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Pathway complexity versus hierarchical self-assembly in *N*-annulated perylenes. Structural effects in seeded supramolecular polymerization

Elisa E. Greciano, Beatriz Matarranz, and Luis Sánchez*

Abstract: We report herein studies on the hierarchical self-assembly *vs*. pathway complexity of *N*-annulated perylenes **1-3**, that differ only in the nature of the linking groups connecting the perylene core and the side alkoxy chains. Despite the structural similarity, compounds **1** and **2** exhibit noticeable differences in their self-assembly. While **1** forms an off-pathway aggregate *I* that converts over time (or by addition of seeds) into the thermodynamic product *A*, **2** undergoes a hierarchical process in which the kinetically trapped monomer species does not lead to a kinetically controlled supramolecular growth. Finally, compound **3**, which lacks the amide groups, is unable to self-assemble under identical experimental conditions and highlights the key relevance of the amide groups and their position to govern the self-assembly pathways.

Supramolecular polymerization is a research area in continuous motion to find out new functionalities for organic and organometallic molecular entities able to self-assemble in an organized manner by the operation of non-covalent forces.[1] To achieve this goal, controlling size, polydispersity, and molecular sequence is a must. In analogy to covalent polymers,[2] seeded supramolecular polymerization (*SSP*) has emerged as a very useful technique to construct complex supramolecular structures.[3] A vast majority of supramolecular polymers, formed through an isodesmic or a cooperative mechanism, are investigated under thermodynamic control.[1] There are scarce examples of kinetically controlled supramolecular polymerization that proceeds through the formation of metastable species that, in addition, are crucial for the consecution of seeded supramolecular polymerizations.[4,5] The kinetically trapped species generate an out-of-equilibrium scenario in which the nucleation of the monomers, prior to the subsequent elongation, is retarded.[4] In this situation, the controlled addition of seeds or initiators notably accelerates the formation of the supramolecular polymers.[5,6] A number of examples of *SSP* demonstrate the operation of intramolecular H-bonds to yield kinetically trapped inactive species that do not evolve spontaneously but upon the addition of seeds to afford the corresponding supramolecular polymers.[5,6]

Herein, we investigate the self-assembly of a series of *N*-annulated perylenes (compounds **1-3** in Figure 1a) in which the number and/or the position of the amide functional groups is modified. Dicarboxamides **1** and **2** form kinetically trapped species by intramolecular H-bonding, termed metastable monomers, that evolve in a different outcome (Figure 1b). Compound **1** shows a pathway complexity in which the inactivated monomeric species are stored as an off-pathway aggregate *I* that kinetically switch into on-pathway, helical structures *A*. This out-of-equilibrium process can be accelerated by the addition of seeds (Figure 1c). Compound **2** also forms kinetically trapped monomers that evolve very rapidly and efficiently to form superhelical structures (Figure 1d). The fast evolution of the monomeric species and the high stability of the final interdigitated supramolecular entities impede performing *SSP*. The lack of amide functional groups in compound **3** results in an inefficient self-assembly process despite the large aromatic surface of this perylene derivative. The comparison of these characteristics to those shown for closely related systems (compounds **S1**[7] and **S2**[8] in Figure S1) demonstrates the strong effect of the number and/or position of functional groups, like amides and paraphinic side chains, to program the course of a seeded supramolecular polymerization. The results presented in these studies allows establishing some basic rules about the structural requirements of a self-assembly unit necessary to experience a efficient *SSP* that yields supramolecular polymers of precise size and polydispersity, controlling the different levels of hierarchy.[9]

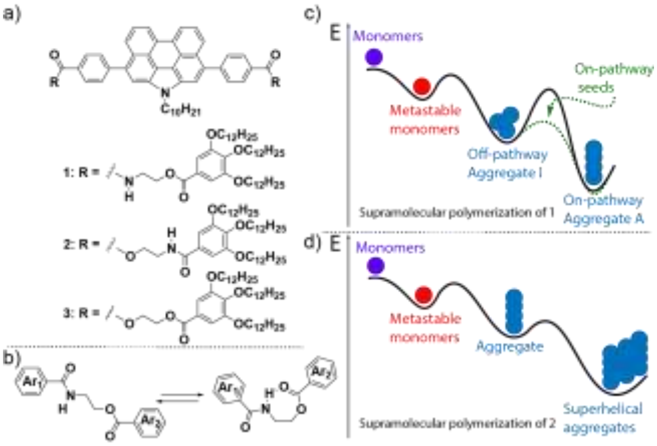

Figure 1. a) Chemical structure of the *N*-annulated perylenes **1-3**; b) Schematic representation of the formation of inactive monomeric species. Energy landscapes of the supramolecular polymerization of **1** (pathway complexity and *SSP* in c) and **2** (hierarchical self-assembly in d).

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N-annulated perylenes **1-3** were synthesized from the dibromo derivative **4** and the corresponding boronic acid (**9**, **12** or **13**) by a Suzuki C–C cross-coupling reaction. The chemical structure of all new reported compounds has been confirmed using NMR, FT-IR, UV-Vis spectroscopy, and HRMS analyses (see Scheme S1 and Supporting Information).

The supramolecular polymerization of **1-3** has been initially investigated by variable temperature (VT) UV-Vis spectra in methylcyclohexane (MCH) as solvent. Compounds **1** and **2** show the characteristic vibronic structure of perylenes, with maxima at 398, 427, and 450 nm at high temperature (Figure 2a, 2b and S2). This pattern coincides with that observed for the tetraester **3** at room temperature, which implies the lack of intermolecular interaction of this compound under these experimental conditions (Figure S3). The UV-Vis spectra at room temperature of **1**, endowed with an inner amide group, and **2**, bearing the amide group at the outer position, experience a broadening effect and a hypsochromic shift characteristic of an aggregation process. Interestingly, a closer inspection in the UV-Vis spectra of **1** and **2** at low temperature shows that the spectroscopic features for the aggregated species are different (Figure S2). In the case of **1**, the spectroscopic pattern consists in two absorption maxima at λ = 432 and 457 nm and a shoulder at λ = 410 nm (Figure 2a). This pattern coincides with that observed for the tetraamide **S2** in toluene as solvent.[8] On the contrary, the aggregated state of **2** exhibits a hypsochromic shift and a hypochromic effect with an absorption maxima at λ = 414 nm and a shoulder at λ = 457 nm (Figure 2b). The spectroscopic features of aggregated **2** are identical to that observed for **S1** and **S2** in MCH as solvent.[7,8] To elucidate the mechanism governing the supramolecular polymerization of both **1** and **2**, we have registered cooling curves of these compounds at different concentrations (Figure 2c, 2d, S4 and S5). These cooling curves, are composed by two segments intersecting in a temperature that increases with increasing the concentration, cannot be fitted neither to an isodesmic nor to a cooperative model.[1a] In addition, the heating curves of freshly prepared **1** are similar in shape to that registered in the cooling process but with different UV-Vis spectra (Figure 2c and S4). Noteworthy, the heating curve of **2** presents two clear points in which the mechanism changes but with identical UV-Vis spectra at low temperatures for the heating and cooling processes (Figure 2d and S5). All these findings imply the operation of more complex supramolecular polymerization mechanisms, other than isodesmic or cooperative, in which a hierarchical organization of the supramolecular structures could take place (see below).[10]

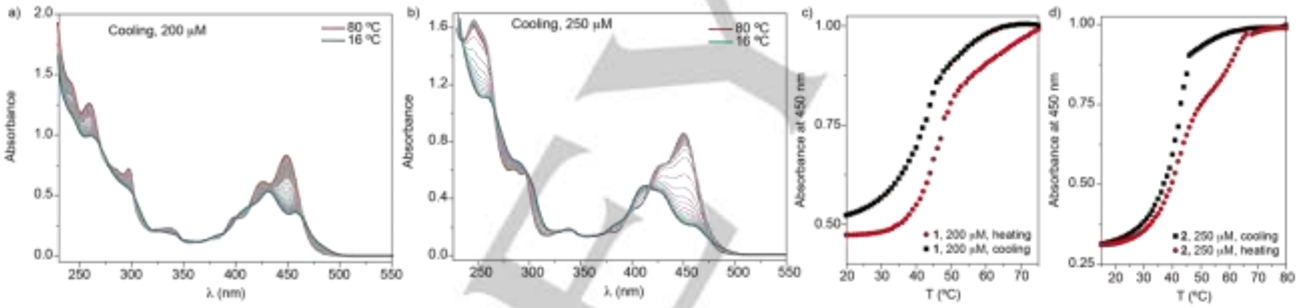

Figure 2. UV-Vis spectra of **1** (a) and **2** (b) in MCH as solvent registered after cooling the sample at 1K/min; Cooling and heating curves of **1** (c) and **2** (d) obtained upon monitoring the absorbance at 450 nm (MCH, 1K/min)

The broadening effect and the hypsochromic shift observed in the UV-Vis spectra of **1** and **2** upon decreasing the temperature are diagnostic of the formation of *H*-like aggregates from the molecularly dissolved state (Figures 2a, 2b and S6). Similarly to compounds **S1** and **S2**, the π-stacking of the aromatic skeletons is visualized by the upfield shift of the resonances corresponding to the *N*-annulated perylene moiety. The deshielding effect experienced by the triplet corresponding to the amide protons upon increasing the concentration implies the intermolecular H-bonding interaction between the amides (Figure 3).[11] Interestingly, the singlet ascribable to the protons of the trialkoxyphenyl rings experiences no shift for **1** but shifts downfield in **2**, which indicates a slightly different packing of these two *N*-annulated perylenes (Figure 3).

Taking into account all the above spectroscopic evidences, it is possible to shed some light on the aggregation mode of both **1** and **2**. Thus, the lower wavelength observed in the UV-Vis spectrum of aggregated **1** implies a more ideal *H*-type packing in comparison to **2**. In addition, the presence in both **1** and **2** of a shoulder at $\lambda \sim 480$ nm implies a rotational displacement of the molecules in the stack.[12] Considering that the distance from the amide group to the core and the flexibility of the spacers are the main differences between the two molecules, this should have an important effect to determine the molecular packing in both cases. In both *N*-annulated perylenes, the formation of a double H-bonding array is essential to maintain the longitudinal order.[7b]

The presence of the amide and ester groups in **1** and **2** should allow the intramolecular N-H$\cdots$O=C H-bonding interaction to form a seven-membered pseudocycle that affords kinetically trapped monomeric species.[5b,5c,5d,8] We have demonstrated that both **1** and **2** afford this inactive monomeric form by using different spectroscopic techniques. The spectroscopic pattern of 2 mM solutions of **1** and **2** in $CDCl_3$ coincides with that observed for the molecularly dissolved state (Figure S7). VT-^{1}H NMR spectra shows the shielding effect experienced by the triplet corresponding to the protons of the amide group upon increasing

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the temperature. However, all the aromatic and aliphatic resonances experience no shift (Figure S8). The upfield shift of the amide protons at high temperatures is indicative of the rupture of the intramolecular H-bonds in the pseudocycle. The formation of the inactivated monomers has been confirmed by 2D-ROESY experiments in which both **1** and **2** show through space contacts between the amide protons and the aromatic protons of the external 3,4,5-trialkoxybenzamide moiety (Figure S9). The additional through-space contacts between the *ortho* proton of the benzamide unit with the trialkoxy ring and also with the methylene joint to the oxygen in this same unit corroborates this structure (Figure S9).

In the examples reported so far, the formation of kinetically trapped monomers guarantees the performance of *SSP*.[5b,5c,5d,8]

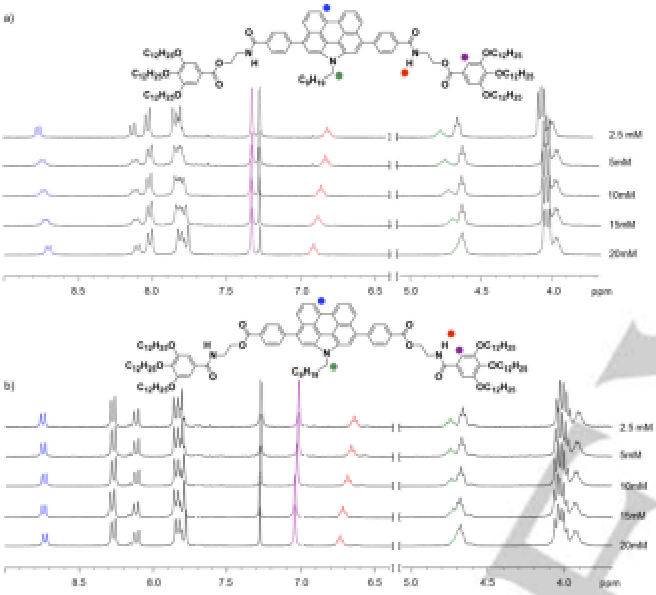

Figure 3. a Concentration-dependent ^1H NMR spectra of **1** (a) and **2** (b) in $CDCl_3$ (300 MHz, 298 K) showing the aromatic, the amide and the methylene linked to the nitrogen and oxygen atom protons.

Consequently, we have investigated the time course of the inactivated monomers of **1** and **2**. The heating-cooling cycles performed for **1** show the formation of different aggregates in both cycles (Figure S2), indicative of the storing of the inactivated monomeric form into an initial intermediate aggregate (*I* in Figure 1c) that evolves spontaneously to a different aggregated state (*A* in Figure 1c). The kinetic profile of a 300 μM solution of **1** in MCH heated at 85 ºC and rapidly cooled shows a sigmoidal shape characteristic of an autocatalytic process that yields the supramolecular polymerization of **1** after a lag time (Figure 4a). This lag time decreases upon decreasing the temperature (Figure 4a) but increases upon increasing the concentration (Figure 4b). The influence of temperature and concentration on the kinetics confirms the initial formation of off-pathways aggregate *I* that evolves to the on-pathway aggregate *A* (Figure 1c and S10).[5a,5d,6a,8] The addition of seeds, prepared by the sonication of a freshly prepared solution of **1** in MCH at c_T = 300 μM for 5 min, accelerates the kinetics of the transformation of the off-pathway aggregate into the on-pathway supramolecular structure (Figure 4c). The ratio between the off-pathway aggregate and the on-pathway seeds plays a determinant role in the acceleration of the transformation between these two states and only at relatively high percentage of seeds it is possible to speed up the conversion.

The situation is completely different in compound **2**. This dicarboxamide form kinetically trapped species and exhibits a complex supramolecular polymerization mechanism. The UV-Vis spectra obtained for **2** in aggregated state experience a severe broadening effect in comparison to the molecularly dissolved species, with practically no differences between the spectra registered for the aggregates of a freshly prepared solution at 20 ºC (Figure S2). In fact, monitoring the kinetic evolution of the conversion of these aggregated species at 30 ºC results in an exponential decay with no lag time (Figure S11).[13] At lower temperature, the UV-Vis spectrum of the aggregate of **2** undergoes no changes. To the best of our knowledge, this is the first example of a system in which the formation of kinetically trapped monomeric species do not afford kinetically controlled supramolecular processes and, consequently, it is not possible to perform *SSP.*

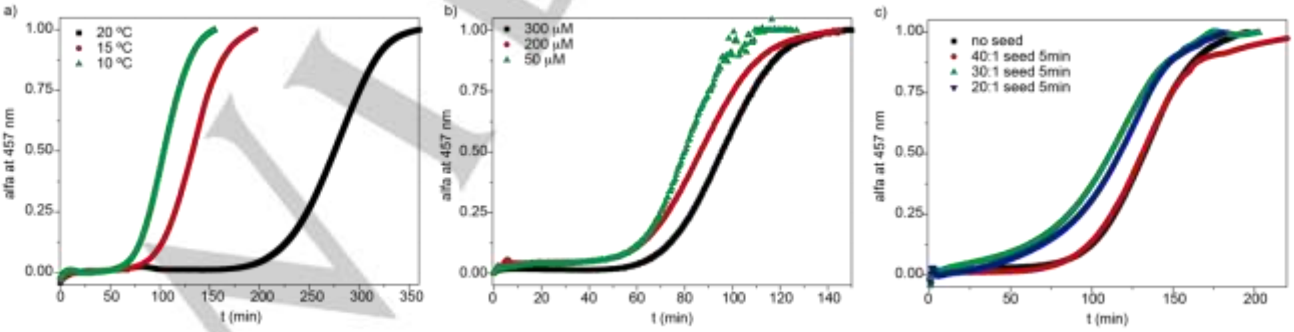

Figure 4. Kinetic profiles of the evolution of the off-pathway aggregate *I* of compound **1** at different temperatures at c_T = 300 μM (a), different concentrations at 10 ºC (b); and after the addition of seeds at different ratios (c_T = 300 μM; T = 15 ºC) (c).

Atomic force microscopy (AFM) imaging contributes to clarify the differences found in the supramolecular polymerization of **1** and **2** and to stablish structural rules to control the consecution of *SSP*. AFM images of **1** show the formation of bundles of short, helical fibers of ~4.5 Å demonstrating the low trend of the fibrillary structures of **1** to pack (Figure 5a, 5b and S12). The AFM images of **2** show a dense network of superhelical structures that strongly bundle into thick filaments of several micrometers length and minimal heights of 12 Å (Figure 5c, 5d and S13). The AFM images of **2** demonstrate the strong tendency of this unit to undergo a preferred hierarchical self-assembly that rapidly shifts all the equilibria involved in its aggregation. The high stability of the final aggregates results in a rapid shift along the energy landscape from the monomers to the superhelical aggregates (Figure 1d).

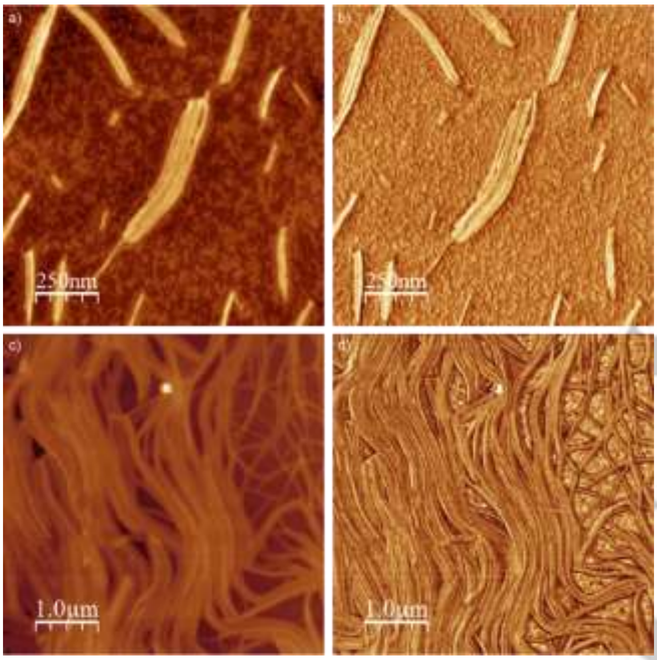

Figure 4. Height (a and c) and phase (b and d) AFM images of the helical aggregates formed by the supramolecular polymerization of **1** (a and b) and **2** (c and d) (c_T= 10 μM; mica, 298 K; z scale = 7 and 60 nm for (a) and (c), respectively).

In summary, we report herein how slight structural changes in the chemical structure of *N*-annulated perylenes produce drastic changes in the supramolecular polymerization outcome. The synergy of all the experimental data obtained from **1** and **2** allows extracting some basic rules about the molecular requirements of a self-assembling unit to develop a *SSP*. In **1**, the formation of the intermolecular H-bonds between the amide groups induces a conformational freedom of the lateral aromatic wedges. This lack of interaction is shown by the concentration dependent ^{1}H NMR experiments. Besides, this conformational freedom provokes a less efficient π-stacking of the central aromatic skeleton as well as a lower trend of the helical structures to interdigitate. Compound **1** forms off-pathway intermediate aggregates that evolve to afford on-pathway helical aggregates. This transformation can be accelerated by a seeding process. However, in **2**, the formation of the H-bonds between the outer amides cancels the conformational freedom of the peripheral units that favors, firstly, a efficient π-stacking of the central perylene moiety and, in addition, the disposition of the external paraphinic chains to interdigitate. The dissimilar packing of the self-assembling units and the further intertwining of the external chains produce a hierarchical process that finally generates superhelical structures.[14] The results presented herein validate that a fine-tuned molecular design determines the out-of-equilibrium outcome during the supramolecular polymerization and allow stablishing some basic rules about the structural requirements of a self-assembly unit necessary to experience a efficient *SSP* that yields supramolecular polymers of controlled size and polydispersity tuning the different hierarchical levels of organization.

Acknowledgements

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Keywords: hierarchy • out-of-equilibrium • pathway complexity • seeded self-assembly • supramolecular polymers

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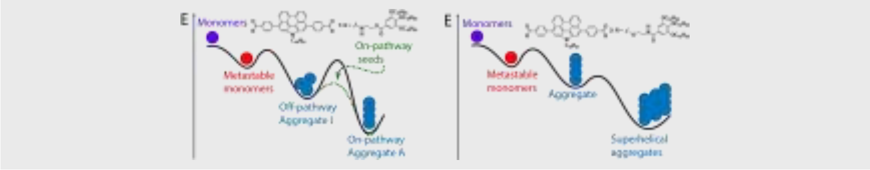

The number and position of amide functional groups exerts a determinant role in the self-assembly outcome of *N*-annulated perylenes. The inner amides favour an out-of-equilibrium system in which the pathway complexity can be accelerated by seeding. The outer amides generate more planar molecular systems that experience a rapid hierarchical self-assembly to produce superhelical structures.

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