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Abstract. The crystal structure of ferrichrome A ($C_{41}H_{58}N_9O_{20}Fe \cdot 4H_2O$) has been determined by x-ray diffraction. The amino acid sequence in the hexapeptide ring is confirmed to be -Orn-Orn-Orn-Ser-Ser-Gly-, and the configuration of this ring is trans at each peptide linkage. The absolute configuration of the three hydroxamate rings at the iron atom is that of a left-handed propeller. Disorder is found concerning the positions of some of the side chains and one of the four water molecules.

Ferrichrome A, a product of the metabolism of the smut fungus Ustilago sphaerogena, is a ferric hydroxamate and a cyclic hexapeptide consisting of residues of the amino acids glycine, serine, and ornithine (1). It is related in structure to several substances which are growth factors for certain micro-organisms (2-4). Its structure is also of interest for possible clues to the structures of proteins. By x-ray diffraction methods we have determined the crystal structure and have found the molecular structure (Fig. 1) to be in agreement with deductions from chemical evidence (1,5).

Crystals of composition $C_{41}H_{58}N_9O_{20}Fe \cdot 4H_2O$ are monoclinic, space group $P2_1$, with $a = 11.02 \pm 0.02$, $b = 13.26 \pm 0.03$, $c = 18.22 \pm 0.01$ Å, $\beta = 99.48^\circ$, $Z = 2$. The density calculated from the x-ray data, $D_x = 1.42$, is to be compared with $D_m = 1.45$ g cm⁻³ (2). Diffraction measurements were made by scintillation counting with a crystal about

0.1 X 0.1 X 0.2 mm in size. Because MoK α radiation gave low counting rates, we recorded the intensities of 3115 independent reflections with FeK α radiation; of these, only 56 were recorded as zero. To determine the absolute configuration of the structure we measured the intensities of 71 pairs (hkl and $h\bar{k}l$) with CuK α radiation, which iron atoms scatter with a large phase shift (anomalous dispersion effect). Significant intensity differences were observed for 40 pairs, and in each case the sign of the difference is explained by our final structure. This test shows that we have the correct absolute configuration and at the same time is strong evidence for the correctness of the structure determination.

The position of the iron atom was guessed correctly from the Patterson function and later confirmed with the anomalous dispersion data. A superposition of the Patterson function with the Fe-Fe vector as the shift vector suggested positions for the six oxygen neighbors of iron and for several other atoms. The rest of the structure was determined by repeated electron density calculations alternated with least-squares refinement.

The discrepancy index $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ was reduced to 0.14 with 75 atoms in the structure. The electron density maps were excellent for most of the structure, but suggested disorder for a few atoms. With some atoms distributed at random between alternate sets of positions R was reduced to 0.11. One water molecule was distributed among three

sites so close together that only one at a time could be occupied. The oxygen atom of one serine side chain, the methyl carbon and alpha carbon of one methyl glutaconic acid residue, and the oxygen atoms of the terminal carboxyl group of another glutaconic acid were each assigned two sites corresponding to two ways of twisting each of these groups. An electron-density-difference function calculated at this point showed peaks

which can be explained as the result of anisotropic thermal motion or as the result of slight shifts associated with the disorder of neighboring atoms. Other peaks were found in correct positions for about 40 hydrogen atoms on those parts of the structure for which the effects of disorder and anisotropic motion are less severe. Further calculations taking account of these hydrogen atoms and some of the anisotropic motion effects have reduced R to 0.09.

The molecular shape is shown in Fig. 2. The sequence of amino acid residues in the cyclic peptide is -Orn-Orn-Orn-Ser-Ser-Gly-. The configuration of the ring is trans at each peptide linkage. The absolute configuration of each of the five asymmetric alpha carbon atoms is the same as that commonly found in other peptides of biological origin and which is described conventionally as left-handed. The absolute configuration of the three hydroxamate rings at the iron atom (Fig. 3) is that of a left-handed propeller. In such a ring structure there are two distinct ways in which the polarities of the C-N bonds can be arranged: either all the same way or one different from the other two. We find the more symmetrical structure in which the polarities are the same in the three rings, as shown in Fig. 3.

We recognize two hydrogen bonds within the molecule. One of length 2.99 Å bridges the peptide ring and joins the alpha nitrogen of one ornithine residue to the carbonyl oxygen of one serine residue. This bond distance corresponds to a weak bond. In the flat representation of this ring (Fig. 1) there seems to be the possibility of a second hydrogen bond across the ring, but the folding of the ring in the actual structure does not permit this. A second hydrogen bond of length 2.79 Å joins the alpha nitrogen of the second ornithine residue to the oxygen atom of the delta nitrogen of this same residue.

Several other hydrogen bonds connect various oxygen atoms with water molecules which in turn are connected to other ferrichrome molecules. There is disorder in some of these bonds, because they involve some of the atoms with alternate sites.

Bond distances and angles which do not involve hydrogen atoms are in good agreement with the expected values, with standard deviations of the distances of $\sim 0.02 \text{ \AA}$. The six oxygen neighbors of the iron atom are at distances ranging from 1.96 to 2.07 \AA . The bond angles at the iron atom which would be 90° for a regular octahedron range from 78° to 101° .

We thank Prof. J. B. Neilands for providing the crystals for this investigation and for helpful discussions concerning the molecular structure. (6).

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References and Notes

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6. This work was done under the auspices of the U. S. Atomic Energy

Figure captions

Fig. 1. Ferrichrome A.

Fig. 2. Molecular shape of ferrichrome A; only one of the two configurations is shown for the disordered atoms, which are the oxygen at the upper left corner, the carboxyl at the far right, and the center of the methyl glutaconic acid residue at the lower left.

Fig. 3. Absolute configuration around the iron atom.

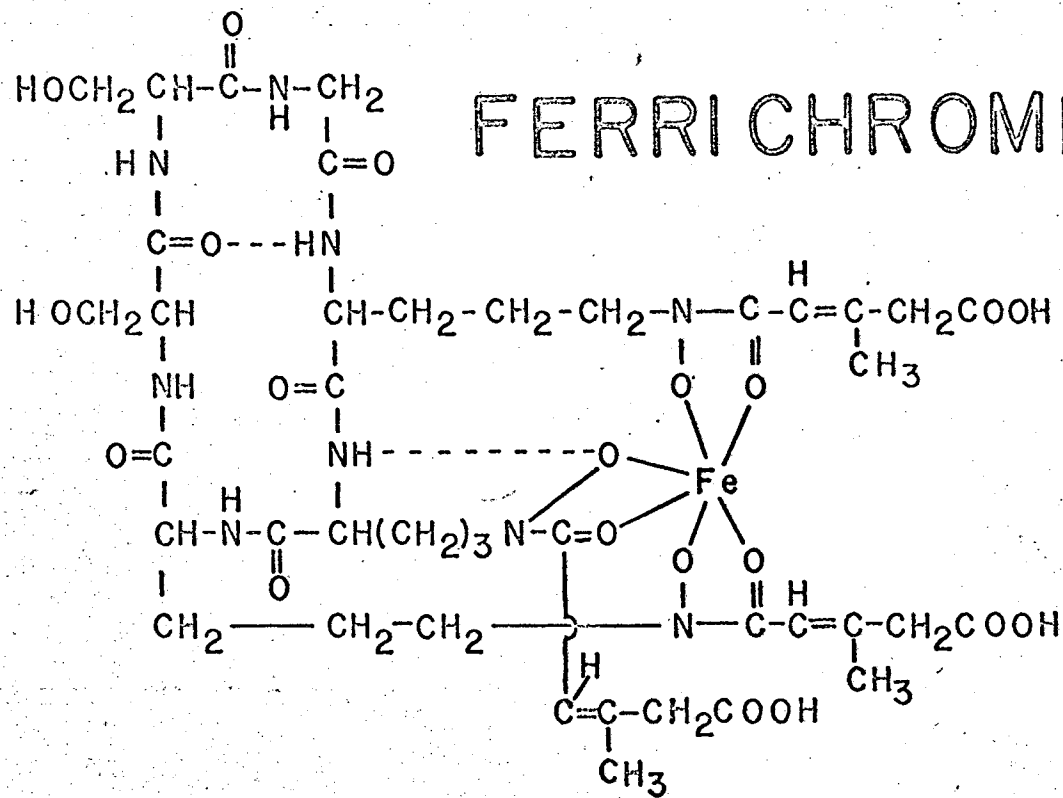
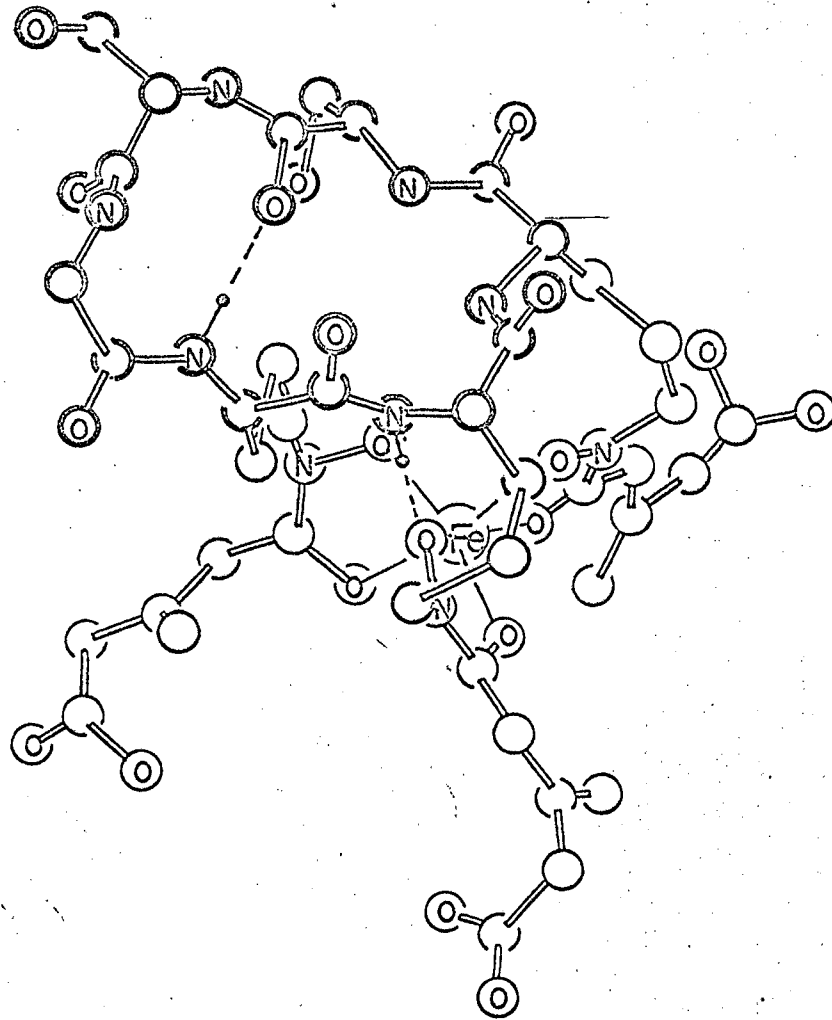


Fig. 1.

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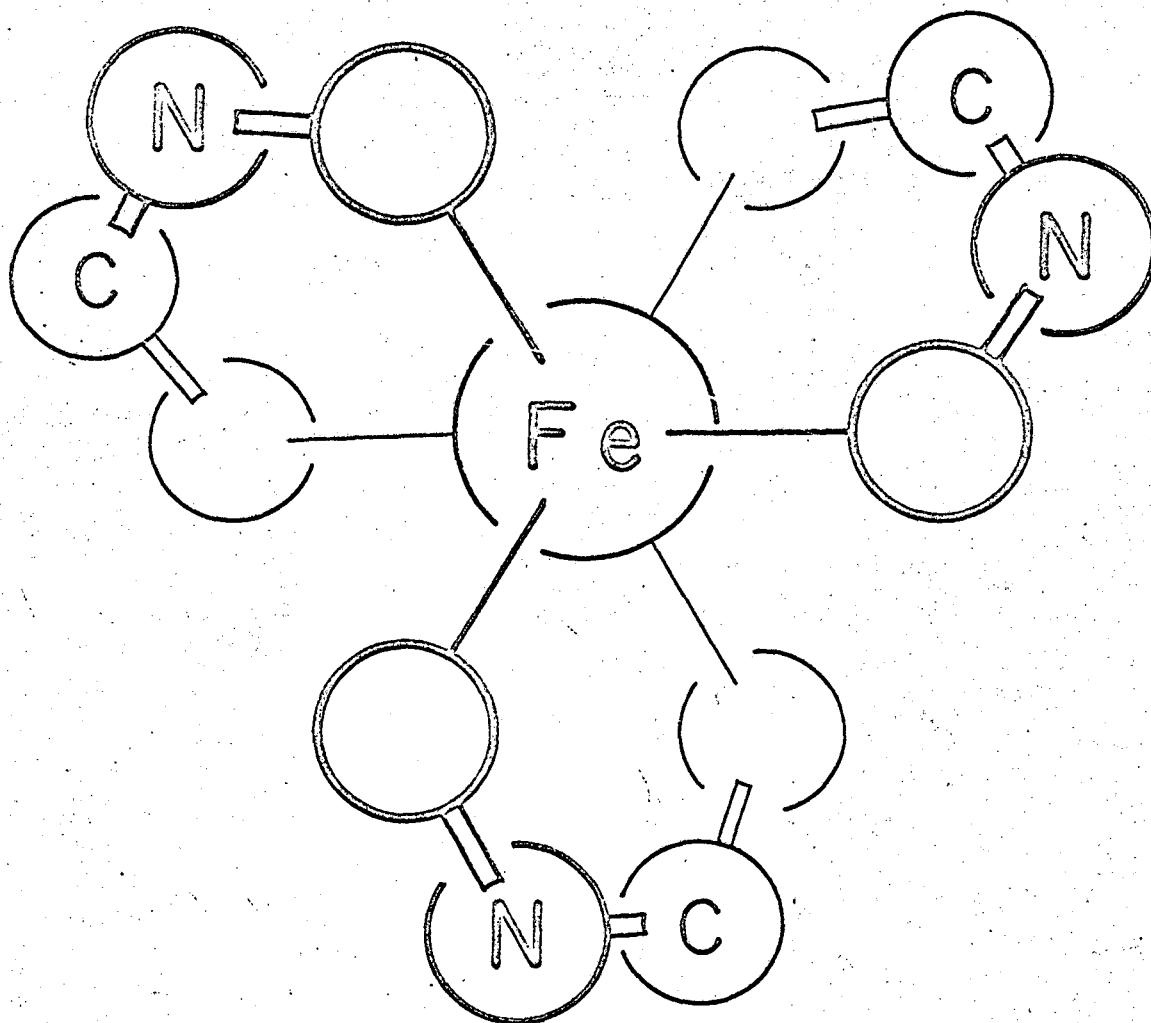
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FERRICHROME - A

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Fig. 2.



Left-handed Co-ordination
Propeller About Fe In Ferrichrome-A

MUB-2916

Fig. 3.

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