Synthesis of Vitamin-B_{12} Derivatives with Peripheral Tris(oxyethylene) Chains

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The new derivatives **7a–c**, of vitamin B_{12}, with a peripheral tris(oxyethylene) chain linked to the corrin ring by an amide or ester group, are prepared, and their ligand-exchange reactions are investigated. Upon reduction of the aqua-cyano complexes **8a–c** with $NaBH_4$, cleavage of the 'outer' ester and amide group is observed.

Introduction. – We are interested in models for vitamin-B_{12}-dependent rearrangements that mimic the apoenzyme-substrate interaction [1–6]. In our first model, the vitamin-B_{12} derivative catalyst and the substrate were modified by aliphatic side chains for association with each other by noncovalent interactions in appropriate solvents [7][8]. It has been shown that this peripheral association between the catalyst and the substrate enhances the methylmalonyl-succinyl rearrangement in aqueous methanol. In the adenine-thymine model, it has been demonstrated that the base pairing, used as recognition and binding sites, leads to increased rearrangement in a nonpolar solvent [9]. A new model system has been designed for cation-mediated association between poly(oxyethylene) groups (podands) attached to the vitamin-B_{12}-derived catalyst and the methylmalonyl substrate. In this way, the association might be controlled by the presence of cations, bringing the reactive site of the substrate and the catalytic Co-centre in close contact to each other enhancing the reactivity and – in our case – rearrangement.

Cations chelate with podands; however, their association is weaker than with crown ethers or cryptates [10][11]. These strong chelating compounds have been extensively studied in the context of enzyme models [12], whereas polyethers have found less attention in the design of bioorganic functions [13]. In our podand model, the association between the two tris(oxyethylene) moieties is assumed to lead to binding prior to the interaction between the Co-centre and the reactive site of the substrate. The complexation might be at its maximum, when the bromomethyl-methylmalonyl substrate is covalently bonded to the Co-centre (*Fig. 1*).

As a first step towards a model where peripheral association between the substrate and the catalyst is controllable by cations, we describe here the synthesis of vitamin-B_{12} derivatives **7a–c** containing different tris(oxyethylene) side chains, their ligand-exchange reactions, and the unexpected reactivity of **8a–c** with $NaBH_4$ in MeOH.

Results and Discussion. – *Syntheses.* The podand-bearing amino amide **2** and hydroxy ester **3** were prepared by condensation of 2-[2-(2-methoxyethoxy)ethoxy]acetic acid (**1**; activated by reaction with dichloro(methoxy)methane [14]) with the diamine **4** and the diol **5**, respectively (*Scheme 1*).

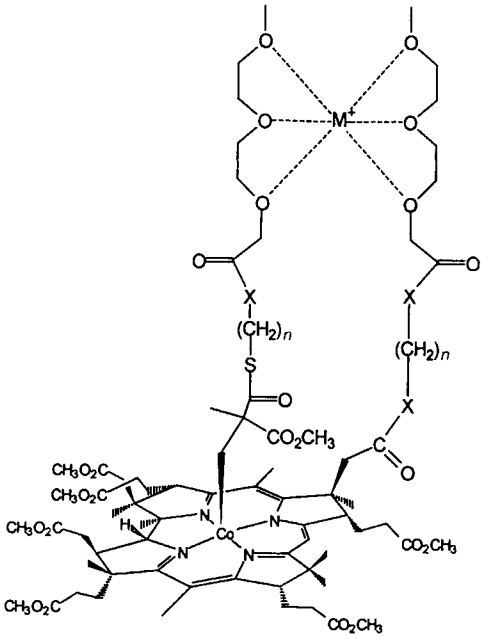
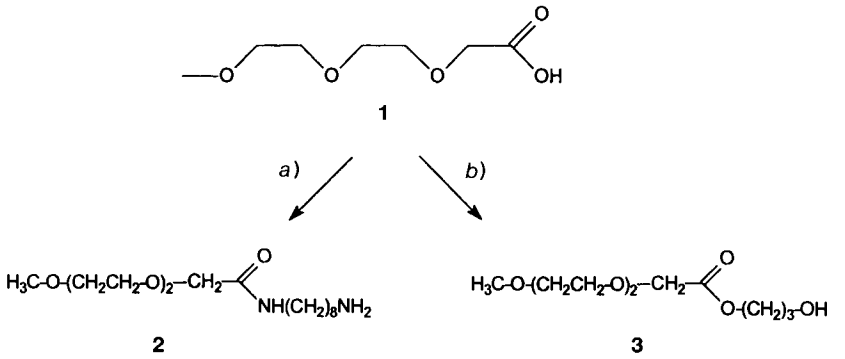


Fig. 1. *Podand model and covalent interaction between substrate and Co-centre*

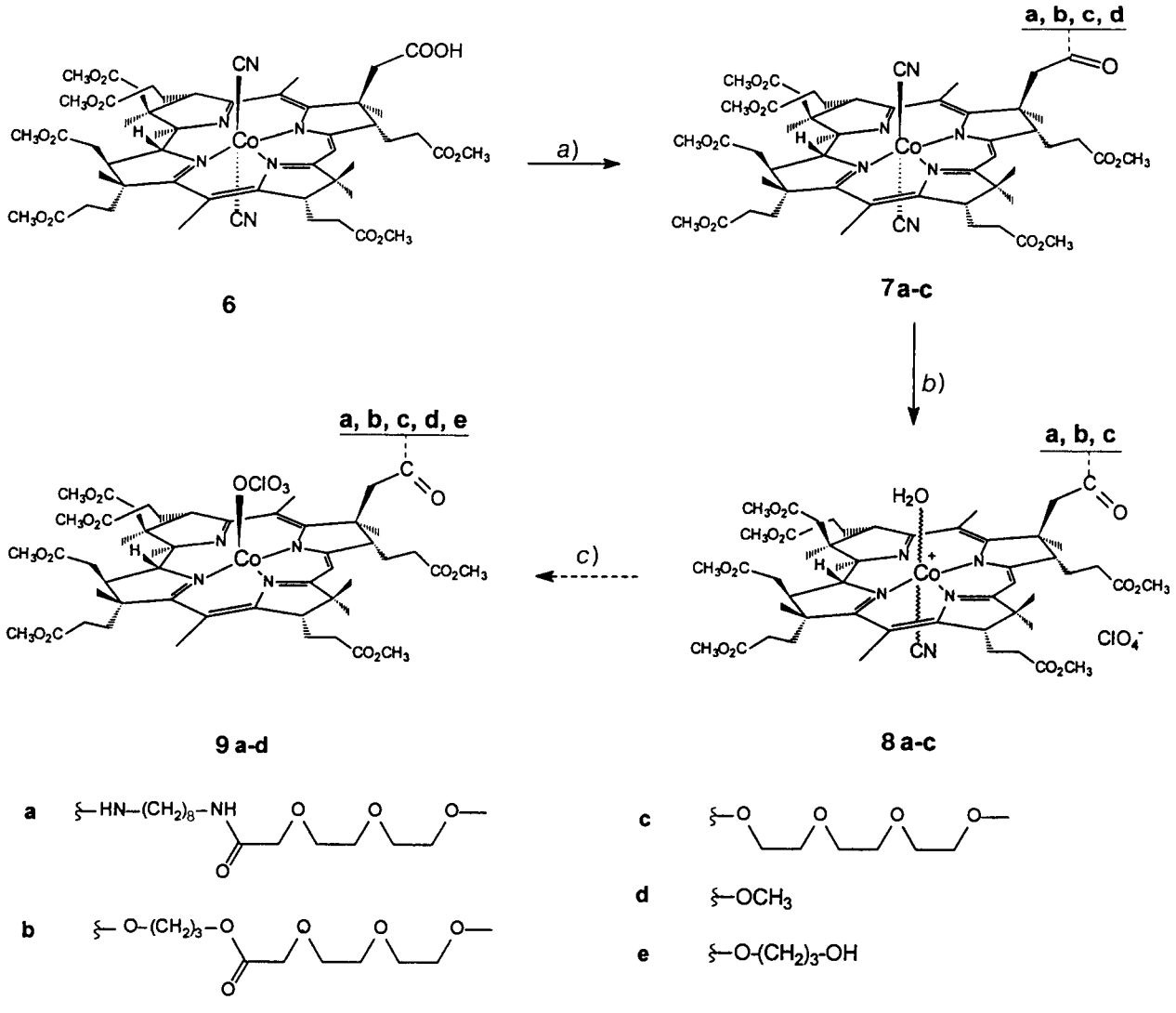
Scheme 1



a) Cl_2CHOMe, $H_2N-(CH_2)_8-NH_2$ (**4**), CH_2Cl_2. *b*) Cl_2CHOMe, $HO-(CH_2)_3-OH$ (**5**), Et_3N.

The amino amide **2** and the hydroxy ester **3** were then attached to the cobester *c*-monoacid **6** (= dicyanocob(III)yrinic acid *a,b,d,e,f,g*-hexamethyl ester) *via* the mixed anhydride formed with 2,2,2-trichloro-1,1-dimethylethyl carbonochloridate to give 88% of **7a** and 40% **7b** (*Scheme 2*).

Alternatively, the condensation could be achieved with EDC/DMAP (*N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide/4-(dimethylamino)pyridine) [15][16], giving the compounds **7b** and **7c** in yields of 58 and 64%, respectively. The new vitamin-B_{12} complexes **7a–c** were identified by ^1H- and ^{13}C-NMR, IR, and electrospray ionization (ESI) mass spectrometry [17].



a) **7a,b**: $ClCOOC(Me)_2CCl_3$, Et_3N, **2** or **3**; **7b,c**: EDC, DMAP, **3** or $MeO(CH_2CH_2O)_2CH_2CH_2OH$. *b*) 30% $HClO_4$ soln. *c*) $NaBH_4$ in MeOH; 30% $HClO_4$ soln.

In the ^{1}H-NMR of **7a**, the signal of H–C(10) appears at 5.52 ppm and lies within the narrow range observed for dicyanocobyrinates (*Fig. 2*). The two signals at 6.95 and 6.99 ppm are due to the H-atoms of the two amide functions and can be slowly exchanged in CD_3OD. The ESI-MS (positive mode) of **7a** gives a peak at *m/z* 1335 assigned to $[M - CN]^+$ (*Fig. 3*). Expansion of this signal gave the expected isotope distribution. A doubly charged peak at *m/z* 668 can be assigned to $[MH - CN]^{2+}$. Similarly, **7b** shows a peak at *m/z* 1266.8, assigned to

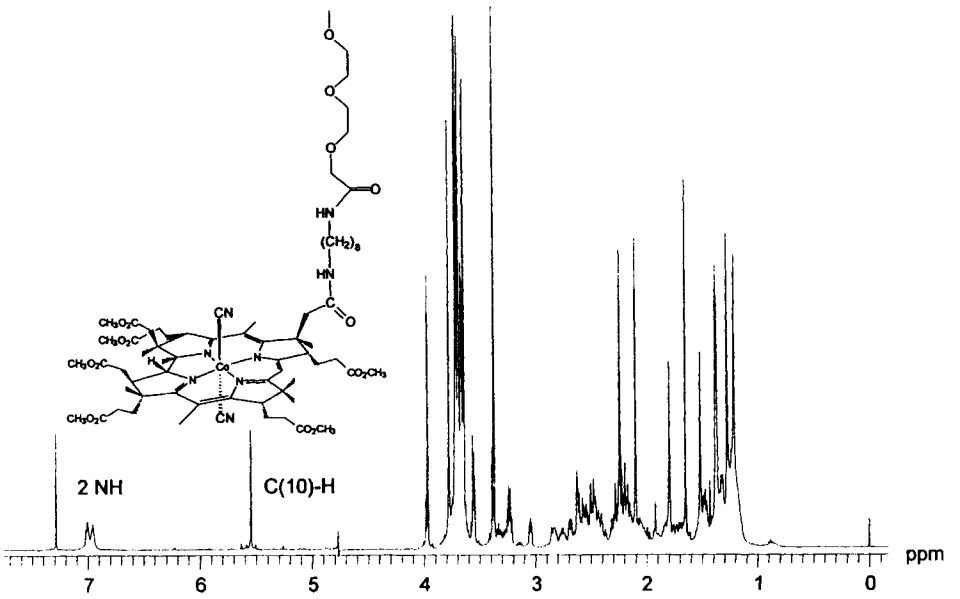


Fig. 2. *^{1}H-NMR Spectrum* (500 MHz, $CDCl_3$) *of* Coα,Coβ-*di(cyano-*κC*)-*N^c-*(10-oxo-12,15,18-trioxa-9-azonon-adec-1-yl)cob(III)yrinic acid*-c-*amide* a,b,d,e,f,g-*hexamethyl ester* (**7a**)

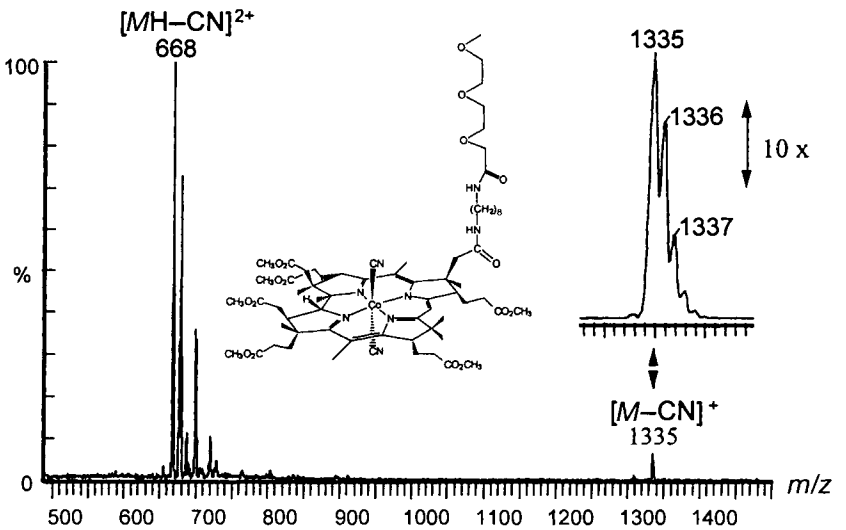


Fig. 3. *Positive-ion ESI mass spectrum of* **7a**

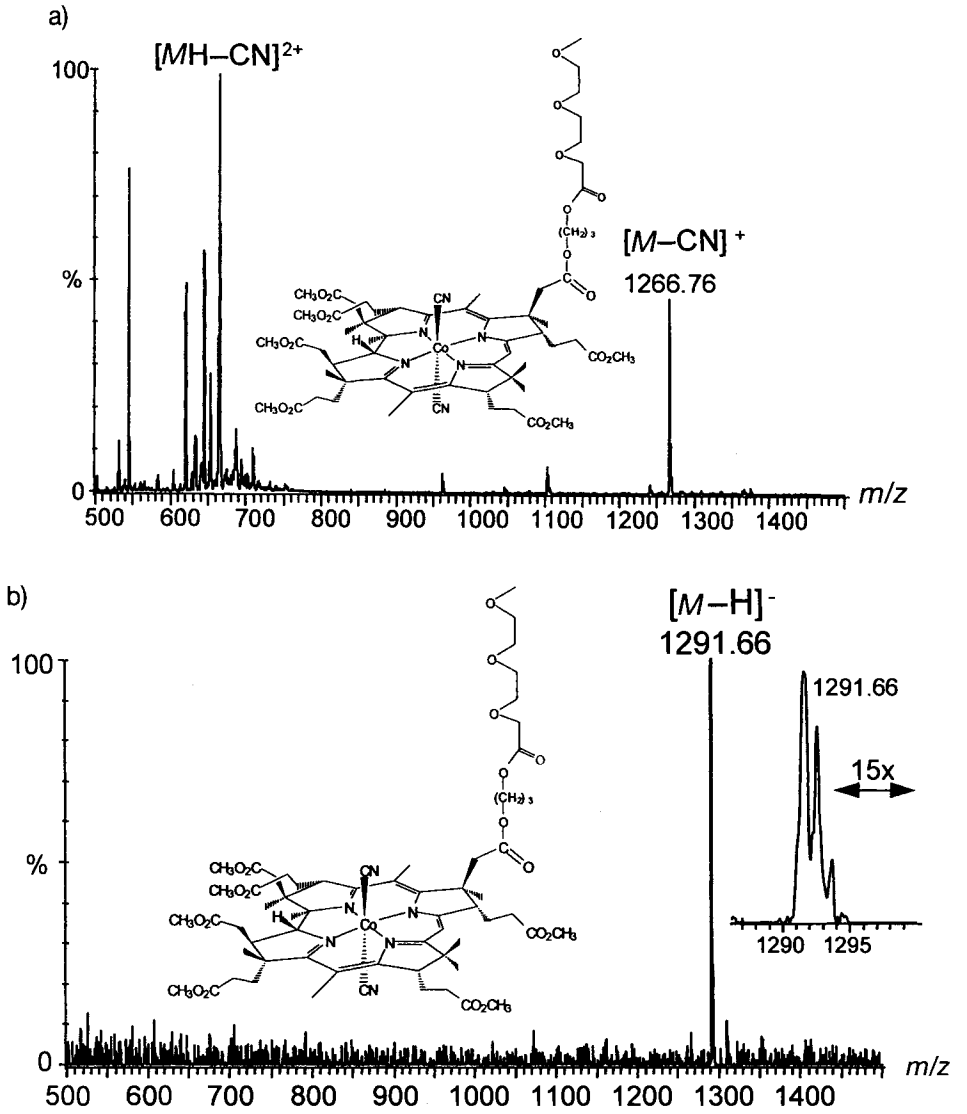


Fig. 4. a) *Positive-ion and* b) *negative-ion ESI mass spectrum of* **7b**. Matrix: MeCN/H_2O 1:1 with 2% Et_3N.

$[M - CN]^+$ and a doubly charged peak at *m/z* 634.4 for $[MH - CN]^{2+}$ (*Fig. 4, a*). The mass of **7b** is further apparent from the corresponding negative-ion ESI-MS, which shows only a peak at *m/z* 1291.7 for $[M - H]^-$ (*Fig. 4, b*). Apart from the peak for $[M - CN]^+$ at *m/z* 1194.7, no other peaks are observed for **7c** (*Fig. 5*).

Ligand Exchange. Treatment of the dicyano complexes **7a–c** with 30% $HClO_4$ solution gave the corresponding aqua-cyanocobyrinates **8a–c** as a mixture of the *Coα*- and *Coβ*-coordination isomers (*Scheme 2*). The presence of these two isomers was confirmed by the presence of two sets of signals appearing in the ^1H- and ^{13}C-NMR spectra for each of the complexes **8a–c**.

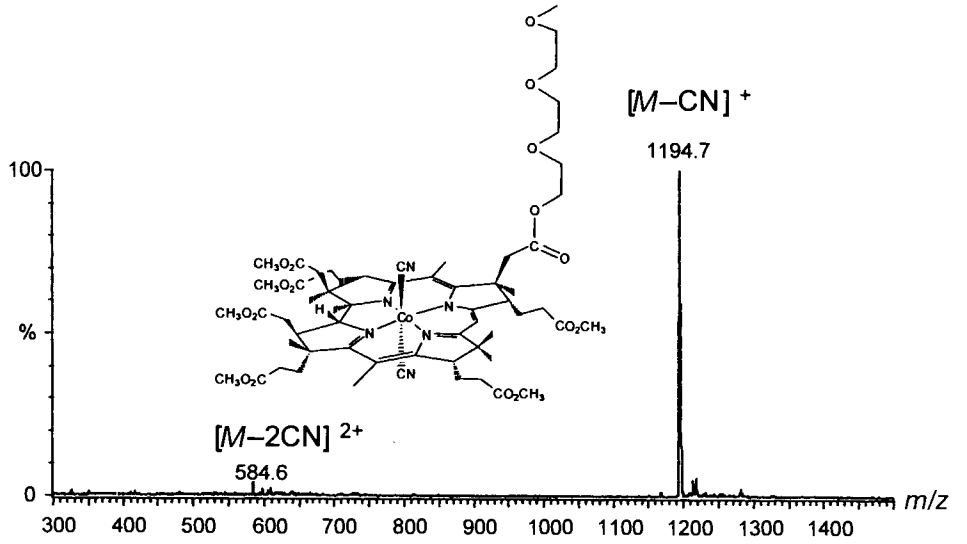


Fig. 5. *Positive-ion ESI mass spectrum of* **7c**

An interesting feature was observed in the ^{1}H-NMR spectra of the aqua-cyano complex **8a**. Due to the two stereoisomers (*Coα*/*Coβ*), the signal of H–C(10) appears as 2*s* at 6.36 and 6.42 ppm. Although 4 signals are expected for the 2 amide groups, the large chemical shifts of 2 of these 4 signals are unexpected (*Fig. 6*). These 4 H-atoms were completely exchanged upon vigorously shaking a solution of **8a** in $CDCl_3$ with D_2O for 2 min. Treatment with H_2O restored the 4 ^{1}H-NMR peaks[1]).

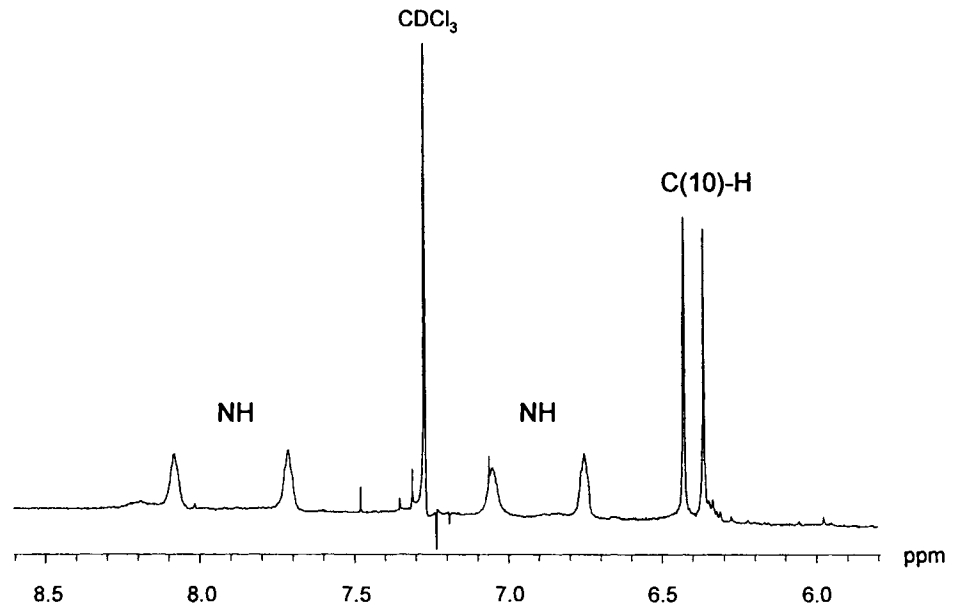


Fig. 6. *Partial ^{1}H-NMR spectrum* (500 MHz, $CDCl_3$) *of* **8a**

[1]) In contrast to this fast exchange, the amide protons in the dicyano complex **7a** were not exchanged under these heterogeneous conditions.

Reduction $Co^{III} \rightarrow Co^{I}$. To prepare the Co^{II} perchlorates **9a–c**, the aqua-cyanocobyrinates **8a–c** were reduced with $NaBH_4$ and subsequently treated with $HClO_4$. According to the ESI- and FAB-MS, the aqua-cyano complex **8a** gave the expected (perchlorato)cobalt(II) complex **9a**. In addition to the parent peak at *m/z* 1335, peaks are detected at *m/z* 1020.3 for a singly charged species and at *m/z* 510 for a doubly charged species. These peaks are assigned to products formed by cleavage of the side chain at the outer functionality.

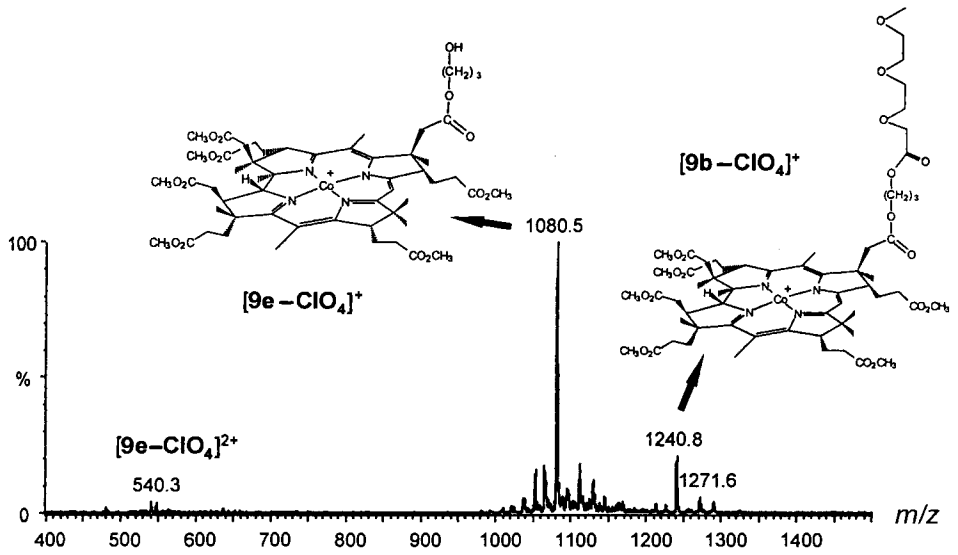


Fig. 7. *Positive-ion ESI mass spectrum of crude* **9b**

In the reaction of complex **8b**, first with $NaBH_4$ and subsequently with 30% $HClO_4$ solution, the expected (perchlorato)cobalt(II) complex **9b** could only be detected as a minor product in the ESI-MS (*Fig. 7*). The major peak at *m/z* 1080.5 and *m/z* 540.3 can be assigned to $[\mathbf{9e} - ClO_4]^+$ and $[\mathbf{9e} - ClO_4]^{2+}$, formed by cleavage of the trioxadecanoic-acid moiety.

In the case of **8c**, where the polyether group is attached to the carboxylic group of **1** without a spacer, the expected complex **9c** is cleanly formed under identical conditions (*Fig. 8*). The small peak at *m/z* 1036.6 observed in the ESI-MS is assigned to the heptamethyl cobester derived ion $[\mathbf{9d} - ClO_4]^+$, most likely formed by transesterification, the remaining ESI-MS peaks are identical with those of complex **9d** prepared independently.

The presence of Co^{I} is necessary for the cleavage of the outer ester group of **8b**. Indeed, when the dicyano cobester **7b** – which is very slowly reduced to Co^{I} under the reaction conditions used – was treated with $NaBH_4$ in MeOH followed by 30% $HClO_4$ solution, the ESI-MS revealed that the original corrin structure had remained intact, with only traces of *m/z* 1080.5 being detected for the $[M - ClO_4]^+$ ion of the cleavage product **9e**. This implies that the hydrolysis of the outer ester group is not due to complexation of the podand with Na^+ ions in MeOH. To exclude the Co^{I}-induced ligand

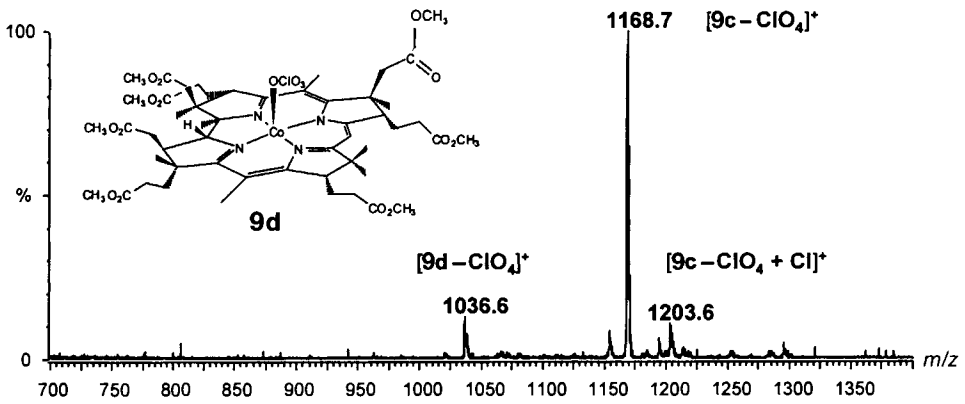


Fig. 8. *Positive-ion ESI mass spectrum of* **9c**

labilization with a subsequent reduction to Co^{I}, the dicyanocobester **7d** was stirred in MeOH for 5 min with vitamin B_{12s}, obtained by reduction of hydroxycobalamin with $NaBH_4$. No ligand exchange or reduction of **7d** could be detected under these conditions. Thus, we suggest that the reaction of the outer amide or ester group occurs by an intramolecular process, with the corrinatocobalt(I) acting as a supernucleophile towards the outer carbonyl group leading to an acyl-Co complex. The acyl complex can then be homolytically cleaved to generate the acyl radical and Co^{II} or it can react with MeOH to give the corresponding methyl ester and Co^{I}. In the case of **8c** without an alkyl spacer, the intramolecular reaction is not favoured, and the Co^{II} complex **8c** can be obtained. The ester functionality of **8b** is more easily cleaved than the amide group present in **8a**, and the octyl spacer thereof might further reduce the intramolecular hydrolysis.

Concluding Remarks. – Vitamin-B_{12} derivatives with a polyether side chain are readily prepared. In the course of the preparation of Co^{II} complexes *via* Co^{I} intermediates, the outer ester moiety in **8b** and the amide group of **8a** are cleaved to a major and minor extent, respectively. There is precedent for reduction of methyl esters with $NaBH_4$ [18]. However, these reactions have been performed in refluxing MeOH, and the esters which underwent such reductions contained neighbouring functional groups. Electrospray mass spectrometry (ESI-MS) was used to identify the new compounds and was found to be a useful tool for the characterization of vitamin-B_{12} derivatives. Further studies for understanding the observed cleavage reactions are under way, with the aim to optimize the syntheses of the desired catalysts.

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Experimental Part

General. The reactions were carried out with reagents and solvents of *puriss.* grade from *Fluka* under Ar. The solns. were degassed by sonication under reduced pressure. Flash chromatography (FC): distilled commercial-grade solvents; silica gel (30–60 μm) from *Baker* (analysed reagents). TLC: *Merck-F-254* precoated sheets,

visualization by 5% phosphomolybdic acid hydrate/EtOH or by UV. Eluent for FC and TLC: if not stated otherwise, CH_2Cl_2/MeOH (0.1% HCN) 10:1. UV/VIS: *Hewlett-Packard 8451 A*; $\lambda_{max}(\varepsilon)$ in nm. IR: *Perkin-Elmer PE 782*; $CHCl_3$ soln. in 0.2-mm path NaCl cells; in cm^{-1}. NMR: *Bruker-AC-300* (^1H, 300 MHz; ^{13}C, 75 MHz) and *Bruker-AC-500* (^1H, 500 MHz; ^{13}C, 125 MHz); δ in ppm rel. to $CDCl_3$ (δ(H) 7.24, δ(C) 77.00) in Hz; ^{13}C multiplicities from DEPT spectra. MS: *Varian MAT-CH-7A*, 70 eV; in *m/z* (%). LSI-MS: *Fision Autospec-Q*; acceleration voltage 8 kV, ionization Cs^+ (32 keV); matrix: dithiothreitol (DTT)/dithioerythriol(DTE); in *m/z* (%). ESI-MS: *Fisions Instrument VG Platform II*; positive-ion measurements (3.5 kV) and negative-ion measurements (2.5 kV); in *m/z* (%) in the solvents given. Acronyms: DMPA, 4-(dimethylamino)pyridine; EDC · HCl: N-[3-(dimethylamino)propyl]-*N'*-ethyl-carbodiimide hydrochloride.

Cyclic Voltammetry: Potentiostat *AMEL 553*; reference electrode *Metrohm 6.0724.000* (SCE), electrolyte bridge *Metrohm 6.1231.000* and *6.1227.000*; working electrode *Metrohm 6.0804.010* (glassy carbon electrode, pretreated by mechanical polishing with Al_2O_3 *Metrohm 6.2802.000*); auxiliary electrode was a Pt wire; scan rates 100 mVs^{-1}; *E* in V. The solns. were deoxygenated by passing a stream of Ar (purified over a *BASF*-BTS catalyst) through the soln.

Coα,Coβ-*Di(cyano-κC)cobyrinic Acid* a,b,d,e,f,g-*Hexamethyl Ester* (**6**). The procedure described in [19][20] was modified: *N*-Bromosuccinimide (5 × 0.52 g, 3.0 mmol) was added in five portions to a stirred soln. of crystalline vitamin B_{12} (15.88 g, 12.18 mmol) in 2M aq. AcOH (1 l) over 2 h in the dark. After 3½ h stirring at r.t. in the dark under Ar, the solvent was evaporated. To the residue, taken up in MeOH (400 ml) and sonicated for 10 min under Ar, a soln. of conc. H_2SO_4 in 100 ml MeOH was added. The soln. was degassed, then slowly heated to gentle reflux, and stirred for 5 days (oil bath: 80°). The mixture was concentrated to 80 ml and taken up in H_2O and ice (400 ml). Upon addition of solid $NaHCO_3$, (→ pH 7) and KCN (1.4 g, 21.5 mmol), the colour changed from red to dark-violet. After extraction with CH_2Cl_2 (3 × 200 ml), the combined org. phase was dried (Na_2SO_4) and evaporated and the residue submitted to FC: 9.5 g (70%) of cobester-*c*-lactone containing a small amount of heptamethyl *Coα,Coβ*-di(cyano-κ*C*)cobyrinate (**9d**): R_f 0.73. To a degassed soln. of crude cobester-*c*-lactone (1.12 g, 1.03 mmol) in toluene (60 ml) and conc. AcOH (10 ml), activated Zn (3 g, 45.9 mmol) was added under Ar [21]. After stirring at r.t. for 30 min, the colour changed to brown and brown-green. The mixture was treated with 1M phosphate buffer (pH 7; 200 ml) and KCN (1.4 g, 21.5 mmol) and filtered. After extraction with CH_2Cl_2 (350 ml), the combined org. phase was filtered over *Celite* and evaporated and the residue submitted to FC: 0.89 g (80%) of **6**. R_f 0.44.

Coα,Coβ-*Di(cyano-κC)*-N^c-*(10-oxo-12,15,18-trioxa-9-azanonadec-1-yl)cob(III)yrinic Acid*-c-*amide* a,b,d,e,f,g-*Hexamethyl Ester* (**7a**). Acid **6** (200 mg, 0.186 mmol) was dried by repeated (3 ×) evaporation of a soln. in CH_2Cl_2 (10 ml). To the soln. in CH_2Cl_2 (20 ml) was added 2,2,2-trichloro-1,1-dimethylethyl carbonochloridate (100 mg, 0.4 mmol) and, dropwise, Et_3N (0.19 ml, 14 mmol) at −10°. Ater 10 min at −10°, the soln. was warmed to r.t. and stirred for 1 h. Amine **2** (170 mg, 0.558 mmol) in CH_2Cl_2 (10 ml) was added dropwise and the mixture refluxed for 18 h. After evaporation, the violet residue was submitted to FC: 224 mg (88%) of **7a**. R_f 0.60. UV/VIS ($c = 1.39 \cdot 10^{-5}$ M, CH_2Cl_2): 227 (sh, 34892), 278 (8992), 316 (7913), 352 (10790), 370 (sh, 21582), 420 (2230), 508 (4892), 548 (6834), 588 (8633). IR: 3440*w*, 3360*w*, 3000*s*, 2960*s*, 2940*s*, 2140*w*, 1740*vs*, 1670*vs*, 1590*vs*, 1540*s*, 1510*vs*, 1440*vs*, 1410*m*, 1370*s*, 1360*m*, 1210*s*, 1160*s*, 1110*s*, 1020*m*, 920*vs*, 790*vs*, 740*vs*, 670*vs*. ^1H-NMR (500 MHz): 1.16–1.83 (*m*, superimposed 1.20 (*s*), 1.26 (*s*), 1.36 (*s*), 1.37 (*s*), 1.51 (*s*), 1.79 (*s*), total 34 H); 1.85–2.62 (*m*, superimposed 2.08 (*s*), 2.21 (*s*), total 24 H); 2.63–3.88 (3*m*, 3 H); 2.98–3.03 (*m*, 1 H); 3.20–3.25 (*m*, 4 H); 3.36 (*s*, 3 H); 3.53–3.75 (*m*, 2 H); 3.63–3.77 (*m*, superimposed 3.64 (*s*), 3.66 (*s*), 3.68 (*s*), 3.70 (*s*), 3.71 (*s*), 3.77 (*s*), total 25 H); 5.52 (*s*, 1 H); 6.9–7.08 (2*m*, 2 H). ^{13}C-NMR (125 MHz): 15.27 (*q*); 15.30 (*q*); 16.86 (*q*); 18.40 (*q*); 19.22 (*q*); 19.71 (*q*); 21.96 (*q*); 24.81 (*t*); 25.69 (*t*); 25.76 (*t*); 26.85 (*t*); 26.90 (*t*); 29.05 (*t*); 29.19 (*t*); 29.25 (*t*); 29.56 (*t*); 29.61 (*t*); 30.73 (*t*); 30.83 (*t*); 31.42 (*q*); 31.72 (*t*); 32.40 (*t*); 33.65 (*t*); 38.81 (*t*); 39.15 (*d*); 39.69 (*t*); 41.58 (*t*); 46.07 (*s*); 46.96 (*s*); 47.24 (*t*); 51.36 (*s*); 51.57 (*q*); 51.59 (*q*); 51.80 (*q*); 51.86 (*q*); 52.38 (*q*); 53.50 (*d*); 56.56 (*d*); 58.42 (*s*); 58.65 (*d*); 58.96 (*q*); 70.14 (*t*); 70.34 (*t*); 70.48 (*t*); 70.89 (*t*); 71.82 (*t*); 74.61 (*d*); 82.59 (*s*); 91.35 (*d*); 102.16 (*s*); 106.67 (*s*); 161.53 (*s*); 163.45 (*s*); 169.45 (*s*); 169.68 (*s*); 171.31 (*s*); 171.48 (*s*); 171.61 (*s*); 172.48 (*s*); 172.83 (*s*); 173.57 (*s*); 173.81 (*s*); 175.31 (*s*); 175.74 (*s*); 175.85 (*s*). LSI-MS (calc. for $C_{68}H_{101}CoN_8O_{17}$: 1361.54): 1334 (65, $[M - CN]^+$), 1308 (100, $[M - 2CN]^+$), 1293 (3), 1148 (5), 962 (20). ESI-MS (pos.; MeCN/H_2O 1:1, 2% formic acid): 1361 (1, M^+), 1335 (16, $[M - CN]^+$), 702 (35), 679 (58), 668 (100, $[M + H - CN]^{2+}$).

Coα,Coβ-*Di(cyano-κC)cob(III)yrinic Acid* a,b,d,e,f,g-*Hexamethyl* c-*(5-Oxo-4,7,10,13-tetraoxa-1-tetradec-1-yl) Ester* (**7b**). Analogously to **7a**, **6** (700 mg, 0.65 mmol) was dissolved in CH_2Cl_2 (50 ml) and treated with DMAP (200 g, 1.6 mmol) and **3** (460 mg, 1.95 mmol) at 0°. After addition of EDC · HCl (0.4 g, 2.08 mmol), the mixture was stirred for 30 min at 0° and 5 h at r.t. The org. phase was washed with 5% HCOOH soln. (20 ml), sat. $NaHCO_3$ soln. (20 ml), and 1% KCN soln. (10 ml), dried (Na_2SO_4), and evaporated and the violet residue submitted to FC (AcOEt/CH_2Cl_2/MeOH (0.1% HCN) 10:10:1): 0.485 g (58%) of **7b**. R_f 0.34 (AcOEt/CH_2Cl_2/

MeOH (0.1% HCN) 10:10:1). UV/VIS ($c = 1.62 \cdot 10^{-6}$ M, CH_2Cl_2): 232 (sh, 34280), 280 (12520), 316 (10830), 372 (sh, 27350), 424 (4490), 512 (6370), 550 (9370), 590 (11410). IR: 3010*w*, 2980*m*, 2960*m*, 2940*w*, 2340*w*, 2140*w*, 1740*vs*, 1585*m*, 1500*m*, 1445*s*, 1370*m*, 1360*m*, 1200*s*, 1160*m*, 1110*m*, 1020*w*. ^{1}H-NMR (500 MHz): 1.16 (*s*), 1.22 (*s*), 1.30 (*s*), 1.34 (*s*), 1.46 (*s*), 1.52 (*s*, total 18 H); 1.60–1.90 (*m*, 3 H); 1.91–2.75 (*m*, superimposed 2.14 (*s*), 2.18 (*s*), total 27 H); 2.71–2.82 (*m*, 1 H); 2.98–3.09 (*m*, 1 H); 3.37 (*s*, 3 H); 3.41–3.48 (*m*, 1 H); 3.52–3.79 (*m*, superimposed 3.63 (*s*), 3.67 (*s*), 3.69 (*s*), 3.70 (*s*), 3.72 (*s*), 3.76 (*s*), total 28 H); 4.11–4.28 (*t*, superimposed 4.16 (*s*) and 4.22 (*t*, $J = 6.14$), total 6 H); 5.58 (*s*, 1 H). ^{13}C-NMR (125 MHz): 15.19 (*q*); 15.88 (*q*); 16.88 (*q*); 18.42 (*q*); 19.13 (*q*); 19.71 (*q*); 21.98 (*q*); 24.87 (*t*); 25.62 (*t*); 26.36 (*t*); 27.83 (*t*); 29.64 (*t*); 30.63 (*t*); 30.96 (*t*); 31.04 (*q*); 31.75 (*t*); 32.49 (*t*); 33.66 (*t*); 39.16 (*d*); 41.03 (*t*); 42.14 (*t*); 45.53 (*s*); 46.96 (*s*); 48.53 (*s*); 51.54 (*q*); 51.55 (*q*); 51.73 (*q*); 51.77 (*q*, 2 × int.); 52.32 (*q*); 53.52 (*d*); 53.96 (*d*); 56.53 (*d*); 58.24 (*s*); 58.97 (*q*); 60.98 (*t*); 61.10 (*t*); 68.49 (*t*); 70.48 (*t*); 70.57 (*t*); 70.88 (*t*); 71.83 (*t*); 74.70 (*d*); 82.49 (*s*); 91.15 (*d*); 102.14 (*s*); 103.50 (*s*); 163.38 (*s*); 163.45 (*s*); 170.28 (*s*); 170.40 (*s*); 171.28 (*s*); 171.67 (*s*); 171.87 (*s*); 172.69 (*s*); 172.88 (*s*); 173.48 (*s*); 173.85 (*s*); 175.18 (*s*); 175.54 (*s*); 176.20 (*s*). ESI-MS (pos. MeCN/H_2O 1:1, 2% formic acid, $C_{63}H_{89}CoN_6O_{19}$, calc. 1293.37): 1266.7 (50, $[M - CN]^+$), 633.8 (30, $[MH - CN]^{2+}$). ESI-MS (neg. ion, MeCN/H_2O 1:1, 2% Et_3N): 1291.7 (100, $[M - H]^-$).

Co*α*,Co*β*-*Di(cyano-κC)cob(III)yrinic Acid* c-*{2-[2-(2-Methoxyethoxy)ethoxy]ethyl}* a,b,d,e,f,g-*Hexamethyl Ester* (**7c**). As described for **7a**, with **6** (400 mg, 0.37 mmol), DMAP (90 mg, 0.74 mmol), triethylene glycol monomethyl ether (183 mg, 1.12 mmol), and EDC (220 mg, 1.4 mmol): 293 mg (65%) of **7c**. Violet powder. R_f 0.34 (AcOEt/CH_2Cl_2/MeOH (0.1% HCN) 10:10:1). UV/VIS ($c = 7.2 \cdot 10^{-5}$ M, CH_2Cl_2): 234 (sh, 18925), 280 (7350), 318 (590), 372 (sh, 18045), 424 (1876), 510 (2914), 550 (5635), 590 (7290). IR ($CHCl_3$): 3400*w*, 2970*m*, 2920*w*, 1740*vs*, 1585*m*, 1500*m*, 1440*m*, 1370*m*, 1200*m*, 1150*m*, 1100*m*, 1030*w*. ^{1}H-NMR (300 MHz): 1.17, 1.22 (2*s*, total 6 H); 1.31, 1.34 (2*s*, total 6 H); 1.48 (*s*, 3 H); 1.54 (*s*, total 3 H); 1.62–1.92 (*m*, 3 H); 1.95–2.08 (*m*, superimposed 2.14 (*s*), 2.18 (*s*), total 14 H); 2.31–2.82 (*m*, 13 H); 2.98–3.09 (*m*, 1 H); 3.34 (*s*, 3 H); 3.41–3.48 (*m*, 1 H); 3.48–3.58 (*m*, 2 H); 3.58–3.79 (*m*, superimposed 3.59 (*s*), 3.63 (*s*), 3.66 (*s*), 3.68 (*s*), 3.73 (*s*), 3.76 (*s*), total 27 H); 4.16–4.28 (*m*, 2 H); 5.55 (*s*, 1 H). ^{13}C-NMR (75 MHz): 15.20 (*q*); 15.88 (*q*); 16.87 (*q*); 18.41 (*q*); 19.05 (*q*); 19.77 (*q*); 21.99 (*q*); 24.93 (*t*); 25.66 (*t*); 26.50 (*t*); 29.67 (*t*); 30.68 (*t*); 31.04 (*t*); 31.10 (*q*); 31.77 (*t*); 32.54 (*t*); 33.77 (*t*); 39.21 (*d*); 41.06 (*t*); 42.20 (*t*); 45.57 (*s*); 46.97 (*s*); 48.50 (*s*); 51.53 (*q*, 2 × int.); 51.71 (*q*); 51.77 (*q*, 2 × int.); 52.32 (*q*); 53.59 (*d*); 54.05 (*d*); 56.59 (*d*); 58.26 (*s*); 58.97 (*q*); 63.65 (*t*); 68.95 (*t*); 70.48 (*t*); 70.51 (*t*); 70.57 (*t*); 71.88 (*t*); 74.72 (*d*); 82.51 (*s*); 91.24 (*d*); 102.10 (*s*); 103.52 (*s*); 163.44 (*s*); 163.66 (*s*); 170.45 (*s*); 171.48 (*s*); 171.70 (*s*); 171.89 (*s*); 172.69 (*s*); 172.89 (*s*); 173.47 (*s*); 173.85 (*s*); 175.22 (*s*); 175.54 (*s*); 176.17 (*s*). ESI-MS (pos. MeCN/H_2O 1:1; calc. for $C_{60}H_{85}CoN_6O_{17}$: 1221.31): 1194.6 (100, $[M - CN]^+$), 584.6 (5, $[M - CN]^{2+}$).

Co*α*(*or* Co*β*)-*Aqua*-Co*β*(*or* Co*α*)-(*cyano*-κC)-N^c-*(10-oxo-12,15,18-trioxa-9-azanonadec-1-yl)cob(III)yrinic Acid*-c-*amide* a,b,d,e,f,g-*Hexamethyl Ester Perchlorate* (**8a**). A 30% $HClO_4$ soln. (90 ml) and **7a** (1.5 g, 1.1 mmol) in CH_2Cl_2 (100 ml) were sonicated for 15 min under periodic evacuation (3 ×) to eliminate HCN. The aq. phase was extracted with CH_2Cl_2 (3 × 150 ml), the combined org. phase washed with H_2O (80 ml) and evaporated, and the residue dissolved in CH_2Cl_2 (4 ml) and precipitated with Et_2O/hexane 1:2 (100 ml). The precipitate was dried under high vacuum to give 1.53 g (95%) of **8a**. Brownish red powder. UV/VIS ($c = 1.238 \cdot 10^{-5}$ M, CH_2Cl_2): 235 (19789), 270 (7100), 352 (10255), 405 (2524), 487 (3944), 523 (3392). IR ($CHCl_3$): 3120*w*, 2980*m*, 2960*vs*, 2940*s*, 2140*w*, 1790*w*, 1740*vs*, 1660*vs*, 1580*vs*, 1490*s*, 1440*vs*, 1380*s*, 1260*s*, 1050–1200*s*, 1020*m*, 910*vs*, 800*w*, 700*vs*, 650*vs*, 620*m*. ^{1}H-NMR (500 MHz): 1.41–1.60 (*m*, superimposed 1.19 (*s*), 1.34 (*s*), 1.38 (*s*), 1.39 (*s*), 1.46 (*s*), 1.54 (*s*), total 27 H); 1.60–1.96 (*m*, superimposed 1.73 (*s*), 1.76 (*s*), 1.91 (*s*), total 7 H); 1.90–2.45 (*m*, superimposed 2.23 (*s*), 2.32 (*s*), 2.35 (*s*), 2.39 (*s*), total 16 H); 2.50–2.80 (*m*, total 9 H); 3.02–3.11 (*m*, 1 H); 3.18–3.40 (*m*, superimposed 3.36 (*s*), total 7 H); 3.36 (*s*, 3 H); 3.52–3.58 (*m*, 2 H); 3.60–3.76 (*m*, superimposed 3.61 (*s*), 3.63 (*s*), 3.64 (*s*), 3.69 (*s*), 3.70 (*s*), 3.71 (*s*), 3.73 (*s*), 3.74 (*s*), total 16 H); 3.78–4.20 (*m*, superimposed 3.79 (*s*), 3.80 (*s*), total 8 H); 4.12, 4.15 (2*s*, 2 H); 6.36, 6.42 (2*s*, 1 H); 6.75, 6.06, 7.71, 8.08 (4*m*, 2 H). LSI-MS (calc. for $C_{67}H_{103}ClCoN_7O_{22}$: 1452.98): 1451 (3, M^+), 1352 (14, $[M - ClO_4]^+$), 1334 (65, $[M - H_2O - ClO_4]^+$), 1308 (100, $[M - H_2O - CN - ClO_4]^+$), 1293 (3), 1149 (5), 963 (20), 802 (5), 473 (4), 309 (14). ESI-MS (pos., MeCN/H_2 1:1, 2% formic acid): 1334 (100, $[M^+ - H_2O - ClO_4]^+$), 1334 (6), 1064 (6).

Co*α*(*or* Co*β*)-*Aqua*-Co*β*(*or* Co*α*)-(*cyano*-κC)*cob(III)yrinic Acid* a,b,d,e,f,g-*Hexamethyl c-(5-Oxo-4,7,10,13-tetraoxatetradec-1-yl) Ester Perchlorate* (**8b**). As described for **8a**, with **7b** (450 mg, 0.345 mmol), CH_2Cl_2 (50 ml), and 30% $HClO_4$ soln. (40 ml). The residue was dissolved in CH_2Cl_2/MeOH 10:1 (10 ml) and injected into hexane (100 ml). The precipitation procedure was repeated twice: **8b** (448 mg, 93%). Brownish red powder. UV/VIS ($c = 3.0373 \cdot 10^{-5}$ M, CH_2Cl_2): 232 (sh, 29080), 324 (14480), 356 (sh, 18350), 406 (8420), 484 (7700). IR ($CHCl_3$): 3500–3100*w*, 2990*s*, 2940*m*, 2360*w*, 1740*vs*, 1638*w*, 1585*s*, 1500*s*, 1445*s*, 1360*m*, 1240*vs*, 1200*s*, 1140*m*, 1050*m*, 1020*w*, 860*w*. ^{1}H-NMR (500 MHz): 1.10–1.70 (*m*, total 21 H); 1.71–2.05 (*m*, 3 H); 2.12–2.40 (*m*, superimposed 2.26 (*s*), 2.32 (*s*), total 15 H); 2.45–2.76 (*m*, 10 H); 2.95–3.07 (*m*, 1 H); 3.27–3.58 (*m*, superimposed 3.30 (*d*), total 4 H); 3.46–3.50 (*m*, 2 H); 3.52–3.72 (*m*, total 25 H); 4.01–4.36 (*m*, superimposed 4.09 (*s*) and 4.16 (*t*),

total 7 H); 4.27 (*d*, 1 H); 6.47 (2*s*, 1 H). ESI-MS (pos., $MeCN/H_2O$ 1:1, 2% formic acid; calc. for $C_{62}H_{91}ClCoN_5O_{24}$: 1384.82): 1266.7 (10, $[M - H_2O - ClO_4]^+$), 645.1 (100), 634.1 (30), 620.7, 545.2 (60). ESI-MS (pos., $MeCN/H_2O$ 1:1, 2% $LiClO_4$): 1372.8 (10, $[M + Li]^+$), 1266.7 (100, $[M - H_2O - ClO_4]^+$), 637.1 (85, $[M - H_2O - ClO_4 + Li]^{2+}$).

Coα(or Coβ)-Aqua-Coβ(or Coα)-(cyano-κC)cob(III)yrinic Acid-c-{*2-[2-(2-Methoxyethoxy)ethoxyl]ethyl*} a,b,d,e,f,g-*Hexamethyl Ester Perchlorate* (**8c**). As described or **8a**, with **7c** (280 mg, 0.229 mmol): **8c** (290 mg, 96%). Dark-red powder. UV/VIS ($c = 3.81 \cdot 10^{-5}$ M, CH_2Cl_2): 234 (sh, 34120), 275 (13960), 327 (14800), 356 (24030), 406 (7435), 488 (9520). IR ($CHCl_3$): 3500–3100*w*, 2990*s*, 2940*m*, 1740*vs*, 1640*s*, 1585*s*, 1500*s*, 1450*s*, 1355*m*, 1240*vs*, 1200*s*, 1140*m*, 1050*m*, 860*w*. ^{1}H-NMR (300 MHz): 1.15–1.68 (*m*, overlapped 1.19 (*s*), 1.41 (*s*), 1.43 (*s*), 1.48 (*s*), 17 H); 1.72–2.00 (*m*, 6 H); 2.00–2.42 (*m*, overlapped 2.30 (*s*), 2.37 (*s*), 2.40 (*s*), 14 H); 2.48–2.98 (*m*, 11 H); 3.40–3.48 (*m*, 4 H), 3.63–3.80 (*m*, with overlapping *s*, 27 H); 4.00–4.39 (*m*, 4 H); 6.52, 6.63 (2*s*, 1 H). ESI-MS (pos. $MeCN/H_2O$ 1:1); calc. for $C_{59}H_{87}ClCoN_5O_{22}$: 1312.75): 1194.6 (100, $[M - H_2O - ClO_4]^+$), 597.8 (30, $[M + H - H_2O - ClO_4]^{2+}$), 584.78 (30, $[M - H_2O - CN - ClO_4]^{2+}$).

N^c-*(10-Oxo-12,15,18-trioxa-9-azanonadec-1-yl)-Coβ-(perchlorato)cob(II)yrinic Acid*-c-*amide* a,b,d,e,f,g-*Hexamethyl Ester* (**9a**). A soln. of **8a** (1.5 g, 1.1 mmol) in $H_2O/MeOH$ 1:1 (50 ml) was sonicated for 15 min under Ar, treated with $NaBH_4$ (0.95 g; 25.07 mmol) in portions, and stirred for 20 min. Upon addition of 30% $HClO_4$ soln. (20 ml), the colour turned immediately from brownish to orange. After evaporation and addition of a phosphate buffer (0.5M, pH 7; 50 ml), the soln. was extracted with CH_2Cl_2 (300 ml) to yield a dark-orange powder which was dissolved in MeOH (2–3 ml) and precipitated by hexane. The crude **9a** was dried under high vacuum (150 mg, 81%). UV/VIS ($c = 5.68 \cdot 10^{-5}$ M, CH_2Cl_2): 230 (19373), 316 (7044), 350 (sh, 9510), 416 (1162), 500 (3751), 516 (3698). IR ($CHCl_3$): 3720*w*, 3640*w*, 3020*s*, 2980*s*, 2940*s*, 2920*w*, 1740*vs*, 1680*m*, 1580*m*, 1540*s*, 1520*s*, 1440*vs*, 1400*m*, 1210–1300*vs*, 1110*m*, 630*m*. LSI-MS (calc. for $C_{66}H_{101}ClCoN_6O_{21}$: 1408.95): 1307 (40, $[M - ClO_4]^+$), 963 (10), 890 (8).

Reduction of **8b**. $NaBH_4$ (0.95 g, 25.07 mmol) was added in portions to degassed $H_2O/MeOH$ 5:1 (15 ml) at −6° under Ar. After addition of **8b** (5 mg, 0.004 mmol), the colour turned from red to green and changed immediately to orange when degassed, cooled 30%. $HClO_4$ soln. (20 ml) was added. After addition of phosphate buffer (1M, pH 7; 20 ml), the aq. phase was extracted with CH_2Cl_2 (80 ml) and the combined org. phase washed with H_2O (160 ml) and 1% $NaClO_4$ soln. (160 ml), dried (Na_2SO_4), and evaporated. The product mixture (3 mg) was dried under high vacuum. UV/VIS ($c = 7.6 \cdot 10^{-5}$ M, CH_2Cl_2): 230 (sh, 17443), 268 (sh, 18418), 316 (sh, 21547), 409 (6576), 470 (10407). IR ($CHCl_3$): 3440*w*, 2980*vs*, 2920*s*, 1740*vs*, 1580*s*, 1505*s*, 1445*vs*, 1350*s*, 1290*s*, 1200*m*, 630*m*. ESI-MS (pos. $MeCN/H_2O$ 1:1, 2% formic acid; calc. for $C_{61}H_{89}ClCoN_4O_{23}$: 1340.78): 1240.8 (100, $[M - ClO_4]^+$), 1080.5 (2, [by-product]$^+$). CV (reversible waves): in MeCN (0.1M $LiClO_4$): E_p^{red} (Co^{II}/Co^{I}) = −0.75 V, E_p^{ox}(Co^{I}/Co^{II}) = −0.67 V; in MeOH (0.1M $LiClO_4$): E_p^{red}(Co^{II}/Co^{I}) = −0.72 V; E_p^{ox}(Co^{I}/Co^{II}) = −0.68 V.

Coβ-(Perchlorato)cob(II)yrinic Acid-c-{*2-[2-(2-Methoxyethoxy)ethoxy]ethyl*} a,b,d,e,f,g-*Hexamethyl Ester* (**9c**). To $NaBH_4$ (130 mg, 3.4 mmol) in MeOH (40 ml) under Ar a soln. of **8c** (150 mg, 0.11 mmol) in degassed MeOH (4 ml) was added at 0° (→ green). After 10 s, degassed 30% $HClO_4$ soln. (20 ml) was added, and the colour turned immediately to orange. After addition of phosphate buffer (0.1M, pH 7, 50 ml), the aq. phase was extracted with CH_2Cl_2 (150 ml), the combined org. phase washed with H_2O (200 ml), 1% $NaClO_4$ soln. (200 ml), dried, and evaporated, and the residue dissolved in CH_2Cl_2 and precipitated with hexane. The precipitate was dissolved in CH_2Cl_2 (10 ml), and, after evaporation, dried under high vacuum: 130 mg (89%) of **9c**. UV/VIS ($c = 3.3 \cdot 10^{-5}$ M, CH_2Cl_2): 232 (sh, 23969), 268 (sh, 21240), 318 (sh, 28422), 409 (8484), 470 (13350). IR ($CHCl_3$): 3600–3100*w*, 2980*s*, 2915*s*, 1750*vs*, 1580*s*, 1495*s*, 1440*s*, 1360*vs*, 1100*s*, 630*m*. ESI-MS (pos., Me CN/H_2O 1:1; calc. for $C_{58}H_{85}ClCoN_4O_{21}$. 1268.72): 1203.6 (10, $[M - ClO_4 + Cl]^+$), 1168.7 (100, $[M - ClO_4]^+$). CV (reversible waves): MeCN (0.1M $LiClO_4$), E_p^{red}(Co^{II}/Co^{I}) = −0.73 V, E_p^{ox}(Co^{I}7Co^{II}) = −0.66 V; in MeOH (0.1M $LiClO_4$), E_p^{red}8Co^{II}/Co^{I}) = −0.68 V, E_p^{ox}(Co^{I}/Co^{II}) = −0.62 V.

N-*(8-Aminooctyl)-2-[2-(2-methoxyethoxy)ethoxy]acetamide* (**2**). A soln. of dichloro(methoxy)methane (1.59 g, 13.7 mmol) in CH_2Cl_2 (15 ml) was slowly and dropwise added to a mixture of octane-1,8-diamine (**4**; 3.06 g, 21 mmol) and 2-[2-(2-methoxyethoxy)ethoxy]acetic acid (**1**; 1.88 g, 10.6 mmol) in CH_2Cl_2 (25 ml) at −7° under N_2. After 4 h, H_2O (40 ml) was added, the org. phase washed with H_2O (3 × 50 ml) and evaporated, and the residue submitted to FC ($MeOH/AcOEt/CH_2Cl_2$ 8:1:1, 1% Et_3N): **2** (1.7 g, 40%). White powder. R_f 0.15 ($MeOH/AcOEt/CH_2Cl_2$ 8:1:1, 1% Et_3N (ninhydrin)). IR: 3440*s*, 3360*s*, 2940*s*, 2890*vs*, 2840*s*, 1740*s*, 1670*vs*, 1535*vs*, 1460*s*, 1360*m*, 1340*s*, 1280*m*, 1240*s*, 1120*vs*, 1030*m*, 855*w*, 580*w*. ^{1}H-NMR: 1.31 (br. *s*, 8 H); 1.34–1.59 (2*m*, superimposed 1.54 (*s*), total 6 H); 2.67 (*dt*, *J* = 2.9, 6.9, 2 H); 3.23–3.28 (*m*, 2 H); 3.37 (*s*, 3 H); 3.54–3.57 (*m*, 2 H); 3.58–3.68 (*m*, 6 H); 3.96 (*s*, 2 H); 7.12 (*s*, 1 H). ^{13}C-NMR: 26.79 (*t*); 26.87 (*t*); 29.25 (*t*); 29.36 (*t*); 29.60 (*t*); 33.62 (*t*); 38.84 (*t*); 42.20 (*t*); 58.90 (*q*); 70.16 (*t*); 70.38 (*t*); 70.47 (*t*); 70.94 (*t*); 71.84 (*t*); 169.7 (*s*). MS: 304

(4, M^+), 275 (5), 273 (6), 260 (7), 201 (66), 184 (8), 172 (25), 155 (11), 142 (41), 133 (9), 128 (16), 114 (92), 100 (62), 8 (51), 72 (47), 59 (100), 44 (32), 30 (76). HR-MS: 304.233343 ($C_{15}H_{32}O_4N_2^+$; calc. 304.236208).

3-Hydroxypropyl 2-[2-(2-Methoxyethoxy)ethoxy]acetate (**3**). A mixture of **1** (2.00 g, 11.2 mmol) and dichloro(methoxy)methane (1.66 g, 14.5 mmol) was stirred at 35° for 24 h under Ar. Excess dichloro(methoxy)methane was evaporated, the acyl chloride added dropwise to propane-1,3-diol (**5**; 8.82 g, 89.6 mmol) and Et_3N (1 ml) at 0°, and the mixture stirred overnight at r.t. CH_2Cl_2/H_2O 1:1 (80 ml) was added to the mixture, the org. layer separated, and the aq. layer extracted with CH_2Cl_2 (90 ml). The combined org. phase was washed with Na_2CO_4 soln. (100 ml) and brine (100 ml), dried (Na_2SO_4), and evaporated. The residue was submitted to FC (AcOEt/MeOH 4:1): **3** (1.44 g, 55%). R_f 0.48 (AcOEt/MeOH 4:1). IR: 3690*w*, 3630*m*, 3600–3200*m*, 2920*vs*, 2900*vs*, 1750*vs*, 1630*w*, 1460*s*, 1430*m*, 1400*m*, 1360*m*, 1280*s*, 1240*vs*, 1180–1080*vs*, 1050*vs*, 980*s*, 940*s*, 860*s*. ^{1}H-NMR (300 MHz): 1.85–1.93 (*m*, 2 H); 2.30 (br. *s*, 1 H); 3.37 (*s*, 3 H); 3.54–3.58 (*m*, 2 H); 3.63–3.75 (*m*, 8 H); 4.14 (*s*, 2 H); 4.31 (*t*, J = 6.14, 2 H). ^{13}C-NMR (75 MHz): 31.55 (*t*); 58.98 (*q*); 59.06 (*t*); 61.91 (*t*); 68.68 (*t*); 70.50 (*t*); 70.64 (*t*); 70.94 (*t*); 71.88 (*t*); 170.80 (*s*). MS: 236 (1, *M*, $C_{10}H_{20}O_6^+$), 204 (1), 179 (4), 161 (10), 133 (12), 117 (18), 103 (54), 89 (32), 75 (14), 59 (100), 45 (60), 31 (40).

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