Bacterial Catecholate Siderophores

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Abstract: Soil bacteria as well as those infecting other organisms have developed systems to secure iron necessary for their metabolism, which is generally not available in its free ionic form. As one of the possible strategies they learnt to produce secondary metabolites able to bind Fe^{3+} as water soluble complexes, so-called siderophores. A prominent group of these siderophores are compounds, which contain at least one catecholate unit. A survey of compounds isolated from bacterial cultures will be presented.

Keywords: Iron metabolism, siderophores, catecholates.

1. INTRODUCTION

In the beginning, life on earth developed in a reductive atmosphere where iron was available abundantly in its divalent form. Salts of Fe^{2+} are sufficiently water soluble to provide an adequate supply of this element, which is essential for many physiological processes. But as a consequence of the photolytic cleavage of water initiated by cyanobacteria, oxygen was set free and soon only trivalent iron abounded. Due to the low dissociation constants of its various oxide hydrates in the soil the concentration of free Fe^{3+} at *pH*-values around 7 is at best 10^{-17} mol/liter[1] while about 10^{-6} mol/liter would be needed to maintain the necessary supply for living cells. Bacteria infecting animals or man are in a similar situation: here iron is bound strongly to peptidic substances such as transferrins. Bacteria learnt to circumvent this problem either by reduction of Fe^{3+} to Fe^{2+} (for a summary see [1]) or by the production of Fe^{3+} chelating substances, so-called siderophores. Siderophores are secondary metabolites with a molecular mass below 2000 Da.

Due to its high charge density, small ion radius, and low polarisability Fe^{3+} is a hard *Lewis* acid and can bind strongly hard *Lewis* bases such as oxide ions. Fe^{3+} forms octahedral d^5 high spin complexes providing six coordination sites, which can accommodate three bidentate ligands. The ligand types encountered most frequently among siderophores are catecholate or hydroxamate units. Because of their higher charge density, catecholates form stronger complexes at *circum*-neutral *pH* values, but they are more acid labile than hydroxamate complexes. Mixed systems are not uncommon and other ligand types such as α-hydroxy carboxylates are observed occasionally. Three bidentate ligands are often connected by aliphatic segments keeping them in place for complexation. This results in an entropic advantage over three non-connected ligands.

Siderophore-mediated iron transport occurs through compound-unspecific porins or compound-specific receptor proteins built up by β-barrel protein structures ([2-4]). Small Fe^{3+} complexes can cross the cell membrane through unspecific narrow porins. Larger complexes require a more or less specific transport protein, which recognizes the ferri-siderophore at the cell surface. By this interaction the tertiary protein structure is changed to allow an active transport through the cell membrane. Iron is released mostly by reduction to the less strongly bound Fe^{2+}, and the free siderophore is re-exported. This transport process into the cell is referred to as "shuttle-mechanism". Rarely the siderophore is degraded in the periplasmic space as in the case of the enterobactin, the siderophore of *Escherichia coli*.

As mentioned above one of the major ligand types of siderophores are catecholate systems. They can be found incorporated in various types of siderophores such as *e. g.* in the pyoverdins typical for fluorescent *Pseudomonas* spp., peptidic structures bound N-terminally to a dihydroxyquinoline moiety [6]. The typical catecholate siderophores to be covered in this review are derived however from 2,3-dihydroxybenzoic acid (DHB, or less frequently from 3,4-dihydroxybenzoic acid) attached to amino acids, amino alcohols, or aliphatic diamines. Structurally related siderophores with an α-hydroxybenzoyl (salicylate) instead of a DHB substituent are not the topic of this review, but they will be mentioned when of special interest.

When DHB or salicylic acid is bound to Thr condensation of the Thr hydroxyl group with the amide bond results in the formation of an oxazoline ring (cf. below Scheme **2**). Occasionally the open form is also observed, possibly a precursor or a hydrolysis product or both. Regarding the stereochemistry of the oxazoline ring see Section **3***g*. For analogous reaction products with other hydroxy acids or Cys see Section **4***c* and **4***d*.

As mentioned above siderophores with three catecholate units are the most efficient siderophores. They are frequently accompanied by their free subunits and there are examples where the complete siderophore rather than these subunits is produced only when the iron supply drops under a critical limit.

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[1]In a recent theoretical study it is claimed that the concentration of Fe^{3+} in an aqueous solution at *pH* 7 is $1.4 \bullet 10^{-9}$ mol/liter. Experimental evidence is not given [5].

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2. DIHYDROXYBENZOIC ACIDS

Free 2,3-dihydroxybenzoic acid (DHB) as the essential building block of the catecholate siderophores has been encountered in the culture solutions of a series of bacterial strains (amongst others *Aerobacter aerogenes* [7], *Azotobacter vinelandii* [9], *Escherichia coli* [10], *Micrococcus denitrificans* [11], *Nocardia asteroides* [12], *Salmonella typhimurium* [13]). It can act by itself as a siderophore for *E. coli* [14]. For a mutant of *Aerobacter aerogenes* [7], *Azomonas macrocytogenes* [15] and *Mycobacterium smegmatis* [7] the production of 3,4-dihydroxybenzoic acid has been reported.

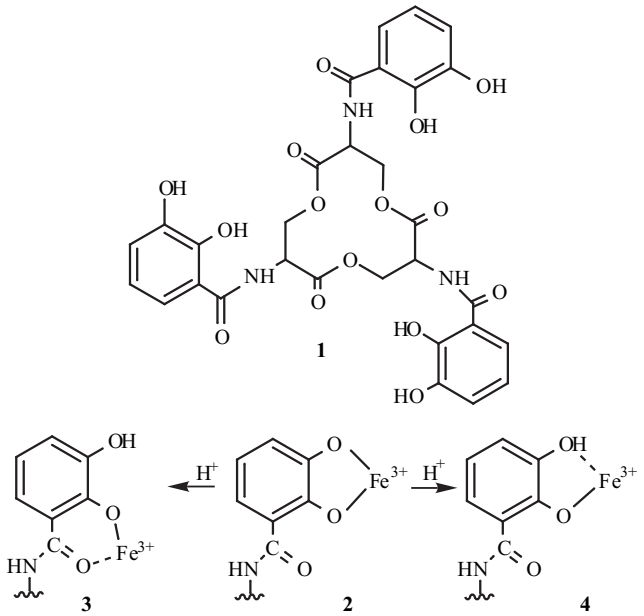
3. CATECHOLATE SIDEROPHORES DERIVED FROM AMINO ACIDS, AMINO ALCOHOLS, OR ALIPHATIC DIAMINES

a. Itoic Acid

From *Bacillus subtilis* under iron starvation 2,3-dihydroxybenzoylglycine was obtained and later on referred to as itoic acid [16]. Factors governing its formation wre studied [17] and an enzymatic method for its quantitation was developed [18].

b. Enterobactin and its Constituents

Enterobactin (also called enterochelin) is the typical siderophore of enterobacteria. It comprises in a cyclic structure three units of DHB-L-Ser (**1**). Enterobactin was isolated first in 1970, from culture filtrates of *Escherichia coli* [10] and from various *Salmonella* spp.[10, 19]. It forms a 1:1 complex with Fe^{3+}. The complexing constant originally estimated as *ca*. 10^{-52} was later on determined as 10^{-49} [20]. $[Fe(ent)_3]^{3-}$ (**2**) is present only in alkaline solutions; with decreasing pH the *m*-phenolate oxygens get protonated stepwise. Two possible structures have been discussed: the originally favored salicylato- (**3**) [21] and subsequently the protonated catecholato-structure (**4**) [22] (Scheme **1**). At pH values below 3 also the *o*-oxygen functions become protonated and the complex starts to dissociate. The color of the complex is pH-dependant: $[Fe(ent)_3]^{3-}$ is red, $[Fe(H\text{-}ent)_3]^{0}$ is violet [21]. In solution enterobactin shows preferentially a Δ-configuration [23], and there is evidence that the Fe^{3+} complex is Δ-*cis* configured [24].



Scheme 1. Enterobactin and its Fe^{+} complex modified by H^{+} addition.

In the culture solutions of *Escherichia coli* also the degradation products of enterobactin were found [10], *viz.* DHB-Ser (**5**) as well as the condensation products of two (**6**) and three (**7**) of these units obtained by hydrolysis, and the elimination product (**8**) (Fig. **1**).

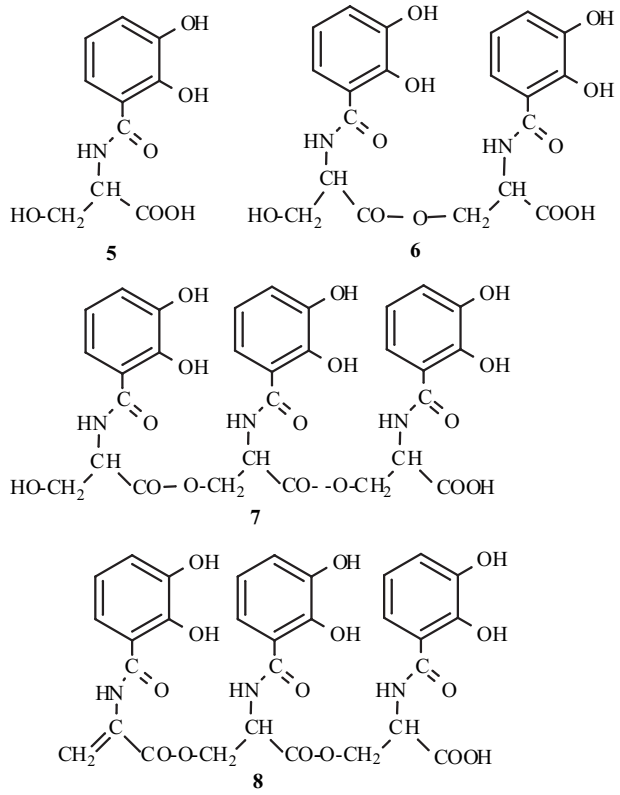


Fig. (1). Degradation products of enterobactin **(1)**.

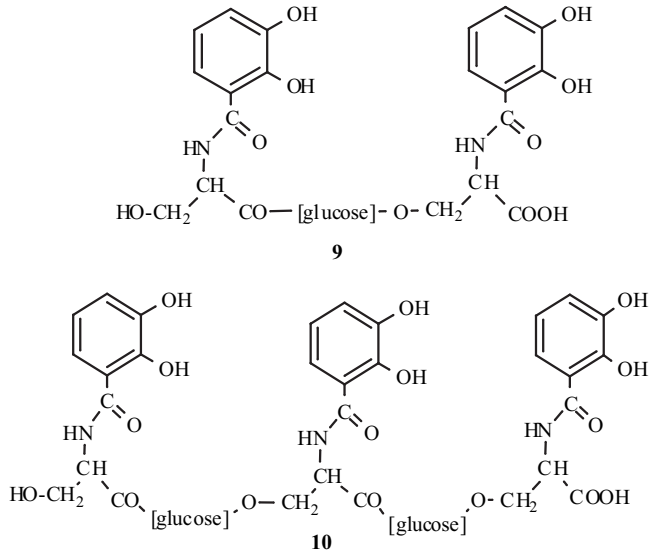


Fig. (2). Salmochelins.

Enterobactin binds to serum albumin. This limits the iron supply of the bacterium when infecting higher organisms and thus its growth there is restricted [25]. A bacterial strategy against this defense mechanism could be the formation of salmochelins, the glucose derivatives of (**6**) and (**7**), *viz.* (**9**) and (**10**) (Fig. **2**), produced by *Salmonella enterica* [26].

c. Myxochelin A and Amonabactins

Myxochelin A (**11**) consists of lysinol (stereochemistry not determined) substituted at both amino groups with DHB [27] (Fig. **3**). Myxochelin could be a reduction product of azotochelin **17** below.

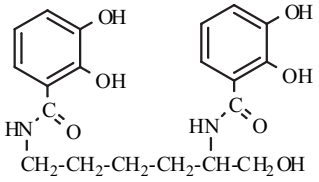


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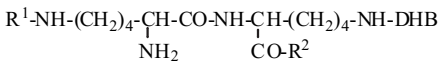
Fig. (3). Myxochelin A.

The amonabactins from *Aeromonas hydrophila* are derived from L-Lys-L-Lys substituted at the free carboxyl group with D-Phe (**13**, **15**) or D-Trp (**12**, **14**) and at the ε-amino groups of the N-terminal Lys with DHB (**14**, **15**) or DHB-Gly (**12**, **13**) (Fig. **4**) [28].



12: R^1 = DHB-Gly, R^2 = Trp (Amo T 789)
13: R^1 = DHB-Gly, R^2 = Phe (Amo P 750)
14: R^1 = DHB, R^2 = Trp (Amo T 732)
15: R^1 = DHB, R^2 = Phe (Amo P 693)

Fig. (4). Amonabactins.

d. Protochelin and its Constituents (see Scheme 2) (Fig. 5)

Azotobacter vinelandii forms DHB, the monocatecholate aminochelin (**18**) [9], the dicatecholate azotochelin (**17**) [29, 30] and the combination product of the two, the tricatecholate protochelin (**16**) [32] (which had been isolated before from a methanol bacterium [31]). Which type of siderophore is actually produced depends on the amount of Fe^{3+} available: At concentrations >7 μmol 2,3-dihydroxybenzoic and in a range between 7 and 3 μmol the di- and tri-catecholate siderophores are used. When the iron concentration drops still lower, the high-affinity peptidic azotobactins are resorted to [32]. Cepaciachelin (**19**) obtained from *Burkholderia cepacia* is lacking the 2,3-dihydroxybenzoyl residue from the aminochelin part of protochelin [33]. The amino acid incorporated in these catecholates is L-Lys.

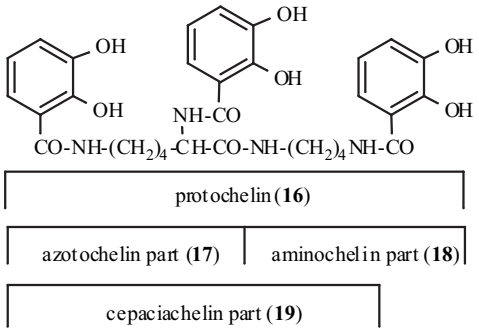


Fig. (5). Protochelin and its constituents.

e. Chryseomonin and Chrysobactin (Fig. 6)

From *Serratia marcescens* [34] and from *Erwinia chrysanthemi* [35] chrysobactin (**20**) was obtained where DHB is bound to D-Lys-L-Ser. From *Chryseomonas luteola* besides chrysobactin a siderophore (chryseomonin **21**) could be isolated where a pyridinium ring is attached to the catecholate ring of chrysobactin [36]. Both compounds form 2:1 complexes with Fe^{3+}.

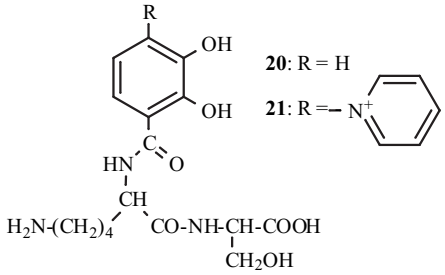


Fig. (6). Chrysobactin (**20**) and chryseomonin (**21**).

f. Photobactin (Fig. 7)

The nematode *Heterorhabditis bacteriophora* transmits the enterobacterium *Photorhabdus luminiscens* to insect larvae where the nematode needs the pathogenic bacterium for growth and reproduction. The bacterium produces the siderophore photobactin (**22**) structurally somewhat related to vibriobactin below; (**22**) seems however not to be essential for pathogenicity [37].

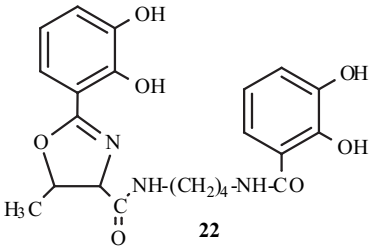


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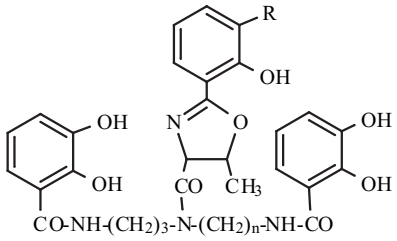
Fig. (7). Photobactin.

g. Agrobactin and Related Compounds (Figs. 8 and 9)

Agrobactin (**23**) is a spermidine derivative substituted with L-Thr at the central nitrogen atom and containing three DHB substituents. It was isolated from *Agrobacterium tumefaciens* [38]. Its structure derived from hydrolysis and NMR studies was confirmed by X-ray analysis [39] and synthesis [40]. The hydrolysis products DHB, agrobactin without the central DHB-Thr unit and the open form (agrobactin A) (cf. Scheme **2**). were obtained by treatment with acid [38].The complexing constants of agrobactin and of its relatives approach that of enterobactin.

The closely related parabactin (**24**) from *Paracoccus* (*Micrococcus* [9]) *denitrificans* has a salicylate instead of a DHB unit bound to L-Thr. The open form (parabactin A) as well as DBH and a precursor with a free central amino group were found [11, 43]. Two syntheses were reported [40, 41, 44]. Parabactin A forms a 1:1 Fe^{3+} complex and also complexes with other trivalent cations [11]. The mechanism of the iron transport was investigated [42].

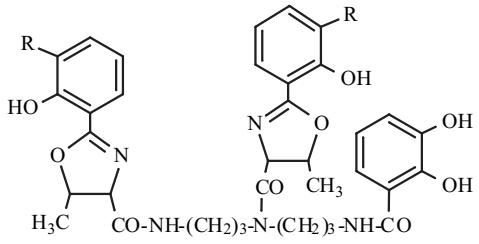
Fluvibactin (**25**) from *Vibrio fluvialis* differs from agrobactin by replacement of spermidine by norspermidine [45].



23: n = 4, R = OH
24: n = 4, R = H
25: n = 3, R = OH

Fig. (8). Agrobactin (**23**), parabactin (**24**), and fluvibactin (**25**).

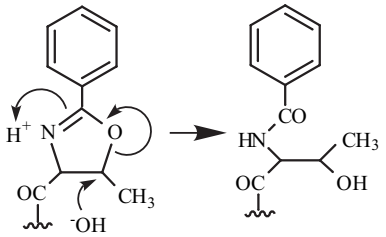
Vibriobactin (**26**) from *Vibrio cholerae* contains two cyclized DHB-L-Thr substituents [46]. In vulnibactin (**27**) from *Vibrio vulnificus* two of the DHB units of vibriobactin are replaced by salicylic acid residues [47]. The constituent units formed by the cleavage of the central amide bond were also found.



26: R = OH
27: R = H

Fig. (9). Vibriobactin (**26**) and vulnibactin (**27**).

In all four sidrophores the H-atoms of the oxazoline ring are in *trans* position corresponding to an incorporated L-*allo*-Thr. Yet in every case after hydrolysis only L-Thr was found. Inversion at the β-carbon of Thr must occur during the alkaline hydrolysis. A mechanism has not been proposed. It is reasonable to assume that either L-*allo*-Thr is the biosynthetic precursor of the siderphores, or in case L-Thr is the actual precursor an inversion must takes place during the enzymatic step governing the ring closure. In any case hydrolysis has to occur by a S_N2 mechanism resulting in the inversion at the β-carbon (Scheme **2**).



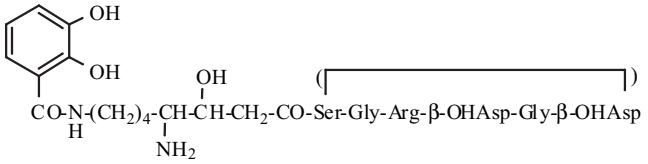
Scheme 2. Opening of the oxazoline ring.

There is evidence that one of the binding sites for Fe^{3+} in agrobactin is the *o*-phenolate ion and the nitrogen of the oxazoline ring [39], but a definitive proof is still missing [48]. This type of complexation would however explain why the replacement of DHB by salicylic acid as in parabactin etc. does not impair the complexing ability of the siderophores.

4. COMPLEX CATECHOLATE SIDEROPHORES

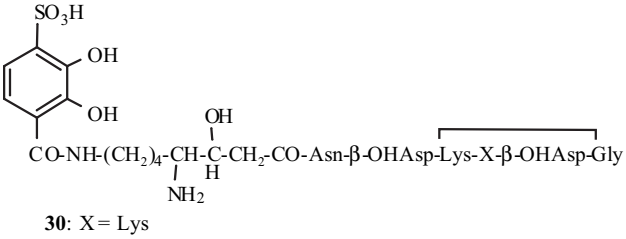
a. Alterobactin (Fig. 10) and Pseudoalterobactin (Fig. 11)

From the marine bacterium *Alteromonas luteoviolacea* a compound was obtained where DHB is bound amidically to the ω-amino group of the peptide 4*S*,8-diamino-3*R*-hydroxyoctanoyl-D-Ser-Gly-L-Arg-L-*threo*-β-hydroxy-Asp-Gly-L-*threo*-β-hydroxy-Asp (alterobactin B (**28**)). Alterobactin B is the hydrolysis product of a cyclodepsipeptide where the C-terminal carboxyl group forms an ester bond with the hydroxyl group of Ser (alterobactin A, (**29**)). The structure was established *i.a.* by NMR studies [49] and confirmed by total synthesis [50]. An unexpectedly high complexing constant (10^{49} - 10^{53}) was reported for alterobactin A, equal to or even higher than that of enterobactin, though only one of the binding sites is a catecholate and the other two α-hydroxy carboxylic acid units which bind Fe^{3+} less strongly. There is however a dispute about the complexing constant (ref. 12 in [51]).



28: without ester bond between OHAsp and Ser
29: with ester bond between OHAsp and Ser

Fig. (10). Alterobactin A (**29**) and B (**28**).



30: X = Lys
31: X = Arg

Fig. (11). Pseudoalterobactin A (**30**) and B (**31**).

From *Pseudoalteromonas* sp. two related siderophores were obtained [51]. DHB carries as an additional substituent an $-SO_3H$ group.[2]The C-terminus of the peptide part is a cyclic substructure with an amide bond between the carboxyl

[2]This is only the third example of a bacterial metabolite with an aromatic sulfonic acid. The other two are the *Pseudomonas* metabolites aeruginosin B and a precursor of the pyoverdin siderophore [6].

group of the C-terminal Gly and the ε-amino group of Lys. Pseudoalterobactin B (**31**) differs from A (**30**) by the replacement of one Lys by Arg. Also here a high complexing constant comparable to that of enterobactin (**1**) (10^{49}) is reported.

b. Petrobactin (Fig. 12)

In the siderophore of the marine bacterium *Marinobacter hydrocarbonoclasticus* two catecholate units bound to spermidine are linked by the 1,3-carboxyl groups of a citrate unit. Originally it had been assumed [52] that 2,3-dihydroxybenzoic acid (DHB) is the constituent, but synthetic studies [53] revealed that in petrobactin (**32**) 3,4-dihydroxybenzoic acid is incorporated.

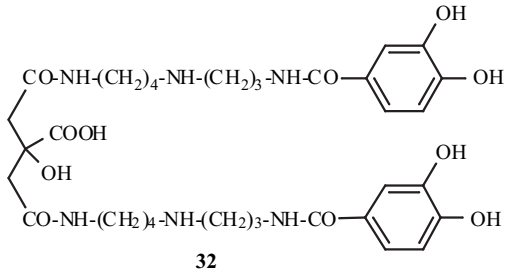


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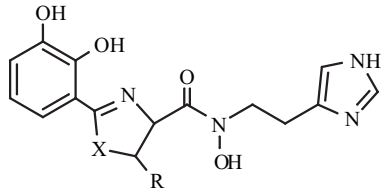
Fig. (12). Petrobactin.

c. Acinetobactin and Anguibactin (Fig. 13)

In acinetobactin (**33**) from *Acinetobacter baumannii* DHB is bound cyclically to Thr (stereochemistry not determined) and N-hydroxy-histamine [54]. It is structurally closely related to anguibactin (**34**) from *Vibrio anguillarum* [55] where Thr is replaced by Cys (stereochemistry also not determined). The two compounds belong to a group of siderophores with a α-hydroxy benzoyl instead of a DHB unit, the best known of which is pyochelin (**35**) from *Pseudomonas aeruginosa* and from several other bacteria (for details see [6]).



33: X = O, R = CH_3
34: X = S, R = H

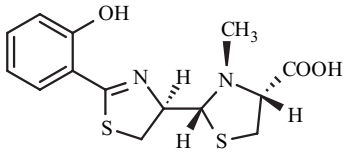


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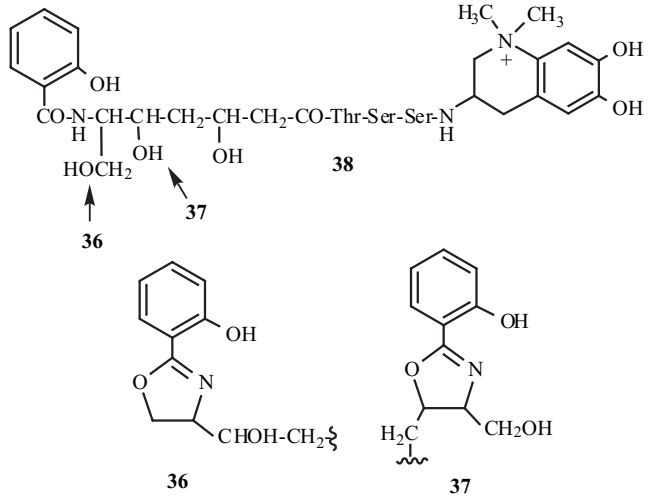
Fig. (13). Acinetobactin (**33**), anguibactin (**34**), and pyochelin (**35**).

d. Anachelin

Two siderophores (**36**, **37**) were obtained from the cyanobacterium *Anabena Cylindrica,* which are actually isomeric cyclization products (indicated by arrows in Scheme **3**) of the open form (**38**) where salicylic acid is bound to the amino group of 6-amino-3,5,7-trihydroxyheptanoic acid (the orientation of the three chiral centers is not known), which in turn is bound to L-Thr-D-Ser-L-Ser. The C-terminus is substituted by a 1,1-dimethyl-3-amino-1,2,3,4-terahydro-7,8-dihydroxy-quinolinium residue (stereochemistry at C-3 not known) [56, 57]. NMR experiments indicate a compact folded structure of the molecule in solution [58].



Scheme 3. Anachelin.

5. INCOMPLETELY CHARACTERIZED SIDEROPHORES

In several instances substances with siderophore activity were found containing DHB and one or two amino acids, viz. Gly (itoic acid) from *Bacillus subtilis* (Section **3***a*), Ser from *Klebsiella oxytoca* [59] (cf. also enterobactin, Section **3***b*), Thr from *Klebsiella oxytoca* [60] and *Rhizobium* spp. [60, 61], Arg from *Pseudomonas stutzeri* [62], Orn plus Ser from *Azospirillum brasiliense* (spirilobactin, ratio DHB, Orn, Ser 1.1:1) [63], Leu plus Lys [64] as well as Lys plus Thr [65] from *Azospirillum lipoferum*, Gly plus Thr from *Rhizobium* sp. [66], and unknown amino acids from *Rhizobium* sp. [8]. Only itoic acid was properly characterized *i.a.* by synthesis, in all the other cases the siderophore was isolated, hydrolized, and its constituents were determined by paper chromatography. The chirality of the amino acids has never been determined and relative ratio of the constituents only once. Condensation products as in the case of enterobactin have not been reported.

6. CONCLUDING REMARKS

A series of bacteria uses the ability of the catecholate system for complexing Fe^{3+} in order to sequester iron present only in low concentrations. Systems with three catecholate units accommodating the six corners of the octahedral structure of Fe^{3+} can be found, but mixed systems using in addition to one catecholate *e.g.* two α-hydroxy acids are known as well. In several cases the isolation of constituent parts of the complete siderophore has been reported. They may be artifacts formed by hydrolysis in the cultural medium or during work-up, but they may as

well be genuine metabolites excreted to cope with a less severe iron deficiency. For *Azotobacter vinelandii* this has been shown conclusively. In those cases where only "monomers" have been reported (esp. Section 4), it could be worthwhile to test the strains reported there under stringently iron deficient conditions.

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