Palladium(II) Complexes with Trans Bis(carbon-metal) Bonds.[1] Ligand Syntheses, Complexation, X-ray Analysis, and Biochemical Activity with Supercoiled DNA

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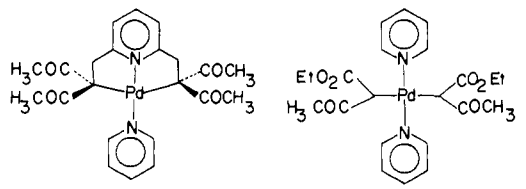
Abstract: A new series of trans bis(carbon-palladium) complexes has been prepared. The initial ligands were synthesized from 2,6-bis(chloromethyl)pyridine upon treatment with an appropriate activated methylene compound. When the 2:1 ligands are treated with potassium tetrachloropalladate(II) in the presence of pyridine, the corresponding complexes are formed. A single-crystal X-ray structure analysis was conducted on $PdC_{26}H_{32}N_2O_8$, which revealed that the molecule has exact C_2 symmetry, the two heteroaromatic rings are *exactly trans* and essentially orthogonal, and the palladium coordination is distorted somewhat from ideal square-planar geometry. Refinement in space group *Pbcn* fitting 1231 observed diffractometer data yielded R = 0.024. Cell constants are a = 9.6261 (12) Å, b = 17.7003 (17) Å, c = 15.7943 (14) Å, and Z = 4. Bond lengths involving Pd are 2.140 (5) Å for Pd-C, 2.050 (5) Å for Pd-N(pyridine), and 1.967 (5) Å for Pd-N to the tridentate ligand. The external pyridine ligand can be readily exchanged with other amines, e.g., γ-picoline. From the DNA nicking assay it appears that these trans-palladium complexes do not act on DNA, whereas the related cis-organopalladium reagents are highly active, a relationship analogous to the well-known platinum(II) series.

Recently, we described the synthesis of the first stable member of a class of palladium(II) complexes (e.g., **14**) containing two



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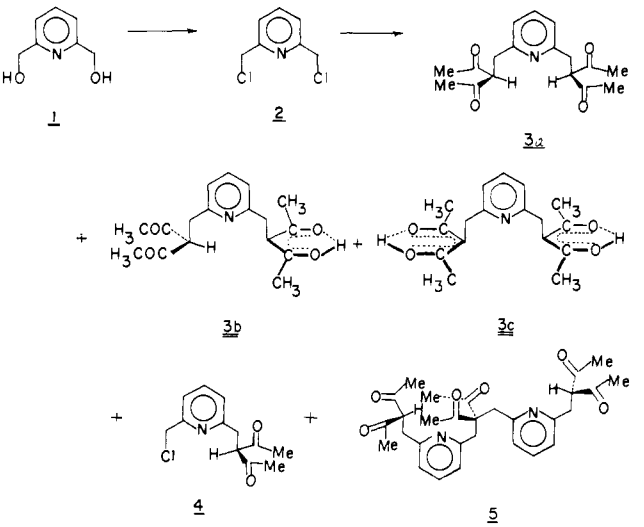
central carbon-bonded acetylacetonato ligands.[3] In 1976, Okeya and Kawaguchi reported the preparation of the related bis(ethyl acetoacetate) (etacH) analogue, as a cis-trans mixture, from a yellow compound of the formula $Pd(etac)_2 \cdot {}^1/_2H_2O$ upon treatment with excess nitrogen bases such as pyridine (py).[4] Although the corresponding anionic platinum(II) complex $Na_2[PtCl_2(\gamma\text{-acac})_2]$[5] and the $Pt(\gamma\text{-acac})_2(py)_2$ complex[6] are known, little is known about the related palladium series. We herein expand our original communication[3] and describe the synthesis of the pyridine ligands, their conversion to the neutral palladium complexes, the conformational orientations of functionality, and the biological correlation to the cis analogues[7] as well as the diamminedichloroplatinum(II) salts.[8]

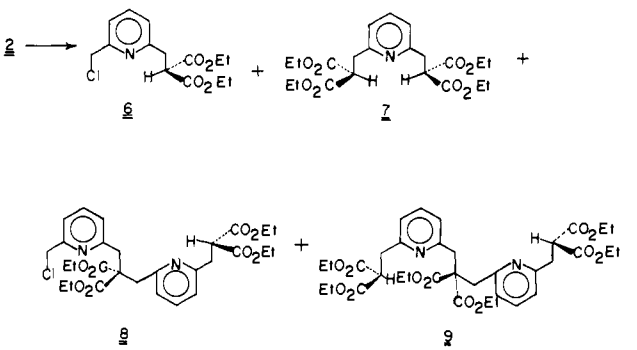
Ligand Preparations. The starting dihalide **2** was prepared from the readily available **1** upon treatment with excess thionyl chloride by the procedure described by Baker et al.[9] After a mixture of **2**, acetylacetone (acac), potassium *tert*-butoxide, and potassium iodide in anhydrous *tert*-butyl alcohol was stirred for 12 h, the desired ligand **3** was isolated (53%) as a pale yellow oil. The NMR spectrum[3] was interpreted as showing **3** to exist as a mixture of



1 **2** **3a** **3b** **3c** **4** **5**

tautomers **3a**, **3b**, and **3c** in a ratio of 43, 48, and 9%, respectively. A 1:1 adduct of **4** was isolated (3%) and characterized by its NMR spectrum, which showed both the multiplet centered at δ 7.2 for the unsymmetrical pyridine pattern and two singlets at δ 4.62 and 4.67 for the pyridyl CH_2 groups. The intensity ratio of these methylene singlets, coupled with the $-CH_2CH-$ pattern, indicate that the keto-enol tautomeric ratio for the acac moiety of **4** in $CDCl_3$ is approximately 72:28, respectively. A 2:3 adduct of **5** was also isolated (30%) and characterized via spectral analyses.

Treatment of **2** with diethyl sodiomalonate gave (30%) the



6 **7** **8** **9**

desired 2:1 ligand **7**, along with several adducts (**6**, **8**, **9**), which resemble those previously isolated from the acac reaction. The

(1) Part 67 of the Chemistry of Heterocyclic Chemistry Series.
(2) (a) On leave from Kyushi University, Fukuoka, Japan (1977-1979). (b) Undergraduate Researcher. (c) On leave from the Institute Di Mineralogia, 10123 Torino, Italy. (d) Department of Biochemistry.
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NMR of 7 showed a doublet (J = 7.5 Hz) at δ 3.24 for the pyridyl CH_2 and a triplet at δ 4.00 for the vicinal methine proton; both are indicative of the desired disubstituted ligand. Unlike **3**, **7** does not exhibit any enolic characteristics at 30 °C in $CDCl_3$. In order to increase the yield of **7**, we devised an alternate procedure using dry *N,N*-dimethylformamide (DMF) as the solvent and potassium carbonate as the base. After 40 h at 25 °C, **7** could be obtained in yields greater than 80%, along with traces of **6** and **8**; this general modification was used in all subsequent ligand preparations.

Construction of the unsymmetrical ligand **10** was accomplished by treatment of ligand **6** with acetylacetone and potassium carbonate in anhydrous DMF. The NMR spectrum of **10** suggests the acac moiety to be ca. 66% enolized (**10b**) in $CDCl_3$ as evidenced by the integration ratio due to the -CH(acac) peaks. Treatment of **2** with ethyl acetoacetate using the potassium carbonate–DMF procedure gave (61%) **11**, as a colorless oil, which existed as an *RR* (*SS*) or an *RS* diastereoisomeric mixture as shown by the two singlets for the acetyl methyl groups. Even though the methine hydrogen underwent facile deuterium exchange in methylene chloride at room temperature with D_2O and traces of pyridine, **11** exists exclusively as the ketonic tautomer since no enolic patterns are evidenced in the NMR spectrum.

Conversion of **2** to the cyano ligands **12** and **13** was accomplished by treatment with ethyl cyanoacetate and malononitrile, respectively. Although **12** is relatively stable to solvent, **13** was found to rapidly decompose in solution or on attempted purification.

Complex Formation. An aqueous solution of potassium tetrachloropalladate(II), **3**, potassium hydroxide, and excess pyridine was stirred for several hours and then extracted with methylene chloride to afford the organic soluble palladium complex **14**, which was crystallized from methylene chloride–cyclohexane as chunky needles ideal for our X-ray studies. The NMR of **14** showed a first-order spectrum[3] in which the up-field shift of the doublet of doublets for the 2,6-pyridine (external) ligand is (1) indicative of an orthogonal orientation relative to the internal pyridine nucleus and (2) nearly identical with the chemical shift of the 2,6-hydrogens in pyridine *N*-oxide[10] and close to those of $Pt(\gamma\text{-acac})_2(pyr)_2$.[6] Equivalence of the methyl groups demonstrated by the spike at δ 1.90, presence of the coordination-free carbonyl bonds (1635 cm^{-1}) in the IR, and the high solubility in nonpolar organic solvents are in accord with the trans structure **14**.

Table I. Selected Bond Distances (Å)

Pd-N1	2.050 (5)	C7-C8	1.556 (6)
Pd-N2	1.967 (5)	C7-C9	1.481 (6)
Pd-C7	2.140 (5)	C7-C10	1.478 (7)
N1-C1	1.345 (6)	C9-O1	1.217 (6)
C1-C2	1.386 (8)	C9-O2	1.343 (6)
C2-C3	1.362 (8)	O2-C11	1.443 (6)
N2-C4	1.348 (5)	C11-C12	1.447 (8)
C4-C5	1.400 (6)	C10-O3	1.200 (6)
C5-C6	1.389 (6)	C10-O4	1.355 (7)
C4-C8	1.482 (7)	O4-C13	1.432 (6)
		C13-C14	1.463 (8)

Treatment of the bis(diethyl malonate) ligand **7** with K_2PdCl_4 under similar reaction conditions in the presence of pyridine afforded the yellow crystalline complex **15**. The NMR spectrum of **15** (Figure 1) exhibits a spike at δ 3.85 for the pyridine CH_2 groups evincive of a plane of symmetry through the internal pyridine nucleus. In view of the symmetry exhibited by **15**, the magnitude of magnetic nonequivalence of the ester methylene groups was unexpected. Double irradiation studies confirm the geminal coupling of these methylene groups. There seems to be little doubt that the magnetic nonequivalence is attributable to the unequal conformer populations. In other words, conformational preference with respect to a dissymmetric center must be responsible for the major contribution to the magnetic nonequivalence. The magnitude of the nonequivalence may further support the orthogonality of the external pyridine ligand. For more precise conformational data on the complex **15** to be obtained, the single-crystal X-ray analysis was undertaken.

The molecule has exact C_2 symmetry in the crystal. Figures 2 and 3 illustrate the structure of **15**, which may be described by the relative orientation of three planes: the coordination plane, the plane of the pyridine (external) ligand, and the plane of the pyridine portion of the tridentate ligand. The two heteroaromatic rings are exactly trans and essentially orthogonal, forming a dihedral angle of 90.5°. The coordination plane forms a dihedral angle of 14.1° with the disubstituted pyridine plane and is distorted somewhat from ideal square-planar geometry. The Pd–C bond is bent 8.2° away from perpendicular; whereas the Pd–N1 (external pyridine) bond distance of 2.050 (5) Å is comparable to those found in similar palladium(II)–pyridine complexes.[11] The Pd–N bond to the tridentate ligand, 1.967 (5) Å, is considerably shorter apparently as a result of geometrical constraints imposed by chelation. The Pd–C bond length, 2.140 (5) Å, is typical of Pd(II)–C(sp^3) bonds.[11b,12] No unusual bond distances or angles are noted within the remainder of the structure, and no unusually short intermolecular contacts exist. Tables I and II show the important bond distances and angles, respectively.

The magnetic nonequivalence exhibited by the ethyl methylene hydrogens in the NMR is more easily rationalized after inspection of Figure 2, in which the inner (H_A) and outer (H_B) hydrogens

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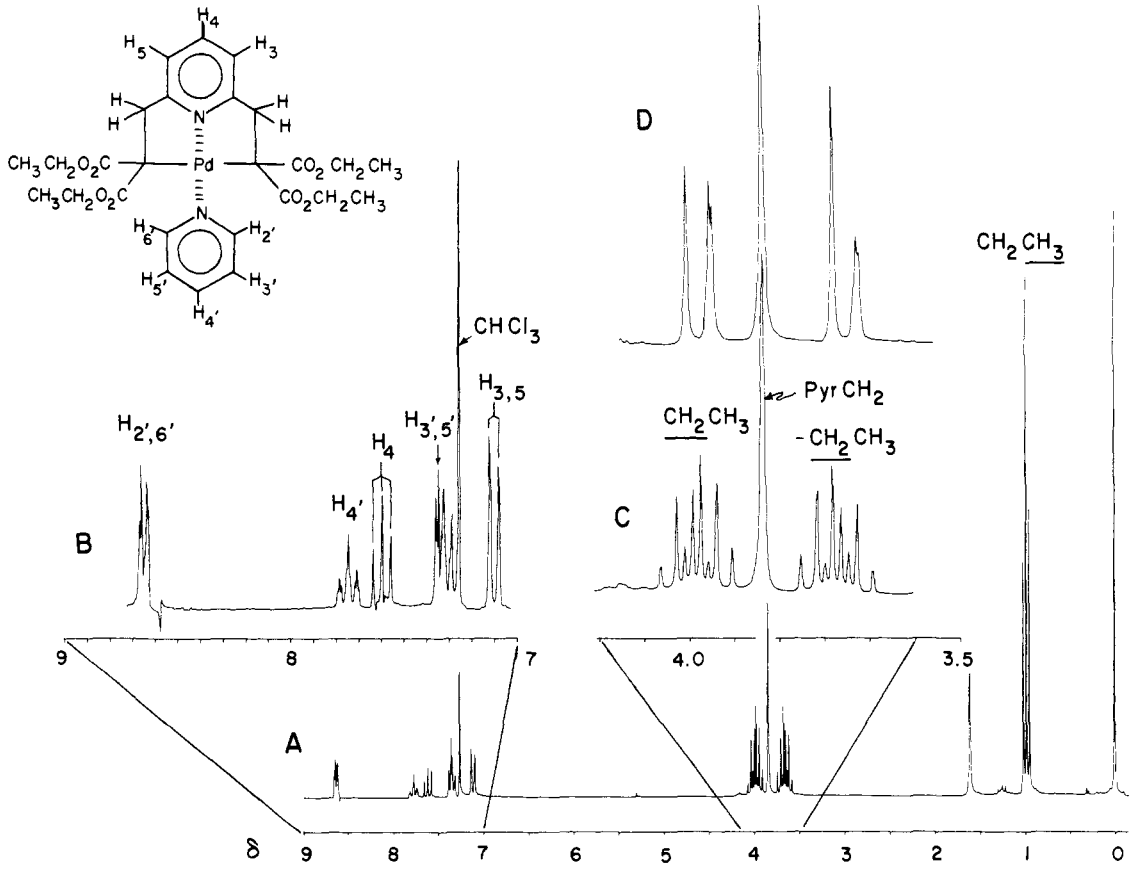


Figure 1. 200-MHz ^1H NMR spectrum (A) of complex **15** in $CDCl_3$ at 40 °C expanded aromatic and methylene regions (B, C) and the decoupled methylene region (D).

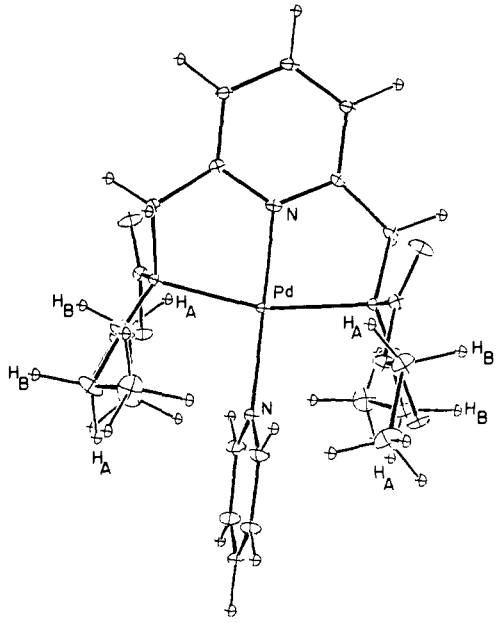


Figure 2. Perspective drawing[17] of complex **15**. Nonhydrogen atoms are represented by thermal ellipsoids drawn at the 30% probability level, and hydrogen atoms are drawn as spheres of arbitrary radius.

are in obviously different chemical environments. The diastereotopic character is evident due to the molecular symmetry of the molecule, and the magnitude of this difference results from the unique orthogonal juxtaposition of the external pyridine ligand or palladium center to that of H_A. Alternatively, H_B is always alien to the environment of the core groups.

Treatment of the isomeric mixture of **11** with potassium tetrachloropalladate(II) in the presence of pyridine gave a mixture of **16**, in which cis and trans isomers could not be separated. The doublets (J = 14 Hz) at δ 3.53 and 3.61 for the pyridine CH_2 groups are suggestive of the adjacent enantiotopic center. Similarly reaction of **10** under identical conditions generated **18**, in which the plane of symmetry (through the pyridine tridentate ligand) results in two singlets (δ 3.80 and 4.02) for the pyridine methylene groups. Both **16** and **18** possess diastereotopic ester methylene groups, as suggested by the complex methylenic region (around δ 3.95). During the course of complex formation, complex **16** underwent hydrolysis of one of the ester functions to generate **19**. The NMR spectrum (Figure 4) of **19** is complex; however, these data can be interpreted in light of the proposed structure. Since the 2- and 6-pyridine hydrogens of the external pyridine ligand of **19** exhibit different chemical shifts in the NMR spectrum, rotation of the Pd–N (external pyridine) bond must be fixed or slow on the NMR time scale. Cyano complex **17** was prepared by this procedure in lower yields due to the instability of the ligand; the singlet at δ 3.83 due to the CH_2 groups suggests symmetrical structure of this complex.

Table II. Selected Bond Angles (Deg)

N1-Pd-N2	180	C4-C8-C7	111.1 (4)
N1-Pd-C7	98.2 (1)	Pd-C7-C8	102.8 (3)
N2-Pd-C7	81.8 (1)	Pd-C7-C9	107.1 (3)
C7-Pd-C7'	163.6 (1)	Pd-C7-C10	105.0 (3)
Pd-N1-C1	120.2 (3)	C7-C9-O1	123.9 (5)
C1-N1-C1'	119.5 (7)	C7-C9-O2	114.9 (5)
N1-C1-C2	120.5 (7)	O1-C9-O2	121.1 (5)
C1-C2-C3	120.5 (7)	C9-O2-C11	116.9 (5)
C2-C3-C2'	118.5 (6)	O2-C11-C12	108.5 (5)
Pd-N2-C4	117.9 (3)	C7-C10-O3	127.8 (6)
C4-N2-C4'	124.3 (5)	C7-C10-O4	111.2 (5)
N2-C4-C5	118.6 (5)	O3-C10-O4	120.9 (5)
N2-C4-C8	114.5 (4)	C10-O4-C13	117.7 (4)
C5-C4-C8	126.8 (5)	O4-C13-C14	107.9 (5)
C4-C5-C6	118.8 (5)		
C5-C6-C5'	121.0 (5)		

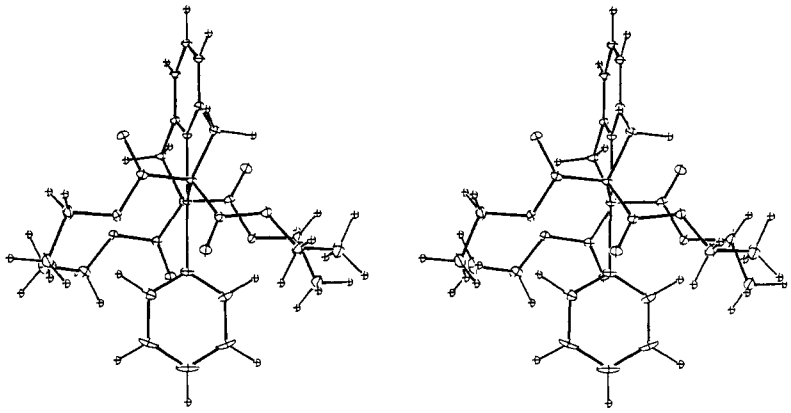
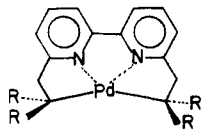


Figure 3. Stereoprojection of complex **15** orthogonal to the external pyridine ligand.

Exchange of the external pyridine ligand was readily accomplished by treatment of **15** with excess γ-picoline at 25 °C for 12 h. The reaction can be monitored by the down-field shift (Δ = δ 0.1) of singlet for the 4-pyridyl methyl upon complexation; the reaction is complete after 12 h. The ligand exchange probably proceeds by a distorted trigonal-bipyramidal intermediate in which an excess of γ-picoline and its marginally stronger basicity drive the exchange to completion.

Analysis of DNA Damage. Previous reports on the action of antitumor drugs such as diamminedichloroplatinum(II) and bleomycin indicate that the target molecule for their toxic effects is DNA.[8,13] Consistent with this, a logical extension of the structural studies reported herein was to establish whether the trans-palladium(II) complexes act on DNA. We previously reported that **15**, whose synthesis is herein described, was inactive on DNA. However, the related cis analogue **20** was found to be



20 : R=CO_2Et

active on DNA by causing DNA strand scissions.[7] It therefore appeared from these initial findings that the cis geometry was essential for the palladium complexes to be active on DNA. Beyond **15**, we also analyzed each of the trans-organometallic reagents whose syntheses are reported herein to find that none were causing strand breaks in DNA, thus supporting our original contention that the cis geometry appeared to be required for nicking of the DNA phosphodiester backbone. We feel it is unlikely that other DNA lesions produced by the trans organometallic reagents are escaping our detection procedure. *The system we have utilized for detecting DNA strand breaks is extremely sensitive, in which one nick per DNA molecule can be easily monitored.* Furthermore, if the trans complexes were binding to DNA or causing DNA interstrand cross-links, these events would have been detected. For example, in vitro studies indicate that the antitumor drug *cis*-diamminedichloroplatinum(II) produces DNA interstrand cross-links within the first 15 min of incubation with DNA.[14] This phenomenon has not been observed for any of the palladium complexes now under investigation nor have we detected any binding of the complexes to DNA. It therefore appears from our initial studies that the trans-palladium complexes do not act on DNA, whereas the related cis-organopalladium complexes are highly active.[7,15] Our results clearly suggest that the palladium(II) complexes might be analogous to the platinum(II) series, in which only the cis configuration is active toward a broad spectrum of animal tumors.[8]

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. NMR spectra were determined on either a Varian Associates A-60A or a Bruker WP-200 NMR spectrometer by using $CDCl_3$ solutions, except where noted with tetramethylsilane as the internal standard. IR spectra were recorded on a Perkin-Elmer 621 grating-infrared spectrophotometer. Mass spectral (MS) data were determined by Mr. D. Patterson on a Hewlett-Packard HP 5992 GC/mass spectrometer. X-ray diffraction data were collected with graphite-monochromatized Mo Kα radiation on an Enraf-Nonius CAD-4 diffractometer.

Reported R_f values were ascertained by a standardized thin-layer chromatography (TLC) procedure: 0.25-mm Brinkmann silica gel HF-254-366 plates eluting with the stipulated solvents.

For the preparative thick-layer chromatography (ThLC), 2-mm silica gel PF-254-366 plates were used. Elemental analyses were performed by Mr. R. Seab in these laboratories.

2,6-Bis(chloromethyl)pyridine (2) was prepared by the procedure of Baker et al.[9] from 2,6-bis(hydroxymethyl)pyridine and thionyl chloride: mp 76–77 °C (lit.[9] mp 74–75 °C).

2,6-Bis(2,2-diacetylethyl)pyridine (3). To a stirred refluxing solution of potassium *tert*-butoxide (2.36 g, 20 mmol) in *tert*-butyl alcohol (40 mL) was added acetylacetone (3 g, 30 mmol) dropwise. After 30 min, 2,6-bis(chloromethyl)pyridine (1.76 g, 10 mmol) was added over 30 min; 1 h after the addition, potassium iodide (400 mg, 2.4 mmol) was added. The mixture was refluxed with stirring for 12 h. The solvent and excess acetylacetone were then removed in vacuo. The residue was extracted with dichloromethane, washed with water, and chromatographed (ThLC) on silica gel eluting with ethyl acetate–cyclohexane (1:1) to give three major components.

Fraction A gave the 1:1 adduct **4**, as a plae yellow oil: 80 mg (3%); R_f 0.46; NMR δ 2.13 (s, CH_3, 1.7 H), 2.29 (s, CH_3, 4.3 H), 2.38 (d, pyridyl CH_2, J = 7.5 Hz, 1.4 H) 3.83 (s, pyridyl CH_2, 0.56 H), 4.50 (t, pyridyl CH_2CH, J = 7.5 Hz, 0.72 H), 4.62 and 4.67 (2 s, pyridyl CH_2, 2 H), 7.03–7.43 (m, 3,5-pyridyl H, 2 H), 7.57–7.87 (m, 4-pyridyl H, 1 H); IR (neat) 1725 (C=O), 1700 (C=O), 1595 (C=C–O), 1575 (C=C) cm^{-1}; MS (70 eV) *m/e* (assignment, relative intensity) 241 (M^+, 0.7), 239 (M^+, 2.7), 198 ($M^+ - C_2H_3O$, 12.9), 196 ($M^+ - C_2H_3O$, 46.5), 156 (C_8H_9NCl, 37.0), *154* (C_8H_9NCl, *100*), 43 (C_2H_3O, 11.5).

Anal. Calcd for $C_{12}H_{14}NO_2Cl$: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.21; H, 5.99; N, 5.85.

Fraction B afforded the desired ligand **3**: 1.6 g (53%); R_f 0.31; NMR δ 2.10 and 2.12 (2 s, CH_3, 4 H), 2.22 and 2.23 (2 s, CH_3, 8 H), 3.75 (d, pyridyl CH_2CH, J = 7.5 Hz, 1.7 H), 3.43 (d, pyridyl CH_2CH, J = 7.5 Hz, 0.96 H), 3.76 (s, pyridyl CH_2, 0.36 H), 3.73 (s, pyridyl CH_2, 0.96 H), 4.38 (t, pyridyl CH_2CH, J = 7.5 Hz, 0.48 H), 4.31 (t, pyridyl CH_2CH, J = 7.5 Hz, 0.86 H), 6.92–7.03 (4 d, 3,5-pyridyl H, J = 8.0 Hz, 2 H), 7.46–7.56 (2 t, 4-pyridyl H, J = 8.0 Hz, 1 H); IR (neat) 1725 (C=O), 1695 (C=O), 1590 (C=C–O), 1575 (C=C) cm^{-1}; MS (70 eV) *m/e* (assignment or see above, relative intensity) 303 (M^+, 8.6), 260 ($M^+ - C_2H_3O$, 74.8), *218* ($C_{13}H_{16}NO_2$, *100*), 176 ($C_{11}H_{14}NO$, 63.6), 109 ($C_7H_{11}N$, 83), 43 (60.8).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 66.94; H, 6.94; N, 4.41.

Fraction C yielded the 2:3 adduct **5**, as thick oil: 750 mg (30%); R_f 0.19; NMR δ 2.13, 2.19, and 2.25 (3 s, CH_3, 18 H), 2.89, 2.96, and 3.01

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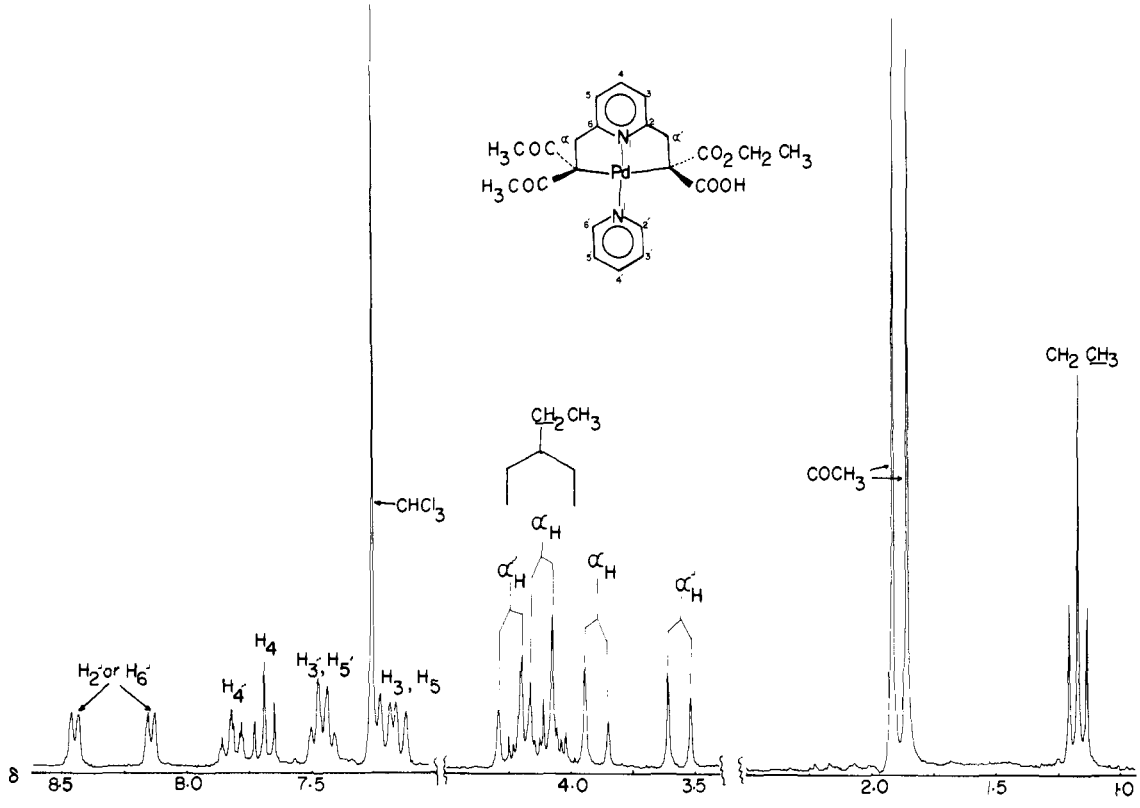

Figure 4. 200-MHz ^{1}H NMR spectrum of complex **19** in $CDCl_3$ at 40 °C.

(3 b s, pyridyl CH_2, 4 H), 3.34 and 3.39 (2 d, pyridyl CH_2CH, 2.6 H), 3.78 and 3.83 (2 s, pyridyl CH_2, 1.4 H), 4.40 and 4.45 (2 t, pyridyl CH_2CH, 1.3 H), 6.95–7.13 (m, 3,5-pyridyl H, 2 H), 7.38–7.71 (m, 4-pyridyl H, 1 H); IR (neat) 1720 (C=O), 1700 (C=O), 1590 (C=C–C=O), 1575 (C=C); MS (70 eV) *m/e* (assignments or see above, relative intensity) 463 ($M^+ - C_2H_3O$, 0.3%), 260 ($C_{15}H_{18}NO_3$, 30.0), 218 (44.0), 176 (28.3), 43 (*100*).

2,6-Bis(2,2-dicarbethoxyethyl)pyridine (7). Method A. Small chips of sodium metal (580 mg, 25 mmol) were placed in absolute ethanol (10 mL) under nitrogen. When all the metal had reacted, the solution was cooled and diluted with anhydrous diethyl ether (30 mL) and then diethyl malonate (4 g, 25 mmol) in anydrous ether (30 mL) was added dropwise. After 30 min, a solution of 2,6-bis(chloromethyl)pyridine (2.2 g, 12 mmol) in anhydrous diethyl ether (40 mL) was added dropwise over 30 min. After the addition was complete, the mixture was refluxed for 2 h, cooled, and washed twice with water (10 mL). The pH of the aqueous extract was adjusted to 7 with 4 N hydrochloric acid, and the mixture was extracted with chloroform. The combined organic extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to give a thick yellow oil (5.5 g), which was chromatographed (ThLC) on silica gel eluting with ethyl acetate–cyclohexane (1:5) to provide five major fractions.

Fraction A gave the unreacted starting material **2**: mp 75–76 °C; 310 mg (15%); R_f 0.4 [ethyl acetate–cyclohexane (1:5)].

Fraction B yielded the 1:1 adduct **6**: 1.09 g (28%); R_f 0.20; NMR (CCl_4) δ 1.22 (t, CH_3CH_2, J = 7.0 Hz, 6 H), 3.30 (d, pyridyl CH_2CH, J = 7.5 Hz, 2 H), 4.00 (t, pyridyl CH_2CH, J = 7.5 Hz, 1 H), 4.15 (q, CH_3CH_2, J = 7.5 Hz, 4 H), 4.58 (s, pyridyl CH_2Cl, 2 H), 7.07–7.76 (m, pyridyl H, 3 H); IR (neat) 1750 (C=O), 1730 (C=O), 1597 (C=C), 1580 (C=C) cm^{-1}.

Anal. Calcd for $C_{14}H_{18}NO_4Cl$: C, 56.08; H, 6.05; N, 4.67. Found: C, 56.24; H, 6.42; N, 4.57.

Fraction C afforded the desired ligand **7**: 1.54 (g (30%) R_f 0.13; NMR (CCl_4) δ 1.22 (t, CH_2CH_3, J = 7.5 Hz, 12 H), 3.24 (d, pyridyl CH_2CH, J = 7.5 Hz, 4 H), 4.00 (t, pyridyl CH_2CH, J = 7.5 Hz, 2 H), 4.13 (q, CH_2CH_3, J = 7.5 Hz, 8 H), 6.95 (d, 3,5-pyridyl H, J = 7.5 Hz, 2 H), 7.45 (dd, 4-pyridyl H, J = 6.5, 8.5 Hz, 1 H); IR (neat) 1750 (C=O), 1730 (C=O), 1580 (C=C), 1545 (C=C) cm^{-1}.

Anal. Calcd for $C_{21}H_{28}NO_8$: C, 59.56; H, 6.90; N, 3.30. Found: C, 59.23; H, 6.77; N, 3.30.

Fraction D gave the 2:2 compound **8**, as a colorless oil: 790 mg (11%); R_f 0.1; NMR (CCl_4) δ 1.21 (t, CH_2CH_3, J = 7.0 Hz, 12 H), 3.21 (d, pyridyl CH_2CH, J = 7.0 Hz, 2 H), 3.30 (s, pyridyl CH_2, 4 H), 4.14 (q, J = 7.0 Hz, $COCH_2CH_3$, 4 H), 4.17 (t, CH, J = 7.0 Hz, 1 H), 4.20 (q, $COCH_2CH_3$, J = 7.0 Hz, 4 H), 4.56 (s, CH_2Cl, 2 H), 6.82–7.72 (m, pyridyl H, 6 H); IR (neat) 1726 (C=O), 1550 (C=C) cm^{-1}.

Anal. Calcd for $C_{28}H_{35}N_2O_8Cl$: C, 59.73; H, 6.26; N, 4.97. Found: C, 59.40; H, 6.59; N, 4.57.

Fraction E gave the 2:3 compound **9**, as colorless oil: 620 mg (8%); NMR δ 1.05–1.35 (3 t, $COCH_2CH_3$, J = 7.0 Hz, 18 H), 3.37 (d, pyridyl CH_2, J = 7.5 Hz, 4 H), 3.40 (s, pyridyl CH_2, 4 H), 4.0–4.23 (2 q, CH_2CH_3, J = 7.0 Hz, 14 H), 6.78–7.60 (m, pyridyl H, 6 H); IR (neat) 1725 (C=O), 1550 (C=C) cm^{-1}.

Method B. 2,6-Bis(2,2-dicarbethoxyethyl)pyridine. A mixture of 2,6-bis(chloromethyl)pyridine (1 g, 5.7 mmol), diethyl malonate (4.0 g, 23 mmol), and potassium carbonate (4.0 g, 30 mmol) in dry dimethylformamide (15 mL) was stirred at room temperature for 40 h. The reaction mixture was filtered, and the residue was thoroughly washed with dichloromethane. The combined organic extract was concentrated in vacuo to afford a thick yellow oil (2.33 g), which was column chromatographed on silica gel eluting with ethyl acetate–cyclohexane (1:3) to afford **7**, as a colorless oil: 1.98 g (82%). This sample was identical with the sample prepared by method A.

2-Bis(2,2-dicarbethoxyethyl)-6-bis(2,2-diacetylethyl)pyridine (10). A mixture of **6** (200 mg, 0.66 mmol), acetylacetone (260 mg, 2.64 mmol), and potassium carbonate (450 mg, 3.3 mmol) in dry dimethylformamide (4 mL) was stirred at room temperature for 48 h and then worked up as in method B. Chromatography (ThLC) eluting with ethyl acetate–cyclohexane (1:2) provided the desired ligand **10**, as the major component: 126 mg (56%); R_f 0.36; NMR δ 1.23 (t, OCH_2CH_3, J = 7.0 Hz, 6 H), 2.12 (s, C=C(OH)CH_3, 1.66 H), 2.25 (s, C(O)CH_3, 4.34 H), 3.30 (d, $CH_2CH(COOEt)_2$, J = 7.0 Hz, 2 H), 3.35 (d, $CH_2CH(COCH_3)_2$, J = 7.0 Hz, 1.34 H), 3.75 (s, $CH_2C(COCH_3)$=C(OH)CH_3, 0.66 H), 4.05 (t, $CH(COOEt)_2$, J = 7.0 Hz, 1 H), 4.20 (q, $COOCH_2CH_3$, J = 7.0 Hz, 4 H), 4.47 (t, $CH(COCH_3)_2$, J = 7.0 Hz, 1 H), 7.05 (d, 3(5)-pyridyl H, J = 7.5 Hz, 2 H), 7.52 (2 d, 4-pyridyl H, J = 7.5 Hz, 1 H); IR (neat) 1752–1690 (b, vs, C=O), 1585, 1568 (C=C) cm^{-1}; MS (70 eV) *m/e* (assignment, relative intensity) 363 (M+, 6.8), 345 (19.4), 320 (34.5), 304 (25.5), 278 (26), 272 (47.7), 232 (26.3), 228 (*100*), 186 (66.4), 132 (55.3), 43 (80.3).

2,6-Bis(2-carbethoxy-3-ketobutyl)pyridine (11). To a mixture of potassium carbonate (6.25 g, 45.2 mmol) and ethyl acetoacetate (7.3 g, 56.6 mmol) in dry dimethylformamide (35 mL) was added 2,6-bis(chloromethyl)pyridine (2.0 g, 11.3 mmol). The mixture was stirred at 25 °C for 20 h, filtered, and concentrated in vacuo. The crude product was chromatographed (ThLC) on silica gel eluting with ethyl acetate–cyclohexane (1:2) to give the desired 2:1 product along with numerous side products.

The major (61%) fraction gave **11**, as a colorless oil: R_f 0.31; NMR δ 1.23, 1.24 (2 t, CH_3CH_2, J = 7.5 Hz, 6 H), 2.30, 2.31 (2 s, $COCH_3$, 6 H), 3.24, 3.35 (2 dd, pyridyl CH^AH^B, J = 15, 7.5 Hz, 4 H), 4.19 (q, OCH_2CH_3, J = 7.5 Hz; t, pyridyl CH_2CH, J = 7.5 Hz, 6 H), 7.02 (d, 3,5-pyridyl H, J = 7.5 Hz, 2 H), 7.48 (2 t, 4-pyridyl H, J = 7.5 Hz, 1 H); IR ($CHCl_3$) 1745 (C=O), 1725 (C=O), 1595, 1577, 1250 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 363 (M+, 10.6), 321 (33), 320 (*100*), 318 (34), 274 (45), 248 (51), 202 (70), 160 (51), 132 (76), 43 (42).

Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.54; H, 7.09; N, 3.67.

2,6-Bis(2-cyano-2-carbethoxyethyl)pyridine (12). To a suspension of potassium carbonate (790 mg, 5.7 mmol) and ethyl cyanoacetate (770 mg, 68 mmol) in acetonitrile (10 mL) was added 2,6-bis(chloromethyl)pyridine (200 mg, 1.1 mmol). The suspension was stirred at 25 °C for 24 h and filtered and the filtrate was concentrated in vacuo to give an oil, which was chromatographed (ThLC) on silica gel eluting with ethyl acetate–cyclohexane (1:5) to give the cyanoester **12**, as a colorless oil: 160 mg (41%); NMR (60 MHz) δ 1.28 (t, OCH_2CH_3, J = 7 Hz, 6 H), 3.41 (d, pyridyl CH_2, J = 6 Hz, 4 H), 4.28 (q, OCH_2CH_3, J = 7 Hz; t, pyridyl CH_2CH, J = 6 Hz, 6 H), 7.15 (d, 3,5-pyridyl H, J = 8 Hz, 2 H), 7.65 (2 t, 4-pyridyl H, J = 8 Hz, 1 H).

2,6-Bis(2,2-dicyanoethyl)pyridine (13). To a suspension of potassium carbonate (2.07 g, 15 mmol) and malononitrile (1.00 g, 15 mmol) in acetonitrile (30 mL) was added 2,6-bis(chloromethyl)pyridine (1.32 g, 7.5 mmol). The suspension was stirred at 25 °C for 8 h, filtered, and concentrated in vacuo to give a crude oil which was chromatographed (ThLC) on silica gel eluting with cyclohexane–ethyl acetate (1:2) to give the desired ligand **13**, which was found to be very unstable and decomposed rapidly in solution or on extended purification: 630 mg (36%); NMR δ 3.52 (d, pyridyl CH_2, J = 7.5 Hz, 4 H), 4.55 (t, pyridyl CH_2CH, J = 7.5 Hz, 2 H), 7.38 (d, 3,5-pyridyl H; J = 7.5 Hz, 2 H), 7.86 (t, 4-pyridyl H, J = 7.5 Hz, 1 H); IR (KBr) 2255 (C≡N) cm^{-1}.

Palladium(II) Complex with 3 and Pyridine (14). General Procedure. An aqueous solution (20 mL) of K_2PdCl_4 (108 mg, 0.33 mmol) was added to a solution of the bis(acac) ligand **3** (100 mg, 0.33 mmol) in ethanol (10 mL), followed by the addition of KOH (70 mg, 1.2 mmol). After 20 min, excess of pyridine (1 mL) was added and the mixture was stirred at 25 °C for 3 h. The mixture was concentrated in vacuo, and the Pd(II) complex was extracted with dichloromethane, washed with water, and dried over anhydrous sodium sulfate. After solvent concentration, the residue was chromatographed (ThLC) on silica gel eluting with ethyl acetate to give **14** as yellow crystals, which were recrystallized from dichloromethane–cyclohexane: mp 190–195 °C (dec); 100 mg (62%); R_f 0.05 (ethyl acetate); NMR δ 1.90 (s, CH_3, 12 H), 4.00 (s, pyridyl CH_2, 4 H), 7.22 (d, 3,5-pyridyl H, J = 7.5 Hz, 2 H), 7.43–7.51 (m, 3′,5′-pyridyl H, 2 H), 7.61 (t, 4-pyridyl H, J = 7.5 Hz, 1 H), 7.77–7.87 (m, 4′-pyridyl H, 1 H), 8.27–8.32 (m, 2′,6′-pyridyl H, 2 H); IR (KBr) 1635 (C=O), 1605 (vs, C=O) cm^{-1}.

Anal. Calcd for $C_{22}H_{24}N_2O_4Pd \cdot {}^1/_4CH_2Cl_2$: C, 52.59; H, 4.86; N, 5.51. Found: C, 52.68; H, 5.03; N, 5.51.

Palladium(II) Complexes, which were prepared by the above procedure, were the following.

15: from the bis(diethyl malonate) ligand **7**; yellow brick crystals; mp 148–153 °C (dec) (benzene–cyclohexane); NMR δ 0.99 (t, CH_3CH_2O, J = 7.5 Hz, 12 H), 3.67 (dq, $CH_AH_BCH_3$, J = 7.5, 10.5 Hz, 4 H), 3.85 (s, pyridyl CH_2, 4 H), 3.99 (dq, $CH_AH_BCH_3$, J = 7.5, 10.5 Hz, 4 H), 7.12 (d, 3,5-pyridyl H, J = 8 Hz, 2 H), 7.36 (dd, 3′,5′-pyridyl H, J = 8, 5 Hz, 2 H), 7.62 (t, 4-pyridyl H, J = 8 Hz, 1 H), 7.78 (dt, 4′-pyridyl H, J = 8, 2 Hz, 2 H), 8.63 (dt, 2′,6′-pyridyl H, J = 5, 2 Hz, 2 H); IR (KBr) 1684, 1670 (b, vs, C=O), 1601 (w, C=C).

Anal. Calcd for $C_{26}H_{32}N_2O_8Pd \cdot {}^1/_3H_2O$: C, 50.70, H, 5.40; N, 4.55. Found: C, 50.49; H, 5.39; N, 4.31.

16: from the bis(ethyl acetoacetate) ligand **11**; mp 140–145 °C (dec); 100 mg (45%); R_f 0.31; NMR δ 1.05 (t, OCH_2CH_3, J = 7.5 Hz, 3 H), 1.07 (t, OCH_2CH_3, J = 7.5 Hz, 3 H), 1.56 (s, $COCH_3$, 3 H), 1.65 (s, $COCH_3$, 3 H), 3.53 (d, pyridyl CH^A, J = 14 Hz, 2 H), 3.61 (d, pyridyl CH^B, J = 14 Hz, 2 H), 3.80–4.20 (m, OCH_2CH_3, 4 H), 7.11 (d, 3,5-pyridyl H, J = 8 Hz, 2 H), 7.48 (dd, 3′,5′-pyridyl H, J = 7, 5 Hz, 2 H), 7.61 (t, 4-pyridyl H, J = 8 Hz, 1 H), 7.83 (dt, 4′-pyridyl H, J = 7, 2 Hz, 1 H), 8.52 (dd, 2′,6′-pyridyl H, J = 5, 2 Hz, 2 H); IR ($CHCl_3$) 1660 (C=O), 1600 (C=C) cm^{-1}.

17: from the bis(dicyano) ligand **13**; mp 160–170 °C (dec); 20% NMR δ 3.83 (s, pyridyl CH_2, 4 H), 7.25 (d, 3,5-pyridyl H, J = 8 Hz, 2 H), 7.55 (dd, 3′,5′-pyridyl H, J = 6, 7.5 Hz, 2 H), 7.78 (t, 4-pyridyl H, J = 8 Hz, 1 H), 7.90 (dt, 4′-pyridyl H, J = 7.5, 1.5 Hz, 1 H), 8.84 (dd, 2′,6′-pyridyl H, J = 6.5, 1.5 Hz, 2 H); IR ($CHCl_3$) 2250 (C≡N) cm^{-1}.

Anal. Calcd for $C_{18}H_{12}N_6Pd(Et_2O)$: C, 53.61; H, 4.50; N, 17.05. Found: C, 52.94; H, 4.15; N, 16.14.

18: from ligand **10**; yellow solid (very hygroscopic); 55%; NMR δ 1.02 (t, OCH_2CH_3, J = 7 Hz, 6 H), 1.92 (s, $COCH_3$, 6 H), 3.67, 3.72 (2 q, OCH^ACH_3, J = 7 Hz, 2 H), 3.80 (s, pyridyl CH_2, 2 H), 3.93, 3.99 (2 q, OCH^BCH_3, J = 7 Hz, 2 H), 4.02 (s, pyridyl CH_2, 2 H), 7.17 (dd, 3,5-pyridyl H, J = 7.5, 2.5 Hz, 2 H), 7.42 (t, 3′,5′-pyridyl H, 2 H), 7.67 (t, 4-pyridyl H, J = 7.5 Hz, 1 H), 7.82 (t, 4′-pyridyl H, J = 7.5 Hz, 1 H), 8.45 (d, 2′,6′-pyridyl H, J = 5 Hz, 2 H); IR (KBr) 1665, 1660 (C=O), 1275, 1075 (C—O) cm^{-1}.

Anal. Calcd for $C_{24}H_{28}N_2O_6Pd \cdot H_2O$: C, 51.03; H, 5.35; N, 4.96. Found: C, 51.21; H, 5.26; N, 4.49.

19: isolated as a side product from the reaction with ligand **10**: yellow crystalline solid; mp 168–169 °C; 20%; NMR (see Figure 4); IR (KBr) 1710 (C=O), 1600, (C=C), 1070 (COC) cm^{-1}.

Anal. Calcd for $C_{22}H_{24}N_2O_6Pd \cdot {}^1/_2H_2O$: C, 50.06; H, 4.67; N, 5.30. Found: C, 49.81; H, 4.58; N, 5.12.

Ligand-Exchange Reaction. γ-Picoline. A solution of **15** (50 mg, 0.08 mmol) and γ-picoline (100 mg) in methylene chloride (5 mL) was stirred at 25 °C for 12 h. The solvent was removed in vacuo, and the residue was chromatographed (ThLC) on silica gel eluting with ethyl acetate–cyclohexane (1:2) to give **20**, as a yellow solid: 49 mg (100%); mp 167–168 °C; NMR δ 1.0 (t, OCH_2CH_3, J = 7 Hz, 12 H), 2.42 (s, 4′-pyridyl Me, 3 H), 3.65, 3.70 (2 q, OCH^ACH_3, J = 7 Hz, 4 H), 3.82 (s, pyridyl CH_2, 4 H), 3.95, 4.00 (2 q, OCH^BCH_3, J = Hz, 4 H), 7.10 (d, 3,5-pyridyl H, J = 7.5 Hz, 2 H), 7.15 (d, 3′,5′-pyridyl H, J = 8.0 Hz, 2 H), 7.6 (t, 4-pyridyl H, J = 7.5 Hz, 1 H), 8.45 (d, 2′,6′-pyridyl H, J = 8 Hz, 2 H); IR (KBr) 1665 (C=O), 1635, 1250, 1090 (COC) cm^{-1}.

Anal. Calcd for $C_{27}H_{34}N_2O_8Pd$: C, 55.22; H, 5.52; N, 4.51. Found: C, 52.43; H, 5.93; N, 4.37.

X-ray Experimental Data. Diffraction quality crystals of **15** were prepared by recrystallization from methylene chloride–cyclohexane. A yellow crystal of dimensions 0.40 × 0.30 × 0.18 mm was mounted in random orientation on an Enraf-Nonius CAD-4 diffractometer. All measurements were made by using graphite-monochromatized Mo Kα radiation (λ = 0.710 73 Å). Unit cell dimensions and crystal orientation were determined from diffractometer coordinates of 25 reflections having $16° < \theta < 22°$. Crystal Data for $PdC_{26}H_{32}N_2O_8$: mol wt 606.9; orthorhombic space group *Pbcn*; a = 9.6261 (12) Å, b = 17.7003 (17) Å, c = 15.7943 (14) Å; Z = 4; d_c = 1.498 (2) g cm^{-3}; μ(Mo Kα) = 7.22 cm^{-1}.

Intensity data were collected by the ω–2θ scan technique employing variable scan rates in order to measure all significant reflections with approximately equal precision. Scan rates varied from 0.45 to 10.0 deg min^{-1}. Reflections having $I_o < 0.5\sigma(I_o)$ in a rapid (10 deg min^{-1}) prescan were flagged as unobserved and not scanned slowly. Scan widths varied with scattering angle to account for $\alpha_1 - \alpha_2$ splitting; $\Delta\omega = (0.80 + 0.35 \tan\theta)$. The scan was extended by 25% at each extreme, with the extents serving as background measurements. Standard reflections which were periodically remeasured during the course of data collection showed no decline in intensity. All data in one octant having $2° \le \theta \le 25°$ were measured. Of the 2724 data measured 1231 had $F_o > 3\sigma(F_o)$ and were used in the refinement. Background, Lorentz, and polarization corrections were applied to the data; no absorption correction was deemed necessary.

Structure Solution and Refinement. The space group is uniquely determined by systematic absences $0kl$ with k odd, $h0l$ with l odd, and $hk0$ with $h + k$ odd. The structure was solved with some difficulty by heavy-atom methods. The Pd atom near $0,0,{}^1/_4$ forms a pseudosymmetric array which caused Fourier maps to contain images of the correct structure and its enantiomer superimposed. The structure was refined by full-matrix least squares on the basis of F with unit weights. Nonhydrogen atoms were treated anisotropically. Hydrogen atoms were fixed in calculated positions with 1.08-Å bond lengths, and a common isotropic temperature factor was refined for them. Convergence was achieved with R = 0.024; the maximum residual on a difference map was 0.41 e $Å^{-3}$, near the Pd atom. Refined coordinates are listed in Table III; hydrogen atom coordinates and anisotropic thermal parameters are given in the supplementary material.

Detection of DNA Damage. Reaction mixtures (0.05 mL) contained 60 fmol of PM2 [^{3}H] DNA molecules (197 cpm/fmol), 25 mM Tris–HCl (pH 7.5), 10 mM $MgCl_2$, and the organometallic reagent. After 5 min at 37 °C, an SE buffer (150 μL; 0.01% sodium dodecylsulfate, 2.5 mM EDTA–NaOH; pH 7.0) was added and reaction tubes were placed on ice. For detection of single-stranded nicks in DNA, reaction tubes were equilibrated at room temperature; DNA was then exposed to 200 μL of 0.3 M K_2HPO_4–KOH (pH 12.4) for 2 min and then neutralized with 100 μL of 1 M KH_2PO_4–HCl (pH 4.0). After addition of 200 μL of 5 M NaCl and 4 mL of NT buffer (1 M NaCl, 50 mM Tris–HCl; pH 8.1), the solution was filtered through nitrocellulose filters (Schleicher

and Schuell, type BA-85). The filters were then washed with 4 mL of 0.3 M NaCl and 0.03 M sodium citrate and dried, and the radioactivity was determined by liquid scintillation counting. The average number of DNA strand breaks was calculated by assuming a Poisson distribution of target sites.[16]

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Supplementary Material Available: Tables of coordinates and anisotropic thermal parameters for complex **15** and a listing of observed and calculated structure factors for complex **15** (11 pages). Ordering information is given on any current masthead page.

Kinetic Studies and a Molecular Orbital Interpretation of Reactions at Bridging Sulfur Ligands in Dimeric Molybdenum Complexes

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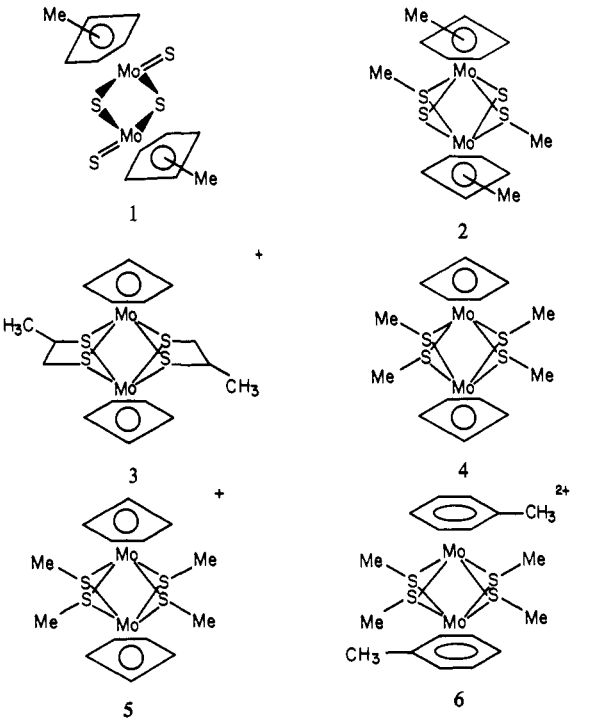
Abstract: Kinetic studies of previously reported exchange reactions at the bridging sulfur atoms in cyclopentadienylmolybdenum dimers have been carried out. The kinetics of the reaction of $[CH_3C_5H_4Mo^{IV}(S)SH]_2$ (I) with benzyl isocyanide which results in the formation of H_2 and $[CH_3C_5H_4MoS_2CNCH_2C_6H_5]_2$ (II) have been studied by the method of initial rates. The reaction shows a first-order dependence on the molybdenum dimer I and a first-order dependence on isocyanide with $k = (7.8 \pm 1.0) \times 10^{-4}$ L mol^{-1} s^{-1} at 31.5 °C. Activation parameters have been derived from rate studies of the reaction over a temperature range of 0-55 °C. The $\Delta H^{\ddagger}$ for the reaction is 7.9 kcal/mol and $\Delta S^{\ddagger} = -38$ cal K^{-1} mol^{-1}. The reaction of $[CH_3C_5H_4Mo^{III}SC_2H_4S]_2$ (III) with benzyl isocyanide results in the formation of the same dithiocarbonimidate complex, II, and ethylene. Studies of the initial rates of the latter reaction reveal a first-order dependence on the molybdenum complex III, but a zero-order dependence on isocyanide with $k = (1.0 \pm 0.1) \times 10^{-4}$ s^{-1} at 31.5 °C. Studies over the temperature range 20-55 °C established the following activation parameters: $\Delta H^{\ddagger} = 24.3$ kcal/mol and $\Delta S^{\ddagger} = 11$ cal K^{-1} mol^{-1}. The work suggests that the Mo(IV) dimer reacts by an associative mechanism, while the reaction of the Mo(III) derivative proceeds by a dissociative pathway. Extended Hückel calculations for a series of molybdenum dimers with bridging sulfur ligands have been completed. The different mechanisms of reaction for the Mo(IV) and -(III) dimers are discussed in terms of the molecular orbitals involved. An analogy is made between the molecular orbitals of the sulfur ligands in these dimers and those of 16- and 18-electron metal centers in organometallic complexes. The observed structure of the Mo_2S_4 core changes as the metal oxidation state varies from V to IV or III, and this structural difference is interpreted in terms of the relative energies of the frontier molecular orbitals.

The presence of sulfur ligands coordinated to molybdenum in enzyme systems[1-4] and in heterogeneous desulfurization catalysts[5,6] has led to the investigation of a large range of molybdenum sulfur complexes.[7-9] Of particular interest to us are the dimeric complexes of the general formula $[Me_nCpMoS_2R_i]_2$, where R is a hydrogen atom or alkyl or aryl group and $i = 0$, 1, and 2, $n =$ 0, 1, and 5. Many of these complexes have interesting structural and reactivity patterns. The structures of complexes **1**-**5**[10-13] and a related π-toluyl derivative, **6**,[14] have been determined by X-ray diffraction techniques. It is interesting that **1** assumes the structure with two bridging and two terminal sulfur atoms while **2**-**6** all



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