BioMetals 1995, **8**, 193–196

Suggestion for a new, semirational nomenclature for the free chelators of ferrioxamines

Gottfried J. Feistner

Beckman Research Institute of the City of Hope, Duarte, CA, USA

Received 14 July 1994; accepted for publication 1 September 1994

The author proposes that the free chelators of ferrioxamines should be referred to as proferrioxamines (pFOs) and the corresponding structural and regulatory genes as pfoA, pfoB, pfoC, etc. He furthermore suggests that individual proferrioxamines should be distinguished by subscripts that indicate the number and sizes of the constituting diamines, and, where applicable, a cyclic structure or a C-terminal acetic acid substitution. Modifications to the basic structures can be accomodated by standard nomenclature rules. The new semirational nomenclature features the best of the old alphabetical and the Chemical Abstracts nomenclatures; it is structure-based and thus chemically informative but still quite concise.

Keywords: proferrioxamine; desferrioxamine; deferrioxamine; deferoxamine

Introduction

Many microorganisms acquire iron from their environment in the form of ferrioxamines, two examples of which are shown in Figure 1. Figure 2 shows the general structure of the free chelators. They belong to the general category of trihydroxamate siderophores, and in their simplest forms consist of repeating units of *N*-hydroxylated diamines and succinic acid only. The free chelators were originally named desferri-ferrioxamine, which is descriptive but inconvenient, and soon led to the 'sloppy' term desferrioxamine (Keller-Schierlein *et al.* 1964). Further trimming led to 'deferrioxamine' or even 'deferiox-amine' and there is no uniformly accepted term in the current literature.

When we first encountered these siderophores (Feistner *et al.* 1993a), we therefore chose to refer to the ferrioxamine precursors as *pro*ferrioxamines (pFOs), in analogy to proferrorosamine A, the precursor of the iron(II) complex, ferrorosamine A (Feistner *et al.* 1983). The prefix 'des' is not satisfactory because by itself 'des' indicates only the absence of something but in no way specifies what is missing. This may result in ambiguous nomenclature and in fact, it already has. For example, the use of *desA*, *desB*, *desC*, etc., to describe the structural genes that code for proferrioxamine biosynthesis (Schupp 1988) is in conflict with the use of *desA* to describe a gene for a fatty acid desaturase from a cyanobacterium (Wada *et al.* 1993). The designations *pfoA*, *pfoB*, *pfoC*, etc., would avoid this ambiguity and are suggested instead.

The second suggestion I would like to make concerns the differentiation of individual proferriox-amines by alphabetical letters (Keller-Schierlein *et al.* 1964). This system has served its purpose for as long as basically only one research group contributed to the knowledge of proferrioxamines. However, due to the practical applications that proferrioxamines have found as metal detoxification agents, bifunctional chelators, etc., other research groups have now entered this field and it becomes difficult to coordinate the naming of novel proferrioxamines using the alphabetical method. The alphabetical letters also do not reveal anything about the corresponding chemical structures, not even indicating chemical relationships between individual proferrioxamines. I therefore suggest to adopt a system that has previously been introduced for the description of polyamines (Hamana & Matsuzaki 1992), i.e. to use the carbon chain length of the constituting diamines for characterization. Specifically, I suggest using the corresponding numerical numbers as subscripts to 'pFO'. As can be seen from Table 1, this system leads to rational descriptions for all of the natural proferrioxamines, but is much more concise than the nomenclature used by the

Address for correspondence: G. J. Feistner, Beckman Research Institute of the City of Hope, 1450 East Duarte Road, Duarte, CA 91010, USA. Tel: (+1) 818 357 9711; Fax: (+1) 818 301 8186.

Chemical Abstract service. For example, the *Chemical Abstract* name for the acyclic proferrioxamine G_1 is 32 - amino - 5,16,27 - trihydroxy - 4,12,15,23,26 -pentaoxo - 5,11,16,22,27-pentaazadotriacontanoic acid, but simply pFO_{555} under the new nomenclature. To distinguish acyclic from cyclic proferrioxamines, the latter will be identified by the subscript-suffix 'c'. Proferrioxamine E thus becomes pFO_{555c}, the tetra-hydroxamate pFO T_1 becomes pFO_{5555c} and the dihydroxamate bisucaberin becomes pFO_{55c}.

This simple number system is possible because most chemical features in natural proferrioxamines are apparently conserved. For example, since the *N*-hydroxamate functions are required for metal binding, they hardly need to be specified. In those rare cases where an *N*-hydroxy group is indeed missing (such as in pFO X_4), this may be discussed as a desoxy-derivative. Also, succinic acid appears to be a largely invariant component of proferrioxamines since all natural proferrioxamines contain it and efforts in Tübingen (Meives 1989) and by ourselves to substitute succinic acid by directed fermentation, e.g. with malic acid, have failed. An exception to the rule is the C-terminal substitution of succinic by acetic acid, e.g. in pFO B. Such acetyl derivatives can easily be accommodated by the subscript-suffix 'Ac'. Thus pFO B would be described as pFO_{555Ac}.

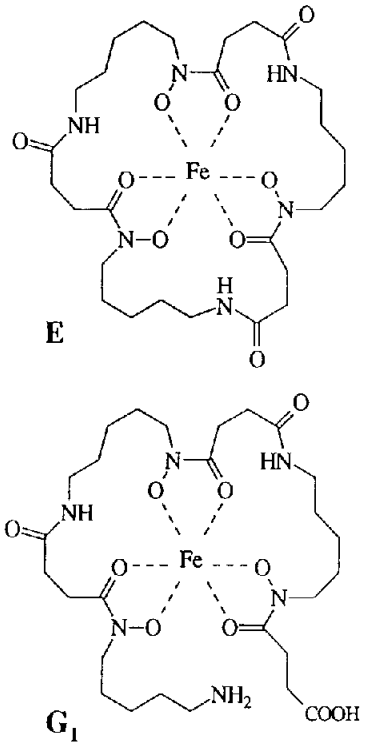

Figure 1. Examples of a cyclic (E) and an acyclic (G_1) ferrioxamine, illustrating the metal binding via the hydroxamate groups. Other ferrioxamines differ in the size of the constituting diamines, the number of hydroxamate groups, and, in a few cases, C-terminal succinic to acetic acid substitution.

Having found a concise description for the composition of proferrioxamines, the next step is to refine the nomenclature to include sequence information and allow for substitutions. Borrowing from the corresponding convention in peptide chemistry, I suggest that the specific number sequence shall indicate the order of the constituting diamines when the proferrioxamine is written with the amino terminus at the left and the carboxyl terminus at the right. If, on the other hand, the diamine sequence is not known, this fact may be indicated by listing the numbers in parenthesis, e.g. $pFO_{(455)}$ would describe pFO G_2 in general, whereas pFO_{554} would specifically describe pFO

Cyclic proferrioxamines have, of course, no termini and thus more than one sequence of numbers may describe a cyclic proferrioxamine correctly. However, in order to be consistent with the IUPAC rule to always use the lowest possible numbers to describe the position of substitutions, it is suggested to start numbering with the shortest diamine. Thus pFO D_2 becomes pFO_{455c}, pFO X_7 becomes pFO_{355c} and pFO X_1 becomes pFO_{445c}. For the same reason, the numbering of acyclic proferrioxamines should start with the carboxyl (or carbonyl) terminus. Following these conventions, alcaligin (Nishio *et al.* 1988) (Figure 3) can be described as 8,18-dihydroxy-pFO_{44c}, and a number of substituted proferrioxamines such as pFO Et_3, pFO Te_3 and pFO P_1, recently obtained by directed fermentation (Meives *et al.* 1990) (Figure 3), can be described as 9-oxa-pFO_{555c}, 9,20,31-trithia-pFO_{555c} and 10-oxo-9-aza-pFO_{555c}, respectively.

What remains to be considered are those acyclic proferrioxamines, in which either the terminal amino or carboxyl group or both are derivatized. The description of these derivatives does not require special rules except the convention that the backbone proferrioxamine shall be the one consisting of complete succinylamino-hydroxyaminoalkane moieties. Thus the acetyl derivative of pFO G_1 may be described as Ac-pFO_{555}, pFO H as succinyl-pFO_{55Ac} and pFO D_1 as Ac-pFO_{555Ac}. Proferrioxamine I, which has been reported without data (Konetschny-Rapp 1990), could be described as pFO_{55}-NH-$(CH_2)_2$-COOH.

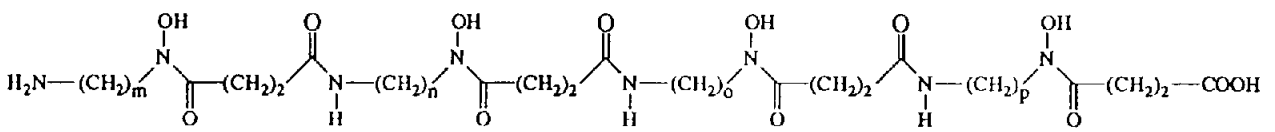

Figure 2. General structure of linear proferrioxamines. The hydroxamate and internal succinic acid groups are conserved, the number and sizes of the constituting succinylamino-hydroxyaminoalkane groups are variable.

Table 1. Comparison between the old and new nomenclature for proferrioxamines

pFO	Cyclic	m	n	o	p	N-terminal modification	C-terminal modification	Semirational nomenclature	Reference
A_1	—	5	5	4	0	—	Ac for Suc	pFO_{554Ac}	Keller-Schierlein *et al.* (1964)
A_2		5	4	4	0	—	Ac for Suc	pFO_{544Ac}	Keller-Schierlein *et al.* (1964)
B	—	5	5	5	0	—	Ac for Suc	pFO_{555Ac}	Keller-Schierlein *et al.* (1964)
D_1	—	5	5	5	0	Ac	Ac for Suc	Ac-pFO_{555Ac}	Keller-Schierlein *et al.* (1964)
D_2	+	4	5	5	0	—	—	pFO_{455c}	Keller-Schierlein *et al.* (1964)
E	+	5	5	5	0		—	pFO_{555c}	Keller-Schierlein *et al.* (1964)
G_1	—	5	5	5	0			pFO_{555}	Reissbrodt *et al.* (1990)
G_{2a}		5	5	4	0	—	—	pFO_{554}	Feistner *et al.* (1993b)
G_{2b}	—	5	4	5	0	—	—	pFO_{545}	Feistner *et al.* (1993b)
G_{2c}	—	4	5	5	0	—	—	pFO_{455}	Feistner *et al.* (1993b)
H	—	5	5	0	0	Suc	Ac for Suc	Suc-pFO_{55Ac}	Adapa *et al.* (1982)
T_1	+	5	5	5	5	—	—	pFO_{5555c}	Feistner *et al.* (1993b)
T_2	+	4	5	5	5	—	—	pFO_{4555c}	Feistner *et al.* (1993b)
T_3	+	3	5	5	5	—		pFO_{3555c}	Feistner *et al.* (1993b)
T_7	+	(4)	(4)	(5)	(5)	—	—	$pFO_{(4455)c}$	Feistner *et al.* (1993b)
T_8	+	3	3	3	5			pFO_{3335c}	Feistner *et al.* (1993b)
X_1	+	4	4	5	0	—	—	pFO_{445c}	Meives *et al.* (1990)
X_2	+	4	4	4	0	—	—	pFO_{444c}	Meives *et al.* (1990)
X_3	+	5	5	6	0	—	—	pFO_{556c}	Meives *et al.* (1990)
X_4	+	5	6*	6	0	—	—	22-desoxy-pFO_{566c}	Meives *et al.* (1990)
X_7	+	3	5	5	0			pFO_{355c}	Feistner *et al.* (1993b)

The subscripts m, n, o and p refer to the number of methylene units as shown in the general proferrioxamine structure given in Figure 2. Ac = acetyl; Suc = succinyl; an asterisk indicates lack of the corresponding *N*-hydroxy oxygen. The structures of proferrioxamines C and F (Bickel *et al.* 1960, Adapa *et al.* 1982), and X_8, X_9, T_4, T_5 and T_6 (Feistner *et al.* 1993) have not yet been determined.

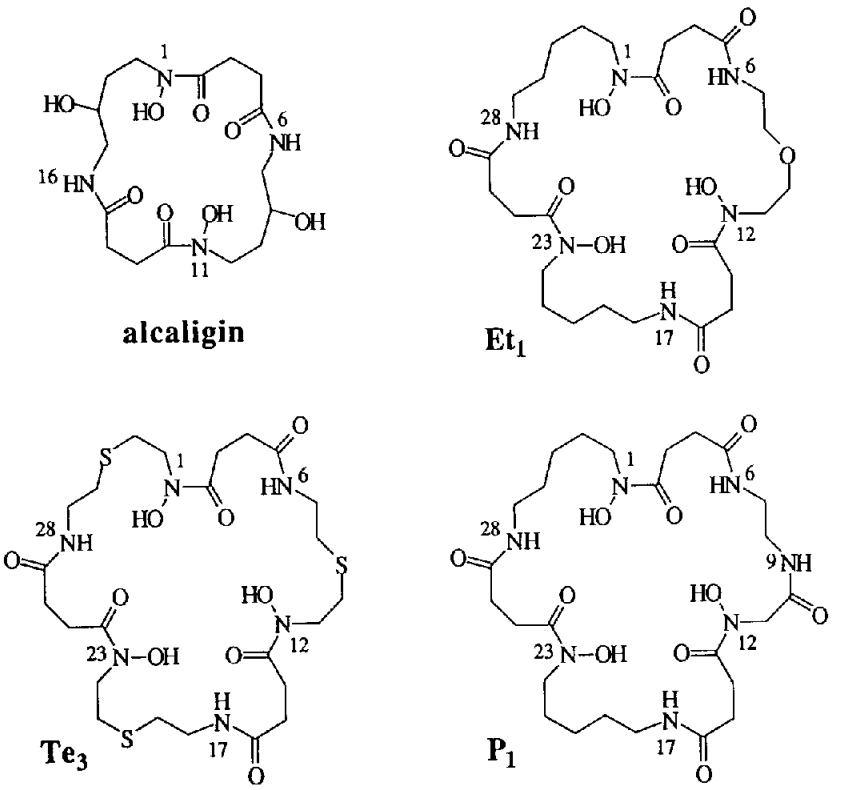

Figure 3. Structures of alcaligin, pFO Et_1, pFO Te_3 and pFO P_1.

References

Adapa S, Huber P, Keller-Schierlein W. 1982 Isolierung, Strukturaufklärung und Synthese von Ferrioxamin H. *Helv Chim Acta* **65**, 1818–1824.

Bickel H, Bosshardt R, Gäumann E, *et al.* 1960 Über die Isolierung und Charakterisierung der Ferrioxamine A-F, neuer Wuchsstoffe der Sideramin-Gruppe. *Helv Chim Acta* **43**, 2118–2128.

Feistner GJ, Korth H, Ko H, Pulverer G, Budzikiewicz H. 1983 Ferrorosamine A from *Erwinia rhapontici*. *Curr Microbiol* **8**, 239–243.

Feistner GJ, Gabrik AH, Beer SV. 1993a Application of capillary liquid chromatography-electrospray mass spectrometry to identify major siderophores of *Erwinia amylovora* as proferrioxamines and their potential role in virulence. In: Kado CI, Crosa JH, eds. *Molecular Mechanisms of Bacterial Virulence*. Dordrecht: Kluwer; 429–444.

Feistner GJ, Stahl DC, Gabrik AH. 1993b Proferrioxamine siderophores of *Erwinia amylovora*. A capillary liquid chromatographic/electrospray tandem mass spectrometric study. *Org Mass Spectrom* **28**, 163–175.

Hamana K, Matsuzaki S. 1992 Polyamines as a chemotaxonomic marker in bacterial systematics. *Crit Rev Microbiol* **18**, 261–283.

Keller-Schierlein W, Prelog V, Zähner H. 1964 Siderochrome (Natürliche Eisen(III)-trihydroxamat-Komplexe). *Prog Chem Org Nat Prod* **22**, 279–322.

Konetschny-Rapp S. 1990 *PhD thesis*, Eberhard-Karls-Universität Tübingen.

Meives J. 1989 *PhD thesis*, Eberhard-Karls-Universität Tübingen.

Meives J, Fiedler H-P, Zähner H, Konetschny-Rapp S, Jung G. 1990 Production of desferrioxamine E and new analogues by directed fermentation and feeding fermentation. *Appl Microbiol Biotechnol* **32**, 505–510.

Nishio T, Tanaka N, Hiratake J, Katsube Y, Ishida Y, Oda J. 1988 Isolation and structure of the novel dihydroxamate siderophore alcaligin. *J Am Chem Soc* **110**, 8733–8734.

Reissbrodt R, Rabsch W, Chapeaurouge A, Jung G, Winkelmann G. 1990 Isolation and identification of ferrioxamine G and E in *Hafnia alvei*. *Biol Met* **3**, 54–60.

Schupp T, Toupet C, Divers M. 1988 Cloning and expression of two genes of *Streptomyces pilosus* involved in the biosynthesis of the siderophore desferrioxamine B. *Gene* **64**, 179–188.

Wada H, Avelange-Macherel M-H, Murata N. 1993 The *desA* gene of the cyanobacterium *Synchocystis* sp. strain PCC6803 is the structural gene for Δ12 desaturase. *J Bacteriol* **175**, 6056–6058.