Journal of Organometallic Chemistry, 363 (1989) 393–399
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands
JOM 09536

Cyclopalladation of bis(pyrazolyl)methane derivatives. Synthesis of a stable 5.6.5 chelate ring system with C_{sp^3}–Pd bonds

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(Received August 2nd, 1988)

Abstract

A bis(pyrazolyl)methane derivative functionalized with malonyl residues to form intramolecular C–Pd bonds is described. Complexation of the ligand with palladium is favored by the arrangement of the nitrogen donor atoms. The boat conformation observed for the six-membered chelate-ring is attributed to the bulk of the lateral chains. Double cyclopalladation of the ligand affords a 5.6.5 fused-ring system. A ^{1}H NMR study of this metallocycle shows two rigid five-membered lateral rings and a more flexible six-membered central ring.

Introduction

Much attention has been focused on the study of new classes of stable organopalladium(II) complexes containing electron pair coordinate donors, usually nitrogen atoms, and carbon atom donors [1–4]. Interest in such complexes is in part due to the possibility of activating a remote site of an organic molecule via carbon–metal bonds, so providing new reagents for organic synthesis [5–7].

Six-membered nitrogen heteroaromatic compounds, in the form of pyridine derivatives, have long been used as ligands in transition metal coordination chemistry, and recently 2,2-bipyridinepalladium complexes have been shown to be of value for the synthesis of cyclometallated compounds [8,9]. However, the arrangement of the nitrogen donors in these structures appears not to be optimal for the square planar coordination requirements of palladium(II) complexes [9,10].

The importance of pyrazole and other azoles as ligands in coordination chemistry is broadly recognized, since they display significantly different π-donor–acceptor characteristics from pyridine and other azines [11]. Among azolyl ligands, bis(pyrazolyl)methane derivatives have received comparatively little attention [12,13], despite the optimal disposition of the donor atoms for achieving a 90° coordination angle with the metal in a six-membered ring chelate. Moreover, from the synthetic

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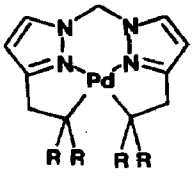

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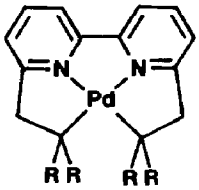

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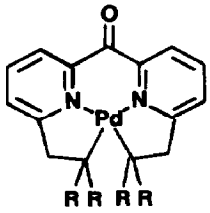


3

R = CO_2Et

point of view, use of this class of ligands as reactive subunits in the design of more elaborated structures would require only the addition of a suitable lateral chain to the central methylene bridge.

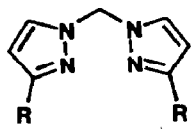
We describe here the synthesis of the cyclometallated bispyrazolyl compound **1**. Inspection of a model revealed that the 5.6.5 fused ring system of **1** would be less distorted and involve considerable less bond angle strain than the 5.5.5 fused ring system of its 2,2′-bipyridine analogue **2** [9]. Similar considerations recently led Newkome and coworkers to the synthesis of the 5.6.5 chelated 2,2′-bipyridine derivative **3**. The interest in this ligand was somewhat limited, however, by the low yield of the synthesis and by the presence of the electron-withdrawing ketone function [14].

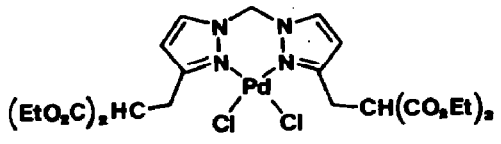
Results and discussion

The synthesis of **1** was accomplished in a five-step sequence from 3(5)-ethoxycarbonylpyrazole. Thus, alkylation with diiodomethane in the heterogeneous system potassium hydroxide/acetonitrile afforded bis(3-ethoxycarbonyl-1-pyrazolyl)methane (**4a**). Under these conditions, the formation of the two other possible regioisomers bis(5-ethoxycarbonyl-1-pyrazolyl)methane (**4b**) and (3-ethoxycarbonyl-1-pyrazolyl)(5-ethoxycarbonyl-1-pyrazolyl)methane (**4c**) was minimized (ratio **4a**/**4b**/**4c** = 51/15/34), and these undesirable side products were easily removed by flash column chromatography. The yield of pure **4a**, after purification, was 40%. Assignment of ^1H NMR spectra of the isomers was based upon chemical shift differences of the central methylene group, the signal in the 1,5-disubstituted isomer **4b** being shielded by ca. 0.8 ppm with respect to the signal of the 1,3-disubstituted one **4a**.

Reduction of **4a** (lithium aluminium hydride/tetrahydrofuran) to the bis-alcohol **5** followed by reaction with phosphorous tribromide yielded the bis-bromomethyl derivative **6**, which was subsequently transformed into the tetraester derivative **7** by reaction with diethyl malonate. The overall yield from this sequence was 65%.

Treatment of tetraester **7** with sodium tetrachloropalladate in acetonitrile afforded the palladium(II) complex **8** in 94% yield. Important differences were observed between the ^1H NMR spectrum of **8** (Fig. 1) and that of the uncomplexed ligand **7**. Thus, both protons of the central methylene were split into well resolved separated signals (J_{gem} 14.7 Hz), and shielded by 0.4 and 1.3 ppm with respect to those in the free ligand. Moreover, the AB system was unaffected by changing the temperature, which suggests a conformationally-rigid boat structure for the six-membered ring chelate (see Fig. 1). On the other hand, an ABX pattern was





8

4a R = CO_2Et

5 R = CH_2OH

6 R = CH_2Br

7 R = $CH_2CH(CO_2Et)_2$

observed for the lateral $-CH_2CH-$ chains, owing to the restricted rotation imposed by the bulky chlorine atoms bound to the central palladium metal. This effect was also clearly evident from the splitting of the terminal methyl groups into two well differentiated triplets. The ^{13}C NMR spectrum was in good agreement with these observations, in two separate signals for the ester carbonyl groups being observed, at 168.9 and 168.7 ppm.

The slow interconversion of boat-shaped conformers in the NMR time scale is a common observation for this class of palladium(II) complexes and is closely connected with steric hindrance. For example, the complex of bis(3,5-dimethyl-1-pyrazolyl)methane [15] shows a similar AB system as **8** at room temperature, whereas the complex of the parent bis(1-pyrazolyl)methane shows a sharp singlet, revealing a fast conformational exchange at the NMR time scale. Steric effects have also been reported for transition metal complexes of 3,3′-dimethyl-2,2′-biindazole [16] or 3,3′- [17], and 6,6′-disubstituted 2,2′-bipyridines [10]. In the case of palladium(II) complexes, a marked distortion of the square planar coordination was also observed [18,19].

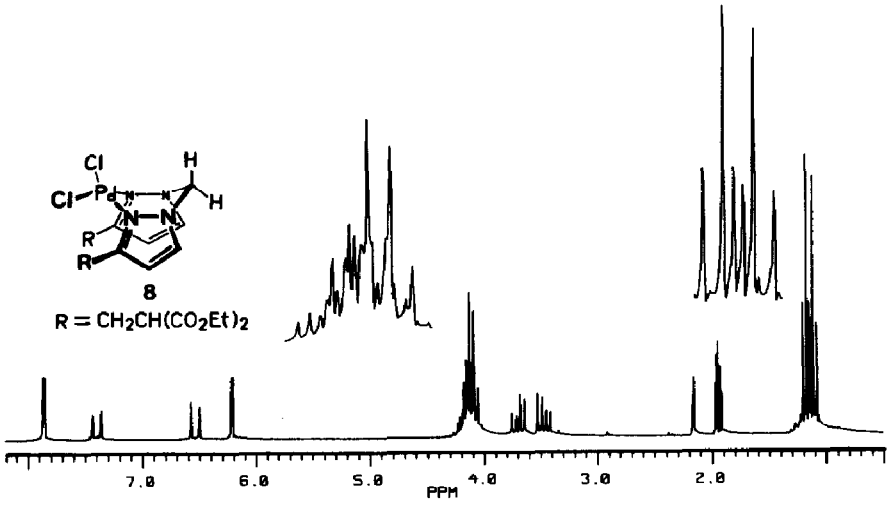


Fig. 1. ^1H NMR spectrum of the palladium(II) complex **8**.

Cyclometallation of dichloropalladium(II) complex **8** to **1** was attempted by treatment with a base. In the case of 2,2′-bipyridyl malonate derivatives reported by Newkome, deprotonation of the malonyl residues was performed under mild conditions by use of potassium carbonate; in the case of incomplete C–Pd bond formation, addition of silver nitrate was necessary to achieve a quantitative transformation [8,9]. In our case, however, all attempts to carry out the cyclometallation by deprotonation of **8** (K_2CO_3, $K_2CO_3/AgNO_3$, $NaOCH_3$, NaOH, NaH) were unsuccessful, the starting compound being recovered quantitatively in all cases. The crowded structure of **8**, in which access of the base to the malonyl protons is inhibited, is probably the reason for this lack of reactivity. Indeed, no hydrogen/deuterium exchange was observed in the ^1H NMR spectrum of **8** after treatment with D_2O/K_2CO_3. Cyclometallation was thus carried out directly with the free ligand **7** by treatment with butyllithium at $-78°C$, followed by addition of sodium tetrachloropalladate. Yields of **1** were high (~ 75%), and the compound was found stable to air in the solid state, though it slowly decomposed in solution. For this reason we were unable to obtain an analytically pure sample of **1** by recrystallization.

The ^1H NMR spectrum of **1** showed dynamic behaviour. At room temperature the signals from the methylene groups of the lateral chains (five-membered rings of the metallocycle) appeared as a very broad singlet, which split into an AB system at lower temperatures. In contrast to this observation and to the spectrum of the complex **8**, the signal corresponding to the central methylene group (six-membered chelate ring) of **1** was a broad singlet over the whole range of temperatures explored, suggesting an easy inversion of this ring in the metallocycle. Only one signal was observed for the ester groups at room temperature, but clean-cut splitting was evident at $-40°C$. Single ester carbonyl signals were observed in the ^{13}C NMR spectrum. Finally, the ^{13}C chemical shifts effects caused by the palladium were in good agreement with those described for other metallocycles ($+8.1$ ppm for CH_2C and -3.4 ppm for C–Pd) [9].

Experimental

Melting points are uncorrected. The ^1H and ^{13}C NMR spectra were registered on a Bruker WP 200 SY spectrometer, mass spectra on Hewlett–Packard 5985 (70 eV, EI mode), and IR spectra on a Perkin–Elmer 257 instrument. Abbreviations used are as follows: s, singlet; d, doublet, t, triplet, q, quartet, m, multiplet, br, broad. Elemental analyses were carried out at the Instituto de Química Orgánica General, CSIC, Madrid.

Merck 230–400 mesh silica gel and DC-Alufolien 60 were used for flash and analytical chromatography, respectively. Thin layer plates were examined under UV light. Most chemicals were purchased from Aldrich Co., and used as received without purification. Organic solvents were purified by standard procedures. *N*,*N*-Dimethylformamide (DMF) was dried over 3Å molecular sieves before use. Acetonitrile was dried by distillation over calcium hydride. Anhydrous tetrahydrofuran (THF) was distilled from benzophenone and sodium under argon immediately before use.

Preparation of ligands

Reaction of 3-ethoxycarbonylpyrazole with diiodomethane. A mixture of 3-ethoxycarbonylpyrazole (1.00 g, 7.1 mmol) and potassium hydroxide (0.56 g, 14.3 mmol) was stirred under reflux for 30 min in dry acetonitrile (50 ml). Diiodomethane (0.29 ml, 3.6 mmol) was then added, and refluxing was continued for one hour. Potassium iodide was filtered off and the solvent evaporated to leave a colorless oil. The oil was shaken with water and dichloromethane, and the organic phase was dried ($MgSO_4$) and evaporated to give a crude mixture of the three isomers **4a**, **4b** and **4c** (0.83 g, 80%). The isomers were separated by flash chromatography. Elution with hexane/ether (1/6) gave first bis(5-ethoxycarbonyl-1-pyrazolyl)methane (**4b**), m.p. 96–98°C. (Nujol) 1730, 1520 cm^{-1}. ^1H NMR ($CDCl_3$) 1.38, t, *J* 8.0 Hz, 6H, CH_3; 4.39, q, *J* 8.0 Hz, 4H, OCH_2; 6.85, d, *J* 1.9 Hz, 2H, H(4); 7.28, s, 2H, NCH_2N; 7.54, d, *J* 1.9 Hz, 2H, H(3). ^{13}C NMR ($CDCl_3$) 14.1, CH_3; 61.3, OCH_2; 62.2, NCH_2N; 11.8, C(4); 133.5, C(5); 139.8, C(3); 159.6, CO. Further elution afforded (3-ethoxycarbonyl-1-pyrazolyl)(5-ethoxycarbonyl-1-pyrazolyl)methane (**4c**), m.p. 131–132°C. (nujol) 1710, 1515 cm^{-1}. ^1H NMR ($CDCl_3$) 1.37 and 1.41, t, *J* 8.0 Hz, 6H, CH_3; 4.38 and 4.41, q, *J* 8.0 Hz, 4H, OCH_2; 6.80, d, *J* 2.8 Hz, 1H, H(4); 6.84, s, 2H, NCH_2N; 6.90, d, *J* 1.9 Hz, 1H, H(4′); 7.61, d, *J* 1.9 Hz, 1H, H(3′); 7.72, d, *J* 2.8 Hz, 1H, H(5). ^{13}C NMR ($CDCl_3$) 14.0 and 14.2, CH_3; 61.2 and 61.5, OCH_2; 64.3, NCH_2N; 110.9, C(4); 111.4, C(4′); 131.1, C(5); 133.3, C(5′); 139.7, C(3′); 145.8, C(3); 159.5 and 162.8, CO. Finally, elution with ether gave bis(3-ethoxycarbonyl-1-pyrazolyl)methane (**4a**), m.p. 140–142°C. (Nujol) 1720, 1490 cm^{-1}. ^1H NMR ($CDCl_3$) 1.39, t, *J* 8.0 Hz, 6H, CH_3; 4.40, q, *J* 8.0 Hz, 4H, OCH_2; 6.47, s, 2H, NCH_2N; 6.82, d, *J* 2.8 Hz, 2H, H(4); 7.77, d, *J* 2.8 Hz, 2H, H(5). ^{13}C NMR ($CDCl_3$) 14.3, CH_3; 61.2, OCH_2; 66.2, NCH_2N; 110.3, C(4); 131.3, C(5); 145.4, C(3); 161.8, CO. Found: C, 53.1; H, 5.5; N, 19.5. $C_{13}H_{16}N_4O_4$ calc: C, 53.4; H, 5.5; N, 19.2%. Yield of pure **4a** was 0.41 g (40%).

Bis(3-hydroxymethyl-1-pyrazolyl)methane (5). Lithium aluminium hydride (0.19 g, 5.1 mmol) was added to a cooled (−10°C) solution of **4a** (1.00 g, 3.4 mmol) in THF (100 ml) and the mixture was stirred for 6 h at −10°C. Water (12 ml) was cautiously added and the solvent then removed in vacuo. The residual solid was treated with methanol (250 ml) and solid carbon dioxide then added in portions until the mixture was acid. Inorganic salts were separated by centrifugation, and washed with methanol. The combined methanol extracts were evaporated to give **5** (0.90 g, 90%), colorless crystals, m.p. 136–137°C. IR (Nujol) 3240, 1520 cm^{-1}. ^1H NMR (CD_3OD): 4.57, s, 4H, OCH_2; 6.20, s, 2H, NCH_2N; 6.33, d, *J* 2.8 Hz, 2H, H(4); 7.75, d, *J* 2.8 Hz, 2H, H(5). ^{13}C NMR (CD_3OD): 58.8, OCH_2; 65.4, NCH_2N; 106.4, C(4); 132.8, C(5); 155.5, C(3). Found: C, 51.2; H, 6.2; N, 26.4. $C_9H_{12}N_4O_2$ calc.: C, 51.9; H, 5.7; N, 26.9%.

Bis(3-bromomethyl-1-pyrazolyl)methane (6). To a suspension of **5** (1.00 g, 4.8 mmol) in anhydrous ether (250 ml) was added 0.3 ml (0.3 mmol) of phosphorous tribromide. The mixture was stirred at 30°C for two days. The solvent was evaporated, the residue treated with a 10% aqueous solution of sodium bicarbonate, and the resulting solution extracted with dichloromethane (3 × 100 ml). The organic solution was dried ($MgSO_4$) and evaporated to give crude **6**, which recrystallized from carbon tetrachloride/methanol (7/3). Yield of pure **6** was 0.93 g (90%), colorless needles, m.p. 177–178°C. IR (Nujol): 1520 cm^{-1}. ^1H NMR ($CDCl_3$): 4.51, s, 4H, CH_2Br; 6.19, s, 2H, NCH_2N; 6.39, d, *J* 2.5 Hz, 2H, H(4); 7.66, d, *J* 2.5

Hz, 2H, H(5). ^{13}C NMR ($CDCl_3$): 24.2, CH_2Br; 65.3, NCH_2N; 107.2, C(4); 131.1, C(5); 150.1, C(3). Found: C, 31.3; H, 3.1; N, 15.6. $C_9H_{10}N_4Br_2$ calc.: C, 32.3; H, 3.0; N, 16.7%.

Bis[3-(2,2-bis(ethoxycarbonyl)ethyl)-1-pyrazolyl]methane (7). A mixture of diethyl malonate (0.64 g, 4 mmol), the bis-bromomethyl derivative **6** (0.33 g, 1.0 mmol), and anhydrous potassium carbonate (0.48 g, 3.5 mmol) in dry DMF (3 ml) was stirred for two days at room temperature. Solid materials were filtered off and washed with dichloromethane. The combined liquids were evaporated in vacuo and the residue purified by flash chromatography (dichloromethane/methanol, 97/3) to give **7** as a pale yellow oil (0.39 g, 80%). (Nujol) 1740, 1530 cm^{-1}. ^1H NMR ($CDCl_3$): 1.24, t, *J* 7.1 Hz, 12H, CH_3; 3.21, d, *J* 8.0 Hz, 4H, CCH_2C; 3.77, t, *J* 8.0 Hz, 2H, CH; 4.15 and 4.17, q, *J* 7.1 Hz, 8H, OCH_2; 6.09, d, *J* 2.8 Hz, 2H, H(4); 6.10, s, 2H, NCH_2N; 7.47, d, *J* 2.8 Hz, 2H, H(5). ^{13}C NMR ($CDCl_3$) 13.9, CH_3; 27.2, CCH_2C; 51.7, CH; 61.3, OCH_2; 64.9, NCH_2N; 106.3, C(4); 130.3, C(5); 150.2, C(3); 168.7, CO. Found: C, 55.7; H, 6.8; N, 11.3. $C_{23}H_{32}N_4O_8$ calc.: C, 56.1; H, 6.5; N, 11.4.

Palladium complexes

Dichloro{bis[3-(2,2'-bis(ethoxycarbonyl)ethyl)-1-pyrazolyl]methane}palladium(II) (8). To a solution of tetraester **7** (0.30 g, 0.61 mmol) in 30 ml of acetonitrile was added sodium tetrachloropalladate (0.27 g, 0.91 mmol). The mixture was stirred at 50 °C for 4 h under argon, and then kept at room temperature for a further 12 h. Solid materials were filtered off, and the filtrate evaporated in vacuo to give the complex (0.38 g, 94%), m.p. 194–196 °C. (Nujol) 1710, 1525 cm^{-1}. ^1H NMR (CD_3CN) 1.08 and 1.15, t, *J* 8.0 Hz, 12H, CH_3; 3.58, m, 4H, CCH_2C; 4.10, m, 10H, OCH_2, CH; 6.20, d, *J* 3.0 Hz, 2H, H(4); 6.61 and 7.37, AB system, *J* 15.2 Hz, 2H, NCH_2N; 7.90, d, *J* 3.0 Hz, 2H, H(5). ^{13}C NMR (CD_3CN) 13.8, CH_3; 27.4, CCH_2C; 52.1, CH; 62.0, OCH_2; 64.5, NCH_2N; 108.7, C(4); 135.0, C(5); 155.1, C(3); 168.7 and 168.9, CO. Found: C, 35.8; H, 4.2; N, 7.3. $C_{23}H_{32}N_4O_8Cl_2Pd \cdot 2NaCl$ calc.: C, 35.1; H, 4.1; N, 7.1.

{[Bis(1-pyrazolyl)methane]3,3'-diylbis[1,1-bis(ethoxycarbonyl)-2,1-ethanediyl]C,C',N,N'}palladium(II) (1). To a well stirred solution of tetraester **7** (0.32 g, 0.65 mmol) in THF (25 ml) under argon was added a 1.6 *M* hexane solution of butyllithium (0.81 ml, 1.3 mmol) at −78 °C and sodium tetrachloropalladate (0.28 g, 1.0 mmol). After 2 h at −78 °C the mixture was allowed to warm slowly to room temperature and then was stirred for 12 h. Evaporation left a residue, which was purified by flash chromatography (acetonitrile) to give 0.29 g (75%) of **1**, as a brownish-orange powder, m.p. 133–134 °C. (Nujol): 1740, 1525 cm^{-1}. ^1H NMR (CD_3CN): 1.17 m, 12H, CH_3; 3.05, br s, 4H, CCH_2C; 4.05, m, 8H, OCH_2; 6.26, d, *J* 2.8 Hz, 2H, H(4); 7.96, br s, 2H, NCH_2N; 8.75, br s, 2H, H(5). ^{13}C NMR (CD_3CN): 14.5, CH_3; 35.3, CCH_2C; 49.3, CH; 60.9, NCH_2N; 61.5, OCH_2; 105.2, C(4); 137.2, C(5); 159.1, C(3); 164.9, CO. MS *m/z* 598 M^+ (^{108}Pd), 595 M^+ (^{105}Pd), 553, 550, 549, 492, 447, 419, 253, 179, 121, 81, 55.

Acknowledgement

Financial support of this research was provided by "Comisión Asesora de Investigación científica y Técnica" (CAICYT). One of us (O.J.) gratefully acknowledges a research fellowship of "Ministerio de Educación y Ciencia".

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