

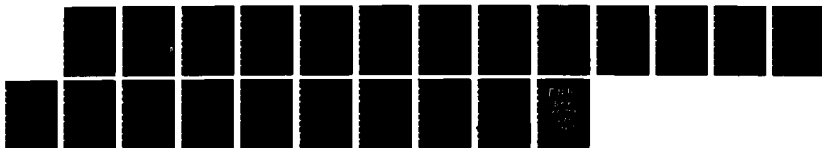
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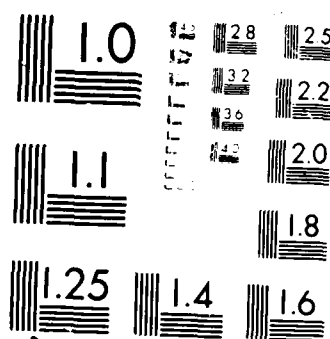
ANTI-CYANIDE DRUGS(U) HOWARD UNIV WASHINGTON DC DEPT OF 171
CHEMISTRY P HAMBRIGHT 81 MAY 86 DAND17-85-C-5086

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Anti-Cyanide Drugs

Annual Summary Report

Peter Hambright
Department of Chemistry
Howard University
Washington, D.C. 20059

May 1, 1986

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD-17-85-C-5086

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Both metal ion complexes and unsaturated organic compounds are being explored as potential <u>in vivo</u> anti-cyanide drugs. Certain water soluble metalloporphyrins containing cobalt(III), silver(II), chromium(III), rhodium(III), palladium(II) or iron(III), and cobalt(II) and (III) sulfonated phthalocyanines have been shown to rapidly complex cyanide at physiological pH. Detailed kinetic work indicates that both cyanide and HCN are reactants. A number		

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SUMMARY

The purpose of this work is to develop a prophylactic drug that will act against the CW agent cyanide. This involves the identification of chemicals that have a high in vitro affinity for cyanide at physiological pH, the kinetic study of their reactions with cyanide in order to determine reaction mechanisms, and the modification of such drugs to gain maximal cyanide affinities. Twenty such drugs will be synthesized each year and submitted to WRAIR for further testing.

Cyanide has a high affinity for iron(III) heme proteins in the body. Thus cyanide complexes with the iron porphyrins in cytochrome oxidase, inhibiting electron transfer and thus respiration. One form of cyanide therapy involves the injection of sodium nitrite, to oxidize a certain amount of iron(II) into the high cyanide affinity iron(III) hemoglobin. The Fe(III)-Hb binds with cyanide, removing it from the cytochrome complex, and subsequent reaction with thiosulfate forms thiocyanate, which is relatively non toxic and can be excreted. Hydroxocobalamin, a porphyrin like complex, binds cyanide forming cyanocobalamin, a form of Vitamin B₁₂, and this agent has been suggested as a cyanide scavenger.

The iron(III) in hemoglobin and the cobalt(III) in hydroxocobalamin are coordination compounds in which the metal ion is bound in a four coordinate fashion to the four nitrogen donor functions of a porphyrin type molecule, the porphyrin being a cyclic conjugated tetrapyrrole pigment. One idea was to determine what other metal ions when bound to porphyrin molecules would have a high affinity for cyanide at physiological pH, and to investigate by rapid kinetic methods the mechanisms of cyanide uptake by such metalloporphyrins. Phthalocyanines have a ring system similar to the porphyrin molecule, and were included in this study because they often stabilize different oxidation states of metal ions than are found in metalloporphyrin derivatives.

To this end, we synthesized several cobalt(III) and palladium(II) complexes of natural porphyrin derivatives which are water soluble by virtue of the ionization of two carboxylic acid functions. Cobalt(III), rhodium(III), silver(II), iron(III) and chromium(III) were incorporated into a variety of synthetic porphyrins, made water soluble with carboxylic acid groups, sulfonated phenyl groups, or N-alkylated pyridyl groups. Cobalt(III) and cobalt(II) derivatives of tetrasulfonated phthalocyanines were also synthesized, and all of the complexes were found to rapidly bind cyanide at pH 7.4.

Solution kinetic work was done on cyanide incorporation into cobalt(III) and rhodium(III) tetrasulfonated porphyrins from pH 4 to 10. For the cobalt adduct, the kinetics of the uptake of the first cyanide were first order in porphyrin and cyanide. The rate was maximal at pH 8, in accord with a mono-hydroxy, mono-aquo cobalt species being more reactive than the di-hydroxy or di-aquo cobalt forms. A dissociative mechanism is suggested, where the hydroxy dissociates the trans aquo group, leading to cyanide complexation. The rate, ca. $2200 \text{ M}^{-1}\text{s}^{-1}$, is as fast as that

shown by Vitamin B₁₂ under the same conditions. The intermediate cyano-hydroxy complex rapidly protonates forming the cyano-aquo species, which incorporates a second cyanide at least 1000 times faster than the first. Around pH 5, where the free cyanide concentration is low, the rate begins to increase due to the presence of undissociated HCN as the reactant. HCN is about one hundred thousand times less reactive than CN⁻ with respect to the di-aquo form. By dropping the pH, we can dissociate the dicyano cobalt porphyrin into the mono cyano form. Even at pH 1, we cannot dissociate the cyanide from the mono-cyano cobalt(III) adduct, an indication of the extreme stability of this species.

In contrast with cobalt(III), the rhodium(III) porphyrin shows maximal reactivity with the di-aquo form, an indication that an associative mechanism is involved. The water leaves and the cyanide enters in a concerted fashion. The cyanide uptake rates at pH 7.4 are about seven hundred times faster for cobalt than rhodium, and the rhodium porphyrin kinetics so far show only one cyanide molecule is bound. However, rhodium(III) begins to react with HCN around pH 7, much earlier than found for cobalt, and the CN⁻ / HCN ratio is ca 2500 for rhodium, as opposed to 10³ for cobalt. Since the pK_a for HCN is 9.2, most of the cyanide at physiological pH is in the form of undissociated HCN, and the reactivity of rhodium is favorable in this regard. Kinetic work is planned on the related iron(III) and chromium(III) derivatives.

Alkylidenes are organic compounds containing an alpha beta unsaturated double bond. By placing electron withdrawing groups on the ends of this functional group, an electron pair can be stabilized on the electron poor end, forming a carbocation on the other, which can react with the electron pair on the highly nucleophilic cyanide anion. We have demonstrated this with cyclohexylidene-alpha-cyanoacetate. The kinetics of cyanide addition at constant pH are first order in cyanide and alkylidene. A subsequent cyanide independent reaction then occurs once cyanide is added, and the final product is the stable species 1-cyano-1-cyanomethyl cyclohexane, formed by the elimination of water and carbon dioxide. A variety of alkylidenes having saturated and unsaturated rings were synthesized, and the same spectral shifts in the UV indicate that the same cyanide bound chromophore is formed by each. Progress was made in the synthesis of intermediate compounds containing two such cyanide trapping functional groups. The low molecular weights and covalently bound cyanide group make such derivatives attractive candidates for cyanide scavengers.

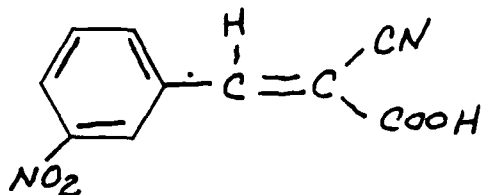
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COMPOUNDS SYNTHESIZED

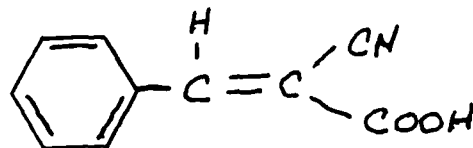
A. m-nitro-alpha-cyano-beta-phenylacrylic acid BK 40851

$C_{10}H_6N_2O_4$ MW = 218 J. Am. Chem. Soc., 63, 3452 (1941)



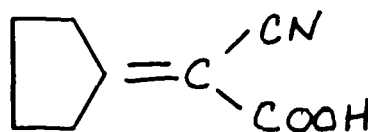
B. alpha-cyano-beta-phenylacrylic acid BK 40860

$C_{10}H_7NO_2$ MW = 173 Organic Synthesis, Vol 1, p 181 1947



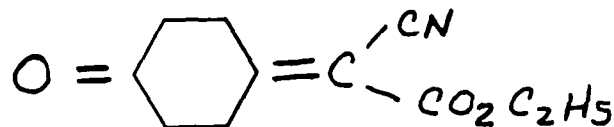
C. Cyclopentylidene-alpha-cyanoacetic acid BK 40879

$C_8H_9NO_2$ MW = 151 J. Am. Chem. Soc., 63, 3452 (1941)



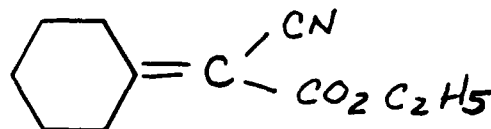
D. Ethyl-alpha-4-oxocyclohexylidene-alpha-cyanoacetate BK 40888

$C_{11}H_{13}NO_3$ MW = 207 J. Am. Chem. Soc., 63, 3452 (1941)



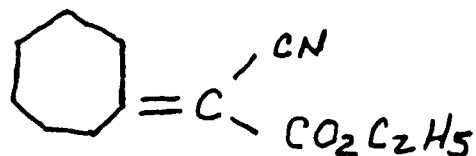
E. Ethyl-alpha-cyclohexylidene-alpha-cyanoacetate BK 40897

$C_{11}H_{15}NO_2$ MW = 193 J. Am. Chem. Soc., 63, 3452 (1941)



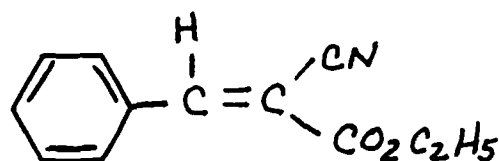
F. Ethyl-alpha-cycloheptylidene-alpha-cyanoacetate BK 40904

$C_{12}H_{17}NO_2$ MW = 207 J. Med. Chem., 28, 413, (1985)



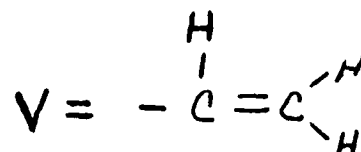
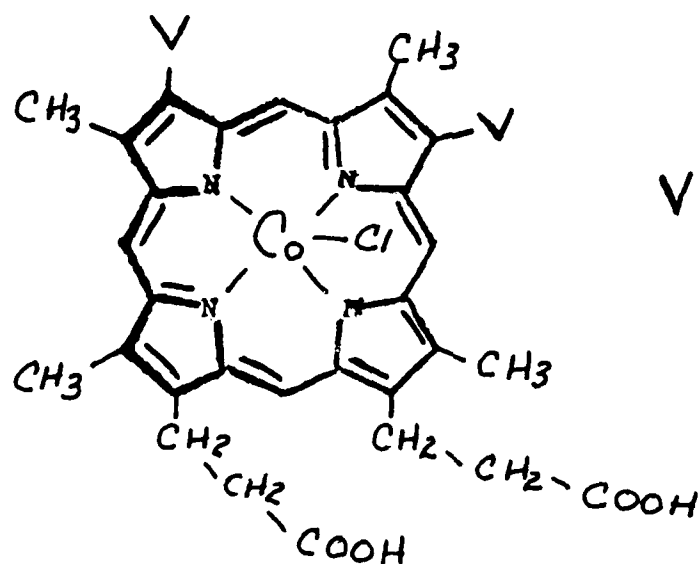
G. Ethyl-alpha-cyano cinnamate BK 40913

$C_{12}H_{11}NO_2$ MW = 201 J. Am. Chem. Soc., 63, 3452 (1941)



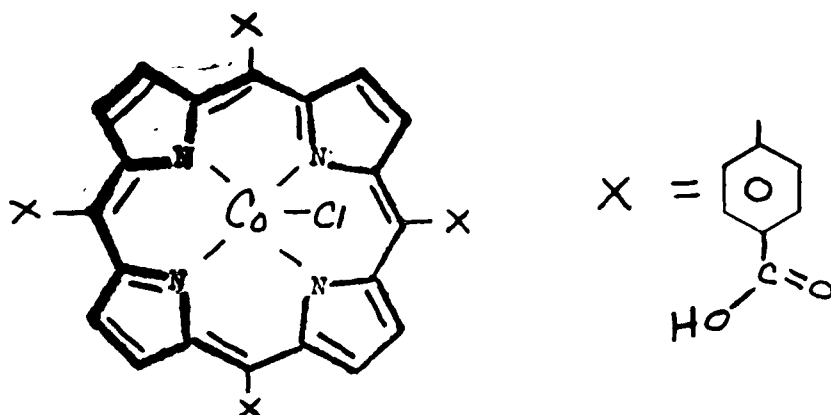
H. Protoporphyrin-IX-Cobalt(III) Chloride BK 40922

$CoN_4O_4C_{34}H_{32}Cl$ MW = 655 J. Biol. Chem., 135, 569 (1940)



I. Tetrakis(4-carboxyphenyl)porphyrincobalt(III) Chloride

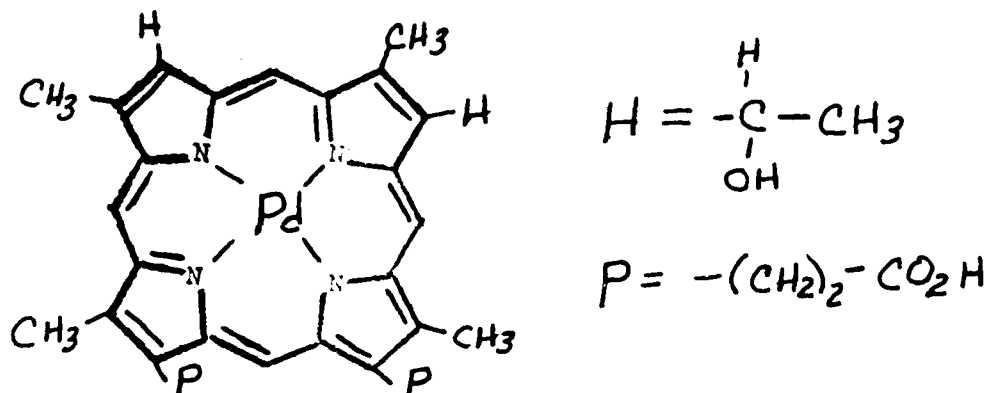
BK 40931 $\text{CoN}_4\text{C}_{48}\text{H}_{40}\text{Cl}$ MW = 895 J. Am. Chem. Soc., 98, 8381
(1976)



J. Hematoporphyrin-IX-palladium(II)

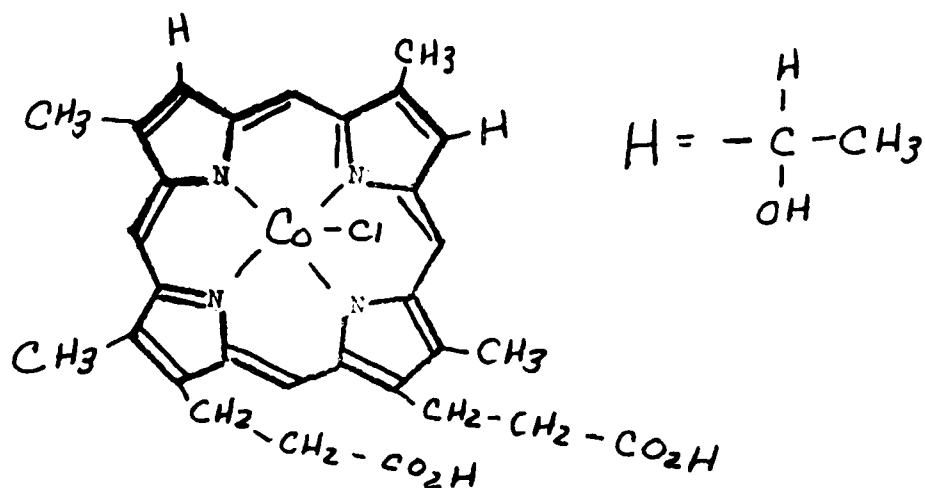
BK 40940

$\text{PdC}_{34}\text{N}_4\text{H}_{36}\text{O}_6$ MW = 703 J. Chem. Soc., 4089 (1964)

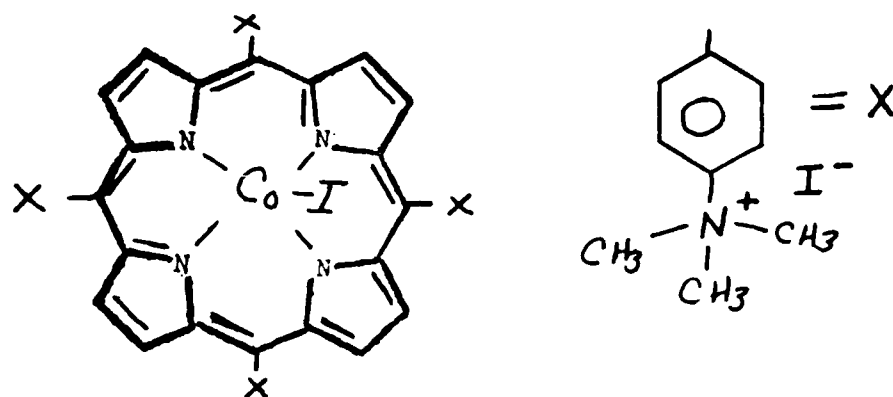


K. Hematoporphyrin-IX-cobalt(III) Chloride BK 40959

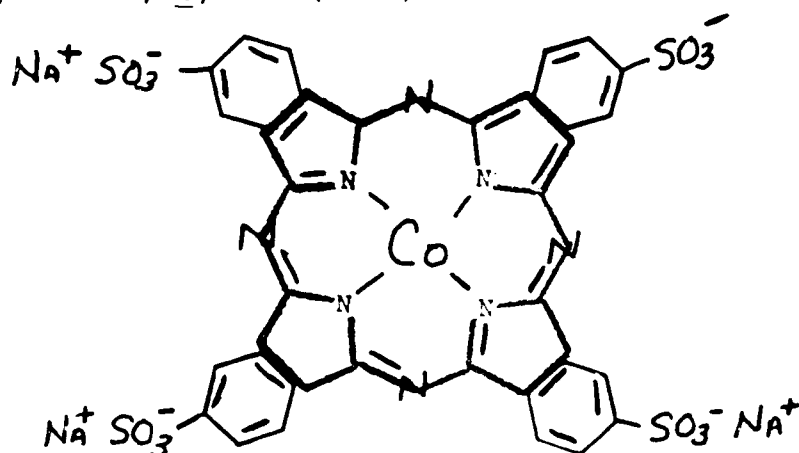
$\text{CoN}_4\text{C}_{36}\text{O}_6\text{H}_{36}\text{Cl} \cdot 2 \text{H}_2\text{O}$ MW = 691 Biochemistry 2, 361 (1963)



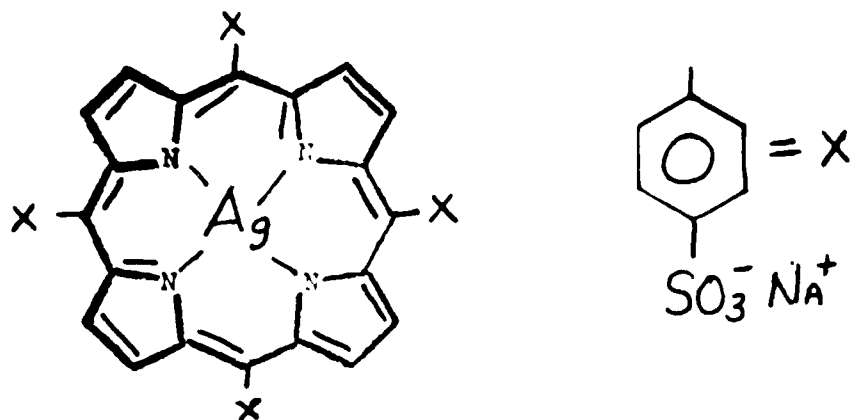
L. Tetrakis(4-(N,N,N-trimethylanilinium))porphyrincobalt(III) Iodide
 BK 40968 $\text{CoN}_8\text{C}_{56}\text{I}_5\text{H}_{60} \cdot 4 \text{H}_2\text{O}$ MW = 1610
 Transition Metal Chemistry, 9, 270 (1984)



M. Trisodium 4,4',4'',4'''-tetrasulfonatophthalocyaninecobaltate(III)
 BK 40977 $\text{CoN}_8\text{C}_{32}\text{H}_{12}\text{S}_4\text{Na}_3\text{O}_{12} \cdot 13 \text{H}_2\text{O}$ MW = 1206
 Inorg. Chem., 4, 472 (1965)



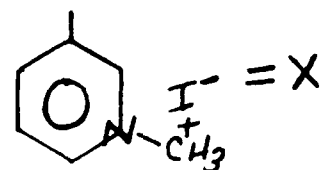
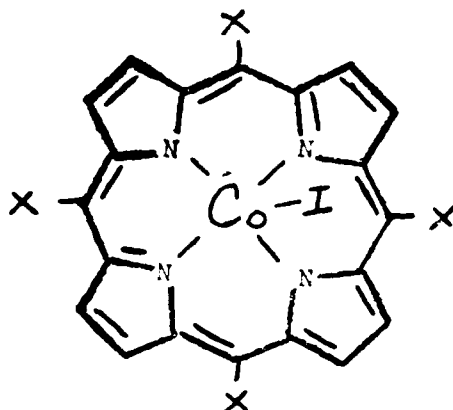
N. Sodium Tetrakis(4-sulfonatophenyl)porphyrinargenate(II)
 BK 40986 $\text{AgC}_{44}\text{N}_4\text{H}_{24}\text{O}_{12}\text{S}_4\text{Na}_4 \cdot 6 \text{H}_2\text{O}$ MW = 1237
 Inorg. Chem., 17, 2242 (1978)



O. Tetrakis(N-Methyl-3-pyridyl)porphyrincobalt(III) Iodide

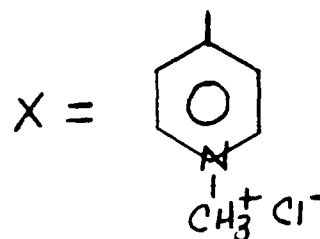
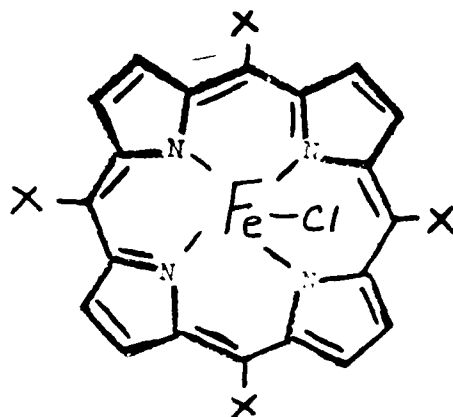
BK 40995 $\text{CoC}_{44}\text{H}_{36}\text{I}_5\text{N}_8 \cdot 3 \text{H}_2\text{O}$ MW = 1424

Bioinorg. Chem., 7, 267 (1977)



P. Tetrakis(N-Methyl-4-pyridyl)porphyriniron(III) Chloride

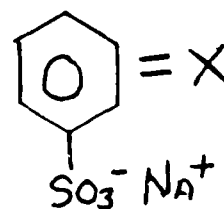
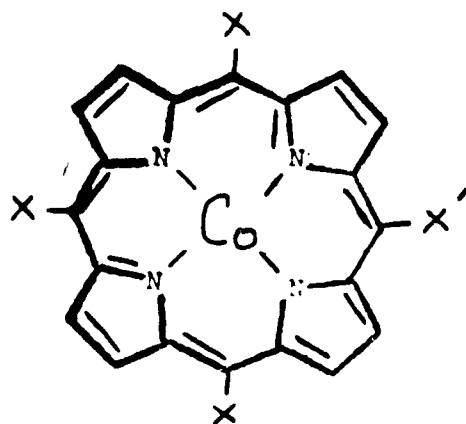
BL 19093 $\text{FeCl}_5\text{C}_{44}\text{N}_8\text{H}_{36} \cdot 10 \text{H}_2\text{O}$ Inorg. Chem., 9, 1757 (1970)



R. Sodium Tetrakis(4-sulfonatophenyl)porphyrincobaltate(III)

BL 19100 $\text{CoN}_4\text{S}_4\text{O}_{12}\text{C}_{44}\text{H}_{32}\text{Na}_3 \cdot 12 \text{H}_2\text{O}$ MW = 1280

J. Am. Chem. Soc., 98, 8381 (1976)

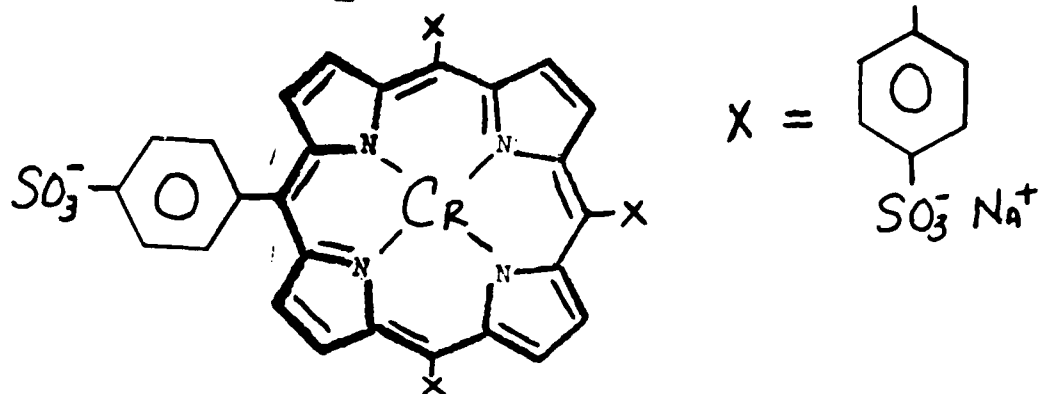


$X' = \text{'' '' (No Na}^+)$

S. Sodium Tetrakis(4-sulfonatophenyl)porphyrinchromate(III)

BL 19119 $\text{CrC}_{44}\text{N}_4\text{H}_{24}\text{S}_4\text{O}_{12}\text{Na}_3 \cdot \text{H}_2\text{O}$ MW = 1067

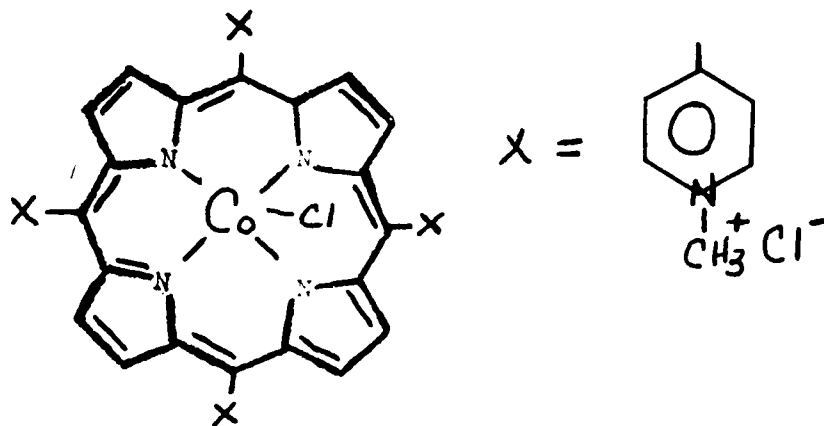
J. Coord. Chem., 2, 89 (1972)



T. Tetrakis(N-Methyl-4-pyridyl)porphyrincobalt(III) Chloride

BL 19128 $\text{CoN}_8\text{Cl}_5\text{C}_{44}\text{H}_{36} \cdot 9 \text{H}_2\text{O}$ MW = 1075

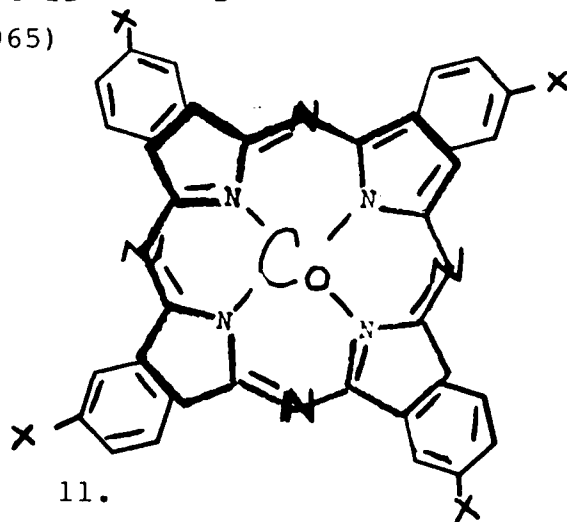
J. Inorg. Nucl. Chem., 35, 4327 (1973)



U. Sodium 4,4',4'',4'''-tetrasulfonatophthalocyaninecobaltate(II)

BL 19137 $\text{CoN}_8\text{C}_{32}\text{H}_{12}\text{S}_4\text{Na}_4\text{O}_{12} \cdot 12 \text{H}_2\text{O}$

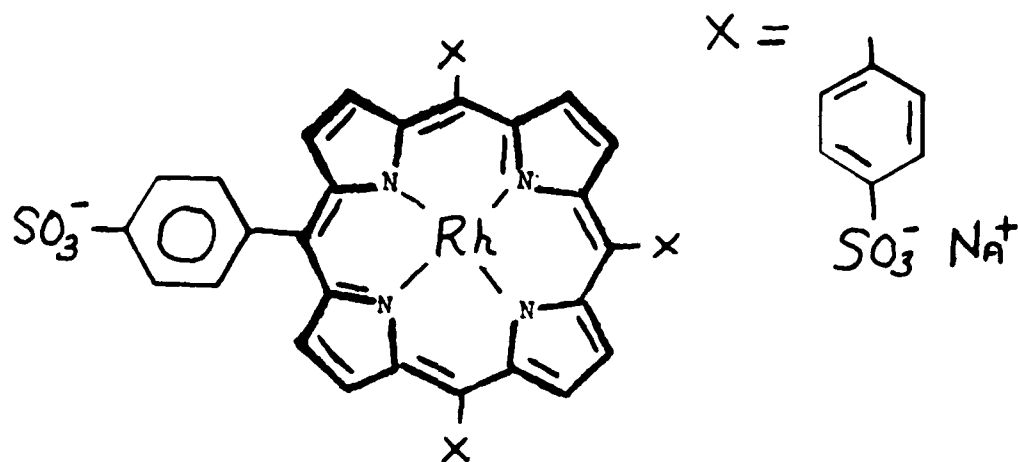
Inorg. Chem., 4, 469 (1965)



V. Sodium Tetrakis(4-sulfonatophenyl)porphyrinrhodate(III)

BL 19146 $\text{RhC}_{44}\text{N}_4\text{H}_{24}\text{S}_4\text{O}_{12}\text{Na}_3 \cdot 23 \text{H}_2\text{O}$ MW = 1513

Inorganica Chimica Acta 25, 215 (1977)



GENERAL REPORT

The ultimate aim of this project is to develop a pill that can be taken to protect against the CW agent, cyanide. One approach is to seek and modify model compounds that have attributes of known cyanide binders in the body, such as iron(III) hemoglobin and the iron(III) porphyrins in cytochrome oxidase. We earlier synthesized 20-30 mg samples of water soluble positive and negatively charged porphyrins and phthalocyanines containing various central metal ions. Using a constant amount of cyanide at pH 7.4, different concentrations of the scavenger drugs were added, and the amount of free cyanide in solution was determined with an autoanalyzer. The parameter of interest was BC 50, which is the molar concentration of the drug that binds half of the cyanide equilibrated with it. Poor scavengers had $BC\ 50 > 10^{-3}M$, and such coordinated metal ions included $VO(IV)$, $Mo(V)$, $W(V)$, $Mn(III)$, $Ni(II)$, $Cu(II)$, $Zn(II)$, $En(IV)$, $Al(III)$, $Mg(II)$, $Au(III)$, $Gd(III)$, $In(III)$, $Cd(II)$, cobalt(II)-myoglobin and certain iron(III) porphyrins. Compounds having $BC\ 50$ ca. $10^{-4}M$ were fairly good scavengers, and were mainly negatively charged complexes containing cobalt(III), silver(II), platinum(II), palladium(II), rhodium(III), certain cobalt(II) and (III) and iron(III) tetrasulfonated phthalocyanines, and hydroxocobalamin. The best cyanide binders had $BC\ 50$ around $10^{-5}M$, and these included cobalt(III) positively charged porphyrins, iron(III) hemoglobin and myoglobin, and di-cobalt(II)-EDTA.

The nature of the metal ion, the charge of the porphyrin and the type of groups coordinated in the axial positions above and below the porphyrin plane all influence the cyanide affinity at physiological pH. Thus, iron(III) hemoglobin and myoglobin, having a water molecule in one axial position bind cyanide, whereas cobalt(III) myoglobin, with an imidazole replacing water, or simple iron(III) porphyrins, which are mainly oxy-bridged dimers at pH 7.2 ($P-Fe-O-Fe-P$) do not rapidly react with cyanide. The cobalt(III) porphyrins, with water or hydroxyl groups in the axial positions react with cyanide, as does a rhodium(III) porphyrin, the metal in Group VIII below cobalt in the periodic table. Based on electrostatics, the negative cyanide should have a higher affinity for positively charged porphyrins as opposed to negative porphyrins, and the data bear this out. Many of these findings, which seem basic to understanding metal complex-cyanide interactions, are outlined in the paper "Mechanisms of Cyanide Inhibition by Scavengers", by P. Hambright, D. Franz and H. Newball, in Proceedings of the Fourth Annual Chemical Defense Bioscience Review, May 1984.

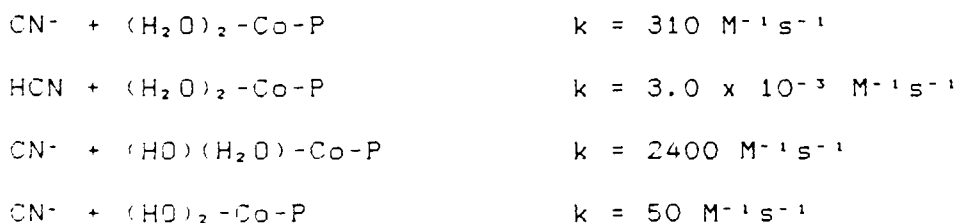
This year we synthesized and purified gram quantities of the better water soluble porphyrins and phthalocyanines, with coordinated $Cr(III)$, $Co(III)$, $Rh(III)$, $Pd(II)$, $Fe(III)$ and $Ag(II)$, and submitted them to WRAIR for further work. It is known that aquo $Co(II)$ is a superior cyanide scavenger, and in fact, $Co(II)$ can be analyzed by reaction with excess cyanide, and titrating the remaining cyanide, taking into account the $Co(CN)_6$,

complex of Co(II) formed. This species rapidly formed species is air sensitive, and a powerful one electron reductant, forming the pentacyanocobalt(III) as the substitution inert product. Di-cobalt(II)-EDTA has the formula $\text{Co}_2[\text{EDTA}] \cdot 6\text{H}_2\text{O}$, and the structure $[\text{Co}(\text{H}_2\text{O})_4][\text{CoEDTA}] \cdot 2\text{H}_2\text{O}$. The commercial drug Kelocyanor contains 300 mg of di-cobalt(II)-EDTA, diluted to 20 ml for (iv injection) with 4 grams of glucose and water. The free Co(II) and bound cobalt in Co-EDTA both scavenge cyanide as above, but any excess Co(II) is cardiotoxic, and the drug should not be given to patients who do not have cyanide intoxication. The cobalt(III) porphyrins and metalloporphyrins in general are strong chelating agents, and as such disguise the inherent toxicity of the free metal ions.

We did a solution kinetic study on the complexation of cyanide to sodium tetrakis(4-sulfonatophenylporphyrin) cobaltate(III) BL 19100] from pH 4 to 10 at 25°C, ionic strength 0.1 (NaNO_3). The rate-pH profile of first cyanide addition reaction is shown in Fig 1. The observed rate law is of the form below, where $k = k_{\text{obs}}/[\text{CN}^-]$:

$$k = \frac{[310 + 4.8 \times 10^6 (\text{H}^+) + 2.0 \times 10^{-4}/(\text{H}^+) + 1.9 \times 10^{-15}/(\text{H}^+)^2]}{1 + 8.3 \times 10^{-6}/(\text{H}^+) + 3.7 \times 10^{-17}/(\text{H}^+)^2}$$

The resolved rate constants are as follows:



In summary, cyanide reacts most rapidly with $(\text{HO})(\text{H}_2\text{O})\text{-Co-P}$, indicating that a dissociative mechanism is in effect. The hydroxide labilizes the trans water molecule, producing a vacant position for cyanide entry. The undissociated HCN (the major cyanide form under physiological conditions) only reacts with the di-aquo cobalt porphyrin, and the relative rates for CN^-/HCN is ca $10^5/1$. Once the first cyanide is bound, its electron density adds to that of the coordinated hydroxide, and a proton is immediately picked up by this hydroxide forming the $(\text{H}_2\text{O})(\text{CN})\text{-Co-P}$. This species then reacts with another cyanide ($k=2 \times 10^7$) to form the di-cyano cobalt porphyrin. This second step is about 10^4 times faster than cyanide addition to any of the species in the first cyanide addition step.

Equilibrium constants for cyanide adding to the mono-cyano porphyrin can be measured by preforming the di-cyano porphyrin at high pH, and monitoring the spectral changes as the pH is

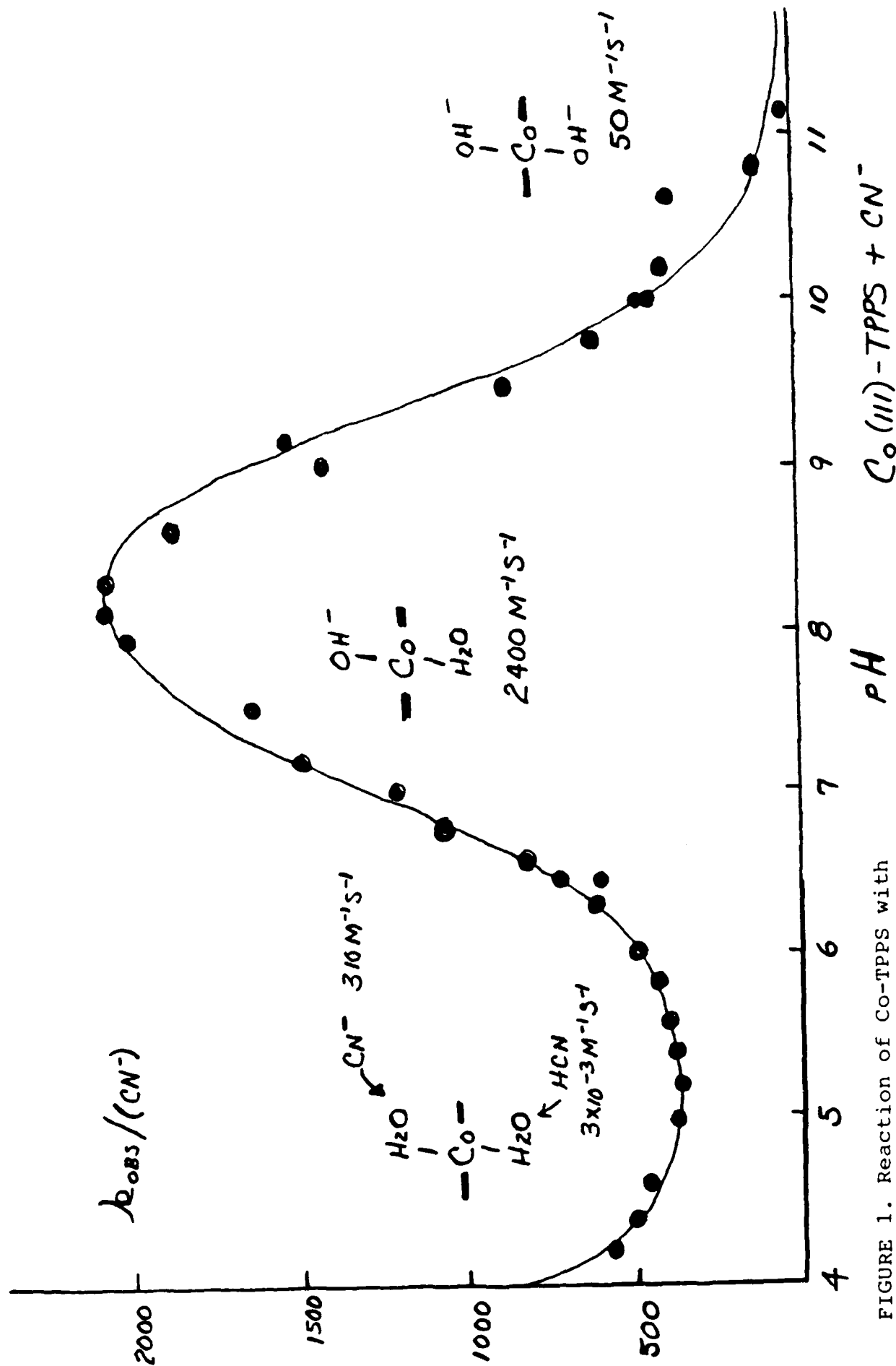


FIGURE 1. Reaction of Co-TPPS with Cyanide, 25°C , $\mu = 0.1 (\text{NaNO}_3)$

lowered. $K = 3.3 \times 10^4$ for the $\text{CN-Co-P} + \text{CN}^- = (\text{CN})_2\text{-Co-P}$ process. Even when the pH is dropped to 1.0, the mono-cyano porphyrin remains, an indication of the very small dissociation constant found for cobalt(III) porphyrins and cyanide. Once the species forms, it is not readily lost in an equilibrium sense by an acid catalyzed dissociation process. The second cyanide is less stable, and can be added or lost depending on the acidity.

We extended this work on the negatively charged Co-TPPS³⁻ to two positively charged cobalt(III) porphyrins, the tetrakis-(N-Methyl-4-Pyridyl)porphyrin [Co-TMPyP³⁺, BL 19128] and tetrakis-(4-N,N,N-trimethylanilinium)porphyrin [Co-TAP³⁺, BL 40968]. At pH 7.4, the specific rates for cyanide addition to Co-TMPyP³⁺, Co-TPPS³⁻ and Co-TAP³⁺ are 1100, 1700 and 2300 M⁻¹s⁻¹ respectively (as compared to 1900 M⁻¹s⁻¹ for hydroxocobalamin). The corresponding equilibrium constants for second cyanide addition are 5.7×10^7 , 3.3×10^4 and 2.2×10^4 . Both the high electron density and positive charge of Co-TAP³⁺ favor the cyanide reaction. The mono-cyano addition rates are all of the same order of magnitude for the three porphyrins and the corrin, and are probably close to the maximal rate possible, which is the water exchange rate of the coordinated water ligand, influenced by the electron density of the group trans to this leaving group. Fortunately the porphyrins have the electron donating hydroxy function stable near physiological pH, and such electron donation favors the reactions. By addition of the reducing agent dithionite ($\text{S}_2\text{O}_4^{2-}$) to the cyano-cobalt(III)porphyrin solutions, the cobalt(II) porphyrin slowly forms, and the initial indication is that this cobalt(II) porphyrin does not strongly bind cyanide. To this end, we investigated the cyanide reactions of a rhodium(III) porphyrin, in that Rh(III)-P cannot be reduced easily to the Rh(II)-P form.

The rate-pH profile for the rhodium(III)-tetrakis(4-sulfonatophenyl)porphyrin (BL 19146) reaction with cyanide from pH 6 to 9 are shown in Fig. 2. Here, the di-hydroxy and mono-hydroxy species have minor reactivity compared to the aquo form. The specific rates at 25°C are 5.0 M⁻¹s⁻¹ for CN⁻ and 2.3×10^{-3} M⁻¹s⁻¹ for HCN. The mechanism appears to be associative interchange in character, where cyanide entry and water leaving occur in a concerted fashion. At pH 7.4, the Rh(III) reacts about 700 times more slowly than does the Co(III) center. Only one cyanide group appears to be attached to the Rh(III)-P. We plan to finish these studies with the aim of publication soon, and extend the solution work with chromium(III) and a monomeric iron(III) porphyrin. Only in such a fashion will the nature of cyanide reactions with metal chelate compounds have a sound basis. Metal chelate compounds are favorable, in that they react extremely rapidly with cyanide, as compared to the classical organic compounds described below. The metalloporphyrins and metallophthalocyanines (and Vitamin B₁₂) are probably too large to be taken orally, and work on similar, but lower molecular weight adducts are planned in the following year.

Organic compounds containing ketone groups such as sodium pyruvate [Green and Williamson, *Biochem. J.*, **31**, 617 (1937)] and more recently alpha ketoglutaric acid [Moore, Norris, Ho and

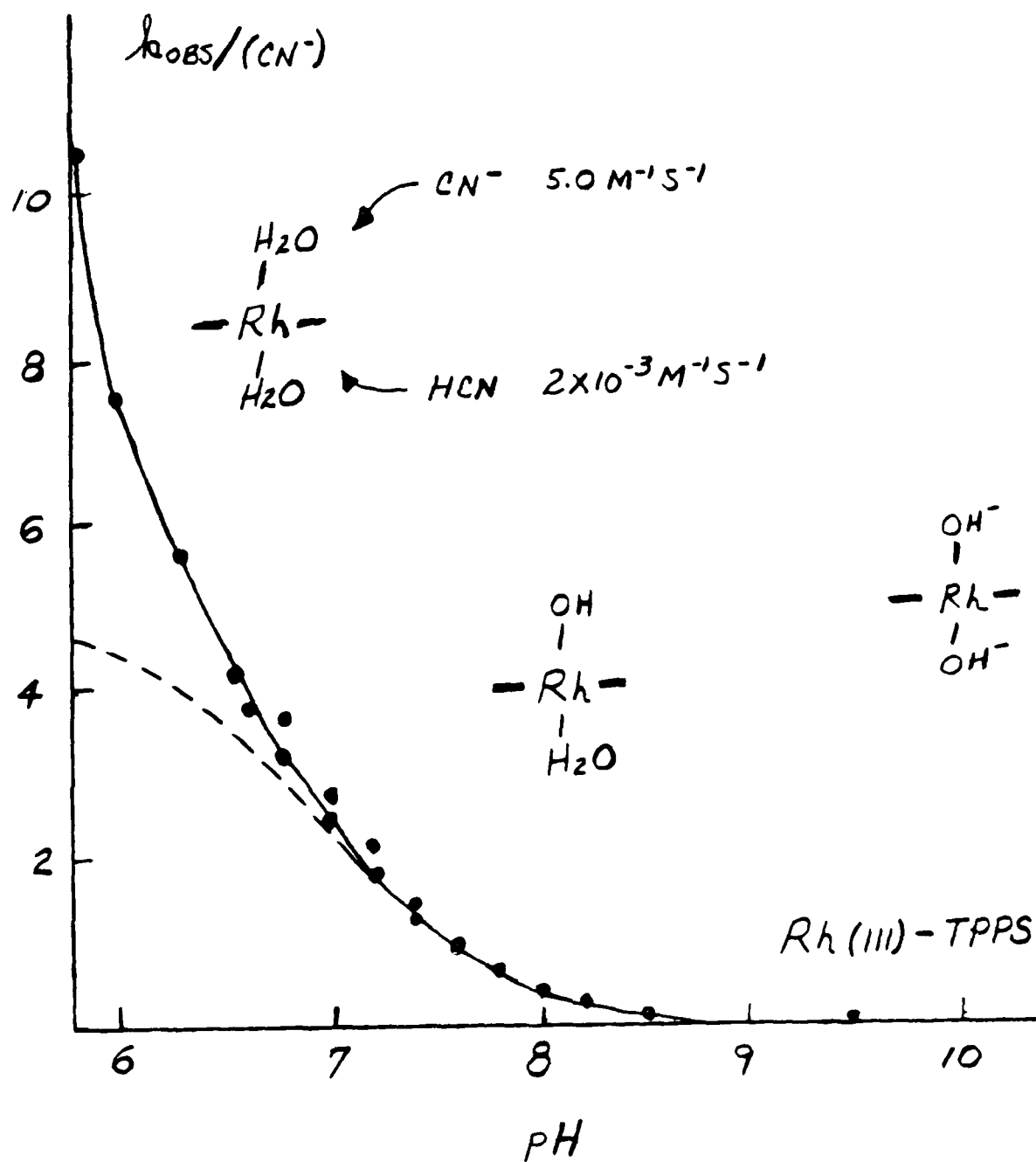
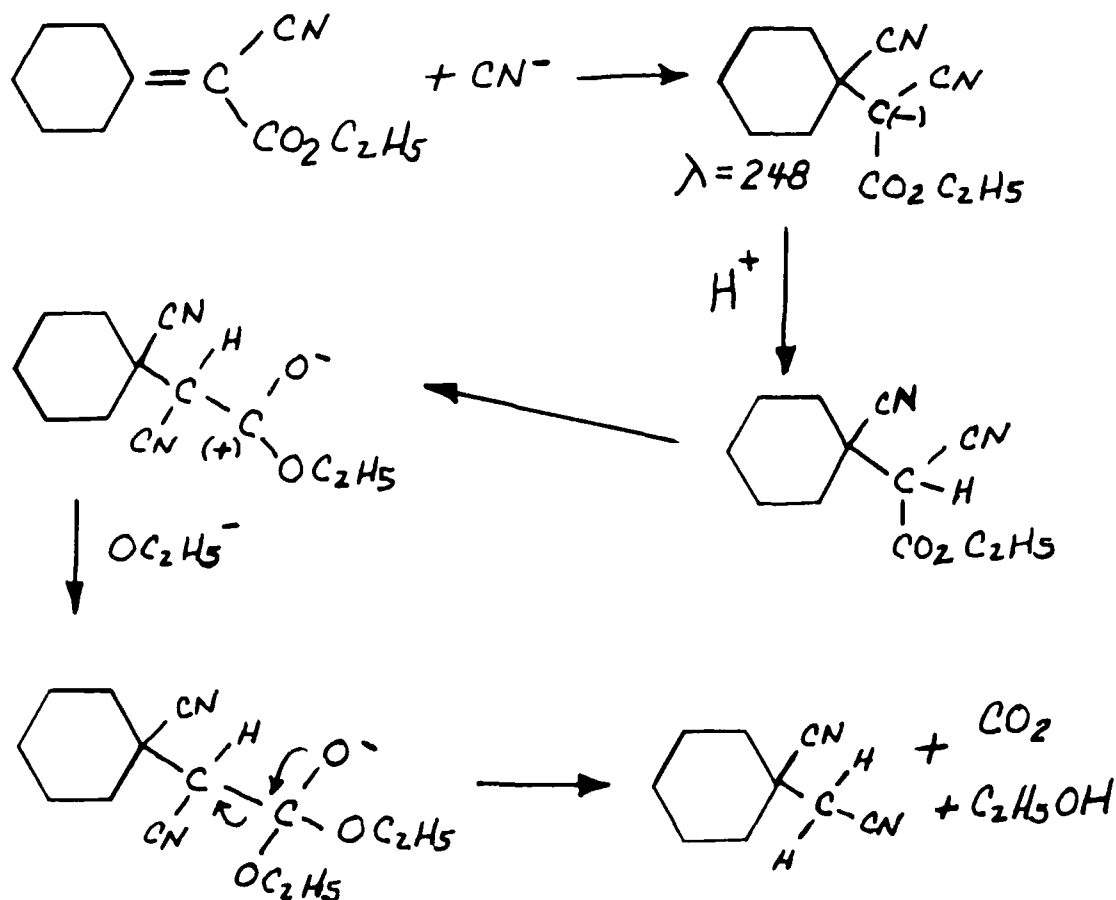


Figure 2. pH profile of the reaction of Rh(III)-TPPS with cyanide, 25°C, $\mu = 1.0$ (NaNO₃)

Hume, Toxicol. Appl. Pharmacol. 82, 40 (1986)] either alone or in conjunction with nitrite/thiosulfate, presumably form cyanohydrins with cyanide in vivo, and provide some protection against the lethal effects of cyanide. Rather than working with cyanohydrin formers, we have concentrated on alpha-beta unsaturated compounds called alkylidenes, which can be made water soluble as the sodium salts of their carboxylic acids. To find if such systems scavenge cyanide at reasonable rates, we did a kinetic study in ethanol/water on the reaction of cyclohexylidene-alpha-cyanoacetate with cyanide at 24.5°C. By following the reaction at 248 nm, the rate was first order in alkylidene and first order in cyanide, with a specific rate constant of $2.0 \text{ M}^{-1}\text{s}^{-1}$. The 248 nm peak slowly disappears, with a $k = 0.10 \text{ min}^{-1}$, with a rate independent of cyanide concentrations. The final stable product is 1-cyano-1-cyanomethyl cyclohexane. The suggested mechanism is as follows :



If the reaction were run in water with the free carboxylic acid, the product would be H_2CO_3 , which is CO_2 and H_2O . In contrast to cyanohydrins which can dissociate back into the carbonyl compound and cyanide, the rearrangement above produces a stable entity from which cyanide cannot be reformed. Such reactions have been studied in water using classical methods by Lapworth [J. Chem.

studied in water using classical methods by Lapworth [J. Chem. Soc., 83, 995 (1903)] and by Jones [J. Chem. Soc. 1547, 1560, (1914)]. These organic drugs appear to react more slowly than do the metal chelates. In fact, using the autoanalyzer and low cyanide concentrations, no cyanide uptake was found within 10 minutes for alpha ketoglutaric acid .Better rate information, in addition to equilibrium constants are needed to characterize these cyanohydrins and alkylidenes. We are in the process of designing alkylidene derivatives capable of picking up several moles of cyanide, and having water soluble dissociated product forms containing the covalently bound cyanide.

Dr. Peter Hambright and Dr. Jesse Nicholson, Howard University, worked full time Summer and 1/4 time the academic year on this project. Dr. Robert Langley, now at Lincoln University, worked full time Summer, and Dr. A. Adeyemo, University of Ibadan, Nigeria worked for six weeks in the Summer. Mr. Kurt Vernon, an Undergraduate, works part time, and Miss Margaret Brown, a high school student, does the library and related technician duties.

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