

## Marine siderophores and microbial iron mobilization

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**Key words:** Photoreactive amphiphilic marine siderophores

### Abstract

Iron is essential for the growth of nearly all microorganisms yet iron is only sparingly soluble near the neutral pH, aerobic conditions in which many microorganisms grow. The pH of ocean water is even higher, thereby further lowering the concentration of dissolved ferric ion. To compound the problem of availability, the total iron concentration is surprisingly low in surface ocean water, yet nevertheless, marine microorganisms still require iron for growth. Like terrestrial bacterial, bacteria isolated from open ocean water often produce siderophores, which are low molecular weight chelating ligands that facilitate the microbial acquisition of iron. The present review summarizes the structures of siderophores produced by marine bacteria and the emerging characteristics that distinguish marine siderophores.

### Introduction

#### *The iron hypothesis*

A third to a half of the world's fixation of carbon dioxide occurs in the oceans as a result of photosynthetic activity by phytoplankton (Field *et al.* 1998). Despite the vast surface area covered by ocean water, the majority of the marine carbon dioxide fixation occurs in coastal environments. In many ocean regimes, chlorophyll levels are low and so too is the level of primary production by photosynthetic activity, even though these waters are replete in major nutrients (e.g., nitrate, phosphate, and silicate). These so called high-nitrate-low chlorophyll (HNLC) regions also coincide with very low iron levels, which range from 20 pM to 1 nM in surface seawater (Martin & Fitzwater 1988; Martin *et al.* 1994; Johnson *et al.* 1997; Morel & Price 2003). The apparent link between low primary production and low iron concentration led to the "Iron Hypothesis" (Martin 1990; Martin *et al.* 1991). If true, then it was reasoned that an influx of iron would not only promote growth of photosynthetic microorganisms but also

significantly reduce atmospheric carbon dioxide levels and lead to the export and sequestration of carbon to the deep oceans.

The region of high primary productivity to the west of the Galapagos Islands provided evidence of the effect of natural iron influx. Iron in the volcanic ash off the Galapagos Islands was being carried by the prevailing winds and currents fertilizing the waters and promoting growth of photosynthetic microorganisms. Thus large-scale *in vitro* supplementation studies were conceived to determine whether iron addition would propagate growth of photosynthetic microorganisms.

The Iron Hypothesis has now been tested at least nine times on large (~70–100 km<sup>2</sup>) patches of ocean water in the equatorial Pacific (Coale *et al.* 1996 and references therein), the eastern subarctic Pacific (Tsuda *et al.* 2003; Boyd *et al.* 2004), and the Southern oceans (Boyd *et al.* 2000; Coale *et al.* 2004 and references therein). In all cases massive blooms occurred, depicted by a substantial increase in chlorophyll levels, a decrease in the concentration of carbon dioxide at the air water interface, and a draw down of various bulk nutrients. The persistence of the blooms however, varied

greatly, from two to greater than 50 days, as did the amount of carbon sequestered to the deep oceans. At this point the variation in the bloom persistence is not entirely understood yet. An important finding of the iron supplementation expeditions was that oceanic heterotrophic bacteria (i.e., that grow on sources of carbon other than carbon dioxide) also increased in numbers and thus heterotrophic bacteria compete successfully for iron against phytoplankton and cyanobacteria.

The iron(III) present in surface ocean waters has been shown to be fully complexed by an organic ligand or class of ligands, "L" (Gledhill & Vandenberg 1994; deBaar *et al.* 1995; Rue & Bruland 1995, 1997; Wu & Luther 1995), although few structural details are known about these ligands (Macrellis *et al.* 2001). An intriguing result of the IronEx II expedition in the equatorial Pacific Ocean was the discovery that the concentration of the organic ligand(s), "L", increased in a relatively short time-span, rising to meet the concentration of added iron. Thus it has been proposed that "L" is biologically derived (Rue & Bruland 1997). Many questions arise about the role and significance of these biologically produced ligands, including a possible relationship between "L" and microbial siderophores (see below). Thus we and others have sought to investigate the molecular mechanisms that microorganisms use to sequester iron.

### *Marine siderophores*

To compete for iron under iron-limited aerobic growth conditions, many microorganisms produce siderophores. Siderophores are low molecular weight, chelating compounds synthesized by bacteria for the purpose of sequestering iron(III) from the environment (Albrecht-Gary & Crumbliss 1998; Winkelmann 2002; Crosa *et al.* 2004). While hundreds of structures of siderophores from terrestrial microorganisms have been reported, the study of open ocean bacteria that produce siderophores is relatively new and thus far fewer structures of marine siderophores are known. Nevertheless, two prominent structural features characterize the majority of the marine siderophores discovered so far. One class of marine siderophores contains  $\alpha$ -hydroxycarboxylic acid moieties, in the form of  $\beta$ -hydroxyaspartic acid or citric acid, which, when coordinated to Fe(III), are photoreactive in the natural sunlight conditions of the mixed layer of the

upper ocean (Barbeau *et al.* 2001, 2002; Bergeron *et al.* 2003) (see aerobactin and the petrobactins in Figure 1 and the marinobactins and aquachelins in Figure 2 below). The other class of marine siderophores that has arisen at this early stage of investigation is comprised of suites of amphiphilic siderophores that contain a unique peptidic head-group appended by one of a series of fatty acids (Martinez *et al.* 2000, 2003) (see Figure 2 below).

### *Photoreactive Fe(III)-siderophore complexes*

The prevalence of siderophores containing photoreactive groups when coordinated to Fe(III) is a newly recognized and intriguing feature of many marine siderophores. Some marine siderophores contain citrate such as aerobactin (*Vibrio* sp. DS40M5, (Haygood *et al.* 1993)), petrobactin (*Marinobacter hydrocarbonoclasticus*, (Barbeau *et al.* 2002; Bergeron *et al.* 2003)) and petrobactin-SO<sub>3</sub> (Hickford *et al.* 2004) (Figure 1). Other marine siderophores such as the alterobactins A and B, the aquachelins and the marinobactins contain  $\beta$ -hydroxyaspartic acid. Photolysis of Fe(III) complexed to  $\alpha$ -hydroxycarboxylic acids in the ultraviolet generates an oxidized ligand and Fe(II) (Figure 1). Thus the photoreactivity of these ferric siderophores in the upper ocean potentially affects the bioavailability of iron. Ferrous ion could be directly taken up by microorganisms or, in aerobic environments, could be oxidized to Fe(III) and rechelated by another siderophore or by the photoproduct itself (Barbeau *et al.* 2001, 2002; Bergeron *et al.* 2003; Hickford *et al.* 2004). Thus, the cycling of iron in the upper ocean could be moderated by the photolysis of photoreactive siderophore ligands that contain the  $\alpha$ -hydroxycarboxylic acid moiety.

Citrate-containing siderophores have been known for a very long time, although the bacteria producing these siderophores are mainly enteric and not likely to experience the UV light conditions required for photolysis; thus the photoreactivity has not been reported until recently (Barbeau *et al.* 2001, 2003).

Photolysis of the Fe(III)-aquachelin complexes in sunlight results in ligand oxidation and truncation as well as reduction of Fe(III) to Fe(II) (Barbeau *et al.* 2001).

The same peptide fragment is formed whether each of the aquachelins is photolyzed separately or photolyzed as the physiologically produced mixture of aquachelins A–D. The only amino acid lost

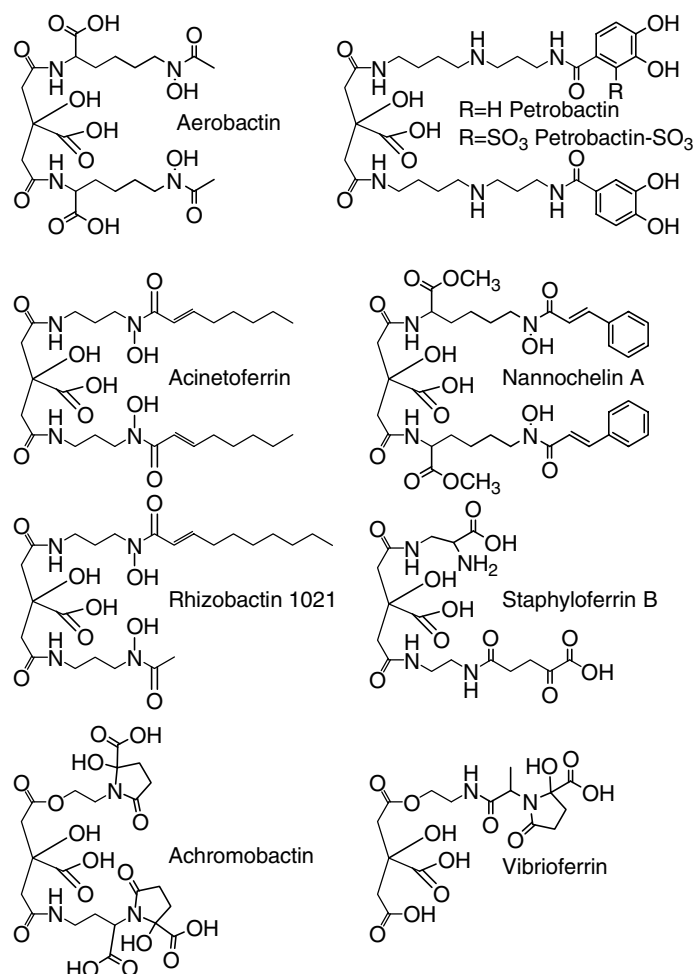


Figure 1. Citric-acid-containing siderophores. Aerobactin is produced by marine (Haygood *et al.* 1993) and terrestrial bacteria. Petrobactin and petrobactin sulfonate are produced by a marine bacterium (Barbeau *et al.* 2002; Bergeron *et al.* 2003; Hickford *et al.* 2004). References for the other siderophores are Acinetoferrin (Okujo *et al.* 1994); Nannochelin A (Kunze *et al.* 1992); Rhizobacterium 1021 (Persmark *et al.* 1993); Staphyloferrin B (Haag *et al.* 1994); Achromobactin (Mnzinger *et al.* 2000); Vibrioferriin (Yamamoto *et al.* 1994).

in the photoreaction is  $\beta$ -hydroxy-aspartate acid. The peptide photoproduct retains the two hydroxamate groups and the ability to coordinate Fe(III) (Barbeau *et al.* 2001). Moreover, only catalytic amounts of Fe(III) are required to effect the complete oxidation of the aquachelins in aerobic conditions.

Petrobactin and petrobactin-SO<sub>3</sub> are citrate-derived marine siderophores with unique 3,4-dihydroxy catecholate appendages. Photolysis of the Fe(III)-petrobactin complex results in photodecarboxylation of the siderophore ligand and reduction of the iron (Barbeau *et al.* 2002).

The ferric complexes of the other  $\beta$ -hydroxyaspartic acid-containing marine siderophores (e.g.,

alterobactins A and B, the marinobactins, etc.) and the other citrate-containing siderophores are currently under investigation. In addition the iron(III) complexes of pseudoalterobactins A and B, which are chemically related to the alterobactins (Kanoh *et al.* 2003), as well as other  $\beta$ -hydroxyaspartic acid-containing siderophores (e.g. ornibactins, corrugatin, etc; see below) are also expected to be photoreactive.

While early results show that  $\alpha$ -hydroxycarboxylic acid-containing microbial Fe(III) chelates can facilitate photochemical cycling of iron in ocean surface waters (Barbeau *et al.* 2001, 2002, 2003), the fate of the photolytically produced iron(II) remains uncertain, as does the fate of the

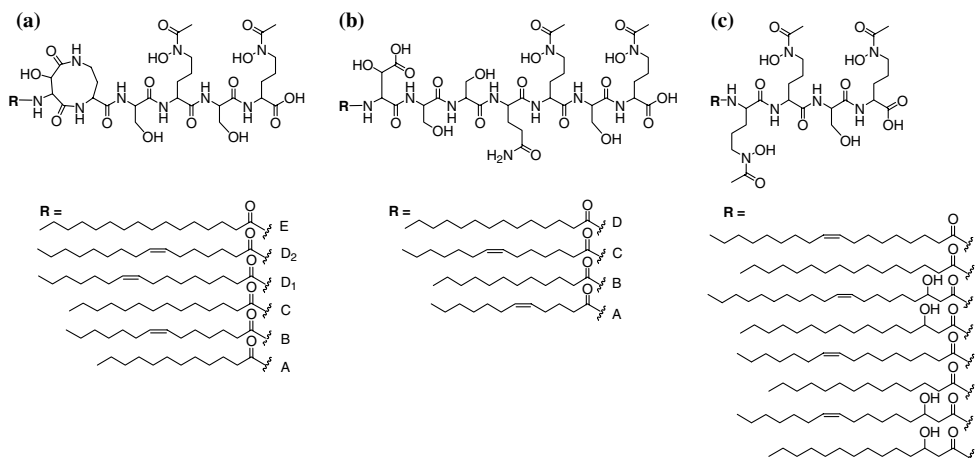


Figure 2. Families of amphiphilic marine bacteria (Martinez *et al.* 2000, 2002). (a) marinobactins, (b) aquachelins and amphibactins.

photooxidized siderophore ligand. Because the hydroxamate and catecholate moieties are not photoactive when coordinated to Fe(III) (Barbeau *et al.* 2003), the photooxidized siderophores coordinate Fe(III) with appreciable affinity. Initial results suggest that iron bound by the oxidized siderophore ligand may be more available for biological uptake by bulk microorganisms, since the conditional stability constant of Fe(III)-photoproduct is reduced relative to that of the original ferric ligand (Barbeau *et al.* 2001).

#### Amphiphilic siderophores

The aquachelins, marinobactins and amphibactins are distinct families of amphiphilic peptidic siderophores produced by different genera of marine bacteria (Figure 2) (Martinez *et al.* 2000).

These siderophores contain a peptidic head group that coordinates iron(III) as well as one of a series of different fatty acids that is appended at the amine terminus (Martinez *et al.* 2000, 2003). The amphiphilicity of each of these siderophores is defined by both the peptide size (e.g., six, seven or four amino acids, respectively) and the fatty acid chain length (e.g., C12–C18). The amphibactins with a short peptide head group of only four amino acids and relatively long C18 fatty acids remain cell associated and are extracted from the bacterial pellet during isolation in contrast to the marinobactins and aquachelins which are isolated from the supernatant following centrifugation of the bacterial culture to pellet the cells. Another

smaller suite of amphiphilic peptide siderophores are the ornibactins, isolated from *Burkholderia cepacia*, a terrestrial bacterium (Stephan *et al.* 1993; Meyer *et al.* 1995). The ornibactins, like the marinobactins and aquachelins contain  $\beta$ -hydroxy aspartic acid, but are distinguished by their quite short fatty acid appendages: C4, C6, and C8.

Relatively few terrestrial bacteria have been found to produce suites of amphiphilic siderophores, although in addition to the ornibactins produced by *B. cepacia* (Stephan *et al.* 1993; Meyer *et al.* 1995), mycobacteria produce both suites of lipophilic siderophores and amphiphilic siderophores (Gobin *et al.* 1996; Ratledge & Dale 1999; Ratledge *et al.* 1999). In addition to the mycobactins, other known cell-associated siderophores include the structurally related formobactins (Murakami *et al.* 1996), nocobactins (Ratledge and Patel 1976), and amamistatins (Suenaga *et al.* 1999; Kokubo *et al.* 2000).

Acinetoferrin and rhizobactin 1021 are two amphiphilic siderophores that also contain a citrate backbone. These siderophores are each composed of citrate, 1,3-diaminopropane, and monounsaturated acyl appendages. Acinetoferrin is produced by the opportunistic pathogen *Acinetobacter haemolyticus* (Figure 1; Okujo *et al.* 1994), however it is reported as a single amphiphilic siderophore with two short C8 fatty acid groups. Rhizobactin 1021 is produced by the nitrogen fixing alfalfa symbiont *Rhizobium meliloti* 1021; it is reported also as a single siderophore with one C10 fatty acid appendage (Figure 1)

(Persmark *et al.* 1993). Finally, corrugatin produced by *Pseudomonas corrugata* (Risse *et al.* 1998) is one other amphiphilic peptide siderophore that is reported as a single siderophore, as opposed to a suite like the marinobactins, aquachelins, amphibactins and ornibactins:

Investigations of the amphiphilicity of the marinobactins, the amphibactins and acinetoferrin to date have centered on the self-assembling characteristics (e.g. the marinobactins (Martinez *et al.* 2000) and the partitioning of the marinobactins, amphibactins and acinetoferrin into 1,2-dimyristoyl-*sn*-3-glycero-phosphocholine (DMPC) vesicles (Xu *et al.* 2002; Fadeev *et al.* 2004; Luo *et al.* 2005). As expected, the siderophores with longer fatty acids partition more than those with shorter fatty acids and siderophores with saturated fatty acids partition more than those with the *cis* double bonds, but otherwise the same chain length. However, unexpectedly the apo-marinobactin E shows a 50-fold increase in partition coefficient over the Fe(III) marinobactin E complex (Xu *et al.* 2000). This increase partitioning of apo over Fe(III)-siderophore has also been observed with the acinetoferrin (Luo *et al.* 2005). The biological significance of these partition trends between apo and the ferric complexed is under investigation.

## Conclusion

Based on the results of the mesoscale iron expedition experiments, many now refer to the “Iron Hypothesis” as the “Iron Theory”. Iron added to HNLC regions of the world's oceans has clearly been shown to promote growth of autotrophic as well as heterotrophic microorganisms, yet these “iron expedition” results also raise many new questions. Of principal interest in the vein of this review is the question of the molecular mechanisms by which marine microorganisms compete for the added iron. We have found a preponderance of  $\alpha$ -hydroxycarboxylic-acid-containing siderophores produced by open ocean bacterial isolates as well as a prevalence of amphiphilic siderophores. The amphiphilicity is an intriguing feature that could function to keep siderophores in close contact with the bacteria or to increase surface reactivity, such as on iron-containing particles. The wide diversity of marine bacteria from which amphiphilic siderophores have been isolated suggests this property

evolved as a common iron acquisition strategy for marine bacteria, the details of which remain to be elucidated (Martinez *et al.* 2003). The photoreactivity of the ferric complexes of  $\alpha$ -hydroxycarboxylic acid-containing siderophores also suggests this property evolved as an advantageous strategy for iron acquisition. We look forward to the results of the ensuing experiments on the biological significance of these properties.

## Acknowledgements

Support from the National Institutes of Health GM38130 and The Center for Environmental BioInorganic Chemistry (CEBIC), an NSF Environmental Molecular Science Institute (NSF CHE-0221978) is gratefully acknowledged.

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