PCCP

Cite this: *Phys. Chem. Chem. Phys.*, 2011, **13**, 3385–3393

www.rsc.org/pccp

**PAPER**



# Microenvironment-switchable singlet oxygen generation by axially-coordinated hydrophilic ruthenium phthalocyanine dendrimers†

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***Received 28th June 2010, Accepted 19th November 2010***
**DOI: 10.1039/c0cp01015d**

A series of new metallodendrimers built around a ruthenium phthalocyanine core has been prepared. Employing a convergent synthetic strategy, pyridine-containing ligands were prepared and then assembled onto the ruthenium phthalocyanine through axial ligand coordination. The growing shell of oligoethylene glycol chains surrounding the lipophilic core allows solubilisation in water. Photophysical studies show that all the metallodendrimers are strongly phosphorescent and the deactivation pathway of their triplet state depends on the medium in which the compounds are dissolved. On one hand, quenching of the triplet state by the dendritic shell is observed and found to be substantially enhanced in aqueous media. On the other, the dendrimer shields the phthalocyanine from oxygen. This notwithstanding, the phthalocyanines are able to generate singlet oxygen in less polar environments such as in $CHCl_3$ or THF solution, while in water the generation of singlet oxygen is almost completely switched off.

## Introduction

Since the first report in 1978 by Vögtle *et al.*,[1] a plethora of dendrimers has been described in the literature.[2] The tremendous advances in the preparation and modification of these branched structures have allowed dendrimers in recent years to move on from academic research and to enter the market in a variety of applications.[3] Generally, the use of dendrimers is closely related to their precisely controlled size and symmetry.[1,4] Within their regularly branched architecture selected chemical units can be introduced in predetermined sites, namely in the core, within the branching units or at the surface.[1,4] Consequently, the size and more importantly the properties of the macromolecule can be tailored. The steadily growing interest in dendrimer structures is based on their potential for molecular design, which offers numerous possibilities, particularly in the field of biomedicine, *e.g.* as markers for magnetic resonance imaging (MRI),[5] as gene transfection agents,[3c,6] or for the treatment of cancer.[7]

Phthalocyanines and their metalloderivatives are two-dimensional 18 π-electron aromatic porphyrin synthetic analogues.[8] One of the outstanding characteristics of this kind of dye molecules is their exceptionally high absorption in the visible region of the UV/vis spectrum from 630 to 750 nm. This so-called Q-band makes them valuable in different fields of science and technology.[9] However, phthalocyanines have another interesting feature: the generation of singlet oxygen. Metallophthalocyanines are being studied as photosensitizers for the treatment of cancer by photodynamic therapy, which takes advantage of the interaction between light and a photosensitizing agent to selectively kill cancer cells.[10] The growing popularity of this therapeutic method can be attributed to the high selectivity of destruction of diseased tissues and tumors through the localized generation of cytotoxic singlet oxygen while surrounding healthy cells remain unaffected. Among others, phthalocyanines comprising zinc,[11] silicon,[12] or ruthenium as the metal in the central cavity have been found to exhibit the PDT effect.[13] Ruthenium phthalocyanines have the added advantage that they are strongly phosphorescent,[14] providing a convenient means for assessing the mechanistic details of singlet oxygen production in microheterogeneous environments, *e.g.*, cells.[15]

The phthalocyanine macrocycle has also been part of dendritic structures.[16] In most cases this porphyrin analogue is embedded in a dendritic environment thereby aiming at creating a hydrophilic surface.[11a,17] In this context, dendritic modification of phthalocyanines is possible by two distinct methods, being (i) the functionalization of the phthalocyanine outer rim or (ii) *via* axial ligand coordination. Hydrophilic

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† Electronic supplementary information (ESI) available: $^1$H NMR spectra of dendritic pyridine ligands **5–7** and **RuP1–3**; phosphorescence spectra at 1140 nm of **RuP1–3**; singlet oxygen luminescence at 1270 nm of **RuP1–3** in $CHCl_3$, THF and $D_2O$. See DOI: 10.1039/c0cp01015d

systems described in the literature deal for instance with a charged surface consisting of carboxylate moieties of Fréchet-[18] or Newkome-type,[19] or with terminal oligoethylene chains.[20] The latter approach of assembling the dendritic units in the axial positions, which is applicable in the case of *e.g.*, silicon or ruthenium metal centres, has been exploited to a lesser degree. Nonetheless, this strategy is particularly appealing as such ligands can be incorporated in the last step of the synthetic methodology. Furthermore, in the case of ruthenium phthalocyanines in which the ligand is bound in a non-covalent manner to the central metal atom, high yields are usually obtained while assembling the final dendritic structures.

Here, we report the high yield synthesis of a new series of monodisperse and well-defined ruthenium phthalocyanine-based dendrimers **RuP1–3** (Chart 1) obtained through orthogonal coordination of pyridine-containing ligands, with the largest dendrimers being readily soluble in aqueous solution. The photophysics and singlet oxygen generation ability of encapsulated photoactive phthalocyanine core moieties have been investigated in organic and aqueous media. The results lead to the surprising finding that the engineering of a ruthenium phthalocyanine with oligoethylene-terminated Fréchet-type dendrimer shells provides a straightforward means to switch their ability to produce singlet oxygen on and off between non-polar and polar environments. Theoretical calculations have been conducted to support the isolation phenomenon of the centre by the dendritic environment, thus demonstrating that aggregation is effectively prevented upon dendritic encapsulation at least for the highest generation specimens.

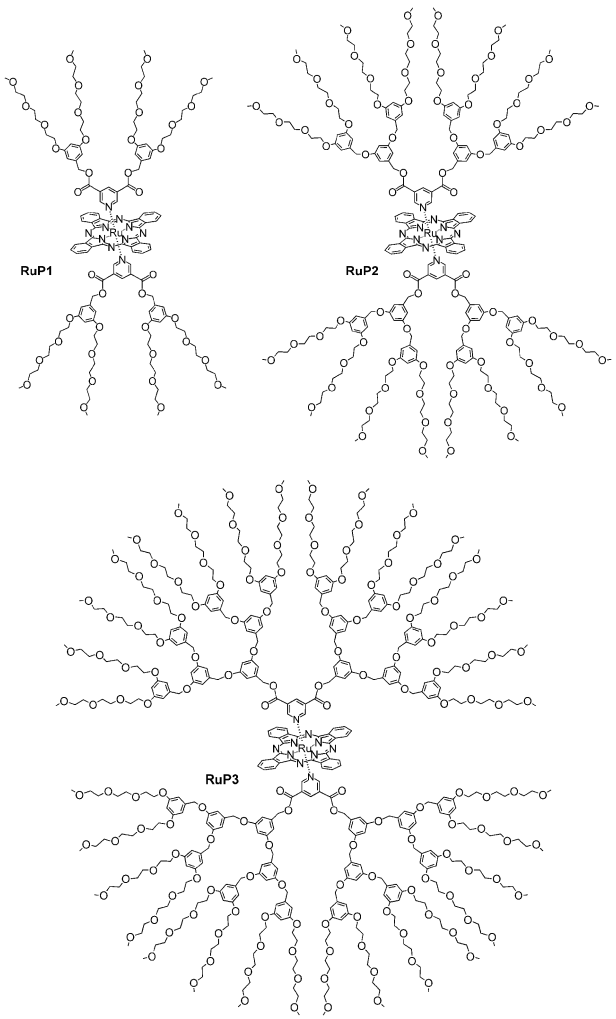


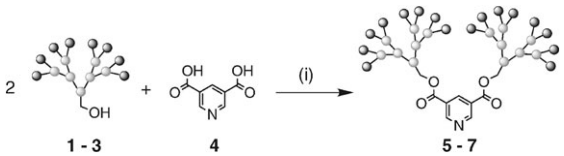

**Chart 1**

## Results and discussion

### Synthesis

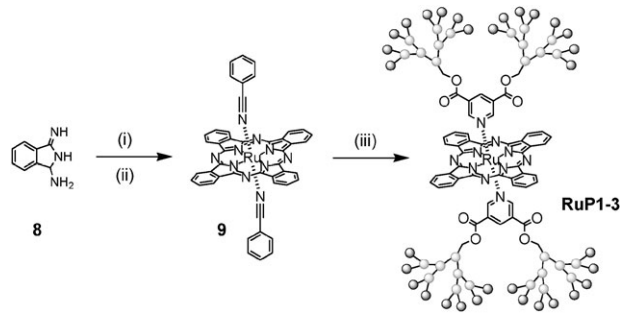
Under the use of the convergent methodology for the construction of dendrimers, branched pyridine-containing ligands have been prepared. Accordingly, first to third Fréchet-type dendrons with terminal oligoethylene glycol chains have been obtained *via* the well-established protocol as reported in the literature.[20,21] The first generation intermediate **1** bearing a benzylic alcohol function at the focal point was then coupled to a 3,5-disubstituted pyridine derivative using two different strategies. Initial attempts were based thereby on the transformation of the diacid into the corresponding diacid dichloride under the use of thionyl chloride and a catalytic amount of dimethylformamide and subsequent reaction with **1** to give diester **5** in 68% yield after purification by chromatography. On the contrary, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDCI) hydrochloride-mediated esterification with pyridine diacid **4** in the presence of dimethylaminopyridine (DMAP) in dichloromethane resulted in the formation of target structure **5** in a significant higher yield of 85% (Scheme 1). The latter reaction conditions have then been applied to the conjugation of pyridine diacid **4** with the oligoethylene glycol-modified higher generation dendritic wedges **2** and **3** (Scheme 1). The two diesters of second, **6** and third generation, **7** have been obtained in high to moderate yields of 83 and 51%, respectively, and similar to the smallest pyridine-containing ligand as colourless highly viscous oils.

On the other hand, ruthenium phthalocyanine **9** was synthesized following a modified protocol as described by Hanack *et al.* Accordingly, formation of the ruthenium phthalocyanine was accomplished by reaction of 1,3-diiminoisoindoline (**8**) in 2-ethoxyethanol (EE) and in the presence of ruthenium(III) chloride and a catalytic amount of diaza(1,3)-bicyclo[5.4.0]undecane (DBU) as base.[22] The crude product obtained after workup was then heated to 100 °C for 4 hours in benzonitrile to yield ruthenium phthalocyanine **9** with two




**Scheme 1** Preparation of dendritic pyridine ligands **5–7** with terminal oligoethylene glycol chains (light spheres represent the polyarylether branching units, darker spheres represent triethylene glycol monomethyl ether end groups). *Reagents and conditions*: (i) EDCI–HCl, DMAP, $CH_2Cl_2$, rt, 1 d (**5**; **6**: 2 d; **7**: 4 d).




**Scheme 2** Preparation of dendritic **RuP1–3**. *Reagents and conditions*: (i) $RuCl_3 \cdot 3H_2O$, DBU, EE, 140 °C, 24 h; (ii) PhCN, 100 °C, 5 h; (iii) THF, 60 °C, 7 h (**RuP1**; **RuP2**: 10 h; **RuP3**: 24 h).

axial benzonitrile ligands (Scheme 2) after purification by chromatography. In the final step, as a result of the weaker association constant of the benzonitrile moieties to the ruthenium metal centre, replacement by the dendritic pyridine-based ligands was feasible. Consequently, simple heating at 60 °C in tetrahydrofuran for several hours gave the monodisperse dendrimers **RuP1–3** in excellent yields of 89 to 93% (Scheme 2). It is important to notice that reaction times required to ensure complete orthogonal complexation were longer due to the higher steric demand of the ligands to allow the pyridine subunit to access the ruthenium centre. All target dendrimers **RuP1–3** could be easily separated from the slight excess of the corresponding pyridine ligands by size exclusion chromatography and were obtained as intense blue coloured highly viscous compounds.

### Structural characterization

Due to the presence of the oligoethylene glycol chains at the surface of the ruthenium phthalocyanine macromolecules, all structures are very soluble in common organic solvents such as $CH_2Cl_2$, $CHCl_3$ or THF, thus facilitating spectroscopic characterization by NMR, UV/Vis, and MS techniques. Furthermore, the largest dendrimers **RuP2** and **RuP3**, *i.e.* the entities of second and third generation, are soluble in neat water, while **RuP1** can still be solubilized if small amounts of organic solvents are added. The increasing amount of hydrophilic surface moieties creates an amphiphilic environment in which the hydrophobic core is shielded by the oligoethylene glycol termini. Elucidation of all structures was easily possible as all signals of the various parts of the dendrimers appear in specific regions and do thus assist the assignments of sets of signals (see ESI†). Additionally, it proved advantageous to incorporate the highly symmetric peripherally unsubstituted phthalocyanine centrepiece whose signals were located as two sets of signals at 9.1 and 7.8 ppm, respectively.

The protons of the 3,5-disubstituted pyridine moieties coordinated in the axial positions are significantly shifted while being affected by the phthalocyanine ring current and can be found as signals at 7.2 and 3.1 ppm, respectively. This is in good agreement with similar systems described in the literature.[23] Concerning the signals of the branches the inner protons are slightly *upfield* shifted in contrast to the outer protons which hardly notice the influence of the ring current of the phthalocyanine subunit. Likewise, proton shifts remain unaffected upon changing the solvent from $CDCl_3$ to deuterated THF. As expected, the $^{13}C$ NMR spectra of the series of dendrimers showed analogous shifts for the corresponding carbon atoms.

### Absorption spectra

The absorption spectra of the series of **RuP1–3** dendrimers are depicted in Fig. 1. For comparison purposes, a simple model phthalocyanine **RuPy** consisting of two pyridine moieties orthogonally coordinated to the ruthenium centre has been included. The spectra have been recorded in THF (Fig. 1a) and $CHCl_3$ (Fig. 1b) as examples of common organic solvents, and in neat water (Fig. 1c).

In general, these spectra show many features archetypical of aggregation phenomena in these dyes: broad Q bands and with lower absorption coefficients than the typical monomer phthalocyanines. While phthalocyanine molecules have indeed a high tendency to aggregate, thereby showing coplanar association under formation of dimers, trimers, and higher oligomers, respectively,[24] the introduction of bulky peripheral substituents or axial ligands should effectively prevent this phenomenon. Indeed, the defined signal patterns as observed for the NMR spectra of all samples and the lack of concentration effects on the spectra rule out such putative formation of aggregated species. However, the appearance of broad Q-bands for the whole series of phthalocyanines regardless of the polarity of the solvent appears to be a particular intrinsic phenomenon apparent in bis-pyridyl-coordinated ruthenium phthalocyanines. This is in line with findings that have been observed before for similar orthogonally

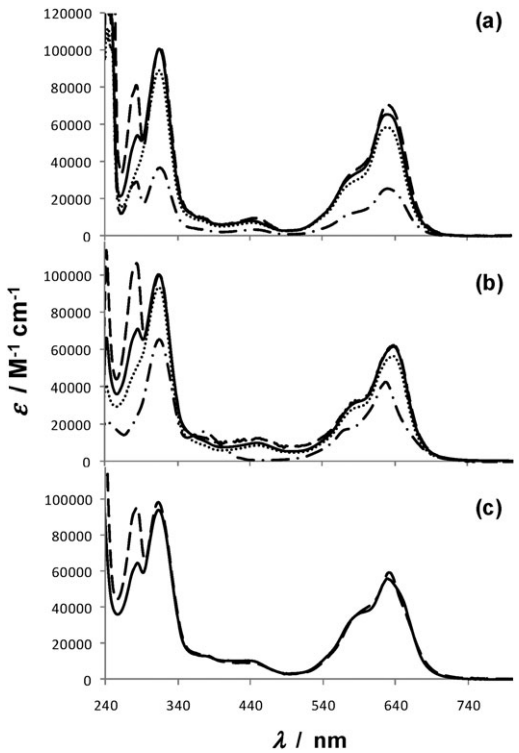



**Fig. 1** UV/Vis spectra of **RuPy** (---), **RuP1** (· · · · · ·), **RuP2** (——) and **RuP3** (---) in (a) THF and (b) $CHCl_3$; (c) UV/Vis spectra of **RuP2** (——) and **RuP3** (---) in $H_2O$.

constructed species,[23] including dendrimers with thiophene-derived ligands in axial positions.[23a]

However, other spectral variations are apparent upon closer inspection of Fig. 1. First, an increasing contribution of the dendrimers is observed around 280 nm on passing from **RuP1** to **RuP3**. Additionally, small changes in the absorption coefficients can be spotted throughout the UV/Vis spectral range. In THF, the Q-band maxima for all compounds under study are identical and can be found at $\lambda_{max}$ = 630 nm. Nonetheless, intensities are increasing upon going from **RuPy** to **RuP3** and are at least two-fold with respect to the model compound **RuPy**. Likewise, in $CHCl_3$ a similar trend of higher absorption coefficients for the dendrimers has been observed. However, it is interesting to note that coordination with the fractal pyridine ligands in this solvent provokes a bathochromic shift of ~10 nm, thus giving rise to Q-bands centered at $\lambda_{max}$ = 638 nm for all dendrimers. These findings cannot be attributed to changes in phthalocyanine/solvent interactions, but to an increasing intramolecular interaction between the phthalocyanine core and the dendrimer part of the series of fractal structures, similar to that described for related fullerodendrimers.[25] Finally, the intensity ratio of the two Q bands (590 and 638 nm) decreases when the solvent polarity is increased. At present we cannot ascertain whether this stems from the interaction between the phthalocyanine core and the dendrimers or from the interaction between the phthalocyanine and the pyridyl ligands.

## Theoretical calculations

In line with the idea of structurally not aggregated and thus independent phthalocyanine chromophores are results obtained by theoretical calculations. Random Branching Theory (RBT) constructs a model solution structure for a branched polymer by random assembly from units that may be oligomers or larger clusters. It has been shown to describe accurately the structures of a variety of synthetic and natural, regular and randomly branched polymers.[26,27] Remarkably, the assembly of a model structure based on random branching provides a good model of the density distributions of dendrimers,[26b] though perhaps this is understandable now that we know that monomers of the outermost generation are often distributed through the dendrimer. Here we do not seek to construct a detailed picture of the distribution of different groups within the metallodendrimers. Rather, we use RBT to estimate the thickness of the dendrimer distribution around the metal centre.

We estimate that the dendron's groups may approach no closer than 0.4 nm to the metal centre, and that the dendrons are attached to the metal complex no more than 1 nm from the ruthenium atom. The monomers in the dendron are of the $AB_2$ type, and we assume that in the fluctuating solution structure a monomer's B group has a Gaussian distribution about its A group, with a width of $\sigma$ = 0.24 nm. The distribution of mass in the oligoethylene glycol chains is also assumed to be Gaussian, with a width estimated at $\sigma$ = 0.35 nm. This led us to assume that the chain can completely reorient over three bonds. The maximum number density permitted for monomers is the random close packed density of spheres with the same radius of gyration: $\rho = 0.03\ \sigma^{-3}$,[26b] which is 2.2 $nm^{-3}$ for the lipophilic groups. RBT normally takes into account interactions through the Flory–Huggins parameters, but here we neglect this for brevity ($\chi$ = 0). Our results are not sensitive to any of these choices or approximations.

Our estimate of the maximum permitted density of lipophilic monomers is 2.2 $nm^{-3}$. Fig. 2 shows the density profiles for metallodendrimers of all three generations. For **RuP2** and **RuP3** the density of lipophilic groups is 1 $nm^{-3}$ or more over a considerable range. For two metal centres to approach each other closely, either their dendron groups would have to overlap, or they would have to move out of the way. In either case, the density of lipophilic groups would approach this maximum density. This would have a large entropy cost. The use of the random close packed density as a maximum here is conservative: we have neglected the effects of regular branching, which is likely to further constrain the distribution of lipophilic groups. We feel that this calculation is useful evidence that the metal centres cannot aggregate, being surrounded by a lipophilic shell, but experimental confirmation is clearly desirable.

## Phosphorescence

All dendrimers show strong triplet phthalocyanine phosphorescence at 1140 nm as depicted in Fig. 3. It has been previously reported for similar compounds that the dendritic wedges are able to partially shield the photoactive core from molecular oxygen, increasing the triplet lifetime upon increasing the dendrimer complexity.[25,29] Interestingly, a different trend is observed for **RuP1–3**. The phosphorescence decays are monoexponential in $CHCl_3$ and THF, with lifetimes $\tau_T$ ranging from 1 to 1.5 μs. A clear trend, *i.e.* a negative dendritic effect, can be noticed on passing from **RuP1** to **RuP3**, *i.e.*, $\tau_T$ decreased upon increasing the dendrimer complexity. This confirms that the electron-rich dialkoxyphenyl moieties of

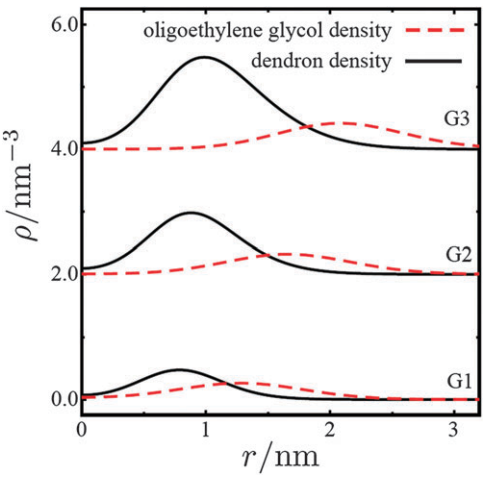



**Fig. 2** Random Branching Theory estimates of the distributions of lipophilic groups (solid lines), and polyether chains (dashed), about the ruthenium atom at $r$ = 0. For the lipophiles, the density integrates to the number of aromatic rings. For the polyethers, the density integrates to the number of oligomers. Our estimate of the maximum achievable density monomers is 2.2 $nm^{-3}$ in these units. Density at less than $r$ = 0.4 nm is an artefact of the mean-field approximation.

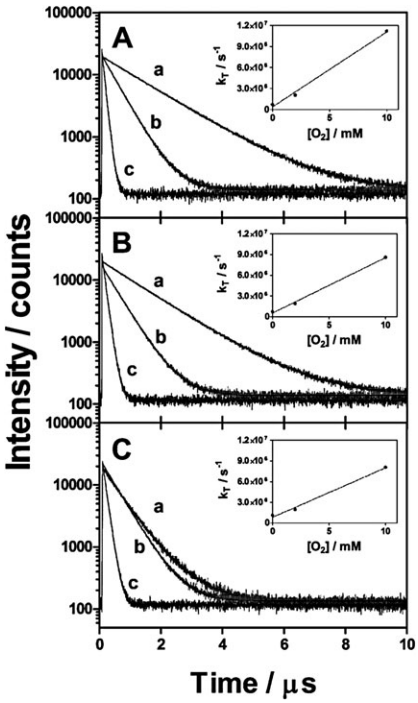



**Fig. 3** Time-resolved near-IR phosphorescence measurements at 1140 nm for (A) **RuP1**, (B) **RuP2**, and (C) **RuP3** in THF, under (a) argon-saturated atmosphere, (b) air-saturated atmosphere, and (c) oxygen-saturated atmosphere. Insets: oxygen concentration dependence of the rate constant for triplet decay, $k_T$. Oxygen concentrations have been calculated from published solubility data after correcting for the oxygen partial pressure above the solutions.[28] The quenching rate constant $k_q$ has been derived from the slope of the linear fit of the equation $k_T = 1/\tau_T + k_q[O_2]$ to the data points, where $\tau_T$ is the triplet lifetime in argon-saturated solutions.

the dendrimer branches interact with the phthalocyanine providing an additional deactivation pathway for the excited states. The rate constants for this process ($k_D$) can be calculated as $k_D = 1/\tau_T - 1/\tau_T(0)$, where $\tau_T(0) = 12$ μs is the triplet lifetime of a ruthenium phthalocyanine axially coordinated with two pyridyl units.[23a–c] The values are collected in Table 1. The decays are more complex in aqueous media, **RuP2** showing the longest phosphorescence lifetime of the three compounds (see ESI†). The complex decays suggest a distribution equilibrium between conformers, the decay kinetics likely reflecting the outcome of the interactions between the dialkoxy groups and the phthalocyanine core, the rest of the dendrimer, and the solvent. The outcome of these complex ternary interactions differs among the three compounds. Compared to those in organic solvents, the lifetimes are substantially shorter in aqueous media, which is consistent with a more extensive interaction as already observed in the absorption spectra. It is worth noting that this process reflects a dynamic quenching of the triplet excited state, as only the triplet lifetime, and not the signals' intensity, is modified.

### Generation of singlet oxygen

Photoirradiation of organic dyes often leads to the formation of singlet oxygen (molecular oxygen in its electronically excited state $O_2(a^1\Delta_g)$) through energy transfer from a photoexcited dye to molecular oxygen.[30] The efficiency of this process is determined, among others, by the ability of oxygen to trap the dye's metastable electronically excited states. As such, singlet oxygen is an ideal probe for studying the effects of the dendrimer on the phthalocyanine photophysics, particularly the extent to which the dendrimer shields the phthalocyanine from its surroundings. These processes are best studied by time-resolved near-IR phosphorescence spectroscopy.[31,32]

Notwithstanding the shielding effect exerted by the dendrimers, the phthalocyanine phosphorescence can be quenched by oxygen. The increasing complexity of the dendrimer core is reflected in the values of the quenching rate constants ($k_q$, *cf.* Table 1), which decrease concomitantly, as already observed by other authors with similar compounds.[25,29,33] In all cases the quenching rate constants are slightly below the diffusional limit while oxygen quenching is diffusional for **RuPy**.[23b,34] In addition, formation of singlet oxygen $O_2(a^1\Delta_g)$ is unequivocally demonstrated by its emission at 1270 nm (see ESI†). Basically, as observed in Table 1, the singlet oxygen quantum yields ($\Phi_\Delta$) are not affected by the oligoethylene glycol chains. However, the situation in organic solvents is different than that in $D_2O$,

**Table 1** Photochemical properties of **RuP1–3**

| Compound | Solvent | $\tau_T$[a]/μs | $k_D$[b]/$s^{-1}$ | $k_q$[c]/$M^{-1}$ $s^{-1}$ | $\Phi_\Delta$[d] | $F^{O_2}{}_T$[e] | $\tau_\Delta$[f]/μs |
|---|---|---|---|---|---|---|---|
| **RuP1** | $CHCl_3$ | 1.51 ± 0.01 | $5.8 \times 10^5$ | $8.1 \times 10^8$ | 0.60 ± 0.05 | 0.68 | 200 ± 2 |
| **RuP1** | THF | 1.43 ± 0.01 | $6.2 \times 10^5$ | $1.1 \times 10^9$ | 0.60 ± 0.05 | 0.67 | 20.5 ± 0.5 |
| **RuP1**[g] | $D_2O$ | 0.80 (0.54)<br>0.21 (0.46) | $1.8 \times 10^6$ | $5.3 \times 10^8$ | 0.005 ± 0.003 | 0.02 | 65.2 ± 0.5 |
| **RuP2** | $CHCl_3$ | 1.43 ± 0.01 | $6.1 \times 10^5$ | $7.3 \times 10^8$ | 0.57 ± 0.05 | 0.58 | 190 ± 2 |
| **RuP2** | THF | 1.38 ± 0.01 | $6.4 \times 10^5$ | $8.1 \times 10^8$ | 0.60 ± 0.05 | 0.61 | 20.1 ± 0.5 |
| **RuP2** | $D_2O$ | 0.75 (0.79)<br>0.29 (0.21) | $1.5 \times 10^6$ | $3.8 \times 10^8$ | 0.010 ± 0.005 | 0.05 | 58.8 ± 0.5 |
| **RuP3** | $CHCl_3$ | 1.26 ± 0.01 | $7.1 \times 10^5$ | $6.1 \times 10^8$ | 0.53 ± 0.05 | 0.56 | 166 ± 2 |
| **RuP3** | THF | 0.93 ± 0.01 | $9.9 \times 10^5$ | $7.2 \times 10^8$ | 0.50 ± 0.05 | 0.44 | 20.1 ± 0.5 |
| **RuP3** | $D_2O$ | 0.30 | $3.3 \times 10^6$ | $1.5 \times 10^8$ | 0.006 ± 0.003 | 0.04 | 52.1 ± 0.5 |

[a] Lifetime of 1140 nm posphorescence in argon-saturated solutions. Relative amplitudes in parentheses. [b] Rate constant for dendrimer-mediated triplet decay. [c] Rate constant for triplet quenching by oxygen. Error bar 10%. [d] Singlet oxygen quantum yield in air-saturated solutions. [e] Fraction of phthalocyanine triplet excited states deactivated by oxygen in air-saturated solutions. Error bar 5%. [f] Singlet oxygen lifetime in air-saturated solutions. [g] **RuP1** was dissolved in a 0.3 : 99.7 THF : $D_2O$ mixture.

where the $\Phi_\Delta$ values are roughly two orders of magnitude smaller. In addition, the $\Phi_\Delta^{D_2O}$ values of **RuP2** and **RuP3** increased *ca.* five-fold upon solvent saturation with oxygen. These results can be rationalized in the light of eqn (1):

$$\Phi_\Delta = \Phi_T S_\Delta \times \frac{k_q[O_2]}{\frac{1}{\tau_T} + k_q[O_2]} \quad (1)$$

where $\Phi_T$ is the quantum yield for triplet state formation, $S_\Delta$ is the efficiency of energy transfer from the triplet phthalocyanine, and the quotient yields the fraction of triplets trapped by oxygen at a given oxygen concentration.[31] Thus, trapping of the phthalocyanine triplets is quantitative in THF for all compounds, despite their differences in $\tau_T$ and $k_q$ (Table 1). In $D_2O$, the simultaneous decrease of $\tau_T$, $k_q$ and $[O_2]$ leads to $1/\tau_T \gg k_q[O_2]$ and the $\Phi_\Delta$ values increase proportionally to the oxygen concentration. In sum, our results reveal a previously unnoticed opposite effect of the dendritic ligands on the triplet lifetime of the core macrocycle. On one hand, the dendrimer shields the phthalocyanine from oxygen, leading to lower $k_q$ values. On the other, the dendrimer interacts with the phthalocyanine, perturbing its electronic structure, and quenching its excited states. This effect is strongly solvent dependent. The combination of structural and solvent effects has dramatic consequences for the compounds' ability to photosensitise the production of singlet oxygen, which can be almost switched on and off by changing the environment of the compounds.

With regards to the singlet oxygen lifetime ($\tau_\Delta$)values, the results in $CHCl_3$ and $D_2O$ indicate that $^1O_2$ is partially quenched by the dendrimer cage, as deduced from the lower lifetime values relative to those in neat solvents (240 μs in $CHCl_3$, 68 μs in $D_2O$, and 20 μs in THF)[35] and by the clear trend observed on passing from **RuP1** to **RuP3**. A similar effect was observed by Nierengarten *et al.* in fullerodendrimers.[29]

## Conclusions

Here, we report the convergent synthesis of a new series of monodisperse ruthenium phthalocyanine-based dendrimers obtained through axial coordination of pyridine-containing ligands. All dendrimers comprising triethylene glycol monomethyl ether end groups show excellent solubility in common organic solvents. In addition, owing to the increasing shell of such hydrophilic moieties, the largest dendrimers are readily soluble in aqueous solution. The encapsulated photoactive phthalocyanine core moieties have been investigated by means of photophysics exhibiting a rather broad Q-band centred at 638 nm. Theoretical calculations have been conducted to support the idea of suppression of aggregation as exerted by the dendritic environment. These calculations are based on conservative estimates of the number of monomers that can occupy a given volume, and an argument based on the entropic cost of this random close packing. Further calculations including the effects of solvent would be useful, as would experimental tests of our theoretical predictions. All phthalocyanines are strongly phosphorescent and the triplet lifetimes are shorter than for the model compound **RuPy**, revealing interactions of the phthalocyanine with its dendrimer shell. In organic solvents, the triplet lifetimes decrease following the trend **RuP1** > **RuP2** > **RuP3** while the trend is more complex in aqueous media. The dendrimer does not isolate the phthalocyanine from oxygen though a noticeable shielding effect can be observed. Notwithstanding, singlet oxygen is readily produced in organic solvents, the quantum yields decreasing by two orders of magnitude in $D_2O$ due to the short lifetime of the triplet state and of the oxygen quenching rate constants in this solvent. The results disclose the surprising finding that the engineering of a ruthenium phthalocyanine with oligoethylene-terminated Fréchet-type dendrimer shells provides a straightforward means to switch their ability to produce singlet oxygen on and off between non-polar and polar environments.

Based on these results, the design of further hydrophilic phthalocyanine dendrimers is currently underway in our labs. In these attempts, the nature of the centrepiece as well as the dendritic surrounding will be subject to modification.

## Experimental

### Materials and methods

Reagents and solvents were purchased as reagent grade and used without further purification. The synthesis of dendritic oligoethylene-terminated branches **1–3** has been accomplished according to literature procedures.[20,21] All reactions were performed in standard glassware under an inert argon atmosphere. Column chromatography: silica gel 60 (230–400 mesh, 0.040–0.063 mm) from E. Merck. TLC: glass sheets coated with silica gel 60 $F_{254}$ from E. Merck; visualization by UV light. UV/Vis spectra were measured on a Perkin Elmer Lambda 19 spectrophotometer. NMR spectra were recorded on Bruker AM 300 (300 MHz) instruments with solvent signal as reference ($H_{pc}$: phthalocyanine protons, $H_{py}$: pyridine protons, $H_{ar}$: aromatic protons, $H_{PhCN}$: benzonitrile protons). Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra were obtained in the positive ion mode from a Applied Biosystem 4700 instrument or a Bruker Ultraflex III TOFTOF both equipped with a Nd:YAG laser operating at 355 nm.

### Synthesis

**Compound 9.** DBU (0.5 mL) was added dropwise to a preheated (140 °C) mixture of 1,3-diiminoisoindoline (**8**, 250 mg, 1.72 mmol) and $RuCl_3 \cdot 3H_2O$ (113 mg, 0.43 mmol) in EE (7 mL) under argon. The resulting intense blue coloured solution was kept at 140 °C for 18 h. After cooling to room temperature, the solution is poured onto water and the forming precipitate filtered. The remaining solid is dried at 120 °C for several hours and then transferred into a 100 mL one-neck flask. Benzonitrile (10 mL) was added and the solution heated to 100 °C for 5 h. The residual benzonitrile was eliminated by distillation and the crude mixture purified by gradient column chromatography on silica gel ($CH_2Cl_2$) to give **9** (118.9 mg, 34%) as intense blue coloured solid which was collected as first fraction. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 9.30 (m, 8H, $H_{pc}$), 7.98 (m, 8H, $H_{pc}$), 6.84

(t, $J$ = 8 Hz, 2H, $H_{PhCN}$), 6.51 (t, $J$ = 8 Hz, 4H, $H_{PhCN}$), 5.52 (d, $J$ = 8 Hz, 4H, $H_{PhCN}$).

**General procedure for the preparation of 5 to 7.** EDCI (2.2 equiv.) was added to a stirred solution of 3,5-pyridinedicarboxylic acid (**4**, 1 equiv.), the dendritic benzylic alcohol of the respective generation (2.05 equiv.), DMAP (0.2 equiv.) in $CH_2Cl_2$ at 0 °C. After 1 h, the mixture was allowed to slowly warm to rt and then stirred at this temperature for several days (**5**: 1 d, **6**: 2 d and **7**: 4 d). The arising solid was filtered off, the solvent evaporated, and the crude product purified as outlined in the following text.

*Compound* **5**. Prepared from **1** (615.0 mg, 1.42 mmol) and **4** (115.9 mg, 0.69 mmol). Gradient column chromatography on silica gel ($CH_2Cl_2$ to $CH_2Cl_2$/MeOH 15 : 1) and gel permeation chromatography (Biorad, Biobeads SX-1, $CH_2Cl_2$) yielded **5** (410.0 mg, 85%) as a colourless highly viscous oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.37 (d, $J$ = 2 Hz, 2H, $H_{py}$), 8.88 (t, $J$ = 2 Hz, 1H, $H_{py}$), 6.58 (d, $J$ = 2 Hz, 4H, $H_{ar}$), 6.47 (t, $J$ = 2 Hz, 2H, $H_{ar}$), 5.31 (s, 4H, $CO_2CH_2$), 4.10 (t, $J$ = 5 Hz, 8H, $CH_2$), 3.83 (t, $J$ = 5 Hz, 8H, $CH_2$), 3.69–3.73 (m, 8H, $CH_2$), 3.61–3.68 (m, 16H, $CH_2$), 3.51–3.55 (m, 8H, $CH_2$), 3.35 (s, 12H, $CH_3$) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ = 164.0, 160.0, 154.2, 138.0, 137.2, 125.8, 106.9, 101.4, 71.8, 70.6, 70.5, 70.4, 69.5, 67.4, 67.1, 58.8 ppm. MALDI-TOF-MS (dithranol + NaI): $m/z$ (%) calcd. for $C_{49}H_{74}NO_{20}$: 996.5 $[M + H]^+$; found: 1018.5 (100) $[M + Na]^+$, 996.5 (28) $[M + H]^+$.

*Compound* **6**. Prepared from **2** (600.0 mg, 619 µmol) and **4** (50.5 mg, 302 µmol). Gradient column chromatography on silica gel ($CH_2Cl_2$ to $CH_2Cl_2$/MeOH 15 : 1) and gel permeation chromatography (Biorad, Biobeads SX-1, $CH_2Cl_2$) yielded **6** (521.0 mg, 83%) as a colourless highly viscous oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.38 (br s, 2H, $H_{py}$), 8.91 (br s, 1H, $H_{py}$), 6.65 (d, $J$ = 2 Hz, 4H, $H_{ar}$), 6.57 (m, 10H, $H_{ar}$), 6.43 (t, $J$ = 2 Hz, 4H, $H_{ar}$), 5.33 (s, 4H, $CO_2CH_2$), 4.95 (s, 8H, $CH_2$), 4.10 (t, $J$ = 5 Hz, 16H, $CH_2$), 3.83 (t, $J$ = 5 Hz, 16H, $CH_2$), 3.69–3.74 (m, 16H, $CH_2$), 3.62–3.68 (m, 32H, $CH_2$), 3.51–3.55 (m, 16H, $CH_2$), 3.36 (s, 24H, $CH_3$) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ = 164.2, 160.7, 154.3, 138.9, 138.2, 137.4, 107.3, 106.0, 102.0, 101.1, 71.9, 70.8, 70.6, 70.5, 70.0, 69.6, 67.5, 67.3, 58.9 ppm. MALDI-TOF-MS (dithranol + NaI): $m/z$ (%) calcd. for $C_{105}H_{154}NO_{40}$: 2070.1 $[M + H]^+$; found: 2092.1 (100) $[M + Na]^+$, 2070.1 (28) $[M + H]^+$.

*Compound* **7**. Prepared from **3** (200.0 mg, 98 µmol) and **4** (8.0 mg, 48 µmol). Gradient column chromatography on silica gel (ethyl acetate/acetone 1 : 1 to 1 : 3 to $CHCl_3$/acetone 1 : 1 to 1 : 10) and gel permeation chromatography (Biorad, Biobeads SX-1, $CH_2Cl_2$) yielded **7** (103.5 mg, 51%) as a colourless highly viscous oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.36 (d, $J$ = 2 Hz, 2H, $H_{py}$), 8.91 (t, $J$ = 2 Hz, 1H, $H_{py}$), 6.68 (d, $J$ = 2 Hz, 4H, $H_{ar}$), 6.65 (d, $J$ = 2 Hz, 8H, $H_{ar}$), 6.60 (t, $J$ = 2 Hz, 2H, $H_{ar}$), 6.56 (d, $J$ = 2 Hz, 16H, $H_{ar}$), 6.52 (t, $J$ = 2 Hz, 4H, $H_{ar}$), 6.43 (t, $J$ = 2 Hz, 8H, $H_{ar}$), 5.33 (s, 4H, $CO_2CH_2$), 4.96 (s, 8H, $CH_2$), 4.93 (s, 16H, $CH_2$), 4.09 (t, $J$ = 5 Hz, 32H, $CH_2$), 3.81 (t, $J$ = 5 Hz, 32H, $CH_2$), 3.68–3.73 (m, 32H, $CH_2$), 3.60–3.67 (m, 64H, $CH_2$), 3.49–3.54 (m, 32H, $CH_2$), 3.34 (s, 48H, $CH_3$) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ = 164.3, 160.1, 154.4, 139.1, 138.4, 137.5, 126.1, 107. 5, 106.5, 106.2, 102.0, 101.7, 101.2, 72.0, 70.9, 70.7, 70.6, 70.2, 70.1, 69.7, 67.6, 67.4, 59.1 ppm. MALDI-TOF-MS (dithranol + NaI): $m/z$ (%) calcd. for $C_{217}H_{314}NO_{80}$: 4216.8 $[M + H]^+$; found: 4238.1 (100) $[M + Na]^+$, 4216.2 (4) $[M + H]^+$.

**General procedure for the preparation of RuPy and RuP1–3.** A solution of pyridine or the appropriate dendritic pyridine-containing ligand (2.1 equiv.) and **9** (1 equiv.) in THF was heated to 60 °C for a certain time (**RuPy**: 1 h; **RuP1**: 7 h; **RuP2**: 10 h; **RuP3**: 24 h). The solvent was evaporated to dryness and the crude mixture purified as outlined in the following text.

*Compound* **RuPy**. Prepared from pyridine (4.1 µL, 51.3 µmol) and **9** (20.0 mg, 24.4 µmol) in THF (4 mL). Column chromatography ($SiO_2$, $CH_2Cl_2$) yielded **RuPy** (14.6 mg, 78%) as a deep blue solid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.12 (br m, 8H, $H_{pc}$), 7.88 (br m, 8H, $H_{pc}$), 6.02 (tt, $J$ = 6 Hz, $J$ = 2 Hz, 2H, $H_{py}$), 5.23 (t, $J$ = 6 Hz, 4H, $H_{py}$), 3.08 (dd, $J$ = 6 Hz, $J$ = 2 Hz, 4H, $H_{py}$) ppm.

*Compound* **RuP1**. Prepared from **5** (63.7 mg, 64.0 µmol) and **9** (25.0 mg, 30.5 µmol) in THF (20 mL). Gel permeation chromatography (Biorad, Biobeads SX-1, $CH_2Cl_2$) yielded **RuP1** (68.4 mg, 93%) as a deep blue solid. UV/Vis ($CHCl_3$): $\lambda$/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) = 314 (96 340), 450 (10 990), 590 (sh, 31 878), 638 (59 060); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.06 (br m, 8H, $H_{pc}$), 7.82 (br m, 8H, $H_{pc}$), 7.17 (t, $J$ = 2 Hz, 2H, $H_{py}$), 6.52 (t, $J$ = 2 Hz, 4H, $H_{ar}$), 6.21 (d, $J$ = 2 Hz, 8H, $H_{ar}$), 4.62 (s, 8H, $CO_2CH_2$), 4.06 (t, $J$ = 5 Hz, 16H, $CH_2$), 3.88 (t, $J$ = 5 Hz, 16H, $CH_2$), 3.72–3.77 (m, 16H, $CH_2$), 3.62–3.70 (m, 32H, $CH_2$), 3.50–3.55 (m, 16H, $CH_2$), 3.35 (s, 24H, $CH_3$), 3.08 (d, $J$ = 2 Hz, 4H, $H_{py}$) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ = 161.0, 160.2, 154.5, 143.9, 140.6, 136.4, 134.8, 128.3, 125.1, 121.7, 107.6, 101.9, 72.1, 71.0, 70.8, 70.7, 69.9, 67.7, 67.6, 59.2 ppm. MALDI-TOF-MS (DCTB): $m/z$ (%) calcd. for $C_{130}H_{162}N_{10}O_{40}Ru$: 2605.0 $[M]^{+\bullet}$; found: 2604.9 (15) $[M]^{+\bullet}$, 1609.5 $[M - 1\ \text{ligand}]^{+\bullet}$ (32).

*Compound* **RuP2**. Prepared from **6** (120.0 mg, 58.0 µmol) and **9** (22.6 mg, 27.6 µmol) in THF (20 mL). Gel permeation chromatography (Biorad, Biobeads SX-1, $CH_2Cl_2$) yielded **RuP2** (118.1 mg, 90%) as a deep blue viscous oil. UV/Vis ($CHCl_3$): $\lambda$/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) = 284 (70 940), 313 (100 420), 450 (9540), 590 (31 960), 638 (61 350); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.10 (br m, 8H, $H_{pc}$), 7.75 (br m, 8H, $H_{pc}$), 7.18 (t, $J$ = 2 Hz, 2H, $H_{py}$), 6.60 (m, 20H, $H_{ar}$), 6.43 (t, $J$ = 2 Hz, 8H, $H_{ar}$), 6.30 (d, $J$ = 2 Hz, 8H, $H_{ar}$), 4.90 (s, 16H, $CH_2$), 4.64 (s, 8H, $CO_2CH_2$), 4.07 (t, $J$ = 5 Hz, 32H, $CH_2$), 3.79 (t, $J$ = 5 Hz, 32H, $CH_2$), 3.67–3.71 (m, 32H, $CH_2$), 3.60–3.66 (m, 64H, $CH_2$), 3.49–3.53 (m, 32H, $CH_2$), 3.34 (s, 48H, $CH_3$), 3.10 (d, $J$ = 2 Hz, 2H, $H_{py}$) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ = 160.9, 160.2, 160.1, 154.4, 143.8, 140.6, 139.1, 136.5, 134.8, 128.2, 125.1, 121.6, 107.7, 106.2, 102.3, 101.3, 72.0, 70.9, 70.7, 70.6, 70.1, 69.7, 67.6, 59.1 ppm. MALDI-TOF-MS (DCTB): $m/z$ (%) calcd. for

$C_{242}H_{322}N_{10}O_{80}Ru$: 4750.1 $[M]^{+\bullet}$; found: 4752.4 (2) $[M]^{+\bullet}$, 2683.0 $[M - 1\ ligand]^{+\bullet}$ (100).

*Compound* **RuP3**. Prepared from **7** (95.0 mg, 22.5 μmol) and **9** (8.8 mg, 10.7 μmol) in THF (20 mL). Gel permeation chromatography (Biorad, Biobeads SX-1, $CH_2Cl_2$) yielded **RuP3** (86.6 mg, 89%) as a deep blue viscous oil. UV/Vis ($CHCl_3$): $\lambda$/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) = 283 (102 870), 314 (96 470), 450 (9040), 590 (29 130), 638 (58 690); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.14 (br m, 8H, $H_{pc}$), 7.76 (br m, 8H, $H_{pc}$), 7.10 (t, $J$ = 2 Hz, 2H, $H_{py}$), 6.72 (d, $J$ = 2 Hz, 16H, $H_{ar}$), 6.63 (t, $J$ = 2 Hz, 4H, $H_{ar}$), 6.52 (m, 40H, $H_{ar}$), 6.40 (t, $J$ = 2 Hz, 16H, $H_{ar}$), 6.35 (d, $J$ = 2 Hz, 8H, $H_{ar}$), 4.92 (s, 16H, $CH_2$), 4.98 (s, 32H, $CH_2$), 4.62 (s, 8H, $CO_2CH_2$), 4.04 (t, $J$ = 5 Hz, 64H, $CH_2$), 3.78 (t, $J$ = 5 Hz, 64H, $CH_2$), 3.66–3.71 (m, 64H, $CH_2$), 3.59–3.65 (m, 128H, $CH_2$), 3.47–3.53 (m, 64H, $CH_2$), 3.34 (s, 96H, $CH_3$), 3.16 (d, $J$ = 2 Hz, 4H, $H_{py}$) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ = 160.9, 160.20, 160.16, 154.3, 151.6, 143.9, 140.6, 139.2, 139.1, 136.6, 135.9, 135.8, 128.4, 125.6, 125.0, 121.7, 107.8, 106.6, 106.2, 102.0, 101.7, 101.2, 72.0, 70.9, 70.7, 70.6, 70.1, 69.7, 68.1, 67.6, 59.1 ppm. MALDI-TOF-MS (DCTB): $m/z$ (%) calcd. for $C_{466}H_{642}N_{10}O_{160}Ru$: 9040.2 $[M]^{+\bullet}$; found: 9044.0 $[M]^{+\bullet}$ (80), 4829.4 $[M - 1\ ligand]^{+\bullet}$ (100), 4213.1 $[ligand + H]^+$.

### Spectroscopic techniques and methods

Phosphorescence of $^1O_2$ and **RuP1–3** were detected by means of a customized PicoQuant Fluotime 200 system described in detail elsewhere.[32] Briefly, a diode-pumped pulsed Nd:Yag laser (FTSS355-Q, Crystal Laser, Berlin, Germany) working at 10 kHz repetition rate at 532 nm (12 mW, 1.2 μJ per pulse) was used for excitation. A 1064 nm rugate notch filter (Edmund Optics, UK) was placed at the exit port of the laser to remove any residual component of its fundamental emission in the near-IR region. The luminescence exiting from the side of the sample was filtered by a cold mirror (CVI Melles Griot, USA) to remove any scattered laser radiation, and focused on the entrance slit of a Science Tech 9055 dual grating monochromator. A near-IR sensitive photomultiplier tube assembly (H9170-45, Hamamatsu Photonics Hamamatsu City, Japan) was used as a detector at the exit port of the monochromator. Photon counting was achieved with a multichannel scaler (PicoQuant's Nanoharp 250). The time-resolved emission signals were analyzed using the FluoFit software to extract lifetime values. The $O_2(a^1\Delta_g)$ quantum yields ($\Phi_\Delta$) were determined by comparing the intensity of the 1270 nm signals to those of optically-matched solutions of the reference photosensitizers 5,10,15,20-tetraphenylporphine (TPP; $\Phi_\Delta^{TPP}$ = 0.62 in benzene,[36] assumed to hold in THF; $\Phi_\Delta^{TPP}$ = 0.50 in $CHCl_3$)[37] and 5,10,15,20-tetrakis(4-sulfonatophenyl)porphine (TPPS, $\Phi_\Delta^{TPPS,\ D_2O}$ = 0.64).[36] Measurements were carried out in standard 1 × 1 cm quartz fluorescence cuvettes at 295 K. The concentration of the phthalocyanines was in the range 1–5 μM. The concentration of oxygen in the solutions was changed by gentle bubbling with solvent-saturated argon or oxygen for at least 30 min.

## Acknowledgements

Financial support for work by the MEC, Spain (CTQ2008-00418/BQU and CONSOLIDER-INGENIO 2010 CDS 2007-00010), and CAM (MADRISOLAR-2, S2009/PPQ/1533) is gratefully acknowledged. U.H. thanks the MEC (Spain) for a "Ramón y Cajal" research contract.

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