* **2020**, 14 (4), 1030–1041.
151. C. Heryakusuma, D. Susanti, H. Yu, et al. A Reduced F420-Dependent Nitrite Reductase in an Anaerobic Methanotrophic Archaeon. *J. Bacteriol.* **2022**, 204 (7), 7822.
152. M.F. Haroon, S. Hu, Y. Shi, et al. Anaerobic oxidation of methane coupled to nitrate reduction in a novel archaeal lineage. *Nature* **2013**, 500 (7464), 567–570.
153. B.L. Hu, L.D. Shen, X. Lian, et al. Evidence for nitrite-dependent anaerobic methane oxidation as a previously overlooked microbial methane sink in wetlands. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, 111 (12), 4495–4500.
154. A. Arshad, D.R. Speth, R.M. de Graaf, et al. A Metagenomics-Based Metabolic Model of Nitrate-Dependent Anaerobic Oxidation of Methane by Methanoperedens-Like Archaea. *Front. Microbiol.* **2015**, 6 (DEC).
155. S. Berger, A. Cabrera-Orefice, M.S.M. Jetten, U. Brandt, C.U. Welte. Investigation of central energy metabolism-related protein complexes of ANME-2d methanotrophic archaea by complexome profiling. *Biochim. Biophys. Acta - Bioenerg.* **2021**, 1862 (1), 148308.
156. C. Argentino, C. Wittig, J. Peckmann, G. Panieri. Nitrogen uptake by methanotrophic consortia in deep-water gas hydrate-bearing sediments. *Chem. Geol.* **2023**, 636, 121638.
157. J. Wu, J. Bian, Q. Wang, D. Ruan. Degradation of benzene in anaerobic groundwater in the typical cold industrial region: Identification, interactions, and optimization of nitrate-/sulfate-reducing assemblages. *Biochem. Eng. J.* **2023**, 192, 108833.
158. K. Zhang, X. Wu, W. Wang, et al. Anaerobic oxidation of methane (AOM) driven by multiple electron acceptors in constructed wetland and the related mechanisms of carbon, nitrogen, sulfur cycles. *Chem. Eng. J.* **2022**, 433, 133663.
159. Y. Chen, C. Xu, N. Wu, et al. Diversity of Anaerobic Methane Oxidizers in the Cold Seep Sediments of the Okinawa Trough. *Front. Microbiol.* **2022**, 13.
160. O. Rasigraf, N.A.G.M. van Helmond, J. Frank, et al. Microbial community composition and functional potential in Bothnian Sea sediments is linked to Fe and S dynamics and the quality of organic matter. *Limnol. Oceanogr.* **2020**, 65 (S1), S113–S133.
161. B. Thamdrup, H.G.R. Steinsdóttir, A.D. Bertagnolli, et al. Anaerobic methane oxidation is an important sink for methane in the ocean's largest oxygen minimum zone. *Limnol. Oceanogr.* **2019**, 64 (6), 2569–2585.
162. L.J. Hamdan, K.P. Wickland. Methane emissions from oceans, coasts, and freshwater habitats: New perspectives and feedbacks on climate. *Limnol. Oceanogr.* **2016**, 61, S3–S12.
163. G.C. Zhuang, A. Montgomery, R.J. Sibert, et al. Effects of pressure, methane concentration, sulfate reduction activity, and temperature on methane production in surface sediments of the Gulf of Mexico. *Limnol. Oceanogr.* **2018**, 63 (5), 2080–2092.
164. E.I. Valenzuela, C. Padilla-Loma, N. Gómez-Hernández, et al. Humic Substances Mediate Anaerobic Methane Oxidation Linked to Nitrous Oxide Reduction in Wetland Sediments. *Front. Microbiol.* **2020**, 11 (587).
165. Y. Bai, Y. Wang, L. Shen, et al. Equal importance of humic acids and nitrate in driving anaerobic oxidation of methane in paddy soils. *Sci. Total Environ.* **2024**, 912, 169311.
166. R. Sun, M. Fu, L. Ma, Y. Zhou, Q. Li. Iron reduction in composting environment synergized with quinone redox cycling drives humification and free radical production from humic substances. *Bioresour. Technol.* **2023**, 384, 129341.

AUTHOR BIOGRAPHY

Prof. S. M. S. Chauhan is a retired professor for University of Delhi, India. He served as the Head, Department of Chemistry, University of Delhi. He was also awarded UGC-BSR Faculty Fellow, at University of Delhi. His current research interests include chemistry and biology of coenzymes and cofactors, and natural products.