Accepted Article

Title: Small Molecules Organic Co-Assemblies as Functional
Nanomaterials

Authors: Ivan R. Sasselli and Zois Syrgiannis

WILEY-VCH

WILEY-VCH

Small Molecules Organic Co-Assemblies as Functional Nanomaterials

Ivan R. Sasselli,[a] and Zois Syrgiannis*[b, c]

[a]   Dr Ivan R. Sasselli
        Center for Cooperative Research in Biomaterials (CIC biomaGUNE), Basque Research and Technology Alliance (BRTA), Paseo de Miramon 182, 20014, Donostia San Sebastián, Spain
[b]   Dr. Zois Syrgiannis,
        Centre of Excellence for Nanostructured Materials (CENMAT), INSTM, unit of Trieste, Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Trieste, via L. Giorgieri 1, 34127, Trieste (Italy).
        E-mail: zois.syrgiannis@gmail.com
[c]   Present Address: ¹Simpson Querrey Institute, Northwestern University, 303 East Superior Street, 11ᵗʰ floor, Chicago, IL 60611, USA; Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208, USA.

Abstract: Supramolecular co-assemblies are an emerging class of materials that have evolved over the last 30 years. These materials demonstrate compelling structures and properties, so they became increasingly promising for different applications. Their dynamic character, the reversibility of the interactions, and the possibility of using a wide variety of building blocks attract the interest of the scientists. In this minireview, we highlight the different types of co-assemblies between low molecular weight organic molecules, mentioning the progress in materials preparation and control, as well as some of the characterization techniques that are used for such materials. Our goal is to unify the classification of peptide and non-peptide-based co-assemblies and to give some guidelines for their control in terms of stability and properties.

1. Introduction

Precise control of shape and dimensions in a soft matter down to the molecular and nanoscale is recognized as a critical scientific goal in the development of new materials. Bottom-up methodologies based on non-covalent interactions provide pathways to ordered supramolecular architectures either on interfacial surfaces or in solution ranging from the molecular to the mesoscale.[1] Nature, through biopolymers, such as proteins and nucleic acids, is working as the guide. These polymers consist of assemblies from smaller units (amino acids, peptides, chromophores, inorganic compounds) in orchestrated architectures yielding to active nanomaterials.[2] Key to this structural formation is the use of multiple non-covalent interactions such as hydrophobic effect, hydrogen bonding, ionic, van der Waals, and π-π interactions to facilitate self-assembly of a single molecule or co-assembly of multiple molecular building blocks in a thermodynamically driven process.

Such polymers work as inspiration for the scientists through the last years and have led to lots of works dealing with self-assemblies of different molecules.[3] The controlled nanoscale morphology gives rise to materials with interesting properties that have been explored in different applications such as catalytic systems, energy storage, light-emitting devices, solar cells, sensors, bio-electronics, drug delivery, cell culture, *etc*.[4] However, to extend the number of available functionalities in

Dr. Sasselli graduated in chemistry from the University of Basque Country (UPV/EHU) after completing his final year at the University of Strathclyde in Glasgow (2012). During his Ph.D. at the University of Strathclyde as Marie Curie ESR, he studied the synergistic effect of combining computational and experimental methods for the study of supramolecular peptide polymers under the supervision of Prof. Tell Tuttle and Prof. Rein V. Ulijn. In 2016, he moved to Northwestern University to study, under the supervision of Prof. Sam I. Stupp, the direct connection between predicted computational parameters and the biological performance of peptide-based supramolecular materials. Currently, as a research associate at CIC biomaGUNE, his research is focussed on improving the on-demand design of these materials by understanding how supramolecular polymers interact with biomolecules and stabilizing the key parameters affecting their bioactivity.
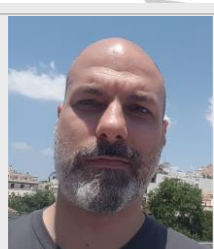
Dr. Syrgiannis is currently a Researcher Fellow at Northwestern University (USA) at the group of Prof. Sam I. Stupp, and he is working in different co-assemblies between peptide-based amphiphilic materials for different biological applications. He studied in Greece (University of Ioannina) Chemistry were also got his MSc in the field of Polymers. He obtained his Ph.D. at the University of Erlangen-Nuremberg (Germany) under the supervision of Prof. Andreas Hirsch, where he examined the chemical modification of carbon nanomaterials. He carried out postdoctoral research at the University of Trieste (Italy) and the IMT-CNR (Padua, Italy), (supervisors: Prof. Mauricio Prato and Prof. Marcella Bonchio) dealing with the chemical manipulation of carbon nanomaterials and the synthesis of organized supramolecular structures for energy applications. In 2016 he was awarded from the Italian Chemical Society with the Medaglia Giacomo Ciamician for his contribution to the field of Carbon Nanomaterials.

MINIREVIEW

supramolecular systems, we must enhance the complexity of systems.

Nature builds up complex supramolecular systems such as membranes by combining different building blocks where the interplay between the components determines the final properties of the structure. Supramolecular co-assembly between two or more components can result in architectures of wide structural complexity and chemical diversity without complicating the nanostructure synthesis. Therefore, supramolecular co-assembly is a simple way of building complex systems. The non-covalent interactions between the components can be tuned to give, through simple and reversible procedures, the demanded nanomaterials with the appropriate properties without having the synthetic difficulties of the covalent systems. Using supramolecular co-assemblies, the complexity to facilitate multiple tasks can be achieved by simply combining additional building blocks or by tuning their ratio. Despite the difficulties, these unique characteristics have attracted scientists to explore the assemblies of more than one component and to try to control the supramolecular interactions between them.

The concept of co-assembly is quite general, meaning any combination of two components into an assembly. As well as small organic molecules, this includes a large variety of other components such as polymers, oligomers, metals, aptamers and other nucleic acid-based systems, which are not the focus of this minireview. If the reader is interested in more detail in peptide co-assemblies or different types of co-assemblies, there are already some very interesting reviews in peptides,[3b, 5] aromatic molecules,[6] and metallosupramolecular polymers.[7] This review aims to shed light on the co-assemblies between small organic molecules showing the differences between peptide and non-peptide-based systems. Within this context, there are some reviews that focus on the peptides co-assemblies and donor-acceptor systems.[5a, 5b] Herein, we are going to unify the nomenclature for the co-assemblies of small organic molecules and try to classify them in different categories with the use of characteristic examples from the literature. We will comment on preparative procedures, structural analysis, and properties, always having in mind the aspects of applications. Then, present what we believe will be the future directions in the field.

1.1 Co-Assembly classification

Supramolecular self-assembling systems have commonly been classified based on the nature of the building block. With this criterion, we can identify peptide and non-peptide-based molecules. While the former can also include other moieties such as aromatic groups, the latter usually have aromatic groups, because π-stacking interactions become crucial for the self-assembly of non-amide-rich monomers. As peptide-based assemblers, we can find pure peptides (PP), peptide amphiphiles (PAs), and aromatic peptide amphiphiles (APAs), and non-peptide based monomers can be aromatic or non-aromatic assemblers.[3b, 8]

However, the definition becomes more complex with co-assemblies, given the multicomponent character. Co-assemblies classification is based in the interplay between two (or more) monomers present in the assembly and can meet structural, chemical, or functional criteria.

Based on the work from Ulijn *et al.*[8a] we can recognize the co-assemblies in the following categories: Orthogonal, where the components segregate into district structural components; Cooperative, where building blocks adhere to a common mode of self-assembly; Random where there is not any precise order and Disruptive, where partial incorporation and mismatches between building blocks result in the occurrence of defects/discontinuities in the structure (Figure 1). A different nomenclature refers only to the degree of mixing of the components: self-sorted (equivalent to orthogonal) and co-assembled, which does not differentiate between random and cooperative.[6b] Thus, the later nomenclature requires a lower knowledge of the exact interplay of the monomers.

The chemical nature of building blocks differentiates co-assemblies in homo-co-assemblies, where the different monomers have similar chemical nature or hetero-co-assemblies, where they differ. Co-assemblies between the same types of peptide-based monomers are homo-co-assemblies despite the amino acid sequence differs. In the same way, we can call co-assemblies between aromatic monomers homo-co-assemblies if the aromatic group is the same, which is not often the case. The combinations of peptides with PAs or APAs are hetero-co-assemblies, as the additional moiety plays a key role in driving the assembly of the building blocks. Therefore, co-assemblies
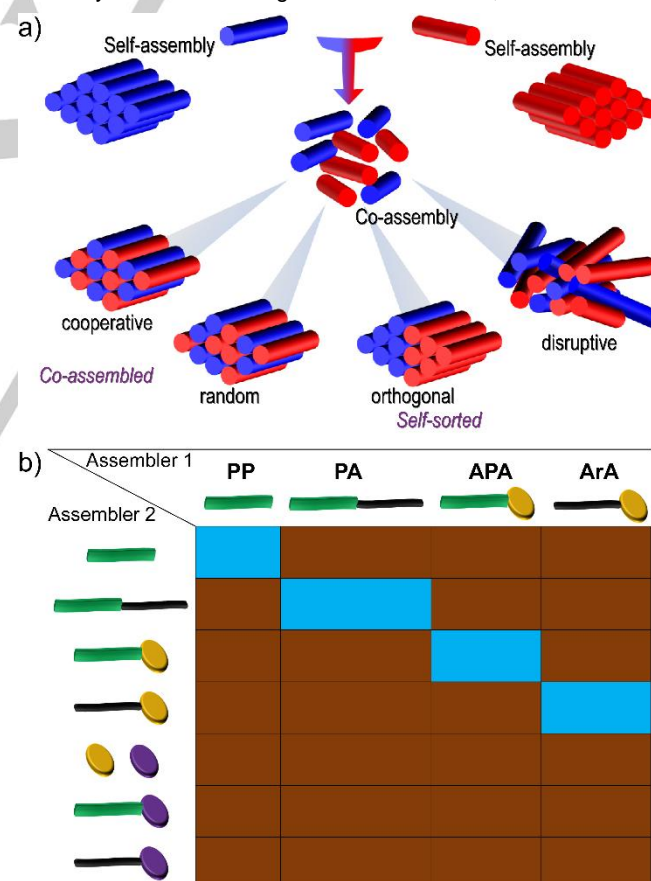
Figure 1. (a) Schematic representation of how two building blocks (blue and red bricks) can assemble into an ordered architecture; mixing them results in a complex co-assembled architecture via four possible categories such as cooperative, orthogonal, random and disruptive co-assembly. (b) Table explaining how the different combinations of the discussed assemblers can give hetero-co-assemblies (brown) or homo-co-assemblies. Peptides are shown in green, aliphatic chains in black, and two different aromatic examples in yellow and purple.

between monomers, where the nature of the interaction motifs driving the self-assembly differ, are hetero-co-assemblies (Figure 1b). For example, PP self-assembly depends on hydrogen bonding between amides, PAs add the aliphatic chain hydrophobic effect, and APAs also π-stacking. It is also convenient to distinguish between different aromatic groups, as the strength of the interactions can strongly differ.

The role of the monomers in the co-assembly classifies them in: structural, if all monomers have a relevant structural role in the assembly, usually intending to obtain a third structure that differs from the self-assembled of each monomer by itself; functional, where one of the monomers act as a structural template for a second, or more, a monomer that incorporates some functionality; and co-functional co-assemblies, where all the monomers contribute to both the structure and the function, either because the functionality is the result of the interplay between both co-assemblers or because the overall function is the result of the addition of properties from both assemblers. Herein we are going to assign different works according to the functionality of the co-assemblies, and then we will try to adjust the examples with the other classifications.

2 Peptide-based co-assemblies

The natural tendency of peptides to form self-assembled structures, as proteins do to form their hierarchical structure, has been largely exploited in nanotechnology.[5a, 8b, 9] The high availability of the building blocks, their biocompatibility, and relatively easy synthesis make them desirable materials. Peptides require hydrophobic side chains to drive self-assembly but can also be helped by other moieties that can be aliphatic or aromatic giving, respectively PAs or APAs. While it is often difficult to assign the exact role of the monomers in the co-assembly given the difficulties to characterize two chemically similar molecules inside the same structures, peptide-based co-assemblies can be easily classified based on the overall structural changes and functionality incorporation.

2.1 Structural Peptide-based Co-assemblies

The combination of building blocks in supramolecular assemblies has been extensively used as a way of gaining complexity and increasing the available types of structures. The role and the structural interplay of the monomers in the co-assemblies have been an object of study, and, as mentioned above, was used by Ulijn et al. to establish four types of co-assemblies (Figure 1). They studied combinations of self-assembling and non-self-assembling (surfactant) APAs, showing different types of structural relationships between them,[5a] to later study how to control the process using an enzymatically triggered system. [10] They show that nanostructure forming APAs serve as nucleation points to surfactant-like APAs favoring their assembly into their structures without affecting the initial order of the fiber-forming molecule. Using these definitions, Tuttle et al. later use molecular dynamic simulations to predict the type of co-assembly between a given tripeptide and different dipeptides.[11] Gazit et al. were able to rationalize the different types of structural relationships based on their crystal structure, showing that single amino acids that crystalize with similar interlayer distance are more prone to form

cooperative co-assemblies.[12] These studies show that both of the co-assemblers must gain stability to favor cooperative co-assembly.

Cooperative assemblies allow for the formation of structures distinct from both individual monomers' assemblies. Wei et al. showed how cooperative homo-co-assemblies between FF and FFF gives different structures depending on their ratio (Figure 2a).[13] On the other hand, Reches et al. exploited orthogonal co-assembly of FF with different C-terminus (tert-butyloxylcarbonyl and amide protected) to build modular structures.[14] The extension of the structural libraries has also been applied to combinations of tripeptides, where the cooperative mixture of a non-nanostructure forming and a ribbon forming tripeptide gives rise to fibers.[15] However, co-assemblies can, in some cases, be disruptive when a non-assembling monomer acts as a surfactant, increasing the solubility of the self-assembling monomer, inhibiting the formation of extended supramolecular structures.[16] Ulijn et al. also observed disruptive effects when same aromatic moiety was used in self-assembling and surfactant APAs, suggesting that favoring the π-stacking enhanced disruption in the hydrogen bonding.[5a] Similarly, Zhang et al. pointed out the need for using different driving forces to favor the formation of orthogonal co-assemblies. In this case, these are hetero-co-assemblies between an Fmoc-dipeptide and a coumarin, but as the previous example, the difference in the aromatic groups seems to be key to avoid interference between the two assemblies[17] Hamachi et al. exploited the orthogonal co-assembly between building blocks of different nature to observe
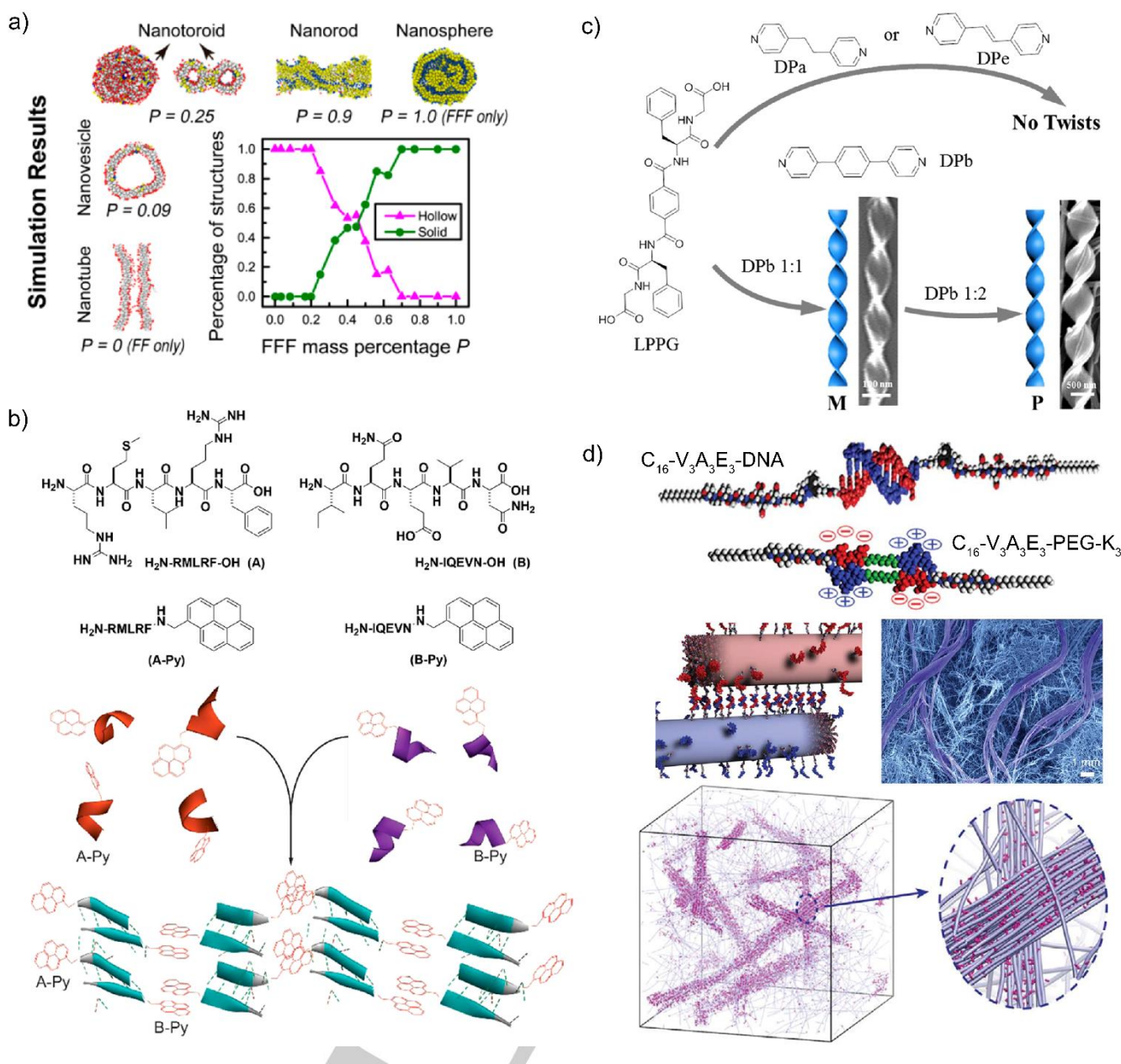
MINIREVIEW

Figure 2. (a) Simulated structural transformation at different ratios of FF/FFF homo-co-assembly. Reproduced from ref.,[13] Copyright (2016), with permission from ACS. (b) β-sheet secondary structure transformation upon homo-co-assembly of two α-helix forming APAs. Reproduced from ref.,[19] Copyright (2016), with permission from ACS. (c) Supramolecular ellipticity effects upon hetero-co-assembly of a peptide derivative (LPPG) with different bipyridines (DPa, DPe and DPb) showing how the ratio of DPb switches from left at 1:1 to right handed ellipticity at 1:2. Reproduced from ref., [25] (d) Superstructure formation induced by supramolecular interactions of functional PAs co-assembled in the fibers. They use DNA functionalized PAs or zwitterionic PAs to enhance interfiber interactions and induce bundling. Reproduced from ref.,[29] Copyright (2018), with permission from AAAS.

the fibers' self-sorting event using confocal fluorescence with propped building blocks. They observed that despite these building blocks formed distinct nanostructures, there are cooperative effects through the assembly process.[18]

Co-assemblies have not only been used to tune the nanoscale morphology but also the intermolecular order. Xu *et al.* found two pyrene based APAs with a helical secondary structure that transformed into a β-sheet upon co-assembly(Figure 2b).[19] Stupp *et al.* combined PAs with the aliphatic tail in opposite termini of the peptide to give rise to PAs of opposite polarity and favor the formation of antiparallel instead of parallel β-sheets.[20] The formation of more stable secondary structures suggests cooperative effects. Lynn *et al.* co-assembled similar amyloid-like

PPs with opposite charge in an orthogonal way to give zwitterionic tubes with the inner and outer walls of opposite charges.[21] The combination of building blocks allowed Hartgerink and co-workers to modify the stability of collagen-like supramolecular assemblies.[22] In this study, they can distinguish between orthogonal (or non-co-assembled) and cooperative co-assembly depending on the mixture conditions of some of the systems using the melting temperatures of the components followed by temperature-dependent circular dichroism.

[17, 23]The hetero-co-assemblies between peptide derivatives and small molecules have been shown to have interesting effects in supramolecular ellipticity. The cooperative co-assembly between tetraleucine with tartaric acid gives rise to twisted ribbons where

4

Figure 3. (a) Orthogonal Co-assembly of Fmoc-FF and Fmoc-S showing the effect in the fiber network to form gels of different stiffness (bottom). Reproduced from ref.,[30] Copyright (2016), with permission from Elsevier. (b) Random co-assembly of a PA and a functionalized PA with different epitope spacers (Gn PA) showing its effect in the presentation of the epitopes on the fiber surface. Reproduced from ref.,[36] Copyright (2015), with permission from RSC. (c) Cyclic peptide co-assembly with small molecule (hetero-co-assembly). Reproduced from ref.,[39] Copyright (2017), with permission from ACS. (d) Homo-co-assembly of oppositely charged PAs (E2 and K2) and APAs (E2-TA and K2-TA) conductive version and the corresponding effect in the cell cultures. Reproduced from ref.,[40] Copyright (2016), with permission from ACS.

the chirality of the small monomer controls the overall ellipticity of the nanostructures formed.[24] In addition to this, the ellipticity of the co-assembled structure of a chiral peptide derivative with a non-chiral bipyridine shift from left to right depending on the ration of the non-chiral monomer(1:1 and 1:2, respectively, Figure 2c).[25] Hetero-co-assemblies can also happen between small peptides and big organic molecules. Yan and co-workers used dilysine to induce order in porphyrins cooperative co-assembly that tuned the electronic properties of the macrocycle.[23]

The hetero-co-assembly of peptide derivatives with small molecules can carry out important structural transformations and even allow reaching high order organization. Zhao *et al.* co-assembled APAs with the hydrogen bonding melamime and showed that depending on the amino acid geometry, this could cause the thickening or thinning of the one-dimensional nanostructures.[26] Mata *et al.* used crosslinking between fibers to tune the dimensionality of the nanostructures. They used a strong hydrogen bonding molecule to interact with hydrogen bonding groups on PA nanofibers surfaces to favor interfiber interactions leading to bundling and gelation.[27] They used a different

approach by introducing host or guest moieties on the surface of the fibers. The modified fibers crosslinked upon the formation of host-guest complexes inducing fiber bundling and gelation, where the mechanical properties are a function of the ratio of functionalized monomers in the fibers.[28] The crosslinking using fibers functionalized with complementary interactions has also been carried out with DNA strands and charged peptide sequences (Figure 2d).[29] While these systems are based in PA homo-co-assemblies, given the different nature of the crosslinking interactions, once the hierarchical architecture is formed, they can be considered hetero-co-assemblies. Interestingly, these works modifying the hierarchical structure and fiber bundling have focused in improving the material properties for cell culture applications and have revealed the importance of mechanical properties for these applications.
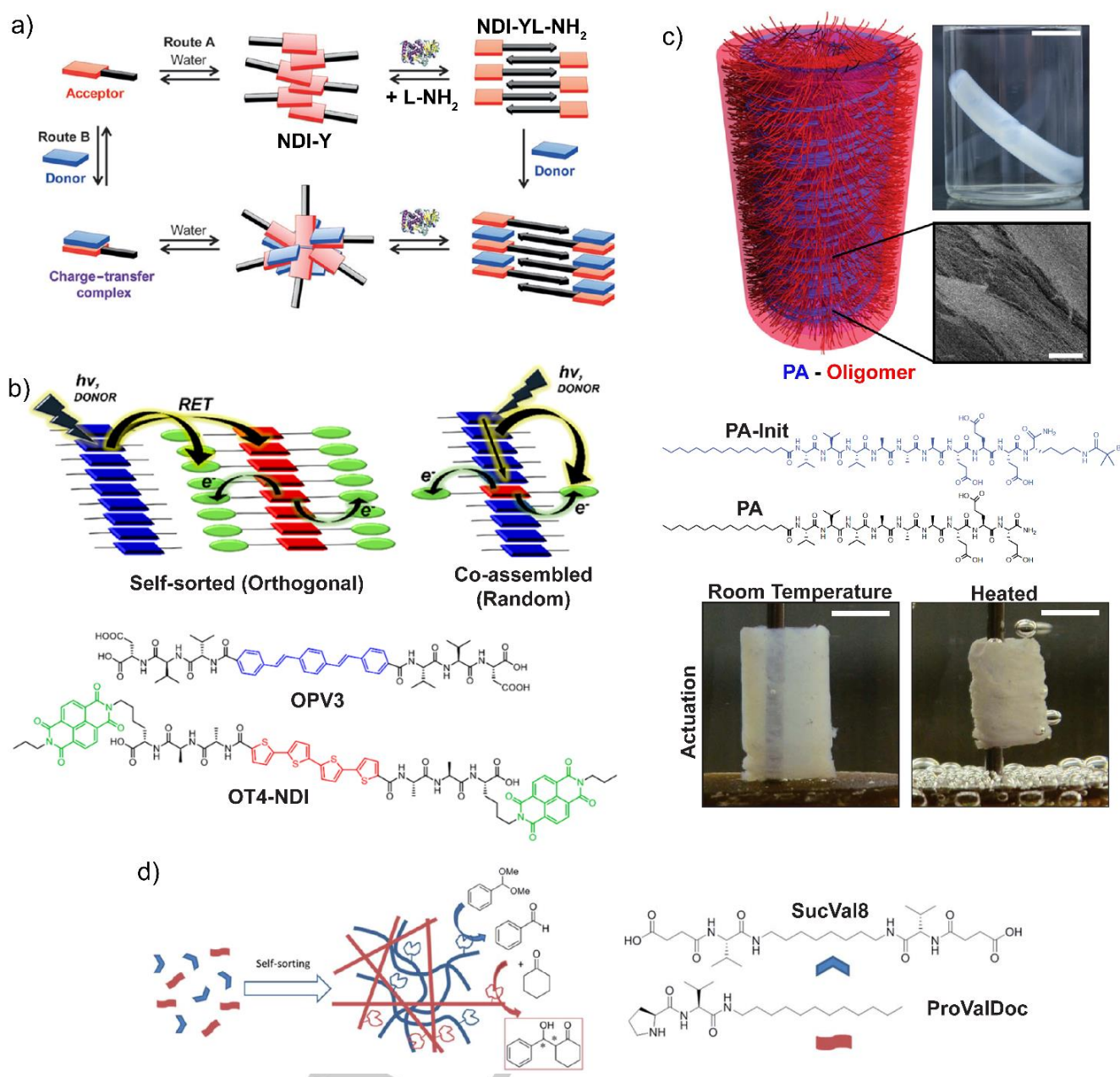
Figure 4. (a) Effect of donor addition to a enzymatically driven assembly of an acceptor APA (NDI-YL-NH2). Reproduced from ref.,[42] (b) Charge transfer differences in orthogonal and random co-assemblies of OPV3 and OT4-NDI. Reproduced from ref.,[44] Copyright (2017), with permission from ACS. (c) Oligomer growth from the functional co-assembly of PA and PA-Init gives rise to the co-functional orthogonal co-assembly of PA with PA-Oligomers. The resulting material is an actuator that contracts upon heating. Reproduced from ref.,[49] Copyright (2018), with permission from Springer Nature. (d) Orthogonal co-assemblies to carry out tandem catalytic reactions. Reproduced from ref.,[46] Copyright (2016), with permission from RSC.

2.2 Functional Peptide-based Co-assemblies

Unlike the examples of the previous section, functional co-assemblies do not aim to induce changes in the structure but to add functional groups to a given scaffold, which acts as a structural part. Ulijn *et al.* orthogonally co-assembled Fmoc-FF-OH fibers with Fmoc-S-OH, a surfactant that on its own forms micelles, to increase the number of charges on the surface of the nanostructures (Figure 3a).[30] The highly charged surface of this core-shell homo-co-assembly facilitated the crosslinking between fibers upon the addition of calcium, driving the formation of hydrogels. Variations in the concentration of the 1:1 co-assembly

could be used to adjust the stiffness of the material for its use in the differentiation of stem cells into different types of tissues. They followed a similar approach for the functionalization of Fmoc-FF-OH fibers with RGD. They orthogonally co-assembled the non-self-assembling Fmoc-RGD-OH on the surface of the fibers.[31] In this way, they combine the advantages of the 3D scaffold for cell culture with the cell signaling of the RGD group to activate integrin α5β1.

The Stupp group has developed a wide range of PA co-assemblies for multiple nanomedical applications. The robustness and well-defined orientation of the monomers in the supramolecular fibers, perpendicular to the axis, allows them to expose functional groups of a great variety of hydrobicities

MINIREVIEW

effectively. The functionalized PA keeps the structural part and attaches the active sequence in the charged exposed terminus. The inclusion of the structural sequence in the active monomers facilitates their incorporation into the nanostructures in a random way that can get disruptive at high percentages of the active monomer if the epitope has a destabilizing effect in the structure.[32] This type of homo-co-assemblies has been used to incorporate active sequences to target proteins for neuronal cell maturation,[32-33] bone generation,[34], and cartilage regeneration.[35] They have used peptide sequences as well as functionalized monosaccharides.[33-34] They found that the functional sequences were more active when co-assembled into the nanostructures than on their free states, supporting the use of the nanofibers scaffold.[32] The ratio of functionalized PA in the co-assembly and the linker length between the active group and the structural part of the functional monomer is critical for their bioactivity (Figure 3b).[33, 36]

Stupp *et al.* also exploited the epitope-protein recognition to target atherosclerotic plaque for drug delivery.[37] This system added the hetero-co-assembly of a hydrophobic drug in the aliphatic core of the PA fibers to the homo-co-assembly between structural and functional PAs. The functional epitope targets the plaque concentrating the fibers containing the drug around the atherosclerotic plaque, where it needs to be delivered.[37] Amyloid-like supramolecular assemblies have also been used to incorporate drugs on the hydrophobic space between β-sheets.[38] Granja *et al.* used a similar hetero-co-assembly approach to incorporate drugs in the inner space of cyclic peptide nanostructures.[39] Cyclic peptides allow for the design of specific interactions with the drug, making a cooperative co-assembly with the drug (Figure 3c), which is more specific than the previous examples.

Guler *at al.* showed how the functionalization of the aliphatic region of PAs with tetraaniline could make the hydrophobic core conductive favoring neurite outgrowth in neural differentiation from stem cells. This is the homo-co-assembly between oppositely charged peptides to strengthen the structure, but as both are functionalized, this system is not strictly what we called a functional co-assembly (Figure 3d).[40]

In summary, the functional co-assemblies are based on the addition of functionalized molecules into assemblies with minimum effect on the structure. These are, hence, orthogonal or random co-assemblies where the structural monomers act as scaffold templating the functional ones. However, drug delivery where the drug can be included in the hydrophobic core of nanostructures or incorporated into the structure can be cooperative. In general, the research on these materials aims to develop robust structural monomers that can be functionalized without affecting the structural part so they can be used as versatile scaffolds for multiple applications where only the functional groups differ.

2.3 Co-Functional Peptide-based Co-assemblies

In co-functional co-assemblies, the monomers do not have clear different roles; both contribute to the functionality and the structure of the system. This can be either because the function is the result of direct interaction between both monomers or because both contribute separately to the material functionality.

APAs can hetero-co-assemble with other aromatic groups (peptide-based or not) to form charge-transfer complexes.[41] The donor-acceptor interactions strengthen the π-stacking contributing to the APA assembly stability, and hence, these are often cooperative co-assemblies. Ulijn *et al.* investigated the effect of this interaction in the self- assembly tendency of Naphthalenediimide (NDI) functionalized dipeptide using enzymatically controlled self-assembly by comparing the yields in the condensation reaction of the dipeptide upon the addition of different donor molecules. They observed the increment in the condensation yield to be proportional to the donor amount up to 1:1 (Figure 4a).[42] They further exploited the charge-transfer hetero-co-assemblies in dynamic combinatorial libraries to show how the additional interaction increases the yield differences in the competition experiment.[43] Tovar *et al.* developed a more complex system co-assembling symmetric APAs. They combined three different aromatic groups by including in one of the monomers NDI and quaterthiophene, where the later one can act as a donor with the former. The second monomer with oligo(p-phenylenevinylene) could act as a donor to both aromatics in the first monomer (Figure 4b). They can control the formation of orthogonal (self-sorting) and random co-assemblies depending in the acidification process and studied that charge transfer between the monomers was more effective in the random co-assemblies (than in the orthogonal), due the closer proximity of the aromatic groups.[44]
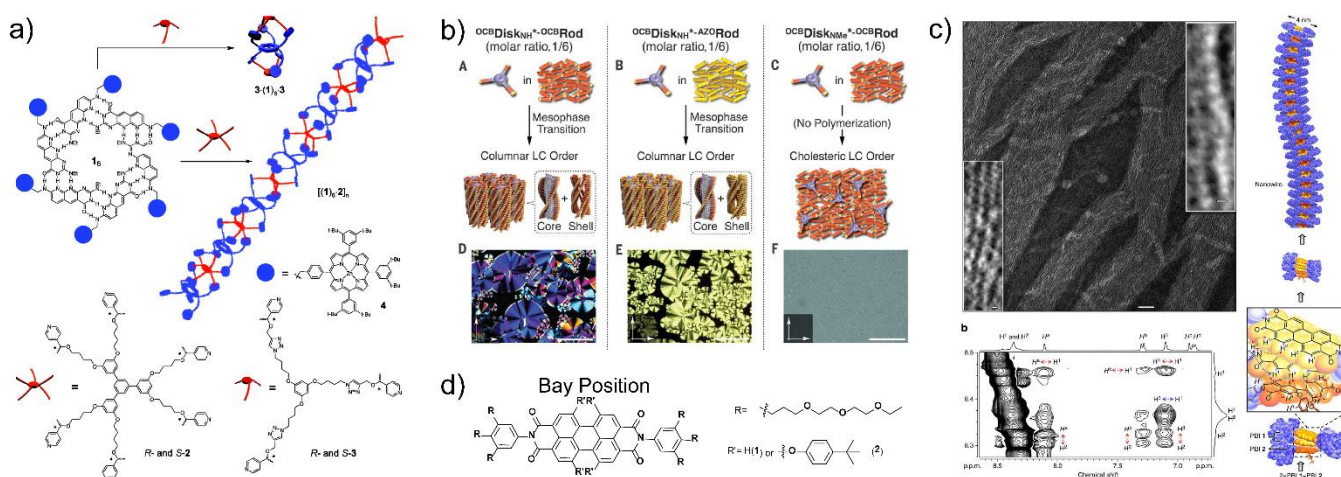
The structural interplay between different peptide sequences forming β-sheet secondary structures has been exploited by Otto *et al.* to favor diversification in their peptide-based macrocycle replicators. They used random and orthogonal homo-co-assemblies to give rise to the selection of new replicators, not selected in the mono-assemblies.[45] The orthogonal co-assembly driven selection was carried out by adding preformed seeds of a first monomer assembly to a solution with the second monomer.[45b]

Catalytic co-assemblies where the final material function is the result of two distinct monomers have also been developed. Escuder *et al.* developed hydrogels able to carry out tandem reactions by orthogonally assembled peptide-derivatives where each assembly carried out a separate reaction on the same substrate (Figure 4d).[46] They showed how the cooperative co-assembled systems could not complete the tandem reactions. In a different work, they were able to catalyze the formation of a second assembly using catalytic supramolecular nanostructures.[47] Cooperative catalytic systems have also been developed where the catalysis is carried out from two functional groups in different monomers.[48]

Stupp and co-workers developed a different type of co-functional hetero-co-assembly. They grew oligo ethylene glycol, which contracts upon heating, from aligned PA nanofibers using a PA functionalized with an initiator (Figure 4c). In this way, oligomer actuation was directed perpendicular to the aligned fibers, building a hydrogel-based artificial muscle triggered with temperature.[49]

Overall, these systems are more difficult to design because the interplay between the different monomers must be well understood as it is critical to the functionality of the material. This can be either a strong interplay for cooperative systems or minimum interplay for those systems based in additive functions from orthogonally assembled functional monomers. In addition to this, they must be redesigned for every different function, unlike

MINIREVIEW

Figure 5.a) Non-homo and chiral co-assembly in which the final polymer is affected from the number of dentates of the ligands. Reproduced from ref.,[53] Copyright (2016), with permission from ACS. b) The nematic to columnar mesophase transformation based on the ratio between the two monomers. Reproduced from ref.,[66] Copyright (2019), with permission from AAAS. [66] c) Homogeneous co-assemblies between a planar and a twisted perylene bisimide (TEM images and Roesy NMR spectrum and the proposed model. Reproduced from ref.,[61] Copyright (2016), with permission from Nature Springer. d) Chemical structures from Perylene Bisimides which used in ref. [61]

the functional assemblies in the previous section, which can be applied for multiple functions with minimum modifications. However, this is the best approach to give rise to systems that mimic the complexity of natural systems.

3 Non-peptide Co-assemblies

Non-peptide co-assemblies have been examined up to now in a different way, following the classification by Meijer *et al.,* who described them mostly as polymers giving five different groups of co-assemblies.[50] In such a way, they described that the formation of the structures requires the generation of a nucleus to initiate the cooperative formation of the supramolecular copolymer. The nucleus and the external factors such as impurities, solvent, temperature, dictate the average molecular weight and microstructure. The composition of these polymers is of utmost importance because it can affect the stability and the dynamicity. The five different categories that are described in this work are the following: Block, Blocky, Periodic, Statistical, and Alternating. An additional point for the non-peptide co-assemblies is the difficulty of the structural characterization. During the last years, different techniques appeared, some of them will be mentioned herein, to give a more accurate characterization of the co-assemblies. However, we suggest here the homogenization of nomenclature for the co-assemblies formed from peptide and non-peptide monomers, framing some literature examples. Thus, in this part, we have three subparts based on the aforementioned different categories of co-assemblies: Structural, Functional, and Co-functional. In most cases, the concept for the formation of co-assemblies based on the use of hydrogen bonds and π-π stacking at the same time. The combination of such interactions is responsible for the formation of the nucleus (mainly hydrogen bonding) and the microstructures (π-π interactions) yielding in a variety of supramolecular architectures.

3.1 Structural non-Peptide based co-assemblies

Hetero and Homo-Co-assemblies of non-peptide building blocks have been presented in different examples dealing with the stability and the differentiation in the structures. One of the first works that appeared in this field was from Lehn in 1990 involving diaminopyridine with uracil or tartaric acid giving columnar triple helical superstructures.[51] This example can be considered as a heterogeneous co-assembly and leaded the way for the preparation of co-assemblies using non-peptide small organic molecules. However, the pioneering work of Isaacs established the field of small-size finite co-assemblies.[52] In this work, the self-sorting materials are based mainly on hydrogen bonding recognition sequences. On the other hand, up to date, only a few examples of different small organic molecules forming infinite self-assemble units have appeared in the literature.

A work from Li *et al.* reports the hierarchical interactions and gives us an example of heterogeneous co-assembly between zinc porphyrins and a C3-symmetric chiral hexadentate molecule forming columnar structures (Figure 5a).[53] It is essential to mention that in this example, the starting dynamically controlled self-sorted structures of the porphyrin converted to thermodynamically controlled co-assemblies through time.

Meijer group, besides the model and the insights in the classification of the co-assemblies, have presented different examples of structural co-assemblies. The mixing of C3-organic molecules yielding in heterogeneous copolymers either by cooling or heating procedures, based on the balance between favorable hydrogen-bonding and the mismatch penalty between the two monomers (Figure 5d).[54] In such a way, it is presented that the block length distribution is closely related to the enthalpy of counteraction of the different monomers with respect to the enthalpy of the related homo-interaction. An additional point of this work is the use of super-resolution microscopy technique for visualizing the formed architectures. Further examples were
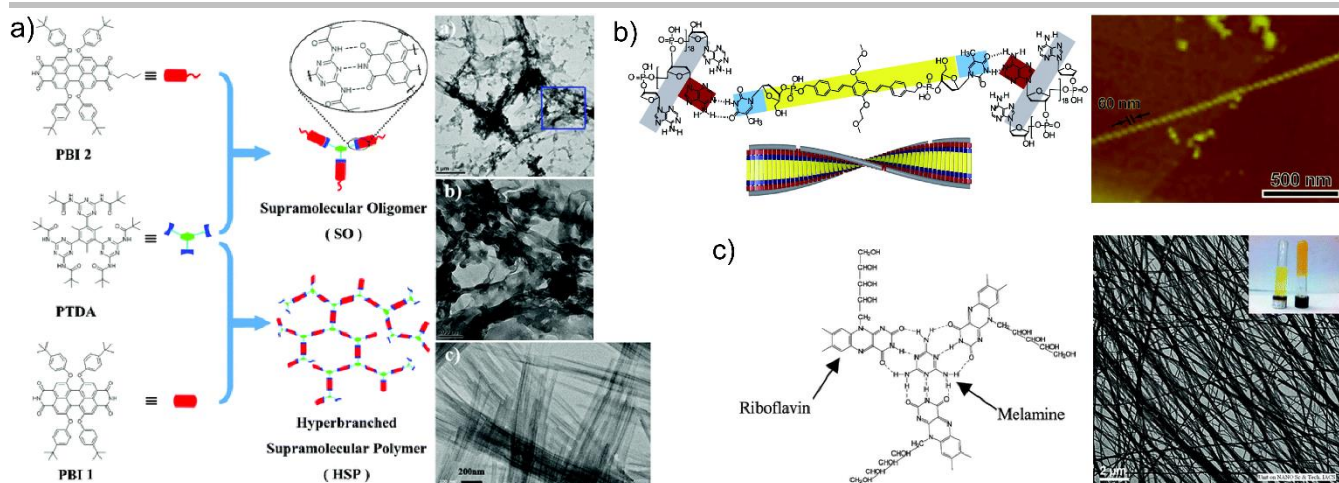
Figure 6. a) Schematic representation and TEM images from the oligomers of the co-functional perylene bisimides monomers and the three arm "glue". Reproduced from ref.,[72] Copyright (2016), with permission from RSC. b) Schematic model of the riboflavin-melamine complex in 2D dimensions and the TEM image presenting the 3D structures, Reproduced from ref.,[78] Copyright (2006), with permission from ACS and c) Schematic representation of the self-assembly between nucleotide-appended OPV and its complementary single-stranded 20-meric oligodeoxyadenylic acid. Reproduced from ref.,[74] Copyright (2006), with permission from RSC.

presented from monomers that have different supramolecular units or different cores.[55] The same group showed examples of dyads of C3 monomers and a co-assembly of a chiral benzene tricarboxamide with achiral benzene trisurea that gives a kinetically trapped copolymer that can evolve into self-sorted homopolymers during the time.[55a] This work presented different characterization techniques, such as Small-Angle Neutron Scattering (SANS), Infrared Spectroscopy, Circular dichroism, in a way to get a "closer" insights in the formed structures. On the other hand, a simple change of the core of the benzene tricarboxamides allowed them to form stable copolymers.[56] A very interesting example of structural co-assemblies reported from the Meijer group and discussed the hetero-co-assembly in two steps. Firstly, the use of a chiral oligo(p-vinylene phenylene)s (OPV) for the formation of supramolecular structures of specific chirality. At the second step, chiral dibenzoyl tartaric acid was added, and upon the addition at a second step, the other monomer yielding in different thermodynamic preference of the assembly process of the OPV. In such a way can be formed only metastable assemblies. [57]

For the structural co-assemblies, the scientist did not use any bulky group, believing that this will prevent co-assembly. However, an interesting example from the Meijer group present that the use of a bulk side chain, which does not allow the self-sorted supramolecular polymer, can give copolymers after being mixed with a different monomer.[58] The ratio of the monomers is responsible for the formation of these heterogeneous co-assemblies, providing the appropriate space between the bulky monomers.

A molecule's family, which appears very often in either homo and hetero co-assemblies is the rylene (Figure 5d). The group of Würthner keeps a central role in the scientific scene dealing with such molecules and with co-assemblies of such ones. Several examples of hetero-co-assemblies are described. In most of the cases, one of the two molecules is a rylene chromophore. In the first example, a perylene bisimide is mixed with melamine linked azobenzene. The ratio between the two molecules is responsible for changes in the types of interactions, hydrogen bonds, and π-stacking, yielding in thermodynamically stable helically-coiled architectures.[59] In a similar system, same perylene bisimide is

mixed with a diarylethene derivative, and through hydrogen-bonding and strong π-π interactions forms parallel conformers.[60] These nanosystems, due to their photoresponsiveness, undergo nanomorphology transition of the formed J-type of dimers. Upon irradiation, the nanofibers turn into nanoparticles. A very interesting example of structural co-assembly from this group is the use of a bay unsubstituted perylene bisimide with a tetrasubstituted one (Figure 5d).[61] The unsubstituted perylene bisimides in most of the cases form nanorods while this tetrasubstituted one gives nanoworms (depending on the bulkiness of the bay substituents). The mix of these two monomers gives kinetically controlled co-assemblies that can be segregated with time in organic solvents. This segregation of the supramolecular polymers can be prevented by inducing the π-π interactions when water is used as solvent. Furthermore, in this work, they introduce the use of ROESY NMR as a characterization technique for the co-assemblies. (Figure 5c)

An additional characteristic example of homo-co-assemblies between perylene-cored molecules is given from Li's group where monosubstituted perylene molecules, having complementary hydrogen bonding sites, form different assembled structures depending on the solvent (mixtures of MeOH and THF).[62] This is a distinctive example of how to change the kinetically formed assemblies by tuning the strength of the hydrogen bonding with a mixture of polar/nonpolar solvents.

The effect of the solvent in the kinetically controlled or thermodynamically controlled co-assemblies is of utmost importance. Mainly water can act as a structural component that unlocks impressive adhesive properties of supramolecular polymers (between the monomers and between different polymers). In addition, to the work of co-assemblies of the perylene bisimides molecules, a representative example is reported from the Schalley group, where they employed crown ether functionalized benzene tricarboxamides.[63] Additional examples are again from the Meijer group, where they presented the co-assemblies of benzene tricarboxamides trisubstituted with different monosaccharides.[64] The different monomers, because of their hydrophilicity, can be affected by the aqueous environment and form different supramolecular structures. The intramolecular interactions, mainly the peripheral

monosaccharide moieties, are tuned from their hydrophobic/hydrophilic character, yielding in the formation of hydrogels. An additional example comes from the group of Sijbesma, where the use of chiral trans-bisureido bolaamphiphiles in water yield the formation of segregated enantiomeric dynamic rods.[65]

The last example in this category of co-assemblies that evidence the importance of the tunability of the supramolecular polymer is coming from Aida's group. They aim to examine the co-assembly of a molecule that forms disks and one that forms rods. In general, such procedures yield to phase separation of the two molecules. However, in the specific example, the polymerization of the disk-shaped chiral monomer in nematic liquid crystals comprising rod-shaped molecules yields in order- increasing mesophase transition into a single mesophase with a core-shell columnar geometry. These systems can be affected and transformed upon the application of an external electric field (Figure 5b).[66]

Living supramolecular polymerization is still a very demanding procedure, but there are only a few examples in the literature. Here, we would like to insert an instance from the Würthner group, where they used properly designed perylene bisimides, which under kinetic control form supramolecular block copolymers.[67] The substitution of such molecules at 1,7 bay positions (Figure 5d) with different moieties can tune the formed aggregates between H and J, based on the kinetically trapped states. The use of another perylene bisimide molecule seeds leads to the formation of the required block copolymers. This is a work that paved the road for living supramolecular polymerization and that the careful kinetic control of different building blocks can yield in different co-assemblies.

Most of the aforementioned examples are based on the aromatic /hydrophobic interactions between the building blocks. Several examples that form co-assemblies are based on complementary hydrogen bonds. The interesting point with the complementary hydrogen bonding polymerization is that they often form chiral supramolecular polymers. We just mention here some examples to present hydrogen-bonding based co-assemblies; however, it has been discussed in more detail in a recent review.[3d] Lehn presented one of the first examples using complementary hydrogen bonding. The two chiral monomers form a supramolecular polymer with optical activity.[68] All these examples give us directions on how to prepare supramolecular co-assemblies, focusing on how the kinetic and the thermodynamic control of the supramolecular interactions between the monomers can affect the type of the formed structures and their stability. The most important factors for such control of the adhesive interactions are the differentiation of the hydrophobic and/or hydrophilic character, the used solvents and the externally applied energy, such as heating and electric field. These examples provide an overview of how they can be built co-assemblies with advanced properties. The next point is to see not only if we can tune the structures, but it can introduce a functional part that can provide the functionality to the systems.

3.2 Functional non-Peptide based co-assemblies

Examples of the formation of Functional co-assemblies are based on the use of molecules that interact through hydrogen bonding and π-stacking at the same time. The combination of these two types of interactions forms functional supramolecular polymers (enhanced emission, organization of polymers in solar cells, etc.) A very characteristic molecular example for the preparation of functional co-assemblies is the melamine and its analogues. Based on the first work from Ringsdorf *et al.* yields in the formation of non-homo-co-assemblies ones. [69] In such co-assemblies, can be used different groups that can be attached to the melamine moiety and through hydrogen bonding can form dyads (hydrogen bonding donor-acceptor). This dyad is now the new building block for the supramolecular polymers using the interactions of the whole dyad for the preparation of the architecture. Examples in the category of functional co-assemblies are reported in the literature yielding in the formation of dyads based on the hydrogen bonds of melamine and then the use of π-π interactions in a second step the formation of supramolecular polymers. A characteristic example is the interaction of a perylene bisimide with substituted melamine in equimolar ratio yield in the formation of hetero-assemblies based supramolecular fibers.[70]

Additional examples were given from the Meijer group on the use of melamine as one part of co-assemblies. The first example is the use of oligo(p-vinylene phenylene)s (OPVs) bearing ureido-pyrimidinone and diisocytosine derivative, forming non-homo-co-assembled polymers. These materials present photoinduced charged -separated states, something that does not take place in the monomers.[71] Another characteristic example was given by Qu *et al.* with the use of two different perylene bisimides analogues and a tris-triazine analogue (Figure 6a).[72] The heterogeneous polymers formed either nanospheres (when is used monotopic PBI) or hyperbranched polymers, which at higher concentrations form nanobelts (ditopic PBI). Both structures present very strong emission, which is not present in the starting PBI analogues. An additional example of the use of PBI analogues with melamine for the preparation of functional co-assemblies is reported in a focused review from Yagai.[73] In these examples, the synthesized co-assemblies present, in the most of the cases, enhanced emission, which is based on the orientation of the π-stacking between the perylene cores from the hydrogen bonding of the imide part of PBI and the melamines and changes between H- and J aggregates.

A very interesting category of the functional co-assemblies is the formation of gels with the use of two different components, where one component can yield into the supramolecular structure, and the second plays the interconnection role. In most of the cases, the interconnection molecule or the "glue" for the formation of gels is the melamine and its analogues. Nandi *et al.* present a gel which is formed with the use of riboflavin and melamine in ratio 3 to 1.[74] These heterogeneous co-assembled gels are affected by the environmental pH and present high photoluminescence (Figure 6c). The same group expands the examples with the use of salicylic acid,[75] dihydroxybenzoic acid[76], and acetoguanamine with riboflavin.[77] These co-assemblies differ in the structural formation from bar, tape, and helical tubes and, as a consequence, in the mechanical properties. All these works mention the importance of the choice of the gelator molecule that is used with riboflavin in optoelectronic properties (for example, acetoguanamine with riboflavin present stronger gel with higher shielding of protons and enhanced photoluminescence). Another example has been reported from Shimizu *et al.* using a nucleotide-appended OPV and its complementary single-stranded 20-meric oligodeoxyadenylic acid in a hetero-co-assembly that double helical structure.[78] This work presents a
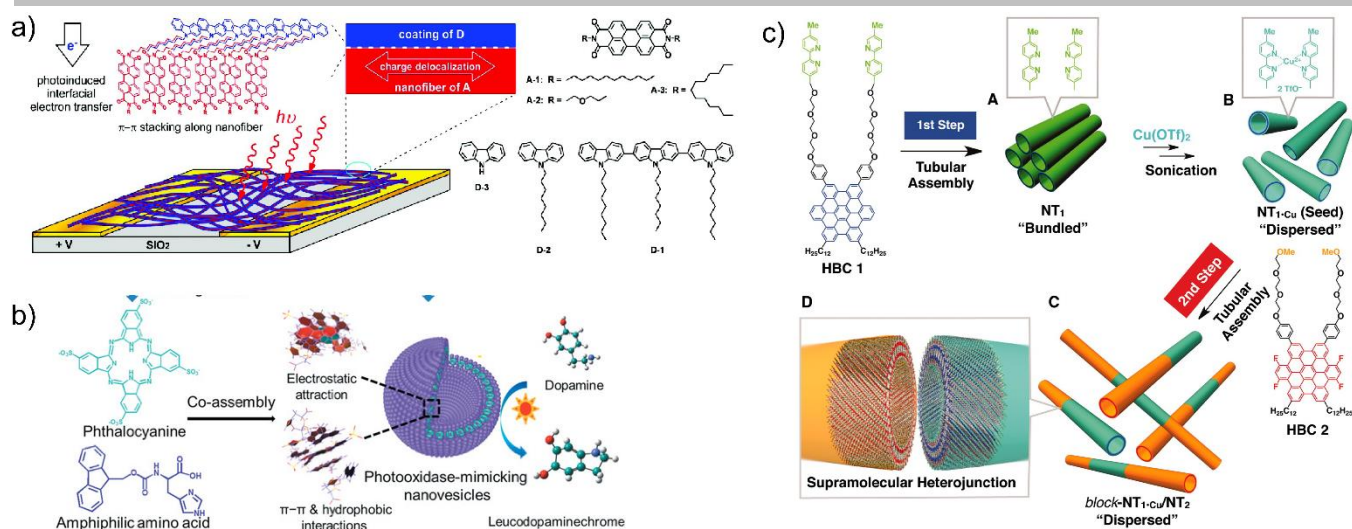
MINIREVIEW

Figure 7. a) Heterogeneous co-assembly based of Donor-Acceptor dyad, based on the hydrophobic interactions of the alkyl chains that they bare. Reproduced from ref.,[85] Copyright (2011), with permission from ACS. b) Photocatalytic vesicles with tuneable size and membrane thickness. Reproduced from ref.,[92] c) Homotropically assembled nanotubes from two different benzocoronenes with energy transfer and charge transport properties. Reproduced from ref.,[89] Copyright (2011), with permission from AAAS.

very characteristic example of how a supramolecular structure can work as a template and then, by the addition of an active molecule (such the OPV here), can lead to useful co-assemblies (herein electronic wires (Figure 6b).

There are additional examples of hetero-co-assemblies, which form strong or less strong gels based on the mixing of one structural and one active molecule. Almost all the examples that we referred here deal with hetero-co-assemblies, which in most of the cases combine hydrogen bonding and π-π interactions. The additional point is that most pairs deal with hydrogen donor-acceptor dyads, and most of the reports focus on the properties and not on the effects of the structure and how the structure can be connected with the applications. In this direction, there is still a lot of room for understanding this type of co-assemblies. For example, the mixing of new monomers, the examination of the structural effect on the properties, and with insights into different directions like applications in bioelectronics and catalysis. This can work as an initial point for the preparation of Functional co-assemblies based on well-known scaffolds, from monomers that can form stable supramolecular polymers, and varying only the functional part of the co-assemblies depending on the application. As for the functional peptide-based co-assemblies.

3.3 Co-Functional non-Peptide based co-assemblies

Co- functional co-assemblies aim to induce changes in the structure from the mixing of at least two functional groups, in which each part plays an essential role in terms of properties (i.e., donor-acceptor) and at the same time cooperate in the formation of supramolecular polymers.[5b] An additional fact that we realized by scanning the literature is that much previous work on co-functional -co-assemblies has focused on the properties of these systems. Because this study conducted in order to deal with the structural properties of co-assemblies and how these can affect the properties, we mention only such examples. ,
Based on the number of works that appeared in the literature, we are going to mention at the beginning of this part some donor-

acceptor examples. Different mixing examples of donor(D)-acceptor(A) co-assemblies have been reported, *i.e.,* DAD, ADA, DADA, or ADADA. In most of these cases, an aromatic-charge transfer takes place, which guides the interactions between the monomers and competing with the π-π interactions.[5b] One of the first and most important examples for the formation of functional co-assemblies came from MacKenzie, where the use of a perylene bisimide and a hexabenzocoronene form hetero-co-assemblies and yield in the formation of crystalline and crystalline-conjugated materials.[79] The materials are segregated in vertical structures, probably due to different solubilities, surface energies, and the solvent evaporation processes. One of the characteristic examples of co-functional co-assembly is coming from Schenning *et al.,* where the mixing of two different fluorene oligomers with naphthalene and with benzothiadiazole, gives supramolecular fluorescent organic nanoparticles and homo- co-assemblies.[80] In these systems, π-stacking is the driving force for the interactions between the molecules, but the side chains are responsible for the stability, fluorescent dynamics, and, most importantly, for the self-sorting between the two monomers.

An example of co-functional co-assemblies is given from Martin's group, where n-type (tetrathiafulvalene) and p-type molecules (perylene bisimide) are used in a mixture for the formation of segregated and alternately stacked donor-acceptor nanodomains which present enhanced photoconductivity.[81] The formation of such nanostructures based on the aromatic interactions between the two molecules but controlled from the electrostatic interactions. A similar example of a donor-acceptor mixture describes the use of C3-symmetrical donor yielding in the formation of super-coiled helical ropes.[82] The interesting point with this example is that the two monomers polymerize following different paths (C3-oligo(p-phenylenevinylene polymerize through an isodesmic mechanism while the C3-PBI with nucleation-elongation mechanism). So again, here we have the involvement of two different types of interactions that affect the final structures (hydrogen bonding and π-π interactions)—these supramolecular structures used as sensors for the detection of aromatic compounds.

11

MINIREVIEW

An additional example from Ajayaghosh presents the design of a homo co-assembly with the ability to harvest light and have tunable emission.[83] This donor-acceptor system is based on the rational choice of motifs by having the appropriate HOMO-LUMO gaps and the donor to exhibit efficient antenna effects. Additionally, the donor plays the role of the gelator yielding in FRET tunable emission. A similar system is reported from Bhattacharya, where they used similar monomers, and the formed gels have a wide-range light-harvesting ability.[84]

A distinctive example of hetero co-assembly, which gives a photoconductive material, is from the Zang group, where perylene bisimides and substituted carbazoles from nanofibrils.[85] The interfacial engineering of the electron donor (carbazole) with the acceptor (perylene bisimide) is based on the hydrophobic interactions of the long alkyl chains, forming these hetero-co-assemblies with high photoconductivity and fast photo-response (Figure 7a).

Several hetero-co-assemblies examples are based on the work from Fukuzumi, where perylene bisimides and different other chromophores, such as porphyrins, are used in an aqueous environment based on the balance between hydrophobic (π-π interactions) and the hydrophilic (ionic) interactions, tuned by the ratio of the molecules.[86] These co-assemblies were examined mainly in terms of optical properties. Older work from Meijer presented the use of a perylene bisimide which, through hydrogen bonding, forms helical p-n heterojunctions with oligo(p-phenylene vinylene)s (OPV).[87] Of utmost importance in these materials is the conjugation length of the OPVs. while they open the field for different types of organic/organic or/and organic /inorganic co-assemblies for optoelectronic applications and catalysis.[88]

A further example is given from Aida's group, where two different substituted Hexa-peri-benzacoronene form a nanoscale organic heterojunction.[89] This system prepared from the stepwise nanotubular co-assembly (each of the monomers forms nanotubular segments) through a heating-cooling procedure. The disparate tubular structures presented electronic communication over the heterojunction interface and exhibit excitation energy transfer, and charge transport properties that are not present in the monomers or the homotropically assembled nanotubes (Figure 7b). An additional example comes from Stupp and Stoddart, where they reported the crystalline co-assemblies of two monomers, presenting room temperature ferroelectricity.[90] These hetero-co-assemblies polymerize in an alternating way between the donor-acceptor monomers.

In addition to the donor-acceptor co-functional assemblies, in the literature, there are examples of light-harvesting materials with complementary light absorption. These co-assemblies have the ability to absorb light in a broader range and can be useful for artificial photosynthesis, mimicking the natural photosystems. Once more, the co-assembly is formed from perylene cored molecules.[91] These have different moieties at the bay position, which tune the optical properties. The specific mixture in ratio 10/3/3/3 of four different monomers gives a material that can harvest light in the whole visible range of light.

Yan gives one of the few examples that combine two organic molecules with being used in catalysis, imitating enzymes.[92] Obtained nanovesicles from phthalocyanine and aromatic amino acid can mimic photooxidase and having tunable particle size and membrane thickness (Figure 7c). This is one of the most interesting approaches to the evolution of supramolecular photocatalytic membrane systems.

Another interesting approach to such co-assemblies is the preparation of fluorescent pH sensors from Würthner.[93] Perylene bisimides vesicles loaded with bispyrene-based energy donors in an aqueous environment, stabilized with *in situ* photopolymerization, presenting pH-dependent fluorescence resonance energy transfer from the encapsulated donors to the bilayer dye membrane. These co-assembled vesicles show ultrasensitive pH information of their environment. This is an indicative example where the pure perylene bisimide vesicles do not present such behavior in aqueous solution.

Co-Functional co-assemblies is the most studied part based mainly on donor-acceptor systems. Such systems-based mainly on π-π interactions and form in most of the cases 1D supramolecular structures. However, there is still plenty of space in the direction of co-assemblies for catalysis or biological application with the use of the appropriate monomers. In all these cases, the interplay between the different parts of the co-assemblies must be well examined, as it is crucial to the functionality of the material.

5 Outlook and Future Directions

In this minireview, we have given an overview of the efforts made through the last 30 years to develop the field of supramolecular co-assemblies, focusing on peptide and non-peptide based low molecular weight molecules. The summarized work shows how the co-assembly between different building blocks is a simple way of synthesizing complex supramolecular systems with new properties and functions which are far beyond those achievable by the self-assembly of single monomers. Through these years, the development has focused on the development of monomers with the appropriate hydrophobic/hydrophilic balance. In addition to this, advances have been made in controlling the interactions between monomers to favor interactions between either equal or different monomers, to give rise to orthogonal (self-sorted) or cooperative co-assemblies, respectively. The structural control is not exclusively thermodynamic; kinetics has been shown to be key to tune the type of co-assembly.

The work presented here shows how the exact interplay between monomers is vital to understand their contribution (structural, functional, or both) to the co-assembled structure. Therefore, we believe that efforts should focus in this direction to provide detailed structural information of the systems, paying particular attention to how specific interactions affect the properties of the co-assemblies. Given the technological advances that continuously arise to study the nanoscale, we understand that this will require revisiting some of the known systems to gain deeper insights. This is especially challenging for peptide-based assemblies given their chemical similarities, while different aromatic groups usually help in studying the interactions. The control of co-assembly will require tuning chemical systems to introduce specific interactions between the monomers to control the relative A-B and A-A/B-B affinities, key in determining their interplay. In addition to this, the development of models to define these interplays to rationalize and predict the mechanism of co-assemblies is a need for the applicability of nanotechnology-based in co-assemblies.

Therefore, the deep understanding of the systems and the role of each monomer are prerequisites to exploit the potential of supramolecular co-assembly, which the authors believe is a

MINIREVIEW

promising tool to build up complexity towards creating synthetic systems that mimic the behavior of natural systems. The combination of functionalities in a given material where these operate cooperatively is definitely the future of both bioactive and energy-related assemblies. In addition to this, it is critical for the next step in the field to deal with the dynamicity of the supramolecular polymers and the dynamic behavior of the non-covalent nature of the formed bonds. In this direction also the characterization procedure must be evolved because this dynamism can be a critical factor for the applications.

Acknowledgments

References

[1]   G. M. Whitesides, B. Grzybowski, *Science* **2002**, *295*, 2418-2421.
[2]   R. Croce, H. van Amerongen, *Nat. Chem. Biol.* **2014**, *10*, 492-501.
[3]   a) O. Zozulia, M. A. Dolan, I. V. Korendovych, *Chem. Soc. Rev.* **2018**, *47*, 3621-3639; b) D. M. Raymond, B. L. Nilsson, *Chem. Soc. Rev.* **2018**, *47*, 3659-3720; c) H.-Q. Peng, L.-Y. Niu, Y.-Z. Chen, L.-Z. Wu, C.-H. Tung, Q.-Z. Yang, *Chem. Rev.* **2015**, *115*, 7502-7542; dE. Yashima, N. Ousaka, D. Taura, K. Shimomura, T. Ikai, K. Maeda, *Chem. Rev.* **2016**, *116*, 13752-13990.
[4]   a) S. Zhang, *Nat. Biotechnol.* **2003**, *21*, 1171-1178; bM. Reches, E. Gazit, *Nat. Nanotech.* **2006**, *1*, 195-200; c) K. Tao, B. Xue, Q. Li, W. Hu, L. J. W. Shimon, P. Makam, M. Si, X. Yan, M. Zhang, Y. Cao, R. Yang, J. Li, E. Gazit, *Mater. Today* **2019**, *30*, 10-16; d) X. Du, J. Zhou, O. Guvench, F. O. Sangiorgi, X. Li, N. Zhou, B. Xu, *Bioconj. Chem.* **2014**, *25*, 1031-1035; eE. Gazit, *Chem. Soc. Rev.* **2007**, *36*, 1263-1269.
[5]   a) S. Fleming, R. V. Ulijn, *Chem. Soc. Rev.* **2014**, *43*, 8150-8177; b) Y. Han, Y. Tian, Z. Li, F. Wang, *Chem. Soc. Rev.* **2018**, *47*, 5165-5176; c) B. O. Okesola, A. Mata, *Chem. Soc. Rev.* **2018**, *47*, 3721-3736.
[6]   a) K.-T. Wong, D. M. Bassani, *NPG Asia Materials* **2014**, *6*, e116-e116; b) M. M. Safont-Sempere, G. Fernández, F. Würthner, *Chem. Rev.* **2011**, *111*, 5784-5814; c) J. Matern, Y. Dorca, L. Sánchez, G. Fernandez, *Angew. Chem. Int. Ed.* **2019**, *58*, 16730-16740.
[7]   a) L.-J. Chen, H.-B. Yang, M. Shionoya, *Chem. Soc. Rev.* **2017**, *46*, 2555-2576; b) A. Winter, U. S. Schubert, *Chem. Soc. Rev.* **2016**, *45*, 5311-5357.
[8]   a) S. Fleming, S. Debnath, P. W. J. M. Frederix, N. T. Hunt, R. V. Ulijn, *Biomacromolecules* **2014**, *15*, 1171-1184; b) M. P. Hendricks, K. Sato, L. C. Palmer, S. I. Stupp, *Acc. Chem. Res.* **2017**, *50*, 2440-2448.
[9]   M. Reches, E. Gazit, *Science* **2003**, *300*, 625-627.
[10]   P. W. J. M. Frederix, G. G. Scott, Y. M. Abul-Haija, D. Kalafatovic, C. G. Pappas, N. Javid, N. T. Hunt, R. V. Ulijn, T. Tuttle, *Nat. Chem.* **2014**, *7*, 30.
[11]   I. P. Moreira, G. G. Scott, R. V. Ulijn, T. Tuttle, *Mol. Phys.* **2019**, *117*, 1151-1163.

[12]   S. Bera, S. Mondal, Y. Tang, G. Jacoby, E. Arad, T. Guterman, R. Jelinek, R. Beck, G. Wei, E. Gazit, *ACS Nano* **2019**, *13*, 1703-1712.
[13]   C. Guo, Z. A. Arnon, R. Qi, Q. Zhang, L. Adler-Abramovich, E. Gazit, G. Wei, *ACS Nano* **2016**, *10*, 8316-8324.
[14]   S. Yuran, Y. Razvag, M. Reches, *Acs Nano* **2012**, *6*, 9559-9566.
[15]   Y. M. Abul-Haija, G. G. Scott, J. K. Sahoo, T. Tuttle, R. Ulijn, *Chem. Commun.* **2017**, *53*, 9562-9565.
[16]   I. Sasselli, I. Moreira, R. Ulijn, T. Tuttle, *Org. Biomol. Chem.* **2017**, *15*, 6541-6547.
[17]   W. Ji, S. Zhang, S. Yukawa, S. Onomura, T. Sasaki, K. i. Miyazawa, Y. Zhang, *Angew. Chem. Int. Ed.* **2018**, *57*, 3636-3640.
[18]   S. Onogi, H. Shigemitsu, T. Yoshii, T. Tanida, M. Ikeda, R. Kubota, I. Hamachi, *Nat. Chem.* **2016**, *8*, 743.
[19]   J. Li, X. Du, S. Hashim, A. Shy, B. Xu, *J. Amer. Chem .Soc* **2016**, *139*, 71-74.
[20]   H. A. Behanna, J. J. Donners, A. C. Gordon, S. I. Stupp, *J. Amer. Chem .Soc* **2005**, *127*, 1193-1200.
[21]   S. Li, A. K. Mehta, A. N. Sidorov, T. M. Orlando, Z. Jiang, N. R. Anthony, D. G. Lynn, *J. Amer. Chem .Soc* **2016**, *138*, 3579-3586.
[22]   a) V. Gauba, J. D. Hartgerink, *J. Amer. Chem .Soc* **2007**, *129*, 2683-2690; b) V. Gauba, J. D. Hartgerink, *J. Amer. Chem .Soc* **2007**, *129*, 8921-8921.
[23]   K. Liu, R. Xing, C. Chen, G. Shen, L. Yan, Q. Zou, G. Ma, H. Möhwald, X. Yan, *Angew. Chem. Int. Ed.* **2015**, *54*, 500-505.
[24]   S. Biswas, A. K. Das, *Langmuir* **2019**, *35*, 2383-2391.
[25]   F. Wang, C. L. Feng, *Chem. European J. Chem.* **2018**, *24*, 1509-1513.
[26]   P. Xing, P. Li, H. Chen, A. Hao, Y. Zhao, *ACS nano* **2017**, *11*, 4206-4216.
[27]   B. O. Okesola, Y. Wu, B. Derkus, S. Gani, D. Wu, D. Knani, D. K. Smith, D. J. Adams, A. Mata, *Chem. Mater.* **2019**, *31*, 7883-7897.
[28]   C. Redondo-Gómez, Y. Abdouni, C. R. Becer, A. Mata, *Biomacromolecules* **2019**.
[29]   R. Freeman, M. Han, Z. Álvarez, J. A. Lewis, J. R. Wester, N. Stephanopoulos, M. T. McClendon, C. Lynsky, J. M. Godbe, H. Sangji, *Science* **2018**, *362*, 808-813.
[30]   E. V. Alakpa, V. Jayawarna, A. Lampel, K. V. Burgess, C. C. West, S. C. Bakker, S. Roy, N. Javid, S. Fleming, D. A. Lamprou, *Chem* **2016**, *1*, 298-319.
[31]   M. Zhou, A. M. Smith, A. K. Das, N. W. Hodson, R. F. Collins, R. V. Ulijn, J. E. Gough, *Biomaterials* **2009**, *30*, 2523-2530.
[32]   A. N. Edelbrock, Z. Àlvarez, D. Simkin, T. Fyrner, S. M. Chin, K. Sato, E. Kiskinis, S. I. Stupp, *Nano Lett.* **2018**, *18*, 6237-6247.
[33]   E. J. Berns, Z. Álvarez, J. E. Goldberger, J. Boekhoven, J. A. Kessler, H. G. Kuhn, S. I. Stupp, *Acta Biomater.* **2016**, *37*, 50-58.
[34]   a) S. S. Lee, T. Fyrner, F. Chen, Z. Álvarez, E. Sleep, D. S. Chun, J. A. Weiner, R. W. Cook, R. D. Freshman, M. S. Schallmo, *Nat. Nanot.* **2017**, *12*, 821; b) S. S. Lee, E. L. Hsu, M. Mendoza, J. Ghodasra, M. S. Nickoli, A. Ashtekar, M. Polavarapu, J. Babu, R. M. Riaz, J. D. Nicolas, *Adv. Health. Mater.* **2015**, *4*, 131-141.
[35]   R. N. Shah, N. A. Shah, M. M. D. R. Lim, C. Hsieh, G. Nuber, S. I. Stupp, *Proc. Nat. Acad. Sci.* **2010**, *107*, 3293-3298.
[36]   S. Sur, F. Tantakitti, J. B. Matson, S. I. Stupp, *Biomater. Sci.* **2015**, *3*, 520-532.
[37]   M. M. So, N. A. Mansukhani, E. B. Peters, M. S. Albaghdadi, Z. Wang, C. M. Rubert Pérez, M. R. Kibbe, S. I. Stupp, *Adv. Biosys.* **2018**, *2*, 1700123.
[38]   D. Roberts, C. Rochas, A. Saiani, A. Miller, *Langmuir* **2012**, *28*, 16196-16206.
[39]   N. Rodriguez-Vazquez, R. Garcia-Fandino, M. J. Aldegunde, J. Brea, M. I. Loza, M. Amorín, J. R. Granja, *Org. Lett.* **2017**, *19*, 2560-2563.
[40]   I. Arioz, O. Erol, G. Bakan, F. B. Dikecoglu, A. E. Topal, M. Urel, A. Dana, A. B. Tekinay, M. O. Guler, *ACS Appl. Mater. Inter.* **2017**, *10*, 308-317.
[41]   M. A. Khalily, G. Bakan, B. Kucukoz, A. E. Topal, A. Karatay, H. G. Yaglioglu, A. Dana, M. O. Guler, *ACS Nano* **2017**, *11*, 6881-6892.
[42]   S. K. M. Nalluri, C. Berdugo, N. Javid, P. W. Frederix, R. V. Ulijn, *Angew. Chem. Int. Ed.* **2014**, *53*, 5882-5887.
[43]   S. K. M. Nalluri, R. V. Ulijn, *Chem. Sci.* **2013**, *4*, 3699-3705.
[44]   H. A. M. Ardoña, E. R. Draper, F. Citossi, M. Wallace, L. C. Serpell, D. J. Adams, J. D. Tovar, *J. Amer. Chem .Soc* **2017**, *139*, 8685-8692.

MINIREVIEW

[45] a) J. W. Sadownik, E. Mattia, P. Nowak, S. Otto, *Nat. Chem.* **2016**, *8*, 264; b) Y. Altay, M. Tezcan, S. Otto, *J. Amer. Chem .Soc* **2017**, *139*, 13612-13615.

[46] N. Singh, K. Zhang, C. A. Angulo-Pachón, E. Mendes, J. H. Van Esch, B. Escuder, *Chem. Sci.* **2016**, *7*, 5568-5572.

[47] N. Singh, C. Maity, K. Zhang, C. A. Angulo‐Pachón, J. H. van Esch, R. Eelkema, B. Escuder, *Chem. European J.Chem. European J.Chem. Europ. J.* **2017**, *23*, 2018-2021.

[48] Z. Huang, S. Guan, Y. Wang, G. Shi, L. Cao, Y. Gao, Z. Dong, J. Xu, Q. Luo, J. Liu, *J. Mater. Chem. B* **2013**, *1*, 2297-2304.

[49] S. M. Chin, C. V. Synatschke, S. Liu, R. J. Nap, N. A. Sather, Q. Wang, Z. Álvarez, A. N. Edelbrock, T. Fyrner, L. C. Palmer, *Nat. Commun.* **2018**, *9*, 2395.

[50] B. Adelizzi, N. J. Van Zee, L. N. J. de Windt, A. R. A. Palmans, E. W. Meijer, *J. Amer. Chem .Soc* **2019**, *141*, 6110-6121.

[51] C. Fouquey, J.-M. Lehn, A.-M. Levelut, *Adv. Mater.* **1990**, *2*, 254-257.

[52] A. Wu, L. Isaacs, *J. Amer. Chem .Soc* **2003**, *125*, 4831-4835.

[53] S.-G. Chen, Y. Yu, X. Zhao, Y. Ma, X.-K. Jiang, Z.-T. Li, *J. Amer. Chem .Soc* **2011**, *133*, 11124-11127.

[54] B. Adelizzi, A. Aloi, A. J. Markvoort, H. M. M. Ten Eikelder, I. K. Voets, A. R. A. Palmans, E. W. Meijer, *J. Amer. Chem .Soc* **2018**, *140*, 7168-7175.

[55] aJ. J. van Gorp, J. A. J. M. Vekemans, E. W. Meijer, *J. Amer. Chem .Soc* **2002**, *124*, 14759-14769; bP. A. Korevaar, C. Grenier, E. W. Meijer, *J. Polym. Sci., Part A: Polym. Chem.* **2015**, *53*, 385-391.

[56] P. J. M. Stals, J. C. Everts, R. de Bruijn, I. A. W. Filot, M. M. J. Smulders, R. Martín-Rapún, E. A. Pidko, T. F. A. de Greef, A. R. A. Palmans, E. W. Meijer, *Chem. European J.* **2010**, *16*, 810-821.

[57] P. A. Korevaar, S. J. George, A. J. Markvoort, M. M. Smulders, P. A. Hilbers, A. P. Schenning, T. F. De Greef, E. Meijer, *Nature* **2012**, *481*, 492-496.

[58] B. N. S. Thota, X. Lou, D. Bochicchio, T. F. E. Paffen, R. P. M. Lafleur, J. L. J. van Dongen, S. Ehrmann, R. Haag, G. M. Pavan, A. R. A. Palmans, E. W. Meijer, *Angew. Chem. Int. Ed.* **2018**, *57*, 6843-6847.

[59] S. Yagai, S. Hamamura, H. Wang, V. Stepanenko, T. Seki, K. Unoike, Y. Kikkawa, T. Karatsu, A. Kitamura, F. Wurthner, *Org. Biomol. Chem.* **2009**, *7*, 3926-3929.

[60] S. Yagai, K. Iwai, M. Yamauchi, T. Karatsu, A. Kitamura, S. Uemura, M. Morimoto, H. Wang, F. Würthner, *Angew. Chem. Int. Ed.* **2014**, *53*, 2602-2606.

[61] D. Gorl, X. Zhang, V. Stepanenko, F. Wurthner, *Nat Commun* **2015**, *6*, 7009-.

[62] Z. Guo, K. Wang, P. Yu, S. Zhang, K. Sun, Z. Li, *Phys. Chem. Chem. Phys.* **2017**, *19*, 23007-23014.

[63] S. Dong, J. Leng, Y. Feng, M. Liu, C. J. Stackhouse, A. Schönhals, L. Chiappisi, L. Gao, W. Chen, J. Shang, L. Jin, Z. Qi, C. A. Schalley, *Science Advances* **2017**, *3*, eaao0900.

[64] S. I. S. Hendrikse, L. Su, T. P. Hogervorst, R. P. M. Lafleur, X. Lou, G. A. van der Marel, J. D. C. Codee, E. W. Meijer, *J. Amer. Chem .Soc* **2019**, *141*, 13877-13886.

[65] A. Pal, P. Besenius, R. P. Sijbesma, *J. Amer. Chem .Soc* **2011**, *133*, 12987-12989.

[66] K. Yano, Y. Itoh, F. Araoka, G. Watanabe, T. Hikima, T. Aida, *Science* **2019**, *363*, 161-165.

[67] W. Wagner, M. Wehner, V. Stepanenko, F. Würthner, *J. Amer. Chem .Soc* **2019**, *141*, 12044-12054.

[68] T. Gulik-Krzywicki, C. Fouquey, J. Lehn, *Proc. Nat. Acad. Sci.* **1993**, *90*, 163-167.

[69] T. M. Bohanon, S. Denzinger, R. Fink, W. Paulus, H. Ringsdorf, M. Weck, *Angew. Chem. Inter. Ed. Eng.* **1995**, *34*, 58-60.

[70] F. Würthner, C. Thalacker, A. Sautter, W. Schärtl, W. Ibach, O. Hollricher, *Chem. European J.Chem. European J.Chem. Europ. J.* **2000**, *6*, 3871-3886.

[71] A. El-ghayoury, A. P. H. J. Schenning, P. A. van Hal, J. K. J. van Duren, R. A. J. Janssen, E. W. Meijer, *Angew. Chem. Int. Ed.* **2001**, *40*, 3660-3663.

[72] X. Fu, Q. Zhang, G. Wu, W. Zhou, Q.-C. Wang, D.-H. Qu, *Polymer Chem.* **2014**, *5*, 6662-6666.

[73] T. Seki, X. Lin, S. Yagai, *Asian J. Org. Chem.* **2013**, *2*, 708-724.

[74] S. Manna, A. Saha, A. K. Nandi, *Chem. Commun.* **2006**, 4285-4287.

[75] Y. Li, L. Cheng, C. Liu, W. Liu, L. Zhu, Y. Fan, Y. Wu, X. Li, Q. Zeng, X. Fan, *RSC Advances* **2015**, *5*, 97629-97634.

[76] A. Saha, B. Roy, A. Esterrani, A. K. Nandi, *Org. Biomol. Chem.* **2011**, *9*, 770-776.

[77] A. Saha, S. Manna, A. K. Nandi, *Langmuir* **2007**, *23*, 13126-13135.

[78] R. Iwaura, F. J. M. Hoeben, M. Masuda, A. P. H. J. Schenning, E. W. Meijer, T. Shimizu, *J. Amer. Chem .Soc* **2006**, *128*, 13298-13304.

[79] L. Schmidt-Mende, A. Fechtenkötter, K. Müllen, E. Moons, R. H. Friend, J. D. MacKenzie, *Science* **2001**, *293*, 1119-1122.

[80] A. Kaeser, I. Fischer, R. Abbel, P. Besenius, D. Dasgupta, M. A. J. Gillisen, G. Portale, A. L. Stevens, L. M. Herz, A. P. H. J. Schenning, *ACS Nano* **2013**, *7*, 408-416.

[81] J. López-Andarias, M. J. Rodriguez, C. Atienza, J. L. López, T. Mikie, S. Casado, S. Seki, J. L. Carrascosa, N. Martín, *J. Amer. Chem .Soc* **2015**, *137*, 893-897.

[82] A. Sandeep, V. K. Praveen, K. K. Kartha, V. Karunakaran, A. Ajayaghosh, *Chem. Sci.* **2016**, *7*, 4460-4467.

[83] A. Ajayaghosh, C. Vijayakumar, V. K. Praveen, S. S. Babu, R. Varghese, *J. Amer. Chem .Soc* **2006**, *128*, 7174-7175.

[84] S. K. Samanta, S. Bhattacharya, *Chem. European J.* **2012**, *18*, 15875-15885.

[85] Y. Che, H. Huang, M. Xu, C. Zhang, B. R. Bunes, X. Yang, L. Zang, *J. Amer. Chem .Soc* **2011**, *133*, 1087-1091.

[86] a) M. Supur, S. Fukuzumi, *J. Phys. Chem. C* **2012**, *116*, 23274-23282; b) M. Supur, S. Fukuzumi, *Phys. Chem. Chem. Phys.* **2013**, *15*, 2539-2546.

[87] F. Würthner, Z. Chen, F. J. M. Hoeben, P. Osswald, C.-C. You, P. Jonkheijm, J. v. Herrikhuyzen, A. P. H. J. Schenning, P. P. A. M. van der Schoot, E. W. Meijer, E. H. A. Beckers, S. C. J. Meskers, R. A. J. Janssen, *J. Amer. Chem .Soc* **2004**, *126*, 10611-10618.

[88] a) M. Bonchio, Z. Syrgiannis, M. Burian, N. Marino, E. Pizzolato, K. Dirian, F. Rigodanza, G. A. Volpato, G. La Ganga, N. Demitri, S. Berardi, H. Amenitsch, D. M. Guldi, S. Caramori, C. A. Bignozzi, A. Sartorel, M. Prato, *Nat. Chem.* **2019**, *11*, 146-153; b) V. Strauss, J. T. Margraf, K. Dirian, Z. Syrgiannis, M. Prato, C. Wessendorf, A. Hirsch, T. Clark, D. M. Guldi, *Angew. Chem. Int. Ed.* **2015**, *54*, 8292-8297.

[89] W. Zhang, W. Jin, T. Fukushima, A. Saeki, S. Seki, T. Aida, *Science* **2011**, *334*, 340-343.

[90] A. S. Tayi, A. K. Shveyd, A. C.-H. Sue, J. M. Szarko, B. S. Rolczynski, D. Cao, T. J. Kennedy, A. A. Sarjeant, C. L. Stern, W. F. Paxton, *Nature* **2012**, *488*, 485-489.

[91] K. Sugiyasu, N. Fujita, S. Shinkai, *Angew. Chem. Int. Ed.* **2004**, *43*, 1229-1233.

[92] J. Han, K. Liu, R. Chang, L. Zhao, X. Yan, *Angew. Chem. Int. Ed.* **2019**, *58*, 2000-2004.

[93] X. Zhang, S. Rehm, M. M. Safont-Sempere, F. Würthner, *Nat. Chem.* **2009**, *1*, 623.

WILEY-VCH

Entry for the Table of Contents
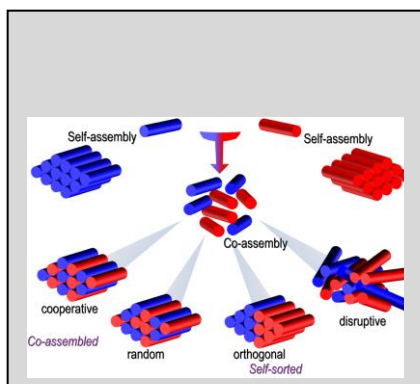
Key Topic: Supramolecular Chemistry

This Minireview focused on the supramolecular co-assemblies of small organic molecules. Specific examples of peptide and non-peptide building blocks are highlighted in a way to understand the interactions of the building blocks and how these can be utilized in different applications.

@IRSasselli, @zoissyrgiannis