# Water-Soluble Star Polymers with a Phthalocyanine as the Core and Poly(ethylene glycol) Chains as Branches

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**ABSTRACT:** Uncharged water-soluble phthalocyanines (Pc's) and some metallophthalocyanines (Me-Pc's) were prepared by means of a chemical modification of a commercial Pc or by a cyclic tetramerization reaction starting from 4-nitrophthalonitrile derivatives. The necessary hydrophilicity for the water solubility of these Pc derivatives was achieved by the binding of eight 9-methoxytriethyleneoxy branches on peripheral Pc positions or, alternatively, four or eight linear poly(ethylene glycol) methyl ether (PEGME; weight-average molar mass = 350 or 750 g/mol) units. The chemical structure of these products was characterized by ^{1}H-NMR and matrix-assisted laser desorption/ionization–time -of -flight mass spectrometric analysis. Finally, their solutions were examined by ultraviolet–visible and luminescence spectroscopy and dynamic light scattering experiments. All of the samples were water soluble, although the formation of small aggregates was ascertained by dynamic light scattering measurements. Furthermore, a lower scattered light intensity was measured for Pc derivatives with longer PEGME branches, which, probably playing a more negative role in the self-assembly process, hindered the aggregation phenomenon. Preliminary data on their sensing ability are also reported. © 2012 Wiley Periodicals, Inc. J Appl Polym Sci 000: 000–000, 2012

**Key words:** light scattering; MALDI; star polymers

## INTRODUCTION

Phthalocyanine (Pc) derivatives are a versatile class of colored macrocyclic compounds widely used as artificial organic pigments and dyes. In the past 20–30 years, their peculiar chemical and physical properties, essentially due to the extended delocalization of the 18 π electrons of their conjugated ring system and to the kind of metal atom in their Pc core, have attracted considerable attention for applications in catalytic, electronic, and optical fields.[1–8] More recently, for their photochemical properties, Pc's have also been investigated as potential photosensitizers in the photodynamic therapy (PDT) of oncological diseases.[9,10] In this regard, Pc's appear to be potentially better candidates than porphyrins for their higher molar light absorption corresponding to the Q bands, which (depending on chemical structure, solvent, acidity, and metal atom in the Pc core) appear at wavelengths in the 500–800-nm range (radiations that also have better tissue penetra-

tion with minimal damage to exposed healthy cells), and for their higher triplet quantum yields.[10]

Generally, both the poor solubility of Pc's (which is essentially due to the strong hydrophobic nature of the hyperconjugate rings and their tendency to form molecular self-aggregates) and the easy quenching of the excited state (necessary for singlet oxygen formation) often limit Pc applications, as in the case of the biomedical PDT of tumors,[4–6] where solubility in aqueous media is considered a prerequisite.

As for porphyrins,[7] the Pc water solubility has been improved by the introduction of solubility-enhancing substituents in peripheral positions of its skeleton; this increases the molecular hydrophilicity (for ionic groups, e.g., pyridinium salts, carboxylate, sulfonate units) and/or reduces the molecular approach by steric hindrance and limits the self-stacking phenomenon.[9] However, although the presence of the free charges does not seem to modify the properties of porphyrins and pthalocyanines, the possibility of undesirable effects, with respect to the uncharged species, cannot be excluded, so there has been attention directed toward alternative solutions.[11(a,b)]

In this article, we report the synthesis of some water-soluble, uncharged metal-free Pc's and metallophthalocyanines (Me-Pc's) containing hydrophilic and biocompatible multiethyleneoxyl branches [triethylene glycol methyl ether (TEGME), poly(ethylene glycol) methyl ether (PEGME), weight-average molar

mass = 350 g/mol (PEGME$_{350}$) or 750 g/mol (PEGME$_{750}$)] covalently bound on Pc peripheral positions. Step by step, the chemical structures of the intermediate species and final Pc derivatives were investigated by NMR (compounds without paramagnetic metal in the molecule only) and by matrix-assisted laser desorption/ionization (MALDI)–time-of-flight (TOF) mass spectrometry. Moreover, their behavior in water solutions and their spectroscopic features were tested by ultraviolet–visible (UV–vis), luminescence, and dynamic light scattering measurements. Finally, preliminary measures of the behavior of our Pc's in sensing fields were performed.

## EXPERIMENTAL

### General

The chemical structures of the Pc's were investigated by MALDI–TOF mass spectrometry. The spectra were acquired with a Voyager DE-STR (PerSeptive Biosystems, Foster City, California) with a delay extraction procedure (25 kV applied after 2600 ns with a potential gradient of 454 V/mm and a wire voltage of 25 V) and detection in linear mode.[12] The instrument was equipped with a nitrogen laser (emission at 337 nm for 3 ns) and a flash Analog to Digital (AD) converter (time base = 2 ns). The samples were prepared by the mixture of the compound (ca. 0.1 nmol) with trans-3-indoleacrylic acid (used as a matrix, ca. 40 nmol) on the sampler target with tetrahydrofuran (THF) as a solvent. Mass spectrometer calibration was performed as reported in previous cases.[13] The mass-to-charge ratio ($m/z$) values reported in the spectra and in text refer to molecular ions of the most abundant isotope of each element in the molecule. ^{1}H-NMR spectra were acquired on a Bruker AC 200 F (Fremont, California) spectrometer interfaced with an Aspect 3000 computer with Bruker DISR 90 acquisition software. Samples were dissolved in $CO(CD_3)_2$ or $CDCl_3$, and the chemical shifts are expressed in parts per million compared to the signal of tetramethylsilane (TMS), which was used as an internal standard. UV–vis spectra were recorded at room temperature with a Shimadzu model 1601 (Kyoto, Japan) spectrophotometer in quartz cells with chloroform, THF, or water as a solvent. Luminescence measurements were carried out with a Varian (Santa Clara, California) Cary Eclipse fluorescence spectrophotometer with a $\lambda_{excitation}$ of 325 nm. Light-scattering measurements were performed with a duplicated Nd:YAG laser source ($\lambda = 532$ nm) at a power of 50 mW, linearly polarized orthogonally to the scattering plane. The scattered light at an angle of 90° was collected through two cooled Hamamatsu R943-02 (Iwata-City, Japan) photomultipliers positioned at the same scattering angle (pseudo-cross-correlation mode), and the signals were sent to a Malvern 4700 (Worcestershire, United Kingdom) correlator,

which built up the intensity autocorrelation function.[14] From the mean decay rate of the correlation function, it was possible to obtain the translation diffusion coefficient ($D$) of the scatterers and, from it, the hydrodynamic radius ($R_H$) through the Einstein–Stokes relation:

$$R_H = k_B T / (6\pi\eta D)$$

where $k_B$ is the Boltzmann constant, $T$ is the absolute temperature, and $\eta$ is the viscosity of the solvent.[15,16] The size distribution was obtained by inversion of the correlation function with the CONTIN algorithm.[17] The temperature was set at 22°C. All of the solvents and basic materials were commercial products (obtained from Sigma-Aldrich, Saint Louis, Missouri) and were appropriately purified before use. Triethylene glycol monomethyl ether, linear PEGME$_{350}$ and PEGME$_{750}$, having both a methoxy and hydroxyl unit as end groups, and 4-nitrophthalonitrile were pure products (from Aldrich, Saint Louis, Missouri). The weight-average molar masses of PEGME$_{350}$ and PEGME$_{750}$ were 350 and 750 g/mol, respectively, with a narrow molecular weight distribution (ca. 1.01). 9-Methyltriethyleneoxy-1-chloride (TEGMEC) and ω-methylpolyethyleneoxy-1-chloride (PEGMEC$_{350}$ or PEGMEC$_{750}$) were obtained by the chlorination of TEGME, PEGME$_{350}$, and PEGME$_{750}$, respectively, with thyonil chloride, as previously described.[11(a)]
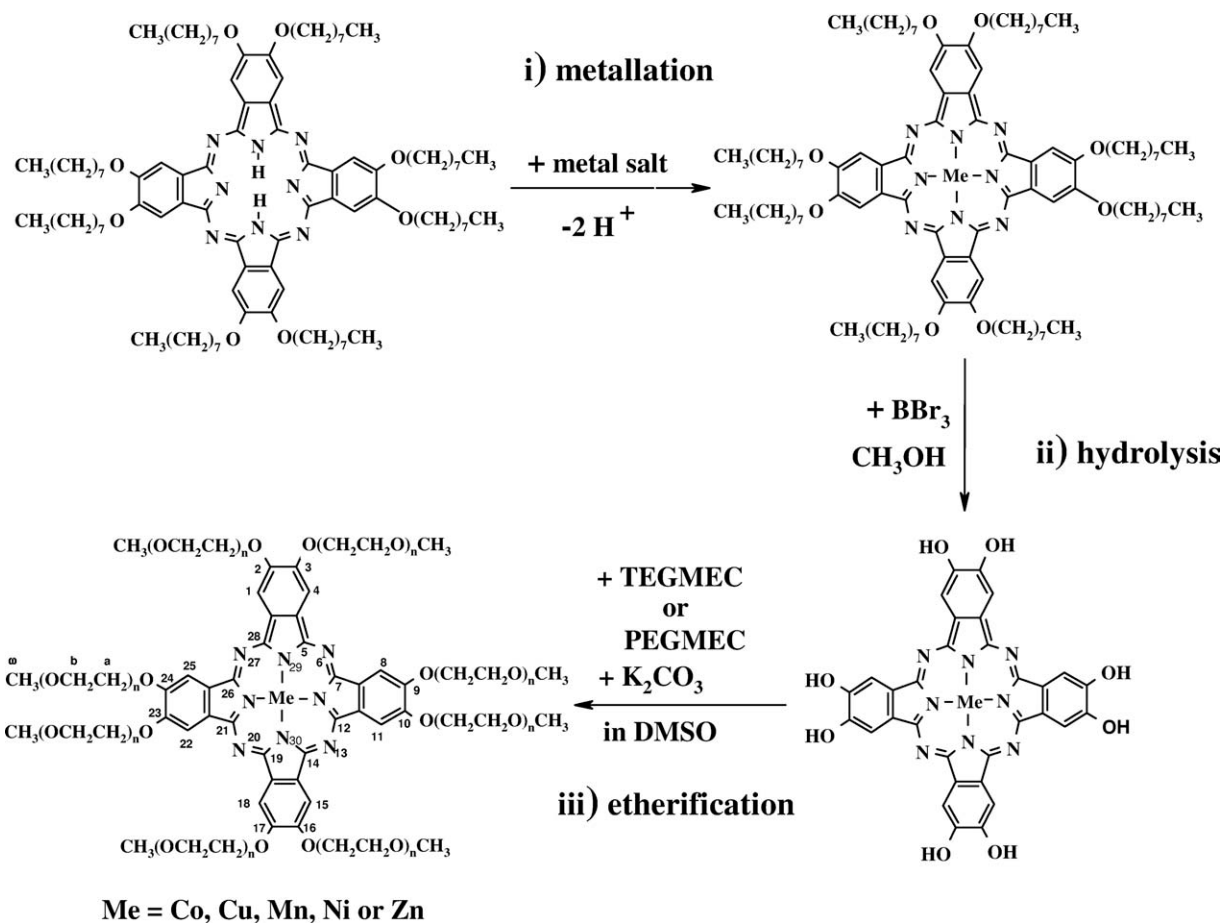
### Synthesis of 2,3,9,10,16,17,23,24-octakis (9-methoxytriethyleneoxy)-29H,31H-phthalocyanine (2H–Pc–8TEGME)

The synthesis of 2H–Pc–8TEGME was attempted by the hydrolysis of the 8-octyloxy groups of commercial 2,3,9,10,16,17,23,24-octakis(octyloxy)-29H,31H-phthalocyanine (2H-Pc-8Octyl; Aldrich) and subsequent reaction with TEGMEC, but because of the very low yield, the procedure was dropped, and the small amount of obtained product was used for spectroscopic comparisons only.

### Synthesis of 2,3,9,10,16,17,23,24-octakis (9-methoxytriethyleneoxy)-metallophthalocyanines (Me-Pc–8TEGME; Scheme 1)

Me-Pc–8TEGMEs were synthesized with commercial 2H-Pc-8Octyl by a three-step process according to Scheme 1. The steps were as follows: (i) insertion of metal atoms [Mn(II), Co(II), Ni(II), Cu(II), or Zn(II)] into the 2H-Pc-8Octyl core, (ii) hydrolysis of the 8-octyloxy groups to obtain corresponding 8-hydroxyl Me-Pc's, and (iii) etherification of the free hydroxyl groups by condensation with TEGMEC to obtain the Me-Pc–8TEGMEs. In a typical synthetic procedure, for example, for the Mn derivative

1. Step i: Octakis(octyloxy)-29H,31H-phthalocyanine (40 mg, 26.0 mmol) and manganese acetate

**Scheme 1** Synthetic procedure adopted for the 2,3,9,10,16,17,23,24-octakis (9-methoxytriethyleneoxy)-metallophthalocyanines and 2,3,9,10,16,17,23,24-octakis (ω-methoxypolyethyleneoxy)-metallophthalocyanine Me-Pc's. The atom numeration for the $^1$H-NMR assignments is also shown.

(45 mg, 0.26 mol) were dissolved in pyridine (4 mL). Then, the solution was maintained at reflux under vigorous stirring for 12 h. The octakis(octyloxy)-Mn-phthalocyanine was recovered by precipitation in water (yield = 60% with respect to the initial Pc amount), and its structure was confirmed by MALDI–TOF mass spectrometry analysis.

2. Step ii: To octakis(octyloxy)-Mn-phthalocyanine (29 mg, 18.2 mmol) dissolved in $CH_2Cl_2$ (10 mL), a solution of $BBr_3$ in $CH_2Cl_2$ (1$M$ solution) was added under stirring at room temperature. After 2 h, the mixture was refluxed for 18 h and then treated with $CH_3OH$ and cooled to stop the reaction. After filtration, the material contained in the solution was recovered by rotoevaporation *in vacuo* and dried *in vacuo*, and its structure was confirmed by MALDI–TOF.

3. Step iii: To a solution of octa(hydroxyl)-Mn-phthalocyanine (10.44 mg, $1.5 \times 10^{-2}$ mmol) in dimethyl sulfoxide (5 mL) placed in a vial, TEGMEC (44 mg, 0.24 mmol) and $K_2CO_3$ (33 mg, 0.24 mmol) were added. Then, the vial was sealed *in vacuo* and heated at 120°C for 6 days.

After cooling, the material contained in the vial was poured into ethyl ether and centrifuged. The solution was dried *in vacuo*, and the residue was extracted by $CHCl_3$. The final product was then obtained by drying *in vacuo* (yield ≈ 80%), and it was analyzed by MALDI–TOF mass spectrometry.

**Synthesis of 2,3,9,10,16,17,23,24-octakis (ω-methoxypolyethyleneoxy)-Cu-phthalocyanine (Cu–Pc–8PEGME₇₅₀)**

Cu–Pc–8PEGME₇₅₀ was synthesized according to the procedure reported previously and in Scheme 1 with PEGMEC₇₅₀ instead of TEGMEC in the third phase of the process.

**Synthesis of tetrakis(ω-methoxypolyethyleneoxy)-metallophthalocyanines (Me-Pc–4PEGME₃₅₀) by the metal-assisted cyclotetramerization of a phthalonitrile derivative [Scheme 2(i)]**

Tetra(polyethylenoxy)phthalocyanine complexes with cobalt or zinc were synthesized according to procedure i of Scheme 2. As an example, in the case of the
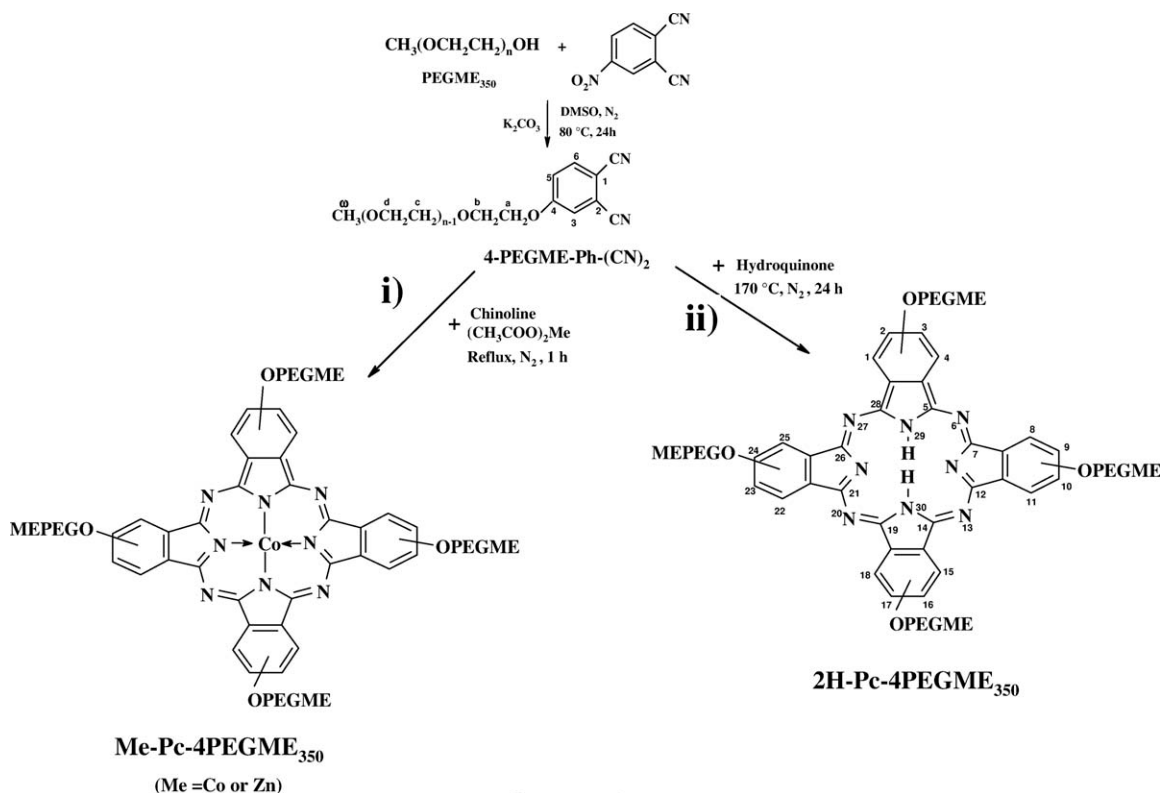
**Scheme 2** Synthetic procedure adopted for the (i) Me-Pc–4PEGME and (ii) 2H–Pc–4PEGME Pc's. The atom numeration for the ^{1}H-NMR assignments is also shown.

Co complex, 4-(ω-methoxypolyethyleneoxy)phtaloni-trile [4-PEGME$_{350}$–Ph(CN)$_2$] was initially prepared[18] by the reaction between 4-nitrophthalonitrile (6.19 g, 30.0 mmol) dissolved in dimethyl sulfoxide (50 mL) and PEGME$_{350}$ (14 g, 40.0 mmol) and K$_2$CO$_3$ (7.31 g, 53.0 mmol) under stirring in a nitrogen atmosphere at 80°C for 24 h. After cooling, the material, extracted with ethyl ether, was recovered by rotoeva-poration *in vacuo* and dried *in vacuo* at 50°C. Pure 4-PEGME$_{350}$–Ph(CN)$_2$ was then collected by column chromatography with Al$_2$O$_3$ as the stationary phase and CH$_2$Cl$_2$ as the eluent (viscous liquid, yield = 64%). Its structure was confirmed by MALDI–TOF mass spectrometry (the spectrum showed a series of peaks at $m/z = 159 + n44$, corresponding to the molecular ions as MH$^+$ of species with an increasing number of ethyleneoxy repetitive units in the Polyeth-ylene glycol (PEG) branch) and ^{1}H-NMR analyses. In particular, the ^{1}H-NMR spectrum in CO(CD$_3$)$_2$ showed the following signals (for the assignments, see Scheme 2): a doublet at 12.98 ppm (1 H, phenyl proton in position 6), a doublet at 12.31 ppm (1 H, phenyl proton in position 3), a double doublet at 11.95 (1 H, phenyl proton in position 5), a broad triplet at 5.75 ppm (2 H, methylene protons a), a broad triplet at 4.77 ppm (2 H, methylene protons b), a broad signal between 4.34 and 3.88 ppm (36 H, methylene protons c and d), and a singlet at 3.54 ppm (3

H methyl protons ω). Then, to a solution of 4-PEGME$_{350}$–Ph(CN)$_2$ (0.2 g, 0.392 mmol) in quinoline (25 mL) placed in a three-necked flash, cobalt(II) acetate tetrahydrate (0.25 g, 1.0 mmol) was added under a nitrogen atmosphere, and the mixture, under stirring, was refluxed for 1 h. The crude product, obtained by the removal of quinoline *in vacuo*, was dissolved in THF, and the solution was fractionized by column chromatography with silica gel as the stationary phase and a CHCl$_3$/MeOH/Triethylamine (98 : 1:1) mixture as the eluent. The final product was a tetra(ω-methoxypolyethylenoxy)–cobalt–phthalocya-nine isomer mixture (yield = 7.4%).

## Synthesis of metal-free tetrakis (ω-methoxypolyethyleneoxy)phthalocyanine (2H–Pc–4PEG$_{350}$) by cyclotetramerization of phthalonitrile [Scheme 2(ii)]

This metal-free Pc was obtained by procedure ii[18] in Scheme 2. In this case, 4-PEGME$_{350}$–Ph(CN)$_2$ (0.3 g, 0.59 mmol) was treated with hydroquinone (0.13 g, 1.18 mmol) in a vial sealed under nitrogen flow at 170°C for 48 h. After the cooling and breaking of the ampule, the material contained therein was treated with a 0.5$M$ NaOH aqueous solution (6 mL) before being dried *in vacuo*. The residue was then solubi-lized in CH$_2$Cl$_2$, and the final product was recovered by column chromatography with silica gel as the

stationary phase and a $CH_2Cl_2$/EtOH mixture (with a gradient from 90/10 to 60/40) as the eluent. The structure of 2H–Pc–4PEG$_{350}$ (yield = 55%) was confirmed by NMR and MALDI–TOF mass spectrometry analysis.

## RESULTS AND DISCUSSION

Because of their photochemical properties, Pc's are potential photosensitizers in the PDT of oncological diseases.[9,10] They also appear to be potentially better candidates than porphyrins[19] (currently used in PDT) for their higher molar light absorption corresponding to the Q bands (in the 500–800-nm range, radiations that also have better tissue penetration with minimal damage to exposed healthy cells) and for their higher triplet quantum yields.[10]

On the other hand, the stronger hydrophobic nature of these macrocycles amplifies the self-stacking phenomenon and often reduces their solubility.[4–6] In this article, we describe the synthesis of some uncharged water-soluble Pc derivatives characterized by the presence of hydrophilic linear oligoethyleneoxyl branches [in different numbers (4 or 8) and/or of different lengths (from 3 to >16 ethylenoxyl repetitive units)] bound on the peripheral positions of their skeleton.

Some Me-Pc's with eight triethylene glycol monomethyl ether units bound on their 2, 3, 9, 10, 16, 17, 23, and 24 Pc positions (indicated as Me-Pc–8TEGMEs) were prepared by the modification of 2H-Pc–8Octyl according to the three-step process reported in Scheme 1. Briefly, in the first step, a metal atom [Mn(II), Co(II), Ni(II), Cu(II), or Zn(II)] was inserted into the macrocyclic core. The eight octyl units were then removed by hydrolysis with BBr$_3$ in the second step, and, finally, in the third step, the obtained eight hydroxyl groups were subjected to an etherification reaction with TEGMEC.[11(a)]

For the case of the Mn(II) derivative, for example, the MALDI–TOF mass spectra of the starting 2H-Pc–8Octyl and the products obtained after each stage of the process are shown in Figure 1. The spectra were essentially composed of peaks corresponding to the molecular ions of the expected products, which were almost exclusively detected as MH$^+$ species. In particular, for 2H-Pc–8Octyl [Fig. 1(a)] a peak at $m/z$ = 1539 ($C_{96}H_{147}N_8O_8$) was obtained. For 2,3,9, 10,16,17,23,24-octakis (ω-methoxypolyethyleneoxy)-Mn-phthalocyanine (Mn–Pc–8Octyl) (step i), a peak [Fig. 1(b)] at $m/z$ = 1592 ($C_{96}H_{145}N_8O_8Mn$) was obtained with a difference of 53 Da with respect the 2H-Pc–8Octyl due to the substitution of the two hydrogens of the Pc core with an Mn atom. For octakis(octahydroxy)-Mn-phthalocyanine (Mn–Pc–8OH) (step ii), a peak [Fig. 1(c)] at $m/z$ = 696
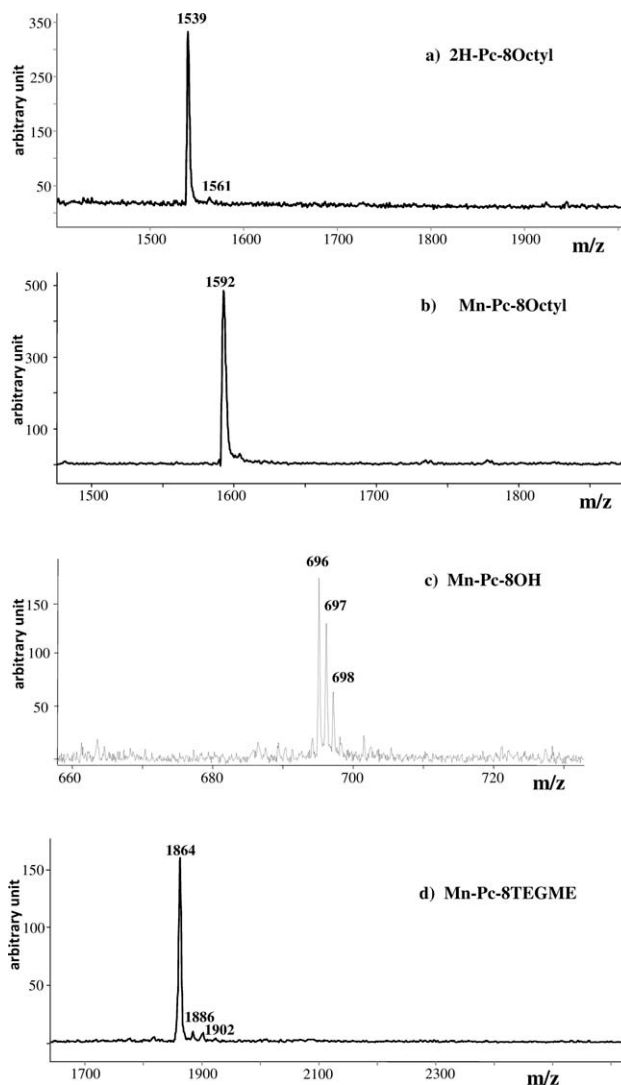


**Figure 1** Positive MALDI–TOF mass spectra of (a) 2H–Pc–8Octyl, (b) Mn–Pc–8Octyl, (c) Mn–Pc–8OH, and (d) Mn–Pc–8TEGME.

($C_{32}H_{17}N_8O_8Mn$) was obtained. Finally (step iii), for 2,3,9,10,16,17,23,24-octakis(9-methoxytriethyleneoxy)–Mn–phthalocyanine (Mn–Pc–8TEGME), a peak [Fig. 1(d)] at $m/z$ = 1864 ($C_{88}H_{129}N_8O_{32}Mn$) was obtained. The presence of the manganese(II) prevented NMR analysis. However, it was possible examine the Ni–Pc–8TEGME derivative, whose spectrum (omitted for brevity) confirmed the expected structure.

A similar synthetic procedure, with PEGMEC$_{750}$ instead of TEGMEC in phase iii of the process, was adopted to prepare Me-Pc derivatives with linear PEGME$_{750}$ branches. As an example, the MALDI–TOF mass spectrum of Cu–Pc–8PEGME$_{750}$ is shown in Figure 2.

Because of the polydispersity of PEGME$_{750}$, this spectrum, differently from the previous case [Fig. 1(d)], consisted of a large cluster of peaks between about 4500 and 7500 Da, which appeared at
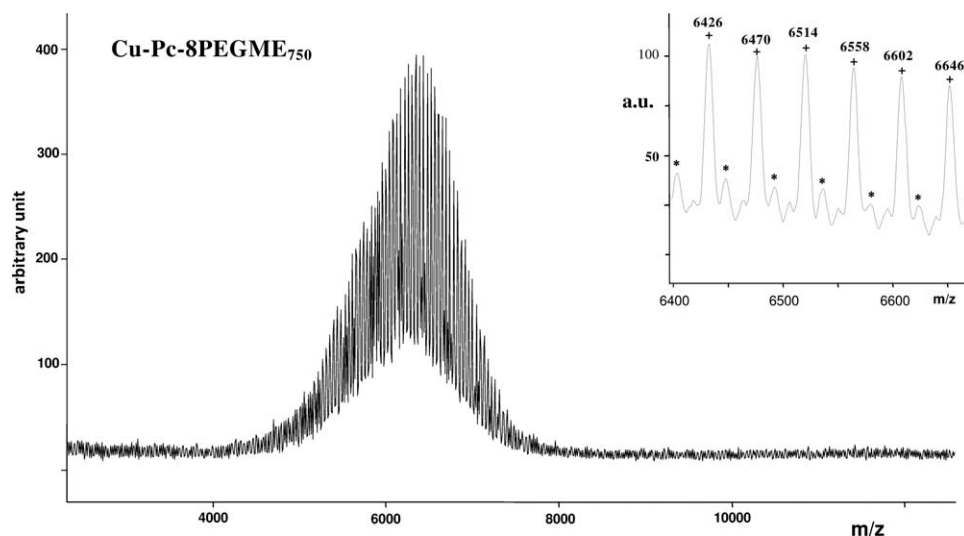
**Figure 2** Positive MALDI–TOF mass spectra of Cu–Pc–8PEGME$_{750}$.

increasing $m/z$ values of 44 Da as a consequence of the increasing total number of repetitive ethylene oxide units in the PEGME groups. We observed that each signal in the spectrum corresponded to more Pc species, all having the same molecular mass and then the same total number of repetitive ethylene glycol units but with a different distribution among the eight PEGME branches. In particular, the more intense signals, appearing at $m/z$ values of 838 + $n$44 (with $n$ = 75–150) and indicated by a plus sign in the inset of Figure 2, corresponded to the sodiated species {MNa$^+$ [C$_{40}$H$_{32}$CuNaN$_8$O$_8$ + $n$(C$_2$H$_4$O)]}. As an example, the peak at 6426 Da corresponded to the sodiated Pc isomers with a total number of 127 ethylene glycol units in the eight branches (i.e., C$_{294}$H$_{540}$CuNaN$_8$O$_{135}$). Peaks due to potassiated species were also present in the spectrum with lower intensities at $m/z$ = 854 + $n$44 [signals indicated with an asterisk in the inset], whereas protonated species were absent.

Cobalt and zinc Pc derivatives with four PEGME branches only were also prepared by means of a metal-assisted cyclic tetramerization reaction of 4-PEG$_{350}$–phthalonitrile (prepared by the reaction between 4-nitrophthalonitrile and PEGME$_{350}$, see Experimental section) according to procedure i of Scheme 2 with Co or Zn acetate as a template catalyst. The corresponding metal-free 2H–Pc–4PEGME$_{350}$ was instead synthesized by a reaction[19] between 4-PEG$_{350}$–phthalonitrile and hydroquinone at about 170°C in a sealed vial, according to procedure ii in Scheme 2.

The MALDI–TOF mass spectra of 2H–Pc–4PEGME$_{350}$ and tetrakis (omega-methoxypolyethyleneoxy)-Co-phthalocyanine 2H–Pc–4PEG$_{350}$ are compared in Figure 3. The spectrum of Co–Pc–4PEGME$_{350}$ [Fig. 3(a)] consisted of two overlapped clusters of peaks, both centered at about $m/z$ =

2000. This lower value with respect to the cluster present in the spectrum of Cu–Pc–8PEGME$_{750}$ in Figure 2 was due to both the smaller size and lower number of PEG groups in the Pc molecules. In particular, the peaks of the more intense species (indicated with a plus sign), appearing at $m/z$ = 692 + $n$44 [C$_{36}$H$_{25}$CoN$_8$O$_4$ + $n$(C$_2$H$_4$O) with $n$ = 20÷40), were due to the protonated species MH$^+$, whereas the peaks at $m/z$ = 714 + $n$44 (indicated with an asterisk) were due to the same oligomers ionized as sodiated species (MNa$^+$). A similar spectrum (omitted for brevity) was obtained for Zn–Pc–4PEGME$_{350}$.

In the MALDI–TOF mass spectrum of 2H–Pc–4PEGME$_{350}$ [Fig. 3(b)], the peaks due to MH$^+$ species, indicated with a number sign, appeared at $m/z$ = 635 + $n$44 [corresponding to C$_{36}$H$_{27}$N$_8$O$_4$ + $n$(C$_2$H$_4$O)]. At $m/z$ = 657 + $n$44 and 673 + $n$44 appeared, respectively, the MNa$^+$ species [indicated with a plus sign] and MK$^+$ species [indicated with a black circle]. With the presence of two H atoms instead of Co in the Pc core, the signals appeared at $m/z$ values lower by 57 Da with respect to the corresponding signals in Figure 3(a).

We also observed that unlike the Pc derivatives with 8-PEGME groups, each $m/z$ value in the spectra of Figure 3 matched more possible isomeric structures different by the position of the four PEG branches (i.e., Pc positions 2 or 3, 9 or 10, 16 or 17, and 23 or 24, see the formula in Scheme 2). Furthermore, with the presence of more isomeric structures, the $^1$H-NMR spectra of the Pc derivatives with only four ethyleneoxy branches (omitted for brevity) showed some very broad signals. So, as an example, the spectrum [in CO(CD$_3$)$_2$] of 2H–Pc–4PEGME$_{350}$ (see pertinent structure in Scheme 2) showed a broad signal at 7.73 ppm (4 H, phenyl protons 2 or 3, 9 or 10, 16 or 17, and 23 or 24), a
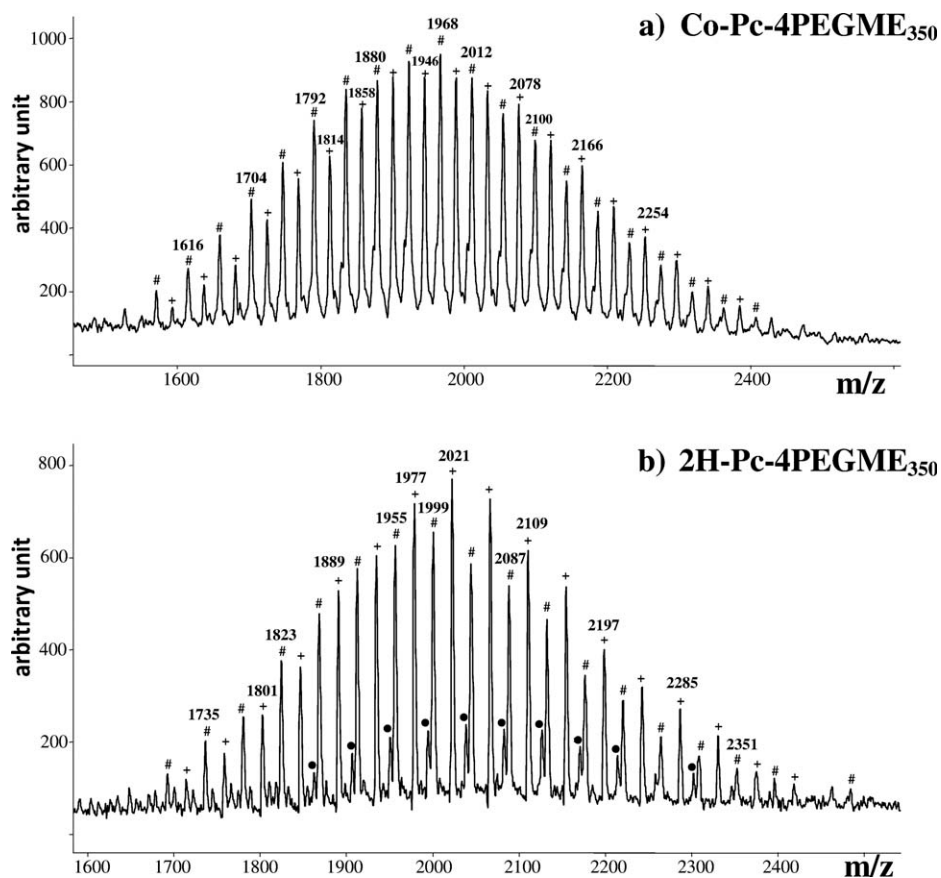
**Figure 3** Positive MALDI–TOF mass spectra of (a) Co–Pc–4PEGME$_{350}$ and (b) 2H–Pc–4PEGME$_{350}$.

broad signal at 7.25 ppm (8 H, phenyl protons 1, 4, 8, 11, 15, 18, 22, and 25), a broad signal between 4.54 and 3.38 ppm (144 H, methylene protons c and d), a singlet at 3.27 ppm (12 H methyl protons ω), and a broad singlet at −3.21 (2H, N—H protons 29 and 31).

With the hydrophilicity of the triethylene glycol (TEG) and PEG units (uniformly bound around the Pc core), our Pc derivatives (with and without metal atoms in the core) were soluble in water in addition to common organic solvents. In Figure 4, the UV–vis spectra of 2H–Pc–4PEGME$_{350}$ and Cu–Pc–8PEGME$_{750}$ in water, THF, and CHCl$_3$ solution are compared (similar spectra, omitted for brevity, were obtained for the all of the Pc samples). All of the spectra showed a strong light absorbance corresponding to the Q bands between 550 and 750 nm. Furthermore, the different lengths of the branches (TEG, PEG$_{350}$, and PEG$_{750}$) and the presence of a metal atom in the Pc core affected, in some cases significantly, the spectral features and induced changes in the number of Q bands[18] (which were less numerous with the metals) and both the wavelength of the maximum values of absorption and the intensity of the signals. In agreement with the literature data,[18,20] the molar absorption values in organic solvents fell between $1.5 \times 10^5$ and $2.0 \times 10^5$ L mol$^{-1}$

cm$^{-1}$, whereas those in aqueous solutions appeared at lower values, between $4.0 \times 10^4$ and $8.0 \times 10^4$ L mol$^{-1}$ cm$^{-1}$.

The photoluminescence of these compounds was also investigated, and as an example, in the inset of Figure 4(a), the fluorescence spectrum of 2H–Pc–4PEGME$_{350}$ in THF solution (Concentration = 7.34 × $10^{-7}$ M), exhibiting a strong emission centered at 705 nm upon excitation with 325 nm of radiation, is shown. As expected, water solutions were much less fluorescent (data omitted for brevity), and no photoluminescence phenomena were observed for the Me-Pc solutions.

In principle, both worse resolved UV–vis signals and lower photoluminescent emissions in water should be indicative of molecular self-assembly phenomena with respect to THF and CHCl$_3$ solutions. The dynamic light-scattering experiments on aqueous solutions of metal and metal-free Pc derivatives with 8TEGME or 8PEGME showed the formation of aggregated species having almost the same size. However, although the average hydrodynamic radii of the aggregates were about 100 nm with a size polydispersity of 20% (see a typical size distribution in Fig. 5), the Cu–Pc–8PEGME$_{750}$ solution displayed a lower light-scattered intensity (ca. half) with respect to the derivative with TEGME branches. This was
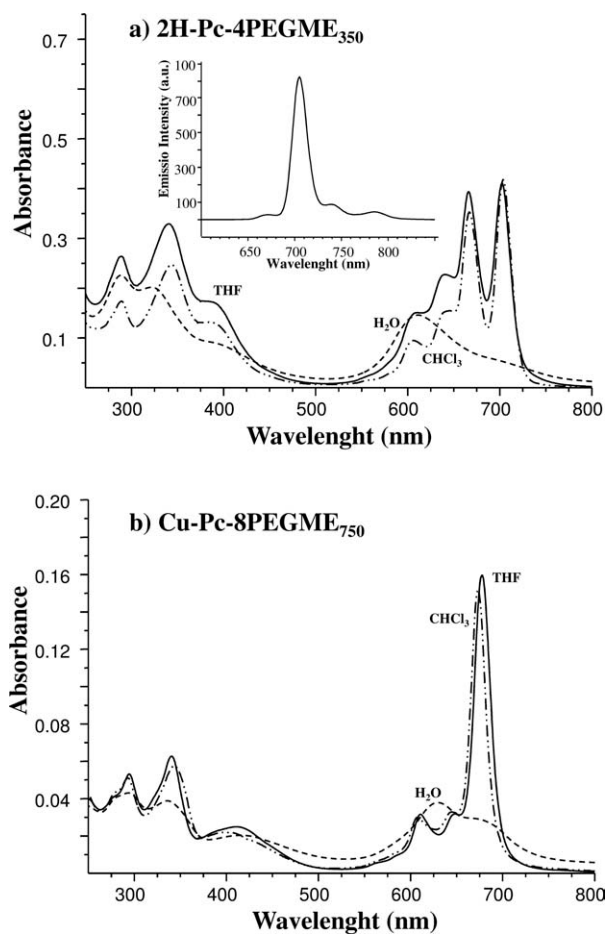
**Figure 4** UV–vis solution spectra in (- - -) H₂O, (— · · —) THF, and (—) CHCl₃ of (a) 2H–Pc–4PEGME₃₅₀ and (b) Cu–Pc8PEGME₇₅₀. In the inset, the fluorescence spectrum of 2H–Pc–PEGME₃₅₀ in THF solution upon excitation with 325 nm of radiation is also shown.

consistent with the presence of a smaller number of aggregates (ca. half, with the consideration that the absorbance and aggregate size were the same) in aqueous solution; this was probably due to a stronger steric hindrance of $PEGME_{750}$ chains (each corresponding to about 16 ethylenoxyl repetitive units) in the face-to-face stacking phenomenon.[21]

The potential applications of these water-soluble Pc's were preliminarily verified by examination of the ability of the metal derivatives to recognize amino acids (AAs) in aqueous solution.

For example, the molecular interactions between 2,3,9,10,16,17,23,24-octakis (ω-methoxypolyethyleneoxy)-Co-phthalocyanine (Co–Pc–8PEGME) and some AAs were evidenced by specific changes in UV–vis spectra of their aqueous solutions, as shown in Figure 6.

More marked modifications (in the position, shape, and/or intensity of the signals) occurred in the B-band regions. However, all of the changes were characteristic of each AA, probably because of
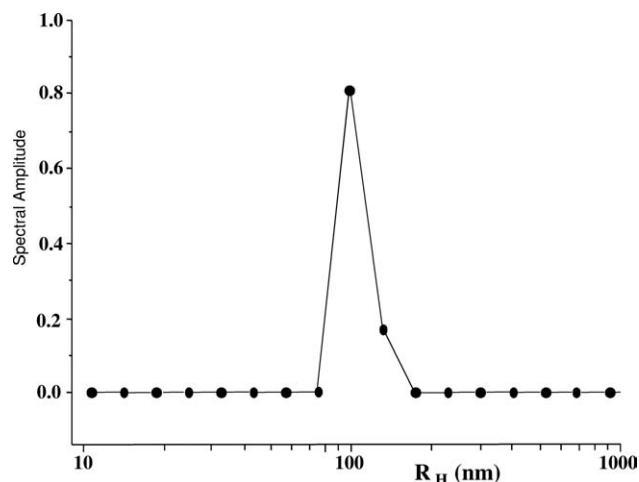
**Figure 5** Cu–Pc–8TEGME hydrodynamic radius size distribution from the light-scattering experiments in aqueous solution.

specific interaction between the AA and the cobalt atom and/or the π-electronic Pc system.[22]

The metal-free Pc's, not suitable for AA sensing, were tested as pH sensors. In particular, their behavior in acidic solutions was tested by examination of both the absorption and emission spectral changes of a 2H-Pc–PEGME₃₅₀ ($7 \times 10^{-6}$ M) aqueous solution upon addition of increasing amounts of acid. Both an intensity decrease of all bands and a relevant bathochromic shift of the Q-band region (whose main peak shifted from 613.4 to 636.7 nm) were observed.[20] As already reported for similar systems, these effects could have been due to the protonation (at pH < 6.5) of the nitrogens of the Pc core and to the protonation of the nitrogen in the meso position.[23]
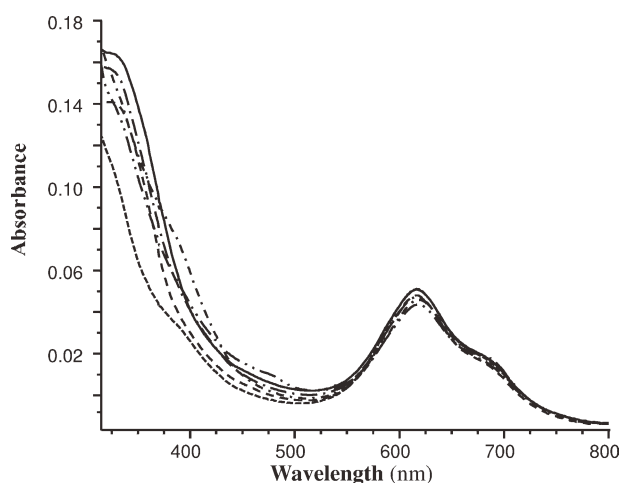


**Figure 6** UV–vis spectra of aqueous solutions of (– –) pure Co–Pc–8PEGME (Concentration = $1 \times 10^{-6}$ M) and its mixtures (molar ratio = 1 : 10) with (— · · —) tryptophan, (— · —) cysteine, (—) phenylalanine, (– · –) methionine, and (- - -) alanine.
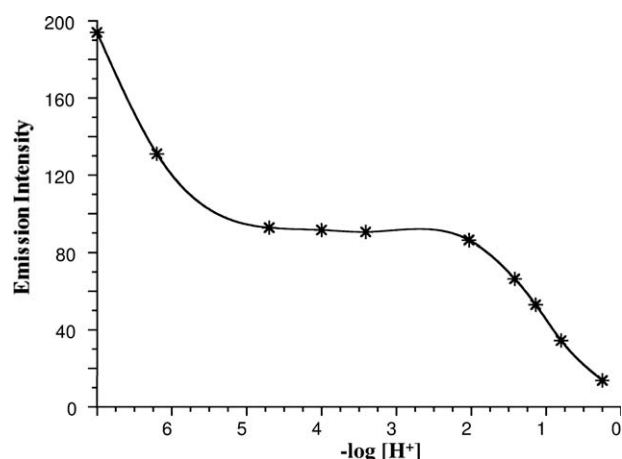
**Figure 7** Spectrophotometric titration of a 2H-Pc–PEGME$_{350}$ aqueous solution: emission intensity at 435.8 nm as a function of the added HCl amount. The spectra were corrected to take into account the dilution effect after each addition.

Changes were also observed in fluorescence spectra of this 2HPc–PEGME$_{350}$ ($7 \times 10^{-6}$ M) water solution upon excitation with 325 nm of radiation.[20] By comparison with the spectrum of the pure 2HPc–PEGME$_{350}$, which exhibited a strong emission at 453.8 nm, the first emission intensity reduction (47%, see Fig. 7) was observed when acid (HCl) was added up to about pH 6; this as due to nitrogen core protonation. A further strong intensity decrease (due to the protonation of the meso N atoms) appeared at about pH 2 with the almost disappearance of the fluorescence signal (down to 10% of the starting emission intensity). Remarkably, the starting system was regenerated by the addition of NaOH.

## CONCLUSIONS

In summary, we reported the synthesis of some new uncharged, water-soluble Pc's and Me-Pc's with TEG, PEGME$_{350}$, or PEGME$_{750}$ branches covalently bound on their peripheral positions. The chemical structure of these compounds was achieved by means of $^{1}$H-NMR and MALDI–TOF mass spectrometry. Despite a modest molecular aggregation phenomenon, evidenced by UV–vis, luminescence, and light-scattering data, all of the Pc derivatives were water soluble. In particular, dynamic light-scattering measurements indicated a lower aggregation for the samples with longer PEGME branches. Remarkably, to the best of our knowledge, these Pc compounds represent one of the few cases of uncharged, hydrosoluble Pc's, and a study is in progress of their possible applications in sensing and especially the biological fields.

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