Phase-transfer-catalysed Preparation of *N*-Alkylated Trihydroxamic Acids†

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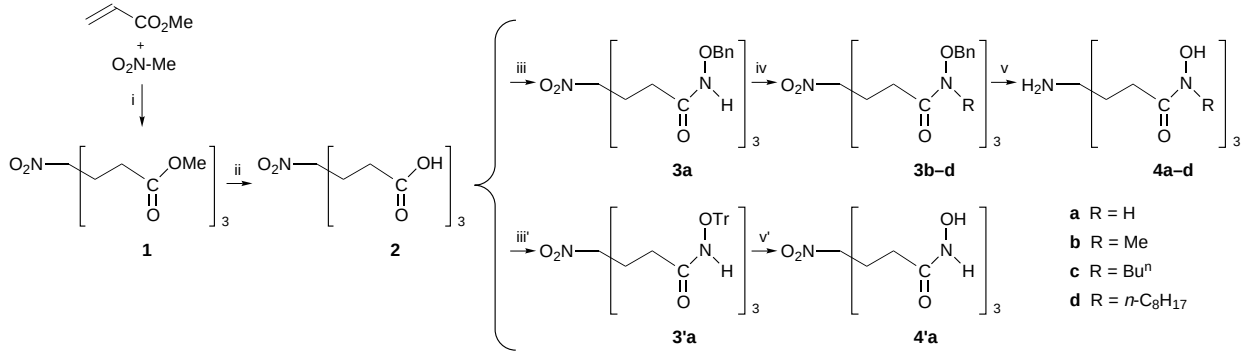
We describe a synthetic route involving phase transfer catalysis leading to a series of tripodal *N*-alkylated hydroxamic acids as models of desferrioxamine; iron(III) exchange reactions between their iron complexes and EDTA were investigated.

Naturally occurring hydroxamic acids act variously as growth factors, antibiotics, tumour inhibitors, cell division factors or lipoxygenase inhibitors, and play a major role as iron transfer agents.[1] Most of these biological activities are due to their complexing properties towards transition metal ions, particularly with iron(III). Desferrioxamine, a natural trihydroxamic acid, is used therapeutically for the treatment of iron-overloaded patients,[2] particularly in patients with AIDS, but the lack of oral activity and its short biological half-life limits its use. Otherwise, iron chelation by desferrioxamine, and other chelators, protects against the cytotoxic and reactivating effects of hydrogen peroxide,[3] and thus decreases NF-κB activation due to oxidative stress, and subsequent activation of HIV-1 transcription. The natural products with an iron(III)trihydroxamate centre form a class comprised of many known members. When three hydroxamate functions are present in the same molecule with an appropriate spacing between the hydroxamic acid units, the complex tends to retain the 1:1 structure, even at low pH.

In this work, we report the synthesis of a series of *N*-H or *N*-alkylated tripodal hydroxamic acids **4** (Scheme 1) as simple models of desferrioxamine. We use phase transfer catalysis[4] (PTC) on the one hand to access the triester **1**, and on the other hand to perform the *N*-alkylation reactions. The relative stabilities of the iron(III) complexes were investigated.

PTC was used for the first step to synthesize the triester **1**, a building block that is often used as a starting material for dendrimeric macromolecule synthesis.[5] Michael-type addition of nitromethane to methyl acrylate, without added organic solvent but in the presence of potassium carbonate and with benzyltriethylammonium chloride as phase-transfer reagent, followed by saponification of the triester **1** afforded the triacid **2**. Condensation of *O*-protected hydroxylamines with the triacid chloride gave the *O*-benzylated trihydroxamic acid **3a**, and the *O*-tritylated trihydroxamic acid **3′a**. As the deprotection conditions of the benzyl group are often incompatible with the presence of other functional groups, we used two different protective groups for the synthesis of compounds **3**. Although synthetic methods for hydroxamic acids are well documented,[6] direct acylation of *O*-protected hydroxylamine derivatives with acid chlorides remains the most commonly used method. A direct condensation with unprotected hydroxylamine gave a mixture of *N*- and *O*-acylated products. Hydroxamic acids have been alkylated with a large variety of electrophiles. Phase-transfer catalysis in the *N*-alkylation of organic molecules seems to be effective especially when the nitrogen atom has a low basicity which renders it less reactive towards alkylating agents. Here, we used PTC in the absence of solvent for the *N*-alkylation[4c] of **3a** with methyl iodide, *n*-butyl bromide, and *n*-octyl bromide in the presence of potassium *tert*-butoxide and Aliquat 336 (tricaprylylmethylammonium chloride) to yield respectively the *N*-alkylated-*O*-protected hydroxamic acids **3b–d**. Finally, deprotection of the benzylated derivatives **3a–d** by catalytic hydrogenation with ammonium formate and 10% palladium–carbon gave the amino hydroxamic acids **4a–d** in moderate yields (20–35%), while removal of the trityl group of compounds **3′a** in acidic diethyl ether gave the nitro derivative **4′a**. The *N*-*n*-octylated product (**4d**) was isolated by chromatography on silica gel, whereas **4a–c** and **4′a** were purified by reversed-phase preparative TLC with a mixture of methanol and water as eluent.

All final hydroxamic acids gave a deep red colour in the presence of Fe^{3+} with a wide characteristic absorption band



Scheme 1 *Reagents and conditions:* i, PTC: benzyltriethylammonium chloride, K_2CO_3, RT; ii, NaOH–methanol, reflux; iii, $SOCl_2$, reflux; *O*-benzylhydroxylamine, Et_3N–THF, RT; iii′, $SOCl_2$, reflux; *O*-tritylhydroxylamine, Et_3N–THF, RT; iv, PTC: methyl iodide, *n*-butyl bromide or *n*-octyl bromide, Aliquat 336, potassium *tert*-butoxide, 50 °C (reflux for methyl iodide, 42 °C); v, ammonium formate, 10% Pd/C–methanol, reflux; v′, HCl–diethyl ether, RT (RT = room temperature)

in the visible range with a maximum located between 420 and 440 nm.

In order to investigate the relative stabilities of the iron complexes, the pseudo-first-order constants for iron(III)

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exchange reactions between the Fe^{III}–**4** complexes and EDTA were determined by following the decrease in absorbance at 425 nm in the presence of a large excess of EDTA. The relative stability constants of the iron(III) complexes of **4′a**, **4a**, **4b**, **4c** and **4d** were respectively 0.8×10^{-2}, 1.5×10^{-2}, 1.0×10^{-2}, 0.2×10^{-2} and 0.4×10^{-2} s^{-1}, suggesting that the lipophilic compounds **4c** and **4d** hold iron a little more tightly than do the other ligands. However, the order of magnitude of the observed constants indicates that the tripodal ligands **4** form much less stable complexes than does desferrioxamine, a linear trihydroxamic acid that has an optimal nine-atom spacing between hydroxamate moieties, and whose exchange constant towards EDTA is 6.5×1^{-6} s^{-1} under the same experimental conditions. The shape of the molecule (linear or tripodal) and the spacing between the hydroxamic acid units seem to play a major role in creating stable iron(III) complexes.

The final hydroxamic acids will be tested as potent antiviral agents in future work; moreover, as part of a program to develop novel chelators for the radioimaging of organs and tumours, the affinity of the trihydroxamic acids **4** towards gallium(III) and indium(III) will be measured.

Experimental

NMR spectra were recorded on a Bruker AC 250 instrument at 250 MHz and UV spectra with a UVIKON 931 spectrometer (Kontron instruments).

Compound **1**. Yield: 97%, oil; δ_H ($CDCl_3$) 2.26–2.28 (12 H, m, CH_2CH_2), 3.66 (9 H, s, CH_3).

Compound **2**. Yield: 65%, solid, mp 175 °C; δ_H [$^2H_6$]DMSO) 2.16–2.17 (12 H, m, CH_2CH_2), 12.31 (3 H, s, COO*H*).

Compound **3a**. Yield: 77%, solid, mp 107 °C; δ_H ([$^2H_6$]DMSO) 1.93–2.13 (12 H, m, CH_2CH_2), 4.78 (6 H, s, PhCH_2), 7.34–7.40 (15 H, m, C_6H_5), 11.09 (3 H, s, N*H*).

Compound **3′a**. Yield: 58%, oil; δ_H ([$^2H_6$]DMSO) 1.88–2.08 (12 H, m, CH_2CH_2), 7.25–7.48 (15 H, m, C_6H_5), 10.89 (3 H, s, NH).

General Procedure for PTC N-*alkylation*.—To a dry mixture of **3a** (9 mmol) and potassium *tert*-butoxide (45 mmol) was added Aliquat 336 (0.1 g). After 2 h under stirring at 50 °C, methyl iodide, *n*-butyl or *n*-octyl bromide (5–10 mol equiv.) were added and the mixture was stirred for 2 h at 50 °C. Chromatography on silica gel with a silica gel with a mixture of dichloromethane and methanol as eluent (ranging from 99:1 to 95:5) provided the desired compounds. **3b** (yield: 67%), oil, δ_H ($CDCl_3$ 2.15–2.20 (12 H, m, CH_2CH_2), 3.17 (9 H, s, NCH_3), 4.77 (6 H, s, PhCH_2), 7.36 (15 H, s, C_6H_5). **3c** (yield: 55%), oil, δ_H ($CDCl_3$) 0.87–0.93 (9 H, t, CH_3), 1.25–1.35 (6 H, m, CH_2), 1.54–1.63 (6 H, m, CH_2), 2.08–2.27 (12 H, m, CH_2CH_2), 3.58–3.64 (6 H, t, NCH_2), 4.75 (6 H, s, PhCH_2), 7.36 (15 H, s, C_6H_5). **3d** (yield: 48%) oil 0.87 (9 H, s, CH_3), 1.25–1.30 (36 H, m, CH_2), 2.08–2.23 (12 H, m, CH_2CH_2), 3.56–3.60 (6 H, t, NCH_2), 4.75 (6 H, s, PhCH_2), 7.36 (15 H, s, C_6H_5).

General Procedure for Debenzylation.—To a solution of **3a–d** (9 mmol) in methanol (50 ml) was added under argon 10% Pd–C (2.5 g) and a solution of ammonium formate (90 mmol) in methanol (100 ml). The mixture was heated at 65 °C for 12 h under argon. After cooling, the mixture was filtered through a Celite pad. The palladium was washed three times with methanol, and the filtrate was evaporated. **4a–c** were chromatographed on reversed-phase TLC and **4d** on silica gel. **4a** (yield: 59%), solid (hygroscopic): δ_H ([$^2H_6$]DMSO) 1.75–2.18 (14 H, m, $CH_2CH_2+NH_2$), 5.02 (3 H, br s, O*H*), 7.35 (3 H, s, N*H*). **4b** (yield: 70%), oil δ_H ([$^2H_6$]DMSO) 2.02–2.27 (14 H, m, $CH_2CH_2+NH_2$), 3.02 (9 H, s, NCH_3), 7.87 (3 H, br s, O*H*). **4c** (yield: 95%), oil: δ_H ([$^2H_6$]DMSO) 0.82–0.88 (9 H, t, CH_3), 1.19–1.34 (6 H, m, CH_2), 1.42–1.53 (6 H, m, CH_2), 2.05–2.32 (14 H, m, $CH_2CH_2+NH_2$), 3.43–3.48 (6 H, t, NCH_2), 6.70 (3 H, br s, O*H*). **4d** (yield: 79%), oil, δ_H ([$^2H_6$]DMSO) 0.85–0.87 (9 H, t, CH_3), 1.26–1.33 (36 H, m, CH_2), 2.10–2.30 (14 H, m, $CH_2CH_2+NH_2$), 3.51–3.59 (6 H, t, NCH_2), 8.43 (3 H, br s, O*H*). R_F values on reversed-phase TLC (C_{18}): **4a** 0.75 (H_2O–MeOH, 80:20); **4b** 0.62 (H_2O–CH_3OH, 60:40); **4c**: 0.17 (H_2O–MeOH, 40:60). R_F value on silica gel TLC: **4d**: 0.20 (CH_2Cl_2–MeOH, 95:5).

Compound **4′a**. To a solution of **3′a** (5.6 g, 5.34 mmol) in dichloromethane (190 ml) was added a solution of hydrochloric acid (1.1 M) in diethyl ether (30 ml). The solution was stirred for 2 h at room temperature. The precipitate was filtered off, washed with dichloromethane and dried under reduced pressure. The residue was dissolved in water, filtered and lyophilised to give **4′a** (yield: 74%), solid (hygroscopic); δ_H ([$^2H_6$]DMSO) 1.92–2.10 (12 H, m, CH_2CH_2), 9.90 (3 H, br s, O*H*), 10.66 (3 H, s, N*H*). $R_F = 0.70$ [reversed-phase TLC (C_{18}); H_2O–MeOH, 80:20].

Iron-exchange Reactions with EDTA.—The exchange reactions between the iron complexes and EDTA were carried out by UV spectroscopy, noting the decrease in the absorbance at 425 nm in the presence of an excess of EDTA as previously described.[7]

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References

1 J. B. Neilands, *Science*, 1967, **156**, 1443; R. J. Bergeron, *Chem. Rev*., 1984, **84**, 587.
2 R. J. Bergeron, C. Z. Liu, J. S. McManis, M. X. B. Xia, S. E. Algee and J. Weigand, *J. Med. Chem*., 1994, **37**, 1411.
3 C. Sappey, J. R. Boelaert, S. Legrand-Poels, C. Forceille, A. Favier and J. Piette, *AIDS Res. Hum. Retroviruses*, 1995, **11**, 1049.
4 (*a*) E. V. Dehmlow, *Angew. Chem*., *Int. Ed. Engl*., 1977, **16**, 493; (*b*) for Michael addition *via* PTC, see for example: V. Dryanska, K. Popandova and C. Ivanov, *Synth. Commun*., 1987, **17**, 211; G. Bram, H. Galons, S. Labidalle, A. Loupy, M. Miocque, A. Petit, P. Pigeon and J. Sansoulet, *Bull. Soc. Chim. Fr*., 1989, 247; (*c*) for PTC *N*-alkylation, see for example: R. J. M. Nolte and D. J. Cram, *J. Am. Chem. Soc*., 1984, **106**, 1416; E. V. Dehmlow and Y. R. Rao, *Synth. Commun*., 1988, **18**, 487.
5 G. R. Newkome, C. N. Moorefield and G. R. Baker, *Aldrichim. Acta*, 1992, **25**, 31.
6 A. M. Lobo, M. M. Marques, S. Prabhakar and H. S. Rzepa, *J. Org. Chem*., 1987, **52**, 2925; R. J. Bergeron and J. S. McManis, *Tetrahedron*, 1990, **46**, 5881; J. M. Altenburger, C. Mioskowski, H. d'Orchymont, D. Schirlin, C. Schalk and C. Tarnus, *Tetrahedron Lett*., 1992, **33**, 5055; M. A. Staszak and C. W. Doecke, *Tetrahedron Lett*., 1994, **35**, 6021; J. Zhu, S. Robin, C. Goasdoué, A. Loupy and H. Galons, *Synth. Commun*., 1995, **25**, 2515; S. S. Nikam, B. E. Kornberg, D. R. Johnson and A. M. Doherty, *Tetrahedron Lett*., 1995, **36**, 197.
7 M. Akiyama, A. Katoh and T. Ogawa, *J. Chem. Soc*., *Perkin Trans. 2*, 1989, 1213.