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External Ligand - Exchange in Cyclometalated Complexes Possessing Pd(II)-C(sp^3) Bond

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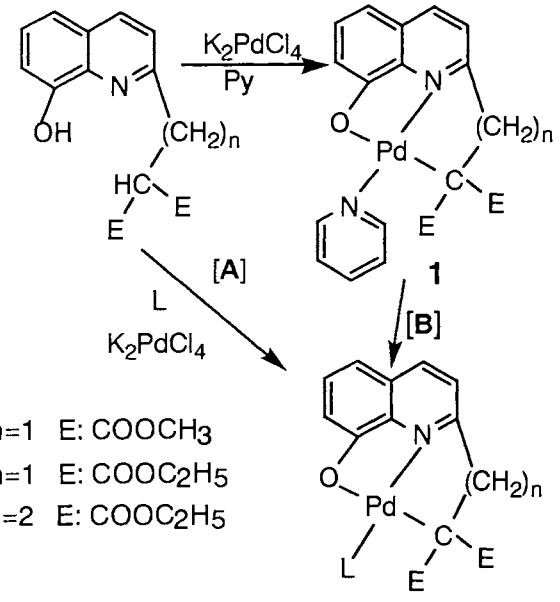
A stable class of σ- bonded palladium(II) complexes was synthesized from exchange of the external pyridine ligand upon treatment with excess of metronidazole. The crystal structure of metronidazole[2-{2,2-bis(methoxycarbonyl)ethyl}-8-quinolinol-*C, N, O*]palladium(II) was determined by the X-ray analysis.

There has been increasing interest in cyclometalated palladium compounds of N-donor ligand.[1] Recently, we reported[2,3] the synthesis and X-ray crystal structure of a stable class of palladium complexes (**1**), which were characterized by the Pd(II)-C(sp^3) σ-bond and fused 5,5- or 5,6-chelate ring system. To further expand that original communication, we have now prepared an attractive series of palladium complexes possessing diverse *N*-bases, such as: vinylpyridine (**2**), metronidazole (**3**),[4] 1-phenylethylamines (**4**-**6**), and (–)- nicotine (**7**).

Treatment of **1b** with amines e.g., 4-vinylpyridine caused replacement of the pyridine ligand (Method B in Scheme 1). A typical experimental procedure is as follows.[5] A benzene (20 ml) solution of **1b** (100 mg, 0.2 mmol) and 4-vinylpyridine (1 ml) was stirred at 25 °C for 12 h. The reaction mixture, after removal of the solvent and the amines in vacuo, was chromatographed (TLC) on a silica gel eluting with ethyl acetate to give **2b** (74 mg, 70%) as yellow crystals and unchanged **1b** (27 mg). Other results are summarized in Table 1.[6]



a: n=1 E: $COOCH_3$
b: n=1 E: $COOC_2H_5$
c: n=2 E: $COOC_2H_5$

Scheme 1. **2 - 7**

Thus, the pyridine ligand in **1** is readily replaced by the other amines in high yields (> 71%) without Pd-C bond cleavage during the reaction. Preparation of these palladium(II) complexes by the cyclometalation of the 2-substituted 8-quinolinols with K_2PdCl_4 in the presence of L(−)-1-phenylethylamine (Method A) gives complex **5b** in a low yield (30%).

Table 1. Exchange reactions of pyridine external ligand

External ligand L	Compd.	Yield %	Mp °C
Pyridine	**1a**		132-134
	1b		124-125
	1c		182-184
4-Vinylpyridine	**2b**	70.2	158-161
Metronidazole[a)]	**3a**	94.8	215-217
	3b	84.5	84-85
D(+)-1-Phenylethylamine	**4b**	79.9	184-187
	4c	73.9	170-175
L(−)-1-Phenylethylamine	**5b**	76.9	185-189
	5c	77.4	177-179
D,L-1-Phenylethylamine	**6b**	78.3	196-200
(−)-Nicotine	**7b**	84.5	95-99
	7c	71.6	68-72

a) 1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole.

The infrared spectra of these palladium complexes showed a very strong carbonyl absorption in the range of 1642-1726 cm^{-1} corresponding to the general range for C-bonded malonato complexes.[7)] The ^1H NMR spectrum of **5b** showed two broad doublets at δ 3.16 and 3.82 indicative of N-H···O interaction;[8)] these protons were not readily exchanged with D_2O at 25 °C.

The molecular structure of **3a** as determined by X-ray crystallography[9)] is shown in Fig. 1. Important bond lengths and angles are presented in Tables 2 and 3. The geometry at palladium is slightly bow-shaped planar with bond angles in the range 81.6-102.1°, which is 10° broader than expected due to the 5,5-fused chelate ring. The dihedral angles between the plane [A] of the imidazole ring and the best plane [B] of the quinoline ring for the square plane [C] around palladium were [A]-[C], 83.4°; [B]-[C], 5.0°; [A]-[B], 80.7°. The Pd-N and Pd-C distances are all within the normal range for Pd(II) complexes.[3,4)] The properties of metronidazole are modified by coordination to Pd(II). Withdrawal of the electron density from the imidazole ring results in low field shifts of the 4-H resonance in the ^1H NMR spectrum (δ 8.05 in **3a** compared with δ 7.87 in metronidazole).

The area of metal-based radiosensitizers using nitroimidazole derivatives, e.g. misonidazole and metronidazole, is one of current interest.[4)] The antitumor activity of **3a** and **1c** against P-388 leukemia in mice has been investigated.[10)] As shown in Table 4, it was proved that these cyclometalated Pd(II) complexes are considerably positive in lower dose.

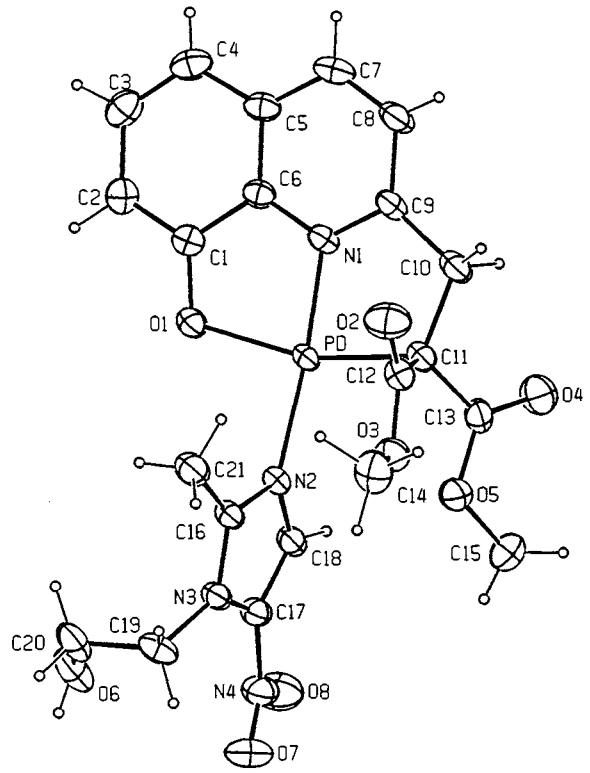


Fig. 1. ORTEP drawing of **3a** showing the atomic labelling scheme.

Table 2. Selected bond lengths (Å)

Pd-N_1	1.936 (2)	Pd-N_2	2.050 (2)
Pd-O_1	2.098 (1)	Pd-C_{11}	2.098 (2)
C_{11}-C_{12}	1.501 (3)	C_{11}-C_{13}	1.505 (3)

Table 3. Selected bond angles (°)

O_1-Pd-N_1	81.63 (6)
O_1-Pd-N_2	93.57 (5)
O_1-Pd-C_{11}	163.86 (7)
N_1-Pd-N_2	174.69 (6)
N_1-Pd-C_{11}	82.57 (7)
N2-Pd-C11	102.08 (7)
Pd-O_1-C_1	109.3 (1)
Pd-N_1-C_6	115.0 (1)
Pd-N_1-C_9	121.5 (1)
Pd-N_2-C_{16}	124.4 (1)
Pd-N_2-C_{18}	128.2 (1)
C_9-C_{10}-C_{11}	113.0 (2)
Pd-C_{11}-C_{10}	107.2 (1)
Pd-C_{11}-C_{12}	100.0 (1)
Pd-C_{11}-C_{13}	111.3 (1)
C_{10}-C_{11}-C_{12}	110.1 (2)
C_{10}-C_{11}-C_{13}	109.7 (2)

Table 4. Antitumor activity of cyclometalated palladium(II) complexes against P388

Complexes	JCI No.	Doses (mg/Kg)	T/C (%)	
1c[a]	6406	200	toxic	
		100	toxic	
		50	102	
		25	126	positive
3a[b]	6836	100	105	
		50	109	
		25	128	positive

a) N.C.I code NSC-633641 X. b) N.C.I code NSC-639223 Q.

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6) The properties for new complexes are as follows. **1b**: ^{1}H NMR ($CDCl_3$) δ 1.02 (t, C*H*$_3$, J=7.1 Hz, 6H), 3.96 (s, α -CH_2, 2H), 3.91-4.08 (m, -C*H*$_2$CH$_3$, 4H), 6.88 (d, 5-quiH, J=7.8 Hz, 1H), 6.92 (d, 7-quiH, J=8.3 Hz, 1H), 7.31 (d, 3-quiH, J=8.8 Hz, 1H), 7.35 (t, 6-quiH, J=7.8 Hz, 1H), 7.43 (t, 3,5-pyrH, J=6.8 Hz, 2H), 7.83 (t, 4-pyrH, J=7.6 Hz, 1H), 8.11 (d, 4-quiH, J=8.3 Hz, 1H), 8.96 (d, 2,6-pyrH, J=5.4 Hz, 2H); IR(KBr) 1672, 1642 (C=O), 1602, 1572 (C=C) cm^{-1}. **2b**: ^{1}H NMR ($CDCl_3$) δ 5.63 (d, (E)-CH*H*, J=10.9 Hz, 1H), 6.06 (d, (Z)-CH*H*, J=17.5 Hz, 1H), 6.68 (d,d, vinCH, J=11.2, 10.9 Hz, 1H).; IR (KBr) 1672, 1646 (C=O), 1615, 1572 (C=C) cm^{-1}. **3a**: ^{1}H NMR ($CDCl_3$) δ 3.02 (s, metCH$_3$, 3H, 3.92-3.96 (m, metCH$_2$C*H*$_2$, 2H), 4.54 (t, metC*H*2CH2, J=4.6 Hz, 2H), 8.05 (s, 4-metH, 1H); IR (KBr) 1692, 1661 (C=O), 1578 (C=C), 1559 (N=O) cm^{-1}. **3b**: ^{1}H NMR ($CDCl_3$) δ 3.05 (s, metCH$_3$, 3H), 4.10 (t, metCH$_2$C*H*$_2$-, J=7.1 Hz, 2H), 4.56 (t, met-C*H*$_2$CH$_2$, J=4.6 Hz, 2H), 8.17 (s, 4-metH, 1H); IR (KBr) 1718, 1692 (C=O), 1578 (C=C), 1560 (N=O) cm^{-1}. **4b**: $[\alpha]^{25}_D$ +38.1°(c 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.13 (t, CH_3, J=7.3 Hz, 3H), 1.27 (t, CH_3, J=7.3 Hz, 3H), 1.79 (d, HC*H*$_3$, J=6.9 Hz, 3H), 3.18 (d, N*H*$_A$H$_B$, J=8.9 Hz, 1H), 3.83 (dd, NH$_A$*H*$_B$, J=11.4, 11.4 Hz, 1H); IR (KBr) 1714, 1687 (C=O), 1572 (C=C) cm^{-1}. **4C**: $[\alpha]^{25}_D$ +127.6° (c 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.15 (t, CH_3, J=7.3 Hz, 3H), 1.31 (t, CH_3, J=7.3 Hz, 3H), 1.74 (d, HC*H*$_3$, J=5.9 Hz, 3H); IR (KBr) 1710 (C=O), 1573 (C=C) cm^{-1}. **5b**: $[\alpha]^{25}_D$ -73.7° (c 0.28, $CHCl_3$). **5c**: $[\alpha]^{25}_D$ -96.6° (0.27, $CHCl_3$). **7b**: $[\alpha]^{25}_D$ -121.9° (c 0.45,$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.69-2.02 (m, 4-nicH, 2H), 2.12 (d, 2-nicH, J=5.0 Hz, 1H), 2.12 (s, nicCH$_3$, 3H), 2.12-2.39 (m, 3-nicH, 2H), 3.05-3.13 (m, 5-nicH, 2H), 7.86 (d, 4-pyrH, J=7.9 Hz, 1H), 8.80 (d, 6-pyrH, J=5.6 Hz, 1H), 8.81 (s, 2-pyrH, 1H); IR (KBr) 1726 (C=O), 1578 (C=C) cm^{-1}. **7c**: $[\alpha]^{25}_D$ -45.6° (c 0.15 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.67-1.38 (m, 4-nicH, 2H), 1.65-1.90 (m, 3-nicH, 2H), 2,23 (s, nicCH$_3$, 3H), 2,23-2.37 (m, 2-nicH, 2H), 3.19-3.31 (m, 5-nicH, 2H), 7.85 (d, 4-pyrH, J=7.9 Hz, 1H), 8.93 (d, 6-pyrH, J=5.6 Hz, 1H), 8.94 (s, 2-pyrH, 1H); IR (KBr) 1691 (C=O), 1572 (C=C) cm^{-1}.

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9) Crystal data for **3a**; $C_{21}H_{22}N_4O_8Pd$, F. W. = 564.8, space group monoclinic $P2_1/c$; Z=4 ; a=9.8802(4), b=13.9379(6), c=16.5416(7)Å, β=102.317(3)° ; V=2225.5(4)Å^3;Dc=1.685g cm^{-3}; crystal size 0.52x0.52x0.65 mm. Data were collected using MoKα radiation on an Enlaf-Nonius CAD4 diffractometer to θ = 25° and were corrected for absorption. The structure was solved by direct method (heavy-atom method) and refined by full-matrix least squares (MolEN) to R = 0.023 for 4420 observed data.

10) Cancer Chemotherapy Center, Japanese Foundation for Cancer Research.

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