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The cooperative supramolecular polymerization of 1 and 2 show very similar thermodynamic parameters ($\Delta H_{
m elo}^0$, ΔS^0 , and ΔH^0_{nucl}), but very different organization of the self-assembling



Helical Structures

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Thermodynamics of the Helical, Supramolecular Polymerization of Linear Self-Asembling Molecules: Influence of Hydrogen Bonds and π Stacking



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Thermodynamics of the Helical, Supramolecular Polymerization of Linear Self-Asembling Molecules: Influence of Hydrogen Bonds and π Stacking

Fátima Aparicio and Luis Sánchez^{*[a]}

Supramolecular polymers integrate order and dynamics to achieve important functions such as high and efficient response to stimuli, environmental adaptation, amplification of chirality, and self-repair ability.^[1] These functions are the consequence of the hierarchical organization of relatively small, and simple molecules that exhibit defined molecular properties that are strongly amplified upon their organized self-assembly process.^[2] Artificial membranes,^[3] polyvalent scaffolds for binding and detecting bacteria,^[4] aggregates capable to transport charges or with optical wave-guiding properties,^[5] organogels with light transmittance and refractive index suitable to fabricate flexible optical lens,^[6] are some of the outstanding applications shown by supramolecular polymers generated upon the self-assembly of the appropriate organic molecules. To achieve such applications, the supramolecular polymerization process of the constitutive building blocks must be efficiently controlled and. hence, an accurate understanding of this process is of great significance. The influence on the stability and dynamics of relevant factors such as the solvent-a crucial parameter in the performance of supramolecular materials^[7]—or the pathways that yield kinetically metastable aggregates that subsequently evolve into their thermodynamically favored form have been recently examined for a number of supramolecular polymers.^[8]

Herein, we report on the influence of small structural changes on the supramolecular polymerization and amplification of chirality of simple linear, self-assembling molecules **1–3** (Figure 1). These compounds, being structurally similar, differ in the number and class of non-covalent interactions that favor their self-assembly into organized linear structures. At relatively high concentrations, all compounds investigated—except chiral **1b**—self-assemble efficiently and form transparent gels with non-polar solvents. At high-diluted conditions, only compounds **2** and **3**, with dissimilar number of H-bonding interactions and π surface, self-assemble into helical structures in a cooperative manner.^[2,9] The elongation and nucleation thermodynamic parameters of the

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Figure 1. Chemical structure of the self-assembling molecules 1-3.

aggregating systems are very similar but these aggregates differ in stability. The internal structure of the aggregates formed from compounds **2** or **3** is very different as suggested by the corresponding sergeants-and-soldiers (SaS) experiments performed to investigate the amplification of chirality phenomenon.^[10,11] The dissimilar organization of the constitutive self-assembling molecules to yield the final helical aggregates has been demonstrated by NOE experiments. The results presented herein increase the knowledge and control on supramolecular polymerization processes and could contribute to develop optimized strategies to achieve functional supramolecular systems.

Compounds 1 and 3 were prepared in five synthetic steps starting from commercially available 3,4,5-trihydroxymethylbenzoate following a similar procedure to that reported previously for compounds 2 and other closely related naphthalenediimides (NDIs).^[12,13] The chemical structure of all new compounds has been unequivocally demonstrated by NMR, FTIR and mass spectrometry (Scheme S1 and Supporting Information).

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To investigate the influence of the different non-covalent interactions participating in the supramolecular polymerization and amplification of chirality of the reported self-assembling molecules, we have utilized compounds 2 as reference systems. We have recently reported that these linear compounds self-assemble into helical, columnar supramolecular structures that further aggregate to form bundles of fibers. These bundles capture solvent molecules to originate the corresponding organogels.^[14] Analogously to 2, the achiral ester 1a and both NDIs 3 form organogels with different critical gelation concentration (CGC) in non-polar solvents such as methylcyclohexane (MCH) or toluene (Table S1 and Figure S1) which imply that the reported self-assembling molecules are able to form organized supramolecular structures. These supramolecular structures have been visualized by scanning electron microscopy (SEM). As it was observed for compounds 2,^[14] the SEM images display uniform, long, and intertwined wires for achiral 1a and 3a (Figure S1) but globular aggregates joint together by an undefined, viscous mass for chiral **3b** (Figure S1). The fine structure of the aggregates have been visualized at more diluted conditions by using atomic force microscopy (AFM) (Figure 2, S2-S4).



Figure 2. AFM images of the diluted gels of 3a (a and b) and 3b (c and d) (HOPG, 1×10^{-5} M, toluene; the z scale values are 35, 20, 20, and 8 nm for a), b), c), and d), respectively). The black lines in b) are to guide the eye in the chirality of the fibers.

The ester derivatives **1** exhibit a low trend to form organized supramolecular structures at concentrations as low as 1×10^{-5} M. Achiral **1a** self-assembles into isolated straight rods of several micrometers length (Figure S2a) but chiral **1b** form smaller intertwined fibrils together with deposits of thin cylindrical micelles underneath (Figure S2b,c). Analogously to compounds **2**,^[12] NDIs **3** exhibit a stronger trend to aggregate into well-defined fibrillar structures at highly diluted conditions than esters **1** (Figure 2a, b and S3). The aggregates of achiral NDI **3a** appear as long nanowires of 4 nm height (Figure S3) that intertwine efficiently to form

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thicker rods with height of 12 and 16 nm (Figure S3). A closer inspection on the AFM images of 3a demonstrates the helical character of the nanowires formed by this achiral NDI that self-assembles into a mixture of right- and left-handed helical structures (Figure 2b). The peripheral chiral chains in 3b induce the aggregation of this NDI into twisted filaments of 1.5 nm height that further interdigitate into thicker fibers (Figure 2c, d and S4). The dissimilar critical gelation concentration (CGC) required to form the corresponding organogels and also the differences observed in the AFM images of the aggregates formed by compounds 1, 2, and 3 suggest the influence that the number and/or type of non-covalent interactions exert on the aggregation phenomenon.

The self-assembly of the compounds in solution has been investigated by applying the novel equilibrium model reported for BTA-based systems in which the dynamic equilibrium between free monomers and the supramolecular polymer and the growth of the corresponding polymer is considered.^[15] The formation of supramolecular polymers is simplified by a two-reaction model: the nucleation and the elongation. In the former, the equilibrium between the free monomers and the nucleated seed is described. The latter describes the fast growth of the nucleus that extends to gives rise to the final aggregate. These two reactions are described by two different constants, K_1 and K_2 , and the parameter σ that expresses the degree of cooperativity. If $\sigma = 1$ the mechanism is isodesmic being cooperative for values of $\sigma \neq 1.^{[2,9]}$ The Arrhenius' law, $K = e^{-\Delta G^0/RT}$, relates the equilibrium constants K_1 and K_2 , as well as σ with an enthalpy of elongation ΔH^0_{elo} , an entropy of elongation ΔS^0 , a nucleation penalty ΔH_{nucl}^0 and a mismatch penalty ΔH_{mm}^0 . ΔS^0 is considered independent of the supramolecular process, but the value of ΔH_{elo}^0 is penalized by the ΔH_{nucl}^0 and/or ΔH_{mm}^0 . The former term, which is independent of the chirality of the aggregate, expresses the energetic cost required to generate active nucleus, and the latter penalizes a mismatch when a chiral monomer is introduced into a stack of its unpreferred helicity.^[15] The three equations that relate all these parameters are:

$$K_1 = \mathrm{e}^{-(\Delta H^0 - T\Delta S^0)/RT} \tag{1}$$

$$K_2 = K_1 e^{\Delta H_{\rm mm}^0/RT} \tag{2}$$

$$\sigma = e^{\Delta H_{\text{nucl}}^0/RT} \tag{3}$$

The new equilibrium model reported by ten Eikelder, Meijer and co-workers^[15] has allowed us to perform an accurate analysis of the supramolecular polymerization of compounds **1–3** quantifying the influence of the number and type of non-covalent interactions. The cooling curves obtained by variable temperature circular dichroism (VT-CD) measurements of pristine chiral compounds yield the corresponding values of ΔH^0_{elo} , ΔS^0 , and ΔH^0_{nucr} We started these studies recording the CD spectra of compound **1b** in MCH

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GaA, Weinheim www.chemeurj.org ______3 These are not the final page numbers! as solvent. Although the AFM images of compounds **1** show the formation of aggregates, the CD spectra of **1b** at a concentration as high as 1×10^{-4} M did not show any dichroic response (Figure S5). These spectroscopic features contrast with that reported for compound **2b** that displays a bisignated dichroic signal—with a positive maximum at 222 nm and a negative maximum at 266 nm^[12]—and are a clear indication of the enormous effect exerted in the self-assembly process by the presence of two additional H-bonding amide units in **2b** in comparison to **1b**. The global analysis of the cooling curves obtained by VT-CD experiments at different concentrations of **2b** (Figure S6) shed values for ΔH^0_{elo} , ΔS^0 , and ΔH^0_{nucl} of -104.9, -0.21, and -36.7 kJ mol⁻¹, respectively (Table 1).

Table 1. Thermodynamic parameters calculated for the cooperative supramolecular polymerization of compounds **2b** and **3b** in MCH.

	$\Delta H_{ m elo}^0$ [kJ mol ⁻¹]	ΔS^0 [kJ mol ⁻¹]	$\Delta H_{ m nucl}^0$ [kJ mol ⁻¹]	σ	T _e [K]
2b	-104.95 (±0.96)	-0.21 (±0.002)	-36.75 (±2.06)	3.6×10^{-7}	355.1 $(5 \times 10^{-5});$ 339.7 $(1 \times 10^{-5});$ 333.5 (5×10^{-6})
3b	-101.99 (±1.84)	-0.23 (±0.005)	-36.43 (± 6.05)	4.1×10^{-7}	322.8 (5×10^{-5}) ; 309.7 (1×10^{-5}) ; 308.9 (9×10^{-6})

A first indication of the efficient self-assembly of NDIs 3 is inferred from the corresponding UV/Vis spectra in poor and good solvents like MCH or CHCl₃, respectively (Figure S7). In CHCl₃ a solvent in which the self-assembling molecules are in a molecularly dissolved state, the UV/Vis spectra of compounds 3 appear intense and well defined. In contrast, in MCH the UV/Vis spectra appear less intense and poorly defined due to the efficient aggregation.^[7] To achieve the complete thermodynamic analysis, we have performed VT-CD of compound 3b in MCH. Compound 3b is also CD-active at high diluted conditions showing two signals of opposite sign at 227 and 260 nm together with two other smaller signals at 339 and 365 nm (Figure S8). The bisignated Cotton effect observed in the CD spectra of NDI **3b** at room temperature and the non-sigmoidal shape of the corresponding cooling curve express the cooperative aggregation of **3b** into helical stacks (Figure S8).^[9,12] The calculated values of ΔH_{elo}^0 , ΔS^0 , and ΔH_{nucl}^0 extracted from the global fitting of the cooling curves obtained at different concentrations of **3b**—are of -101.9, -0.23and $-36.43 \text{ kJ} \text{mol}^{-1}$, respectively (Table 1). These values are very similar to that calculated for 2b, which suggest that these two self-assembling molecular building blocks exhibit an analogous trend to form supramolecular polymers regardless the non-covalent interactions participating in this process. Apparently, the replacement of two H-bonding amides by a relatively large π surface has no influence on the supramolecular polymerization thermodynamic parameters and also in the degree of cooperativity of the process but changes sensibly the stability of the aggregates as indicates the corresponding $T_{\rm e}$ values (Table 1).

However, the different type and/or number of non-covalent forces does exert a remarkable effect in the supramolecular polymerization as demonstrate the experiments of amplification of chirality. The lack of dichroic response in compound 1b impedes performing the corresponding studies of amplification of chirality. Even by mixing achiral 1a with chiral 2b or vice versa resulted in a null dichroic response thus indicating the strong effect that the presence of only two H-bonding amide functionalities has on the ability to form aggregates with a preferred helical orientation in solution.^[16] This situation is very different for compounds 2 and 3. We have previously described that the helicity of the racemic mixture formed by achiral 2a can be biased by adding increasing amounts of chiral 2b being the maximum CD effect obtained upon the addition of 30% of the chiral sergeant (Figure 3a).^[12]

The SaS experiments accomplished for NDIs **3** show that the maximum handedness value is achieved in the racemic mixture of aggregates formed from achiral **3a** by adding only 10% of the chiral sergeant **3b** (Figure 3b). The different amount of chiral sergeant required to achieve the maximum chirooptical response in compounds **2** and **3** indicates that the internal structure of the aggregates formed from tetra-amides **2** or NDIs **3** is very different and the intercalation of the chiral sergeant in the aggregates formed from **2a** is more impeded in comparison to the aggregates of **3a**.

To elucidate the molecular organization of compounds 2 and 3 during aggregation, we have carried out selective NOE experiments with solutions of 2a and 3a at different concentrations (Figure 4 and S9).^[17] The irradiation of the protons corresponding to the ethylene spacer in a concentrated CDCl₃ solution of **2a** (20 mM) resulted in clear NOE effects with both protons at the central and peripheral aromatic units as well as the expected interaction with the amide functional groups. These NOE effects suggest the aggregation of compounds 2 into columnar, rotated aggregates by the operation of amide C=O···H-N H-bonds and with negligible π stacking between the small aromatic units (Figure 4, top). The columnar aggregates grow longitudinally to form the fibers observed in the AFM images.^[12] The irradiation of the ethylene spacer protons in a diluted solution of 2a (2 mm) only show NOE effects with the amide N-H resonances being the NOE effects with the aromatic units completely cancelled, which unambiguously demonstrate the intermolecular character of the interactions (Figure S9, top). The irradiation of a concentrated solution of NDI 3a (20 mM in CDCl₃) at $\delta \approx 8.7$ ppm, corresponding to the aromatic protons of the NDI moiety, shows NOE effect with the resonances at $\delta \approx 6.9$ and 3.9 ppm, ascribable to the peripheral trialkoxybenzene unit and the methylene group joint to the oxygen in the peripheral chains (Figure 4, bottom). These NOE effects disappear by using a diluted solution of 3a (2 mm) that demonstrates the intermolecular character of the NOE effect (Figure S9, bottom). The spatial proximity of the NDI and trialkoxybenzene aromatic moiet-

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Figure 3. Sergeants-and-soldiers experiments performed by mixing a) achiral **2a** and chiral **2b** and b) achiral **3a** and chiral **3b** (MCH, 298 K, 1×10^{-5} M).



Figure 4. Partial ¹H NMR spectra (300 MHz, 298 K) (black) and NOE experiments (gray) of **2a** (top) and **3a** (bottom) irradiating at $\delta = 3.7$ and 8.7 ppm for **2a** and **3a**, respectively (298 K, CDCl₃, 20 mM). Curved arrows represent the NOE contacts and a schematic model of the aggregation of **2a** and **3a** is depicted.

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ies can be justified by considering the formation of linear aggregates in a head-to-tail fashion by the H-bonding interaction of the amide functional groups (Figure 4, bottom). The further π - π interactions between the aromatic units of these linear aggregates give rise to the intertwined fibers observed in the AFM images. The dissimilar internal organization of the aggregates formed from 2 and 3 justifies the differences found in the incorporation of a chiral sergeant into the corresponding helical aggregates and demonstrates the strong influence exerted by the number and type of non-covalent interactions involved in the formation of supramolecular polymers.

In summary, we have applied the mathematical model recently described for cooperative self-assembly-that considers the dynamic equilibrium between the growth of the supramolecular polymer and the monomer pool-to quantify the influence of the different number and/or types of non-covalent forces on the supramolecular polymerization of simple linear molecules 1-3. The presence of only two Hbonding units allows the aggregation into fibrillar structures of esters 1, however, the self-assembly of compounds 1 in solution is so weak that it cannot be investigated by the above mentioned model. Compounds 1a, 2, and 3 also form fibers that further interact to constitute gels. The elongation and nucleation thermodynamic parameters of 2 and 3 are very similar but the corresponding SaS experiments show that an increasing amount of the chiral sergeant with increasing the number of H-bonds functionalities is required to achieve the maximum handedness of the helical supramolecular struc-

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tures. The experimental data extracted from the amplification of chirality studies, together with NOE experiments, demonstrate a very different organization of the constitutive self-assembling molecules to yield the final helical aggregates. The results presented herein get an insight into supramolecular polymerizations and could contribute to develop optimized strategies to achieve functional supramolecular systems.

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