Acta Cryst. (1983). B39, 258–263

The Structure of Deferriferrioxamine E (Nocardamin),* a Cyclic Trihydroxamate

BY M. B. HOSSAIN, DICK VAN DER HELM AND M. POLING

Department of Chemistry, University of Oklahoma, Norman, OK 73019, *USA*

(*Received* 29 *April* 1982; *accepted* 16 *November* 1982)

Abstract

The structure of deferriferrioxamine E, a cyclic trihydroxamate type of siderophore, has been determined as part of a study of conformational differences between the siderophores and deferrisiderophores. Deferriferrioxamine E hexahydrate, $C_{27}H_{48}N_6O_9.6H_2O$, $M_r = 708{\cdot}8$, crystallizes in the trigonal space group $P3$, with $a = 24{\cdot}346\ (6)$, $c = 5{\cdot}392\ (1)$ Å, $Z = 3$, $V = 2767{\cdot}8$ Å^3 at 138 K; $a = 24{\cdot}610\ (9)$, $c = 5{\cdot}410\ (2)$ Å, $V = 2837{\cdot}6$ Å^3, $D_x = 1{\cdot}244$, $D_m = 1{\cdot}237$ Mg m^{-3} at 293 K. The structure was determined by direct methods from 3825 diffractometer data (Cu $K\bar{\alpha}$ radiation at 138 K) and refined to a final R factor of 0·067. The molecule consists of a 33-membered macrocycle formed by condensation of three groups of 1-amino-5-pentylhydroxylamine and three succinyl groups through peptide and hydroxamate linkages. The macrocyclic ring is essentially flat with an average thickness of about 4·0 Å. There are major conformational differences between the three equivalent segments of the molecule, particularly in the pentane chain and in the orientation of the peptide linkages, leading to substantial asymmetry for the potentially symmetric molecule. The three hydroxamate groups are all *trans* with all the oxime O atoms lying outwards while all the carbonyl O atoms are directed inwards of the macrocyclic ring. The three peptide bonds are all *trans*. All six water molecules in the asymmetric unit lie inside the macrocyclic ring and form extensive hydrogen bonding.

Introduction

The antibioticum nocardamin was originally isolated from a *Nocardia* species (Stoll, Renz & Brack, 1951). It was not until the discovery of the ferrioxamines (Bickel *et al.*, 1960), and their proof of structure, that nocardamin was shown to be identical with deferriferrioxamine E (Keller-Schierlein & Prelog, 1961). The structure of ferrioxamine E was also proven by synthesis of ferrioxamine G (Prelog & Walser, 1962).

The ferrioxamines form one family of siderophores. Siderophores are low molecular-weight compounds of microbial origin, which act as cellular transport agents for iron in aerobic fungi and bacteria (Emery, 1971; Neilands, 1973; Raymond & Carrano, 1979). In the ferrioxamines the Fe^{III} is chelated by hydroxamate groups. These groups occur commonly in natural products (Maehr, 1971). The ferrioxamine family of siderophores is produced by several species of *Streptomyces* and *Nocardia* and are characterized as A, B, C, D_1, D_2, E, F and G (Bickel *et al.*, 1960). They are either cyclic (D_2 and E) or linear. A characteristic structural feature of the ferrioxamines is repeating units of α-amino-ω-hydroxyamino alkane and succinate or acetate. A very stable octahedral ferric complex is formed using the three hydroxamate groups. Deferriferrioxamine E is optically inactive and neutral. The NMR spectrum has been investigated (Maehr, Benz, Smallheer & Williams, 1977).

It has been reported (Emery, 1967; Llinas, Klein & Neilands, 1970) that for siderophores drastic conformational changes of the ligands occur upon chelation with iron. The conformational differences between the complexed and the free ligand may furnish a selective device at the cell surface for excretion of the deferrisiderophore into the medium and transport of the siderophore itself into the cell. The structure of deferriferrioxamine E (Fig. 1) has been determined as a part of our study of conformational differences between siderophores and deferrisiderophores. The structure of the corresponding iron chelate, ferrioxamine E, has been reported earlier (van der Helm & Poling, 1976).

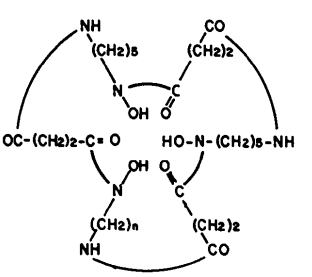

Fig. 1. A schematic drawing of the deferriferrioxamine E molecule.

* 1,12,23-Trihydroxy-1,6,12,17,23,28-hexaazacyclotritriacontane-2,5,13,16,24,27-hexone.

0567-7408/83/020258-06$01.50

Table 1. *Parameters for intensity-data collection*

Radiation	Cu $K\bar{\alpha}$	Maximum scan time	90 s
Data range	$0 \le 2\theta \le 150°$	Total number of reflections	3825
Temperature	138 (2) K		
Scan width	$(1{\cdot}10 + 0{\cdot}20 \tan\theta)°$	Number of observed reflections	2960
Aperture width	$(5{\cdot}50 + 0{\cdot}86 \tan\theta)$ mm	$[I > 2\sigma(I)]$	
Aperture height	6 mm		

Experimental

Thin needle-shaped crystals of deferriferrioxamine E were obtained from an acetonitrile solution by slow evaporation at room temperature. The crystals, though stable, showed in general large mosaic spread ranging between 1·3–3·0°. A crystal of dimensions 0·45 × 0·09 × 0·07 mm and smallest available mosaic spread was selected for X-ray diffraction measurements. Photographic investigation and preliminary diffractometer studies confirmed the crystal to be trigonal, belonging to space group $P3$ with pseudo $R3$ symmetry.

The cell parameters were obtained by a least-squares fit to the $+2\theta$ and -2θ values of 24 reflections (2θ range 20–40°) measured at 138 K using Cu $K\alpha_1$ (λ = 1·54051 Å) radiation. The density was determined by flotation in a mixture of carbon tetrachloride and hexane. Intensities of all unique reflections with $2\theta \le 150°$ were measured at 138 (2) K on a Nonius CAD-4 automatic diffractometer equipped with a cold-N_2-stream cooling device, using Cu $K\bar{\alpha}$ radiation. A $\theta/2\theta$ scan technique was employed with variable scan width and variable scan speed. Specific parameters related to the data collection are listed in Table 1. Of the total scan time two thirds was spent scanning the peak and one sixth the time was spent scanning each of the left and right backgrounds. The detector aperture was opened to its maximum width to allow for the large mosaic spread of the crystal. The intensity of a monitor reflection, measured after every 3600 s of X-ray exposure, showed a maximum variation of 7·5%. The orientation matrix was checked after every 200 measurements. Lorentz and polarization corrections were applied to the individual structure amplitudes, but no absorption correction was made. An experimental weight estimated on the basis of counting statistics was assigned to each structure amplitude (Ealick, van der Helm & Weinheimer, 1975).

Structure determination and refinements

The structure was determined by direct methods and difference Fourier syntheses. During the initial run of the direct-method program *MULTAN* (Germain, Main & Woolfson, 1971), one of the E maps (475 reflections, $E > 1{\cdot}47$) led to a very interesting and puzzling result. The map showed 48 large peaks which correspond to the 42 non-hydrogen atoms in the deferrioxamine E molecule and six water oxygens. The bond distances and angles were all reasonable, but the overall structure consisted of an endless spiral along the c crystallographic axis, instead of the expected macrocyclic molecule. The problem was finally resolved by excluding different fragments of the spiral, in turn, from structure factor calculations and evaluating a difference Fourier map in each case. After several attempts, the complete structure was obtained which refined smoothly. The refinement of the structure was carried out in stages using isotropic thermal parameters at the beginning and anisotropic thermal parameters in the

Table 2. *Final positional parameters* ($\times 10^4$) *and equivalent isotropic thermal parameters of non-hydrogen atoms*

Standard deviations for the last digit are in parentheses.

$U_{eq} = (\frac{1}{6}\pi^2) \sum_i \sum_j \beta_{ij}\, \mathbf{a}_i \cdot \mathbf{a}_j$.

	x	y	z	U_{eq} (Å^2)
O(11)	421 (2)	1146 (2)	4622 (10)	0·032 (2)
O(12)	1940 (2)	1811 (2)	2086 (9)	0·030 (2)
O(13)	1661 (2)	144 (2)	1526 (10)	0·036 (3)
O(21)	5510 (2)	2651 (2)	1537 (9)	0·034 (3)
O(22)	4864 (2)	3488 (2)	−1341 (9)	0·030 (2)
O(23)	6533 (2)	4825 (2)	−1444 (10)	0·036 (3)
O(31)	4021 (2)	6249 (2)	304 (9)	0·028 (2)
O(32)	3199 (2)	4727 (2)	2929 (10)	0·032 (2)
O(33)	1843 (2)	5015 (2)	3167 (12)	0·041 (3)
N(11)	1059 (3)	1588 (3)	4211 (1)	0·027 (3)
N(12)	2352 (2)	761 (2)	−1422 (10)	0·024 (3)
N(21)	5062 (3)	2834 (3)	909 (11)	0·027 (3)
N(22)	5980 (3)	4961 (3)	−4529 (11)	0·028 (3)
N(31)	3831 (3)	5612 (3)	734 (10)	0·027 (3)
N(32)	1730 (2)	4265 (2)	5889 (11)	0·027 (3)
C(11)	1373 (3)	1458 (3)	2465 (13)	0·028 (3)
C(12)	978 (3)	860 (3)	946 (12)	0·028 (3)
C(13)	1377 (3)	777 (3)	−1057 (12)	0·025 (3)
C(14)	1810 (3)	542 (3)	−151 (14)	0·027 (3)
C(15)	2794 (3)	534 (3)	−1022 (12)	0·027 (3)
C(16)	3267 (3)	885 (3)	1084 (13)	0·029 (3)
C(17)	3701 (3)	1584 (3)	643 (13)	0·029 (3)
C(18)	4138 (3)	1901 (3)	2853 (13)	0·032 (4)
C(19)	4532 (3)	2616 (3)	2667 (12)	0·028 (3)
C(21)	5206 (3)	3259 (3)	−841 (12)	0·023 (3)
C(22)	5812 (3)	3451 (3)	−2311 (12)	0·026 (3)
C(23)	5937 (3)	3953 (3)	−4296 (12)	0·027 (3)
C(24)	6165 (3)	4609 (3)	−3254 (12)	0·024 (3)
C(25)	6216 (3)	5629 (3)	−3864 (13)	0·030 (3)
C(26)	5837 (3)	5700 (3)	−1759 (14)	0·031 (3)
C(27)	5142 (3)	5449 (3)	−2371 (12)	0·032 (3)
C(28)	4812 (3)	5618 (3)	−373 (12)	0·029 (3)
C(29)	4117 (3)	5351 (3)	−936 (13)	0·034 (4)
C(31)	3412 (3)	5305 (3)	2528 (12)	0·023 (3)
C(32)	3213 (3)	5685 (3)	4099 (12)	0·024 (3)
C(33)	2706 (3)	5269 (3)	6009 (12)	0·026 (3)
C(34)	2065 (3)	4835 (3)	4875 (13)	0·030 (3)
C(35)	1075 (3)	3817 (3)	5176 (14)	0·031 (3)
C(36)	1023 (3)	3390 (3)	3052 (13)	0·034 (4)
C(37)	1333 (4)	2981 (3)	3511 (12)	0·033 (3)
C(38)	1075 (3)	2557 (3)	5762 (13)	0·034 (4)
C(39)	1330 (3)	2103 (3)	6003 (13)	0·034 (4)
W(1)	4926 (2)	4368 (3)	−7834 (11)	0·041 (3)
W(2)	2827 (3)	1822 (3)	−4621 (11)	0·046 (3)
W(3)	2396 (3)	3890 (3)	−773 (10)	0·039 (3)
W(4)	2777 (3)	2995 (2)	173 (11)	0·040 (3)
W(5)	3628 (3)	3880 (3)	3466 (11)	0·045 (3)
W(6)	3656 (2)	3061 (3)	−3094 (10)	0·042 (3)

Table 3. *Bond lengths* (Å)

	$i=1$	$i=2$	$i=3$	Average	Equivalent average distance in ferrioxamine E
O(i1)–N(i1)	1·396 (8)	1·410 (6)	1·398 (5)	1·401 (4)†	1·381 (3)†
N(i1)–C(i1)	1·346 (8)	1·312 (8)	1·331 (9)	1·330 (5)	1·307 (4)
C(i1)–O(i2)	1·225 (8)	1·241 (6)	1·252 (5)	1·239 (4)	1·275 (3)
C(i1)–C(i2)	1·522 (8)	1·528 (9)	1·502 (7)	1·517 (5)	1·495 (4)
C(i2)–C(i3)	1·532 (9)	1·536 (8)	1·536 (9)	1·535 (5)	1·520 (4)
C(i3)–C(i4)	1·510 (7)	1·513 (6)	1·509 (9)	1·511 (4)	1·502 (4)
C(i4)–O(i3)	1·240 (8)	1·249 (8)	1·253 (8)	1·247 (5)	1·228 (4)
C(i4)–N(i2)	1·339 (8)	1·340 (7)	1·326 (6)	1·335 (4)	1·331 (4)
N(i2)–C(i5)	1·451 (6)	1·473 (6)	1·463 (8)	1·462 (4)	1·455 (4)
C(i5)–C(i6)	1·537 (9)	1·526 (9)	1·509 (9)	1·524 (5)	1·492 (5)
C(i6)–C(i7)	1·507 (7)	1·520 (9)	1·541 (6)	1·523 (4)	1·513 (5)
C(i7)–C(i8)	1·525 (10)	1·519 (8)	1·512 (9)	1·519 (5)	1·482 (5)
C(i8)–C(i9)	1·514 (7)	1·509 (9)	1·520 (6)	1·514 (4)	1·534 (5)
C(i9)–N(i + 1,1)*	1·470 (9)	1·464 (7)	1·454 (8)	1·463 (5)	1·463 (4)

* (i + 1) to be read as (i + 1)[mod 3].
† The figure in parentheses is the standard deviation of the mean, $\sigma = \bar{\sigma}/\sqrt{n}$; $\bar{\sigma}$ is the mean of the individual standard deviations.

final stages. An attempt to locate H atoms from a difference map was frustrated by the presence of several spurious peaks of height ranging between 0·3–0·6 e Å^{-3}. Contributions from 45 H atoms placed at their ideal positions were included in the structure factor calculations during the final cycles of refinement. The refinement converged to an R ($\sum ||kF_o| - |F_c||/\sum |kF_o|$) factor of 0·067 for 2960 reflections included in the least-squares calculations. All refinements were carried out by using a full-matrix least-squares routine as incorporated in the program *SHELX* (Sheldrick, 1976). The rather high R factor for the structure may largely be due to the poor quality of the crystal. The final atomic parameters of all non-hydrogen atoms are listed in Table 2.*

Description and discussion of the structure

A stereoview of a single molecule of deferriferrioxamine E is shown in Fig. 2. The molecular structure consists of a 33-membered macrocycle, formed by condensation of three groups of 1-amino-5-pentylhydroxylamine and three succinyl groups through three peptide and three hydroxamate linkages. The macrocyclic ring is essentially flat. The maximum deviation of the ring atoms from the least-squares plane through the 33 atoms is 2·06 Å. The three hydroxamate groups are all *trans* with all the oxime O atoms pointing outwards while the carbonyl O-atom bonds are directed inwards of the ring system. The potentially symmetric molecule assumes an asymmetric conformation. Of the three pentane chains, one is skewed, while the other two are extended. All three peptide bonds are *trans*, and the peptide carbonyl groups are pointed approximately perpendicular to the plane of the macrocyclic ring, two pointing to one side while the third points to the opposite side of the plane of the ring.

The bond lengths, bond angles and torsion angles for the deferriferrioxamine E molecule are listed in Tables 3, 4, and 5 respectively. These results are arranged so that the three equivalent segments of the molecule can be easily compared. Dimensionally there are no significant differences between the three segments. The major differences in equivalent bond lengths, N(11)–C(11) of 1·346 (8) Å and N(21)–C(21) of 1·312 (8) Å, and C(11)–O(12) of 1·225 (8) Å and C(31)–O(32) of 1·252 (5) Å, are within 4σ of one another. Differences in equivalent bond angles in the three segments are all within 3σ.

There are major conformational differences in the three equivalent segments of the molecule (Table 5). Segment III has the opposite conformation for bonds C(i2)–C(i3), C(i3)–C(i4), N(i2)–C(i5), C(i5)–C(i6) and C(i9)–N(i + 1, 1), when compared to segments I and II. The pentane chain is completely extended in segment II, while the segment I is the same, but for a

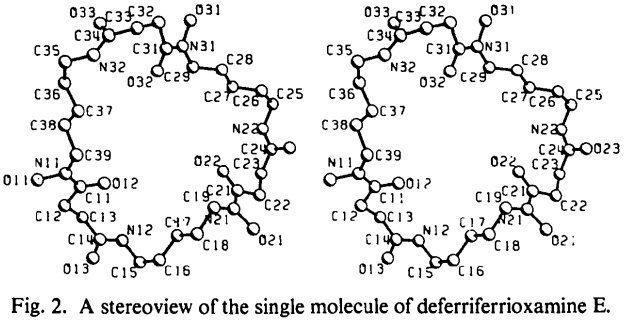

Fig. 2. A stereoview of the single molecule of deferriferrioxamine E.

* Lists of anisotropic thermal parameters, structure factors and calculated H-atom positions have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38240 (21 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 4. *Bond angles* (°)

	$i=1$	$i=2$	$i=3$	Average	Equivalent average angle in ferrioxamine E
O(*i*1)–N(*i*1)–C(*i*1)	118·3 (5)	118·6 (5)	118·6 (4)	118·5 (3)‡	116·9 (2)‡
O(*i*1)–N(*i*1)–C(*i* − 1,9)*	114·2 (5)	114·1 (4)	114·5 (5)	114·3 (3)	113·8 (2)
C(*i*1)–N(*i*1)–C(*i* − 1,9)	127·0 (6)	126·1 (5)	126·9 (4)	126·7 (3)	128·7 (2)
N(*i*1)–C(*i*1)–O(*i*1)	121·7 (5)	122·4 (6)	121·8 (5)	122·0 (3)	118·8 (2)
N(*i*1)–C(*i*1)–C(*i*2)	116·1 (6)	116·8 (5)	117·2 (4)	116·7 (3)	120·8 (2)
O(*i*2)–C(*i*1)–C(*i*2)	122·2 (5)	120·8 (5)	121·0 (6)	121·3 (3)	120·4 (2)
C(*i*1)–C(*i*2)–C(*i*3)	111·5 (5)	112·4 (4)	111·9 (4)	111·9 (3)	113·4 (2)
C(*i*2)–C(*i*3)–C(*i*4)	115·5 (5)	113·8 (5)	113·5 (5)	114·3 (3)	112·8 (2)
C(*i*3)–C(*i*4)–O(*i*3)	123·0 (6)	122·8 (4)	121·9 (4)	122·6 (3)	121·6 (3)
C(*i*3)–C(*i*4)–N(*i*2)	114·8 (5)	114·9 (5)	116·4 (5)	115·4 (3)	115·2 (3)
O(*i*3)–C(*i*4)–N(*i*2)	122·0 (5)	122·1 (4)	121·5 (6)	121·9 (3)	123·1 (3)
C(*i*4)–N(*i*2)–C(*i*5)	122·9 (4)	120·7 (6)	122·9 (5)	122·2 (3)	123·7 (3)
N(*i*2)–C(*i*5)–C(*i*6)	113·0 (4)	112·5 (5)	113·4 (5)	113·0 (3)	112·7 (3)
C(*i*5)–C(*i*6)–C(*i*7)	114·8 (5)	114·0 (6)	115·1 (5)	114·6 (3)	116·0 (3)
C(*i*6)–C(*i*7)–C(*i*8)	111·5 (5)	111·7 (5)	113·6 (5)	112·3 (3)	113·4 (3)
C(*i*7)–C(*i*8)–C(*i*9)	114·3 (5)	111·8 (5)	112·6 (5)	112·9 (3)	115·8 (3)
C(*i*8)–C(*i*9)–N(*i* + 1,1)†	113·3 (4)	111·3 (5)	113·3 (5)	112·6 (3)	111·5 (3)

* When $i - 1 = 0$, it refers to atom C(39).
† $i + 1$ to be read as $(i + 1)$[mod 3].
‡ See second footnote to Table 3.

Table 5. *Torsion angles in the macrocyclic ring of deferriferrioxamine E and ferrioxamine E*

	Deferriferrioxamine E			Ferrioxamine E‡		
	(I)	(II)	(III)	(I)	(II)	(III)
C(*i*8)–C(*i*9)–N(*i* + 1,1)–C(*i* + 1,1)*	119·3 (6)	131·1 (6)	−110·2 (7)	−92	−78	−77
C(*i* − 1,9)–N(*i*1)–C(*i*1)–C(*i*2)†	175·8 (5)	175·1 (5)	176·7 (7)	−8	−3	−8
N(*i*1)–C(*i*1)–C(*i*2)–C(*i*3)	177·3 (5)	−179·7 (5)	177·2 (5)	−138	−135	−139
C(*i*1)–C(*i*2)–C(*i*3)–C(*i*4)	76·5 (5)	73·9 (6)	−71·6 (5)	66	61	64
C(*i*2)–C(*i*3)–C(*i*4)–N(*i*2)	−147·6 (5)	−147·5 (6)	143·5 (5)	−163	−169	−155
C(*i*3)–C(*i*4)–N(*i*2)–C(*i*5)	−172·7 (5)	−174·2 (5)	173·3 (5)	177	176	−176
C(*i*4)–N(*i*2)–C(*i*5)–C(*i*6)	−86·0 (5)	−83·6 (5)	89·1 (6)	−101	−97	−130
N(*i*2)–C(*i*5)–C(*i*6)–C(*i*7)	−62·8 (7)	−62·2 (6)	58·6 (7)	58	64	54
C(*i*5)–C(*i*6)–C(*i*7)–C(*i*8)	177·9 (5)	−171·6 (4)	57·6 (8)	179	−178	68
C(*i*6)–C(*i*7)–C(*i*8)–C(*i*9)	−173·1 (5)	−178·1 (4)	173·2 (6)	−179	−179	175
C(*i*7)–C(*i*8)–C(*i*9)–N(*i* + 1,1)*	−74·8 (7)	−169·4 (4)	−73·4 (4)	−56	−57	59

* $i + 1$ to be read as $(i + 1)$[mod 3].
† When $i - 1 = 0$, it refers to atom C(39).
‡ Standard deviations of ferrioxamine E angles range between 0·4 and 0·8°.

skewed conformation around C(*i*8)–C(*i*9); segment III is skewed around both C(*i*6)–C(*i*7) and C(*i*8)–C(*i*9). One can conclude, therefore, that segments I and II are similar, but that segment III is quite different, with as one of the results the observation that the peptide oxygen of segment III is directed downwards (Fig. 2), while for segments I and II that group is directed upwards.

The average bond distances in the hydroxamate groups are N–OH = 1·401 (5), C–N = 1·330 (5) and C–O = 1·239 (5) Å. These values compare well with those found in other *trans* hydroxamic acids, as in *N*,*N*′-dihydroxy-*N*,*N*′-diisopropylhexanediamide [1·396 (2), 1·328 (2) and 1·241 (2) Å] (Smith & Raymond, 1980), and in hydroxyurea [1·390 (1), 1·347 (1) and 1·255 (1) Å] (Thiessen, Levy & Flaig, 1978). The hydroxamate groups are planar, but the deviation from the ideal *trans* conformation is noticeable in segment II of the molecule [torsion angle, O(21)–N(21)–C(21)–O(22) is −173·1 (5)°]. The r.m.s. deviation of the C, N and O atoms from the least-squares plane of the hydroxamate group is 0·011, 0·036 and 0·015 Å, as compared to 0·014 Å in *N*,*N*′-dihydroxy-*N*,*N*′-diisopropylhexanediamide. The *trans* peptide bonds [torsion angles, −172·7 (5), −174·2 (5) and 173·3 (5)° for segments I, II and III respectively] have normal C–N distances of 1·339 (8), 1·340 (7) and 1·326 (6) Å.

Neither ferrioxamine E nor deferriferrioxamine E is optically active. The first crystallizes in the centrosymmetric space group $P\bar{1}$, while the present compound crystallizes in the noncentrosymmetric space group $P3$.

A comparison of the bond lengths and angles of the present structure with those for its iron chelate, ferrioxamine E (Tables 3 and 4) shows that dimensionally there are only minor differences and most of these are, as expected, in the hydroxamate groups. The

molecular structures of the two compounds are illustrated in idealized drawings in Fig. 3. A stereoview of the least-squares fit of the positional parameters of the equivalent atoms in the two structures is shown in Fig. 4. It is quite apparent from these illustrations that drastic conformational changes occur in the free ligand as it forms the iron chelate. Both the chelate and the free-ligand molecules are relatively flat. In the free ligand all the hydroxamate groups are *trans* with the three oxime oxygens pointing outwards from the periphery of the macrocyclic ring, while the carbonyl groups are directed inwards. Two of the peptide carbonyls are directed upwards from one of the flat faces, while the third peptide carbonyl group points in the opposite direction. It appears that in the ligand molecule, the overall disposition of the polar groups is such that they virtually shield the lipophylic pentane chains from the environment. In the iron chelate, the situation is quite different. The hydroxamate groups are *cis* and all three peptide carbonyl groups and all the oxime O atoms lie on one side of the flat molecule. These polar groups are interlaced by the pentane chains giving both hydrophylic and lipophylic characteristics to that surface of the chelate molecule. The iron chelation brings the ligand into a more rigid and relatively more symmetric conformation. There are much fewer conformational differences between the three segments in the chelate molecule. The only differences are for bonds C(*i*6)–C(*i*7) and C(*i*8)–C(*i*9) (Table 5). The conformational changes in the ligand due to chelation involve a rotation of the hydroxamate bond to turn a *trans* hydroxamate into a *cis*, so that all three oxime O atoms move inwards to coordinate to the metal. In segment III of the ligand molecule, additional conformational changes are required to reverse the direction of the peptide carbonyl group.

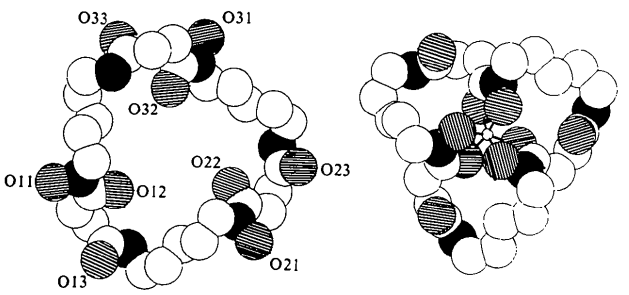

Fig. 3. Deferriferrioxamine E (left) and ferrioxamine E (right). Open circle carbon, striped circle oxygen, and dark circle nitrogen.

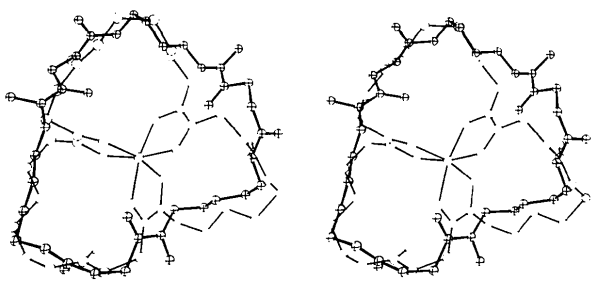

Fig. 4. Stereoview of the superimposed molecules of deferriferrioxamine E and ferrioxamine E.

Packing and hydrogen bonds

Fig. 5 shows the environment of a single molecule of deferriferrioxamine E in the unit cell. The flat face of the molecule lies approximately perpendicular to the *c* crystallographic axis. A molecule is surrounded by six neighbors and is linked to each of them through a strong hydrogen bond, forming a two-dimensional

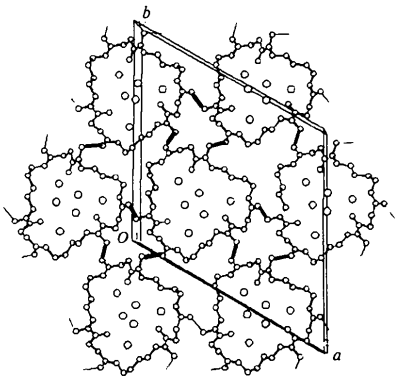

Fig. 5. Crystal structure of deferriferrioxamine E hexahydrate, showing the environment of a single molecule. The water molecules are indicated by open circles. Intermolecular hydrogen bonds are indicated by thick lines.

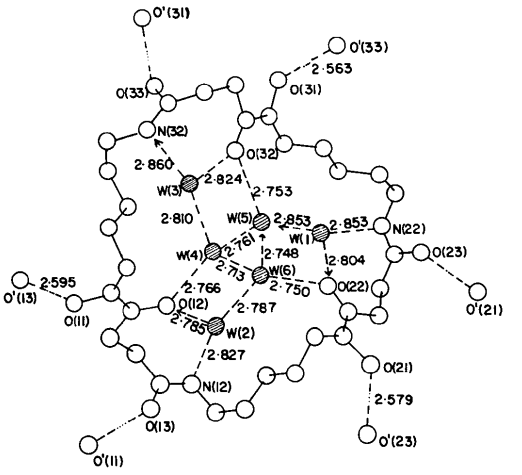

Fig. 6. Hydrogen-bond distances in the deferriferrioxamine E structure (Å). Standard deviations range between 0·008 and 0·009 Å. Atom O'(13) is O(13) [$-y, x-y, z$], O'(23) is O(23) [$1-y, x-y, z$], and O'(33) is O(33) [$1-y, 1+x-y, z$]. Hydrogen bonds are indicated by dashed lines. An arrow points to an atom belonging to the neighboring cell ($x, y, z-1$).

sheet perpendicular to the *c* axis. Three of the intermolecular hydrogen bonds are unique. They connect the *N*-hydroxyl of the hydroxamate groups with the peptide carbonyl of a neighboring molecule. All three bonds are very strong, O(11)···O′(13) = 2·595, O(21)···O′(23) = 2·579, and O(31)···O′(33) = 2·563 Å (Fig. 6). Fig. 5 also shows the nature of the pseudosymmetry (*R*3) in the crystal structure of deferriferrioxamine E. Along the *c* axis, the molecules stack on top of each other forming infinite cylinders. Within each cylinder, a molecule is linked to its nearest neighbors by hydrogen bonds *via* the water molecules.

All six water molecules in the asymmetric unit lie inside the macrocyclic ring of the deferriferrioxamine E molecule and are involved in extensive hydrogen bonding. The water molecules fall into two distinct groups: inner and outer. The three outer molecules [*W*(1), *W*(2), and *W*(3)] have a trigonal environment. Each of these forms three hydrogen bonds, two to the deferriferrioxamine E molecule and one to a water molecule belonging to the inner group. The three water molecules connect the peptide amino group of one molecule to the hydroxamate carbonyl of an adjacent molecule in the stack. The three inner water molecules [*W*(4), *W*(5) and *W*(6)] each form four hydrogen bonds in a tetrahedral environment: one to the deferriferrioxamine E molecule and three to other water molecules. The three inner water molecules are hydrogen bonded to each other in such a fashion that they form an infinite spiral along the *c* axis. The six water molecules are related to each other by a pseudo threefold screw axis at the center of the deferriferrioxamine E molecule. The hydrogen bonding, therefore, is quite efficient and involves all the O atoms, the peptide N atoms and water molecules.

We thank Drs W. Keller-Schierlein and H. Maehr for samples of nocardamin. This work was supported by a grant from the National Institute of General Medical Sciences (GM-21822).

References

BICKEL, H., BOSSHARDT, R., GÄUMANN, E., REUSSER, P., VISCHER, E., VOSER, W., WETTSTEIN, A. & ZÄHNER, H. (1960). *Helv. Chim. Acta*, **43**, 2118–2128.

EALICK, S. E., VAN DER HELM, D. & WEINHEIMER, A. J. (1975). *Acta Cryst.* B**31**, 1618–1626.

EMERY, T. F. (1967). *Biochemistry*, **6**, 3858–3866.

EMERY, T. F. (1971). *Adv. Enzymol. Relat. Subj. Biochem.* **35**, 135–185.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A**27**, 368–376.

KELLER-SCHIERLEIN, W. & PRELOG, V. (1961). *Helv. Chim. Acta*, **44**, 1981–1985.

LLINAS, M., KLEIN, M. P. & NEILANDS, J. B. (1970). *J. Mol. Biol.* **52**, 399–414.

MAEHR, H. (1971). *Pure Appl. Chem.* **28**, 603–636.

MAEHR, H., BENZ, W., SMALLHEER, J. & WILLIAMS, T. H. (1977). *Z. Naturforsch. Teil B*, **32**, 937–942.

NEILANDS, J. B. (1973). *Inorganic Biochemistry*, Vol. I, edited by G. L. EICHHORN, pp. 167–202. New York: Elsevier.

PRELOG, V. & WALSER, A. (1962). *Helv. Chim. Acta*, **45**, 1732–1734.

RAYMOND, K. N. & CARRANO, C. J. (1979). *Acc. Chem. Res.* **12**, 183–190.

SHELDRICK, G. M. (1976). *SHELX*76. Program for crystal structure determination. Univ. Chemical Laboratory, Cambridge, England.

SMITH, W. L. & RAYMOND, K. N. (1980). *J. Am. Chem. Soc.* **102**, 1252–1255.

STOLL, A., RENZ, J. & BRACK, A. (1951). *Helv. Chim. Acta*, **34**, 862–873.

THIESSEN, W. E., LEVY, H. A. & FLAIG, B. D. (1978). *Acta Cryst.* B**34**, 2495–2502.

VAN DER HELM, D. & POLING, M. (1976). *J. Am. Chem. Soc.* **98**, 82–86.

Acta Cryst. (1983). B**39**, 263–266

Polymorphism of Crystalline Poly(hydroxymethyl) Compounds. VII.* Structure and Twinning of 2-(Hydroxymethyl)-2-methyl-1,3-propanediol

BY DONNA EILERMAN, ROBERT LIPPMAN AND REUBEN RUDMAN

Department of Chemistry, Adelphi University, Garden City, New York 11530, *USA*

(*Received* 18 *August* 1982; *accepted* 19 *November* 1982)

Abstract

Crystals of the title compound, $CH_3C(CH_2OH)_3$, grown from solution or by sublimation, exhibit fourfold twinning thereby forming a pseudo-body-centered-tetragonal unit cell (cell II) in which the (*eee*) reflections have an average intensity 76 times greater than the other observed reflection types. Each of the fourlings contributes to the (*eee*) reflections, but only one fourling contributes to each of the other reflections. The structure reported here is an averaged, disordered structure determined from the (*eee*) reflections only.

* Part VI: Sake Gowda & Rudman (1982).

0567-7408/83/020263-04$01.50