

N-Hydroxy Amides. Part 8.† Synthesis and Iron(III)-holding Properties of Di- and Tri-hydroxamic Acids Extending from Benzene-di- and -tri-carbonyl Units Through Oligo(ethyleneoxy) Arms

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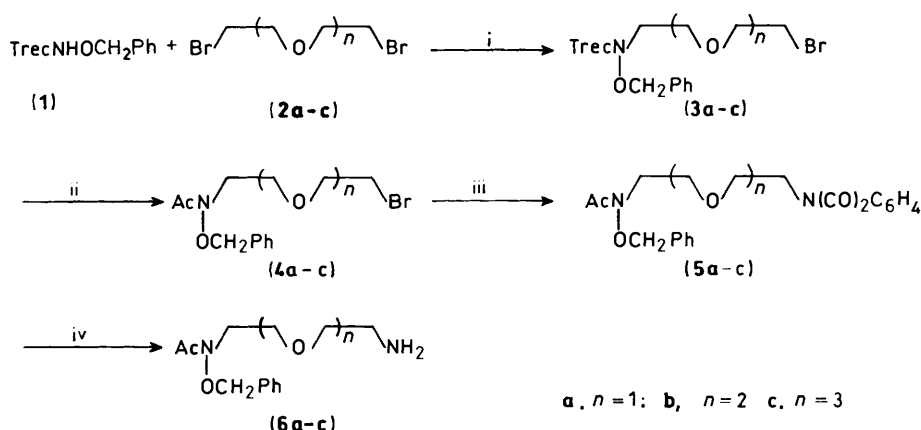
Benzene-ring centred di- and tri-hydroxamic acids (**9a–c** and **10a–c**) having oligo(ethyleneoxy) chains are prepared by reaction of benzene-di- and -tri-carbonyl chlorides with amino[oligo(ethyleneoxy)ethylhydroxylamine derivatives (**6a–c**). Trihydroxamic acids (**10a–c**) form more stable iron(III) complexes than dihydroxamic acids (**9a–c**) in several respects. In iron(III) transport experiments using a H₂O–CHCl₃/CCl₄ system, however, compounds (**9a–c**) show greater rates than compounds (**10a–c**). The number of ethyleneoxy units in the arm apparently influences these iron(III) holding properties and the iron-transport rates.

Synthetic iron-sequestering agents^{1–4} are of current interest for use as drugs or models of siderophores, naturally occurring iron-chelating compounds. Siderophores in general possess three functional groups of hydroxamate or catecholate type to form hexadentate, octahedral iron(III) complexes in order to solubilize the ion for cell membrane transport.^{5–9} In the design and synthesis of new iron-chelating agents, efforts have been directed to the utilization of these siderophore-ligating groups.^{1–4,10–15} In particular, several synthetic ligands contain a 1,3,5-trisubstituted benzene unit as a basic building block for making a trifunctional molecule.^{16–18} Benzene derivatives, such as this, tend to lose hydrophilicity which is a desirable property of siderophores. Ether linkages, however, have considerable affinity for water. We describe here an interesting combination of a rigid lipophilic benzene unit with hydroxamic acid units carrying flexible hydrophilic oligo(ethyleneoxy) chains. Under favourable circumstances, iron(III) transport through aqueous

Results and Discussion

Synthesis.—Benzene-ring centred di- (**9a–c**) and tri- (**10a–c**) hydroxamic acids were prepared by condensation of benzene-di- and -tri-carbonyl chlorides with amino[oligo(ethyleneoxy)]-hydroxylamine derivatives (**6a–c**). Scheme 1 depicts the synthesis of amino hydroxamic acid derivatives (**6a–c**).

Alkylation of *N*-trichloroethoxycarbonyl-*O*-benzylhydroxylamine (**1**)²⁰ with oligo(ethyleneoxy)ethyl dibromides (**2a–c**) in the presence of sodium hydride gave the monosubstituted products (**3a–c**) along with disubstituted ones. The mixtures were treated with zinc in acetic acid, allowed to react *in situ* with acetic anhydride, and then separated by column chromatography to give mono-*N*-acetyl-*N*-benzyloxy derivatives (**4a–c**) in good yields. Compounds (**4a–c**) were converted into phthaloylimido derivatives (**5a–c**). Treatment of compounds (**5a–c**) with methylamine gave oily amino[oligo(ethyleneoxy)]-hydroxylamine derivatives (**6a–c**) also in good yields. The

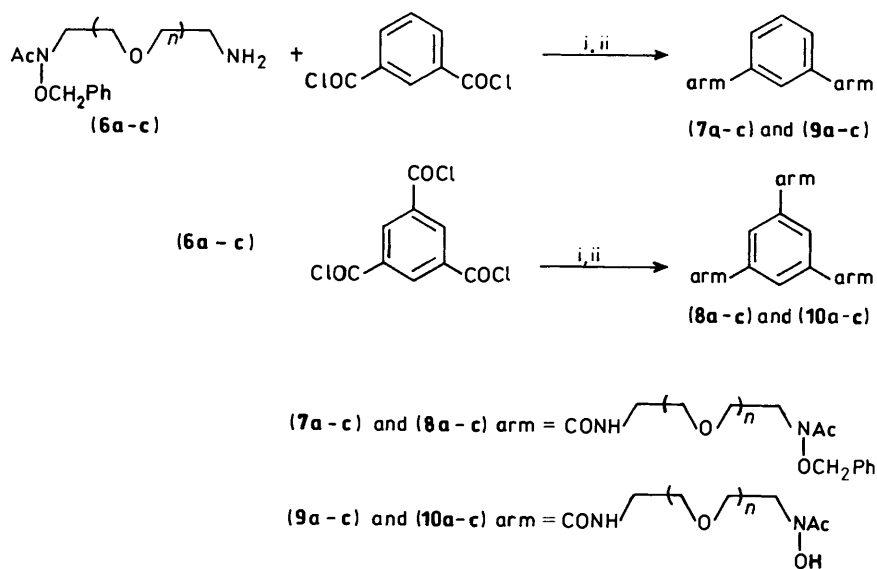


Scheme 1. Synthesis of amino[oligo(ethyleneoxy)ethylhydroxylamine derivatives (**6a–c**). Reaction conditions: (i) NaH in DMF; (ii) Ac₂O and Zn in AcOH; (iii) potassium phthalimide in DMF; (iv) 40% MeNH₂ in EtOH.

and organic phases may be carried out with these molecules as is often done by alkali-metal cation transport with crown- and related ethers.¹⁹

desired benzene-ring centred 1,3-di- (**9a–c**) and 1,3,5-tri- (**10a–c**) hydroxamic acids were obtained by reaction of benzene-1,3-di- and benzene-1,3,5-tri-carbonyl chlorides with amines (**6a–c**), after deprotection of the *O*-benzyl groups by hydrogenation (10% Pd–C). Hydroxamic acid derivatives (**9a–c**) and (**10a–c**) were viscous oils and soluble in methanol, DMF, and chloroform.

† Part 7, M. Akiyama, A. Katoh, and T. Mutoh, *J. Org. Chem.*, 1988, 53, 6089.



Scheme 2. Synthesis of benzene-ring centred di-(**9a-c**) and tri-(**10a-c**) hydroxamic acids. Reaction conditions: i, for (**7**), (**8**), (**9**), and (**10**), Et_3N in CH_2Cl_2 ; ii, for (**9**) and (**10**), H_2 -Pd/C in MeOH.

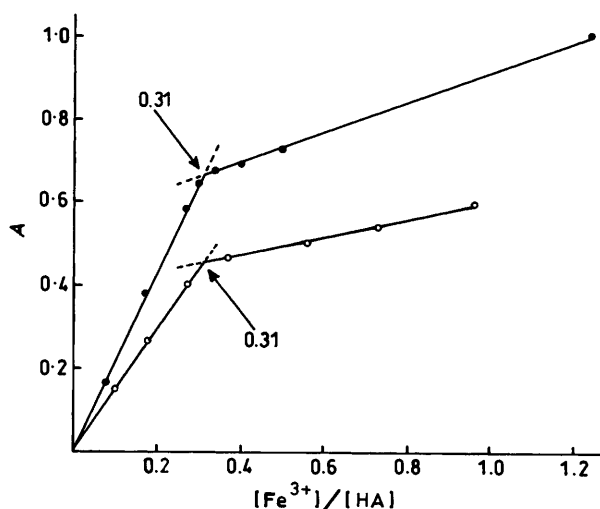


Figure 1. Plot of absorbance (A) vs. ratio of iron(III) to the hydroxamic acid unit (HA) for compounds (**9a**) (—○—) and (**10a**) (—●—) in 50% aqueous DMF at 25 °C; [**9a**] = 2.5×10^{-4} mol dm^{-3} at pH 7, [**10a**] = 2.9×10^{-4} mol dm^{-3} at pH 4.

Table 1. Data at the intersection in mole ratio plots for iron(III) complex formation.^a

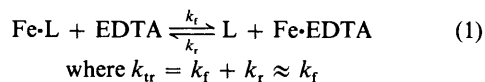
Compound	pH	Mole ratio	$\lambda_{\text{max}}/\text{nm}$	$\epsilon/\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$
(9a)	7	0.31	420	2 900
(9b)	7	0.25	420	3 300
(9c)	7	0.25	420	3 400
(10a)	4	0.31	424	2 400
(10b)	4	0.28	424	2 890
(10c)	4	0.29	424	2 830

^a Conditions: 50% aqueous DMF solution at 25 °C; compounds (**9a-c**) indicated the formation of 2:1 complexes at pH 4.

Iron(III) Complex Formation.—The iron(III)-complex-forming tendency of compounds (**9a-c**) and (**10a-c**) was examined in 50% aqueous DMF solution by plotting the absorbance at λ_{max} as a function of the mole ratio of iron(III) to the hydroxamic acid

group, as shown for representative examples (Figure 1). The results are summarized in Table 1. Compounds (**10a-c**) showed an intersection at a ratio of 0.3 both at pH 4 and 7, indicating formation of 1:3 complexes of iron(III) with the hydroxamic acid units. The 1:3 iron-complex formation is also supported by its characteristic λ_{max} and ϵ values.⁸ Compounds (**9a-c**) indicated formation of 1:2 iron(III) complexes at pH 4, but at pH 7 the 1:3 iron(III) complex was formed for compound (**9a**). The λ_{max} and ϵ values for compounds (**9b**) and (**9c**) indicated formation of a 1:3 iron(III) complex, although their mole ratios were 0.25. The differences are interpreted as being due to one hydroxamic acid group remaining uncomplexed when two molecules approach prior to complex formation.

Relative Stability of Iron(III) Complexes.—The pseudo-first-order rate constants (k_{tr}) of iron(III) exchange reactions from complexes to EDTA were obtained following a decrease in absorbance at 420 nm in the presence of a large excess of EDTA, and the results are summarized in Table 2. The exchange reactions are reversible,^{21,22} but under the present conditions we can estimate relative kinetic stability (k_f) for these complexes from the initial rates (k_{tr}) of iron(III) transfer from Fe-ligand to EDTA [equation (1)]. Compounds (**10a-c**) hold iron(III) more



firmly than compounds (**9a-c**), which is attributed to the entropically favourable (relative to intermolecular complexation) intramolecular complexation. The relative stability falls in order of (**10b**) > (**10a**) > (**10c**) for the trihydroxamic acid series, and (**9a**) > (**9b**) > (**9c**) for the dihydroxamic acid series. Differences in the number of ethyleneoxy units of the hydroxamic acid arms affect the stability of complexes formed, although the optimum length of the arms is different for each type of ligand, *i.e.* di- or tri-substituted benzenes. The iron(III)-holding capacity of these benzene derivatives is not strong. Table 2 also contains data for a siderophore, deferriferrioxamine B, at pH 5.3. The benzene derivatives release the ion much more readily at pH 5.3, so the experiments were carried out at pH 6.75. Proton-assisted iron(III)-exchange reactions have been demonstrated.²²

Table 2. Iron(III) exchange reactions with EDTA.^a

Ligand (L)	k_{tr}/s^{-1}	Relative rate
(9a)	1.0×10^{-2}	36
(9b)	1.5×10^{-2}	54
(9c)	1.6×10^{-2}	57
(10a)	1.3×10^{-3}	4.6
(10b)	2.8×10^{-4}	1
(10c)	9.0×10^{-4}	3.2
DFB ^b	7.1×10^{-5c}	

^a An exchange reaction rate (k_{tr}) was observed under the pseudo-first-order conditions; $[Fe-L]_0 = 9 \times 10^{-5} \text{ mol dm}^{-3}$, $[EDTA]_0 = 1.7 \times 10^{-3} \text{ mol dm}^{-3}$ at pH 6.75 in tris-HCl buffer at 25 °C. ^b DFB, deferriferrioxamine B. ^c See ref. 10; $[Fe-DFB]_0 = 3.2 \times 10^{-5} \text{ mol dm}^{-3}$, $[EDTA]_0 = 8.3 \times 10^{-4} \text{ mol dm}^{-2}$ at pH 5.3 in acetate buffer at 25 °C.

Electrochemistry of Iron(III) Complexes.—The electrochemical properties of iron(III) complexes²³ of compounds (10a–c) were determined by cyclic voltammetry to give unsymmetrical waves, and the results are summarized in Table 3. Electron-transfer processes are not reversible since ΔE_p values are smaller than 60 mV and i_{pc}/i_{pa} ratios are larger than unity. Their standard redox potentials (E_3°) are somewhat higher than that of an *N*-benzoyl derivative of ferrioxamine B, hence they are less stable. Values of smaller ΔE_p suggest the adsorption of the complexes on to the carbon electrode through a benzene ring, as suggested for the *N*-terminus benzoyl derivative of ferrioxamine B.¹¹

Iron(III) Transport.—We thought that a molecule having both lipophilic and hydrophilic moieties would be favourable for transport experiments between aqueous and organic phases. Experiments of this kind are rare. Emery conducted iron(III) transport (passage) by ferrichrome or ferrichrome A through a water–benzyl alcohol–chloroform system at 55 °C.²⁴ Present iron complexes were much too soluble in the benzyl alcohol–chloroform mixture. A less polar organic layer was needed. Two types of experiments, extraction and transport, were performed [apparatus shown in Figure 2(a) and (b)]. Iron(III) transport through $CHCl_3/CCl_4$ liquid membrane coupled with an ascorbic acid–ferrous complex agent [3-(2-pyridyl)-5,6-bis(4-sulphophenyl)-1,2,4-triazine] system was carried out at 25 °C, and the results are summarized in Table 4. In iron(III) transport, a metal complex in the source phase (pH 6.7) moves across the liquid membrane to the receiving phase (pH 2.6), where the metal is reduced by ascorbic acid and trapped by the complexing agent as iron(II). The concentration of iron(II) in the receiving phase was determined by absorbance at 562 nm, characteristic of the iron(II) complex. Iron(III) was completely transported across the liquid membrane when subjected to these reducing conditions, as demonstrated with (10a). For the apparatus in Figure 2(b), it must be noted that the area from B to C is 3 times larger than that from A to B. In extraction experiments the equilibrium was attained within 3–5 h, and the position of the equilibrium varied with different complexes. It was observed that the reduction was rapid and complete within minutes and that the transport tendency paralleled the extraction tendency. It may be said that a critical factor for the present iron(III) transport is the initial transfer of an iron(III) complex from aqueous to organic phases and not the formation of a strong iron(III) complex, although the entrance to the organic phase is narrower than the exit from it. It is difficult to compare the efficiency of the present iron(III) passage with that of the previous example²⁴ because of differences in experimental conditions. It seems that the present compounds are more suitable to this kind of transport, since the liquid membrane is less polar.

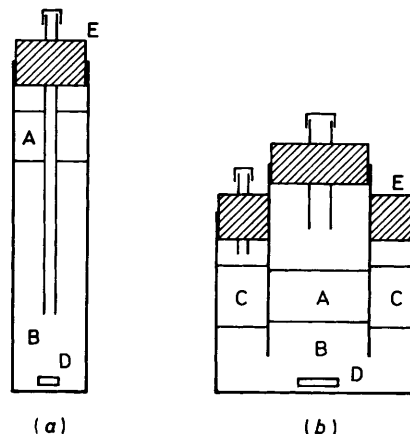


Figure 2. Apparatus for ion extraction (a) and transport (b) experiments: A, phase I (source phase); B, phase II (membrane phase); C, phase III (receiving phase); D, magnetic stirring bar; E, silicon cap. For (b): A, 1.8 cm²; C, 5.4 cm².

Table 3. Cyclic voltammetry for iron(III) complexes.^a

Ferric complex	E_3° vs. SCE/mV	ΔE_p /mV	i_{pc}/i_{pa}
(10a)–Fe(III)	–615	30	1.9
(10b)–Fe(III)	–640	45	1.3
(10c)–Fe(III)	–630	40	1.9
<i>N</i> -Benzoyl-DFB ^b –Fe(III)	–710	35	1.3

^a Conditions: electrode, basal plain graphite (0.196 cm²); ferric complex concentration, ca. 1 mmol dm⁻³ in 1 mol dm⁻³ KCl with 0.1 mol dm⁻³ KH_2PO_4 –0.05 mol dm⁻³ $Na_2B_4O_7$ buffer solution at pH 7.0. ^b DFB, deferriferrioxamine B; reported in ref. 11.

Table 4. Iron(III) transport through a $CHCl_3/CCl_4$ liquid membrane.

Ferric complex	Extraction ^a (%)	Transport ^b (%)
(9a)–Fe(III)	25	38
(9b)–Fe(III)	16	32
(9c)–Fe(III)	12	16
(10a)–Fe(III)	9	12 ^c
(10b)–Fe(III)	5	10
(10c)–Fe(III)	13	25

^a At equilibrium (after 3–5 h); carried out in an apparatus shown in Figure 2(a). ^b After 3 h; in an apparatus shown in Figure 2(b). ^c Fe(III) was completely transported after 70 h.

Experimental

M.p.s are uncorrected. I.r. spectra were recorded on JASCO Model A-302 and FT/IR-5M spectrometers. ¹H N.m.r. spectra were obtained on a JEOL JNM-FX 200 spectrometer with $SiMe_4$ as an internal standard in $CDCl_3$. U.v. spectra were recorded on a Hitachi 320 A spectrometer. The pH of solutions was measured with a TOA Model HM-20B digital pH meter. T.l.c. was carried out using Merck silica gel 60 F₂₅₄. Gel chromatography was performed using Sephadex LH-20 with methanol as the eluant, and Wako gel C-300 was used for column chromatography. *O*-Benzyl-*N*-trichloroethoxycarbonylhydroxylamine (1)²⁰ was prepared according to the literature. *N,N*-Dimethylformamide (DMF) was treated with both BaO and ninhydrin before use.

***O*-Benzyl-*N*-(11-bromo-3,6,9-trioxaundecyl)-*N*-(trichloroethoxycarbonyl)hydroxylamine (3c).**—Sodium hydride (4.8 g, 12 mmol) was washed with dry hexane with stirring under a nitrogen atmosphere, and hexane was removed by decantation.

O-Benzyl-*N*-trichloroethoxycarbonylhydroxylamine (1) (3 g, 10 mmol) in DMF (10 cm³) was added dropwise to a suspension of NaH in DMF (15 cm³) with stirring at -18 °C; the mixture was stirred for a further 0.5 h. This was added to a solution of 1,11-dibromo-3,6,9-trioxaundecane (2c) (3.2 g, 10 mmol) in DMF (15 cm³), and the mixture was stirred at -18 °C for 1 h, and then overnight at room temperature. DMF was removed under reduced pressure to give an oil, which was dissolved in AcOEt. The organic layer was washed with H₂O, dried (Na₂SO₄), and evaporated to give a crude product (3c), which was chromatographed on silica gel with benzene-AcOEt (8:1), 3.3 g (71%); *R*_F 0.34 (AcOEt-benzene 1:6) (Found: C, 38.75; H, 4.75; N, 2.3. C₁₈H₂₅Br-Cl₃NO₆·H₂O requires C, 38.9; H, 4.9; N, 2.5%); *v*_{max}(neat) 1 721, 1 134, 748, and 700 cm⁻¹; *δ*_H 3.45 (2 H, t), 3.66 (12 H, m), 3.76 (2 H, t), 4.80 (2 H, s), 4.96 (2 H, s), and 7.36 (5 H, s).

General Procedure for Compounds (4a-c).—A typical example: *N*-Acetyl-*O*-benzyl-*N*-(5-bromo-3-oxapentyl)hydroxylamine (4a). Compound (1) (4.5 g, 15 mmol) was treated with 1,5-dibromo-3-oxapentane (2a) (3.5 g, 15 mmol) in the presence of NaH (720 mg, 18 mmol) in DMF (60 cm³) as above. A mixture of *O*-benzyl-*N*-(5-bromo-3-oxapentyl)-*N*-(trichloroethoxycarbonyl)hydroxylamine (3a) and 1,5-di[trichloroethoxycarbonyl(benzyloxy)amino]-3-oxapentane obtained (total 5.8 g) was used directly for further reaction. The mixture (5.8 g) and acetic anhydride (2.6 g, 25 mmol) in acetic acid (70 cm³) was treated with Zn dust (8.4 g) with stirring for 4 h at room temperature. Filtration of the catalyst, followed by evaporation of acetic acid under reduced pressure gave a residue, which was taken up in chloroform. The organic layer was washed consecutively with saturated aqueous Na₂CO₃ and H₂O, dried (MgSO₄), and evaporated to give a residue, which was chromatographed on silica gel with AcOEt-hexane (1:1) to afford (4g), 1.8 g overall yield 38%; *R*_F 0.31 (AcOEt-hexane 2:1) (Found: C, 48.9; H, 5.85; N, 4.3. C₁₃H₁₈BrNO₃ requires C, 49.4; H, 5.75; N, 4.45%); *v*_{max}(neat) 1 670, 1 120, 750, and 700 cm⁻¹; *δ*_H 2.08 (3 H, s), 3.43 (2 H, t), 3.67 (4 H, t), 3.76 (2 H, t), 4.90 (2 H, s), and 7.39 (5 H, s). *N*-Acetyl-*O*-benzyl-(8-bromo-3,6-dioxaoctyl)hydroxylamine (4b), yield 37%; *R*_F 0.33 (AcOEt-hexane 2:1) (Found: C, 50.25; H, 6.05; N, 4.0. C₁₃H₂₂BrNO₄ requires C, 50.0; H, 6.1; N, 3.9%); *v*_{max}(neat) 1 665, 1 200, 750, and 700 cm⁻¹; *δ*_H 2.08 (3 H, s), 3.43 (2 H, t), 3.67 (8 H, m), 3.79 (2 H, t), 4.89 (2 H, s), and 7.39 (5 H, s). *N*-Acetyl-*O*-benzyl-*N*-(11-bromo-3,6,9-trioxaundecyl)hydroxylamine (4c), yield 49%; *R*_F 0.28 (AcOEt-hexane 2:1) (Found: C, 50.65; H, 6.35; N, 3.5. C₁₇H₂₆BrNO₅ requires C, 50.5; H, 6.5; N, 3.5%); *v*_{max}(neat) 1 650, 1 130, 755, and 700 cm⁻¹; *δ*_H 2.11 (3 H, s), 3.41 (2 H, t), 3.61 (12 H, m), 3.80 (2 H, t), 4.89 (2 H, s), and 7.35 (5 H, s).

General Procedure for Compounds (5a-c).—A typical example: *N*-acetyl-*O*-benzyl-*N*-(11-phthalimido-3,6,9-trioxaundecyl)hydroxylamine (5c). Compound (4c) (1.35 g, 3.3 mmol) and potassium phthalimide (750 mg, 4 mmol) in DMF (22 cm³) were heated at 120 °C for 18 h, and evaporated under reduced pressure to give a residue, which was dissolved in chloroform. The chloroform layer was washed consecutively with 0.1 mol dm⁻³ NaOH and H₂O, and dried (MgSO₄). Evaporation of the solvent gave (5c) as a colourless oil (1.5 g, 96%); *R*_F 0.18 (AcOEt-hexane 2:1) (Found: C, 62.85; H, 6.4; N, 5.85. C₂₅H₃₀N₂O₇·½H₂O requires C, 62.6; H, 6.5; N, 5.85%); *v*_{max}(neat) 1 773, 1 715, 1 665, 1 110, 758, 722, and 699 cm⁻¹; *δ*_H 2.07 (3 H, s), 3.05 (2 H, t), 3.15 (12 H, m), 3.35 (2 H, t), 4.89 (2 H, s), 7.35 (5 H, s), 7.69 (2 H, m), and 7.85 (2 H, m).

N-Acetyl-*O*-benzyl-*N*-(5-phthalimido-3-oxapentyl)hydroxylamine (5a). (97%), m.p. 76–77 °C; *R*_F 0.38 (AcOEt-hexane 2:1) (Found: C, 65.5; H, 5.65; N, 7.3. C₂₁H₂₂N₂O₅ requires C, 66.0; H, 5.8; N, 7.35%); *v*_{max}(KBr) 1 775, 1 710, 1 670, 1 120, 750, 710,

and 700 cm⁻¹; *δ*_H 2.07 (3 H, s), 3.05 (2 H, t), 3.13 (4 H, t), 3.43 (2 H, t), 4.85 (2 H, s), 7.34 (5 H, s), 7.68 (2 H, m), and 7.85 (2 H, m).

N-Acetyl-*O*-benzyl-*N*-(8-phthalimido-3,6-dioxaoctyl)hydroxylamine (5b) (98%), *R*_F 0.26 (AcOEt-hexane 2:1); *v*_{max}(CCl₄) 1 775, 1 710, 1 670, 1 120, 710, and 700 cm⁻¹; *δ*_H 2.07 (3 H, s), 3.05 (2 H, t), 3.13 (8 H, m), 3.34 (2 H, t), 4.87 (2 H, s), 7.34 (5 H, s), 7.69 (2 H, m), and 7.85 (2 H, m).

General Procedure for Compounds (6a-c).—A typical example: *N*-acetyl-*N*-(11-amino-3,6,9-trioxaundecyl)-*O*-benzylhydroxylamine (6c). Compound (5c) (1.9 g, 4 mmol) and methylamine (40% aqueous solution; 1.9 g, 23.9 mmol) were dissolved in ethanol (25 cm³); the mixture was stirred for 36 h at room temperature, and evaporated to give a residue, which was taken up in dichloromethane, washed with H₂O, and then dried (MgSO₄). An oil was obtained on removal of the solvent, which was chromatographed on silica gel with chloroform-methanol (4:1) to give *N*-[11-acetyl(benzyloxy)amino-3,6,9-trioxaundecyl]-*N'*-methylbenzene-1,2-dicarboxamide (840 mg) and (6c). The former (840 mg, 1.7 mmol) and 40% methylamine (1 g, 12.6 mmol) in ethanol was stirred for 60 h at room temperature. A similar work-up as that described above gave additional (6c) (240 mg). The combined yield was 0.8 g (58%); *R*_F 0.13 (CHCl₃-MeOH 7:1) (Found: C, 59.5; H, 8.15; N, 8.1. C₁₇H₂₈N₂O₅ requires C, 60.0; H, 8.3; N, 8.25%); *v*_{max}(neat) 3 350, 1 660, 1 115, 760, and 700 cm⁻¹; *δ*_H 2.08 (3 H, s), 2.33 (2 H, br s), 3.50 (2 H, t), 3.62 (12 H, m), 3.82 (2 H, t), 4.87 (2 H, s), and 7.39 (5 H, s).

N-Acetyl-*N*-(5-amino-3-oxapentyl)-*O*-benzylhydroxylamine (6a): 50%; *R*_F 0.19 (CHCl₃-MeOH 7:1); *v*_{max}(neat) 3 420, 1 640, 755, and 700 cm⁻¹; *δ*_H 1.97 (2 H, br s), 2.09 (3 H, s), 2.83 (2 H, t), 3.50 (2 H, t), 3.66 (2 H, t), 3.81 (2 H, t), 4.87 (2 H, s), and 7.39 (5 H, s).

N-Acetyl-*N*-(8-amino-3,6-dioxaoctyl)-*O*-benzylhydroxylamine (6b), 61%; *R*_F 0.18 (CHCl₃-hexane 7:1); *v*_{max}(neat) 3 350, 1 655, 1 110, 755, and 700 cm⁻¹; *δ*_H 1.60 (2 H, br s), 2.11 (3 H, s), 3.51 (2 H, t), 3.63 (8 H, m), 4.72 (2 H, s), and 7.38 (5 H, s).

General Procedure for Compounds (7a-c) and (8a-c).—A typical example: *N,N,N'*-tris[11-acetyl(benzyloxy)amino-3,6,9-trioxaundecyl]benzene-1,3,5-tricarboxamide (8c). A mixture of compound (6c) (260 mg, 0.8 mmol) and triethylamine (71 mg, 0.7 mmol) in dichloromethane (15 cm³) was cooled to 0 °C. Benzene-1,3,5-tricarbonyl chloride (61 mg, 0.2 mmol) in dichloromethane (5 cm³) was added dropwise to the mixture with vigorous stirring. The mixture was stirred for 1 h at 0 °C and for 2 h at room temperature, washed consecutively with 5% NaHCO₃ and H₂O, dried (MgSO₄), and evaporated. The residue was chromatographed on silica gel with chloroform-methanol (15:1) to give (8c) as a viscous oil, (234 mg, 86%); *R*_F 0.35 (CHCl₃-MeOH 15:1) (Found: C, 60.3; H, 7.15; N, 7.2. C₆₀H₈₄N₆O₁₈·H₂O requires C, 60.3; H, 7.25; N, 7.05%); *v*_{max}(neat) 3 300, 1 660, 1 110, 845, 755, and 700 cm⁻¹; *δ*_H 2.05 (9 H, s), 3.60 (42 H, m), 3.76 (6 H, t), 4.84 (6 H, s), 7.35 (18 H, s), and 8.43 (3 H, s).

N,N,N'-Tris[5-acetyl(benzyloxy)amino-3-oxapentyl]benzene-1,3,5-carboxamide (8a): 90%; *R*_F 0.32 (CHCl₃-MeOH 20:1) (Found: C, 62.5; H, 6.62; N, 9.15. C₄₈H₆₀N₆O₁₂·½H₂O requires C, 62.55; H, 6.65; N, 9.1%); *v*_{max}(neat) 3 290, 1 645, 1 110, 840, 745, and 695 cm⁻¹; *δ*_H 2.03 (9 H, s), 3.65 (18 H, m), 3.81 (6 H, m), 4.83 (6 H, s), 7.33 (18 H, s), and 8.52 (3 H, s).

N,N,N'-Tris[8-acetyl(benzyloxy)amino-3,6-dioxaoctyl]benzene-1,3,5-tricarboxamide (8b): 96%; *R*_F 0.56 (CHCl₃-MeOH 7:1) (Found: C, 61.65; H, 7.05; N, 8.0. C₅₄H₇₂N₆O₁₅ requires C, 62.05; H, 6.95; N, 8.05%); *v*_{max}(neat) 3 300, 1 660, 1 120, 850, 760, and 700 cm⁻¹; *δ*_H 2.05 (9 H, s), 3.60 (36 H, m), 4.84 (6 H, t), 7.29 (15 H, s), 7.67 (3 H, br s), and 8.47 (3 H, s).

Compounds (7a-c) were prepared by reaction of compounds (6a-c) with benzene-1,3-carbonyl chloride.

N,N'-Di[5-acetyl(benzyloxy)amino-3-oxapentyl]benzene-1,3-dicarboxamide (**7a**): 88%; R_F 0.4 (CHCl₃-MeOH 15:1) (Found: C, 61.95; H, 6.6; N, 8.8. C₃₄H₄₂N₄O₈· $\frac{3}{2}$ H₂O requires C, 61.7; H, 6.85; N, 8.45%); ν_{max} (neat) 3 335, 1 660, 1 120, 755, and 699 cm⁻¹; δ_H 2.03 (6 H, s), 3.64 (12 H, m), 3.82 (4 H, m), 4.83 (4 H, s), 7.31 (2 H, br s), 7.34 (10 H, s), 7.48 (1 H, t), 8.09 (2 H, dd), and 8.32 (1 H, t).

N,N'-Di[8-acetyl(benzyloxy)amino-3,6-dioxaoctyl]benzene-1,3-dicarboxamide (**7b**): 85%; R_F 0.49 (CHCl₃-MeOH 15:1); ν_{max} (neat) 3 340, 1 660, 1 115, 755, and 699 cm⁻¹; δ_H 2.06 (6 H, s), 3.61 (20 H, m), 3.80 (4 H, m), 4.84 (4 H, s), 7.36 (10 H, s), 7.40 (2 H, br s), 7.47 (1 H, t), 8.01 (2 H, dd), and 8.34 (1 H, t).

N,N'-Di[11-acetyl(benzyloxy)amino-3,6,9-trioxaundecyl]benzene-1,3-dicarboxamide (**7c**): 82%; R_F 0.49 (CHCl₃-MeOH 10:1); ν_{max} (neat) 3 340, 1 660, 1 110, 755, and 699 cm⁻¹; δ_H 2.06 (6 H, s), 3.62 (28 H, m), 3.77 (4 H, m), 4.85 (4 H, s), 7.30 (2 H, br s), 7.36 (10 H, s), 7.47 (1 H, t), 7.97 (2 H, dd), and 8.27 (1 H, t).

General Procedure for Compounds (9a-c) and (10a-c).—A typical example: N,N',N''-tris[8-acetyl(hydroxy)amino-3,6-dioxaoctyl]benzene-1,3,5-tricarboxamide (**10b**).—Compound (**8b**) (315 mg, 0.3 mmol) in methanol (20 cm³) was treated with 10% Pd-C (40 mg) and hydrogen under atmospheric pressure for 6 h at room temperature. Filtration to remove the catalyst and evaporation of the solvent gave a crude product (**10b**), which was chromatographed on silica gel with chloroform-methanol (9:1) and further by gel chromatography with methanol (162 mg, 72%), R_F 0.3 (CHCl₃-MeOH 7:1) (Found: C, 50.85; H, 7.05; N, 10.55. C₃₃H₅₄N₆O₁₅ requires C, 51.15; H, 7.0; N, 10.85%); ν_{max} (neat) 3 350, 1 635, and 1 120 cm⁻¹; δ_H 2.03 (9 H, s), 3.63 (30 H, m), 3.74 (6 H, t), 7.93 (3 H, br s), and 8.49 (3 H, s).

N,N'-Di[5-acetyl(hydroxy)amino-3-oxapentyl]benzene-1,3-dicarbamide (**9a**): 69%; R_F 0.38 (CHCl₃-MeOH 9:1); ν_{max} (neat) 3 280, 1 631, and 1 127 cm⁻¹; δ_H 2.10 (9 H, s), 3.63 and 3.76 (16 H, m), 7.56 (1 H, t), 7.76 (1 H, br s), 7.88 (1 H, br s), 8.07 (2 H, t), 8.68 (1 H, br s), and 9.33 (3 H, s).

N,N'-Di[8-acetyl(hydroxy)amino-3,6-dioxaoctyl]benzene-1,3-dicarboxamide (**9b**): 80%; R_F 0.43 (CHCl₃-MeOH 7:1) (Found: C, 50.4; H, 7.05; N, 10.15. C₂₄H₃₈N₄O₁₀· $\frac{3}{2}$ H₂O requires C, 50.6; H, 7.25; N, 9.85%); ν_{max} (neat) 3 300, 1 631, and 1 113 cm⁻¹; δ_H 2.04 (6 H, s), 3.62 (24 H, m), 7.49 (1 H, t), 7.76 (1 H, br s), 7.88 (1 H, br s), 8.02 (2 H, t), and 8.36 (1 H, br s).

N,N'-Di[11-acetyl(hydroxy)amino-3,6,9-trioxaundecyl]benzene-1,3-dicarboxamide (**9c**): 74%; R_F 0.46 (CHCl₃-MeOH 7:1) (Found: C, 51.2; H, 7.15; N, 8.6. C₂₈H₄₆N₄O₁₂· $\frac{3}{2}$ H₂O requires C, 51.15; H, 7.5; N, 8.5%); ν_{max} (neat) 3 300, 1 635, and 1 110 cm⁻¹; δ_H 2.06 (6 H, s), 3.65 (32 H, m), 7.47 (1 H, t), 7.60 (1 H, br s), 7.96 (2 H, t), 8.30 (1 H, br s), and 8.88 (1 H, br s).

N,N',N''-Tris[5-acetyl(hydroxy)amino-3-oxapentyl]benzene-1,3,5-tricarboxamide (**10a**): 77%; R_F 0.24 (CHCl₃-MeOH 7:1) (Found: C, 49.2; H, 6.55; N, 12.7. C₂₇H₄₂N₆O₁₂·H₂O requires C, 49.1; H, 6.7; N, 12.7%); ν_{max} (neat) 3 350, 1 640, and 1 130 cm⁻¹; δ_H 2.03 (9 H, s), 3.61 (6 H, t), 3.65 (6 H, t), 3.69 (6 H, t), 3.77 (6 H, t), 8.18 (3 H, br s), and 8.52 (3 H, s).

N,N',N''-Tris[11-acetyl(hydroxy)amino-3,6,9-trioxaundecyl]benzene-1,3,5-tricarboxamide (**10c**): 66%; R_F 0.34 (CHCl₃-MeOH 8:1) (Found: C, 51.15; H, 7.3; N, 9.0. C₃₉H₆₆N₆O₁₈· $\frac{1}{2}$ H₂O requires C, 51.15; H, 7.35; N, 9.15%); ν_{max} (neat) 3 350, 1 635, and 1 105 cm⁻¹; δ_H 2.06 (9 H, s), 3.63 (42 H, m), 3.72 (6 H, t), 7.82 (3 H, br s), and 8.44 (3 H, s).

Mole-ratio Determination of Iron(III) Complexes.—To a solution (2.5–4.5 × 10⁻³ mol dm⁻³; 1 cm³) of each compound (**9a-c**) and (**10a-c**) in DMF, was added an appropriate amount of an aqueous ferric nitrate solution (3.01 × 10⁻³ mol dm⁻³) and an equal volume of DMF to the ferric solution. KNO₃ (1.0 cm³; 0.2 mol dm⁻³) was added to make a 50% aqueous solution of constant ionic strength. The pH of the solution was adjusted to

an apparent pH value, 4 or 7, by adding 0.01 or 0.1 mol dm⁻³ KOH. The resulting solution was diluted to a volume of 10.0 cm³ with 50% aqueous DMF. After 2 h the visible spectrum of the solution was measured. The absorbance at λ_{max} (usually 424 nm) was plotted as a function of the mole ratio of iron(III) to the hydroxamic acid group (Figure 1).

Iron(III) Exchange Reactions with EDTA.—A sample solution of each compound (**9a-c**) and (**10a-c**) in DMF was prepared; 4.5 × 10⁻³ mol dm⁻³ for compounds (**9a-c**) and 3.0 × 10⁻³ mol dm⁻³ for compounds (**10a-c**). In a 5.0 cm³ flask were placed a sample solution (1.5 cm³), KNO₃ (0.2 mol dm⁻³; 1.5 cm³), an appropriate amount of ferric nitrate solution (1.7 × 10⁻² mol dm⁻³) and a volume of DMF equal to that of the ferric solution. The resulting solution was adjusted to pH 7.0 and diluted with 50% aqueous DMF to 5.0 cm³ (solution A, [iron complex] = 9.0 × 10⁻⁴ mol dm⁻³). An EDTA solution in buffer was prepared by dissolving EDTA Na₂·2H₂O in tris-HCl buffer (ionic strength 0.2, pH 6.76) to give a concentration of 1.9 × 10⁻² mol dm⁻³ (solution B). In a cell were mixed solution A (0.3 cm³) and solution B (2.7 cm³) and the iron(III) exchange reaction was monitored at 25 °C and the decrease in absorbance at 420 nm was observed. The pseudo-first-order rate constant (k_t) was obtained from the plot of ln[(OD₀ - OD_∞)]/[(OD_t - OD_∞)] versus time.

Cyclic Voltammetry of the Iron(III) Complexes.—To a 5.0 cm³ aliquot of a solution of each compound [**10(a-c)**] in DMF (2.3 × 10⁻² mol dm⁻³) was added 0.93 equivalent of an aqueous Fe(NO₃)₃ solution. The resulting solution was adjusted to pH 7. After 2 h at room temperature, the solvent was evaporated. To the residue were added potassium chloride (746 mg), potassium dihydrogenphosphate (79 mg), and sodium tetraborate (80 mg). After filtration to remove insoluble materials, the filtrate was adjusted to pH 7.0 and diluted to a volume of 10.0 cm³ with H₂O. Cyclic voltammetry was carried out for these solutions generating triangular waves at an ambient temperature. A carbon electrode was used together with a saturated calomel electrode as a reference and a platinum wire as an auxiliary electrode.

Extraction of Iron(III) Complexes.—In a cylindrical tube, as shown in Figure 2(a), the aqueous phase I contained a phosphate buffer solution (1 cm³; pH 6.7) of an iron(III) complex of compounds (**9a-c**) and (**10a-c**) (7.0 × 10⁻⁴ mol dm⁻³), and the lower phase II contained chloroform (4.0 cm³) and carbon tetrachloride (4.0 cm³). Both phases were stirred constantly at 25 °C. The concentration of the iron(III) complex in phase II was determined by measurement of the absorbance of an aliquot of the solution (3.0 cm³) at 420 nm at appropriate intervals; the solution was returned to phase II through a central glass tube by a syringe. When equilibrium was reached an aliquot (0.5 cm³) of aqueous phase I was taken out, and diluted to 5.0 cm³. The concentration of iron(III) complex of the solution was determined by means of visible spectroscopy.

Iron(III) Transport.—In a cylindrical glass cell, shown in Figure 2(b), the inner aqueous phase I contained an iron(III) complex (7.0 × 10⁻⁴ mol dm⁻³; pH 6.7; 1.0 cm³) for compounds (**9a-c**) and (**10a-c**) and the outer aqueous phase III contained 3-(2-pyridyl)-5,6-bis(4-sulphophenyl)-1,2,4-triazine (5.0 mmol dm⁻³; 4.0 cm³) and ascorbic acid (100 mmol dm⁻³; 4.0 cm³) (pH = 2.6). The two phases were separated by the lower phase II which contained a chloroform-carbon tetrachloride mixture (1:1 v/v; 8 cm³). Each phase was stirred at a constant rate and 25 °C. After 3 h, an aliquot (2.5 cm³) of phase III was collected, and the concentration of iron was determined by the absorbance 562

nm. As a typical run, the transport was followed for the (10a)-iron(III) complex at appropriate time intervals and complete transfer was confirmed.

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