Oxygenation Equilibria of Cobalt(II) Complexes of Amino Acids and Dipeptides[1a]

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Abstract: The oxygenation reactions of cobalt complexes of the amino acids glycine, L-alanine, L-proline, L-valine, L-leucine, and L-histidine, and the dipeptides glycylglycine, glycyl-L-serine, L-serylglycine, glycyl-L-alanine, L-alanylglycine, glycyl-L-tyrosine, glycyl-L-leucine, glycyl-L-valine, and L-alanyl-L-alanine, have been investigated. The stoichiometry of the oxygenated complexes has been determined, and the thermodynamic equilibrium constants which describe the oxygenation reaction are reported. Some factors influencing the thermodynamics of oxygenation are discussed, and the results are compared with previous work on cobalt dioxygen complexes.

Although it has been known for some time that amino acid and dipeptide complexes of cobalt(II) react with molecuar oxygen, much of the earlier work suffers from the mistaken identification of the oxidized cobalt(III) complex as the final, stable species still containing the dioxygen moiety.[2-6] It has now been amply demonstrated that the actual oxygenated species is the "brown intermediate" observed by some of the early workers at high pH.[7-10] This intermediate eventually loses the bridging peroxo group to form red, unoxygenated, mononuclear cobalt(III) chelates. The confusion arose because at low pH the irreversible oxidation of these complexes is so rapid that the rate of the appearance of the cobalt(III) complexes is essentially identical with the rate of oxygen uptake. However, despite the identification of the species involved, there is still a scarcity of quantitative data describing the equilibria between the various forms of the cobalt(II) chelates and molecular oxygen. Such data are necessary if one is to identify the primary factors influencing the thermodynamics of such systems. In this paper equilibrium data on the oxygenation of the cobalt(II) complexes of the amino acids glycine, L-alanine, L-proline, L-valine, L-leucine, L-histidine, and the dipeptides glycylglycine, glycyl-L-alanine, L-alanylglycine, glycyl-L-serine, L-serylglycine, glycyl-L-tyrosine, glycyl-L-valine, glycyl-L-leucine, and L-alanyl-L-alanine are presented.

Experimental Section

All equilibria were studied at 25.0 ± 0.05 °C and at 0.10 M (KNO_3) ionic strength. Base uptake experiments, which were run to determine the proton stoichiometry of the oxygenation reaction, and potentiometric equilibrium measurements, were carried out in a sealed, jacketed cell under both nitrogen and oxygen atmospheres using carbonate free KOH. The nitrogen was bubbled through alkaline pyrogallol solutions to remove any trace of oxygen. Hydrogen ion concentrations were determined using a Beckman research model pH meter equipped with glass and calomel electrodes and standardized with dilute HCl to read $-\log [H^+]$ directly.

Base uptake experiments were run by first raising a solution of the appropriate ligand to a given pH under either a nitrogen or oxygen atmosphere. Sufficient cobalt(II) was added so that a 10–30-fold excess of ligand was attained, and any drop in the pH was countered by the addition of standardized KOH, such that the pH before and after the addition of cobalt was the same. From the amount of base required for such an adjustment, the number of moles of hydrogen ions released per mole of cobalt added was calculated.

Oxygen uptake experiments were conducted in a similar manner using a polarographic YSI Model 53 biological oxygen monitor to measure the percent of oxygen saturation before and after the addition of cobalt(II) to a basic solution containing a 10–30-fold excess of ligand. The value of 1.32×10^{-3} was used as the molar concentration of oxygen in a saturated 0.10 M (KNO_3) aqueous solution at 25.0 °C.[11] Because of the smaller volumes used in the determination of oxygenation equilibria, the hydrogen ion concentrations of these solutions were measured using a combination electrode in place of separate glass and calomel electrodes.

Electronic spectra were recorded on a Cary 14 recording spectrophotometer using 1.000-cm matched quartz cells.

Results

In order to describe the equilibrium data in terms of the actual species involved, it is necessary to assign a ligand/metal stoichiometry to both the oxygenated and unoxygenated complexes. Because of the very low equilibrium constants for the addition of the third amino acid or dipeptide ligand to cobalt(II), the unoxygenated metal ion was present only as the bis chelate, even in the presence of fairly large excesses of ligand. The ligand/metal ratios in the dipeptide oxygen complexes were determined experimentally by the method of continuous variation (Job's plot). Figure 1 shows the absorbance at 380 nm of oxygen-saturated solutions of cobalt(II) glycyclglycine at pH 11 as a function of X, where $X = T_L/(T_L + T_M)$. T_L and T_M refer to the analytical concentrations of ligand and cobalt, and for all solutions $T_L + T_M$ is equal to a constant. The maximum in Figure 1 occurs at $X = 0.67$, indicative of a 2:1 ligand to metal stoichiometry in the cobalt–dipeptide oxygen complexes. For reasons put forth in the Discussion, the oxygen complexes of the amino acids were assumed to also have a 2:1 ligand to metal ratio.

As previously mentioned, the irreversible oxidation of the oxygen complexes of amino acids and dipeptides is fairly rapid, with half-lives ranging from 1 min to a few hours, depending on the ligand and the pH of the solution. The histidine dioxygen complex is exceptional in that it appears to be much more stable toward irreversible oxidation than the other ligands investigated. Therefore, it was not possible to determine the hydrogen ion stoichiometry or the equilibrium constants of the oxygenation reaction by the widely used method of potentiometric equilibrium measurements. Instead, the H^+ stoichiometry was determined by base uptake. For the amino acids other than histidine, the addition of cobalt(II) to an oxygen-saturated ligand solution at high pH resulted in the release of 0.50 mol of H^+ per mole of cobalt. Such a half-integer number of protons released is characteristic of μ-peroxo-μ-hydroxo-dibridged complexes, which have already been described for cobalt complexes of several ligands having fewer than five coordinating groups.[9,12-15] Since no change in pH was observed when cobalt was added to similar amino acid solutions under a nitrogen atmosphere, the oxygenation reaction must involve the net release of 0.50 mol of hydrogen ion per mole of cobalt. Since it has already been shown that the amino acid and dipeptide oxygen complexes of cobalt in aqueous solution are binuclear,[9,10] this corresponds to the release of 1.0 mol of hydrogen ion per mole of oxygen complex formed. Thus the

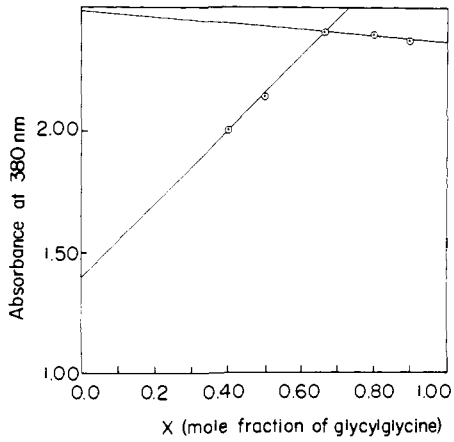

Figure 1. Continuous variation of cobalt(II) glycylglycine under an oxygen atmosphere at $-\log [H^+] = 11.0$. Total concentration of ligand and metal, 0.0100 M. $\mu = 0.10$ M KNO_3; $t = 25.0$ °C.

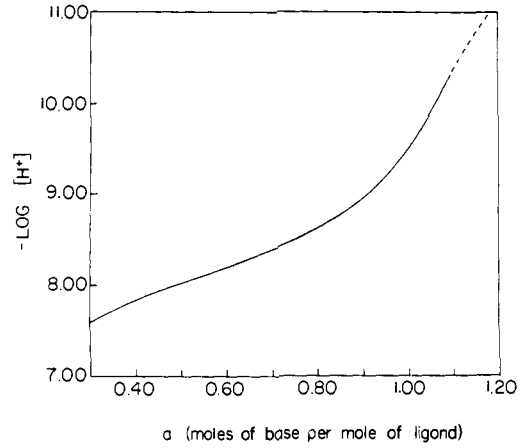

Figure 2. Potentiometric equilibrium curve for a 20:1 ratio of glycylglycine to Co^{2+} under a nitrogen atmosphere. The dashed line indicates precipitation of $Co(OH)_2$. $\mu = 0.10$ M KNO_3; $t = 25.0$ °C.

equilibrium can be written as shown in the equation

$$2\,Co^{2+}(L^-)_2 + O_2 \underset{}{\overset{K_{O_2}}{\rightleftharpoons}} [(L^-)_2Co^{3+}(O_2^{2-})(OH^-)Co^{3+}(L^-)_2]^- + H^+ \quad (1)$$

We have adopted the standard formalism of writing the oxygen complex as a reduced peroxide group bound to two oxidized cobalt(III) ions,[9,13] although the determination of the equilibrium constants does not depend on the validity of this description.

In the case of histidine, no protons were released by the addition of cobalt to ligand solutions under either nitrogen or oxygen atmospheres, so the oxygenation reaction (eq 2) of the cobalt(II) complex of this ligand is pH independent when written similarly to eq 1.

$$2\,Co^{2+}(His^-)_2 + O_2 \overset{K_{O_2}}{\rightleftharpoons} [(His^-)_2Co^{3+}(O_2^{2-})Co^{3+}(His^-)_2] \quad (2)$$

The oxygenation equilibrium constants were determined by the measurement of oxygen uptake, which was carried out as described in the Experimental Section. From the percent of oxygen saturation of the ligand solution before and after the addition of cobalt, and from the pH of the final solution, one can determine the concentrations of all the species represented in eq 1, and thus can calculate the equilibrium constant in the form shown in the equation

$$K_{O_2} = \frac{[L_4{}^-Co_2{}^{3+}(O_2{}^{2-})(OH^-)][H^+]}{[CoL_2]^2[O_2]} \quad (3)$$

The constant for histidine differs only in the hydrogen ion dependence, as shown in

$$K_{O_2}{}' = \frac{[(His^-)_4Co_2{}^{3+}(O_2{}^{2-})]}{[Co^{2+}(His^-)_2]^2[O_2]} \quad (4)$$

The values of the equilibrium constants for the oxygenation of the cobalt(II) complexes of amino acids determined in this research are shown in Table I, with the average deviation in the final decimal place listed in parentheses.

Base uptake experiments were also run with a 10–30-fold excess of glycylglycine between pH 10 and 11. When cobalt was added under a nitrogen atmosphere, between 1 and 2 equiv of hydrogen ion were released. Potentiometric equilibrium measurements were also made on solutions with a 20-fold excess of glycylglycine over cobalt under a nitrogen atmosphere. The potentiometric equilibrium curve shown in Figure 2 has an obscure break shortly after the addition of 1 mol of base per mole of ligand, followed by precipitation immediately after the addition of 1.10 mol of base per mole of ligand. Since the terminal amino group is fully deprotonated above pH 10, the protons released in the base uptake runs could come only from hydrolysis of the chelate or amide proton dissociation. The aquo cobalt(II) ion has a hydrolysis constant, log $K_{M^{2+}}{}^{H}$ ($K_{M^{2+}}{}^{H} = [M^{2+}]/[MOH^+][H^+]$) of 9.5.[16] Since the replacement of water molecules by the more strongly coordinating dipeptide ligands would be expected to result in an even higher hydrolysis constant for the dipeptide chelate, it is unlikely that such a complex would be involved in a second hydrolysis step less than 1 pH unit above the first log $K_M{}^H$ of the aquo ion. Therefore the dipeptide data have been interpreted in terms of two consecutive amide proton dissociations.

Table I. Logarithms of the Oxygenation Constants for Some Cobalt(II) Complexes of Amino Acids[a,b]

Ligand	Log K_{O_2}	Ligand	Log K_{O_2}
Glycine	*c*	Leucine	−4.01 (1)
Alanine	−4.03 (3)	Valine	−3.8 (2)
Proline	−4.41 (1)	Histidine	6.50 (10)[d]

[a] All values at 25.0 °C and 0.10 M (KNO_3). [b] K_{O_2} defined in eq 3. [c] Formation too low for accurate determination. [d] $K_{O_2}{}'$ as defined in eq 4.

Base uptake runs carried out in oxygen-saturated solutions of glycylglycine and glycylserine under conditions such that the oxygen complexes are fully formed showed that 2.0 mol of hydrogen ion were released per mole of cobalt added. Thus, the final oxygenated species contains both amide nitrogens in the deprotonated form. The integral number of hydrogen ions released rules out μ-hydroxy bridging in the dipeptide complexes.

The presence of two different deprotonated forms of the cobalt(II) chelates allows for the possibility of two separate oxygenation equilibria involving the same product, but differing in their proton stoichiometry, as shown in the equations.

$$2[Co^{2+}(H_{-1}L^{2-})(L^-)]^- + O_2 \overset{K_{O_2}{}^2}{\rightleftharpoons} [Co_2{}^{3+}(H_{-1}L^{2-})_4(O_2{}^{2-})]^{4-} + 2H^+ \quad (5)$$

$$2[Co^{2+}(H_{-1}L^{2-})_2]^{2-} + O_2 \overset{K_{O_2}{}^0}{\rightleftharpoons} [Co_2{}^{3+}(H_{-1}L^{2-})_4(O_2{}^{2-})]^{4-} \quad (6)$$

Following the same general procedures as outlined for the amino acid complexes, it is possible to determine the equilibrium constants for the reactions shown in eq 5 and 6. These constants are defined in the equations

$$K_{O_2}{}^2 = \frac{[Co_2{}^{3+}(H_{-1}L^{2-})_4(O_2{}^{2-})][H^+]^2}{[Co^{2+}(H_{-1}L^{2-})(L^-)]^2[O_2]} \quad (7)$$

$$K_{O_2}{}^0 = \frac{[Co_2{}^{3+}(H_{-1}L^{2-})_4(O_2{}^{2-})]}{[Co^{2+}(H_{-1}L^{2-})_2]^2[O_2]} \quad (8)$$

In order to calculate values of $K_{O_2}{}^2$ and $K_{O_2}{}^0$, one must also take into consideration the amide dissociation constants for the cobalt(II) chelate. Since base uptake experiments showed that at pH values at or below those at which oxygen uptake measurements were run, between 1 and 2 mol of hydrogen ion was released, the equilibrium most strongly influencing the calculation of the oxygenation constants was the second amide dissociation, for which the equilibrium constant is written as shown in the equation

$$K_{A_2} = \frac{[Co^{2+}(H_{-1}L^{2-})_2][H^+]}{[Co^{2+}(H_{-1}L^{2-})(L^-)]} \quad (9)$$

The value of K_{A_2} was determined as being that unique value which would simultaneously minimize the average deviations in the calculated values of $K_{O_2}{}^2$ and $K_{O_2}{}^0$. Oxygen uptake runs were made at as high a pH as possible to minimize the error which results from the lack of consideration of the first amide dissociation. The equilibrium constants determined for the dipeptide systems are shown in Table II, with the average deviation in the final decimal place listed in parentheses. In the case of alanylglycine, the average deviation in the calculation was minimized by assuming $K_{A_2} = 0.0$, indicating that in the pH range of oxygen uptake measurements the second amide dissociation was already complete. Therefore only $K_{O_2}{}^0$ could be calculated.

Table II. Logarithms of the Second Amide Dissociation and Oxygenation Constants of Bis(dipeptide)cobalt(II) Complexes[a,b]

Ligand	Log K_{A_2}	Log $K_{O_2}{}^2$	Log $K_{O_2}{}^0$
Glycylalanine	−9.55 (5)	−11.68 (3)	7.43 (3)
Glycylserine	−9.60 (5)	−11.19 (1)	8.01 (1)
Serylglycine	−9.75 (5)	−10.70 (2)	8.80 (2)
Alanylalanine	−10.00 (5)	−12.16 (3)	7.84 (3)
Glycyltyrosine	−10.20 (5)	−12.6 (2)	8.4 (2)
Glycylglycine	−10.3 (1)	−12.2 (2)	8.4 (2)
Alanylglycine			7.8 (2)
Glycylvaline[c]		−13.5 (5)	
Glycylleucine[c]			

[a] All values at 25.0 °C and 0.10 M (KNO_3) ionic strength. [b] Constants defined in eq 7–9. [c] Formation too low for an accurate determination.

Discussion

The stoichiometry $((H_{-1}L)_2(Co)_2O_2$ of the peptide oxygen complexes exemplified by Glygly is in agreement with the titrimetric results of Michailidis and Martin.[10] A 1:1 cobalt(II) glycylglycine dioxygen complex, $(Co(Glygly))_2O_2$, has been identified as a kinetic intermediate in the formation of the stable bis(peptide) dioxygen complex, but exists in negligibly small equilibrium concentration under the conditions employed in this study.

The stoichiometry of the amino acid dioxygen chelates is somewhat less well defined. The method of continuous variation, used successfully for the peptide complexes, is invalid for the low stability amino acid cobalt dioxygen complexes, since K_{O_2} is insufficiently large to overcome K_{sp} of cobalt(II) hydroxide, and thus precipitation occurs even with excess ligand present. However, our potentiometric results unambiguously demonstrated that μ-hydroxo bridging is present for ternary cobalt amino acid dioxygen complexes when the amino acids do not possess liganding side chains. This result is supported by the UV-visible spectra, which show a single charge-transfer peak at ca. 355 nm, characteristic of dibridged dioxygen complexes. (Monobridged complexes are known to exhibit two charge-transfer bands,[17] consistent with the greater splitting of the in-plane (π_h*) and out-of-plane (π_v*) components of the π_{O_2}* orbitals, for the larger dihedral angles permitted in the absence of dibridging.[18]) Thus, with two sites occupied by μ-peroxo and μ-hydroxo bridges, the availability of four remaining sites strongly suggests a simple bis amino acid complex as the oxygen active species. Although coordination by such weak donors is unusual, precedent for "two nitrogen" oxygen complexes is well established.[15] Recent arguments relating ligand donor properties and the thermodynamics of oxygenation[20] would suggest a quite low stability for such complexes (that oxygenated species are formed at all may be attributed to secondary hydroxo bridging, which "locks in" the dioxygen in a five-membered ring, thereby shifting the equilibrium toward oxygenation). The presence of hydroxo bridging in such systems has been overlooked in some previous studies of cobalt aino acid oxygen complex formation.[20]

It is interesting to note, therefore, that the equilibrium constant for oxygenation of the $Co(aa)_2$ species ($\log K_{O_2,OH} \simeq -4.0$) is of the same order as that found for the cobalt ethylenediaminediacetate dioxygen complexes[15] ($\log K_{O_2} \simeq -4.3$), which contain similar donor groups.

A curious exception is afforded by the glycine complex, which possesses extremely low stability. For this system, while dioxygen complex formation can be detected by UV-visible measurements at high P_{O_2} (760 mm), the small amount of dioxygen complex formation attained precludes accurate polarographic determination of the oxygenation equilibria. The reasons for this strong dependence of reactivity on the nature of the noncoordinating side chain are unclear. Work on this problem is continuing.

In the case of the dipeptides, it is not possible to use the regression equation[19] to predict the values for the oxygenation constants for two reasons. First, no hydroxo bridging is involved, and secondly, it is impossible to assign accurate values to the proton dissociation constant for the amide group.

Although the variation in the values of $K_{O_2}{}^0$ is wider than one might have expected for complexes with ligands so structurally similar and with essentially identical acid dissociation constants, the scatter of values is roughly the same as that observed in the values of K_{ML} and K_{ML_2} for these ligands with cobalt(II). Since complexes of glycylvaline and glycylleucine display exceptionally low affinity for molecular oxygen, one possible explanation for the variation in oxygenation constants is steric interference from the side groups in the dimerization reaction. However, among the remaining seven dipeptides studied, the size of the side group does not appear to be an important factor, with even glycyltyrosine having a typical value of $K_{O_2}{}^0$. Therefore it does not appear that a bulky side group is sufficient to reduce the affinity of the complex for molecular oxygen.

The value of the second amide dissociation constant for the glycylglycine complex agrees fairly well with the value reported by Michailidis and Martin.[10] The potentiometric equilibrium curve for this system shown in Figure 2 demonstrates the necessity of obtaining such values from the oxygenation data. The absence of an appreciable break in the curve after the addition of 1 mol of base per mole of ligand indicates significant overlap between chelate formation, ligand deprotonation, and amide dissociation equilibria. The large excess of ligand necessary to prevent precipitation in the oxygen-free systems severely complicates any attempt to calculate the amide dissociation

constants from these potentiometric data.

In most cases the values of the oxygenation constants calculated by varying the value of K_{A_2} were determined to precisions within the limits of experimental error, so that the introduction of a second adustable parameter, K_{A_1}, cannot be justified. The small average deviations observed in most systems is taken as strong evidence that the first amide dissociation can be neglected without introducing any appreciable error. However, in the glycylglycine and glycyltyrosine systems, where amide dissociation does not occur until higher pH values are attained, the larger average deviations may be due to incomplete deprotonation of the first amide group.

Morris and Martin[21] have recently described a cobalt(II) promoted amide dissociation in dipeptides involving a spin-state equilibrium between high- and low-spin complexes, both of which have both amides deprotonated. They cite as primary evidence of the change to a low-spin complex a color change from pink to blue around pH 11.5 for cobalt glycylglycine solutions containing a 20-fold excess of ligand. However, our own efforts to reproduce these data result in precipitation of cobalt(II) hydroxide around pH 10.5, as indicated in Figure 2. Upon going to a 40-fold excess of glycylglycine, which prevents any precipitation of cobalt, no blue color was observed even at pH 11.5. Although the absence of a visible blue color could be the result of using more dilute solution, the fact that a 20:1 excess is not sufficient to prevent precipitation above pH 10.5 casts serious doubt upon any spectral data obtained at these conditions. For this reason we have omitted any spin-state equilibria from consideration in our calculations.

References and Notes

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Mechanisms of Reduction of Cobaltic Porphyrins with Various Reducing Agents

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Abstract: In this paper, tetra(*p*-sulfonatophenyl)porphinatocobalt(III), tetra(*p*-carboxyphenyl)porphinatocobalt(III), and tetra(4-pyridyl)porphinatocobalt(III) were reduced with hexaaquochromium(II), hexaaquovanadium(II), and hexaammineruthenium(II). The reduction kinetics were studied with stopped-flow techniques. The rate law is: rate = k[reductant][cobaltic porphine] = $\{k_1' + (k_1^*/[H^+]) + k_2[Cl^-] + k_2'[SCN^-]\}$ [reductant][$Co^{III}P$]. For the vanadium(II) reductions, the term k_1' was of the order of 1350 $M^{-1}\,s^{-1}$ for all three of the cobaltic porphines and the mechanism was proposed to be an outer-sphere pathway. For the chromium(II) reduction of Co^{III}-TPPS, $k_1' = 0.0$, $k_1^* = 4.9\ s^{-1}$, and $k_2 = 2.9 \times 10^4\ M^{-2}\,s^{-1}$ and $k_2' = 1.1 \times 10^6\ M^{-2}\,s^{-1}$. For the chromium(II) reduction of Co^{III}-TCPP, $k_1^* = 3\ M^{-1}\,s^{-1}$, $k_2 = 4.4 \times 10^4\ M^{-2}\,s^{-1}$, and $k_2' = 1.3 \times 10^6\ M^{-2}\,s^{-1}$. Finally, for the chromium(II) reduction of Co^{III}-TPyP, $k_1' = 49\ M^{-1}\,s^{-1}$, $k_1^* = 0.4\ s^{-1}$, $k_2 = 2.3 \times 10^3\ M^{-2}\,s^{-1}$, and $k_2' = 1.8 \times 10^5\ M^{-2}\,s^{-1}$. Since the electron-transfer reactions were always faster than the axial ligand substitution of the cobaltic porphines, the axial inner-sphere pathway was precluded. The reduction products were analyzed with cation-exchange columns. Using radioactive chromium tracer techniques, the chromium was observed to be bound to the Co^{II}-TPPS and Co^{II}-TCPP after the reductions. Since the axial ligands of cobaltic porphyrins are labile, this experimental result firmly establishes the peripheral inner-sphere pathway with attack at the para substituents. Consequently, the path of the electron transfer is via the porphyrin π cloud and not via the metalloporphyrin axial ligand positions. For the chromium(II) reduction of Co^{III}-TPyP, steric and electrostatic effects precluded the peripheral inner-sphere pathway. Finally the inverse acid term is assigned to be due to the deprotonation of the para substituents. The halide and thiocyanate catalysis is attributed to nonbridging ligand effects.

Metalloporphyrins participate in the electron-transfer steps of many essential metabolic processes. However, the metalloporphyrin electron-transfer reaction mechanism remains to be confirmed unambiguously. The aim of this paper is to systematically investigate the possible paths of electron-transfer reactions involving metalloporphyrins and to establish the mechanisms operative in these systems.[1-18] Theoretically, the electron-transfer mechanisms involving metalloporphyrins can be classified into axial inner-sphere, peripheral inner-sphere, axial outer-sphere, and peripheral outer-sphere pathways. In this paper we employ the reducing agents hexaaquochromium(II), hexaaquovanadium(II), and hexa-