

Through the challenging synthesis of tetraphenylporphyrin derivatives bearing nitroxide moieties

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> **ABSTRACT:** Tetraphenylporphyrin derivatives a synthetic heterocycles with convenient preparation and a richness of properties which make them attractive in broad fields such as energy, life and materials sciences. Thus, in the quest for new radical architectures, tetraphenylporphyrins are prime candidates. To this end, we designed free-base tetraphenylporphyrins bearing nitronyl and imino nitroxide moieties covalently bonded to the *para*-position of the *meso*-phenyl substituent. Their detailed synthesis and characterization are reported here.

KEYWORDS: porphyrin, nitronyl and imino nitroxide, EPR, UV-vis, MALDI-TOF.

INTRODUCTION

Free radicals in general, and more particularly nitroxide, have witnessed a renewed interest due to the prospect that they may bring new technology such as organic batteries, molecular electronic or OFF–ON fluorescent probes, to name just a few. From the very famous commercial 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) through complicated architecture such as polyradical molecules [1, 2] or polymers [3], integration of nitroxide radicals into original architectures opens the way for novel applications.

The success of nitroxide free radicals is held in their relatively easy synthesis associated with incredible stability. In the case of tetraphenylporphyrins (TPP), nitroxides have most often been used as a decoration through carbon–carbon linkages to add some magnetism to their exceptional intrinsic electrochemical and photophysical properties [4, 5]. Surprisingly, incorporation of nitroxide into the skeleton of a porphyrin macrocycle has not been achieved so far. To do this, the nitronyl (NN) and imino (IN) nitroxide radicals, so called Ullman radicals, are particularly appealing. First, for decades they have proven very versatile as spin-carrying ligands in the design of state-of-the-art molecular-based magnetic materials [6]. Second, incorporation of Ullman radicals into the skeleton of a porphyrin is assumed to give a platform with much connectivity for 3D building while the π -conjugated system of the macrocycle should favor magnetic interactions among the radicals as well the metal center. This is fundamental to building up state-of-the-art magnetic materials.

Although there are a few examples of metalloporphyrins with axially-coordinated nitronyl nitroxide (NN) radicals [7], Ullman radical-appended porphyrins have been investigated only theoretically [8]. This pushes us to develop a synthetic pathway to handle free-base tetraphenylporphyrins bearing nitronyl (**TPP-NN**) and imino (**TPP-IN**) nitroxides on the *para*position of the *meso*-phenyl substituent (Scheme 1). Here, as model compounds, we describe the synthesis of porphyrins incorporating one unique Ullman radical

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Scheme 1. Syntheses pathways to porphyrin nitroxides TPP-NN and TPP-IN

well characterized by electron paramagnetic resonance (EPR), UV-vis and MALDI-TOF spectra, thus paving the way for promising applications.

RESULTS AND DISCUSSION

The detailed syntheses of free-base porphyrins bearing nitroxide moieties TPP-NN and TPP-IN, shown in Scheme 1, start from the formation of the precursor 5-(4-bromophenyl)-10,15,20-triphenylporphyrin (TPP-Br) which is obtained via the Adler method by condensation of 4-bromobenzaldehyde and benzaldehyde in a 1:10 ratio in the presence of pyrrole. These conditions gave a mixture of 5-10,15,20-tetraphenylporphyrin (TPP) and 5-(4-bromophenyl)-10,15,20-triphenylporphyrin (**TPP-Br**) which were inseparable by the usual chromatography technique (see Fig. S2). Thus post-modification was carried out on this mixture. This had no inconveniences, as **TPP** is inactive vs. halogen-lithium exchange reactions as involved in the insertion of the formyl group [9]. After the usual chromatography technique and with the help of characterization tools (see Figs S1, S3, S4), TPP-CHO was obtained in 35% yield.

The syntheses of **TPP-NN** and **TPP-IN** require more know-how. Indeed, the highly aromatic character of **TPP** induces (i) stabilization of the formyl group by resonance which restricts efficient condensation with the 2,3-bis(hydroxylamine)-2,3-dimethylbutane (**BHA**) and (ii) a decrease in solubility of the resulting 1,3-dihydroxyimidazolidine derivative which forestalls its oxidation [10].

Consequently, as for each novel molecule, the conventional Ullman's synthetic route [11-13] had to be adapted. The best condensation condition was achieved by refluxing TPP-CHO and BHA in a mixture of toluene/methanol (1:1). The completion of the reaction was determined by FT-IR observation until the disappearance of the CHO stretching band at 1698 cm⁻¹ (Fig. S5). The condensation product **TPP-NOH** was used without further purification. Only a small amount was chromatographed and characterized by MALDI-TOF mass and ¹H-NMR spectroscopy (Figs S6–S7). Interestingly, the choice of the oxidant was a determinant, as PbO₂ allowed only **TPP-NN** to be obtained, whereas NaIO₄ favored access to **TPP-IN**. The structures of the radicals were highlighted by EPR spectroscopy. The low yields of the reactions were attributed to the multichromatography purification process required to isolate and characterize the radical character without doubt. Upscaling is in progress.

TPP-NN and **TPP-IN** are fairly soluble in polar organic solvents, allowing for electron paramagnetic resonance (EPR) and UV-vis analyses in solution (Figs 1a, 1b and 1c). The EPR spectra of **TPP-NN** and **TPP-IN** and spectral simulations are presented in Fig. 1b. Characteristic features of nitroxide radicals are the



Fig. 1. (a) Chloroform solutions (10×10^{-6} M) of **TPP-CHO**, **TPP-NOH**, **TPP-NN**, **TPP-IN** from left to right. (b) X-band EPR spectra of **TPP-NN** and **TPP-IN** in chloroform recorded at 298 K. Each plot includes a simulated spectrum, bottom (blue), and an experimental spectrum, top. (c) Absorption spectra of **TPP-CHO** (**purple**), **TPP-NOH** (blue), **TPP-NN** (**pink**) and **TPP-IN** (orange) in chloroform solutions of 2–10 µM concentration range. Insets: absorbance *vs.* concentration

nitrogen hyperfine couplings with well-resolved bands that allow non-ambiguous determination of the radical identity. TPP-NN and TPP-IN have splitting patterns that contain unresolved proton hyperfine interactions, typically from the alkyl groups neighboring the nitroxide moiety. Regarding the nitrogen hyperfine couplings, the EPR spectrum of TPP-NN exhibits a quintet pattern with the relative intensities of 1:2:3:2:1 arising from the hyperfine coupling of electron spin (S = 1/2) with two equivalent ¹⁴N atoms (nuclear spin I = 1) in the imidazoline ring, characteristic of nitronyl nitroxide radicals. In case of TPP-IN, it has seven line motifs with an intensity ratio of 1:1:2:1:2:1:1 which is reasoned to be due to the interaction of the unpaired electron (S =1/2) with two inequivalent ¹⁴N nitrogen atoms (nuclear spin I = 1) in the ring, characteristic of imino nitroxide radicals. The splitting analyses of EPR spectra of porphyrin nitroxides TPP-NN and TPP-IN undeniably confirm their identities.

By comparing the nitrogen hyperfine coupling constants (HFCCs) of **TPP-NN** and **TPP-IN** with those of **Ph-NN** (2-phenyl-4,4,5,5-tetramethyl-2-imidazoline-3oxide-1-oxyl) and **Ph-IN** (2-phenyl-4,4,5,5-tetramethyl-2-imidazoline-1-oxyl) almost identical constants are found, suggesting that the porphyrin moieties are not influencing the radical character (Table 1). Splitting patterns, isotropic hyperfine coupling constants (α_N) and linewidth (ΔH_{p-p}) values are also in harmony with reported studies [1–2].

The typical absorption spectra of a porphyrin skeleton has characteristic bands [14] from $\pi \rightarrow \pi^*$ transitions (respectively, $1a_{1u} \rightarrow 1e_g^*$ and $1a_{1u} \rightarrow 1e_g^*$ seen as one

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Table 1. *g* Value and HFCCs (a_N) obtained from EPR studies in CHCl₃ solution

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	Giso	αN1 (Gauss)	$\alpha N2$ (Gauss)	Δ Hp-p (G)
TPP-NN	2.0087	7.58		1.78
TPP-IN	2.0072	9.21	4.33	1.62
Ph-NN ²	2.0089	7.5	_	2.0
Ph-IN ¹	2.0084	9.2	4.3	1.55

Table 2. UV-vis data in CHCl₃ at 10×10^{-6} M (λ_{max} in nm, ϵ in cm⁻¹ M⁻¹) for the B band at room temperature

Compound $λ_{Bmax}$ ε in CHCl ₃ (10 μM) TPP-CHO 420158400	
ТРР-СНО 420 158400	log ε
	(5.19)
TPP-NOH 420 167000	(5.22)
TPP-NN 416 227100	(5.35)
TPP-IN 416 229600	(5.37)

intense B band at 395–425 nm and up to four weaker Q bands at 480–700 nm). In contrast, characteristic bands by $n \rightarrow \pi^*$ transitions of nitroxide radicals are observed at 610 nm for NN derivatives and at 443 nm for INs [1–2]. The UV-vis spectra of **TPP-NN** and **TPP-IN** present the characteristic features of free-base tetraphenylporphyrin with an extreme intense B band at 416 nm and four weaker Q bands, however, they simply shade the $n \rightarrow \pi^*$ transition bands of radical moieties (Fig. 1c). Moreover, the nature of the substituents on the



Fig. 2. MALDI-TOF mass spectrum of 5-[4-(4,4,5,5-tetramethyl-2-imidazoline-3-oxide-1-oxyl-2-yl)]-phenyl-10,15,20-triphenyl-porphyrin (**TPP-NN**)



Fig. 3. MALDI-TOF mass spectrum of 5-[4-(4,4,5,5-tetramethyl-1-oxyl-2-imidazoline-2-yl)]-phenyl-10,15,20-triphenyl-porphyrin (**TPP-IN**)

para-position of the *meso*-phenyl substituent for **TPP**-**CHO**, **TPP-NOH**, **TPP-NN**, **TPP-IN** induces a small bathochromic effect (4 nm) and a hyperchromic effect (represented by the increase of the molar absorptivity ε of the band, Table 2).

TPP-NN and **TPP-IN** were also characterized by MALDI-TOF mass spectroscopy. Both compounds presented similar fragmentation of the radical moieties (Figs 2 and 3). **TPP-NN** was detected as $[M]^+$ whereas **TPP-IN** was detected as $[M + 2H]^+$ ion peaks at m/z = 769.751 and m/z = 755.814, respectively.

CONCLUSION

In summary, for the first time free-base tetraphenylporphyrins bearing NN and IN on the paraposition of the *meso*-phenyl substituent were prepared. This is an advancement towards achieving promising novel radical architectures. TPP-CHO was obtained by lithium-halogen exchange in 35% yield. Conversely, the challenging incorporation of NN and IN moieties was a success in spite of the high porphyrin aromaticity and low solubility of **TPP-CHO** in methanol. The use of a co-solvent, toluene, overcomes these disadvantages. Moreover, the oxidation either by PbO₂ or NaIO₄ allows access specifically to one targeted radical. The novel compounds were non-ambiguously characterized by EPR and UV-vis spectroscopy as well as MALDI-TOF mass spectrometry. Further studies are underway to obtain some metallated counterpart porphyrins and to study the metal-radical interaction.

EXPERIMENTAL SECTION

Synthetic procedures

The syntheses of **TPP-Br** [15], **TPP-CHO** [9] and **BHA** [16] were achieved according to published methods, slightly modified. Synthetic procedures and characterizations of **TPP-Br**, **TPP-CHO**, **TPP-NOH**, **TPP-NN**, and **TPP-IN** are provided in the supporting information.

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ABBREVIATIONS

Dimethylformamide (DMF), dichloromethane (DCM), *n*-buthyllithium (*n*-BuLi), 5-(4-bromophenyl)-10,15,20triphenylporphyrin (**TPP-Br**), 5-(4-formylphenyl)-10,15, 20-triphenylporphyrin (**TPP-CHO**), 5-[4-(4,4,5,5-tetramethyl-1,3-dihydroxy-2-imidazoline-2-yl)]-phenyl-10,15,20-triphenyl-porphyrin (**TPP-NOH**), 5-[4-(4,4,5,5tetramethyl-2-imidazoline-3-oxide-1-oxyl-2-yl)]-phenyl-10,15,20-triphenyl-porphyrin (**TPP-NN**), 5-[4-(4,4,5,5tetramethyl-1-oxyl-2-imidazoline-2-yl)]-phenyl-10,15,20-triphenyl-porphyrin (**TPP-IN**). 5

Supporting information

Detailed experimental procedures and Figs (S1–S7) not included in the text for brevity are given in the supplementary material. This material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml.

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