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Characterization of Cobalt(III) Hydroxamic Acid Complexes Based on a Tris(2-pyridylmethyl)amine Scaffold: Reactivity toward Cysteine Methyl Ester

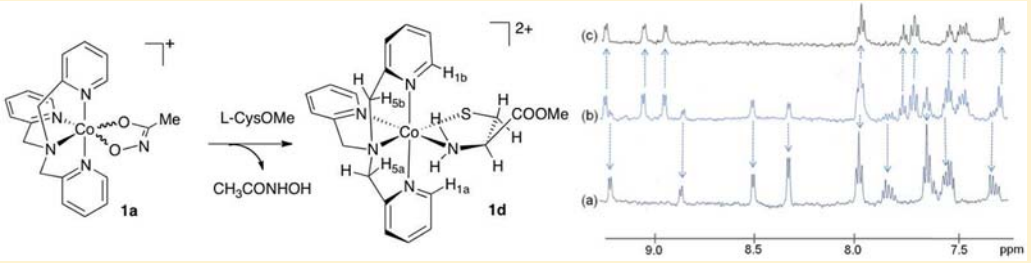
Mickael Alimi,[†] Anas Allam,[†] Mohamed Selkti,[‡] Alain Tomas,[‡] Pascal Roussel,[§] Erwan Galardon,[†] and Isabelle Artaud*,[†]

[†]Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR 8601 CNRS, Université Paris Descartes, Sorbonne Paris Cité, 45 rue des Saints Pères, 75270 Paris Cedex 06, France

[‡]Laboratoire de Crystallographie et RMN Biologiques, UMR 8015 CNRS, Université Paris Descartes, Sorbonne Paris Cité, 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France

[§]Unité de Catalyse et Chimie du Solide, UMR 8012 CNRS, Ecole Nationale Supérieure de Chimie de Lille BP 90108, 59652 Villeneuve d'Ascq Cedex, France

Supporting Information



ABSTRACT: Six Co(III) complexes based on unsubstituted or substituted TPA ligands (where TPA is tris(2-pyridylmethyl)amine) and acetohydroxamic acid (**A**), *N*-methyl-acetohydroxamic acid (**B**), or *N*-hydroxy-pyridinone (**C**) were prepared and characterized by mass spectrometry, elemental analysis, and electrochemistry: [Co(III)(TPA)(A-2H)](Cl) (**1a**), [Co(III)((4-Cl_2)TPA)(A-2H)](Cl) (**2a**), [Co(III)((6-Piva)TPA)(A-2H)](Cl) (**3a**), [Co(III)((4-Piva)TPA)(A-2H)](Cl) (**4a**) and [Co(III)(TPA)(B−H)]$(Cl)_2$ (**1b**), and [Co(III)(TPA)(C−H)]$(Cl)_2$ (**1c**). Complexes **1a**−**c** and **3a** were analyzed by ^{1}H NMR, using 2D (^{1}H, ^{1}H) COSY and 2D (^{1}H, ^{13}C) HMBC and HSQC, and shown to exist as a mixture of two geometric isomers based on whether the hydroxamic oxygen was *trans* to a pyridine nitrogen or to the tertiary amine nitrogen. Complex **3a** exists as a single isomer that was crystallized. Its crystal structure revealed the presence of an H-bond between the pivaloylamide and the hydroximate oxygen. Complexes **1a**, **2a**, and **4a** are irreversibly reduced beyond −900 mV versus SCE, while complexes **1b** and **1c** are reduced at less negative values of −330 and −190 mV, respectively. The H-bond in **3a** increased the redox potential up to −720 mV. Reaction of complex **1a** with L-cysteine methyl ester CysOMe was monitored by ^{1}H NMR and UV−vis at 2 mM and 0.2 mM in an aqueous buffered solution at pH 7.5. Complex **1a** was successively converted into an intermediate [Co(III)(TPA)(CysOMe-H)]$^{2+}$, **1d**, by exchange of the hydroximate with the cysteinate ligand, and further into Co(III)(CysOMe-H)$_3$, **5**. An authentic sample of **1d** was prepared and thoroughly characterized. A detailed ^{1}H NMR analysis showed there was only one isomer, in which the thiolate was *trans* to the tertiary amine nitrogen.

INTRODUCTION

Development of metallodrugs as prodrugs to deliver an active molecule to its target appears as a challenging alternative to access new pharmaceuticals.[1−3] The major examples reported so far refer to cobalt(III) complexes of drugs with anticancer activity, such as those based on nitrogen mustards[4] and more recently marimastat.[5] The release of the drug inside the cells was first proposed to proceed by reduction of the Co(III) metallodrug to a Co(II) state and dissociation from this unstable Co(II) complex.[6] While the activity of mustard complexes follows this trend,[4] in the case of the hydroxamic acid, marimastat,[5] the reduction with biological reductants is hardly possible because the redox potential required is very low and beyond the redox value inside the cell (around −250 mV vs NHE[7]). More recently, Hambley and co-workers proposed that reductants could also act via ligand exchange, and that, in Co(III)(TPA)(hydroximate) metallodrugs, the drug could be displaced inside the cell by an endogenous ligand.[8] However, the limitation of this second hypothesis is the well-known inertness of Co(III) complexes, while ligands are labile in the Co(II) state.[9] In this paper, using model complexes based on

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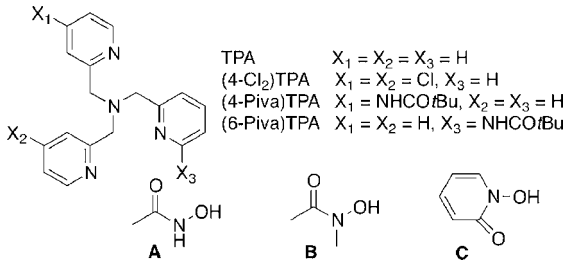
substituted or unsubstituted TPA (tris(2-pyridylmethyl)amine) and hydroxamic acids, we provide some new evidence regarding the mode of dissociation of the drug from the original complex, i.e., reduction or ligand exchange. We first detail a complete study, on the influence on the Co(III)/Co(II) reduction, of the two partners of the Co(III)(TPA)(hydroximate), the ancillary ligand TPA, and the hydroxamic acid. Using acetohydroxamic acid, we introduced chloro substituents on the TPA ligand to try to tune the redox potential by electronic effects, but without any success. However, introduction of a pivaloylamido group in *ortho* position of one pyridine ring nitrogen promotes a more drastic change of the redox value. Then, using the unsubstituted TPA, we turned to *N*-methyl-acetohydroxamic acid and *N*-hydroxy-pyridinone as other models of inhibitors of this class[10] to investigate their influence on the reduction potential. All the complexes were thoroughly characterized by ^{1}H NMR, mass spectrometry, elemental analysis, and cyclic voltammetry. In a second part, we focused on the Co(III)(TPA)(acetohydroximate) complex, and we discussed the outcome of its reaction with L-cysteine methyl ester (CysOMe) as model of intracellular thiol reductants. In this study, we prepared and characterized a new complex, [Co(III)(TPA)(CysOMe-H)]$(BPh_4)_2$, the intermediate resulting from the ligand exchange between the cysteine derivative and the hydroximate ligand.

RESULTS AND DISCUSSION

Synthesis of Ligands and Complexes. Ligands and complexes used in this study are depicted in Scheme 1.

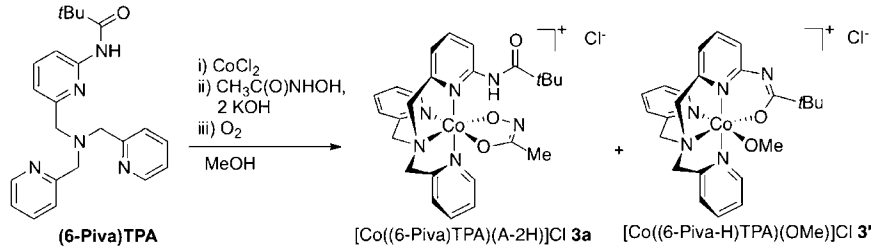
Scheme 1. Ligands and Hydroxamic Acids Used in This Study



Syntheses of ligands TPA,[11] (4-Cl_2)TPA,[12] and (6-Piva)TPA[13] have been previously reported in the literature except *N*-((4-(pivaloylamido)-2-pyridyl)methyl)-*N*,*N*′-bis((2-pyridyl)-methyl)amine, (4-Piva)TPA, that we prepared from *N*-((4-nitro)-2-pyridyl)methyl)-*N*,*N*′-bis((2-pyridyl)methyl)amine[12] in two steps upon reduction in ethanol with hydrazine hydrate in the presence of a catalytic amount of Pd/C[14] followed by condensation in CH_2Cl_2 of the resulting amine with pivaloyl chloride. Synthesis of the Co(III) complexes was achieved by dioxygen oxidation of the Co(II) species formed upon treatment of the Co(II)((X)TPA)Cl_2 complexes (X = H, 4-Cl_2, 4-Piva, and 6-Piva), prepared *in situ* in methanol, with acetohydroxamic acid (**A**), *N*-methyl-acetohydroxamic acid (**B**), or *N*-hydroxy-pyridinone (**C**), in the presence of 2 (**A**) or 1 (**B** and **C**) equiv of KOH. Five complexes were readily obtained and characterized: [Co(III)(TPA)(A-2H)](Cl) (**1a**), [Co(III)((4-Cl_2)TPA)(A-2H)](Cl) (**2a**), [Co(III)((4-Piva)-TPA)(A-2H)](Cl) (**4a**), [Co(III)(TPA)(B−H)]$(Cl)_2$ (**1b**), and [Co(III)(TPA)(C−H)]$(Cl)_2$ (**1c**). Unlike complexes **2a** and **4a** for which there are numerous isomers, complexes **1a**, **1b**, and **1c** exist only as a mixture of two geometric isomers, based on whether the hydroxamic oxygen is *trans* to a pyridine nitrogen or to the tertiary amine nitrogen. Thus, **2a** and **4a** were only characterized by mass spectrometry (ESI$^+$ in CH_3CN) and elemental analysis, and the other complexes were in addition thoroughly characterized by ^{1}H NMR spectroscopy, since a complete assignment of their ^{1}H NMR resonances was possible using homonuclear 2D (^{1}H, ^{1}H) COSY and heteronuclear 2D (^{1}H, ^{13}C) HMBC and HSQC correlations. All the spectra of the complexes are shown with proton assignment in Supporting Information (Figure S1). Complex **1a** appears as a 50:50 mixture of the two isomers on the basis of the integration ratio of the signals attributed to protons in *ortho* position of the pyridine nitrogens. For the pyridine ring in the mean plane containing the hydroximate, this proton is highly deshielded and appears in the two isomers as a doublet at 9.33 and 9.18 ppm, while the two corresponding protons of the pyridines in axial position are equivalent and appear as doublets at 8.20 and 8.52 ppm in the two isomers, respectively. The methyl of the hydroximate is located at 1.91 and 1.36 ppm in the two isomers. Similarly, complexes **1b** and **1c** were isolated as 40:60 and 30:70 mixtures of the two isomers.

Characterization of Complex [Co((6-Piva)TPA)(A-2H)]Cl (3a). Following the procedure aforementioned, reaction of (6-Piva)TPA with $CoCl_2$ and acetohydroxamic with two base equivalents did not result in the unique formation of the expected complex **3a**, [Co((6-Piva)TPA)(A-2H)]Cl. ^{1}H NMR analysis of the raw material obtained at the end of the reaction revealed a 60:40 mixture of complexes **3a** and **3′**, this latter was identified as [Co(III)(6-Piva-H)(TPA)(OMe)]Cl (Scheme 2). An authentic sample of complex **3′** was synthesized by adding 2 equiv of KOH to a methanolic solution of (6-Piva)TPA and $CoCl_2$, followed by air oxidation. Mass spectrometry, elemental analysis, and ^{1}H NMR spectroscopy are consistent with the proposed structure. Owing to the strong Lewis acidity of the cobalt(III) ion, in this complex, the pivaloylamide is likely deprotonated, resulting in the coordination of the iminolate oxygen to the Co(III) as previously observed in the X-ray structures of related TPA complexes such as [Ni(II)(6-Piva-

Scheme 2. Preparation of [Co(III)(6-Piva)TPA)(A-2H)]Cl, 3a



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H)TPA)]^{15} and [Zn(II)(6-Piva-H)TPA)].^{13} This is supported by the FTIR spectrum of **3′**, in which the C═O stretching vibration was shifted to a lower energy relative to the free ligand (1609 cm^{-1} for **3′** and 1683 cm^{-1} for (6-Piva)TPA)) and relative to a pivaloylamide carbonyl oxygen bound to a Co(II)^{16} (ν_{CO} = 1618 cm^{-1}). The sixth ligand in **3′** is likely a methanolate since the mass spectrum, recorded in acetonitrile or dichloromethane, showed a parent peak at m/z = 478 corresponding to [Co(III)(6-Piva-H)(TPA)(OMe)]$^+$. Complex **3a** was readily separated from **3′** by chromatography over Sephadex LH-20, eluting first with methanol as a green band. Its ^{1}H NMR analysis (Figure S1) revealed the presence of a single stereoisomer that was crystallized as its BPh_4 salt. The X-ray structure of **3a(BPh$_4$)** shown in Figure 1 is quite similar to

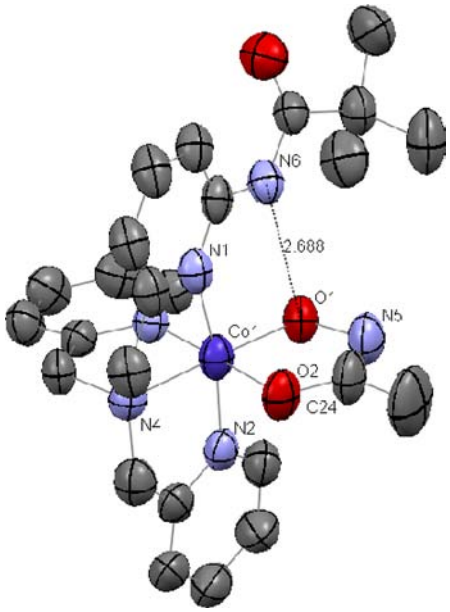

Figure 1. ORTEP view of **3a(BPh)$_4$** showing thermal ellipsoid at 50% probability and atom labeling. Hydrogen atoms and BPh_4 anions are omitted for clarity. Selected bond distances (Å) and angles (deg): Co(1)−O(1) 1.842(2), Co(1)−O(2) 1.862(2), Co(1)−N(1) 1.978(3), Co(1)−N(2) 1.914(3), Co(1)−N(3) 1.902(3), Co(1)−N(4) 1.943(3), O(1)−N(5) 1.423(4), N(5)−C(24) 1.292(5), C(24)−O(2) 1.302(5), O(1)−Co(1)−N(4) 178.35(12), N(1)−Co(1)−N(2) 168.88(13), O(2)−Co(1)−N(3) 177.53(12), O(1)−Co(1)−O(2) 85.86(11), N(2)−Co(1)−N4) 85.18(13), N(2)−Co(1)−O(1) 93.21(12), N(4)−Co(1)−O(2) 93.79(12).

those previously reported by Failes et al. for similar [Co(III)(TPA)(hydroximate)]$^+$ complexes.^{5,17} The geometry around the Co(III) is slightly distorted octahedral, and the acetohydroximate adopts a bidentate chelation mode to the Co(III) with the hydroximate oxygen *trans* to the tertiary amine nitrogen and the carbonyl oxygen *trans* to the pyridine nitrogen. The main difference with the structure of [Co(III)-(TPA)(A-2H)]$^+$, **1a**,^{17} is the existence of a hydrogen bond between the NH of the pivaloylamide and the hydroximate oxygen (N6···O1 2.688 Å), which induces a slight elongation of the corresponding cobalt nitrogen axial bond (Co···N1 1.978 and Co···N2 1.914 Å). The other bond lengths are in the range of those previously reported.^{17} This complex is a new example in which a metal ligand interaction is stabilized through intramolecular hydrogen bonding.^{18,19}

Electrochemistry. The cyclic voltammogram of all the complexes **1a−c**, **2a**, **3a**, and **4a** in DMF displayed an irreversible reduction attributed to the Co(III)/Co(II) couple (Figure S2 and Table 1). In the acetohydroximate series, while

Table 1. E_{pc} Values for the Co(III) Complexes Derived from Hydroxamic Acids

complex	E_{pc} vs SCE (mV)
[Co(III)(TPA)(A-2H)](Cl), **1a**	−990[a]
[Co(III)(TPA)(B−H)](Cl)$_2$, **1b**	−330
[Co(III)(TPA)(C−H)](Cl)$_2$, **1c**	−190
[Co(III)((4-Cl$_2$)TPA)(A-2H)](Cl), **2a**	−960
[Co(III)(6-Piva)TPA)(A-2H)]Cl, **3a**	−720
[Co(III)((4-Piva)TPA)(A-2H)](Cl), **4a**	−1060

[a]This value is in the range of that previously reported for **1a** by Failes et al. in ref 17.

complexes **1a**,^{17} **2a**, and **4a** exhibited E_{pc} values in the range −990 to −1060 mV versus SCE, E_{pc} value of **3a** was less negative (+270 mV shift relative to **1a**). The hydroxamate derivatives, **1b** and **1c**, were also reduced at a more anodic potential, −330 mV for [Co(III)(TPA)(B−H)](Cl)$_2$ (**1b**), and −190 mV for [Co(III)(TPA)(C−H)](Cl)$_2$ (**1c**). Introducing an electron withdrawing group in *para* position of the TPA pyridine moieties does not affect the Co(III)/Co(II) reduction, and clearly, stabilization of the Co(III) state by the hydroximate prevails over electronic effect on the TPA ligand. However, replacing the hydroximate by a hydroxamate results in an increase of the overall charge of the complex and destabilizes the Co(III) state. We previously observed the same tendency with [Fe(III)(TPA)(hydroximate)]$^+$ relative to [Fe(III)(TPA)-(hydroxamate)]$^{2+}$ complexes,^{20} and during the submission of this paper, P. D. Bonnitcha et al. reported a similar result, upon conversion of Co(III)(TPA)(hydroximate) to Co(III)(TPA)-(hydroxamate) by protonation.^{21} Interestingly, the hydrogen bond between the hydroximate oxygen and the pivaloylamide in complex **3a**, by decreasing the charge of the bound hydroximate, makes the Co(III)/Co(II) reduction easier. So, introducing a hydrogen bond donor in the coordination sphere of the Co(III)(hydroximate) complexes appears as an alternative to tune the reduction potential of hydroximate-based metallodrugs.

Reactivity of Complex 1a toward L-Cysteine Methyl Ester. Even though the reduction potentials measured by electrochemistry are not thermodynamic, since the processes are irreversible, they indicate that some cobalt(III) complexes could be reduced within a range of potential accessible to biological reductants. However, this could not be the case of the hydroximato derivatives which are reduced at much lower potentials. To get some insights on the possible release of the hydroxamic acid by an alternative ligand exchange pathway as previously suggested,^{8} we focused on the reactivity of **1a** toward L-cysteine methyl ester in Tris buffer solution at pH 7.5. Compound **1a** was stable in this buffer, and no degradation was observed over 24 h by UV−vis spectroscopy. Reaction of **1a** with 10 equiv of L-cysteine methyl ester hydrochloride was monitored, under argon, by ^{1}H NMR and UV−vis spectroscopy at concentrations of **1a** of 2 mM. At this concentration, we observed by NMR the disappearance of the typical signals attributed to **1a** (9.33 and 8.20 for one isomer, and 9.18 and 8.52 for the other) and the appearance of those of the free TPA ligand. The conversion was complete within 3 h (Figure 2). In

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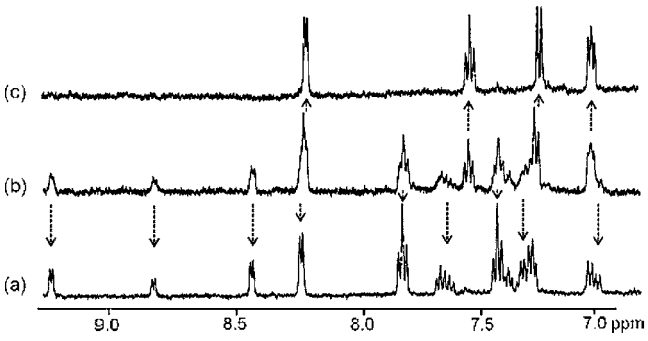

Figure 2. ^{1}H NMR monitoring of the reaction of complex **1a** (2 mM in 200 mM Tris buffer, pH = 7.5) with 10 equiv of L-cysteine methyl ester hydrochloride: (a) spectrum of complex **1a**, (b and c) spectra recorded after 1 and 3 h, respectively.

UV−vis, we observed in the cuvette the progressive formation of a green precipitate. Its spectrum, in Tris buffer pH 7.5/DMSO 9:1, which displayed bands at 280, 450, and 586 nm (Figure 3), was identical to that of an authentic sample of

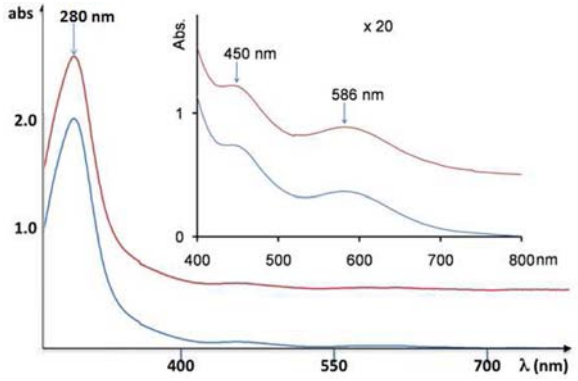

Figure 3. Superposition of the UV−vis spectra (1.2 mM in 200 mM Tris buffer pH 7.5/DMSO, 90:10) of the precipitate formed upon reaction of **1a** with 10 equiv of L-cysteine methyl ester: precipitate (blue trace), reference complex **5** (red trace).

Co(III)(CysOMe-H)$_3$ (**5**), prepared by reaction, in water, of CysOMe·HCl with $Na_3[Co(CO_3)_3]\cdot 3H_2O$ as previously reported.[22] Direct identification of the released hydroxamic acid in the final NMR spectrum was difficult due to the excess of cysteine methyl ester, and we put it in evidence thanks to the specific assay with iron(III) chloride.[23] The cobalt cation was first trapped with Chelex. Evaporating the solvent and adding $FeCl_3$ to an acetone solution of the residue, once filered, promoted the appearance of the expected deep magenta color of the tris hydroxamate iron(III) complex. Then, to try and identify an intermediate before the complete ligand exhange leading to the formation and precipitation of **5**, we performed experiments in more dilute conditions, and monitored the reaction, by UV−vis spectroscopy, between **1a** at 0.2 mM and CysOMe·HCl at different pH. We indeed observed the clean conversion of **1a** into an intermediate with bands at 260 and 310 nm, whose rate of formation decreased as the buffer became more acidic, showing that the reactive species was the deprotonated form of the cysteine methyl ester. The conversion was complete within 2 h at pH 8.0 for a CysOMe·HCl/**1a** ratio of 5 (Figure S3), while it required about 7 h with a CysOMe.HCl/**1a** ratio of 10 at pH 6.5 (Figure S4). The reaction was then monitored by ^{1}H NMR (Figure 4A) and UV−vis (Figure 4B) at pH 7.5. The species with bands at 260 and 310 nm, formed within 3 h, displayed in ^{1}H NMR signals at 9.19, 9.01, and 8.89 ppm. This complex, supposed to be $[Co(III)(TPA)(CysOMe\text{-}H)]^{2+}$, was prepared by reaction, in methanol, of $[Co(III)(TPA)(Cl)_2](ClO_4)$ with cysteine methyl ester hydrochloride in the presence of 2 equiv of KOH, followed by counteranion exchange with $NaBPh_4$. This new complex **1d**, $[Co(III)(TPA)(CysOMe\text{-}H)](Cl)_{0.75}(BPh_4)_{1.25}$, was characterized by mass spectrometry and elemental analysis. It showed the same ^{1}H NMR and UV−vis characteristics as those of the intermediate discussed above. Although we could not get crystals of **1d** suitable for X-ray analysis, since it is very sensitive to dioxygen, we determined its structure in solution by classical NMR experiments under argon (Scheme 3). In contrast to complexes **1a−c**, which were obtained as mixture of two stereoisomers, **1d** was formed as a single stereoisomer. This is highlighted by the presence of only one set of doublets corresponding to the three *ortho* pyridine protons at 9.19, 9.01, and 8.89 ppm, **1d(BPh$_4$)** (Figure S1). The 2D NOESY experiment, which revealed several correlations between the TPA and the cysteine fragments, supported the expected bidentate N/S cordination of the cysteine to the cobalt(III) center and allowed us to conclude that the thiolate was *trans* to the tertiary amine nitrogen atom. This assignement was based on (i) correlations observed between each of the *ortho* pyridine protons in axial position, H_{1a} at 9.19 ppm and H_{1b} at 9.01 ppm, and one diastereotopic proton from the CH_2 group of the

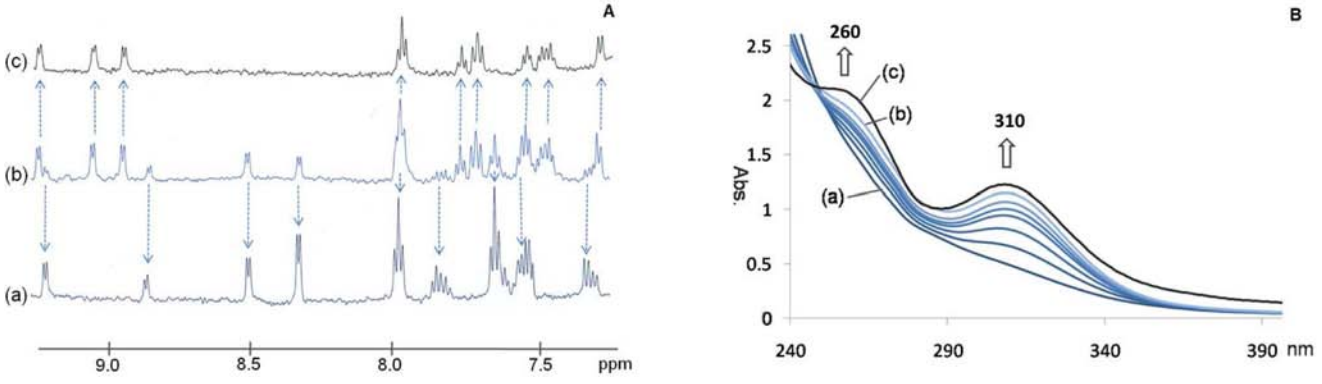

Figure 4. Reaction of complex **1a** (0.2 mM in 200 mM Tris buffer, pH 7.5) with 10 equiv of L-cysteine methyl ester hydrochloride. Evolution of the (A) ^{1}H NMR (500 MHz) and (B) UV−vis spectra: (a) spectrum of **1a**, (b) traces after 3 h of reaction, (c) spectrum of the reference complex **1d**.

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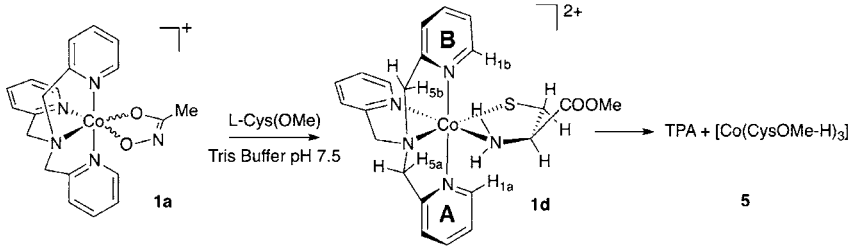
Scheme 3. Reaction of [Co(TPA)(A-2H)]Cl, 1a, with L-Cysteine Methyl Ester in an Aqueous Buffered Solution at pH 7.5



cysteine fragment at 2.57 and 2.63 ppm, respectively (see Scheme 3 for the labeling), (ii) correlations between each of the NH_2 protons at 5.34 and 5.18 ppm, and one proton of the two benzylic moieties from TPA apart from the mean plane containing the cysteine, H_{5a} and H_{5b} at 5.70 and 5.93 ppm, respectively. Then, due to the chirality of the cysteine methyl ester, there is only one enantiomer, and, therefore, only one correlation between one axial pyridine *ortho* proton, namely H_{1a}, and the CH of the cysteine at 3.49 ppm. Clearly, reaction of complex **1a** with the cysteine ester proceeded through ligand exchange, hydroximate/L-cysteine methyl ester, as shown in Scheme 3. We did not observe, by EPR, under argon the formation of any Co(II) species. Reaction of **1d** at 0.2 mM with an excess of CysOMe·HCl led to the slow release of TPA as shown by ^{1}H NMR (Figure S5).

To complete this study, we also monitored by ^{1}H NMR the reaction of **1b** (0.2 mM) with 10 equiv of CysOMe·HCl at pH 7.5; **1b** was equally converted into **1d**, and after 3 h, the conversion rate was roughly similar to that of **1a** into **1d** (Figure S6).

CONCLUSION

In this paper, we have shown that the reduction potential of Co(III) metallodrugs built on TPA and hydroxamic acids is mainly governed by the state of deprotonation of the hydroxamic acid. With *N*-substituted hydroxamic acid or *N*-hydroxypyridinone, which act as monoanionic hydroxamato ligands, the Co(III)/Co(II) reduction potential can fall in the range of those of biological reductants. On the contrary, hydroxamic acids, which bind to the Co(III) center in their dianionic hydroximato form, are reduced at very low potentials. However, introducing a hydrogen bond donor on the TPA ligand such as a pivaloylamide in *ortho* position of a pyridine nitrogen, appears as a suitable alternative to raise the potential to a less negative value. With, by far less reducible complexes, the hydroxamic acid is very likely released from the $[Co(III)(TPA)(hydroximate)]^+$ metallodrug, inside the cell, by a ligand exchange with a biological thiol. Monitoring the reaction of such a complex with L-cysteine methyl ester, in a buffered solution at pH 7.5, by ^{1}H NMR and UV−vis spectroscopies, is in agreement with the intermediate formation of the $[(Co(III)(TPA)(CysOMe\text{-}H)]^{2+}$ complex, without any reduction of the Co(III) to the Co(II) state. An excess of L-cysteine methyl ester ultimately leads to the release of the TPA ligand and to the formation of $Co(III)(CysOMe\text{-}H)_3$.

EXPERIMENTAL SECTION

Physical Measurements. ESI-MS spectra were recorded on a Thermo Finnigan LCD Advantage spectrometer. UV−vis spectra were recorded on a Jasco V-570 spectrometer. Elemental analyses were carried out in CNRS at Gif-sur-Yvette. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker ARX-250 or AVANCEII-500 spectrometers, with chemical shifts reported in ppm relative to the residual solvent. Cyclic voltammetry experiments were performed at room temperature on a PGZ100/HVB100 setup (radiometer analytical) with a three-electrode system which consists of a NaCl saturated calomel electrode (SCE), a platinum auxiliary electrode, and a glassy carbon working electrode. The samples were dissolved in deaerated DMF (0.01 M). nBu_4NClO_4 was used as supporting electrolyte (0.10 M). The potential sweep rate was 100 mV s^{-1}, and ferrocene was used as internal standard ($E_{1/2}$ = 342 vs mV/SCE). IR spectra were obtained with a Perkin-Elmer Spectrum One FT-IR spectrometer equipped with a MIRacleTM single reflection horizontal ATR unit (Zirconium−Selenium crystal).

Materials. Organic solvents were dried and freshly distilled before use following standard procedures. Tris buffer (200 mM, pH = 7.5) was prepared by dissolving the required amount of TRIS AMINO in deionized water, and by adjusting the pH with concentrated aqueous HCl.

Synthesis of *N*-((4-(Pivaloylamido)-2-pyridyl)methyl)-*N*,*N*′-bis((2-pyridyl)methyl)amine, (4-Piva)TPA). To a solution of *N*-((4-nitro)-2-pyridyl)methyl)-*N*,*N*′-bis((2-pyridyl)methyl)amine[12] (100 mg, 0.30 mmol) in dry ethanol (5 mL) under argon was added a catalytic amount of Pd/C (10 mg). After stirring under reflux for 1 h, hydrazine hydrate (20 equiv, 302 mg, 5.96 mmol) was added, and the mixture was stirred under reflux for 2 additional hours. After cooling and filtration through Celite, ethanol was removed under reduced pressure, and then the residue was dissolved in CH_2Cl_2 and washed 3 times with water. After drying over $MgSO_4$ the organic layer was evaporated to give an oily residue which was triturated with diethyl ether to afford *N*-((4-amino-2-pyridyl)methyl)-*N*,*N*′-bis((2-pyridyl)-methyl)amine as a colorless solid (91 mg, quantitative yield). ^{1}H NMR (δ, 250 MHz, $CDCl_3$): 8.51 (d, 2H, ^3J = 4.9 Hz), 8.11 (d, 1H, ^3J = 5.9 Hz), 7.58 (m, 4H), 7.12 (t, 2H, ^3J = 6,4 Hz), 6.83 (d, 1H, ^3J = 2.0 Hz), 6.36 (dd, 1H, ^3J = 5.9 Hz, ^4J = 2.0 Hz), 4.15 (s, 2H), 3.85 (s, 4H), 3.72 (s, 2H). ^{13}C NMR (δ, 62.5 MHz, $CDCl_3$): 160.0, 159.6, 153.5, 149.8, 149.3, 136.6, 123.3, 122.1, 108.7, 108.6, 60.4, 60.3. MS (ESI$^+$, CH_3CN, m/z): 306.1 (100%, $[C_{18}H_{19}N_5 + H]^+$).

Triethylamine (1 equiv, 415 μL, 2.91 mmol) was added to a solution of *N*-((4-amino-2-pyridyl)methyl)-*N*,*N*′-bis((2-pyridyl)-methyl)amine (900 mg, 2.91 mmol) in dry CH_2Cl_2 (10 mL). Then, pivaloyl chloride (1 equiv, 362 μL, 2.91 mmol) was added dropwise at 0 °C over 10 min. After stirring for 12 h at room temperature (rt), the solvent was removed under reduced pressure, and the residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH (100:0 to 95:5)) to yield **(4-Piva)TPA** as a colorless oil (940 mg, 80%). ^{1}H NMR (δ, 500 MHz, $CDCl_3$): 8.51 (d, 2H, ^3J = 5.0 Hz), 8.38 (d, 1H, ^3J = 5.7 Hz), 7.62 (m, 3H), 7.59 (s, 1H), 7.54 (m, 3H), 7.12 (t, 2H, ^3J = 6.2 Hz), 3.86 (s, 4H), 3.82 (s, 2H), 1.31 (s, 9H). ^{13}C NMR (δ, 125 MHz, $CDCl_3$): 177.4, 160.5, 159.3, 150.3, 149.3, 145.9, 136.7, 123.6, 122.4, 112.9, 112.5, 60.5, 60.4, 40.2, 27.7. MS (ESI$^+$, CH_3CN, m/z): 390.2 (100%, [(4-Piv)TPA + H]$^+$). Anal. Calcd (Found) for $C_{23}H_{27}N_5O{\cdot}0.7H_2O$: C, 68.70 (68.80); H, 7.12 (7.05); N, 17.42 (17.35).

Typical Experiment for the Preparation of Hydroximato and Hydroxamato Complexes. A mixture of ligand (0.35 mmol) and $CoCl_2$ (45 mg, 0.35 mmol) in methanol (10 mL) was stirred under argon at rt for 15 min. A mixture of the hydroxamic acid (0.35 mmol) and solid KOH (0.70 mmol for complexes **1a**, **2a**, **3a**, and **4a**, or 0.35

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mmol for complexes **1b** and **1c**) in methanol (2 mL) was then added. After 15 min the reaction vessel was flushed with dioxygen and stirred overnight at rt. The greenish solution was concentrated, and the residue was purified over Sephadex LH-20 using methanol as eluent. Complexes were isolated as mixtures of diastereoisomers by adding diethyl ether to a methanol solution of the complexes.

Complex [Co(III)(TPA)(A-2H)](Cl), 1a.[17] Green powder (79 mg, 47%). ^{1}H NMR (δ, 500 MHz, DMSO) major isomer: 9.18 (d, 1H, ^3J = 5.8 Hz), 8.52 (d, 2H, ^3J = 5.9 Hz), 7.98 (t, 2H, ^3J = 7.6 Hz), 7.84 (dd, 1H, ^3J = 8.0 Hz, ^3J = 7.8 Hz), 7.62 (d, 2H, ^3J = 7.6 Hz), 7.56 (dd, 1H, ^3J = 7.8 Hz, ^3J = 5.8 Hz), 7.50 (dd, 2H, ^3J = 7.6 Hz, ^3J = 5.9 Hz), 7.29 (d, 1H, ^3J = 8.0 Hz), 5.39 (d, 2H, ^2J = −16.1 Hz), 5.27 (d, 2H, ^2J = −16.1 Hz), 5.10 (s, 2H), 1.36 (s, 3H). Minor isomer: 9.33 (d, 1H, ^3J = 5.8 Hz), 8.20 (d, 2H, ^3J = 6.0 Hz), 7.98 (t, 2H, ^3J = 7.6 Hz), 7.90 (dd, 1H, ^3J = 8.1 Hz, ^3J = 7.7 Hz), 7.64 (dd, 1H, ^3J = 7.7 Hz, ^3J = 5.8 Hz), 7.60 (d, 2H, ^3J = 7.6 Hz), 7.47 (dd, 2H, ^3J = 7.6 Hz, ^3J = 6.0 Hz), 7.35 (d, 1H, ^3J = 8.1 Hz), 5.24 (d, 2H, ^2J = −16.4 Hz), 5.00 (d, 2H, ^2J = −16.4 Hz), 4.95 (s, 2H), 1.91 (s, 3H). UV−vis (Tris buffer, pH = 7.5): λ (ε, M^{-1} cm^{-1}) 581 (118) and 461 (sh). Cyclic voltammetry: E_{pc} −990 mV vs SCE. MS (ESI$^+$, CH_3CN, m/z): 421.9 (100%, [Co(III)(TPA)(A-2H)]$^+$). Anal. Calcd (Found) for $C_{20}H_{21}ClCoN_5O_2\cdot1.2H_2O$: C, 50.11 (50.35); H, 4.92 (5.00); N, 14.61 (14.36).

Complex [Co(III)(TPA)(B−H)](Cl)$_2$, 1b. Purple powder (90 mg, 45%). ^{1}H NMR (δ, 500 MHz, DMSO) major isomer: 8.74 (d, 1H, ^3J = 5.9 Hz), 8.60 (d, 2H, ^3J = 6.1 Hz), 8.15 (t, 2H, ^3J = 7.6 Hz), 7.98 (dd, 1H, ^3J = 8.1 Hz, ^3J = 7.6 Hz), 7.80 (d, 2H, ^3J = 7.6 Hz), 7.70 (dd, 1H, ^3J = 7.6 Hz, ^3J = 5.9 Hz), 7.67 (dd, 2H, ^3J = 7.6 Hz, ^3J = 6.1 Hz), 7.38 (d, 1H, ^3J = 8.1 Hz), 5.46 (d, 2H, ^2J = −15.9 Hz), 5.30 (d, 2H, ^2J = −15.9 Hz), 5.29 (s, 2H), 3.73 (s, 3H), 1.93 (s, 3H). Minor isomer: 9.14 (d, 1H, ^3J = 5.9 Hz), 8.32 (d, 2H, ^3J = 6.1 Hz), 8.15 (t, 2H, ^3J = 7.6 Hz), 8.00 (dd, 1H, ^3J = 8.1 Hz, ^3J = 7.6 Hz), 7.80 (d, 2H, ^3J = 7.6 Hz), 7.75 (dd, 1H, ^3J = 7.6 Hz, ^3J = 5.9 Hz), 7.62 (dd, 2H, ^3J = 7.6 Hz, ^3J = 6.1 Hz), 7.40 (d, 1H, ^3J = 8.1 Hz), 5.29 (d, 2H, ^2J = −15.8 Hz), 5.25 (s, 2H), 5.20 (d, 2H, ^2J = −15.8 Hz), 3.15 (s, 3H), 2.47 (s, 3H). Cyclic voltammetry: E_{pc} −330 mV vs SCE. MS (ESI$^+$, CH_3CN, m/z): 218.5 (100%, [Co(III)(TPA)(B − H)]$^{2+}$). Anal. Calcd (Found) for $C_{21}H_{24}Cl_2CoN_5O_2\cdot3.7H_2O$: C, 43.87 (43.85); H, 5.50 (5.29); N, 12.18 (12.14).

Complex [Co(III)(TPA)(C−H)](Cl)$_2$, 1c. Red powder (143 mg, 63%). ^{1}H NMR (δ, 500 MHz, DMSO), major isomer: 8.90 (d, 1H, ^3J = 5.9 Hz), 8.83 (d, 1H, ^3J = 6.5 Hz), 8.62 (d, 2H, ^3J = 5.9 Hz), 8.15 (t, 2H, ^3J = 7.7 Hz), 8.04 (dd, 1H, ^3J = 8.1 Hz, ^3J = 7.6 Hz), 7.85 (d, 2H, ^3J = 7.7 Hz), 7.70 (dd, 1H, ^3J = 7.6 Hz, ^3J = 5.9 Hz), 7.62 (dd, 2H, ^3J = 7.7 Hz, ^3J = 5.9 Hz), 7.55 (dd, 1H, ^3J = 8.4 Hz, ^3J = 7.6 Hz), 7.43 (d, 1H, ^3J = 8.1 Hz), 7.03 (dd, 1H, ^3J = 7.6 Hz, ^3J = 6.5 Hz), 6.90 (d, 1H, ^3J = 8.4 Hz), 5.55 (d, 2H, ^2J = −16.5 Hz), 5.37 (s, 2H), 5.32 (d, 2H, ^2J = −16.5 Hz). Minor isomer: 9.19 (d, 1H, ^3J = 5.7 Hz), 8.41 (d, 2H, ^3J = 5.7 Hz), 8.15 (t, 2H, ^3J = 7.7 Hz), 8.12 (d, 1H, ^3J = 6.4 Hz), 8.04 (dd, 1H, ^3J = 8.1 Hz, ^3J = 7.6 Hz), 7.85 (d, 2H, ^3J = 7.7 Hz), 7.78 (m, 1H), 7.73 (m, 1H), 7.58 (m, 2H), 7.54 (m, 1H), 7.43 (d, 1H, ^3J = 8.1 Hz), 6.82 (dd, 1H, ^3J = 7.4 Hz, ^3J = 6.4 Hz), 5.43 (d, 2H, ^2J = −16.4 Hz), 5.36 (s, 2H), 5.30 (d, 2H, ^2J = −16.4 Hz). Cyclic voltammetry E_{pc}: −190 mV vs SCE. MS (ESI$^+$, CH_3CN, m/z): 229.5 (100%, [Co(III)(TPA)(C − H)]$^{2+}$). Anal. Calcd (Found) for $C_{23}H_{22}Cl_2CoN_5O_2\cdot3H_2O$: C, 47.28 (47.23); H, 4.83 (4.74); N, 11.99 (11.97).

Complex [Co(III)((4-Cl$_2$)TPA)(A-2H)](Cl), 2a. Green powder (104 mg, 51%). Cyclic voltammetry E_{pc}: −960 mV vs SCE. MS (ESI$^+$, CH_3CN, m/z): 245.4 (100%, [Co(III)((4-Cl$_2$)TPA)(A − H)]$^{2+}$), 489.9 (60%, [Co(III)((4-Cl$_2$)TPA)(A − 2H)]$^+$). Anal. Calcd (Found) for $C_{20}H_{19}Cl_3CoN_5O_2\cdot3.2H_2O$: C, 41.11 (41.27); H, 4.38 (4.56); N, 11.99 (12.28).

Complex [Co(III)(6-Piva)TPA)(A-2H)]Cl, 3a. Green powder (78.5 mg, 39%). ^{1}H NMR (δ, 500 MHz, CD_3OD): 9.30 (d, 1H, ^3J = 6.1 Hz), 8.56 (d, 1H, ^3J = 6.0 Hz), 8.18 (d, 1H, ^3J = 8.4 Hz), 7.90 (dd, 1H, ^3J = 7.9 Hz, ^3J = 7.2 Hz), 7.85 (dd, 1H, ^3J = 8.0 Hz, ^3J = 6.9 Hz), 7.78 (dd, 1H, ^3J = 8.4 Hz, ^3J = 7.4 Hz), 7.55 (dd, 1H, ^3J = 6.9 Hz, ^3J = 6.1 Hz), 7.51 (d, 1H, ^3J = 7.9 Hz), 7.43 (dd, 1H, ^3J = 7.2 Hz, ^3J = 6.0 Hz), 7.33 (d, 1H, ^3J = 8.0 Hz), 7.21 (d, 1H, ^3J = 7.4 Hz), 5.59 (d, 1H, ^2J = −14.8 Hz), 5.55 (d, 1H, ^2J = −16.1 Hz), 5.11 (d, 1H, ^2J = −19.0 Hz), 5.05 (d, 1H, ^2J = −14.8 Hz), 5.10 (d, 1H, ^2J = −16.1 Hz), 5.02 (d, 1H, ^2J = −19.0 Hz), 1.61 (s, 3H), 1.55 (s, 9H). Cyclic voltammetry E_{pc}: −720 mV vs SCE. MS (ESI$^+$, CH_3CN, m/z): 521.1 (100%, [Co((6-Piva)TPA)(A-2H)]$^+$). Anal. Calcd (Found) for $C_{25}H_{30}ClCoN_6O_3\cdot H_2O$: C, 52.23 (51.98); H, 5.61 (5.71); N, 14.62 (14.66).

Crystals suitable for X-ray analysis were obtained after exchange of the counteranion as follows: sodium tetraphenylborate (1.2 equiv) was added to a concentrated solution of **3a** in methanol, and the complex was isolated by filtration. Crystals of **3a(BPh$_4$)** were grown by slow diffusion of methanol in a concentrated solution of complex in CH_2Cl_2.

Complex [Co(III)((4-Piva)TPA)(A-2H)](Cl), 4a. Green powder (86.8 mg, 40%). Cyclic voltammetry E_{pc}: −1060 mV vs SCE. MS (ESI$^+$, CH_3CN, m/z): 521.1 (100%, [Co(III)((4-Piva)TPA)(A-2H)]$^+$). Anal. Calcd (Found) for $C_{25}H_{30}ClCoN_6O_3\cdot3.5H_2O$: C, 48.43 (48.35); H, 6.02 (5.80); N, 13.56 (13.27).

Complex [Co(III)(6-Piva-H)(TPA)(OMe)]Cl, 3′. After stirring for 15 min a mixture of $CoCl_2$ (32 mg, 0.26 mmol) and (6-Piva)(TPA) (100 mg, 0.26 mmol) in methanol (3 mL) and 2 equiv of solid KOH (34 mg, 0.52 mmol) were added to the purple solution. Then the reaction vessel was opened to air, and the orange solution gradually turned red. Two hours later, the solution was concentrated and the mixture purified over Sephadex LH-20 (eluent methanol) to afford after precipitation in diethyl ether a red powder (119 mg, 85%). ^{1}H NMR (δ, 500 MHz, CD_3OD): 9.02 (d, 1H, ^3J = 5.9 Hz), 8.13 (dd, 1H, ^3J = 8.1 Hz, ^3J = 7.6 Hz), 8.04 (d, 1H, ^3J = 6.0 Hz), 7.86 (t, 1H, ^3J = 7.7 Hz), 7.78 (dd, 1H, ^3J = 8.3 Hz, ^3J = 7.6 Hz), 7.74 (dd, 1H, ^3J = 7.6 Hz, ^3J = 5.9 Hz), 7.70 (d, 1H, ^3J = 8.1 Hz), 7.49 (dd, 1H, ^3J = 7.7 Hz, ^3J = 6.0 Hz), 7.37 (d, 1H, ^3J = 7.7 Hz), 7.16 (d, 1H, ^3J = 7.6 Hz), 7.00 (d, 1H, ^3J = 8.3 Hz), 5.10 (d, 1H, ^2J = −15.1 Hz), 4.97 (d, 1H, ^2J = −14.4 Hz), 4.85 (m, 2H), 4.58 (d, 1H, ^2J = −15.1 Hz), 4.55 (d, 1H, ^2J = −14.4 Hz), 2.15 (s, 3H), 1.56 (s, 9H). Cyclic voltammetry E_{pc} −850 mV vs SCE. IR (cm^{-1}): 1609 for the complex and 1683 for the free ligand. MS (ESI$^+$, CH_3CN, m/z): 478.0 [100%, [Co(III)(6-Piva-H)(TPA)(OMe)]$^+$). Anal. Calcd (Found) for $C_{24}H_{29}ClCoN_5O_2\cdot1.5H_2O$: C, 53.29 (53.15); H, 5.96 (5.89); N, 12.95 (12.67).

Complex [Co(III)(CysOMe-H)$_3$], 5. To a suspension of sodium (tris-carbonato)cobaltate(III) trihydrate[24] (500 mg, 1.40 mmol) in deionized water (10 mL) was added at rt under argon L-cysteine methyl ester hydrochloride (704 mg, 4.10 mmol). The mixture was stirred for 20 min, and the green precipitate was filtered and washed with distilled water, methanol, and then diethyl ether. The green powder thus obtained was dried under reduced pressure to give complex **5** as a blue-green powder (320 mg, 40%). UV−vis (Tris buffer with 10% DMSO, pH = 7.5): λ (ε, M^{-1} cm^{-1}) 586 (164), 450 (270), 279 (16 600). Anal. Calcd (Found) for $C_{12}H_{24}CoN_3O_6S_3\cdot1.9NaCl$: C, 25.18 (25.25); H, 4.23 (4.41); N, 7.34 (7.48).

Complex [Co(III)(CysOMe-H)(TPA)](Cl)$_{0.75}$(BPh$_4$)$_{1.25}$, 1d. To a purple solution of complex [Co(TPA)(Cl)$_2$].(ClO$_4$)[25] (150 mg, 0.29 mmol) in degassed methanol (20 mL) under argon were successively added solid KOH (38 mg, 0.58 mmol) and L-cysteine methyl ester hydrochloride (50 mg, 0.29 mmol). After stirring for 30 min, the brown-green solution was concentrated and the residue purified over Sephadex LH-20 using methanol as eluent. The first brown band was collected, and shown to contain the complex [Co(III)(CysOMe-H)(TPA)](Cl)$_{1.5}$(ClO$_4$)$_{0.5}$ (**1d**) by elemental analysis (Anal. Calcd (Found) for $C_{22}H_{26}Cl_2CoN_5O_4S\cdot1.6H_2O$: C, 42.95 (42.97); H, 4.78 (5.01); N, 11.38 (11.35)). To try to crystallize this complex, we exchanged the anion by addition of a slight excess of NaBPh$_4$, leading to complex **1d(BPh$_4$)**, (93 mg, 35%). ^{1}H NMR (δ, 500 MHz, DMSO): 9.19 (d, 1H, ^3J = 6.1 Hz), 9.01 (d, 1H, ^3J = 6.0 Hz), 8.89 (d, 1H, ^3J = 6.3 Hz), 8.00 (t, 1H, ^3J = 7.4 Hz), 7.98 (t, 1H, ^3J = 7.4 Hz), 7.82 (dd, 1H, ^3J = 8.4 Hz, ^3J = 7.5 Hz), 7.72 (d, 2H, ^3J = 7.4 Hz), 7.52 (dd, 1H, ^3J = 7.4 Hz, ^3J = 6.1 Hz), 7.49 (dd, 1H, ^3J = 7.5 Hz, ^3J = 6.3 Hz), 7.45 (dd, 1H, ^3J = 7.4 Hz, ^3J = 6.0 Hz), 7.27 (d, 1H, ^3J = 8.4 Hz),

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7.18 (m, 10H), 6.91 (t, 10H, ^3J = 7.4 Hz), 6.78 (t, 5H, ^3J = 7.4 Hz), 5.93 (d, 1H, ^2J = −16.4 Hz), 5.70 (d, 1H, ^2J = −16.4 Hz), 5.39 (d, 1H, ^2J = −16.4 Hz), 5.38 (d, 1H, ^2J = −16.4 Hz), 5.34 (m, 1H), 5.32 (m, 2H), 5.18 (m, 1H), 3.49 (ddd, 1H, ^3J = 8.9 Hz, ^3J = 6.4 Hz, ^3J = 4.6 Hz), 3.42 (s, 3H), 2.63 (dd, 1H, ^3J = 6.4 Hz, ^2J = −12.4 Hz), 2.57 (dd, 1H, ^3J = 4.6 Hz, ^2J = −12.4 Hz). UV−vis (Tris buffer, pH = 7.5) $\lambda(\varepsilon, M^{-1}\ cm^{-1})$ 656 (sh), 451 (sh), 310 (5430), and 257 (8900). Cyclic voltammetry $E_{1/2}$ −270 mV vs SCE (ΔE = 170 mV). MS (ESI$^+$, CH_3CN, m/z): 482.0 [100%, {[Co(III)(TPA)(CysOMe-H)] − H}$^+$. Anal. Calcd (Found) for $C_{52}H_{51}B_{1.25}Cl_{0.75}CoN_5O_2S{\cdot}0.2H_2O$: C, 68.43 (68.51); H, 5.68 (5.55); N, 7.67 (7.93).

Structural Data for Complex [Co((6-Piva)TPA)(A-2H)](BPh$_4$), 3a(BPh$_4$). Data collection was performed with monochromated Mo Kα radiation (λ = 0.710 73 Å) on a Nonius Kappa detector at 293 K, by using the HKL package for data collection and reduction.[26] The structure was solved by direct methods in the space group $P\bar{1}$ using SHELXS-9727 and refined by least-squares methods on F^2 using SHELXL-97.[27] Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were placed in their geometrically generated positions and were allowed to ride on their parent atom with an isotropic thermal parameter equal to 1.2 times those of the attached atoms. In the final cycles of refinement, the peak pattern of electron density suggested that part of solvent was highly disordered; attempts to model this disorder were unsuccessful. In the final cycles of refinement, the contribution to electron density corresponding to the disordered solvent was removed from the observed data using the SQUEEZE option in PLATON.[28] The resulting data seriously improved the precision of the geometric parameters for the remaining structure. Crystal data and structure refinements are listed in Table S4.

UV−Vis and NMR Studies. Reactions between **1a** and L-cysteine methyl ester hydrochloride were carried out in degassed nondeuterated Tris buffer solution (pH = 7.5). Typically, for UV studies 800 μL of a 0.25 mM or 2.5 mM solution of complex **1a** and 200 μL of a 10^{-2} M or 10^{-1} M solution of L-cysteine methyl ester hydrochloride were mixed in a UV cuvette. For NMR studies, 400 μL of a 0.25 mM or 2.5 mM solution of complex **1a** and 100 μL of a 10^{-2} M or 10^{-1} M solution of L-cysteine methyl ester hydrochloride were mixed in an NMR tube. The green precipitate resulting from the reaction under concentrated conditions (2.5 mM) was filtered and washed with water, methanol, and diethyl ether before being dried under vacuum.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figure S1, ^{1}H NMR spectra of complexes **1a−c**, **3a**, **3′**, and **1d**; Figure S2, cyclic voltammograms in DMF of complexes **1a−c**, **2a**, **3a**, and **4a**; Figures S3 and S4, time dependent conversion of **1a** into **1d** at pH 6.5 and 8.0, respectively; Figure S5, ^{1}H NMR spectra, at 0.2 mM in 200 mM Tris buffer pH 7.5, of the reaction of complex **1d** with L-CysOMe·HCl in excess; Figure S6, ^{1}H NMR reaction of **1b** (0.2 mM) with CysOMe·HCl (10 equiv) in 200 mM Tris buffer pH 7.5. Table S1, crystal data and structure refinements of complex **3a**(BPh$_4$). X-ray crystallographic file for complex **3a(BPh$_4$)** (CCDC 879870) (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: isabelle.artaud@parisdescartes.fr. Phone: (33) 1 42 86 21 89. Fax: (33) 1 42 86 83 87.

Notes

The authors declare no competing financial interest.

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