MULTINUCLEAR NMR STUDIES OF PALLADIUM(II) DIHALIDE COMPLEXES OF DIBUTYL {α-[4-(PHENYLDIAZENYL)ANILINO]BENZYL}PHOSPHONATE

Ljerka TUSEK-BOZIC[a1], Manda CURIC[a2], Drazen VIKIC-TOPIC[a3] and Antonin LYCKA[b]

[a] *Department of Chemistry, Ruder Boskovic Institute, Bijenicka 54, 10000 Zagreb, Croatia; e-mail:* [1] *tusek@olimp.irb.hr,* [2] *curic@olimp.irb.hr,* [3] *vikic@faust.irb.hr*

[b] *Research Institute of Organic Syntheses, 532 18 Pardubice-Rybitvi, Czech Republic; e-mail: slnmr@pol.upce.cz*

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The ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR studies of two types of palladium(II) dihalide complexes of dibutyl {α-[4-(phenyldiazenyl)anilino]benzyl}phosphonate (L) are reported: those with the monodentate *trans*-bonded ligands through the azo nitrogen, *trans*-$Pd(L)_2X_2$ (X = Cl, Br), and a cyclopalladated binuclear complex in which chloride ions bridge two metal centers, $[Pd(L–H)(\mu\text{-}Cl)]_2$. The ^{15}N-enriched organophosphorus compound and its palladium(II) complexes were also prepared to enable unambiguous determination of the nitrogen ligation site by ^{15}N NMR. The NMR analysis was accomplished by one- and two-dimensional homo- and heteronuclear experiments including ^{1}H-^{1}H COSY, long-range ^{1}H-^{1}H COSY, NOESY, ^{1}H-^{13}C COSY, long-range ^{1}H-^{13}C COSY, HMQC and HMBC. With the mononuclear complexes, the formation of isomeric species was observed, which are interpreted as rotational isomers caused by restricted rotation around the metal–ligand bond.

Key words: Chelates; Phosphonates; Aminophosphonate ligands; Palladium complexes; ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR spectroscopy; Two-dimensional NMR.

Aminophosphonic acids and their derivatives are very attractive complex-forming agents because of their relevance to the natural systems[1]. Hence, the investigation of their interaction with various metal ions may contribute to a better understanding of their biological activity[2–4]. In an effort to obtain a new class of metal complexes with potential antitumor and antiviral activity, we have recently reported studies on coordination behaviour of various (quinolylmethyl)phosphonates and (α-anilinobenzyl)phosphonates towards palladium(II) ion[5–7]. The preliminary screening tests showed that most of these complexes exhibit a certain inhibitory effect against human and animal tumor cell lines. The greatest activity was found for complexes of dialkyl esters of {α-[4-(phenyldiazenyl)anilino]benzyl}phosphonic acid. These potential chelate ligands form two types of the square-planar palladium(II) halide complexes: dihalide adducts and the cyclopalladated binuclear complexes. The former contain *trans*-bonded ligands through the azo nitrogen while in the latter the deprotonated ligand undergoes palladation at the azo nitrogen and the *ortho*-carbon producing a complex with the metal–metal

chloro bridge. The anilino and phosphoryl groups do not participate in metal coordination and are free to be involved in hydrogen bonding which is known to play a key role in DNA binding interactions[8]. In this paper we investigated the structure of palladium(II) dihalide complexes of dibutyl {α-[4-(phenyldiazenyl)anilino]benzyl}phosphonate in chloroform solution by ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR. To facilitate the NMR studies, the ^{15}N-enriched phosphorus ligand and its complexes were also prepared, and their properties discussed.

EXPERIMENTAL

Compounds

Dibutyl {α-[4-(phenyldiazenyl)anilino]benzyl}phosphonate (**1**, L) was prepared as previously described by addition of dibutyl phosphite to 4-benzeneazo-*N*-benzylideneaniline[9]. Palladium(II) dihalide adducts **2** and **3**, *trans*-$Pd(L)_2X_2$ (X = Cl, Br), were obtained by reaction of dichloro-bis(acetonitrile)palladium(II) complex and dibromo-bis(benzonitrile)palladium(II) complex, respectively, with **1** under refluxing in dichloromethane, while the cyclopalladated complex $[Pd(L–H)(\mu\text{-}Cl)]_2$ (**4**) was prepared by reacting with Na_2PdCl_4 in methanol at room temperature according to the reported procedure[7]. The ^{15}N-triply-labelled ligand was obtained from the triply-labelled 4-aminoazobenzene with different degree of enrichment of nitrogens (*ca* 25, 96 and 25% in N-α, N-β and NH_2, respectively). The labelled 4-aminoazobenzene was prepared *via* rearrangement of diphenyltriazene from aniline (95.7% ^{15}N) and sodium nitrite (96.0% ^{15}N). During the synthesis, the ^{15}N-nitrogen content from sodium nitrite (N-β) retained the same, while those derived from aniline (N-α and NH_2) were reduced to *ca* 1/3, as the non-labelled aniline and aniline hydrochloride were added to ^{15}N-triply-labelled diphenyltriazene formed in the first reaction step[10]. By reaction with benzaldehyde, 4-aminoazobenzene afforded a Schiff base which was used for preparation of the organophosphorus ligand. In this way, different relative degrees of enrichment were retained in the ligand molecule which was then used as the ^{15}N-labelled precursor for preparation of complexes **3** and **4**.

NMR Spectra

The ^{1}H and ^{13}C one- and two-dimensional NMR spectra were recorded with Varian broadband Gemini 300 and Bruker AMX 360 spectrometers, operating at 75.46 and 90.56 MHz for the ^{13}C resonance, respectively. The compounds were dissolved in $CDCl_3$ (20–50 mg/0.5 cm^3 $CDCl_3$) at 276 K in 5 mm NMR tubes. The ^{1}H and ^{13}C chemical shifts were referred to tetramethylsilane as an internal standard. Digital resolution in ^{1}H NMR spectra was 0.25 Hz, while in ^{13}C NMR it was 0.60 Hz per point. The following techniques were performed: proton-noise decoupling, gated decoupling, APT, ^{1}H-^{1}H COSY, NOESY and ^{1}H-^{13}C COSY with a Varian Gemini 300 spectrometer and long-range ^{1}H-^{1}H COSY, TOCSY, long-range ^{1}H-^{13}C COSY, HMQC and HMBC with a Bruker AMX spectrometer. The ^{1}H-^{1}H COSY spectra were obtained in the magnitude mode, while NOESY spectra in the phase-sensitive mode. For both, ^{1}H-^{1}H COSY and NOESY, 1 024 points in *F2* dimension and 256 increments in *F1* dimension were used. The latter were subsequently zero-filled to 1 024 points. Each increment was obtained with 16 scans, using 2 750 Hz spectral width and a relaxation delay of 1 s. The resolution was 5.4 Hz/point and 10.7 Hz/point in *F1* and *F2* dimension, respectively. The NOESY spectra were measured with several mixing times (0.45–0.80 s). The ^{1}H-^{13}C COSY spectra were measured with one-bond C-H coupling value set to 140 Hz, using 2 048 points in *F2* dimension and 256 increments in *F1* dimension. The latter were zero-filled to 512 points. Increments were ob-

tained using 128 scans and relaxation delay of 1 s. Spectral widths were 20 000 Hz in *F2* and 4 500 Hz in *F1* dimension. The resulting resolution was 19.53 Hz/point in *F2* and 17.6 Hz/point in *F1* dimension. The delay time in long-range ^{1}H-^{1}H COSY was 100 ms, while in TOCSY 30 ms and 100 ms. The long-range ^{1}H-^{13}C COSY, HMQC and HMBC were measured with C-H coupling values set to 145 Hz/8 Hz, 145 Hz and 8 Hz, respectively. All two-dimensional experiments were performed by standard pulse sequences, using Gemini Data System software Version 6.3 Revision A (for VXR-4000) and Bruker microprograms of UXNMR software Version 940501.3 (ref.[11]). For proton decoupling Waltz-16 modulation was used.

The ^{15}N (36.50 MHz) and ^{31}P (145.78 MHz) NMR spectra were recorded in $CDCl_3$ at 300 K on a Bruker AMX 360 spectrometer equipped with a 5 mm broadband probe or a 5 mm broadband inverse probe. The proton-noise decoupling was applied during the measurements. The ^{15}N chemical shifts were referred to external nitromethane (δ = 0.0), while ^{31}P shifts to 85% H_3PO_4 (δ = 0.0), placed in coaxial capillaries. Positive values of chemical shifts denote downfield shifts with respect to standards. In ^{15}N NMR measurements the tris(acetylacetonato)chromium(III) was used as a relaxation agent[12].

RESULTS AND DISCUSSION

We have shown that dibutyl {α-[4-(phenyldiazenyl)anilino]benzyl}phosphonate (**1**) binds the palladium(II) ion either in a monodentate manner through the azo nitrogen forming dihalogenopalladium(II) adducts **2** and **3**, or acts as a bidentate ligand forming a five-membered chelate **4** by metallation at the azo nitrogen and the *ortho*-carbon atom[7]. In the present study, the ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR have been used for full characterization of both types of these complexes. These data along with those for the free ligand are summarized in Tables I–III. The numbering scheme is shown in Fig. 1.

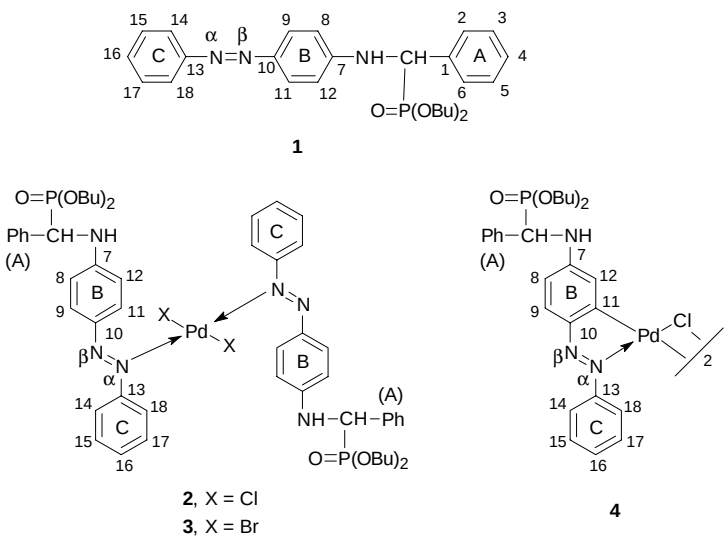

FIG. 1
Structure and numbering scheme for dibutyl {α-[4-(phenyldiazenyl)anilino]benzyl}phosphonate (**1**) and its complexes **2–4**

The signal assignments were performed on the basis of substituent effects, spin–spin coupling constants, splitting patterns and signal intensities, as well as by using a combination of the 1D and 2D homo- and heteronuclear NMR techniques.

In an unsymmetrically substituted azobenzene derivative, the coordination to metal atom can occur in either azo nitrogens, giving rise to the possibility of isomeric mixture. ^{15}N NMR spectroscopy provides a very sensitive method for determination of the coordination position[13,14]. For this purpose, the triply-labelled ligand with different degrees of nitrogen enrichment was prepared from the appropriate triply enriched 4-aminoazobenzene (*ca* 25, 96 and 25% in N-α, N-β and NH_2, respectively). The ^{15}N NMR spectrum of the labelled 4-aminoazobenzene, presented in Fig. 2, shows a singlet of high intensity at 119.0 ppm for N-β with appropriate satellites due to $^1J(^{15}N^{15}N)$ coupling and a doublet of lower intensity at 103.1 ppm for the partially enriched N-α. Doublet arises from the coupling to almost completely enriched N-β, with the coupling constant amounting to 15.3 Hz. This splitting pattern was retained in the spectra of the free ligand and its complexes enabling undoubted determination of the ligation nitrogen from changes in the ^{15}N chemical shifts and the signal multiplicity. The ^{15}N data obtained for the free ligand, its adduct **3** and cyclopalladated complex **4** are given in Table I. The small differences between the values obtained for the unlabelled and the labelled ligand could be explained by the influence of a relaxation agent[12]. As expected, the azo-type nitrogen signals in **1** are found near 100 ppm (N-α) and 118 ppm (N-β), respectively, while the amine-type nitrogen signal appears at –311.4 ppm (ref.[15]). A large upfield shift of the N-α resonance ($\Delta\delta$ = 102–146 ppm) in the spectra of complexes may be ascribed to lowering in energy of the nitrogen lone pair due to bonding to palladium. In both types of complexes, the coordination takes place only through this nitrogen (Fig. 1). Similar chemical shift changes were obtained on protonation (an upfield shift of about 100 ppm) of various heterocycles[16] (*e.g.* pyridine, purine, indolizine). Relatively small changes observed for N-β (up to 17 ppm) and NH (up to 13 ppm)

TABLE I
Nitrogen-15 NMR data (δ, ppm) for compounds **1**, **3** and **4**[a]

Compound	N-α	N-β	NH
1[b]	99.9 (101.15)	118.0 (118.5)	–311.4 (–311.4)
3[c]	–3.6 (–2.3)[d]	132.7 (132.6)[d]	–303.1 (–307.5)
4	–46.2	100.2	–298.6

[a] Spectra of the triply-^{15}N-labelled compounds. [b] Values for the non-labelled ligand measured with addition of $Cr(acac)_3$ are given in parentheses. [c] Data for two most abundant rotamers. Values for the minor rotamer are given in parentheses. [d] $^1J(^{15}N\text{-}\alpha,^{15}N\text{-}\beta)$ *ca* 12 Hz.

signals confirm the non-participation of these nitrogens in the metal coordination and can be ascribed to the substitution effect.

The ^{1}H and ^{13}C data in $CDCl_3$ solution are summarized in Tables II and III. ^{1}H NMR results presented herein as well as recently reported ^{13}C NMR spectral data on the free benzeneazoanilino phosphorus ligand[17] provided a basis for interpreting spectra of its palladium complexes. We have shown that two ester groups in phosphonate molecule are non-equivalent, since two sets of separate proton and carbon resonances have been observed for the diastereotopic butyl groups of the $P(O)(OBu)_2$ moiety that is adjacent to a chiral benzyl carbon atom. Although the non-equivalency of methylene protons within each butoxy group further complicates the proton spectra, the connectivities in ^{1}H-^{1}H COSY and TOCSY spectra enable the differentiation of proton signals of two butoxy groups (see Table II). Similar spectral features were observed for some diethyl phosphonate derivatives having chiral center attached to phosphorus atom[18].

In ^{13}C NMR gated decoupled spectra of **1**, the alkyl carbons show two distinctive complex quartets for the methyl and two closely spaced complex triplets for the methylene carbons. Beside one-bond (^{1}J(CH) = 126–151 Hz) and two-bond (^{2}J(CH) = 3.9–4.5 Hz) carbon-proton couplings, the complexity of these resonances arises from the additional two- and three-bond carbon-phosphorus couplings (^{2}J(POC) ≈7 Hz; ^{3}J(POCC) ≈5.5 Hz). The proton of the PCH group appears as a broaden doublet due to simultaneous coupling with phosphorus and NH proton. The carbon of this group with couplings of 151.1 Hz to phosphorus and of 136.4 Hz to the directly bonded proton shows a doublet of doublets, which with the three-bond coupling of 3.9 Hz to protons H-2,6, gives a pattern of four triplets of equal intensities. In the spectrum of free ligand all *ortho* and *meta* protons and carbons of the aromatic rings are magnetically equivalent as a consequence of the fast ring rotation on the NMR time scale. The assignment of the aromatic protons, especially partially overlapped H-3,5, H-4 and H-16, were unambiguously confirmed by one-bond ^{1}H-^{13}C COSY experiment, as it is shown in Fig. 3.

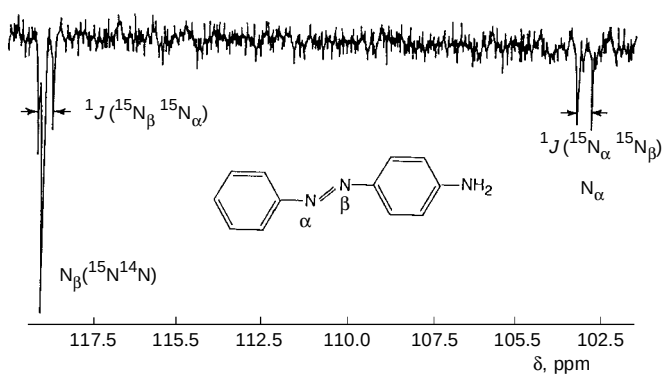

FIG. 2
Part of the ^{15}N NMR spectrum of triply-^{15}N-labelled 4-aminoazobenzene

TABLE II

^{1}H NMR data (δ, ppm; *J*, Hz) for compounds **1–4**[a]

Hydrogen	**1**			**2**[b]			**3**[b]			**4**
	ID	COSY[c]	NOESY[d]	ID	COSY[c]	NOESY[d]	ID	COSY[c]	NOESY[d]	
H-2,6	7.56 d *J*(HH) = 7.0	7.36	4.92; 7.36	7.52 d[e,f] *J*(HH) = 7.1	7.49	4.90 (4.80)	7.51 d[e,f] *J*(HH) = 7.1	7.49	4.90 (4.80)	[g]
H-3,5	7.36 t *J*(HH) = 7.2	7.56; 7.32	0.84; 7.56	7.49[e,h]	7.52; 7.30		7.49[e,h]	7.51; 7.33		[g]
H-4	7.32 t[i] *J*(HH) = 7.1	7.36		7.30[e,j]	7.49		7.33[e,j]	7.49		[g]
H-8	6.76 d *J*(HH) = 8.8	7.81	0.90; 4.92; 5.83; 7.81	6.76 (6.41) d *J*(HH) = 8.9 (8.8)	9.13 (8.07)	4.90; 9.13 (8.07)	6.77 (6.42) d *J*(HH) = 8.7 (8.8)	9.15 (8.02)	4.90; 9.15 (8.02)	6.33 d *J*(HH) = 6.8
H-12	6.76 d *J*(HH) = 8.8	7.81	0.90; 4.92; 5.83; 7.81	6.76 (6.41) d *J*(HH) = 8.9 (8.8)	9.13 (8.07)	4.90; 9.13 (8.07)	6.77 (6.42) d *J*(HH) = 8.7 (8.8)	9.15 (8.02)	4.90; 9.15 (8.02)	6.56 s
H-9,11	7.81 d *J*(HH) = 8.7	6.76	6.76	9.13 (8.07) d *J*(HH) = 8.7 (8.7)	6.76 (6.41)	6.76; 8.20 (6.41)	9.15 (8.02) d *J*(HH) = 8.7 (8.7)	6.77 (6.42)	6.77; 8.16 (6.42)	[g]
H-14,18	7.85 d *J*(HH) = 7.6	7.47	7.47	8.20 (7.92) d *J*(HH) = 7.7 (7.6)	7.21 (7.50)	7.21; 9.13 (7.50)	8.16 (7.92) d *J*(HH) = 7.7 (7.6)	7.20 (7.50)	7.20; 9.15 (7.50)	[g]

TABLE II
(*Continued*)

Hydrogen	**1**			**2**[b]			**3**[b]			**4**
	ID	COSY[c]	NOESY[d]	ID	COSY[c]	NOESY[d]	ID	COSY[c]	NOESY[d]	
H-15,17	7.47 t *J*(HH) = 7.3	7.85; 7.39	7.85	7.21 (7.50) dt[k] *J*(HH) = 7.5 (7.5)	8.20;7.33 (7.92; 7.38)	8.20 (7.92)	7.20 (7.50) dt[k] *J*(HH) = 7.5 (7.4)	8.16; 7.35 (7.92; 7.38)	8.16 (7.92)	[g]
H-16	7.39 t[i]	7.47		7.33 (7.38)[l]	7.21 (7.50)		7.35 (7.38)[l]	7.20 (7.50)		[g]
PC**H**	4.92 d *J*(PH) = 23.9	5.83	6.76; 7.56	4.90 (4.80) dd *J*(PH) = 24.1 (23.0) *J*(HH) = 7.2 (6.0)	5.89 (5.55)	6.76; 7.52 (7.52)	4.90 (4.80) dd *J*(PH) = 24.2 (24.1) *J*(HH) = 6.3 (5.9)	6.17 (5.76)	6.77; 7.51 (7.51)	4.85 dd *J*(PH) = 20.5 *J*(HH) = 7.2
N**H**	5.83 br s	4.92	6.76	5.89 (5.55) t *J*(PH), *J*(HH) = 7.5 (6.9)	4.90 (4.80)		6.17 (5.76) t *J*(PH), *J*(HH) = 8.6 (7.8)	4.90 (4.80)		5.89 br s
OC**H**$_2$CH$_2$– CH$_2$CH$_3$	3.64, 3.91 m	1.42; 3.64, 3.91[m]	3.64, 3.91[m]	3.56, 3.90 m[e]	1.45; 3.56, 3.90[m]	3.56, 3.90[m]	3.58, 3.89 m[e]	1.43; 3.58, 3.89[m]	3.58, 3.89[m]	3.49, 3.84 br s
OC**H**$_2$CH$_2$– CH$_2$CH$_3$′	4.12 m	1.63	1.63	4.10 m[e]	1.68	1.68	4.09 m[e]	1.64	1.64	4.05 br s
OCH$_2$C**H**$_2$– CH$_2$CH$_3$	1.42 m[n]	1.23; 3.64, 3.91	1.23	1.45 m[e,o]	1.25; 3.56, 3.90	1.25	1.43 m[e,o]	1.22; 3.58, 3.89	1.22	1.39 m[o]

TABLE II
(*Continued*)

Hydrogen	1			2[b]			3[b]			4
	ID	COSY[c]	NOESY[d]	ID	COSY[c]	NOESY[d]	ID	COSY[c]	NOESY[d]	
$OCH_2C\mathbf{H}_2$–CH_2CH_3'	1.63 m[p]	1.38; 4.12	1.38; 4.12	1.68 m[e]	1.43; 4.10	1.43; 4.10	1.64 m[e]	1.38; 4.09	1.38; 4.09	1.62 m
OCH_2CH_2–$C\mathbf{H}_2CH_3$	1.23 m[r]	0.84; 1.42	0.84; 1.42	1.25 m[e]	0.84; 1.45	0.84; 1.45	1.22 m[e]	0.83; 1.43	0.83; 1.43	1.21 m
OCH_2CH_2–$C\mathbf{H}_2CH_3'$	1.38 m[s]	0.90; 1.63	0.90; 1.63	1.43 m[e,t]	0.89; 1.68	0.89; 1.68	1.38 m[e,t]	0.89; 1.64	0.89; 1.64	1.35 m[t]
OCH_2CH_2–$CH_2C\mathbf{H}_3$	0.84 t *J*(HH) = 7.3	1.23	1.23; 7.36	0.84 (0.82) t[u] *J*(HH) = 7.2	1.25	1.25	0.83 (0.82) t[u] *J*(HH) = 7.3	1.22	1.22	0.82 t *J*(HH) = 7.1
OCH_2CH_2–$CH_2C\mathbf{H}_3'$	0.90 t *J*(HH) = 7.3	1.38	1.38; 6.76	0.89 (0.90) t[u] *J*(HH) = 7.2	1.43	1.43	0.89 (0.90) t[u] *J*(HH) = 7.3	1.38	1.38	0.90 t *J*(HH) = 7.1

[a] Multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad signal. [b] Data for two most abundant rotamers. Values for the minor rotamer are given in parentheses. [c] Cross-peaks obtained from a ^{1}H-^{1}H COSY experiment. [d] Cross-peaks obtained from a NOESY experiment. [e] Signals of two rotamers are overlapped. [f] Partly overlapped with H-3,5. Value obtained from a longe-range ^{1}H-^{13}C HMBC experiment. [g] Resonance not resolved due to broadening and extensive overlap of signals of aromatic protons between 7.30–7.80 ppm. [h] Partly overlapped with H-2,6 and with H-15,17 of the minor rotamer. Value obtained from a longe-range ^{1}H-^{13}C HMBC experiment. [i] Partly overlapped with H-3,5. Value obtained from a ^{1}H-^{13}C COSY experiment. [j] Partly overlapped with H-16. Value obtained from a ^{1}H-^{1}H COSY experiment. [k] Major rotamer appears as quartet, minor is overlapped with H-3,5. Value taken from ^{1}H-^{1}H COSY and longe-range ^{1}H-^{13}C HMBC experiments. [l] Partly overlapped with H-4. Values obtained from ^{1}H-^{1}H COSY and longe-range ^{1}H-^{13}C HMBC experiments. [m] Interaction between geminal protons. [n] Appears as quintet with *J*(HH) ≈ 7.2 Hz. Partly overlapped with $OCH_2CH_2C\mathbf{H}_2CH_3'$. [o] Partly overlapped with $OCH_2CH_2C\mathbf{H}_2CH_3'$. [p] Appears as quintet with *J*(HH) ≈ 7.2 Hz. [r] Appears as sextet with *J*(HH) ≈ 7.4 Hz. [s] Appears as sextet with *J*(HH) ≈ 7.4 Hz. Partly overlapped with $OCH_2C\mathbf{H}_2CH_2CH_3$. [t] Partly overlapped with $OCH_2C\mathbf{H}_2CH_2CH_3$. [u] Closely spaced triplets of two rotamers. Their interactions in 2D NMR experiments are not visible separately.

TABLE III
Carbon-13 NMR data (δ, ppm; *J*, Hz) for compounds **1**–**4**[a]

Carbon	**1**		**2**[b]		**3**[b]		**4**	
C-1	135.50 m	$^{2}J(PC)_{d}$ = 2.4	134.83 m[c]	$^{2}J(PC)_{d}$ = 2.4	134.9 (135.05) m	$^{2}J(PC)_{d}$ = 2.4 (2.3)	135.19 br s	^{2}J(PC) = 2.8
C-2,6	127.79 dq[e]	^{3}J(PC) = 5.5 ^{1}J(CH) = 159.0 ^{3}J(CH) = 5.5, 7.1	127.85 br dd[c]	^{3}J(PC) = 5.7 ^{1}J(CH) = 157.7	127.77 br dd[c]	^{3}J(PC) = 5.2 ^{1}J(CH) = 157.8	128.15 br d	^{1}J(CH) = 155.5
C-3,5	128.54 ddd	^{4}J(PC) = 2.4 ^{1}J(CH) = 161.3 ^{3}J(CH) = 7.8	129.11 dd[c]	^{1}J(CH) = 160.2 ^{3}J(CH) = 7.2	128.96 dd[c]	^{1}J(CH) = 160.2 ^{3}J(CH) = 7.1	129.03 br d	^{1}J(CH) = 159.7
C-4	127.95 ddt	^{5}J(PC) = 3.1 ^{1}J(CH) = 161.3 ^{3}J(CH) = 7.1	127.82[c,f]	[g]	127.75[c,f]	[g]	128.42 br d	[g]
C-7	149.08 m	$^{3}J(PC)_{d}$ = 13.7	151.90 (150.42) m	$^{3}J(PC)_{d}$ = 13.4 (13.8)	151.84 (150.30) m	$^{3}J(PC)_{d}$ = 13.4 (13.8)	149.14 br d	^{3}J(PC) = 13.9
C-8	113.31 dd	^{1}J(CH) = 158.2 ^{3}J(CH) = 5.5	113.15 (112.83) br d	^{1}J(CH) = 160.2	113.15 (112.90) br d	^{1}J(CH) = 160.4	110.24 br d	^{1}J(CH) = 158.0
C-12	113.31 dd	^{1}J(CH) = 158.2 ^{3}J(CH) = 5.5	113.15 (112.83) br d	^{1}J(CH) = 161.15	113.15 (112.90) br d	^{1}J(CH) = 160.4	118.10 br d	^{1}J(CH) = 156.3
C-9	124.79 dd	^{1}J(CH) = 160.9 ^{3}J(CH) = 5.8	127.72 (127.62) dd	^{1}J(CH) = 161.5 ^{3}J(CH) = 5.2	128.01 (127.90) dd	^{1}J(CH) = 161.7 ^{3}J(CH) = 5.2	131.95 br d	^{1}J(CH) = 161.5
C-11	124.79 dd	^{1}J(CH) = 160.9 ^{3}J(CH) = 5.8	127.72 (127.62) dd	^{1}J(CH) = 161.5 ^{3}J(CH) = 5.2	128.01 (127.90) dd	^{1}J(CH) = 161.7 ^{3}J(CH) = 5.2	159.78 br s	

TABLE III
(*Continued*)

Carbon	1		2[b]		3[b]		4	
C-10	145.19 m	[d]	141.95 (145.09) m	[d]	142.00 (145.89) m	[d]	151.32 br s	
C-13	152.88 m	[d]	154.41 (153.28) m	[d]	155.18 (153.46) m	[d]	155.74 br s	
C-14,18	122.16 ddd	^1J(CH) = 161.0 ^3J(CH) = 5.8, 7.5	124.36 (121.53) br dt	^1J(CH) = 163.3 ^3J(CH) = 5.9	124.57 (121.56) br dt	^1J(CH) = 163.7 ^3J(CH) = 6.0	123.62 br d	^1J(CH) = 164.3
C-15,17	128.77 dd	^1J(CH) = 159.7 ^3J(CH) = 7.8	128.58 (128.78) dd[h]	^1J(CH) = 162.3 ^3J(CH) = 8.0	128.47 (128.66) dd[h]	^1J(CH) = 162.1 ^3J(CH) = 8.0	128.59 br d	^1J(CH) = 160.6
C-16	129.52 dt	^1J(CH) = 161.3 ^3J(CH) = 7.8	129.84 (129.08) dt[i]	[j]	129.86 (128.89) dt[i]	[j]	129.43 br d	[j]
P**C**H	55.99 ddt	^1J(PC) = 151.1 ^1J(CH) = 136.4 ^3J(CH) = 3.9	55.54 (55.49) ddt	^1J(PC) = 150.7 ^1J(CH) = 137.2 ^3J(CH) = 3.9	55.71 (55.65) ddt	^1J(PC) = 150.5 ^1J(CH) = 136.8 ^3J(CH) = 3.9	55.34 br dd	^1J(PC) = 151.6 ^1J(CH) = 137.6
(O**C**H$_2$CH$_2$–CH$_2$CH$_3$)$_2$	66.99, 67.10 tm	^2J(POC) = 7.1 ^1J(CH) = 144.3	66.92, 67.36 tm[c]	^2J(POC) = 7.1 ^1J(CH) = 145.2	67.16, 67.49 tm[c]	^2J(POC) = 7.3 ^1J(CH) = 144.8	67.01, 67.24 tm	^2J(POC) = 6.8 ^1J(CH) = 146.1
(OCH$_2$**C**H$_2$–CH$_2$CH$_3$)$_2$	32.19, 32.40 tm	^3J(POCC) = 5.5 ^1J(CH) = 126.3	32.13, 32.25 tm[c]	^3J(POCC) = 5.5 ^1J(CH) = 126.7	32.27, 32.49 tm[c]	^3J(POCC) = 5.6 ^1J(CH) = 126.2	32.04, 32.43 td	^3J(POCC) = 5.5 ^1J(CH) = 127.2
(OCH$_2$CH$_2$–**C**H$_2$CH$_3$)$_2$	18.37, 18.52 tm	^1J(CH) = 126.1	18.35, 18.52 tm[c]	^1J(CH) = 125.8	18.48, 18.65 tm[c]	^1J(CH) = 126.0	18.22, 18.42 td	^1J(CH) = 126.8
(OCH$_2$CH$_2$–CH$_2$**C**H$_3$)$_2$	13.39, 13.43 qm	^1J(CH) = 126.6	13.35, 13.42 qm[c]	^1J(CH) = 126.2	13.48, 13.55 qm[c]	^1J(CH) = 126.3	13.28, 13.55 q	^1J(CH) = 126.4

[a] Multiplicities refer to those in fully coupled spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. [b] Data for two most abundant rotamers. Values for the minor rotamer are given in parentheses. [c] Signals of two rotamers are overlapped. [d] Complex overlap of lines. J(CH) values could not be determined. [e] Appears as doublet of quintets. [f] Overlapped with C-2,6. Tentative value obtained from a ^{1}H-^{13}C COSY experiment. [g] Overlapped in coupled spectrum. ^1J(CH) value could not be determined. [h] Value for the minor rotamer obtained from a ^{1}H-^{13}C COSY experiment. [i] Minor rotamer overlapped with C-3,5, tentative value taken from a longe-range ^{1}H-^{13}C HMB experiment. [j] Partly overlapped in coupled spectrum. ^1J(CH) value could not be determined.

In the spectra of the complexes, the most pronounced chemical shift changes were observed for atoms involved in metal binding and those in vicinity of the ligation site, which is due to the electronic and steric effects. In all the complexes, significant proton and carbon chemical shift differences were revealed in the B-phenyl and C-phenyl rings, supporting the coordination at the azo group. In accordance with it, resonances corresponding to the PCH, $PO(OBu)_2$ and A-phenyl groups which are far from the metal ligation place, show small changes upon complexation.

Pd(II) Dihalide Adducts

The NMR spectra of complexes **2** and **3** showed the presence of several isomeric species arising from hindered rotation around the metal–ligand bond. On the basis of relative intensity of signals, it could be seen that in both complexes two rotamers predominate, in the chloro complex in the 1 : 1.5 ratio, while in the bromo complex their ratio is close to 1 : 2. The existence of rotamers and their relative abundance in complex **3** are clearly visible in its ^{31}P NMR spectrum. There are six signals in the region of 21.63–22.15 ppm, giving doublet-like patterns at 21.66, 21.76 and 21.88 ppm, and two of them are more intense as was shown in Fig. 4. The ratio of two most intense signals, ascribed to two main isomeric forms, is approximately 1 : 2. The total abundance of the third component and of the remaining non-splitted signals at the lower field is less than 10% of the intensity of the most populated component. The difference between signals in doublet-like patterns is very small, amounting to 0.012–0.014 ppm.

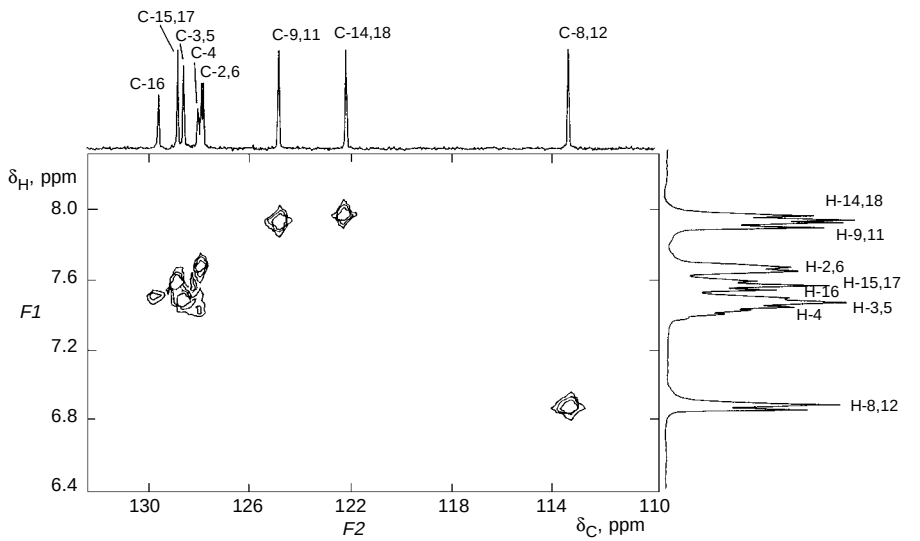

FIG. 3
Part of the one-bond ^{1}H-^{13}C COSY spectrum of ligand **1**

It might be related to the existence of two ligand molecules negligibly differing magnetically in each of these species or to the presence of two diastereoisomeric pairs (*RR–SS* and *RS–SR*) with very small chemical shifts difference, as the distance between chiral centers in the two ligand molecules is very far away[19]. Free phosphonate ligand **1** shows only one signal in ^{31}P NMR spectrum at 22.55 ppm. The ^{15}N NMR spectrum of the ^{15}N-triply-labelled complex **3** displays 1 : 2 ratio of two main rotamers as well. There is no doubt that palladium is bound to N-α in both rotamers with almost equal upfield coordination chemical shift of 103.5 and 102.2 ppm (Table I). The same intensity ratio of signals is observed in the corresponding ^{1}H and ^{13}C NMR spectra. Differences in some chemical shifts between rotamers are caused by different spatial arrangement of ligand molecules in each rotamer. The separated signals are visible for the CH_3, PCH and NH resonances as well as for those of the B-phenyl and C-phenyl rings. The ^{1}H and ^{13}C NMR data for two most abundant rotamers are summarized in Tables II and III.

In the ^{1}H NMR spectra, the most pronounced changes caused by complexation were observed for the aromatic protons H-9,11 and H-14,18 which are in *ortho* positions with respect to the azo group. In the major rotamer, their downfield shifts are *ca* 1.3 and 0.3 ppm, respectively, while in the minor one, they are only 0.2 and 0.1 ppm, respectively. These differences are related to various proximity of these protons to the Pd(II) center as this area is recognized to be very anisotropic, bringing about deshielding effects[20]. The separated rotamers signals are also visible for the H-8,12 and H-15,17 protons, while the other aromatic protons give a complex multiplet pattern in the region of 7.30–7.60 ppm. However, the connectivities from 2D homo- and heteronuclear experiments enabled the assignment of aromatic protons in two sets of rotamers. Thus, the H-4 and H-16 could be identified *via* their homonuclear correlations with the H-3,5 and H-5,17, respectively. The H-2,6 were assigned *via* the long-range heterocorrelation to carbon of the PCH group, the H-3,5 to the C-1, the H-8,12 to the C-10, the H-9,11 to the C-7, the H-15,17 to the C-13 and the H-16 to carbons C-14,18, as shown in Fig. 5, which presents a part of the HMBC spectrum of complex **3**. Proton/carbon resonances

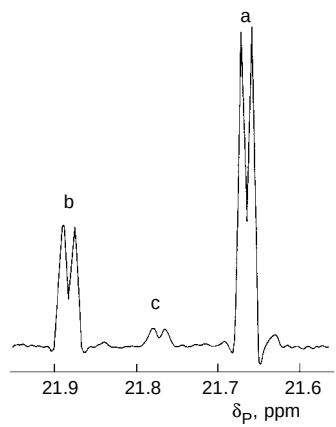

FIG. 4
^{31}P NMR spectrum of complex **3** (for a, b, c see text)

of small intensity corresponding to the third rotamer which are visible for the atoms H,C-8,12 at 6.93/112.80 ppm and for H,C-9,11 at 8.34/127.90 ppm are worth to note. In the non-aromatic region, the methyl resonances display two closely spaced triplets for each rotamer, the methylene resonances exhibit only slight broadening of signals with respect to those in free ligand, while PCH and NH protons give two sets of separate signals. The former gives two doublet of doublets with couplings to phosphorus of 23–24 Hz and to NH proton of 6–7 Hz, while the NH resonance appears as two triplets showing proton-proton and proton-phosphorus couplings of 7–8.5 Hz. Different spatial orientation of ligand molecules in two rotamers is confirmed by the NOESY experiments. The aromatic part of the NOESY spectrum of complex **3** is displayed in Fig. 6. In both the chloro and bromo complex, the main cross-peaks of the major rotamer are those of protons H-8,12 to H-9,11 and PCH, as well as those of protons H-14,18 to H-9,11 and H-15,17. A relatively strong interligand (but intramolecular) NOESY cross-peak between H-9,11 and H-14,18 suggests the *anti*-orientation of two ligand molecules bonded to palladium(II) in the major rotamer of both complexes. In the minor rotamer, the main cross-peaks are those between H-8,12 and H-9,11 as well as between H-14,18 and H-15,17, while that of H-9,11 and H-14,18 was not observed.

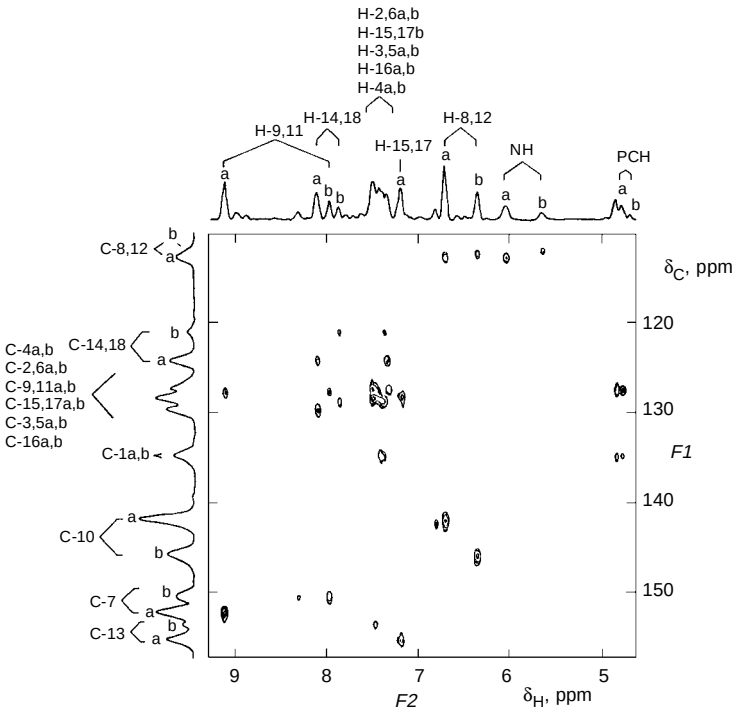

FIG. 5
Part of the long-range ^{1}H-^{13}C HMBC spectrum of complex **3**

Carbon chemical shifts of complexes **2** and **3** were assigned by the correlation experiments and by comparison with the data for the free ligand[17]. The chemical shift and the splitting patterns of carbons of the PCH and butoxy groups are almost the same as in the free ligand. In the aromatic region, a downfield shift of 0.4–3.2 ppm was observed for the quaternary carbons C-7 and C-13 as well as for carbons C-9,11 and C-14,18 (only for the main rotamer). Most of the other aromatic carbons show an upfield shift since coordination to palladium reduces the resonance influence of the electronegative azo group. Comparing the coupling patterns of the aromatic resonances in complexes with those in the free ligand, it could be noticed that some resonances, *i.e.* C-2,3, C-3,5 and C-8,12, do not show long-range proton and phosphorus couplings. The most pronounced differences in the chemical shifts between two rotamers are found for C-14,18 and the quaternary carbons C-10 and C-13. However, there is no change of the C-9,11 shift in contrast to the corresponding H-9,11 shift. This may be related to the greater sensitivity of ^{1}H compared to ^{13}C nucleus to the interligand shielding and to the paramagnetic anisotropy effect of the palladium atom.

Cyclopalladated Complex

The cyclopalladated complex **4** is a binuclear compound with the metal–metal chloro bridging configuration. Its NMR spectra indicate metal bonding with the azo N-α and

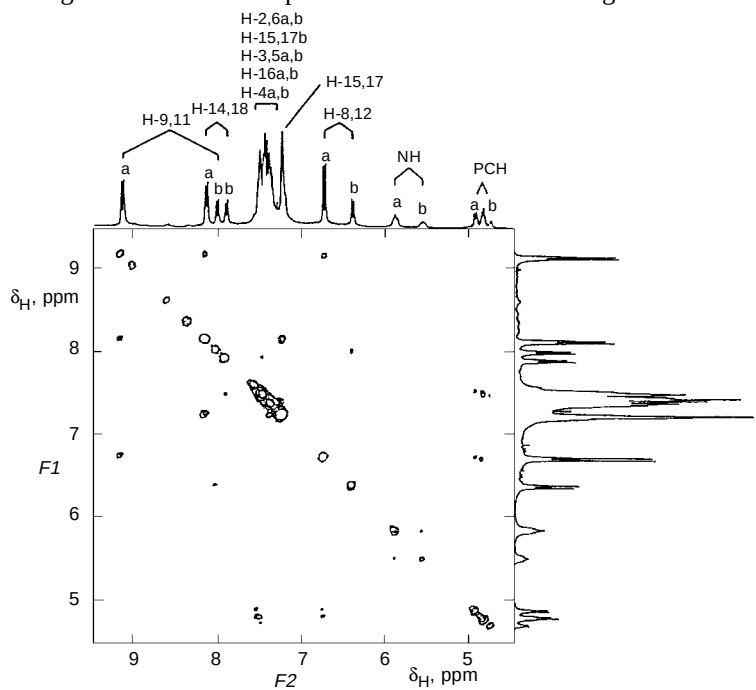

FIG. 6
Part of the NOESY spectrum of complex **3**

the *ortho*-carbon of the B-phenyl ring. It is in agreement with previous results on some palladium complexes with the substituted azobenzene derivatives in which palladation occurs in the aromatic ring with the highest electron density[21,22]. In the ^{15}N NMR spectrum of the ^{15}N-labelled complex, the signals are relatively broad with no visible $^1J(^{15}N^{15}N)$ coupling. Nitrogen resonances were differentiated on the basis of the relative integral intensities. Changes in chemical shift of signals belonging to azo N-β and anilino NH amounting to 16.8 and 12.8 ppm, respectively, are rather small relative to those of the free ligand. A much greater upfield shift of 146.1 ppm was found for the azo N-α supporting its coordination to palladium[23]. In accordance with that, the non-equivalence of aromatic protons H-8 and H-12 in the proton NMR spectrum and their upfield shift of 0.43 and 0.20 ppm, respectively, suggests the metallation at the B-phenyl ring. The flow of electron density from the d orbitals of palladium atom into this aromatic ring causes shielding of its protons[24]. The other aromatic protons could not be clearly resolved due to an extensive overlapping of resonances between 7.20–7.80 ppm.

The ^{13}C NMR spectra confirm formation of one isomeric form displaying only one resonance for each carbon atom. The most important differences appear in resonances related to carbons C-7–C-12 of the B-phenyl ring, as an indication of changes in the electron density of this aromatic ring due to *ortho*-metallation. A comparison with the spectrum of the free ligand shows that none of these carbons in the complex are equivalent. The palladium-bound C-11 is greatly shifted downfield by 34.99 ppm, the C-9 and C-12 are shifted downfield by 7.16 and 4.79 ppm, respectively, while the C-8 shows an upfield shift of 3.07 ppm, in agreement with data reported for various cyclopalladated compounds[25–28]. The quaternary carbons C-10 and C-13 from the both sides of the azo group show downfield shifts of 6.13 and 2.86 ppm, respectively. The signals of the other carbons of the C-phenyl ring exhibit small changes. Thus, the *ortho* carbons C-14,18 are shifted downfield by 1.46 ppm, while the other carbons show an upfield shift of only 0.1–0.2 ppm. As expected, the overall pattern of the carbon chemical shifts at the remote A-phenyl ring is quite similar to that of the free ligand.

CONCLUSION

A combination of ^1H, ^{13}C, ^{15}N and ^{31}P NMR was used to characterize dibutyl {α-[4-(phenyldiazenyl)anilino]benzyl}phosphonate and its dihalide mononuclear and binuclear Pd(II) complexes, which might be of interest as anticancer agents. The ^{15}N-enriched ligand and its palladium complexes enabled unambiguous determination of the bonding mode of the organophosphorus ligand which may be coordinated to a metal center through several donor sites: the anilino and azo nitrogens as well as the phosphoryl oxygen. In both types of palladium complexes, the coordination through the azo N-α nitrogen was established. A coordination induced ^{15}N chemical shifts vary from *ca* 102 ppm in the adducts **2** and **3** to 146 ppm in the cyclopalladated complex **4**. The NMR analyses have revealed several isomeric species for **2** and **3**, arising from

hindered rotation around the metal–ligand bond. Two rotamers predominate with relative abundance of *ca* 1 : 1.5 for the chloro and 1 : 2 for the bromo adduct. Various 2D homo- and heteronuclear correlated experiments enabled a complete signal assignment in each rotamer. The *J*(HH) and *J*(CH) values were determined for the majority of the resonances. A relatively strong interligand NOESY cross-peak between protons H-9,11 and H-14,18 suggests the *anti*-orientation of the two ligand molecules bonded to palladium(II) ion in the major rotamer of both complexes. The NMR spectra of **4** show the presence of one isomer formed by palladation at the azo N-α nitrogen and the *ortho*-carbon of the B-phenyl ring. This was supported by non-equivalence of the aromatic protons H-8 and H-12 in the ^{1}H NMR spectrum as well as by a significant downfield shift for the Pd-coordinated C-11 in the ^{13}C NMR spectrum.

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