Konrad-Zuse-Zentrum
für Informationstechnik Berlin

Takustraße 7
D-14195 Berlin-Dahlem
Germany

MICHAEL MEYER*, RÜDIGER SCHNURRE†,
ROLF REISSBRODT‡, WOLFRAM TROWITZSCH-KIENAST†

Computer-aided design of novel siderophores: Pyridinochelin

* Konrad-Zuse-Zentrum
† Technische Fachhochschule Berlin
‡ Robert-Koch-Institut

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Computer-aided design of novel siderophores: Pyridinochelin

Michael Meyer*, Rüdiger Schnurre†,
Rolf Reissbrodt‡, Wolfram Trowitzsch-Kienast†

Abstract

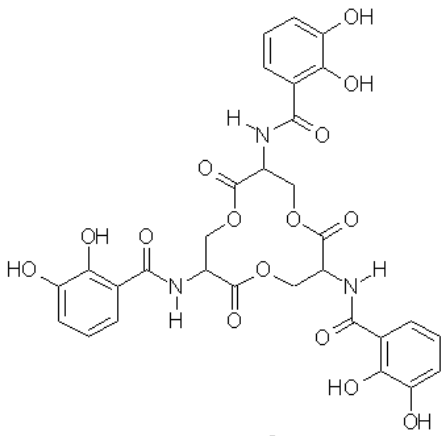
Pyridinochelin, a novel catecholate type siderophore, has been designed on the basis of the active analog enterobactin. Growth promotion tests indicate that this synthetic siderophore feeds various pathogenic bacteria effectively with iron even though it lacks one catecholate group compared to enterobactin. The superposition of the siderophore structures suggests that the structure of the skeleton connecting the catecholate groups might be an important factor for the iron transport.

Introduction

Bacteria produce siderophores, highly specific low molecular weight ligands, for iron supply.[1a−f] We have designed novel ligands because it is a promising strategy to use conjugates of siderophores and antibiotics as a Trojan horse in order to increase the concentration of the latter only at the site of action.[1f] Furthermore, siderophores can be used to promote the growths of bacteria to facilitate diagnostics. They can be used also in the medical treatment of patients suffering from an excess of iron ions and they are useful for the medication of viral infections. Cinatl et al. proved siderophores to interfere with the uridine uptake into the viral DNA.[2] Shanzer and others[3a−e] demonstrated antibiotic activities of siderophores, especially for lipophilic complexing agents, against the Plasmodium falciparum causing malaria. Most applications require that a synthetic ligand has a specific structure to be able to form complexes with iron *and* to be recognized by the receptor.

We have designed and synthesized an effective novel iron transporter of the catecholate [2,3-dihydroxy benzoate(DHB)]-type termed pyridinochelin[4] (Bis-2,3-dihydroxybenzoyl-2,6-dimethylamino-pyridin, **1**) using an active analog approach. The enterobactin receptor FepA seems to be an unique bacterial receptor of siderophores recognizing the DHB group in nature. The structure of FepA has been determined recently,[5] but as the electron density in the putative enterobactin binding region was not well defined, structure based design techniques could not be used. Furthermore, these methods focus on the design of molecules which bind specifically to a protein with a high affinity,[6a−e] but

*Konrad-Zuse-Zentrum für Informationstechnik Berlin, Takustr. 7, D-14195 Berlin
†Technische Fachhochschule Berlin, FB II, Luxemburger Str. 10, D-13353 Berlin
‡Robert-Koch-Institut, D-38855 Wernigerode



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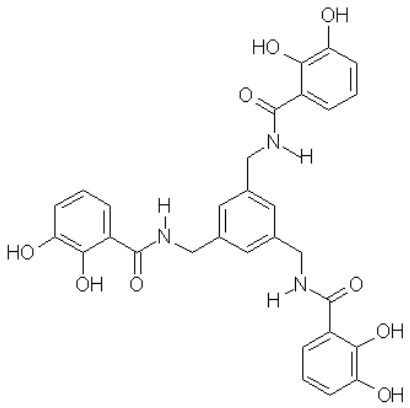

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ligands derived this way might be poor iron transporters. Enterobactin (ent, **2**) provides an ideal basis for active analog modeling because the formation constant of $[Fe(ent)]^{3-}$ is about 10^{52} while the affinity towards alkali and alkaline earth metals tends to be much lower. The structures of the $[M(ent)]^{3-}$ anions do not have rotatable bonds eliminating the problem to find out the bioactive conformation from a set of potential conformations for active analog modeling.

2 is a natural catecholate-type siderophore with a trilactone ring anchoring skeleton consisting of three L-serine residues, which induce a Δ-configuration of the three bidentate catechol groups at the metal nucleus (right handed propeller). In addition to Fe^{III}, enterobactin forms isostructural complexes with Ga^{III}, Cr^{III} and V^{IV}.[7a-e] These ions have been used often in theoretical and experimental studies as a model for iron, because the ionic radii are very similar to that of the ferric ion. The X-ray structure of the V^{IV}-enterobactin complexes[7d,e] and the computed structures of Ga^{III} with **2** and MECAM, **3**,[8] a synthetical siderophore with a non-chiral backbone, have been taken as active analogs.

Results and Discussion

Computations

The structures of the Ga^{III} complexes with the ligands **2** (Figure 1) and **3** have been optimized at HF/6-31G(d) level[9a-c] with Gaussian94[10] for the Δ-configuration. The V^{IV}[7d,e] and Ga^{III} complexes with **2** and **3** have been superimposed using a least squares fit of the metal atoms and all catechol oxygen atoms in order to generate a pseudo receptor with LUDI.[11a-c] The pseudo receptor, a cavity which is complementary to the shape of the superimposed active siderophores described above, restricts the size of the ligands created by the program similar to the real binding pocket of the FepA receptor. Then interaction sites, donor or acceptor sites located at the corresponding atom positions within the cavity, are derived from the enterobactin metal complexes. In the next step pharmacophores assumed to be important for metal binding and transport were selected and placed inside the cavity. The selection of the phar-