# Siderophores: New Understanding of Strong Metal Chelation

Dewain K. Garner Literature Seminar October 30, 2003

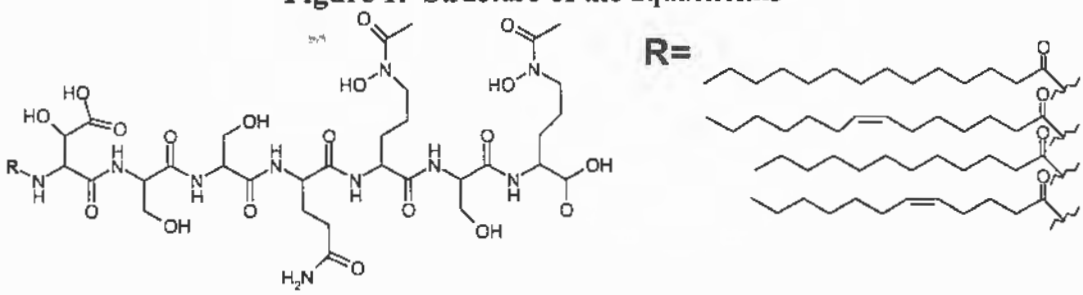
Iron, the most abundant transition metal in the earth's crust, has been widely exploited by living organisms to effect essential chemical transformations including photosynthesis, respiration, nitrogen fixation, electron transport and oxidase activity.[1,2] Due to the oxidizing nature of Earth's atmosphere nearly all surface iron exists as iron(III)hydroxide or oxide species with very low solubility at biological pH.[1,3] Bacteria counter this low solubility by creating organic ligands with high specificity toward and strong binding of ferric ion. These organic ligands, called siderophores, usually have a molecular weight less than 1,000 and employ a variety of oxygen rich functional groups such as catecholates, hydroxamates, carboxylates, α-hydroxy carboxylates, and even phenolates.[4]

Siderophores are of interest because of their exceptionally strong binding and high selectivity for ferric ion. In addition, they have applications in medicine as anti-biotic and anti-tumor drugs and for the decorporation of iron and aluminum in cases of toxic overload.[3,4] Siderophores also display interesting non-iron chemistry with other hard lewis-acids found among the lanthanides and actinides.[4,5] These properties have lead to the proposed use of siderophores in purification of nuclear fuel stocks[4] and remediation of heavy metal contamination,[5] as well as raising questions about their effect on the environmental mobility of heavy metals.[6]

Over 200 siderophores have been characterized[4] most of which come from terrestrial organisms. In 1995 Rue and Bruland determined that >99.9% of the iron in ocean surface water was complexed by organic ligands and was not inorganic iron hydroxides as previously believed[7]. Further investigation revealed that the iron binding constants of these unknown organic ligands were similar to known iron complexing siderophores and porphyrins.[8] Siderophore complexed iron was shown to be more bioavailable to prokaryotes while porphyrin iron was favored by eukaryotic bacteria.[9] These studies provide support for the presence of siderophores in oceanic waters.

The likelihood that many of these unknown ligands are siderophores directed recent efforts toward isolation and characterization of siderophores produced by oceanic bacteria.[10,11] Of particular interest are the photochemical reactivity[11] and amphiphilic nature[10] of the recently isolated siderophore classes marinobactin,[10] peterobactin,[11c] amphibactin,[10c] and aquachelin[10a,c,11a,b] **(figure 1)**.

**Figure 1.** Structure of the aquachelins



Iron binding has been shown to influences the association of these siderophore with the cell membrane.[10b,c] The ability to synthesize a suite of siderophores with differing membrane affinities may create a siderophore gradient centered on the bacteria[10c]. Iron binding has also been demonstrated to decreases the photostability of siderophores containing α-hydroxy-carboxylates[11] leading to increased rates of siderophore oxidative cleavage and ferric ion reduction. Siderophore mediated photo-cycling of iron may be very significant to overall iron availability in the ocean.

Similarities in lewis acidity of $Fe^{3+}$ and actinides, notably $Pu^{4+}$, have lead to investigations of siderophores as actinide specific ligands.[5] The crystallographic characterization of $Pu^{4+}$ bound by a siderophore[12], Desferrioxamine E (DFOE), suggests that siderophores may contribute to environmental mobilization of plutonium. Overlaid structures of DFOE iron and plutonium complexes reveal several similarities. In particular, the polar amide bonds implicated in bacterial siderophore recognition are oriented in the same direction (opposite visible carbonyl bonds) in both structures (figure 2). Experimentation with siderophore mediated $Pu^{4+}$ accumulation by bacteria revealed that the plutonium and iron siderophore complexes each inhibit cellular accumulation of the other.[6] This indicates that the plutonium complex is recognized by bacterial iron acquisition proteins. With the exact cellular location of accumulated plutonium still uncharacterized further studies are necessary for complete assessment of the effect of siderophores on plutonium mobility.

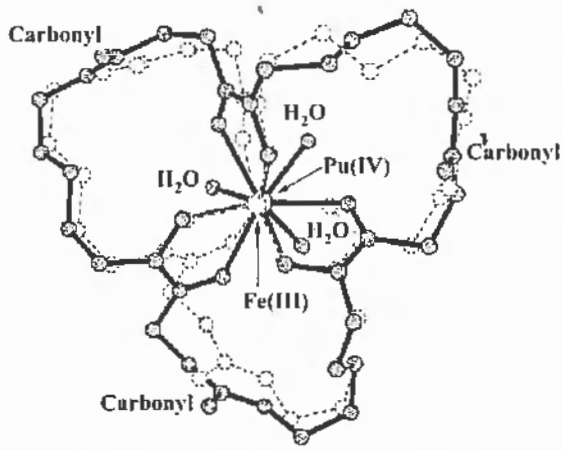



**Figure 2.** Overlay of Fe-DFOE (dashed) and Pu-DFOE (solid).

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