Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Self-Assembling of an Amphiphilic Iron(III) Chelator : Mimicking Iron Acquisition in Marine Bacteria.

Mariana Apostol, Paul Baret, Guy Serratrice, Jacques Desbrières, Jean-Luc Putaux, Marie-José Stébé, Dominique Expert and Jean-Louis Pierre. *

Synthesis of ligands L^a and L^b.

The protected 2,3-dimethoxybenzoic acid was activated with thionyl chloride and coupled with respectively n-octylamine and n-dodecylamine. Then phenol groups were deprotected with boron tribromide.

2,3-dimethoxybenzoyl chloride

2,3-dimethoxybenzoic acid (2 g ,10.9 mmol) was dissolved in $SOCl_2$ (20 ml). The mixture was refluxed for 4 h. and then the excess of $SOCl_2$ was removed under vacuum. 2,3-dimethoxybenzoyl chloride was washed with hexane and the beige powder was used immediately.

Coupling with amines

Under nitrogen at room temperature, a solution in CH_2Cl_2 (50 mL) of 2,3-dimethoxybenzoyl chloride, prepared as described above, was added dropwise to a solution of the amine (11 mmol) in CH_2Cl_2 (75 mL) and triethyl amine (2.25 mL). The mixture was stirred overnight then washed with brine, dried (Na_2SO_4) and concentrated.

2,3-dimethoxy-*N*-octyl-benzamide

The product was purified by column chromatography (silica, hexane – ethyl acetate). A whitish solid was obtained : 2.8 g., yield = 84 %.

^{1}**Hnmr** (300 MHz, $CDCl_3$)

δ: 0.87 (3H, t, J = 6.7Hz); 1.28-1.40 (10 H, m); 1.6 (2H, m); 3.45 (2H, dd, J_1 = 1.2, J_2 = 6.9 Hz); 3.88 (6H, OCH_3); 7.02 (1H, dd, J_1 = 1.6, J_2 = 8 Hz); 7.12 (1H, m) ; 7.8 (1H, dd, J_1 = 1.7, J_2 = 7.8); 7.9 (1H, brd, NH)

^{13}Cnmr (300 MHz, $CDCl_3$)

14.1 (CH_3); 22.6 (CH_2); 27.1 (CH_2); 29.2 (CH_2); 29.3 (CH_2); 29.6 (CH_2); 31.8 (CH_2); 39.7 (CH_2); 56.1 (OCH_3); 61.3 (OCH_3); 115.2 (CH); 122.8 (CH_A); 124.4 (CH) ; 127.1 (Cq); 147.4 (Cq); 152.6 (Cq); 165 (CO).

IR ($CHCl_3$, cm^{-1}): 3380; 1721 (ν C=O); 165.1 (ν C=O)

MS (DCI, NH_3 + isobutane): 294 ($M + H^+$)

Anal. Calcd. (found) for $C_{17}H_{27}NO_3$: C = 69.59 (69.71); H = 9.28 (9.33); N= 4.77 (4.90)

2,3-dimethoxy- *N*-dodecyl-benzamide

Treatment of the crude product with hexane – ether 4 :1 gave the pure product 4.1g yield = 95 %.

^{1}Hnmr (300 MHz, $CDCl_3$)

δ: 0.88 (3H, t, J = 6.7 Hz); 1.26-1.36 (18 H, m) ; 1.60 (2H, m) ; 3.46 (2H, m) ; 3.88 (3H, s, OCH_3); 3.89 (3H, s, OCH_3) ; 7.03 (1H, dd, J_1 = 1.7, J_2 = 8.0Hz) ; 7.14 (1H, t, J = 8.0 Hz) ; 7.68 (1H, dd, J_1 = 1.7, J_2 = 8.0 Hz); 7.95 (1H, brd t, NH)

^{13}Cnmr (300 MHz, $CDCl_3$)

14.2 (CH_3) ; 22.8 (CH_2); 27.2 (CH_2); 29.4 (CH_2); 29.6 (CH_2); 29.7 ($2CH_2$); 29.8 ($3\ CH_2$); 32.0 (CH_2); 39.8 (CH_2); 56.2 (OCH_3); 61.4 (OCH_3); 115.2 (CH); 122.9 (CH); 124.5 (CH); 127.2 (Cq); 147.5 (Cq); 152.7 (Cq); 165.1 (CO).

IR ($CHCl_3$, cm^{-1}): 3380; 1721 (ν C=O); 1650 (ν C=O)

MS (DCI, NH_3 + isobutane): 395 ($M + H^+$)

Deprotection of phenol groups

At 0°C under nitrogen, BBr_3 (1.1 eq) in CH_2Cl_2 was slowly added to a solution of the (methoxy protected) compound in CH_2Cl_2. The mixture was stirred for 6 h. and then treated with methanol. The solvents were evaporated under vacuum. Addition and evaporation of methanol were repeated five times.

2,3-dihydroxy- *N*-octyl-benzamide , $\mathbf{L^b}$

1.450 g of $\mathbf{L^b}$ was obtained (starting with 1.8 g. of the dimethoxy precursor) in the pure form; yield = 89 %.

^{1}**Hnmr** (300 MHz, $CDCl_3$) ;

δ: 0.86 (3H, t, J = 7 Hz); 1.26 (10 H, brd m); 1.59 (2H, m); 3.26 (2H, m); 6.1 (1H, brd s); 6.4 (1H, brd s); 6.6 (1H, dd, J_1 = 7.8, J_2 = 8.1 Hz); 6.9 (1H, dd, J_1 = 1.5, J_2 = 8.1 Hz); 7.1 (1H, dd, J_1 = 1.5, J_2 = 7.8 Hz)

^{13}**Cnmr** (300 MHz, $CDCl_3$)

14.2 (CH_3); 22.7 (CH_2); 27.1 (CH_2); 29.3 (CH_2); 29.4 (CH_2); 29.6 (CH_2); 31.2 (CH_2); 39.9 (CH_2); 114.3 (Cq); 115.9 (CH); 118.1(CH); 118.6 (CH); 146.1 (Cq); 149.2 (Cq); 170.0 (CO).

IR (KBr, cm^{-1}): 3500-3050; 1646 (ν C=O)

MS (DCI, NH_3 + isobutane): 266 (M + H^+)

Anal. Calcd. (found) for $C_{15}H_{23}NO_3$: C = 67.90 (66.82); H = 8.74 (8.69); N= 5.28 (5.18)

2,3-dihydroxy- *N*-dodecyl-benzamide , L^a

3.18 g of $\mathbf{L^a}$ was obtained quantitatively (starting with 3.9 g. of the dimethoxy precursor).

^{1}**Hnmr** (300 MHz, $CDCl_3$)

δ: 0.92 (3H, t, J = 6.7 Hz); 1.31-1.39 (18 H, brd m); 1.64 (2H, m); 3.39 (2H, t, J = 7.1 Hz); 6.74 (1H, t, J = 8 Hz); 6.93 (1H, dd, J_1 = 1.4, J_2 = 7.9 Hz); 7.24 (1H, dd, J_1 = 1.5, J_2 = 7.9 Hz)

^{13}**Cnmr** (300 MHz, $CDCl_3$)

15.3 (CH_3); 24.6 (CH_2); 28.9 (CH_2); 31.2 -31.6 (7 CH_2); 33.9 (CH_2); 41.4 (CH_2); 117.4 (Cq); 119.5 (CH); 120.4(2 CH); 148.2 (2 Cq); 172.3 (CO)

IR (KBr, cm^{-1}): 3458 - 3100; 1650 (ν C=O)

MS (D/IC, NH_3 + isobutane): 322 (M + H^+)

Synthesis of the ligand L^T

Hexadecyl 2,2,2-tris[3-(2,3-dimethoxybenzamido)propyl]-amide

At room temperature under nitrogen, DAST (diethylaminosulfurtrifluoride) (200 ? L, 1.63 mmol) in 5 mL of CH_2Cl_2 was slowly added to a solution of 2,2,2-tris[-(2,3-dimethoxybenzamido)propyl] ethanoic acid (500 mg, 0.68 mmol) in 25 mL of CH_2Cl_2. The mixture was stirred for 45 min. and then treated with water. The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The crude product (beige solid) was dissolved in THF (5 mL) and slowly added to a solution of hexadecylamine (130 mg, 0.54 mmol) and 0.25 mL of triethylamine in THF (25 mL). The mixture was stirred overnight at room temperature. The solvent THF was evaporated and the crude product was taken into CH_2Cl_2, then washed twice with brine. Purification by column chromatography (silica gel ; 1-2% methanol in CH_2Cl_2) afforded the product (410 mg, yield = 64%)

^{1}H nmr (300 MHz, $CDCl_3$)

δ: 0.88 (3 H, t, J = 6 Hz); 1.23-1.66 (40 H, m,); 3.18 (2H, m); 3.42 (6H, m); 3.86 (s, 9H); 3.88 (s, 9H); 6.02 (1 H, brd t, NH amide) ; 7.02 (1H, dd, J_1 = 1.6 Hz, J_2 = 8 Hz); 7.1 (6H, t, J=8 Hz); 7.63 (3H, dd, J_1 = 1.6, J_2 = 8 Hz); 8.0 (3H, brd t**,** NH amide)

^{13}C nmr (300 MHz, $CDCl_3$)

13.9 (CH_3); 22.5-32.0 (CH_2); 39.6 (CH_2); 39.8 (CH_2); 55.8 (OCH_3); 61.1 (OCH_3); 115.0 (CH); 122.4 (CH); 124.0(CH); 126.6 (Cq); 147.2 (Cq); 152.3(Cq); 165.0 (CO); 175.4 (CO).

MS (DCI, NH_3 + isobutane): 947 ($M + H^+$)

Anal. Calcd. (found) for $C_{54}H_{82}N_4O_{10}$, 0.5 CH_2Cl_2: C = 66.14 (65.60); H = 8.45 (8.57); N=5.66 (5.64)

Hexadecyl 2,2,2-tris[3-(2,3-dihydroxybenzamido)propyl]-amide (L^T)

At 0°C under nitrogen, BBr_3 (0.86 mL, 5 mmol) in 7 mL of CH_2Cl_2 was slowly added to a solution of the (methoxy protected) compound (400 mg, 0.42 mmol) in 30 mL of CH_2Cl_2. The mixture was stirred for 6 h. and then treated with methanol. The solvents were evaporated under vacuum. Addition and evaporation of methanol were repeated five times. The product $\mathbf{L^T}$ was obtained pure as a beige powder (350 mg, yield = 96 %).

F = 98 – 100°C

^{1}H nmr (300 MHz, CD_3OD)

δ: 0.89 (3H, t, J = 6.6 Hz); 1.21 – 1.63 (40 H, m); 3.16 (2H, t, J_1 = 6.9 Hz); 3.34 (6H, t, J_1 = 6.9 Hz); 6.7 (3H, t, J_1 = 8.0 Hz); 6.9 (3H, dd, J_1 = 8 Hz, J_2 = 1.5 Hz); 7.1 (3H, dd, J_1 = 8 Hz, J_2 = 1.5 Hz)

^{13}C nmr (75 MHz, CD_3OD)

δ: 14.8 (CH_3); 24.1 - 41.3 (CH_2) ; 41.3 (CH_2); 117.1 (Cq); 119.1 (CH); 120.0 (2CH); 148.7 (Cq); 150.5 (Cq); 172.0 (CO); 179.2 (CO)

IR (KBr): 3536-3073 (ν O-H_a + ν N-H); 1642 (ν C=O_{amide}) cm^{-1}

MS (DCI, NH_3 + isobutane): M = 863

Anal. Calcd. (found) for $C_{48}H_{70}N_4O_{10}$.1.5 H_2O: C = 64.77(64.72); H = 8.27 (8.02); N = 6.29 (6.26)

Cryo-TEM images of Fe(III)-L^a complexes 10^{-3} M in water/methanol 95/5 (v/v) solution at pH=7.4 (MOPS buffer) embedded in vitreous ice (10) five minutes after addition of 1 % octanol.