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ORIGINAL PAPER

Metallophores and Trace Metal Biogeochemistry

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Abstract Trace metal limitation not only affects the biological function of organisms, but also the health of ecosystems and the global cycling of elements. The enzymatic machinery of microbes helps to drive critical biogeochemical cycles at the macroscale, and in many cases, the function of metalloenzyme-mediated processes may be limited by the scarcity of essential trace metals. In response to these nutrient limitations, some organisms employ a strategy of exuding metallophores, biogenic ligands that facilitate the uptake of metal ions. For example, bacterial, fungal, and graminaceous plant species are known to use Fe(III)-binding siderophores for nutrient acquisition, providing the best known and most thoroughly studied example of metallophores. However, recent breakthroughs have suggested or established the role of metallophores in the uptake of several other metallic nutrients. Furthermore, these metallophores may influence environmental trace metal fate and transport beyond nutrient acquisition. These discoveries have resulted in a deeper understanding of trace metal geochemistry and its relationship to the cycling of carbon and nitrogen in natural systems. In this review, we provide an overview of the current state of knowledge on the biogeochemistry of metallophores in trace metal acquisition, and explore established and potential metallophore systems.

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1 Introduction

Our views on metal cycling in the Earth's surface environments are largely informed by geochemical investigations of processes that lead to massive metal translocations in the context of ore formation, weathering, diagenesis, and environmental pollution. However, cellular-scale processes associated with metal uptake by plants and microorganisms form the base of the nutritional food web. Furthermore, processes driven by enzymes containing trace metals drive many key biogeochemical processes at the local to global scale. The importance of inorganic trace nutrients has long been a focus of disciplines such as agronomy and marine sciences. For example, biological activity in oxic terrestrial systems and the photic zone of the marine water column can be iron-limited due to the low solubility and slow dissolution kinetics of iron oxides. In carbonate mineral-bearing soils with alkaline pH values, these constraints on iron solubilization lead to clear ecosystem responses and to agricultural losses (Kraemer et al. 2006; Schenkeveld et al. 2008; Schenkeveld et al. 2010). In marine systems, Fe limitation of marine primary productivity in high-nutrient, low-chlorophyll (HNLC) ocean areas may have a profound effect on global carbon cycling (Martin and Fitzwate 1988).

A particularly efficient iron acquisition strategy employed by a phylogenetically diverse range of organisms is to influence its solution speciation via the exudation of organic ligands with high affinity for the ferric iron. The role of siderophores in iron uptake has been recognized for more than half a century (Garibaldia and Neilands 1956). Siderophores are produced by bacteria (Neilands 1995) [including cyanobacteria (Kranzler et al. 2013)], fungi (Winkelmann 2007), and graminaceous plants (Kraemer et al. 2006). Data suggest that soluble Fe in the photic zone of Fe-limited ocean areas is almost quantitatively bound by strong ligands that form iron complexes of similar stability as siderophore complexes, and that the concentrations of these ligands increase when iron salts are added (iron fertilization) (Boye et al. 2005; Rue and Bruland 1995). Whether these strong ligands are indeed siderophores is difficult to ascertain due to their low concentrations, but marine organisms that potentially produce siderophores have been identified (Gärdes et al. 2013; Gledhill et al. 2004; Kraemer et al. 2005; Martinez and Butler 2007; McCormack et al. 2003; Mucha et al. 1999; Reid et al. 1993; Vraspir and Butler 2009) and siderophores have been directly detected in seawater (Boiteau et al. 2013; Mawji et al. 2008; Velasquez et al. 2011). The role of siderophores in iron acquisition in terrestrial environments (Kraemer et al. 2006; Romheld and Marschner 1986) and by pathogenic organisms (Abergel et al. 2006b) is also well established. Numerous excellent reviews exist on the topic of high-affinity Fe uptake and the biogeochemistry of siderophores (Ahmed and Holmstrom 2014; Albrecht-Gary and Crumbliss 1998; Boukhalfa and Crumbliss 2002; Butler and Martin 2005; Butler and Theisen 2010; Crumbliss 1990; Crumbliss and Harrington 2009; Harrington and Crumbliss 2009; Hider and Kong 2010; Kraemer 2004; Kraemer et al. 2005, 2006; Neilands 1995; Raymond et al. 1984; Stone 1996; Vraspir and Butler 2009; Winkelmann 2007).

Recent studies suggest that high-affinity nutrient acquisition systems akin to siderophores are not unique to Fe. Many metals that are considered toxic at high concentrations are also essential nutrients that are required in trace concentrations for proper biological function, and strategies have been developed by organisms to acquire them from the environment. In this sense, the environmentally ubiquitous siderophores are simply the best-known examples of a larger class of "metallophores" (Kraepiel et al. 2009) that are employed by organisms to promote the uptake of a range of metal ions. Metallophores are herein defined as low-molecular-weight organic ligands that function to supply a metal ion nutrient to an organism, which regulates ligand biosynthesis and exudation based on the nutritional status with respect to this metal ion. By this definition, siderophores are metallophores that are exuded to promote Fe(III) uptake; however, phytochelins and other species that are involved in metal detoxification are not (Bundy et al. 2013). Despite the broad interest in siderophore–Fe(III) interactions, much less work has focused on the chemistry and biology of other metallophores (Kraepiel et al. 2009; Schalk et al. 2011).

In this article, we will explore the geochemistry of metallophores. We will introduce the chemical concepts that control the solubilization and binding of specific metal ions, and evaluate how metallophores may affect the bioavailability of trace metal ions in the environment. Because siderophores are currently the most prominent and well-studied metallophores by far, we will discuss siderophore chemistry as it reflects on the more general definition of metallophores. Additionally, we will review the roles of metallophores in solubilization, binding, and uptake of other target nutrients, including Cu, which is important in oxygen-dependent methanotrophy, and Mo and V, which play important roles in nitrogen fixation. We will also discuss metallophore interactions with metal ions for which the existence of metallophores has been suggested (but not definitively proven), such as Ni and Co. Finally, we will discuss the involvement of metallophores in the biogeochemical cycling of metals that are presumed not to be target metal ions of the complexing metallophore, including Mn, contaminant metals, and actinides.

2 Structural Factors Controlling Metallophore Complexation of Ions

High affinity and specificity for a target trace metal nutrient are considered to be typical properties of a metallophore. Table 1 shows literature values for stability constants of a number of proposed metallophores with a variety of metals, demonstrating the range of metallophore affinities for specific metals. However, specificity of a ligand for a target metal is difficult to obtain because the affinity of ligating groups for metal ions is controlled by a number of factors related to both the structure of the metallophore and the characteristics of the individual metal.

An important parameter in this context is the degree of covalence of the coordinative bond as expressed by Pearson's principle of hard and soft acids and bases (HSAB) (Pearson 1963). The hardness or softness of metals and ligands refers to their tendency to form bonds with more ionic or covalent character, respectively. Hard acid ions such as Pu^{4+}, Ga^{3+}, Mn^{3+}, Cr^{3+}, Fe^{3+}, and Co^{3+} are characterized by a high ratio of the ionic charge to the ionic radius (z/IR, which is often referred to as ionic potential and will be referred to as "charge-to-radius ratio" in the following text), a high electronegativity, and a low polarizability. They exhibit a high affinity for hard ligating groups containing donor atoms such as oxygen. Hard acid ions generally form coordinative bonds with a more ionic character. The binding affinity of ligands with hard oxygen-binding groups, such as microbial siderophores and carboxylate chelators, is often strongly correlated to the charge-to-radius ratio of the metal ion (Fig. 1), which is a surrogate for a metal ion's hardness (Duckworth et al. 2009b, 2014; Hernlem et al. 1999; Hider 1984). The difficulty in overcoming this trend in affinity in favor of a target metal is illustrated by the

Table 1 Selected logβ for a selection of metallophores with diverse metal ions (Akafia et al. 2014; Anderegg et al. 1963; Bellenger et al. 2007; Buglyo et al. 1995; Carrano et al. 1996; Choi et al. 2006; Duckworth et al. 2009c; Duckworth and Sposito 2005b; Enyedy et al. 2004; Evers et al. 1989; Farkas et al. 2003; Harrington et al. 2012b; Hernlem et al. 1996; Jarvis and Hancock 1991; Kim et al. 2009; Murakami et al. 1989; Pesch et al. 2012; Shenker et al. 1996; Szabo and Farkas 2011; Whisenhunt et al. 1996; Yoshimura et al. 2011)

Metallophore	Al(III)	Co(II)	Co(III)	Cu(II)	Fe(II)	Fe(III)	Mn(II)	Mn(III)	Mo(IV)[a]	Ni(II)	Zn(II)
DFOB	25.5	10.1	37.4	14.6	11.1	31.9	7.68	29.9	56.0	11.8	10.4
Rhizoferrin		6.2	34.9	6.2	7.5	25.3	5.9	29.8			4.4
DMA				19.98	11.73	20.3	9.57			16.06	14.12
MA	15.3			19.38	11.42	19.63	9.58			16.2	13.97
epiHMA	14.0			19.2	11.3		9.31			15.67	13.72
Desferricoprogen	24.9	11.3	44.52	16.9	10.6	31.8	9.89	30.5		13.0	13.4
Azotochelin		17.7		27.8			15.0		49.2		20.3
Methanobactin		6.04		34.5		5.99	5.88			5.69	6.65

When necessary, constants are corrected to $I = 0$ with the Davies equation (Pankow 1991)

[a] Equilibrium constants for Mo(VI) are of the form $MoO_4 + L + 4H^+ \leftrightarrow MoO_2L + 2H_2O$. A true log$\beta$ is not physically relevant due to the existence of Mo in the oxyanion form. Methanobactin is from *Methylosinus trichosporium* OB3b, and the constants are conditional constant (pH 6.8). In the case of the Cu(II) complex, the constant describes the overall reaction including Cu(II) binding and reduction to Cu(I) (Choi et al. 2006)

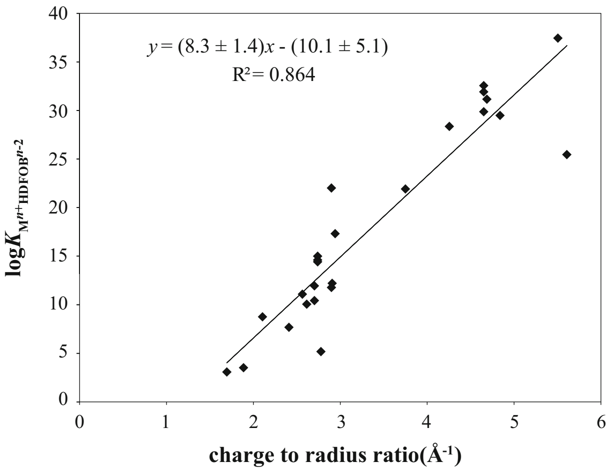

Fig. 1 Correlation between ionic charge-to-radius ratio (*z*/IR) and stability constants for $M^{n+}HDFOB^{2-n}$ complexes (Duckworth et al. 2009b, 2014; Hernlem et al. 1999; Hider 1984). Literature stability constant (Anderegg et al. 1963; Buglyo et al. 1995; Duckworth et al. 2009c; Duckworth and Sposito 2005b; Evers et al. 1989; Hernlem et al. 1996; Jarvis and Hancock 1991; Kim et al. 2009; Whisenhunt et al. 1996)

siderophore desferrioxamine-B (DFOB). DFOB has a strong affinity for Fe(III), but it exhibits an even stronger affinity for presumed nontarget metal ions with larger charge-to-radius ratios, such as Pu(IV) (Boukhalfa et al. 2007; Whisenhunt et al. 1996). Also, even when the affinity for the target metal is largest, other metals can compromise binding selectivity. For example, pyoverdine PV1 has been shown to be able to bind non-ferric metals with lesser affinity than Fe(III), but non-ferric metals are still able to disrupt the ability of *Pseudomolnas aeruginosa* to acquire iron from its environment (Braud et al. 2009). Similarly, in calcareous agricultural soils, deoxymugineic acid (DMA) tends to favor binding of metal ions such as Cu, Co, and Ni over binding the presumed target metal Fe (Schenkeveld et al. 2014a).

In contrast, soft acid ions, such as Cu^+, Cd^{2+}, and Hg^{2+}, are characterized by a smaller charge-to-radius ratio, a smaller electronegativity, and a large degree of polarizability. They exhibit a larger affinity for soft ligating groups containing reduced sulfur and nitrogen, such as thiolates and cyanide, and form bonds with a more covalent character. By the Pearson HSAB concept, nitrogen is an important donor atom for ions of intermediate hardness such as divalent Fe(II), Co(II), Ni(II), Cu(II), and Zn(II). The usefulness of this concept is illustrated by the observation that Fe(III)-binding siderophores typically contain oxygen donor atoms such as found in the hydroxamate, catecholate, and α-hydroxycarboxylate groups in siderophores, whereas the Cu(I)-binding chalkophores contain sulfur and nitrogen donor atoms (Fig. 2). This analysis clearly demonstrates that the selectivity of a metallophore for a target metal may result from a chemical match between the properties of the metal ion and the binding moieties in the metallophore.

Whereas Pearson's HSAB concept only addresses the nature of the coordinative bond, the geometry of the ligand also plays a role in controlling its metal-binding properties. The nature and number of binding moieties partially controls the fit of the metallophore to the metal ion relative to the ion size and electron configuration of the metal ion (Harrington et al. 2012b). For example, the hexadentate siderophore DFOB forms octahedral iron complexes, completely satisfying the coordinative requirements of Fe(III). Synthetic derivatives of DFOB that incorporate an additional bidentate functional group possess increased specificity for actinide ions, which exhibit higher coordination numbers than Fe(III) (Whisenhunt et al. 1996). Additionally, ring structures formed between donor

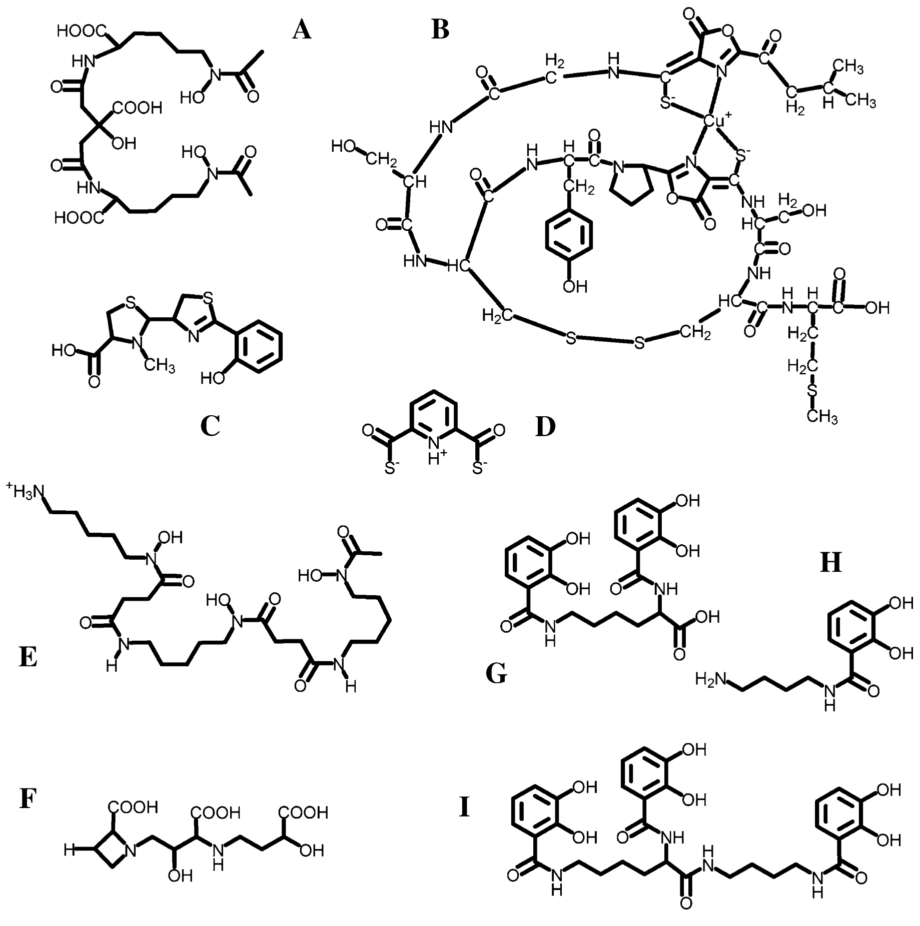

Fig. 2 Figure is based on Shenkeveld et al. (2014b). Examples of metallophore structure*s*: **a** aerobactin, **b** Cu complex of methanobactin from *Methylosinus trichosporium* OB3b, **c** pyochelin, **d** pyridine-2,6-bisthiocarboxylic acid (PTBC), **e** desferrioxamine-B (DFOB), **f** mugineic acid (a phytosiderophore), **g** azotochelin, **h** aminochelin, and **i** protochelin

groups and metal ions with more members in the chelate ring will be better able to interact with smaller metal ions. Thus, six-membered chelate rings such as those seen in citrate are well suited for binding smaller metal ions such as Fe (IR $\leq$ 0.6 Å). Meanwhile, four-membered chelate rings are more effective at binding larger metals (IR $\geq$ 1.0 Å) (Cukrowski et al. 1995; Thom et al. 1985). Copper has an intermediate ionic radius and occurs in six-membered and five-membered (as in chalkophores) chelate rings (Ambundo et al. 1999).

How well a metallophore matches the requirements of the central metal ion also depends on its overall ligand geometry and structural flexibility. The composition and length of the chain that connects the binding moieties, although intuitively less important than the moieties themselves, may also influence the relative binding constants for different metals by accommodating specific ion sizes or geometric configurations (Farkas et al. Farkas et al. 2002, 2004). In addition, the size of the chelate ring connecting donor groups to the metal ion relates the bite angle of a donor group to its ability to interact with the bonding orbitals of the metal ion, resulting in the formation of coordinative bonds (Martell et al. 1994). The effect of flexibility of multidentate binding groups can be demonstrated in the case of the most commonly observed binding groups in siderophores. Catecholate donor groups are very rigid owing to the hybridization of the phenyl ring incorporated into the donor group and the delocalization of electron density throughout the conjugated ring system. This structural rigidity is ideally suited to octahedral coordination of metal ions, such as in the case of iron. The α-hydroxycarboxylate donor group has a minimal amount of electron delocalization, making the geometry of the donor group relatively flexible. This flexibility can accommodate coordination geometries that deviate from octahedral, such as is observed in Jahn–Teller distorted d^4, d^9, and low-spin d^7 coordination systems. In addition, flexible chalkophores form complexes with a distorted tetrahedral with five-membered chelate rings favors Cu(I) while Cu(II) is stabilized in distorted six-coordinate tetragonal geometries (Ambundo et al. 1999). Preferences regarding the coordination geometry can be found by the comparison of the stability constants of the same metallophore with different metal ions and oxidation states (Harrington et al. 2012b).

The concept of specificity of metallophores for certain metals was explored by relating the design of a number of siderophores to their stability constants with Fe(III) and Mn(III), two metal ions with similar charge-to-radius ratio (Harrington et al. 2012b). The study used the model siderophores protochelin (a triscatecholate), DFOB (a trishydroxamate), and rhizoferrin (containing both carboxylate and α-hydroxycarboxylate) to compare complex stability. Results suggested that catecholate siderophores exhibited preferential binding for Fe(III), which has a d^5 electronic configuration and prefers binding in an octahedral geometry that can be more easily accommodated by the preorganized and rigid catecholate donor groups. It was also suggested that rhizoferrin was better suited to binding Mn(III), which has a d^4 electronic configuration that experiences Jahn–Teller distortion, due to the flexibility of the donor groups of the siderophore. This case study thus reinforces some of the structural factors that may help to favor the binding of one metal over another.

Depending on the structure of the siderophore, the binding reaction may or may not exhibit a significant chelate effect, that is, the stability of the chelate complex is not significantly elevated compared to a complex formed by several ligands of lower denticity possessing the same functional groups (Albrecht-Gary and Crumbliss 1998; Carrano et al. 1979). A comparison of the Fe(III)-binding constants of a hydroxamate donor group molecule (NMAHA, log $\beta_3 = 29.44$) and a trishydroxamate donor group molecule (DFOB, log $\beta = 30.9$) displays a relatively insignificant chelate effect. Meanwhile, a comparison of the Fe(III)-binding constant of some monocatecholate donors (aminochelin, log $\beta_3 = 41.3$) and triscatecholate siderophores (protochelin, log $\beta = 44.6$) demonstrates a modest chelate effect.

In addition, a steric preorganization, often through the use of a macrocyclic or tripodal backbone, can force the functional groups into optimal position with respect to the coordinative requirements of the central metal ion, resulting in elevated affinities (Hou et al. 1998; Spasojevic et al. 1999). The reaction of preorganized ligands with metal ions provides less of a decrease in entropy than comparable reactions of non-preorganized ligands, providing a greater degree of stability of the complex (Hancock et al. 2007). Preorganization has been used to the benefit of rational design of selective binding agents for medical and environmental applications (Datta and Raymond 2009; Gorden et al. 2003; Hider and Kong 2010). It is important to distinguish between the concepts of the chelate effect and preorganization in ligand design.

There are some similarities in the two effects, as both provide entropic benefits to the binding reaction over bidentate, tridentate, or tetradentate chelators. However, there are a number of specific examples that require that we distinguish between the two. In the class of catecholate metallophores, protochelin is a triscatecholate ligand that exhibits a log $\beta = 44.6$ for Fe(III), actually slightly lower than the log β_3 of catecholate (log $\beta_3 = 44.9$) and slightly higher than aminochelin (log $\beta_3 = 41.3$) (Harrington et al. 2012a; Khodr et al. 2002; Martell et al. 2005). Enterobactin (log $\beta = 49$) has an additional increase in complex stability due to the preorganization of the donor groups, suggesting that the two effects should be distinguished from each other (Loomis and Raymond 1991). There are additional demonstrations of the preorganization effect in a study of synthetic cyclic trishydroxamates (the effect of arm placement around a central ring and the effect of retrohydroxamate vs. hydroxamate donor orientation) (Dhungana et al. 2007) and the comparison of ferrichrome, basidiochrome, and the cyclic hydroxamate mimics (Harrington et al. 2011).

3 Metallophores and the Geochemistry of Metal Bioavailability

By definition, organisms draw nutrients only from pools that are bioavailable. However, the bioavailability of a nutrient is neither a generic nor a static parameter: nutrient pools that are available to one organism may not be available to another (Romheld and Marschner 1986), and nutrients that are not available at one time may become available under different conditions (Black et al. 2012). Conceptually, nutrients in environmental systems can be distributed over three pools: (1) a directly bioavailable pool in which the nutrient is in a form that can be directly taken up by the organism (referred to as the bioavailable pool); (2) a potentially bioavailable pool that can replenish the directly available pool on relevant timescales (the potentially bioavailable pool); and (3) a non-bioavailable pool (the bioinaccessable pool), consisting of nutrients that cannot become bioavailable to an organism within a relevant time frame (e.g., because they are incorporated in a mineral matrix) (Peijnenburg et al. 2007). When the kinetics involved with nutrient uptake are rapid in comparison with the processes involved with replenishment of the surrounding environment (e.g., desorption and dissolution), the nutrient will become depleted in proximity of the organism, resulting in a concentration gradient (Santner et al. 2012; van Leeuwen et al. 2005).

Upon exudation, metallophores will engage in environmental processes that affect the efficiency of nutrient acquisition from the bioavailable and potentially bioavailable pools (Fig. 3). Metals can be found in a variety of forms in the environment, including solid phases, colloids, dissolved complexes, and biota (Adriano 2001). A large fraction of the nutrients in an ecosystem can be immobilized as a part of the solid and colloidal phases (Hilger et al. 1999; Kraemer et al. 2006; Weng et al. 2001); nutrients associated with these phases are typically considered to be part of the potentially bioavailable or bioinaccessable pools. In these phases, the target metal can either be present as an adsorbed or a precipitated species associated with natural organic matter, clay minerals, and (hydr)oxide minerals (Weng et al. 2001). Because metallophores are exuded to increase the bioavailability of trace metals, the principal process in which they are involved is the complexation and mobilization of metals from environmental reactive compounds. For example, metallophores have been demonstrated to complex adsorbed metals through a ligand exchange reaction (Pesch et al. 2013) and to solubilize metal ions from mineral phases via ligand-promoted dissolution (Kraemer 2004).

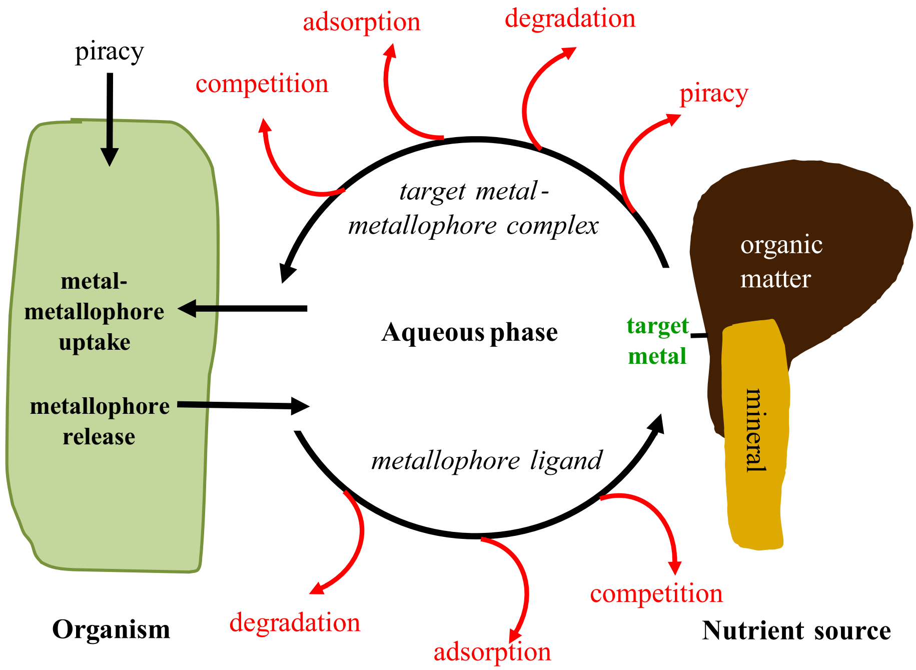

Fig. 3 Mode of action of metallophores. The metallophore ligand is exuded by the organism into the aqueous environment, binds and mobilizes the target metal from either a mineral or organic nutrient source, and the formed target metal–metallophore complex is subsequently taken up by the organism. However, the metallophore ligand and metal–metallophore complexes are exposed to or participate in environmental processes that reduce the efficiency of the mode of action. These processes include adsorption (both of the ligand and of complexes), degradation (including biodegradation and (photo)chemical degradation), competition (either the ligand binds a nontarget metal, or a nontarget metal displaces the target metal from the metallophore complex), and piracy (uptake of metal–metallophore complexes by (other) organisms not producing the metallophore ligand). Piracy can also be an additional source of nutrients for the organism itself, when it takes up metals complexed to metallophore ligands it does not produce itself

Adsorption and dissolution reactions can both profoundly affect the ability of metallophores to solubilize metals. Adsorption of the metallophore is considered a prerequisite in the process of ligand-controlled dissolution (Stumm 1997), and several studies have shown metallophore-promoted dissolution rates to be proportional to the concentration of the ligand adsorbed on the mineral surface (Cheah et al. 2003; Duckworth et al. 2014; Duckworth and Sposito 2005a; Reichard et al. 2005). However, adsorption retains metallophores and metal–metallophore complexes at the surfaces of environmental reactive compounds, thereby reducing the diffusive flux of the target metal toward the organism (Duckworth et al. 2008; Haack et al. 2008; Kraemer et al. 2002; Siebner-Freibach et al. 2004, 2006). The extent to which metallophores are retained depends on how strongly the ligands and complexes interact with environmental reactive compounds and on the abundance of reactive surfaces. These interactions can be electrostatic, hydrophobic, chemical, or mixed in nature. The charge of the metallophore ligands and metal–metallophore complexes plays an important role in electrostatic interactions (Kraemer et al. 2002). Most environmental surfaces, including natural organic matter and clay minerals, have a net negative charge. This negative charge will result in repulsion of negatively charged ligands and complexes, and attraction of positively charged ligands and complexes. The substantially higher adsorption of the positively charged DFOB to a montmorillonite clay in comparison with the negatively charged synthetic ligand *o*, *o*-EDDHA (ethylenediamine di-*o*-hydroxyphenylacetic acid) illustrates this principle (Siebner-Freibach et al. 2004). Conversely, metal (hydr)oxide minerals that exhibit a net positive surface charge at environmental pH values will repel positively charged and attract negatively charged ligands and complexes (Kraemer et al. 1999).

Ligand-promoted mineral dissolution rates, and thus the relative availability of the metals contained in the surface layers of the mineral, are controlled by environmental factors including pH, temperature, element substitution, particle size, surfactant adsorption (Barton et al. 2012; Carrasco et al. 2007; Cervini-Silva and Sposito 2002; Cocozza et al. 2002; Reichard et al. 2007a), as well as the presence of other organic molecules and exudates. Dissolution rates of oxyhydroxide minerals in the presence of metallophores and low-molecular-mass organic acids (LMMOA) have been shown to exhibit a synergistic effect, i.e., the sum of the dissolution rates of the mineral in the presence of LMMOA and of the mineral in the presence of the metallophore is smaller than the dissolution rate when both are present at the same time (Cervini-Silva and Sposito 2002; Cheah et al. 2003). These synergistic effects are particularly pronounced in the presence of the LMMOA oxalate and have been proposed to arise by both ligand-based and reductive pathways. In the ligand-based pathway, the initial step involves adsorption of the LMMOA to the mineral surface; the rate-limiting step of the dissolution reaction in this pathway is the detachment of a kinetically labile metal surface complex. After detachment into solution, the metal undergoes rapid ligand exchange with the metallophore and the LMMOA is available to readsorb (Reichard et al. 2007a, b). Synergistic reductive dissolution reactions also may occur for oxyhydroxide minerals. In this pathway, the LMMOA has been proposed to act as a chemical or photo-induced electron donor that reduces surface metal ions to a more labile lower valence form, which can be readily transferred into solution by a metallophore (Borer et al. 2005; Saal and Duckworth 2010). In environmental systems, ligands are often present in mixtures, and therefore, such synergistic effects may play an important role in nutrient acquisition. Furthermore, because the effectiveness of dissolution in the presence of different combinations of exudates varies between metal hydroxides, the production of differing combinations of exudates may affect which metals are preferentially solubilized (Akafia et al. 2014).

The production of metallophores is thought to result from low availability of a particular nutrient in the environment. However, the selectivity of metallophores for this target nutrient is often limited. As discussed in the "*Structural Factors Controlling Metallophore Complexation of Ions*" section, binding selectivity is related to the match between structural features of the metallophore and ionic charge, ionic radius, and electron configuration of the metal ion. Thus, if metallophores are exuded into the environment in the presence of ions that exhibit similar chemical properties as the limited metal, the efficiency of chelation of the required nutrient may be decreased due to competition from the nontargeted metals (Duckworth et al. 2009a; Schenkeveld et al. 2014a). In the case of phytosiderophores, the principal competitors are other first-order transition metals (Cu, Ni, Zn, Co, Mn) (Schenkeveld et al. 2014a, b; Treeby et al. 1989). Competition reduces the amount of free ligand available for binding the target metal and may force the organism to expend additional energy to produce higher concentrations of metallophores and other exudates to obtain the required nutrients.

The extent to which the efficiency is decreased by complexation of nontargeted metals can be considered from either a thermodynamic or a kinetic standpoint. From a thermodynamic perspective, the impact of competition can be assessed through equilibrium modeling. Equilibrium competition models should take into account the affinity of the metallophore for the target metal and for competing metals, and should describe the free ion activity of these metals in the environmental system of interest. However, within a biologically relevant time frame, the metallophore speciation may not reach equilibrium (Schenkeveld et al. 2014a) due to a number of factors including differences in mobilization kinetics among the metals and relatively slow exchange kinetics. For example, mercury may be preferentially bound by chalkophores in the presence of copper despite a thermodynamic preference for copper, which has been attributed to the rapid complexation kinetics of mercury (Vorobev et al. 2013).

Under such conditions, a kinetic model may prove more suitable for describing metal mobilization. From a kinetic perspective, both the abundance of a metal and the intrinsic rate at which it is complexed and mobilized by metallophores must be taken into account to predict its mobilization in the environment. Further, metal exchange reactions can continue to alter metallophore speciation after the free ligand concentration has become negligible. In the case where the target metal is displaced by a competing metal, the exchange reaction produces a detrimental effect on the nutrient acquisition process (Schenkeveld et al. 2014b). The rate of the displacement reaction determines the extent to which nutrient acquisition by metallophores is compromised. For certain complexes, these exchange reactions have been shown to be surface-catalyzed (Duckworth et al. 2008; Schenkeveld et al. 2012).

Metallophores can be degraded, either microbially (Pierwola et al. 2004; Villavicencio and Neilands 1965; Zaya et al. 1998) or chemically via photochemical or heterogeneous redox reactions (Borer et al. 2005; Duckworth and Sposito 2005a; Parker et al. 2007). The dominant degradation mechanisms and rates under natural conditions for most metallophores are unknown, but degradation rates presumably depend on a combination of environmental factors, including the size and composition of the microbial community (von Wirén et al. 1993). However, microorganisms have been shown to utilize certain metallophores as a carbon source (Takagi et al. 1988). According to Römheld (1991), the phytosiderophore concentration in the rhizosphere of graminaceous plants could decrease by as much as a factor of three as a result of microbial degradation. Microorganisms may require an adaptation time for the utilization of metallophores in catabolic processes, manifesting in a lag time with regard to the degradation of metallophore ligands (Schenkeveld et al. 2014b). Degradation lowers the total metallophore concentration in solution and may limit the diffusive flux of the target metal toward the organism.

4 Metallophores and the Uptake of Metals from Environmental Pools

Metallophores can enhance the biological acquisition of metals through several interrelated geochemical and biological effects. First, they can facilitate the solubilization of the target nutrient (Kraemer 2004). Solubilization can induce the transition of a nutrient from the potentially bioavailable pool to the bioavailable pool. A higher (bulk) solution concentration of the nutrient may lead to less relative depletion and a higher concentration of the nutrient at the organism's surface. Furthermore, it can increase the diffusional gradient toward the organism's surface, accelerating the rate of transport of the nutrient into the direct surroundings of the organism (van Leeuwen et al. 2005). Finally, organisms may have specific receptors facilitating nutrient uptake from nutrient–metallophore complexes (Inoue et al. 2009).

In the free ion activity model (FIAM), the free ion activity is considered a measure for bioavailability because the free ion is a form that can readily be taken up (Campbell 1995; Knauer et al. 1997). The free ion activity in an environmental system may either remain unaffected by the binding of metal ions by metallophores (because the activity is imposed by the solubility of a mineral phase), or decrease (due to the increase in metal-binding capacity related to the exudation of metallophores). In order to contribute to the uptake of the target nutrient, the metal–metallophore complex must be either

(a) directly bioavailable, so that it can be taken up by an organism as a complex (e.g., in plants utilizing Strategy II Fe acquisition, specific membrane transporters for Fe–phytosiderophore complexes have been identified) (Inoue et al. 2009; Murata et al. 2006).
(b) sufficiently labile such that it can either (rapidly) dissociate in the vicinity of the organism as a result of the low activity of the target nutrient ion, thereby contributing to an increase in activity and uptake (van Leeuwen et al. 2005), or transfer the metal through a ligand exchange reaction to a surface membrane-bound ligand (Fukushima et al. 2013).
(c) susceptible to modification by the organism, so that the target nutrient is converted to a bioavailable form. For example, certain membrane-bound enzymes can alter the properties of the metallophore complex by reducing the complexed metal, resulting in a thermodynamically less stable complex (Chaney et al. 1972; Yehuda et al. 2000).

Individual organisms, which may or may not be of the same species or strain, may be affected by metallophore production of other organisms in their proximity. In order to benefit from metallophore production by other organisms (piracy), bacteria and fungi have evolved transporters for xenosiderophores (siderophores they do not produce themselves) (Nevitt 2011). For example, several Yersinia bacteria species do not produce catecholate or hydroxamate siderophores, but are well able to take up their Fe complexes (Rabsch and Winkelmann 1991; Schubert et al. 1999). It appears that certain taxonomical groups of bacteria, unable to produce siderophores, even rely on neighboring siderophore-producing species for growth (Lewis et al. 2010), demonstrating that certain bacterial strains chemically depend on other strains for the production of growth factors (D'Onofrio et al. 2010). Furthermore, in a study on actinomycete bacteria by Traxler et al. (2012), the down-regulation of siderophore-related genes was observed in the one species when grown near a second species that produced siderophores which could be utilized by the first species. This suggests that competition for iron via siderophore piracy and species-specific siderophores can alter gene expression patterns as a result of interactions between bacterial strains.

Both among plants and microorganisms, species not producing metallophores have been shown to take up metals associated with the metallophores (Griffin et al. 2004; Xiong et al. 2013). Intercropping plants exuding phytosiderophores with plants that do not on soils of low Fe availability have been shown to substantially increase Fe uptake by the latter (Zuo and Zhang 2008). However, if the metal associated with the metallophore is not bioavailable for an organism, introduction of a strong binding ligand may have a detrimental effect by decreasing the free metal ion activity. This effect of selectively promoting and reducing bioavailability may be part of the disease-suppressing ability of some bacteria that are known to promote plant growth, which is postulated to occur both by starving pathogenic organisms of trace metals and instead providing them to the plant (Robin et al. 2008).

5 Examples of Environmental Metallophore Biogeochemistry

The previous sections focused on the nature of metallophores, their basic chemistry, and their general interactions with trace metals in the environment. We will now focus on specific examples of metallophores and their roles in the biologically mediated binding, solubilization, and uptake of specific nutrients, as well as their influence on the fate, transport, and potential application to the remediation of toxic metals.

5.1 Copper, Chalkophores, and Methane Cycling

Copper is an essential nutrient for a range of prokaryotic and eukaryotic organisms due to the widespread use of Cu-containing oxidoreductases (Fraústo da Silva and Williams 2001). Also, it is a component of a metalloenzyme involved in the uptake of iron by diatoms, and thus, it is conceivable that primary productivity in the ocean could suffer from Cu/Fe co-limitation (Maldonado et al. 2006; Peers et al. 2005). Additionally, there are indications of possible Cu limitation of ammonia oxidation by Archaea (Jacquot et al. 2014). In the seawater column, Cu exhibits nutrient-type concentration profiles with concentrations ranging from 0.5 nmol/kg in the photic zone to 5 nmol/kg in bottom waters (Bruland 1980). Throughout the water column, Cu is strongly complexed by two classes of ligands of unknown structure: a stronger binding class with a conditional binding constant $\log K_c = 12\text{–}14$ and a weaker binding class with $\log K_c = 9\text{–}12$ (Vraspir and Butler 2009).

Methanotrophic methane oxidation illustrates how metallophores (i.e., chalkophores) can play a key role in Cu acquisition for a specific class of bacteria (Balasubramanian and Rosenzweig 2008). Methane is a potent greenhouse gas, and its release from marine or terrestrial systems to the atmosphere hinges, to a large degree, on the balance between microbial methanogenesis and methanotrophy. Methanotrophs oxidize methane by a soluble or a membrane-bound particulate form of methane monooxygenase enzyme (MMO). Under copper replete conditions, high intracellular concentrations of the copper-containing particulate methane monooxygenase (pMMO) are found in methanotrophic bacterial species (Kenney and Rosenzweig 2012). Some methanotrophs react to Cu limitation by expressing soluble MMO (sMMO) containing a di-iron center. This “copper switch” to the copper-free sMMO is only observed at very low copper-to-biomass ratios (Semrau et al. 2013). Other methanotrophic bacteria possess a high-affinity Cu acquisition system involving methanobactins, a structurally distinct class of chromopeptide metallophore first detected in *Methylosinus trichosporium* OB3b culture media (DiSpirito et al. 1998; El Ghazouani et al. 2012; Tellez et al. 1998; Zahn and DiSpirito 1996). Operons encoding methanobactin-like precursor peptides have been identified in the genome of methanotrophs and a range of non-methanotrophic proteobacteria (Kenney and Rosenzweig 2013). The uptake of Cu–methanobactin complexes by methanotrophs has been directly observed (Balasubramanian et al. 2011), and thus, methanobactin’s function as a metallophore has been demonstrated unambiguously. Readers interested in the general chemistry and biology of chalkophores are referred to a number of recent review articles (Balasubramanian and Rosenzweig 2008; Bandow et al. 2011; Graham and Kim 2011; Kenney and Rosenzweig 2012; Semrau et al. 2010). In this section, we will briefly introduce some properties of chalkophores and then focus the discussion on how these properties may influence the copper geochemistry in natural systems.

Methanobactins from methanotrophs, including *Methylosinus trichosporium* OB3b, *Methylocystis* strains M, SB2, hirsute CSC-1, and roseaSV97T, have been structurally characterized (Bandow et al. 2012; Behling et al. 2008; El Ghazouani et al. 2012; Kim et al. 2004; Krentz et al. 2010). Observations of the stimulation of growth of the *Methylocystis* strain SB2 in the presence of methanobactin produced by *Methylosinus trichosporium* OB3b suggest that methanobactin can be involved in metallophore piracy (Vorobev et al. 2013), a concept well known for promiscuous siderophore uptake by bacteria (D'Onofrio et al. 2010). Copper selectivity of methanobactin is imparted by a combination of complex geometry and the nature of the binding moieties, which differs from siderophores and other metallophores. In all known cases, the methanobactin backbone is peptidic and the ligating donors are two nitrogen atoms in heterocycles and two sulfur atoms in neighboring thioamide groups. These soft ligating donor atoms increase the selectivity of methanobactin for Cu(I) binding (Choi et al. 2006; Tellez et al. 1998) and structurally distinguish it from siderophores. The distorted tetrahedral coordination geometry of methanobactin favors binding of Cu(I) over Cu(II) by increasing the stability field of monovalent copper. Indeed, X-ray photoelectron spectroscopy (Kim et al. 2004) and XANES observations (Hakemian et al. 2005) suggest that copper is primarily present as Cu(I) in this complex, even if the chalkophore reacts with soluble Cu(II). The redox potentials of various methanobactins have been determined by cyclic voltammetry to range from 483 to 745 mV, which reflects differences in Cu(II) affinities between methanobactins, and is indicative of a strong preference for Cu(I) binding in all cases (El Ghazouani et al. 2012). The authors conclude that the differences in Cu(II) affinities are not due to differences in the ligating groups, but are primarily a consequence of variations in the second coordination sphere caused by differences in the overall ligand structures. Detailed studies of the protonation of methanobactin from *Methylosinus trichosporium* OB3b and its affinity for Cu-binding demonstrated that at environmentally relevant low Cu concentrations, methanobactin forms a 1:1 cuprous complex (Table 1) (Pesch et al. 2011, 2012). Although methanobactin exhibits a high binding affinity for Cu, it was demonstrated that it also complexes a range of other metal ions, including Ag(I) and Au(III) (Choi et al. 2006). Chelation of mercury by methanobactin has been demonstrated to decrease toxicity both for the species exuding the compound as well as for other methanotrophic species (Vorobev et al. 2013).

Whereas much research has been performed on the topic of chalkophore chemistry and biology, there is currently no information available regarding chalkophore concentrations and their effect on metal speciation and bioavailability in natural systems. Field and laboratory experiments have failed to correlate methane oxidation with the bioavailability of copper (Bender and Conrad 1995; Lidstrom and Semrau 1995), possibly implying that the copper switch and the use of chalkophores increase the bioavailability of Cu, effectively solving the problem of low copper availability (Knapp et al. 2007). However, the sources from which Cu is solubilized by methanobactin in natural systems are not currently known. It has been demonstrated that methanobactin promotes the dissolution of copper-containing carbonates, hydroxides, oxides, and borosilicate glasses, and that this process relieved Cu stress in *Methylosinus trichosporium* OB3b (Chi Fru et al. 2011; Knapp et al. 2007; Kulczycki et al. 2007). However, these phases are not thought to control copper bioavailability most in environments where methanotrophy occurs. Rather, previous research consistently has found Cu to be bound in stable organic complexes, except in highly Cu-polluted waters (Croot et al. 2000; Leal et al. 1999; Moffett and Brand 1996; Town and Filella 2000; Xue et al. 1996; Xue and Sigg 1999).

In order to illustrate the potential effect of chalkophores in such a natural aquatic system, we have modelled Cu speciation in Lake Greifen, a eutrophic lake in which methanotrophy occurs, using the data from Xue and Sigg (1999) (see Supporting Information for modelling details). In Fig. 4, Cu speciation in the lake is presented as a function

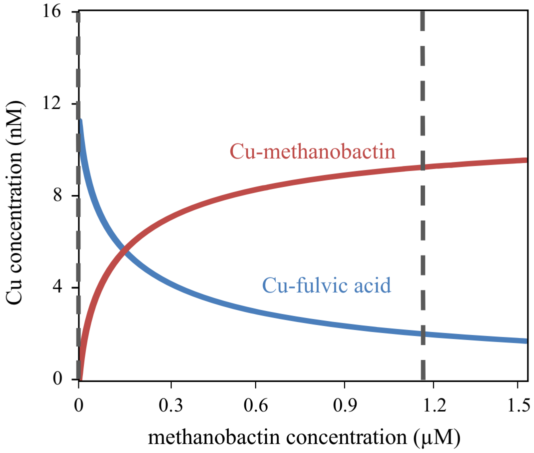

Fig. 4 Modelled Cu speciation in Lake Greifen as a function of added methanobactin concentration

of added concentrations of methanobactin (from Methylosinus trichosporium). If the DOC in the lake is modelled to exclusively consist of generic fulvic acid, the predicted free Cu^{2+} activity in the absence of methanobactin ($pCu^{2+} = 13.5$, where pCu^{2+} is the −log of the free dissolved Cu^{2+} concentration) is two orders of magnitude higher than the measured activity in the lake water ($pCu^{2+} = 15.5$). Introduction of methanobactin into the model results in the formation of methanobactin Cu complexes and a decrease in free Cu^{2+}. Adding 1.15 µM methanobactin causes ca. 80 % of the Cu to be bound by methanobactin instead of FA, indicating that chalkophores efficiently compete with natural organic matter. Also, the modelled free Cu^{2+} activity matches the value observed by Xue and Sigg (1999) ($pCu^{2+} = 15.5$). Xue and Sigg (1999) found that copper was complexed by strong ligands with log $K_c = 13$–15.5 and weaker ligands with log $K_c = 11$–13 in eutrophic Swiss lakes. The strong ligand concentrations varied with season and biological activity, suggesting that the strong ligand is of biological origin (Xue et al. 1996). Furthermore, no obvious correlation between Cu complexation and DOC concentration was observed, indicating the Cu complexing ligands are specific organic compounds. Similarly, our modelling results indicate the presence of a Cu-binding ligand with an affinity comparable to chalkophores in Lake Greifen.

Acquiring Cu from natural organic matter (NOM) complexes requires Cu–methanobactin complexes to be of sufficiently high affinity to compete with NOM, and that the ligand exchange kinetics be rapid. In a recent study, it was shown that Cu exchange reactions between humic substances and methanobactin were rapid, but that the rate decreased with decreasing temperature and Cu concentration. Therefore, it is conceivable that methanotrophic Cu acquisition in organic-rich systems with low Cu concentrations may be kinetically limited by such exchange reactions (Pesch et al. 2013). Clearly, the understanding of chalkophore geochemistry in natural systems remains a challenge for future research.

5.2 Iron, Molybdenum, and Vanadium in Nitrogen-Fixing Bacteria

Metallophores that have been previously classified as siderophores may be directly involved with regulation and uptake of Mo and V. Nitrogen-fixing bacteria, such as Cowpea *Rhizobia* (Patel et al. 1988), *Azospirilium lipoferum* (Saxena et al. 1989), and

Azotobacter vinelandii (Cornish and Page 1995), are known to produce several catecholate and mixed-moiety siderophores. These organisms have a high nutritional requirement for Mo or V because of their utilization of these elements in nitrogenases, the key enzymes for N fixation (Bellenger et al. 2008b; Kraepiel et al. 2009). Nitrogenases contain Fe and Mo or just Fe, although in some cases V may substitute for Mo under conditions of Mo deficiency (Cammack 1988; Howard and Rees 2006; Robson et al. 1986). Nitrogen is often the limiting nutrient in terrestrial and marine environments (Vitousek and Howarth 1991), and because of this limitation, there is considerable interest in factors, from the molecular to ecosystem scale, that limit N fixation (Vitousek et al. 2002). The scarcity of Mo (typically 0.5–5 mg kg^{-1} in soil) (Adriano 2001), and thus the efficiency of its uptake system, may be a critical factor that contributes to the limitation of nitrogen fixation in forests (Barron et al. 2009; Jean et al. 2013; Silvester 1989; Wurzburger et al. 2012) and agroenvironments (Srivastava 1997).

The free living diazotroph *A. vinelandii* is the best-studied nitrogen-fixing bacterium and is capable of producing a triscatecholate (protochelin), a biscatecholate (azotochelin), and a mixed-moiety siderophore (azotobactin), which contains a catecholate, a hydroxamate, and an α-hydroxycarboxylate moiety (Fig. 2) (Duhme et al. 1998); additionally, two monocatecholate ligands, aminochelin and 2,3 dihydroxybenzoic acid (DHBA), may also be produced. The presence of multiple siderophores, in conjunction with the relatively high intercellular quotas for Mo, has led to much interest in their possible roles as metallophores in the uptake of Mo, as well as the effect of Mo binding on Fe uptake. Catecholate ligands are known to associate with molybdate at circumneutral pH; however, the stability constants of the molybdate complexes are significantly lower than those of the corresponding Fe(III) complexes (Table 1) (Bellenger et al. 2007; Cornish and Page 2000; Duhme et al. 1998; Khodr et al. 2002). Furthermore, molybdate activity affects the ratios of metallophores produced during *A. vinelandii* growth (Cornish and Page 1995, 2000). These observations led to the early observation that azotochelin may be a molybdophore (Duhme et al. 1998; Page and von Tigerstrom 1982), a metallophore utilized in the uptake of molybdenum.

Recent work has painted a more complicated picture of metallophore-mediated metal uptake and detoxification in *A. vinelandii* (Kraepiel et al. 2009). Azotochelin, protochelin (Bellenger et al. 2008b), and azotobactin (Wichard et al. 2009a) can promote the uptake of molybdate for use in nitrogenase (Bellenger et al. 2011; Holler et al. 2009) when it is present at low concentrations ($<10^{-8}$ M), even in iron replete media. In addition, at high molybdate concentrations ($>10^{-6}$–10^{-5} M), the uptake of Mo is stopped, possibly to avoid the toxic effects of the metal (Bellenger et al. 2008a; Cornish and Page 2000). Under Mo-depleted conditions, these metallophores promote the uptake of V at low concentrations, but uptake is halted in Mo-replete media (Bellenger et al. 2008a, b). The selectivity in uptake, which may function as a detoxification mechanism to exclude excess or toxic metals (e.g., W) (Kraepiel et al. 2009; Wichard et al. 2008), suggests that independent transport systems are used for each metal complex (Page and von Tigerstrom 1982). In *A. vinelandii*, a membrane-bound ABC-type transporter to facilitate Mo uptake has been identified (Grunden and Shanmugam 1997), but its relationship to Mo–metallophore complexes has not been established.

In most oxic environments, Mo and V typically exist as oxyanions [e.g., molybdate ($Mo(VI)O_4^{2-}$) and vanadate ($V(V)O_4^{3-}$)] (Kraepiel et al. 2009), although V(IV) species are possible (Butler and Carrano 1991). From a coordination chemistry perspective, the most obvious difference between Fe(III) and these oxyanions is the presence of strongly bound oxygen atoms; thus, Mo and V coordination by ligands is typically tetradentate, with two oxygen atoms that are not part of the ligand structure retained in the inner coordination sphere of *cis*-dioxo Mo(VI) (Cornelis 2005; Duhme-Klair 2009). Indeed, an X-ray spectroscopic analysis of a 1:1 azotochelin–Mo(VI) complex formed at pH > 5 revealed 2 short bonds associated with Mo–O oxyanion bonds, in addition to four longer bonds associated with metal–ligand bonds (Bellenger et al. 2007). At lower pH, a multimeric complex may be formed (e.g., a 6:3 Mo–azotochelin complex), although the detailed structure of this complex has not been explored. The structure of the Mo–protochelin complex has not been carefully characterized, but is likely also a tetradenate *cis*-dioxo Mo(VI) species (Duhme-Klair 2009), at least at pH > 5. The structures of the protochelin and azotochelin complexes with V have not been explored, but by analogy to V(V)–DFOB complexes, it is reasonable to postulate that the circumneutral pH species is a tetradentate chelate of the *cis*-dioxo $V(V)O_2^{3-}$, with a possible increase in the ligand coordination number at lower pH (Buglyo et al. 1995). However, it is worth noting that the structurally similar hexadentate catecholate siderophore enterobactin forms stable octahedral complexes with V(IV) (Karpishin et al. 1993). It is unknown how a possible salicylate-type coordination shift may affect the binding of Mo and V, compared to a catecholate-type coordination. The later has been found for Fe(III) and Mn(III) protochelin complexes at pH < 7 (Harrington et al. 2012a), as well as for other catecholamide siderophores (Abergel et al. 2006a).

The ability of these biogenic ligands to function as metallophores for Mo and V hinges on not only their ability to selectively bind but also to solubilize these metals in the environment. This may seem problematic considering the low complexation constants for the oxyanions as compared to Fe(III), which is typically orders of magnitude more abundant than V and Mo. However, the chemical speciation of these metals may allow for kinetic, in addition to thermodynamic, factors to play a role in metal selectivity (Kraepiel et al. 2009). In oxic environments, the dominant iron species are likely to be mineral phases (viz., oxides and hydroxides), although organic complexes may also be present. Molybdate is likely to sorb to the surface of minerals as monomers or polymers (Arai 2010), or be bound to natural organic matter (Wichard et al. 2009b); vanadium is likely to be found in similar pools in most environments (Adriano 2001; Bellenger et al. 2008a). The surface sorbed pool of oxyanions is likely to be more labile than the Fe(III) associated with mineral phases, and rates of exchange of the oxyanions from organic ligands greatly exceed those of Fe(III) (Kraepiel et al. 2009). In addition, aminochelin has been shown to dissolve Mo from a Mo–Fe silicate glass designed to simulate hornblende (Liermann et al. 2005), suggesting that it may be able to solubilize molybdenum from more recalcitrant silicate minerals. These observations suggest that these oxyanions may be able to kinetically compete with Fe for metallophores in the environment. Furthermore, these complexes may be persistent even in the presence of iron despite their relatively low-affinity constants. In the presence of $Mo(VI)O_2^{2-}$, aminochelin (Khodr et al. 2002), azotochelin (Khodr et al. 2002), and protochelin (Duhme et al. 1997) dissolve Fe(III) hydroxide more slowly than in Mo-free systems, with dissolution most inhibited for azotochelin (Khodr et al. 2002). In culture, the complexes are stable in the presence of EDTA bound iron (Kraepiel et al. 2009). These observations suggest that if Mo or V is initially in a more kinetically labile form than Fe(III) (a plausible environmental scenario), it may be able to form kinetically stable complexes with metallophores, despite having lower affinities as compared to Fe(III).

5.3 Nickel in *Escherichia coli*

Nickel is an essential nutrient for plants including legumes (Eskew et al. 1984) and non-legumes (Brown et al. 1987), as well as for bacteria, archaea, fungi, and algae (Boer et al. 2014; Mulrooney and Hausinger 2003) due to its function in enzymes, including hydrogenases (Fraústo da Silva and Williams 2001), superoxide dismutases (Dupont et al. 2008), and those involved in methanogenesis and methanotrophy (Li and Zamble 2009). Ni concentrations in rivers vary considerably from 2.2 to 35 nM (Cameron and Vance 2014), and marine Ni concentrations exhibit a nutrient-like distribution with concentrations increasing from 1.5 to 2 nM in the photic zone to10–11 nM in the deep ocean (Bruland 1980; Cameron and Vance 2014) with only partial complexation by strong organic ligands in coastal and open ocean waters (Vraspir and Butler 2009). In surface waters, Ni speciation is dominated by complexation with organic ligands (Xue et al. 2001). Ni limitation has been observed in the marine diatom *Thalassiosira weissflogii* when provided with urea as nitrogen source, as the diatom requires Ni for use as a cofactor with the urease enzyme (Egleston and Morel 2008; Price and Morel 1991). It has been suggested that in marine systems, partial complexation of Ni to organic ligands and the slow reaction kinetics of Ni exchange reactions may result in Ni limitation (Price and Morel 1991). Ni limitation to methanogenic bacteria in bioreactors as a result of the formation of soluble Ni–sulfide complexes and precipitates with low bioavailability has been well documented (Jansen et al. 2007).

Ni cellular uptake and homeostasis are tightly regulated (Li and Zamble 2009). Detailed characterization of the Ni uptake system in *Escherichia coli* has led to the assertion that Ni uptake may be mediated by a metallophore, although direct detection of the putative metallophore has not been accomplished. It has been shown that *E. coli* possesses an ABC-type membrane-bound receptor for Ni (Dosanjh and Michel 2006), and homologous receptors have been identified in the genomes of several other bacterial species (Li and Zamble 2009). A membrane-bound protein (*NikA*) functions as the Ni receptor for the transporter. Initially, it was believed that this receptor interacted with the pentaaquonickel species (Heddle et al. 2003). However, Fe(III)–EDTA complexes bind strongly to a site in *NikA*, suggesting the formation of a persistent ternary metal–ligand receptor complex, leading to the belief that the transport of Ni is mediated by a carboxylate-bearing metallophore (Cherrier et al. 2005). Mass spectrometry also suggests the presence of a small molecule bound in addition to the metal (Cherrier et al. 2008). Based on a model fit to the structure of the receptor, butane-1,2,4-tricarboxylate (BTC) was proposed to be the best match of candidate ligands (Cherrier et al. 2008). However, a Ni-BTC-*NikA* complex has not been constructed and *E. coli* lacks an obvious synthetic pathway for BTC, and thus, the putative metallophore structure has yet to be elucidated (Cherrier et al. 2008; Li and Zamble 2009). More recently, it has been shown that addition of L-histidine to a minimal growth medium lead to uptake of a $\mathrm{Ni(L{-}His)_2}$ complex via the *NikA* receptor (Chivers et al. 2012), and the binding of the complex to the *NikA* site was elucidated by X-ray crystallography (Lebrette et al. 2013). Although these studies do not establish the physiological relevance of this complex, they further point toward the role of Ni complexes in uptake by E. *coli*.

5.4 Cobalt in Marine Bacteria and Cyanobacteria

Cobalt is not widely utilized in prokaryotic enzymes. However, it is present in cobalamin (B_{12}), can substitute for other metals in enzymes (e.g., carbonic anhydrase), and may be involved in as yet unknown metabolic pathways (Morel et al. 2006). Furthermore, several species of cyanobacteria require Co for growth (Saito et al. 2002; Sunda and Huntsman 1995). Because Co is found in the ocean and most other environments in very low concentrations (pM) (Butler 1998; Donat and Bruland 1995; Vraspir and Butler 2009), it is possible that a metallophore-like uptake system may be used to acquire it, particularly in marine environments.

This assertion is supported by several corroborating lines of evidence. Most Co in the ocean is complexed by high-affinity ligands (Vraspir and Butler 2009), which may be of biogenic origin (Ellwood and van Der Berg 2001; Saito and Moffett 2001). In addition, cyanobacteria are known to produce Co-binding ligands in culture. Preconditioned media that contained cyanobacteria grown in low Co media (which was presumed to contain biogenic ligands) promoted Co uptake compared to fresh media (Saito et al. 2002). Cobalt binding ligands may be found in deep water, suggesting that these complexes are long-lived and stable (Saito and Moffett 2001). However, the structure of these ligands in the ocean or in culture is unknown (Vraspir and Butler 2009). One possibility is that cobalamin, or its degradation products, is the predominant Co-binding ligand in the ocean. The corrin ring at the core of the molecule forms strong complexes with Co, and the stability of cobalamine-like complexes in seawater is consistent with some of the measurements of the stability of Co complexes in seawater. However, because Co(III) forms exceptionally stable complexes with hard bases, other biomolecules may also be candidate ligands (Cotton et al. 1999). Trivalent Co has the largest known stability constants for 1:1 complexes with the α-hydroxycarboxylate rhizoferrin and the trishydroxamates DFOB and desferricoprogen, possibly due to short Co–O bonds between the siderophores and low-spin Co(III) (Akafia et al. 2014; Duckworth et al. 2009c; Farkas and Szabo 2012). Additionally, several siderophores have been shown to promote the dissolution of CoOOH at a much faster rate than FeOOH and, in certain cases, can preferentially solubilize Co from Co-doped FeOOH (Akafia et al. 2014; Bi et al. 2010); however, the dominant dissolution pathway for siderophore-promoted dissolution of CoOOH is reductive, with only DFOB at pH > 7 producing Co(III)–siderophore complexes (Akafia et al. 2014; Bi et al. 2010). Taken as a whole, these results suggest the possibility that metallophores could be involved with cycling and uptake of cobalt in the ocean and other environments. However, this assertion is far from certain as many gaps exist in our understanding of the environmental speciation of Co and its interactions with siderophores. Additional work is required to identify the structure of the Co-binding ligands and to confirm their role in metal uptake in order to definitively determine whether cobalt biogeochemistry and uptake is mediated by metallophores.

5.5 Siderophores and Manganese Biogeochemical Cycling

A discussion of manganese interactions with biogenic ligands should be prefaced by noting that metallophore-mediated uptake of Mn has not been demonstrated, despite the importance of Mn in many redox enzymes (Armstrong 2008; Fraústo da Silva and Williams 2001). Therefore, by the definition presented in this manuscript, there are no currently known putative Mn metallophores. However, a wide structural range of siderophores may interact strongly with Mn and can thus affect its chemical speciation, reactivity, and cycling. Because Mn is abundant in soils and natural waters, it is possible that it may compete effectively for biogenic ligands, thus disrupting the metallophore-mediated transport of other metals [viz., Fe (Duckworth et al. 2009a)]. We thus frame our discussion of manganese–metallophore interactions around these topics.

Manganese is typically found in the environment as ions in oxidation states of +II, III, or IV. Mn(IV) forms a wide variety of minerals but typically does not form dissolved species (Morgan 2000); although the same tenets were until recently widely held for Mn(III), dissolved Mn(III) may be stabilized by strong ligands (Morgan 2000), and it has long been thought to exist in soils (Bartlett 1988; Bartlett and James 1993; Dion and Mann 1946; Heintze and Mann 1949). Recent studies have detected the presence of dissolved Mn(III) in suboxic basins and marine sediments (Madison et al. 2013; Pakhomova et al. 2009; Trouwborst et al. 2006), although Mn(III) is not thought to exist in significant concentrations in the surface ocean (Wuttig et al. 2013). Mn(III) complexes may be involved in diverse, essential redox chemistry, including the maintenance of suboxic zones (Trouwborst et al. 2006). Although the composition of Mn(III) complexes in the environment is unknown, a possible class of ligands which may stabilize these Mn(III) complexes are Fe(III)-binding siderophores. A wide range of siderophore structures, including those with differing binding moieties, have been shown to form temporally stable complexes with Mn(III) that have affinity constants that are near or exceed the corresponding affinity constants for Fe(III) complexes (Duckworth and Sposito 2005b; Faulkner et al. 1994; Harrington et al. 2012a, b; Parker et al. 2004; Szabo and Farkas 2011). In the cases where they are known, Mn(II) complexes exhibit stability constants that are approximately 20–30 orders of magnitude lower than the Mn(III) complexes with the corresponding siderophore (Duckworth and Sposito 2005b; Harrington et al. 2012b; Szabo and Farkas 2011).

Siderophore complexes with Mn(III) may be formed in a number of environmental processes. The siderophore-promoted dissolution of a wide variety of manganese minerals may yield both Mn(III) and Mn(II) complexes. At circumneutral to alkaline pH, DFOB has been shown to dissolve Mn(II,III,IV) oxides by a complex-forming dissolution mechanism that results in Mn(III)–siderophore complexes. At pH < 7, DFOB-promoted dissolution proceeds via a reductive mechanism, resulting solely in Mn(II) (Akafia et al. 2014; Duckworth and Sposito 2005a, 2007; Faulkner et al. 1994; Lloyd 1999; Peña et al. 2007; Saal and Duckworth 2010). In contrast, the catecholate siderophore protochelin and the α-hydroxycarboxylate siderophore rhizoferrin dissolve MnOOH exclusively by a reductive dissolution mechanism (Akafia et al. 2014). Interestingly, the presence of low-molecular-weight organic acids may not only increase the rate of siderophore-promoted dissolution but may also affect whether Mn(II) or Mn(III) complexes are formed (Akafia et al. 2014; Saal and Duckworth 2010). In general, the dissolution rates of Mn (hydr)oxides as promoted by a variety of siderophores exceed those of common Fe(III) (hydr)oxides by approximately two orders of magnitude under corresponding conditions (Akafia et al. 2014; Duckworth et al. 2009a).

Mn(III)–siderophore complexes may also be produced by oxidation of Mn(II) in the environment. Although the conversion of Mn(II) to higher valence states is thermodynamically favorable over a range of oxic conditions, it is typically kinetically slow unless promoted by microbes, surfaces, or organic ligands (Morgan 2000). Catecholate, hydroxamate, and α-hydroxycarboxylate siderophores promote air oxidation of Mn(II) to Mn(III) complexes, with oxidation rates one to two orders of magnitude faster than in the absence of siderophores (Duckworth and Sposito 2005b; Faulkner et al. 1994; Harrington et al. 2012a, b; Parker et al. 2004; Szabo and Farkas 2011). The effect can be explained by noting that the ligand donates charge to Mn(II), potentially lowering the activation energy required for the oxidation reaction (Morgan 2005). It should be noted that the precursor Mn(II)–siderophore complexes exhibit low-affinity constants (Duckworth and Sposito 2005b; Faulkner et al. 1994; Harrington et al. 2012a, b; Parker et al. 2004; Szabo and Farkas 2011), and thus, competition with other common metals may inhibit the formation and subsequent oxidation of Mn(II) complexes in seawater (Wuttig et al. 2013) and other environments with abundant reactive metals. However, siderophores are frequently produced by Mn-oxidizing organisms (Andrews et al. 2014; Parker et al. 2004; Sudek et al.

2009), and siderophores may play a role in the Mn-handling biomachinery of these organisms (Parker et al. 2007).

It has been suggested that the presence of Mn oxides, which are common in soils, sediments, and aquatic environments, may disrupt the siderophore-mediated solubilization, transport, and uptake of Fe(III) in soils and natural waters (Duckworth et al. 2009a). Mn oxides are effective sorbents of metals, and layer-type Mn oxides have been shown to remove iron from Fe(III)HDFOB$^+$ complexes, providing a direct means of affecting complex transport (Duckworth et al. 2008). Manganese may also indirectly affect siderophore-mediated Fe(III) acquisition by competing for a limited pool of siderophores. The relatively rapid kinetics of siderophore-promoted Mn oxide dissolution, which can result in oxidative degradation of siderophores and the formation of high-affinity Mn(III)–siderophore complexes, could result in a decrease in the concentration of free siderophores available to bind Fe(III). For example, a recent study revealed that DFOB in the absence or presence of oxalate and citrate promoted the dissolution of Mn from an oxisol at $\mathrm{pH} = 5$ to a greater extent than the dissolution of Fe, despite the fact that the soil contained <10-fold more labile Fe than Mn (Zhong et al. 2013). Similar antagonistic effects may be possible for other uptake systems that utilize metallophores with similar structures (viz., Mo and V), but no information on this topic is currently available.

5.6 Metallophores and Contaminant Metals: Mobilization, Uptake, and Remediation

As previously discussed in Structural Factors Controlling Metallophore Complexation of Ions section, many chemical, biological, and environmental factors affect the binding and transport of ions by metallophores, and ultimately, the selectivity of a metallophore for a target metal may, for certain metals, be difficult to attain. Thus, metallophores may affect the fate and transport of metals that are not necessarily the target of biological uptake. Metallophores have been shown to bind (Anderegg et al. 1963; Batka and Farkas 2006; Boukhalfa et al. 2007; Christenson and Schijf 2011; Dahlheimer et al. 2007; Farkas et al. 2008; Frazier et al. 2005; Hakemian et al. 2005; Hernlem et al. 1996, 1999; Jarvis and Hancock 1991; Mishra et al. 2009; Moll et al. 2008a, b, c; Whisenhunt et al. 1996) and solubilize (Biver and Shotyk 2012; Brainard et al. 1992; Cornejo-Garrido et al. 2008; Dahlheimer et al. 2007; Frazier et al. 2005; Hakemian et al. 2005; Hepinstall et al. 2005; Kraemer et al. 1999, 2002; Manecki and Maurice 2008; Mishra et al. 2010; Schenkeveld et al. 2014b; Wolff-Boenisch and Traina 2007b) a number of metals (e.g., Al, Am, Bi, Cm, In, Ru, Pb, Pd, Pt, Pu, Sb, Th, U, and a number of rare earth elements) which are not currently thought to have significant intracellular metabolic roles in most organisms and may even be toxic. These observations have led to the assertion that metallophores may affect the rate of dissolution and transport of these toxic metals in the environment, as well as to the suggestion that metallophores may have utility as remediative agents in environmental systems contaminated with toxic metals.

Much of the work in this area has focused on common radioactive metals that may be mobilized from mining operations or legacy waste sites. Metallophores can form strong complexes with U(IV) (Frazier et al. 2005; Moll et al. 2008a), Cm (Moll et al. 2008b, c), Th(IV) (Whisenhunt et al. 1996), Pu(IV) (Boukhalfa et al. 2007; Whisenhunt et al. 1996), and Co(III) (Akafia et al. 2014; Duckworth et al. 2009c; Farkas and Szabo 2012). For Pu(IV)HDFOB^{2+} and Co(III)HDFOB$^+$, the complex stability was shown to exceed that of Fe(III)HDFOB$^+$. Based on these high affinities, it has been suggested that metallophores and related ligands may have value in the reprocessing of nuclear fuel (Ahmed and Holmstrom 2014; Taylor et al. 1998) and in the design of specific synthetic chelating agents for the treatment for patients exposed to Pu and other actinides (Abergel et al. 2010; Gorden et al. 2003). Complexation by metallophores could enhance contaminant mobility not only by increasing metal solubility, but also by inhibiting the sorption of metals to mineral phases. This phenomenon was demonstrated by the inhibition of Eu(III) [a model for the radioactive contaminant Am(III)] sorption onto goethite by DFOB (Kraemer et al. 2002). In addition, DFOB has been shown to promote the dissolution of Pu (Brainard et al. 1992), U (Edberg et al. 2010; Frazier et al. 2005), and Co (Akafia et al. 2014; Bi et al. 2010) minerals, and promote U desorption from kaolinite and goethite (Wolff-Boenisch and Traina 2007a, b).

Despite the evidence for strong interactions between siderophores and potentially toxic metals under laboratory conditions, it is currently unclear whether metallophores significantly contribute to the mobilization of such metals in a field environment. This is largely due to the lack of field studies in this area, driven by the analytical difficulties in working with the low environmental concentrations of metallophores. However, one field study attributed the mobilization of low concentrations (pM) of plutonium from a legacy waste site to colloidal particles with siderophore-type binding moieties (Xu et al. 2008). In general, low metallophore concentrations may serve to limit the maximum flux of metals mobilized by metallophores. In contrast, metallophores may enhance uptake of contaminant metals, despite the specificity of receptors, providing another mechanism of altering the mobility of contaminants. For example, the uptake of the Pu(IV)HDFOB^{2+} complex by the high-affinity iron uptake system of *Microbacterium flavescens* (JG-9) has been observed, most likely a result of the chemical similarity of Pu(IV) and Fe(III) (John et al. 2001). Taken as a whole, these studies raise the possibility that metallophores may function as natural dispersive agents that affects the fate, transport, and uptake of important radionuclides by enhancing mobility. However, significant improvement of kinetic and thermodynamic databases as well as improvements in our understanding of the environmental occurrence and persistence of siderophores will be necessary before these effects can be quantified and modeled.

The fact that metallophores can increase the solubility and bioavailability of metals has led to much interest in potential technological (Ahmed and Holmstrom 2014; Rajkumar et al. 2010) and medical (Foley and Simeonov 2012; Hider and Kong 2010) applications. From a geochemical perspective, it has been suggested that metallophores and metallophore-producing organisms may be utilized in environmental remediation schemes based on phytoextraction. This approach utilizes vascular plants, including metal hyperaccumulating plants (Callahan et al. 2006; Milner and Kochian 2008; Sheoran et al. 2010), to remove metals from contaminated soils. Although phytoextraction is attractive because of the relatively low cost and the lack of site disturbance (Tack and Meers 2010), significant barriers exist to its implementation, including the slow rate of the extraction process (Robinson et al. 2003; Van Nevel et al. 2007). Chelate-enhanced phytoextraction, where chelating agents are added to the soil to enhance bioavailability and uptake, may increase the speed of the process, but also increases the likelihood of leaching and transport of metals in the area of application. This risk is particularly acute with environmentally persistent synthetic chelators, and thus, there is an interest in the development and application of biodegradable chelating agents with shorter residence times in soils (Evangelou et al. 2007; Nowack et al. 2006).

A class of more appropriate chelating agents for use in enhanced phytoextraction is metallophores. In most cases, the introduction of a metallophore is accomplished by the addition of bacteria and their subsequent stimulation to produce metallophores, which may also provide benefits beyond the simple act of producing metallophores (Glick 2010).

Microbes (including plant growth-promoting bacteria and metal tolerant bacteria isolated from serpentine soil) may promote phytoextraction by enhancing metal uptake and increasing the biomass of the plant (Braud et al. 2009; Lebeau et al. 2008; Rajkumar et al. 2009a, b, 2010, 2012). Although the results have been mixed and vary with plant, microbial, and edaphic factors, a recent review generally suggests significant increases in both plant tissue concentration and total amounts of metal extracted (Lebeau et al. 2008). Although the mechanisms of these processes are currently poorly understood, siderophores are generally believed to play important roles in bacterially enhanced phytoextraction processes (Lebeau et al. 2008; Rajkumar et al. 2010). In addition to the geochemical dynamics of the metals in the rhizosphere, plant–soil interactions and processes associated with assimilation and translocation of the metal are critical to the effectiveness of this approach (Rajkumar et al. 2012) and optimization of the system can be complex (Lebeau et al. 2008). Future applications of enhanced phytoextraction may hinge on developing a more detailed understanding of the biogeochemical processes involved to further optimize remediation systems.

6 Summary and Outlook

Siderophores are widely recognized as having broad importance to many disciplines, including oceanography (Kraemer et al. 2005; Vraspir and Butler 2009), agronomy (Kraemer et al. 2006), environmental science (Kraemer 2004), and medicine (Hider and Kong 2010). However, in recent years, geoscientists and environmental scientists have become increasingly interested in metallophores and their broad effects on the speciation, bioavailability, and uptake of non-ferric metals. The motivation for these studies has not only come from fundamental interest in the effects of biogenic agents on metal cycling, but also from the insight that trace metal scarcity may be more widespread and impactful than previously thought. This scarcity can lead to shifts in microbial communities (Basiliko and Yavitt 2001), the utilization of alternate enzymes that utilize more accessible metals (Bellenger et al. 2014; Semrau et al. 2010), or the limitation of environmental processes (Barron et al. 2009; Ho 2013; Jean et al. 2013; Martin and Fitzwater 1988), and thus presents scenarios where small changes in nutrient availability in the presence of metallophores (e.g., increasing soluble iron concentrations in the ocean from sub-nanomolar to nanomolar concentrations) can have major effects on element cycling.

"Are metallophores a general response of microorganisms to trace metal limitation?" is an open and critical question to the field of biogeochemistry. The broad literature described in this review on metals such as Mo and Cu has established that metallophore-mediated metal transport is not limited to Fe. In addition, recent studies with Co and Ni, although currently less definitive, suggest that metallophores may also be involved in solubilization, transport, and uptake of these metals. However, beyond these candidate elements, there is a potentially wide range of metals that have significant interactions with previously identified siderophores or biogenic exudates (cf. Table 2). Because of the potential importance of metalloenzymes in environmental processes, the discovery of an unknown high-affinity metal uptake system may aid in elucidating the function of the molecular-scale machinery of ecosystems and perhaps the Earth system. In the search for unknown metallophores, it is critical to consider the coordination chemical, evolutionary, and ecological principles discussed above.

Table 2 Summary of enzymatic utilization and metallophore-mediated uptake of trace metals

Metal	Notable metalloenzymes in microbes	Known, putative, or possible metallophores
Fe	Many diverse enzymes (Fraústo da Silva and Williams 2001)	Over 500 currently known structures of siderophores (Kraemer et al. 2005)
Cu	Many diverse enzymes (Fraústo da Silva and Williams 2001); particulate methane monooxygenase (Balasubramanian and Rosenzweig 2008) specifically linked to metallophores	Methanobactin promotes solubilization and uptake; this Cu(I)-binding ligand is structurally distinct from Fe(III)–siderophores (Behling et al. 2008; Kim et al. 2004)
Mo	Redox enzymes, most notably Fe–Mo nitrogenase (Howard and Rees 2006) and other N-cycle enzymes (Self et al. 2001)	Azotochelin, protochelin, and aminochelin promote solubilization and uptake (Bellenger et al. 2008b; Cornish and Page 1995); pyrochelin may affect transport in *Pseudomonas aeruginosa* (Visca et al. 1992)
V	Fe–V nitrogenase (Robson et al. 1986)	Azotochelin and protochelin promote uptake (Bellenger et al. 2008a)
Ni	Nine metalloenzymes (Mulrooney and Hausinger 2003), most notably urease (Fraústo da Silva and Williams 2001), nitrogenase (Fraústo da Silva and Williams 2001), and superoxide dismutase (Dupont et al. 2008)	No metallophores have been identified, but an uptake system is suspected in *E. coli* (Dosanjh and Michel 2006); pyrochelin may affect Ni(II) uptake in *Pseudomonas aeruginosa* (Visca et al. 1992); interactions with known Fe(III)-siderophores are of moderated strength (Hernlem et al. 1996)
Co	B_{12}, substitution into urease or carbonic anhydrase; other unknown functions (Fraústo da Silva and Williams 2001; Morel 2008; Morel et al. 2006)	Uptake is accelerated by unknown biogenic ligands for cyanobacteria (Saito et al. 2002, 2005); Co(III) is bound very strongly by Fe(III)–siderophores, and thus natural marine metallophores may be structurally similar (Duckworth et al. 2009c); pyrochelin may affect Co(II) transport in *P. aeruginosa* (Visca et al. 1992)
Mn	Redox enzymes, most notably superoxide dismutase and water-splitting enzymes (Fraústo da Silva and Williams 2001)	Siderophore-mediated uptake is not known; aqueous Mn(III) is stabilized and strongly bound by known Fe(III)–siderophores (Duckworth and Sposito 2005b; Farkas and Szabo 2012; Faulkner et al. 1994; Harrington et al. 2012a, b; Parker et al. 2004)
B	B is an essential element to plants and may be beneficial to bacteria and animals (Adriano 2001)	B is bound by several iron siderophores and may be associated with signaling in the ocean (Harris et al. 2007)
W	Some prokaryotic redox enzymes, most notably in thermophilic bacteria (Kletzin and Adams 1996)	No metallophores have been identified; however, W binds to azotochelin and protochelin, but is not taken up by *A. vinelandii* (Wichard et al. 2008)
Zn	Many diverse enzymes (Morel et al. 2006)	No metallophores have been identified; however, there is a possible role of pyridine-2,6-bisthiocarboxylic acid (PDTC) in uptake (Leach et al. 2007) by *Pseudomonas putida*
Cd	Carbonic anhydrase (Price and Morel 1990)	No metallophores have been identified

Table 2 continued

Metal	Notable metalloenzymes in microbes	Known, putative, or possible metallophores
Ti	Currently, no known natural role in biology; however, it is environmentally common and may play as yet unknown metabolic roles (Tinoco et al. 2008)	No metallophores have been identified; however, aqueous Ti(IV) is stabilized by citrate (Collins et al. 2005) and triscatecholate ligands (Borgias et al. 1984)
Cr	Known enzymatic use confined to mammals (Fraústo da Silva and Williams 2001)	No metallophores have been identified; however, Cr(III) binds to known Fe(III)–siderophores (Akafia et al. 2014; Budzikiewicz et al. 2002; Leong and Raymond 1975)

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