

Proceeding Paper

# Synthesis, Self-Assembling and Photophysical Properties Exploration of Water Self-Dispersible, Grafted Poly(p-Phenylene Vinylene)s with Nonionic, Hydrophilic and Biocompatible Side Chains <sup>†</sup>

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**Abstract:** Conjugated polymers (CPs), in particular poly(p-phenylene vinylene)s (PPVs) are recognized as “smart” materials with potential applications ranging from opto-electronic devices to emergent technologies and to precision medicine. The present communication reports on the synthesis and structural characterization of new dibrominated macromonomers and their derived PPVs, of rod-graft-coil architecture, whose the grafted, biocompatible and hydrophilic side chains are either PEG-2000 or poly(2-methyl-2-oxazoline) or poly(2-ethyl-2-oxazoline). The Suzuki-Heck cascade reaction was used for PPVs’ obtainment. After PPVs’ structural characterization using specific techniques (as <sup>1</sup>H-NMR;GPC), the micellar, fluorescent nanoparticles formed by spontaneous self-assembling at simple direct dissolution in water were evaluated by dynamical light scattering for their size, complementary combined with Atom Force Microscopy (AFM) for their shape assessing. The PPVs’ micelles photophysical properties were revealed by UV-Vis spectroscopy and fluorescence measurements.

**Keywords:** biophotonics; poly(p-phenylene vinylene)s (PPV)s; macromonomers; rod-graft-coil architecture; poly(2-alkyl-2oxazoline)s; self-assembling; Suzuki-Heck cascade

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## 1. Introduction

Photonic nanomedicine promotes the progress of early detection and diagnosis of diseases, new modalities of light-guided and light-activated therapies, providing opportunities to advance healthcare technology with unprecedented precision and safety [1]. As such, there is an increasing demand to develop and optimize materials platform for biophotonic applications. Particularly, the design of biocompatible and biodegradable materials with desired optical properties, improved biocompatibility and biological functionalities is required [2]. Originally designed for the use in electronic and optoelectronic devices, conjugated polymers (CPs) have emerged as one of the most appropriate agents for biophotonics [3]. Typical examples are PPVs, recognized as representative of electroluminescent polymers, used for the construction of the first polymer light emitting diode [4]. Later on, it turned out that they could be the materials of choice for various type of

bioapplications. Taking the advantages of light harvesting, of light emitting and of photosensitizing capabilities, PPVs found applications for in vivo bioimaging [5], for photodynamic- [6], gene- [7] and immunotherapy [8], for drug delivery [9], as interesting biodegradable afterglow imaging agent [10], or for afterglow imaging-guided photothermal therapy [11]. It has previously been found that when the polymer side chains attached to the conjugated backbone are hydrophilic and biocompatible, better interaction with biological entities is occurring [12]. The resulting amphiphilic rod-graft-coil topology mediated an enhanced physiological stability for their derived micellar nanoparticles, while preserving the CPs' optical properties; this can be an optimized alternative to CPs nanoparticles encapsulation in amphiphilic biocompatible matrix by nanoprecipitation [13]. Following a similar strategy, the present communication introduces new amphiphilic, grafted poly(p-phenylene vinylene)s (*g*-PPVs), having hydrophilic side chains, differing in length, chemical nature and in attaching way. Using the "grafting through" approach [14], the new *g*-PPVs were synthesized by the Suzuki-Heck cascade polycondensation [15] of macromonomers derived from PEG or poly(2-alkyl-oxazolines) (POXA). The macromonomers and new *g*-PPVs were structurally confirmed by <sup>1</sup>H-NMR spectroscopy, whereas complementary use of DLS and AFM evidenced the size and shape of the micellar nanoparticles formed by spontaneous self-assembling in water. The formed micelles are fluorescent and the values of absorption and of emission maxima wavelengths were established by UV-vis and fluorescence measurements. To the best of our knowledge only a few *g*-PPVs with hydrophilic polymer side chains, aimed at bioapplications, have been reported [10,11,16], but this is the first one regarding *g*-PPVs having poly(2-alkyl-2-oxazoline) side chains.

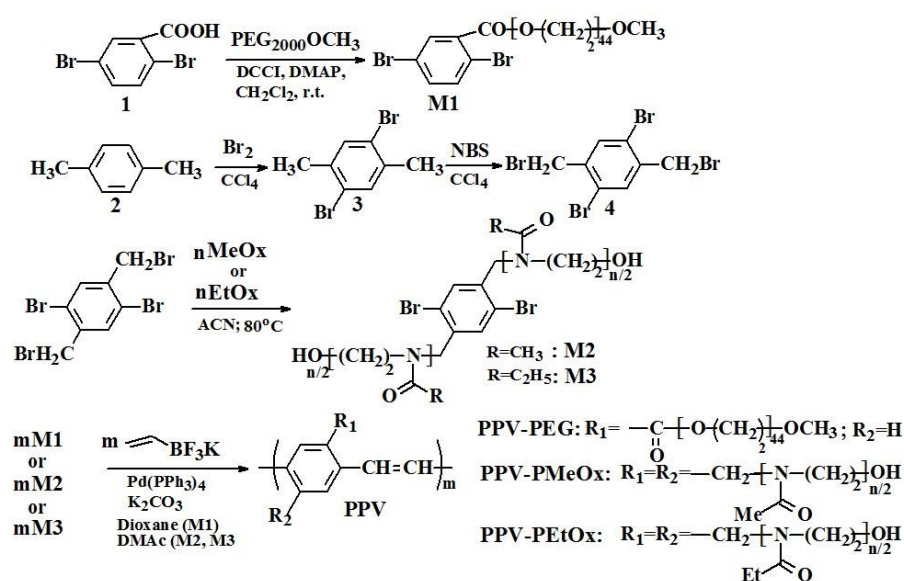
## 2. Materials and Methods

### 2.1. Materials

All chemicals were purchased from Sigma-Aldrich and used without further purification. All the solvents were purified and dried by usual methods before use.

### 2.2. Syntheses

Macromonomer **M1** in Scheme 1 was prepared by following a procedure previously described in detail [12]. 1,4-Dibromo-2,5-bis(bromomethyl)benzene (compound **4** in Scheme 1), used as initiator for synthesis of macromonomers **M2** and **M3**, was synthesized following the steps described in reference [17]. For polymers synthesis, in each case, an equimolar amount of potassium vinyltrifluoroborate and of macromonomer was used following a slightly modified protocol reported in reference [15]. The crude *g*-PPVs were obtained by precipitating the reaction mixture in cold diethylether. They were purified by reprecipitation from methanol to cold diethylether for three times followed by draying in vacuum oven at room temperature for 24 h.



**Scheme 1.** The route for synthesis of macromonomers (**M1**, **M2** and **M3**) and of their derived *g*-PPVs.

### 2.3. Methods

Nuclear Magnetic Resonance (NMR) Spectroscopy was performed on a Bruker Avance NEO 400 MHz spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany,) operating at 400.1 MHz for <sup>1</sup>H nuclei. All the experiments were recorded at room temperature (24 °C) by using, CD<sub>3</sub>OD and CDCl<sub>3</sub> as deuterated solvents. The relative molecular weight (M<sub>n</sub>) and index of polydispersity (IPD) were determined by gel permeation chromatography (GPC). The measurements were performed by using a WGE SEC-3010 multidetection system, consisting of a pump, two PL gel columns (PL gel 5 micro Mixed C Agilent and PL gel 5 micro Mixed D Agilent), dual detector refractometer/viscometer (RI/VI) WGE SEC-3010 and flow rate of 1.0 mL/min at 30 °C. The RI/VI detector was calibrated with PS standards (580–467,000 DA) having narrow molecular weight distribution. UV–vis absorption spectra were measured using a Specord 200 Analytik Jena spectrophotometer. Fluorescence measurements were carried out using a Perkin Elmer LS 55 apparatus. Particles size measurement was carried out by dynamic light scattering (DLS) using a Malvern Zetasizer Nano ZS instrument equipped with a 4.0 mW He–Ne laser operating at 633 nm and a detection angle of 173°. AFM micrographs of the polymers films were taken in air, on a SPM SOLVER Pro-M instrument. A NSG10/Au Silicon tip with a 35 nm radius of curvature and 255 kHz oscillation mean frequency was used. The apparatus was operated in semi-contact mode. The polymers films were prepared by drop casting the aqueous dispersion of the polymers at concentration of 0.01mg/mL on mica support.

## 3. Results and Discussion

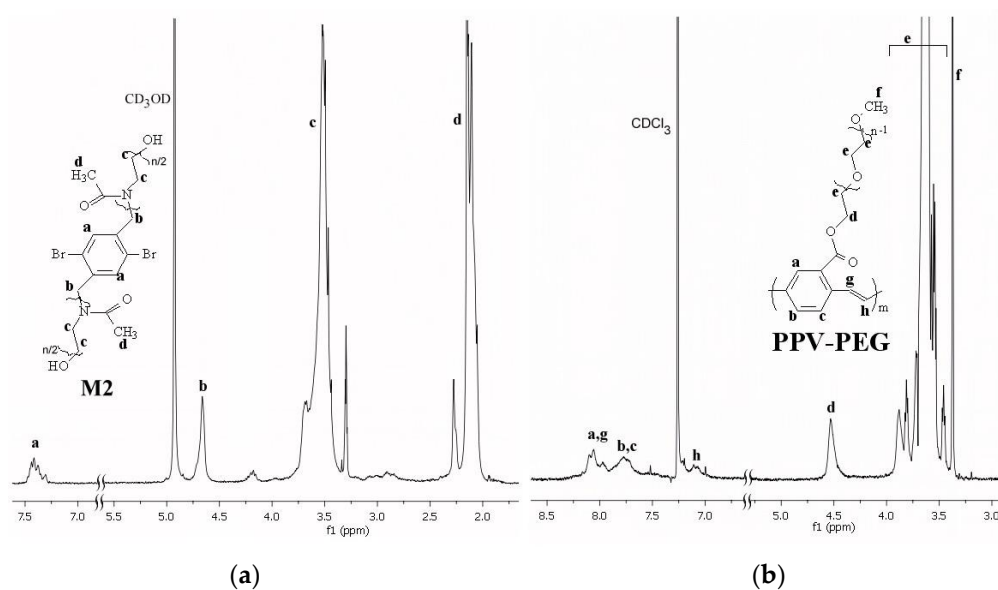
### 3.1. Syntheses of Macromonomers and of *g*-PPVs Based on Them-Structural Characterization

Macromonomer **M1** was obtained by end-group functionalization, through esterification of the hydroxyl function of PEG2000 monomethylether with 2,5-dibromobenzoic acid, in a similar manner as reported in [12]. By cationic ring-opening polymerization (CROP) of 2-methyl- or 2-ethyl-2-oxazoline, respectively were synthesized macromonomers **M1** and **M2**, using the initiator **4** (Scheme 1) in a ratio to the monomer (I/M) of 10/1 and 15/1, respectively.

The expected structure of the three macromonomers was confirmed, beside another techniques (like FT-IR, DSC), by <sup>1</sup>H-NMR spectroscopy. In Figure 1a, the spectrum of **M2** shows all the signals belonging to the protons characterizing the structure and exemplified in the enclosed molecular formula. By using the values of the integrals of peaks **a** or

**b** in conjunction with the ones for protons **c** or **d**, the polymerization degree of obtained PMeOx was evaluated as  $n = 10$ . In a similar manner for **M3** the degree of polymerization **n** of PEtOx was calculated as 14. For synthesis of amphiphilic *g*-PPVs, the versatile protocol of Suzuki-Heck cascade reaction was chosen, as it was claimed that percentage of structural 1,1-diarylenevinylene defects can be minimized [15]. In Figure 1b is given the  $^1\text{H-NMR}$  spectrum of polymer **PPV-PEG**, which shows, beside the signals characteristic to the starting macromonomer **M1**, also the peaks for protons **g** and **h** of the newly formed vinylene linkage.

The apparent molecular weight of the synthesized polymers was measured by GPC and the obtained values are given in Table 1.



**Figure 1.**  $^1\text{H-NMR}$  spectrum of (a) macromonomer **M2** in  $\text{CD}_3\text{OD}$  and of (b) **PPV-PEG** in  $\text{CDCl}_3$ .

The increased number of the electron withdrawing carbonyl groups in the structures of **M2** and **M3** could decrease the reactivity of bromine functionality, resulting in lower values of  $M_{n,\text{GPC}}$  for **PPV-PMeOx** and **PPV-PEtOx**, respectively.

**Table 1.** GPC data of PPV grafted polymers.

| Sample    | $M_{n,\text{GPC}}$ (IPD) <sup>a</sup> | $M_{n,\text{GPC}}$ (IPD) <sup>b</sup> |
|-----------|---------------------------------------|---------------------------------------|
| PPV-PEG   | 3825 (1.13)                           | 44,580 (1.13)                         |
| PPV-PMeOx | 276 * (1.02)                          | 8834 (1.07)                           |
| PPV-PEtOx | 705 * (1.07)                          | 10,950 (1.1)                          |

<sup>a</sup>—GPC measured in THF; <sup>b</sup>—GPC-measured in DMF; IPD—index of polydispersity; \*—unrealistic values.

### 3.2. Self-Assembling of PPVs in Water by Direct Dissolution

New amphiphilic *g*-PPVs self-assemble upon simple “dissolution” in water.

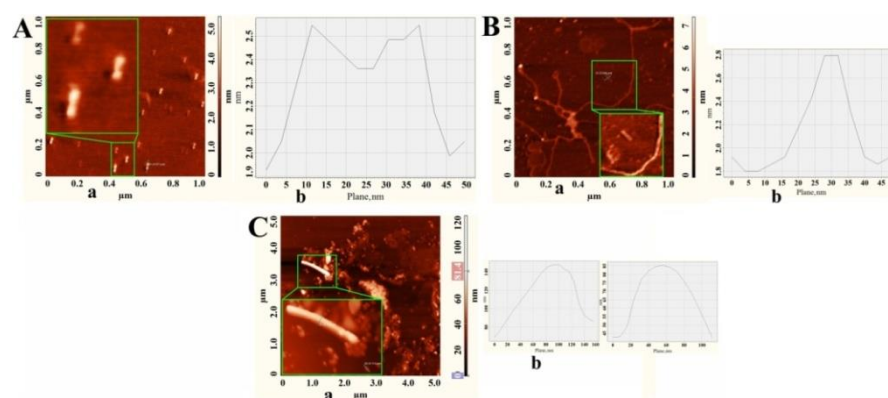
The visual confirmation of the formation of the self-assembled structures was done by AFM (Figure 2), which supports the obtained results of DLS (Table 2).

**Table 2.** Dependence of particle size on polymers’ concentration in water and some optical data.

| Sample  | Concentration (mg/mL) | Size (nm) | $\lambda_{\text{abs}}/\lambda_{\text{em}}$ (nm) <sup>a</sup> |
|---------|-----------------------|-----------|--|
| PPV-PEG | 0.001                 | - *       | nd   |
|         | 0.01                  | 6.1; 806  | 418/524  |
|         | 0.1                   | - *       | nd   |

|                  |       |            |              |
|------------------|-------|------------|--------------|
| <b>PPV-PMeOx</b> | 0.001 | 600; 4830  | nd           |
|                  | 0.01  | - *        | nd           |
|                  | 0.1   | 28         | 331/403      |
|                  | 1     | 373; 5290  | nd           |
| <b>PPV-PEtOx</b> | 0.001 | 72.5; 4960 | nd           |
|                  | 0.01  | 16.5; 4430 | nd           |
|                  | 0.1   | 1.58; 134  | 267/403; 420 |
|                  | 1     | 383; 4030  | nd           |

\* Obtained values exceeded the apparatus maximum limit; nd-not determined; <sup>a</sup> the values of the peak maxima, obtained in water, by UV-vis and fluorescence spectroscopy.

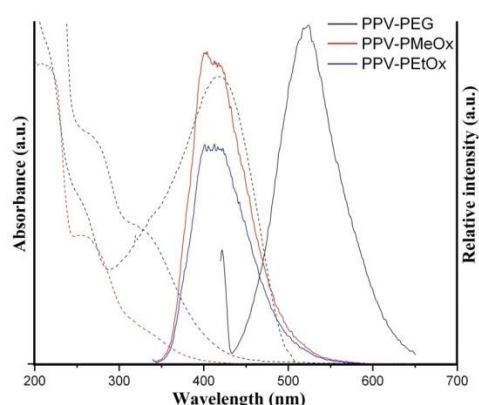


**Figure 2.** AFM micrographs of (A)—PPV-PEG; (B)—PPV-PMeOx;(C)—PPV-PEtOx; (a)—height contrast and (b)—cross-sectional traces.

The data from Table 2 suggest a dependence of the formed particles' size on the concentration of the polymers in water, with higher values both for the lowest concentrations and for the highest ones. **PPV-PEG** self-assembled in an interesting dumbbell-like shape (Figure 2A), while for **PPV-PMeOx** and **PPV-PEtOx** a heterogeneous, mixed morphology can be seen, dominated by the "rod-like" structures and by the sinuous fibers (Figure 2B,C).

### 3.3. Optical Properties of the PPVs' Self-Assembled Micellar Nanoparticles

As expected, the formed micellar structures are fluorescent in water, the side chains preserve the optical properties typical for PPVs but significantly influenced them. All polymers showed large emission bands (200 nm). While **PPV-PEG** micelles absorb light in visible region (Table 2) and emit in green-yellow range, with a maximum centered at around 524 nm, those formed by **PPV-PMeOx** and **PPV-PEtOx** absorb light in UV range and emit in visible with the maximum in blue range (Table 2). When comparing with the values reported for bare PPV [18], there are practical no differences for **PPV-PEG**, but the introduction of the POXA side chains produced a relevant hypsochromic effect, the emission maxima being blue shifted with more than 100 nm. This phenomenon was noticed by us [19,20] and by others [21] for *g*-PPVs. It could be due to the effect of the synergistic combination of the steric hindrance, imposed on the conjugated chain by the side chains, with the grafts' electronic peculiarities; in this case, the electron-withdrawing nature of the carbonyl groups in the side chains of POXA.



**Figure 3.** UV-vis (left side) and fluorescence (right side) spectra of g-PPVs, in water at 0.01 mg/mL.

The dependence of the photophysical properties on the size of the micelles as well as on the presence of some biomolecules (like proteins) will be studied in the future.

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