

# Solvophobic Effects in the Self-Assembly of Triangular-Shape Amphiphilic Oligo(phenylene ethynylenes)

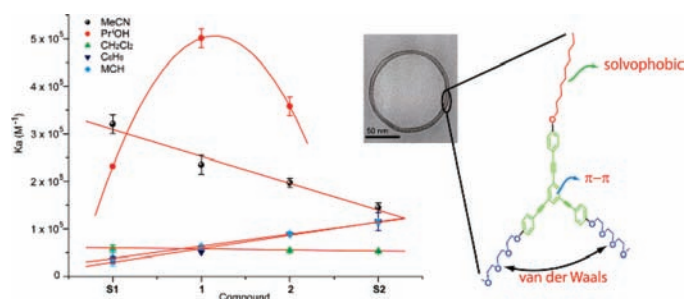
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## ABSTRACT



Triangular-shape OPEs, decorated in their periphery with a variable number of hydrophilic and hydrophobic substituents, have been synthesized to evaluate the influence of the solvent–solute and solute–solute interactions involved in their self-association. The similar size and electronic properties for these radial OPEs allow a direct evaluation of the solvophobic component of the  $\pi$ – $\pi$  stacking since any preferential Coulombic or dispersion effect can be discarded. In addition, the formation of aggregates in solution is efficiently transferred to surfaces and the formation of hollow vesicles can be observed.

The formation of helices from natural biomolecules like proteins or polynucleotides is guided by the participation of a number of noncovalent interactions and, significantly, by solvophobic effects.<sup>1</sup> Given that the flat  $\pi$ -surface of aromatic moieties and the aliphatic chains possess a nonpolar character, polar solvents favor their stacking to minimize the contact with solvent molecules, and as a consequence, solvophobic forces play a pivotal role in the stability and organization of supramolecular structures with natural<sup>1,2</sup> or synthetic<sup>3</sup> substrates, many of them presenting an amphiphilic character.

Nonspecific forces like  $\pi$ – $\pi$  interactions and, more specifically its solvophobic component,<sup>4</sup> also participate and control the creation of architectures with different morphology and dimensionality from self-assembled amphiphilic aromatic molecules. Vesicles, micelles, or (helical) fibers can be obtained from a variety of aromatic amphiphiles in which the aromatic core is constituted by hexabenzocoronenes,<sup>5</sup> perylenebisimides,<sup>6</sup> or different classes of  $\pi$ -conjugated oligomers.<sup>7,8</sup> We have recently reported on the formation

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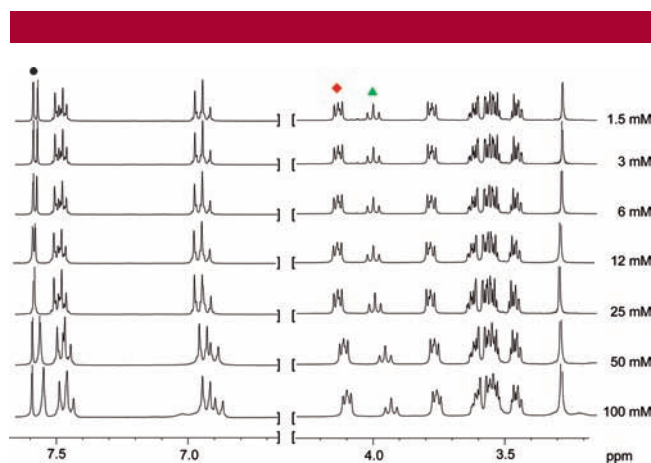
of supramolecular structures of different morphology and dimensionality (vesicles, toroids, networks or wires) from simple radial oligo(phenylene ethynylenes) (OPEs).<sup>9</sup>

Herein, we report on the synthesis, redox properties, and self-assembling features of a series of triangular-shape amphiphilic OPEs decorated with a variable number of polar triethyleneglycol (TEG) and aliphatic decyl chains in their periphery. The similar size and electronic properties of the new amphiphiles reported discard any preferential dispersion or Coulombic effect in their  $\pi$ -stacking, and therefore, a direct evaluation of the influence of solvophobic effects in the self-assembly can be extracted from this type of discrete amphiphilic systems.

Compounds **1** and **2**, endowed with a variable number of TEG and decyl chains and, therefore, with a modulated hydrophilia/hydrophobia relationship, have been readily obtained by following a one-pot Sonogashira cross-coupling protocol<sup>10</sup> in which the decyloxyphenyl units are first attached to the central aromatic fragment. Thus, for the synthesis of **1**, endowed with two TEG and only one decyl chains, 1,3,5-triethynylbenzene (**3b**)<sup>11</sup> was reacted with 1 equiv of the 1-(decyloxy)-4-iodobenzene **4a**<sup>12</sup> in the presence of triethylamine, copper iodide, and Pd(PPh<sub>3</sub>)Cl<sub>2</sub> as catalyst. The reaction was monitored by TLC until all starting materials **3b** and **4a** disappeared. After that, an excess of **4b**<sup>9a</sup> was added to the reaction mixture to afford **1** in 26% yield (Scheme 1). A similar strategy was followed to obtain

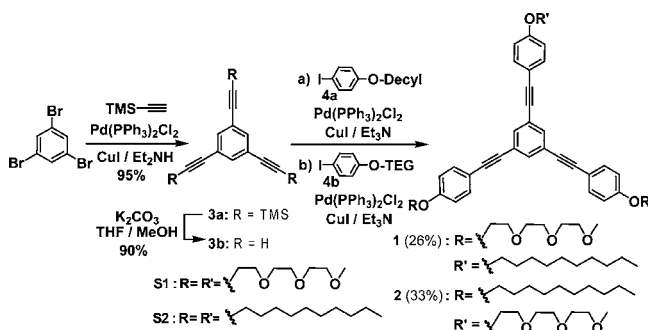
the heptamer ( $m/z = 5964$ ) are distinguishable for **1** and **2**, respectively (Figures S1 and S2, Supporting Information). Similar results have been obtained for the previously reported congeners **S1**<sup>9a</sup> and **S2**<sup>12</sup> (see the Supporting Information) bearing three TEG or three decyl chains, respectively (Figure S3, Supporting Information).

The self-assembly features of **1** and **2** in solution were first investigated by concentration-dependent <sup>1</sup>H NMR experiments (Figures 1 and S4, Supporting Information).



**Figure 1.** Partial <sup>1</sup>H NMR spectra (CD<sub>3</sub>CN, 300 MHz) of **1** at different concentrations (1.5–100 mM).

#### Scheme 1. Synthesis of Triangular-Shape Amphiphiles **1** and **2**



**2**, which possesses two decyl and one TEG chains, in 33% yield (Scheme 1). Compounds **1** and **2** have been fully characterized by NMR, FTIR, and UV–vis spectroscopy and MALDI-TOF spectrometry (see the Supporting Information).

A first insight into the self-assembly ability of compounds **1** and **2** was obtained from the corresponding MALDI-TOF spectra. Both amphiphiles show no preferential self-assembling properties in the gas phase since the presence of aggregated species up to the pentamer ( $m/z = 4290$ ) and to

Concentration-dependent <sup>1</sup>H NMR studies of **1** in CD<sub>3</sub>CN (300 MHz, 298 K, 1.5–100 mM)<sup>13</sup> show slight upfield shifts of most resonances upon increasing concentration, indicative of an eclipsed face-to-face  $\pi$ – $\pi$  stacking (Figure 1).<sup>4</sup> However, only the resonance corresponding to the protons of the central aromatic ring experienced a small shielding effect with increasing concentration when similar studies were carried out with **1** and **2** in C<sub>6</sub>D<sub>6</sub> (300 MHz, 298 K, 1.5–100 mM) (Figure S4, Supporting Information), which can be attributed to a rotated offset  $\pi$ -stacking.<sup>4</sup> Plotting the variation of the chemical shifts versus concentration reveals the different participation of the aromatic moieties in

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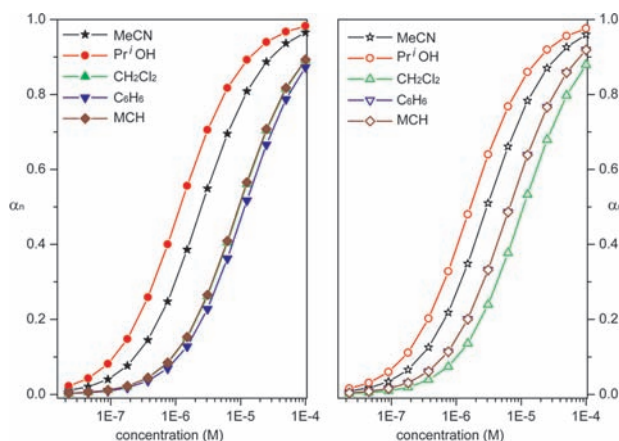
(13) The scarce solubility of less polar **2** in CD<sub>3</sub>CN at concentrations above of 10 mM has prevented a concentration-dependent <sup>1</sup>H NMR study in this solvent.

comparison with the peripheral chains in the self-assembly process of **1** and **2** (Figure S4, Supporting Information).

The small variation of the chemical shifts observed upon increasing concentration impedes the calculation of an accurate value for the association constant ( $K_a$ ). Thus, in order to attain the value of  $K_a$  and also to evaluate the influence of the solvent on this thermodynamical parameter, we have carried out concentration-dependent UV–vis investigations in a number of solvents of increasing polarity (Figures S5–8 and Table S1, Supporting Information).

The concentration-dependent UV–vis experiments carried out for **1** and **2** show identical spectroscopical features. As occurs in our previous described amphiphilic OPEs,<sup>9</sup> the appearance of bands of low energy is accompanied by the depletion of the higher energetic band at  $\sim 260$  nm. These features are diagnostic of the  $\pi$ -stacking of these amphiphiles to form supramolecular structures. In addition, we have calculated the  $K_a$  values for **1** and **2** and also for **S1** and **S2** by applying the isodesmic model<sup>14</sup> to the molar extinction coefficient (Figures S5–8 and Table S1, Supporting Information).<sup>9,15</sup>

The calculation of the molar fraction of  $n$ -mer aggregates ( $\alpha_n$ ) corroborates the applicability of the isodesmic mechanism for the self-assembly of the studied compounds (Figures 2 and S9, Supporting Information).<sup>14–16</sup> As expected, the

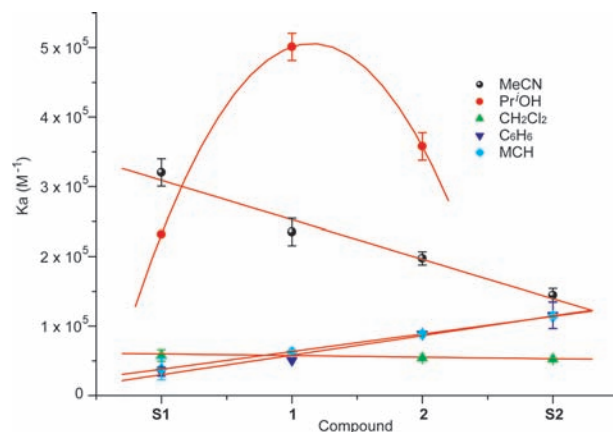


**Figure 2.** Molar fraction of  $n$ -mer aggregates ( $\alpha_n$ ) of **1** (left) and **2** (right) as a function of concentration in different solvents.

increase of  $\alpha_n$  for those amphiphiles bearing polar TEG chains (**S1**, **1**, and **2**) starts at lower concentration for polar solvents, which is diagnostic of their strong propensity to stack.

A detailed inspection on the  $K_a$  values calculated for the studied compounds in polar  $\text{CH}_3\text{CN}$  ( $\epsilon = 37$ ,  $E_{\text{T}(30)} = 45.6$

$\text{kcal/mol}$ )<sup>17</sup> reveals that this thermodynamic parameter decreases linearly with the increasing number of alkyl chains (Table S1 (Supporting Information) and Figure 3). As



**Figure 3.** Plot of the variation of the calculated  $K_a$  (UV–vis, 298 K) values in solvents of different polarity. Error bars are associated with an estimated maximum error of  $\pm 5\%$ .

expected, the opposite trend is observed for the  $K_a$  values determined for nonpolar solvents like benzene ( $\epsilon = 2.3$ ,  $E_{\text{T}(30)} = 34.3$   $\text{kcal/mol}$ )<sup>17</sup> or methylcyclohexane (MCH) ( $\epsilon = 2$ ,  $E_{\text{T}(30)} = 30.9$   $\text{kcal/mol}$ )<sup>17</sup> in which the  $K_a$  values increase linearly from compound **S2**, endowed with three aliphatic chains, to **S1** that bears three TEG substituents. Using a solvent of intermediate polarity as  $\text{CH}_2\text{Cl}_2$  ( $\epsilon = 9.1$ ,  $E_{\text{T}(30)} = 40.7$   $\text{kcal/mol}$ )<sup>17</sup> results in nearly identical  $K_a$  values regardless of the number of hydrophilic and hydrophobic chains. It is well-established that chlorinated compounds are “bad” solvents for favoring  $\pi$ – $\pi$  interactions which accounts for the low binding constants observed in  $\text{CH}_2\text{Cl}_2$ .<sup>3</sup>

Interestingly, when 2-propanol ( $\epsilon = 18$ ,  $E_{\text{T}(30)} = 48.4$   $\text{kcal/mol}$ )<sup>17</sup> is utilized to perform the concentration-dependent UV–vis investigations, the  $K_a$  values follow a parabolic trend (Figure 3) with a maximum value for the binding constant of compound **1** ( $\sim 5 \times 10^5$   $\text{M}^{-1}$ ) and a significant  $K_a$  value for compound **2** of  $\sim 3.5 \times 10^5$   $\text{M}^{-1}$ , higher than that determined for **S1** that possesses three peripheral polar chains. Under these conditions, solvent–solvent interactions are energetically favorable and give rise to a solvent cage that surrounds the arrays formed by positive solute–solute solvophobic interactions among the nonpolar aromatic moieties and the coiled decyl chains. These solvent–solvent and solute–solute interactions enhance the global  $\pi$ -stacking of the aromatic rings and increase the  $K_a$  values.<sup>3,4</sup>

The exothermicity of the self-assembly of amphiphile **1** in isopropanol has been studied by the van’t Hoff analysis of the  $K_a$  values determined by concentration-dependent UV–vis experiments at different temperatures (Figure S10). The obtained thermodynamic parameters are  $\Delta H = -27.07$

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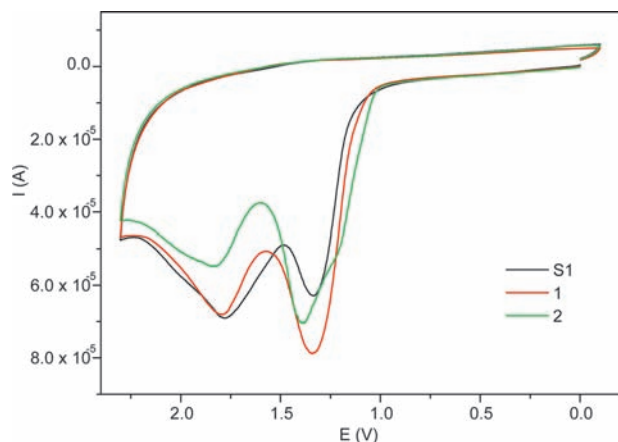
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$\text{kJ mol}^{-1}$  and  $\Delta S = -14.21 \text{ J mol}^{-1}$ . These negative thermodynamical values demonstrate that the enthalpy is the driving force in the aggregation of **1** in this solvent.<sup>18</sup>

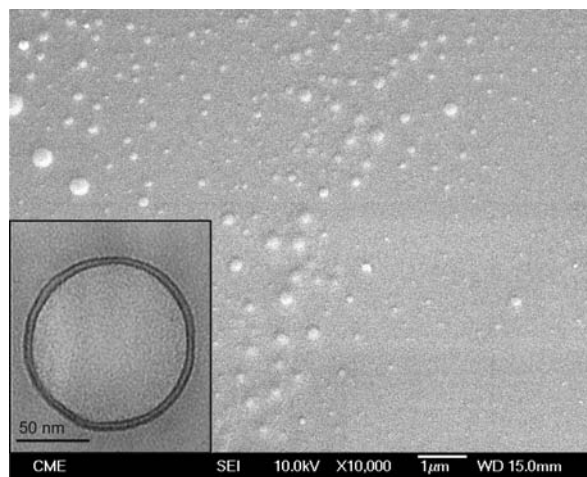
The redox characteristics of amphiphilic compounds **1**, **2**, and **S1**<sup>19</sup> have been examined by cyclic voltammetry in acetonitrile at room temperature (Figure 4). The similar



**Figure 4.** Cyclic voltammograms of amphiphiles **1**, **2**, and **S1** in acetonitrile (0.5 mM) at room temperature and at  $100 \text{ mV s}^{-1}$ .

electrochemical behavior—characterized by the appearance of two broad irreversible oxidation waves at  $\sim 1.3$  and  $\sim 1.7 \text{ V}$ <sup>20</sup>—discard any preferential Coulombic factor in the self-association features of the studied compounds.

Finally, we have also investigated the formation of organized supramolecular architectures onto surfaces for the case of amphiphile **1** in polar acetonitrile. Scanning electron microscopy (SEM) images of **1** on mica plates ( $\sim 10^{-4} \text{ M}$ , 298 K) reveal the formation of flattened spherical objects with diameters in the range of  $\sim 200 \text{ nm}$  (Figure 5). The vesicular character of these structures has been confirmed by transmission electron microscopy (TEM). The vesicles observed in TEM images present a membrane thickness of around  $8 \text{ nm}$  (inset in Figure 5) in good correlation with the previous results observed for amphiphile **S1**.<sup>9a</sup> These dimensions could imply the interaction between the hydrophobic decyl chains of two arrays of molecules of **1** pointing the corresponding hydrophilic TEG chains toward the interior and the exterior of the membrane. This arrangement guar-



**Figure 5.** SEM image (298 K) of a drop-cast of a  $\sim 10^{-4} \text{ M}$  solution of **1** in MeCN on a mica plate. The inset shows the TEM image, stained with uranyl acetate, of a hollow vesicle of **1** under the same experimental conditions.

antees the maximum contact for the polar chains with the polar environment remaining the apolar aromatic frameworks and decyl tails occult.

In conclusion, we have reported on the synthesis and self-assembling features of a series of triangular-shaped OPEs decorated in the periphery with a variable number of polar TEG and apolar decyl chains. The calculated  $K_a$  values for these compounds in a number of solvents (MeCN,  $\text{CH}_2\text{Cl}_2$ , benzene, and MCH) present a linear correlation between the number and nature of the peripheral substituents and the polarity of the solvent due to the input of  $\pi$ – $\pi$  and van der Waals interactions. Unexpectedly, this trend fails for the case of protic 2-propanol, in which the solvophobic contribution, not only between the aromatic frameworks but also between the decyl tails, raises the  $K_a$  value for **1** and **2**, despite the fact that all of the studied OPEs present a similar electronic character. van't Hoff analysis for compound **1** in this solvent demonstrates that the exothermicity of the self-assembly process is enthalpy-driven. Finally, the solvophobic effects experienced by the aromatic frameworks and the decyl chains of compound **1** result in the formation of hollow vesicles with a membrane thickness of  $\sim 8 \text{ nm}$ .

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**Supporting Information Available:** Experimental details and supplementary figures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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