Synthesis of amidine complexes by metal-mediated addition of amino acid esters to coordinated nitriles

A. V. Makarycheva-Mikhailova, E. A. Tronova, and V. Yu. Kukushkin★

Department of Chemistry, St. Petersburg State University,
26 Universitetsky prosp., 198504 Stary Petergof, Russian Federation.
Fax: +7 (812) 428 6939. E-mail: kukushkin@VK2100.spb.edu

The reaction of the nitrile platinum(IV) complex *trans*-$[PtCl_4(EtCN)_2]$ with amino acid esters $H_2NC(R^1)(R^2)CO_2Me$ (R^1 = R^2 = H, H—Me, Me—Me, H—Ph) and $H_2NCH_2CH_2CO_2Me$ in CH_2Cl_2 produces the amidine complexes *trans*-$[PtCl_4\{Z\text{-}NH{=}C(Et)NHC(R^1)(R^2)CO_2Me\}_2]$ and *trans*-$[PtCl_4\{Z\text{-}NH{=}C(Et)NHCH_2CH_2CO_2Me\}_2]$, which were isolated in 70—80% yields and characterized by elemental analysis, mass spectrometry, IR spectroscopy, and ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. The structures of the complexes with $R^1 = R^2 = H$ (**1**), $R^1 = H$, $R^2 = Me$ (**2**), and $R^1 = H$, $R^2 = Ph$ (**4**) were established by X-ray diffraction analysis.

Key words: nitriles, amino acid esters, amidines, platinum(IV) complexes, nucleophilic addition, reactivity of ligands.

The nucleophilic addition to the CN group is a widespread reactivity mode of nitriles. This reaction is used to prepare compounds of industrial (for example, acrylamide) and/or pharmaceutical (for example, nicotinamide or *S*-(+)-ibuprofen) importance. The reactivity of RCN species in nucleophilic additions can be enhanced in a number of ways, among which coordination to metal centers plays a great role. Metal-mediated transformations of nitriles were considered in the reviews.[1—3]

Examples were given of metal-mediated reactions of nitrile ligands with *N*-nucleophiles containing the sp^3-hybridized nitrogen atom (ammonia,[4] primary and secondary amines;[5] for recent studies, see Refs 6—9). These reactions afford amidine complexes with the [M]—N(H)=C(R)NHR′ structural moiety. In most cases, only simple amines (R′ = H, Alk, Ar) were used as nucleophiles. The reactions with functionalized amines were studied only for amino alcohols.[10] However, the introduction of various peripheral groups (for example, hydrophilic) into the substituent R′ could, first, lead to an increase in solubility of amidine complexes in water, which is of importance in tests for antitumor activity of these biologically active compounds,[11] and, second, provide the possibility to use the peripheral groups in further synthetic transformations (for example, for the synthesis of metallaligands[12]).

As part of continuing studies (see the reviews[1,2] and recent publications[9,10,12—16]) of the reactions of *N*-nucleophiles with nitrile platinum(IV) complexes, we investigated the nucleophilic addition of amino acid esters $H_2NC(R_1)(R_2)CO_2Me$ (R^1 = R^2 = H; R^1 = H, R^2 = Me; R^1 = R^2 = Me; R^1 = H, R^2 = Ph) and $H_2NCH_2CH_2CO_2Me$ to the nitrile ligands of the *trans*-$[PtCl_4(EtCN)_2]$ complex giving rise to compounds with functionalized amidine ligands.

Results and Discussion

The reactions of nitriles in the platinum(IV) complex *trans*-$[PtCl_4(EtCN)_2]$ with amino acid esters $H_2NCR^1R^2CO_2Me$ and $H_2NCH_2CH_2CO_2Me$ proceed at room temperature in a CH_2Cl_2 solution and are completed in one hour (Scheme 1).

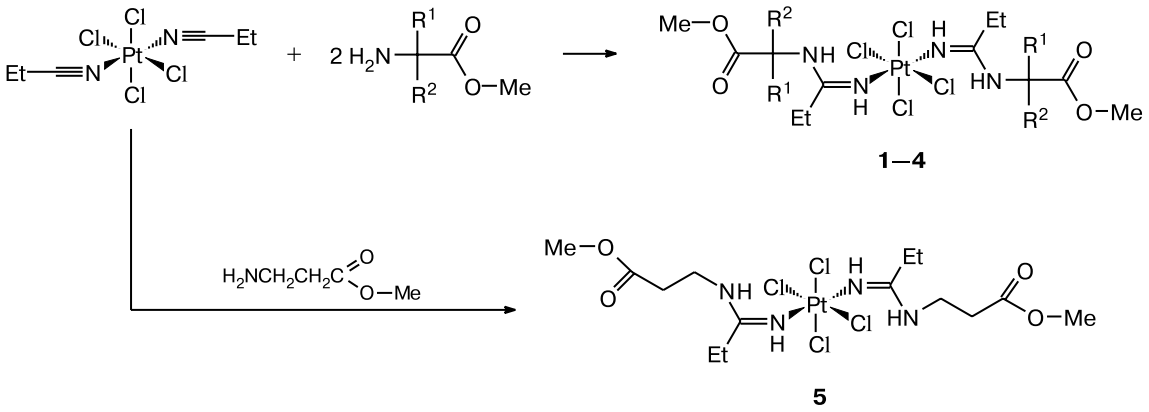
Complexes **1**—**4** and *trans*-$[PtCl_4\{NH{=}C(Et)\text{-}NHCH_2CH_2CO_2Me\}_2]$ (**5**) were isolated in 70—80% yields and characterized by elemental analyses (C, H, and N), mass spectrometry, IR spectroscopy, and ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. In the reaction mixture, we also found small amounts of the iminol platinum(IV) complex *trans*-$[PtCl_4\{NH{=}C(OH)R\}_2]$, which has been characterized earlier.[17] Apparently, the latter is formed by hydrolysis of the propionitrile ligands in $[PtCl_4(EtCN)_2]$, which occurs in undried dichloromethane.

The results of elemental analyses of complexes **1**—**5** showed that all these compounds contain two amidine ligands formed by the nucleophilic addition of the amino acid esters to the coordinated nitriles. The observed fragmentation and the character of isotopic patterns in the electrospray mass spectra of the complexes, which were measured in acetone solutions at concentrations of $\sim 2 \cdot 10^{-6}$ mol L^{-1}, are similar to those expected for amidine

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 601—605, March, 2005.

1066-5285/05/5403-0610

Scheme 1



$R^1 = R^2 = H$ (**1**); $R^1 = H$, $R^2 = Me$ (**2**); $R^1 = R^2 = Me$ (**3**); $R^1 = H$, $R^2 = Ph$ (**4**).

derivatives; $[M - H]^-$ and $[M + Na]^+$ are characteristic fragments.

The IR and NMR spectroscopic data also confirm the hypothesis of the addition of amino acid esters to the RCN ligands. A comparison of the IR spectra of the resulting compounds with the spectra of the starting complexes shows the absence of the absorption band ν(C≡N) at 2350—2300 cm^{-1} (in the *trans*-$[PtCl_4(EtCN)_2]$ complex, ν(C≡N) 2340 cm^{-1})[17] and reveals a very intense stretching band ν(C=N) at 1642—1625 cm^{-1} and weaker bands ν(N—H) in the range of 3387—3317 cm^{-1}, which are absent in the IR spectrum of the *trans*-$[PtCl_4(EtCN)_2]$ complex. An analogous situation is observed for the addition of other *N*-donors (ammonia,[4] amino alcohols $H_2NCH(R')CH(R'')OH$,[10] imino esters NH=C(R)OR′,[15] or benzophenone imine $HN=CPh_2$ [18]) or OH-nucleophilic agents (for example, oximes HON=CRR [19—21] or alcohols HOR′ [22]) to nitriles in the $[PtCl_4(RCN)_2]$ complexes.

The addition products of amino acid esters $H_2NCR^1R^2CO_2Me$ and $H_2NCH_2CH_2CO_2Me$ to nitriles in the *trans*-$[PtCl_4(EtCN)_2]$ complex were studied by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. The spectra of compounds **1—5** show fragments corresponding to the NH=C(Et) group and the amide moiety of the ligand. In the $^{13}C\{^1H\}$ NMR spectra of the complexes, the signal for the C atom of the imino group NH=C emerges at δ ~170, *i.e.*, at substantially lower field compared to the signal for the nitrile carbon atom (δ 119) in the spectrum of the starting *trans*-$[PtCl_4(EtCN)_2]$ complex. The ^1H NMR spectra show signals for the hydrogen atom of the NH=C group at δ 5.4—5.7 and the signals for the proton of the —NH— amide group at δ 7.5—8.1 (assignment of the signals for NH was made based on the NOESYTP NMR experiment). The downfield shift of the signal of the amide group indicates that the proton of the —NH— group is involved in hydrogen bonding. X-ray diffraction study (see below) demonstrated that all complexes in the solid state have an intramolecular hydrogen bond between the H atom of the amido group and the chloride ligand.

The NOE spectra were recorded for all complexes. These data revealed a correlation between the signal for the proton of the imino group [Pt]—NH=C(CH_2CH_3) and the signal for the methylene protons in [Pt]—NH=C(CH_2CH_3). This is evidence that[22] the amidine ligands in solutions of complexes **1—5**, like those in the solid state (see below), have a *Z* configuration.

Light-orange crystals of complexes **1**, **2**, and **4** were prepared by evaporation of solutions of these compounds in a mixture of toluene and methanol. The coordination polyhedra of these compounds are slightly distorted octahedra. The amidine ligands adopt a *Z* configuration. The C=N bond lengths vary in the range of 1.275—1.319 Å and are consistent with the average lengths in other imino platinum complexes.[10,13] X-ray diffraction analysis confirmed the presence of a hydrogen bond between the amide hydrogen atom and the chloride ligand. The Pt—Cl bond lengths (2.303—2.327 Å) are typical of chloride derivatives of platinum(IV).[17,19]

The nucleophilic addition of amino acid esters to nitriles observed in the present study is promoted by

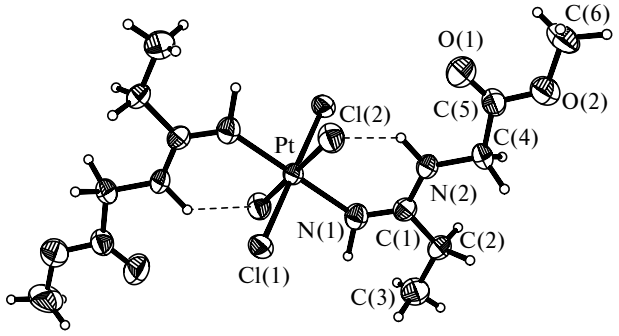


Fig. 1. Molecular structure of complex **1**.

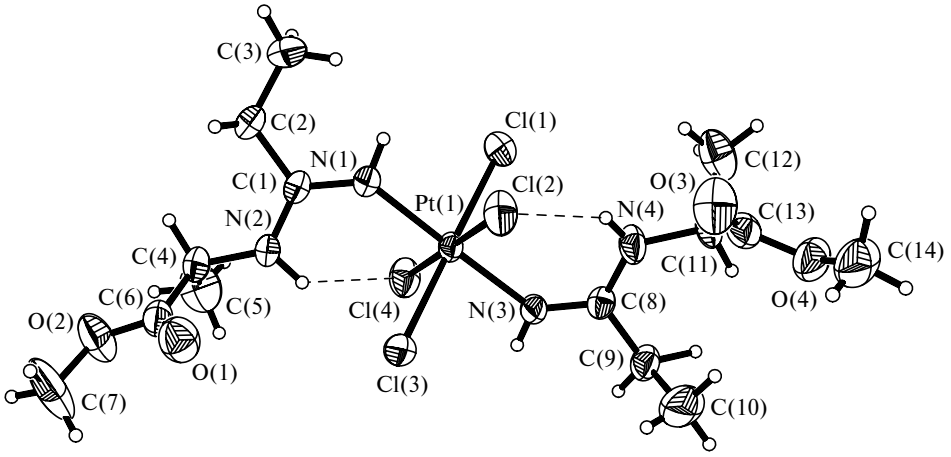


Fig. 2. Molecular structure of complex **2**.

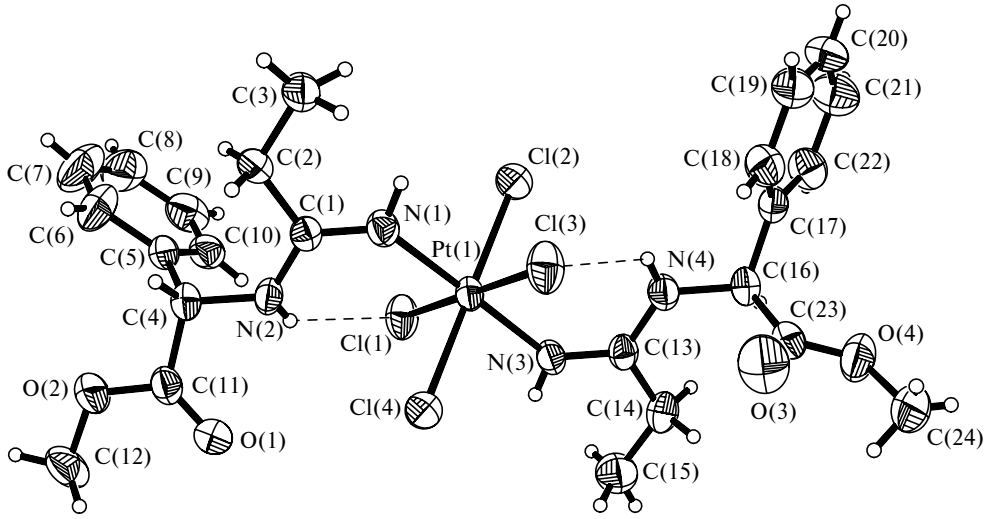


Fig. 3. Molecular structure of complex **4**.

platinum(IV) because free reactants do not react with each other even under much more drastic conditions (2 days, 40 °C).

Experimental

The *trans*-$[PtCl_4(EtCN)_2]$ complex was prepared according to a procedure described earlier.[17] Amino acid ester hydrochlorides were synthesized from the corresponding amino acids according to a known procedure.[23] The melting points were determined on a Büchi B-540 instrument. The TLC analysis was carried out on Merk 60 F_{254} plates. The electrospray mass spectra were measured on a Bruker *Esquire*$_{3000}^{TM}$ instrument. The IR spectra were recorded on a Perkin Elmer FTIR instrument in the 4000—400 cm^{-1} region in KBr pellets. The ^1H and $^{13}C\{^1H\}$ NMR spectra were measured on a Bruker DPX 400 spectrometer at ambient temperature.

Addition of amino acid esters to coordinated nitriles. An aqueous $NaHCO_3$ solution (16.8 mg, 0.20 mmol) was added to a solution of amino acid ester hydrochloride (0.190 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was vigorously shaken in a separatory funnel and the organic layer was separated. Then a solution of the amino acid ester in CH_2Cl_2 (2 mL) was added to a suspension of *trans*-$[PtCl_4(EtCN)_2]$ (40.0 mg, 0.089 mmol) in CH_2Cl_2 (1 mL), and the reaction mixture was stirred at room temperature for 30 min. After removal of the solvent, the orange oily residue was washed with diethyl ether (3×3 mL), and the orange crystalline powder was obtained. The powder was dried at room temperature in air. The yields were 70—80%.

Tetrachloro[bis(methyl-*N*-propanimidoyl-*N*-glycinato)]platinum(IV), $[PtCl_4\{NH=C(Et)NHCH_2CO_2Me\}_2]$ (1). Found (%): C, 22.81; H, 3.65; N, 8.67. $C_{12}H_{24}N_4Cl_4O_4Pt$. Calculated (%): C, 23.05; H, 3.87; N, 8.96. MS, *m/z*: 648 $[M + Na]^+$. M.p. 159 °C, R_f = 0.54 (Et_2O—CH_2Cl_2, 1 : 25, as the eluent). IR, ν/cm^{-1}: 3387 (N—H); 1748 (C=O); 1625 (C=N). ^1H NMR ($CDCl_3$), δ: 8.00 (t, 1H, NH); 5.75 (t, 1 H, NH); 3.83 (s, 1 H, OCH_3); 2.86 (q, 2 H, CH_2NH); 2.53 (q, 2 H, CH_2); 1.30 (t, 3 H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 171.87 (COO); 170.01 (C=N); 53.28 (OCH_3); 44.75 (CH_2NH); 27.09 (CH_2); 10.11 (CH_3).

Table 1. Crystallographic data and parameters of structure refinement of complexes **1**, **2**, and **4**

Parameter	**1**	**2**	**4**
Molecular formula	$C_{12}H_{24}N_4Cl_4O_4Pt$	$C_{14}H_{28}N_4Cl_4O_4Pt$	$C_{24}H_{32}N_4Cl_4O_4Pt$
M	625.23	653.28	777.42
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	*P*2(1)/*n*	*P*2(1)	*P*2(1)
a/Å	10.721(2)	7.788(2)	8.561(2)
b/Å	8.835(2)	18.839(4)	13.881(3)
c/Å	11.373	8.485	12.381
β/deg	104.13(2)	107.19(3)	95.66(3)
V/Å^3	1044.7(5)	1189.3(5)	1464.1(5)
Z	2	2	2
d_{calc}/g cm^{-3}	1.990	1.824	1.763
μ/mm^{-1}	7.25	6.37	5.19
Radiation		Mo-Kα (λ)	
Scan range	2.3—25.0	2.1—25.0	2.4—25.0
Number of measured reflections	1972	2145	2502
Number of reflections with $I \geq 2\sigma$	1195	1995	2339
R_1	0.039	0.019	0.015
wR_2	0.094	0.049	0.015

Tetrachloro[bis(methyl-*N*-propanimidoyl-*N*-alaninato)]platinum(IV), [$PtCl_4${NH=C(Et)NHCH(Me)CO_2Me}$_2$] (2). Found (%): C, 25.56; H, 4.31; N, 8.63. $C_{14}H_{28}N_4Cl_4O_4Pt$. Calculated (%): C, 25.74; H, 4.32; N, 8.58. MS, *m/z*: 676 $[M + Na]^+$. M.p. 149 °C, R_f = 0.68 (Et_2O—CH_2Cl_2, 1 : 25, as the eluent). IR, ν/cm^{-1}: 3317 (N—H); 1746 (C=O); 1642 (C=N). ^{1}H NMR ($CDCl_3$), δ: 8.10 (d, 1 H, NH); 5.41 (t, 1 H, NH); 4.25—4.19 (m, 1 H, CH); 3.81 (s, 1 H, OCH_3); 2.53 (q, 2 H, CH_2); 1.58 (d, 3 H, CH_3CH); 1.29 (t, 3 H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$), δ: 171.16 (COO); 169.36 (C=N); 53.42 (CH); 52.44 (OCH_3); 26.69 (CH_2); 18.96 (CH_3CH); 10.54 (CH_3).

Tetrachloro[bis(methyl-2-methyl-*N*-propanimidoyl-*N*-alaninato)]platinum(IV), [$PtCl_4${NH=C(Et)NHC(Me)$_2$$CO_2$Me}$_2$] (3). Found (%): C, 27.98; H, 4.86; N, 8.34. $C_{16}H_{32}N_4Cl_4O_4Pt$. Calculated (%): C, 28.21; H, 4.73; N, 8.22. MS, *m/z*: 680 $[M - H]^-$. M.p. 186 °C (decomp.), R_f = 0.34 (CH_2Cl_2, as the eluent). IR, ν/cm^{-1}: 3341 (N—H); 1733 (C=O); 1628 (C=N). ^{1}H NMR ($CDCl_3$), δ: 7.95 (t, 1 H, NH); 5.54 (t, 1 H, NH); 3.79 (s, 1 H, OCH_3); 2.36 (q, 2 H, CH_2); 1.63 (s, 6 H, CH_3); 1.28 (t, 3 H, CH_3 from Et). ^{13}C{^{1}H} NMR ($CDCl_3$), δ: 174.55 (COO); 170.37 (C=N); 58.50 ($C(Me)_2$); 53.46 (OCH_3); 27.75 (2 CH_3); 26.14 (CH_2); 11.03 (CH_3).

Tetrachloro{bis[methylphenyl(propanimidoyl-*N*-amino)acetato]}platinum(IV), [$PtCl_4${NH=C(Et)NHCH(Ph)CO_2Me}$_2$] (4). Found (%): C, 37.45; H, 3.95; N, 7.02. $C_{24}H_{32}N_4Cl_4O_4Pt$. Calculated (%): C, 37.08; H, 4.15; N, 7.21. MS, *m/z*: 799 $[M + Na]^+$. M.p. 176 °C (decomp.), R_f = 0.33 (Et_2O—CH_2Cl_2, 1 : 20, as the eluent). IR, ν/cm^{-1}: 3385 (N—H); 1735 (C=O); 1637 (C=N). ^{1}H NMR ($CDCl_3$), δ: 8.80 (d, 1 H, NH); 7.55 (d, 2 H, Ph); 7.42—7.37 (m, 3 H, Ph); 5.79 (t, 1 H, NH); 5.21 (d, 1 H, CH); 3.78 (s, 3 H, OCH_3); 2.47 and 2.26 (both m, 1 H each, CH_2); 1.15 (t, 3 H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$), δ: 169.22 (C=N); 136.39 (Ph—C_{ipso}); 129.74, 129.44, and 127.52 (Ph—$C_{meta,ortho,para}$); 60.39 (CH); 53.76 (OCH_3); 27.00 (CH_2); 10.02 (CH_3).

Tetrachloro[bis(methyl-*N*-propanimidoyl-*N*-β-alaninato)]platinum(IV), [$PtCl_4${NH=C(Et)NH$CH_2CH_2CO_2$Me}$_2$] (5). Found (%): C, 25.56; H, 4.25; N, 8.36. $C_{14}H_{28}N_4Cl_4O_4Pt$. Calculated (%): C, 25.74; H, 4.32; N, 8.57. MS, *m/z*: 651 $[M - H]^-$, 689 $[M + Cl]^-$. M.p. 146 °C, R_f = 0.44 (MeCOMe—CH_2Cl_2, 1 : 20, as the eluent). IR, ν/cm^{-1}: 3332 (N—H); 1720 (C=O); 1630 (C=N). ^{1}H NMR ($CDCl_3$), δ: 7.54 (t, 1 H, NH); 5.45 (t, 1 H, NH); 3.72 (s, 1 H, OCH_3); 3.58 (q, 2 H, CH_2NH); 2.62 (t, 2 H, CH_2); 2.55 (q, 2 H, CH_2); 1.30 (t, 3 H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$), δ: 171.33 (COO); 169.68 (C=N); 52.66 (OCH_3); 38.98 (CH_2NH); 34.57 (CH_2); 26.82 (CH_2 from Et); 10.53 (CH_3).

X-ray diffraction study. X-ray diffraction data sets for compounds **1**, **2**, and **4** were collected on an automated Enraf-Nonius CAD-4 diffractometer (monochromator, Mo-Kα radiation, 293(2) K, θ/2θ scanning technique). Principal crystallographic parameters and details of structure refinement are given in Table 1.

All calculations were carried out with the use of the SHELX-97 program package.[24] The atomic coordinates and complete tables of the bond lengths and bond angles were deposited with the Cambridge Structural Database.

We thank Prof. V. K. Belsky (L. Ya. Karpov Institute of Physical Chemistry) for performing X-ray diffraction analysis, Prof. B. K. Keppler (University of Vienna) for putting ESMS facilities at the our disposal, and M. Galanski (University of Vienna) for performing the NOESYTP NMR experiment.

This study was financially supported by the Russian Foundation for Basic Research (Project No. 03-03-32362) and the Competitive Center of Fundamental Natural Sciences (Grants A03 2.11-61, M03-2.5K-91, and PD 03-1.3-28).

References

1. V. Yu. Kukushkin and A. J. L. Pombeiro, *Chem. Rev.*, 2002, **102**, 1771.
2. A. J. L. Pombeiro and V. Yu. Kukushkin, in *Comprehensive Coordination Chemistry*, 2nd ed., Elsevier, 2003, **1**, 639.
3. R. A. Michelin, M. Mozzon, and R. Bertani, *Coord. Chem. Rev.*, 1996, **147**, 299.
4. V. Yu. Kukushkin, I. V. Ilichev, G. Wagner, M. D. Revenco, V. H. Kravtsov, and K. Suwinska, *Eur. J. Inorg. Chem.*, 2000, 1315.
5. U. Belluco, F. Benetollo, R. Bertani, G. Bombieri, R. A. Michelin, M. Mozzon, O. Tonon, A. J. L. Pombeiro, and F. C. Guedes da Silva, *Inorg. Chim. Acta*, 2002, **334**, 437.
6. B. Longato, G. Bandoli, A. Mucci, and L. Schenetti, *Eur. J. Inorg. Chem.*, 2001, 3021.
7. S. Du, J. A. Kautz, T. D. McGrath, and F. G. Stone, *J. Chem. Soc., Dalton Trans.*, 2002, 1553.
8. S. V. Kryatov, A. Y. Nazarenko, M. B. Smith, and E. V. Rybak-Akimova, *Chem. Commun.*, 2001, 1174.
9. M. N. Kopylovich, A. J. L. Pombeiro, A. Fischer, L. Kloo, and V. Yu. Kukushkin, *Inorg. Chem.*, 2003, **42**, 7239.
10. A. V. Makarycheva-Mikhailova, V. Yu. Kukushkin, A. A. Nazarov, D. A. Garnovskii, A. J. L. Pombeiro, M. Haukka, B. K. Keppler, and M. Galanski, *Inorg. Chem.*, 2003, **42**, 2805.
11. R. A. Michelin, M. Mozzon, U. Belluco, R. Bertani, F. Baccichetti, F. Bordin, and C. Marzano, *Int. Conf. Coord. Chem.,* Heidelberg, 2002, 242.
12. D. A. Garnovskii, A. J. L. Pombeiro, M. Haukka, P. Sobota, and V. Yu. Kukushkin, *Dalton Trans.*, 2004, 1097.
13. A. V. Makarycheva-Mikhailova, N. A. Bokach, M. Haukka, and V. Yu. Kukushkin, *Inorg. Chim. Acta*, 2003, **356**, 382.
14. N. A. Bokach, T. B. Pakhomova, V. Yu. Kukushkin, M. Haukka, and A. J. L. Pombeiro, *Inorg. Chem.*, 2003, **42**, 7560.
15. N. A. Bokach, V. Yu. Kukushkin, M. Haukka, J. J. R. Fraústo da Silva, and A. J. L. Pombeiro, *Inorg. Chem.*, 2003, **42**, 3602.
16. A. V. Makarycheva-Mikhailova, N. A. Bokach, V. Yu. Kukushkin, P. F. Kelly, L. M. Gilby, M. L. Kuznetsov, K. E. Holmes, M. Haukka, J. Parr, J. M. Stonehouse, M. R. J. Elsegood, and A. J. L. Pombeiro, *Inorg. Chem.*, 2003, **42**, 301.
17. K. V. Luzyanin, M. Haukka, N. A. Bokach, M. L. Kuznetsov, V. Yu. Kukushkin, and A. J. L. Pombeiro, *J. Chem. Soc., Dalton Trans.*, 2002, 1882.
18. D. A. Garnovskii, V. Yu. Kukushkin, M. Haukka, G. Wagner, and A. J. L. Pombeiro, *J. Chem. Soc., Dalton Trans.*, 2001, 560.
19. V. Yu. Kukushkin, T. B. Pakhomova, Yu. N. Kukushkin, R. Herrmann, G. Wagner, and A. J. L. Pombeiro, *Inorg. Chem.*, 1998, **37**, 6511.
20. V. Yu. Kukushkin, T. B. Pakhomova, N. A. Bokach, G. Wagner, M. L. Kuznetsov, M. Galanski, and A. J. L. Pombeiro, *Inorg. Chem.*, 2000, **39**, 216.
21. A. V. Makarycheva-Mikhailova, M. Haukka, N. A. Bokach, D. A. Garnovskii, M. Galanski, B. K. Keppler, A. J. L. Pombeiro, and V. Yu. Kukushkin, *New J. Chem.*, 2002, **26**, 1085.
22. N. A. Bokach, M. L. Kuznetsov, D. A. Garnovskii, G. Natile, V. Yu. Kukushkin, and A. J. L. Pombeiro, *Inorg. Chem.*, 2002, **41**, 2041.
23. A. A. Danilin, P. P. Purygin, N. V. Makarova, and I. K. Moiseev, *Zh. Obshch. Khim.*, 1999, **11**, 1846 [*Russ. J. Gen. Chem.*, 1999, **11** (Engl. Transl.)].
24. G. M. Sheldrick, *SHELX-97 Program Manual*, University of Göttingen, Germany, 1997.

Received June 15, 2004;
in revised form October 6, 2004