

Feature Article

Toward Rational and Modular Molecular Design in Soft Matter Engineering^{*}

Wen-Bin Zhang^{a**} and Stephen Z.D. Cheng^{b**}

^a Key Laboratory of Polymer Chemistry & Physics of Ministry of Education, Center for Soft Matter Science and Engineering, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

^b Department of Polymer Science, College of Polymer Science and Polymer Engineering, The University of Akron, Akron, OH 44325-3909, U.S.A.

Abstract This essay discusses some preliminary thoughts on the development of a rational and modular approach for molecular design in soft matter engineering and proposes ideas of structural and functional synthons for advanced functional materials. It echoes the Materials Genome Initiative by practicing a tentative retro-functional analysis (RFA) scheme. The importance of hierarchical structures in transferring and amplifying molecular functions into macroscopic properties is recognized and emphasized. According to the role of molecular segments in final materials, there are two types of building blocks: structural synthon and functional synthon. Guided by a specific structure for a desired function, these synthons can be modularly combined in various ways to construct molecular scaffolds. Detailed molecular structures are then deduced, designed and synthesized precisely and modularly. While the assembled structure and property may deviate from the original design, the study may allow further refinement of the molecular design toward the target function. The strategy has been used in the development of soft fullerene materials and other giant molecules. There are a few aspects that are not yet well addressed: (1) function and structure are not fully decoupled and (2) the assembled hierarchical structures are sensitive to secondary interactions and molecular geometries across different length scales. Nevertheless, the RFA approach provides a starting point and an alternative thinking pathway by provoking creativity with considerations from both chemistry and physics. This is particularly useful for engineering soft matters with supramolecular lattice formation, as in giant molecules, where the synthons are relatively independent of each other.

Keywords: Molecular design; Materials genome; Molecular nanoparticles; Soft matter; Synthon.

INTRODUCTION

“An idea, like a ghost, must be spoken to a little before it will explain itself.”

---- Charles Dickens^[1]

In the cause of soft matter material development, the “trial-and-error” approach has been frequently used to establish the structure-property relationships for further performance optimization. It is now well recognized that the performance of functional materials does not depend only on their chemical structures, but also on how they are organized across multiple length scales^[2, 3]. In other words, to achieve a desired function, we need to control not only the primary chemical structures, but also the hierarchical structures at different length scales, especially

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^{**} Corresponding authors: Wen-Bin Zhang (张文彬), E-mail: wenbin@pku.edu.cn

Stephen Z.D. Cheng (程正迪), E-mail: scheng@uakron.edu

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from 1–100 nm^[4]. Constructing such hierarchical structures demands an understanding of the molecular and supramolecular interactions in the formation of crystals, liquid crystals, plastic crystals, mesophases and other complex supramolecular lattices^[5]. The phase formation is determined by the difference between its initial and final free energy states (the driving force), yet the pathway in which the phase transformation is pushed through relies entirely on the kinetic barriers^[3]. Very often, soft materials are trapped at various metastable states and could not reach the final thermodynamic equilibrium state. Thus, the final macroscopic properties are determined by the organization and aggregation of molecules following a specific assembling pathway. Therefore, although it is hoped that all of the functions intrinsic at the molecular level are additive (linear or nonlinear) toward a collective macroscopic property, this is not necessarily true.

To illustrate the translation of molecular functions intrinsic in microscopic functional groups into materials' macroscopic properties across different length scales, a few examples are briefly discussed here. First, polyethylene (PE) consists of $-\text{CH}_2-$ chemical repeating units with C–H non-polar bonds. Hence, a low dielectric constant is intrinsically expected ($\epsilon = 2.3$)^[6]. When the polarity of the component chemical bonds increases, the dielectric constant is predicted to also increase. If all the hydrogen atoms are replaced by fluorine atoms in PE, the polymer, polytetrafluoroethylene (PTFE), only exhibits an ϵ of 2.1^[6], although the C–F chemical bonds in PTFE are much more polar than C–H bonds. It can be explained by the slightly bulkier size of fluorine atoms that changes the zigzag conformation of the PE to a 13_7 helical conformation in PTFE and cancelling out the polarity of individual C–F bonds^[7]. The second example is concerned with a technologically important polymer called poly(vinylidene fluoride) (PVDF) with a chemical repeating unit of $-\text{CH}_2-\text{CF}_2-$. It is known that PVDF has four different polymorphism, among which only the β form exhibits strong ferroelectricity that is extremely useful for sensors and device applications^[8]. The rationale lies in the structure of the β form, which possesses a zigzag chain conformation and can align the dipoles collectively towards one direction under an electric field. Note that, in this case, the dielectric constant can be as large as 12.2^[6]. The other three crystalline forms have helical conformations, which cancel out partially the dipole moments of the bonds and compromise the ferroelectricity. The third example is the chirality transfer and amplification across hierarchical structures in soft matters^[9, 10]. The chirality transfer and amplification are important in the translation of chiral information at the atomic level to macroscopic assemblies. This has been demonstrated in a series of non-racemic liquid crystalline polyesters PETs (R^*-n). The polymers contain chiral centers at the main chain spaced by different numbers of methylene units (from 7 to 11)^[9]. The atomic chiral centers in these polymers determine the local helical conformations. The chains further pack into helical lamellar crystals to exhibit a unique double-twisted helical single crystal. However, the chirality has been lost during the aggregation process due to the uncooperative packing of chains in the higher structure level. Based on our experiences, macroscopic properties of materials are always a combined outcome of the primary chemical bonding and the hierarchical structures. In order to make accurate translation of molecular designs into final materials properties, it is not only important to consider the molecular chemical structures, but also the physical interactions that dominate at length scales beyond that of molecules.

Recognition of the possibility to engineer supramolecular interactions and “make crystals by design” has led to the vigorous field of crystal engineering and stimulated enormous research interest in the past decades^[11]. As defined by Desiraju, it refers to “the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties^[12].” The paradigm in designing periodical supramolecules thus shifted from a focus on chemical covalent bond formation within a molecule to an emphasis on noncovalent interactions among molecules^[13]. A striking parallelism was found between organic synthesis and crystal engineering. The concept of “supramolecular synthon” was proposed^[14] to describe the structural unit in the analysis, design, and synthesis of molecular crystals *via* supramolecular retro-synthesis^[15]. This modular approach captures the essence of the molecular recognition in building crystals and has achieved considerable success in the field. With interdisciplinary efforts among chemistry, physics and biology, crystal engineering has tremendously advanced the field of materials science and expanded into a global discipline with far-reaching implications, providing the

basis for understanding structure-property relationships of materials in general.

Besides molecular crystalline solids, there are many other materials that are of technological significance and practical importance, yet not traditionally considered or treated within the scope of crystal engineering. Soft matter is a class of materials that shall deserve such attention. Proposed by de Gennes^[16] as molecular systems giving a large response to small foreign stimuli, soft matters usually form hierarchical structures that are critical to their functions. Such systems typically include colloids, amphiphiles, liquid crystals, polymers, bio-macromolecules and many other functional materials^[17]. While many of them do not possess the precise atomic order as seen in crystals, they are also “organized entity of higher complexity held together by intermolecular forces”^[18] as crystals, but with varying degree of order across multiple length scales^[19]. The striking parallelism calls for a similar approach to material creation and optimization by rational design to deal with the ever-increasing complexity and diversity of soft matters. The endeavors have led to a recent burgeoning field of “soft matter engineering”^[20].

The exploration of new functional materials starts with molecular design. While engineering is simple and effective in improving current materials, we often rely on serendipity in the discovery of new materials with novel structures/compositions and exotic properties/functions. Fullerenes, carbon nanotubes and graphenes are only a few examples. It is not apparent how materials can be rationally designed until they have been actually found. For example, each gene sequence encodes a protein of specific function. Although people are good at engineering natural sequence by directed evolution^[21], it is still difficult to “write” from scratch a meaningful sequence. The same holds true for molecular materials. While methods are available for modifying the molecules both covalently and noncovalently, the *de novo* design of a molecular material remains more or less a mysterious process. By saying so, it does not mean that we have to create unique sequence (molecular structures) for each of the functions we desire. Nature combines modular and evolutionary protein domains^[22] (which are proteins with relatively conserved sequence and folded structure that can exist, function and evolve independently) to create new functions. In that sense, Nature is more like a tinker than an inventor. Similarly, we may also combine various synthetic building blocks for creating new materials. Inspired by Corey’s 1967 article entitled “General Methods for the Construction of Complex Molecules”^[23] and Desiraju’s concept of “supramolecular synthon” in crystal engineering^[14], we propose a “retro-functional analysis” (RFA) as a tentative and preliminary approach for molecular design in soft matter engineering using synthetic domains called “structural and functional synthons”^[24]. In this essay, we discuss the strategy, strengths and weaknesses of RFA, the idea of “structural and functional synthons”, and several exemplary analyses from our recent researches. We aim to develop a rational and modular approach toward molecular design in soft matter engineering that can provide intriguing and potentially useful targets for research.

RETRO-FUNCTIONAL ANALYSIS

“In order to be acceptable, the solution to a scientific problem must satisfy exacting criteria and demands.

These constraints, however, do not eliminate creativity. They provoke it.”

---- Ilya Prigogine^[25]

Basic Philosophy

The retro-functional analysis is intended as a function-oriented, modular approach for molecular design. It takes into consideration two important factors: (1) function of the motifs and (2) their structures. This approach is meaningful only when the functions of the motifs are relatively independent of each other and are additive toward a collective macroscopic property. For example, through proper arrangement of protein domains of different functions, new functions can be created^[22]. A similar strategy in synthetic materials is highly desired. Hence, the basic philosophy underlying this approach (also, the ultimately desired characteristics of) this approach can be described as follows: (1) it should be function-oriented; (2) it should be modular and efficient; (3) the building blocks are independent of each other and have well-defined molecular functions, precise chemical structures and preferred secondary interactions/packing schemes. Although the requirements may not

be all satisfied at first and at once, the merit of RFA lies in its ability to yield novel functional molecular scaffolds that are otherwise not obvious from a conventional point of view. Beginning with the end in mind, it provides dynamic targets for research.

Figure 1 is an outline of the RFA. Starting from the desired property, the molecular design identifies the corresponding molecular functions and potentially useful hierarchical structures. The molecular building blocks are thus categorized into two types: functional synthons and structural synthons (similar to domains in protein science)^[24]. The functional synthons shall possess certain specific molecular functions, such as redox activity, π -conductivity, hydrophilicity, catalytic activity *etc.*, while the structural synthons shall possess well-defined physical interactions responsible for selectively directing and controlling the formation of various structures. The definition and scope will be further elaborated in section of Synthetic Domains. Selected synthons from both groups can be joined to create a molecular scaffold and convert to a family of detailed chemical structures. The emergence of “click chemistry” and other highly efficient transformations^[26–28] is a natural ingredient of RFA since it facilitates the precise, modular and reliable construction of the designed molecules from the precursor domains/synthons. Hence, one can focus more on the function of the molecular design rather than the complex synthesis. Although the “black magic” of structure formation is the delicate balance among the free energy pathways and their transformation barriers, it is difficult to predict structure formation accurately. Nevertheless, the RFA approach provides intriguing targets for research. With the knowledge gained from the cycles of study, it guides further refinement of the molecular design. Both features shall eventually make it a viable approach.

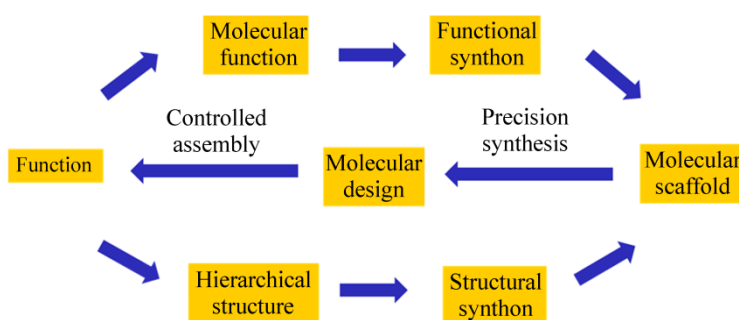


Fig. 1 Strategy for retro-functional analysis in the molecular design of functional soft matter materials^[24]

Physical Principles

Before discussions on the details of RFA and its components, it is necessary to briefly look into the fundamental physical principles that are core in materials science. They include physical interactions, ordered hierarchical structures, and the thermodynamics and kinetics of structural formation. The development of supramolecular chemistry and crystal engineering has tremendously advanced our understanding of physical interactions in terms of their origin, strength, and how they are related to chemical structures. Table 1 briefly summarizes the general aspects of major secondary interactions, which include van der Waals forces, hydrogen bonding, halogen bonding, π - π interaction, and many others.

The van der Waals interactions are profound in nature. It is not only used to explain the attraction or repulsion between molecules as described in textbooks, but also widely adopted by living creatures. For example, Gecko’s power to defy gravity has been attributed to van der Waals forces that act in concert^[29]. Being small individually, it creates a huge adhesion force when used and aligned collectively. Moreover, the weak nature still makes it easy to peel off under certain conditions. Hydrogen bonding, regarded as the master key of supramolecular science, is ubiquitous in Nature with varying strengths. Combination of multiple complementary donor-acceptor (D-A) hydrogen bonding pairs can generate dynamic linkages as strong as, if not weaker than, a single covalent bond. Not only has it been used to construct supramolecular polymers and other synthetic assemblies as demonstrated by Lehn^[30] and Meijer *et al.*^[31], it is also essential in maintaining the life form by keeping the DNA double helix and rendering proteins active through proper folding. By contrast, the recognition

of halogen bonding and its significance is relatively recent^[32]. Dipole-dipole interactions are useful in generating relatively strong physical bonds. For example, the antiparallel packing of cyanobiphenyl derivatives due to strong quadruple-quadruple interactions is responsible for the formation of liquid crystalline phases in its alkyl derivatives, which plays a key role in liquid crystal display technologies. Due to the high directionality of metal-ligand coordination and the easily tunable interactions depending on the type of metal and ligand, it has been a favorite subject in supramolecular chemistry to assemble into pre-organized supramolecules as demonstrated by Stang^[33], Fujita^[34], and Newkome *et al.*^[35], and in crystal engineering^[36] to construct metal-organic frameworks (MOFs)^[37] of various dimensionality. The ionic interactions are non-directional, relatively strong, yet difficult to handle, but they are very important and useful since they have comparable strength to covalent bonds. The ion-dipole interactions are also prevalent. The field of supramolecular chemistry was actually initiated by the discovery of crown ethers and cavitands that selectively bind to certain types of cations *via* this type of interaction^[38]. Finally, π - π interaction covers a broad spectrum of bonding energy, ranging from close to zero to around 50 kJ/mol, depending on how the two π - systems interact with each other (*e.g.*, face to edge or face to face), their sizes and electronic structures^[39]. For example, electron-rich benzene ring and electron-deficient hexafluorobenzene ring can form a complex with a much higher melting temperature (23.7 °C) than each component (5.5 °C for benzene and 3.7 °C for hexafluorobenzenes)^[40]. While discrete π - π stacked species are occasionally observed^[41], the large and anisotropic π - π interactions usually lead to a preferred face-to-face continuous stacking as seen in many discotic liquid crystals, giving rise to low-dimensional organic semiconductors^[42].

Table 1. Summary of various non-covalent interactions^[24, 38, 56]

Name	Energy	Directionality	Origin	Length scale	Note
van der Waals interaction	< 5 kJ/mol	No	Weak electrostatic attraction in nature; Induced by electron cloud polarization	Several Å	Ubiquitous; decays rapidly with distance
Hydrogen bonding (D-H...A)	~ 1–161.5 kJ/mol	Yes	Weakly electrostatic	0.5 nm	Master key in supramolecular chemistry
Halogen bonding (D-X...A) ^[32, 57]	~ 5–180 kJ/mol	Yes	The tendency of halogen atoms to interact with atoms possessing lone electron pair	~ 0.2–0.5 nm	Effective and reliable, similar to hydrogen bonding
Ion-Dipole interactions ^[58]	~ 40–600 kJ/mol	Yes	Electrostatic attraction between an ion and a neutral molecule that has a dipole	~ 0.1–10 nm	Medium range interactions ($\sim 1/r^2$), important in solvation processes
Ion-Ion interactions ^[56]	~ 100–350 kJ/mol	No	Electrostatic attraction/repulsion	~ 0.1–10 nm	Basis for the formation of ionic structures and colloids
Dipole-Dipole interactions ^[58]	~ 5–25 kJ/mol	Yes	Type I: from a single pair of poles on adjacent molecules; Type II: from dipoles with opposing alignment	~ 0.1–10 nm	Significant in solid state; relatively weak in solution
Cation- π interactions ^[59]	~ 5–80 kJ/mol	Yes	The face of an electron-rich π system with an adjacent cation	< 1 nm	Strong in transition metals; weak in alkaline and alkaline earth metal cations
π - π interactions ^[39]	~ 0–50 kJ/mol	Yes	Electrostatic intermolecular overlapping of p-orbitals in π -conjugated systems	~ 0.3–0.5 nm	Important in understanding organic electronic materials
Metal-Ligand coordinations ^[60]	Varies with metal, ligand, and coordination number	Yes	Lone electron pair occupying the empty orbitals	Several Å	Important in crystal engineering, MOF, and supramolecular chemistry
Hydrophobic effect	< 40 kJ/mol	No	Nonpolar molecules that tend to minimize unfavorable interaction with solvent	—	—

The following set of questions is: “*How do weak, non-covalent bonds influence the structure and behavior of materials at larger length scales? And what is the driving force to form these hierarchical structures?*” The key is the collective, cumulative, and cooperative response as a result of multiple secondary interactions. For example, the hydrophobic effects, the close packing of molecules with specific geometries and shapes, and the microphase separations, are all the major collective interactions that drive self-assemblies. They can be viewed as a result of collective van der Waals, hydrogen bonding and other interactions at the molecular scale. To be more specific, hydrophobic effects are generally related to the exclusion of water from the weakly solvated entities, which is originated in van der Waals force^[38]. Such collective interactions are usually treated without considering molecular details. As a result, the detailed molecular arrangements at smaller length scales are often independent from the structures at higher length scales, leading to the formation of hierarchical structures. For example, the protein domains have conserved sequences and folding structures, which are not directly related to the structures at the larger length scale^[22]. In those structures at the larger length scale, the domains interact through collective physical bonding on the surface of the domain, but not from within. In other words, in designing materials, it is sometimes possible to leave out details on the length scales that are smaller than that of interest. For example, phase separation of block copolymers in the melt leads to the formation of sphere, cylinder, bicontinuous structure and lamellae. It depends on the volume fractions of the block and is irrespective of the detailed chemical structure of the blocks as long as the two blocks are incompatible due to the strong interactions (the enthalpic contribution as described by the Flory-Huggins factor, χ) and the long chain nature (the entropic contribution influenced by the degree-of-polymerization, N)^[43].

The second set of questions is: “*How does size matter? Will molecules that are analogous in terms of shape and topology, but with distinct sizes, behave and function similarly? What are the consequences of changing molecular sizes?*” Self-assembly is believed to occur across all length scales^[2]. There is a striking resemblance (or parallelism, or similarity) in objects with similar geometry and shape at different length scales. The most significant difference may be associated with thermal fluctuation during structure formations. At larger length scales, the collective, cumulative and cooperative physical interactions take over chemical bonding as the major form of interactions. It is intriguing to seek for the differences in structure formations and functions between analogous molecules with same overall shapes and geometry but distinct sizes. The recent development of colloidal molecules^[44, 45] and giant molecules^[46–48] are excellent examples in this direction. These attempts raise an intriguing philosophical inquiry: “*How big can a well-defined molecule be?*”

The third set of questions is: “*What are the structures and how do they form and change?*” In order to form a specific macrophase structure, the physics of phase transitions should be understood. When a phase transition takes place from an unstable state to an equilibrium state, the process is the so-called spinodal decomposition, and the transition happens without an activation barrier. On the other hand, if a phase transition is from a metastable state toward an equilibrium state, this transition requires molecules to overcome a free energy barrier (nucleation), and it is a nucleation and growth process^[3]. Most of the kinetics of phase transitions belong to the nucleation and growth process dominated by the free energy barrier. More than often, it is necessary to steer the assembly pathway either toward various metastable states or to reach the final thermodynamic equilibrium state. In small molecules and macromolecules, their phase transition processes have seldom taken place at the equilibrium transition temperature but in the supercooled fluids (particularly in crystallization). Profound experimental observations have revealed that “...in the course of transformation of an unstable (or metastable) state into a stable one the system does not go directly to the most stable conformation (corresponding to the modification with the lowest free energy) but prefers to reach intermediate stages (corresponding to other metastable modifications) having the closest free energy to the initial state^[49].” This “stage rule” was first recognized over one hundred years ago by Ostwald^[50]. Consequently, the phase transitions proceed *via* a series of metastable states of increasing stability. In fact, many useful properties of soft matter are landed on metastable states and many functional systems often operate in states far from equilibrium^[3]. The functional hierarchical structure is maintained at these states due to very high transition barriers towards the equilibrium states. However, there are few developed ways to quantitatively understand, describe and predict such phase transition

systems since after all, the transition kinetics is determined by how high the free energy barrier is and how large the thermal fluctuation of the molecules or motifs possess. Particularly, when the size of molecules or motifs becomes increasingly large, the magnitude of thermal fluctuation must be increased accordingly to help them overcome the free energy barrier. Thus, more than often, “self”-assembly would require certain assistance, especially in complex environments or when spatial-/temporal-controls over the self-assembly are desired. The concept of “catalyzing” the assembly, or “catassembly”, with the aim to decrease the free energy barrier and speed up the kinetics of phase transitions, has thus become more and more popular and shall play an increasing important role in the formation of functional structures^[51, 52].

Synthetic Domains: Structural and Functional Synthons

In analogy to the concept of structural domains in protein science, we propose the idea of “synthetic domains” or “synthons” in soft matters^[24]. The modular feature is reminiscent of the “nanoscale atoms”^[53] or “nano-elements”^[54, 55] or “nano-atoms”^[48] described in literature. According to their roles in final materials, they can be categorized as structural synthons and functional synthons. Functional synthons are molecular entities that possess specific and intrinsic functions/properties, while structural synthons refer to molecular entities that possess well-defined physical interactions for supramolecular engineering into specific structures and phases at specific length scales. They are hierarchical in nature and do not discriminate on the basis of size (Fig. 2). The functional synthons with the smallest sizes are atoms, functional groups (such as carboxylic acids, amines, thiols) possessing specific reactivity and functionality. They can also be part of the molecule or a particular arrangement of a set of functional groups, such as the active sites in an enzyme, conjugated π -segments (capable of absorbing light, transporting electrons, *etc.*), peptide sequences (for recognition by cells, for binding and signaling, *etc.*), or fluorescent chromophores. Individual molecules may also serve as functional synthons, such as fullerene (*e.g.*, C₆₀), polyhedral oligomeric silsesquioxanes (POSS), signaling molecules, ligands, hormones and others. Ever larger functional synthons are supramolecular assemblies, such as protein complexes, metal clusters, inorganic nanoparticles (*e.g.* gold particles), quantum dots and micelles. Future materials are believed to have complex and sophisticated structures involving supramolecular entities as part of the building blocks.

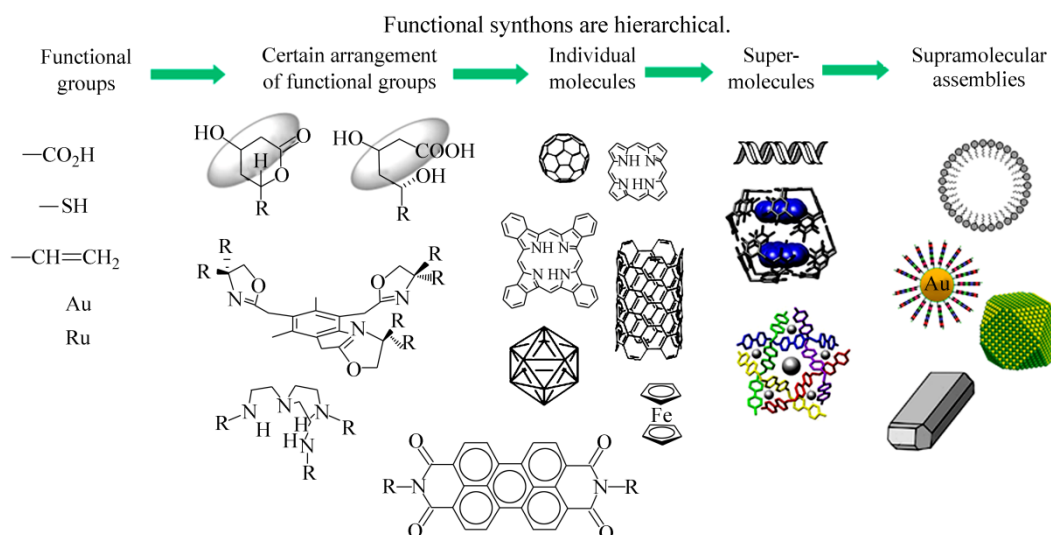


Fig. 2 Examples of functional synthons at different length scales

With noncovalent interactions well understood, the next step would be to identify and engineer the units that may lead to or aid in the formation of specific structures and phases at specific length scales. These units are thus referred to as “structural synthons” and are further divided based on their structures and features sizes. At

the sub-molecular level, the structural synthon are like the “supramolecular synthons” proposed by Desiraju^[14] in that they have a kinetically fixed structure-forming pattern and typically are a fraction of a nanometer in size. At the molecular level, the building blocks responsible for crystals, liquid crystals, liquid formations are usually hard to identify since the structure is the result of a network of supramolecular synthons. For example, calamitic and discotic mesogens are typical classes of structural synthons that are responsible for liquid crystal and columnar phase formations^[61–63]. At the macromolecular level, collective responses from those supramolecular interactions dominate and drive self-assembly. Nano-sized molecules, such as polymers, dendrimers, nanoparticles, are typical synthons at this level and nanophase separations often occur^[55]. According to corresponding nanostructure, they may be referred to as lamellae synthon, cylinder synthon, sphere synthon, *etc.* Shape also becomes a critical factor for determining the outcome of self-assembly if the molecules are rigid in conformation^[64]. Recently, a road map of possible structures from different shapes has been outlined by Glotzer *et al.*^[5] via computer simulation. At multi-molecular level, highly specific, strong interactions should be responsible for any controlled structure formation. This is best demonstrated by DNA-templated ordered superlattice formation of nanoparticles as reported by Mirkin^[65, 66], Gang^[67, 68], and others. Their phase structures exhibit a strikingly similarity to those of the crystals formed by ions, which again demonstrates that there is a similarity in physics between different length scales, as long as the interaction energies are engineered to match that length scale and are strong enough to direct the assembly. Figure 3 summarizes typical structural synthons at different length scales.

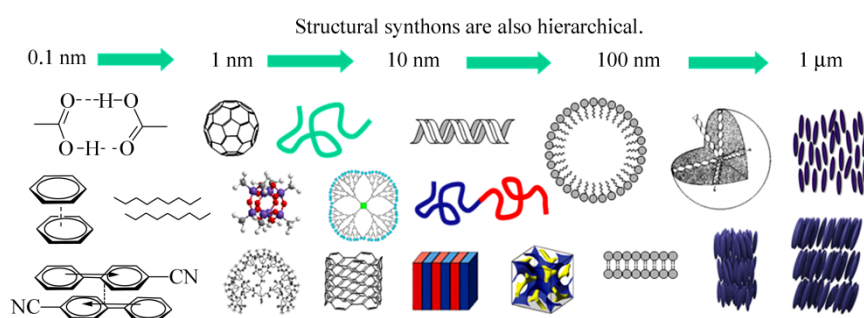


Fig. 3 Examples of structural synthons across different length scales

The idea is inspired by Nature. For example, in perhaps the simplest way to understand, the organization of a living creature starts from the single molecules, such as lipids and proteins, which self-assemble into bilayered membranes and folded functional structures, respectively. These constitute the cells that are responsible for various tasks (*e.g.* red blood cell, osteoblast, T-cell, *etc.*). The cells form tissues to perform a complex function at a larger scale as a whole. Then, organs are a collection of tissues joined to serve a common, but complex function, such as the circulatory system and the endocrine adjusting system. The cooperative workings of organs finally leads to a living creature with intelligence. The categorization of building blocks shall be helpful for understanding and constructing such systems. While the molecular entities are the sources of function, the structures by which they organize are also of fundamental importance. The structural synthons may also be understood as principles to guide structural formation. Although complications may arise when molecular entities are multifunctional and with close interactions, we believe that it provides a clear scheme to consider the molecular entities in the context of its function and the desired structure.

Strengths and Weaknesses

There are many intrinsic weaknesses in the RFA approach. First, to start analysis by RFA, a rough prior knowledge about the relationship between structure and function should be in place to guide the initial design. However, this is usually not the case in brand new materials. One might have no idea about the molecular basis of the function, not to mention the hierarchical structures that are beneficial for such functions. Second, structure

and function are never fully decoupled in materials. The roles of molecular segments in the final materials are usually two-fold. Moreover, any subtle change in chemical structure may lead to drastic change in the assembled structures and perhaps, completely different functions. In other words, the RFA seems to oversimplify the situation. Then, under which circumstances, can it be useful?

The hierarchy of structures suggests that the structures at larger length scales can often form irrespective of the molecular details at smaller length scales. This is especially true when the interactions at larger length scales are much stronger. Typical examples are the DNA-mediated super-lattice formation from nanoparticles^[65, 67] and the nanophase separation of diblock copolymers at the strong segregation region^[43]. Thus, in order to be valid, the structural synthons should preferably be at a larger length scale than the functional synthons. In other words, functional synthons should preferably have function-bearing structures that are independent of other synthons and shall interact with the rest of the molecules *via* collective interactions on the surface. Combining functional and structural synthons in specific ways gives a family of structures that shall shed light into the structure-property relationship of this class of materials. By thinking hierarchically with the importance of structure in mind, the RFA can often yield novel molecular designs that are otherwise not apparent from conventional approach. We also believe that the effort will rationalize and facilitate the modular design of materials by providing libraries of synthons, similar to the Cambridge Crystallographic Data Centre^[69] and Protein Data Bank^[70], in computer-aided design. This approach echoes the proposal of the Materials Genome Initiative^[71] by offering a user-friendly thinking pathway and a comprehensive tool box, especially useful for new-comers in the field, and shall provoke creativity in interdisciplinary study in advanced materials.

More specifically, the RFA is a coarse-grained molecular design principle that is particularly suitable for engineering mesoscale structure/supramolecular lattice formation at 2–100 nm feature sizes in soft matters. This is the length scale where the feature sizes of most soft matters are in^[4]. This is also the length scale that is critical in the correct transfer and amplification of molecular information into a desired macroscopic physical property. For molecular design, more than often, the molecular details at smaller scales may be neglected since these synthons can act as relatively independent synthetic domains, similar to that of protein domains. This is reflected in the dependence of their structures on the chemical structures. For example, while a triazole linkage in small molecules would completely alter the crystal packing scheme, its presence in block copolymers linking two strongly segregated incompatible blocks of symmetric composition may not change the lamellae structure formation. While crystal engineering is mostly concerned with optimizing sub-nanometer interactions toward a precisely defined 3D network structure, the RFA for soft matter engineering takes advantage of the different interactions at distinct length scales to control the superlattice and hierarchical structure formation. In recent years, our group has utilized RFA to reveal many intriguing soft materials as described in the following section.

EXEMPLARY MOLECULAR DESIGNS

“Unanticipated novelty, the new discovery, can emerge only to the extent that his anticipations about nature and his instruments prove wrong. . . . There is no other effective way in which discoveries might be generated.”

---- Thomas S. Kuhn^[72]

When designing functional materials, the RFA emphasizes two important factors: the molecular function, and the hierarchical structures. While the first one concerns the properties of molecular segments such as electronic structure, redox activities, electron (or hole) conductivity, magnetic spin and fluorescent properties, *etc.*, the second one is associated with the atomic organization and secondary interactions. With a holistic view from both chemistry and physics, novel molecular structures can be designed in the pursuit of a specific function, as demonstrated in the following examples.

Alternating Conductive and Insulating Nano-layers

Alternating conductive and insulating layers are useful in fabricating conventional capacitors for energy storage. Since capacitance is inversely proportional to layer spacing, it is of great interest to create “nanocapacitors” with layer spacing as small as only a few nanometers. Using the RFA approach, the functional synthons are identified

as electron-conducting units and electron-insulating units, while the structural synthon is lamellar synthon at the nanometer scale. Most organic compounds are insulators. Electron-conducting synthons are less common and typically include π -conjugated materials, such as hexabenzocoronene, C_{60} , C_{70} , and conjugated polymers. The lamellar synthon can be selected from different classes of soft matters since many of them do self-assemble into layered structures. For example, semi-crystalline polymers are known to grow 2D lamellar crystal from dilute solutions with non-crystalline units excluded and tethered onto the lamellar basal surface^[73, 74]. Block copolymers can form lamellar structures at the strongly segregated region when the volume fractions of both blocks are symmetric^[43]. Molecules with rigid conformation and well-defined shape can form lamellar structure if they are linked to an incompatible counterpart with similar size and conformational rigidity. In polymer processing, multi-layer extrusion technique has been developed recently as an industrial solution for fabricating alternating conducting/insulating layers^[75]. These structural synthons can be combined with functional synthons with careful balance of their interactions to afford a molecular scaffold. Here, the functional synthon, C_{60} , is chosen because of its excellent electronic properties.

Fullerene is a class of carbon allotrope with fascinating nanostructures and has received wide-ranging applications^[76, 77]. To improve fullerene's compatibility, chemical modifications are often utilized to create many derivatives that greatly expand the scope of fullerene materials^[78]. However, the chemical modification should be minimal in order to preserve the electronic properties. As a result, C_{60} in the final material still maintains its rigid shape and strong hydrophobicity, which affects the structure formation. The following aspects need to be considered for C_{60} : (1) it is largely spherical and conformationally rigid with a well-defined, incompressible scaffold; (2) it is impenetrable to most atoms and functional groups; (3) it tends to aggregate due to strong π - π interaction. In order to make C_{60} an integrated part in newly designed materials, one can either take advantage of the strong aggregation of C_{60} to interplay with other interactions to guide the formation of ordered structures, or use strong interactions of other structural synthons to override that of C_{60} and template the arrangement of C_{60} . Alternatively, one can also use a conformationally rigid, incompressible, impenetrable counterpart of C_{60} to assist their ordered packing.

Crystallization has been known to possess the strongest physical interactions in self-assemblies. It is firstly utilized to template the ordered arrangement of C_{60} . The molecular scaffold is thus the combination of C_{60} (functional synthon) attached to a semicrystalline poly(ethylene oxide) (PEO, the structural synthon), as shown in scaffold **a** in Fig. 4. There are of course other ways to link them, for example, tethering C_{60} at the middle of the chain, or at both ends of the polymer chain, or to a cyclic polymer at any positions. But the physical picture will basically be the same. We will thus start from the simplest scaffold **a**. To ensure facile synthesis and high functionality, the design of molecular structure takes "click" chemistry into consideration. The detailed molecular structure of **1** is shown in Fig. 4 and synthesized by a combination of living anionic polymerization and "click" chemistry^[79, 80]. Dilute solution crystallization yields PEO lamellar single crystal with its top and bottom both covered by C_{60} to form sheets of C_{60} with varying degree of surface coverage depending on the molecular weight of PEO^[24]. It is also found that the self-assembly of PEO- C_{60} in the bulk generates lamellae structures with half-fold stems^[81].

The strongly segregated block copolymers, such as polystyrene-block-poly(ethylene oxide) (PS-*b*-PEO) can also serve as the lamellae structural synthon to guide the self-assembly of C_{60} . The molecular scaffold **b** is designed with C_{60} at the junction point of PS-*b*-PEO so that the C_{60} will be confined to the interface and takes the shape of the interface as defined by the phase structure of the block copolymer^[80]. The interaction between C_{60} s at the interface may lead to hierarchical structures. Again, the molecular structure **2** was designed and synthesized with the help of "click" chemistry to ensure a precise structure. Preliminary results have shown that C_{60} is indeed confined to interface and leads to an unusual change in *d*-spacing^[24]. It should also be noted that in the above approaches, the coverage of C_{60} at the lamellae is dependent on the composition of the polymer. To ensure a quantitative coverage of C_{60} , another strategy can be used.

Polyhedral oligomeric silsesquioxanes (POSS) are considered as perhaps the smallest shape-persistent silicon nanoparticles. With cage diameters of ~ 1.0 nm, they are an inorganic counterpart of C_{60} in terms of their sizes and shapes^[82–86]. By covalently linking them together, a cube-sphere shape amphiphile, POSS- C_{60} , is

created as shown in molecular scaffold **c** and molecular structure **3**^[87–89]. The linkage in this case is chosen to be a very simple ester bond and the synthesis is simple and straightforward. Upon crystallization, **3** exhibits polymorphism by the formation of two types of crystals having either hexagonal or orthorhombic lattices^[87]. The double-layered structure is seen in both crystal forms. Since POSS is generally considered as insulating and C₆₀, conducting or even superconducting upon doping, such an alternating structure of POSS and C₆₀ could be viewed as an as-assembled “nano-capacitor”. Therefore, it is evident that RFA is a rational and modular approach that provides different molecular scaffolds, each of which forms structures with varying degree of order as directed or assisted by the chosen structural synthon. In literature, many other structural synthons have also been used to direct the lamellae formation of C₆₀ layers^[90, 91].

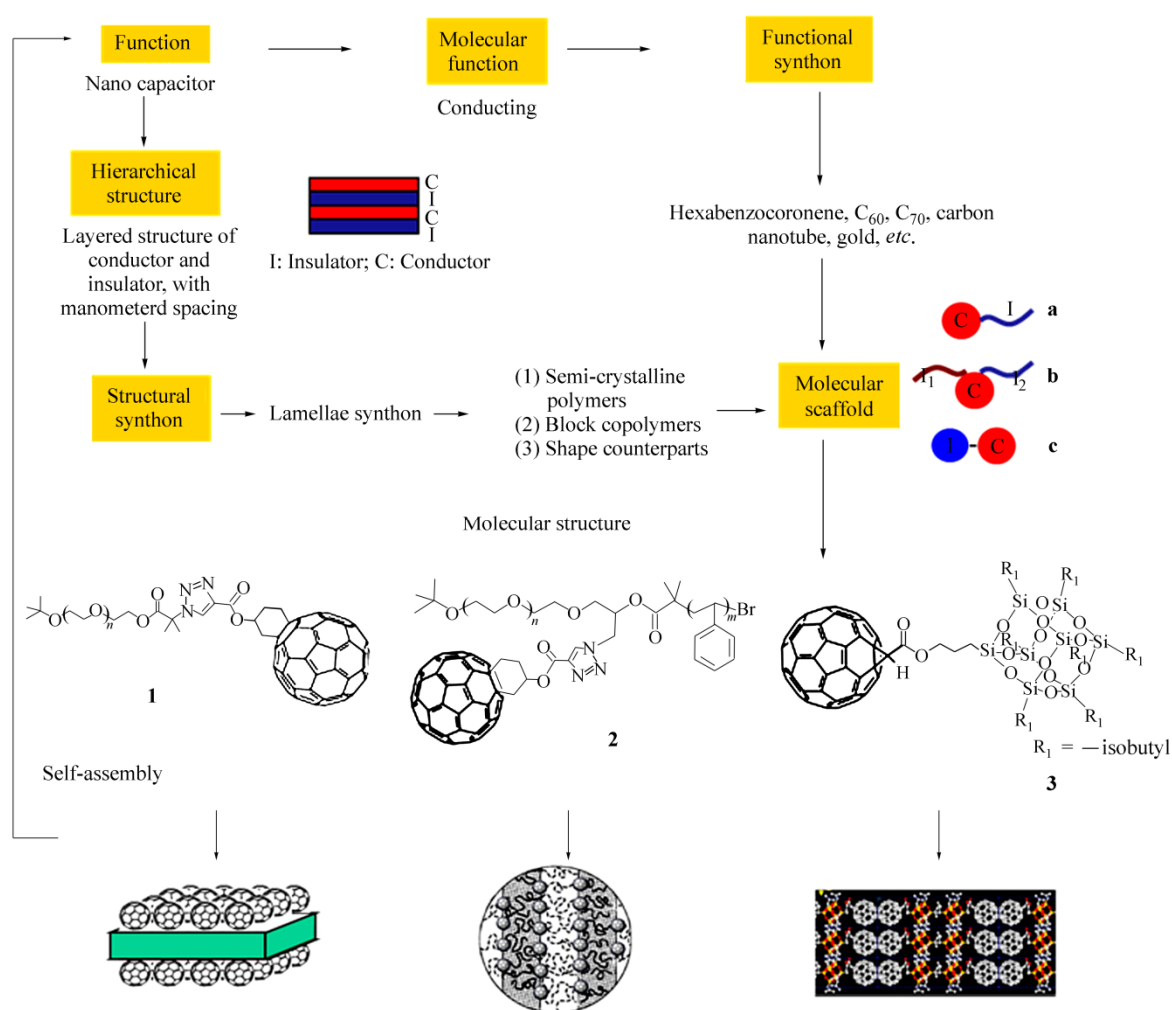


Fig. 4 Retro-functional analysis for nanocapacitor materials (Adapted with permission from Ref. [24] and Ref. [87]; Copyright 2011 The Royal Society of Chemistry)

Bulk Heterojunction Organic Photovoltaic Materials

In order to produce efficient organic photovoltaic materials, a bicontinuous nano-phase-separated structure of donors and acceptors is highly desired^[92]. The functional synthons in this case are donor synthons and acceptor synthons, each corresponding to a large class of chemical structures. Typical donors in bulk heterojunction organic photovoltaic materials are *p*-type π -conjugated oligomers/polymers such as porphyrin, polythiophene derivatives, and other low-band-gap materials while typical acceptors are *n*-type π -conjugated materials such as

C_{60} and perylene diimides. The concept of double-cable polymers has been popular since the middle of 1990s^[77]. They are typically composed of a *p*-type conjugated polymer donor backbone and *n*-type acceptor moieties, such as [60]fullerene (C_{60}), as the side chain. Ambipolar transporting properties were expected in this type of materials since they are anticipated to self-assemble into phase-separated D/A nano-structures. However, due to the lack of control over primary chemical structure and secondary physical structure in the traditional “grafting-to” synthesis, the double cable polymers are rarely well-defined and their device performances have been disappointing^[93].

Recently, supramolecular double cable approach has been realized and shown promises in the generation of such structures with improved photovoltaic performances. When structural synthon is properly chosen, one shall be able to construct such double cable structures. For example, the block copolymer synthon may also be used with proper choice of volume fraction to form bicontinuous structure of donors and acceptors. The result is a molecular scaffold **d** or **f** in Fig. 5, a scenario similar to the formation of C_{60} layers by block copolymer synthon in the previous section. Also, columnar liquid crystals with *p*-type channel in the center can be derived into

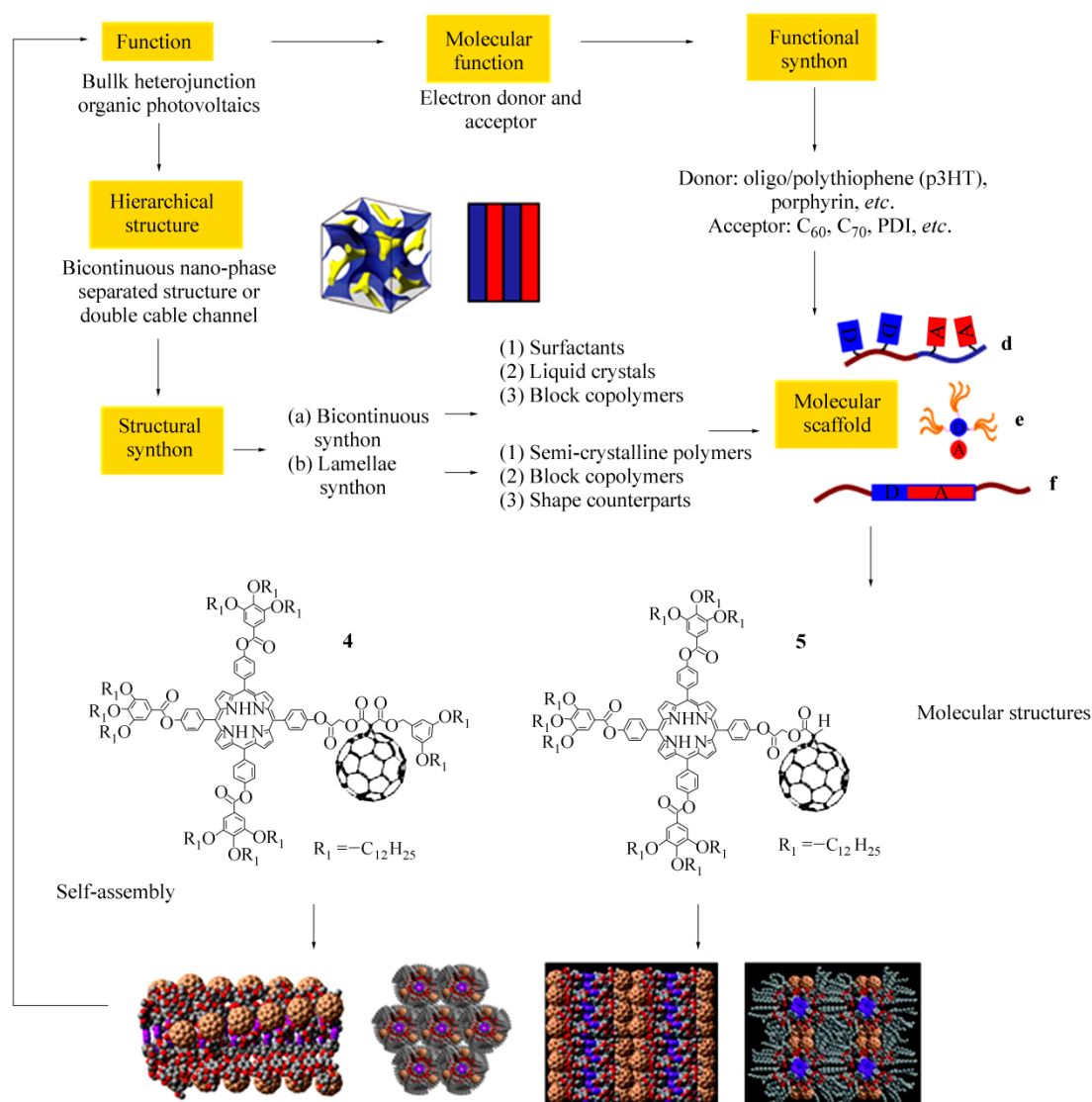


Fig. 5 Retro-functional analysis for bulk heterojunction organic photovoltaic materials (Adapted with permission from Ref. [24], [61] and [63]; Copyright 2012 Wiley-VCH)

a double cable structure by adding the *n*-type channels around it. The *p*-type functional synthon is chosen to be porphyrin and the *n*-type functional synthon is chosen to be C₆₀. To make a columnar liquid crystal structure, alkyl chains of varying length is attached to the periphery of porphyrin. The simplest molecular scaffold **e** is thus constructed by linking donor porphyrin with acceptor C₆₀ in the hope of that they will form columnar liquid crystal. It again can be reduced to a class of molecular structures with varying side chain lengths, linkages and modifications on C₆₀. The molecular structures **4** and **5** are presented, differing by the presence of two long alkyl chains modification on C₆₀ in **4**, but not **5**. The results show that the π - π stacking of porphyrin overrides the aggregation of C₆₀s, leading to the formation of columnar liquid crystals in both cases^[61–63, 94]. In the former, it forms a hexagonal columnar phase with an unusual 129₄₄ helical structure for each column^[61]. The C₆₀s were found to interact intra-columnly to form three pendant, continuous channels along the column. This is a typical well-defined supramolecular double cable structure containing parallel arrays of hole and electron transport channels. However, the removal of the alkyl groups on C₆₀ leads to preferentially intercolumnar C₆₀-C₆₀ interactions and thus, compound **5** forms a rectangular columnar liquid crystal phase in an orthorhombic unit cell^[63]. In this case, the C₆₀s form separate continuous domains parallel to the column of porphyrin, exhibiting another type of supramolecular double cable structure. Although their performance may be further optimized by engineering their electronic structure and matching the energy levels, preliminary device tests have shown higher photovoltaic conversion efficiency than their PCBM counterpart. Therefore, it is evident that the same molecular scaffold with identical structural synthon and functional synthon gives a class of molecular structures depending on the choice of linkages and detailed chemical structures. Although precise prediction of physical structure is unlikely, the key structural features at larger length scales are apparently dominated by structural synthon. It should also be noted that not every molecular design from the same molecular scaffold would yield the desired supramolecular structure. It may still require cycles of iteration to understand structure-property relationship and optimize materials property (Fig. 1).

Information Storage Materials

The previous two examples are straightforward and provide molecular design that may not seem so different from conventional design. With desired supramolecular structure in mind, RFA may sometimes give rise to molecular structures that are not as common and may not be readily accessible through current synthetic methods. However, they do provide intriguing targets for research and inspire future innovations in related subjects. An example is given below.

In the information age, the materials for information storage are very important, particularly those of high capacity and high reading/writing speeds^[95, 96]. Molecules with strong dipole moments may be used as information storage materials if the dipole moments can be manipulated to change the states on demand^[97]. At the molecular level, dipole moment arises from the displacements of the centers of positive and negative charges. If the displacements are large and permanent, a giant dipole could be created. From such an analysis, the functional synthons are apparently positively or negatively charged groups. To maintain the dipole moment across length scales, they should be aligned in a way that does not cancel each other. A directional lamellar synthon may be used, such as the block copolymer synthon with symmetric volume fractions. However, their flexible conformations would be easily disturbed by the strong ionic interactions among giant dipoles and it would be difficult to align and maintain the desired ordered arrangement of giant dipoles. This issue may be addressed by keeping the charges spatially separated in a rigid scaffold. In this case, lamellae structural synthons with rigid conformations shall serve the purpose. This is possible by combining incompressible, shaped counterparts, such as molecular nanoparticles (*e.g.* C₆₀ and POSS), in structural synthons. There are two ways to arrange the functional synthons (the positive charged and negative charged groups) on structural synthons (C₆₀ and/or POSS): they can be located (1) on each individual MNP, as shown in the molecular scaffold **g**, or (2) on the same MNP, as shown in the molecular scaffold **h** (Fig. 6). The former is a “dumbbell” molecule with segregated opposite charges generating a large dipole moment. This is actually an interesting molecular Janus particle that possesses symmetry breakings not only in the sense of geometry but also chemistry. Self-assembly

of this type of Janus molecules is expected to yield layered structures with dipole moments aligned towards the same direction parallel to the layer normal. However, the synthesis of such molecules is not easy. During the cause of its development, a class of similar molecular Janus particles based on the conjugation of one hydrophilic and one hydrophobic POSS have been synthesized by sequential click chemistry^[98, 99]. Among them, BPOSS-APOSS was found to self-assemble into a bilayered structure (Fig. 7)^[98]. Other molecular Janus particles, such as snowman- and Mickey-mouse-typed, were also designed and synthesized in a similar way^[88]. The molecular scaffold **h** is even more unique in that the MNP is now a patched particle with half surface bonded with positive charges and the other half with negative charges. Considering that regioselective modification of C₆₀ is relatively well-established^[78], it is reduced to a molecular structure **7**. Although the synthesis of this novel structure may not be straightforward, it does offer a novel molecular design in challenging the synthetic chemists. It should be noted that although these novel materials are designed for a particular application, they are by no means limited to it; instead, they are bound to find more applications due to their unique structures.

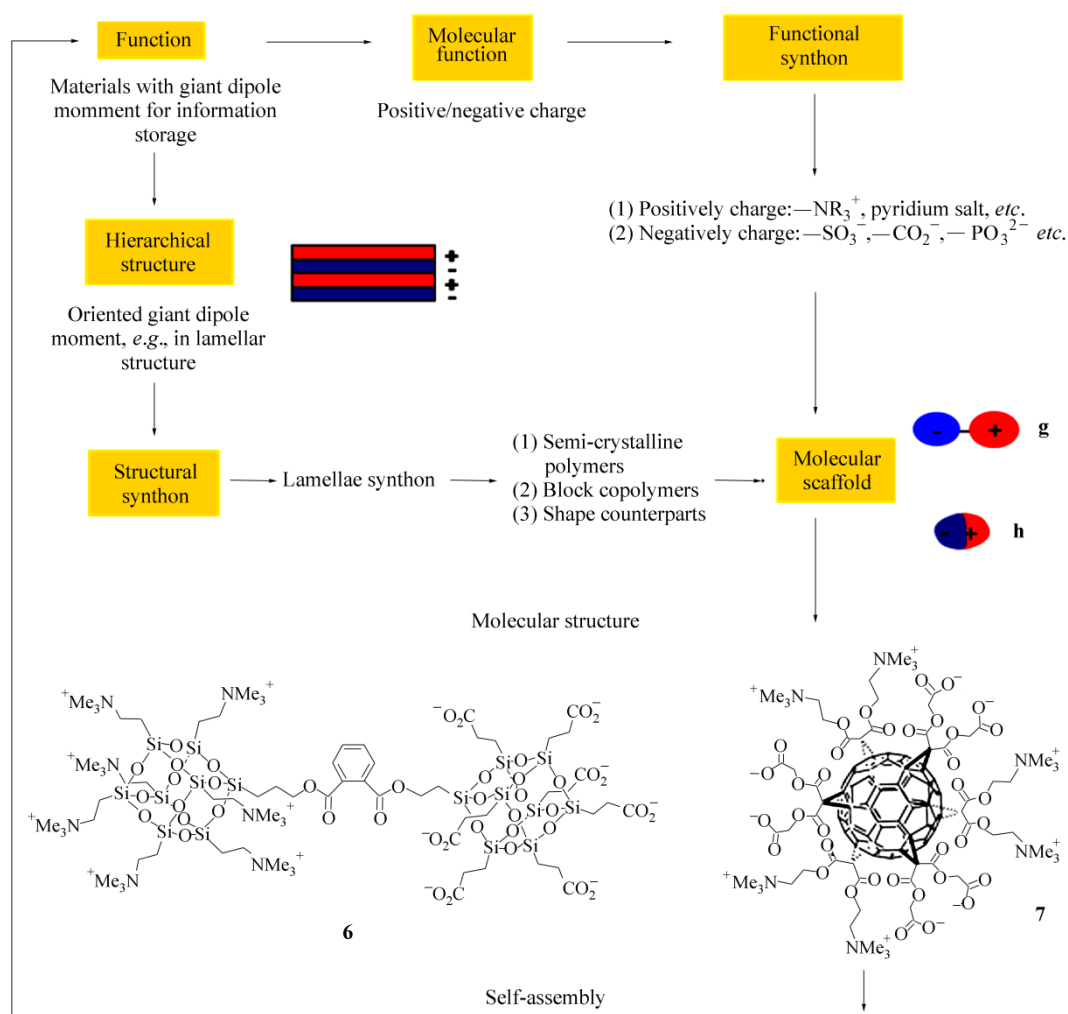


Fig. 6 Retro-functional analysis for information storage materials^[24]

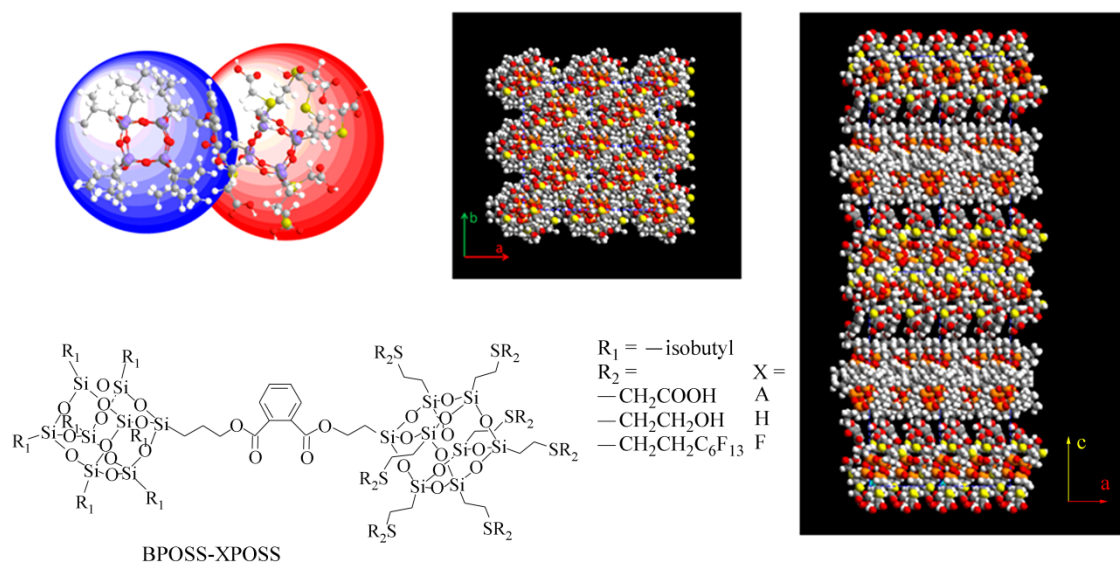


Fig. 7 Molecular Janus particles and the self-assembled hierarchical structure^[98] (Adapted with permission from Ref. [98]; Copyright 2011 American Chemical Society)

SUMMARY AND PERSPECTIVES

“It does not matter how slowly you go so long as you do not stop.”

---- Confucius^[100]

Through the above examples, the features of the RFA are clear. In summary, it provides a rational and modular approach for the molecular design of novel functional materials from the combination of two sets of building blocks: functional synthons and structural synthons. The synthons include libraries of molecular and supramolecular entities that either possess certain functions (functional synthons) or lead to/aid in the formation of specific structures and phases (structural synthons). Note that these structural synthons shall guide the formation of “useful” structures that can transfer and amplify molecular functions across different length scales to become desired macroscopic properties. The emergence of “click” chemistry provides simple access to these compounds through precision synthesis. Sometimes novel architectures and designs can be created that are otherwise not so obvious from conventional design and may not be readily available by current synthetic techniques. Hence, it presents intriguing challenges to material scientists. Overall, it emphasizes the importance of structure control in materials science and allows one to focus more on function but less on synthesis. This is demonstrated by examples in the molecular design for nanocapacitor materials, bulk heterojunction organic photovoltaic materials, and information storage materials. Among them, soft matters play a critical role. Supramolecular soft matter engineering will be the next step to go, just as what crystal engineering has achieved in creating novel crystalline solid materials. This is an exciting research area with a lot of new opportunities. Although current RFA as described in this article is still very crude and may oversimplify the situation, it is our hope that this can serve as a starting point to the development of a tentative molecular design principle toward new functional materials of novel architecture and exotic compositions. In writing this article, we are constantly thrilled by the talents of the pioneers in the field whose insightful and deep comprehension of chemical and physical sciences and methodology has inspired us continuously and tremendously. This article is thus a tribute to them in the hope of invoking further valuable contributions from other ingenious scientists in all related fields. The road to an effective, rational, and modular materials design is bound to be long and bumpy, but, as long as we do not stop, progress can be made, slowly but steadily.

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