

Morphological changes in the self-assembly of a radial oligo-phenylene ethynylene amphiphilic system†

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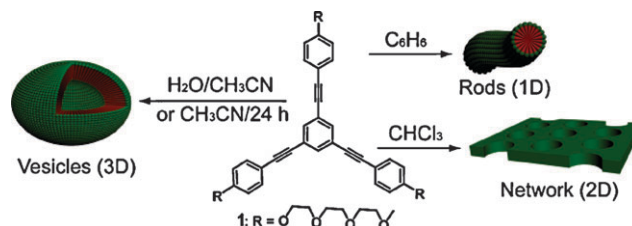
Varying polarity of the solvent leads to the formation of vesicles, planar networks or rod-like objects by the spontaneous self-assembly of a simple C_3 -radial oligophenylene ethynylene amphiphile.

The construction of supramolecular structures with specific size, shape and function by chemical self-assembly is ubiquitous in chemistry, materials science and biology.¹ The interaction of small molecules by non-covalent forces generates well-defined structures that can show interesting properties not presented by the isolated block molecules.² Small amphiphilic molecules, *i.e.* those comprising both hydrophilic and hydrophobic parts in the same molecule, are able to spontaneously self-assemble to form objects of different morphology, which, in some cases can be modified by varying some external factors.^{3–5} Hollow vesicles are especially interesting due to their potential application as molecular containers. A number of molecular amphiphilic systems, like those bearing squaraines,^{5b} perylene bisimides,⁶ biphenyl fragments,⁷ or oligophenylene ethynylene (OPE)^{5a,8} hydrophobic cores, has been successfully applied in the construction of supramolecular assemblies.

In this communication we report on the synthesis and self-assembling behaviour of a C_3 -radial OPE amphiphilic system **1** (Scheme 1 and Scheme S1†). Compound **1** self-assembles into nanoaggregates of different morphology—hollow vesicles, a planar network or rod-like objects—depending on the nature of the solvent used.

Compound **1**, unlike many other organic amphiphiles, was readily synthesized from commercially available 4-iodophenol and 1,3,5-tribromobenzene in only four steps with an overall yield of 45%. The structure of **1** was confirmed by NMR, FT-IR, UV-Vis and MALDI-TOF techniques (see ESI†).

The calculated Israelachvili critical packing parameter (P_c) value for **1** is 0.3—as expected for an equilateral triangle—which suggests that **1** can form spherical objects in polar solvents.⁹ First evidence of the self-assembly of **1** came from its MALDI-TOF spectra in which up to the pentamer is clearly distinguishable (Fig. S1†). Self-association of **1** was also studied by ¹H NMR dilution experiments in deuterated acetonitrile, chloroform and benzene (Fig. S2†). In polar solvents, such as CD₃CN and CDCl₃, most of resonances, the corresponding to the aromatic region and the triethyleneglycol (TEG) chains, were slightly shifted upfield with increasing concentration (Fig. S2a and S2b†).



Scheme 1 Chemical structure of **1** and cartoon representation of the morphology of the ensembles in different solvents.

In contrast, in a non-polar and aromatic solvent as benzene, only the aromatic signals shift upfield with increasing concentration whereas the TEG chains remain unaltered (Fig. S2c†). Furthermore, the central aromatic protons split into two sets of resonances that implies an offset face-to-face stacked structure¹⁰ in which the molecules of **1** are gradually rotated with respect to the axis formed by the central aromatic ring. This organization minimizes the contacts of the polar TEG chains and gives rise to the π - π arrangement of **1** into rod-like architectures (Scheme 1). The shielding of all resonances of **1**, observed in variable temperature (VT) ¹H NMR studies (298–238 K, 4 mM, CD₃CN, 300 MHz), also corroborates its self-assembly. Interestingly, the broadening of the NMR signals corresponding to the TEG chains with decreasing temperature demonstrates their significance in the formation of the supramolecular arrays (Fig. S3†).

The calculation of the association constant (K_a) of **1** in solution has been carried out by UV-Vis dilution experiments in acetonitrile (Fig. 1), chloroform and benzene (Fig. S4†), with

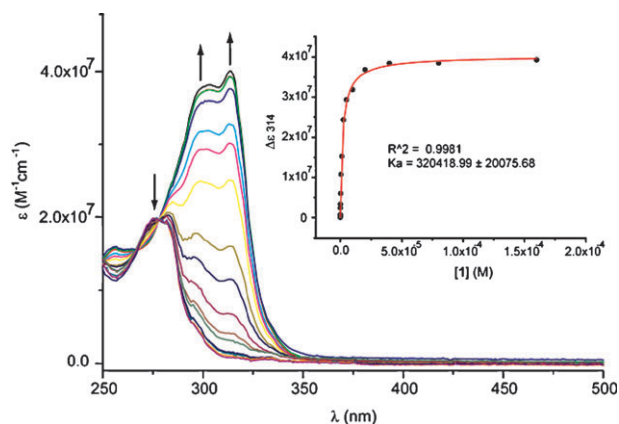


Fig. 1 Concentration dependent UV-Vis absorption spectra of **1** (CH₃CN, 298 K, 1.6×10^{-4} to 4.5×10^{-9} M). Arrows indicate the direction of change with increasing concentration. The inset shows the fit of $\Delta\epsilon$ (314 nm) to the isodesmic model.^{11,12}

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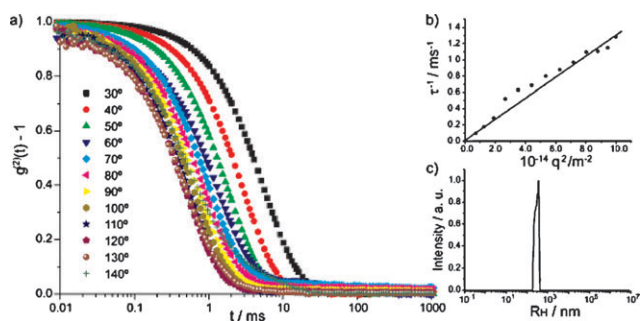


Fig. 2 Autocorrelation functions (a), linear correlation of the inverse of time *vs.* the square of the scattering vector (b), and normalized distribution of R_H (c) of **1** (H_2O -acetonitrile (1 : 1) $\sim 10^{-4}$ M).

values for K_a of $\sim 3.2 \times 10^5$, $\sim 6.1 \times 10^4$ and $\sim 3.4 \times 10^4 M^{-1}$, respectively.^{11–13}

The large K_a values, especially those calculated in acetonitrile, can be justified by considering the effect that van der Waals and solvophobic interactions between the TEG tails, together with the π - π stacking of the hydrophobic aromatic part of the molecule, exert in the association of **1**, as suggest the corresponding NMR studies.

CONTIN analysis of the dynamic light scattering (DLS) autocorrelation function has been carried out to determine the value for the vesicle size in a $H_2O/MeCN$ ($\sim 10^{-4}$ M) solution (Fig. 2). The linear fit obtained by plotting the inverse of time *vs.* the square of the scattering vector (q) shed a value for the diffusion coefficient (D) of $1.32 \times 10^{-8} cm^2 s^{-1}$ and, therefore, a calculated hydrodynamic radius (R_H) of 340 nm. These values are in a very good agreement with previous values of D reported for other vesicles.^{4c}

With the principal goal of visualizing vesicles, we carried out atomic force microscopy (AFM) imaging in polar solvents. AFM images of **1** from a 1 : 1 mixture of H_2O -acetonitrile ($\sim 10^{-6}$ M) on a freshly cleaved mica surface showed flattened spherical objects with an average diameter of 422 ± 7 nm,¹⁴

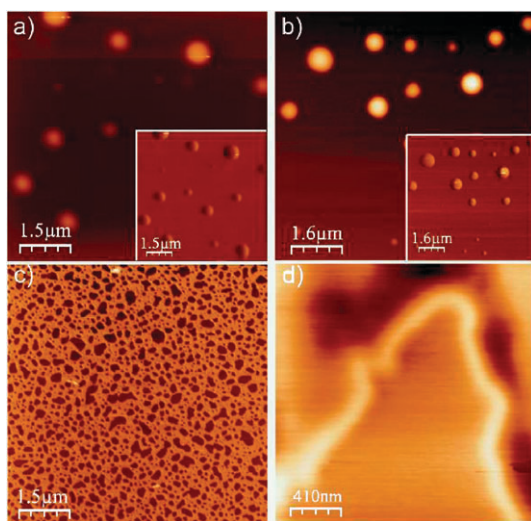


Fig. 3 Tapping-mode AFM images of **1** (air, 298 K, mica, $\sim 10^{-6}$ M) in H_2O -MeCN (1 : 1) (Z scale = 80 nm) (a); aged MeCN (Z scale = 50 nm) (b); chloroform (Z scale = 10 nm) (c), and benzene (Z scale = 10 nm) (d). The inset in (a) and (b) shows the corresponding phase AFM images.

calculated from the fitted histograms of the particle size after subtracting the tip-broadening parameter¹⁵ (Lorentzian distribution, $R^2 = 0.97$, Fig. 3(a) and S5†) and mean height of 71.8 ± 1 nm. Similar results have been obtained by scanning electron microscopy (SEM) imaging in which spherical objects are also observed (Fig. 4(a) and S6†). In contrast, a dropcast of a freshly prepared solution of **1** in acetonitrile ($\sim 10^{-6}$ M) onto mica showed the coexistence of a predominant network with circular in-plane holes and a profile height of around 10 nm together with isolated spherical objects of ~ 400 nm (Fig. S7†). Upon aging the same sample onto mica for 24 h, the porous network evolves to form flattened vesicular clusters with mean diameter of 384 ± 6 nm and height of 28.3 ± 0.3 nm as shown by AFM images (Fig. 3(b) and S8†). Such experimental evidence support that the self-assembly kinetics of **1** is slower in acetonitrile than in the more polar acetonitrile- H_2O mixture and vesicles are thermodynamically favored in comparison with the network.

The association of **1** to form vesicles in acetonitrile- H_2O has also been studied at different concentrations in order to estimate an approximate value for the critical concentration for vesicle formation. Thus, we first utilized a $\sim 10^{-4}$ M solution of **1** for AFM investigations. In these conditions, most vesicles collapse giving rise to mixtures of large and ellipsoidal aggregates together with isolated vesicles (Fig. S9a†). Regarding lower concentrations, an important insight about this critical concentration comes from the concentration-dependent UV-Vis investigations. The binding isotherm in any of the studied solvent reveals that at concentration below 10^{-8} M, compound **1** is practically unbound and, therefore, no supramolecular ensembles should be visualized in AFM images. That's indeed what we observe when studying the self-organization of **1** at low concentrations. Whereas at 10^{-7} M the vesicular assemblies are still observed although to a lesser extent (Fig. S9b†), at concentrations of 10^{-8} M and below, these aggregates are completely disrupted into small particles of nanometric size, thus demonstrating the prediction that self-assembly does not take place at concentrations below 10^{-8} M.

The hollow nature of the vesicular assemblies was confirmed by confocal fluorescence microscopy and transmission electron microscopy (TEM). Fluorescence microscopy images of **1** (1 : 1 mixture of H_2O -acetonitrile, $\sim 10^{-4}$ M) showed hollow spherical aggregates (Fig. 4(b)). TEM images of **1** (H_2O -acetonitrile (1 : 1), $\sim 10^{-4}$ M) confirm the spherical shape and the hollow nature for the vesicles (Fig. 4(c)). Moreover, TEM images provided evidence for the formation of vesicles with a wall thickness value of around 10 nm (Fig. 4(c)). This membrane could be formed by the π - π stacking of the hydrophobic cores

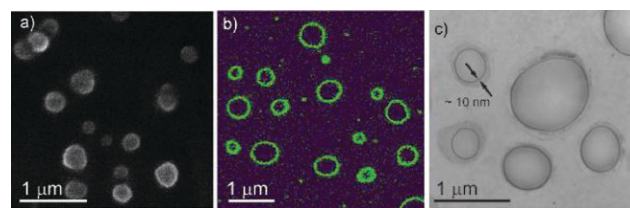


Fig. 4 SEM image (a), fluorescence micrograph (b) and TEM image onto a copper grid without staining (c) obtained from a H_2O -acetonitrile (1 : 1) solution of **1** ($\sim 10^{-4}$ M).

which is favoured by the extended conformation of the TEG chains, induced by the hydrophilic solvent. In addition, the solvophobic favourable interactions between the TEG chains^{16,17}—which have been experimentally proven by the VT ¹H NMR experiments—likely gives rise to a complex framework of the OPE **1** that finally yields spherical hollow vesicles (Scheme S1†).

Considering the dependence of the NMR features and K_a values for **1** on solvent polarity, we have also visualized that the morphology of the self-assembly of **1** can be modulated by using solvents other than polar acetonitrile or acetonitrile–H₂O mixtures. AFM images obtained upon dropcasting a freshly prepared solution of **1** in chloroform ($\sim 10^{-6}$ M) onto mica showed the presence of a network with irregular holes (Fig. 3(c) and S10†), similarly to that observed for freshly prepared acetonitrile. The lack of vesicles or other curved objects, together with the average profile height for the network (~ 2 nm), suggests the π -stacking of a very few molecules coplanar to the mica surface and intertwined with other molecules of **1** by the TEG chains. This molecular organization, probably influenced by the hydrophilic character of the mica surface, induces the network growing in-plane but not in height (Scheme 1 and S1†). However, for the case of dropcasting a benzene solution, AFM images display long wires of different heights, ranging from ~ 3.5 to ~ 100 nm (Fig. 3(d) and S11†). SEM images also prove the formation of wires under equivalent conditions (Fig. S12†). According to these dimensions, non-polar benzene induces the coiling of the hydrophilic TEG chains which, in turn, rotates the molecules of **1**—an effect that has been confirmed by concentration dependent ¹H NMR experiments in deuterated benzene—that self-assemble by π - π interactions to form wire-like assemblies.

In summary, the self-assembly ability of a radial OPE amphiphile, readily available in only four synthetic steps from commercial reagents, is reported. A number of techniques (MALDI-TOF, variable concentration and temperature ¹H NMR studies, dilution UV-Vis experiments, and DLS measurements) demonstrates the association of amphiphile **1**. The high value for the calculated association constant ($\sim 3.2 \times 10^5$ M⁻¹ in acetonitrile) accounts for the strong tendency of **1** to self-assemble as a consequence of the contribution of several classes of non-covalent forces, namely, π - π stacking, van der Waals and solvophobic interactions. AFM images demonstrate the morphological changes produced in the self-association of **1** by modifying the solvent polarity. Thus, the dimensionality of the ensembles obtained from **1** is directly proportional to the polarity of the solvent and rods, networks or vesicles can be unambiguously observed.

Work is in progress to explore the self-assembly of compound **1** in other conditions as well as for the synthesis of new amphiphilic congeners of **1** useful to attain vesicles and other supramolecular objects.

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