Synthesis of Linear and Cyclic Trihydroxamic Acids as Models for Ferrioxamines E and G

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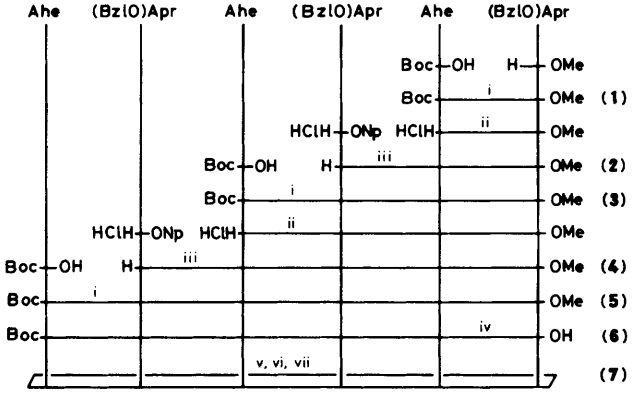
Linear and cyclic trihydroxamic acids including the 6-aminohexanoyl-3-(hydroxyamino)propanoyl sequence have been synthesized in a stepwise manner from the appropriately protected acyl derivatives and used as iron(III) chelating compounds.

There is keen interest in synthetic iron sequestering compounds for use as drugs or models of naturally occurring compounds.[1—3] Ferrioxamines, an important class of microbial iron transport agents, are stable octahedral iron(III) complexes of linear and cyclic trihydroxamic acids (deferriferrioxamines).[4,5] The methanesulphonate salt of deferriferrioxamine B (DFB) is used as the drug of choice in treating iron overload.[5] A characteristic structural feature of the trihydroxamic acids is the presence of repeating 1-amino-5-(hydroxyamino)pentane and succinic acid units.[5] It is possible to design and synthesize trihydroxamic acids of a similar nature but of a different constitution. We report here a simple synthesis of the linear and cyclic trihydroxamic acids (**8**) and (**9**) containing repeating units of 6-aminohexanoic acid (H-Ahe-OH) and 3-(hydroxyamino)propanoic acid [H-(HO)Apr-OH] as models for ferrioxamines E and G. The only difference between the models and the natural products is the direction of the hydroxamic acid moiety, –CON(OH)– and –N(OH)CO–.[6]

The synthesis was carried out by the reactions in Scheme 1. The hydroxy moiety of the *N*-hydroxyamino group was protected by a benzyl group. The *N*-benzyloxyamino group was acylated by the mixed anhydride method. *p*-Nitrophenyl 3-(benzyloxyamino)propanoate[7] was used to acylate the terminal amino group. Application of these procedures produced the protected oligoamides (**1**) (oil; 93%), (**2**) (oil; 77%), (**3**) (oil; 97%), (**4**) (oil; 93%), and (**5**) (m.p. 63—65 °C; 93%), in turn. Hydrolysis of the methyl ester (**5**) gave the acid (**6**). Removal of the benzyl groups (10% Pd–C in MeOH) and of the Boc group (CF_3CO_2H) and neutralization gave the desired linear trihydroxamic acid (**8**) (77%), m.p. 161—162 °C (decomp.); 42% total yield. Conversion of (**6**) into the *N*-hydroxysuccinimide (HOSu) ester with *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodi-imide (WSC) and deprotection of the Boc group (CF_3CO_2H), followed by intramolecular cyclization at high dilution gave the cyclohexamer (**7**); the Su ester CF_3CO_2H salt (2.0 mmol) in dimethylformamide (DMF) (20 ml) was added slowly to pyridine (640 ml) and stirred for 12 h at room temperature. The resulting residue (**7**)



Scheme 1. *Reagents and Conditions:* i, $ClCO_2Bu^i$–Et_3N, −15 °C (5 h), then room temp. (20 h); ii, 4 M HCl–dioxane, room temp. (2 h); iii, Et_3N in DMF, 30 °C (30 h); iv, 1 M NaOH (2 equiv.) in MeOH, room temp. (5 h); v, HOSu–WSC, −5 °C (2 h), then 5 °C (12 h); vi, CF_3CO_2H, 0 °C (30 min); vii, 3 × 10^{-3} M in pyridine.

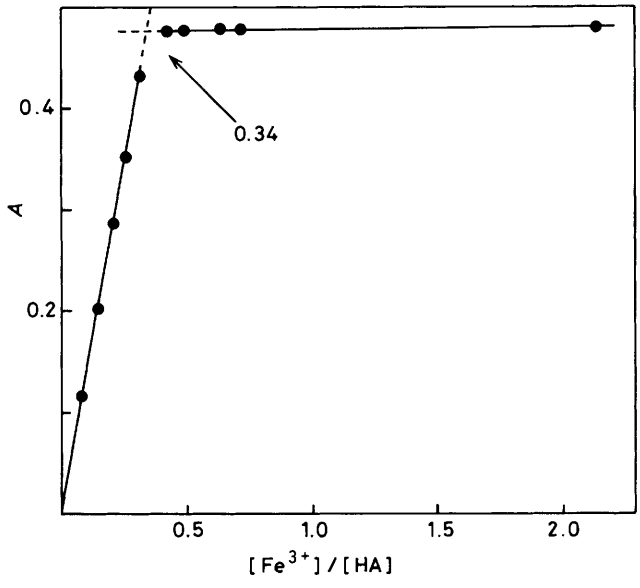


Figure 1. Absorbance (*A*) *vs.* ratio of iron(III) to the hydroxamic acid unit (HA) of (**8**); H_2O, [(**8**)] = 1.6 × 10^{-4} M; 25 °C; pH = 3; $\lambda_{max.}$ 425—440 nm.

$H_2N[CH_2]_5N(OH)\text{-}CO[CH_2]_2CO\text{-}NH[CH_2]_5N(OH)\text{-}CO[CH_2]_2CO\text{-}NH[CH_2]_5N(OH)\text{-}CO[CH_2]_2CO_2H$
Deferriferrioxamine G

$H_2N[CH_2]_5CO\text{-}N(OH)[CH_2]_2CO\text{-}NH[CH_2]_5CO\text{-}N(OH)[CH_2]_2CO\text{-}NH[CH_2]_5CO\text{-}N(OH)[CH_2]_2CO_2H$
(**8**)

$\overline{HN[CH_2]_5N(OH)\text{-}CO[CH_2]_2CO\text{-}NH[CH_2]_5N(OH\text{-}CO[CH_2]_2CO\text{-}NH[CH_2]_5N(OH)\text{-}CO[CH_2]_2CO}$
Deferriferrioxamine E

$\overline{HN[CH_2]_5CO\text{-}N(OH)[CH_2]_2CO\text{-}NH[CH_2]_5CO\text{-}N(OH)[CH_2]_2CO\text{-}NH[CH_2]_5CO\text{-}N(OH)[CH_2]_2CO}$
(**9**)

was purified by ion exchange (Dowex-1 and -50 with 90% aq. MeOH) and gel (Sephadex LH-20 with MeOH) chromatography (oil; 45%). Hydrogenolysis of (**7**) and chromatographic purification (Toyopearl HW-40 with DMF) afforded the desired cyclic trihydroxamic acid (**9**) (75%), m.p. 190—191 °C (decomp.); 18% total yield; M^+, *m/z* 601. The use of the active ester without *N*-protection facilitated the synthesis.

The complex forming ability of (**8**) and (**9**) was determined by measuring the change of absorbance as a function of the molar ratio of iron(III) to the hydroxamic acid unit, as shown in Figure 1. A sharp inflection at 0.34 for (**8**) [and 0.33 for (**9**); not shown] indicates the ready formation of a 1 : 3 complex. In fact, a crystalline 1 : 1 complex of (**9**) ($\lambda_{max.}$ 430 nm; ε 2900) was obtained when (**9**) and $FeCl_3 \cdot 6H_2O$ were mixed in methanol. In acetate buffer (pH 5.3) at 25 °C, iron(III) was transferred from ethylenediaminetetra-acetic acid (EDTA) to DFB, (**8**), and (**9**) with pseudo-first order rate constants ($k_{tr} = k_f + k_r$) of 5.6×10^{-5}, 7.3×10^{-5}, and 5.2×10^{-5} s^{-1}, and conversely from DFB, (**8**), and (**9**) to EDTA with $k_{tr} = 7.1 \times 10^{-5}$, 7.8×10^{-5}, and 6.4×10^{-6} s^{-1}, respectively. The transfer was virtually complete with the present concentration gradient (from 0.32 mM to 8.3 mM) except for the case of (**9**) to EDTA where 15% of the iron remained unremoved. These preliminary data suggest that the cyclic compound (**9**) takes up Fe^{3+} rather slowly but more firmly than the linear derivatives.

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