Preparation, characterization and activity of palladium(II) halide complexes with diethyl 8-quinolylmethylphosphonate (8-dqmp). X-ray crystal structure of $[8\text{-dqmpH}]_2[PdCl_4]\cdot 2H_2O$ and $[8\text{-dqmpH}]_2[Pd_2Br_6]$

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Abstract

The synthesis, spectroscopic and biological properties of the novel palladium(II) halide complexes with diethyl 8-quinolylmethylphosphonate (8-dqmp) have been reported. It was shown that the square planar complexes *trans*-$[Pd(8\text{-dqmp})_2X_2]$ were obtained by reaction of 8-dqmp with PdX_4^{2-} (X = Cl, Br) in the neutral ethanolic/aqueous solution. In the HX acidic medium the quinolinium salt complexes [8-dqmp H]$_2[PdX_4]$ were isolated. They were converted by heating in methanol into the corresponding hexahalodipalladium salt complexes $[8\text{-dqmpH}]_2[Pd_2X_6]$. The new complexes were characterized on the basis of elemental and thermogravimetric analysis, magnetic and conductance measurements, by the IR and ^1H NMR spectra and some X-ray crystal structure determinations. The complexes were tested for their cytostatic activity on KB and L1210 cell lines. The coordination behaviour of 8-dqmp as well as the spectral and biological properties of its complexes were compared with the results reported for the diethyl ester of 2-quinolylmethylphosphonic acid (2-dqmp) and its palladium(II) halide complexes. The molecular structures of the complexes $[8\text{-dqmpH}]_2[PdCl_4]\cdot 2H_2O$ (**3**) and $[8\text{-dqmpH}]_2[Pd_2Br_6]$ (**6**) have been fully characterized by X-ray diffraction studies. The crystals of both complexes are triclinic, space group $P\bar{1}$, $Z = 2$, with lattice parameters for **3**: $a = 9.438(2)$, $b = 9.481(2)$, $c = 11.082(2)$ Å, $\alpha = 83{,}4(1)$, $\beta = 107.5(1)$, $\gamma = 77.0(1)°$, the final R factors are $R = 0.0481$ and $R' = 0.0551$ for 3208 observed diffractometer collected reflections; and for **6**: $a = 11.943(2)$, $b = 10.644(2)$, $c = 8.873(2)$ Å, $\alpha = 102.08(2)$, $\beta = 85.56(2)$, $\gamma = 69.54(2)°$, the final R factors are $R = 0.0725$ and $R' = 0.0804$ for 2584 observed diffractometer collected reflections. The structure of **3** is composed of the square planar $PdCl_4^{2-}$ anion lying in a centre of symmetry (average Pd–Cl = 2.330 Å), of two quinolinium phosphonate cations and two water molecules. The structure of **6** consists of two quinolinium moieties as a cationic part separated by the Pd_2Br_6 centrosymmetric dianionic dimer.

Introduction

The importance of palladium complexes of 8-(substituted) quinoline derivatives in analytical chemistry is well known [1, 2]. Some of them are also important in biological systems [3]. Recently an increasing number of studies including various structural and spectroscopic investigations have been concerned with the cyclopalladated complexes of 8-methylquinolines and their use in organic synthesis [4–10].

In our earlier paper we reported the synthesis, spectroscopic studies and some X-ray crystal structure determinations of the palladium(II) halide complexes with the diethyl ester of 2-quinolylmethylphosphonic acid (2-dqmp) [11]. The preliminary screening tests showed that most of these complexes exhibit some cytostatic activity. In continuation of this work in

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the present paper we wish to describe the coordination behaviour of diethyl 8-quinolylmethylphosphonate (8-dqmp) with respect to Pd(II) ion as well as the spectral properties and the inhibitory activities of the novel complexes. Diethyl quinolylmethylphosphonates have two potential donor atoms, the quinoline nitrogen and the phosphoryl oxygen, however, while 2-dqmp can act as monodentate N-bonded or as bidentate N,O-bonded chelate ligand, 8-dqmp binds the palladium ion only through the nitrogen atom. In acidic media both ligands form salt complexes containing the protonated quinolylmethylphosphonate ligand as cation and the tetrahalopalladium(II) complex as anion. Upon heating in methanol the 2-dqmp salt complexes decomposed to the molecular dihalopalladium complexes PdL_2X_2, while the 8-dqmp salt complexes are converted into the corresponding hexahalodipalladium salt complexes. The molecular structure of both types of salt complexes was determined by a single crystal X-ray diffraction study.

Experimental

Starting materials

Diethyl ester of 8-quinolylmethylphosphonic acid (8-dqmp) prepared as described [12] was freshly distilled. All other reagents and solvents were analytical grade purity products and were used without purification.

Preparation of the complexes

[Pd(8-dqmp)$_2$Cl$_2$] (1)

A concentrated aqueous solution of K_2PdCl_4 (0.219 g, 0.67 mmol) was added dropwise to an ethanolic solution of 8-dqmp (0.373 g, 1.34 mmol). The reaction mixture was vigorously stirred for 2 h. The yellow–green precipitate which formed was filtered off, washed with cold ethanol and dried under vacuum over P_2O_5. Yield 0.197 g (80%).

[Pd(8-dqmp)$_2$Br$_2$] (2)

A mixture of K_2PdCl_4 (0.184 g, 0.56 mmol) and LiBr (0.292 g, 3.36 mmol) in water (10 ml) was stirred for 1 h before adding to a stirred solution of 8-dqmp (0.314 g, 1.12 mmol) in ethanol (3 ml). The oil initially formed resulted in the formation of an ochre precipitate after an additional stirring of 1 h with 50% ethanol (5 ml). Yield 0.189 g (82%).

[8-dqmpH]$_2$[PdCl$_4$]·2H$_2$O (3)

To a stirred solution of 8-dqmp (0.342 g, 1.22 mmol) in ethanol (3 ml) was added dropwise a mixture of K_2PdCl_4 (0.200 g, 0.61 mmol) and 1:1 HCl (0.4 ml) in water (5 ml). After stirring for 4 h, the light brown precipitate which formed was separated, washed with acetone and dried in air. Crystals used for X-ray analyses were obtained by recrystallization from methanol.

[8-dqmpH]$_2$[PdBr$_4$]·2H$_2$O (4)

A mixture of K_2PdCl_4 (0.225 g, 0.69 mmol) and 1:1 HBr (1.35 ml, 5.5 mmol) in water (5 ml) was stirred for 1 h and then was slowly added to a solution of 8-dqmp (0.385 g, 1.38 mmol) in ethanol (3 ml). After an additional stirring of 4 h, a brick red precipitate was formed (0.567 g, 80%).

[8-dqmpH]$_2$[Pd$_2$Cl$_6$] (5)

The tetrachloropalladium complex **3** was refluxed overnight in methanol under a stream of N_2. The crystal precipitate obtained on cooling was determined as a mixture of the complexes **3** and **5**. The much more soluble complex **3** was separated by sohxlet extraction with chloroform.

[8-dqmpH]$_2$[Pd$_2$Br$_6$] (6)

The tetrabromopalladium complex **4** was refluxed for 30 min in methanol. On cooling reddish brown monocrystals of **6** suitable for X-ray analysis were obtained.

Physical measurements and analyses

Melting points were determined on a hot-stage microscopy and are uncorrected. IR spectra were recorded on a Perkin-Elmer 580B spectrophotometer in KBr disks (4000–250 cm^{-1}) and as Nujol mulls in polyethylene (400–200 cm^{-1}). ^1H NMR spectra were determined in $CDCl_3$ and d_7-DMF solutions with tetramethylsilane as the internal standard. Conductivity measurements were carried out using a CD 7A Tacussel conductivity bridge at 25 °C for 10^{-3} mol l^{-1} solutions in methanol and dimethylformamide. Thermogravimetric measurements were performed with a Cahn RG electromicro balance applying a heating rate of 2° min^{-1} in an atmosphere of static air. Magnetic susceptibilities were determined by the standard Gauy method at 22 °C using $CuSO_4 \cdot 5H_2O$ as calibrant.

Elemental analyses were performed in the Laboratory of Complex Compounds and the Microanalytical Laboratory of the Rudjer Bošković Institute.

X-ray crystal structure determination

For both complexes [8-dqmpH]$_2$[PdCl$_4$]·2H$_2$O (**3**) and [8-dqmpH]$_2$[Pd$_2$Br$_6$] (**6**) the intensity data were collected on a Siemens AED diffractometer with

ω–2θ scan, $\theta < 70$ °C with Cu Kα radiation (Ni filtered).

$C_{28}H_{38}Cl_4N_2O_6P_2Pd \cdot 2H_2O$ (**3**), $M = 8.44.81$, triclinic, space group $P\bar{1}$, $a = 9.438(2)$, $b = 9.481(2)$, $c = 11.082(2)$ Å, $\alpha = 83.4(1)$, $\beta = 107.5(1)$, $\gamma = 77.0(1)°$, $U = 903.5(9)$ Å^3, $Z = 2$, $F(000) = 432$, μ(Cu Kα) = 82.94 cm^{-1}, $D_x = 1.553$ g cm^{-3}. Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement of 30 reflections ($\theta = 14$–$35°$). A total of 3428 reflections was measured and 3208 with $I \geq 2\sigma(I)$ were used in the refinement. The intensity data were corrected for Lorentz and polarization effects. Absorption corrections were made with the procedure of Walker and Stuart [13] using ABSORB [14]. The structure was solved by the heavy-atom method and refined by full-matrix least-squares. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were located or calculated and refined in the last cycles isotropically. The final cycle refinement included 233 variable parameters with an agreement R factor of 0.0481 and R' of 0.0551 (weighting scheme $w = 1/\sigma^2(F) + gF^2$). Scattering factors of SHELX76 [15] and anomalous dispersion factors taken from the International Tables for X-ray Crystallography [16] were used.

$C_{14}H_{19}Br_3NO_3PPd$ (**6**), $M = 626.40$, triclinic, space group $P\bar{1}$, $a = 11.943(2)$, $b = 10.644(2)$, $c = 8.873(2)$ Å, $\alpha = 102.8(2)$, $\beta = 85.56(2)$, $\gamma = 69.54(2)°$, $U = 1019.3(4)$ Å^3, $Z = 2$, $F(000) = 600$, μ(Cu Kα) = 153.75 cm^{-1}, $D_x = 2.041$ g cm^{-3}. The same procedure for data collection, solving and refining was performed as for the previous compound. A total of 2584 observed reflections (out of 3874 measured) was used and the final R factors for 262 variable parameters were $R = 0.0725$ and $R' = 0.0804$.

in vitro Cytostatic evaluation

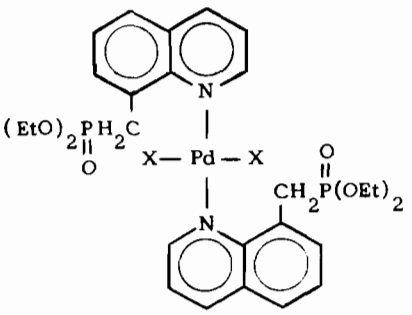
The cytostatic activity of the complexes was estimated against KB cell line derived from a human epidermoid carcinoma [17], and on murine leukemia L1210 cell line [18] by the standard screening procedures described in refs. 11 and 19. The KB cells were cultivated in Eagle's Minimum Essential Medium (MEM) [20] supplemented with 10% newborn calf serum and 1% non-essential amino acids. The cell population doubling time was approximately 24 h. The cells were adherent to the substratum.

The L1210 cells were maintained as cultures in suspension in Roswell Park Memorial Institute 1640 (RPMI) [21] supplemented with 10% fetal calf serum. Under these conditions the cell population doubling time was approximately 12 h.

For the cytostatic assay a cell culture in exponential growth phase was used for both lines according to the experimental Protocols of the National Cancer Institute (Bethesda, MD, U.S.A.) [22]. The compounds were dissolved or suspended immediately before use in a sterile dimethylsulfoxide. Further dilutions were carried out using a culture medium until the required concentration of the compound was obtained. The final percentage of the solvent in the culture medium was always tested for non-toxicity. For each compound at least five different concentrations were used and five samples were used for each one. The incubation of the cultures in the presence of the compounds being examined was set at 37 °C for 72 h, the time interval during which the exponential growth occurred. This growth was calculated by counting the vital cells (trypsin blue exclusion test). The cytostatic activity was calculated as the growth inhibition percentage of the samples treated with respect to the growth of the control cultures. The significance of the results was evaluated using Student's 't' test ($p < 0.01$). The cytostatic activity was expressed as concentration of the complex in μg ml^{-1} (ID_{50}) at which the tumor cells showed a 50% inhibition of growth, and was calculated by linear regression analysis [23].

Results and discussion

Investigations of the interaction of diethyl 8-quinolylmethylphosphonate with PdX_4^{2-} (X = Cl, Br) have shown that either the molecular or the ionic complexes could be formed depending on the acidity of the alcoholic/aqueous reaction solution. While in neutral medium dihalopalladium complexes PdL_2X_2 containing N-bonded ligand in a *trans* square-planar fashion were obtained, from HX acidic medium the salt complexes $[LH^+]_2[PdX_4^{2-}]$ were isolated. The ligand is protonated forming quinolinium ion, while palladium remains in the form of square planar monomeric tetrahalopalladium complexes PdX_4^{2-}. By heating in methanol they were converted into the planar dimeric halobridged complexes $Pd_2X_6^{2-}$, and therefore the salt complexes $[LH^+]_2[Pd_2X_6^{2-}]$ were obtained.



X = Cl (1); X = Br (2)

We failed to isolate the metal-to-ligand 1:1 palladium complexes of 8-dqmp regardless of the various preparative conditions such as the temperature at which the reaction was carried out, kind of solvent applied (methanol or ethanol), duration of reaction, or the extent of the excess of PdX_4^{2-} used in the reaction process. The 1:1 complexes with the bidentate N,O-bonded 8-dqmp ligand should contain a seven membered ring, and although the formation of such chelate ring is possible in some palladium complexes with nitrogen containing donors [24–26], it is unlikely that the much less electronegative and basic phosphoryl oxygen could stabilized the formation of the seven membered chelate complex. Furthermore it is well known that 8-methylquinoline and some of its derivatives are capable of forming chelate complexes by palladation at the 8-methyl group [4, 10]. It may be presumed that the bulky diethyl phosphonato group in 8-dqmp prevents metallation at the 8-methylene position and formation of such cyclopalladated complexes with a five membered ring.

Physical properties, analytical and conductance data of the novel palladium complexes are reported in Table 1. The most important IR and ^1H NMR data are listed in Tables 2 and 3. The prepared complexes are microcrystalline, coloured from yellow to brown, diamagnetic compounds, stable under normal laboratory conditions. Palladium bromide complexes are more soluble than the corresponding chloride complexes, as are the ionic salt complexes with respect to the molecular dihalopalladium complexes. The low molar conductance values of dihalopalladium complexes **1** and **2** in DMF indicate their non-electrolytic behaviour. In methanol they are almost insoluble. Salt complexes containing PdX_4^{2-} and $Pd_2X_6^{2-}$ ions, complexes **3–6**, exhibit methanol conductivities comparable to those of diunivalent electrolytes ($\Lambda_M \sim 190\ \Omega^{-1}\ cm^2\ mol^{-1}$) [27]. The corresponding conductance data obtained in DMF are considerable lower than expected for 2:1 electrolytes, especially for chloride complexes, presumably due to the small ion-pair dissociation in less polar DMF. In methanol they are completely dissociated.

Spectral studies

The IR spectra of diethyl 8-quinolylmethylphosphonate and its palladium complexes are too complex to allow the precise assignment of all absorption bands, therefore only the frequencies associated with the characteristic functional groups are given in Table 2. Generally, the most significant differences between spectra of the free ligand and its complexes may be noticed in the region of 1600–1500 cm^{-1} where bands arising from the stretching modes of the C=C and C=N bands of the quinoline ring are present. While free 8-dqmp has three rather weak bands around 1600 cm^{-1} and a more intense one at 1500 cm^{-1} associated with these vibrations, dihalopalladium complexes **1** and **2** are characterized by only one weak to medium band around 1600 cm^{-1} and a medium to strong band around 1512 cm^{-1} as a result of the coordination of the quinoline nitrogen to the palladium(II) ion. On the other hand the absorption bands attributed to the phosphonic ester groups

TABLE 1. Analytical and physical data for the palladium halide complexes

Complex	Colour	Melting point (°C)	Analysis (%)[a]						Λ_M[b] ($cm^2\ \Omega^{-1}\ mol^{-1}$)
			Pd	C	H	N	P	Halogen	
$Pd(8\text{-dqmp})_2Cl_2$ (**1**)	yellow–green	160–161	14.7 (14.5)	45.5 (45.7)	4.8 (4.9)	3.9 (3.8)	8.3 (8.4)	9.8 (9.6)	5.1/–
$Pd(8\text{-dqmp})_2Br_2$ (**2**)	ochre	131–133	12.8 (12.9)	40.5 (40.8)	4.2 (4.4)	3.5 (3.4)	7.6 (7.5)	19.5 (19.4)	6.0/–
$[8\text{-dqmpH}]_2[PdCl_4]\cdot 2H_2O$ (**3**)	light brown	130 dec.	12.6 (12.6)	39.9 (39.8)	4.7 (5.0)	3.5 (3.3)	7.3 (7.3)	16.9 (16.8)	72.4/195.2
$[8\text{-dqmpH}]_2[PdBr_4]\cdot 2H_2O$ (**4**)	brick red	94 dec.	10.1 (10.4)	32.8 (32.9)	4.0 (4.1)	2.7 (2.7)	6.2 (6.1)	31.1 (31.3)	127.2/193.5
$[8\text{-dqmpH}]_2[Pd_2Cl_6]$ (**5**)	red	151–153	21.2 (21.6)	34.2 (34.1)	3.9 (3.9)	3.1 (2.8)	6.4 (6.3)	21.5 (21.6)	92.3/174.2
$[8\text{-dqmpH}]_2[Pd_2Br_6]$ (**6**)	reddish brown	136–138	16.8 (17.0)	26.5 (26.8)	2.8 (3.1)	2.1 (2.2)	5.2 (4.9)	38.4 (38.3)	121.1/177.5

[a]Calculated values are given in parentheses. [b]At room temperature in *c.* 1×10^{-3} mol l^{-1} dimethylformamide/methanol solutions.

TABLE 2. Selected infrared spectroscopic data (cm^{-1})[a]

Compound	ν(OH)[b]	ν(NH^+)	ν(C=C), ν(C=N)	ν(P=O)	ν(PO–C)	δ(P–OC)	ν(Pd–X)[c]	ν(Pd–N)
8-dqmp			1616w 1598w-m 1578w 1500m-s	1265sh 1245vs(br)	1160m 1130w	1050vs 1022vs		
1			1602w-m 1514m-s	1260vs	1156w 1140vw	1036s 1018s	340m	260w
2			1600w-m 1512m-s	1260vs	1157w 1138vw	1037s 1018s	285w	260w
3	3480s 3320s	2900–2400m(br)	1637s 1597s 1562s	1242s 1231vs 1220vs	1154w 1142w	1051vs 1020vs	320s	
4	3480s 3320s	2900–2400m(br)	1637s 1600s 1563s	1241s 1230vs 1218vs	1157w 1139w-m	1060s 1051vs 1024vs	247s	
5		2900–2500m(br)	1638m-s 1602m-s 1570m-s	1258vs 1228s	1147w 1154w-m	1060s 1024vs	329s 249m	
6		2900–2500m(br)	1639m-s 1604m-s 1572m-s	1251vs 1226s	1160w-m 1147w	1061s 1022vs	252s	

[a]KBr pellets. Abbreviations: vs = very strong, s = strong, m = medium, w = weak, br = broad. [b]From H_2O. [c]X = Cl, Br.

TABLE 3. Proton NMR data[a]

Compound	^1H (δ ppm)
8-dqmp	1.10 [t, 6 H, J(HH) 7.0, CH_3], 3.91 (m, 4 H, $POCH_2$), 3.93 [d, 2 H, J(PH) 21.0, PCH_2], 7.13–8.18 (m, 5H, aryl H), 8.83 [m, 1 H, aryl H(2)]
2	1.21 [t, 12 H, J(HH), 7.1, CH_3], 4.10 (m, 8 H, $POCH_2$), 4.13 [d, 4 H, J(PH) 21.0, PCH_2], 7.54–8.14 (m, 8 H, aryl H), 9.09 [dd, 2 H, J(HH) 5.9, aryl H(3)], 10.14 [dd, 2 H, J(HH) 5.8, aryl H(2)]
3	1.24 [t, 12 H, J(HH), 7.0, CH_3], 4.14 (m, 8 H, $POCH_2$), 4.26 [d, 4 H, J(PH) 21.6, PCH_2], 6.67 (br s, 6 H., NH^+, OH)[b], 7.78–8.38 (m, 8 H, aryl H), 9.05 [dd, 2 H, J(HH) 5.1, aryl H(3)], 9.40 [dd, 2 H, J(HH) 5.0, aryl H(2)]
4	1.24 [t, 12 H, J(HH) 7.1, CH_3], 4.15 (m, 8 H, $POCH_2$), 4.26 [d, 4 H, J(PH) 21.1, PCH_2], 5.20 (br s, 6 H, NH^+, OH)[b], 7.91–8.54 (m, 8 H, aryl H), 9.33 [dd, 2 H, J(HH) 4.2 , aryl H(3)], 9.54 [dd, 2 H, J(HH) 4.3, aryl H(2)]
6	1.18 [t, 12 H, J(HH) 7.0, CH_3], 4.10 (m, 8 H, $POCH_2$), 4.11 [d, 2 H, J(PH) 21.5, PCH_2], 5.28 (br s, 2 H, NH^+)[b], 7.59–8.62 (m, 8 H, aryl H), 8.50 [dd, 2 H, J(HH) 4.4, aryl H(3)], 9.07 [dd, 2 H, J(HH) 4.4, aryl H(2)]

[a]Spectra recorded in d_7-DMF: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet, br = broad signal. Coupling constants in Hz. [b]D_2O exchangeable protons.

remain almost unchanged upon complex formation confirming the non-involvement of the phosphoryl oxygen atom in the metal coordination. In the far IR region, the spectra of dihalopalladium complexes show a band of palladium–halogen stretching vibrations in the expected range for terminal halides in *trans* square planar complexes with D_{2h} stereochemistry [11, 28].

Tetrahalopalladium complexes **3** and **4** as well as hexahalodipalladium complexes **5** and **6** which contain the protonated ligand as a counterion show a sharp strong band at about 1638 cm^{-1} and a very broad complex progression of absorptions covering the whole 2900–2400 cm^{-1} region due to the vibrations of the protonated quinoline nitrogen. In tetrahalopalladium complexes the broad absorption is displaced to lower frequencies than in the hexahalodipalladium complexes most probably because of the weak intermolecular hydrogen bonding between the NH^+ and the lattice water present in tetrahalopalladium complexes. Furthermore on the basis of X-ray data for complex **3** it is evident that the water molecules are also bonded to the phosphoryl groups by intramolecular hydrogen bonding. The water bonded to the P=O group may change the polarity of the oxygen atom and brings about the appearance of multiple bands of phosphoryl stretching vibrations shifted to lower frequencies by *c.* 25 cm^{-1} with respect to the free ligand. In the ν(O–H) region the spectra of hydrated complexes exhibit two rather strong bands at 3480 and 3320 cm^{-1}. The far IR spectra of the ionic palladium complexes are consistent with the spectral results obtained for various compounds containing the planar monomeric tetrahalopalladium anions PdX_4^{2-} or the dimeric halo-bridged $Pd_2X_6^{2-}$ anions [29, 30].

While all bromopalladium complexes are sufficiently soluble in DMF for observing the ^1H NMR spectra, among the chloro complexes only for the tetrachloropalladium complex **3** could a satisfactory spectrum be obtained. Our measurements confirm that the complexes retain their structural integrity in solution. Chemical shifts and coupling constants for 8-dqmp and its palladium complexes are given in Table 3. In the spectra of complexes the resonances of all kind of protons show a certain downfield shift with respect to the free ligand. These differences may be explained by the lowering in electronic density of the aromatic ring caused by the coordination to the metal ion, complexes **1** and **2**, or by protonation of the quinoline nitrogen, complexes **3–6**, as well as by the magnetic anisotropy of the palladium atom [31]. The magnitude of the shift decreases with the distance from the coordination or protonation site. Therefore the protons of the methyl groups exhibit a downfield shift of only 0.08–0.14 ppm, methylene ester protons of 0.9–0.24 ppm, benzyl methylene protons of 0.18–0.33 ppm and the most pronounced downfield shift of 0.24–1.30 ppm could be observed for the aromatic protons. While there is no appreciable difference in the methyl and methylene region of the spectra between all three types of palladium complexes, significant differences can be observed in the aromatic region for the H(2) aromatic proton. In the dibromopalladium complex **2** the large downfield shift of 1.31 ppm obtained for this proton may arise partially from its proximity to the Pd(II) atom, and partially from the lower electronic density of the aromatic ring. Less remarkable but a still significant shift of 0.65 and 0.78 ppm, respectively, is found for tetrachloro- and tetrabromopalladium complexes **3** and **4**, while a downfield shift of only 0.24 ppm could be observed in the hexabromodipalladium complex **6**. Proton bonded directly to nitrogen gives a broad absorption most probably due to the slower dissociation rate of these ion-pair complexes in DMF, which is confirmed by the conductance measurements. The presence of only one set of resonances for each proton in the spectra of the complexes is due to the equivalence of the two either coordinated or protonated ligand molecules in the examined complexes.

X-ray studies

The atomic coordinates for complexes [8-dqmp $H]_2[PdCl_4]\cdot 2H_2O$ (**3**) and [8-dqmp $H]_2[Pd_2Br_6]$ (**6**) are given in Tables 4 and 5 and selected interatomic distances and bond angles in Table 6. Perspective views of the molecules with the atom numbering are shown in Figs. 1 and 2.

The structure of complex **3** is built up of planar $PdCl_4^{2-}$ anions, protonated 8-methylquinolinium phosphonate cations and water molecules. The Pd atom is situated at the crystallographic center of symmetry, so this implies that the $PdCl_4^{2-}$ anions are planar. The anions are nearly regular square, having Pd–Cl bond lengths near the normal values 2.30–2.34 Å found for bis(propylammonium)-tetrachloropalladate(II) [32], [cytosine $H]_2[PdCl_4]$ [33] and diguanidinium tetrachloropalladate(II) [34]. The angles Cl–Pd–Cl are almost right angles, 91.3(2) and 88.7(2)°, and hence the deviation from regular square planar coordination is dominated by the presence of long 2.342(3) and short 2.317(1) Å Pd–Cl bonds.

The protonated 8-methylquinoline ring is planar with the greatest deviation from the least-squares plane being 0.048(7) Å for the C(3) atom. Each ring is hydrogen-bonded to the water molecule with the

TABLE 4. Atomic fractional coordinates ($\times 10^4$) for complex **3**

	x/a	*y/b*	*z/c*
Pd	0	0	0
Cl(1)	−2604(1)	292(1)	−346(1)
Cl(2)	−511(1)	2384(1)	−1172(1)
P	604(1)	2311(1)	3661(1)
O(1)	2096(4)	1135(4)	3708(4)
O(2)	1167(4)	3740(4)	3738(4)
O(3)	−50(4)	1894(4)	4634(4)
O(W1)	1637(5)	673(5)	7200(5)
N	−3628(5)	2063(5)	2019(4)
C(2)	−4911(7)	1639(7)	1935(6)
C(3)	−6288(7)	2693(8)	1739(7)
C(4)	−6307(7)	4151(7)	1626(6)
C(5)	−4963(8)	6080(6)	1503(6)
C(6)	−3669(9)	6455(7)	1513(6)
C(7)	−2281(7)	5347(6)	1690(5)
C(8)	−2206(6)	3870(5)	1863(4)
C(9)	−3558(5)	3478(5)	1865(4)
C(10)	−4971(6)	4588(6)	1667(5)
C(11)	−711(6)	2731(6)	2037(5)
C(12)	2226(7)	−439(7)	3918(7)
C(13)	3797(8)	−1268(7)	4120(8)
C(14)	2098(8)	3955(8)	4985(6)
C(15)	2718(9)	5210(8)	4749(7)

TABLE 5. Atomic fractional coordinates ($\times 10^4$) for complex **6**

	x/a	*y/b*	*z/c*
Pd	4376(1)	6812(1)	5971(1)
Br(1)	6035(1)	4732(1)	6193(1)
Br(2)	4918(1)	8217(1)	8080(2)
Br(3)	2679(1)	8757(1)	5670(2)
P	10328(2)	3725(2)	2749(2)
O(1)	10784(6)	2690(8)	1108(8)
O(2)	9959(5)	5181(7)	2390(8)
O(3)	11213(5)	3429(7)	3822(8)
N	7385(6)	6688(7)	3938(8)
C(2)	6788(9)	8054(10)	4220(11)
C(3)	5985(8)	8588(10)	3253(12)
C(4)	5804(8)	7723(10)	2055(12)
C(5)	6261(7)	5334(10)	515(11)
C(6)	6861(8)	3948(11)	276(10)
C(7)	7682(7)	3430(9)	1276(10)
C(8)	7903(7)	4309(9)	2482(9)
C(9)	7251(6)	5754(8)	2748(9)
C(10)	6420(7)	6263(9)	1732(10)
C(11)	8860(7)	3751(8)	3450(10)
C(12)	11898(11)	1444(15)	721(16)
C(13)	11669(24)	345(19)	1274(45)
C(14)	10832(9)	5742(12)	1898(13)
C(15)	10300(13)	7290(12)	2553(16)

N–H···O(1w) [$-x$, $-y$, $1-z$] distance of 2.706(7) Å and an angle of 154°. There are also O(1w)–H···O (3) hydrogen bonds of 2.766(7) Å with an angle of

TABLE 6. Selected bond distances (Å) and angles (°) for complexes **3** and **6**[a]

	Complex **3**	Complex **6**
Pd–X(1)	2.317(1)	2.458(2)
Pd–X(2)	2.342(3)	2.419(2)
Pd–X(3)		2.418(2)
Pd–X(1′)		2.453(2)
P–O(1)	1.570(4)	1.555(6)
P–O(2)	1.565(4)	1.565(8)
P–O(3)	1.453(5)	1.474(7)
P–C(11)	1.793(5)	1.802(9)
O(1)–C(12)	1.455(8)	1.467(13)
O(2)–C(14)	1.462(8)	1.451(16)
N–C(2)	1.340(9)	1.334(11)
N–C(9)	1.352(7)	1.352(11)
X(1)–Pd–X(2)	91.3(2)	90.2(1)
X(1)–Pd–X(1′)		86.1(1)
X(2)–Pd–X(1′)	88.7(2)	176.1(1)
X(2)–Pd–X(3)		93.3(1)
X(3)–Pd–X(1′)		90.3(1)
Pd–X(1)–Pd′		93.9(1)
O(3)–P–C(11)	114.3(4)	114.7(4)
O(2)–P–C(11)	101.6(3)	100.6(4)
O(2)–P–O(3)	116.1(3)	116.3(4)
O(1)–P–C(11)	107.3(3)	107.3(4)
O(1)–P–O(3)	114.1(3)	112.8(4)
O(1)–P–O(2)	102.0(4)	103.9(4)
P–O(1)–C(12)	121.9(5)	123.9(6)
P–O(2)–C(14)	119.5(4)	123.4(6)
P–C(11)–C(8)	112.4(4)	113.8(6)

[a]X refers to Cl in complex **3** and Br in complex **6**.

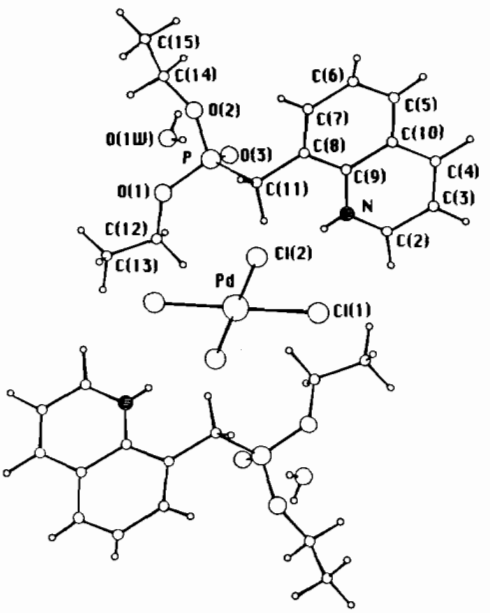


Fig. 1. A perspective drawing of bis(diethyl 8-quinoliniummethylphosphonate)tetrachloropalladium(II)dihydrate (**3**) with atom numbering scheme.

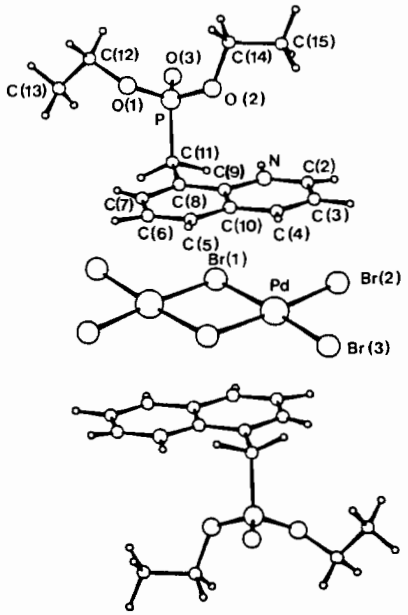


Fig. 2. A perspective drawing of bis(diethyl 8-quinoliniummethylphosphonate)hexabromodipalladium(II) (**6**) with atom numbering scheme.

174°. There are no short N–H···Cl or O–H···Cl contacts.

The structure of complex **6** consists of a 'sandwich' association of two cationic quinolinium moieties with a Pd_2Br_6 dianionic unit in the middle, so the dihedral angle between the best planes through the quinoline ring and dinuclear anionic unit is 10.3(1)° with an interplanar distance of about 3.74 Å.

The bromo-bridged dimer lies on a crystallographic center of symmetry and has a Pd–Br bridging bond (2.458(2) Å) longer than those with the terminal Br atoms (2.419(2) and 2.418(2) Å). These values are similar to those observed in 1,3,8-trimethylxanthinium tribromopalladate(II) [30], 2.452 and 2.413, 2.424 Å; in bis(pyridine-*N*-oxide)bis(pyridine-*N*-hydroxide)-tetrabromo-bis(μ-bromo)-di-palladium(II) [35], 2.452 and 2.398, 2.405 Å; and also with those of 2.455 and 2.463 Å found in a similar bridging bromide palladium complex [36].

The bond distances and angles around the phosphorus atom in both complexes are all close to those found in diethyl 4-ethoxycarbonyl-3,4-dihydrobenzo [f] quinoline-3-phosphonate [37].

in vitro Cytostatic activity

The results obtained by screening the new complexes for their cytostatic activity expressed as concentration of the complex required to inhibit the tumor cell growth by 50% (ID_{50}) are reported in Table 7. Comparing these results of the *in vitro* assay with those obtained for the corresponding complexes

TABLE 7. *in vitro* Cytostatic activity of the complexes

Complex	ID_{50} (μg ml^{-1})[a]	
	KB cells	L1210 cells
1	6.65 (9.00×10^{-6})	7.92 (1.08×10^{-5})
2	10.03 (1.22×10^{-5})	12.72 (1.54×10^{-5})
3	16.00 (1.94×10^{-5})	11.51 (1.40×10^{-5})
4	9.89 (9.70×10^{-6})	9.83 (9.60×10^{-6})
6	17.61 (2.82×10^{-5})	14.79 (2.36×10^{-5})

[a]Molar concentration of the complexes are given in parentheses.

of 2-dqmp [11], it could be concluded than the 8-dqmp ligand is more cytotoxic than its 2-analogue. It was shown that for complexes of 2-dqmp in general the L1210 line was more responsive than the KB cell line, and the bromo complexes much more effective than their chloro analogues. However, for complexes of 8-dqmp there are no significant differences in response between the two cell lines, neither between the chloro and bromo complexes. In these investigations more attention should be paid to the neutral complexes with the Pd-coordinated ligands as in ionic complexes their cytotoxicity most probably reflects the combined activity of the protonated ligand and the tetrahalopalladium anionic complex. Neutral 8-dqmp complexes display a higher activity than the corresponding 2-dqmp complexes, especially against the KB cell line, which may partly be ascribed to the greater leaving ability of the halogen ligands in the 8-dqmp complexes. It is known that the breaking of Pt,Pd–X bonds is important for the reaction mechanism in the cell and when the leaving ability of the halogen is lower, the activation reaction occurs to a minor extent [38]. The much higher initial decomposition temperature of 2-dqmp complexes, as well as the position of the palladium–halogen stretching vibrations at the higher frequencies than those obtained for the 8-dqmp complexes, confirm the assumption that the halogens are stronger bonded to the palladium atom in these complexes. Comparing the cytostatic effect between the ionic complexes it could be observed once again that the 2-derivatives display a much lower activity than the 8-derivatives.

Supplementary material

Tables of H atom coordinates, thermal parameters and remaining bond distances and angles are available from the authors on request.

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References

1 F. E. Beamisch and J. C. Van Loon, *Analysis of Noble Metals,* Academic Press, New York, 1977.
2 V. K. Gustin and T. R. Sweet, *Anal. Chem., 34* (1963) 44; H. Hashitani, H. Yoshida and M. Motojima, *Bunseki Kagaku, 18* (1969) 136.
3 S. Chaberck and A. E. Martell, *Organic Sequestering Agents,* Wiley, New York, 1959.
4 G. E. Hartwell, R. L. Lawrence and M. J. Smas, *Chem. Commun.,* (1970) 912; A. Deeming and I. P. Rothwell, *J. Chem. Soc., Chem. Commun.,* (1978) 344.
5 A. J. Deeming, I. P. Rothwell, M. B. Hursthouse and K. M. Malik, *J. Chem. Soc., Dalton Trans.,* (1980) 1974, and refs. therein.
6 C. G. Auklin and P. S. Pregosin, *J. Organomet. Chem., 243* (1983) 101.
7 H. Motschi, P. S. Pregosin and H. Ruegger, *J. Organomet. Chem., 193* (1980) 397.
8 F. Massarani, M. Pfeffer and G. Le Borgue, *Organometallics, 6* (1987) 2043.
9 P. Braunstein, J. Fischer, D. Matt and M. Pfeffer, *J. Am. Chem. Soc., 106* (1984) 410.
10 D. W. Evans, G. R. Baker and G. R. Newkome, *Coord. Chem. Rev., 93* (1989) 155, and refs. therein.
11 Lj. Tušek-Božić, I. Matijašić, G. Bocelli, G. Calestani, A. Furlani, V. Scarcia and A. Papaioannou, *J. Chem. Soc., Dalton Trans.,* (1991) 195.
12 V. Jagodić, B. Božić, Lj. Tušek-Božić and M. J. Herak, *J. Heterocycl. Chem., 17* (1980) 685.
13 M. Walker and D. Stuart, *Acta Crystallogr., Sect. A, 39* (1983) 158.
14 F. Ugozzoli, *Comput. Chem., 11* (1986) 109.
15 G. M. Sheldrik, *SHELX76,* program for crystal structure determination, University of Cambridge, U.K., 1976.
16 *International Tables for X-ray Crystallography,* Vol. IV, Kynoch Press, Birmingham ,U.K., 1974, p. 149. (Present distributor Kluwer, Dordrecht, The Netherlands.)
17 H. Eagle, *Proc. Soc. Exp. Biol. Med., 89* (1955) 362.
18 D. J. Hutchinson, O. L. Ittensohn, M. R. Bjerregaard, *Exp. Cell Res., 42* (1966) 157.
19 A. Furlani, V. Scarcia, G. Faraglia, L. Sinderllary, L. Trincia and M. Nicolini, *Eur. J. Med. Chem.–Chim. Ther., 21* (1986) 261; V. Cherchi, G. Faraglia, L. Sindellari, S. Sitran, A. Furlani and V. Scarcia, *Inorg. Chim. Acta, 155* (1989) 267.
20 H. Eagle, *Science, 130* (1959) 432.
21 G. E. Moore, R. E. Gerner and H. A. Franklin, *J. Am. Med. Assoc., 199* (1967) 519.
22 R. I. Geran, N. H. Greenberg, M. M. McDonald, A. M. Schumacher and B. J. Abbott, *Cancer Chemother. Rep., 3* (1972) 1.
23 R. J. Tallarida and R. B. Murray, *Manual of Pharmacological Calculations with Computer Programs,* Springer, New York, 1987.
24 P. R. Bontchev, M. Boneva, M. Arnaudov and V. I. Nefedov, *Inorg. Chim. Acta, 81* (1984) 75.
25 H. C. Freeman, in G. L. Eichhorn (ed.), *Inorganic Biochemistry,* Vol. 1, Elsevier, New York, 1973, Ch. 4.
26 E. W. Wilson, Jr and R. B. Martin, *Inorg. Chem., 9* (1970) 528.
27 W. J. Geary, *Coord. Chem. Rev., 7* (1971) 81.
28 J. R. Ferraro, *Low Frequency Vibrations of Inorganic and Coordination Compounds,* Plenum, New York, 1971.
29 K. Nakamoto, *Infrared and Raman Spectra of Inorganic and Coordination Compounds,* Wiley, New York, 1978.
30 M. I. Moreno-Vida, E. Colacio-Rodrigues, M. N. Moreno-Carretero, J. M. Salas-Peregrin, M. Simard and A. Beauchamp, *Inorg. Chim. Acta, 157* (1989) 201.
31 G. R. Newkome, D. K. Kohli an F. R. Fronzek, *J. Am. Chem. Soc., 104* (1982) 994; B. E. Mann, P. M. Bailey and P. M. Maitlis, *J. Am. Chem. Soc., 97* (1975) 1275.
32 R. D. Willett and J. J. Willett, *Acta Crystallogr., Sect. B, 33* (1977) 1639.
33 B. L. Kindberg and E. L. Amma, *Acta Crystallogr., Sect. B, 31* (1975) 1492.
34 H. Kiriyama, N. Matsushita and Y. Y. Yamagata, *Acta Crystallogr., Sect. C, 42* (1986) 1492.
35 Ya. A. Letuchij, I. P. Lavrentiev, M. L. Khidekel, O. N. Krasochka, D. D. Makitova and L. O. Atovmyan, *Izv. Akad. Nauk SSSR, Ser. Khim.,* (1978) 1002.
36 R. Uson, J. Fornies, M. Tomas, B. Menjon and A. J. Welch, *Organometallics, 7* (1988) 1318.
37 Y. Yokota, T. Tsukihara, K. I. Sakaguchi, Y. Hamada and I. Takeuchi, *Acta Crystallogr., Sect. C, 46* (1990) 167.
38 N. Farrell, *Transition Metal Complexes as Drugs and Chemotherapeutic Agents,* Kluwer, Dordrecht, The Netherlands, 1989.