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The Structure of Ferrioxamine D₁–Ethanol–Water (1/2/1)

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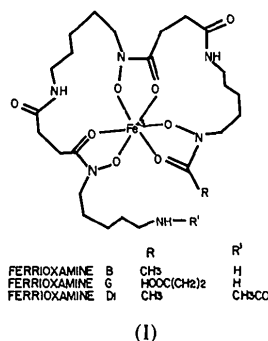
Abstract. C₂₇H₄₇FeN₆O₉, $M_r = 737.7$, $P\bar{1}$, $a = 15.035$ (20), $b = 16.240$ (17), $c = 7.852$ (8) Å, $\alpha = 89.30$ (9), $\beta = 100.01$ (11), $\gamma = 101.82$ (10)°, $V = 1847$ (1) Å³, $Z = 2$, $D_x = 1.325$ Mg m⁻³, $Mo K\alpha$, $\lambda = 0.71069$ Å, $\mu = 0.43$ mm⁻¹, $F(000) = 784$, $T = 138$ K, $R = 0.064$ for 3532 observed reflections [$I > 2\sigma(I)$]. The crystal structure contains a racemic mixture of *A-cis* and Δ -*cis* coordination isomers. The parameters of the iron coordination geometry, Fe–O(N) = 1.961 (4), Fe–O(C) = 2.049 (4) Å, ligand bite = 1.27, twist angle = 42.9°, agree well with those observed in crystal structures of other trihydroxamate siderophores. Conformational features of ferrioxamine D₁ are compared with those of ferrioxamine E, a cyclic analog of D₁.

Introduction. Siderophores are low-molecular-weight iron-chelating compounds of microbial origin, which act as cellular transport agents for iron in aerobic fungi and bacteria (Emery, 1971; Neilands, 1973, 1981; Raymond, Müller & Matzanke, 1984; Hider, 1984).

Although there is considerable evidence that the siderophore uptake is a receptor-mediated process requiring a structure–function relationship between the siderophores and the membrane ‘carriers’, our understanding of the mechanism of siderophore-mediated iron transport in microorganisms is still very fragmentary. This is partly due to insufficient knowledge concerning the conformation and configuration of the siderophore molecules and largely because of the lack of information about the nature of the transport system in the cell membranes.

The ferrioxamine family, an important class of siderophores, is produced by several species of *Streptomyces* and *Nocardia*. They are characterized as A, B, C, D₁, D₂, E, F and G (Bickel, Bosshardt, Baumann, Reusser, Vischer, Voser, Wettstein & Zähler, 1960). All the ferrioxamines are trihydroxamates and the deferriferrioxamines are either cyclic or linear, consisting of units of α -amino- ω -hydroxyamino alkane and succinate or acetate. Ferrioxamine D₁ is a member of the linear ferrioxamines and is the *N*-acetyl

derivative of ferrioxamine B (I). It is also a linear analog of the cyclic ferrioxamine E.



The structural study of the ferrioxamines has been a subject of considerable chemical and pharmaceutical interest. Deferriferrioxamine B (DFB), which is currently used in the clinical treatment of iron toxicity, has been studied extensively. DFB, marketed as Desferral (deferriferrioxamine B methanesulfonate) by Ciba-Geigy Corporation, is used in the treatment of acute iron poisoning and in chronic iron overload resulting as a side effect of transfusion therapy in patients suffering from Cooley's anemia. The chemical properties of the ferrioxamines and their deferriferrioxamines have been described by Prelog (1963) and others (Bickel *et al.*, 1960). The chelation of iron(III) with deferriferrioxamine B has also been examined by thermodynamic and kinetic methods (Monzyk & Crumbliss, 1982; Kazmi & McArdle, 1981). Although ferrioxamines have never been isolated from fungi, in growth-promotion tests they can act as fungal growth factors (Bickel *et al.*, 1960; Prelog, 1963). Ferrioxamines are also antagonists to the structurally related ferrimycins (Bickel *et al.*, 1960). It has also been shown that the deferriferrioxamines have a bacteriostatic effect on most microbial strains (van Asbeck, Marcelis, Marx, Struyvenberg, van Kats & Verhoef, 1983). Despite the wide interest, the structural results of ferrioxamines are limited. The only reported crystal structures are those of ferrioxamine E (van der Helm & Poling, 1976) and deferriferrioxamine E (Hossain, van der Helm & Poling, 1983). Because of its kinetic lability, the structural features of ferrioxamine B could not be characterized from solution studies, but it has been shown that the more stable Cr³⁺ complex of deferriferrioxamine B (and also of D₁) exists as a mixture of two geometrical isomers, with *cis* and *trans* configuration (Leong & Raymond, 1975). The presence of two distinct coordination isomers (one *cis* and one *trans*) in Ga³⁺ and Al³⁺ complexes of deferriferrioxamine B has also been reported (Borgias & Raymond, 1984). As a part of our continuing investigation of the structures of siderophores in the solid state, we present here the crystal and molecular structure of ferrioxamine D₁.

Experimental. Reddish-brown plates from ether/methanol, unstable at room temperature and stable at low temperature, 0.70 × 0.18 × 0.08 mm; triclinic, $P\bar{1}$ from intensity statistics and structure refinement; all X-ray measurements on Enraf-Nonius CAD-4 automatic diffractometer fitted with a liquid-N₂ low-temperature set-up; cell parameters from 46 reflections, 2θ range 11–20°, Mo $K\alpha$. 5131 unique reflections, $2\theta_{\max} = 46^\circ$, $-17 \leq h \leq 17$, $0 \leq k \leq 17$, $-8 \leq l \leq 8$, collected at 138 (2) K, Mo $K\alpha_1$ (graphite monochromator), θ - 2θ scan technique, variable scan width $(0.80 + 0.20 \tan \theta)^\circ$ and variable horizontal aperture $(4.50 + 0.86 \tan \theta)$ mm; three standard reflections measured every 2 h of X-ray exposure, max. fluctuation less than 5%; 3532 observed data [$I \geq 2\sigma(I)$]; Lorentz and polarization correction, no absorption correction; structure determined by heavy-atom technique and successive difference Fourier syntheses; refinement by full-matrix least squares on F ; 43 H atoms (out of 57) from difference Fourier map, refined isotropically; atoms C(16) and C(18) disordered, both refined isotropically at two sites with 0.5 occupancy; non-H atoms including solvent molecules refined anisotropically; $R = 0.064$, $wR = 0.063$ for 3532 observed reflections, $w = 1/\sigma^2(F)$, $S = 1.6$; $(\Delta/\sigma)_{\max} = 0.5$, $(\Delta/\sigma)_{\text{av}} = 0.15$; max. electron density in final difference map $0.5 \text{ e } \text{Å}^{-3}$ around methanol solvent; atomic scattering factor and anomalous-dispersion corrections (Fe) from *International Tables for X-ray Crystallography* (1974); all calculations with *SHELX76* (Sheldrick, 1976).

Discussion. The final atomic parameters are listed in Table 1.* Fig. 1(a) shows a schematic drawing of the ferrioxamine D₁ molecule along with the numbering scheme followed in this report. A perspective view of the molecule is shown in Fig. 1(b). The chelate molecule consists of two macrocycles (each of which is formed by condensation of a 5-hydroxyamino-1-pentylamine and a succinyl group) and an open chain end. The conformation of the chain part is such that the dangling chain is bent backward towards the surface of the molecule which contains all the oxime O atoms. The chain is held in its position by an intramolecular N–H...O hydrogen bond, $\text{N}(32)\cdots\text{O}(13) = 2.800(7) \text{ Å}$.

The crystal structure of ferrioxamine D₁ contains a racemic mixture of *A-cis* and *A-cis* coordination isomers as observed in the crystal structure of its cyclic analog, ferrioxamine E (van der Helm & Poling, 1976). The geometry and dimensions of the coordination

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and a list of bond angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 43016 (22 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

octahedron are given in Fig. 2. Other bond distances are listed in Table 2. The six hydroxamate donor O atoms form the familiar distorted octahedral geometry around the Fe atom. The deviation from perfect octahedral symmetry is reflected in the O—Fe—O angles: The average of three chelate angles is $78.7(1)^\circ$ and the average of the three axial O—Fe—O angles is $165.8(1)^\circ$. The metal to oxime O atom distances are systematically shorter than the metal to carbonyl O atom distances. The average Fe—O(N) distance of $1.962(4) \text{ \AA}$ and Fe—O(C) distance of $2.049(4) \text{ \AA}$ compare well with the equivalent distances in other trihydroxamates like ferrichrome [$1.983, 2.034 \text{ \AA}$] (van der Helm, Baker, Eng-Wilmot, Hossain & Loghry, 1980), ferrioxamine E [$1.953, 2.055 \text{ \AA}$] (van der Helm & Poling, 1976) and ferricrocin [$1.981, 2.041 \text{ \AA}$] (Barnes, Eng-Wilmot & van der Helm, 1984). The

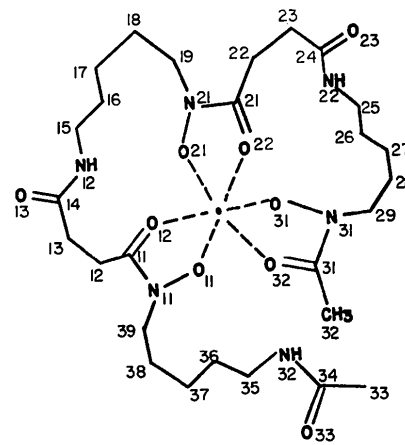
Table 1. Atomic parameters and equivalent isotropic thermal parameters (\AA^2)

| | x | y | z | U_{eq}^* |
|---------|-------------|-------------|------------|------------|
| Fe(1) | 0.85803 (6) | 0.80726 (6) | 0.6066 (1) | 0.0149 (3) |
| O(11) | 0.9806 (2) | 0.8664 (2) | 0.7163 (4) | 0.018 (1) |
| O(12) | 0.9121 (2) | 0.8579 (2) | 0.3966 (4) | 0.017 (1) |
| O(21) | 0.8929 (3) | 0.6976 (3) | 0.6082 (5) | 0.022 (2) |
| O(22) | 0.7434 (2) | 0.7359 (3) | 0.4563 (5) | 0.018 (1) |
| O(31) | 0.8168 (2) | 0.7889 (2) | 0.8327 (5) | 0.018 (1) |
| O(32) | 0.7868 (2) | 0.9014 (2) | 0.6133 (5) | 0.019 (1) |
| N(11) | 1.0357 (3) | 0.9017 (3) | 0.6004 (6) | 0.016 (2) |
| C(11) | 0.9966 (4) | 0.8949 (4) | 0.4343 (7) | 0.016 (2) |
| C(12) | 1.0498 (4) | 0.9326 (4) | 0.2978 (7) | 0.018 (2) |
| C(13) | 1.0153 (4) | 0.8876 (4) | 0.1215 (7) | 0.018 (2) |
| C(14) | 1.0458 (4) | 0.8047 (4) | 0.1150 (7) | 0.019 (2) |
| O(13) | 1.1255 (3) | 0.7989 (3) | 0.1829 (5) | 0.032 (2) |
| N(12) | 0.9841 (3) | 0.7414 (3) | 0.0333 (6) | 0.024 (2) |
| C(15) | 1.0026 (5) | 0.6582 (4) | 0.0084 (8) | 0.031 (3) |
| C(16A)† | 0.9352 (8) | 0.5897 (8) | 0.071 (1) | 0.021 (3) |
| C(16B) | 1.004 (1) | 0.605 (1) | 0.177 (2) | 0.044 (4) |
| C(18A) | 0.8653 (8) | 0.5332 (8) | 0.331 (2) | 0.023 (3) |
| C(18B) | 0.9309 (9) | 0.5577 (9) | 0.439 (2) | 0.036 (4) |
| C(17) | 0.9303 (5) | 0.5992 (4) | 0.2660 (8) | 0.036 (3) |
| C(19) | 0.8486 (4) | 0.5533 (4) | 0.5212 (8) | 0.028 (2) |
| N(21) | 0.8234 (3) | 0.6360 (3) | 0.5265 (6) | 0.020 (2) |
| C(21) | 0.7472 (4) | 0.6582 (4) | 0.4473 (7) | 0.018 (2) |
| C(22) | 0.6671 (4) | 0.5961 (4) | 0.3517 (7) | 0.024 (2) |
| C(23) | 0.5766 (4) | 0.6087 (4) | 0.3959 (7) | 0.022 (2) |
| C(24) | 0.5726 (4) | 0.5925 (4) | 0.5867 (8) | 0.023 (2) |
| O(23) | 0.6220 (3) | 0.5492 (3) | 0.6690 (5) | 0.035 (2) |
| N(22) | 0.5113 (4) | 0.6238 (4) | 0.6520 (6) | 0.031 (2) |
| C(25) | 0.4980 (4) | 0.6153 (4) | 0.8336 (8) | 0.031 (3) |
| C(26) | 0.4913 (4) | 0.6989 (4) | 0.9098 (8) | 0.031 (3) |
| C(27) | 0.5709 (4) | 0.7721 (5) | 0.9091 (8) | 0.035 (3) |
| C(28) | 0.6591 (4) | 0.7615 (5) | 1.0241 (8) | 0.033 (3) |
| C(29) | 0.7387 (4) | 0.8363 (4) | 1.0391 (7) | 0.028 (2) |
| N(31) | 0.7729 (3) | 0.8511 (3) | 0.8753 (6) | 0.021 (2) |
| C(31) | 0.7578 (4) | 0.9054 (4) | 0.7551 (8) | 0.021 (2) |
| C(32) | 0.7085 (5) | 0.9758 (4) | 0.7794 (9) | 0.038 (3) |
| C(33) | 1.3638 (5) | 0.8141 (5) | 0.1865 (9) | 0.045 (3) |
| C(34) | 1.3536 (5) | 0.7595 (4) | 0.3423 (8) | 0.033 (3) |
| O(33) | 1.4238 (3) | 0.7448 (3) | 0.4400 (6) | 0.046 (2) |
| N(32) | 1.2690 (4) | 0.7316 (4) | 0.3711 (7) | 0.030 (2) |
| C(35) | 1.2493 (4) | 0.6870 (4) | 0.5288 (9) | 0.035 (3) |
| C(36) | 1.2484 (4) | 0.7479 (4) | 0.6752 (9) | 0.034 (3) |
| C(37) | 1.1828 (4) | 0.8074 (4) | 0.6201 (8) | 0.031 (3) |
| C(38) | 1.1819 (4) | 0.8717 (4) | 0.7571 (7) | 0.024 (2) |
| C(39) | 1.1299 (4) | 0.9387 (4) | 0.6801 (7) | 0.019 (2) |
| O(H1) | 0.5941 (4) | 0.8460 (4) | 1.4117 (8) | 0.083 (2) |
| O(M1)‡ | 0.6925 (4) | 0.4961 (4) | 0.9803 (6) | 0.062 (2) |
| C(M1) | 0.7234 (8) | 0.4271 (7) | 0.921 (1) | 0.074 (5) |
| O(M2) | 0.6040 (6) | 0.9746 (5) | 1.188 (1) | 0.124 (4) |
| C(M2) | 0.5620 (7) | 1.0371 (7) | 1.257 (2) | 0.115 (6) |

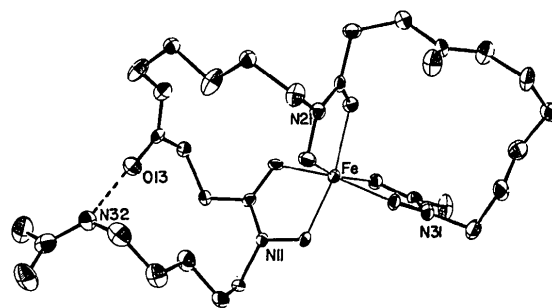
$$* U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

† Atoms C(16) and C(18) are disordered.

‡ O(M1) indicates O atom of methanol molecule 1 etc.



(a)



(b)

Fig. 1. (a) A schematic drawing of the ferrioxamine D_1 molecule showing the atom-numbering scheme. (b) An ORTEP (Johnson, 1965) drawing of the molecule. The intramolecular hydrogen bond is indicated by the dashed line.

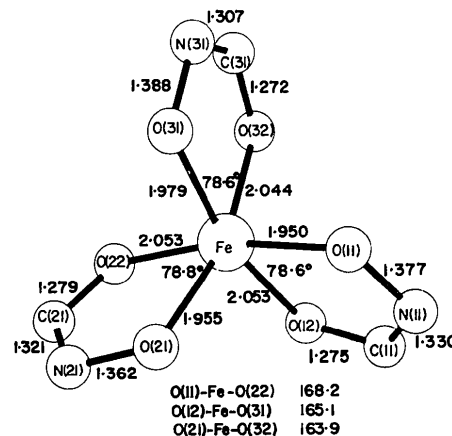


Fig. 2. Fe coordination geometry in ferrioxamine D_1 . E.s.d.'s for the bond lengths range between 0.003 and 0.007 \AA , and for the angles between 0.1 and 0.2 $^\circ$.

Table 2. Bond distances (Å) with e.s.d.'s in parentheses

| | <i>i</i> = 1 | <i>i</i> = 2 | <i>i</i> = 3 | Ferrioxamine E (average of 3) |
|------------------------------------|--------------|--------------|--------------|----------------------------------|
| O(<i>i</i> 1)—N(<i>i</i> 1) | 1.377 (5) | 1.363 (6) | 1.388 (5) | 1.381 (3) |
| N(<i>i</i> 1)—C(<i>i</i> 1) | 1.330 (6) | 1.321 (7) | 1.307 (7) | 1.307 (4) |
| C(<i>i</i> 1)—O(<i>i</i> 2) | 1.275 (7) | 1.279 (7) | 1.272 (6) | 1.275 (3) |
| C(<i>i</i> 1)—C(<i>i</i> 2) | 1.498 (7) | 1.495 (8) | 1.514 (8) | 1.495 (4) |
| C(<i>i</i> 2)—C(<i>i</i> 3) | 1.529 (7) | 1.514 (8) | — | 1.520 (4) |
| C(<i>i</i> 4)—O(<i>i</i> 3) | 1.246 (7) | 1.225 (7) | 1.255 (8) | 1.228 (4) |
| C(<i>i</i> 4)—N(<i>i</i> 2) | 1.322 (7) | 1.316 (7) | 1.317 (8) | 1.331 (4) |
| N(<i>i</i> 2)—C(<i>i</i> 5) | 1.456 (7) | 1.476 (7) | 1.471 (7) | 1.455 (4) |
| C(<i>i</i> 5)—C(<i>i</i> 6)* | 1.484 (12) | 1.519 (8) | 1.530 (8) | 1.492 (5) |
| | 1.570 (13) | | | |
| C(<i>i</i> 6)—C(<i>i</i> 7) | 1.557 (11) | 1.505 (9) | 1.525 (9) | 1.513 (5) |
| | 1.399 (15) | | | |
| C(<i>i</i> 7)—C(<i>i</i> 8) | 1.450 (13) | 1.509 (9) | 1.512 (8) | 1.482 (5) |
| | 1.506 (13) | | | |
| C(<i>i</i> 8)—C(<i>i</i> 9) | 1.601 (11) | 1.510 (9) | 1.525 (8) | 1.534 (4) |
| | 1.482 (14) | | | |
| C(<i>i</i> 9)—N(<i>i</i> + 1,1)† | 1.472 (7) | 1.466 (7) | 1.454 (7) | 1.463 (4) |

* Atoms C(16) and C(18) are disordered.

† *i* + 1 to be read as (*i* + 1) (mod 3).

differences between Fe—O(N) and Fe—O(C) distances indicate that the majority of the negative charges reside on the oxime O atoms. The corresponding N—O and C—O distances [average 1.376 (6) and 1.275 (6) Å, respectively] are also in good agreement with those observed in the trihydroxamates referred to above. The coordination geometrical parameters, ligand bite (ratio of O—O distance to the Fe—O distance) and twist angle (60° for an ideal octahedron and 0° for a trigonal prism) for ferrioxamine D₁ are 1.27 and 42.9°, respectively, which compare well with the values observed in ferrichrome (1.26, 42.9°), ferrioxamine E (1.27, 45.1°) and ferricrocin (1.26, 40.4°). Bond distances in the ligand are normal and are in agreement with the average values of the corresponding bonds in ferrioxamine E (Table 2).

In Table 3 torsion angles of the ligand chain are compared with those observed in ferrioxamine E. A least-squares fit of the two molecules obtained using 19 atoms is shown in Fig. 3. The metal coordination and the two macrocycles in ferrioxamine D₁ fit quite smoothly with those in ferrioxamine E. Conformations of the pentane chains are somewhat different, indicating their flexibility. The major difference between the two molecules lies in the open-chain part of the D₁ molecule, in particular in the torsion angles about the bonds N(11)—C(39) and C(35)—C(36) (Table 3). Such a conformation of the dangling chain leads to an asymmetric environment for the metal coordination in D₁, while in ferrioxamine E the three macrocycles form an approximately symmetric environment around the coordination octahedron. It is interesting to note that a rotation of about 170° about the N(11)—C(39) bond and of -120° about the C(35)—C(36) bond in ferrioxamine D₁ would bring the chain nearly on the top of the third macrocycle in ferrioxamine E.

The packing of the ferrioxamine D₁ molecules is quite compact and gives rise to three short Fe—Fe distances, 7.18, 7.85 and 8.74 Å. The three shortest

Fe—Fe distances in the ferrioxamine E structure are 8.03, 9.09 and 10.51 Å. The two centrosymmetrically related molecules are arranged so that they give the appearance of a dimeric pair (Fig. 4), although there is no intermolecular hydrogen bond between the two molecules. The crystal structure is stabilized by a number of hydrogen bonds involving ferrioxamine D₁ molecules and both water and methanol solvates. There are two intermolecular N—H...O hydrogen bonds, one along the *a* axis, N(22)...O(33)(*x* + 1, *y*, *z*) = 2.926 (6) Å, and the other along the *c* axis, N(12)...O(31)(*x*, *y*, *z* + 1) = 2.964 (6) Å. The water molecule forms four hydrogen bonds, three with ferrioxamine D₁ molecules, O(*W*)...O(33)(*x* + 1, *y*, *z* - 1) = 2.744 (8) Å, O(*W*)...O(32)(*x*, *y*, *z* - 1) = 3.004 (8) Å, and O(*W*)...O(22)(*x*, *y*, *z* - 1) = 3.097 (8) Å, and with a methanol molecule, O(*W*)...O(*M*1) = 2.744 (10) Å. The second methanol molecule also forms a hydrogen bond, O(*M*2)...O(23) = 2.694 (9) Å.

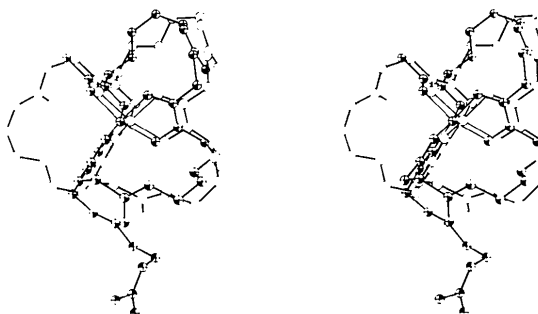
Table 3. Torsion angles (°) in ferrioxamine D₁ and ferrioxamine E

E.s.d. range: 0.5–1.0°.

| | Ferrioxamine D ₁ | | | Ferrioxamine E | | |
|----------------------------------------------------------------------|-----------------------------|--------------|--------------|----------------|--------------|--------------|
| | <i>i</i> = 1 | <i>i</i> = 2 | <i>i</i> = 3 | <i>i</i> = 1 | <i>i</i> = 2 | <i>i</i> = 3 |
| C(<i>i</i> -1,9)*—N(<i>i</i> 1)—C(<i>i</i> 1)—C(<i>i</i> 2) | -4 | 7 | 9 | 8 | 8 | 3 |
| N(<i>i</i> 1)—C(<i>i</i> 1)—C(<i>i</i> 2)—C(<i>i</i> 3) | 153 | 134 | — | 139 | 138 | 135 |
| C(<i>i</i> 1)—C(<i>i</i> 2)—C(<i>i</i> 3)—C(<i>i</i> 4) | -76 | -64 | — | -64 | -66 | -61 |
| C(<i>i</i> 2)—C(<i>i</i> 3)—C(<i>i</i> 4)—N(<i>i</i> 2) | 140 | 161 | — | 155 | 163 | 169 |
| C(<i>i</i> 3)—C(<i>i</i> 4)—N(<i>i</i> 2)—C(<i>i</i> 5) | 177 | -179 | -172 | 176 | -177 | -176 |
| C(<i>i</i> 4)—N(<i>i</i> 2)—C(<i>i</i> 5)—C(<i>i</i> 6) | 126† | 134 | 88 | 130 | 101 | 94 |
| | 76 | | | | | |
| N(<i>i</i> 2)—C(<i>i</i> 5)—C(<i>i</i> 6)—C(<i>i</i> 7) | -58 | -58 | 54 | -54 | -58 | -63 |
| | 50 | | | | | |
| C(<i>i</i> 5)—C(<i>i</i> 6)—C(<i>i</i> 7)—C(<i>i</i> 8) | 180 | -66 | -177 | -68 | -179 | 179 |
| | -173 | | | | | |
| C(<i>i</i> 6)—C(<i>i</i> 7)—C(<i>i</i> 8)—C(<i>i</i> 9) | -170 | -175 | 169 | -175 | 179 | 180 |
| | -179 | | | | | |
| C(<i>i</i> 7)—C(<i>i</i> 8)—C(<i>i</i> 9)—N(<i>i</i> + 1,1)‡ | 53 | -68 | 58 | -59 | 56 | 57 |
| | -50 | | | | | |
| C(<i>i</i> 8)—C(<i>i</i> 9)—N(<i>i</i> + 1,1)—C(<i>i</i> + 1,1)‡ | 67 | 100 | -111 | 92 | 78 | 77 |
| | 116 | | | | | |

* When *i* - 1 = 0, it refers to C(39).

† Upper values correspond to C(16A) and C(18A) and lower values to C(16B) and C(18B), the two disordered atoms.

‡ *i* + 1 to be read as (*i* + 1) (mod 3).Fig. 3. A stereoview of the superimposed molecules of ferrioxamine D₁ (half-shaded circles) and ferrioxamine E (open circles) separated from each other by a translation of 0.54 Å.

With the present structure we now have solid-state structures of two of the ferrioxamines, E and D₁, and both of them appear as a racemic mixture of two optical isomers, *A* and *Δ*, and as only one geometrical isomer, *cis*. Indeed, one can expect that, owing to the achiral nature of the ligand, the ferrioxamines will exist as a racemic mixture of *A* and *Δ* isomers. For linear trihydroxamates where hydroxamate groups are part of a long chain, one can expect as well greater flexibility in the configuration of the chelate as compared to the ferrichrome-type trihydroxamates where the ligand backbone is a rigid cyclic peptide and the three hydroxamate groups are attached to the side chains. The presence of both *cis* and *trans* isomers for the Cr³⁺ and Ga³⁺ complexes of deferriferrioxamine B (and also of D₁) in solution have been reported (Leong & Raymond, 1975; BORGAS & Raymond, 1984) and it is further suggested that the ferric complex of the deferriferrioxamines B and D₁ exhibits similar coordination isomerism, but so far only *cis* isomers have been observed in the solid state. A *trans* isomer has been observed in the case of Neocoprogen I (ferric isotriornicin), a linear trihydroxamate siderophore, whose structure has been determined in our laboratory (Hossain, Jalal, Benson, Barnes & van der Helm, 1984). The occurrence of the *trans* geometry in this complex can possibly be attributed to head-to-head condensation of two of the ornithine moieties in the ligand.

Conformational and topological similarities and differences between the molecules of ferrioxamine E and ferrioxamine D₁ as illustrated in the present report could be useful in understanding structure–function relationships and discrimination of the siderophores by their membrane carriers. Suitable experiments could be set up to compare uptake of the two siderophores. The fact that ferrioxamine E and D₁ have almost identical Fe coordination geometries but different environments for the metal coordination could be a useful guide in elucidating which part of the molecule is more important for iron uptake.

In a recent investigation of stereospecificity and mechanism of ferrioxamine-mediated iron transport, Müller & Raymond (1984) have shown that the uptake

system in *Streptomyces pilosus* does not discriminate between ferrioxamine E and D₁, whereas ferrioxamine B shows a higher uptake rate. In an associated study, Müller, Matzanke & Raymond (1984) reported that in *S. pilosus* ferrichrome and the ferrioxamines use the same carrier system and that the uptake rate of ferrioxamine B and ferrichrome are comparable. Considering the structural differences between ferrioxamine E and D₁ illustrated in this report, there could be two plausible explanations for the similarity in their uptake. (i) Under physiological conditions the open chain in D₁ undergoes conformational changes, *i.e.* rotation about the N(11)–C(39) and C(35)–C(36) bonds to make D₁ look more like ferrioxamine E. Although such changes are likely to happen, the presence of the intramolecular hydrogen bond, N(32)···O(13), makes it less probable. (ii) The surface of the coordination octahedron containing the three oxime O atoms is less important in regard to recognition by the membrane carrier system and the surface containing the hydroxamate carbonyls is the determining factor for recognition, because in ferrioxamine D₁ the ‘oxime face’ is partially shielded by the chain end of the molecule and the ‘carbonyl face’ is open and in ferrioxamine E both faces are open.

This latter explanation seems more plausible because it also correlates with the similar uptake rates of ferrichrome and ferrioxamines in *S. pilosus*. In all ferrichrome-type trihydroxamate siderophores, the ‘oxime surface’ of the metal coordination is shielded by the peptide ring and the ornithine side chains, while the ‘carbonyl face’ is either relatively open (as in ferrichrome, ferrichrysin *etc.*) or partially shielded by the acyl groups (as in ferrichrome A, ferrirubin *etc.*). Our suggestion that the membrane transport system recognizes the ‘carbonyl face’ of the Fe coordination in trihydroxamate siderophores is in fact an affirmation of the observations made by Müller, Matzanke & Raymond (1984) that the Fe coordination and its immediate environment and not the backbone structure are the determining factors for specific siderophore recognition. However, the overall uptake rate of a trihydroxamate siderophore by a transport system is not dependent on recognition alone, but also on the trans-membrane transport and post-transport release of the siderophore. These latter processes may be influenced by factors such as structure substituents at the hydroxamate carbonyls, presence of polar and/or charged functional groups in the ligand molecules and also the conformation of the parts of the molecule away from the Fe coordination center (Huschka, Jalal, van der Helm & Winkelmann, 1986). This may explain why ferrioxamine D₁ and ferrioxamine B have different uptake rates in *S. pilosus* (Müller & Raymond, 1984) although their recognition center (the ‘carbonyl face’) could very well be similar. It needs to be clarified that the terms ‘oxime face’ and ‘carbonyl face’ are applicable only in the case of a *cis* isomer.

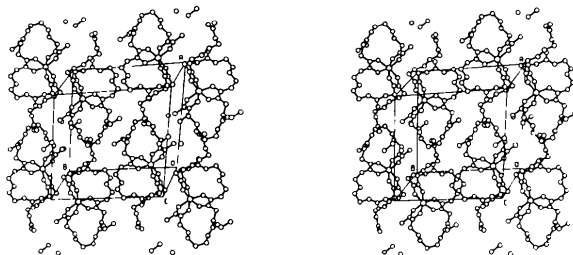


Fig. 4. A stereoview of the packing in ferrioxamine D₁.

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Structure of Hydronium*–1,4,7,10,13,16-Hexaoxacyclooctadecane (18-Crown-6)–Hexamolybdate(VI) (2/2/1)

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Abstract. $[\text{Mo}_6\text{O}_{19}]^{2-} \cdot (\text{C}_{12}\text{H}_{24}\text{O}_6 \cdot \text{H}_3\text{O}^+)_2$, $M_r = 1446 \cdot 30$, monoclinic, $P2_1/m$, $a = 11 \cdot 571$ (13), $b = 11 \cdot 222$ (11), $c = 9 \cdot 150$ (9) Å, $\beta = 101 \cdot 98$ (8)°, $V = 1162$ (2) Å³, $Z = 1$, $D_m = 2 \cdot 09$ (1), $D_x = 2 \cdot 07$ g cm⁻³, $\lambda(\text{Mo } K\alpha) = 0 \cdot 71069$ Å, $\mu = 16 \cdot 28$ cm⁻¹, $F(000) = 714$, $T = 293$ (2) K, final $R = 0 \cdot 069$ for 1265 observed reflections (47 left out because of twinning). The $[\text{Mo}_6\text{O}_{19}]^{2-}$ polyanion has the geometry previously reported: it consists of six distorted MoO_6 octahedra fused together, with the central O atom, which is at a center of symmetry, shared by all six. The average distances in Å are: Mo–Mo 3.285 (5), Mo–O_t (terminal) 1.649 (7), Mo–O_c (central) 2.323 (7), Mo–O_b (bridging) 1.933 (38). The average angles in degrees are: Mo–O_c–Mo 90.0 (1) and 180.0, Mo–O_b–Mo 116.4 (1.0), O_c–Mo–O_t 178.4 (1.5), O_c–Mo–O_b 76.8 (9), O_b–

Mo–O_b 87.0 (1.4) and 153.5 (1.7), O_t–Mo–O_b 103.2 (1.4). Two O atoms of the 18-crown-6 are on a mirror plane; the symmetry of the crown is approximately $\bar{3}m$ (D_{3d}). The hydronium ion is on the mirror plane close to the center of the crown. H atoms are presumed to be between this ion and the three alternating O atoms of the crown that are located, on average, 0.11 Å closer to this ion than the other three O atoms of the crown. The hydronium ion has a large component of thermal motion perpendicular to the ring, which may indicate disorder and does not exclude a pyramidal shape of this ion. The average distances and angles in the crown in Å and degrees are: C–C 1.473 (33), C–O 1.418 (20), O–C–C 108.8 (1.6), C–O–C 112.6 (1.3).

Introduction. The title compound was formed in a study of co-condensation products of MoO_3 with various

* IUPAC name: oxonium.