# Tetra-2,3-pyrazinoporphyrazines with externally appended pyridine rings. 18. Physicochemical properties and photochemical behavior of new uncharged water soluble low symmetry macrocycles [{$Pd(OAc)_2$}$_3$($PtCl_2$)LM] (M = $Mg^{II}(H_2O)$, $Zn^{II}$, $Pd^{II}$)

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Dedication to Professor Claudio Ercolani on the Occasion of his 80th Birthday

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**ABSTRACT**: The synthesis and physicochemical characterization of a new class of low symmetry water soluble heteropentanuclear porphyrazine complexes are described. The investigated compounds, represented as [{$Pd(OAc)_2$}$_3$($PtCl_2$)LM]·x$H_2O$ where L = tetrakis-2,3-[5,6-di(2-pyridyl)pyrazino]porphyrazinato dianion, M = $Mg^{II}(H_2O)$, $Zn^{II}$ or $Pd^{II}$ and x = 3-8, were prepared under mild experimental conditions from the previously described heterobimetallic compounds [($PtCl_2$)LM]. Peripheral binding of one $PtCl_2$ and three $Pd(OAc)_2$ units in the new series of compounds occurs at the vicinal pyridine N atoms of each dipyridinopyrazine fragment via a "py–py" coordination. The newly synthesized porphyrazines were characterized by IR measurements in the solid state and UV-visible absorption spectroscopy in the low-donor nonaqueous solvents pyridine, dimethyl sulfoxide and dimethylformamide as well as in water, the enhanced solubility in this medium being due to the presence of the external $Pd(OAc)_2$ moieties. Data on the photosensitizing activity of the compounds for the generation of singlet oxygen, $^1O_2$, were also obtained in DMF and should be of interest to researchers in the area of photodynamic therapy.

**KEYWORDS:** Tetrapyrazinoporphyrazines, Uncharged low-symmentry water soluble heteropentanuclear complexes. UV-visible Spectra. Photoactivity for Singlet Oxygen Generation

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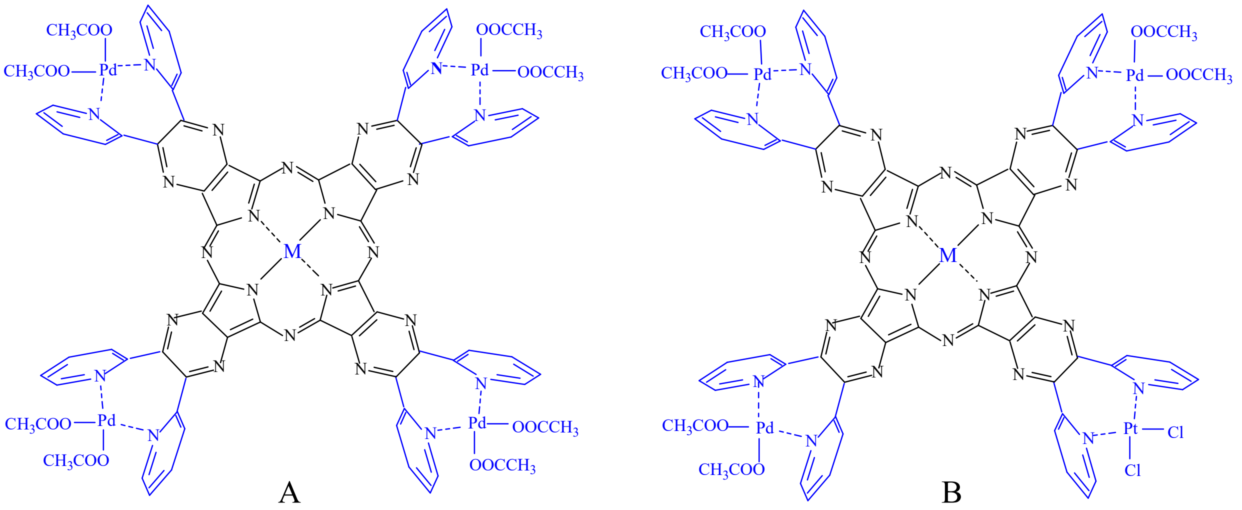
## INTRODUCTION

An important aspect which needs to be addressed when considering the use of phthalocyanines (tetraaza analogues of porphyrins) for practical and technological applications [1], especially in the area of biochemical and biomedical fields, is their very low or complete insolubility in water. Attempts have been made to obtain water-soluble derivatives of these compounds by introducing a variety of peripheral substituents which were selected on the basis of their potential use in a specific application. Phthalocyanines, as well as porphyrazines in general, have often been studied as photosensitizers (PS) in photodynamic therapy (PDT), one of the most widely expanding anticancer curative modalities [2]. This therapy requires the combined action of light, dioxygen and a photosensitizer which is able to absorb energy in the phototherapeutic window (600-850 nm) as well as release energy to dioxygen to generate singlet oxygen, $^1O_2$, the citotoxic agent in PDT. In connection with this therapeutic approach and other closely related fields of research, water solubility has generally been achieved by the synthesis of phthalocyanines having multiply charged cationic or anionic groups [3]. Water soluble sulfonated, carboxylated and octaphosphonilated phthalocyanines were in the past largely studied as anionic PSs in PDT [4]; parallel studies were also conducted with the use of cationic pyridinoporphyrazines [5] and pyrazinoporphyrazines [6]. A number of reports have confirmed the potential PS activity of phthalocyanine [7] and porphyrazine [8] derivatives, most of which have contained $Zn^{II}$ or $Mg^{II}$ central metal ions and, less frequently, $Pd^{II}$ or $Pt^{II}$. The selection of a specific metal ion was often based on data obtained in nonaqueous solvents (which was most often DMF) but it should be noted that aggregation quite often occurs in nonaqueous solvents as well as in water and this severely limits the reactivity of the phthalocyanines or porphyrazines, thus diminishing their role as photosensitizers in PDT in terms of the response of $^1O_2$ quantum yields ($\Phi_\Delta$).

We recently demonstrated that the $Zn^{II}$ octacationic $[(CH_3)_8LZn]^{8+}$ complex where L = tetrakis-2,3-[5,6-di(2-pyridyl)pyrazino]porphyrazinato dianion was able to act as a photosensitizer in PDT (DMF; $\Phi_\Delta$: 0.29 in DMF, 0.39 in DMF/HCl) [9]. The same octacation was also shown to bind to a G-quadruplex (G4) structure which is formed in the presence of $K^+$ by the guanine-rich telomeric sequence 5'-d[AGGG(TTAGGG)3]-3', 22mer [10]. Moreover, the related $Zn^{II}/Pt^{II}$ heterobimetallic porphyrazine hexacation $[(PtCl_2)(CH_3)_6LZn]^{6+}$, characterized by the presence of an external *cis*-platin-like functionality, was separately shown to exhibit excellent photosensitizer activity ($\Phi_\Delta$: 0.46 in DMF/HCl) [11]. This compound was also examined as to the type of interaction which occurs in water medium with the same G-quadruplex structure, under similar experimental conditions [12]. Despite the presence of "bothersome" aggregation (and formation of a monomer-dimer composite), it was established that the monomeric unit of both multicharged $Zn^{II}$ complexes forms a stable 2:1 complex/G4 sandwich-type complex in which G4 is stabilized in its "parallel form". Information could also be obtained that some type of interaction occurs between the monomer of each complex and a ds model of B-DNA [13]. Thus, the observed behaviour of these compounds all suggest that the multicationic species (salted by $I^-$ ions) have potential in terms of bi-multimodal anticancer activity.

In a recent study [14], the synthesis of a series of symmetrical homo/heteropentametallic porphyrazine macrocycles bearing four peripherally coordinated $Pd(OAc)_2$ units was reported. Structures of these compounds are shown in Scheme 1A and have the formula $[\{Pd(OAc)_2\}_4LM]\cdot xH_2O$, where L represents the tetrakis-2,3-[5,6-di(2-pyridyl)pyrazino]porphyrazinato dianion, M = $Mg^{II}(H_2O)$, $Zn^{II}$, $Cu^{II}$, $Co^{II}$, $Pd^{II}$ or $Pt^{II}$ and x = 11–22. These complexes represent a rare, if not unique, class of uncharged water soluble porphyrazine macrocycles which possess a "compact" pentanuclear molecular framework; their solubility in water was made possible by the four external acetate ($OAc^-$) groups, as is also clearly suggested by the fact that analogues of these compounds carrying externally $PdCl_2$ [8a] or $PtCl_2$ [15], units are completely insoluble in a water medium. Solid state properties for the series of compounds represented as $[\{Pd(OAc)_2\}_4LM]\cdot xH_2O$ were previously described [14] in a study which also included a characterization of their UV-visible spectral and electrochemical behavior in aqueous and nonaqueous solvents, as well as their photoactivity in DMF for the production of singlet oxygen, $^1O_2$.

In the present paper, we report the synthesis and physicochemical characterization of a new class of low symmetry (3:1) water soluble heteropentanuclear porphyrazine complexes having the formula $[\{Pd(OAc)_2)\}_3(PtCl_2)LM]\cdot xH_2O$, where (M = $Mg^{II}(H_2O)$, $Zn^{II}$ or $Pd^{II}$ and x = 13-22 (Scheme 1B). These compounds are related to the above cited symmetrical $[\{Pd(OAc)_2\}_4LM]\cdot xH_2O$ species in that they have three peripheral $Pd(OAc)_2$ units and one $PtCl_2$ unit, this latter group forming a *cis*-platin-like coordination site $N_{2(py)}PtCl_2$. It should be noted that the newly described series of porphyrazines represents a rare example of neutral low-symmetry macrocycles which exhibit relatively high solubility in water (ca. $10^{-3}$-$10^{-4}$ M), thus paralleling the previously reported behavior for the corresponding symmetrical species, $[(Pd(OAc)_2)_4LM]$ [14]. UV-visible spectral data for the triad of new complexes indicate that they are soluble in the polar non aqueous solvents pyridine, dimethylsulfoxide and dimethylformamide as well as water, where they exist in their monomeric form. Their photosensitizing activity for the generation of singlet oxygen was also examined in DMF and the estimated quantum yields ($\Phi_\Delta$) are presented and discussed. The presence of a *cis*-platin-like functionality in these new macrocycles opens up the possibility for their potential use in the area of bi/multimodal anticancer therapy.



**Scheme 1**. A) $[\{Pd(OAc)_2\}_4LM]$ and B) $[\{Pd(OAc)_2\}_3(PtCl_2) LM]$ (M = $Mg^{II}(H_2O)$, $Zn^{II}$, $Pd^{II}$) .

## EXPERIMENTAL

**Solvents and reagents**. Solvents and reagents were commercial materials and used as received unless otherwise indicated. Elemental analyses of samples of the bimetallic species $[(PtCl_2)LM]\cdot xH_2O$ (M = $Mg^{II}(H_2O)$, $Zn^{II}$, $Pd^{II}$; x = 3-10), prepared as described previously from the $[LM]\cdot xH_2O$ complexes [11], gave the following results:

**$[(PtCl_2)LMg(H_2O)]\cdot 3H_2O$** (yield: 84%). Calcd for $C_{64}H_{40}Cl_2MgN_{24}O_4Pt$: C, 51.26; H, 2.69; N.22.42, Pt, 13.01. Found: C, 51.59, H, 2.71; N, 22.23; Pt, 12.77%.

**$[(PtCl_2)LZn]\cdot 10H_2O$** (yield: 71%). Calcd for $C_{64}H_{52}Cl_2N_{24}O_{10}PtZn$: C, 46.63; H, 3.18; N, 20.39; Pt, 11.83. Found, C, 46.54; H, 2.51; N, 19.93; Pt, 12.59%.

**$[(PtCl_2)LPd]\cdot 9H_2O$** (yield: 49%). Found for $C_{64}H_{50}Cl_2N_{24}O_9PdPt$: C, 49.58; H, 3.01; N, 20.11; Pd, 6.37; Pt, 11.67: Found: C, 45.50; H, 2.67; N, 19.23; Pd, 6.92; Pt, 11.25%.

The triad of pentanuclear complexes, $[\{Pd(OAc)_2\}_3(PtCl_2)LM]\cdot xH_2O$, schematically shown in Scheme 1B, were obtained from the corresponding bimetallic species $[(PtCl_2)LM]\cdot xH_2O$ as follows:

**$[\{Pd(OAc)_2\}_3(PtCl_2)LMg(H_2O)]\cdot 9H_2O$**. A mixture of $[(PtCl_2)LMg(H_2O)]\cdot 3H_2O$ (20.5 mg 0.014 mmol) and $Pd(OAc)_2$ (10.7 mg, 0.048 mmol) was stirred for 3 h in DMSO (1 mL) at 50 °C. After cooling and addition of acetone (3 mL), the suspension was kept in a refrigerator for 24 h. The solid was then separated by centrifugation, washed with acetone and brought to constant weight under vacuum ($10^{-2}$ mmHg) (21.4 mg, yield 67%). Calcd for $[\{Pd(OAc)_2\}_3(PtCl_2)LMg(H_2O)]\cdot 9H_2O$, $C_{76}H_{70}Cl_2MgN_{24}O_{22}Pd_3Pt$. Calcd: C, 40.02; H, 3.09; N, 14.74; Pd, 14.00; Pt, 8.55. Found: C, 40.38; H, 2.94; N, 14.06; Pd, 14.35; Pt, 8.48%. IR (KBr, $cm^{-1}$): 3433 (very broad) vs, 1627 sh, 1599 s, 1560 vs, 1485 w-m, 1412 m, 1363 m, 1331 vw, 1296 vw, 1246 vs, 1190 m, 1163 w-m, 1122 w-m, 1107 w-m, 1092 w, 1034 vw, 1020 vw, 957 w-m, 777 w-m, 759 w-m, 710 s, 669 w, 656 w-m, 627 w, 588 vw, 565 vw, 557 w, 521 w, 494 w-m, 479 w-m, 465 w-m, 447 w-m, 440 w, 434 w, 418 w, 393 w, 370 w, 351 s, 336 s (split $\nu_{Pt-Cl}$). TGA shows a loss of 10 water molecules in the range of 25-130 °C (calcd. 7.90%; found 7.77%).

**$[\{Pd(OAc)_2\}_3(PtCl_2)LZn]\cdot 21H_2O$**. A mixture of $[(PtCl_2)LZn]\cdot 10H_2O$ (21.1 mg 0.013 mmol) and $Pd(OAc)_2$ (10.5 mg, 0.047 mmol) was stirred for 3 h in DMSO (1 mL) at 50 °C. After cooling, the suspension was added of acetone (3 mL) and kept in a refrigerator for 24 h. The solid was then separated by centrifugation, washed with acetone and brought to constant weight under vacuum ($10^{-2}$ mmHg) (24.1 mg, yield 75%). Calcd for $[\{Pd(OAc)_2\}_3(PtCl_2)LZn]\cdot 21H_2O$, $C_{76}H_{92}Cl_2N_{24}O_{33}Pd_3PtZn$: C, 36.22; H, 3.68; N, 13.34; Pd, 12.67; Pt, 7.74. Found: C, 36.16; H, 2.91; N, 12.75; Pd, 12.58; Pt, 7.42%. IR (KBr, $cm^{-1}$): :3400 (very broad) s, 1678 w-m, 1627 sh, 1599 vs, 1568 s, 1485 m, 1400 w-m, 1361 s, 1327 w-m, 1292 vw, 1244 vs, 1190 m-s, 1161 m, 1122 m, 1107 m, 1093 w-m, 1034 w, 1020 w, 957 s, 856 vw, 823 vw, 775 m-s, 760 m, 710 vs, 656 m, 631 vw, 557 w-m, 519 vw, 494 w, 468 vw, 463 vw, 442 w, 434 w, 415 w, 368 w, 351 m, 345 w (split $\nu_{Pt-Cl}$).

**Synthesis of $[\{Pd(OAc)_2\}_3(PtCl_2)LPd]\cdot 22H_2O$**. A mixture of $[(PtCl_2)LPd]\cdot 9H_2O$ (15.0 mg 0.009 mmol) and $Pd(OAc)_2$ (7.1 mg, 0.031 mmol) was stirred for 3 h in DMSO (1 mL) at 50 °C.After cooling, the suspension was added of acetone (3 mL) and kept in a refrigerator for 24 h. The solid was then separated by centrifugation, washed with acetone and brought to constant weight under vacuum ($10^{-2}$ mmHg) (9.8 mg, yield 42%). Calcd for $[\{Pd(OAc)_2\}_3(PtCl_2)LPd]\cdot 22H_2O$, $C_{76}H_{94}Cl_2N_{24}O_{34}Pd_4Pt$: C, 35.39; H, 3.67; N, 13.03; Pd, 16.50; Pt, 7.56; Found: C, 34.90; H, 3.30; N, 12.13; Pd, 15.94; Pt, 6.64%. IR (KBr, $cm^{-1}$): 3410 (very broad) m, 1627 sh, 1599 vs, 1560 s, 1520 w, 1485 m, 1400 w, 1361 s, 1333 m, 1248 vs, 1192 m-s, 1163 w-m, 1132 s, 1036 w, 970 m-s, 881 w, 812 w, 777 m-s, 756 m, 715 s, 694 w-m, 658 m, 621 vw, 615 vw, 557 w-m, 525 vw, 505 w-m, 472 vw, 467 vw, 438 w, 418 w, 395 m, 368 m, 355 m, 342 m (split $\nu_{Pt-Cl}$).

**Conversion of $[\{Pd(OAc)_2\}_3(PtCl_2)LMg(H_2O)]$ to $[(PdCl_2)_3(PtCl_2)LMg(H_2O)]$**. A water solution (4 mL) of the $Mg^{II}$ complex $[\{Pd(OAc)_2\}_3 (PtCl_2) LMg(H_2O)]\cdot 9H_2O$ (9.0 mg) was added of 0.2 mL of HCl 0.2 M ([HCl] $\cong 10^{-2}$ M) and stirred at room temperature for 24 h, during which time the progressive formation of a precipitate was observed. At the end of the reaction, the solid was separated from the colorless aqueous solution by centrifugation, washed with water until neutrality and brought to constant weight under vacuum ($10^{-2}$ mmHg). Calcd for $[(PdCl_2)_3(PtCl_2)LMg(H_2O)]\cdot 8H_2O$, $C_{64}H_{50}Cl_8MgN_{24}O_5Pd_3Pt$: C, 36.23; H, 2.38; N, 15.85. Found: C, 36.62; H, 2.85; N, 15.48%.

**Conversion of $[\{Pd(OAc)_2\}_3(PtCl_2)LPd]$ to $[(PdCl_2)_3(PtCl_2)LPd]$**. The complex $[\{Pd(OAc)_2\}_3(PtCl_2)LPd]\cdot 22H_2O$ (8.0 mg) was dissolved in 4 mL of water containing 0.2 mL of added HCl 0.2 M ([HCl] $\cong 10^{-2}$ M) and the solution was stirred for 24 h at room temperature. During the reaction, the progressive formation of a precipitate was observed. At the end of the reaction the solid was separated from the colorless aqueous solution by centrifugation, washed with water until neutrality and brought to constant weight under vacuum ($10^{-2}$ mmHg). Calcd for $[(PdCl_2)_3(PtCl_2)LPd]\cdot 5H_2O$, $C_{64}H_{42}Cl_8N_{24}O_5Pd_4Pt$: C, 36.06; H, 1.99; N, 15.77. Found: C, 36.55; H, 2.52; N, 14.99%.

**Singlet oxygen quantum yield measurements**. Measurements of singlet oxygen quantum yield ($\Phi_\Delta$) were carried out in DMF and/or DMF/HCl ([HCl] $\cong 1\text{x}10^{-4}$ M) by a modified procedure [16] based on an absolute method earlier reported in the literature [17]. 1,3-Diphenylisobenzofuran (DPBF) was used as the scavenger of $^1O_2$. Solutions of the complexes (ca. $10^{-6}$-$10^{-5}$ M) and DPBF (ca. $5\text{x}10^{-5}$ M) in DMF and/or DMF/HCl were irradiated with monochromatic light (Premier LC Lasers/HG Lens, Global Laser). The irradiation wavelength ($\lambda_{irr}$ = 635 or 660 nm) was close to the maximum of the Q-band absorption peaks for the examined species. The light intensity was set to 0.300 mW and accurately measured with a radiometer (ILT 1400A/SEL100/F/QNDS2, International Light Technologies).

The $\Phi_\Delta$ values were obtained from the quantum yield of the photoreaction ($\Phi_{DPBF}$) calculated with respect to different concentrations of DPBF, on the basis of Equation 1

$$\frac{1}{\Phi_{DPBF}} = \frac{1}{\Phi_\Delta} + \frac{k_d}{k_r}\frac{1}{\Phi_\Delta}\frac{1}{[DPBF]} \qquad (1)$$

where $k_d$ is the decay rate constant of $^1O_2$ in the solvent and $k_r$ is the rate constant of the reaction of DPBF with $^1O_2$. The $1/\Phi_\Delta$ value was obtained as the intercept of the Stern-Volmer plot ($1/\Phi_{DPBF}$ vs 1/[DPBF]).

**Other Physical Measurements.** IR spectra of the solid materials were recorded on a Varian 660-IR FT-IR spectrometer by using KBr pellets in the range 4000-400 cm$^{-1}$ and nujol mulls between CsI disks in the range 400-300 cm$^{-1}$. UV-visible solution spectra were recorded with a Varian Cary 5E spectrometer using 1-cm quartz cuvettes. Thermogravimetric analyses (TGA) were performed on a Stanton Redcroft model STA-781 analyzer under a $N_2$ atmosphere (0.5 L/min). Elemental analyses for C, H, and N were provided by the "Servizio di Microanalisi" at the Dipartimento di Chimica, Università "Sapienza" (Rome) on an EA 1110 CHNS-O instrument. The ICP-PLASMA analysis of palladium and platinum was performed on a Varian Vista MPX CCD simultaneous ICP-OES.

## RESULTS AND DISCUSSION

### Synthetic Aspects and Properties

As reported in the Experimental Section, the complexes $[\{Pd(OAc)_2\}_3(PtCl_2)LM]$ where M = $Mg^{II}(H_2O)$, $Zn^{II}$ or $Pd^{II}$ were synthesized under mild experimental conditions by reaction of $Pd(OAc)_2$ with the respective bimetallic $[(PtCl_2)LM]$ compound in DMSO at 50 °C for 3 h. The final products were obtained as air stable hydrated dark-green solid species in fairly good yield (65-75%) for the Mg(II) and Zn(II) derivatives, but the yield was lower (42%) for the $Pd^{II}$ complex.

Support for coordination of the $PtCl_2$ and $Pd(OAc)_2$ units to the N atoms of the peripheral vicinal 2-pyridyl rings ("py-py" coordination) with formation of $N_{2(py)}PtCl_2$ and $N_{2(py)}Pd(OAc)_2$ coordination sites is given by published information on previously characterized $[(CN)_2Py_2PyzMCl_2]$ (M = $Pd^{II}$, $Pt^{II}$), whose structure was confirmed by X-ray crystallography [8a,18], as well as by $^1H$-$^{13}C$ NMR data on both a series of heterobimetallic pyrazinoporphyrazine macrocycles $[(PtCl_2)LM]$ ($Mg^{II}(H_2O)$, $Zn^{II}$, $Pd^{II}$) [11] and pentanuclear $[(PtCl_2)_4LPt]$ [15]. The same type of coordination was assigned to the $Pd(OAc)_2$ units of the symmetrical $[\{Pd(OAc)_2\}_4LM]$ derivatives, as confirmed by $^1H$–$^1H$ COSY and $^1H$–$^{13}C$ HSQC NMR experiments on $[\{Pd(OAc)_2\}_4LZn]$ in DMF-$d_7$ where the prevalent conformational isomer which was synthesized in DMSO has all four external $N_{2(py)}Pd(OAc)_2$ coordination sites oriented on the same side of the plane of the pyrazinoporphyrazine framework [14]. This assignment of orientation agrees with previous findings for analogs of this compound carrying externally bound $PdCl_2$ units [8a,19]. The strict relationship of both $PdCl_2$ and $Pd(OAc)_2$ in terms of peripheral "py-py" coordination is in keeping with the facile conversion of $[\{Pd(OAc)_2\}_3(PtCl_2)LM]$ to $[(PdCl_2)_3(PtCl_2)LM]$ (M = $Mg^{II}(H_2O)$, $Pd^{II}$), analogous to what was earlier reported for the symmetrical $[\{Pd(OAc)_2\}_4LZn]$ complex in its transformation to $[\{PdCl_2\}_4LZn]$ [14].

Retention of clathrated water molecules is a common feature of porphyrazine macrocycles in the solid state and has been known since Linstead's early work [20] more than six decades ago. For the currently examined compounds, the amount of water content after stabilization in air (x = 13-22) is higher than that normally found for the related monometallic complexes [LM]·x$H_2O$ (x = 3-8) [21,8a,15], for the parent dinuclear [($PtCl_2$)LM]·$H_2O$ (x = 3-10) [11] or for the pentanuclear species [$(PdCl_2)_4$LM]·x$H_2O$ (x = 1-14) [8a,19]. It is, however, similar to what was observed for the corresponding symmetrical species [$\{Pd(OAc)_2\}_4$LM] (x = 11-22) [14]. This high value of $H_2O$ content for compounds in the current study can be rationalized by the presence of the acetate groups which are able to hydrogen bond with water molecules and the numerous attracting N atoms. Clathrated water is normally eliminated from the compounds by heating under vacuum at mild temperatures (< 100°C), but water is again, at least partially, recovered by exposure of the porphyrazines to the air, as verified in the present study. In any event, the number of retained water molecules in the examined compounds was variable, the exact number depending on the specific prepared batch of the compound. Thermogravimetric analysis shows that all of the synthesized metal complexes, once desolvated, were stable under an inert atmosphere up to temperatures of ca. 200 °C or slightly higher. Figure 1 shows a thermogravimetric analysis curve for the $Mg^{II}$ complex, [$\{Pd(OAc)_2\}_3(PtCl_2)$ LMg($H_2O$)]·9$H_2O$, which exhibits a weight loss of 7.7% over a range of temperature changes from 25-130 °C, this value of weight decrease corresponding to the loss of ca. 10 water molecules (which would give a calculated weight loss of 7.90%).

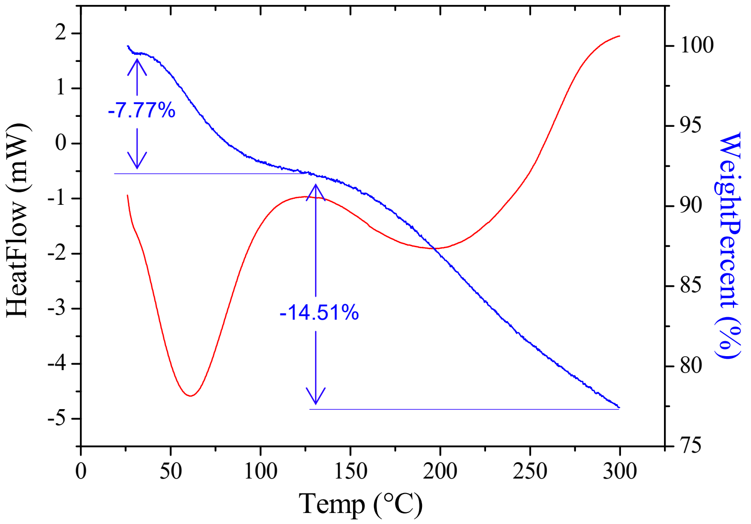


**Fig. 1.** . Thermogravimetric analysis of [$\{Pd(OAc)_2\}_3(PtCl_2)LMg(H_2O)$]·9$H_2O$.

Since chlatrated water was shown to not significantly influence the behavior of the porphyrazine macrocycles, the currently investigated complexes are formulated without external water molecules and water will be given in the formula only if it is important for quantitative aspects or if it is bound to the central metal ion, as occurs, for instance, in the case of the $Mg^{II}$ derivative which contains one water molecule directly ligated to the central metal ion.

Formulation of the $Mg^{II}$ porphyrazine as containing one axially coordinated $H_2O$ molecule is in line with similar formulations for the mono-, bi- and pentanuclear $Mg^{II}$ derivatives of the same macrocycle [21,11,19,9]. The presence of a bound water molecule in these species is difficult to prove directly, since attempts to obtain single crystals suitable for X-ray analysis were unsuccessful. Nevertheless, the presence of water is implied by the fact that the $Mg^{II}(H_2O)$ moiety is commonly observed in a number of $Mg^{II}$ porphyrazine macrocycles. Examples of this are given by the structures of (aquo)(octakis(methylthio)porphyrazinato)magnesium(II), [(omtp)Mg($H_2O$)] [22] and [PcMg($H_2O$)]$_2$·py [23] (Pc = phthalocyaninatodianion, $C_{32}H_{16}N_8^{2-}$). Additional support for the mono-aquo moiety Mg($H_2O$) is given by its presence in $Mg^{II}$ complexes of the tetrakis(thia/selenodiazole)porphyrazines [24] and tetrakis-2,3-(5,7-diphenyl-6*H*-diazepino)porphyrazine [25]. Interestingly, a $Mg^{II}$ bis-hydrated, $[PcMg(H_2O)_2]$ species has also been reported [26] and a dimerized monohydrate of a low-symmetry porphyrazine macrocycle has been structurally elucidated [27], both examples again proving the tendency of $Mg^{II}$ to coordinate water molecules when present in the cavity of a porphyrazine macrocycle.

The IR spectrum of $[\{Pd(OAc)_2\}_3(PtCl_2)LPd]$, is illustrated in Figure 2C over the wavelength range of 1800-400 cm$^{-1}$, together with the spectrum of the corresponding monometallic [LPd] derivative (Figure 2A) and the bimetallic complex $[(PtCl_2)LPd]$ (Figure 2B).

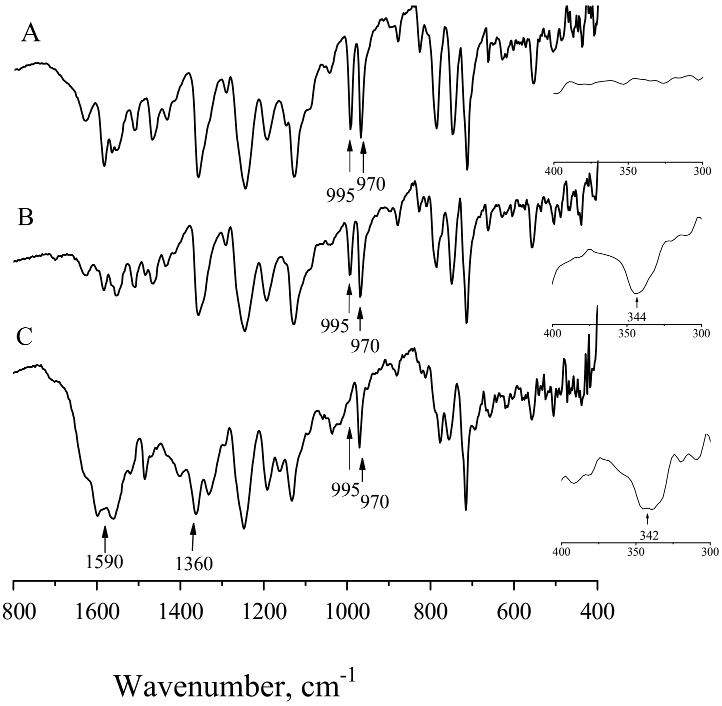


**Fig. 2**. IR spectra in KBr of (A) [LPd], (B) $[(PtCl_2)LPd]$ and (C) $[\{Pd(OAc)_2\}_3(PtCl_2)LPd]$.

The spectrum of $[\{Pd(OAc)_2\}_3(PtCl_2)LPd]$ shows a medium-to-low intensity absorption at 970 cm$^1$, a band also present but with higher intensity in spectra of the parent compounds, $[(PtCl_2)LPd]$ and [LPd]. A conversion of the monometallic [LPd] derivative to the mono-platinated $[(PtCl_2)LPd]$ complex results in a decreased intensity of the absorption at 995 cm$^{-1}$ and this band completely disappears upon going to the pentanuclear $[\{Pd(OAc)_2\}_3(PtCl_2)LPd]$ species. This absorption can then be used as a reference peak to monitor formation of the pentanuclear complex. The spectrum of $[\{Pd(OAc)_2\}_3(PtCl_2)LPd]$ (Figure 2C) also shows a strong broad peak centered at ca. 1590 cm$^{-1}$ and a peak of lower intensity at ca. 1360 cm$^{-1}$. Both absorptions are due to the presence of the $CH_3COO^-$ groups and assigned as ν(C=O) and ν (C-O), respectively. In addition, a split absorption is seen in the range of 400-300 cm$^{-1}$ for the $PtCl_2$ unit (see inset in Figure 2) and is due to stretching of the Pt-Cl bond. Finally, a broad absorption is present in the range of 3000-3500 cm$^{-1}$ (not shown in Figure 2) and is due to the presence of clathrated water.

**UV-Visible Spectra**. The $[\{Pd(OAc)_2\}_3(PtCl_2)LM]$ complexes are all insoluble in the non-donor solvents $CH_2Cl_2$ and $CHCl_3$ and only very slightly soluble in the polar solvents pyridine, DMSO and DMF ($c = 10^{-4} \div 10^{-5}$ M). However, despite the low solubility in DMSO and pyridine, the compounds are generally stable in these two solvents as indicated by the presence of an unchanged UV-visible spectrum over a period of 24-48 h. Interestingly, all three metal complexes

($Mg^{II}$, $Zn^{II}$ and $Pd^{II}$) exhibit good solubility in water, with relatively high concentrations obtained for the saturated solutions ($c \cong 10^{-4}$ M). This level of water solubility is similar to what was earlier reported for the analogous symmetrical series of $[\{Pd(OAc)_2\}_4LM]$ [14] compounds and is rare, especially if account is taken of the fact that the complexes are neutral species which exhibit a more "compact" structure as compared to previously characterized porphyrazines containing peripherally long branched chains [28].

The UV-visible spectra of the $[\{Pd(OAc)_2\}_3(PtCl_2)LM]$ complexes all have similar clean profiles in pyridine, DMSO and DMF, with well-defined absorptions in the Soret region of the spectrum (340-450 nm) and sharp narrow Q bands in the region of 620-670 nm, these latter bands being accompanied by vibrational peaks at higher energies. The UV-vis spectra clearly indicate that the compounds are in their monomeric form (see a representative spectrum of the $Mg^{II}$ complex in DMF and $H_2O$ in Figure 3), approaching closely spectra of related monomeric phthalocyanine or porphyrazine macrocycles, where the main absorption peaks are attributable to ligand-centered $\pi$ - $\pi^*$ transitions.

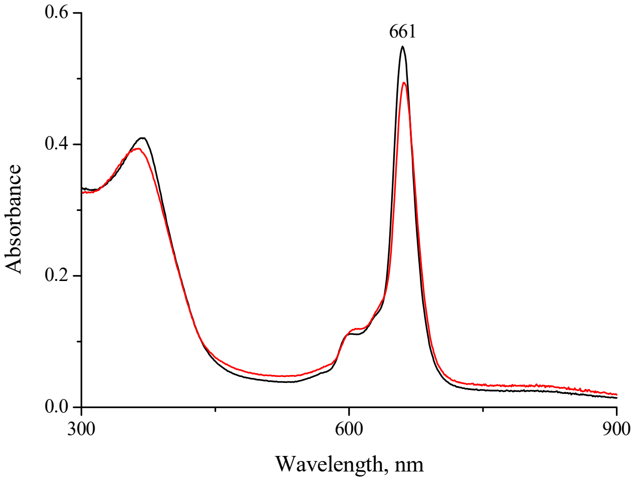


**Fig. 3**. UV-visible spectra of $[\{Pd(OAc)_2\}_3(PtCl_2)\ LMg(H_2O)]$ in DMF (black line) and $H_2O$ (red line).

The currently investigated compounds remain stable and unchanged in pyridine solutions for 2-4 days. Worthy of notice, this behavior duplicates what was observed in the same solvent for the symmetrical parent complexes of $[\{Pd(OAc)_2\}_4LM]$, but it is different from that of the analogous complexes carrying externally bound $PdCl_2$ groups, i.e. $[(PdCl_2)_4LM]$, where a dissociation of the bound external $PdCl_2$ units occurs immediately after dissolution in pyridine, with a consequent formation of the corresponding [LM] species [8a,19]. Moreover, it was observed that among the currently investigated complexes, the one carrying the central $Pd^{II}$ ion, tends to undergo a one-electron reduction to its corresponding -1 charged species in DMF at a concentration of $c \cong 10^{-5}$ M or lower (see Figure 4). This behavior parallels what was previously reported for related $[\{Pd(OAc)_2\}_4LM]$ (M = $Zn^{II}$, $Pd^{II}$, $Pt^{II}$) [14] and $[(PdCl_2)_4LM]$ species (M = $Pd^{II}$, $Co^{II}$, $Cu^{II}$) [8a,19]. It was verified that a reducing agent (dimethylamine?), present in trace amounts in DMF (ca. $10^{-5}$ M) is able to convert the neutral compounds to their one-electron reduced state. Reoxidation of the generated monoanions to their neutral form could be accomplished in DMF by adding a slight excess of HCl to the solution ($c = 1 \times 10^{-4}$ M, which is approximately ten times the concentration of the macrocycle). Moreover, dissolution of $[\{Pd(OAc)_2\}_3(PtCl_2)LPd]$ in preacidified DMF ($[HCl] = 1 \times 10^{-4}$ M) gives a well defined spectrum for the monomeric species in its neutral and unreduced form, thus indicating that the added HCl prevents reduction.

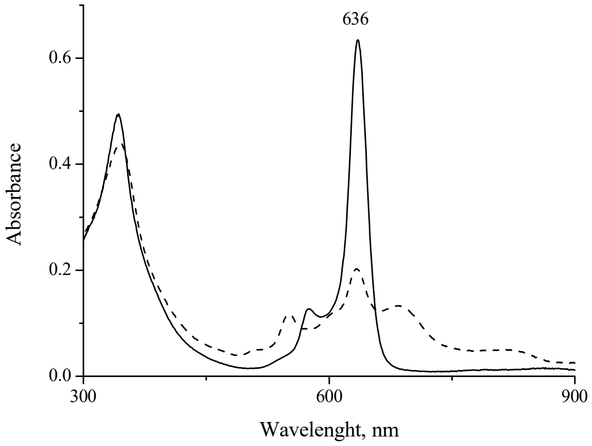


**Fig. 4.** UV-visible spectrum of [{Pd(OAc)$_2$}$_3$(PtCl$_2$) LPd] in DMF before (dashed line) and after addition of HCl to solution (solid line).

**Table 1**. Quantitative UV-visible spectral data of the complexes [{Pd(OAc)$_2$}$_3$(PtCl$_2$)LM] (chlatrated water taken into account) and the related species [{Pd(OAc)$_2$}$_4$LM] (M = Mg$^{II}$(H$_2$O), Zn$^{II}$, Pd$^{II}$) in different solvents.

| **Complex** | **Solvent** | **Soret band** | **Q-band region** | | | **ref.** |
|---|---|---|---|---|---|---|
| | | **λ, nm (log ε)** | | | | |
| [{Pd(OAc)$_2$}$_3$(PtCl$_2$)LMg(H$_2$O)] | Py | 372 (4.83) | 601 (4.25) | 637sh (4.40) | 661 (4.98) | tw |
| | DMSO | 370 (4.74) | 600 (4.18) | 640sh (4.27) | 660 (4.86) | tw |
| | DMF | 366 (4.79) | 603 (4.25) | 632sh (4.34) | 661 (4.91) | tw |
| | H$_2$O | 364 (4.79) | 604 (4.27) | 638sh (4.41) | 661 (4.89) | tw |
| [{Pd(OAc)$_2$}$_4$LMg(H$_2$O)] | Py | 372 (5.02) | 599 (4.40) | | 660 (5.13) | 14 |
| | DMSO | 372 (4.91) | 599 (4.42) | 632sh (4.51) | 661 (5.31) | 14 |
| | DMF | 369 (4.87) | 598 (4.33) | | 660 (5.05) | 14 |
| | H$_2$O | 367 (4.91) | 603 (4.43) | | 658 (5.11) | 14 |
| [{Pd(OAc)$_2$}$_3$(PtCl$_2$)LZn] | Py | 376 (4.84) | 599 (4.30) | 630sh (4.34) | 659 (5.05) | tw |
| | DMSO | 371 (4.78) | 602 (4.28) | | 661 (4.98) | tw |
| | DMF | 373 (4.80) | 598 (4.28) | | 659 (5.03) | tw |
| | H$_2$O | 368 (4.49) | 608 (4.11) | | 664 (4.55) | tw |
| [{Pd(OAc)$_2$}$_4$LZn] | Py | 375 (4.93) | 596 (4.35) | 628sh (4.36) | 658 (5.20) | 14 |
| | DMSO | 371 (4.85) | 599 (4.34) | | 661 (5.03) | 14 |
| | DMF/HCl | 377 (4.87) | 600 (4.38) | 631sh (4.41) | 662 (5.26) | 14 |
| | H$_2$O | 367 (4.95) | 597 (4.38) | | 656 (5.17) | 14 |
| [{Pd(OAc)$_2$}$_3$(PtCl$_2$)LPd] | Py | 341 (5.06) | 573 (4.45) | 611sh (4.49) | 633 (5.19) | tw |
| | DMSO | 343 (5.11) | 577 (4.50) | 620sh (4.79) | 636 (5.16) | tw |
| | DMF/HCl | 343 (5.06) | 576 (4.48) | | 636 (5.20) | tw |
| | H$_2$O | 342 (4.89) | 581 (4.35) | | 632 (4.91) | tw |
| [{Pd(OAc)$_2$}$_4$LPd] | Py | 341 (4.89) | 572 (4.23) | | 636 (4.86) | 14 |
| | DMSO | 342 (4.94) | 576 (4.23) | 606sh (4.28) | 636 (4.99) | 14 |
| | DMF/HCl | 341 (4.99) | 575 (4.29) | | 632 (4.94) | 14 |
| | H$_2$O | 342 (4.97) | 577 (4.27) | | 638 (4.85) | 14 |

Quantitative spectral data of the examined [$\{Pd(OAc)_2\}_3(PtCl_2)LM$] compounds is summarized in Table 1, together with data for the corresponding [$\{Pd(OAc)_2\}_4LM$] species (M = $Mg^{II}(H_2O)$, $Zn^{II}$, $Pd^{II}$). The spectral data of the [$\{Pd(OAc)_2\}_3(PtCl_2)LM$] compounds in nonaqueous solvents deserves special attention. In general, only a small solvent effect is observed on the position of the Soret and Q bands but there is a marked change in the spectrum with changes of the central metal ion. For example, as seen in Table 1, the Q-band maximum is located in the range of 632-635 nm for the $Pd^{II}$ complex but this band shifts to 659-664 nm for the complexes with $Mg^{II}$ or $Zn^{II}$ central metal ions; a parallel shift of the B-band is observed upon going from the $Pd^{II}$ complex (341-343 nm) to the $Mg^{II}$ or $Zn^{II}$ complexes (366-376 nm). A comparable dependence on the central metal ion is also exhibited by the parent monometallic [LM] [15,21] derivatives, the analogous monoplatinated [$(PtCl_2)LM$] [8a,19] complexes and the symmetrical pentanuclear [$\{Pd(OAc)_2\}_4LM$] analogues [14].

Noteworthy, the position of the Q band is slightly red-shifted upon going from the LM series of compounds to compounds in the corresponding [$\{Pd(OAc)_2\}_3(PtCl_2)LM$] series of porphyrazines. This result is similar to what was earlier observed when comparing the spectral properties of [LM] with that of the related [$\{Pd(OAc)_2\}_4LM$] [14] and [$(PdCl_2)_4LM$] compounds [8a,19]. This shift in the spectral absorption bands results from the electron withdrawing effect caused by external coordination of the $Pd(OAc)_2$, $PtCl_2$ or $PdCl_2$ units on the conjugated macrocyclic framework. This effect is especially remarkable, if account is taken of the fact that coordination of $Pd^{II}$ and $Pt^{II}$ occurs at the extreme periphery of the macrocycle, with the $N_{2(py)}Pd(OAc)_2$, $N_{2(py)}PtCl_2$ or $N_{2(py)}PdCl_2$ coordination sites oriented almost perpendicular to the plane of the central tetrapyrazinoporphyrazine core, as previously proposed for the symmetrical [$\{Pd(OAc)_2\}_4LM$] derivatives [14] as well as for the entire series of [$(PdCl_2)_4LM$] [8a,19] and [$(PtCl_2)_4LM$] complexes [9,15].

As indicated above, the currently described class of neutral low symmetry pentanuclear porphyrazine macrocycles exhibits good solubility in water due to the presence of the externally coordinated $Pd^{II}$-acetate groups, and this water solubility is often higher than that observed in the nonaqueous solvents, pyridine, DMSO or DMF. This result is in line with findings for the symmetrical analogues [$\{Pd(OAc)_2\}_4LM$] [14]. Practically no changes of the spectral band positions are observed for these compounds in water as compared to the peak positions of these absorptions in the nonaqueous solvents (Table 1). However, the effect of the central metal ion has a significant influence on the UV-vis spectra, in a way similar to that described above when the measurements were carried out in nonaqueous solvents. One example of this is seen by comparing the changes in wavelength upon going from the $Pd^{II}$ complex (Q and B bands at 632 nm and 342 nm, respectively) to the $Mg^{II}$ or $Zn^{II}$ complexes (Q-bands at 661/664 nm and B-band at 364/368 nm). The compounds are stable in the water and no significant changes in the position or intensity of the spectral bands was seen as a function of time (over a period of hours). Also, it should again be pointed out that the present triad of [$\{Pd(OAc)_2\}_3(PtCl_2)LM$] complexes exhibits solution UV-visible spectra in water which are typical of monomeric species (see Figure 3 for spectrum of the $Mg^{II}$ complex). This was also observed for the symmetrical parent compound [$\{Pd(OAc)_2\}_4LM$], the monomeric form of the macrocycle persisting even at the highest examined concentrations (saturated solutions). This contrasts with what was earlier reported for the $Zn^{II}$ octacationic [10] and the hexacationic species [11] sharing the same central pyrazinoporphyrazine macrocycle, where the spectra in water are characterized by the presence of aggregation, proven by the appearance of two peaks of comparable intensity in the Q-band region, the peak at lower wavelength belonging to the aggregated form of the compound [10,11].

**Singlet Oxygen Quantum Yield Measurements**. The involvement of porphyrins and phthalocyanines [2d,e,7] as photosensitizers for the generation of singlet oxygen is of expanding interest for studies in the area of photodynamic therapy, whereas porphyrazines, in general, have so far received only limited attention in this area, pertinent work having being mostly devoted to the photoactivity of seco- [29], benzonaphtho- [30], and pyrazinoporphyrazines [8b,9,10,15,31]. The efficiency of a macrocyclic photosensitizer depends upon its tendency to undergo excitation, upon irradiation, from the ground state $S_0$ to the triplet state $T_1$ with a high quantum yield and to also have an adequate $T_1$ energy and lifetime, to allow for a proper energy transfer to dioxygen for the process $^3O_2 \rightarrow {}^1O_2$ to occur; complementary effects are due to the recovery of the ground states from the $S_1$ and $T_1$ excited states. The type of central metal ion in the macrocycle can strongly influence this process and, in this regard, it is known that closed shell metal ions like $Zn^{II}$ and $Mg^{II}$ lead to high photoactivity, as do, in some cases open shell diamagnetic $d^8$ metal centers like $Pd^{II}$ and $Pt^{II}$.

In the present study, results are presented on the photosensitizing activity of $[\{Pd(OAc)_2\}_3(PtCl_2)LM]$ for the generation of singlet oxygen. Singlet oxygen quantum yields ($\Phi_\Delta$) were obtained in DMF ([complex] ≅ $10^{-5}$ M) and/or in DMF acidified with HCl (DMF/HCl; [HCl] = $10^{-4}$ M) by the above mentioned absolute method [16,17], using a laser source at values close to the maxima of the Q-band absorption peaks for the corresponding $Zn^{II}$ and $Mg^{II}$ complexes (in this case at 600 nm) and at 635 nm for the $Pd^{II}$ species. UV-visible spectral features and Stern-Volmer plot from a typical experiment used to calculate the $\Phi_\Delta$ values of the sensitizers according to Eq. 1 (see Experimental section), are shown in Figure 5 for the $Zn^{II}$ derivative. The inset of the figure illustrates the absorption decay recorded at 414 nm for the $^1O_2$ scavenger, DPBF, during irradiation. Table 2 lists the singlet oxygen quantum yields ($\Phi_\Delta$) of $[\{Pd(OAc)_2\}_3(PtCl_2)LM]$. Data for the related $[\{Pd(OAc)_2\}_4LM]$ complexes [14] are also included in this table for comparison purposes.

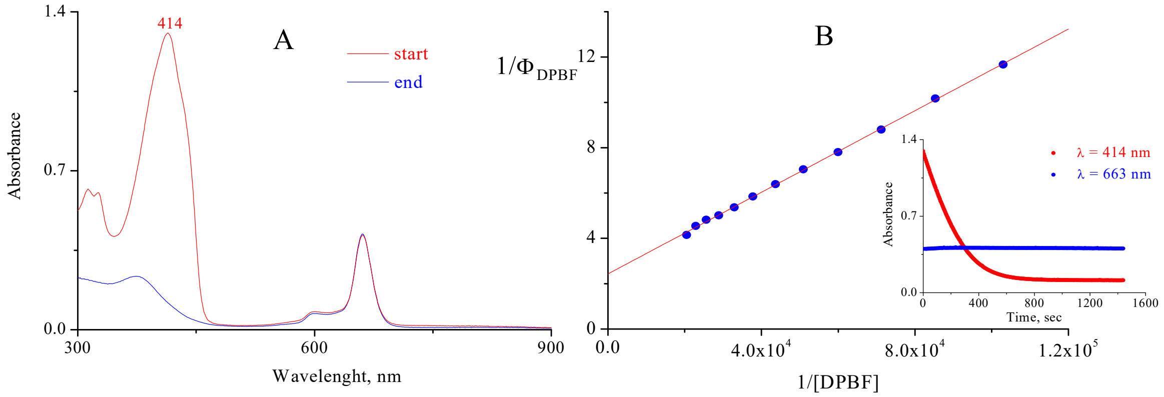


**Fig. 5**. **A)** UV-visible spectra of a DMF solution containing $[\{Pd(OAc)_2\}_3(PtCl_2)LZn]$ and DPBF before (red line) and after (blue line) laser irradiation and B) Stern-Volmer data analysis of the DPBF photooxidation (shown in inset).

In order to prevent the one-electron reduction of $[\{Pd(OAc)_2\}_3(PtCl_2)LPd]$ in DMF, the $\Phi_\Delta$ values of this compound were measured in preacidified DMF. For the $Zn^{II}$ and $Mg^{II}$ complexes, which were stable in DMF, measurements of $\Phi_\Delta$ were made in both DMF and DMF/HCl. All of the complexes in DMF and/or DMF/HCl were generally stable in solution under irradiation.

**Table 2.** Singlet oxygen quantum yields ($\Phi_\Delta$) of [$\{Pd(OAc)_2\}_3(PtCl_2)LM$] and the related species [$\{Pd(OAc)_2\}_4LM$] (M = $Zn^{II}$, $Mg^{II}(H_2O)$, $Pd^{II}$) in DMF and/or DMF preacidified with HCl ($1\times10^{-4}$ M).

| Photosensitizer | HCl [M] | $\lambda_{max}$ (Q band) [nm] | Singlet oxygen | | Ref. |
|---|---|---|---|---|---|
| | | | $\lambda_{irr}$[nm] | $\Phi_\Delta$ [a] | |
| [$\{Pd(OAc)_2\}_3(PtCl_2)LZn$] | 0 | 661 | 660 | 0.40 | tw |
| | 1 x $10^{-4}$ | 663 | 660 | 0.53 | tw |
| [$\{Pd(OAc)_2\}_4LZn$] | 1 x $10^{-4}$ | 662 | 660 | 0.43 | 14 |
| [$\{Pd(OAc)_2\}_3(PtCl_2)LMg(H_2O)$] | 0 | 662 | 660 | 0.16 | tw |
| | 1 x $10^{-4}$ | 665 | 660 | 0.18 | tw |
| [$\{Pd(OAc)_2\}_4LMg(H_2O)$] | 0 | 660 | 660 | 0.05 | 14 |
| | 1 x $10^{-4}$ | 660 | 660 | 0.29 | 14 |
| [$\{Pd(OAc)_2\}_3(PtCl_2)LPd$] | 1 x $10^{-4}$ | 637 | 635 | 0.39 | tw |
| [$\{Pd(OAc)_2\}_4LPd$] | 1 x $10^{-4}$ | 636 | 635 | 0.34 | 14 |

[a] Mean value of at least three measurements. Uncertainty is half-dispersion and is typically ±0.03.

The measured $\Phi_\Delta$ values for the $Zn^{II}$ and the $Mg^{II}$ complexes follow the order: $Zn^{II} > Mg^{II}$. This is in agreement with the "heavy atom effect" which enhances the triplet excited state quantum yield for $Zn^{II}$ with respect to $Mg^{II}$. The $\Phi_\Delta$ values of the $Zn^{II}$ complex [$\{Pd(OAc)_2\}_3(PtCl_2)LZn$] in DMF with and without added HCl (0.40 and 0.53) are in the range of 0.4 to 0.7, values previously reported for a number of $Zn^{II}$ phthalocyanines [7,32] and porphyrazines [27,29,33] (including macrocycles of this latter type studied by us) [9,15,19]. This result thus qualifies these compounds as a highly active photosensitizers for the generation of singlet oxygen. The $\Phi_\Delta$ value for the complex with a central $Pd^{II}$ ion, [($\{Pd(OAc)_2\}_3(PtCl_2)LPd$], measured exclusively in DMF/HCl (0.39) is lower than the value of the $Zn^{II}$ complex measured under the same experimental conditions. The $\Phi_\Delta$ value measured for the $Mg^{II}$ compound shows similar values in the DMF and DMF/HCl solution.

## CONCLUSION

The newly synthesized low symmetry heterometallic pentanuclear complexes of formula [$\{Pd(OAc)_2\}_3(PtCl_2)LM$] (M = $Mg^{II}(H_2O)$, $Zn^{II}$, $Pd^{II}$), bearing three exocyclic $Pd(OAc)_2$ units and one $PtCl_2$ coordinated to N atoms of the vicinal pyridine rings ("py-py" coordination), are stable in air and characterized by the presence of several chlathrated water molecules, most probably interacting with the external $OAc^-$ groups. All of the examined compounds exhibited poor solubility ($10^{-4}$-$10^{-5}$ M) in pyridine, DMSO or DMF, but higher solubility was achieved in water at concentrations up to $10^{-4}$ M or higher, which is a rare occurrence for neutral porphyrazine or phthalocyanine macrocycles. It is noteworthy to point out that the examined compounds were always present in their monomeric form, even at the highest examined concentrations both in solutions of low donor solvents and in water with no evidence for detectable aggregation. An examination of the UV-visible spectral behavior of the compounds in different solvents indicates that coordination of the $Pd(OAc)_2$ units leads to more electron-deficient macrocycles as shown by red shifts of the Q-band positions as compared to both the related mononuclear [LM] derivatives and the parent bimetallic $[(PtCl_2)LM]$ compounds. Studies performed in DMF prove that the $[\{Pd(OAc)_2\}_3(PtCl_2)LM]$ derivatives (M = $Mg^{II}(H_2O)$, $Zn^{II}$, $Pd^{II}$) behave as active photosensitizers for the generation of singlet oxygen, $^1O_2$, the quantum yields ($\Phi_\Delta$), measured in DMF or in acidified DMF ([HCl] = (1 x $10^{-4}$ M)), moving along the series $Zn^{II} > Pd^{II} > Mg^{II}(H_2O)$. This observed sequence reproduces findings for the related series of parent compounds $[\{Pd(OAc)_2\}_4LM]$, [LM] and $[(PtCl_2)LM]$. Measurements of $\Phi_\Delta$ in water are seen as an important target for the currently investigated neutral water soluble porphyrazines and additional studies in this direction will be reported in due course. Furthermore the presence in these macrocycles of a cis-platin-like funcionality, opens up the possibility for future applications in the field of bi-modal anticancer therapy.

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