# Bis(triphenylphosphine)copper(I) Complexes of Orotate and L-Dihydroorotate

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## Introduction

Orotic acid derivatives and their complexes with metal ions have recently been investigated by several research groups.[1] The importance of orotic acid as a metal ion carrier and as a precursor in the biosynthesis of the pyrimidine nucleotides of DNA has spawned this interest. The pathway of the biosynthesis of thymidine and cytosine proceeds through the function of several enzymes that have active sites containing various metal ions. For instance, the enzyme dihydroorotase which cyclizes the *N*-carbamyl-L-aspartase unit to form dihydroorotic acid has an active site containing Zn,[2] and investigations of the binding of Zn to dihydroorotic acid have recently been published by two research groups.[3,4] Another example of an enzyme along the biosynthetic pathway of orotic acid that contains a metal at the active site is that of dihydroorotate dehydrogenase. A recently obtained crystal structure of this enzyme by Nielsen and co-workers has shown that this enzyme contains an iron−sulfur cluster as a cofactor.[5] In addition to the importance of metal complexes of orotic acid derivatives in the biosynthesis of pyrimidine nucleotides, some other metal complexes have been found to show significant anticancer activity.[6] Alternative studies reported from our laboratories have examined the binding of orotate and dihydroorotate derivatives in organometallic derivatives, namely, group 6 metal carbonyls.[7] These studies have demonstrated that the chelated, deprotonated nitrogen of the uracil ring can exhibit significant $\pi$-donating capability and thus greatly enhance CO lability in these metal carbonyl complexes.[8] Yet, despite the obvious importance of metal complexes of orotic acid and its derivatives, their coordination chemistry heretofore has been relatively underexplored.

As a further study into the various binding modes of orotic acid derivatives with metals, we describe in this communication the synthesis of a bis(triphenylphosphine)copper(I) orotate complex, as well as a bis(triphenylphosphine)copper(I) dihydroorotate complex and examine their crystal structures. These compounds are the first examples of orotic acid derivatives of copper in the +1 oxidation state. Copper(I) is isoelectronic with the biologically more relevant zinc(II) species, and this study provides the first structural data of complexes containing the same $d^{10}$ metal fragment bound separately to the orotate and dihydroorotate ligands.

## Experimental Section

**Materials and Methods.** All manipulations were performed on a double-manifold Schlenk vacuum line under an atmosphere of argon or in an argon-filled glovebox. All of the solvents used were dried and deoxygenated by distillation from the appropriate reagent under a nitrogen atmosphere. Infrared spectra were collected on a Matteson 6022 spectrometer with DTGS and MCT detectors in a 0.10-mm $CaF_2$ cell. Copper(I) acetate and copper(I) bis(triphenylphosphine) acetate were prepared according to previously reported methods.[9] Orotic acid monohydrate was purchased from Aldrich Chemical and used without further purification. Triphenylphosphine was purchased from Lancaster Synthesis, Inc., and used without further purification. L-Dihydroorotic acid was purchased from Sigma Chemical and used as received. Microanalyses were performed by Canadian Microanalytical Service, Ltd. (Delta, B.C., Canada).

**Synthesis of Cu(I) Bis(triphenylphosphine) Orotate, 1.** The synthesis of **1** was accomplished in yields in excess of 80% by the reaction of 1 equiv of Cu(I) bis(triphenylphosphine) acetate with 1 equiv of the orotic acid monohydrate in a 1:1 THF/methanol mixture. This affords a greenish-yellow solution from which the solvent is removed, leaving behind a pale greenish-yellow powder. Crystals of **1** were obtained via slow diffusion of diethyl ether into the THF/methanol solution of **1** at −10 °C. Anal. Calcd for $Cu(PC_{18}H_{15})_2(C_5H_3N_2O_4)\cdot MeOH$ [$C_{42}H_{37}P_2N_2O_5Cu$]: C, 65.07; H, 4.81; N, 3.61. Found: C, 64.67; H, 4.82; N, 3.62.

**Synthesis of Cu(I) Bis(triphenylphosphine) Dihydroorotate, 2.** The synthesis of **2** was accomplished in yields in excess of 80% by the reaction of 1 equiv of Cu(I) bis(triphenylphosphine) acetate with 1 equiv of L-dihydroorotic acid in 30 mL of methanol. The resulting product is a clear, nearly colorless solution from which the solvent is removed, leaving behind an off-white powder. Crystals of **2** were obtained by concentrating the reaction solution to 5 mL and refrigerating at 10 °C overnight. Anal. Calcd. for $Cu(PC_{18}H_{15})_2(C_5H_5N_2O_4)\cdot MeOH$ [$C_{42}H_{39}P_2N_2O_5Cu$]: C, 64.90; H, 5.06; N, 3.60. Found: C, 64.37; H, 4.99; N, 3.64.

**X-ray Crystallography of 1 and 2. $Cu(PPh_3)_2$(orotate), 1.** Crystal data and the details of data collection for **1** are given in Table 1. A pale green block of **1** was mounted on glass fibers with epoxy cement at room temperature and then cooled in a liquid-nitrogen cold stream. X-ray diffraction data were collected on a Rigaku AFC5R X-ray diffractometer (Cu K$\alpha$, $\lambda$ = 1.541 78 Å radiation). Cell parameters were calculated from the least-squares fitting of the setting angles for 24 reflections. Data were collected for $3.58° < \theta < 50.00°$. Three control reflections, collected for every 97 reflections, showed no significant trends. Lorentz and polarization corrections were applied to 1895 reflections, and a total of 1766 unique reflections were used in further calculations. The structure was solved by direct methods [SHELXS program package, Sheldrick (1993)], and an empirical absorption correction was applied (difabs). Full-matrix least-squares anisotropic refinement for all non-hydrogen atoms yielded $R = 0.0956$, $R_w = 0.2090$, and $S = 0.980$ for **1**. Hydrogen atoms were placed in

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**Table 1.** Crystallographic Data for Complexes 1

| | 1 | 2 |
|---|---|---|
| empirical formula | $C_{42}H_{37}CuN_2O_5P_2$ | $C_{42}H_{39}CuN_2O_5P_2$ |
| FW | 775.27 | 777.23 |
| space group | $P2_1$ | $P2_1$ |
| $V$, Å$^3$ | 1836.0(6) | 3702(2) |
| $Z$ | 2 | 4 |
| $d_{calc}$, g/cm$^3$ | 1.390 | 1.395 |
| $a$, Å | 10.088(2) | 14.750(3) |
| $b$, Å | 14.727(3) | 14.846(6) |
| $c$, Å | 12.562(3) | 17.382(2) |
| $\alpha$, deg | 90 | 90 |
| $\beta$, deg | 100.34(3) | 103.452(11) |
| $\gamma$, deg | 90 | 90 |
| $T$, K | 191(2) | 191(2) |
| $\mu$[Cu K$\alpha$(1), Mo K$\alpha$(2)], mm$^{-1}$ | 2.058 | 0.725 |
| wavelength, Å | 1.54178 | 0.71073 |
| $R_F$,[a] % | 9.56 | 5.75 |
| $R_{wF}$,[b] % | 20.90 | 14.30 |

[a] $R_F = \sum|F_o - F_c|/\sum F_o$. [b] $R_{wF} = \{[\sum w(F_o^2 - F_c^2)^2]/(\sum wF_o^2)\}^{1/2}$.

idealized positions with isotropic thermal parameters fixed at 0.08. Neutral atom scattering factors and anomalous scattering correction terms were taken from *International Tables for X-ray Crystallography*.

**Cu(PPh$_3$)$_2$(dihydroorotate), 2.** Crystal data and the details of data collection for **2** are given in Table 1. A colorless block of **2** was mounted on glass fibers with epoxy cement at room temperature and then cooled in a liquid-nitrogen cold stream. X-ray diffraction data were collected on a Siemens P-4 X-ray diffractometer (Mo K$\alpha$, $\lambda$ = 0.710 73 Å radiation). Cell parameters were calculated from the least-squares fitting of the setting angles for 24 reflections. Data were collected for $2.06° < \theta < 30.01°$. Three control reflections, collected for every 97 reflections, showed no significant trends. Lorentz and polarization corrections were applied to 11 568 reflections, and a total of 11 181 unique reflections were used in further calculations. The structure was solved by direct methods [SHELXS program package, Sheldrick (1993)], and an empirical absorption correction was applied (difabs). Full-matrix least-squares anisotropic refinement for all non-hydrogen atoms yielded $R = 0.0575$, $R_w = 0.1430$, and $S = 1.017$ for **2**. Hydrogen atoms were placed in idealized positions with isotropic thermal parameters fixed at 0.08. Neutral atom scattering factors and anomalous scattering correction terms were taken from *International Tables for X-ray Crystallography*.

## Results and Discussion

**Synthesis and Spectral and Structural Characterization of Cu(PPh$_3$)$_2$(orotate) and Cu(PPh$_3$)$_2$(dihydroorotate).** The title complexes were synthesized in greater than 80% yield by the reaction of the appropriate acid with Cu(I)(PPh$_3$)$_2$(acetate). The driving force for the reaction depicted in Scheme 1 is the formation of acetic acid, which has a higher p$K_a$ (4.75) than that of the carboxylic acid proton of either orotic acid (2.07)[10] or dihydroorotic acid.

The product obtained in the reaction of orotic acid monohydrate is insoluble and usually precipitates out of the methanol/THF mixture within 5 min. However, with the appropriate concentrations of reactants crystals suitable for single-crystal X-ray diffraction can be grown by the slow diffusion of diethyl ether into the methanol/THF mixture at −10 °C. It should be noted that although the crystals were suitable for X-ray analysis, the overall quality of the crystals was poor. L-dihydroorotic acid is more soluble in methanol than orotic acid, and the product of the corresponding reaction depicted in Scheme 1 for L-dihydroorotic acid remains in solution in methanol for up to 30 min. Concentration of this solution and cooling to 10 °C affords suitable crystals for single-crystal X-ray diffraction. The infrared spectrum of complex **1** (KBr) exhibits four bands in the ketone/carboxylate region. This four-band pattern at 1692, 1666, 1635, and 1354 cm$^{-1}$ for the metal-bound orotic acid species is assigned to the $\nu$(CO)$_{asym}$ and $\nu$(CO)$_{sym}$ (1692 and 1354 cm$^{-1}$) of the carboxylate ligand and the $\nu$(CO) stretches (1666 and 1635 cm$^{-1}$) of the carbonyl groups of the uracil ring. These latter assignments are consistent with the corresponding $\nu$(CO) vibrational modes observed in uracilate derivatives.[7] The infrared spectrum of complex **2** (KBr) exhibits a similar pattern with stretches at 1690, 1622, 1609, and 1391 cm$^{-1}$. These stretches also can be assigned to the $\nu$(CO)$_{asym}$ and $\nu$(CO)$_{sym}$ (1690 and 1391 cm$^{-1}$) of the carboxylate ligand and the $\nu$(CO) stretches (1622 and 1609 cm$^{-1}$) of the carbonyl groups of the ring.

The structure of complex **1** was determined by X-ray crystallography, and a thermal ellipsoid drawing of the complex is provided in Figure 1. The complex consists of an orotate residue bound monodentate through one of its carboxylate oxygens to the metal center. As seen in other orotate complexes,[11] the pyrimidine ring deviates from planarity by only 0.0255 Å. This is consistent with the pseudoaromatic nature of the uracil ring. The Cu(1)−O(1) bond distance is a bit shorter than that of a typical Cu(I) bis(triphenylphosphine) carboxylate complex at 2.08(2) Å. Healy and co-workers have summarized their work and work done in our laboratories with a comparison of bond distances in 15 different monocarboxylate copper(I) bis(triphenylphosphine) complexes.[9,12,13] Among the monocarboxylate complexes, the Cu−O bond distance ranges from 2.051(3) to 2.244(7) Å with the average at 2.151 Å. The Cu−P distances reported by Healy in these complexes range from 2.219(2) to 2.267(5) Å with the average at 2.237 Å. The Cu(1)−P(1) and the Cu(1)−P(1a) bond distances in complex **1** at 2.255(6) and 2.257(8) Å, respectively, are well within that range. Another important comparison that we can make to other monocarboxylate complexes is the metal to distal oxygen distance. This distance ranges from 2.205(2) to 2.643(3) Å in other monocarboxylates, but in complex **1**, we observe no interaction of the metal center with the distal oxygen at a distance of 3.33(3) Å. The geometry at the metal center can best be described as a distorted tetrahedron. The Cu lies out of the plane formed by the two phosphorus atoms and the carboxylate oxygen by 0.5617 Å. This tetrahedral distortion arises from the rather strong interaction of the metal center with one of the exocyclic oxygens on the orotate residue in a neighboring unit cell at a distance of 2.28(2) Å. This interaction coupled with the hydrogen bonding from the methanol solvate as shown in Figure 2 explains why the complex is insoluble in most solvent systems. The insolubility of the compounds precludes further solution state characterization. This exocyclic oxygen interaction also explains the unusually long distance from the metal center to the distal carboxylate oxygen. In the solid state, the copper atom has a full coordination sphere by virtue of its interaction with the two phosphines, the orotate's carboxylate oxygen, and the exocyclic oxygen on a neighboring orotate.

The X-ray structure of complex **2**, which is shown in Figure 3, reveals characteristics similar to those observed in complex **1**, with some minor deviations. One notable difference in the structures is puckering of the uracil ring in complex **2**. This is

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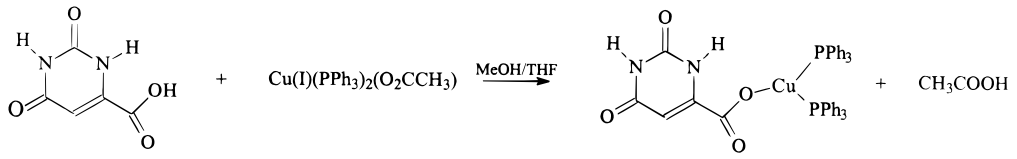
**Scheme 1**



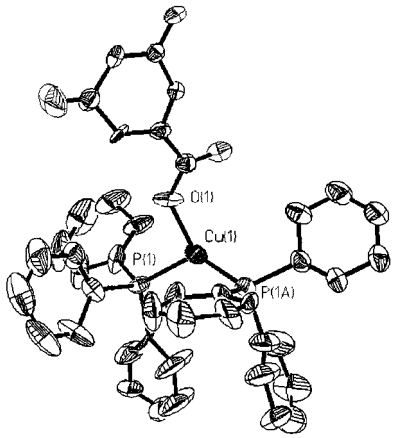




**Figure 1.** Molecular structure of **1** with thermal ellipsoids at 50% probability.

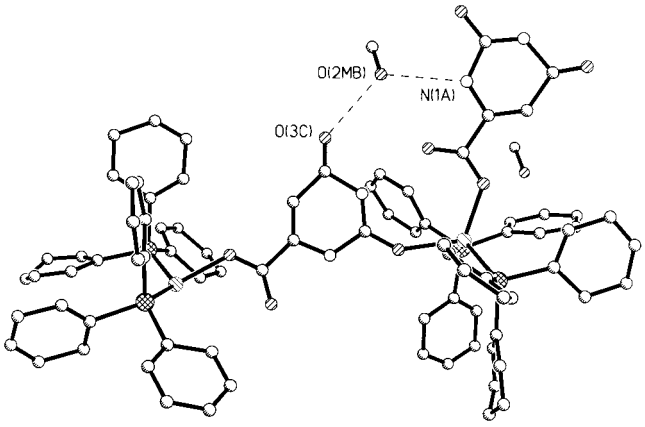



**Figure 2.** Intermolecular interactions observed in the solid-state structure of **1**.

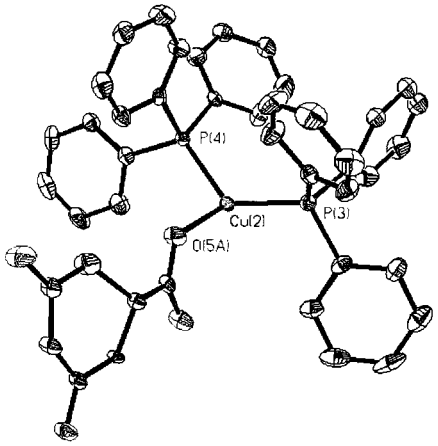



**Figure 3.** Molecular structure of **2** with thermal ellipsoids at 50% probability.

expected because the hydrogenated carbons in the ring are now $sp^3$-hybridized. Another difference in the structures is that in complex **2** there are two molecules of the complex in the asymmetric portion of the unit cell. Both molecules have essentially the same structural parameters. The Cu−O distances for the bound carboxylate oxygen found in complex **2** are similar to those found in **1** at 2.043(4) and 2.044(4) Å. The strong copper−exocyclic oxygen interactions are still present at 2.200(3) and 2.245(4) Å for the respective molecules. The Cu−P bond distances are typical for this type of compound, with the average at 2.260 Å. It is also interesting to note that the interaction of the metal center with the distal carboxylate oxygen is absent as it was in complex **1** with the average distance of 3.30 Å.

The binding mode noted herein for the orotate and dihydroorotate ligands to the metal center in complexes **1** and **2** is rare. Monodentate coordination through a carboxylate oxygen has only been reported for four other orotates or dihydroorotates, and only three of these have been structurally characterized. Terzis and co-workers[14] reported the crystal structure of a $UO_2^{2+}$ complex in which two orotic acid moieties were bound monodentate through the carboxylate oxygens. More recently, Vahrenkamp and co-workers[4] have reported the synthesis of tris(3-cumenyl-5-methylpyrazolyl)borate zinc orotate. This compound could not be characterized crystallographically because of the unavailability of suitable crystals. However based on infrared spectroscopy, it was assumed to be the same as the dihydroorotic acid analogue which was characterized by X-ray crystallography and shown to contain a monodentate-bound carboxylate ligand. It is of interest to note at this point that in the pyrazolylborate zinc derivatives of dihydroorotate the carbonyl stretch occurs at a much higher frequency (1663 $cm^{-1}$) than that which we observed for the copper(I) derivative. This may be the result of the copper(I) interaction with the exocyclic oxygen on the dihydroorotate residue in a neighboring molecule. An interaction of this type is unlikely in the zinc complex because of the bulky pyrazolylborate ligand employed in that study. One other dihydroorotic acid complex has been shown crystallographically to bind monodentate. Hambley and co-workers published the structure of [Zn(dihydroorotate)$_2$-($H_2O$)$_2$] in 1995.[3] This structure contains a zinc center bound monodentate to two dihydroorotates and one from a neighboring unit cell. The zinc also has two water molecules present to fill the trigonal-bipyramidal coordination sphere. Our future plans are to better characterize the solution-state properties of a variety of more soluble metal orotate or dihydroorotate derivatives.

One aspect of our interest in copper(I) carboxylate derivatives which we have not addressed herein is that of metal-catalyzed decarboxylation processes.[15] Currently, the mechanism of the enzyme-catalyzed decarboxylation of orotic acid, which until very recently was presumed not to involve a metal at the active site,[16] is receiving renewed attention.[17] The documented cases of copper(I) involvement in enhanced decarboxylation rates

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indicate an electrophilic catalysis mechanism, e.g., the cyanoacetic acid decarboxylation catalyzed by copper(I) occurs via a nitrile-bound copper(I) intermediate, $(Ph_3P)_2CuNCCH_2CO_2$.[18,19] Although there are sites for metal binding to orotate other than the carboxylate group, whether these interactions in our complexes would survive the conditions necessary for decarboxylation of orotic acid is presently unknown.[20] Decarboxylation rates of orotic acid in the presence of copper(I) complexes and their group 12 analogues are currently under investigation in our laboratories.

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**Supporting Information Available:** Packing diagrams for complexes **1** and **2**, and tables of anisotropic thermal parameters, bond lengths, and bond angles for complexes **1** and **2** (22 pages). Ordering and access information is given on any current masthead pages.

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(19) The rate of decarboxylation of $(Ph_3P)_2CuNCCH_2CO_2$ is 400 times faster than the corresponding rate of $[PPN][NCCH_2CO_2]$ at 55.4 °C. See ref 15.

(20) It should be emphasized that the uncatalyzed decarboxylation of cyanoacetic acid occurs readily at 100 °C whereas the analogous process involving orotic acid takes place slowly at 206 °C. See ref 17a.