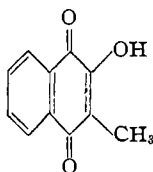


[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

Preparation and Properties of Some Phthiocol Inner Complexes¹BY BRADFORD P. GEYER² WITH GEORGE MCP. SMITH

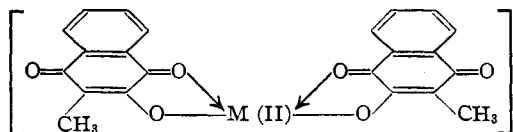
Synthesis of the Inner Complexes

Phthiocol is of interest because it possesses anti-hemorrhagic activity and is the yellow pigment of the human tubercle bacillus. In connection with studies on the relationship between the color and constitution of inner complexes, a series of these compounds was prepared from this *o*-hydroxyquinone, which has the following structural formula.



Some of the inner complexes, it was thought, might possibly prove to be of value from a therapeutic standpoint.

The cobalt(II), copper(II), iron(II), iron(III), magnesium, manganese(II), nickel(II), uranyl and zinc inner complexes of phthiocol were synthesized and obtained pure in crystalline condition. Because phthiocol is an *o*-hydroxyquinone,



it contains the chelating group C,C-O,OH,³ and the inner complexes of this pigment have the representative spiran-type structure, as illustrated, in the case of the four-coördinate, bivalent metal complexes, in which the metal is part of a five-membered ring system and is common to each quinone residue in the molecule.

The inner complexes of phthiocol described in this paper exhibited the characteristics of compounds of this type, being completely stable at temperatures up to 200°, insoluble in water and deeply colored. They were stable in the presence of weak acids, but were immediately decomposed with liberation of the free quinone by hydrochloric

(1) This paper represents an abstract from a portion of a thesis presented by Bradford P. Geyer to the University of Washington in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) Haendler and Geyer, *THIS JOURNAL*, **60**, 2813 (1938).

acid. Sodium hydroxide also decomposed these inner complexes with the formation of the deep-red alkali salt of phthiocol. At room temperature the compounds were insoluble in diethyl ether, acetone, methyl *n*-amyl ketone and chlorobenzene; partially soluble in methanol, *n*-butanol and nitrobenzene and quite soluble in dioxane, in which solvent decomposition apparently occurred. Prepared in methanol solution, the four-coördinate inner complexes, with the exception of copper and magnesium, all crystallized in a solvated condition. When heated to 150°, solvent was liberated and the unsolvated complex was formed with an accompanying change in color. The inner complexes, when first formed, invariably crystallized with a small amount of phthiocol as impurity. To secure them analytically pure, advantage was taken of the fact that the quinone could be removed by sublimation while the complex remained unchanged.

As far as we are aware, the iron(II) and iron(III) inner complexes of phthiocol are the first to have been prepared from an *o*-hydroxyquinone with the chelating group C,C-O,OH.

Experimental

Phthiocol used in this work was prepared by a method essentially that of Fieser,⁴ and formed fine, lemon-yellow needles, m. p. 172°.

For the purpose of correctly naming the inner complexes of phthiocol, this quinone will be referred to also as 3-methyl-1,4-naphthalenedione-2-ol.

All analyses were performed in a crucible furnace by direct combustion of the organic material and determination of the metal as oxide.

3-Methyl-1,4-naphthalenedione-2-olato-cobalt(II).—A cold, filtered solution of 0.25 g. of $\text{Co}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 4\text{H}_2\text{O}$ in 40 ml. of methanol was added to a cold, filtered solution of 0.40 g. of phthiocol, also in 40 ml. of methanol. The color of the liquid became violet-red, but no solid formed at once. Several minutes after mixing the solutions some solid began to appear. The mixture was allowed to stand at room temperature for three days, after which time it was filtered and the solid washed with ether. The solvated material, which then formed deep brownish-red needles, was air-dried. After heating at 184° for four hours in a drying pistol under the vacuum of an efficient water pump to remove any remaining excess free quinone by sublimation, the color of the crystals became violet-black. The unsolvated compound was obtained as fine, slender, violet-black needles; yield 0.35 g. (81%).

(4) Fieser, *J. Biol. Chem.*, **133**, 391 (1940).

Anal. Calcd. for $C_{22}H_{14}O_6Co$: Co, 13.6. Found: Co, 13.9.

3-Methyl-1,4-naphthalenedion-2-olato-copper(II).—A cold, filtered solution of 0.20 g. of $Cu(C_2H_3O_2)_2 \cdot H_2O$ in 40 ml. of methanol was added to 75 ml. of a cold, filtered methanol solution of 0.40 g. of phthiocol. The color of the liquid became dark red, and in a few minutes solid began to form. After standing at room temperature for three days, during which time the quantity of solid increased, the mixture was filtered and the brownish-violet crystals washed with ether. The substance was air-dried and then heated at 184° for four hours in a drying pistol under the vacuum of a water pump. The yield of fine, slender, deep-purple needles was 0.35 g. (80%).

Anal. Calcd. for $C_{22}H_{14}O_6Cu$: Cu, 14.5. Found: Cu, 14.5.

3-Methyl-1,4-naphthalenedion-2-olato-iron(II).—A cold, filtered solution of 0.27 g. of $FeSO_4 \cdot 7H_2O$ in 5 ml. of distilled water was admixed, without delay, to 30 ml. of a hot, filtered 70% aqueous methanol solution containing 0.40 g. of phthiocol. The yellow color of the latter solution turned deep purple without the formation of any solid, but upon the immediate addition of a solution of 0.27 g. of $NaC_2H_3O_2 \cdot 3H_2O$ in 5 ml. of distilled water, the complex began to form almost at once. It was filtered off *immediately* and freed from any quinone by washing repeatedly with cold ether. The solvated brownish-purple microcrystals with a metallic luster were then air-dried. After heating in a drying pistol immersed in an oil-bath at 230° for two hours under the vacuum of a water pump, the unsolvated inner complex was secured in the form of fine, slender, dark violet-black needles; yield 0.36 g. (84%).

Anal. Calcd. for $C_{22}H_{14}O_6Fe$: Fe, 13.0. Found: Fe, 13.0.

3-Methyl-1,4-naphthalenedion-2-olato-iron(III).—To a hot, filtered, clear solution of 0.57 g. of phthiocol in 70 ml. of 50% aqueous methanol, a cold, filtered solution of 0.27 g. of $FeCl_3 \cdot 6H_2O$ in 5 ml. of distilled water was added. The mixture, the color of which had darkened upon intermingling the above solutions, was placed in a refrigerator to cool and to allow the inner complex to crystallize. After two and a half hours at 10° , solid covered the bottom of the containing flask. Yellow needles of the quinone formed afterward also. After standing for sixteen hours at 10° , the reaction mixture was removed from the refrigerator, and the solid filtered off. The yellow quinone was removed by repeated washing with cold ether, leaving the complex as glistening, black crystals with a greenish surface luster. When dry, the compound was heated at 210° for six hours in a drying pistol under the vacuum of an aspirator. The complex then appeared as a black microcrystalline powder with a metallic luster; yield 0.26 g. (42%).

Anal. Calcd. for $C_{33}H_{21}O_9Fe$: Fe, 9.0. Found: Fe, 9.4.

3-Methyl-1,4-naphthalenedion-2-olato-magnesium.—A hot, filtered, saturated solution from 0.22 g. of $Mg(C_2H_3O_2)_2 \cdot 4H_2O$ and 30 ml. of methanol was added to a cold, filtered solution of 0.40 g. of phthiocol, likewise in 30 ml. of methanol. The liquid became deep red in color, but remained clear. When no crystals appeared after standing

in a refrigerator for four days, the solution was concentrated on the steam-bath to one-half its original volume. The mixture was again placed in the refrigerator, and material began to crystallize after several days. After fifteen days at 10° , the solid was filtered off and washed with ether, in which it appeared to be slightly soluble. The complex was air-dried and then heated for five and a half hours at 210° in a drying pistol under the vacuum of an aspirator. This compound formed deep reddish-brown-black crystals. The yield was 0.33 g. (83%).

Anal. Calcd. for $C_{22}H_{14}O_6Mg$: Mg, 6.1. Found: Mg, 6.4.

3-Methyl-1,4-naphthalenedion-2-olato-manganese(II).—To 50 ml. of a hot, clear, filtered, 50% aqueous methanol solution of 0.40 g. of phthiocol, 5 ml. of a cold, filtered solution of 0.25 g. of $Mn(C_2H_3O_2)_2 \cdot 4H_2O$ in distilled water was added. The color of the mixture became deep wine-red and some solid formed soon afterward. After standing overnight at 10° in a refrigerator, the crystalline material was filtered off and washed repeatedly with cold ether until free from admixed crystalline quinone. The solvated complex, when air-dried, formed glistening, short, fine, maroon needles. Upon being heated in a drying pistol inserted in an oil-bath at $200-205^\circ$ for one hour under the vacuum of a water pump, the inner complex was obtained in an unsolvated condition in the form of curved, narrow, black blades with a surface luster; yield 0.30 g. (70%).

Anal. Calcd. for $C_{22}H_{14}O_6Mn$: Mn, 12.8. Found: Mn, 13.0.

3-Methyl-1,4-naphthalenedion-2-olato-nickel(II).—A warm, filtered, saturated solution from 0.25 g. of $Ni(C_2H_3O_2)_2 \cdot 4H_2O$ and 30 ml. of methanol was mixed with a cold, filtered solution of 0.40 g. of phthiocol in 30 ml. of methanol. No immediate crystallization occurred from the resulting deep red-violet solution. The mixture was placed in the refrigerator, and after four hours, crystals began to form. After four days at 10° , the deep maroon-red, crystalline, solvated solid was removed from the mother liquor by filtration, and washed with cold ether in which it was somewhat soluble. It was air-dried and heated under the vacuum of the water-pump at 210° in a drying pistol for one and a half hours. The yield of unsolvated compound in the form of fine, slender, deep brown-violet needles was 0.25 g. (58%).

Anal. Calcd. for $C_{22}H_{14}O_6Ni$: Ni, 13.6. Found: Ni, 13.5.

3-Methyl-1,4-naphthalenedion-2-olato-uranyl.—To a cold, filtered solution of 0.40 g. of phthiocol in 55 ml. of methanol, 65 ml. of a cold, filtered methanol solution containing 0.42 g. of $UO_2(C_2H_3O_2)_2 \cdot 2H_2O$ was added. A deep red color developed, and after swirling the liquid for a short time, solid began to form. The mixture was allowed to stand at 10° overnight, and the crystalline material then filtered off and washed repeatedly with cold ether. When air-dried, the solvated compound was a dark reddish-brown microcrystalline powder. After being heated in a drying pistol immersed in an oil-bath at $200-210^\circ$ for one and a half hours under the vacuum of an aspirator, this inner complex formed unsolvated, dark violet-black microcrystals; yield 0.56 g. (87%).

Anal. Calcd. for $C_{22}H_{14}O_6U$: U, 37.0. Found: U, 36.9.

3-Methyl-1,4-naphthalenedion-2-olato-zinc.—A cold, filtered solution of 0.22 g. of $Zn(C_2H_3O_2)_2 \cdot 2H_2O$ in 5 ml. of distilled water was added to a hot, filtered solution of 0.40 g. of phthiocol in 50 ml. of 50% methanol. The color of the mixture became deep claret-red, and solid formed very soon after mixing the solutions. After standing overnight at 10°, the crystals were filtered off and purified by repeated washing with cold ether. The complex, in a solvated condition, then appeared as glistening, narrow, dark, reddish-brown blades, after being dried in the air. This material, when heated in a drying pistol in an oil-bath at 200° for one hour under the vacuum of a water pump, was transformed into the unsolvated compound in the form of dark violet-black blades; yield 0.38 g. (86.5%).

Anal. Calcd. for $C_{22}H_{14}O_6Zn$: Zn, 14.9. Found: Zn, 14.7.

Absorption Spectra of the Inner Complexes

The absorption of the inner complexes of phthiocol in the visible region of the spectrum was measured qualitatively. Curves were constructed for the copper(II) and iron(III) inner complexes, and for phthiocol itself, by plotting molar extinction coefficient *versus* wave length. These are shown in Fig. 1. The curves for the four-coordinate complexes are all similar in shape.

It appears that the formation of a four-coordinate inner complex from phthiocol gives rise to a marked absorption band in the blue-green region of the spectrum. The intensity of the absorption depends upon the metal present in the complex. In Table I the values of the wave lengths at which maximum absorption occurs and the corresponding molar extinction coefficients, in increasing order of magnitude, are tabulated.

TABLE I

PHTHIOL INNER COMPLEX ABSORPTION SPECTRA DATA			
Inner complex	ϵ	Max., $m\mu$	Atomic no. of metal
Mg	1520	490	12
UO ₂	1630	490	
Cu(II)	1830	490	29
Co(II)	2020	510	27
Ni(II)	2360	520	28
Zn	3625	500	30
Mn(II)	3790	500	25
Fe(II)	6500	470	26
Fe(III)	2220	410	26
	990	490	

From the data given in Table I it is evident that no regularity exists between the displacement of the maxima and any property of the metal in the complex, such as its atomic number or position in the periodic system. Since there is only a slight change in the position of the maxima, it is also apparent that the actual color of the complexes is

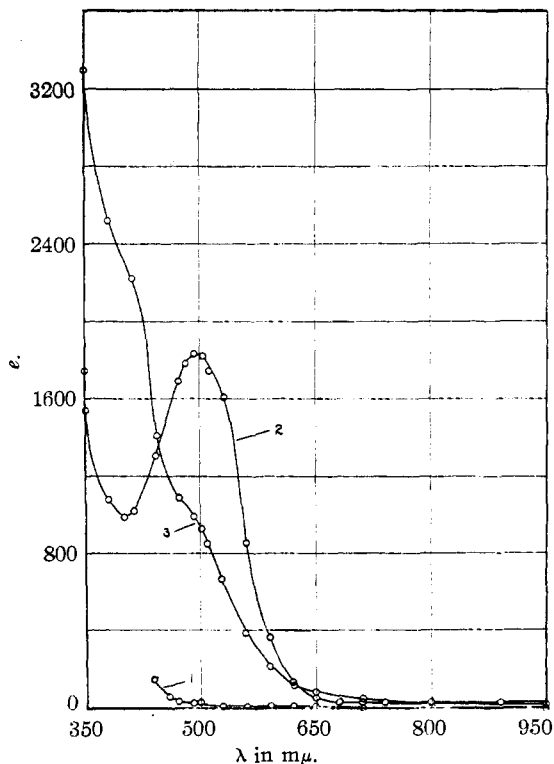


Fig. 1.—Absorption spectra of: (1) phthiocol, (2) phthiocol-Cu(II), (3) phthiocol-Fe(III).

due, not so much to the metal present, as it is to the chelation of phthiocol with the metal and inclusion of the latter in a spiran ring system. A similar conclusion has been reached in studies on the absorption spectra of *o*-quinone monoxime and *o*-hydroxy azo dye inner complexes.⁵

The iron(III) inner complex of phthiocol, being different from all the others in that it is six-coordinate, gives an absorption spectrum curve which exhibits two rather flat maxima, one in the violet and the other in the green-blue region of the spectrum.

Experimental⁶

A Coleman Regional Spectrophotometer was used to measure the absorption spectra of phthiocol and its inner complexes by determining, at definite wave lengths, the percentage transmission of the solutions compared to the pure solvent as a standard. No solvation of the inner complexes was found to occur in *n*-butanol, and this alcohol was therefore employed as the solvent in every case. Because the compounds were so insoluble, even in *n*-butanol, saturated solutions had to be used when measuring the spectra. Upon taking

(5) Haendler with Smith, *THIS JOURNAL*, **62**, 1669 (1940).

(6) With H. M. Haendler,

an aliquot afterward and determining the amount of complex therein by weighing the solid after removal of the solvent, the concentrations of the solutions used were found to range from 0.00007 to 0.00027 *M*. The values of the molar extinction coefficients were calculated with the aid of Beer's law.

Catalytic Behavior of the Inner Complexes

Hemin,⁷ salicylaldehyde-ethylenediimine iron(III) chloride and related compounds,⁸ iron(II) and chloroiron phthalocyanines⁹ and iron chlorophyll derivatives¹⁰ have been observed to catalyze the chemiluminescence of luminol (3-aminophthalhydrazide). These substances are all iron inner complexes in which the metal is coordinated with nitrogen atoms.

In *o*-hydroxyquinone inner complexes the metal is coordinated with oxygen atoms. Since phthiocol has been shown¹¹ to be the oxidant of a reversible oxidation-reduction system, the potential of which is among the lowest reported for biologically occurring systems, and since iron plays an important rôle in biological oxidation processes, it appeared of merit to test the iron(II) and iron(III) inner complexes of phthiocol for catalytic activity in the chemiluminescent oxidation of luminol by hydrogen peroxide.

These iron(II) and iron(III) complexes, indeed, produced a luminescence of much greater intensity than that of a control. The intensity of light produced by each of the iron complexes was about the same, but the duration of the luminescence in the case of the iron(II) compound was more than twice that with the iron(III) complex, being three hours with the former and one and a quarter hours with the latter. Contrary to all expectations, however, the catalytic activity of the iron compounds was surpassed by that of the cobalt(II) and copper(II) inner complexes of phthiocol, cobalt being extremely active. The copper(II) compound produced a luminescence much stronger in intensity than iron(II) and (III), while the cobalt(II) complex caused an emission of intense blue-violet light which lasted for three hours and which was much brighter than that produced by any other of the inner complexes of phthiocol. It was found that the addition of ethanol to the test mixture imparted greater solubility to the cobalt(II) com-

plex, thereby causing the production of a brilliant blue-violet luminescence, visible at the start in a dimly lighted room, and by which in a dark room the time could be read from a watch with a non-luminous dial. In contrast with the cobalt(II) compound in the absence of ethanol, the light caused by the cobalt(II) complex when ethanol was added, although much stronger in intensity, diminished more rapidly and lasted for only one hour. The nickel(II) and manganese(II) inner complexes of phthiocol were found also to produce a weak luminescence in the oxidation of luminol, that is to say, the light emitted was stronger than that from the control. The magnesium, uranyl and zinc complexes produced little or no luminescence. The experimental results describing the catalytic action of the phthiocol inner complexes are given in Table II.

TABLE II
CHEMILUMINESCENCE DATA FOR PHTHIACOL INNER COMPLEXES

Inner complex	Intensity of light in absence of C ₂ H ₅ OH	Intensity of light in presence of C ₂ H ₅ OH	Color of light	Duration of light, hr.
Co(II)	Very strong		Bluish Violet-white	3
Co(II)		Brilliant	Blue-violet	1
Cu(II)	Strong		Bluish-white	2
Cu(II)		Strong	Bluish-white	Weak after 1.5
Fe(II)	Medium		White	Weak after 3
Fe(II)		Medium	White	Weak after 1.5
Fe(III)	Medium		White	1.25
Mg	None	Barely discernible	White	
Mn(II)	Weak	Weak	White	Diminishes rapidly
Ni(II)	Weak	Weak	White	
UO ₂	Discernible		White	
Zn	None	Discernible	White	

The results obtained are surprising and remarkable because this is the first case in which a copper inner complex has been found to be more active than iron and in which a cobalt inner complex of any kind has exhibited catalytic activity in the chemiluminescent oxidation of luminol. The order of effectiveness of the complexes in producing light is: Co(II) > Cu(II) > Fe(II) > Fe(III) > Ni(II) > Mn(II).

As has been shown with iron pigments of the phthalocyanine type,⁹ this catalytic activity of the inner complexes of phthiocol in the oxidation of luminol has its origin in the metal atom and in the inner complex linkage of the metal to the rest of the molecule. To substantiate this, it was found that the free hydroxyquinone, itself, was inactive, and also that the addition of a minute amount of ionizable cobalt(II) nitrate, alone, to the test solution caused only a momentary emission of

(7) Tamamushi, *Naturwissenschaften*, **25**, 318 (1937).

(8) Thielert and Pfeiffer, *Ber.*, **71**, 1399 (1938).

(9) Cook, *J. Chem. Soc.*, 1845 (1938).

(10) Schneider, *THIS JOURNAL*, **63**, 1477 (1941).

(11) Ball, *J. Biol. Chem.*, **106**, 515 (1934).

intense blue-violet light. Also, when cobalt(II) nitrate was added to a test solution containing phthiocol alone, there appeared only a very brief brilliant luminescence which was evidently due to the presence of the ionized salt. Then, too, the light from a brightly glowing test mixture, containing the cobalt(II) complex of phthiocol, was quenched, almost immediately, with the introduction of cobalt(II) nitrate.

The addition of ethanol to the test mixtures caused the complexes to be more soluble therein, and thus gave rise to the production of light of greater intensity. Ethanol alone had no effect upon the luminescence of the control. It would appear from the experimental findings, therefore, that solubility does play some part in the catalysis of chemiluminescence. Those inner complexes which are more readily soluble in the reaction mixture produce greater luminosity. When ethanol is added, the catalytic action is accelerated, as may be observed from the data in Table II. Coupled with the effect of solubility, there is also the factor of stability. The cobalt(II) and copper(II) inner complexes of phthiocol are quite stable, and their catalytic action is rather persistent. On this basis, it would seem that a combination of solubility and stability plays an important rôle in determining the effectiveness of the catalytic activity of an inner complex of phthiocol in the chemiluminescent oxidation of luminol.

It is noteworthy that those complexes containing metals adjacent to or in the first transition series of the periodic table, and having variable valency, are the most active. In this catalysis of chemiluminescence it may be possible that the metal functions as an oxygen-carrier.

Experimental

According to the procedure of Cook,⁹ the control used in the chemiluminescence experiments was a mixture of 10 ml. of a 0.1% solution of 3-aminophthalhydrazide in 0.1% aqueous sodium hydroxide and 3 ml. of a 0.3% solution of hydrogen

peroxide in water. To determine the catalytic activity of an inner complex, approximately 1 mg. of the solid compound was added to an identical sample of the control mixture. The luminescence from the control was designated as discernible. In every case, the intensity of light produced was referred to that of the control, which served as a standard.

In the experiments made to observe the effect solubility upon the catalysis, 1 ml. of 95% ethanol was added to the test mixture, and the luminosity compared with that of the control, to which also 1 ml. of 95% ethanol was added.

In the future, it is hoped that a prospective X-ray study of the crystallographic structure of these phthiocol inner complexes can be undertaken in this Laboratory.

Summary

The preparation and properties of cobalt(II), copper(II), iron(II), iron(III), magnesium, manganese(II), nickel(II), uranyl and zinc inner complexes of phthiocol have been described.

The absorption spectra of these inner complexes in *n*-butanol solution have been determined in the visual region of the spectrum.

The actual color of these inner complexes is due to the chelation of the quinone with the metal.

Certain inner complexes of phthiocol exhibit catalytic activity in the chemiluminescent oxidation of luminol by hydrogen peroxide.

The order of effectiveness of the inner complexes in the catalysis of chemiluminescence is: Co(II) > Cu(II) > Fe(II) > Fe(III) > Ni(II) > Mn(II).

This catalytic behavior of the inner complexes has its origin in the metal atom present and in the chelate linkage of this atom to the rest of the molecule.

The effectiveness of the catalytic action of an inner complex of phthiocol in the chemiluminescent oxidation of luminol would appear to be governed by the factors of solubility and stability.

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