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Complex Formation of $PdCl_2$ with 1-Substituted 3,5-Dimethylpyrazoles

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Abstract—Herein the synthesis of 3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)butanal oxime (L) and its complex formation with $PdCl_2$ is studied. IR and 1H NMR spectroscopic methods as well as X-ray diffraction analysis (CIF file CCDC no. 1531058) elucidate that the nitrogen atoms N(4) and N(15) from pyrazole and imine group of oxime respectively, participate in coordination with $PdCl_2$. Moreover, primarily thermal stability test shows that $[PdCl_2(L)]$ complex (**I**) is quite stable at moderate temperatures and intense decomposition of latter occurs ca 200–210°C. As a consequence of thermal decomposition, both volatile ligand and its dehydration by-product 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)butanenitrile are formed. Afterwards, the anticonvulsant properties of $PdCl_2$, L, and **I** are of interest and well studied in this section.

Keywords: 3,5-dimethylpyrazoles, palladium(II), bidentate ligands, X-ray diffraction analysis, thermal stability, complex formation

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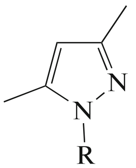
INTRODUCTION

Coordination compounds of pyrazoles with noble metals, unlike complexes with transition metals, are poorly studied. Many azole-based complexes exhibit biological activity and serve as efficient drugs [1–7]. The related materials have high technological and exploitation characteristics [8–13]. Azoles are also of practical interest in catalytic reactions of organic synthesis [14–18]. In this work, we studied for the first time the reactions of $PdCl_2$ with 1-substituted derivatives of 3,5-dimethylpyrazole [19–21] of the general formula presented below and designated as A.



(A)

$R = CH_3CHCH_2COOH$;
CH_3CHCH_2COOEt;
CH_3CHCH_2CN; CH_3CHCH_2COH

EXPERIMENTAL

Analyses to carbon and hydrogen were carried out on a EuroVector EA-3000 analyzer. IR spectra were recorded on a Termo Nicolet Nexus FT-IR spectrometer in Nujol in a range of 400–4000 cm^{-1}. ^1H and ^{13}C NMR spectra were detected on a Varian Mercury spectrometer (300 and 75 MHz, respectively) at 300 K in a DMSO-d_6–CCl_4 (1 : 3) system and in CD_3OD using tetramethylsilane as an internal standard. Melting points were determined on a Boetius apparatus.

Synthesis of 3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)butanal oxime (L). A solution of potassium hydroxide (9 g, 160.4 mmol) in ethanol (30 mL) was added to a solution of hydroxylamine hydrochloride (10 g, 144 mmol). The formed white crystalline precipitate of KCl was filtered. Preliminarily aldehyde A ($R = CH_3CHCH_2COH$) (9.6 g, 57.8 mmol) was dissolved in ethanol (25 mL), and the obtained solution was added to the filtrate. The formed white crystals were filtered off and recrystallized from toluene. The yield

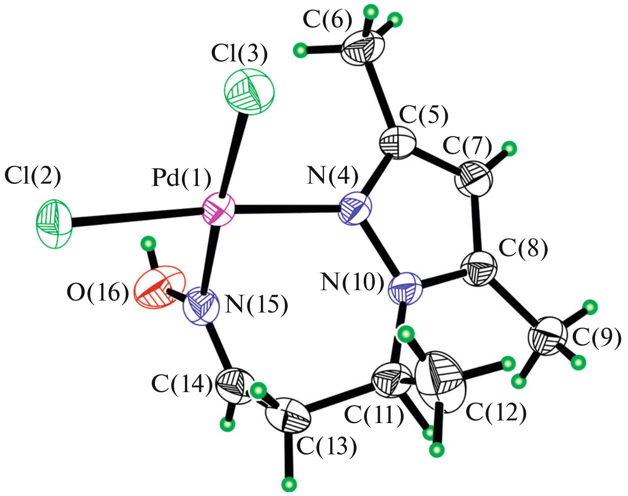


Fig. 1. Molecular structure of compound **I** (thermal vibration ellipsoids are shown at the 50% probability level).

of oxime was 8.1 g (77.1% based on aldehyde), mp = 108–110°C.

For $C_9H_{15}N_3O$ (FW = 181.24)

Anal. calcd., %:	C, 59.64;	H, 8.34;	N, 23.19.
Found, %:	C, 59.61;	H, 8.11;	N, 23.38.

IR (ν, cm^{-1}): 3300–3500 ν(OH), 1654 ν(CH=N), 1546 (Pz). ^1H NMR, δ, ppm: 1.41 d (3H, J = 6.6 Hz, $\underline{CH_3}$–CH), 2.12 and 2.12 s (1.5H each, 3-CH_3), 2.20 and 2.20 d (1.5H each, J = 0.7 Hz, 5-CH_3), 2.46–2.82 m (2H, CH_2), 4.27–4.38 m (0.5H) and 4.39–4.50 m (0.5H, CH–CH_3), 5.63 br.s (1H, 4-CH), 6.36 dd (0.5H, J = 5.8 and 5.0 Hz) and 7.05 dd (0.5H, J = 6.5 and 5.4 Hz, CH=N), 10.23 and 10.71 s (0.5H each, OH). ^{13}C NMR, δ_C, ppm: 10.26 (CH–$\underline{CH_3}$), 13.20 (CH_3), 20.47 (CH_3), 31. 71 (CH–$\underline{CH_2}$), 50.85 ($\underline{CH}$–CH_3), 95.49 (C=N), 103.76 (4-CH), 136.9 (CH^5), 145.85 (CH^3).

Synthesis of complex [$PdCl_2$ (L)] (I). Distilled water (25 mL) and hydrochloric acid (1.0 mL) were added to $PdCl_2$ (0.53 g, 3 mmol), and the mixture was heated to complete dissolution. Then oxime L (0.54 g, 3 mmol) dissolved in distilled water (15 mL) was added. The solution was left to stay over day. The obtained crystals were filtered off, dried, and recrystallized from ethanol. The yield of complex **I** was 0.8 g (72.7% based on oxime).

For $C_9H_{15}N_3OCl_2Pd$ (FW = 358.56)

Anal. calcd., %:	C, 30.15;	H, 4.22;	N, 11.72.
Found, %:	C, 30.65;	H, 4.04;	N, 12.03.

IR (ν, cm^{-1}): 3300–3500 ν(OH), 1672.1 ν($CH=N_{im}$), 1594 (Pz). ^1H NMR (CD_4O, 300 MHz), δ, ppm: 1.85 d (3H, $\underline{CH_3}$–CH), 2.25, 2.88 s (6H, CH_3(Pz)), 3.52–3.92 m (2H, $\underline{CH_2}$–$CH=N_{im}$), 4.75–4.91 m (1H, $\underline{CH–}$$CH_2$), 6.51 br.s ($CH^4$), 7.35 t (1H, J = 6.5 Hz, CH=N). ^{13}C NMR, δ_C, ppm: 11.3 (CH–$\underline{CH_3}$), 14.5, 22.3 (CH_3), 38.3 (CH–$\underline{CH_2}$), 60.3 ($\underline{CH}$–CH_3), 110.3 (C=N), 112.5 (CH^4), 139.5 (CH^5), 149.1 (CH^3).

X-ray diffraction analysis of compound **I** was carried out at room temperature on an Enraf-Nonius CAD-4 automated diffractometer (graphite monochromator, MoK_α radiation, λ = 0.71073 Å, θ/2θ scan mode). The unit cell parameters were determined and refined by 25 reflections with $12.1° < \theta < 13.5°$. The structure was solved by a direct method. An absorption correction was applied by the ψ scan method [22]. The coordinates of hydrogen atoms (except for the hydrogen atoms of the methyl groups) were determined from the difference Fourier syntheses and refined by full-matrix least squares in the isotropic approximation. The coordinates of the hydrogen atoms of the methyl groups were determined geometrically and refined by the riding model: C–H = 0.96 Å, $U_{iso}(H) = 1.5U_{eq}(C)$. The parameters of non-hydrogen atoms were refined by full-matrix least squares in the anisotropic approximation. All structural calculations were performed using the SHELXTL program package [23]. The main crystallographic data for complex **I** are presented in the Table 1. The molecular structure of compound **I** is shown in Fig. 1.

The coordinates of atoms and other parameters of the structure of complex **I** were deposited with the Cambridge Crystallographic Data Centre (CIF file no. CCDC 1531058); deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/data_request/cif).

The anticonvulsant properties of compounds L and **I** synthesized at the Institute of Organic Chemistry of the Scientific Technological Center of Organic and Pharmaceutical Chemistry (National Academy of Sciences of the Republic of Armenia) were studied at the Laboratory of Pharmacology and Pathohistology according to the rules of the Council Directive (86/609/EEC) on the Approximation of Laws, Regulations and Administrative Provisions of the Member States Regarding the Protection of Animals Used for Experimental and Other Scientific Purposes.

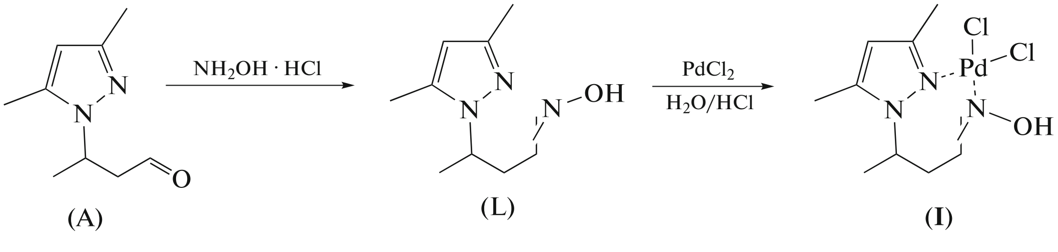
RESULTS AND DISCUSSION

When an aqueous-acid solution of $PdCl_2$ and an ethanolic solution of compound A (R = CH_3CHCH_2COOH, CH_3CHCH_2COOEt, CH_3CHCH_2CN, CH_3CHCH_2COH) were used, it

Table 1. Crystallographic data and experimental and structure refinement parameters for compound **I**

Parameter	Value
Crystal system	Monoclinic
Space group	$C2/c$
a, Å	22.318(5)
b, Å	7.3579(15)
c, Å	15.983(3)
β, deg	103.65(3)
V, Å^3	2550.5(10)
Z	8
ρ_{calcd}, g/cm^3	1.867
$\mu(\text{Mo}K_\alpha)$, mm^{-1}	1.857
$T_{\min}/T_{\max}$	0.64083/0.74078
$F(000)$	1424
Crystal size, mm	0.16 × 0.20 × 0.26
Temperature, K	293
Range of data collection over θ, deg	1.9–30.0
Ranges of reflection indices	$-31 \leq h \leq 30$, $-8 \leq k \leq 10$, $-14 \leq l \leq 22$
Number of measured reflections	3860
Number of independent reflections	3722
Number of observed reflections with $I > 2\sigma(I)$	2925
Number of refined parameters	172
R, wR_2, S	0.0277, 0.0626, 1.03
$\Delta\rho_{\max}/\Delta\rho_{\min}$, e Å^{-3}	0.440/–0.401

turned out that no complex formation occurred in a range of 20–80°C at the 1 : 1 molar ratio of the reactants. However, after the conversion of A (R = CH_3CHCH_2COH) in the reaction with hydroxylamine (by analogy to 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)propanal [24]) to 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)butanal oxime (L) having an additional functional group, complex formation with $PdCl_2$ proceeded via the scheme



A (R = CH_3CHCH_2COH)

The IR spectrum of ligand L exhibits an absorption band of the exocyclic imine group (C=NOH) at 1654 cm^{-1}. A strong absorption band at 1546 cm^{-1} should be assigned to vibrations of the pyrazole ring, and an intense band in a range of 3300–3500 cm^{-1} should be attributed to the ν(OH) stretching vibrations of the N–OH group.

We chose methanol as an appropriate solvent for the ^1H and ^{13}C NMR spectral studies of complex **I**, since compound **I** is insoluble in the most part of

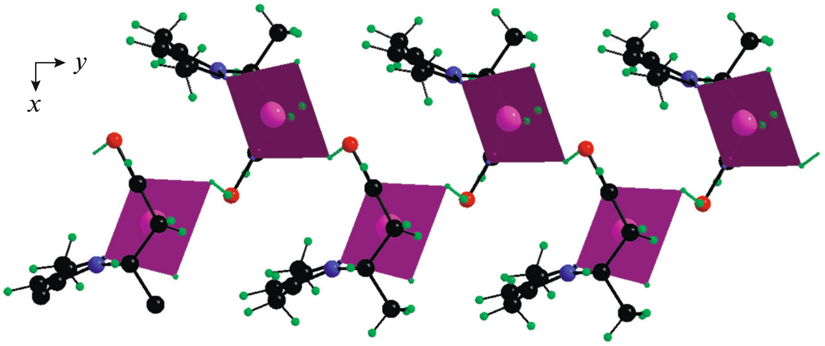


Fig. 2. Infinite chain of molecules in crystal of compound **I** (projection along [010]).

organic solvents (CCl_4, $CDCl_3$), while the starting ligand is eliminated on heating in DMSO. According to the ^1H NMR spectral data, in ligand L the chemical shifts of the 4-H ring proton lie in a weaker field (5.61 ppm) than the chemical shifts of the methyl protons of the heterocycle appeared in a narrow range (2.11–2.31 ppm) in a stronger field. The signals from the protons of the methyl group of the exocyclic chain are presented by a doublet at 1.41 ppm. The signals from the protons of the exocyclic imine group (CH=N) are presented by two triplets at 6.34 and 7.15 ppm, indicating the presence of ligand L in the form of two geometric *syn-* and *anti-*isomers in a ratio of 1 : 1. The formation of two isomers is also indicated by two signals from the protons of the OH group at 10.11 and 10.75 ppm. The signals from other protons have a shape of multiplets, and their integral intensities completely correspond to the structure of ligand L.

It is established by the X-ray diffraction data for complex **I** that the metal atom is coordinated by the nitrogen atoms N(4) (pyrazole) and N(15) (exocyclic imine group) to form a seven-membered metallocycle (Fig. 1). The seven-membered ring has a conformation of a distorted bath. The N(4), N(10), N(15), and C(14) atoms forming the bottom of the bath are shifted from the root-mean-square plane passed through all the seven atoms by 0.24, 0.50, 0.50, and 0.45 Å, respectively, whereas the Pd(1), C(11), and C(13) are shifted from the root-mean-square plane in the opposite direction by 0.77, 0.32, and 0.61 Å, respectively.

In the ^1H NMR spectrum of complex **I**, the peak corresponding to vibrations of the proton of the imine group of the seven-membered metallocycle is not split, unlike the signal of the same hydrogen of ligand L; i.e., complex **I** exists in the form of the *E* or *Z* configuration. The results of X-ray diffraction analysis show that in the studied sample of complex **I** ligand L has the *E* configuration and the chiral center on the asymmetric C(11) atom. Since the structure is centrosymmetric (space group *C*2/*c*), the crystal contains a racemic mixture of *R*(*E*) and *S*(*E*) conformers.

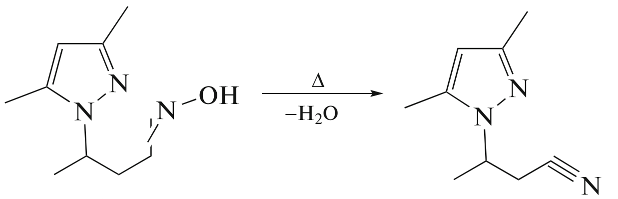
We believe that the participation of the N(10) nitrogen atom of the pyrazole ring in the coordination of Pd is poorly probable, which is consistent with the calculation data [25]. The Pd atom is coordinated by two chlorine atoms at the vertices of the *cis*-square (Pd–Cl 2.2964(8) and 2.2733(8) Å) and two nitrogen atoms of the organic molecule L performing the bidentate chelate function: N(4) (pyrazole) (Pd–N 2.020(2) Å) and N(15) (oxime) (Pd–N 2.023(2) Å). The bond angles are as follows: Cl(2)Pd(1)Cl(3) 91.04(3)°, N(4)Pd(1)N(15) 85.80(9)°, N(4)Pd(1)-Cl(3) 92.00(6)°, and N(15)Pd(1)Cl(2) 91.00(7)°. Unlike the structure of complex **I**, in the dichloro-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-ethylpropan-1-imine)zinc complex, regardless of similarity of organic molecules, the zinc atom is coordinated at the vertices of the tetrahedron [26].

The adjacent molecules of compound **I** bound by the screw axis 2_1 form an infinite chain along the [010] direction due to intermolecular hydrogen bonds O–H···Cl (Fig. 2). The chains are formed of molecules of the same chirality. In the 3D packing, the chains interact mainly by the van der Waals forces.

The thermal study of compound **I**, under the conditions of isothermal heating, was carried out to evaluate thermal stability and possible schemes for the decomposition of the complex. The decomposition of the palladium complex occurs above 200°C with the 50.6% mass loss, which corresponds to the elimination of one ligand molecule via the scheme

$$Pd(L)Cl_2 \longrightarrow PdCl_2 + L.$$

However, the spectral studies (IR, ^1H NMR) shows that not only oxime L but also 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)butanenitrile (A), which is the product of dehydration of L via the scheme presented below [20, 27, 28], are volatile products of thermal decomposition under these conditions.



(L) (A)

A (R = CH_3CHCH_2CN)

The anticonvulsant properties of compounds $PdCl_2$, L, and **I** were studied using the pentylenetetrazole seizure test, (dose 50 mg/kg on mice) with an effect of 40–60%, and compound **I** exerts the maximum effect. However, compounds $PdCl_2$, L, and **I** taken in this dose induce no muscle relaxation according to the rotating rod test. The enhanced activity of compound **I** compared to compounds $PdCl_2$ and L is related, most likely, to the effect of synergism.

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