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Interactions of Cyanide with a Water Soluble Ruthenium Porphyrin

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Abstract

The reactions of cyanide with the mono-carbonyl complex of ruthenium(II)–uroporphyrin-I (CO–Ru(II)–P) were studied in aqueous solution at 25 °C, ionic strength 0.1 (NaCl). The equilibrium constant for mono-cyano (CO, CN)–Ru(II)–P formation was $1.1 \pm 0.1 \times 10^4$ M^{-1}, which was independent of pH between 6 and 12. The kinetics of the incorporation of the first cyanide were first order in porphyrin and cyanide concentration, with a specific rate constant of 2.3 ± 0.2 M^{-1} s^{-1} at pH 11. Under an inert atmosphere, the di-cyano $(NC)_2$–Ru(II)–P forms from the (CO, CN) adduct, with a rate law first order in porphyrin and independent of cyanide concentration. This is ascribed to a rate limiting dissociation of CO, with a specific rate constant of $4.6 \pm 0.3 \times 10^{-5}$ s^{-1}. Upon adding di-oxygen in the presence of excess cyanide at pH 11, both the (CO, CN) and di-cyano–Ru(II) complexes were oxidized to the di-cyano–Ru(III) porphyrin, which could be reduced with dithionite into the di-cyano–Ru(II) adduct. In acid solution, both cyanides were lost from the di-cyano–Ru(II) porphyrin, and addition of carbon monoxide at this stage reformed the starting material, CO–Ru(II)–P. The applications of ruthenium porphyrins as *in vivo* cyanide scavenging drugs is discussed.

Introduction

The elucidation of the coordination chemistry of ruthenium porphyrins is an active area. They exhibit a multiplicity of oxidation states [1, 2], form metal–metal and oxo-bridged dimers [3], react with small gaseous molecules [4–6], and give insight [7] into the biologically important iron porphyrins. Interest in potential *in vivo* water soluble cyanide scavenging agents has led to studies on the interactions of Fe^{III} [8, 9], Rh^{III} [10, 11] and Co^{III} [12] porphyrins with cyanide. Since these air stable oxidation states have substantially less affinity for cyanide in their reduced forms [13], we now consider ruthenium porphyrins, where both the di- and trivalent states bind cyanide [13, 14]. Little is known about water soluble ruthenium porphyrins, and we report the cycles of changes found for cyanide reactions with carbonyl–ruthenium(II)–uroporphyrin-I in aqueous solution.

Experimental

To prepare the carbonyl (uroporphyrin-I)ruthenium(II) complex {CO–Ru(II)–P}, 200 mg of uroporphyrin-I-octamethylester and 200 mg $Ru_3(CO)_{12}$ were dissolved in xylene, and refluxed overnight. The solvent was evaporated, and the solid taken up in CH_2Cl_2, filtered, and passed through an alumina column. A brown impurity was removed with CH_2Cl_2, and the orange ruthenium porphyrin band was eluted with 10:1 $CHCl_3$/MeOH. The solid porphyrin was dissolved in THF and stirred for two days with 3 M NaOH to hydrolyze the ester, bringing the porphyrin into the aqueous phase. After THF removal, the pH was taken to 3 with HCl, and the precipitated complex filtered off, washed with water, and air dried. *Anal.* Calc. for $RuC_{41}H_{36}N_4O_{17} \cdot 4H_2O$: C, 47.82; H, 4.31; N, 5.44. Found: C, 47.83; H, 4.55; N, 5.45%. IR (Nujol): 1923 cm^{-1} (CO). UV–Vis (pH 11.5), 393.5 nm ($\epsilon_{mM} = 305$), 516.5 (20.5), 549.5 (31.4). The metal insertion [15] and ester hydrolysis [16] methods are modifications of literature procedures, and the absorption spectra resembles that of (CO, MeOH)–Ru(II)–OEP (OEP = octaethylporphyrin) in benzene [3].

The kinetic and equilibrium studies were run at 25 °C, at ionic strength 0.1 (NaCl), and monitored on a Beckman DU-70 spectrophotometer. pHs were taken on a London PHM 64 Research Meter, and sodium cyanide was analyzed with $AgNO_3$.

Results

The absorption spectra of CO–Ru(II)–P was independent of pH from 5 to 13. At pH 11.5, making a 3 μM solution of porphyrin 4 mM in cyanide under nitrogen lead to the formation of the mono-cyano adduct, CO–Ru(II)–P–CN, with bands at 403

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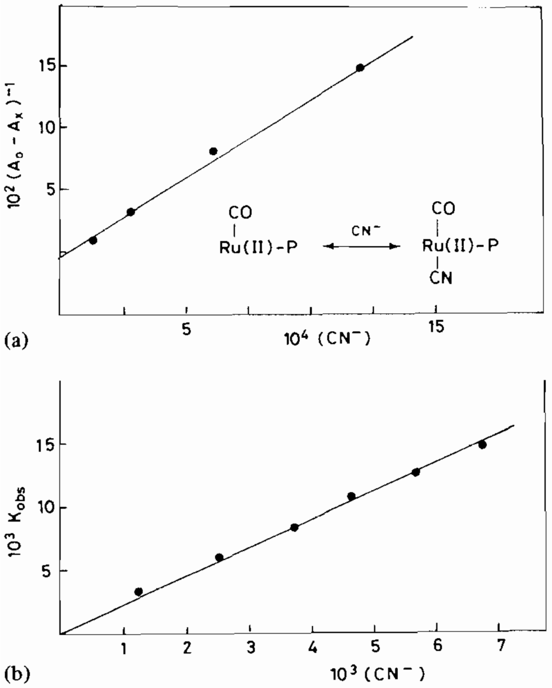

Fig. 1. (a) Equilibrium results for the reaction of cyanide with CO–Ru(II)–P. See eqn. (1) and footnote. (b) Plot of the first-order rate constant, k_{obs} *vs.* cyanide for the addition of cyanide to CO–Ru(II)–P forming (CO, CN)–Ru(II)–P.

(316), 524.5 (19.5) and 554 (10.4) nm. As the pH was lowered step by step, the mono-cyano porphyrin dissociated into the starting material, and isosbestic points were observed during the process. The equilibrium constant, K_1, for reaction (1) was determined using standard spectrophotometric techniques* by varying the pH of a porphyrin solution containing a known amount of cyanide (Fig. 1)

$$\mathrm{CN^- + CO{-}Ru(II){-}P = (CO, CN){-}Ru(II){-}P} \quad K_1 \qquad (1)$$

Using a pK_a for the (HCN)/(H^+)(CN^-) reaction of 9.14 [17], K_1 was calculated to be 1.1 ± 0.1 × 10^4 M^{-1}. This value was independent of pH between 6 and 12.

The kinetics of formation of the mono-cyano species was investigated at pH 11.5 in a nitrogen atmosphere to prevent air oxidation to the trivalent ruthenium state. Under pseudo first-order conditions with more than a fifty fold excess of cyanide to porphyrin, the reaction was first order in porphyrin over three half-lives, and as shown in Fig. 1, first order in cyanide (1.3 to 7.4 mM) concentration. The specific rate constant was 2.3 ± 0.2 M^{-1} s^{-1}.

If the CO–Ru(II)–P–CN complex was allowed to stand under nitrogen for 24 h in the presence of excess cyanide, the carbon monoxide was slowly replaced by cyanide, forming $(NC)_2$–Ru(II)–P (eqn. (2)). The complex has bands at 405 (sh, 101), 414 (148), 503.4 (19.2) and 530 (20.9) nm.

$$\mathrm{(CO, CN){-}Ru(II){-}P + CN^-}$$
$$\mathrm{= (NC)_2{-}Ru(II){-}P + CO} \qquad (2)$$

At pH 11.5, the kinetics of $(NC)_2$–Ru(II)–P formation were first order in porphyrin and independent of cyanide from 1.3 to 16 mM concentration. The half-life was 4.1 h, and the specific rate constant was 4.6 ± 0.3 × 10^{-5} s^{-1}.

If di-oxygen is bubbled through the mono- or di-cyanoporphyrin solutions in the presence of excess cyanide, both are oxidized into $(CN)_2$–Ru(III)–P, which had bands at 400 (127), 512.5 (15.0) and 721 (27.5) nm, similar to the OEP derivative [14]. Addition of sodium dithionite causes reduction to the di-cyano–ruthenium(II) porphyrin. If the pH of this Ru(II) adduct is lowered from 12 to 4, the cyanide is lost, and an uncharacterized ruthenium(II) porphyrin [394 (120) and 525 (15.1) nm] is produced. Addition of carbon monoxide gas at this pH quantitatively forms CO–Ru(II)–P. The cycle of changes observed is shown in Fig. 2.

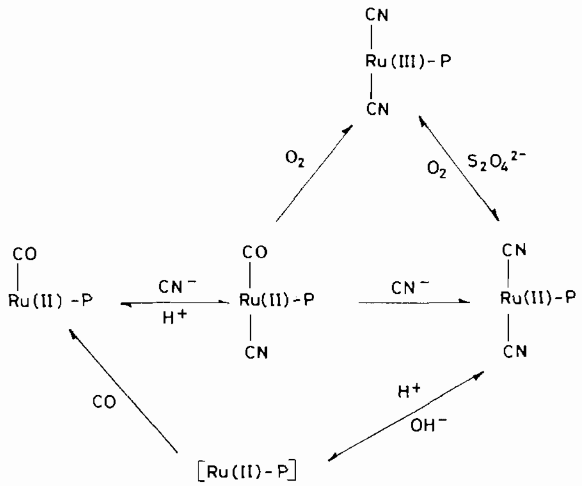

Fig. 2. Reactions of cyanide with the water soluble ruthenium–uroporphyrin-I complexes.

Discussion

In aqueous solution, most trivalent porphyrins [18], such as Fe, Mn, Co, Rh, Cr (but not Au [19]) and the lanthanides [20] hydrolyze at various pHs to form hydroxy, di-hydroxy and oxo-bridged

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*At constant wavelength, A_0, A_∞ and A_x are the absorbances of the porphyrin fully complexed with cyanide, uncomplexed and a mixture of the two species, respectively. In terms of eqn. (1), $(A_0 - A_x)^{-1} = Q + K^1Q(\mathrm{CN^-})$, where $Q = (A_0 - A_\infty)^{-1}$.

complexes. The lack of change of spectra with the present CO—Ru(II)—P over a wide pH range indicates that this divalent oxidation state hydrolyzes to a lesser extent than the aforementioned trivalent states. Such carbonyl porphyrin complexes are usually six-coordinate [21], and thus a water molecule probably occupies the remaining coordination position. The retention of the CO function after the compound stood for days in concentrated hydroxide both indicates its inertness to replacement by hydroxide, and the extreme stability it confers on the divalent state of the ruthenium ion. The substitution reaction chemistry of trivalent Co, Cr and Rh porphyrins have been probed in many cases using the S-bonded SCN^- ligand [22]. We find no spectral evidence for complexation of this Ru(II) porphyrin with thiocyanate. Ru(II) is soft, and the porphyrin apparently makes it softer [19].

The absorption spectra of the (CO, CN)—Ru(II)—P and $(CN)_2$—Ru(III)—P uroporphyrins are similar to those shown by the beta pyrrole substituted OEPs [13, 14] and mesoporphyrins [7]. $(CN)_2$—Ru(II)—P can be produced both by cyanide addition at the divalent level, and by an apparent outer sphere reduction of the trivalent form. Bis(benzyl isocyanide)—Ru(II) porphyrins are well known species [23]. The addition of the negative pi acceptor cyanide to CO—Ru(II)—P makes the metal center more readily oxidized by O_2.

The kinetics of the reaction of the first cyanide with CO—Ru(II)—P is first order in porphyrin and cyanide, and might occur by a dissociative interchange process. The addition of another cyanide to (CO, CN)—Ru(II)—P is first order in porphyrin and independent of cyanide concentration, an indication of dissociative activation. The slow step in this process is ascribed to the loss of CO, followed by rapid uptake of the second cyanide ligand. The kinetics of the first cyanide addition process are unusual in Ru(II)—P chemistry while the rate behavior for second cyanide addition is commonly found for bis-ligated Ru(II) [and Fe(II)] porphyrins, with N- or O-donor ligands such as imidazoles, pyridine or THF [21, 23]. In the present case, the dissociation of a CO *trans* to CN has a specific rate constant of 4.6×10^{-5} s^{-1}, while the dissociation of a cyanide *trans* to the CO group ($k_d = K_1/k_1$) occurs at 21×10^{-5} s^{-1}. Such ligand dissociation rate constants are in the same ranges as found in other Ru(II)—P systems in non-aqueous solutions [6, 21, 23].

TABLE 1. Equilibrium and Rate Constants for Metalloporphyrins and Metalloproteins Reactions with Cyanide

Compound[a]	K_F (M^{-1})	k_F (M^{-1} s^{-1})	Reference
H_2O–Co^{III}–TPPS	$>10^{12}$	3.1×10^2	12
HO–Co^{III}–TPPS		2.4×10^3	12
H_2O–Co^{III}–B12	1.3×10^{14}	2.5×10^2	28, 29
H_2O–Rh^{III}–TPPS	5.4×10^5	5.0	10
CO–Ru^{II}–URO	1.1×10^4	2.3	tp
HO–Cr^{III}–TMPyP	1.5×10^3	7.9×10^{-1}	30
HO–Fe^{III}–Meso		7×10^3	9
HO–Fe^{III}–TPPS		1×10^2	26
Fe^{II}–Mb	1.0	1×10^{-1}	31
Fe^{III}–Mb	5.7×10^4	1.7×10^2	32
Fe^{III}–Mp-8	3.6×10^7	6.0×10^5	33

[a] TPPS, tetra(4-sulfonatophenyl)porphyrin; TMPyP, tetra(*N*-methyl-4-pyridyl)porphyrin; Meso, mesoporphyrin-IX; Mb, myoglobin; MP-8, microperoxidase-8.

Since iron(III) methemoglobin [24] and hydroxocobalamin (a Co(III) corrin, Vitamin B-12 derivative [25]) have been suggested as *in vitro* cyanide scavengers, the cyanide binding interactions of simpler and lower molecular weight Fe^{III} [8, 9, 26], Co^{III} [11] and Rh^{III} [10, 11] porphyrins might be viewed from this standpoint. Although B-12 has been used successfully against cyanide in animal models and in man (in conjunction with other antidotes [27]), the amount of drug that must be administered is massive in comparison to the small amount of cyanide scavenged (1346 mg B-12 binds 26 mg CN^-), and high concentrations of B-12 cause cardiac arrhymthamis. Table 1 shows a comparison of the equilibrium and substitution kinetic rate constants found for various metalloporphyrin containing systems and cyanide [28, 33]. The Co(III) porphyrins and B-12 have large formation constants and rapid reactions at the physiologic pH with the first cyanide ion. Unfortunately, upon reduction to the Co(II) state, both the porphyrins and corrins have little affinity for cyanide [13], and the same trend is found in Fe(III) and Fe(II) hemoglobins and myoglobins. Ruthenium porphyrins are favorable in that they form cyano complexes in both the di- and trivalent states, and the lack of hydrolysis found for CO—Ru(II)—P gives a cyanide equilibrium constant independent of pH. Due to mono- and di-hydroxy and polymer formation, the cyanide affinity of Co(III), Rh(III) and Cr(III) porphyrins usually decrease with an increase in pH [18, 22]. Although the reaction conditions and even the porphyrins are not the same, Table 1 in general indicates that the equilibrium constants for cyanide binding are in the order Co(III) $\gg$ Rh(III) > CO—Ru(II) > Cr(III).

While it appears unprofitable to suggest CO—Ru(II)—P as an anti-cyanide agent, since the liberated CO will also be toxic, other pi acids could be used in place of CO. The Ru(III) porphyrins themselves are not unreasonable candidates. James and coworkers [14] have demonstrated that acid added to the water insoluble $(CN)_2$—Ru(III)—OEP causes the loss of one cyanide, leading to the ultimate isolation of (CN, Py)—Ru(III)—OEP, which is less stable to electrochemical reduction than the dicyano porphyrin. Efforts are continuing in this area.

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