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Research review paper

Sulfide in engineered methanogenic systems – Friend or foe?

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ABSTRACT

Sulfide ions are regarded to be toxic to microorganisms in engineered methanogenic systems (EMS), where organic substances are anaerobically converted to products such as methane, hydrogen, alcohols, and carboxylic acids. A vast body of research has addressed solutions to mitigate process disturbances associated with high sulfide levels, yet the established paradigm has drawn the attention away from the multifaceted sulfide interactions with minerals, organics, microbial interfaces and their implications for performance of EMS. This brief review brings forward sulfide-derived pathways other than toxicity and with potential significance for anaerobic organic matter degradation. Available evidence on sulfide reactions with organic matter, interventions with key microbial metabolisms, and interspecies electron transfer are critically synthesized as a guidance for comprehending the sulfide effects on EMS apart from the microbial toxicity. The outcomes identify existing knowledge gaps and specify future research needs as a step forward towards realizing the potential of sulfide-derived mechanisms in diversifying and optimizing EMS applications.

1. Introduction

Sulfide is undesired in engineered methanogenic systems (EMS), where anaerobic fermentative, organic acids oxidizing, and methanogenic microorganisms convert organic substances to products such as methane, hydrogen, alcohols, and carboxylic acids. Excessive sulfide formation often gives rise to microbial toxicity, disruption of the anaerobic degradation chain, and process instability (Vu et al., 2022). The consequent high sulfide levels in gaseous products such as biogas (i.e., a mixture of mainly methane and carbon dioxide) also cause corrosion of equipment in subsequent applications for heat and power generation, for which sulfide concentrations <100 ppm is demanded (Nguyen et al., 2021). A vast body of research has been dedicated to provide solutions to remove sulfide from the final products of EMS or alleviate its negative impacts on bioprocess performance (reviewed by Vu et al., 2022, Jung et al., 2022, and Pudi et al., 2022). Although the practical significance of these attempts is unquestionable, the established sulfide paradigm as villain of the piece has drawn the attention away from the multifaceted sulfide interactions with minerals, organics, microbial interfaces, and their implications for EMS performance.

Sulfate ions (SO_4^{2-}) and sulfur (*S*)-containing proteins in influent organic substances are the major sources of sulfide formation in EMS. When sulfate ions are available, aqueous sulfide (H_2S, HS^-, and S^{2-}) is formed via the dissimilatory sulfate reduction pathway by sulfate reducing bacteria (SRB), with a broad application in biotechnological settings for treatment of sulfate-rich wastewaters and pollutants removal (Qian et al., 2019). Some SRB are also capable of utilizing organosulfates (RSO_4) as electron acceptors to form sulfide (Jochum et al., 2018). In general, consumption of acetate and hydrogen coupled to dissimilatory sulfate reduction can suppress the growth of acetoclastic and hydrogenotrophic methanogens (Raskin et al., 1996), lowering the overall degree of substrate mineralization to methane. Reader is referred to Qian et al. (2019) and Ruckert (2016) for comprehensive reviews on the dissimilatory sulfate reduction pathway and its biotechnological applications. Along with the microbial sulfate reduction, sulfide originates from enzymatic hydrolysis of proteins and peptides (e.g., by activity of proteases and peptidases). Protein hydrolysis leads to solubilization of amino acids, among which cysteine and methionine contain reduced S. Methionine is demethylated to homocysteine by transmethylases and sulfide is cleaved from cysteine and homocysteine due to desulfhydrase activity to form pyruvate and 2-ketobutyrate, respectively (Gottschalk, 1986). It is notable that the anaerobic turnover of cysteine and

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methionine may follow pathways other than desulfidation; e.g., conversion to volatile organic S such as methanethiol, dimethyl sulfide, and dimethyl disulfide (Khanthongthip et al., 2021; Martínez-Cuesta et al., 2013), (di)methylation of cysteine to penicillamine (Gutensohn et al., 2023), or direct uptake by microorganisms (discussed in section 3), implying that the protein hydrolysis may not always give rise to corresponding sulfide level in EMS.

Sulfide formation via microbial sulfate reduction occurs at a wide range of pH, whereas proteins degradation is particularly favored at circumneutral pH (Duong et al., 2019; Qian et al., 2019), pertinent to the optimum pH for neutrophilic methanogenesis. At circumneutral pH, equilibrium between H_2S and HS^- prevails in the aqueous phase ($H_2S = HS^- + H^+$; $pK_a = 7$; Suleimenov and Seward, 1997). The neutrally charged H_2S evolves to the gas phase (Henry's constant of 0.09 M atm^{-1}; De Bruyn et al., 1995) or permeates across the microbial cell membranes (membrane permeability of 3 cm s^{-1}; Cuevasanta et al., 2012). In the presence of metal ions, kinetically favored metal-sulfide precipitation scavenges HS^- ions, influencing the overall aqueous and gaseous concentration of sulfide. Precipitation of iron sulfide is particularly important in the present context ($Fe^{2+} + HS^- = FeS + H^+$; Rickard, 2006), due to the use of Fe additives in engineered systems (e.g., for phosphate removal in wastewater treatment or sulfide removal in anaerobic digesters; Shakeri Yekta et al., 2014). Among the FeS species, formation of amorphous FeS particles (e.g., FeS_m, mackinawite) prevail in EMS (van Hullebusch et al., 2019), and crystalline structures such as pyrite (FeS_2) may as well be present despite their slow nucleation kinetics (Wang et al., 2020b). The amorphous FeS particles may also act as a precursor for formation of sulfide precipitates with other (trace) metals (e.g., β-HgS, metacinnabar; Skyllberg et al., 2021). Depending on the redox state of Fe present in or supplied to EMS (i.e., Fe^{3+} and Fe^{2+} ratio), the pathway of FeS precipitation may involve intermediate formation of elemental S (S^0) and polysulfides (HS_x^-) (Tekin et al., 1999). Elemental S and polysulfides are also formed through oxidation of sulfide ions in the presence of other transition metals ($HS^- + 2Me^{n+} = S^0 + 2Me^{(n\text{-}1)+} + H^+$; Steudel, 1996). Accordingly, the availability of and toxicity by sulfide for microorganisms are regulated by factors determining the chemical speciation and partitioning of S among various species, including metal-sulfides (MeS_x), polysulfidic (HS_x^-), elemental (S^0), and reduced organic S (RSH, and RS_xR'), summarized in Fig. 1.

The toxicity of sulfide has been extensively studied for mitochondrial cells and aerobic bacteria, primarily related to the activities of cytochromes and metal-containing enzymes, e.g., via reaction with cytochrome *c* oxidase in the electron transfer chain of complex IV and impairment of respiration (Szabo et al., 2014), depletion of antioxidants (e.g., glutathione) involved in cellular immune systems (Truong et al., 2006), or alteration of cellular redox state (Eghbal et al., 2004; Ng et al., 2019). In EMS, sulfide toxicity is commonly interpreted based on inhibition of the desired biological functions such as suppressed methanogenesis or organic acids oxidation by the microbial community (Maillacheruvu and Parkin, 1996; Wang et al., 2020a). The mode of sulfide toxicity in EMS is conventionally attributed to the concentration of neutrally charged H_2S due to its membrane permutability (Speece, 1983). An intensified sulfide toxicity has also been observed at alkaline pH where the H_2S and HS^- equilibrium shifts towards lower levels of the former, pointing at the potential toxicity mechanisms related to HS^- (McCartney and Oleszkiewicz, 1991; O'Flaherty et al., 1999). Nevertheless, insights on the physiology of the anaerobic microorganisms suggest their widespread tolerance and adaptive capacity to high sulfide levels, for which the metabolic elements susceptible to sulfide toxicity such as sulfide-sensitive cytochromes maybe lacking or are substituted (e.g., cytochrome *bd* with a lower sulfide sensitivity compared to cytochrome *c*) (Edgcomb et al., 2004; Forte et al., 2016; Mirzoyan and Schreier, 2014; Truong et al., 2006; Xia et al., 2018).

Although it is important to notice that the elevated concentration of aqueous sulfide disrupts certain microbial functions in EMS, it is reasonable to question whether the impact of sulfide on EMS performance is limited to microbial toxicity considering the multitude of reactions linked to the formation of sulfide (cf. Fig. 1). In this brief review, we bring forward sulfide-derived pathways – other than toxicity – observed in diverse anaerobic ecosystems and with potential significance for organic matter degradation in EMS. We focus on abiotic reactions and microbial pathways commonly overlooked in EMS, including sulfide reactions with organic matter, interactions with microbial metabolisms, and interspecies electron transfer to identify research needs for realizing the potential implications of sulfide-derived mechanisms in diversifying and optimizing the EMS function.

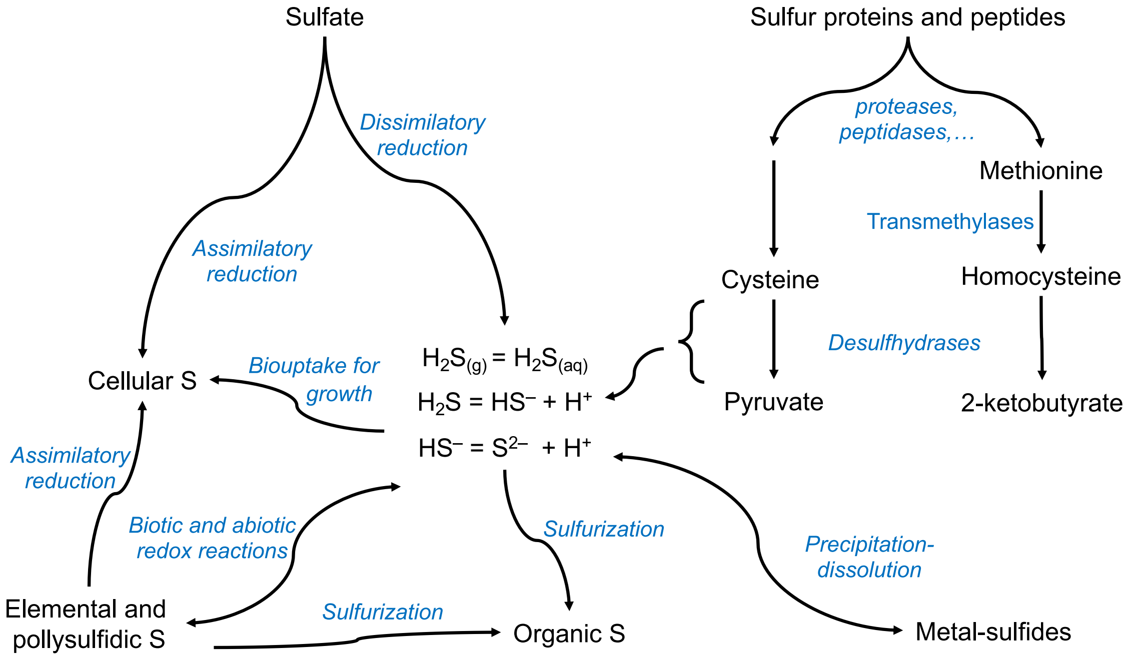

Fig. 1. A simplified scheme of potential pathways underlying the partitioning and turnover of sulfide in engineered methanogenic systems.

2. Sulfide and organic matter

The extent and pathway of sulfide reaction with organic matter depend on properties of the pool of organic molecules such as electron accepting capacity, functional groups, and degree of carbon chain saturation. Different functional groups in complex organic matter can react with sulfide, promoting a rapid chemical oxidation of sulfide to thiosulfate (in a matter of hours; Heitmann and Blodau, 2006), prior to formation of elemental S as the main end product (Valenzuela et al., 2022; Yu et al., 2015). The sulfide-induced reduction of organic matter imposes hydrogenation of the organic structures i.e., $2H_2S + 4OM + 3H_2O = S_2O_3^{2-} + 4OM\text{-}H_2 + 2H^+$ and $H_2S + OM = S^0 + OM\text{-}H_2$, where OM and $OM\text{-}H_2$ represent oxidized and reduced organic functionalities, respectively (e.g., in case of quinones; Yu et al., 2015). As a result, sulfide reaction with the redox active organic functionalities can alter the electron transferring capacity of the pool of organic matter (Valenzuela et al., 2022), with the potential to arbitrate the microbial conversion of organic matter in anaerobic environments such as EMS. In addition, sulfide interaction with organic matter increases the pool of organosulfur compounds via sulfurization. Sulfurization is referred to the abiotic incorporation of sulfide ions into organic structures. The process occurs in different natural environments and is perceived to lower the reactivity of organic molecules towards biological and chemical reactions with substantial implication for organic carbon sequestration and turnover (Kutuzov et al., 2020). The common feature of EMS with respect to biogenic sulfide formation and the presence of structurally complex organic matter would provide conditions for multitude of sulfurization reactions.

2.1. *General pathways of sulfurization*

The strong nucleophilicity of bisulfide anions (HS^-) promotes the sulfurization, particularly with unsaturated, electrophilic carbon bonds (C=C). Such interactions have been exemplified for conjugated α, β unsaturated carbonyl systems (e.g., acrylic, crotonic, methacrylic, and fumaric acids) via nucleophilic addition of HS^- to the β-carbon (Fig. 2a; Vairavamurthy and Mopper, 1987). The reaction is rapid and leads to irreversible formation of thiol groups (RSH). An analogous mechanism has also been observed for addition of sulfide to conjugated α, β systems of quinones at the C2 (or C3) position (Fig. 2b; Perlinger et al., 2002). Similarly, polysulfides are strong nucleophiles and trigger reversible, slower sulfurization of unsaturated bonds compared to the bisulfide-derived reactions (Raven et al., 2015). Polysulfides attack carbon double bonds, forming negatively charged sulfide linkages ($RS_{x\text{-}1}S^-$). The reaction proceeds by coupling of $RS_{x\text{-}1}S^-$ to functional groups of other organic molecules, forming sulfide bridges with two or more S atoms (RS_xR'), or within the same molecule, forming a thiophene-like ring structure (Fig. 2c and d; Raven et al., 2015). The ability of sulfide to substitute N-heteroatoms may as well contribute to sulfurization of organic matter such as those in triazine, amine, and aldehyde-based compounds. This reaction is commonly used to scavenge sulfide from oil and gas streams and it involves substitution of N atoms by S (Fig. 2e; reviewed by Saji, 2021).

Upon sulfurization, formation of thiol functional groups as potent nucleophiles can initiate a suite of subsequent exchange, addition, or substitution reactions with organic matter (comprehensively presented by Lo Conte and Carroll, 2013). Particularly, thiols can trigger the so-called thiolene reaction, leading to their coupling to the unsaturated bonds of other molecules (Fig. 2f). This process has long been utilized to synthesize polymers from e.g., alkenes and linear chain carboxylic acids and it requires a formation of thiyl radicals ($RS^{\bullet}$) by radical initiators such as peroxides or UV exposure (Türünc and Meier, 2013). In the absence of the radical initiators, abiotic oxidation of thiols coupled to reduction of transition metals such as Fe^{3+} can contribute to formation of thiyl radicals and initiation of the thiolene reaction ($RS^- + Fe^{3+} = RS^{\bullet} + Fe^{2+}$; Rontani et al., 2012; Wlodek, 2002). The thiyl radicals are added to the double bonds and form carbon radicals ($RSCC^{\bullet}$), which further abstract the hydrogen of another thiol group leading to elongation of carbon chain and formation of sulfide bridges (RSR').

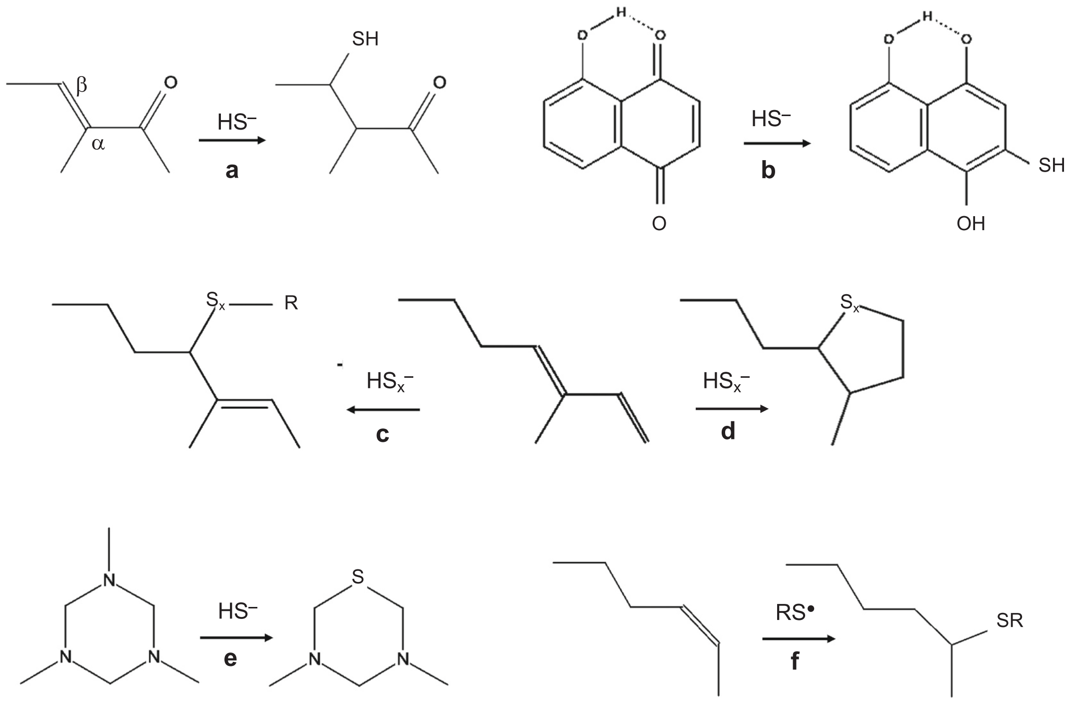

Fig. 2. General pathways of sulfide incorporation into organic matter (adopted from Perlinger et al., 2002; Raven et al., 2015; Saji, 2021; Türünc and Meier, 2013; Vairavamurthy and Mopper, 1987). **a)** Nucleophilic addition of HS^- to the β-carbon of carbonyl groups, **b)** addition of sulfide to 5-hydroxy-1,4-naphthoquinone at C2, **c)** polysulfide (HS_x^-) addition reaction with double bonds and formation of sulfide bridges with other organic molecules, or **d)** formation of thiophene-like ring structure, **e)** substitution of N-heteroatoms in triazine by S, and **f)** coupling of thiyl radicals ($RS^{\bullet}$) to unsaturated bonds via thiolene reaction.

2.2. Sulfurization of organic mixtures in EMS

Engineered methanogenic systems are widely used for handling complex organic waste streams that are categorized based on their proportion of carbohydrates, proteins, and lipids (Ekstrand et al., 2022). Via microbial hydrolysis, carbohydrates are degraded to their oligo and monosaccharides, proteins to amino acids, and lipids to glycerol and long-chain carboxylic acids. In this context, the products of sulfurization are expected to vary for carbohydrates, proteins, and lipids mixtures, occurring in the EMS. The pathway of carbohydrate sulfurization involves a reaction of (poly)sulfide with carbonyl groups at C1 position (Fig. 3a), which has been experimentally observed for a suite of C_4, C_5 and C_6 monosaccharides (Van Dongen et al., 2003). The hydroxyl groups (ROH) of the monosaccharides are likely inert towards sulfide addition, while formation of S-bridged dimer structures with shorter carbon lengths compared to their parent monosaccharides has been observed, implying that sulfide could induce a cleavage of C—C bonds prior to a dimerization reaction (Fig. 3b; Van Dongen et al., 2003).

Sulfide reacts with S bonds in proteins (e.g., CysCys), causing structural modification and aggregation (Cavallini et al., 1970). The overall reaction involves incorporation of sulfide through sulfhydration of thiol groups and formation of persulfide intermediates (RSSH) and trisulfide (RSSSR') products (Fig. 3c) (Nielsen et al., 2010). Sulfide and polysulfides interactions with proteins have gained considerable attention due to their impacts on the physiological functions of proteins (for details on multiple sulfide-protein interactions see reviews by Nielsen et al., 2010 and Kimura, 2020). To exemplify, sulfide can attack the bisulfide bonds in lysozyme, a glycoside hydroxylase catalyzing the hydrolysis of glycosic bonds in sugars, to form trisulfide bridges as a denaturation pathway that prevents lysozyme fibrillation (Rosario-Alomar et al., 2019). Presence of polysulfides and elemental S may as well trigger the sulfurization of cysteine, forming cysteine dimers with polysulfidic linkages ($CysS_xCys$) that are transformed over a short time (i.e., hours) to stable configurations with shorter S chains such as cystine and CysSCys (Fig. 3d; Raven, 2016).

Unsaturated long-chain carboxylic acids (e.g., oleate) as intermediate degradation products of lipids are as well susceptible to sulfurization of the unsaturated carbon bonds, with tentative formation of thiols in diastereotopic configuration over methylene groups (Fig. 3e; Shakeri Yekta et al., 2022). Such interaction has been suggested to influence the kinetics of long-chain carboxylic acids β-oxidation by microorganisms and their conversion to acetate and subsequently to methane in EMS e.g., in case of oleate (Shakeri Yekta et al., 2022, 2019). Furthermore, unsaturated carboxylic acids can undergo cis-trans isomerization in the presence of thiols (Fig. 3f), where the isomerization is prompted by self-initiation of the thiyl radicals as the first step of the thiolene pathway (Samuelsson et al., 2004).

Overall, it can be perceived that the organic matter reduction by sulfide and sulfurization alter the electron transferring properties of organic mixtures and enhance the complexity of organic structures e.g., via formation of S-bridged compounds, structural elongation, or modification of extracellular proteins (cf. Figs. 2 and 3). These reactions are modulated by e.g., the ratio between sulfide and organic matter concentrations, the availability of sulfide-reactive functional groups (e.g., the proportion of carbonyl, carboxyl, and aromatic functional groups) as well as the initial fraction of the sulfurized organic moiety (Graham et al., 2017), indicating the importance of feedstock profiles in terms of organic matter characteristics for the prevalence of sulfurization in EMS. In addition, pH and temperature are expected to influence the charge distribution on carbon functional groups, the chemical speciation of aqueous sulfide as well as the sulfurization kinetics. As factors determining the extent of organic matter and sulfide reactions are poorly explored in relation to the operating conditions of EMS, it is rather unclear whether the degradability of sulfurized organic mixtures in EMS differ from their parent structures.

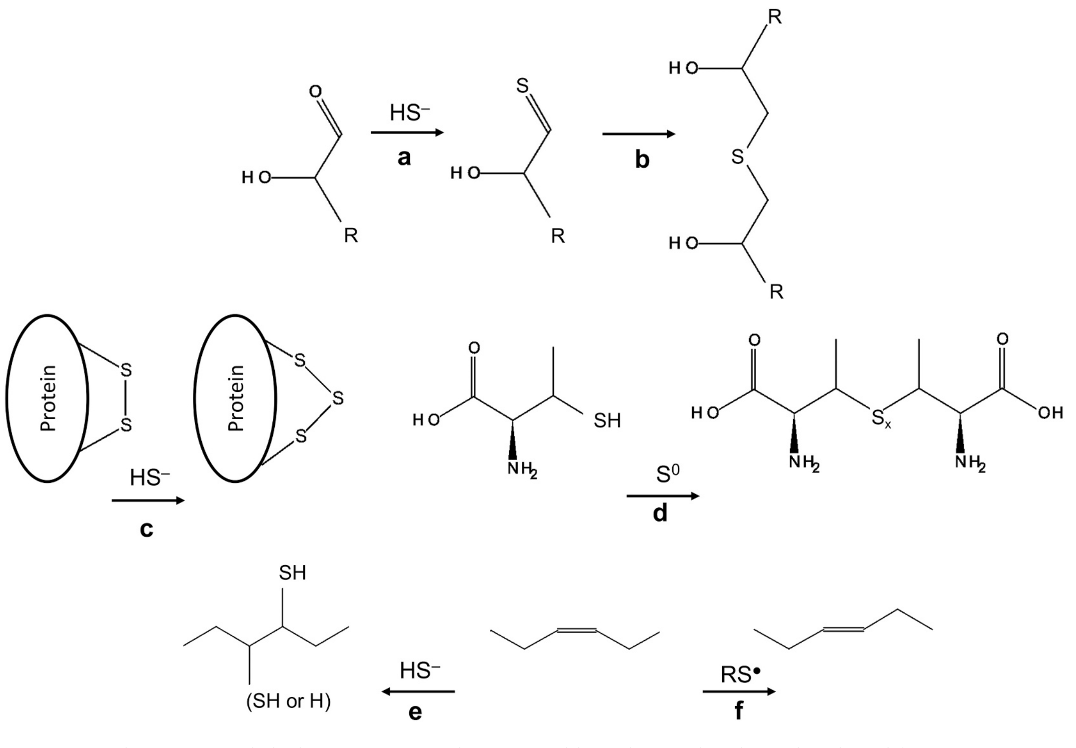

Fig. 3. Sulfide incorporation pathways into carbohydrates, proteins and unsaturated long-chain carboxylic acids (adopted from Van Dongen et al., 2003; Nielsen et al., 2010; Samuelsson et al., 2004; Shakeri Yekta et al., 2022). **a)** Sulfide incorporation into monosaccharides, and **b)** formation of dimer structures, **c)** sulfide reaction with persulfide bonds in proteins and formation of trisulfide, **d)** elemental sulfur (and polysulfide) reaction with cysteine and formation of polysulfidic linkages, **e)** sulfurization of unsaturated bonds of long-chain carboxylic acids, and **f)** their cis-trans isomerization by thiyl radicals.

3. Sulfide and microbial metabolism

Sulfur is an essential nutrient for synthesis of cellular enzymes. During the initial anoxic eras of life, sulfide and elemental S was the dominant S species available for cellular growth, while S uptake and incorporation into biomolecules through sulfate reduction came into play after introduction of oxygen on the Earth (Burini et al., 2018). Sulfate uptake involves transport across the cell membrane via sulfate permeases, formation of adenosine-50-phosphosulfate by ATP sulfurylase and further conversion to intracellular sulfide (Sekowska et al., 2000). Through activities of *O*-acetylserine sulfhydrylase, the intracellular sulfide is converted to cysteine that is utilized by cells as a precursor of S-containing entities such as methionine, Fe—S clusters, and protein persulfides (Hidese et al., 2011). Exogenous cysteine can also be assimilated directly via the cell membrane after aminoacylation of $\mathrm{tRNA}^{\mathrm{Cys}}$ by canonical cysteinyl-tRNA synthetases (Li et al., 1999). Anaerobes generally have a higher content of S-containing groups in their proteomic composition (i.e., cysteine and methionine), compared to the non-anaerobic microorganisms (Bragg et al., 2006). However, a suite of anaerobes such as ancestral methanogens commonly lack the gene repertoires for sulfate and/or cysteine assimilation (Bult et al., 1996; Li et al., 1999; Liu et al., 2012; Rauch et al., 2014), highlighting the potential significance of sulfide as a primary source of S. The metabolic dependency of methanogens to sulfide as a S source has been reported (Rönnow and Gunnarsson, 1981, 1982), indicating that the sulfide deficiency can particularly impair the methanogenic activity. Indeed, direct sulfide addition has since long been proposed for treatment of S deficient industrial waste and wastewater streams by EMS to ensure sufficient S availability for methanogens (Speece, 1983).

3.1. Sulfide as S source of methanogens

Methanogens are dependent on unique S-containing enzymes such as coenzyme M and coenzyme B (Graham, 2011), and a high proportion of their proteomic composition contains Fe—S clusters (up to 8% of the encoded proteins; Christina et al., 2021). The metabolic machinery of methanogens highly relies on Fe—S cluster systems e.g., for hydrogen conversion and storage by hydrogenase, nitrogen reduction to ammonia by nitrogenase, utilization of carbon monoxide and carbon dioxide by dehydrogenases, or regulation of genes involved in osmolyte synthesis in salt tolerance species (Leigh, 2000; Ragsdale and Kumar, 1996; Thauer et al., 2010; Tunçkanat et al., 2022). Examples of EMS that are susceptible to operational disturbances by low sulfide availability are methanation reactors. During the biological methanation, gas streams containing different combinations of CO_2, CO, and H_2 are used as methanogenic substrates. In these systems, rapid evolution of H_2S to the outgoing gas stream continuously purges the S pool available for the methanogenic community. Direct addition of sulfide has shown to mitigate the process disturbances during biological methanation, which was attributed to the role of sulfide as S donor for the methanogenic activities (Cheng et al., 2022; Strübing et al., 2017).

Methanogens that have retained their primitive heredities (e.g., class I Methanobacteriales, Methanopyrales, and Methanococcales) acquire S through direct assimilation of sulfide by tRNA-dependent SepRS/SepCysS or aspartate semialdehyde-mediate pathways (Perona et al., 2018). Sulfide can then be used as a direct S donor for Fe—S cluster assembly and methionine synthesis, as shown for *Methanococcus maripaludis* (Liu et al., 2010). More recent lines of methanogens (e.g., class II Methanomicrobiales, Methanocellales, and Methanosarcinales) have evolved cysteine assimilation capacity, but share sulfide insertion genes such as homologues of MA1821 (L-aspartate semialdehyde sulfurtransferase; Rauch et al., 2014), SepCysS (O-phosphoseryl-tRNA:Cys-tRNA synthase; Fukunaga and Yokoyama, 2007), or MA1715 (ApbE-like S-trafficking proteins; Rauch and Perona, 2016). In addition to the direct use of sulfide, elemental S species can be assimilated and reduced intracellularly by methanogens in the presence of hydrogen as the electron donor (Liu et al., 2012).

Reaction of sulfide with Fe and formation of FeS also promote multiple growth stimulating mechanisms. The use of amorphous FeS as a reducing agent has been suggested for the growth of anaerobic bacteria and archaea in e.g., isolation studies (Brock and Od'ea, 1977). More recently, it has been discovered that the nano-scale FeS particles that are formed in anaerobic environments (Luther and Rickard, 2005), can be transferred across the membrane by either passive or active uptake mechanisms, where methanogens in particular, has the ability to assimilate the FeS nanoparticles as precursors for biosynthesis of FeS-clusters (Payne et al., 2021). Furthermore, it has been suggested the transfer of H_2 produced due to the formation of FeS_2 from FeS and H_2S to methanogens ($4FeS + 4H_2S + CO_2 = 4FeS_2 + CH_4 + 2H_2O$) may catalyze the kinetically-limited formation of FeS_2, while supporting the methanogenic activity in anaerobic environments (Thiel et al., 2019).

Altogether, nutritional role of sulfide, its derivatives and precursors may influence microbial functions in EMS, where sulfide availability below certain thresholds can impair organic matter conversion to methane. Practices such as Fe addition for sulfide precipitation in anaerobic digesters, biological methanation of CO_2, CO, and H_2 and anaerobic digestion of S-deficient industrial wastewater streams are examples of cases where sulfide availability may become an influential factor on EMS performance.

3.2. Sulfide intervention with micronutrients uptake

Biological uptake of micronutrient metals (e.g., Fe, Co, Ni, Cu, and Zn), needed for activity and synthesis of a multitude of metabolic enzymes, is conventionally attributed to complexation of free metal ions with biotic ligands involved in metal trafficking across the cell membrane (Hendriks et al., 2018; Ma et al., 2009). Influence of the metal-sulfide formation on bioavailability of metal ions have been subjected to research, comprising studies on EMS (Aquino and Stuckey, 2007; Callander and Barford, 1983; Shakeri Yekta et al., 2017; van der Veen et al., 2007). In this context, precipitation of metal-sulfides is often considered as a pathway reducing the overall solubility and potential bioavailability of micronutrient metals in EMS. However, the equilibrium chemistry of metal-sulfide minerals particularly at high levels of dissolved sulfide ions include the formation of strong soluble metal-sulfide species with a neutral charge (e.g., $\mathrm{Me}^{2+} + 2\mathrm{HS}^{-} = \mathrm{Me(HS)}^{0}_{2\,\mathrm{aqueous}}$). It has been argued that the neutrally charged soluble metal-sulfide species can permeate across the cell membrane and have the potential to support the passive metal acquisition by microorganisms (Benoit et al., 2001; Shakeri Yekta et al., 2017).

Apart from the reaction of sulfide with metals, thiols as products of sulfurization may impact micronutrients uptake due to their high affinity towards metal ions and formation of stable metal-thiol complexes (Smith et al., 2002). Thiols also inhibit the crystallization of metal-sulfide minerals by stabilizing nanoparticles and clusters of Me_xS_y, as shown for silver and mercury (Deonarine and Hsu-Kim, 2009; Gondikas et al., 2012; Graham et al., 2012). Accordingly, metal-thiol complexation reactions have the potential to substantially regulate the metal solubility and chemical speciation in sulfidic EMS. Metal-thiol complexes can in turn act as biouptake mediators for microorganisms. For example, it has been observed that a modest concentration of Zn-thiol in the presence of strong Zn-EDTA complex can enhance the diffusion rates of Zn towards the cell surface and provide sufficient uptake, presumably via formation and internalization of ternary organometallic complexes at the cell membrane (Aristilde et al., 2012). Available evidence also suggest a complex interplay of intracellular thiol formation and excretion by microorganisms (e.g., formation of cysteine by SRB) with biological uptake rates of metals, which varies with the branching (steric hindrance) of the thiol, but are generally higher than the rate expected at corresponding sulfide concentrations (Adediran et al., 2019; Gutensohn et al., 2023; Schaefer et al., 2011).

Overall, formation of low molecular mass thiols via sulfurization and/or their bacterial excretion is likely an important mechanism, facilitating the biological uptake of micronutrient metals in EMS. As micronutrient metals are commonly added to EMS such as anaerobic digesters (Hendriks et al., 2018), facilitation of the metal uptake mechanisms has important implications for optimizing the metal dosage strategies.

4. Sulfide and interspecies electron transfer

Establishment of syntrophic partnerships between electron donating, organic acid oxidizing bacteria (e.g., butyrate, propionate, and acetate oxidizers) and electron accepting species (e.g., hydrogenotrophic methanogens) is a key for an efficient performance of EMS (Stams et al., 2012). Involvement of sulfide in interspecies electron transfer has long been suggested coupled to the redox cycle of elemental S and sulfide in anaerobic environments. Electrons produced by organic acid oxidizers can reduce elemental S to sulfide (e.g., $CH_3COOH + 4S^0 + 2H_2O = 2CO_2 + 4H_2S$), which is further (re)oxidized to elemental S by shuttling the electrons to the electron accepting microorganisms (e.g., nitrate-reducing or phototrophic S bacteria; Biebl and Pfennig, 1978; Kaden et al., 2002; Pfennig and Biebl, 1976). Considering the redox potential of elemental S/sulfide (i.e., $S^0/HS^- = -275$ mV; Thauer et al., 1977), pertinent to anaerobic environments, and a widespread occurrence of sulfide dehydrogenases that mediate oxidation-reduction of sulfide by anaerobic microorganisms (Hedderich et al., 1998), the elemental S/sulfide redox cycle can be an important mechanism for syntrophic associations in EMS.

In addition, sulfide intervenes with the interspecies electron transfer due to its effect on turnover of reduced organic S species, among which cysteine has the potential to shuffle electrons between syntrophic partners. The cysteine-mediated electron transfer is linked to the oxidation of thiols and formation of disulfide bonds with cystine as the end product (Kaden et al., 2002). The mechanism has been suggested for acetate and propionate oxidation in methanogenic cultures, where the reduction of cystine to cysteine is triggered by electrons generated from the oxidation of carboxylic acids, while the reverse oxidation of cysteine to cystine further shuttles the electrons to the methanogens (Fig. 4a; Kaden et al., 2002; Zhuang et al., 2017). The net effect of cysteine/cystine redox cycle on syntrophic methanogenesis and organic acid oxidation manifests as an accelerated methanogenic activity (Zhuang et al., 2017).

Stimulatory effect of cysteine addition on microbial pathways has been frequently reported in different bioprocesses, including an enhanced activity of enzymes taking part in anaerobic glucose metabolism in EMS (Liu and Chen, 2018) or an increased hydrogen formation by fermentative communities (Yuan et al., 2008). Similarly, an accelerated rate of methanogenic activity upon addition of cysteine to anaerobic cultures has been observed (Shakeri Yekta et al., 2022). Nevertheless, it was shown that the addition of serine, that has a similar structure as cysteine but with a hydroxyl group (ROH) instead of thiol, could equally enhance the rate of methanogenic activity (Shakeri Yekta et al., 2022). Serine can be assimilated by microorganisms as a precursor of cysteine synthesis through *O*-acetylation and substitution of the acetyl group by sulfide (Haitani et al., 2006). The similar effect of cysteine and serine on the methanogenic activity might be related to the direct assimilation of these amino acids and a subsequent stimulation of metabolic functions. Furthermore, cysteine is a reducing agent (Rymovicz et al., 2011), implying that the oxidation-reduction reactions that are thermodynamically favorable at lower redox potentials may be promoted upon cysteine addition. Further studies are therefore needed to distinguish whether the observed stimulatory effects of cysteine on microbial activities in EMS is a result of its assimilation as an essential amino acid and S source, changes in redox potentials of the anaerobic medium, or it relates to the mediation of interspecies electron transfer.

Biogenic sulfide formation and the resultant precipitation of FeS can arbitrate the electron transfer. It is well recognized that the amorphous FeS structures have semiconductive properties (Kondo et al., 2015), and act as electrical conduits, across which the electrons generated by microbial oxidation of organic substances can be conveyed (Nakamura et al., 2010). It can therefore be postulated that the conductive surface area that is formed upon FeS precipitation in EMS could provide an arena for microbial growth, where syntrophic associations between electron donating and accepting members are facilitated. In addition, nanoparticles of FeS that are formed by the reaction of sulfide with Fe can adhere on/between the outer cell membranes as a network of wires, which substantially enhances the conductance between cells (e.g., >100 folds higher electrical conductivity in biofilm of FeS-*Shewanella* compared to the biofilm without FeS; Jiang et al., 2014). The FeS-mediated electron transfer mechanism is presumably coupled to the S respiratory system and the activity of membrane-bound polysulfide and thiosulfate reductases (Psr; Kondo et al., 2015). In this pathway, electrons generated upon oxidation of sulfide to elemental S at the surface of FeS, are conducted to distance electron-acceptors across the FeS network. Thereafter, the elemental S reacts with sulfide to form soluble polysulfide ions (HS_2^-), that are assimilated and reduced to sulfide by Psr in the cell membrane (Fig. 4b).

In light of these observations, the facilitation of electron transfer by FeS offers possibilities for enhancing the kinetics of syntrophic organic acids degradation in EMS, which is conventionally limited by the rate of electron transfer via H_2 and/or formate diffusion (Dolfing, 1992). To this purpose, the engineering of biogenic FeS formation for regulating properties auspicious for electron transfer, such as particle size, surface area and conductivity, may allow developing operating strategies that foster the activities of key syntrophic partners in EMS.

5. Sulfide, pollutants, and antimicrobials

The organic waste streams processed by EMS often contain mixtures

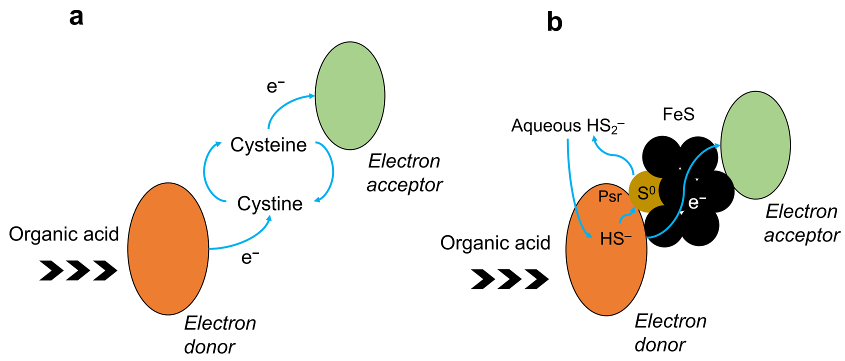

Fig. 4. Schematic representation of cysteine- and FeS-mediated electron transfer (adopted from Kaden et al., 2002; Kondo et al., 2015; Zhuang et al., 2017). Psr: Polysulfide and thiosulfate reductase.

of organic pollutants from municipal, industrial, or agricultural activities with diverse chemical structures. Reactions with sulfide may be important intermediate steps during anaerobic transformation of organic pollutants. Reductive dehalogenation and nucleophilic substitution by sulfide have long been recognized as transformation pathways of halogenated aliphatic pollutants such as carbon tetrachloride (i.e., $CCl_4 + 2H_2S = CS_2 + 4Cl$; De Best et al., 1998; Kriegman-King and Reinhard, 1992). Sulfide has also the ability to rapidly reduce a nitro group in 2,4,6-trinitrotoluene to form (hydrolxyl)aminodinitrotoluene (Qiao et al., 2011), or induce decolorization of monoazo dye, likely due to chemical reduction of azo bonds (RN=NR') and formation of amine functionalities (RNH_2; Yoo et al., 2001). An analogous reaction contributes to the abiotic reduction of azo xenobiotics by biogenic sulfide generated e.g., by microorganisms in human faeces, *E-coli*, and in vivo in mice (Wolfson et al., 2022). In this context, sulfide formation and the consequent precipitation of FeS may as well promote adsorptive removal of organic pollutants from liquid fraction of wastes, particularly those with amine functionalities (Kulandaivelu et al., 2020).

Furthermore, sulfide interacts with emerging pollutants such as polymer nanocomposites, used in industrial and consumer products, or microplastic pollutants in industrial and municipal waste and wastewater streams. Surface precipitation of the metal contents of polymer nanocomposites with sulfide may mitigate the leachability and transfer of metals from these particles to the aqueous phase (e.g. in case of Cd and Ag; Duncan et al., 2022). Interestingly, Zhao et al. (2021) demonstrated that the exposure of microplastic pollutants to sulfide could result in formation of C—S bonds on the surface of the plastic polymers. The authors proposed that the sulfurization occurs via nucleophilic addition after an initial formation of double bonds induced by hydroxyl radical oxidation and may facilitate further transformation of the microplastics by biotic and abiotic processes.

Antibiotic resistant bacteria occur in diverse organic wastes and the EMS used for management of these wastes can contribute as a route for environmental dissemination of antibiotic resistance (Su, 2021). Accordingly, understanding the counteracting mechanisms deems essential to offset the environmental spread of antibiotic resistance upon application of EMS in waste management practices. Sufide-generating bacteria or those with high tolerance against sulfide toxicity commonly show a higher tendency to resist antibiotics. Shatalin et al. (2011) demonstrated that suppression of enzymes responsible for intracellular sulfide production (i.e., cystathionine β-synthase, cystathionine y-lyase, and 3-mercaptopyruvate sulfurtransferase) renders the bacterial cells resistant to antibiotics, suggesting a cytoprotective function of endogenous sulfide. The mechanisms of sulfide-derived antibiotic resistance relate to mitigation of oxidative stress induced by antibiotics, where chromosomal damage via a Fenton-like reaction is suppressed as sulfide scavenges Fe^{2+} (i.e., the catalyst of hydroxyl radical formation), while it favors the activities of antioxidant enzymes (i.e., catalase and superoxide dismutase). Sulfide concentration in the surrounding environment of microorganisms may as well alleviate the antibiotic resistance, as exogenous sulfide in the growth medium could suppress the sensitivity of bacteria to antibiotics (Shatalin et al., 2011). Nevertheless, it has later been argued that the cytoprotective function of sulfide is likely restrained to aminoglycoside antibiotics that primarily target the respiratory chain of the cytoplasmic membrane (Weikum et al., 2018).

The anaerobic and non-respiring microorganisms have inherently low sensitivity to aminoglycoside antibiotics due to their slow growth and the inability/low efficiency to transfer aminoglycosides (Bryan et al., 1979). Furthermore, sulfide stimulation of antibiotic resistance is likely pronounced for bacteria with an endogenous sulfide generation ability. By exposing bacteria lacking the sulfide-generating capability to sodium sulfide (i.e., *Acinetobacter baumannii*), Ng et al. (2020) showed that the bactericidal impact of antibiotics were sensitized (i.e., higher number of cells were killed at copresence of antibiotics and sodium sulfide) and the acquired resistance could be reverted (e.g., against gentamicin). The antibiotic sensitization mechanism was attributed to the interference of sulfide with redox and energy homeostasis, where sulfide exposure upregulates the Fe—S cluster and ATP synthase proteins, while downregulating proteins involved in oxidative stress responses. As a result, capability of sulfide-exposed cells to counter the oxidative stress imposed by the antibiotics is reduced (Ng et al., 2020). These novel findings suggested the potential for administration of exogenous sulfide as a way to mitigate antibiotic resistance, where EMS can offer an arena for targeting antibiotic resistance in wastes upon down-stream treatments.

6. Outlook

High levels of sulfide may upset the EMS performance, however, there are numerous evidence on direct or indirect intervention of sulfide with anaerobic organic matter degradation via redox reactions, sulfurization, influence on micronutrients bioavailability, and interspecies electron transfer. It is therefore reasonable to argue that sulfide is an important molecule in the intricate microbiology of EMS with impacts beyond the toxicity. Nevertheless, there is a need for future studies to address the following questions to enable harnessing the sulfide-mediated abiotic reactions and biotic pathways to improve and diversify the EMS applications:

- To what extent does sulfurization occur in EMS and how does the degradability of sulfurized organic mixtures in EMS differ from their parent structures? Important aspects are profiles of feedstock, including organic matter characteristics, S and Fe speciation as well as process parameters such as retention time and temperature.
- At which operating conditions and applications of EMS does sulfide availability become limiting for microbial activity and particularly methanogenesis?
- Does formation of metal-thiol complexes facilitate the acquisition of micronutrient metals by microorganisms in EMS?.
- Are electron transfer pathways mediated by elemental S/sulfide or cystine/cysteine redox cycles of significance for syntrophic interactions in EMS? A key aspect is to distinguish the contribution of cysteine and elemental S to interspecies electron transfer from their role as nutrients and electron donor/acceptor for microorganisms.
- How can the conductive properties of biogenic FeS be used to enhance the syntropic associations in EMS?
- How does sulfide influence the transformation of different organic pollutant categories (e.g., pharmaceuticals, pesticides, halogenated structures, aromatic pollutants, microplastics, etc.) in EMS?
- The observed synergies between sulfide levels and bactericidal impacts of antibiotics raise the question on how sulfide formation in EMS influences the antibiotic resistance and the transfer of antibiotic resistance genes?

Answers to the latter questions are particularly relevant for improving the application of EMS for pollutants removal along with energy, nutrients, and biomolecules recovery from organic wastes.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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