Pergamon

Tetrahedron Letters 40 (1999) 6383–6387

TETRAHEDRON LETTERS

Synthesis of calix[4]arene podands bearing two and four histidine or glycine groups at the lower rim. Complexation properties towards cobalt(II) chloride

Yann Molard,[a] Cécile Bureau,[a] Hélène Parrot-Lopez,[a] Roger Lamartine [a] and Jean-Bernard Regnouf-de-Vains [b,*]

[a]*Laboratoire de Chimie Industrielle, associée au CNRS, Université Claude-Bernard, 69622, Villeurbanne, France*
[b]*G.E.V.S.M, associé au CNRS, Faculté de Pharmacie, Université Henri Poincaré, 54000, Nancy, France*

Received 27 May 1999; accepted 22 June 1999

Abstract

Four calix[4]arene podands displaying two or four glycine or histidine arms at the lower rim have been synthesised and fully characterised. Their coordinating behaviour towards cobalt(II) chloride has been investigated.

Keywords: calixarene; amino acids; podands; cobalt complexes.

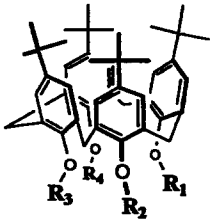
In the field of supramolecular chemistry, the calix[4]arene platform **1** displays interesting organising properties, notably, as recently reviewed by Matt and co-workers[1] for the building of ester- or amide-containing ligands for alkaline and alkaline–earth cations and heterocycle-containing ones for transition metal species. Surprisingly, the chelating behaviour of amino acid pendant arms grafted on such macrocycles has not been investigated until now. Nevertheless, the introduction of amino acids at the upper and lower rims of the calix[4]arene platform has been described, leading to water-soluble chiral entities. At the upper rim, Shinkai and co-workers[2] introduced four L-cysteine subunits, while more recently, Ungaro and co-workers[3] described the selective introduction of two and four alanine groups. At the lower rim, Warner and co-workers[4] grafted, after isolation of the corresponding succinimidoyl activated ester, four alanine units separated from the calixarene platform by an *O*-acetyl link. The resulting chiral podand was used in this case as mobile phase additive in capillary electrophoresis.

As part of our general project dedicated to the building of lipophilic ligands including heterocyclic chelating arms preorganised on a calixarene platform,[5] we attempted to prepare transition metal complexing agents bearing active amino acid subunits which could mimic the activity of some metallo-enzymes. Thus, in parallel to investigations related to the synthesis of a carbonic anhydrase biomimetic, we attempted to prepare a tetra-histidyl calix[4]arene podand in the cone conformation. Our first experiments

* Corresponding author. Fax: (33) 03 83 17 88 63; e-mail: jean-bernard.regnouf@pharma.u-nancy.fr

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01243-5

involved coupling reaction between the tetra-acid chloride **4**,[6] obtained by direct chlorination of the tetra-acid **3**[6] with $SOCl_2$, and histidine methyl ester or, in the presence of DCC and HOBT, between **3** and *N*-benzyl histidine methyl ester. In both cases, the resulting products were in fact mixtures of intermediates we were unable to separate correctly.



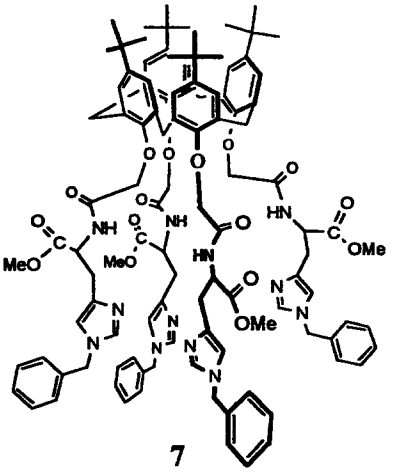
1: $R_1 = R_2 = R_3 = R_4 = H$
2: CH_2COOEt
3: CH_2COOH
4: CH_2COCl
5: CH_2COO-Nsuccinimide
6: $CH_2CONHCH_2COOEt$

8: $R_1 = R_3 = H$; $R_2 = R_4 = CH_2COOEt$
9: H; CH_2COOH
10: H; CH_2COO-Nsuccinimide
11: H; $CH_2CONHCH_2COOEt$

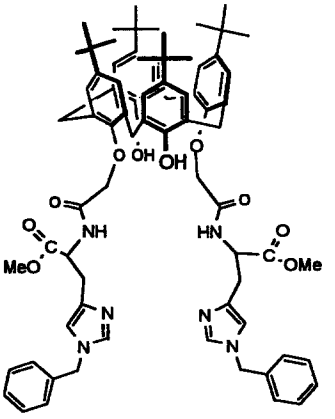
Adapting the DCC/NHS procedure of Warner,[4] which involves the isolation of the tetra-succinimidoyl activated ester **5**, to the synthesis of the model compound tetra-glycyl **6**, did not give reproducible results. The yield of 70% given for **5** was obtained with a longer reaction time (48 h instead of 12 h at 25°C) and after a careful washing of the DCU precipitate. The quadruple peptide-bound formation gave reproducible results but with a longer reaction time (72–120 h instead of 24 h); **6** was thus obtained pure in 60% yield after chromatography.[7]

In parallel, the tetra-*N*-benzyl histidine methyl ester derivative **7** was obtained pure with a yield of 40%; nevertheless, the washing step resulted in the formation of a milky emulsion between CH_2Cl_2 and H_2O, which necessitated decantation times of ca. 72 h. The presence of polluting residual DCU also necessitated a purification by chromatography (Al_2O_3, CH_2Cl_2:MeOH 98:2).[7]

The versatile organising properties of the calix[4]arene platform were also tested with the introduction of two amino acid residues. That was done by using the same synthetic procedure, but without protecting the two residual OH groups located at the 26th and the 28th positions. The bisactivated ester **10** was thus obtained with a yield of 75% as a white solid. Reaction of **10** with GlyOEt or Hist(Bzl)OMe at 25°C during 5 days under anhydrous conditions afforded the bisglycyl and bishistidyl podands **11** and **12**, with respective yields of 65 and 52%, after chromatography.[7]



7



12

^1H NMR analysis of **12** showed that the chirality of the histidyl arms induces a discrimination of the OCH_2 protons which appear as an AB system at 4.15–5.00 ppm (J_{AB}=14.7 Hz); this phenomenon is also observed, but at a lesser degree, with **7**, in which the eight OCH_2 protons appear as a strong AB system at

4.57–4.65 ppm (J_{AB}=14.7 Hz), overloaded by the low field component of the Ar-CH_2-AR AB resonance signal. As expected, no differentiation was observed with the glycyl analogues **6** and **11**.

Thus, the presence of histidyl groups at the lower rim of the calixarene platform generates a prohelical structure which could be strengthened in **12** by hydrogen bonding between the free OH groups and the amide carbonyl subunits; nevertheless, the expected shift of ca. 50 cm^{-1} for the corresponding IR band is not observed. However, the higher space available for the two histidyl groups in **12**, with regard to **7**, explains the expanded AB system observed for the OCH_2 protons.

Attempts to prepare complexes of Co(II) with the glycyl podands **6** and **11** were unsuccessful, but both histidinyl analogues **7** and **12** formed blue-coloured species **13** and **14**, with a tendency to give crystals unfortunately unsuitable for X-ray analysis. UV spectroscopy notably showed the presence of a metal-centred absorption band at 615 nm which was used to determine the corresponding stoichiometries via Job plot experiments. These were carried out in CH_2Cl_2/EtOH and showed that **13** displays an exact M_2L stoichiometry, while **12** gave relatively ambiguous results leading to an $M_{1.5}L$ (M_3L_2). Positive mode ES-MS analyses confirmed the M_2L nature of **13** with, notably, the molecular peak at 2069.7 amu ([**7**+2 $CoCl_2$–Cl^-]$^+$). The M_3L_2 stoichiometry of the isolated complex **14** was not evidenced by this technique, which provides two major peaks at 1340.4 amu ([**12**+$CoCl_2$–Cl^-]$^+$), and 1247.6 amu ([**12**+H]$^+$). Elemental analysis of **14** was consistent with the presence of one cobalt cation, and UV–visible spectroscopy of the isolated complex showed that at 615 nm, with regards to **13**, its stoichiometry is of the ML type. IR analysis (KBr pellets) showed that the complexation of Co(II) should not involve the carbonyl groups, no specific shift of the corresponding elongation bands being observed between the free ligands **7** and **12** and their complexes. A participation of the amide N-H subunits to the complexation process could be related, although ambiguously, to the apparition of a relatively intense band at 1519.0 cm^{-1} (N-H bending).

The grafting of amino acid residues on a calix[4]arene platform lead to potent transition metal complexing agents which could display metallo-enzyme biomimetic activities. The preparation of a tris-histidinyl podand designed to mimic the carbonic anhydrase active centre is now in progress.

Acknowledgements

We are grateful to the MRES for financial support, especially Y.M. for a PhD fellowship; to BRUKER S.A. (France) for WinNMR facilities. The authors wish to thank Mrs. Nicole Marshall for correcting the manuscript.

References

1. Wieser, C.; Dieleman, D. B.; Matt, D. *Coord. Chem. Rev.* **1997**, *165*, 93–161.
2. Nagasaki, T.; Tajiri, U.; Shinkai, S. *Rec. Trav. Chim. Pays Bas* **1993**, *112*, 407–411.
3. Sansone, F.; Barboso, S.; Casnati, A.; Pochini, A.; Ugozzoli, F.; Ungaro, R. *Eur. J. Org. Chem.* **1998**, 897–905.
4. Sanchez Peña, M.; Zhang, Y.; Thibodeaux, S.; McLaughlin, M. L.; Munoz de la Peña, A.; Warner, I. M. *Tetrahedron Lett.* **1996**, *37*, 5841–5844.
5. (a) Regnouf-de-Vains, J.-B.; Lamartine, R. *Helv. Chim. Acta* **1994**, *77*, 1817–1825. (b) Regnouf-de-Vains, J.-B.; Pellet-Rostaing, S.; Lamartine, R. *Tetrahedron Lett.* **1995**, *36*, 5745–5748. (c) Regnouf-de-Vains, J.-B.; Lamartine, R.; Fenet, B.; Bavoux, C.; Thozet, A.; Perrin, M. *Helv. Chim. Acta* **1995**, *78*, 1607–1619. (d) Pellet-Rostaing, S.; Regnouf-de-Vains, J.-B.; Lamartine, R. *Tetrahedron Lett.* **1996**, *37*, 5889–5892. (e) Pellet-Rostaing, S.; Regnouf-de-Vains, J.-B.; Lamartine, R.; Meallier, P.; Guittonneau, S.; Fenet, B. *Helv. Chim. Acta* **1997**, *80*, 1229–1243. (f) Regnouf-de-Vains, J.-B.; Lamartine, R.; Fenet, B. *Helv. Chim. Acta* **1998**, *81*, 661–669. (g) Regnouf-de-Vains, J.-B.; Lamartine, R. *Tetrahedron Lett.* **1996**, *37*, 6311–6314.

6. The tetra-ester **2**, tetra-acid **3**, diester **8**, and diacid **9** were synthesised according to the literature: (a) Iwamoto, K.; Shinkai, S. *J. Org. Chem.* **1992**, *57*, 7066–7073. (b) Cang, S. K.; Cho, I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 211–214. (c) Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaiyner, B.; Lough, A. J.; Mc Kervey, M. A.; Marques, E.; Ruhl, B. L.; Schwing-Weill, M.-J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, *11*, 8681–8691. The acid chloride **4**: Arnaud-Neu, F.; Barret, G.; Cremin, S.; Deasy, M.; Ferguson, G.; Harris, S. J.; Lough, A. J.; Guerra, L.; Mc Kervey, M. A.; Schwing-Weill, M.-J.; Schwinte, P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1119–1124.

7. General: Melting points (°C, uncorrected) were determined on an electrothermal 9100 capillary apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 (300.13 and 75 MHz) or DRX 500 (500.13 and 125.75 MHz), ($CDCl_3$, TMS as internal standard, chemical shifts in ppm, J in hertz). Mass spectra (electrospray, ES) were recorded on a Platform Micromass apparatus at the Service Central d'Analyse du CNRS, Solaize. Infra-red was performed on a Mattson 5000 FT apparatus (ν in cm^{-1}) and UV spectra were recorded on a Shimadzu UV 2401 PC apparatus, λ_{max} in nm, ε in $dm^3\ mol^{-1}\ cm^{-1}$. Elemental analyses were performed at the Service Central de Microanalyse du CNRS, Solaize. Macherey-Nagel TLC plates were used for chromatography analysis (SiO_2, Polygram SIL G/UV254, Ref. 805021). All commercially available products were used without further purification unless otherwise specified. Compound **6**: The tetra-acid **3** (0.88 g, 1 mmol) was added to a solution of *N*-hydroxysuccinimide (0.48 g, 4.2 mmol) in dry ethyl acetate. A solution of DCC (0.87 g, 4.2 mmol) in dry ethyl acetate was added and stirred 48 h at 25°C under anhydrous conditions. The resulting precipitate was filtered and washed three times with ethyl acetate and the filtrate was concentrated in vacuo to give **5** in 70% yield as white product. The calixarene **5** (0.55 g, 0.39 mmol) was suspended in dry CH_2Cl_2. A solution of GlyOEt, HCl (0.24 g, 1.73 mmol) and diisopropylethylamine (0.79g, 6.1 mmol) in dry CH_2Cl_2 was added and the mixture was stirred at 25°C for 5 days. After addition of H_2O, the product was extracted with CH_2Cl_2. The combined organic phases were washed with water and evaporated in vacuo. The mixture was chromatographed (Al_2O_3, CH_2Cl_2:MeOH 98:2) to give **6** (0.28 g, 60%) as white product. M.p.: 193.2°C. IR (KBr): 1663.8 (CO(NH)); 1751.1 (CO(O)); 3329.3 (NH). UV (CH_2Cl_2): 274.5 (3300). ^1H NMR ($CDCl_3$): 1.09 (s, 36H, Me_3C); 1.28 (t, J=7.35, 12H, CH_3CH_2); 3.31, 4.56 (AB, J_{AB} =13.3, 8H, Ar-CH_2Ar); 4.12 (d, J=5.89, 8H, N-CH_2); 4.16 (q, J=7.36, 8H, CH_3CH_2); 4.58 (s, 8H, OCH_2); 6.82 (s, 8H, H-Ar); 7.92 (t, 4H, NH). ^{13}C NMR: 14.12 (CH_3CH_2); 31.12 (Ar-CH_2-Ar); 31.31 (Me_3C); 33.92 (Me_3C); 40.99 (CH_2-NH); 61.31 (CH_3CH_2); 74.18 (OCH_2); 125.96 (3,5-Ar); 132.66, 146.14, 152.49 (1,2,4,6-Ar); 170.11 (CONH); 170.37 (COOEt). ES-MS (pos. mode): 1243.9 [**6**+Na]$^+$. Anal. calcd for $C_{68}H_{92}O_{16}N_4$ (1220): C 66.89; H 7.59; N 4.59; O 20.96; found: C 66.54; H 7.75; N 4.14; O 20.59. Compound **7**: Same procedure, from Hist(Bzl)OMe, 2HCl (0.63g, 1.73 mmol); (**7**: 0.29 g, 40%, white powder). M.p. 189.3°C. IR: 1671.2 (CO(NH)); 1743.5 (CO(O)); 3316 (NH). UV (CH_2Cl_2): 282.0 (3380). ^1H NMR: 1.05 (s, 36H, Me_3C); 3.03 (*br* m, 8H of CH_2-His and 4H of ArCH_2Ar); 3.54 (s, 12H, OCH_3); 4.57, 4.65 (AB, J_{AB}=14.7, 8H, OCH_2), 4.61 (d, J_{AB}=14.7, 4H, ArCH_2Ar); 4.88 (dt, J_1=7.35, J_2=6.61, 4H-C_αHis); 4.98 (s, 8H, CH_2-Ph); 6.69 (s, 4H-Ar); 6.71 (s, 4H, $H_{(2)}$Im); 7.10 (d, J=5.15, 8$H_{(o)}$-Ph); 7.28 (m, 12$H_{(m,p)}$-Ph); 7.39 (s, 4$H_{(4)}$Im); 8.28 (d, J=8.1, 4 N*H*). ^{13}C NMR: 30.62 (CH_2-Im); 31.79 (Me_3C); 32.32 (Ar-CH_2-Ar); 34.22 (Me_3C); 51.09 (CH_2-Ph); 52.57 (O*Me*); 52.83 (C_αHis); 74.19 (OCH_2); 117.53 (4-Im); 125.68, 126.02 (2-Im); 12765, 128.54, 129.32 (2,3,4,5,6-Ph); 136.80 (2,6-Ar); 137.31 (3,5-Ar); 138.6 (4-Ar, 1-Ph); 145.37 (1-Ar); 153.73 (5-Im); 170.49 (CONH); 172.71 (COOMe). ES-MS (pos. mode): 1869.1 [**7**+Na]$^+$, 934.8 [**7**+H+Na]$^{2+}$/2, 923.7 [**7**+2 H]$^{2+}$/2, 1847.1 [**7**+H]$^+$. Anal. calcd for $C_{108}H_{124}O_{16}N_{12}$ (1846.26): C 70.26, H 6.77, N 9.10, O 13.87; found: C 69.96, H 6.96, N 8.99, O 14.33. Compound **10**: Prepared according to **5** (see above). M.p.: 189°C. ^1H NMR ($CDCl_3$): 0.91 (s, 18H, Me_3C); 1.29 (s, 18H, Me_3C); 2.81 (s, 8H, CH_2CH_2); 3.37, 4.36 (AB, J_{AB}=13.6, 8H, Ar-CH_2Ar); 5.20 (s, 4H, OCH_2); 6.58 (s, 2H, O*H*); 6.72 (s, 4H, H-Ar); 7.06 (s, 4H, H-Ar). Compound **11**: The diacid **9** (0.77 g, 1 mmol) was added to a solution of *N*-hydroxysuccinimide (0.25 g, 2.2 mmol) in dry ethyl acetate. A solution of DCC (0.47 g, 2.2 mmol) in dry ethyl acetate was added and stirred 48 h at 25°C under anhydrous conditions. The resulting precipitate was filtered and washed three times with ethyl acetate and the filtrate was concentrated in vacuo to give **10** in 75% yield as a white product. The calixarene **10** (0.60 g, 0.63 mmol) was suspended in dry CH_2Cl_2. A solution of GlyOEt, HCl (0.19 g, 1.38 mmol) and diisopropylethylamine (0.49 g, 3.8 mmol) in dry CH_2Cl_2 was added and the mixture was stirred at 25°C for 5 days. After addition of H_2O, the product was extracted with CH_2Cl_2. The combined organic phases were washed with water and evaporated in vacuo. The mixture was chromatographed (Al_2O_3, CH_2Cl_2:MeOH 98.5:1.5) to give **11** (0.39 g, 65% yield) as a white product. M.p.: 150°C. IR (KBr): 1691.3 (CO(NH)); 1752.2 (CO(O)); 3324.7 (NH). UV (CH_2Cl_2): 289.0 (6700). ^1H NMR ($CDCl_3$): 1.06 (s, 18H, Me_3C); 1.22–1.27 (m, 24H, Me_3C+CH_3CH_2); 3.43, 4.23 (AB, J_{AB}=13.2, 8H, Ar-CH_2Ar); 4.11–4.25 (m, 10H, CH_3CH_2+NCH_2); 4.63 (s, 4H, OCH_2); 6.94 (s, 4H, H-Ar); 7.09 (s, 4H, H-Ar); 7.92 (s, 2H, OH); 9.30 (t, J=5.15, 2H, NH). ^{13}C NMR: 14.06 (CH_3CH_2); 30.99, 31.61 (Me_3C); 32.18 (Ar-CH_2-Ar); 33.90, 34.13 (Me_3C); 41.31 (CH_2NH); 61.39 (CH_3CH_2); 74.83 (OCH_2); 125.51, 126.20 (3,5-Ar); 127.08, 132.44, 142.83, 148.21, 149.37, 149.75 (1,2,4,6-Ar); 169.00 (CONH); 169.35 (COOEt). ES-MS (pos. mode): 957.6 [**11**+Na]$^+$. Anal. calcd for $C_{56}H_{74}O_{10}N_2$+H_2O (952): C 70.11; H 8.22; N 3.29; O 18.38; found: C 70.56; H 8.03; N 2.95; O 18.46. Compound **12**: Same procedure, from Hist(Bzl)OMe, 2HCl (0.50 g, 1.38 mmol); (**12**:

0.41 g, 52%, white powder). M.p. 199.5°C. IR (KBr): 1673.6 (CO(NH)); 1749.6 (CO(O)); 3322.6 (NH). UV (CH_2Cl_2): 290.0 (7400). ^1H NMR: 1.02 (s, 18H, Me_3C); 1.25 (s, 18H, Me_3C); 3.10, 3.18 (AB*d*, J_{AB}=14.0, J=5, 4H, CH_2-His); 3.11, 4.19 (AB, J_{AB}=13, 4H, Ar-CH_2-Ar); 3.35, 4.03 (AB, J_{AB}=14, 4H, Ar-CH_2-Ar); 3.65 (s, 6H, OCH_3); 4.15, 5.00 (AB, J_{AB}=14.7, 4H, OCH_2); 4.25, 4.53 (AB, J_{AB}=15.4, 4H, CH_2Ph); 5.00 (sext, J_1=7.4, J_2=5, 2*H*-C_αHis); 6.54 (d, J=0.5, $2H_{(4)}$Im); 6.86 (AB, J_{AB}=2, 4H-Ar); 6.92 (dd, J_1=7.7, J_2=2, $4H_{(o)}$-Ph); 701 (AB, J_{AB}=2, 4H-Ar); 7.09 (d, J=0.5, $2H_{(2)}$Im); 7.20–7.32 (m, $6H_{(m,p)}$-Ph); 7.86 (s, 2 O*H*); 9.43 (d, J=7.4, 2 N*H*). ^{13}C NMR: 31.37, 32.10 (Me_3C); 32.23, 32.34 (Ar-CH_2-Ar); 32.74 (CH_2-Im); 34.27, 34.45 (Me_3C); 50.44 (CH_2-Ph); 52.50, 52.76 (C_αHis, O*Me*); 75.47 (OCH_2); 116.96, 125.37, 125.66, 125.92, 127.14, 127.30, 128.34, 129.14, 137.07 (3,5-Ar, 2,3,4,5,6-Ph, 2,4-Im); 126.77, 128.15, 132.69, 132.90, 137.13, 137.99, 142.62, 148.11, 150.34 (1,2,4,6-Ar; 5-Im; 1-Ph); 169.30 (*C*ONH); 172.02 (*C*OOMe). ES-MS (pos. mode): 1269.8 [**12**+Na]$^+$; 646.4 [**12**+2 Na]$^{2+}$/2; ES-MS (neg. mode): 1245.9 [**12**-H]$^-$; 1268.0 [**12**+Na-2H]$^-$. Anal. calcd for $C_{76}H_{90}O_{10}N_6$+H_2O (1264): C 72.12; H 7.32; N 6.64; O 13.91; found: C 71.98; H 7.37; N 6.68; O 13.93. Cobalt complexes: To a solution of ligand in CH_2Cl_2 was added solid $CoCl_2$ (3 equiv. for **7**, 2 equiv. for **12**). The solution turned blue immediately and was stirred under N_2 for 2 h. The excess of $CoCl_2$ which remained unsoluble was filtered off and the complexes were directly precipitated by addition of hexane, giving quantitatively blue powders which were collected by filtration, then recrystallised from CH_2Cl_2/CH_3CN/EtOH mixture. Compound **13** (from 3 equiv. of $CoCl_2$ and 1 equiv. of **7**). IR (KBr): 1673.0 (CO(NH)), 1742.6 (CO(O)). UV (CH_2Cl_2): 274.5 (6200), 615 (320). ES-MS (pos. mode): 2127.9 [**7**+$(CoCl_2)_2$+Na^+−H^+]$^+$, 2092.7 [**7**+$(CoCl_2)_2$+Na^+−2H^+−Cl^-]$^+$, 2069.7 [**7**+$(CoCl_2)_2$−Cl^-]$^+$, 2033.7 [**7**+$(CoCl_2)_2$−H^+−2Cl^-]$^+$, 1939.8 [**7**+$CoCl_2$−Cl^-]$^+$, 1904.0 [**7**+$CoCl_2$−H^+−2Cl^-]$^+$. Anal. calcd for $C_{108}H_{124}O_{16}N_{12}$ Co_2Cl_4, $4H_2O$ (2177.94): C 59.51; H 6.06; N 7.71; Cl 6.51; Co 5.41; found: C 59.50; H 5.96; N 7.88; Cl 6.60; Co 5.04. Compound **14** (from 2 equiv. of $CoCl_2$ and 1 equiv. of **12**). IR (KBr): 1680.8 (CO(NH)), 1746.3 (CO(O)). UV (CH_2Cl_2): 281.5 (8000), 615 (185). ES-MS (pos. mode): 1340.4 [**12**+$CoCl_2$−Cl^-]$^+$, 1304.3 [**12**+$CoCl_2$−2Cl^-−0H^+]$^+$, 1248.5 [**12**+H^+]$^+$. Anal. calcd for $C_{76}H_{90}O_{10}N_6$, $CoCl_2$, 4 H_2O (1447.8): C 62.98; H 6.76; N 5.80; Cl 4.89; Co 4.06; found: C 63.19; H 6.49; N 5.96; Cl 5.04; Co 3.67.