

# Synthesis of dendritic iron(II) porphyrins with a tethered axial imidazole ligand designed as new model compounds for globins

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A series of novel dendritic iron(II) porphyrins with an axial imidazole ligand attached to the central porphyrin core was synthesised and fully characterised. The vacancy of the second axial coordination site was demonstrated by their ability to coordinate the diatomic gas molecules CO, O<sub>2</sub> and NO. The formation of NO complexes by dendritic iron(II) porphyrins was observed for the first time.

The peptidic shell around the iron(II) containing heme cofactor in the oxygen-transporting and -storing proteins of the globin family serves two major purposes, namely steric protection against autoxidation under formation of  $\mu$ -oxo-dimers and creation of an appropriate axial coordination to the metal ion centre in order to tune gas binding affinities.<sup>1</sup> Mimicry of the steric protection has been achieved by attachment of bulky substituents onto iron(II) porphyrins or macrocyclic bridging<sup>2</sup> and, recently, by encapsulation of the iron(II) porphyrin core into dendritic shells.<sup>3–5</sup> Modelling the fine tuning of the gas binding affinities by the nature of the axial ligation, however, is more difficult. The T-state of hemoglobin, in which dioxygen affinity is reduced due to distortion of the iron centre out of the porphyrin plane, can be readily mimicked by addition of an external, sterically hindered axial ligand, such as 1,2-dimethylimidazole.<sup>2</sup> This ligand ensures formation of a five-coordinate iron complex with a free axial coordination site available for gas binding. However, the high-affinity R-state cannot be mimicked in this simple way, since addition of a sterically non-encumbered imidazole ligand would exclusively lead to six-coordinate species, that react only slowly with dioxygen.<sup>2a,3b</sup> The preparation of functional hemoglobin R-state mimics requires the synthesis of model compounds with a defined five-coordinate ligation pattern and therefore an elaborate porphyrin core that includes axial ligation.<sup>6</sup> Here, we describe the preparation and characterisation of the first five-coordinate iron(II) porphyrin dendrimers comprising such an elaborate porphyrin core. The title compounds, namely [1·Fe<sup>II</sup>], [2·Fe<sup>II</sup>], and [3·Fe<sup>II</sup>] (*M<sub>r</sub>* = 11553 Da) which are designed to be functional hemoglobin R-state models, have been synthesised up to the second generation. In addition, their ability to bind diatomic gases (O<sub>2</sub>, CO and NO) is demonstrated.<sup>7</sup>

The novel iron porphyrin dendrimers were synthesised by a convergent strategy (Scheme 1). An appropriately protected porphyrin core [4·Zn] was prepared by a high-yielding *Suzuki* cross-coupling between the *meso*-brominated zinc(II) porphyrin [5·Zn]<sup>7</sup> and the imidazole containing boronic ester **6**. The latter was obtained from 4-bromo-2-hydroxytoluene (**7**)<sup>8</sup> by MOM-protection (MOM = methoxymethyl) of the OH-group to give **8**, followed by lithiation, reaction with B(OMe)<sub>3</sub> and transesterification with pinacol to afford **9**. MOM-ether deprotection gave phenol **10** which was alkylated with 1-(6-bromohexyl)-imidazole (**11**)<sup>9</sup> to give **6**. For the synthesis of the zinc(II) porphyrin dendrimers of zero ([1·Zn]), first ([2·Zn]) and second ([3·Zn]) generation, the tetraester [4·Zn] was hydrolysed to give core tetraacid [12·Zn], which was coupled with the triethylene-glycol monomethyl ether-functionalised dendrons **13–15**,

**Table 1** Spectroscopic properties of the complexes formed by [1·Fe<sup>II</sup>], [2·Fe<sup>II</sup>] and [3·Fe<sup>II</sup>] with CO, O<sub>2</sub> and NO, respectively, in CHCl<sub>3</sub>

Complex <sup>a</sup>	Soret-Band $\lambda_{\max}/\text{nm}$ ( $\epsilon/1000 \text{ cm}^2 \text{ mol}^{-1}$ )	Q-Band $\lambda_{\max}/\text{nm}$ ( $\epsilon/1000 \text{ cm}^2 \text{ mol}^{-1}$ )
[1·Fe <sup>II</sup> ]CO	420 (259000)	540 (14000)
[2·Fe <sup>II</sup> ]CO	420 (218000)	540 (15000)
[3·Fe <sup>II</sup> ]CO	420 (196000)	540 (15000)
[1·Fe <sup>II</sup> ]O <sub>2</sub> <sup>b</sup>		
[2·Fe <sup>II</sup> ]O <sub>2</sub>	420 (97000)	544 (15000)
[3·Fe <sup>II</sup> ]O <sub>2</sub>	420 (112000)	544 (15000)
[1·Fe <sup>II</sup> ]NO	426 (167000)	538 (18000)
[2·Fe <sup>II</sup> ]NO	426 (176000)	538 (19000)
[3·Fe <sup>II</sup> ]NO	426 (184000)	538 (21000)

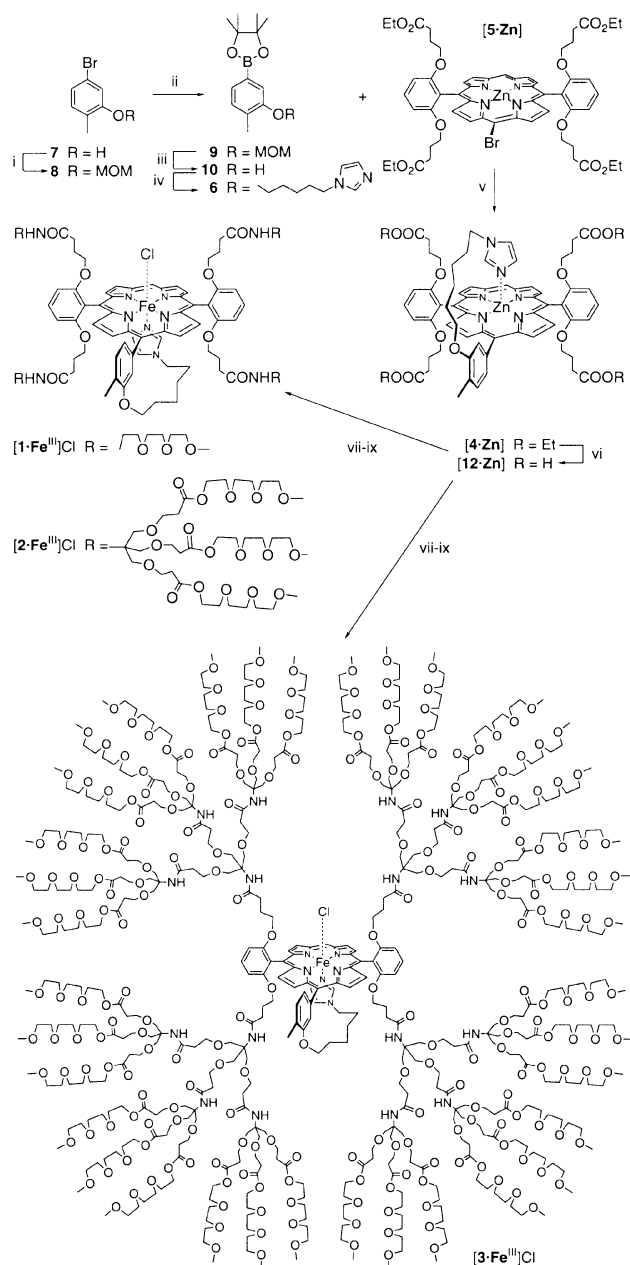
<sup>a</sup> At 20 °C under atmospheric pressure of the corresponding gas.

<sup>b</sup> Decay too rapid for the measurement of a conventional absorption spectrum.

respectively.<sup>7,10</sup> The dendritic zinc(II) porphyrins were purified by repeated preparative gel permeation chromatography (GPC, Biorad Biobeads S-X1; CH<sub>2</sub>Cl<sub>2</sub>) and fully characterised.† Demetallation<sup>7</sup> was achieved with CF<sub>3</sub>COOH and Fe<sup>II</sup> insertion<sup>6a,7</sup> using FeCl<sub>2</sub> and 2,6-dimethylpyridine, followed by autoxidation gave the air-stable dendritic iron(III) porphyrins [1·Fe<sup>III</sup>]Cl, [2·Fe<sup>III</sup>]Cl and [3·Fe<sup>III</sup>]Cl, respectively, which were purified by preparative thin layer chromatography (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>–MeOH 90:10), followed by preparative GPC (Biorad Biobeads S-X3; CH<sub>2</sub>Cl<sub>2</sub>) and fully characterised.‡ The corresponding, highly air-sensitive five-coordinate iron(II) complexes [1·Fe<sup>II</sup>], [2·Fe<sup>II</sup>] and [3·Fe<sup>II</sup>], required for gas binding, were prepared *in situ* by reduction of carefully degassed CHCl<sub>3</sub> solutions of the iron(III) complexes with 0.1 M aqueous sodium dithionite solution under two-phase conditions in an argon atmosphere, and characterised by absorption spectroscopy.§ The three compounds displayed spectra characteristic of five-coordinate high-spin iron(II) porphyrins.<sup>2a,6</sup>

The availability of their sixth coordination site was demonstrated by the reaction with gaseous ligands. All three dendritic iron(II) porphyrins [1·Fe<sup>II</sup>], [2·Fe<sup>II</sup>] and [3·Fe<sup>II</sup>] instantaneously reacted with excess CO, O<sub>2</sub> and NO at 20 °C to yield the corresponding gas complexes. These exhibited absorption spectra (Table 1) and IR-spectra characteristic of six-coordinate low-spin iron(II) porphyrins which compared well with literature data for similar complexes.<sup>2a,11</sup> In particular, clearly assignable IR-absorptions were found for the ligand stretching vibrations of CO and NO ( $\nu_{\max}(\text{C}\equiv\text{O}) = 1970 \text{ cm}^{-1}$ ;  $\nu_{\max}(\text{N}=\text{O}) = 1600 \text{ cm}^{-1}$ ), with frequencies typical for six-coordinate iron(II) porphyrins.<sup>11</sup> Even in the case of NO, which exerts a very strong *trans*-labilising influence,<sup>11b</sup> the axial imidazole ligand remained coordinated. This finding underlines the favorable, non-strained character of the tethered axial ligation.

Whereas both CO and NO adducts did not decompose at all within 3 days, the O<sub>2</sub> complexes all showed gradual



**Scheme 1** Reagents and conditions: i, MOM-Cl,  $K_2CO_3$ , MeCN, 0 °C, 30 min, 99%; ii,  $nBuLi$ , TMEDA, THF, -78 °C, 60 min, then  $B(OMe)_3$ , 20 °C, 2 h, then pinacol, PhH, reflux, 12 h, 74%; iii, conc. HCl, THF-MeOH, 20 °C, 3 d, 84%; iv, **11**,  $Cs_2CO_3$ , DMF, 20 °C, 4 h, 68%; v,  $[Pd(PPh_3)_4]$ ,  $Cs_2CO_3$ , PhMe, 90 °C, 6 h, 81%; vi, NaOH, dioxane-H<sub>2</sub>O, 20 °C, 3 d; vii,  $H_2NCH_2(CH_2OCH_2)_3H$  (**13**),  $H_2NC-[CH_2O(CH_2)_2CO_2CH_2(CH_2OCH_2)_3H]_3$  (**14**) or  $H_2NC[CH_2O(CH_2)_2CONHC[CH_2O(CH_2)_2CO_2CH_2(CH_2OCH_2)_3H]_3]$  (**15**), HATU (*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate),  $Et_3N$ , DMF, -15 °C → 0 °C, 24 h, 91% (**[1-Zn]**), 3 d, 70% (**[2-Zn]**), 5 d, 65% (**[3-Zn]**) (yields from **[4-Zn]**); viii,  $CF_3COOH$ ,  $CHCl_3$ , 0 °C, 5 min; ix,  $FeCl_2$ , 2,6-dimethylpyridine, THF, reflux, 2-4 h, then 1% HCl in  $CHCl_3$ , 20 °C, 5 min, then 'proton sponge' (1,8-bis(dimethylamino)naphthalene), THF, 20 °C, 15 min, 49% (**[1-Fe<sup>III</sup>]Cl**), 53% (**[2-Fe<sup>III</sup>]Cl**), 59% (**[3-Fe<sup>III</sup>]Cl**) (yields from **[1-Zn]**, **[2-Zn]** and **[3-Zn]**).

decomposition to iron(III) species<sup>12</sup> with a dramatic increase in stability with increasing size of the dendritic shell as has been observed previously.<sup>3</sup> In contrast to the zero generation compound, which was oxidised immediately after exposure to the gas, the O<sub>2</sub> complex of the first generation dendrimer was stable for a few minutes ( $t_{1/2} \approx 7$  min) and the corresponding second generation compound decayed only very slowly over the course of several hours ( $t_{1/2} \approx 60$  min), reflecting the increasing suppression of autoxidation. This confirms the nature of the dendrimer as a sterically protecting replacement for the protein shell.

Quantitative gas binding studies to obtain the association constants as well as evaluation of the new, highly water-soluble compounds as dendritic NO sensors<sup>13</sup> are currently under way.

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## Notes and references

† Selected data for **[1-Zn]**: viscous purple oil;  $R_f = 0.34$  ( $SiO_2$ ;  $CH_2Cl_2$ -MeOH 90:10);  $\lambda_{max}$  ( $CHCl_3$ )/nm ( $\epsilon/1000$  cm<sup>2</sup> mol<sup>-1</sup>) 596 (4400), 560 (16500), 512 (2400), 427 (389100), 405 (39300), 313 (19400);  $\delta_H$  (500 MHz,  $CDCl_3$ ) 10.03 (s, 1 H), 9.28 (d,  $J$  4.4, 2 H), 8.98 (d,  $J$  4.4, 2 H), 8.85 (d,  $J$  4.5, 2 H), 8.80 (d,  $J$  4.5, 2 H), 7.85 (d,  $J$  7.1, 1 H), 7.70 (t,  $J$  8.5, 2 H), 7.47 (d,  $J$  7.1, 1 H), 7.04 (d,  $J$  8.5, 2 H), 7.00 (s, 1 H), 6.99 (d,  $J$  8.5, 2 H), 4.99 (s, 1 H), 4.96 (s, 2 H), 4.01 (t,  $J$  6.8, 2 H), 3.78-3.99 (m, 8 H), 3.64 (s, 8 H), 3.54 (s, 8 H), 3.34 (s, 6 H), 3.18 (s, 4 H), 3.04 (s, 8 H), 3.02 (s, 6 H), 2.78-2.99 (m, 8 H), 2.50-2.70 (m, 8 H), 2.49 (s, 3 H), 2.18 (s, 1 H), 1.99 (s, 8 H), 1.72 (s, 1 H), 1.55 (br s, 2 H), 1.12-1.38 (m, 8 H), 0.81-1.05 (m, 8 H), 0.73 (br s, 2 H), 0.56 (br s, 2 H), 0.00 (br s, 2 H);  $\delta_C$  (125 MHz,  $CDCl_3$ ) 172.3, 171.4, 159.9, 159.5, 153.3, 150.5, 150.4, 149.2, 149.0, 142.0, 131.6, 131.6, 131.5, 131.1, 130.8, 130.0, 128.8, 125.6, 124.7, 123.1, 121.4, 119.9, 118.5, 115.8, 112.3, 105.7, 104.9, 104.0, 71.9, 71.2, 70.5, 70.5, 70.1, 69.6, 69.6, 69.5, 69.0, 68.9, 67.4, 66.9, 66.0, 59.0, 58.6, 46.3, 38.6, 37.7, 31.2, 31.1, 29.4, 26.5, 24.9, 24.5, 23.8, 16.3;  $m/z$  (MALDI-TOF MS, matrix: 2-(4-hydroxyphenylazo)benzoic acid (HABA)) 1793.9 (37,  $[M + Na]^+$ , calc. for  $C_{92}H_{124}N_{10}O_{21}Zn \cdot Na^+$ : 1793.8), 1771.5 (100,  $M^+$ , calc. for  $C_{92}H_{124}N_{10}O_{21}Zn^+$ : 1770.8). For **[2-Zn]**: viscous purple oil;  $R_f = 0.42$  ( $SiO_2$ ;  $CH_2Cl_2$ -MeOH 90:10);  $\lambda_{max}$  ( $CHCl_3$ )/nm ( $\epsilon/1000$  cm<sup>2</sup> mol<sup>-1</sup>) 596 (4400), 560 (17000), 522 (3100), 427 (464000), 405 (sh, 39200), 312 (22600);  $\delta_H$  (500 MHz,  $CDCl_3$ ) 9.93 (s, 1 H), 9.20 (d,  $J$  4.4, 2 H), 8.90 (d,  $J$  4.4, 2 H), 8.75 (d,  $J$  4.5, 2 H), 8.71 (d,  $J$  4.5, 2 H), 7.88 (d,  $J$  7.6, 1 H), 7.67 (t,  $J$  8.5, 2 H), 7.45 (d,  $J$  7.6, 1 H), 7.05 (d,  $J$  8.5, 2 H), 7.04 (s, 1 H), 6.98 (d,  $J$  8.5, 2 H), 5.74 (s, 2 H), 5.61 (s, 2 H), 5.04 (s, 1 H), 4.17-4.19 (m, 12 H), 4.02 (t,  $J$  6.8, 2 H), 3.98-4.00 (m, 12 H), 3.82-3.88 (m, 8 H), 3.39-3.65 (m, 168 H), 3.33 (s, 18 H), 3.29 (s, 18 H), 2.78 (br s, 2 H), 2.52 (t,  $J$  6.4, 12 H), 2.47 (s, 3 H), 2.43 (t,  $J$  6.4, 12 H), 2.10 (s, 1 H), 1.88 (s, 1 H), 1.58 (br s, 2 H), 1.22-1.45 (m, 8 H), 0.97-1.21 (m, 8 H), 0.93 (br s, 2 H), 0.76 (br s, 2 H), 0.06 (br s, 2 H);  $\delta_C$  (125 MHz,  $CDCl_3$ ) 172.6, 171.9, 171.3, 171.3, 160.1, 159.5, 153.1, 150.3, 150.0, 149.2, 148.8, 142.7, 131.8, 131.1, 131.0, 130.9, 130.3, 129.5, 128.5, 124.9, 124.9, 123.6, 121.8, 119.2, 118.7, 115.5, 111.5, 105.6, 105.0, 104.1, 71.8, 71.7, 70.5, 70.5, 70.3, 70.3, 69.1, 69.0, 68.8, 67.4, 67.2, 66.6, 66.5, 66.0, 63.5, 63.3, 59.7, 59.6, 58.9, 58.9, 46.1, 34.7, 34.6, 32.3, 32.0, 29.6, 26.6, 24.8, 24.6, 24.4, 23.9, 16.2;  $m/z$  (MALDI-TOF MS, matrix: 2,5-dihydroxybenzoic acid (DHB)) 4245.8 (49,  $[M + Na]^+$ , calc. for  $C_{200}H_{316}N_{10}O_{81}Zn \cdot Na^+$ : 4245.0), 4222.7 (100,  $M^+$ , calc. for  $C_{200}H_{316}N_{10}O_{81}Zn^+$ : 4222.0). For **[3-Zn]**: viscous purple oil;  $R_f = 0.58$  ( $SiO_2$ ;  $CH_2Cl_2$ -MeOH 90:10);  $\lambda_{max}$  ( $CHCl_3$ )/nm ( $\epsilon/1000$  cm<sup>2</sup> mol<sup>-1</sup>) 595 (4300), 558 (17000), 522 (3500), 426 (442600), 405 (sh, 45900), 312 (21900);  $\delta_H$  (500 MHz,  $CDCl_3$ ) 9.85 (s, 1 H), 9.12 (d,  $J$  4.2, 2 H), 8.83 (d,  $J$  4.2, 2 H), 8.68 (d,  $J$  4.3, 2 H), 8.62 (d,  $J$  4.3, 2 H), 7.81 (d,  $J$  7.4, 1 H), 7.63 (t,  $J$  8.5, 2 H), 7.39 (d,  $J$  7.4, 1 H), 4.07 (d,  $J$  8.5, 2 H), 6.97 (s, 1 H), 6.96 (d,  $J$  8.5, 2 H); 6.09 (s, 6 H), 6.08 (s, 6 H), 6.01 (s, 2 H), 5.98 (s, 2 H), 4.99 (s, 1 H), 4.17 (t,  $J$  6.8, 2 H), 4.14 (t,  $J$  4.9, 36 H), 4.11 (t,  $J$  4.9, 36 H), 3.71-3.82 (m, 8 H), 3.38-3.65 (m, 552 H), 3.30 (s, 54 H), 3.27 (s, 54 H), 2.53 (br s, 2 H), 2.49 (t,  $J$  6.3, 36 H), 2.48 (t,  $J$  6.3, 36 H), 2.42 (s, 3 H), 2.33 (br t,  $J$  6.1, 12 H), 2.32 (br t,  $J$  6.1, 12 H), 1.99 (s, 1 H), 1.00-1.81 (m, 19 H), 0.89 (br s, 2 H), 0.72 (br s, 2 H), 0.01 (br s, 2 H);  $\delta_C$  (125 MHz,  $CDCl_3$ ) 172.1, 171.7, 171.3 (2 $\times$ ), 170.8, 170.7, 160.1, 159.3, 153.0, 150.2, 150.0, 149.1, 148.7, 142.7, 131.9, 131.0, 131.0, 130.8, 130.3, 129.5, 128.4, 124.8, 124.7, 123.6, 121.8, 119.1, 118.7, 115.3, 111.4, 105.8, 105.1, 103.9, 71.8, 71.7, 70.4, 70.4 (2 $\times$ ), 70.3, 70.3 (2 $\times$ ), 69.1 (3 $\times$ ), 68.9 (2 $\times$ ), 68.8, 67.9, 67.7, 67.4 (2 $\times$ ), 66.7, 66.6, 59.9, 63.5, 63.4, 60.3 (2 $\times$ ), 59.7, 59.7, 58.9, 58.8, 46.0, 37.0, 36.9, 34.6, 34.6, 31.9, 31.9, 29.5, 26.6, 24.7, 24.1, 23.9, 23.7, 16.2;  $m/z$  (MALDI-TOF MS, matrix: HABA) 11586.1 (100,  $[M + Na]^+$ , calc. for  $C_{524}H_{904}N_{22}O_{249}Zn \cdot Na^+$ : 11584.8), 11562.6 (30,  $M^+$ , calc. for  $C_{524}H_{904}N_{22}O_{249}Zn^+$ : 11561.8).

‡ Selected data for **[1-Fe<sup>III</sup>]Cl**: viscous red-brown oil;  $R_f = 0.12$  ( $SiO_2$ ;  $CH_2Cl_2$ -MeOH (90:10));  $\lambda_{max}$  ( $CHCl_3$ )/nm ( $\epsilon/1000$  cm<sup>2</sup> mol<sup>-1</sup>) 646 (sh, 2100), 577 (sh, 4500), 507 (10400), 415 (90000), 395 (sh, 50300), 350 (sh, 25200);  $g$ -values (X-Band,  $CHCl_3$ )  $g_{\perp} = 5.82$ ,  $g_{\parallel} = 1.99$  (in addition a weak rhombic signal was observed);  $m/z$  (MALDI-TOF MS, matrix: HABA) 1762.4 (100,  $[M - Cl]^+$ , calc. for  $C_{92}H_{124}N_{10}O_{21}Fe^+$ : 1761.8) and for **[1-Fe<sup>III</sup>]Cl**: viscous orange-red oil;  $\lambda_{max}$  ( $CHCl_3$ )/nm ( $\epsilon/1000$  cm<sup>2</sup> mol<sup>-1</sup>) 561 (sh, 7100), 536 (8900), 432 (152400). For **[2-Fe<sup>III</sup>]Cl**: viscous red-brown oil;  $R_f = 0.24$  ( $SiO_2$ ;  $CH_2Cl_2$ -MeOH 90:10);  $\lambda_{max}$  ( $CHCl_3$ )/nm ( $\epsilon/1000$  dm<sup>2</sup> mol<sup>-1</sup>) 645 (sh, 3400), 575 (sh, 5700), 507 (12000), 415

- (96000), 385 (sh, 46600), 350 (sh, 27000);  $g$ -values (X-Band,  $\text{CHCl}_3$ )  $g_{\perp} = 5.86$ ,  $g_{\parallel} = 2.01$  (in addition a weak rhombic signal was observed);  $m/z$  (MALDI-TOF MS, matrix: HABA) 4214.6 (100,  $[M - \text{Cl}]^+$ , calc. for  $\text{C}_{200}\text{H}_{316}\text{N}_{10}\text{O}_{81}\text{Fe}^+$ : 4212.0) and for  $[\mathbf{2}\cdot\text{Fe}^{\text{II}}]$ : viscous orange-red oil;  $\lambda_{\text{max}}$  ( $\text{CHCl}_3$ )/nm ( $\epsilon/1000 \text{ dm}^2 \text{ mol}^{-1}$ ) 560 (sh, 10400), 536 (12600), 432 (150600). For  $[\mathbf{3}\cdot\text{Fe}^{\text{III}}]\text{Cl}$ : viscous red-brown oil;  $R_f = 0.35$  ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$ -MeOH 90:10);  $\lambda_{\text{max}}$  ( $\text{CHCl}_3$ )/nm ( $\epsilon/1000 \text{ dm}^2 \text{ mol}^{-1}$ ) 645 (sh, 2200), 585 (sh, 5700), 507 (12200), 415 (99900), 395 (sh, 74000), 350 (sh, 27400);  $g$ -values (X-Band,  $\text{CHCl}_3$ )  $g_{\perp} = 5.85$ ,  $g_{\parallel} = 2.03$  (in addition a weak rhombic signal was observed);  $m/z$  (MALDI-TOF MS, matrix: HABA) 11552.0 (100,  $[M - \text{Cl}]^+$ , calc. for  $\text{C}_{524}\text{H}_{904}\text{N}_{22}\text{O}_{249}\text{Fe}^+$ : 11551.8) and for  $[\mathbf{3}\cdot\text{Fe}^{\text{II}}]$ : viscous orange-red oil;  $\lambda_{\text{max}}$  ( $\text{CHCl}_3$ )/nm ( $\epsilon/1000 \text{ dm}^2 \text{ mol}^{-1}$ ) 559 (sh, 11900), 536 (14400), 433 (151200).
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