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Solvent-Dependent Disassembly of Amphiphilic OPE-Based Tricarboxamides

Julia Buendía and Luis Sánchez*

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Ciudad Universitaria s/n 28040 Madrid, Spain

lusamar@quim.ucm.es

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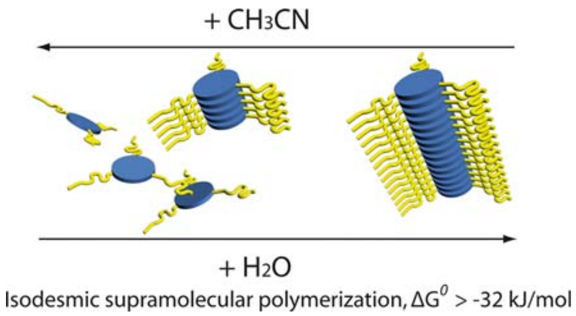
ABSTRACT



A series of water-compatible C_3-symmetric tricarboxamides endowed with a large number of EO side chains separated from the amide groups by different paraffinic linkers has been synthesized. The addition of a small amount of water breaks the N−H···O=C amide H-bonds but induces the formation of aggregates by a solvophobic effect. The lack of highly directional H-bonding interactions results in an isodesmic supramolecular polymerization with a calculated Gibbs free energy of −31.26 and −36.79 kJ mol^{-1} for 1 and 3, respectively.

A subtle balance of hydrophobic/hydrophilic effects dictates the formation of complex and functional natural structures by the assembly of biomolecules.[1] Proteins, nucleic acids, or polysaccharides interact in the aqueous, natural environment by the operation of noncovalent forces like H-bonding, $\pi-\pi$ stacking, or ion-pairing that tune this hydrophobic/hydrophilic balance.[2] However, the weakness of polarized H-bonds that operate efficiently in nonpolar environments is a major drawback for the formation of organized aggregates in water.[3] Tissue engineering[4] or stable hydrogels[5] illustrate the applicability of supramolecular structures formed in water by the combination of a number of noncovalent forces and especially H-bonding arrays. Ethylene oxide (EO) chains have been utilized as solubilizing media of supramolecular aggregates in water.[6] Unfortunately, these EO chains compete with polarizable N−H groups to form H-bonding arrays that disrupt an efficient and organized aggregation. Separating the H donor and acceptor units by a solvophobic pocket can circumvent this effect.[7]

We have described that C_3-symmetric oligo(phenylene ethynylene) tricarboxamides (OPE-TAs) decorated with paraffinic or polar tri(ethelene glycol) (TEG) chains self-assemble cooperatively into helical, columnar stacks by the

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synergy of triple N$-$H$\cdots$O$=$C amide H-bonding motifs and $\pi-\pi$ stacking.[8,9] Herein, we report the synthesis of a series of C_3-symmetric OPE-TAs endowed with a large number of EO side chains that, unlike the previously reported OPE-based tricarboxamides, yield water-compatible systems (compounds **1**$-$**3** in Scheme 1). In order to isolate the amide groups from the TEG peripheral chains, different paraffinic linkers separate these two functionalities. The stability of the intermolecular H-bonding arrays formed between the three amide functional groups that induce the formation of supramolecular aggregates in solution has been studied by different techniques. The addition of a small amount of water breaks the N$-$H$\cdots$O$=$C amide H-bonds but induces the formation of stable aggregates by a solvophobic effect. The stability of these aggregates has been quantitatively investigated by applying the folding–unfolding model recently reported for the disassembly of supramolecular polymers in mixtures of "good" and "poor" solvents.[10]

The synthesis of the amphiphilic tricarboxamides **1**$-$**3** requires a multistep synthetic protocol in which the preparation of the corresponding 4-iodo-*N*-substituted benzamides **6b**, **9b**, and **12** is a key step (Scheme 1). The synthesis of target tricarboxamides **1**$-$**3** starts with the previously reported dendronized alcohol **4**.[11]The sequential reaction of alcohol **4** with tosylate chloride, potassium phthalimide, and hydrazine hydrate results in the corresponding amine **6a** that is further reacted with 4-iodobenzoic acid to yield the iodo derivative **6b**. Compound **9b** was obtained by an analogous methodology for **6b** with the previous esterification reaction between alcohol **4** and the reported carboxylic acid **7**.[12] The preparation of the gallic acid derivative **12** requires two synthetic steps. The first consists of the condensation reaction between 4-iodobenzoic acid and the more nucleophilic amino group of 4-aminobutan-1-ol to attain the 4-iodobenzamide **10**. A subsequent esterification reaction between **10** and the previously reported gallic acid derivative **11**[13] endowed with three TEG chains yields compound **12**. A final three-fold Sonogashira cross-coupling reaction catalyzed by palladium of the 4-iodobenzamides **6b**, **9b**, and **12** with 1,3,5-triethynylbenzene[14] yields the target OPE-based tricarboxamides **1**$-$**3** in 33, 30, and 33%, respectively (Scheme 1).

The chemical structure of the new compounds has been confirmed by ^{1}H NMR, ^{13}C NMR, and FTIR spectroscopy and MALDI-TOF spectrometry. The C_3-symmetry of compounds **1**$-$**3** results in simple ^{1}H NMR spectra in $CDCl_3$ or CD_3CN with only three aromatic resonances at $\delta \sim 7.8$, 7.7, and 7.6 and a triplet at $\delta \sim 6.8$ corresponding to the amide functional groups. In addition, the polar EO and alkyl side chains appear as a complex set of resonances at $\delta \sim 3.5$ and ~ 1, respectively (see Supporting Information). The N$-$H, amide I, and amide II bands at $\nu \sim 3345$, 1650, and 1540 cm^{-1} observed in the FTIR spectra of **1**$-$**3** are a first indication on the relatively weak H-bonds established between the amide groups that finally yield columnar aggregates from the reported C_3-symmetric discotics (Table S1 and Figure S1).[9,15]

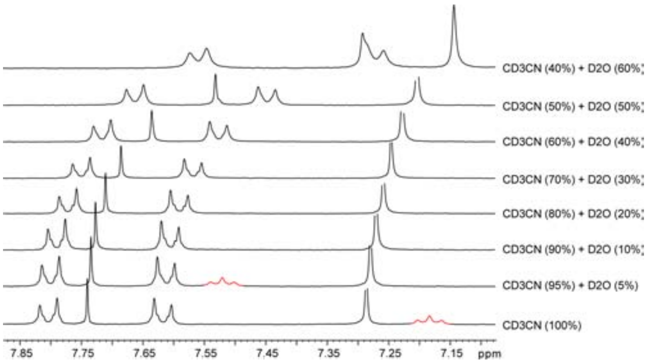

Figure 1. Partial ^{1}H NMR (300 MHz, 298 K, 2 mM) spectra of compound **3** in CD_3CN/D_2O mixtures.

The columnar aggregation induced by the π-stacking of the aromatic OPE units and the formation of a triple array of N$-$H$\cdots$O$=$C H-bonds in compounds **1**$-$**3** are justified by the upfield and downfield shift experienced by the aromatic and the amide resonances, respectively (Figures 1 and S2).[8] However, the challenging task to achieve with the reported tricarboxamides **1**$-$**3** is to attain stable aggregates in aqueous media. Compounds **1** and **3** are relatively soluble in water solution, but unfortunately, this is not the case for **2** in which the large hydrophobic content impedes its solubilization in water even at very low concentration. To estimate the stability of the N$-$H$\cdots$O$=$C H-bonds of compounds **1** and **3**, we have first registered ^{1}H NMR spectra of these tricarboxamides in mixtures of deuterated acetonitrile and water (Figures 1 and S3).

The addition of increasing amounts of water results in the gradual shielding of the aromatic resonances diagnostic of a more efficient π-stacking between the OPE moieties due to the solvophobic effect. At the same time, at low percentage of added water, it is possible to detect the triplet corresponding to the amide H-bonded proton that finally disappears due to the rapid exchange between this proton and the deuterium of the solvent. Interestingly, the amount of added water that breaks the H-bonded amide functional groups is 5 times higher in compound **3** (5%) than in compound **1** or in the amphiphilic tricarboxamides

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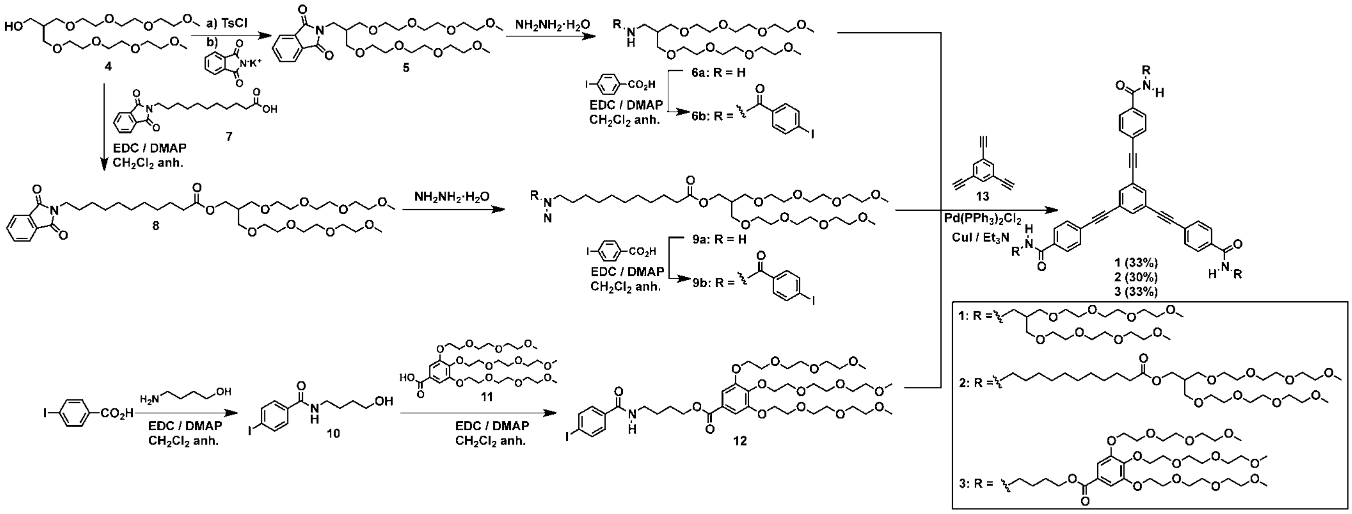
Scheme 1. Synthesis of Amphiphilic Tricarboxamides **1**–**3**



previously reported by our group (1%).[9] The higher stability of the H-bonds between the amide functionalities in compound **3** could be adscribed to the larger paraffinic chain that links the amide groups and the EO chains.

The ^{1}H NMR data indicate that amphiphiles **1** and **3** form aggregates in aqueous solution without the participation of highly directional H-bonds which could exert a relevant influence on the thermodynamics of the self-assembly of these discotics. We have previously demonstrated by variable-temperature measurements that OPE-based tricarboxamides decorated with paraffinic side chains self-assemble cooperatively into helical, columnar stacks.[8] However, to determine the self-assembly mechanism of compounds **1**–**3**, it is not possible to utilize temperature-dependent measurements since increasing the temperature above the lower critical solution temperature (LCST) in nonionic amphiphilic molecules results in turbid dispersions with a strong scattering effect.[7d,16] Figure S4 illustrates this effect for compound **3** that exhibits a LCST value of 40 °C.

To quantify the stability of the aggregates formed from the self-assembly of **1** and **3**, we have applied the folding–unfolding model for the disassembly of supramolecular polymers in mixtures of "good" and "poor" solvents.[10] In this model, the Gibbs free energy gain upon monomer addition in a mixture of solvents ($\Delta G^{0'}$) and the Gibbs free energy in a pure solvent (ΔG^{0}) are linearly correlated by the volume fraction of good solvent f and the m parameter (eq 1).

$$\Delta G^{0'} = \Delta G^{0} + mf \tag{1}$$

Compounds **1** and **3** present broad UV–vis spectra with an absorption maximum at 304 nm in aqueous solution but two well-defined absorption maxima (298 and 315 nm) in acetonitrile (MCN), in good agreement with the spectroscopic features reported for aggregated and molecularly dissolved OPE-TAs, respectively. The addition of small amounts of MCN to aqueous solutions of **1** or **3**, keeping constant the total concentration at 1×10^{-4} M, transforms the band at 304 nm into the two bands at 298 and 315 nm. This conversion implies the dissassembly of the aggregates formed by **1** and **3** in aqueous solutions (Figures 2 and S5).

Plotting the variation of the fraction of aggregates against the volume fraction of acetonitrile as a good solvent results in sigmoidal curves characteristic of an isodesmic mechanism.[10] The derived values of ΔG^0, m, and the cooperativity factor σ obtained from the corresponding denaturation curves of **1** and **3** by using CH_3CN/H_2O mixtures at different concentrations are collected in Table 1. The addition of water to the MCN solutions of **1** and **3** breaks the H-bonding interaction between the amide groups but increases the π-stacking of the aromatic moieties by a solvophobic effect. Despite both amphiphiles possessing the same OPE central core, the Gibbs free energy gain upon monomer addition is around 5 kJ mol^{-1} higher in **3** than in **1**, and the m parameter is also larger for **3** than for **1**. These calculated values can be reasonably accounted for by considering the larger hydrophobic spacer present in amphiphile **3**. Unfortunately, the scarce solubility of compound **2** in aqueous solution impedes the application of the folding–unfolding model to quantify the Gibbs free energy released upon monomer addition.

Tricarboxamide **2** also shows the absorption maxima at 298 and 315 nm in MCN that become a broad band centered at 303 nm upon the addition of water. Unfortunately, increasing the water ratio above 70% produces a

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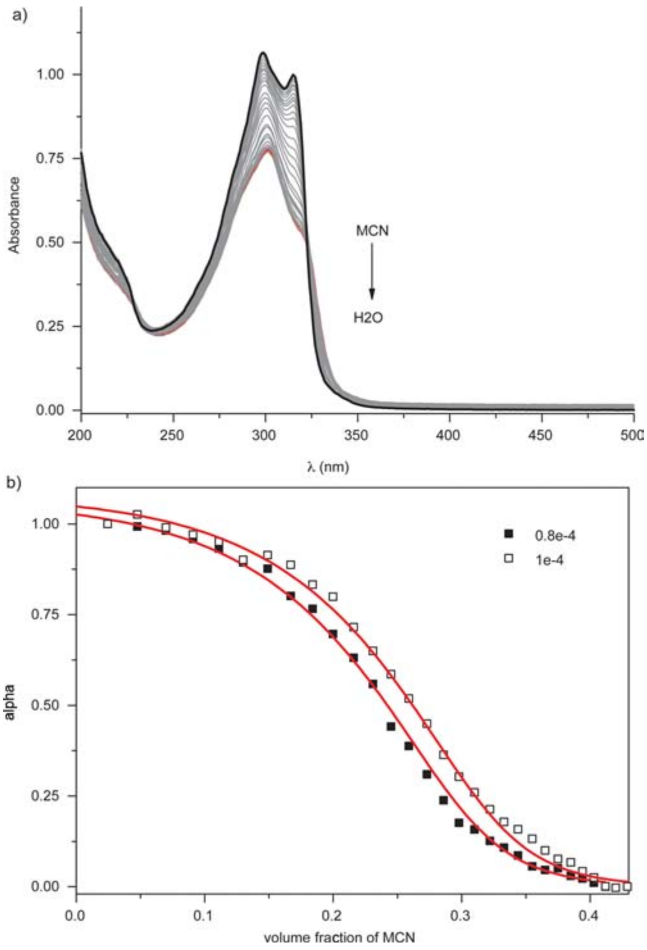

Figure 2. Unfolding of the aggregates formed from compound **1** in aqueous solution upon increasing the ratio of MCN (1×10^{-4} M). The denaturation curves of the isodesmic supramolecular polymerization of **1** are fitted to the equilibrium model reported in ref 10.

turbid solution with a strong scattering. However, the data registered in the interval ranging from 0 to 70% of water fit well with a sigmoidal curve which is indicative of an isodesmic mechanism (Figure S6).

Table 1. Thermodynamic Parameters of **1** and **3** in CH_3CN/H_2O Mixtures (298 K)

compound	ΔG^0 (kJ mol^{-1})	m (kJ mol^{-1})	σ
1	−31.26	29.76	0.09
3	−36.79	39.79	0.3

Dynamic light scattering (DLS) measurements of aqueous 1×10^{-4} M solutions of **1** and **3** show very broad distribution of hydrodynamic radii (R_H) centered at ~90 and ~110 nm for **1** and **3**, respectively (Figure S7). The calculated values of R_H are indicative of the presence of aggregates in solution. Additionally, the broad distribution of R_H implies a high degree of polydispersity, a typical feature of an isodesmic supramolecular polymerization.[17]

To summarize, we report the synthesis of a series of water-compatible C_3-symmetric OPE-TAs endowed with a large number of EO side chains. The polar EO side chains are separated from the amide groups by different paraffinic linkers. The stability of the intermolecular H-bonding arrays formed between the three amide functional groups that induce the formation of supramolecular aggregates in solution has been studied by different techniques. The addition of a small amount of water breaks the $N-H\cdots O{=}C$ amide H-bonds but induces the formation of aggregates by a solvophobic effect. The lack of highly directional H-bonding interactions able to generate large aggregates results in an isodesmic supramolecular polymerization.[18] The Gibbs free energy released in the aggregation of compounds **1** and **3** has been calculated as −31.26 and −36.79 kJ mol^{-1}, respectively, by applying the recently reported folding–unfolding model for the disassembly of supramolecular polymers in MCN/H_2O mixtures as "good" and "poor" solvents, respectively. The results presented herein provide useful information about the structural elements that participate in the formation of supramolecular structures in aqueous media.

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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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The authors declare no competing financial interest.