

# Synthesis and Some Physicochemical Properties of the Aqua Complexes of Covalent Conjugates of Platinum(II) with Octacarboxy-Substituted Cobalt Phthalocyanine

O. V. Dolotova and O. L. Kaliya

*NPO Organic Intermediates and Dyes (NIOPIK), ul. Bol'shaya Sadovaya 1/4, Moscow, 103787 Russia*

Received February 9, 2006

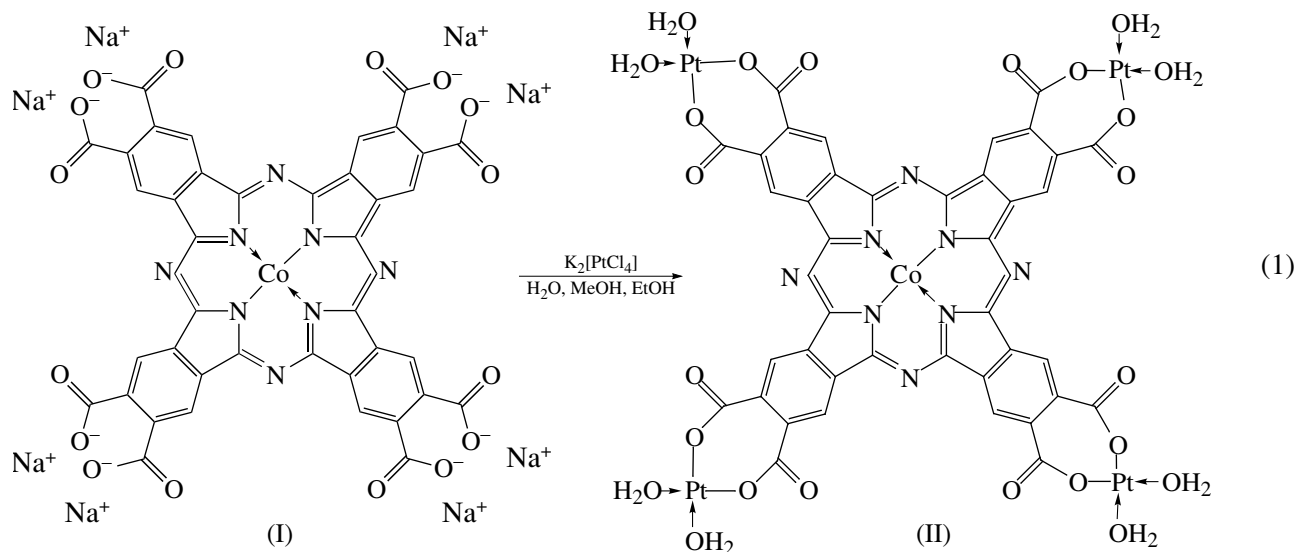
**Abstract**—Aqua complexes of the covalent conjugates of octacarboxy-substituted cobalt phthalocyanine with platinum, which are of interest as components of a catalytic system for cancer therapy, were synthesized. For the tetraplatinated product, elemental analysis data and the data from electronic absorption, IR, and mass spectra are given.

**DOI:** 10.1134/S1070328407020066

During the last decade, studies aimed at combining in one preparation of the cytotoxic activity of platinum complexes with photodynamic activity of porphyrins and their ability to selectively accumulate in a tumor have occupied a prominent place in the research concerned with anticancer therapy [1–8]. It is known [9–11] that platinum complexes are fairly efficient in the therapy of malignant neoplasms at some sites; however, side effects caused by their toxicity create a number of grave problems in the clinical use of these complexes. Studies dealing with combination of the useful properties of platinum-containing preparations and porphyrins resulted in the synthesis of a number of compounds representing platinum complexes (covalent conjugates) with hematoporphyrin and tetraphenylporphyrin derivatives [2, 3, 12–16] and with zinc phthalocyanine [4]. A study of the effect of conjugates on living cells showed an additive effect of porphyrin photodynamic activity and platinum cytotoxic activity.

A new approach to the therapy of cancer [17] (so-called catalytic therapy) makes use of the cytotoxic properties of free radicals formed as intermediate products in the catalytic oxidation of ascorbic acid with oxygen in the presence of transition metal phthalocyanines. During the development of efficient drugs for the catalytic therapy of cancer and the ways of their application, it was shown that combined use of the best catalysts with standard cytostatics often gives an over-additive therapeutic effect [18], which thus allows one to decrease the therapeutic dose of, in particular, platinum drugs. This mitigates the problem of toxicity of these drugs but does not solve it radically.

The purpose of this study is an attempt to prepare a platinum complex with octacarboxy-substituted cobalt phthalocyanine (covalent conjugate) (II) by the following reaction:



The sodium salt of cobalt 2,3,9,10,16,17,23,24-octacarboxyphthalocyanine OCPcCoNa<sub>8</sub> (Teraphthal, **I**) is now under the second phase of clinical tests as a component of a catalytic system for the therapy of cancer.

## EXPERIMENTAL

Teraphthal produced at the pilot plant of the Federal Unitary Enterprise, State Scientific Center, Organic Intermediates and Dyes (NIOPIK) and high-purity grade potassium hexachloroplatinate K<sub>2</sub>[PtCl<sub>6</sub>] were used in the syntheses.

IR spectra were recorded on a FSM-1201 FT spectrometer in the 400–4000 cm<sup>-1</sup> range (KBr pellets). Mass spectra were measured on an LCQ Finnigan spectrometer. The electronic absorption spectra (UV/Vis) of **I** and **II** were measured on a Hewlett Packard 82341C HP spectrometer.

Potassium tetrachloroplatinate was synthesized by a modification of a reported procedure [19]. N<sub>2</sub>H<sub>4</sub> · H<sub>2</sub>SO<sub>4</sub> (0.27 g, 2.06 mmol) was added to K<sub>2</sub>[PtCl<sub>6</sub>] (2 g, 4.12 mmol) dissolved in distilled water (20 ml), and the mixture was brought to boiling and heated on a water bath for 40 min. The resulting solution was filtered, and K<sub>2</sub>[PtCl<sub>4</sub>] was precipitated by an acetone–diethyl ether mixture (1 : 1). The product was washed with acetone and ether. The yield was 1.46 g (86%).

Analysis for platinum was carried out by a known procedure [20]. A sample (18 mg) was dissolved in a buffer solution (20 ml) of a Na<sub>2</sub>HPO<sub>4</sub> and KH<sub>2</sub>PO<sub>4</sub> mixture (pH 8). A 30% aqueous solution of formaldehyde and 10 ml of a 50% aqueous solution of NaOH were added to the resulting solution. After a while, platinum black precipitated, which was filtered through a porous glass filter. The filtrate was intensively aquamarine-colored, i.e., the phthalocyanine chromophore was not destroyed. The platinum black precipitate was washed on a filter with distilled water to pH 7 and dried in a drying oven at 150°C for 2 h. The yield of platinum black was 7.53 mg, which is in good agreement with the elemental analysis data for ash.

As found experimentally when testing the conditions of the synthesis, the preparation of a covalent conjugate containing four platinum atoms requires that the initial cobalt phthalocyanine and a platinum salt be taken in 1 : 7 molar ratio. Since one-time addition of a large excess of K<sub>2</sub>[PtCl<sub>4</sub>] results in the formation of platinum black during the reaction, probably via the reaction of the initial potassium tetrachloroplatinate with methanol, a two-step synthetic procedure was elaborated.

**Synthesis of OCPcCoPt<sub>4</sub>(H<sub>2</sub>O)<sub>8</sub> (**II**).** *Step 1.* Teraphthal OCPcCoNa<sub>8</sub> (**I**) (0.21 g, 0.19 mmol) was dissolved in distilled water (25 ml), and methanol (210 ml) was added. A solution of K<sub>2</sub>[PtCl<sub>4</sub>] (0.32 g, 0.77 mmol) in 50% ethanol (380 ml) prepared immediately prior to the synthesis was added to the solution of salt **I**, and the mixture was stirred for 3 h at room temperature. After

48 h, the precipitate was filtered off, washed with distilled water and dried in air. The yield was 0.27 g.

As judged from the dependence of the elemental analysis data on the particular reactant ratio, the precipitate formed in this reaction is not an individual substance but a mixture of mono-, di- and trisubstituted complexes.

*Step 2.* A solution of K<sub>2</sub>[PtCl<sub>4</sub>] (0.24 g, 0.58 mmol) in 50% ethanol (285 ml) was added to a suspension of the product obtained in step 1 (0.27 g) in a mixture of water (50 ml) with methanol (210 ml). The subsequent operations were similar to those described in step 1 of the synthesis. The solid product was washed with distilled water, ethanol, acetone, and ether and dried in air. The air-dry product was a dark violet-colored crystalline compound with a metallic luster soluble in dimethylformamide and dimethyl sulfoxide. The yield was 0.29 g (81%).

According to elemental analysis data, the composition of the compound can be described by the formula OCPcCoPt<sub>4</sub>(H<sub>2</sub>O)<sub>8</sub>.

For C<sub>40</sub>H<sub>24</sub>N<sub>8</sub>CoO<sub>24</sub>Pt<sub>4</sub>

anal. calcd. (%): C, 26.11; H, 1.31; N, 6.09; Co, 3.20; Pt, 42.40.

Found (%): C, 26.84; H, 1.50; N, 6.94; ash, 46.71.

(with the assumption that the ash consists of Pt and equal amounts of CoO and Co<sub>2</sub>O<sub>3</sub>, the calculated overall percentage of Pt and Co is 45.55).

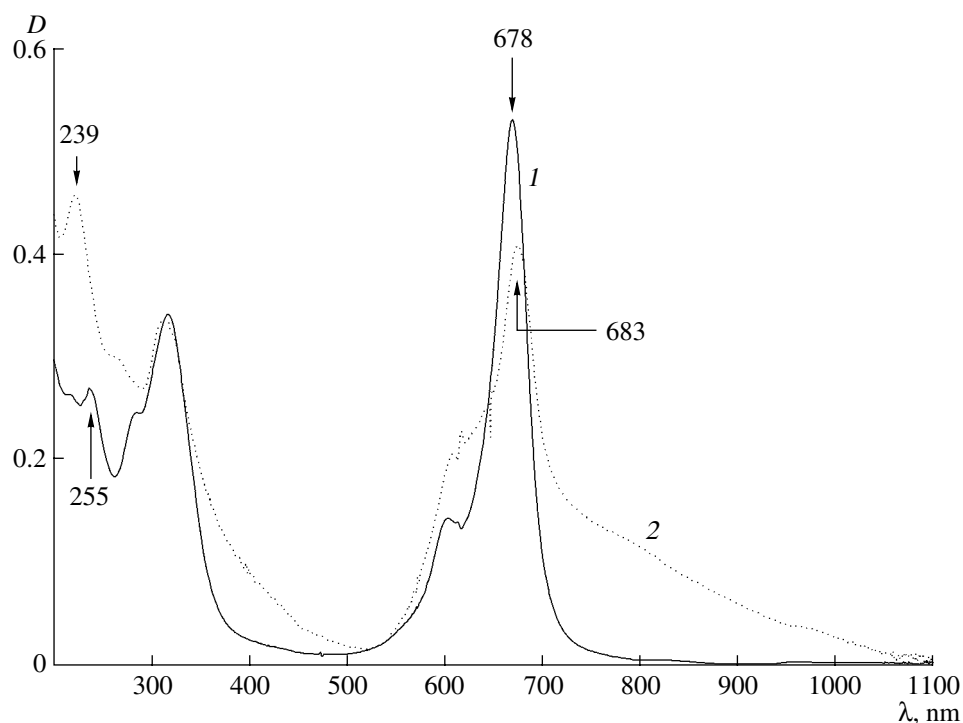
The Beilstein test and the elemental analysis of the reaction product showed the absence of residual chlorine in the sample.

## RESULTS AND DISCUSSION

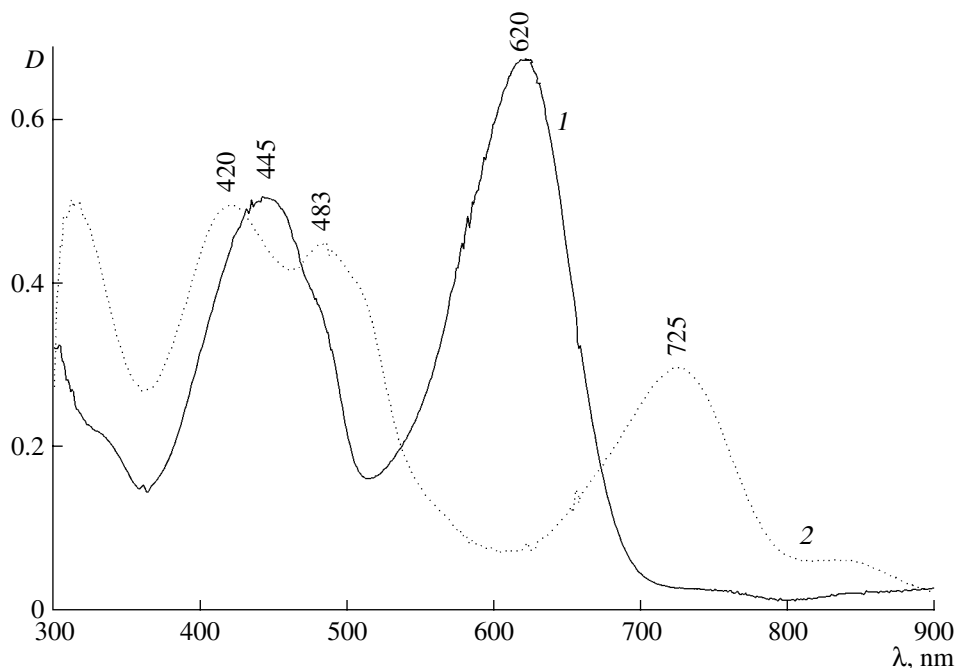
The introduction of platinum at the periphery of cobalt octacarboxyphthalocyanine changes essentially the physicochemical properties of complex **I**. For example, the replacement of the ionic bond, Na<sup>+</sup>O<sup>-</sup>, by the Pt–O covalent bond eliminates almost completely the solubility of the tetraplatinated product **II** in water. The initial complex **I** can be chromatographed on silica gel with a Na<sub>2</sub>HPO<sub>4</sub> – KH<sub>2</sub>PO<sub>4</sub> buffer solution (pH 8); no eluent was selected for the final product **II**, which was sorbed irreversibly on the stationary phase.

A comparison of the UV/Vis spectra of complex **II** and initial salt **I** (Fig. 1) reveals significant changes in the spectral pattern with the general structure being retained. These changes (especially those in the 230–260 nm range) can serve for monitoring the formation of complex **II**.

The presence of platinum in product **II** was confirmed by a qualitative test for Pt(II) with photometric detection [21]. The procedure included the extraction of Pt(II) from an aqueous suspension of a sample of **II** with a diphenylthiocarbazone (dithizone **HDz**) solution in carbon tetrachloride containing SnCl<sub>2</sub> and 2 N HCl. This resulted in a transition of the green color typical of



**Fig. 1.** UV/Vis spectrum of the (1) initial OCPcCoNa<sub>8</sub> and (2) final OCPcCoPt<sub>4</sub>(H<sub>2</sub>O)<sub>8</sub> compounds in water ( $c_{II} = 10^{-5}$  mol/l,  $l = 1$  cm).



**Fig. 2.** UV/Vis spectrum of (1) dithizone and (2) the product of its reaction with OCPcCoPt<sub>4</sub>(H<sub>2</sub>O)<sub>8</sub> in CCl<sub>4</sub> ( $c_{II} = 10^{-5}$  mol/l,  $l = 1$  cm).

a dithizone solution in CCl<sub>4</sub> to brownish-yellow color typical of platinum dithizonate Pt(HDz)<sub>2</sub> and was accompanied by a change in the UV/Vis spectrum (Fig. 2).

The IR spectrum of **II** (Fig. 3, 1) in the 1400–1700 cm<sup>-1</sup> range differs considerably from the spectrum of the initial Teraphthal (Fig. 3, 2), which has two characteristic bands, namely, at 1380 cm<sup>-1</sup> due to

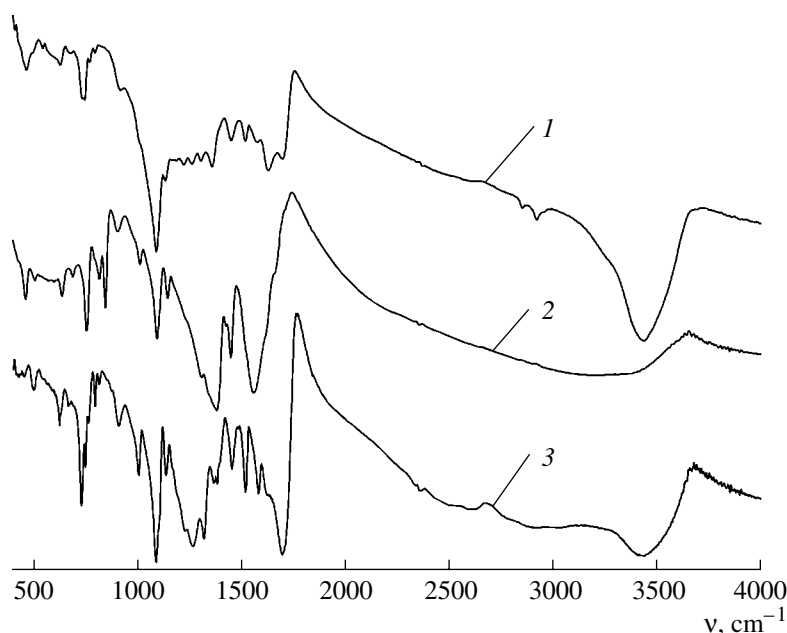


Fig. 3. IR spectra of (1) OCPcCoPt<sub>4</sub>(H<sub>2</sub>O)<sub>8</sub>, (2) Teraphthal, and (3) OCPcCoH<sub>8</sub>.

$\nu_s(\text{COO}^-)$  and at 1570  $\text{cm}^{-1}$  due to  $\nu_{as}(\text{COO}^-)$ , and also from the spectrum of OCPcCoH<sub>8</sub> (Fig. 3, 3) in which the strongest band at 1704  $\text{cm}^{-1}$  is due to the C=O mode of the carboxy group. The 1600–1700  $\text{cm}^{-1}$  range is known to be rather ambiguous for interpretation [22, 23]. This range includes the C=O vibrations of the carboxy groups of carboxylic acids, their salts, or other compounds. According to published data [15, 16, 24, 25], the C=O vibrations of a carboxy group covalently bonded to platinum may be manifested as two or three bands at 1600–1708  $\text{cm}^{-1}$ . Thus, the bands at 1628 and 1699  $\text{cm}^{-1}$  present in the spectrum of product **II** and missing from the spectrum of initial Teraphthal are attributable to these vibrations. Unlike **I**, the platinum-containing conjugate **II** exhibits also a clear-cut band at 3400  $\text{cm}^{-1}$  (Fig. 3, 1), which can be assigned to the OH stretching vibrations of coordinated water molecules.

The mass spectrum of complex **II** contains a peak for the molecular ion that has lost five water molecules, OCPcCoPt<sub>4</sub>(H<sub>2</sub>O)<sub>3</sub> ( $m/z$  1749.9), a peak for anhydrous OCPcCoPt<sub>4</sub> (–2H) ( $m/z$  1693.4), and the fragments, OCPcCoPt<sub>3</sub>(H<sub>2</sub>O)<sub>6</sub> (–2H) ( $m/z$  1606.2) and OCPcCoPt<sub>2</sub> ( $m/z$  1306.2). These data, together with the results of elemental analysis and IR spectra suggest that each of the four platinum atoms coordinates two water molecules, which thus complete the coordination sphere to a planar square typical of Pt(II). It is this hypothetical structure that is given for **II** in the scheme of reaction (1).

The formation of complexes (covalent conjugates) of OCPcCo with platinum is reversible. The addition of a Na<sub>2</sub>HPO<sub>4</sub>–KH<sub>2</sub>PO<sub>4</sub> buffer solution (pH 8) or a solution of NaOH to an aqueous solution of complex **II**

induces the elimination of platinum and the recovery of initial OCPcCoNa<sub>8</sub>, which is accompanied by a characteristic change in the UV/Vis spectrum. The addition of acids to complex **II** also results in the elimination of platinum to give the acid OCPcCoH<sub>8</sub>.

## REFERENCES

1. Kim, Y.S., Song, R., Kim, D.H., et al., *Bioorg. Med. Chem.*, 2003, vol. 11, no. 8, p. 1753.
2. Brunner, H. and Obermeier, H., *Angew. Chem.*, 1994, vol. 106, no. 21, p. 2305.
3. Brunner, H. and Schellerer, K.-M., *Inorg. Chim. Acta*, 2003, vol. 350, p. 39.
4. Nemykin, V., Mytsyk, V., Volkov, S., and Kobayashi, N., *J. Porphyrins Phthalocyanines*, 2000, vol. 4, no. 5, p. 551.
5. Song, R., Kim, Y.S., Lee, C.O., and Sohn, Y.S., *Tetrahedron Lett.*, 2003, vol. 44, no. 8, p. 1537.
6. Winkelman, J., Slater, G., and Grossman, J., *Cancer Res.*, 1967, vol. 27, p. 2060.
7. Woodburn, K.W., Phillips Bellinger G.C.A., Sadek M., et al., *Bioorg. Med. Chem. Lett.*, 1992, vol. 2, no. 4, p. 343.
8. Tronconi, M., Colombo, A., De Cesare, M., et al., *Cancer Lett.*, 1995, vol. 88, no. 1, p. 41.
9. Wong, E. and Giandomenico, C.M., *Chem. Rev.*, 1999, vol. 99, no. 9, p. 2451.
10. Hambley, T.W., *Coord. Chem. Rev.*, 1997, vol. 166, p. 181.
11. Von Hoff, D.D., Schilsky, R., Reichert, C.M., et al., *Cancer Treat. Rep.*, 1979, vol. 63, nos. 9–10, p. 1527.
12. Brunner, H., Maiterht, F., and Treitinger, B., *Chem. Ber.*, 1994, vol. 127, no. 11, p. 2141.

13. Brunner, H., Obermeier, H., and Szeimies, R.M., *Chem. Ber.*, 1995, vol. 128, no. 2, p. 173.
14. Brunner, H., Schellerer, K.-M., and Treitinger, B., *Inorg. Chim. Acta*, 1997, vol. 264, nos. 1–2, p. 67.
15. Lottner, C., Bart, K.-C., Bernhardt, G., and Brunner, H., *J. Med. Chem.*, 2002, vol. 45, no. 10, p. 2064.
16. Lottner, C., Bart, K.-C., Bernhardt, G., and Brunner, H., *J. Med. Chem.*, 2002, vol. 45, no. 10, p. 2079.
17. Vol'pin, M.E., Vorozhtsov, G.N., Gerasimova, G.K., et al., RF Patent 2106146, 1997.
18. Vorozhtsov, G.N., Kuz'min, S.G., Lukyanets, E.A., et al., RF Patent 2114623, 1998.
19. Livingstone, S.E., *The Chemistry of Ruthenium, Rhodium, Palladium, Osmium, Iridium, and Platinum*, New York: Pergamon, 1973.
20. *Sintez kompleksnykh soedinenii metallov platinovoi gruppy. Spravochnik* (Synthesis of Complex Compounds of Platinum Group Metals. Handbook), Chernyaev, I.I., Moscow: Nauka, 1964, p. 330.
21. Lur'e, Yu.Yu., *Spravochnik po analiticheskoi khimii* (Handbook on Analytical Chemistry), Moscow: Khimiya, 1979.
22. Bellamy, L.J., *The Infra-Red Spectra of Complex Molecules*, London: Methuen, 1959.
23. Kazitsyna, L.A. and Kupletskaya, N.B., *Primenenie UF-, IK- i YaMR-spektroskopii v organicheskoi khimii* (Application of UV, IR, and NMR Spectroscopy in Organic Chemistry), Moscow: Vysshaya Shkola, 1971.
24. Kidani, Y., Inagaki, K., Iigo, M., et al., *J. Med. Chem.*, 1978, vol. 21, no. 12, p. 1315.
25. Noji, M., Hanamura, S., Suzuki, K., et al., *Chem. Pharm. Bull.*, 1986, vol. 34, no. 6, p. 2487.