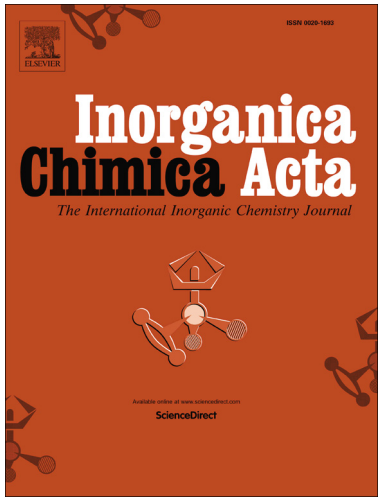

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Tuning the redox potentials of ternary cobalt(III) complexes containing various hydroxamates

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This paper is dedicated to Professor Imre Sóvágó on the occasion of his 70th birthday.

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Abstract

Sixteen cobalt(III) complexes incorporating one of the investigated 4N donor tripodal amines in the presence or absence of differently substituted hydroxamates have been synthesized and the effect of the nature of the N-donor, size of the chelates formed and the effect of the type of the substituent(s) at the hydroxamate moiety on the redox properties of the complexes have been studied. The crystal and molecular structures of the new complexes, [Co(uns-penp)(H_2O)Cl]Cl_2.H_2O (**4**), [Co(tren)(phebha)]$(ClO_4)_2$ (**11**), [Co(tpa)(bha)]$(ClO_4)_2$·C_2H_5OH·H_2O (**15**) and [Co(tpa)(phebha)]$(ClO_4)_2$ (**16**) have also been determined by single crystal X-ray diffraction method. Cyclic voltammetric (CV) results indicated the irreversible reduction of Co(III) in all the investigated complexes. Out of the four studied tripodal amines, abap was found to decrease the Co(III/II) reduction potential far below the region of bioreductants. Decreasing of two of the chains by one CH_2 in tren compared to abap resulted in less negative reduction potential of the corresponding complex. Further positive shift was observed by introducing two (uns-penp), and especially three (tpa) π-back-bonding pyridyl rings into the chains of tetramines. In agreement with literature results, the 3+ oxidation state of the central cobalt ion was found to be extremely stabilized in the ternary complexes containing the doubly deprotonated benzohydroximate, but the metal ion is significantly more reducible in the ternary complexes with mono-deprotonated benzohydroxamate/derivative ligands. Measurable effect was not found on the redox potential via introduction of chloro or nitro substituents in para position into the phenyl moiety of bha^- (Cl-bha^- and NO_2-bha^-). Significant positive shift (ca. 200 mV) was obtained, however, when R_N = H was replaced by a phenyl ring in $phebha^-$ therefore complexes with this latter ligand can be likely candidates for the *in vitro* releasing of hydroxamates with proven biological activity.

Introduction

Hydroxamic acids (HA) with the general formula of $R_CC(O)NR_N(OH)$ (where R_C = alkyl or aryl; R_N = H in primary derivatives, alkyl or aryl in secondary ones) are important class of biomolecules with their significance in a wide array of different applications, *e.g.* in nature and medicine [1-3]. In addition to their well-known roles in the microbial iron-uptake [4] HAs are capable of inhibiting a variety of enzymes, including e. g. matrix metalloproteinases [3, 5, 6]. Extensive studies on hydroxamate-based compounds have resulted in the development of several drug candidates during the past ca. two decades, such

as batimastat and its orally bioavailable analogue, marimastat [7]. Moreover, suberoilanilide hydroxamic acid, SAHA, is an FDA-approved anticancer agent to treat cutaneous T-cell lymphoma [8]. A hydroxamic function, in its deprotonated form, typically bounds to metal ions via the five-membered „so-called" hydroxamate-type (O,O) chelate, but, with certain metal ions and doubly deprotonated primary derivatives, the hydroximate-chelate can also be formed [2,9]. There is no doubt that all the above-mentioned biological activities of HAs are in close correlation with their excellent metal ion binding capability. At least in some part, the selectivity and efficiency problems of hydroxamate-based drug candidates can also be associated with the interaction of their active forms with various endogeneous metal ions during their transportation to the target. To overcome the problem, chaperoning of the small drug molecule to the site of action in an inactive form and activation of it at the site have been investigated in a number of laboratories, e.g. by Hambley and his co-workers [10-14]. In their works, inactivation of the hydroxamate-based MMP (Matrix Metalloproteinases) inhibitors has been achieved via chelation of the hydroxamate binding group to the metal centre of kinetically inert Co(III) complexes. Out of the several known approaches [14-17], the concept of the bioreduction in the environment of hypoxic tumours was envisaged in a number of works to solve selective activation of the chaperon pro-drug at the site of action [10-13, 15-16]. Cobalt complexes are of special interest as hypoxia selective prodrugs since many years, because of the very significant difference in lability between the complexes of cobalt(III) and cobalt(II) [18]. While the former complexes are inert, the latters show labile character. Consequently, reduction of the metal centre to the labile +2 oxidation state at hypoxic environment of tumour tissues allows releasing of the inhibitor molecule in its active form.

Realization of the above concept requires compliance of the redox potential of the cobalt(III) complex with that of hypoxic tumors. To the best of our knowledge, accurately determined redox properties have not reported for hypoxic tumours yet, but a reduction potential range of -200 mV − -400 mV (vs. normal hydrogen electrode, NHE) is given in a paper to match that of cellular reductases [15], while near or lower than ca. -300 mV is suggested as appropriate potential for an ideal hypoxia-acivated pro-drug in another publication [10].

As it is known from the literature, O-donor hydroxamate ligands alone are not able to decrease the redox potential of the $[Co(H_2O)_6]^{3+}/[Co(H_2O)_6]^{2+}$ system (ca. +1.8 V) down to the values above [19], but numerous ternary complexes, prepared by Hambley and his coworkers, consisting of a tripodal tetraamine tetradentate ligand and a hydroxamate have been found to fullfill this requirement [10-12]. Out of the high number of known tripodal

tetraamins [20], tris(2-methylpyridyl)amine (tpa) and tris(2-aminoethyl)amine (tren) were used to sysnthesize chaperons in the works cited in refs. 10-12, while the studied hydroxamic acids were the acetohydroxamic acid, benzohydroxamic acid, propionhydroxamic acid, 2-(naphthalen-1-yl)hydroxamic acid [11,12], as well as the MMP inhibitor marimastate [10]. All of the investigated complexes showed irreversible reduction at the cobalt centre and the reduction potentials for the tren-containing complexes were always considerably lower than for the tpa-containing ones. This trend was suggested to be caused by the π-acceptor behaviour of the tpa-pyridyl rings [12,16]. Significantly more negative reduction potential was found to belong to the hydroximate-containing complexes compared to the hydroxamate ones [12, 21]. The very low reduction potentials for the former complexes are thought to be beyond the redox value inside the cell and reduction of them with biological reductants is hardly possible [21].

As a continuation of our previous investigations on Co(III) complexes of hydroxamic acids [19], synthesis and characterization of numerous ternary complexes of Co(III) formed with tripodal tetraamines involving different types of N-donors and chain lengths, as well as with hydroxamic acids have been performed in the present study. The formulae of the ligands are presented in Scheme 1.

Scheme 1

Because the reduction potential of the complexes is a vital parameter for the activation of the inactivated inhibitor via bioreduction, study of the structural effect of different tetraamines and also various substituents at the hydroxamic function on this parameter has been one of the major goals of this work.

2. Experimental

2.1 Materials and reagents

$CoCl_2 \cdot 6H_2O$, $NaNO_2$, tris(2-aminoethyl)amine (tren), N-acetylethylenediamine, pyridine-2-carboxaldehyde, phthalic acid anhydride, 3,3'-iminobis(propylamine), $NaBH(OAc)_3$, 4-nitro-benzoylchloride, 4-Cl-benzoylchloride, picolyl-amine, picolyl-chloride, nitrobenzene, 4-nitro-toluene, 4-Cl-toluene, zinc powder, benzohydroxamic acid and various solvents were commercial products from Merck, SigmaAldrich, VWR and Reanal; and used as received. Tris(2-pyridylmethyl)amine (tpa) [22], N-phenylhydroxylamine, N-(4-chlorophenyl)-

hydroxylamine, N-(4-nitrophenyl)-hydroxylamine, 4-chlorobenzohydroxamic acid, 4-nitrobenzohydroxamic acid, N-phenylbenzohydroxamic acid, N-(4-methylphenyl)benzohydroxamic acid, N-(4-chlorophenyl)-4-chlorobenzohydroxamic acid) [23, 24], N-(2-bromoethyl)phthalimide [25], $[Co(tren)(NO_2)_2]Cl$, $[Co(tren)Cl_2]Cl$, $[Co(tpa)(NO_2)_2]Cl$, $[Co(tpa)Cl_2]Cl$ [26], $[Co(tpa)(bhaH_{-1})](ClO_4)_2$ [11], $Na_3[Co(CO_3)_3]\cdot 3H_2O$ [27] were synthesized and purified according to literature procedures.

2.2 Synthesis of the precursors and complexes

Compounds **1**–**3** were prepared by the slight modification of the appropriate literature methods. [28-30]

Bis(phtalimidylpropyl)amine (**1**)

Phthalic acid anhydride (59.30 g, 0.40 mol) was heated up to 180 ^oC in a two-neck flask equipped with a dropping funnel and condenser. 3,3'-iminobis(propylamine) (28.0 ml, 0.20 mol) was dropwise added to the melt while vigorous stirring. The reaction mixture was kept at 180 ^oC for further 2.5 h and after cooling it was dissolved in hot abs. ethanol (100 ml). On cooling at 4 ^oC overnight and treatment of the bottom phase separated out with a glass rod resulted in the formation of a sticky solid. After decantation the solid was homogenized with diethylether to obtain a pale brown solid. Recrystallization from hot methanol afforded the title compound as a white solid. Yield: 45.72 g (58 %). ^1H NMR (360 MHz, DMSO): δ/ppm = 8.17–7.50 (m, 8H, Ar-H); 3.62 (t, 4H, $-CH_2$); 2.71 (t, 4H, $-CH_2$); 1.79 (p, 4H, $-CH_2$).

(N-(2-aminoethyl)-N,N-bis(3-aminopropyl)amine, abap (**2**)

1 (3.83 g, 9.82 mmol) was melted in a two-neck flask equipped with a condenser and N-(2-bromoethyl)phthalimide (2.49 g, 9.82 mmol) was added in five portion under vigorous stirring. The reaction mixture was strirred in an oil bath at 165 ^oC for 45 min and let to cool down. The resulting glass-like solid was treated with HCl solution (40 ml, 8 M) and refluxed overnight. The solution was filtered and the solvent was removed. The resulting sticky solid was boiled with ethanol (20 ml) and some drops of water were also added for complete dissolution. On cooling overnight at 4 ^oC the resulting white crystals were filtered, washed with a small amount of ethanol and dried in vacuo. Yield: 400 mg (23 %). ^1H NMR: (400 MHz, D_2O): δ/ppm = 3.65-3.55 (m, 1H $-CH_2$); 3.55-3.45 (m, 1H $-CH_2$); 3.45-3.35 (m, 2H, $-CH_2$); 3.25-3.10 (m, 8H, $(CH_2)_4$); 2.25-2.05 (m, 4H, $-CH_2$).

(2-aminoethyl)bis(2-piridylmethyl)amine, uns-penp (**3**)

N-acetylethylenediamine (3.36 g, 30 mmol) was dissolved in dry $C_2H_4Cl_2$ (150 ml) under nitrogen in a two-neck flask. Pyridine-2-carboxaldehyde (5.7 ml, 60 mmol) was dropwise added and to the yellow solution $NaBH(OAc)_3$ (18.06 g, 84.9 mmol) was added at positive nitrogen pressure. The milky reaction mixture was stirred for 3 h and the reaction was quenched by adding NaOH solution (300 ml, 2 M). The organic phase was separated and extracted twice with 150 ml of CH_2Cl_2. The combined organic phase was washed with 150 ml of saturated NaCl solution and dried over $MgSO_4$ overnight. After filtering and removing the solvent the crude product was recrystallized from acetonitrile. The acetyl protected derivative was subjected to hydrolysis in HCl (120 ml, 5 M) via 24 h reflux. The pH of the resulting solution was set to 12 with solid KOH and the orange oil separated was extracted with 3x 100 ml of CH_2Cl_2. After drying on $MgSO_4$ and filtration the solvent was removed and the resulting crude oil was extracted 3 x 50 ml of diethylether. Removal of the solvent afforded the title compound as pale yellow oil. Yield: 2.50 g, 34 %. ^{1}H NMR: (360 MHz, D_2O): δ/ppm = 8.66 (d, 2H, Py-H); 8.47 (t, 2H, Py-H); 8.01 (d, 2H, Py-H); 7.90 (t, 2H, Py-H); 4.22 (s, 4H, -CH_2); 3.22 (t, 2H, -CH_2); 3.02 (t, 2H, -CH_2).

[Co(uns-penp)(H_2O)Cl]Cl_2·H_2O (**4**)

3 (250 mg, 1.03 mmol) was dissolved in water (11 ml), KOH (173 mg, 3.09 mmol), $CoCl_2$·$6H_2O$ (245 mg, 1.03 mmol) and $NaNO_2$ (142 mg, 2.06 mmol) were added. Via the dark solution oxygen was bubbled for 4 h and the solvent was removed. The black purple nitrito complex was dissolved in conc. HCl (5 ml) and evaporated to dryness in a steam bath. Recrystallization from water afforded the title compound as purple crystalline solid. Slow evaporation of the mother liquor resulted in the formation of single crystals directly suitable for X-ray analysis. Yield: 127 mg, 32 %. ^{1}H NMR (360 MHz, D_2O): δ/ppm = 9.29 (d, 2H, Ar-H); 8.22 (t, 2H, Ar-H); 7.74 (m, 4H, Ar-H); 5.19 (d, 2H, -CH_2); 4.65 (d, 2H, -CH_2); 3.25 (t, 2H, -CH_2); 2.06 (t, 2H, -CH_2). IR (KBr)/cm^{-1}: 3488, 3423, 3030, 2965, 1613, 1446, 775. MS (ESI-TOF): m/z 299.065 [Co(uns-penp)-2H]$^+$ (simulated: 299.070). UV-Vis (λ_{max}(nm)/ε(M^{-1}cm^{-1})) : 371(131), 533(127).

[Co(abap)Cl_2]ClO_4 (**5**)

To $Na_3[Co(CO_3)_3]\cdot 3H_2O$ (400 mg, 1.11 mmol) suspended in water (4 ml) abap (**2**) (419 mg, 1.11 mmol) dissolved in water (2.5 ml) was dropwise added while strirring. The brown reaction mixture was heated up to 75 ^oC within 1 h and kept at 75 ^oC for further 3 h. The resulting dark violet solution was evaporated to ¼ of the volume and treated with $HClO_4$-soltion (0.13 ml, 60 %) and ethanol (5 ml). Cooling at 4 ^oC overnight afforded a dark violet crystalline solid as title compound. It was filtered washed with ether and dried in vacuo. Yield: 220 mg (49 %) ^1H NMR: (400 MHz, D_2O): δ/ppm = 3.23-1.92 (m, 16H, $-CH_2$). IR (KBr)/cm^{-1}: 3199, 3120, 1600, 1543, 1465, 1099, 624. MS (ESI-TOF): m/z 231.102 $[Co(abap)-2H]^+$ (simulated: 231.101). UV-Vis (λ_{max}(nm)/ε($M^{-1}cm^{-1}$)) : 530(69).

$[Co(tren)(bhaH_{-1})]ClO_4$ (**6**)

$[Co(tren)Cl_2]Cl$ (1.00 g, 3.00 mmol) (30 ml) and benzohydroxamic acid (520 mg, 3.8 mmol) were dissolved in water and KOH (10 ml, 1 M) was added dropwise. The reaction mixture was stirred at 70 ^oC for 6 h. The solvent was almost completely removed and the black solid crystallized out was dissolved in ethanol (20 ml). The solution was treated with saturated ethanolic $NaClO_4$ solution (8 ml). On cooling overnight at 4 ^oC the title compound appeared as black needles in a 4:3 mixture of the two isomers. The product was filtered off and dried in vacuo. Yield: 1.04 g, 79 %. ^1H NMR of the major isomer (360 MHz, D_2O): δ/ppm = 7.86 (d, 2H, Ar-H); 7.43 (m, 3H, Ar-H); 3.87 (m, 2H, tren-H); 3.28-2.90 (m, 10H, tren-H). ^1H NMR of the minor isomer (360 MHz, D_2O): δ/ppm = 7.71 (d, 2H, Ar-H); 7.43 (m, 3H, Ar-H); 3.53 (m, 2H, tren-H); 3.28-2.90 (m, 10H, tren-H). IR (KBr)/cm^{-1}: 3312, 3087, 1464, 1348, 1102, 624. MS (ESI-TOF): m/z 340.110 $[Co(tren)(bhaH_{-1})]^+$ (simulated: 340.118). UV-Vis (λ_{max}(nm)/ε($M^{-1}cm^{-1}$)) : 466sh(129), 567(138).

$[Co(tren)(bha)](ClO_4)_2$ (**7**)

6 (200 mg, 0.45 mmol) was suspended in water (4 ml) and $HClO_4$ solution (5 ml, 0.1 M) was added. The red solution was stirred for 20 min, evaporated to 2 ml and the crystalline solid separated out on standing at 4 ^oC overnight was filtered off. The purple solid as a 2:1 mixture of the two isomers was dried in vacuo. Yield: 140 mg, 57 %. ^1H NMR of the major isomer (360 MHz, d^6-DMSO): δ/ppm = 12.76 (s, 1H, NH); 7.90 (d, 2H, Ar-H); 7.54 (m, 3H, Ar-H); 5.11 (m, 4H, NH_2); 4.56 (s, 2H, NH_2); 3.54 (m, 2H, tren-H); 3.34-2.71 (m, 10H, tren-H). ^1H NMR of the minor isomer (360 MHz, d^6-DMSO): δ/ppm = 12.82 (s, 1H, NH); 7.80 (d, 2H,

Ar-H); 7.54 (m, 3H, Ar-H); 5.31 (s, 2H, NH_2); 5.11 (m, 2H, NH_2); 4.76 (s, 2H, NH_2); 3.34-2.71 (m, 12H, tren-H). IR (KBr)/cm^{-1}:3302, 3260, 1611, 1476, 1096, 1046, 925, 697, 623. MS (ESI-TOF): m/z 340.111 $[Co(tren)(bha-H)]^+$ (simulated: 340.118). UV-Vis (λ_{max}(nm)/$\varepsilon(M^{-1}cm^{-1})$) : 390sh(167), 526(169).

$[Co(tren)(NO_2\text{-}bha)]Cl_2$ (**8**)

$[Co(tren)Cl_2]Cl$ (660 mg, 2.00 mmol) was dissolved in water (20 ml) and 4-nitrobenzohydroxamic acid (403 mg, 2.2 mmol) and KOH (123 mg, 2.2 mmol) were added. The reaction mixture was stirred at 70 ^oC for 6 h. The brown solid obtained on standing overnight at 4 ^oC was filtered off and recrystallized from hot methanol. Yield: 140 mg, 15 %. ^1H NMR (360 MHz, D_2O): δ/ppm = 8.35 (d, 2H, Ar-H); 8.09 (d, 2H, Ar-H); 3.85 (m, 2H, tren-H); 3.46-2.89 (m, 10H, tren-H). IR (KBr)/cm^{-1}: 3427, 3187, 3105, 1594, 1523, 1476, 1349, 852. MS (ESI-TOF): m/z 385.109 $[Co(tren)(NO_2\text{-}bha)\text{-}H]^+$ (simulated: 385.103). UV-Vis (λ_{max}(nm)/$\varepsilon(M^{-1}cm^{-1})$) : 548(179).

$[Co(tren)(NO_2\text{-}bha)](ClO_4)_2$ (**9**)

The mother liquor of the reaction to prepare **8** was evaporated, the solid obtained was dissolved in ethanol and treated with saturated ethanolic $NaClO_4$ solution (8 ml). Slow evaporation at 4 ^oC afforded a red microcrystalline solid. Yield: 260 mg, 22 %. ^1H NMR (360 MHz, D_2O): δ/ppm = 8.34 (d, 2H, Ar-H); 7.98 (d, 2H, Ar-H); 3.51 (m, 2H, tren-H); 3.44-2.87 (m, 10H, tren-H). IR (KBr)/cm^{-1}: 3305, 3256, 1590, 1528, 1480, 1351, 1141, 1102, 1034, 625. MS (ESI-TOF): m/z 385.109 $[Co(tren)(NO_2\text{-}bha)\text{-}H]^+$ (simulated: 385.103). UV-Vis (λ_{max}(nm)/$\varepsilon(M^{-1}cm^{-1})$) : 539(214).

$[Co(tren)(Cl\text{-}bha)](ClO_4)_2$ (**10**)

It was synthesized analogously to **9** using $[Co(tren)Cl_2]Cl$ (660 mg, 2.01 mmol), 4-chlorobenzohydroxamic acid (377 mg, 2.21 mmol) and KOH (123 mg, 2.2 mmol). The reaction mixture was almost completely evaporated and the resulting crude crystalline solid was dissolved in ethanol (10 ml) and treated with saturated ethanolic $NaClO_4$ solution (8 ml). On cooling the title compound appeared as claret coloured solid. Recrystallization from methanol resulted in the formation of mainly isomer I. Yield: 430 mg, 37 %. Slow evaporation of the mother liquor afforded dark purple crystals identified as mainly isomer II.

Both products contain a small amount of the other isomer. Yield: 160 mg, 14 %. ^{1}H NMR of isomer I (360 MHz, D_2O): δ/ppm = 7.85 (d, 2H, Ar-H); 7.55 (m, 2H, Ar-H); 3.83 (m, 2H, tren); 3.43-2.88 (m, 10H, tren). ^{1}H NMR of isomer II (360 MHz, D_2O): δ/ppm = 7.74 (d, 2H, Ar-H); 7.55 (m, 2H, Ar-H); 3.49 (m, 2H, tren-H); 3.43-2.88 (m, 10H, tren-H). IR (KBr)/cm^{-1}: 3443, 3217, 3114, 1628, 1143, 1113, 1089, 636, 627. MS (ESI-TOF): m/z 374.086 $[Co(tren)(Cl\text{-}bha)\text{-}H]^+$ (simulated: 374.079). UV-Vis (λ_{max}(nm)/ε($M^{-1}cm^{-1}$)) : 427sh(103), 524(135).

$[Co(tren)(phebha)](ClO_4)_2$ (**11**)

$[Co(tren)Cl_2]Cl$ (270 mg, 0.835 mmol) was dissolved in water (10 ml) and N-phenylbenzohydroxamic acid (176 mg, 0.84 mmol) and KOH (50 mg, 0.90 mmol) were added. The reaction mixture was stirred at 60 ^{o}C for 6 h. Removal of the solvent and treatment of the ethanolic solution of the complex with ethanolic $NaClO_4$ solution afforded the title compound on cooling as purple crystalline solid. Slow evaporation of the mother liquor gave single crystals directly suitable for X-ray diffraction. Yield: 230 mg, 45 %. ^{1}H NMR (360 MHz, D_2O): δ/ppm = 7.93-7.30 (m, 10H, Ar-H); 3.94-3.78 (m, 2H, tren-H); 3.70-2.79 (m, 10H, tren-H). IR (KBr)/cm^{-1}: 3300, 3260, 1591, 1097, 696, 624. MS (ESI-TOF): m/z 416.141 $[Co(tren)(phebha)\text{-}H]^+$ (simulated: 416.149). UV-Vis (λ_{max}(nm)/ε($M^{-1}cm^{-1}$)) : 428sh(152), 520(168).

$[Co(tren)(ClCl\text{-}phebha)](ClO_4)_2$ **(12)**

This was synthesized as **11** using N-(4-chlorophenyl)-4-chlorobenzohydroxamic acid (233 mg, 0.83 mmol). Yield: 260 mg, 46 %. ^{1}H NMR (360 MHz, D_2O) δ: 7.52-7.30 (m, 8H, Ar-H) 3.95-3.77 (m, 2H, tren-H) 3.65-2.69 (m, 10H, tren-H). IR (KBr)/cm^{-1}: 3445, 3201, 3109, 1599, 1142, 1115, 635, 627. MS (ESI-TOF): m/z 484.062 $[Co(tren)(ClCl\text{-}phebha)\text{-}H]^+$ (simulated: 484.071). UV-Vis (λ_{max}(nm)/ε($M^{-1}cm^{-1}$)) : 408sh(242), 513(147).

$[Co(tren)(Me\text{-}phebha)](ClO_4)_2$ **(13)**

This was synthesized as **11** using N-(4-methylphenyl)-benzohydroxamic acid (188 mg, 0.83 mmol). Yield: 210 mg, 40 %. ^{1}H NMR (360 MHz, D_2O) δ/ppm = 7.53-7.18 (m, 9H, Ar-H) 3.97-3.81 (m, 2H, tren-H) 3.70-2.72 (m, 10H, tren-H) 2.39-2.30 (m, 3H, Me). IR (KBr)/cm^{-1}: 3443, 3306, 3270, 1108, 1092, 626. MS (ESI-TOF): m/z = $[Co(tren)(Me\text{-}phebha)]^{2+}$ 215.6

(simulated = 215.6). MS (ESI-TOF): m/z 430.155 $[Co(tren)(Me\text{-}phebha)\text{-}H]^+$ (simulated: 430.165). UV-Vis (λ_{max}(nm)/ε($M^{-1}cm^{-1}$)) : 431sh(115), 509(113).

$[Co(tpa)(bhaH_{-1})](ClO_4)_2$ (**14**)

It was synthesized as **11** using $[Co(tpa)Cl_2]Cl$ (1.00 g, 2.2 mmol), benzohydroxamic acid (310 mg, 2.2 mmol) and KOH (5.5 mmol). Yield: 900 mg, 70 %. ^{1}H NMR (400 MHz, d^6-DMSO): δ/ppm = 9.58 (d, 1H Ar-H); 9.22 (d, 1H, Ar-H); 8.55 (d, 1H, Ar-H); 8.18 (t, 1H, Ar-H); 8.00-7.86 (m, 3H, Ar-H); 7.75-7.60 (m, 3H, Ar-H); 7.52-7.43 (d, 3H, Ar-H); 7.41-7.30 (m, 3H, Ar-H); 7.13 (d, 1H, Ar-H); 5.62 (d, 1H, -CH_2); 5.32 (t, 2H, -CH_2); 5.15 (m, 2H, -CH_2); 5.06-5.00 (m, 1H, CH_2). IR (KBr)/cm^{-1}: 3545, 3420, 3055, 2970, 2016, 1610, 1445, 1341, 773, 624. MS (ESI-TOF): m/z 484.107 $[Co(tpa)(bhaH_{-1})]^+$ (simulated: 484.118). UV-Vis (λ_{max}(nm)/ε($M^{-1}cm^{-1}$)) : 450sh(136), 595(151).

$[Co(tpa)(bha)](ClO_4)_2 \cdot C_2H_5OH \cdot H_2O$ (**15**)

14 (263 mg, 0.45 mmol) was suspended in water (10 ml), $HClO_4$ solution (5 ml, 0.1 M) was added and stirred for 3 h. The color of the reaction mixture turned to pink. The crystalline solid was filtered off, washed with water and dried in vacuo. Slow evaporation of the solution gave single crystals. Yield: 200 mg, 64 %. ^{1}H-NMR (400 MHz, d^6-DMSO): δ/ppm = 8.81 (d, 1H, Ar-H); 8.59 (d, 2H, Ar-H); 8.37-8.24 (dd, 1H, Ar-H); 8.20-8.10 (m, 2H, Ar-H); 7.87-7.57 (m, 8H, Ar-H); 7.57-7.49 (m, 1H, Ar-H); 7.46-7.37 (m, 3H, Ar-H); 5.74 (d, 2H, -CH_2); 5.42-5.12 (m, 4H, -CH_2). IR (KBr)/cm^{-1}: 3525, 3113, 3083, 2017, 1475, 1441, 924, 776, 624. MS (ESI-TOF): m/z 484.107 $[Co(tpa)(bha)\text{-}H]^+$ (simulated: 484.107). UV-Vis (λ_{max}(nm)/ε($M^{-1}cm^{-1}$)) : 443sh(167), 544(246).

$[Co(tpa)(phebha)](ClO_4)_2$ (**16**)

It was synthesized as **11** using $[Co(tpa)Cl_2]Cl$ (0.50 g, 1.1 mmol) and N-phenylbenzohydroxamic acid (235 mg, 1.1 mmol). Yield: 580 mg, 63%. ^{1}H NMR (400 MHz, DMSO): δ/ppm = 9.37 (d, 1H, Ar-H); 8.77 (d, 2H, Ar-H); 8.54 (d, 1H, Ar-H); 8.21 (t, 2H, Ar-H); 8.08-7.93 (m, 1H, Ar-H); 7.89-7.56 (m, 8H, Ar-H); 7.53-7.12 (m, 6H, Ar-H); 6.92 (d, 1H, Ar-H); 5.74 (d, 2H, -CH_2); 5.30 (m, 4H, -CH_2). IR (KBr)/cm^{-1}: 3566, 3420, 3059, 2981, 2007, 1747, 1611, 1549, 1492, 1421, 770, 624. MS (ESI-TOF): m/z 560.136 $[Co(tpa)(phebha)\text{-}H]^+$ (simulated: 560.149). UV-Vis (λ_{max}(nm)/ε($M^{-1}cm^{-1}$)) : 428sh(146), 536(136).

2.3 NMR, IR and ESI-MS measurements

NMR measurements were carried out using Bruker Avance 360 or 400 NMR spectrometers at room temperature on samples prepared in D_2O or d^6-DMSO. Calibration was performed using the isotopic impurities of the solvents. IR spectra as KBr pellets were recorded on a Perkin Elmer FTIR Paragon 1000 PC instrument at the Department of Organic Chemistry, University of Debrecen. ESI-TOF MS measurements in the positive mode were carried out on a Bruker micrOTOF-Q instrument at the Department of Applied Chemistry, University of Debrecen.

2.4 Cyclic voltammetric studies

Cyclic voltammetric experiments were performed at room temperature in aqueous solution using a Metrohm 746-747 VA Trace Analyser equipped with a three-electrode system, which consists of a Ag/AgCl/3M KNO_3 reference electrode ($E_{1/2}$ = 209 mV vs. NHE), a platinum wire auxiliary electrode (ALS Co. Japan), and a glassy carbon (CHI104) working electrode. Aqueous solution of $K_3[Fe(CN)_6]$ was used to calibrate the system ($E_{1/2}$ = 0.458 V versus NHE in 5×10^{-1} mol dm^{-3} KCl) [31]. The samples were degassed before the measurements using argon gas. The concentration of the complexes was 5 or 10 mM, the potential sweep rates were varied within the range 200-500 mV s^{-1} during the determination of the redox potentials. In all cases, KNO_3 (0.20 M) was used as supporting electrolyte.

2.5 Crystal structure analysis

Diffraction intensity data collection was carried out at 293(2) K on a Bruker-Nonius MACH3 diffractometer equipped with an area detector using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) or on a SuperNova diffractometer equipped with an Atlas detector using Cu-Kα radiation (λ = 1.5418 Å) at 293(2) K. The structures were solved by SIR-92 program [32] and refined by full-matrix least-squares method on F^2. Non-hydrogen atoms were refined anisotropically using the SHELX package [33]. Publication material was prepared with the WINGX- suite [34] and publCIF [35]. Hydrogen atoms were placed into calculated positions and refined in the rigid mode except the O-H and N-H protons which could be found at the difference electron density map and the respective O-H and N-H distances were constrained. Complex **11** crystallized in chiral space group of C2 with one molecule in the asymmetric unit. Structure **11** overlayed with its inverted pair is shown in Figure S1. The synthesis route was achiral and no further research was performed to detect the possibility of chiral induction. In structure **15** the solvent ethanol shows slight disorder. Crystallographic and experimental details are summarized in Table 1. Crystallographic data

and refinement details for **4, 11, 15** and **16** are deposited in the Cambridge Crystallographic Data Centre under CCDC 1546197-1546200.

Figure S1.

Table 1.

3. Results and discussion

3.1 Characterization of the precursors and complexes

Some of the already published amine ligands or complexes were synthesized by the slight modification of published methods while for the preparation of most of the novel Co(III) ternary complexes one of the literature methods were used. All the compounds were characterized with NMR and IR methods. For some of the new Co(III) complexes the molecular structure was identified using single crystal X-ray diffraction method.

^{1}H-NMR spectra of the ternary Co(III) complexes showed the expected resonances, although, in agreement with previous findings [12], non-equivalence of the aliphatic protons of tren as well as those in tpa resulted in the appearance of signals with high multiplicity. Although it was beyond the scope of our work, in some cases the isomers of the [Co(tren/tpa)hydroxamate] complexes, being present due to the non-symmetrical structure of the coordinating (O,O) donor hydroxamates, were also identified and quantified. As an example, COSY spectrum of the aromatic region of $[Co(tpa)(bha)]^{2+}$ is shown in Figure 1.

Figure 1.

As it is seen in Fig. 1 two sets of cross peaks belonging to the major and minor isomers (identified by the ratios of the corresponding signal areas) can be detected. For both isomers the presence of two set of signals is the consequence of the presence of a mirror plane within the complex cation making non-equivalent of the pyridyl ring being in this place with the two other symmetry-equivalent pyridyl units out of the plane.

For $[Co(uns\text{-}penp)(H_2O)Cl]Cl_2{\cdot}H_2O$ (**4**), containing the tripodal ligand with an aliphatic and two pypidyl arms, and in the case of some new tren or tpa ternary hydroxamate complexes, **11**, **15** and **16**, the molecular structures were also proven by X-ray diffraction. In every cases, in accordance with previous results on similar Co(III) complexes [12], the expected octahedral geometry around the central metal ion was found with the N-Co-N or N-Co-O

bond angles being around 180°. For the Co-N or Co-O distances (Table 2) the measured values are in the range of the typical values for [Co(tren/tpa)(hydroxamate)] type complexes [12].

Table 2

Although high chloride concentration was used to convert the nitrito precursor to the mixed ligand chlorido complex for **4**, the structure (Fig. 2) indicated the presence of one water and one chloride ligand beside the tripodal amine in the coordination sphere of the metal ion.

Figure 2

As far as the benzohydroxamato (protonated hydroxamate-NH) ternary complex, $[Co(tpa)(bha)](ClO_4)_2 \cdot C_2H_5OH \cdot H_2O$ (**15**), is concerned, due to rigid structures no significant differences in the appropriate bond distances compared to the benzohydroximato (deprotonated hydroxamate-N) species, $[Co(tpa)(bhaH_{-1})]^+$ [11], were found with the exception that in **15** (Fig. 3) H-bonding is detected between the hydroxamate NH as donor and the water molecule as acceptor. Interestingly, the orientation of the benzohydroxamate and benzohydroximate ligands are opposite in the two structures, i.e. the carbonyl O is trans or cis to the aliphatic N of tpa, respectively. Comparison of the two new, phebha-containing stuctures with tren (**11**) (Fig. S2) and tpa (**16**) (Fig. 4) reveals higher steric hindrance of the pyridyl arms of tpa than those of the alphatic ones of tren resulting in significantly different Co-O(N) and Co-O(C) distances in **16** while these values are practically identical for **11** (Table 2). Overlay of the two structures indicates the very similar orientation of the phenyl substituents of the hydroxamic acids in the two complexes (Fig. S3).

Figure 3
Figure S2
Figure 4
Figure S3

3.2 Electrochemical results on some precursor complexes

The electrochemical properties of some precursor Co(III) complexes, as well as those of all the investigated ternary complexes have been analysed under the conditions given in Section

2.4. Catodic peaks (E_{pc}) in all cyclic voltammograms (CVs) were observable indicating clearly the reduction of the complexes, while lack of anodic peaks (E_{pa}) provided evidence about default of anodic, reoxidation upon scan reversal. Namely, irreversible reduction of the complexes occured in all of the investigated systems under the conditions used.

Out of the precursor complexes, the tpa- and tren-containing ones (especially with chloride ancillary ligand(s)) have been previously investigated in some laboratories [11, 12, 21], but, to the best of our knowledge, this is the first time, when some electrochemical results are provided on the complexes $[Co(abap)Cl_2]ClO_4$ and $[Co(uns\text{-}penp)(H_2O)Cl]Cl_2$. With tpa and tren, in addition to their chlorido complexes, also the nitrito ones have been electrochemically studied in the present work. For illustration, CVs registered for $[Co(tren)Cl_2]Cl$, $[Co(tpa)Cl_2]Cl$, $[Co(abap)Cl_2]ClO_4$ and $[Co(uns\text{-}penp)(H_2O)Cl]Cl_2$ are presented in Figure 5. The calculated cathodic peak potentials compared both to Ag/AgCl and NHE reference electrodes are collected in Table 3.

Figure 5

Table 3

As Table 3 and Figure 5 show, the Co(III)/(II) reduction potentials of the complexes with tren are significantly more negative than those of the corresponding tpa complexes. This is in complete agreement with previous literature results [12, 17] and explained by the capability of the three pyridyl rings of tpa for π-back-bonding interaction with the metal centre resulting in lowering of its electron density and positive shift of Co(III)/Co(II) redox potential. This assumption is also supported by the reduction potential of the complex of uns-penp. In this latter ligand only two of the three arms contain pyridyl rings, the third involves amine nitrogen, and, in fact, the E_{pc} value lies between those for the complexes of tpa and tren (see Table 3). Surprising result was obtained, however, with abap. As it is clearly seen in Figure 5, the reduction potential of $[Co(abap)Cl_2]ClO_4$ is far the most negative of the investigated precursors and is significantly more negative even compared to that of the tren-containing complex. If we try to understand the background of this significant decreasing of the redox potential, we can take into account that two arms of abap are longer with one CH_2 moiety compared to tren, what, according to the literature, results in somewhat higher overall basicity [20] and, as a consequence, possibility of a slightly higher σ-donation ability of the amine nitrogens of abap might be reasonable. However, for the more adequate explanation of this, somehow unexpected result needs additional investigation. Anyway, it seems that the redox

potential of the abap-containing complex is far below the region, where reduction of the central Co(III) by biological redox systems would be realistic.

As it can be expected, electron donating capability of the nitrite moiety results in measurably negative shift of the reduction potentials of its complexes (see Table 3) compared to the corresponding choride-containing ones.

3.3 Electrochemical results on the ternary complexes incorporating hydroxamates

All the previous results on Co(III) ternary complexes formed with the involvement of a tripodal tetraamine (tren or tpa) and a mono- or doubly-deprotonated form of benzo- [11,12], aceto- [11, 21], propiono- [11] or 1-napthylacetohydroxamic acid [12] and also our corresponding values (see Table 3) demonstrate that the 3+ oxidation state of the central metal ion is very much stabilized in the complexes containing doubly deprotonated hydroxymato ligands and it can be reduced at far more negative potential than the region of the biological reductants. As Table 3 also shows, with the monoanionic hydroxamate, bha^-, if the ancillary ligand is tpa, the reduction potential is adequate to the region, where biological reductants might be able to reduce the Co(III) ion. This is not the case with tren, however, the complexes of which are far less reducable. It is an interesting question, whether there is some possibility to tune the Co(III)/(II) reduction potential into the above-mentioned region via modification of the hydroxamate ligand. Relevant information to this question was aimed to find, when a series of bhaH derivatives have been synthesized (see Scheme 1 for their formulae) and, first of all, their ternary complexes with tren ancillary ligand have been investigated in electrochemical studies in the present work.

The following conclusion can be drawn by analysing the corresponding redox potential values in Table 3: (i) Only a small, if any effect was found on the redox potential via introduction of chloro or nitrito substituent in para position into the phenyl moiety of bha^- (Cl-bha^- and NO_2-bha^-). To illustrate this conclusion, CV curves recorded for the $[Co(tren)bha](ClO_4)_2$ and $[Co(tren)4\text{-}Cl\text{-}bha](ClO_4)_2$ complexes are shown on the same figure in the Supplementary part (Fig. S4) (This result is in agreement with those obtained for Co(III)-acetohydroxamate-tpa derivative ternary complexes. No effect was found on the redox potential, when introduction of chloro substituents on tpa was made [21]). (ii) Significant positive shift (ca. 200 mV) was obtained, however, when R_N = H was substituted by a phenyl ring in $phebha^-$ and the reduction of this complex may become imaginable by bio-reductants. For comparison, with this ligand, not only the tren-containing ternary complex was investigated, but also the tpa-containing one and exactly the same positive shifts of the values (see Table 3) were identified

for both complexes. (iii) Introduction of chloro or methyl substituent in one or both of the two phenyl moieties of phebha$^-$ did not cause any significant further change in the reducibility of the complexes.

Figure S4

Conclusions

As potential carriers and deactivators of benzohydroxamate-based bioactive molecules, Co(III) complexes of four tripodal tetramines, tris(2-aminoethyl)amine (tren), tris(2-pyridylmethyl)amine (tpa), N-(2-aminoethyl)-N,N-bis(3-aminopropyl)amine (abap) and 2-aminoethyl)bis(2-piridylmethyl)amine (uns-penp), being the ancillary ligands either chloride or nitrite ions, have been prepared and characterized by NMR, IR, ESI-TOF-MS, UV-Vis, cyclic voltammetry, and by X-ray in the case of the complex $[Co(uns\text{-}penp)(H_2O)Cl]Cl_2$, as well as the influence of the structural differences of the amines on the redox activity of the central Co(III/II) couple was also studied. The first two amines have been already used in numerous previous studies to develop hypoxia-selective cobalt complexes, but, to the best of our knowledge, this is the first case, when the latter two are investigated with this goal. Irreversible reduction of Co(III) was observed in all the investigated complexes and the highest reduction potential was identified for the tpa-containing complex (+281 mV vs. NHE), where the three π-back-bonding pyridyl rings produce the highest decrease of the electron density on the metal centre. Compared to this, ca. 250 mV negative shift was detected for the complex of uns-penp containing two pyridyl rings and one amine moiety in the chains. Additional ca. 250 mV negative shift is observed with tren, containing three aliphatic amines. Surprisingly, an increase of two chains by one CH_2 group each in abap compared to tren, results in sharp decrease of the redox potential (-564 mV vs. NHE) making the bioreduction of this complex highly unlikely.

The tren-containing precursor complex was used to prepare and characterize seven ternary complexes with various derivatives of bhaH, while three complexes were prepared and characterized with tpa. For three complexes, $[Co(tren)(phebha)](ClO_4)_2$, $[Co(tpa)(bha)](ClO_4)_2{\cdot}C_2H_5OH{\cdot}H_2O$ and $[Co(tpa)(phebha)](ClO_4)_2$, the molecular structures were also proven by X-ray diffraction. In agreement with the literature results it was found that the +3 oxidation state of the central cobalt-ion is extremely stabilized in the ternary complexes containing the doubly deprotonated benzohydroximate, but the metal ion is significantly more reducible in the ternary complexes with mono-deprotonated

benzohydroxamate/derivative ligands. Measurable effect was not observed on the redox potential via introduction of chloro or nitro substituent in para position into the phenyl moiety of bha^- (Cl-bha^- and NO_2-bha^-). Significant positive shift (ca. 200 mV) was obtained, however, when R_N = H was substituted by a phenyl ring in $phebha^-$ therefore complexes with this latter ligand can be likely candidates for the *in vitro* releasing of hydroxamates with proven biological activity.

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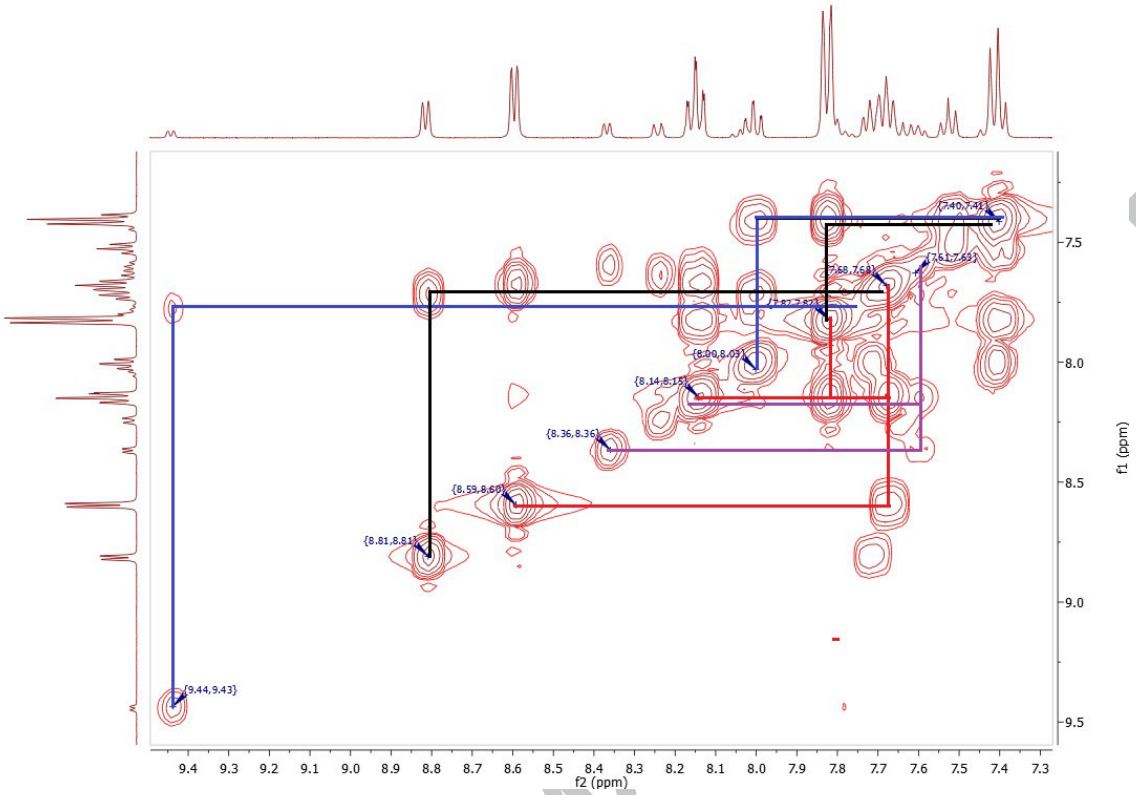


Figure 1. Aromatic region of the COSY spectrum of $[Co(tpa)(bha)](ClO_4)_2$ in d^6-DMSO.

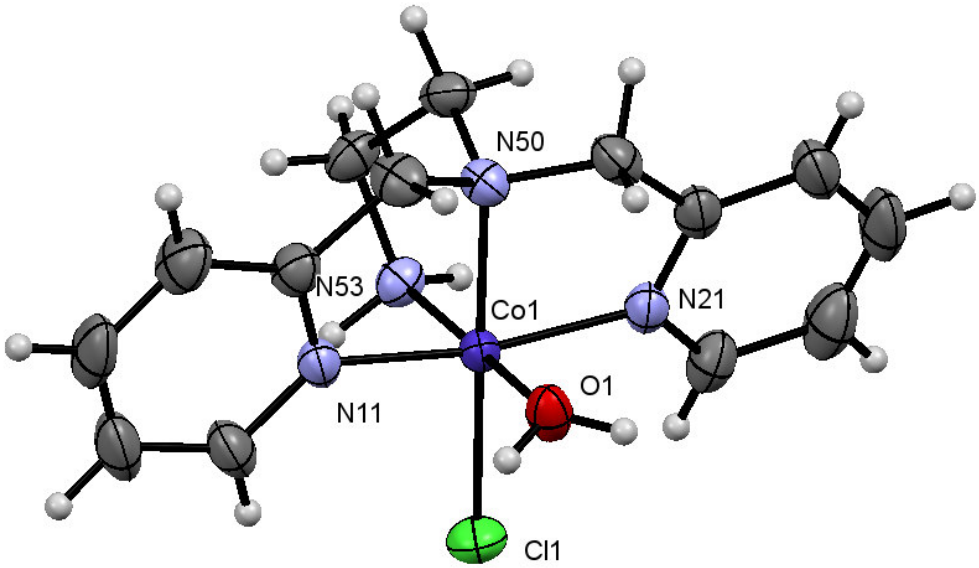


Figure 2. ORTEP view of the $[Co(uns\text{-}penp)(H_2O)Cl]^{2+}$ cation of (**4**) at 50 % probability level. The chloride counter ions and the solvent water molecule are not shown for clarity.

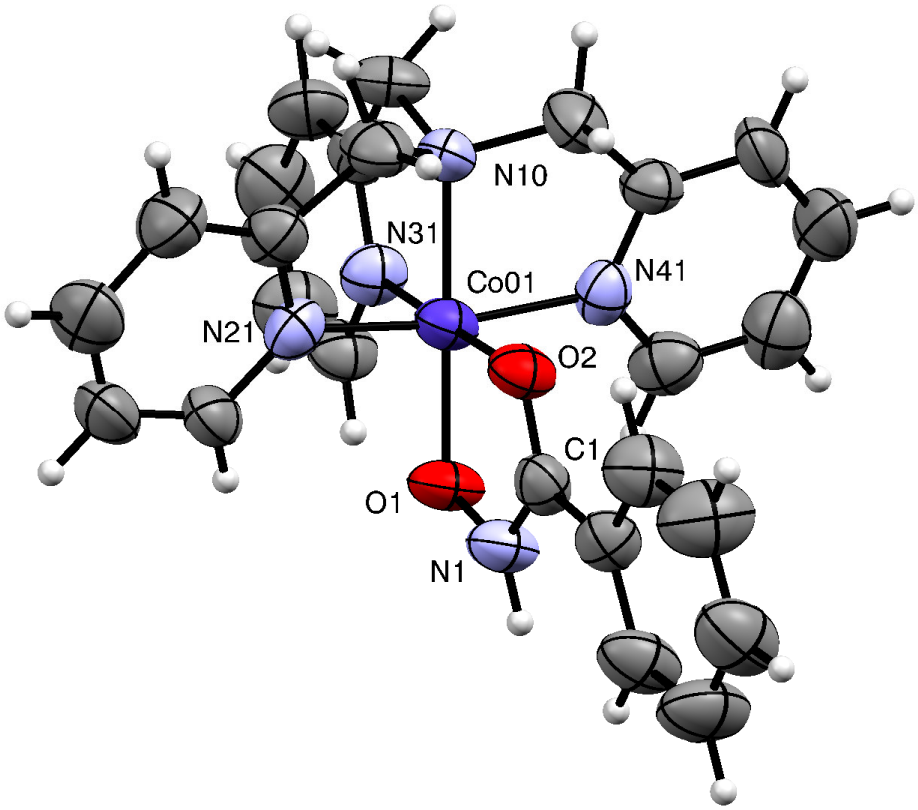


Figure 3. ORTEP view of the $[Co(tpa)(bha)]^{2+}$ cation of **15** at 50% probability level. The perchlorate counter ions, the solvent C_2H_5OH and the water molecule are not shown for clarity.

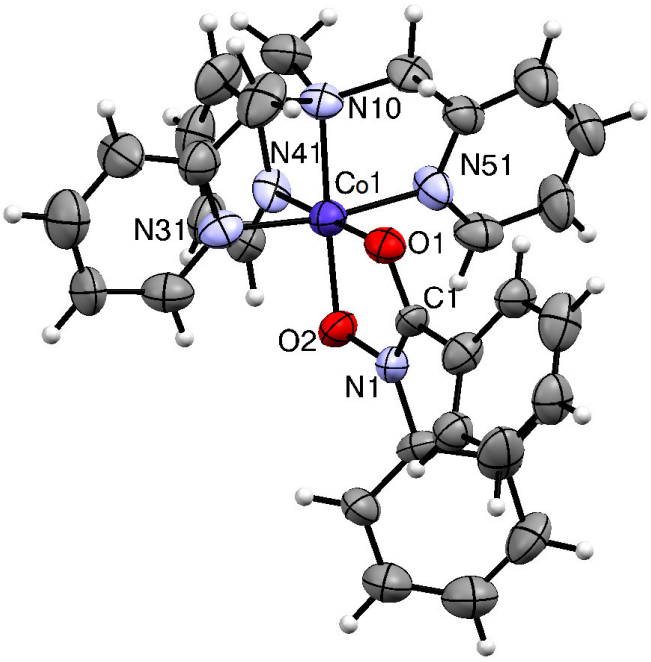


Figure 4. ORTEP view of the $[Co(tpa)(phebha)]^{2+}$ cation of **16** at 50 % probability level. The perchlorate counter ions are not shown for clarity.

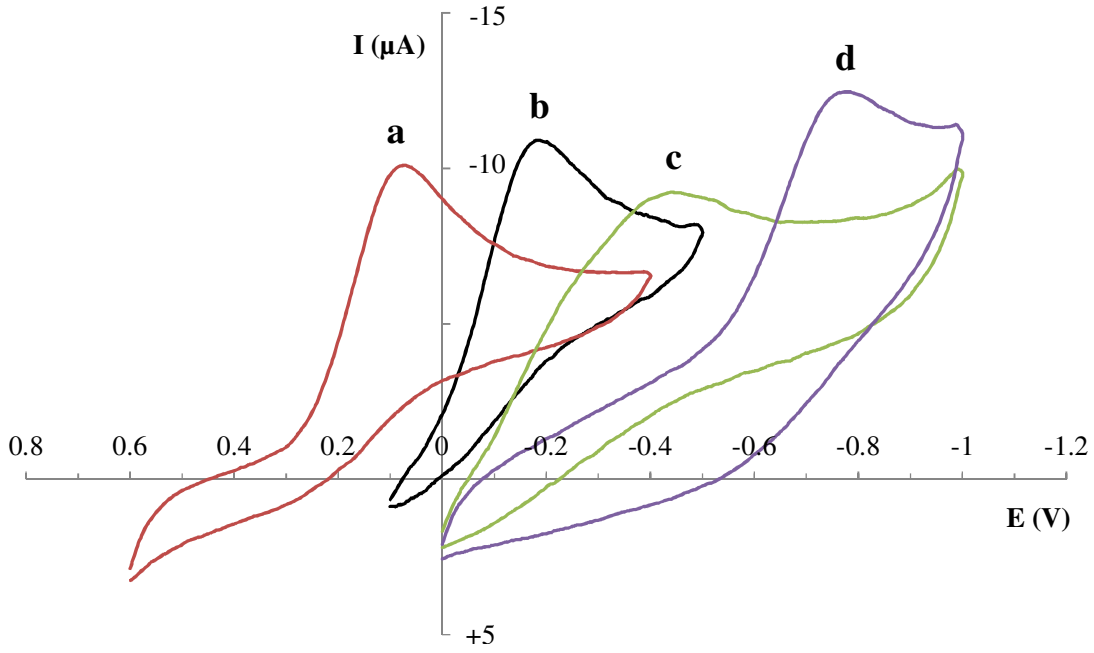
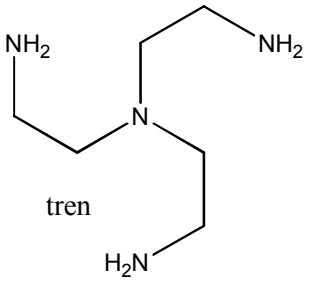


Figure 5. CV curves registered for $[Co(tpa)Cl_2]Cl$ (a), $[Co(uns\text{-}penp)(H_2O)Cl]Cl_2$ (b), $[Co(tren)Cl_2]Cl$ (c) and $Co(abap)Cl_2]ClO_4$ (d) in water, referenced to Ag/AgCl electrode at a potential sweep rate of 200 mV/s and c_M = 1.0 mM.



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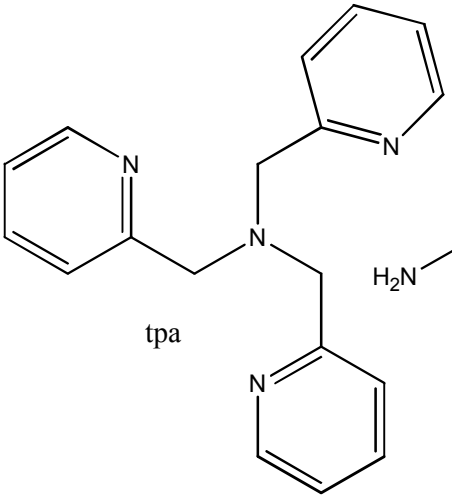

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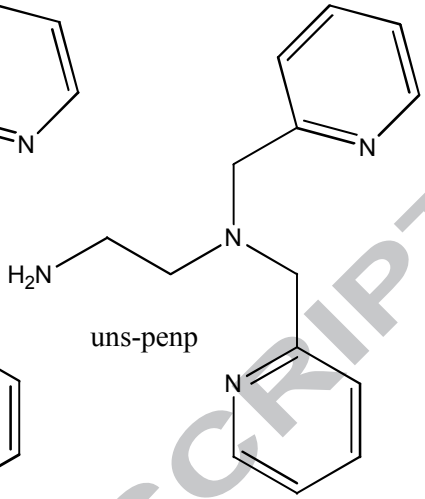

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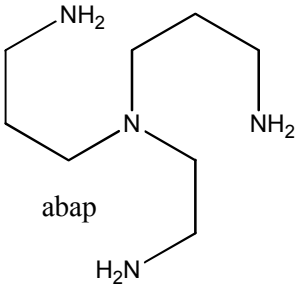
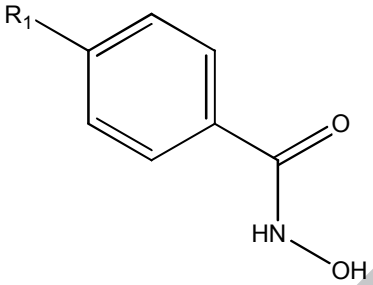
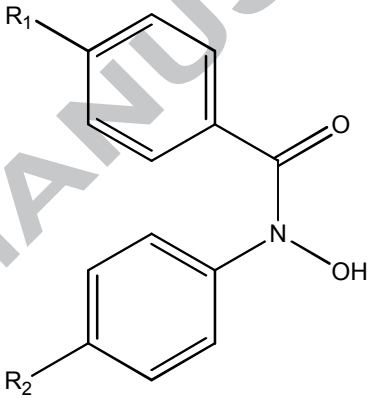


abap





R_1	ligand
H	bhaH
Cl	Cl-bhaH
NO_2	NO_2-bhaH

R_1	R_2	ligand
H	H	phebhaH
Cl	Cl	ClCl-phebhaH
H	CH_3	Me-phebhaH

Scheme 1

Table 1. Crystallographic parameters and refinement details for the Co(III) complexes

Chemical formula	$2(C_{14}H_{20}ClCoN_4O)\cdot Cl_4\cdot H_2O$ (**4**)	$C_{19}H_{28}CoN_5O_2\cdot 2(ClO_4)$ (**11**)	$C_{25}H_{24}N_5O_2Co\cdot 2(ClO_4)\cdot C_2H_6O\cdot H_2O$ (**15**)	$C_{31}H_{28}CoN_5O_2\cdot 2(ClO_4)$ (**16**)
M_r	869.25	616.29	748.4	760.41
Crystal system, space group	Monoclinic, *Cc*	Monoclinic, *C*2	Monoclinic, $P2_1/n$	Monoclinic, *Cc*
Temperature (K)	293	293	298	298
a, *b*, *c* (Å)	12.8726 (2), 7.7648 (1), 18.7982 (3)	16.4658 (3), 7.7014 (1), 21.5468 (4)	12.712 (1), 12.862 (2), 20.234 (3)	9.122 (3), 18.174 (4), 19.752 (5)
β (°)	97.532 (1)	111.214 (2)	98.92 (1)	100.04 (2)
V (Å^3)	1862.73 (5)	2547.19 (8)	3268.3 (7)	3224.5 (15)
Z	2	4	4	4
Radiation type	Cu *K*α	Cu *K*α	Mo *K*α	Mo *K*α
μ (mm^{-1})	11.28	7.78	0.76	0.77
Crystal size (mm)	0.30 × 0.30 × 0.10	0.04 × 0.05 × 0.3	0.4 × 0.3 × 0.25	0.35 × 0.1 × 0.07
Diffractometer	SuperNova, Dual, Cu at zero, Atlas diffractometer	SuperNova, Dual, Cu at zero, Atlas diffractometer	Enraf Nonius MACH3 diffractometer	Enraf Nonius MACH3 diffractometer
Absorption correction	Multi-scan *CrysAlis PRO* 1.171.38.41 (Rigaku Oxford Diffraction, 2015) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.	Multi-scan *CrysAlis PRO* 1.171.38.41 (Rigaku Oxford Diffraction, 2015) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.	ψ scan North A.C.T., Phillips D.C. & Mathews F.S. (1968) Acta. Cryst. A24, 351 Number of ψ scan sets used was 4 Theta correction was applied. Averaged transmission function was used. Fourier smoothing - Window value 5	Part of the refinement model (Δ*F*) Walker, N. & Stuart, D (1983) Acta. Cryst. A39, 158-166
T_{min}, T_{max}	0.148, 1.000	0.322, 1.000	0.647, 0.986	0.295, 0.863
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	6733, 3126, 3077	14501, 4854, 4607	6702, 6083, 2470	4607, 4607, 3135
R_{int}	0.029	0.027	0.052	0.157
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.621	0.622	0.607	0.603
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.038, 0.103, 1.10	0.071, 0.187, 1.06	0.092, 0.221, 0.93	0.097, 0.220, 1.36
No. of reflections	3126	4854	6083	4607
No. of parameters	230	334	432	443
No. of restraints	8	1	5	2
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement	H-atom parameters constrained	H atoms treated by a mixture of independent and constrained refinement	H-atom parameters not refined
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.80, -0.28	2.58, -0.36	0.64, -0.37	0.48, -0.69

Table 2. Key bond length values (Å) of the complexes.

Complex	C=O	N-O	Co-O(N)	Co-O(C)
[Co(tren)(phebha)]$(ClO_4)_2$ (**11**)	1.331(7)	1.348(7)	1.891(4)	1.892(5)
[Co(tpa)(bha)]$(ClO_4)_2 \cdot C_2H_5OH \cdot H_2O$ (**15**)	1.291(8)	1.375(7)	1.864(4)	1.885(5)
[Co(tpa)(phebha)]$(ClO_4)_2$ (**16**)	1.308(18)	1.406(16)	1.864(11)	1.901(11)

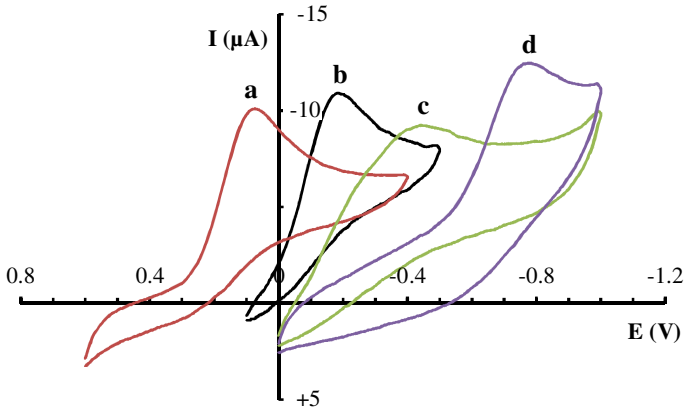
Table 3. Measured cathodic peak potential (Epc) values of the Co(III) complexes referenced to Ag/AgCl and the calculated values against NHE.

Complex	Epc (mV) Ag/AgCl	Epc (mV) H_2/H^+
$[Co(tren)Cl_2]Cl$	-439	-230
$[Co(tpa)Cl_2]Cl$	72	281
$[Co(uns\text{-}penp)(H_2O)Cl]Cl_2$	-182	27
$[Co(abap)Cl_2]ClO_4$	-773	-564
$[Co(tren)(NO_2)_2]Cl$	-568	-359
$[Co(tpa)(NO_2)_2]Cl$	-175	34
$[Co(tren)(bha)](ClO_4)_2$	-780	-571
$[Co(tren)(bhaH_{-1})]ClO_4$	-999	-790
$[Co(tren)(Cl\text{-}bha)](ClO_4)_2$	-782	-573
$[Co(tren)(NO_2\text{-}bha)](ClO_4)_2$	-726	-517
$[Co(tren)(phebha)](ClO_4)_2$	-572	-363
$[Co(tren)(ClCl\text{-}phebha)](ClO_4)_2$	-570	-361
$[Co(tren)(Me\text{-}phebha)](ClO_4)_2$	-550	-341
$[Co(tpa)(bha)](ClO_4)_2$	-427	-218
$[Co(tpa)(bhaH_{-1})](ClO_4)$	-687	-478
$[Co(tpa)(phebha)](ClO_4)_2$	-224	-15

Highlights

- synthesis of Co(III) complexes incorporating hydroxamates as potential hypoxia-activated prodrugs
- CV study of the complexes to explore the structural and electronic effects of the ligands on their redox properties

Graphical Abstract



Synopsis for the graphical abstract

Ternary [Co^{III}(4N)(hydroxamate] complexes as potential hypoxia-activated chaperons were synthesized and the effect of the structural and electronic effects of the ligands on the redox behaviour of the complexes was studied using cyclic voltammetry.