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Anti-Cyanide Drugs

Annual Report

Peter Hambright

May 1, 1988

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701-5012

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

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The extent of cyanide uptake by various molecules at pH 7.4 was monitored with a cyanide specific electrode. Low molecular weight aliphatic aldehydes scavenged cyanide best, followed by aromatic aldehydes with electron withdrawing functions. Palladium(II) complexes rapidly bound four moles of cyanide, gold(III) species bound three, while platinum(II, IV) and trivalent rhodium and ruthenium complexes were less reactive. A ruthenium porphyrin complexed two cyanides in both the +2 and +3 oxidation states. A nickel(II) Schiff-base adduct took up four moles of cyanide through a dissociative process. Nickel(II) cyclams rapidly bound one cyanide, and three more at later times. Keywords:

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SUMMARY

This is the third year of a project to identify and develop compounds that might act in a prophylactic fashion against the rapid acting poison, cyanide. Such compounds include metal ions and metal complexes, aldehydes, ketones, porphyrins, phthalocyanines, and alkylidenes. Although many compounds bind cyanide at high pH, the limitations here are that the molecules must be water soluble and react with cyanide at reasonable rates at the physiologic pH of 7.4. Several such derivatives will be supplied to WRAIR for further testing. The two earlier reports (1,2) give the extensive background and literature for this project.

In earlier work, we studied the kinetics and mechanisms of cobalt(III) and rhodium(III) porphyrins reacting with cyanide. Such compounds have structures similar to the Vitamin B-12 derivative hydroxocobalamin, a known cyanide scavenger. The Rh(III) adduct reacts with cyanide too slowly to be of interest, while the Co(III) porphyrins have high equilibrium constants and show rapid complexation with cyanide at the physiologic pH. The molecular weights of such species are about half that of B-12, and since such porphyrins bind two moles of cyanide (B-12 binds one in-vivo), they are perhaps four times more effective on a per-gram basis. The Co(III) porphyrins and B-12 derivative as well as the Rh(III) system have a high affinity for ligands other than cyanide, such as hydroxide and other nitrogenous bases. This year we studied ruthenium(II) porphyrins, that have no affinity for hydroxide in aqueous solution, due to their low oxidation state, and are specific binders for cyanide. Upon complexation with cyanide, the ruthenium(II) monocyano porphyrins are rapidly oxidized to the ruthenium(III) state, at which time they add one more cyanide to their coordination sphere. Equilibrium and kinetic data are presented for one such ruthenium porphyrin system.

Low molecular weight aldehydes and ketones react with cyanide to form cyanohydrins. We previously demonstrated that aldehydes are more reactive than the corresponding ketones, and such reactions were easily followed using a cyanide selective electrode. Thus 2,6-pyridinedicarboxaldehyde bound two moles of cyanide per mole of ligand, whereas glyoxylic acid (CHO-COOH) reacts with one mole of cyanide per mole of ligand. All other derivatives studied showed lesser cyanide uptake abilities. With aromatic aldehydes, this year we demonstrated that electron withdrawing groups on the ring facilitate cyanohydrin formation. Thus 2,6-difluorobenzaldehyde has a cyanide/ligand ratio of 0.97/1 whereas the 4-hydroxybenzaldehyde shows 0.08/1. The best scavengers were aliphatic aldehydes. For example acetaldehyde (Me-CHO) showed a cyanide to ligand ratio of 1/1.

In terms of simple metal complexes, we found that the relatively non-toxic palladium derivatives rapidly bind four moles of cyanide, whereas gold(III) species bind three moles of cyanide at pH 7.4. Various Pt(IV), Rh(III), and Ru(III) complexes have rather less affinity for cyanide.

We have been seeking agents that strongly complex metal ions and allow release of this metal to form tightly bonded cyanide adducts only in the presence of a certain external tension of cyanide. In this direction, a nickel(II)-cyclam-14 will bind one cyanide ligand with a reasonably high formation constant of log $K = 4.4$, and after standing for days, the very stable tetracyano-nickel(II) is produced. This nickel ion is held in a macrocyclic ring of four nitrogen atoms in the cyclam. We have found a Schiff base nickel derivative that has the metal attached to nitrogen and oxygen atoms, in a ligand-metal-ligand configuration. Upon addition of cyanide, the nickel(II) ion reacts rapidly with four moles of free cyanide and is released from the complex.

TABLE OF CONTENTS

COMPOUNDS SUBMITTED TO WRAIR, MAY 1988

COMPOUND		NUMBER
A-88.	Glyoxal sodium bisulfite addition compound, monohydrate	BL 53620
B-88.	4-Quinolinecarboxaldehyde	BL 53639
C-88.	4-Pyridinecarboxaldehyde-N-oxide	BL 53648
D-88.	Hydrogen tetrachloroaurate trihydrate	BL 53611
E-88.	<u>trans</u>-Dichlorobis(dimethylsulfoxide)-palladium(II)	BL 53657
F-88.	Bis(1,3-dicyanomethylene)-2-keto-4-cyclopentene,4,5-diol, dipotassium salt	BL 53666
G-88.	Ammonium hexachlororuthenium(IV)	BL 53675
H-88.	Tetraamminepalladium(II) nitrate	BL 53684
I-88.	Hexamminerhodium(III) chloride	BL 53693
J-88.	2,5-Dimethoxy-3-tetrahydrofuran-carboxaldehyde	BL 53700

The aim of this project was to explore the chemistry of species that have a high affinity for cyanide at the physiologic pH of 7.4, in order to develop drugs that could counteract the rapid acting CW agent, cyanide. To this end, aldehydes, ketones, metal ions and metal complexes, alkylidenes, metalloporphyrins, and metallophthalocyanines were investigated for their cyanide binding ability. The better compounds were submitted to WRAIR for further testing.

ALDEHYDES AND KETONES: The carbonyl group in aldehydes and ketones has a high affinity for cyanide. The pKa value for the (HCN)/(H+)(CN-) reaction at an ionic strength of 1.0 is 9.1, and thus at pH 7.4, the bulk of the total cyanide is in the undissociated HCN form. The mechanism of cyanide addition is postulated (3) to be:

$$HCN + OH^- = CN^- + H_2O \qquad (fast)$$

$$\text{(slow)}$$

$$\text{(fast)}$$
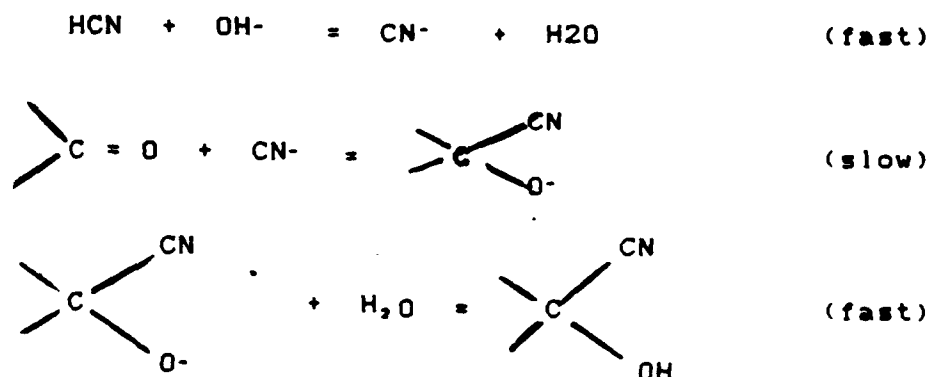
As a rapid method of determining the cyanide affinity of various carbonyl compounds, we used a Radiometer cyanide electrode system. Fifty ml of a 0.2 ionic strength solution (0.1 M in phosphate buffer at pH 7.4 containing 0.1 M NaNO3) was placed in the reaction flask containing the cyanide electrode, a reference electrode and combination pH electrode and magnetic stirring bar. Four 0.25 ml portions of standardized aqueous KCN solution were added from a micropipet, and the potential was noted after each addition. The final cyanide concentration was about $1 \times 10(E-03)$ M, and a linear plot of potential vs log total cyanide concentration was constructed. The compound to be investigated was dissolved in 10 ml of the buffer solution and added in portions to the solution of known cyanide concentration. The new cyanide level was noted two minutes after ligand addition. Plots of cyanide vs ligand concentration were made, and the initial slopes of such plots were used as a measure of relative cyanide

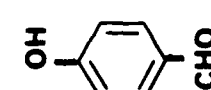TABLE 1. CYANIDE/LIGAND RATIOS FOR AROMATIC ALDEHYDES: KETONES

Structure	Ratio
2-fluorobenzaldehyde (F, CHO)	0.36
3-fluorobenzaldehyde (F, CHO)	0.26
4-fluorobenzaldehyde (F, CHO)	0.20
2,4,6-trimethylbenzaldehyde (Me, Me, Me, CHO)	0.17
4-hydroxybenzaldehyde (OH, CHO)	0.08
2,4-dihydroxybenzaldehyde (OH, OH, CHO)	0.17
2,3-dihydroxybenzaldehyde (OH, OH, CHO)	0.13
4-dimethylaminobenzaldehyde (Me₂N, CHO)	0.06
4-nitrobenzaldehyde (NO₂, CHO)	0.48
2-nitrobenzaldehyde (NO₂, CHO)	0.5
2,6-difluorobenzaldehyde (F, F, CHO)	0.97
4-cyanobenzaldehyde (CN, CHO)	0.42
2-carboxybenzaldehyde (COOH, CHO)	0.18
4-carboxybenzaldehyde (COOH, CHO)	0.15
2-sulfobenzaldehyde (SO₃, CHO)	0.5
benzaldehyde (CHO)	0.11
2-acetylpyridine	0.01
2,6-diacetylpyridine	0.45
pyridine-2,6-dicarboxaldehyde (OHC, CHO)	2.0
6-methylpyridine-2-carboxaldehyde (CH₃, N, CHO)	0.66
pyridine derivative (N, CHO, CH₃)	0.8
pyridine-3-carboxaldehyde	0.5
pyridine-4-carboxaldehyde	0.5

9.

TABLE I. CONT'D

CHO 0.07

HCO—[]—SO₃⁻ 0.08

CH_3 / OCH_3 CHO 0.8

CHO—N[] 0.003

CH_3 CHO (furan) 0.12

CHO / OHO / CH_3 / CH_2OH 0.1

C-10 [quinoline] 0.6

CH=N—OH / CH_3 N⁺ 0.12

[]—COCH₂NH₃⁺ ~0

CHO [isoquinoline] 0.34

O=N[]—CHO 0.82

H—N[]N—CHO 0.01

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7.

affinities of the test samples. This corresponds to the moles of cyanide bound per mole of ligand, when a small amount of ligand is added to a large and constant cyanide concentration. In several cases the compounds to be tested were of such low solubility in water that their stock solutions were prepared in 40% by volume methanol, and such compounds are denoted by a (*) in the accompanying work. Control experiments indicated that the methanol had little effect on the cyanide/ligand ratio measured.

The cyanide vs ligand concentration data obtained this year are in the Data section. Table 1 is a summary of the results on various ring structures containing aldehyde or keto groups. Table 2 is a list of compounds containing aliphatic aldehydes or ketones. Several generalizations can be made.

      (1). Aldehydes have higher tendencies for cyanohydrin formation than related ketones. Thus 2,6-diacetyl-pyridine gives a cyanide/ligand ratio of 0.45 whereas the 2,6-pyridinedicarboxaldehyde is 2/1.

      (2). In a series of substituted benzaldehydes, electron withdrawing groups favor cyanohydrin production. Thus the 4-N,N-dimethylaminobenzaldehyde shows 0.06/1, whereas the 2,6-difluorobenzaldehyde gives 0.97/1.

      (3). In general, aliphatic aldehydes are better cyanohydrin formers than compounds containing aromatic groups. Glyoxylic acid (HOOC-CHO) and acetaldehyde (Me-CHO) both show 1/1 uptake of cyanide.

ALKYLIDENES: Alkylidenes are compounds containing double bonds in which one carbon atom in the bond has strongly electron withdrawing substituents that should draw electrons from the double bond facilitating cyanide addition to the other carbon. Compound A below, alpha-cyano-4-carboxyethylcinnamate, is an example of an alkylidene and shows a cyanide/ligand ratio of 0.1/1. Compound B is the dipotassium salt of 1,3-bis(dicyanomethylene)croconate (4). While formally similar to compound A, the electron delocalization is such that no true keto or double bond character is present, and a ratio of 0.15/1 is obtained. Compound C is croconic acid, and the anion is rather fully delocalized so no real keto groups exist. Again the cyanide/ligand ratio was 0.15/1. Replacing two oxygen groups by sulfur atoms would break up such conjugation, perhaps making for more useful derivatives. For compound B, it has been speculated that (5) the nitrile (-CN) group might saturate biological cyanide binding sites, and thus provide a measure of protection.
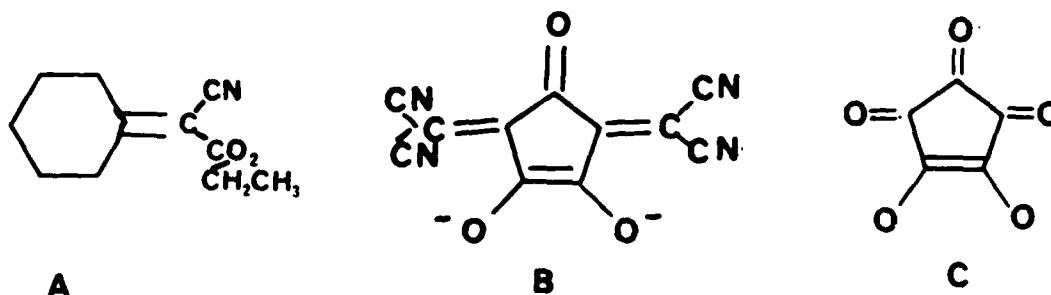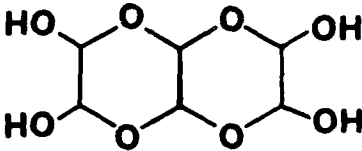

A   B   C

Table 2. Aliphatic aldehydes and ketones, pH 7.4

Compound	Structure	CN / Ligand
Glyoxal trimeric dihydrate	HO–[dioxane bicyclic ring structure with OH, O substituents]	1.9/1
Glyoxylic acid	$HCO-COOH$	1.0/1
Acetaldehyde	CH_3-CHO	1.0/1
Glyoxal sodium bisulfite addition compound	$[O_3S-CH(OH)-CH(OH)-SO_3]Na_2$	0.7/1
Isobutyraldehyde	$(CH_3)_2-CH-CHO$	0.4/1
2-Ketobutyric acid	$C_2H_5-CO-COOH$	0.4/1
Alpha-keto-glutaric acid	$HOOC-(CH_2)_2-CO-COOH$	0.25/1
Ketomalonic acid	$HOOC-C(OH)_2-COOH$	0.17/1
Pyruvic acid	$CH_3-CO-COOH$	0.12/1
Acetone	$CH_3-CO-CH_3$	0.08/1
Oxalacetic acid	$HOOC-CH_2-CO-COOH$	0.06/1

<u>METAL COMPLEXES:</u> The following data was observed for simple metal complexes reacting with cyanide at pH 7.4. The ratio is moles of cyanide bound per mole of metal ion added. In general, such slopes are independent of the metal ion concentration.

COBALT

$[CoCl_2 (H_2O)_4] . 2H_2O$	5/1
$[Co^{II} (H_2O)_4 Co^{II}EDTA] . 2H_2O$ (outdated sample of commercial Kelocyanor)	3/1

NICKEL

trans-$[NiCl_2 (H_2O)_4] . 2 H_2O$	4/1

PALLADIUM

cis-$PdCl_2(NH_3)_2$	4/1
trans-$PdCl_2(NH_3)_2$	4/1
$[PdCl_4] Na_2$	3.8/1
$PdCl_2(DMSO)_2$ -DMSO = (CH_3)$_2$-SO -	4/1
$[Pd(NH_3)_4] (NO_3)_2$	4/1

GOLD

$H[AuCl_4]$	3/1
$AuBr_3$	3/1

PLATINUM

$[Pt^{IV} (en)_3] Cl_4$	0.15/1
cis-$PtCl_2(NH_3)_2$	2.6/1
trans-$PtCl_2(NH_3)_2$	0.9/1

ZINC

$Zn(NO_3)_2 . 6H_2O$	1/1

RUTHENIUM

$[Ru^{IV} Cl_4] (NH_4)_2$	1/1
$[Ru^{III} (NH_3)_4] Cl_3$	1/1

RHODIUM

$[Rh^{III} (NH_3)_4] Cl_3$	0.09/1

RUTHENIUM((II)-PORPHYRINS: Since cobalt(III) hydroxocobalamin, a Vitamin B-12 derivative has been suggested to be useful in cyanide therapy (6), we investigated the kinetics and mechanisms of related rhodium(III) porphyrins (7) and cobalt(III) porphyrin (8) reactions with cyanide. The rhodium system had specific rates too slow to be of interest, whereas the cobalt(III) porphyrins had rapid cyanide formation kinetics at physiologic pH and high stability constants for cyanide addition. On a per/gram basis, the cobalt(III) porphyrins might be four times more effective than the B-12 analogue, a rather small effect.

The cobalt(III) porphyrins and cobalamin and the rhodium(III) porphyrin are in high oxidation states, and react readily with hard ligands such as hydroxide, amines, thiosulfate, etc. Thus the cobalt porphyrins (Co-P) form mono-hydroxy (HO-Co-P) and di-hydroxy species and perhaps oxo bridged dimers (P-Co-O-Co-P) depending upon pH, and such groups need to be removed before the uptake of cyanide. We decided to study the reactions of ruthenium(II) porphyrins, with the notion that the low oxidation state would favor bonding to soft back bonding ligands such as cyanide, rather than the hard hydroxide anion. This proved to be the case.

The reactions of a carbonyl-ruthenium(II) porphyrin with cyanide are shown in Figure 1. The porphyrin studied was uroporphyrin-1, a compound containing eight carboxylic acid groups, making it fully water soluble. The absorption spectra were independent of pH from pH 3 to 13, indicating that the species did not react with hydroxide or hydrolyze in the pH range considered. Upon adding cyanide, the 393.5 nm CO-Ru-P band shifted to 403 nm, indicating the uptake of one mole of cyanide, forming CO-Ru-P-CN. The equilibrium constant for cyanide uptake was found to be Log K = 4. The reaction was found to be first order in porphyrin and cyanide concentration, with a specific rate constant at 25 degrees C of 2.2 M(-1)sec(-1). These data are shown in Figure 2. In the presence of oxygen and excess cyanide, the CO-Ru(II)-P was oxidized to the Ru(III)-dicyano form (400 nm), where the carbon monoxide is lost to the solution upon oxidation. In the absence of cyanide, oxidation into what appears to be a ruthenium(IV) state takes place in days, thus the cyanide facilitates oxidation to the (III) state. If the air-unstable CO-Ru(II)-CN is allowed to stand under nitrogen at room temperature, the carbon monoxide ligand is slowly lost, with the production of dicyano-Ru(II)-P (414 nm). The kinetics of this reaction were first order in porphyrin, and independent of cyanide from 1.3 mm to 16 mm cyanide concentration. The half-life of the reaction is 4.3 hours, giving a specific rate constant of the order of 4.4(E-05) sec(-1). The porphyrin apparently features two modes of cyanide uptake, an associative mechanism when the carbonyl is present, and a dissociative mechanism, wherein the slow step is carbon monoxide loss, followed by the rapid uptake of a second cyanide into the unstable [CN-Ru(II)] form. The dicyano-Ru(II) porphyrin is rapidly air oxidized into the dicyano-Ru(III) state presumably by an outer sphere mechanism in which electron

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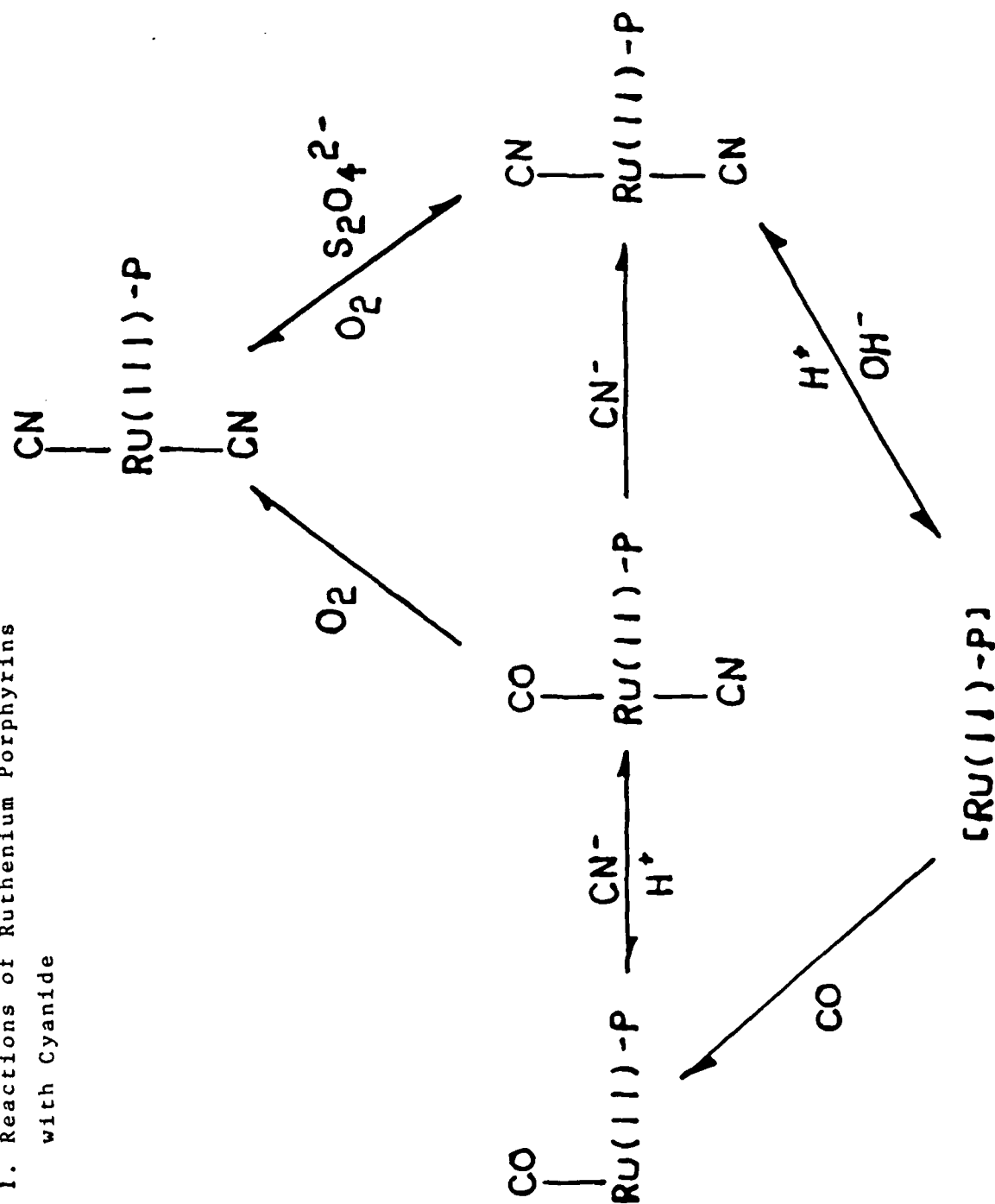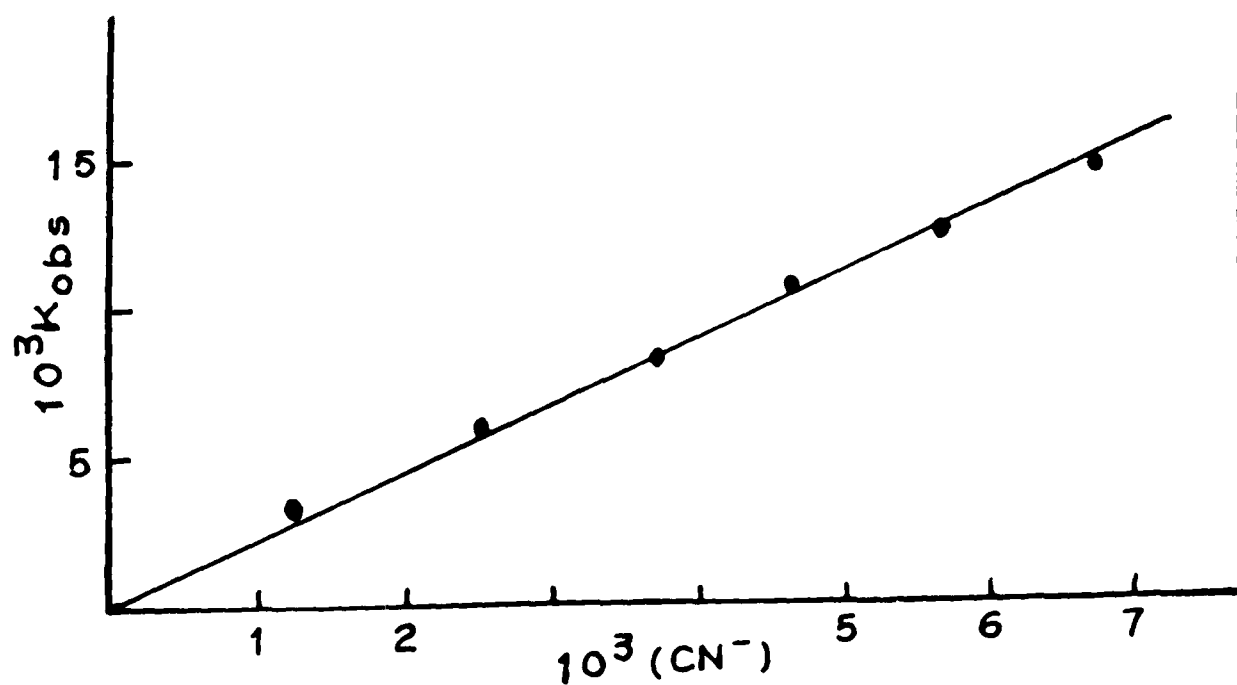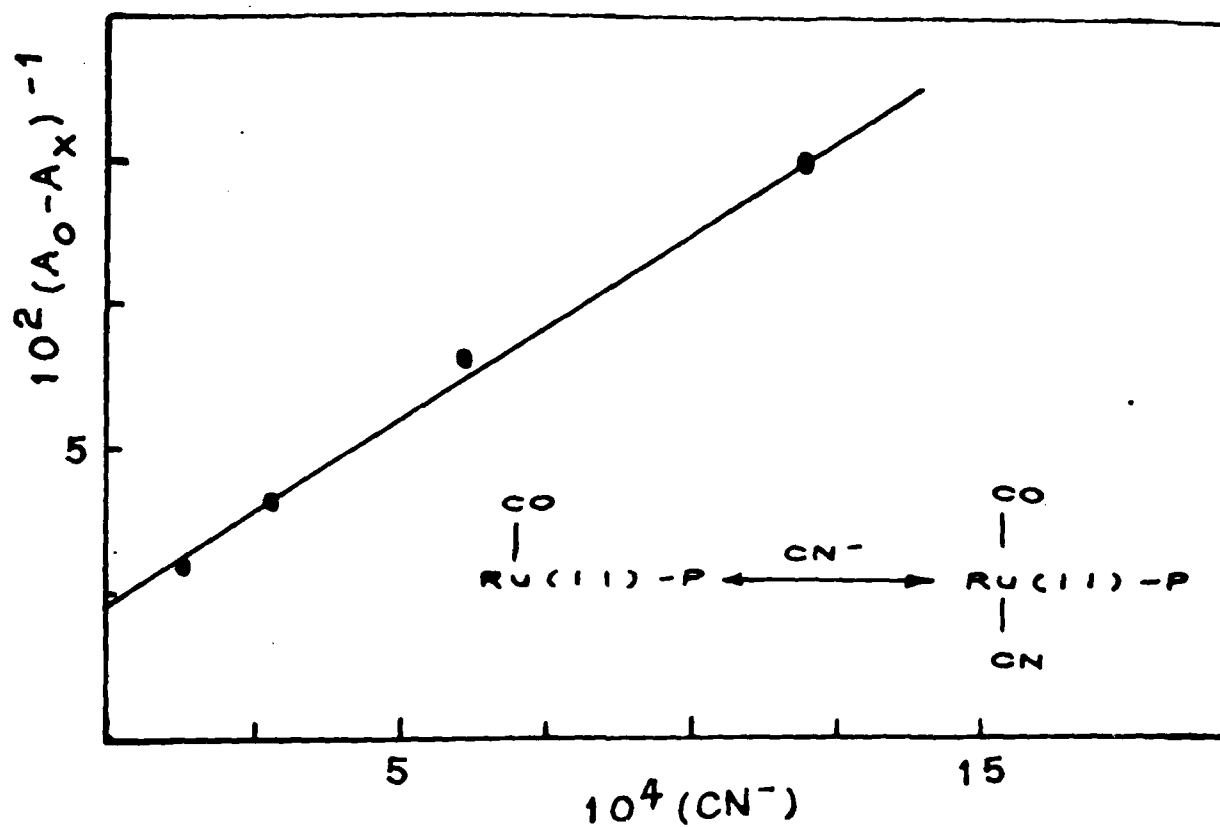FIGURE 1. Reactions of Ruthenium Porphyrins with Cyanide

12.

FIGURE 2.(Top)Equilibrium and (bottom) Kinetic Ruthenium Data

transfer occurs through the intact dicyano-Ru(II) coordination shell. Adding dithionite to the Ru(III) form allows reduction back into the dicyano-Ru(II) state. Addition of acid (pH 2) to the dicyano-Ru(II) porphyrin produces cyanide loss to an uncharacterized [Ru(II)] state, and the passage of CO through this solution reforms the CO-Ru(II)-P.

If the dicyano cobalt(III) porphyrins or corrins are reduced, the cyanide is lost from the coordination sphere, as the Co(II) forms have little cyanide affinity. This was one of the main reasons for investigating the rhodium(III) porphyrins; they are reduced much less readily than the cobalt(III) states. The advantage of the ruthenium porphyrins is that both the reduced and oxidized forms have an affinity for cyanide. In fact, the reduced state is very specific for cyanide and should not interact with any other anionic or nitrogen base biological ligands, or water. The complexation of one cyanide to a Ru(II) porphyrin makes the compound more oxidizable, and the resulting oxidation both retains the coordinated cyanide and adds another due to the oxidation process. The trivalent Ru(III) should have a higher affinity for the negative cyanide than does the reduced divalent state. The equilibrium constant for cyanide uptake is several orders of magnitude less than is desirable for a scavenger at pH 7, and no doubt other differently substituted positively charged porphyrins might raise the equilibrium quotient to reasonable values. The cobalt(III) porphyrins have a huge affinity for cyanide, with log K > 13 for first cyanide addition. This is probably the reason that Co(III)-B12 is active in its diaquo rather than its monocyano form in vivo.

NICKEL(II)-CYCLAM-14: We would like to develop metal containing species that are strongly bonded to the ligand framework, and release the otherwise toxic (but multiple cyanide binding) metal ion only upon demand by a certain tension of cyanide in solution. The high metal-cyanide formation constant might render both the metal and the cyanide itself non-toxic. The first effort in this direction was the synthesis of a nickel(II)-cyclam-14 compound, the structure of which is noted below. The equilibrium constant for cyanide addition was measured spectrophotometrically at pH 7.4, and the results are as follows:

% Ni-[cyclam-14]	(Cyanide)	Log K
47.5	3.5 (E-05)	4.4
71.4	9.4 (E-05)	4.4
90.2	1.4 (E-03)	4.5

14.

Thus, for the reaction:

$$Ni-[cyclam-14]^{2+} \quad + \quad CN^- \quad = \quad Ni-[cyclam-14]-CN^+$$
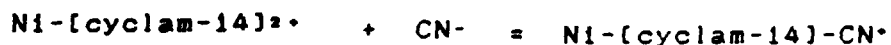
the equilibrium constant is K = 2.5 x 10(E+04), a sizeable effect. If the mM cyanide solution of the complex is allowed to stand for several days, the Ni(II) is removed from the ligand, forming the very stable tetracyanonickelate di-anion:

$$Ni-[cyclam-14]^{2+} + 4\ CN^- \quad = \quad Ni(CN)_4^{2-} \quad + \quad cyclam-14$$

It should be possible to vary the ring sizes of the cyclams and alter the central metal ion to favor immediate dissociation in the presence of cyanide. We will try this approach, and look at the cobalt(III)-sulfite derivative of cyclam, in which the sulfite should labilize the ligand trans to itself, and lead to mono-cyano formation. Such cobalt(III) complexes are substitution inert, and once complexed, the cyanide should be slow to be removed. We attempted this with a $[SO_3-Co(III)(NH_3)_5]^+$ complex, but had difficulty obtaining the pure species in reasonable amounts.
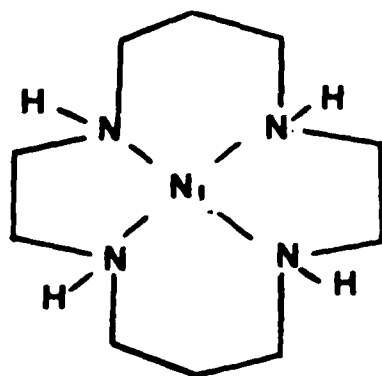
Nickel(II)-Cyclam-14

SCHIFF BASE COMPLEXES: The Schiff base complex below, bis(N,N-dimethylethane-1,2-diammine,2-hydroxy-4-methoxy-5-sulfonic acid benzophenimine)nickel(II) is water soluble. The cyanide electrode indicated an immediate uptake of four moles of cyanide per mole of ligand. The cyclams and porphyrins above have the metal ion in a macrocyclic circle of ligands, and removal of the metal is difficult in that little ligand deformation can occur during the deligation process. In contrast, the present Schiff base is formally a (ligand-metal-ligand) combination, and twisting and

removal of one ligand due to cyanide coordination can occur, followed by a stepwise dechelation of the second ligand. Some effort will be made to develop water soluble frameworks of this sort, that protect the metal ion from reaction, until cyanide is present.
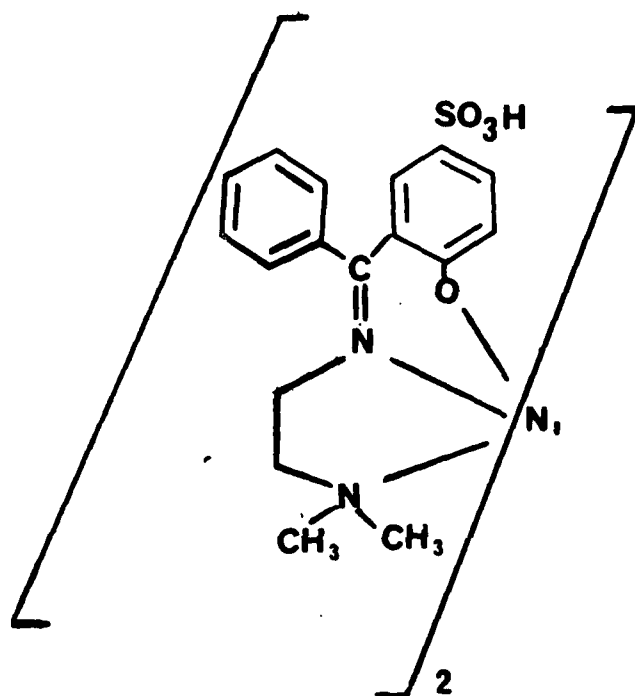
Nickel(II)-Schiff Base
Complex

16.

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Cyanide Scavengers: Kinetics of the Reaction of Rhodium(III)-Tetrakis(4-sulfonatophenyl)porphyrin with Cyanide and Hydrogen Cyanide. Peter Hambright and Robert Langley, Inorg. Chim. Acta, 1987, 137, 209.
[Contribution No. 1809 to the U.S. Army Drug Development Program].

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[Contribution No. xxxx to the U.S. Army Drug Development Program].

PROJECT PERSONNEL

Dr. Hambright worked part time the academic year 1987-1988 and full time summer, 1987. Ms. Shirleyanne Haye worked full time on this project, summer, 1987.

BINDING RATIO DATA

CN/LIGAND RATIO

(CN$^-$) × 10^{-4}

(ligand)

CH$_3$CHO

1 / 1

19.

$(SO_3(CHOH)_2SO_3)Na_2$

0.7/1

$(NH_4)_2RuCl_6$
1/1

$[Pd(NH_3)_4](NO_3)_2$
4/1

$[Ru(NH_3)_6]Cl_3$
1/1

$H[AuCl_4]$
3/1

4/1

10

6

2

CH₃   CH₃

N

CHO

0.06/1

1   2   3 mM

⊖O K⊕   ⊖O K⊕

O

O

O

0.15/1

1   2   3

E

CHO

N

O

8

4

0.82/1

.2   .6   1.0

⊖O K⊕   ⊖O K⊕

CN—C   C—CN

CN   O   CN

10

6

2

0.15/1

8

4

CH=N—OH

N

⊕CH₃ Cl⊖

0.12/1

1   2   3

10

6

2

CH₃

CH₃   CH₃

CHO

0.17/1
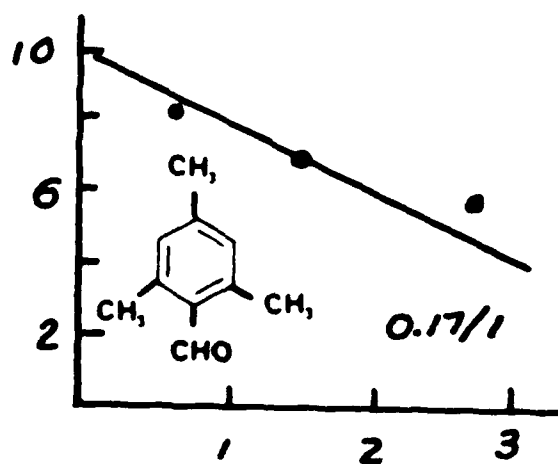
1   2   3
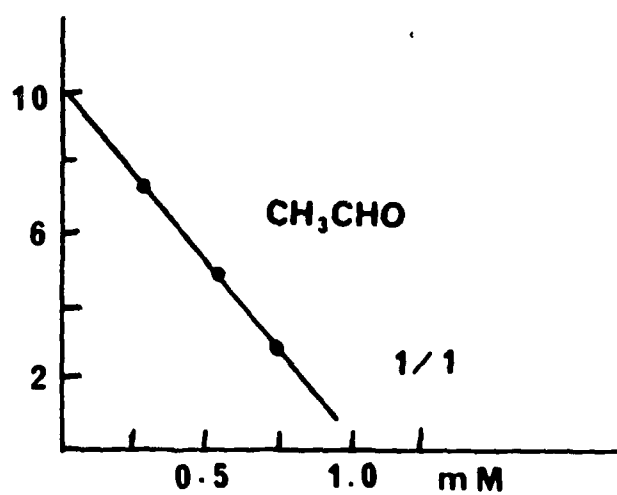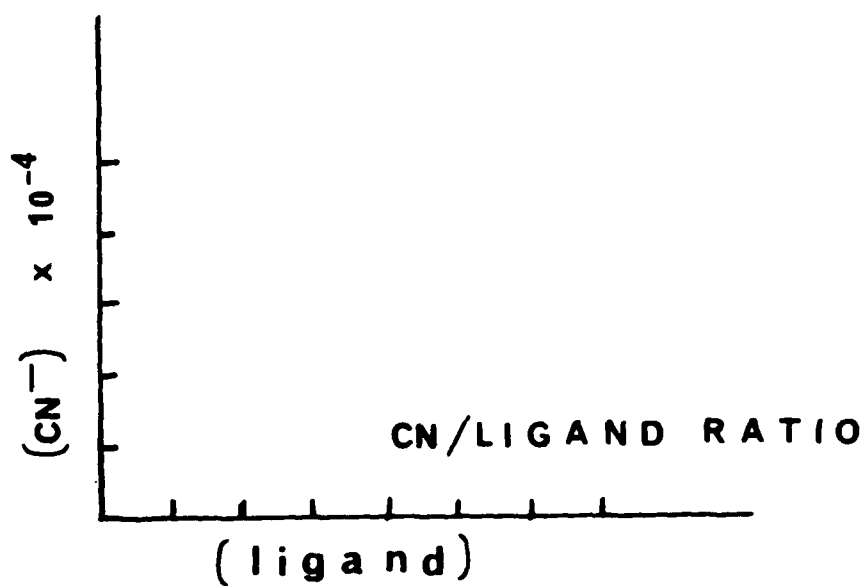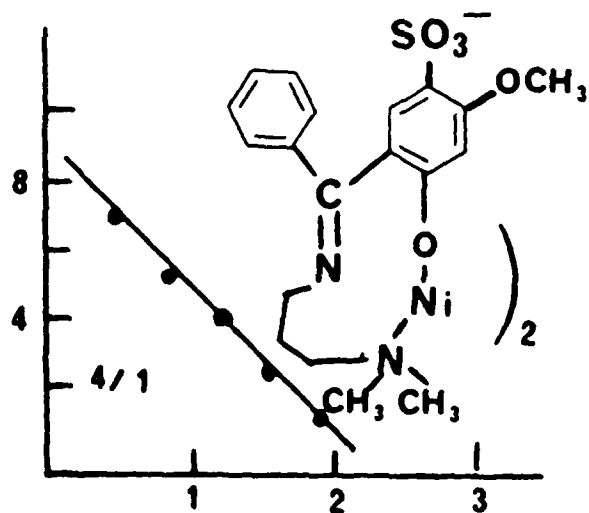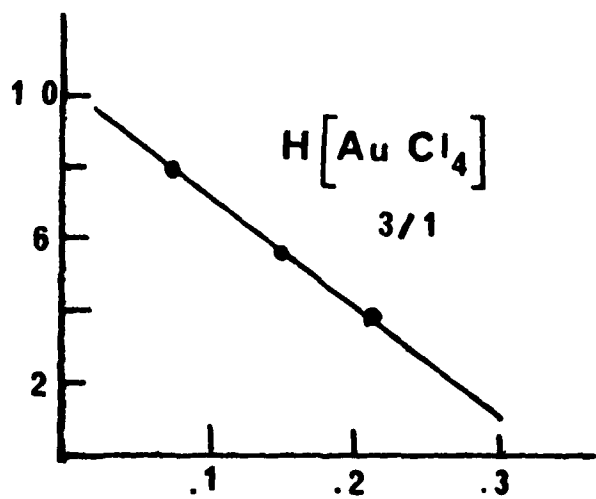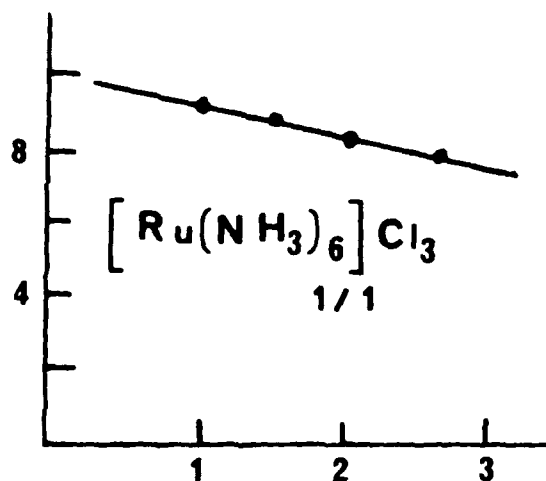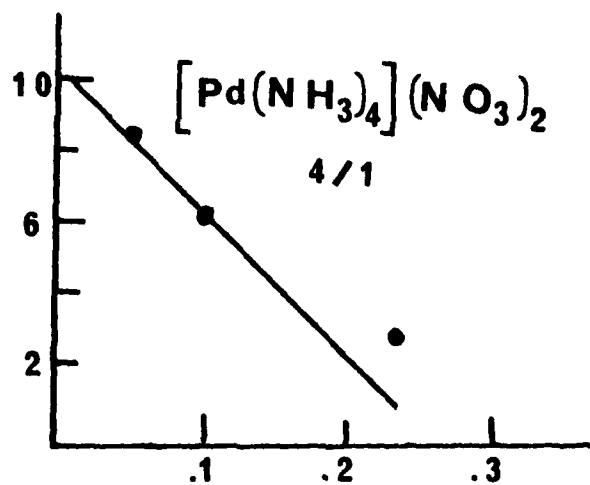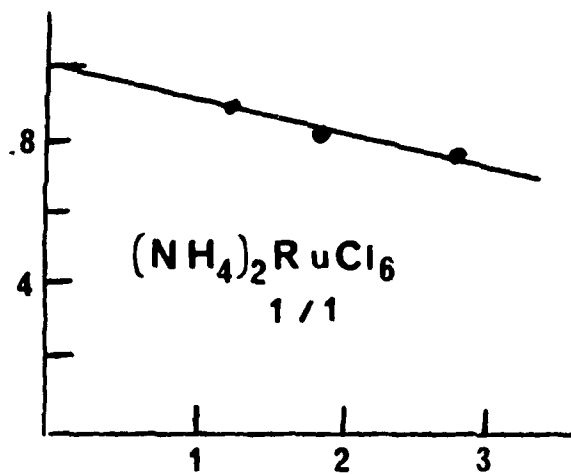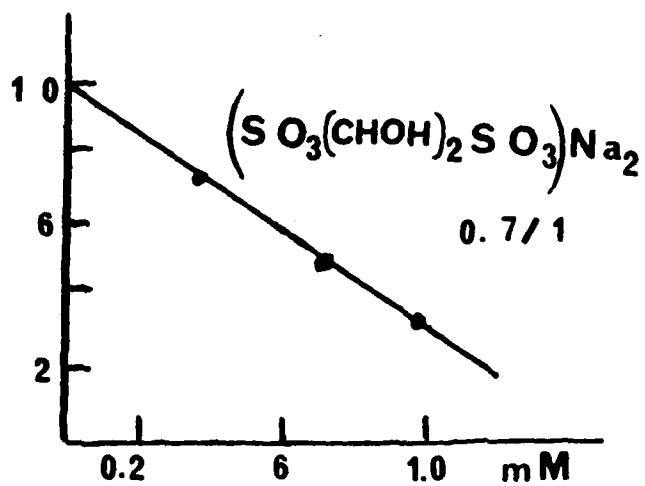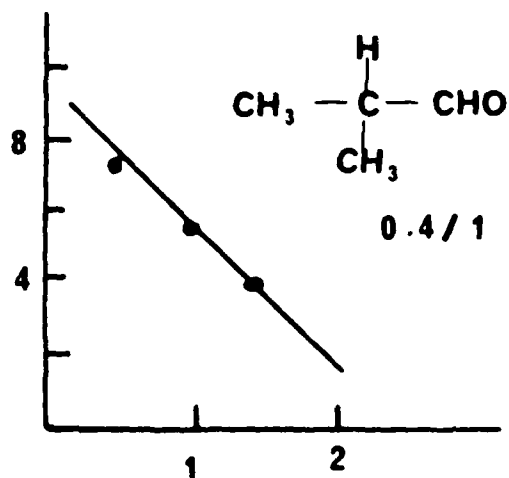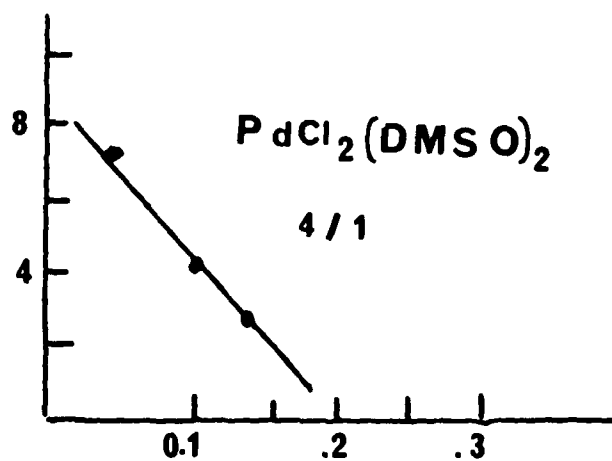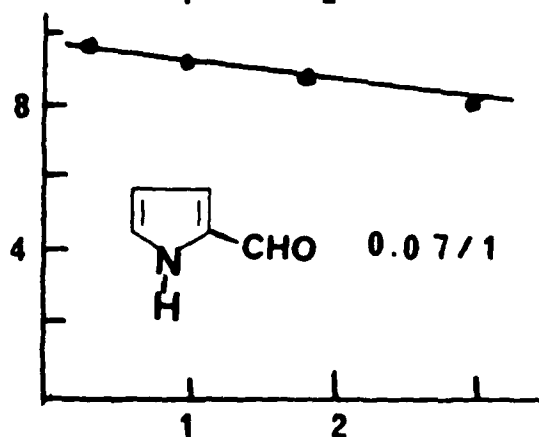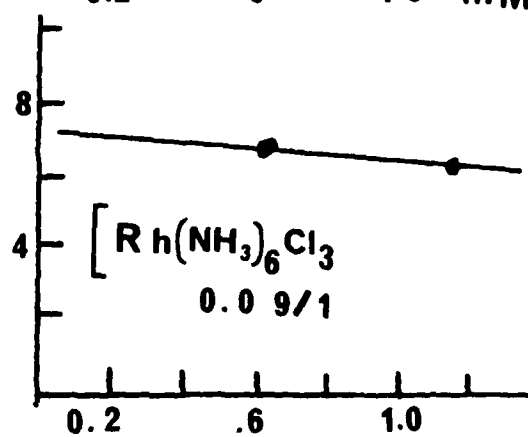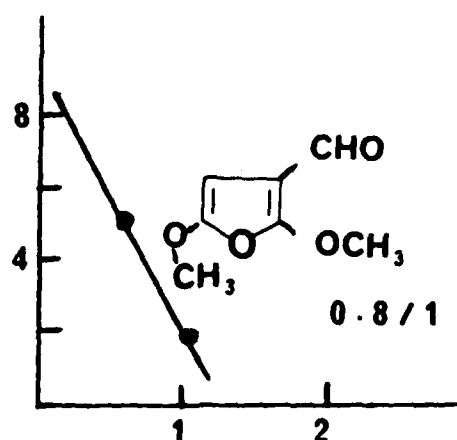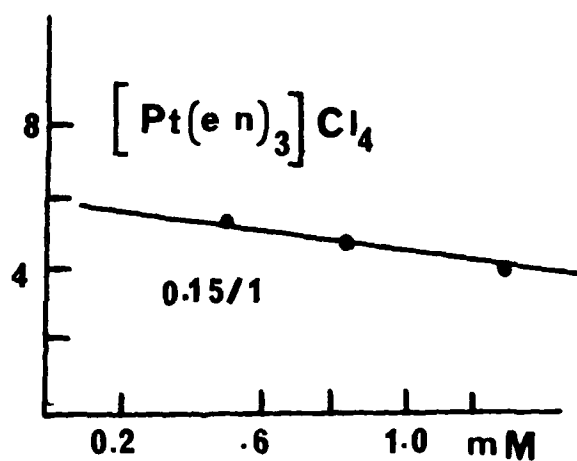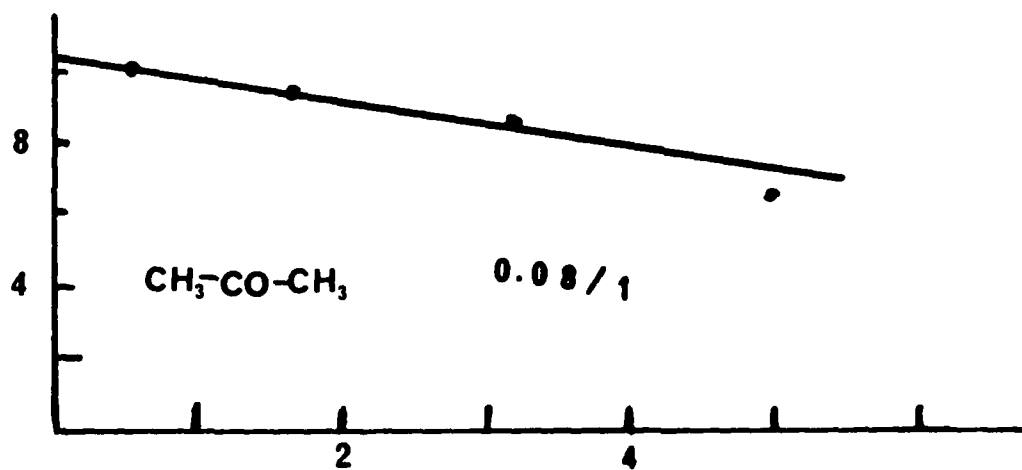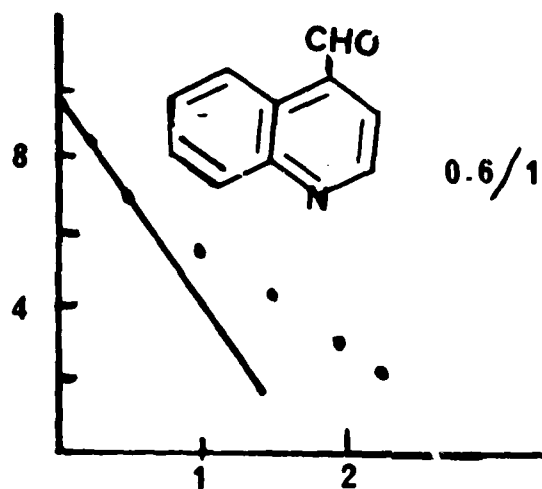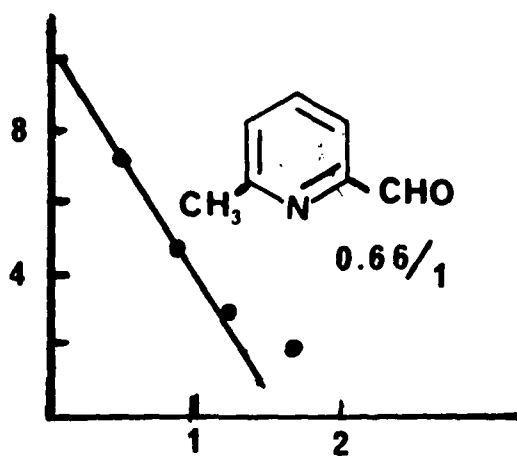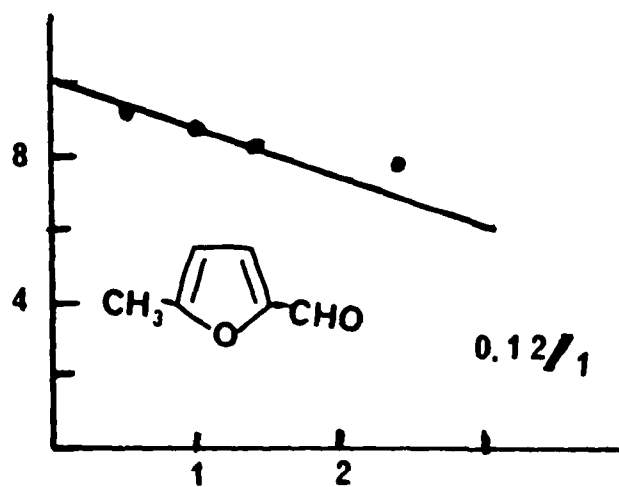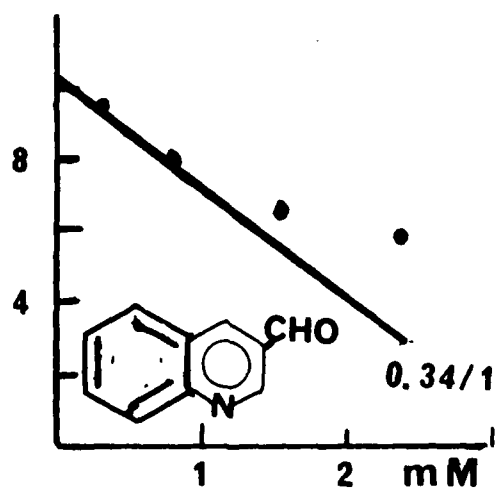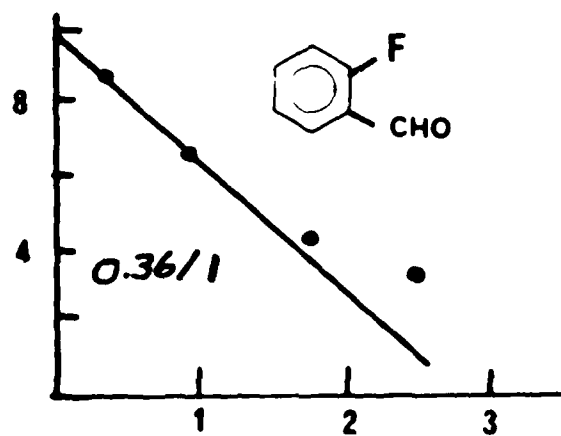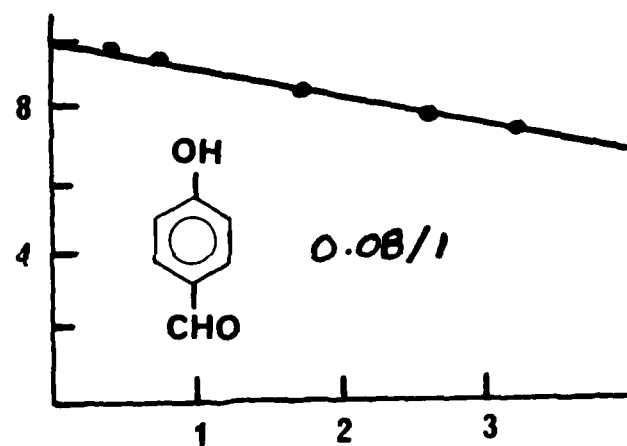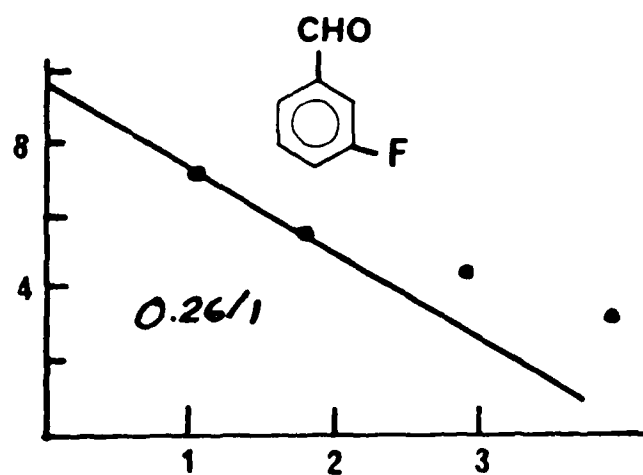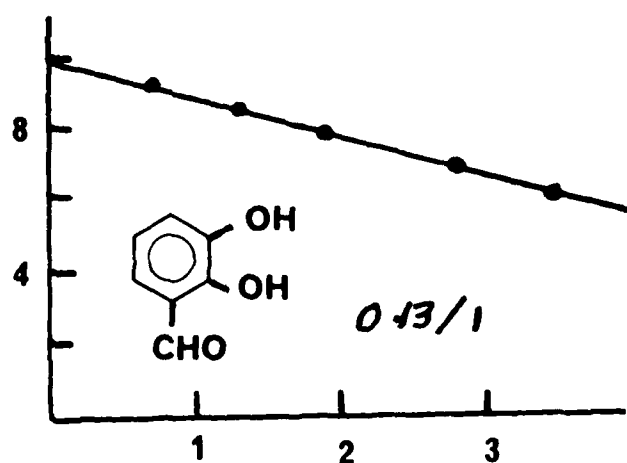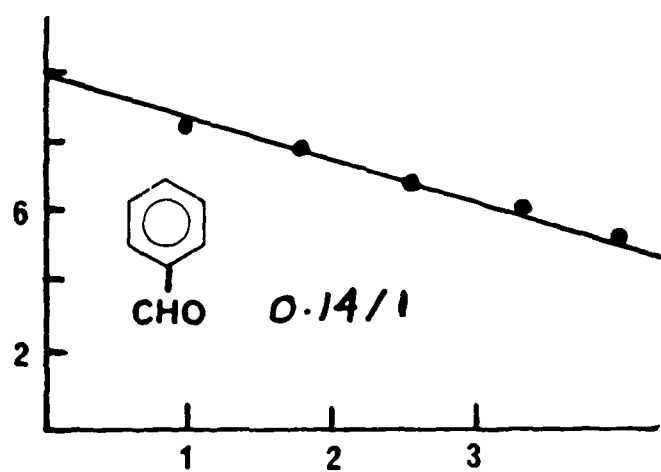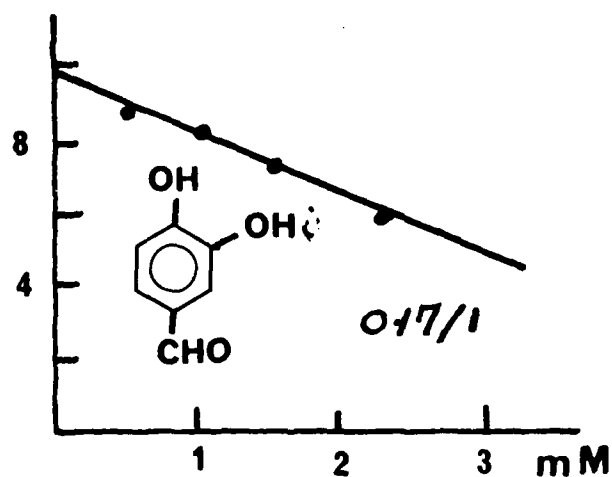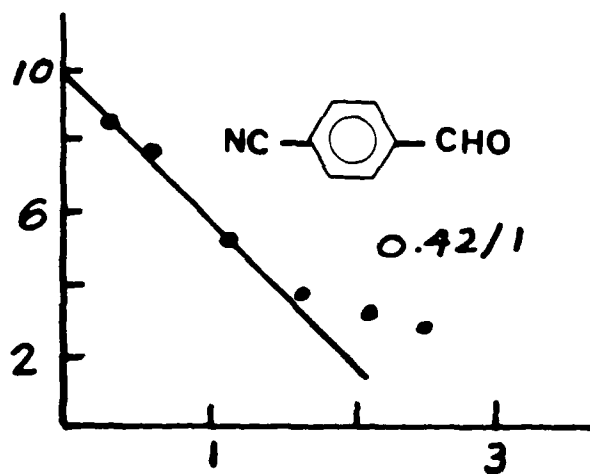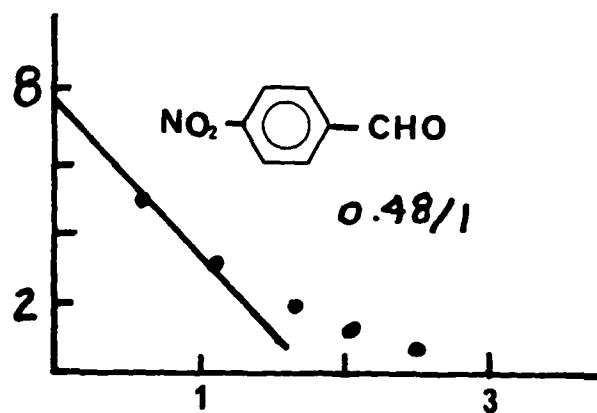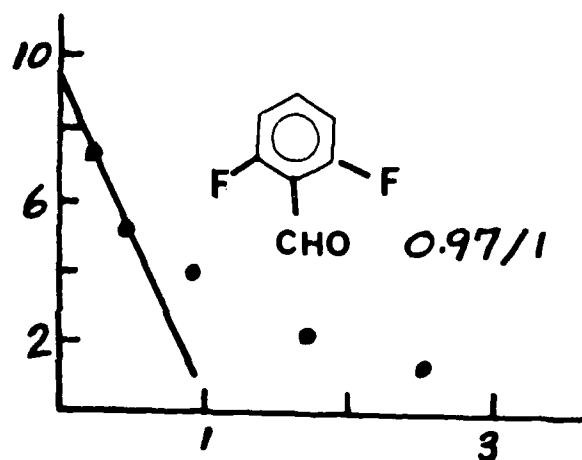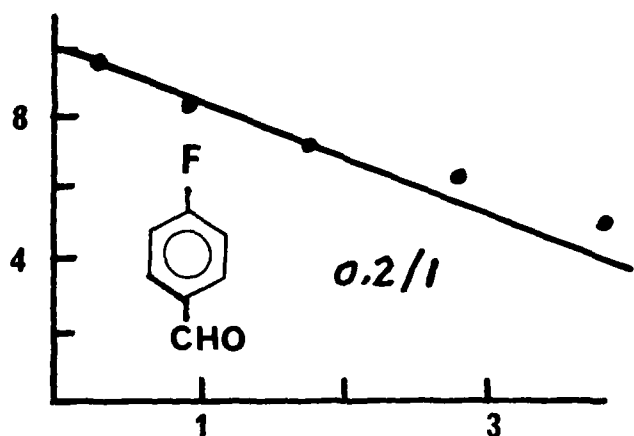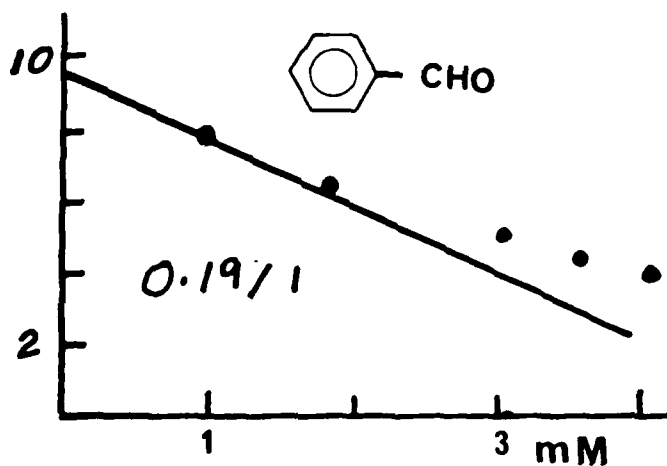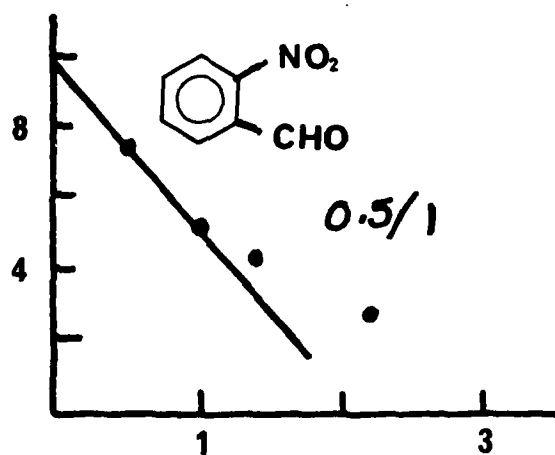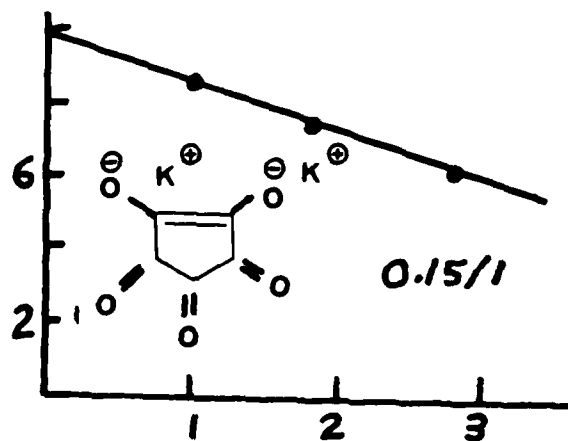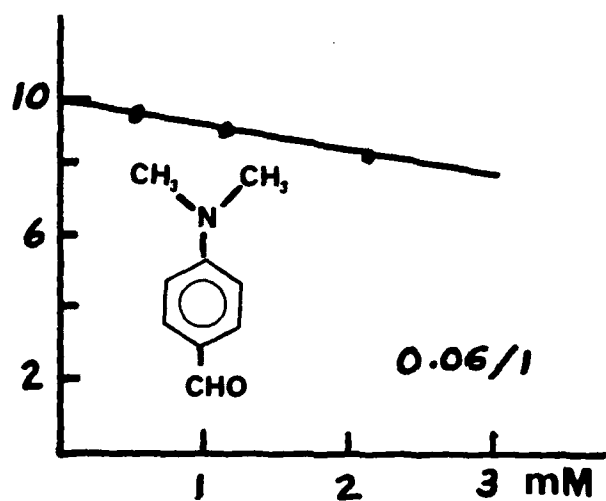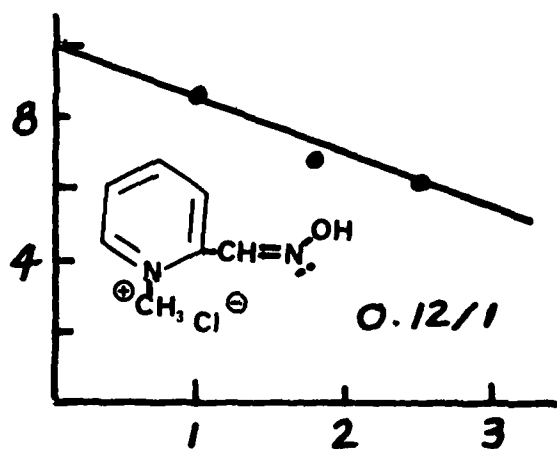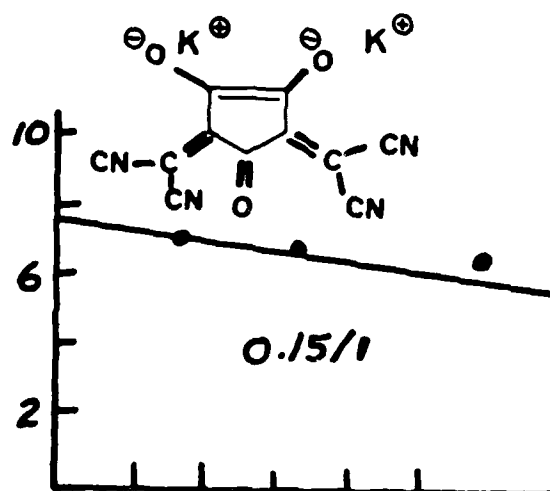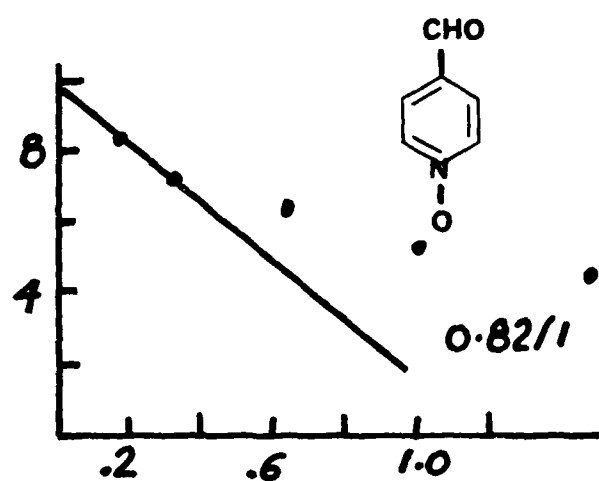
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