Cyanide Scavengers: Kinetics of the Reaction of Rhodium(III)–Tetrakis(4-sulfonatophenyl)porphyrin with Cyanide and Hydrogen Cyanide

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Abstract

The kinetics of the reaction between rhodium(III)–tetrakis(4-sulfonatophenyl)porphyrin and cyanide/hydrogen cyanide were studied at 25 °C, ionic strength 0.5 ($NaNO_3$), from pH 5 to 9. The pK_{a1} for the Rh–TPPS aquo/mono-hydroxy reaction was determined kinetically to be 6.93. The mono and di-hydroxy forms of Rh–TPPS were of negligible reactivity as compared to the aquo species, with the Rh–TPPS$(H_2O)_2/CN^-$ reaction having a specific rate constant of 5.0 M^{-1} s^{-1}, and that of Rh–TPPS$(H_2O)_2$/HCN as 2.3×10^{-3} M^{-1} s^{-1}. With respect to the corresponding cobalt(III) and chromium(III) porphyrin anations, it appears that the Rh–TPPS/CN^- process is associatively activated. Comparisons are made between Rh–TPPS and current medically useful cyanide scavenger drugs.

Introduction

A variety of metal complexes have been explored as possible antidotes for cyanide intoxication. One clinically useful therapy involves the injection of dicobalt–ethylenediamminetetraaceticacid (Co(Co-EDTA)) in aqueous glucose, where the cobaltous ions scavenge cyanide [1]. Unfortunately, cobaltous salts often produce anaphylactic reactions [2], and serious complications may result either later, or if the drug is administered to a patient that has minimal or no cyanide poisoning. In the second regimen, amyl nitrite [3] is inhaled before hospitalization, then sodium nitrite (or the more rapidly acting 4-dimethylaminophenol [4]) is administered to oxidize about thirty percent of the Fe(II)-hemoglobin into the cyanide binding Fe(III)–methemoglobin form, which presumably by mass action considerations removes the cyanide from cytochrome oxidase. This is followed by injection of sodium thiosulfate, which serves as a massive sulfane sulfur source [5] for rhodanase, the enzyme in our bodies which catalyzes the conversion of cyanide into the more benign thiocyanate. The latter treatment renders the patient hypotensive and even more anoxic, and neither therapy can be used prophylactically. Hydroxocobalamin [6] (Co(III), Vitamin B_{12}), cobalt(II) salts (chloride [7], histidine [8]), stroma free methemoglobin [9] and administered rhodanase [10] have all been explored in animals as cyanide antidotes.

We have shown before [11] that certain water soluble metalloporphyrins bind cyanide under *in vitro* conditions at the physiological pH of 7.4. In addition to disguising the toxic effects of the free metal ion, such derivatives can be designed to have lower molecular weights than metmyoglobin or hydroxocobalamin. We report the kinetics of the reaction between rhodium(III) tetrakis(4-sulfonatophenyl)porphyrin [Rh–TPPS] and cyanide between pHs 5 and 9. The results are notably different from the cobalt(III) and chromium(III) derivatives, and comparisons are made between potential metalloporphyrin cyanide binders and current agents.

Experimental

Several methods have been used to prepare rhodium porphyrins [12–15] and we followed the procedure of Krishnamurthy [16] which involved the reaction of $(Rh(CO)_2Cl)_2$ in methanol with H_2-TPPS and oxidation of the resulting Rh(I) complex with hydrogen peroxide. *Anal.* Calc. for $RhC_{44}N_4H_{24}S_4O_{12}Na_3 \cdot 23H_2O$: C, 34.88; N, 3.70; H, 4.65; S, 8.46. Found: C, 35.19; H, 3.79; N, 3.70; S, 8.46%.

The kinetic and equilibrium studies were done at 25 °C on a Beckman Acta III recording spectrophotometer. The ionic strength was kept at 0.5 ($NaNO_3$), and 10 mM phosphate or borate buffers

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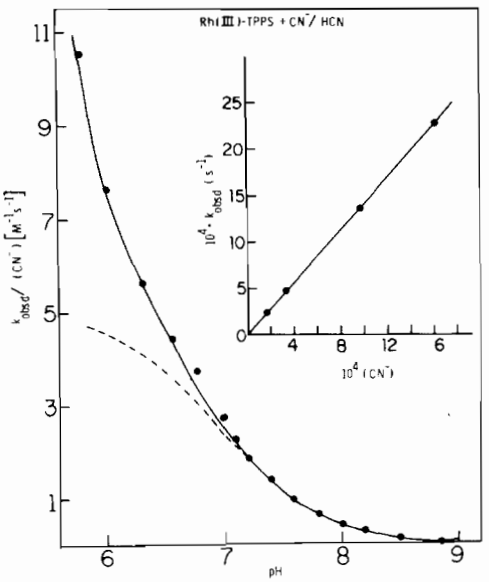

Fig. 1. pH profile of the specific rates of the reaction between Rh(III)–TPPS and cyanide/hydrogen cyanide. The dotted line would be the rate profile if hydrogen cyanide were not a reactant. The solid line is calculated from the parameters in eqn. (5). The Insert shows the first order dependence of the observed rate constant upon free cyanide concentration, at pH 7.4.

were used in the appropriate pH ranges. The KCN was analyzed by the Leibig-Deniges method.

Results

The absorption spectra of Rh–TPPS$(H_2O)_2$ at pH 1.0 showed bands (and molar extinction coefficients) at 417 nm (2.2×10^5 M^{-1} cm^{-1}), 530 nm (2.0×10^4) and 565 nm (5.3×10^3). At pH 7.4 in the presence of excess cyanide, the Rh–TPPS(CN) has a Soret at 427.5 nm (2.3×10^5) and visible peaks at 542 nm (1.6×10^4) and 579 nm (9.8×10^3). Isosbestic points were noted at 600, 565, 537, 500, 450, 422 and 370 nm as the aquo complex is transformed into the mono-cyano derivative at pH 7.4. The spectra of both complexes are similar to those reported by other workers [12, 16].

Solutions of Rh–TPPS at pH 7.4 were equilibrated with total cyanide concentrations from 1 to 10 mM, and an equilibrium constant for mono-cyanide formation of 5.4×10^5 M^{-1} was determined, as compared to 1.9×10^2 M^{-1} found at pH 10.5 [16]. Under pseudo first order conditions with an excess of cyanide to porphyrin, the kinetics of the reaction were first order in porphyrin concentration over three half-lives. Figure 1 shows that the reaction was also first order in cyanide concentration, from 1.6×10^{-3} M to 1.6×10^{-4} M in free cyanide. The pH dependence of the specific rates of this reaction is also shown in the figure. When the fully formed cyano porphyrin at pH 7.4 in 10^{-2} M cyanide was brought to pH 1, the spectra of the aquo species slowly (hours) appears, and some porphyrin decomposition was evident.

Discussion

Although extensive work has been done on the chemistry of water insoluble rhodium porphyrins [15], rather less is known about the water soluble rhodium derivatives. Rh(II)–TPPS dimers [17] have been produced by radiolytic and photochemical means. The anation reactions of the negatively charged Rh–TPPS at a single pH with cyanide (pH 10.5) and SCN^- (pH 4.7) were first studied by Krishnamurthy [16], and later by Ashley *et al.* [12] below pH 4 using SCN^-, I^-, Br^- and Cl^-. Related work [18] was reported on the positively charged rhodium(III)–tetrakis(4-*N*,*N*,*N*-trimethylanilinium)porphyrin. It was noted that both porphyrins showed similar reactivities, and the same was found for the SCN^- reactions of the corresponding Co(III) complexes [19, 20]. While a high pressure kinetic study on the Rh–TPPS reaction with SCN^- gave evidence for an I_d mechanism [21], an associative interchange process has also been suggested [12, 16].

Our interest in Rh–TPPS as a potential cyanide scavenging drug led to the present studies covering the physiological pH range. The following reactions are considered:

$$\text{Rh–TPPS}(H_2O)_2 = \text{Rh–TPPS}(H_2O)(OH)^- + H^+ \quad (1)$$
$$K_{a1}$$

$$\text{Rh–TPPS}(H_2O)(OH)^- = \text{Rh–TPPS}(OH)_2^{2-} + H^+ \quad (2)$$
$$K_{a2}$$

$$\text{Rh–TPPS}(H_2O)_2 + CN^- \longrightarrow \text{products} \quad k_1 \quad (3)$$

$$\text{Rh–TPPS}(H_2O)_2 + HCN \longrightarrow \text{products} \quad k_2 \quad (4)$$

Assuming that the mono and di-hydroxy species have negligible reactivities as compared to the di-aquo form, the theoretical rate law is:

$$k_{obs}/(CN^-) = [k_1 + k_2(HCN)/(CN^-)]Q \quad (5)$$

where $Q = [(H^+)/[K_{a1} + (H^+)]$. The pK_a of HCN was taken as 9.2. As shown in Fig. 1, the k_2 pathway does not substantially contribute below pH 7.2, allowing the determination of $k_1 = 5.0$ M^{-1} s^{-1} and $pK_{a1} = 6.93$. A k_2 of 2.3×10^{-3} M^{-1} s^{-1} could then be calculated from the results below pH 7.2. Using these parameters, Fig. 1 shows the agreement between the observed and calculated specific rates from pH 5.5 to 9. Our pK_{a1} of 6.93 is essentially the same as the 7.03 found before [12] at an ionic strength of 1.0 ($NaClO_4$), where pK_{a2} was 9.8.

TABLE I. Metalloporphyrin Anation Rate Data, 25 °C

Porphyrin/Ligand	P–M–OH_2	P–M–OH^-	k-OH/k-H_2O	Reference
Rh(III)–TPPS/CN^-	5.0[a]	$<10^{-2}$	$<2 \times 10^{-3}$	tp[b]
Co(III)–TPPS/CN^-	3.1×10^2	2.4×10^3	7.7	[c]
Co(III)–TPPS/SCN^-	3.2×10^2	1.4×10^3	4.2	25
Cr(III)–TPPS/SCN^-	4.7×10^{-3}	2.9×10^1	6.1×10^3	26

[a]Rate constants in units of $M^{-1}\ s^{-1}$. [b]tp is this paper. [c]R. Langley and P. Hambright, unpublished results.

The cyanide ion reacts two thousand times more rapidly than does HCN with the aquo rhodium porphyrin. Towards aquo–cobalamin [22], the CN^- (2.5×10^2 $M^{-1}\ s^{-1}$) to HCN (80 $M^{-1}\ s^{-1}$) ratio is 3, whereas HCN is favored [23] over CN^- with $Ni(EDTA)^{2-}$. From our results, the specific rate of the Rh–$TPPS(H_2O)(OH)^-/CN^-$ process is less than 10^{-2} $M^{-1}\ s^{-1}$, which is not inconsistent [16] with the value of 2×10^{-2} $M^{-1}\ s^{-1}$ found before at pH 10.5, 30 °C. Thus cyanide is at least 500 times more reactive with the aquo Rh–TPPS than with the mono-hydroxy species. Similarly, cyanide complexes only with the aquo and not the hydroxy-cobalamin [23].

Table I shows that the hydroxy/aquo rate ratios [24–26] decrease along the porphyrin series Cr(III) [*ca.* 10^3], Co(III) [*ca.* 10^1], Rh(III) [*ca.* 10^{-3}]. In a dissociative framework, the *trans*-hydroxy group places more electron density on the metal center, labilizing the opposite axial water molecule, thus leading to a faster anation rate, as compared to the di-aquo case. In these terms, the reaction of cyanide with Rh–TPPS appears to be associative in character, in line with ligand substitution results on many Werner type rhodium systems [16].

By comparison with hydroxocobalamin, Rh–TPPS is not a particularly attractive candidate as an anti-cyanide drug. At pH 7.4, CN^- and HCN react faster (*ca.* 1900 $M^{-1}\ s^{-1}$) with H_2O–CoB_{12} [22] than with Rh–TPPS (*ca.* 1.4 $M^{-1}\ s^{-1}$). Similarly, while the equilibrium constant for cyanide addition to Rh–TPPS at this pH is 5.4×10^5 M^{-1}, the first cyanide is essentially irreversibly bound [27] in NC–CoB_{12}. The hydroxocobalamin (but not the mono-cyano form) has been shown to protect against cyanide intoxication [6]. About 200 mg of KCN (~3 μg/ml blood) is considered fatal to man. The 200 mg KCN would require 4.1 grams of hydroxocobalamin for neutralization, and in practice [28], at least ten grams would have to be administered; a rather massive amount. With methemoglobin, 49 grams are stoichiometrically required. For Co(CoEDTA) which in the body binds about 2 moles of cyanide per formula weight of complex, 623 mg would neutralize 200 mg KCN. In actual cyanide therapy, up to three injections of a proprietary mixture in which each injection contains 300 mg Co(CoEDTA) [actually $(Co^{II}(H_2O)_4Co^{II}EDTA)\cdot 2H_2O$ in the solid state [29]] is suggested. It is apparent that a non-toxic, low molecular weight water soluble, rapidly reacting multi-cyanide scavenger with prophylactic action has yet to be developed.

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