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First Bivalent Palladium and Platinum Cyanoximates: Synthesis, Characterization, and Biological Activity†

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A series of five cyanoximes (compounds having the general formula NC–C(═NOH)–R, where R is an amide or carboxylic ester group) have been synthesized and spectroscopically and structurally characterized. These are 2-cyano-2-isonitrosoacetamide (later HACO), 2-cyano-2-isonitrosothioacetamide (HTCO), 2-cyano-2-isonitroso-ethylacetate (HECO), 2-cyano-2-isonitroso-*N*-piperidinylacetamide (HPiPCO), and 2-cyano-2-isonitroso-*N*-morpholin-ylacetamide (HMCO). A high yield method of synthesis was developed for the last two previously unknown amidocyanoximes. Variable temperature ^{13}C NMR studies in DMSO-d_6 solutions allowed the determination of rotational energy barriers for these two new cyanoximes. The HPiPCO and HMCO oxime molecules adopt a *trans-anti* configuration in the solid state according to X-ray analysis. Reactions between aqueous solutions of K^+L^- (L = cyanoximate anions: TCO^-, $PiPCO^-$, and MCO^-) and $K_2[MCl_4]$ (M = Pd, Pt) resulted in the formation of ML_2 complexes. The crystal structure of $Pd(MCO)_2$·DMSO was determined and showed the formation of coplanar dimeric $[Pd(MCO)]_2$ units with 3.13 Å Pd···Pd separation. The complex adopts *cis* geometry with anions being in the *nitroso* form. In the presence of bivalent Pd and Pt, ACO^- and ECO^- anions completely or partially hydrolyze in aqueous solutions to the dianion of 2-cyano-2-isonitrosoacetic acid ($AACO^{2-}$). The crystal structure of the product of the hydrolysis reaction, $K_2[Pd(AACO)_2]\cdot 4H_2O$, was determined. Data revealed planar and *cis* geometry of the $[Pd(AACO)_2]^{2-}$ anion where cyanoximes are in the *nitroso* form and adopt a *cis-anti* configuration. All synthesized cyanoxime ligands and nine of their Pd(II) and Pt(II) complexes were tested *in vitro* on antiproliferating activity using human cervical cancer HeLa cell lines, and cisplatin as a positive control substance. Two out of the nine studied complexes, $Pd(MCO)_2$ and Pt(MCO), were found to be active compounds inflicting death on 28% and 16% of the cells, respectively, with 55% value for the cisplatin under the same conditions.

Introduction

Research has proven that the most effective and widely used metal-containing chemotherapy anticancer drugs are *cisplatin*, *oxalylplatin*, and *carboplatin*, all Pt(II)-containing complexes.[1] Despite their high activity, these compounds have significant disadvantages including poor water solubility and serious side effects such as severe nausea and kidney and liver failure typical of heavy metal toxicity.[2] Another problem found in using these platinum compounds is the development of drug tolerance by a tumor.[3] Thus, the design and testing of new platinum metal complexes is an important

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† Dedicated to Prof. Jozsef Andor on occasion of his retirement.

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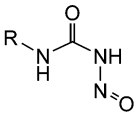
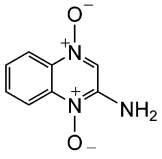
problem with obvious practical applications.[1,4] In this situation, treatment of cancer with a sequence of chemically different active metallocomplexes is desirable and provides an incentive for expanded research to discover a greater variety of new antitumor Pt(II,IV) and lately Pd(II) compounds.[5]

There are two groups of NO-containing simple organic molecules that have been successfully tested as antitumor agents. For example, the *N*-nitroso urea and tirapazamine shown below were found to exhibit strong anticancer activity.



mono-N-nitroso ureas

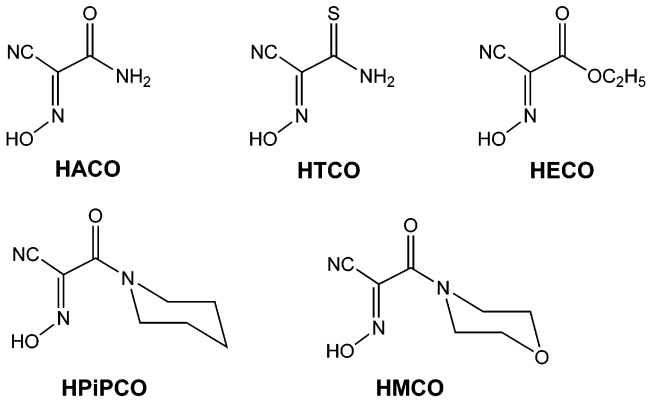


tirapazamine

At the same time, there is an absence of fundamental information about interactions of bivalent Pt and Pd with the oximes, nitroso-group containing compounds and cyanoximes in particular, and the biological activity of the complexes formed. The latter have the general formula NC−C(═N−OH)−R where R represents different types of electron-withdrawing groups that contain donor atoms of nitrogen, oxygen, or sulfur: NC, amide, thioamide, keto, carboxylic ester, substituted aryl, and heteroaryl.[6] Cyanoximes were found to be excellent ligands capable of binding to different metal ions.[7] Also, several previously known cyanoximes have shown pronounced biological activity such as growth-regulating,[8] antimicrobial,[9] and detoxifying agricultural pesticide properties.[10]

It is interesting to combine the anticancer properties exhibited by bivalent platinum and palladium ions with the

Scheme 1



established, beneficial biological effect of cyanoxime ligands. The five amide or carboxylic ester derivatives of 2-cyanoacetic acid, shown in Scheme 1 with their respective abbreviations, were selected for this investigation. Four out of the five ligands are water-soluble compounds where only the HPiPCO is a hydrophobic counterpart to HMCO. In this paper we will report the synthesis and characterization, including *in vitro* studies of antiproliferating activity on human cancer cell lines, of the first bivalent palladium and platinum cyanoximates.

Experimental Section

Materials and Methods. Reagent or analytical grade materials were obtained from commercial suppliers (Aldrich, Mallinckrodt, AlfaAesar) and used without further purification.

Spectroscopic Methods. Routine ^{1}H and ^{13}C spectroscopic studies of the protonated ligands and their K^+ salts were carried out using a Varian Gemini 200 MHz NMR spectrometer. Variable temperature ^{1}H and ^{13}C were recorded on an Avance DRX-500 BRUKER NMR spectrometer using standard pulse methods. All solutions were in dmso-d_6 containing TMS as an internal standard, and temperature increments were 10 °C with ±0.2 °C accuracy of the set point assignment.

IR spectra for solid samples of HL (L = all studied ligands), their K^+ derivatives, and metal complexes were recorded in KBr pellets. Spectra were obtained in the range of 4000 to 400 cm^{-1} with an FT-IR Nicolet Magna 550 spectrometer equipped with Windows OMNIC software.

UV−visible spectra for the ligands were recorded on a Varian Bio 100 UV−visible spectrophotometer in 1 cm quartz cuvettes in the range of 220−800 nm.

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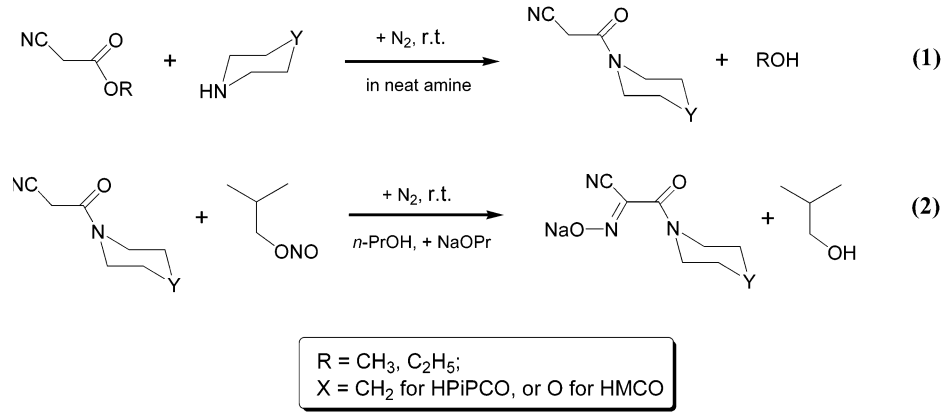
Scheme 2



Mass spectra for all synthesized cyanoximes HL were obtained using Autospec Q and ZAB spectrometers and positive FAB technique. The exact mass determination for molecular ion peaks was used for the identification of the obtained cyanoximes.

Melting points for protonated cyanoximes, HL, and their K^+ salts were determined in open capillary tubes using a Mel-Temp II apparatus (Thomas-Hoover) without correction.

An elemental analysis was performed on the C, H, N, and S content at the MicroMass Laboratory of the University of California (Berkeley). ICP analyses of the metal content in the metal complexes were conducted using a Varian Liberty 150 AX Turbo ICP emission spectrometer. Standard solutions (1000 ppm concentration; pH = 1) of palladium and platinum salts for calibration of the instrument were obtained from Aldrich.

X-ray Crystallography. Structural investigations of the two new cyanoxime molecules HPiPCO and HMCO were conducted at −100 °C on a diffractometer equipped with a Bruker Smart CCD area detector. Both structures were solved by direct methods and refined by full-matrix least-squares techniques. Hydrogen atoms for the HPiPCO structure were located on a difference map, but in the structure of HMCO positions of all H atoms were calculated using a riding model for their refinement. Data collection for the crystal of $[Pd(MCO)_2 \cdot DMSO]$ was conducted at +20 °C K on the above diffractometer. The crystal structure was solved using direct methods and refined by full-matrix least-squares techniques. Crystallographic measurements for the structure determination of palladium complex $K_2[Pd(AACO)_2] \cdot 4H_2O$ was carried out at −50 °C K using a Siemens Stoe STADI-4 diffractometer. A semiempirical absorption correction was based on ψ scans. The structure was solved by direct methods and refined by full-matrix least-squares techniques in the anisotropic approximation using SHELXS-86 and SHELXL-93 program packages.[11] All non-hydrogen atoms with the exception of disordered water molecules were refined anisotropically. One of two unique potassium cations was found to be disordered over two positions. The partial occupancies were 0.5 and both components were refined anisotropically for the sake of overall convergence. Two of the four unique water molecules were also disordered and refinement of partial occupancies led to contributions 0.77 and 0.23 for O(10) and 0.52 and 0.48 for O(11). These atoms were left isotropic. High anisotropy of thermal motion for the rest of solvate water (O(7) and O(9)) also indicated possible disorder, but we were unable to resolve it. Hydrogen atoms of solvate water were not located and were not included in the calculations. The crystal data for all reported structures are presented in Table 4.

Synthesis of Compounds. Cyanoxime Ligands. Synthesis of HACO,[12] HECO,[12,13] and HTCO[14] was carried out according to published procedures. The Meyer reaction[15] was conducted under acidic conditions using 2-cyanoacetamide, 2-cyanothioacetamide, and 2-cyanoethylacetate as starting compounds. Glacial acetic acid with sodium nitrite as a source of nitrous acid, HNO_2, was employed for syntheses. The cyanoximes HACO, HTCO, and HECO are water-soluble substances and form stable aqueous solutions. The two new amidocyanoximes HPiPCO and HMCO cannot be obtained from the respective 2-cyanoacetamides under the above conditions. However, they are available using nitrosation with alkyl nitrites under basic conditions. Preparation of 2-cyano-*N*-piperidinylacetamide and 2-cyano-*N*-morpholinylacetamide was accomplished using the reaction between 2-cyanoacetic acid esters and secondary amines[16] shown in eq 1 (Scheme 2). The general reaction employed for the synthesis of two new amidocyanoximes HPiPCO and HMCO is shown in eq 2 (Scheme 2).

Synthesis of HPiPCO. The reaction (1) between methylcyanoacetate and neat piperidine (at a 1:5 molar ratio, at room temperature, and under nitrogen within 48 h) led to the formation of 2-cyano-*N*-piperidinylacetamide amide with ∼65% yield. The course of the reaction was monitored by the TLC tracing disappearance of the starting ester using an EtOAc/hexane = 1:2 mobile phase. Since there was no chromophore in either reactants or products, development of TLC plates was done in an iodine chamber. An excess of the secondary amine was removed from the reaction mixture, under vacuum, resulting in a white crystalline solid with mp = 88 °C. Mass spectrometry: positive FAB, for 2-cyano-*N*-piperidinylacetamide, $C_8H_{12}N_2O$, calculated $M = 152.12$ (found $M = 152.1$).

The next step, the reaction of 2-cyano-*N*-piperidinylacetamide with isobutyl nitrite or *tert*-butyl nitrite at a 1:1.5 molar ratio in the presence of sodium propoxide in 1-propanol, yields the HPiPCO ligand (Scheme 2). The solution of sodium propoxide was freshly prepared prior to each use: metallic sodium (0.750 g; 2.26×10^{-3} mol) was dissolved under nitrogen in 15 mL of 1-propanol at +30 °C. Solid 2-cyano-*N*-piperidinylacetamide (1.022 g; 6.72×10^{-3}

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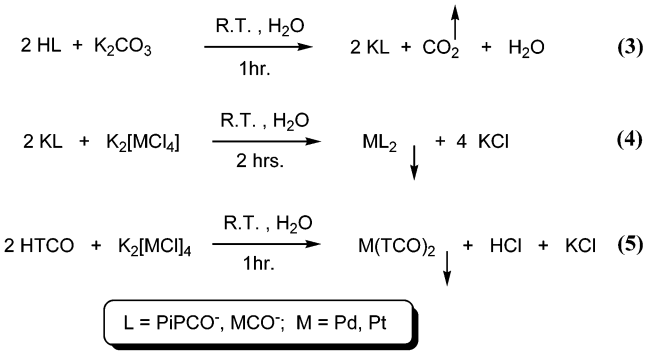
mol) was dissolved in 15 mL of the above sodium propoxide solution, and the resulting mixture gained a light-yellow color. Isobutyl nitrite or *tert*-butyl nitrite (0.854 g; 8.29×10^{-3} mol) was dissolved in 30 mL of 1-propanol under nitrogen. The butyl nitrite solution was slowly added to a basic solution of the 2-cyano-*N*-piperidinylacetamide in 1-propanol. The reaction mixture was stirred for 1 h under slow nitrogen flow, and then closed overnight at +4 °C. The solvent was removed using a rotovapor, resulting in a pale-yellow solid, which then was redissolved in water and acidified with 1.0 M HCl to pH ~4. This acid solution was saturated with solid NaCl, and salted out white powdery 2-cyano-2-isonitroso-*N*-piperidinylacetamide, HPiPCO, was filtered off, washed with water, and dried in a vacuum desiccator over H_2SO_4. Yield: 0.706 g (58%); mp = 159−162 °C; $R_f = 0.55$ (ethanol/$CHCl_3$ = 9:1 mobile phase). Mass spectrometry: positive FAB method for $C_8H_{12}N_3O_2$, calculated $M = 181.0851$ (found $M = 181.0881$). IR: 3415 cm^{-1} (ν_{O-H}), 2945 cm^{-1} (ν^{as}_{C-H}), 2800 cm^{-1} (ν^{s}_{C-H}), 2236 cm-1 ($\nu_{C\equiv N}$), 1630 cm^{-1} ($\nu_{C=O}$), 1036 cm^{-1} (ν_{NO}). The compound is soluble in alcohols, acetonitrile, chlorinated hydrocarbons, acetone, and ether, but insoluble in water, hexane, and aromatic hydrocarbons.

Synthesis of HMCO. Preparation of this ligand was also accomplished in two steps as shown by Scheme 2. The 2-cyano-*N*-morpholinyacetamide was prepared by the reaction (eq 1, Scheme 2) of 2-cyanoethylacetate and neat morpholine at molar ratio 1:10 at room temperature. Ten milliliters 2-cyanoethylacetate (10.63 g; 9.30×10^{-2} mol) were mixed under nitrogen with 20 mL of morpholine under intensive stirring. The reaction was monitored daily by TLC, and plates were developed in an iodine chamber. The disappearance of the starting ethylcyanoacetate indicated a reaction completion that typically required 7 days. The excess of morpholine was removed under vacuum, and the resulting yellowish solid product was further dried using a high vacuum diffusion pump. 2-Cyano-*N*-morpholinylacetamide (17.728 g) was recovered at ~100% yield. Mp = 78−81 °C, $R_f = 0.12$ in EtOAc/hexane = 1:2 mobile phase. Mass spectrometry: positive FAB method. For 2-cyano-*N*-morpholinylacetamide, $C_7H_{10}N_2O_2$: calculated M = 154.0742 (found $M = 154.0826$).

HMCO was synthesized by the reaction between 2-cyano-*N*-morpholinylacetamide and isobutyl nitrite in the presence of a freshly prepared base: sodium propoxide (eq 2, Scheme 2). Therefore, 0.175 g of metallic sodium was dissolved under N_2 in 70 mL of 1-propanol. A solid sample of 2-cyano-*N*-morpholinyl-acetamide (5.433 g; 3.527×10^{-2} mol) was dissolved in the basic sodium propoxide solution at room temperature. Five milliliters (4.35 g; 4.22×10^{-2} mol) of isobutyl nitrite were dissolved in 50 mL of 1-propanol, and then added dropwise under N_2 to the above 2-cyano-*N*-morpholinylacetamide solution. The mixture was stirred for 1 h under nitrogen. The resulting yellow/brown solution was concentrated on a rotovapor, and then all of the solvent was completely removed under a vacuum using an oil pump. The yellow-orange solid residue was redissolved in 100 mL of water, acidified to pH ~4 by the addition of 1.0 M HCl, and the desired cyanoxime was extracted with two portions of ether (75 mL). The organic layers were combined and dried over $MgSO_4$, and the removal of the solvent resulted in 2.56 g of slightly yellow solid HMCO. Yield: 40%; mp = 155−160 °C; $R_f = 0.44$ in EtOAc/hexane = 2:1 mobile phase. Mass spectrometry: positive FAB method, for HMCO, $C_7H_9N_3O_3$ calculated $M = 183.0644$ (found $M = 183.0737$). IR: 3425 cm^{-1} (ν_{O-H}), 2977 cm^{-1} (ν^{as}_{C-H}), 2825 cm^{-1} (ν^{s}_{C-H}), 2236 cm^{-1} ($\nu_{C\equiv N}$), 1627 cm^{-1} ($\nu_{C=O}$), 1006 cm^{-1} (ν_{NO}). The compound is soluble in water, alcohols, acetonitrile, chlorinated hydrocarbons, acetone, and ether, but insoluble in hexane and aromatic hydrocarbons.

Scheme 3



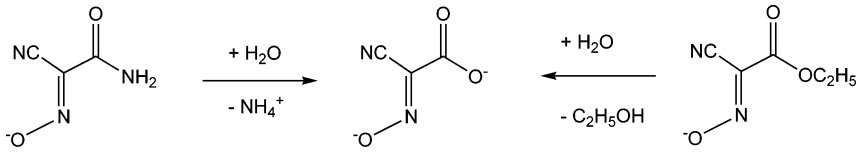
Metal Complexes. The only protonated HTCO ligand was employed for the preparation of TCO^--containing complexes. Potassium salts of the KL composition were used for the synthesis of other bivalent palladium and platinum cyanoximates. General reactions including stoichiometry and some other conditions are shown in eqs 3−5 in Scheme 3. Since all syntheses of Pd(II) and Pt(II) cyanoximates are analogous, only two typical preparations of complexes will be described. Elemental analysis data for all synthesized complexes are shown in the Supporting Information, S1.

$Pt(TCO)_2$. In this synthesis, protonated cyanoxime, 2-cyano-2-isonitrosothioacetamide, HTCO, was used (eq 5, Scheme 3). The platinum source, K_2PtCl_4 (0.200 g; 4.81×10^{-4} mol), was dissolved in 5 mL of deionized water. An aqueous solution of 0.125 g (9.68×10^{-4} mol) of HTCO in 5 mL of water was added dropwise wiht stirring at room temperature to the tetrachloroplatinate solution. The light orange clear solution slowly changed to a dark green suspension after about 1 h with stirring. The green precipitate was filtered off, washed with water, and dried in a vacuum desiccator over H_2SO_4, yielding 0.199 g (4.41×10^{-4} mol) of $Pt(TCO)_2$ with a 92% yield.

$Pd(MCO)_2$. A solution of yellow sodium salt of MCO^- ligand was obtained when 0.224 g (1.22×10^{-3} mol) of the protonated solid cyanoxime HMCO reacted with the exact stoichiometric amount of 1.0 M aqueous NaOH solution. Potassium tetrachloro-palladate, $K_2[PdCl_4]$ (0.200 g; 6.13×10^{-4} mol), was dissolved at room temperature in 5 mL of deionized water and then added dropwise, with stirring, to the above solution of Na(MCO). Upon mixing, the light red color of the solution disappeared and a yellow precipitate formed almost immediately. After 1 h the precipitate was filtered off, washed with 25 mL of water, and then dried in a vacuum desiccator over H_2SO_4, resulting in 0.231 g of $Pd(MCO)_2$ with an 80% yield.

Syntheses of the Pd(II) and Pt(II) complexes with ACO^- and ECO^- ligands unexpectedly resulted in compounds containing completely or partially hydrolyzed cyanoxime anions (Scheme 4). According to data derived from an X-ray analysis of one of the Pd complexes, the ligand 2-cyano-2-isonitroso-ethylacetate, ECO^-, completely hydrolyzed in the metal complex to the dianion of 2-cyano-2-isonitrosoacetic acid, $AACO^{2-}$. A compound of $K_2[Pd(AACO)_2]\cdot 4H_2O$ composition was obtained instead of the expected $Pd(ECO)_2$ complex. A similar result occurred with 2-cyano-2-isonitrosoacetamide anion ACO^- in both Pd(II) and Pt(II) complexes, where analytical (and spectroscopic) data indicated the presence of both ACO^- and $AACO^{2-}$ anions (Supporting Information, S1). The Pt(II) complex containing the ECO^- anion has not been isolated despite several attempts.

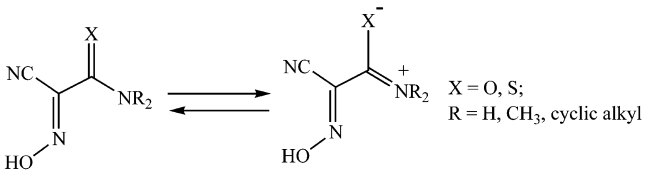
Scheme 4



ACO⁻ **AACO⁻²** **ECO⁻**

Results and Discussion

Spectroscopic Characterization of Cyanoxime Ligands. NMR spectra. The cyanoximes HACO, HECO, and HTCO have been previously synthesized, and some of their properties are well-known.[13,14,18,19] Nevertheless, their Pd and Pt complexes have not been obtained. Ligands such as HPiPCO and HMCO, however, were unknown prior to this investigation. Results of NMR spectroscopic studies of all five cyanoximes are present in Supplementary Information, S2, S3. Four out of five cyanoximes selected for these studies represent amides (Scheme 1). An amido NR_2 group in these ligands has a rotational barrier since the C−N amide bond has a partially double character due to the contribution of the resonance form II as shown below.



I **II**

As a result, there are two nonequivalent and well-separated signals of R groups typically observed in ^{1}H NMR spectra at room temperature. They are located at 7.91 and 7.84 ppm ($\Delta\delta = 0.07$ ppm) for HACO[6a] and at 10.18 and 9.64 ppm ($\Delta\delta = 0.54$ ppm) for HTCO ligands in dmso-d_6 solutions at 293 K. The restricted rotation around the C−N bond is characterized by activation energy to overcome the barrier. Two separate amide protons in the ^{1}H NMR spectrum of HACO coalesce at ∼50 °C resulting in $\Delta G^{\ddagger} = 67.7$ kJ/mol for the restricted rotation of the NH_2 group.[6a] To our surprise, there was no coalescence of the signals of the thioamide protons of HTCO observed at the studied 20−110 °C temperature interval. The absence of the coalescence of signals of the NH_2 group, even at 110 °C, indicates that the contribution of form **II** is dominant in this ligand. It is interesting to note that $\Delta\delta$ for these protons is the same at room temperature and 110 °C (Supporting Information, S4).

The oxime protons of HACO and HTCO are strongly deshielded and were observed at 14.9 and 15.05 ppm, respectively, at 293 K in dmso-d_6. ^{13}C NMR spectra of HACO, HTCO, and HECO, studied in the +20 ↔ +110 °C temperature interval, contained only one set of signals (three lines for the first two ligands[14] and five lines for HECO molecule[13]). This indicates an absence of the *syn/anti* isomeric mixture in dmso-d_6 solutions.

The ^{1}H NMR spectrum of HPiPCO in dmso-d_6 at 293 K contains one highly deshielded oxime proton at 14.22 ppm. The position and splitting pattern of the protons of the piperidine fragment are typical for this group. Analysis of the carbon-13 NMR spectra at room temperature has led to some interesting observations. The presence of only one set of signals for the nitrile carbon, oxime, and amide groups confirmed the absence of the mixture of *syn/anti* isomers. However, the appearance of five distinct peaks instead of three signals for the piperidine group indicates loss of their equivalency due to the aforementioned restricted rotation around C−N amide bond (Figure 1). An interesting peculiarity of this piperidine ring is the presence of fast boat/chair conformation change, that typically is observed[20] at temperatures below 0 °C, but may have an additional contribution into the overall dynamic of the system as shown in Scheme 5. Only the C3 signal remained sharp at all the temperatures in studied range, while carbon atoms 1, 2, 4, and 5 underwent two positional temperature-dependent exchanges. The coalescence temperature for carbon atoms C2 and C4 was determined to be 70 °C. At 95 °C the signals of the C1 and C5 carbon atoms disappeared from the spectrum without coalescence. Calculations of the activation energies were performed only for coalescing signals using eqs 6 and 7. The values of $\Delta G^{\ddagger}$ are presented in Table 1. The k_c is the exchange rate constant at coalescence temperature T_c (K), k_B is Boltzmann's constant, h is Planck's constant, and χ is the transmission coefficient, which equals 1 for cases of the restricted rotation for two positional exchange.[20] Values of ν_a and ν_b represent the frequencies of individual signals that are well-resolved to the baseline in the respective NMR spectrum. A value of $\Delta G^{\ddagger} = 64.9 \pm 2.0$ kJ/mol was

$$k_c = \pi\frac{\sqrt{2}}{2}(\nu_a - \nu_b) \qquad (6)$$

$$k_c = \chi\left(\frac{k_B T_c}{h}\right)e^{-\Delta G^{\ddagger}/RT_c} \qquad (7)$$

obtained for the carbon atoms C2 and C4. This result is in the range of commonly observed activation energies of amides being from 50.0 to 66.7 kJ/mol.[20]

(17) Sliva, T. Yu.; Dobosz, A.; Jerzykiewicz, L.; Karaczyn, A.; Moreeuw, A.; Swiatek-Kozlowska, J.; Glowiak, T.; Kozlowski, H. *J. Chem. Soc., Dalton Trans.* **1998**, 1863−1867.
(18) Gerasimchuk, N. N.; Domasevich, K. V.; Zhmurko, O. A. Proceedings of "VI Conference on Crystallochemistry of Inorganic and Coordination Compounds," Lvov, Ukraine; Sept 22−26, 1992; p 19.
(19) (a) Domashevskaya, O. A.; Skopenko, V. V.; Gerasimchuk, N. N.; Zvereva, G. A.; Larin, G. M. *Koord. Khim.* **1990**, *16* (5), 630−635. (b) Domashevskaya, O. A.; Simonov, Yu. A.; Gerasimchuk, N. N.; Dvorkin, A. A.; Mazus, M. D. *Russ. J. Coord. Chem.* **1990**, *16* (11), 1544−1548. (c) Simonov, Yu. A.; Domashevskaya, O. A.; Skopenko, V. V.; Dvorkin, A. A.; Gerasimchuk, N. N. *Koord. Khim.* **1991**, *17* (5), 702−706.

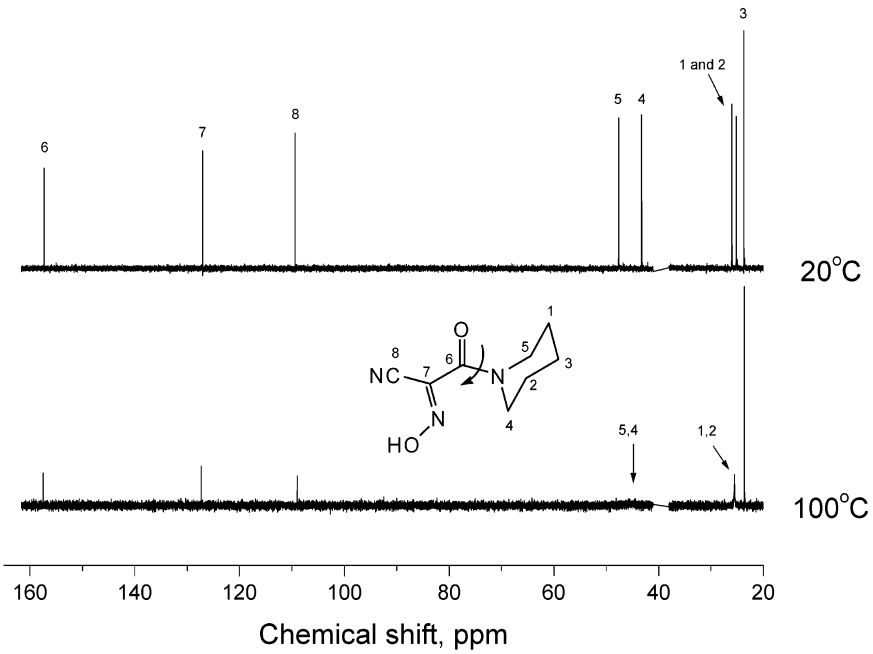
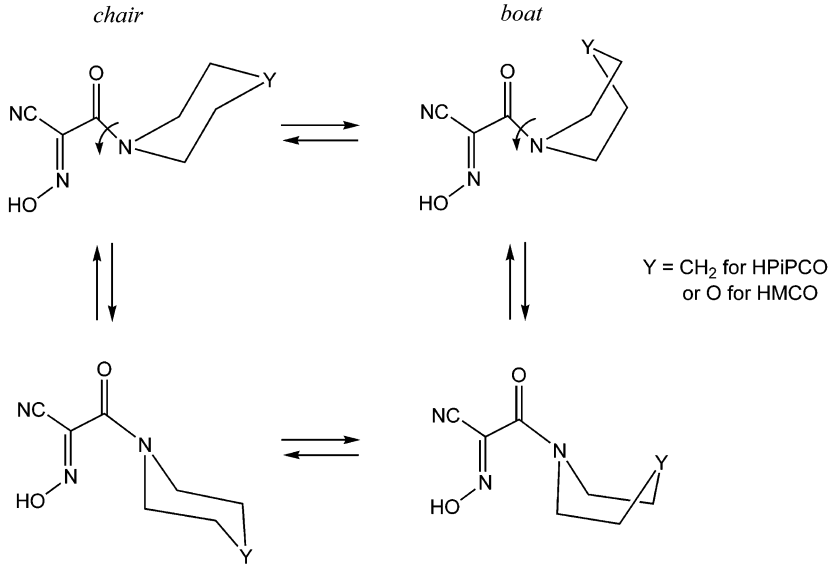


Figure 1. ^{13}C NMR spectra of HPiPCO in dmso-d_6 at two different temperatures showing temperature-dependent restricted rotation around amide bond.

Scheme 5

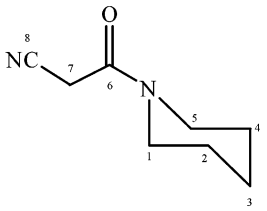
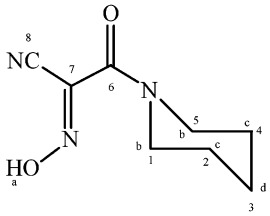
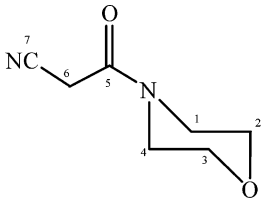
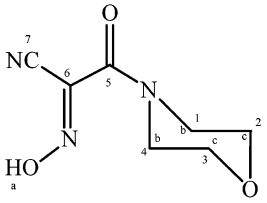


It is important to note that the ^{13}C spectrum of the $K^+(PiPCO^-)$ also in dmso-d_6 at 293 K showed only three types of carbon atoms present in the piperidine group (Supporting Information, S5). The magnetic equivalence of C1,C5 and C2,C4 carbon atoms of $K^+(PiPCO^-)$ indicates rotation of the piperidine group around the C6−N bond that is fast in the NMR time scale (Figure 4) contrary to the protonated ligand HPiPCO at room temperature (Supporting Information, S3).

The ^1H NMR spectrum of the HMCO ligand showed two highly deshielded signals for the oxime hydrogen at 14.29 and 14.10 ppm with a ratio of 3:1, and this evidenced the presence of *syn*- and *anti*-isomers in solution (Supporting Information, S3). The analysis of the ^{13}C NMR spectrum at room temperature in dmso-d_6 confirmed the finding of two isomers in the proton spectrum. Thus, there is a presence of two sets of peaks for nitrile carbon, oxime, and the amide group that indicates the coexistence of *syn/anti* isomers in the solution of the compound (Figure 2). This is a new phenomenon for this class of compounds and was not known for amidocyanoximes. The *syn/anti* isomers were previously detected by ^{13}C NMR spectroscopy for the HTLCO ligand,[7a] a cyanoxime containing a heterocyclic fragment, 2-(4-methyl)thiazoline, and also for its selenium analogue HSLCO.[7e] Another effect leading to a doubling of signals in the NMR spectra was the *nitroso/oxime* tautomeric equilibrium established earlier for HQCO,[21] a heterocyclic cyanoxime contain-

(20) (a) Gordon, A. J.; Ford, R. A. *The Chemist Companion* (Handbook)*;* John Wiley & Sons: New York, Chichester, Brisbane, Toronto, 1972; 304 pp. (b) Zabicky, J. *The Chemistry of Amides*; Interscience: 1970; 925 pp.

Table 1. Coalescence Temperatures, Exchange Rate, and Activation Energies Obtained from Variable Temperature ^{13}C NMR Spectra of HPiPCO, HMCO, and Their Precursors

Compound	T_{coal}, C	k_c, s^{-1}	$\Delta G^{\neq}$ (kJ/mol)
	for $C_{2,4}$: T=85°C for $C_{1,5}$: at 105°C signals disappear	for $C_{2,4}$: 651.9	for $C_{2,4}$: 68.9 ± 2.0
 **HPiPCO**	for $C_{2,4}$: T=70°C for $C_{1,5}$: at 95°C signals disappear	for $C_{2,4}$: 943.9	for $C_{2,4}$: 64.9 ± 1.9
	for $C_{2,3}$: at 105°C signals disappear	----------	----------
 **HMCO**	for $C_{1,4}$: T=100°C for $C_{2,3}$: T= 55°C	for $C_{1,4}$: 4998.4 for $C_{2,3}$: 488.6	for $C_{1,4}$: 65.6 ± 1.8 for $C_{2,3}$: 63.7 ± 2.0

ing a 2-quinoline group. The exact assignment of signals to *syn* and *anti* isomers requires special 2D NOE experiments and was beyond the scope of this investigation. The presence of two sets of four distinct peaks of the morpholine substituent demonstrated loss of equivalency for all four carbon atoms in the group in the ^{13}C spectrum of HMCO at room temperature (Figure 2). As in the case of HPiPCO, this indicated magnetic nonequivalency in the *syn* and *anti* geometrical isomers because of the restriction of free rotation around the C−N amide bond (Supporting Information, S3).

Variable temperature ^{13}C NMR studies of the dmso-d_6 solutions of HMCO allowed for observation of the rotation around the C−N amide bond (Scheme 5) and conversion of the *syn* isomer into a more stable *anti* isomer of the oxime. Carbon atoms C1 and C4, and C2 and C3 underwent two positional temperature-dependent exchanges. This is seen as the coalescence of pairs of the peaks in ^{13}C NMR spectra (Figure 2). Coalescence temperatures for carbon atoms were determined to be 100 °C for carbon atoms C1 and C4 and 55 °C for C2 and C3 of the morpholine group. Calculations of the activation energies were performed using es 6 and 7 and resulted in a value of $\Delta G^{\ddagger}$ as 65.6 ± 1.8 kJ/mol for carbon atoms C1 and C4, and $\Delta G^{\ddagger} = 63.7 \pm 2.0$ kJ/mol for C2 and C3 atoms. These values are typical for rotation energies commonly observed for amides.

Again, the ^{13}C spectrum of deprotonated cyanoxime in its $K^+(MCO^-)$ salt in the dmso-d_6 solution ($T = 296$ K) showed the equivalence of C1, C4 and C2, C3 carbon atoms in the morpholine group. Moreover, there is a presence of only one set of signals for the anion meaning absence of a *syn/anti* isomeric mixture. This indicates free rotation around the C5−N bond of the morpholine fragment (Figure 7) contrary to the protonated form of cyanoxime HMCO (Supporting Information, S3). Chemical shift values for this compound can be found in the Supporting Information, S5.

(21) Tyukhtenko, S. I.; Bernik, N. P.; Pilipenko, A. T.; Volovenko, Yu. M.; Gerasimchuk, N. N. *Dokl. Akad. Nauk UkSSR* **1986**, *B* (1), 58−62.

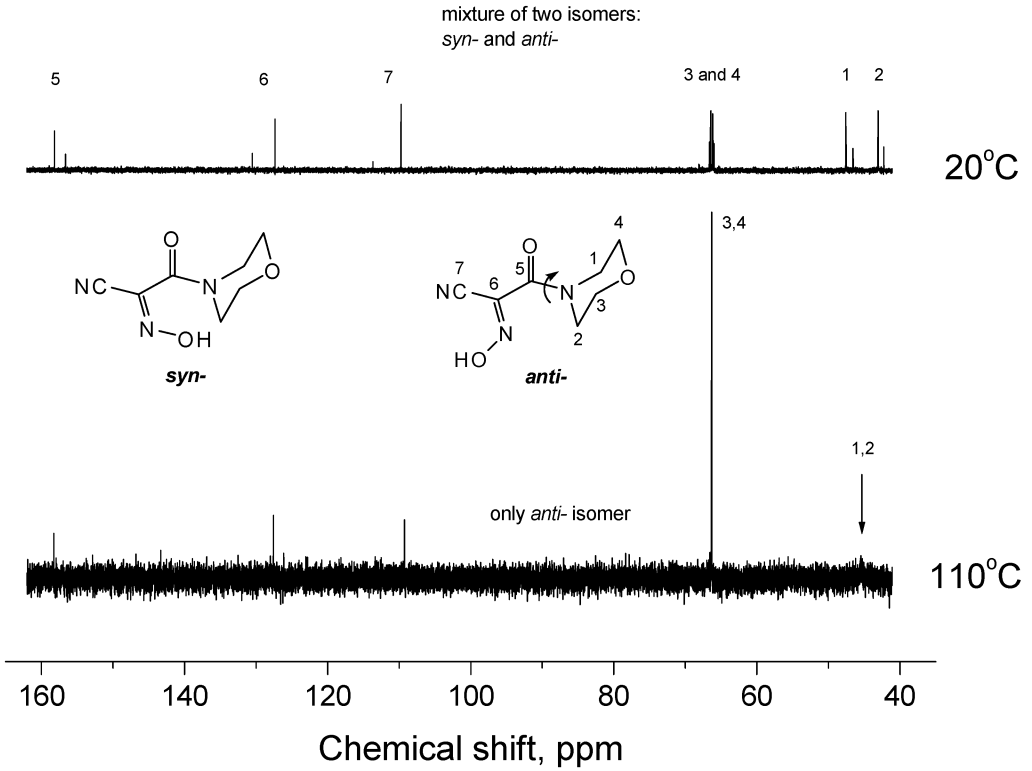


Figure 2. ^{13}C NMR spectra of HMCO in dmso-d_6 solutions at two different temperatures indicating restricted rotation and conformation changes in cyanoxime.

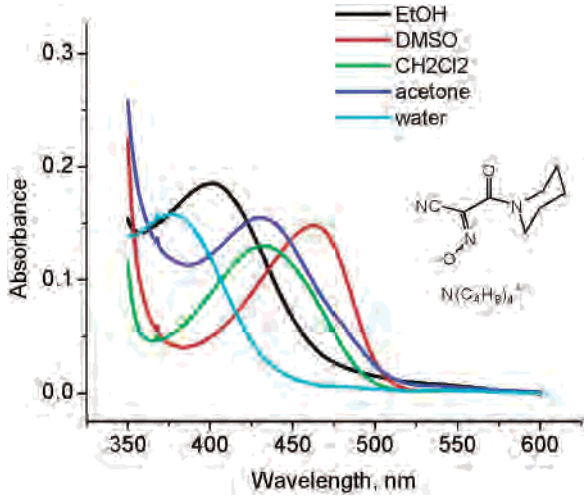


Figure 3. Solvatochromic series for equimolar solutions (5 mM) of NBu_4^+ $PiPCO^-$.

UV−Visible Spectra. Synthesized cyanoximes (with the exception of yellow HTCO) represent colorless microcrystalline compounds. An addition of base leads to the deprotonation of cyanoximes with the formation of yellow conjugated anions[22] that demonstrate weak absorbance in the visible region of the spectrum. The values of molar extinction coefficients, ϵ, typically are in the range of 20−200 depending on a ligand. The origin of color in these anionic compounds is similar to that in NO_2^- and $ONC(CN)_2^-$ anions.[23] There is a transition of $\pi \rightarrow \pi_N^*$ type with a substantial degree of charge transfer in the *nitroso* chromophore. The *nitroso* form of the anion is a dominant resonance form among four possible forms that describe the delocalization of the negative charge in cyanoximate anions.[7d] UV−visible spectra for deprotonated ACO^-, ECO^-, and TCO^- ligands were recorded earlier.[13,14] UV−visible spectra of the $N(C_4H_9)_4^+$ salts of $PiPCO^-$ and MCO^- anions in

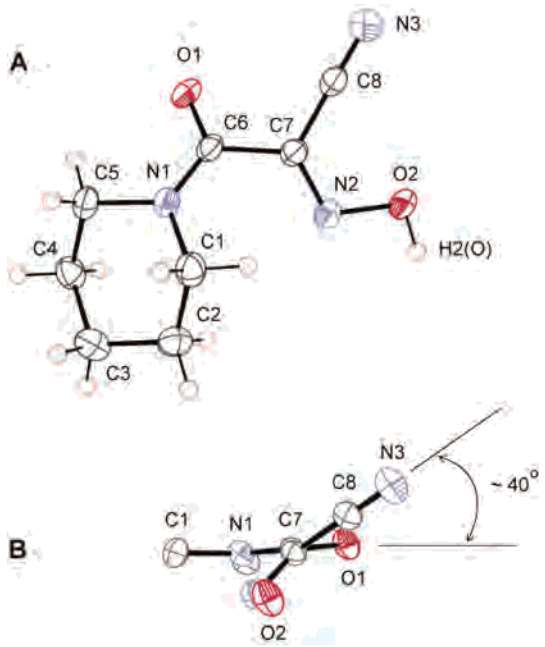


Figure 4. Molecular structure of HPiPCO as an ORTEP representation at 50% probability level. Numbering scheme in the molecule (A), and view along C7−C6 direction with indication of torsion angle between two planar fragments in the structure (B), where carbon atoms C2, C3, C4 and hydrogen atoms of the piperidine group are omitted for clarity.

(22) Kohler, H.; Seifert, B. *Z. Anorg. Allg. Chem.* **1970**, *379* (1), 1−8.

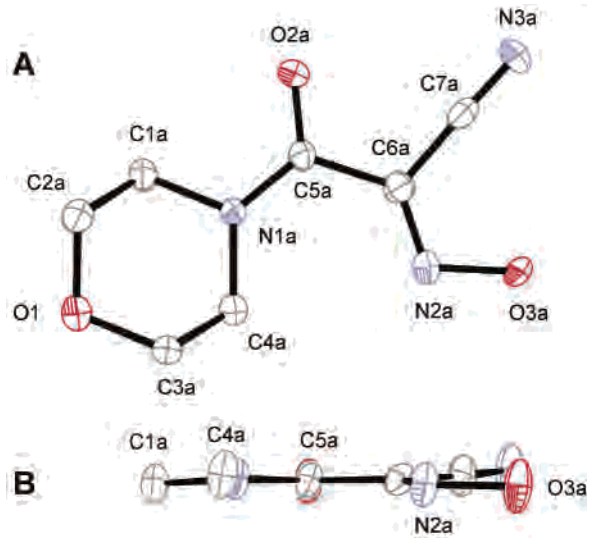


Figure 5. An ORTEP drawing at the 50% probability level of the molecular structure of one of the seven independent molecules of HMCO in the unit cell. The numbering scheme for the molecule (A), and side view along the C5−O2 direction showing planarity of the cyanoxime skeleton of the molecule (B). Carbon atoms C2, C3, oxygen atom O1, and hydrogen atoms of the morpholyl group are omitted for clarity.

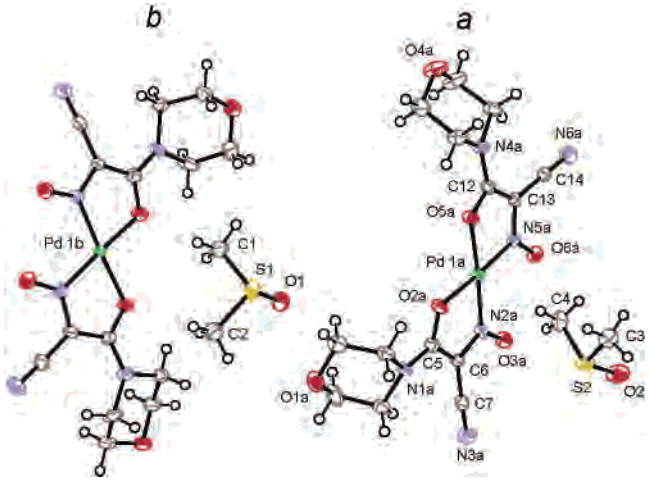


Figure 6. Two independent molecules **a** and **b** of $[Pd(MCO)_2]$·DMSO in the unit cell. An ORTEP drawing at the 50% probability level with the numbering scheme shown for molecule **a**.

different solvents at room temperature were obtained for the first time (Figure 3; Supporting Information, S6). A very pronounced solvent dependence (solvatochromic effect) of λ_{max} is indicative of the charge-transfer character[23a,e] of this transition. Thus, the biggest value of $\Delta\lambda_{max} = 87$ nm was determined between the absorbance of the $PiPCO^-$ anion in water and DMSO solution.

Structural Characterization of Cyanoxime Ligands. Structure of HPiPCO. Single crystals of HPiPCO suitable for X-ray analysis quality were obtained from ether. A clear block crystal with the dimensions 0.35 × 0.35 × 0.25 mm was used for structure determination. Crystal and refinement

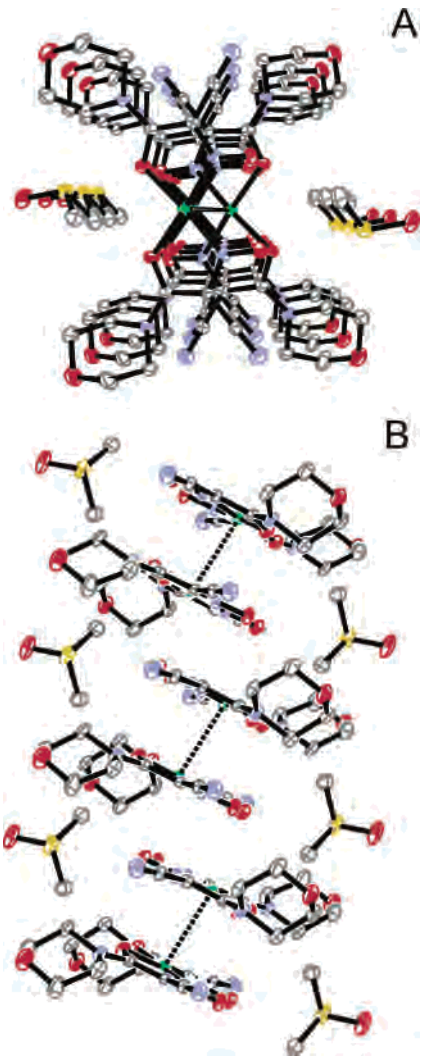


Figure 7. Fragment of packing of one of the independent $[Pd(MCO)_2]$·DMSO molecules into a crystal: (A) top view; (B) side view. Hydrogen atoms are omitted for clarity.

data are shown in Table 2, and selected bond distances and angles for the structure of the HPiPCO ligand are presented in Table 3. The molecular structure of this cyanoxime is shown in Figure 4, and the packing diagram for the compound can be found in the Supporting Information, S7.

The cyanoxime skeleton, in general, adopts a nonplanar *trans-anti* configuration. Nevertheless, there are two practically planar fragments in the core of the molecule excluding the piperidine group. One planar O(1), C(6), N(1), C(5), C(1) fragment involves the amide group where torsion angles are O(1)−C(6)−N(1)−C(5) = −172.8° and O(1)−C(6)−N(1)−C(1) = −173.2°. Another planar fragment is the cyanoxime group N(3), C(8), C(7), N(2), O(2); torsion angles between atoms are even less than in the previous fragment and equal −1.7° and 3.9° for the angles N(3)−C(8)−C(7)−N(2) and O(2)−N(2)−C(7)−C(8), respectively. The two torsion angles (in the structure of HPiPCO) that define nonplanarity of the cyanoxime skeleton are O(1)−C(6)−C(7)−N(2) = −137.7° and O(1)−C(8)−C(7)−C(8) = 31.9°. It is interesting to note that the two carbon atoms C5 and C1 and nitrogen atom N1 of the piperidine group and amide carbon atom C6 are in one plane. This is a different finding than was previously

(23) (a) Sidman, J. W. *J. Am. Chem. Soc*. **1957**, *79*, 2669−2675. (b) Sidman, J. W. *J. Am. Chem. Soc*. **1957**, *79*, 2675−2678. (c) Kohler, H.; Lux, G. *Inorg. Nucl. Chem*. **1968** (4), 133−136. (d) Drago, R. S. *Physical Methods in Inorganic Chemistry*; Reinold: New York, 1976. (e) Feuer, H., Ed. *The Chemistry of the Nitro- and Nitroso- Groups*; R. Krieger Publishing Co.: Huntington, NY, 1981; Part 1, 771 pp.

Table 2. Crystal Data and Structure Refinement Data for Structures of Several Synthesized Compounds

parameter	HPiPCO	HMCO	$K_2[Pd(AACO)_2]\cdot 4H_2O$	$[Pd(MCO)_2]\cdot DMSO$
cheml formula	$C_8H_{11}N_3O_2$	$C_7H_9N_3O_3$	$C_6H_8N_4O_{10}K_2Pd$	$C_{16}H_{22}N_6O_7PdS$
fw (g/mol)	181.20	183.17	480.76	548.86
temperature (K)	173(2)	173(2)	223(2)	293(2)
wavelength (Å)	0.71073	0.71073	0.71073	0.71073
crystal system	orthorhombic	orthorhombic	triclinic	triclinic
space group	$P2_12_12_1$	$P2_12_12_1$	P_1	P_1
a (Å)	6.674	7.3098	6.459	6.768
b (Å)	10.3462	14.435	9.134	13.638
c (Å)	13.2342	54.810	14.204	24.424
α (deg)	90	90	103.193	103.43
β (deg)	90	90	102.519	90.45
γ (deg)	90	90	97.216	104.33
volume ($Å^3$)	913.8	5783.4	782.8	2119.5
Z	4	28	2	4
density (calc), (Mg/m^3)	1.317	1.473	2.040	1.720
abs coeff (mm^{-1})	0.097	0.117	1.772	1.026
F(000)	384	2688	472	1112
final *R* indices	0.0323	0.0727	0.0549	0.0515
$[I > 2\sigma(I)]$	0.846	0.1809	0.1401	0.0851
R indices	0.0358	0.0922	0.0648	0.1087
(all data)	0.0872	0.1914	0.1535	0.1009

Table 3. Selected[a] Bond Distances and Valence Angles for the Structure of HPiPCO

bond length, Å		angle, deg	
C(1)−N(1)	1.475	O(1)−C(6)−N(1)	124.65
N(3)−C(8)	1.142	O(1)−C(6)−C(7)	114.26
O(1)−C(6)	1.248	N(2)−C(7)−C(8)	122.14
O(2)−H2(O)	0.942	N(2)−C(7)−C(6)	121.13
O(2)−N(2)	1.376	C(8)−C(7)−C(6)	115.88
C(5)−N(1)	1.479	N(3)−C(8)−C(7)	179.09
C(6)−O(1)	1.248	C(6)−N(1)−C(1)	126.99
C(6)−N(1)	1.326	C(6)−N(1)−C(5)	120.00
C(6)−C(7)	1.509	C(1)−N(1)−C(5)	113.00
C(7)−N(2)	1.287	C(7)−N(2)−O(2)	111.42
C(8)−C(7)	1.453	H2(O)−O(2)−N(2)	100.77
		N(1)−C(6)−C(7)	121.05

[a] Bonds and angles in the piperidine group are not shown.

Table 4. Selected Bond Lengths and Angles for the Structure of HMCO[a]

bond length, Å		valence angle, deg	
O(1A)−C(2A)	1.429	C(2A)−O(1A)−C(3A)	109.6
O(1A)−C(3A)	1.442	C(5A)−N(1A)−C(1A)	118.8
O(2A)−C(5A)	1.234	C(5A)−N(1A)−C(4A)	129.4
O(3A)−N(2A)	1.378	C(1A)−N(1A)−C(4A)	111.8
N(1A)−C(5A)	1.335	C(6A)−N(2A)−O(3A)	111.5
N(1A)−C(1A)	1.469	N(1A)−C(1A)−C(2A)	109.6
N(1A)−C(4A)	1.472	O(1A)−C(2A)−C(1A)	109.8
N(2A)−C(6A)	1.280	O(1A)−C(3A)−C(4A	111.3
N(3A)−C(7A)	1.146	N(1A)−C(4A)−C(3A)	110.2
C(1A)−C(2A)	1.528	O(2A)−C(5A)−N(1A)	123.5
C(3A)−C(4A)	1.505	O(2A)−C(5A)−C(6A)	114.0
C(5A)−C(6A)	1.521	N(1A)−C(5A)−C(6A)	122.5
C(6A)−C(7A)	1.457	N(2A)−C(6A)−C(7A)	120.6
		N(2A)−C(6A)−C(5A)	126.8
		C(7A)−C(6A)−C(5A)	112.5
		N(3A)−C(7A)−C(6A)	176.9

[a] Data for only one molecule (A) out of seven independent cyanoxime molecules in the unit cell (S9, Supporting Information).

observed in the structures of *N*,*N*′-dimethylamide-cyanoxime, HDCO,[16b] its thio analogue HTDCO,[7c,24] and their numerous complexes.

The oxime group in HPiPCO has a C(7)−N(2) distance of 1.287 Å and is longer than a double bond. The N(2)−O(2) bond is 1.376 Å and much shorter than a single bond (Table 3). The piperidine group adopts the chair conformation in a crystal (Figure 4). The group is twisted with respect to the plane O(1), C(6), N(1), C(1) of the molecule, resulting in different distances between the oxygen atom O(1) of the carbonyl group and the carbon atoms of the piperidine fragment. Thus, the O(1)−C(5) distance is 2.79 Å while the O(1)−C(1) distance is 3.66 Å. That difference accounted for the magnetic nonequivalence of these carbon atoms as well as the C(2), C(3), and C(4) carbon atoms in the ^{13}C NMR spectrum of the compound in the solution at room temperature. Moreover, the bond length of N(1)−C(6) is 1.326 Å (Table 3) and has a substantial double bond character, leading to restricted rotation around the bond observed in ^{13}C NMR spectra.

The crystal structure of the HPiPCO ligand represents a system of chains interconnected by van der Waals forces between piperidine groups. Inside each chain there is a strong intermolecular hydrogen bonding between the oxygen atom of the carbonyl group and carbonyl group and the oxime OH group of the adjacent molecule. Parameters of H bonding in the structure are shown in the Supporting Information, S8.

Structure of HMCO. Single crystals suitable for an X-ray analysis of the HMCO ligand were obtained from acetone. The ligand crystallized as needles, and a single crystal of $0.55 \times 0.55 \times 0.25$ mm dimensions was selected for X-ray analysis (Table 2).

The selected bond distances and angles for the HMCO ligand are presented in Table 4. The molecular structure of the ligand is shown in Figure 5. This crystal structure was found to be quite rare and interesting because of the presence of seven independent, but structurally similar, cyanoxime molecules in the unit cell (Supporting Information, S9). There are other known cases of multiple crystallographically independent molecules in the unit cell.[25] For example, diphenylacetylene (tollane) has even 9 independent molecules

(24) Domasevich, K. V.; Ponomareva, V. V.; Skopenko, V. V.; Tsan, H.; Sieler, J. *Russ. J. Inorg. Chem.* **1997**, *42* (7), 1128−1133.

in its unit cell.[26] All these cases evidence crystal lattices that are not at thermodynamic equilibrium, and typically studied compounds have numerous polymorphs.[27] Another key issue in some of these crystal structures is the possibility for formation of multiple and strong hydrogen bonds. Crystallization of a compound from different solvents usually results in different structures.[27] In the structure of HMCO there is a strong H-bonding between the OH group of the oxime fragment and the carbonyl and morpholine oxygen atoms (Supporting Information, S10). Bond lengths and valence angles were not significantly different between all seven molecules. Thus, the N−O distance of 1.38 Å and the C═N distance of 1.29 Å (Table 4) of the CNO fragment indicated the *oxime* character of HMCO. Other bond lengths in the structure were not different from those known for other protonated cyanoximes.[7a,16b] The cyano group is linear with the C6−C7−N3 angle equal to 177°.

The cyanoxime skeleton of the molecule, with the exception of the morpholine group, adopted a practically planar trans-anti configuration (Figure 5). This finding was opposite to the above-described structure of the HPiPCO, and also the HQCO[7a] and HDCO[16b] ligands. However, the finding is similar to a completely planar HACO structure.[18] It is interesting to note that the latter cyanoxime also had two independent molecules in the unit cell. There are several torsion angles that may define the planarity of the cyanoxime−amide skeleton in the structure of the HMCO with exclusion, by default, of the nonplanar morpholine group. These angles are O2−C5−N1−C6 = 177.8°, N2−C6−C7−C5 = −179.3°, O2−C5−C6−N2 = −174.7°, O3−N2−C6−C5 = 176°. Also, there are slightly different torsion angles, O2−C5−C6−C7 = −7.8° and N1−C5−C6−C7 = 170.2°, with less than 10° deviations from what is typical for reflecting planarity, 180° (or 0°) angles.

The morpholine fragment adopted a *chair* conformation in a solid state. Similar to the HPiPCO ligand, the amide bond length C5−N1 is equal to 1.335 Å (Table 4), indicating a substantial double bond character. The restricted rotation around this bond, certainly, was responsible for the nonequivalence of all carbon atoms of morpholine group in the ^{13}C NMR spectrum of the HMCO solution at room temperature (Supporting Information, S3; Figure 2).

Finally, in a solid state the HMCO exists only as the *anti* isomer contrary to the observed isomeric *syn/anti* mixture in both ^{1}H and ^{13}C NMR spectra of dmso-d_6 solutions of the compound (see NMR discussion above).

Spectroscopic and Structural Characterization of Pd(II) and Pt(II) Cyanoximates. IR Spectra of Synthesized

Table 5. The Most Important Vibrations of Cyanoxime Anions in IR Spectra of Synthesized Compounds

compound	assigned frequencies, cm^{-1}			
	$\nu_{C\equiv N}$	$\nu_{C=O}$	$\nu_{N=O}$	ν_{CNO}
$K^+(ACO)^-$	2210	1676	1280	1175
			1270[a]	1165[a]
$K[Pd(ACO)(AACO)]\cdot 3H_2O$	2220	1616	1331	1175
$K[Pt(ACO)(AACO)]\cdot 2H_2O$	2218	1644	1319	1183
		1636		
$K^+(ECO)^-$	2209	1674	1280	1140
			1265[a]	1115[a]
$K_2[Pd(AACO)_2]\cdot 4H_2O$	2221	1636	1317	1166
$K^+(TCO)^-$	2209	885[b]	1280	1140
			1265[a]	1135[a]
$Pd(TCO)_2$	2217	835, 879[b]	1309	1155
$Pt(TCO)_2$	2218	835, 869[b]	1301	1157
$K^+(PiPCO)^-$	2203	1617	1172	1004
$Pd(PiPCO)_2\cdot H_2O$	2209	1576	1302	1128
$Pt(PiPCO)_2$	2203	1567	1298	1115
$K^+(MCO)^-$	2206	1602	1222	1024
$Pd(MCO)_2$	2210	1576	1310	1114
$Pt(MCO)_2$	2207	1570	1309	1115

[a] Frequencies for ^{15}N isotopomers. [b] $\nu_{C=S}$ vibration for TCO^- anion.

Transition Metal Complexes. In the past, the method of IR spectroscopy has been successfully applied for studies of different metal complexes based on cyanoximes. The IR spectroscopic criteria were developed to determine the binding mode of these ligands to metal centers.[28] The exact assignment of vibrations with participation of the >CNO fragment was conducted using isotopically enriched (53% ^{15}N, >CNO group) cyanoximes. In all of these cases, the source of the stable isotope label was $Na^{15}NO_2$, allowing synthesis of the isotopomeric ligands with reasonably good yields in the range of 50−70%. Therefore, a comparative analysis of IR spectra of labeled and unlabeled compounds allowed unambiguous detection of stretching vibrations with participation of the *oxime/nitroso* fragment. The most important assigned frequencies of vibrations in the IR spectra of the synthesized anionic cyanoximates are shown in Table 5. The IR spectra of bivalent Pd(II) and Pt(II) complexes were matched against the spectra of ionic K^+L^- with the noncoordinated cyanoxime anion.

A lowering of the $\nu_{C=X}$ (X = O, S) vibrations in the IR spectra of transition metal compounds in comparison with those for K^+L^- indicated the involvement of the carbonyl (thiocarbonyl) group in coordination (Table 5). Increasing the frequency of vibrations with the participation of the CNO fragment also evidenced the binding of cyanoximes to Pd(II) and Pt(II) via the nitrogen atom of the nitroso group.[14,16a,28] These changes are similar to the previously observed coordination mode of the other ligands in numerous complexes; structures of some were confirmed by X-ray

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(26) Zorkii, P. M. Supersymmetry of Molecular and Crystal Structures. In *Problems of Crystallochemistry*; Nauka: Moscow, 1984; p 102 and references therein.

(27) (a) Bernstein, J. Conformational Polymorphism. In *Organic Solid State Chemistry*; Desiraju, G. R., Ed.; Elsevier: Amsterdam, 1987; Chapter 13. (b) Brittain, H. G. *Polymorphysm in Pharmaceutical Solids*; Marcel Dekker: New York, 1999. (c) Boldog, I.; Rusanov, E. B.; Chernega, A. N.; Sieler, J.; Domasevich, K. V. *Angew. Chem., Int. Ed.* **2001**, *40* (18), 3435−3438.

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analysis.[7d,17,19] A bidentate chelate function of the cyanoxime anions in transition metal complexes that are synthesized and presented in this paper is offered on the basis of the consistence of our observations and literature data.[31] There is a formation of a five-membered cyclic structure composed of the central metal atom, an oxygen (sulfur) atom of an amide (thioamide) group, and a nitrogen atom of the nitroso group. Structural studies of two of the obtained complexes have confirmed this suggestion.

Structure of [Pd{MCO}$_2$·DMSO] Complex. Yellow needle type single crystals of this complex were obtained from powdery material after recrystallization from DMSO at +95 °C and overnight cooling in a thermostat to +30 °C. It is interesting to note that the crystallization of transition metal complexes from DMSO represents a rare phenomenon. A crystal of 0.55 × 0.01 × 0.01 mm dimensions was selected for structural studies. Yellow transparent crystals of [Pd(MCO)$_2$·DMSO] became opaque after filtering and an overnight exposure to air on a microscope slide due to partial desolvation. The structure of the complex is displayed in Figures 6−8, and selected bond angles and valence angles for this complex are presented in Table 6.

There are two independent molecules **a** and **b** of the complex in the structure (Figure 6). Both molecules adopt essentially the same geometry but have slightly different bond lengths and valence angles. Two independent molecules form columns that have a "staircase" type structure by means of $\pi-\pi$ stacking interactions (Figure 7), and solvent molecules occupying channels between two columns of complexes. Each column consists of distinctive and alternating dimeric [Pd(MCO)$_2$·DMSO]$_2$ units. All Pd atoms in the same column are coplanar forming a zigzag chain with the angle between palladium(II) atoms equal to 131° (Figure 7). Inside of a [Pd(MCO)$_2$·DMSO]$_2$ dimer there is a very close Pd···Pd contact equal to 3.129 Å (Figure 8), while the interdimeric Pd···Pd distance is 4.271 Å. It is interesting to note that the first distance is actually the shortest reported[29] thus far for Pd···Pd interaction, which is significantly shorter than the interatomic distance in metallic palladium, 3.891 Å.[30] Two individual Pd(MCO)$_2$ molecules are oriented in opposite directions in a dimeric unit (Figure 8). The cyanoxime anions are in the *nitroso* form and adopt the *cis-anti* configuration in the structure. Thus, bond length N−O is shorter than the C−N bond in this group in the complex (Table 6) comparing with the structure of uncomplexed ligand (Table 4). Therefore, binding of transition metal to the cyanoxime molecule leads to the conformation change where the ligand demonstrates chelate function upon coordination (Scheme 6). The value of the "bite angles" of the cyanoxime ligands is ∼81°, which is in the normal range for this type of bidentate coordination (Table 6). Bond lengths C(5)−C(6) and C(12)−C(13) for coordinated MCO$^-$ anion in Pd(MCO)$_2$ complex are significantly shorter than the same bond in protonated cyanoxime (Tables 4 and 6). The bond length for the carbonyl group in the complex is slightly longer comparing to that in HMCO molecule. Morpholine groups of cyanoxime anions in the Pd complex adopt the *chair* conformation in the crystal. With the exception of the morpholine fragment, the carbon−nitrogen−oxygen skeleton of the cyanoxime ligand is essentially planar (Figure 8). The monomeric Pd(MCO)$_2$ unit in the complex has *cis* geometry with the palladium(II) central atom being in distorted square-planar surroundings (Figure 8). One of the methyl groups of the DMSO solvate molecule in the crystal is oriented toward the oxygen atoms of the nitroso group of anions. Thus, there was observed close and almost equidistant location of the H(4b) proton of the solvent's CH_3 group between the O(6a) and O(3a) atoms. Parameters of such interaction are the following: distance H(4b)−O(3a) = 2.54 Å with the angle O(3a)−H(4b)−C(4) = 134.8°, and distance H(4b)−O(6a) = 2.55 Å with the angle O(6a)−H(4b)−C(4) = 138.5°.

Table 6. Selected[a] Bond Lengths and Angles for the Structure of One of the Two Independent Molecules (Molecule **a**) of [Pd(MCO)$_2$·DMSO]

Cyanoxime Anions

bond lengths, Å		valence angles, deg	
O(2a)−C(5a)	1.277	C(5a)−N(1a)−C(1a)	126.8
O(3a)−N(2a)	1.253	C(5a)−N(1a)−C(4a)	119.6
O(5a)−C(12a)	1.281	O(3a)−N(2a)−C(6a)	120.5
O(6a)−N(5a)	1.239	O(2a)−C(5a)−N(1a)	119.3
N(1a)−C(5a)	1.323	O(2a)−C(5a)−C(6a)	117.0
N(2a)−C(6a)	1.361	N(1a)−C(5a)−C(6a)	123.5
N(3a)−C(7a)	1.138	N(2a)−C(6a)−C(7a)	118.4
N(4a)−C(12a)	1.332	N(2a)−C(6a)−C(5a)	114.0
N(5a)−C(13a)	1.354	C(7a)−C(6a)−C(5a)	127.1
N(6a)−C(14a)	1.155	N(3a)−C(7a)−C(6a)	177.5
C(5a)−C(6a)	1.463	C(12a)−N(4a)−C(11a)	117.4
C(6a)−C(7a)	1.434	C(12a)−N(4a)−C(8a)	120.3
C(12a)−C(13a)	1.448	O(6a)−N(5a)−C(13a)	121.3
C(13a)−C(14a)	1.438	O(5a)−C(12a)−N(4a)	118.0
		O(5a)−C(12a)−C(13a)	116.5
		N(4a)−C(12a)−C(13a)	125.5
		N(5a)−C(13a)−C(14a)	117.0
		N(5a)−C(13a)−C(12a)	115.0
		C(14a)−C(13a)−C(12a)	127.5
		N(6a)−C(14a)−C(13a)	178.0

Pd Center

distances, Å		angles, deg	
Pd(1a)−N(2a)	1.981	N(2a)−Pd(1a)−N(5a)	103.17
Pd(1a)−N(5a)	1.986	N(2a)−Pd(1a)−O(5a)	175.69
Pd(1a)−O(5a)	2.019	N(5a)−Pd(1a)−O(5a)	80.93
Pd(1a)−O(2a)	2.021	N(2a)−Pd(1a)−O(2a)	81.13
		C(5a)−O(2a)−Pd(1a)	113.7
		C(12a)−O(5a)−Pd(1a)	113.8
		O(3a)−N(2a)−Pd(1a)	125.8
		O(6a)−N(2a)−Pd(1a)	113.6
		O(6a)−N(5a)−Pd(1a)	125.5
		C(13a)−N(5a)−Pd(1a)	113.1

[a] Bond lengths and valence angles for carbon and oxygen atoms of the morpholine group have normal values and are not shown.

Structure of K$_2$[Pd(AACO)$_2$]·4H$_2$O Complex. Single crystals of a complex suitable for X-ray diffraction were grown upon slow concentration of the aqueous mother liquor solution obtained from the reaction of K_2PdCl_4 with $K^+(ECO^-)$ after the small amount of immediate yellow precipitate was filtered off. Needlelike yellow crystals appeared in the vial

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(30) Emsley, J. *The Elements*; Clarendon Press: Oxford, 1991.
(31) (a) Kukushkin, V. Yu.; Pombeiro, A. J. L. *Coord. Chem. Rev.* **1999**, *181*, 147−175. (b) Kopylovich M. N.; Kukushkin, V. Yu.; Haukka, M.; da Silva, J. J. R.; Pombeiro, A. J. L. *Inorg. Chem.* **2002**, *41* (18), 4798−4804.

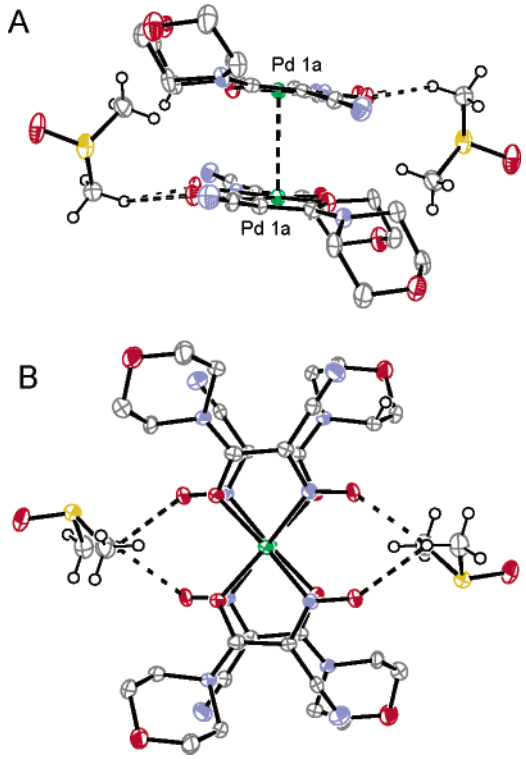
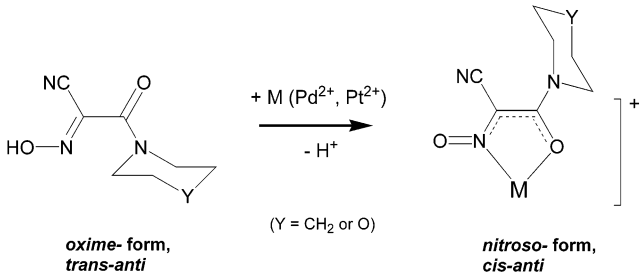


Figure 8. Molecular structure of a dimeric unit $\{[Pd(MCO)_2]\cdot DMSO\}_2$ in the structure of the complex: (A) side view; (B) top view, indicating closest CH···O contacts between the solvent molecules and the oxygen atom of the nitroso group.

Scheme 6



within approximately 4 weeks. A crystal of 0.25 × 0.10 × 0.10 mm dimensions was selected for studies.

As mentioned earlier, the reaction did not lead to the expected "$Pd(ECO)_2$" compound. Instead, cleavage of the C_2H_5 group was observed with the formation of the dianion of 2-cyano-2-isonitrosoacetic acid $AACO^{2-}$ (Scheme 4). The explanation for this hydrolysis might be in the time length of reaction of the complex formation between these catalytically active transition metal ions and cyanoximates ACO^- and ECO^-. Metal complexes that formed with other ligands, such as $PiPCO^-$, TCO^-, and MCO^-, typically precipitated out within 10 min to 2 h after the mixing of components. In the case for the ACO^- and ECO^- anions, some incomplete precipitation took place after ~12 h of stirring and signaled the beginning of the workup procedure. The prolonged exposure to catalytically active metals led to a formation of the Pd(II) and Pt(II) complexes with partially or completely hydrolyzed cyanoxime anions. Hydrolysis of other amidocyanoximes was recently established for the Cu(II) complexes;[17]

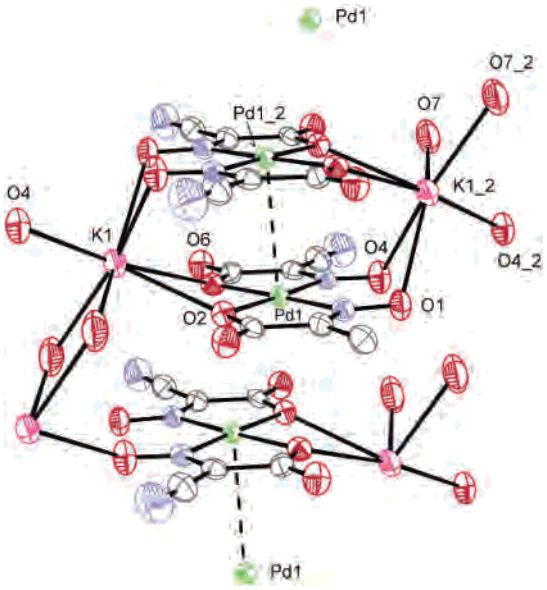


Figure 9. Fragment of the crystal structure of $K_2[Pd(AACO)_2]\cdot 4H_2O$ showing $\pi-\pi$ stacking interaction between dimeric units.

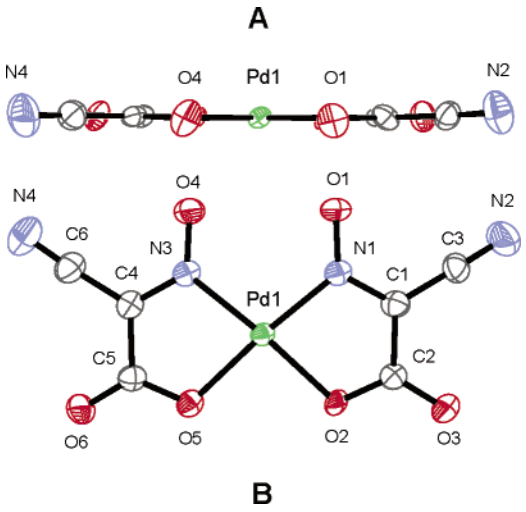


Figure 10. Structure of the $[Pd(AACO)_2]^{2-}$ anion: side view (A), and top view (B) with numbering scheme for the cyanoxime ion.

however, it was never previously observed for the cyanoxime anions listed and described above.

A fragment of the crystal structure of the obtained complex $K_2[Pd(AACO)_2]\cdot 4H_2O$ is shown in Figure 9, and the structure of the dianion $[Pd(AACO)_2]^{2-}$ is displayed in Figure 10. Figure 9 contains only nondisordered K(1) cation, and O(7), O(9) water molecules. Disordered between the two positions, the K(2) ions as well as the O(10) and O(11) water molecules are not shown. They can be viewed using the respective CIF from the Supporting Information. The selected bond distances and angles for the structure of this palladium(II) compound are presented in Table 7. The studied complex can be described as a dimeric dipalladium sandwich polymer. The crystal structure of the complex $K_2[Pd(AACO)_2]\cdot 4H_2O$ represents alternating zigzag columns of $[Pd(AACO)_2]^{2-}$ dianions held together by $\pi-\pi$ interactions between these planar dianions (Figure 9). Columns from the opposite sides are surrounded with hydrated K^+ countercations connected to oxygen atoms of the cyanoxime anions. Palladium(II)

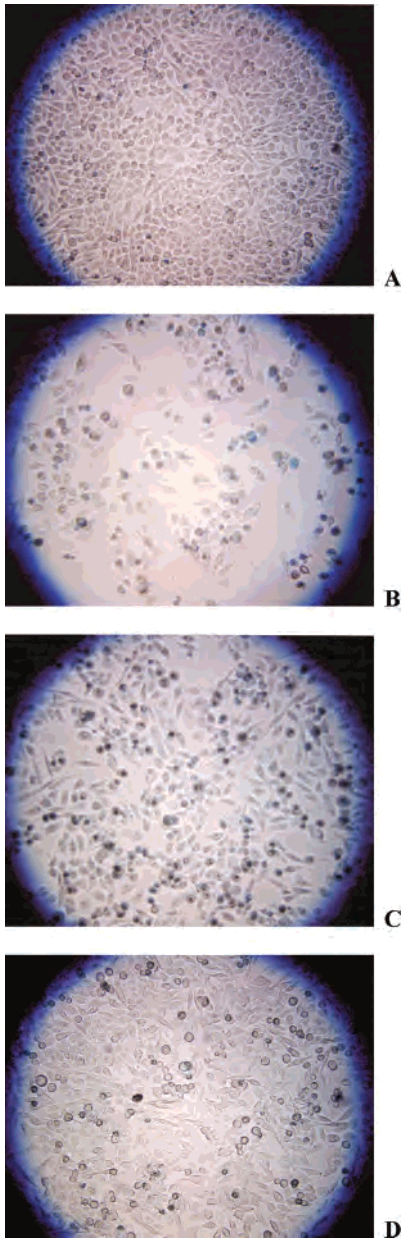


Figure 11. Photographs of fixed and Trypan Blue stained HeLa cells after overnight exposure to (A) cisplatin at 1mM concentration, (B) dmso, 1%, (C) $[Pd(MCO)_2]$, and (D) $[Pt(MCO)_2]$. Metal cyanoximates at 0.1 mM concentrations.

atoms in the structure can be viewed as a zigzag chain with an angle Pd(1)−Pd(1_2)−Pd = 155.4°, and all Pd atoms in this chain are in one plane. There is a pronounced dimeric motif in the structure since there are two alternating Pd···Pd distances 3.202 Å and 3.403 Å in the column of $[Pd(AACO)_2]^{2-}$ dianions (Figure 9). Coplanar cyanoxime anions are oriented in opposite directions in dimeric $[Pd(AACO)_2]_2^{4-}$ units (Figure 9). The shortest distance between the Pd(II) ion and the ordered K(1) cation is 3.802 Å.

The $AACO^{2-}$ ligand is bound to the Pd^{2+} central atom via the oxygen atom of the carbonyl and the nitrogen atom of the nitroso group with the formation of a five-membered metallocycle (Figure 10). The "bite" angles of the chelate cyanoxime anions are ~82° and are normal for this type of

Table 7. Selected Bond Lengths and Angles for the Structure of $K_2Pd(AACO)_2 \cdot 4H_2O$

Anion			
bond lengths, Å		valence angles, deg	
C(1)−N(1)	1.323	N(1)−C(1)−C(3)	120.80
C(1)−C(3)	1.437	N(1)−C(1)−C(2)	116.98
C(1)−C(2)	1.474	C(3)−C(1)−C(2)	122.20
C(2)−O(3)	1.243	O(1)−N(1)−C(1)	120.94
C(2)−O(2)	1.275	O(3)−C(2)−O(2)	124.08
C(3)−N(2)	1.141	O(3)−C(2)−C(1)	119.89
N(1)−O(1)	1.280	O(2)−C(2)−C(1)	115.99
C(4)−N(3)	1.317	N(2)−C(3)−C(1)	177.79
C(4)−C(6)	1.437	N(3)−C(4)−C(6)	119.12
C(4)−C(5)	1.490	N(3)−C(4)−C(5)	117.40
C(5)−O(6)	1.222	C(6)−C(4)−C(5)	123.49
C(5)−O(5)	1.283	O(6)−C(5)−O(5)	125.18
C(6)−N(4)	1.122	O(6)−C(5)−C(4)	119.44
N(3)−O(4)	1.262	O(5)−C(5)−C(4)	115.38
		N(4)−C(6)−C(4)	176.64
		O(4)−N(3)−C(4)	121.78
Metal Cations			
distances, Å		angles, deg	
Pd^{2+}			
N(1)−Pd(1)	1.976	C(1)−N(1)−Pd(1)	112.17
N(3)−Pd(1)	1.980	C(4)−N(3)−Pd(1)	112.06
O(2)−Pd(1)	2.034	C(2)−O(2)−Pd(1)	112.69
O(5)−Pd(1)	2.034	C(5)−O(5)−Pd(1)	112.71
		N(1)−Pd(1)−N(3)	101.93
		N(1)−Pd(1)−O(2)	82.11
		N(1)−Pd(1)−O(5)	175.63
		N(3)−Pd(1)−O(2)	175.93
		N(3)−Pd(1)−O(5)	82.44
		O(2)−Pd(1)−O(5)	93.52
K^+, Ordered			
K(1)−O(1)	2.852	O(1)−K(1)−O(4)	101.50
K(1)−O(2)	2.832	O(1)−K(1)−O(5)	72.90
K(1)−O(4)	2.777	O(1)−K(1)−O(7)	140.26
K(1)−O(4_2)[a]	2.926	O(2)−K(1)−O(1)	105.85
K(1)−O(5)	2.934	O(2)−K(1)−O(4)	116.25
K(1)−O(7)	2.618	O(2)−K(1)−O(5)	61.82
K(1)−O(7_2)[a]	3.193	O(2)−K(1)−O(7)	66.07

[a] Contacts to oxygen atoms of a neighboring Pd-dimeric unit.

binding mode (Table 7). The complex has cis geometry in the planar $[Pd(AACO)_2]^{2-}$ anion. Thus, the O(2)−Pd−N(1)−C(1) atoms demonstrate a torsion angle of 1.3°. The cyanoxime anion $AACO^-$ adopts a planar *cis-anti* configuration[7d,18] and is present in the complex in *nitroso* form (Figure 10). Atoms O(3)−C(2)−C(1)−C(3) form a torsion angle of 177°.

There is one peculiarity, common for both metal complexes examined by X-ray analysis, that should be noted especially. This is a rather short Pd···Pd distance in dimeric units of $[Pd(MCO)_2]$ and $[Pd(AACO)_2]_2^-$ equal to 3.13 Å and 3.20 Å respectively. The matter is that the observed metal−metal separation is significantly shorter than that in metallic palladium with a = 3.89 Å.[30] To the best of our knowledge, the palladium(II) cyanoximates discussed above represent compounds with the shortest Pd···Pd distances found thus far. There is definitely an attractive interaction between two diamagnetic $4d^8$ metal ions (Supporting Information, S11). However, it is unclear yet by means of what type of forces or metal based orbitals this interaction is provided. Several observations of similar binding effect for both diamagnetic homometallic complexes of gold,[33] co-

poper,[34] silver,[35] thallium,[36] platinum,[37] and heterometallic compounds[38] have appeared during recent years.

***In Vitro* Testing of Complexes and Assessment of Their Biological Activity.** The synthesized and characterized cyanoximates of bivalent Pt and Pd represent a new class of chelate complexes. These novel compounds with amide−cyanoximes have never been tested for biological activity. As a cellular model for screening of these compounds, we utilized epithelial cells of the human cervical cancer cell line, HeLa, obtained from ATTC. Unfortunately, there were only two compounds moderately soluble in water: $K_2[Pd(AACO)_2]\cdot 4H_2O$ and $K[Pt(ACO)(AACO)]\cdot 2H_2O$. All other metal complexes were insoluble in alcohol, DMF, aqueous solutions, and buffers at physiological pH. Therefore, the solutions were prepared in pure DMSO (Aldrich). First of all, to determine which complexes were good candidates for the biological screening, a series of solubility tests were completed, and data for these tests are in the Supporting Information (S12, S13). The solubility of the complexes was evaluated at two different concentrations: 100 mM and 10 mM. This was done in parallel to observation of whether or not the complexes kept their integrity in solutions or showed some side reactions, as evidenced by a color change of solutions with time (24 h) or with the appearance of precipitates. It was found that $K[Pd(ACO)(AACO)]\cdot 3H_2O$, $K[Pt(ACO)(AACO)]\cdot 2\ H_2O$, and $K_2[Pd(AACO)_2]\cdot 4H_2O$ were the only complexes that were soluble at 100 mM in DMSO and showed no change in color nor the presence of a precipitate. All but one complex, $Pd(PiPCO)_2\cdot H_2O$, was not soluble at 10 mM in DMSO (Suppporting Information, S7, S8). Solutions of compounds that were stable for 24 h were diluted 1:100 with distilled water to determine if any precipitation would occur. This was done to ensure that the compound stayed in the solution when added to the aqueous cell culture media containing the 1% DMSO. Compounds that were not soluble or that were partially soluble under these conditions were not tested in the *in vitro* viability assay. The compounds that remained soluble and stable and were miscible with buffer and cell culture media were selected for further testing. Results of studies are presented in the Supporting Information, S14.

Two sets of controls were used for the *in vitro* testing. One control contained only the cells with no addition of any compounds, and the second control was the use of cells treated overnight with 1% DMSO for evaluation of the cytotoxic effect of the solvent on the cell culture. Also as a positive control, cells were treated with 1 mM solution of cisplatin, $[Pt(NH_3)_2Cl_2]$, which was the same concentration for the tested cyanoximate complexes.

HeLa cells were maintained in L-15 media containing 10% FBS and penicillin/streptomycin. Equal numbers of cells were plated on a 24 well plate and untreated or cells treated with solvent control, or compounds were incubated for 24 h and then assayed for cell viability. The selected Pt(II) and Pd(II) complexes in the DMSO were added directly to 500 μL of L-15 media. The final concentrations used in the cell plates for the tested complexes were 1 mM and 0.1 mM after the 1:100 dilutions that were made.

To determine cell viability 24−48 h after treatment, cells were stained with the dye Trypan Blue for 2 min at room temperature, washed with phosphate buffered saline (PBS), and fixed using 4% paraformaldehyde. This method relies on a breakdown in membrane integrity that is determined by the uptake of a dye, such as Trypan Blue, which is normally unpermeable.[32] Cells were viewed using phase contrast microscopy. Digital pictures of the cells were analyzed to evaluate compound toxicity. Two fields of cell views (×40 magnification) from two independent dishes were analyzed for each condition. Random fields of cells were counted, and any blue cells were recorded as nonviable. Table S14 of the Supporting Information shows the percent of viable cells. Results of the biological testing revealed that, with the exception of two compounds, none of the tested ligands and complexes had a pronounced biological effect leading to cell death compared to the cisplatin control. The only two complexes that had a significant effect on cell viability and proliferation was $Pd(MCO)_2$, causing 28% death, and its platinum analogue $Pt(MCO)_2$, with 16% death. These compounds will be used for further investigations. Interestingly, both complexes contain the MCO^- anion with the oxygen atom of the morpholine group pointed outward, and that may facilitate formation of intermolecular H bonding and intracellular uptake of these compounds.

The absence of significant biological activity of other synthesized Pd and Pt complexes in general is explained in terms of the stability of the chelate cyanoxime complexes, which precludes the availability of the metal ion to further intracellular reactions with water molecules and then nucleotides of DNA.

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Concluding Remarks

(1) Five cyanoximes based on 2-cyanoacetic acid derivatives have been synthesized and characterized by spectroscopic and structural methods. Two cyanoxime ligands, HPiPCO and HMCO, were obtained for the first time using a high yield reaction between methyl- or ethyl-2-cyanoacetates and secondary amines such as piperidine and morpholine at room temperature. Four out of five cyanoximes represent water-soluble compounds with the exception of HPiPCO, a hydrophobic counterpart to the HMCO molecule.

(2) Variable temperature ^{13}C NMR investigations of HPiPCO and HMCO in dmso-d_6 solutions allowed for the determination of the rotational energy barriers for these amidocyanoximes. The HMCO compound exists as a mixture of *syn* and *anti* isomers with ~1:3 ratio in solutions at room temperature. The variable temperature ^1H studies of HTCO in dmso-d_6 solutions in the range 20−110 °C have not evidenced the rotation of the NH_2 group in the thioamide fragment, contrary to that observed for HACO cyanoxime.

(3) The new amidocyanoximes HPiPCO and HMCO were structurally characterized, and it was found that they adopt a *trans-anti* configuration in the solid state.

(4) Deprotonation of all ligands leads to a formation of yellow anions that exhibit a significant solvatochromic effect in UV−visible spectra recorded in different solvents. The presence of strong solvate dependence evidences a charge-transfer character of absorbance in the visible region of spectra.

(5) Nine bivalent Pd and Pt complexes, containing studied cyanoximes, were obtained and characterized. It was established that both ACO^- and ECO^- anions hydrolyze in aqueous solutions to the dianion of 2-cyano-2-isonitrosoacetic acid ($AACO^{2-}$) in the presence of Pd(II) and Pt(II). The crystal structures of two palladium compounds were determined and showed *cis* geometry of both complexes with central atoms being in distorted square-planar N_2O_2 surroundings. The cyanoxime anions are in the *nitroso* form, adopt a *cis-anti* configuration in both compounds, and demonstrate bidentate chelate coordination to a transition metal in the complex.

(6) All synthesized cyanoxime ligands and their bivalent Pd and Pt complexes were tested *in vitro* on antiproliferating activity using the human cervical cancer HeLa cell lines and cisplatin as a positive control. With the exception of two MCO^- based complexes of Pd and Pt, causing the death of 28% and 16% of the cells, respectively, there was no substantial anticancer activity found for all of the compounds studied. The cytotoxicity of these two complexes is comparable to that of cisplatin (55% death under the same conditions), and is a subject of future investigation. This finding could be especially useful for other researchers seeking to discover the anticancer activity of novel platinum and palladium complexes. The lack of biological activity of the other studied Pd and Pt complexes is explained in terms of the stability of the chelate cyanoxime complexes, precluding the availability of the metal center to further intracellular reactions with water molecules and, subsequently, with nucleotides of DNA.

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Supporting Information Available: Elemental content determination (S1); data of ^1H, ^{13}C NMR characterization of the obtained cyanoximes (S2, S3); variable temperature ^1H NMR spectra of HTCO (S4); ^{13}C NMR spectra of KL where L = $PiPCO^-$ and MCO^- ligands (S5); results of UV−visible spectroscopy for $PiPCO^-$ and MCO^- anions (S6); packing diagram for the structure of HPiPCO (S7) and seven independent molecules in the structure of HMCO (S9); H bonding in structures of HPiPCO and HMCO (S8, S10); views of molecular structures of two complexes exhibiting Pd···Pd interactions (S11); solubility tests in dmso solutions at 100 mM and 10 mM concentrations for all nine obtained Pd(II) and Pt(II) cyanoximates (S12, S13); results of cytotoxicity study of synthesized metal complexes (S14). An X-ray crystallographic file (CIF) for all reported structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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