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Helical Self-Organizations and Emerging Functions in Architectures, Biological and Synthetic Macromolecules[#]

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Abstract

Helical architectures including artwork and monuments, such us the Trajan's column from Rome, were constructed as early as in the year 113 while the assemblies and the self-organizations of biological and synthetic macromolecules, only started to be discovered, elucidated and respectively designed during the early 1950s. This personalized account will first provide a historical journey starting from the Trajan's column, that represents a classic mesoscopic helical architecture, to nanoscale biological macromolecules such as proteins, nucleic acids, carbohydrates and to supramolecular helical co-assemblies of proteins with nucleic acids, such as tobacco mosaic virus (TMV). It will continue with examples of synthetic helical covalent and supramolecular macromolecules. Their emerging functions ranging from mesoscopic scale to nanoscale and the current limitations of synthetic helical self-organizations will be discussed with selected examples mostly from the laboratory of the corresponding author.

Keywords: Helical | Architecture | Biology

1. Introduction

Self-organization by the shortest definition "*order for free*" or "*spontaneous order*" is encountered in all aspects of life and daily activities starting from biology and continuing with society, politics and economics. Numerous reviews,[1–8] including from our laboratory[9–17] provide ample discussions of definitions with examples of molecular self-organizations and of self-organized complex systems. In our opinion the most powerful and rapid way to introduce the reader to the concept of self-organization, self-organizations and complex systems is with the help of two highly dissimilar daily images borrowed from two leading publications in the field (Figure 1).[8,18]

Figure 1a illustrates a self-organized pattern of wind-blown ripples on the surface of a sand dune.[18] Figure 2a provides a photograph demonstrating the constantly evolving highways system.[8] In Figure 1a complexity is created entirely by self-

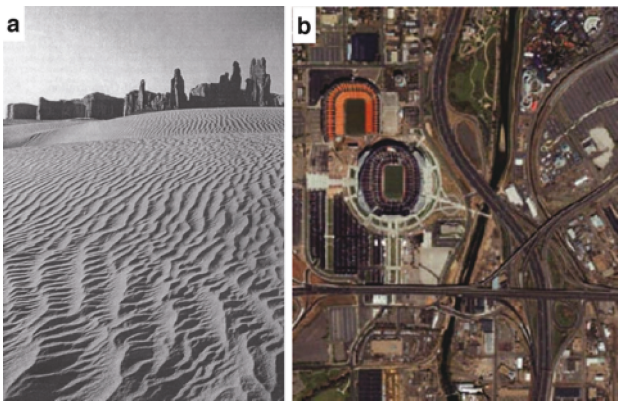

Figure 1. (a) Self-organized pattern of wind-blown ripples on the surface of a sand dune;[18] (b) More than the sum of its parts: complex systems such as highways, are constantly evolving.[8] Credit: SPACE IMAGING.

Figure 2. (a, b) Trajan's Column from Rome, Italy.

organization. In Figure 1b complexity is the result of an attempt to engineer a simple and efficient transportation system. In both Figure 1a and Figure 1b adaptation and self-control are responsible for the emergence of the complex system. However, while in Figure 1a a self-repair process is possible, the self-repair is accessible in a more difficult way in Figure 1b. In Figure 1a adaptation is time independent while in Figure 1b, once the first highway was constructed, adaptation is a requirement during the engineering of the second and subsequent highway(s) as well as of other constructions. According to our knowledge, this personalized perspective represents the first attempt to discuss and bridge between unrelated helical self-organizations and their functions. Helical mesoscopic architectures including artwork and monuments, helical biological macromolecules such as proteins, nucleic acids and carbohydrates as well as helical biological assemblies, containing or not, helical macromolecules such as tobacco mosaic virus and the evolution of their design as well as structural elucidation will be provided first. Knowledge derived from these examples together with historical development will be employed to discuss synthetic helical macromolecules and assemblies and their self-organizations. The mechanisms and the requirements *via* which functions of helical self-organizations emerge will also be discussed.

The length of this paper would have been well beyond that of an account if numerous other topics of helicity including functions in solution such as supramolecular chiral recognition,[19] asymmetric synthesis,[20] chiral separation,[21–23] sensing,[24,25] theoretical work on why helicity,[26–29] helicenes,[30] folding and foldamers[31,32] would have been discussed. Therefore, we apologize to these and other authors who have contributed seminal work on helical self-organizations for not being included in this personalized account.

2. Definition of Self-Organization

What is self-organization? According to Yates "*Technological systems become organized by commands from outside, as when human intentions lead to the building of structures and machines. But many natural systems become structured by their own internal processes: these are the self-organizing systems, and the emergence of order within them is a complex phenomenon that intrigues scientists from all disciplines*."[18] By taking into account this definition we can immediately discriminate between the contents of Figures 1a and 1b.

3. Helical Self-Organizations. From Mesoscopic Scale Architectures to Nanoscale Biological Macromolecules

3.1 Trajan's Column from Rome. An Early Example of Mesoscopic Scale Helical Organization. In back-to-back wars fought between A.D. 101–102 and 105–106 the emperor Trajan of the Roman empire conquered the Dacia empire that was located on the current territory of Romania. These wars were the defining event of Trajan's 19-year rule, A.D. 98 to 117, and brought to the Roman empire at least a half million pounds of gold and a million pounds of silver in addition to the fertile new province that became the Roman Dacia, later to become Romania. To commemorate this victory, Trajan commissioned a forum containing a spacious plaza surrounded by colonnades, two libraries containing Trajan's scroll-written dispatches from his Roman-Dacia wars, a grand civic space known as Basilica Ulpia and a temple. Towering over was a 126 feet-high and 12.1 feet diameter spiral column crowned with a bronze statue of Trajan that was completed in 113 (Figure 2a). The 2,662 carved figures including 55 of Trajan and 155 scenes all in 20 Carrara marble drums each weighing about 32 tons surround the column and tell the history of these wars (Figure 2b). An internal spiral staircase of 185 steps provides access to the viewing platform from the top of the column (Figure 2a). Trajan's column represents an amazing artwork, that is as rich in information as helical proteins or the double helix of DNA, both to be discussed later. The helical arrangement of the artwork on this column was most probably selected to express the continuity of these wars and provides a mesoscopic scale architectural example of the structure and function of helical proteins.

3.2 The Pauling-Corey Hydrogen-Bonded α-Helix Configuration of Proteins and Synthetic Polypeptides. In the introductory parts of a half-page communication submitted and published in JACS in 1950[33] and a seminal PNAS paper submitted and published in 1951,[34] Pauling, and Corey and Pauling, Corey, and Brandson, respectively, in slightly modified sentences combined from both publications, stated. "*During the past fifteen years we have been attacking the problem of the structure of proteins in several ways. One of these ways is the complete and accurate determination of the crystal structure of amino acids, peptides, and other simple substances related to proteins, in order that information about interatomic distances, bond angles, and other configurational parameters might be*

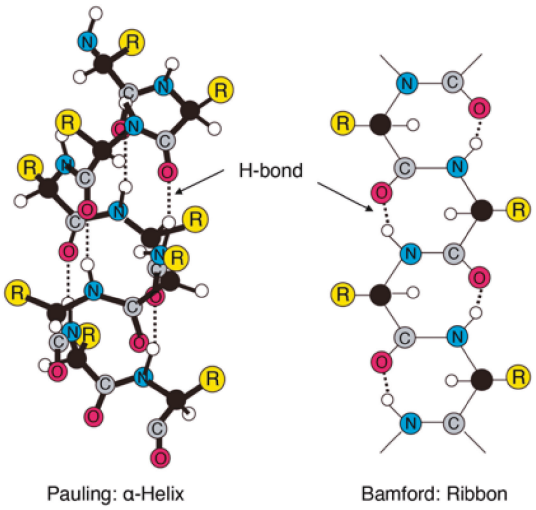

Figure 3. Two models of polypeptide chains: the α-helical structure proposed by Pauling and Corey[34] and ribbon-like planar structure proposed by Bamford.[55]

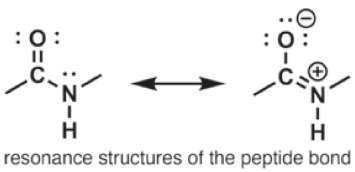

Figure 4. The resonance structures of the peptide bond.

obtained that would permit the reliable predictions of reasonable configurations for the peptide chain. We have attempted to find all configurations for which the residues have the interatomic distances and bond angles found in the simpler model substances and are equivalent, and for which also ***each CO group and NH group is involved in the formation of a hydrogen-bond****. We have now used this information to construct two reasonable hydrogen-bonded helical configurations of the polypeptide chain. One of these spirals is a three-residues spiral, in which there are* ***about 3.7 residues per turn and each residue is hydrogen-bonded to the third residue from it in each direction along the chain****. The third unit translation per residue is 1.47 Å.* The second helical structure with 5.1 residues per turn will not be discussed here (Figure 3). *We think that it is likely that these configurations constitute an important part of the structure of both α-keratin, contracted myosin and other fibrous proteins and also in hemoglobin and other globular proteins, as well as of synthetic polypeptides.*"

Interatomic distances and bond angles and other configurational parameters were determined mostly by Jerry Donohue, a former PhD student of Pauling who spend 5 year after graduation at Caltech,[35–40] and Robert B. Corey.[41–43] The double bond planar character of the peptide bond derived from one of its two resonance structures (Figure 4),[44] together with very precise molecular models constructed in Pauling lab at the scale of 2.5 cm = 1 Å (Figure 5),[45] were most influential in reaching the conclusion of the α-helix based on the 3.7 non-integer number of residues.

"*The stability of our helical structures in a non-crystalline phase depends solely on interaction between adjacent residues*

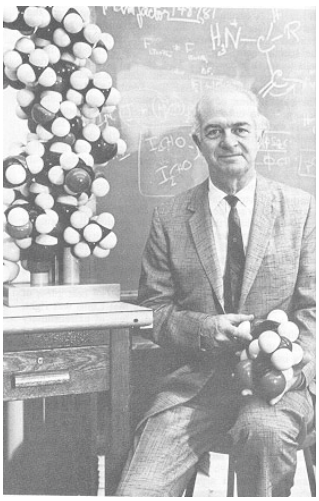

Figure 5. Linus Pauling with his atomic models. Copyright: Caltech Archive.

and does not require that the number of residues per turn be a ratio of small integers.[34] *These helical structures have not previously been described*." In a very important paragraph Pauling, Corey, and Brandson[34] give credit to the authors that suggested protein and polypeptides structures that did not fit the X-ray results. "*In addition to the extended polypeptide chain configuration, which for nearly thirty years has been assumed to be present in stretched hair and other proteins with the β-keratin structure, configurations for the polypeptide chain have been proposed by Astbury and Bell,*[46] *and specially by Huggins*[47,48] *and by Bragg, Kendrew, and* Perutz.[49] *Huggins discussed a number of structures involving intramolecular hydrogen bonds, and Bragg, Kendrew, and Perutz extended the discussion to include additional structures, and investigated the compatibility of the structures with X-ray diffraction data for hemoglobin and myoglobin. None of these authors proposed either our 3.7-residue helix or our 5.1-residue helix.* ***On the other hand, we would eliminate, by our basic postulates, all of the structures proposed by them****.*" Pauling, Corey and Brandson[34] explain that both Bragg and his collaborators and Huggins discussed in great details, by using similar arguments with the Caltech lab, only helical structures containing an integral number of residues per turn and also by using only rough approximations of the interatomic distances, bond angles and planarity of the conjugated peptide bond rather than precise values derived from the crystal structure of the model compounds. Integer helical structures do not provide the stability of the non-integer 3.7-residue helical structure. They also discuss the closest related helical structure that was proposed and dismissed by Bragg, Kendrew, and Perutz. "*Bragg, Kendrew, and Perutz have described a structure topologically similar to our 3.7-residue helix as* ***a hydrogen-bonded helix with 4 residues per turn****. In their thorough comparison of their models with Patterson projections for hemoglobin and myoglobin* ***they eliminated this structure****, and drew the cautious conclusion that the evidence favors the* ***non-helical 3-residue folded*** *α-keratin configuration of Astbury and Bell, in which* ***only one-third of the carbonyl and amide groups are involved in intramolecular hydrogen-bond formation****.*"

We must recall at this point that, in 1915 at the age of 25, Lawrence Bragg was the youngest-ever Nobel laureate, while Kendrew and Perutz were already working on the determination of the crystal structures of the globular proteins, myoglobin and hemoglobin, for which they will be awarded the Nobel Prize in 1962. Therefore, the simple idea of the non-integer α-helix suggested to be available both in fibrous and globular proteins not only that pioneered but also accelerated the development of the field of molecular biology and also, as it will be discussed later, it will immediately initiate the search for a methodology to determine not only the α-helix of natural and synthetic macromolecules as well as of biological and synthetic helical assemblies but also that of the double helix of DNA.

During the same period of time the first synthetic polypeptides started to be synthesized by the ring opening polymerization of *N*-carboxyanhydrides of α-amino acids[50] and the structure of their oriented fibers and films started to be investigated.[50–55] A folded ribbon-like secondary structure stabilized by H-bonding as shown in Figure 3, right side, was proposed from X-ray diffraction and other experiments. Pauling and Corey reinvestigated this model[54] and rejected it since in the ribbon-like secondary structure the peptide group was not assigned a planar configuration with double bond character and a carbon-nitrogen distance of 1.32 Å that corresponds to about 50% double bond character.[56] The reinterpretation of the best X-ray data that were for poly(γ-methyl-L-glutamate) suggested a helical structure with 3.7 residues per turn, as reported already for fibrous proteins.[56] The helical cylinder-like polypeptide crystallizes, as expected, in a structure compatible with a columnar hexagonal symmetry.

3.2.1 The 1.5 Å Reflection Discovered by Perutz Supports the Pauling-Corey α-Helix. Perutz was very unhappy about missing the α-helix when enumerating with Bragg and Kendrew[49] helical configurations into which the polypeptide chain of a protein might fold and therefore, he took the appropriate X-ray diffraction photographs to confirm the existence of Pauling's α-helix in both proteins and polypeptides.[57] His experiments were reported in a communication from 1951 in Nature[58] that stated: "*Polypeptide chains in certain synthetic polymers, in fibrous proteins of the keratin-myosin-fibrinogen group, and also in hemoglobin, appear to be coiled or folded to about half the length of a fully stretched chain. Many different chain configurations have been proposed to account for the X-ray diffraction* data,[49] *the latter being proposed by Pauling, Corey and Branson*.[34] *Until now, however, the lack of any simple and decisive criterion in the X-ray diffraction pattern has made it difficult to test the validity of proposed models. This communication describes a new reflection, not hitherto observed, which is given by the proteins mentioned above.* ***The spacing at which this reflection appears excludes all models except the 3.7 residue helix of Pauling, Corey and Branson, with which it is in perfect concord***."

The 1.5 Å reflection is due to the spacing along the chain of the amino-acid residues. He explains the method used to discover this reflection and makes the very clear statement. "*The appearance of a 1.50 Å reflection from planes perpendicular to the fibre axis is incompatible with any other model so far proposed*." He continues by explaining the reason and subsequently by making an additional strong statement in support of the Pauling, Corey and Branson model. "*It is seen that the only structure to give a 1.5 Å reflection and the simplest is that of Pauling, Corey and Branson; the one that comes closest to it (1.4 Å) is a topographically similar model with a fourfold screw axis proposed by Bragg, Kendrew and Perutz*.[49] "However, in his publication with Bragg and Kendrew this helical model was considered incorrect and was disfavored for a planar model. Perutz observed the 1.5 Å reflection also in the synthetic polypeptides reported by Bamford.[54] He concludes that the 1.5 Å reflection supports the presence of the 3.7 residue helix in hemoglobion and in poly(γ-benzyl-L-glutamate in addition to many fibrous proteins in addition to fibrous proteins. However, he strongly states that when the 1.5 Å reflection is not observed the structure of the protein is not a 3.7 residue helix. This issue will be discussed in a different subchapter. In an additional half column paragraph from the last page of the communication discussed above,[58] Perutz reports the 1.5 Å reflection and the 3.7 residue helix in polypeptide chains from frog Sartorius muscle.[59] A subsequent Nature communication from the same year is dedicated by Perutz entirely to the 1.5 Å reflection from proteins and polypeptides.[60] He finds this reflection in wool, myosin, actomyosin and fibrinogen, indicating the universality of the 1.5 Å reflection and of the 3.7 residue helix in proteins and polypeptides. However, debates on the 3.7 Å helix were provided also in Nature by C. H. Bamford and W. E. Hanby[61] although in a Nature from 1952 Bamford and his colleagues agreed with the 3.7 Å residue helix but maintain some hesitation in some cases.[62] The fundamental dimensions of polypeptide chains[40] and the stable configuration of polypeptide chains were discussed by Pauling and Corey in two comprehensive articles.[40,63]

3.2.2 Definitive Support for the Pauling-Corey α-Helix from the Helical Diffraction Theory The debate over the numerous models of folding in proteins and polypeptides and the development of the α-helix concept by Pauling and Corey inspired experts in X-ray diffraction to develop the helical diffraction theory. Cochran, Crick and Vand (CCV)[64,65] and Stokes[66] independently from each other, developed this theory that briefly, for non-experts, states that an oriented fiber from a macromolecule displaying an α helix should exhibit a St. Andrew cross pattern. This pattern can be used to recognize an α-helix immediately and calculate all parameters of the helix with minimum knowledge of crystallography. This methodology was used to detect and solve the helical structures of proteins, peptides, nucleic acids, carbohydrates,[67] nanotubes,[68,69] synthetic polymers, biological and synthetic supramolecular assemblies and was extended by our laboratory for helical supramolecular dendrimers and helical self-organizable dendronized polymers[70] to be discussed in subchapter **8**.

3.3 Self-Organization of Coiled-Coil Protein Structures Derived from Helical Proteins. Independently from each other Pauling and Corey[71] and Crick[72] have developed the concept of coiled-coil α-helix protein structures. Figure 6 illustrates the coiled-coil protein ropes of Pauling and Corey for 3 and respectively 7 helical proteins. Additional examples of coiled-coil proteins are shown in Figure 7.

Figure 7 also demonstrated the hydrophobic interaction as responsible for the self-organization of coiled-coil architectures

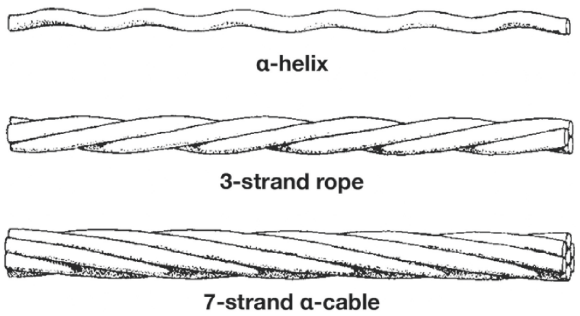

Figure 6. Ropes/coiled coil of polypeptide demonstrated by Pauling[71] and by Crick.[72]

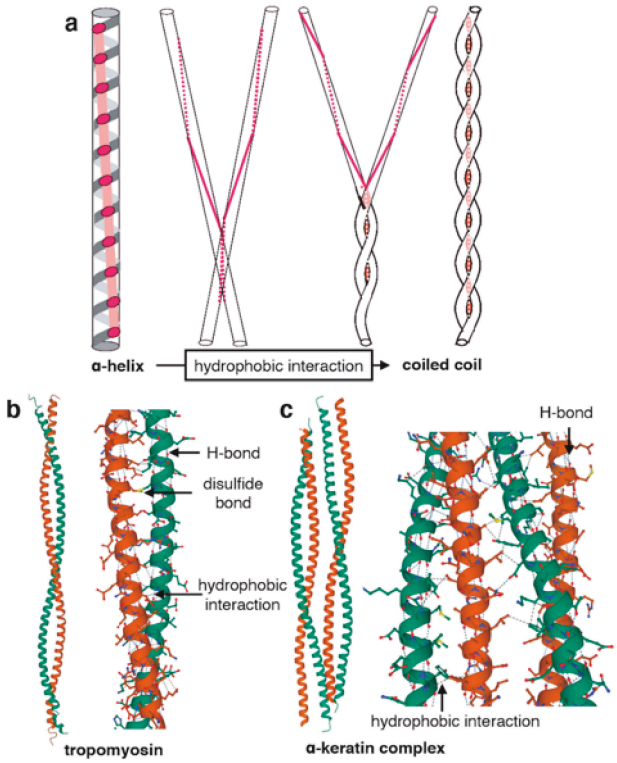

Figure 7. (a) The mechanism of coiling around each other of two polypeptide chains in water *via* hydrophobic interactions. (b) Coiled coil structure of tropomyosin's mid-region (PDB id: 2B9C). (c) Super coil filament from two α-helix coiled coil from α-keratin (PDB id: 6EC0).

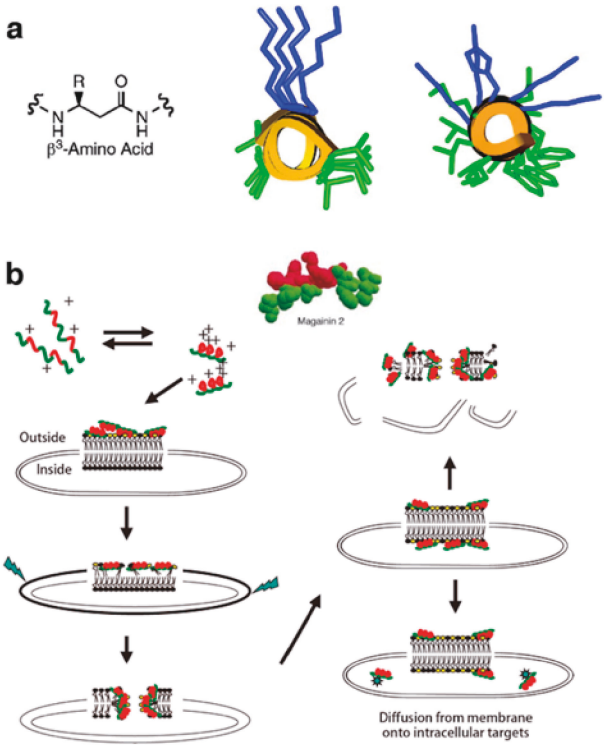

Figure 8. (a) A synthetic β-peptide based helical antimicrobial; (b) The α-peptide natural antimicrobial, magainin, and its mechanism to destroy a bacterial cell.[76,77] Reproduced with permission from ref. 76. Copyright 2011, American Chemical Society.

from helical proteins. Both Pauling and Corey and Crick explained that coiled coils diminish or even eliminate the intensity of some reflections to the point that the 1.5 Å reflection pointed out by Perutz[58] as a requirement for a 3.7 residue helix could be completely absent. Coiled-coil proteins are widely available in biology and a recent periodic table of coiled-coil protein structures was elaborated.[73] In 1954 the Nobel Prize for Chemistry was awarded to Linus Pauling "*for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances*." Several pages of his Nobel lecture discussed the elaboration of the concept of α-helix of proteins and polypeptides.[74] The principles of his work on the elaboration of the α-helix were very simple and employed precise interatomic distances, H-bonding distances, bond angles, and resonance structures, all obtained from the analysis of model compounds, together with his famous molecular models (Figure 5). These principles provided a methodology that was immediately adopted by Kendrew, Perutz, Crick, Watson, Wilkins and Klug, to name just a few who developed the field of molecular biology.

3.4 The Simplest Functions of Helical Proteins. Why are proteins adopting such a precise helical secondary structure and what are the simplest functions that are mediated by a helical rather than by a linear protein structure? Helical structures can be approximated with a column containing a precise distribution of its functional groups on its surface. Antimicrobial proteins may provide the simplest way to demonstrate this concept.[75] Figure 8b illustrates how a helical natural protein, magainin, isolates, due to its precise sequence and helical conformation, hydrophobic and hydrophilic rests of amino acids on the opposite sides of the helix. Figure 8a demonstrates the same concept accomplished with a synthetic polypeptide.[76] In both cases the precise self-organization of the hydrophilic and hydrophobic groups on the surface of the columns facilitates their interactions with the surface of the bacterial cell membrane and ultimately disassemble the bacterial cell thus providing the antimicrobial character of the protein (Figure 8b). Short fragments of helical proteins or synthetic polypeptides and or even polypeptide-like are able to provide access to antimicrobial proteins.[75,76]

3.5 The Structure of Globular Proteins Hemoglobin and Myoglobin. Pauling and Corey stated in their communica-

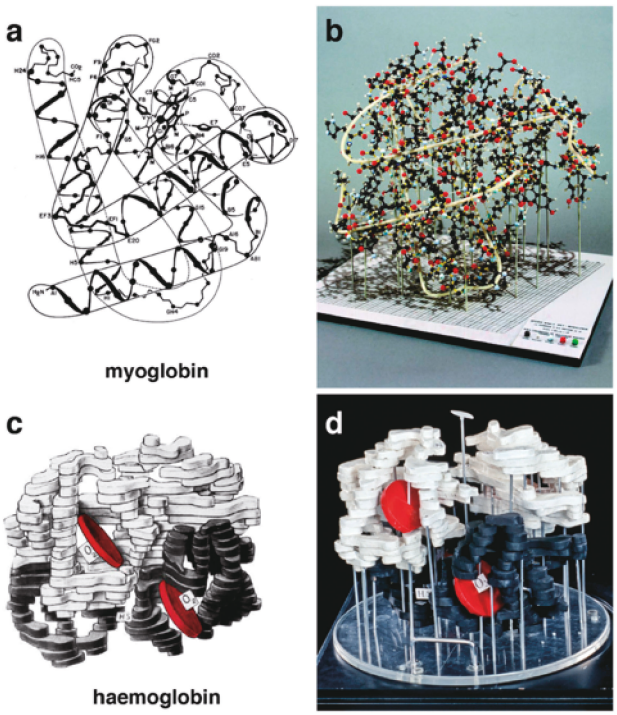

Figure 9. Crystal structure of globular proteins containing mainly α-helical proteins: (a) myoglobin and (b) its models by Kendrew (c) (d) hemoglobin and its models by Perutz.

tion[33] and in their first paper[34] that the 3.7 residue helix is not only part of the fibrous proteins but also of the globular proteins such as hemoglobin. This was indeed demonstrated by the work of Perutz and Kendrew who solved the structures of hemoglobin[77–86] and myoglobin[87–89] respectively, to explain the diffusion of oxygen in red blood cells and in the muscle and were awarded a joint Nobel Prize in Chemistry in 1962 (Figure 9).[86,90] Most unusual was that this Nobel Prize was for a mentor, Perutz, and for his former doctoral student, Kendrew. What is interesting and most probably less known is that Perutz, while an undergraduate organic chemistry student in Vienna, was advised by the future polymer chemist, Hermann F. Mark, who was his professor of physical chemistry, to join the lab of J. D. Bernal at Cavendish laboratory in Cambridge for graduate studies. During a visit to the Bernal lab Mark also made the arrangements that Perutz would join the Bernal lab. At that time Bernal was trying to elucidate the secret of life by determining the structure of proteins with X-ray diffraction.[57,91] In September 1936 Perutz's father sent his son to Cambridge together with 500 pounds that were supposed to cover all his living expenses and university fees for the 2.5 years doctoral work in the UK. When Perutz asked Bernal: "*How can I solve the secret of life*?", he replied: "*The secret of life lies in the structure of proteins, and X-ray crystallography is the only method to solve it*".[92] When Perutz returned to Vienna for summer vacation in 1937 he did not have yet a subject for his thesis. The husband of one of his cousins from Prague, who was a biochemist, advised him that it would be interesting to study the structure of hemoglobin. He also recommended to Perutz that the Cambridge physiologist, Gilbert Adair, knew how to grow hemoglobin crystals.[91] Back in Cambridge, Perutz obtained the hemoglobin crystals from Adair and soon after, excellent X-ray diffraction pictures showing thousands of reflections were generated from them.[93] Bernal already had demonstrated that wet protein crystals could provide good X-ray diffraction photographs.[57,94] Impressed by these results, Sir Lawrence Bragg,[95,96] the founder of X-ray crystallography who was appointed to lead the Cavendish lab in 1937, obtained a grant for Perutz from the Rockefeller Foundation and appointed him as his research assistant, since Bernal was moving as chair of physics at Birkbeck College, London. It would take 22 year of hard work, frustration, and inspiration for Perutz to solve the structure of hemoglobin. WWII interrupted this research. In October 1945 a young man dressed in a smart Wing Commander's uniform walked into the office of Perutz at the Cavendish Laboratory, introduced himself as John Kendrew, and said that he wanted to become his research student to do a doctoral degree in protein crystallography. For several reasons Perutz was hesitant. Kendrew was going to be his first research student, was close in age to himself, and the progress on the structure of hemoglobin was not fast enough to lead to a doctoral degree in the expected period of time.[97] The only positive was that Kendrew had some part of his doctoral fellowship money left from before the war. Ultimately, Kendrew joined Perutz's lab and demonstrated to be an outstandingly able, resourceful, meticulous, brilliantly organized, knowledgeable, and hard worker who decided to solve the structure of myoglobin rather than work with Perutz on hemoglobin and obtained his PhD in 1949. There were no positions for Perutz and Kendrew in the Cavendish Physics labs since Perutz was trained as a chemist and therefore, Bragg convinced the Medical Research Council (MRC) that their work could provide an insight into the working of life. As a consequence, on October 1, 1947 Perutz and Kendrew became the "*MRC Unit for the Study of the Molecular Structure of Biological Systems.*" Nine year later Perutz shortened the name to "*Laboratory of Molecular Biology (LMB)*." Francis Crick[98] joined the MRC Unit in 1949 as a doctoral student of Perutz to study the structure of hemoglobin, Jim Watson joined in 1951 and others in the meantime. In 1953 Perutz demonstrated the isomorphous replacement in protein crystallography, a method predicted by Bernal in 1939. The history of the development of the MRC Laboratory for Molecular Biology has been briefly presented by Perutz himself.[91] In addition to solving the structures of myoglobin and hemoglobin, Perutz also discovered during his studies the role of aromatic rings as H-bonding acceptors in molecular recognition.[99–101] This became very soon an independent research field in supramolecular chemistry.[101–110] The working conditions and the enthusiasm, that may have created one of the most efficient research operations ever, was described by the scientists who were part of it[91,111–114] and are highly recommended to be consulted by the current generation of young scientists.

The hut in which this laboratory generated the work leading to 5 Nobel Prizes in 1962, together with the photos of HF Mark, JD Bernal, and Sir L Bragg, the most influential scientists who impacted Perutz's professional career at different stages of his life, are shown in Figure 10. The 50th anniversary of the determination of the crystal structure of the first two globular proteins by Perutz and Kendrew was beautifully

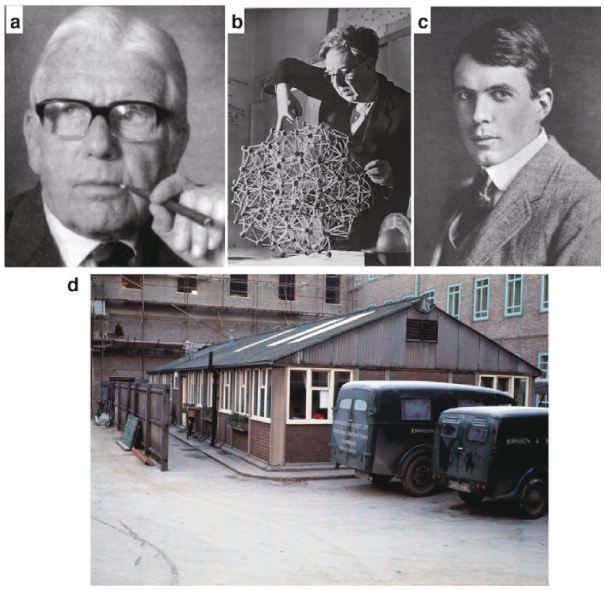

Figure 10. Portraits of (a) H.F. Mark, (b) J.D. Bernal and (c) Sir L. Bragg together with the (d) Hut Building from Cambridge.

written by Philip Ball in an article entitled "Complexity Crystallized".[115]

4. The DNA Double Helix

The discovery of the double helix of DNA, is in my opinion, a much simpler story than that of the α-helix of proteins even if much more has been written about it. Crick[64,65] and Stokes[66] were already equipped with the helical diffraction theory that was required to recognize and determine the structure of an α or a double helix. Wilkins and Rosalind Franklin at King's college in London were already investigating fibers of oriented DNA. Jerry Donohue from Pauling Laboratory at Caltech, who knew everything about bond length and bond angles,[35–40] was sharing an office with Crick and Watson at Cavendish laboratory for six months. On January 2, 1953 Pauling and Corey submitted to Nature a communication on less than one quarter of a page entitled "Structure of the Nucleic Acids." This communication was published in the February 21 issue of Nature in 1953.[116] This Nature communication mentioned that the detailed description of the structure of the three interlocked polynucleotide chain structure will appear in the February 1953 issue of PNAS. The PNAS paper entitled "A proposed Structure for the Nucleic Acids" was submitted for publication on December 31, 1952.[117] The structure reported in the PNAS report was based on their own X-ray data as well as those of Astbury[118,119] and Wilkins.[120] The PNAS paper of Pauling and Corey stated: "*This is the first precisely described structure for the nucleic acids that has been suggested by any investigator. The structure accounts for some of the features of the X-ray photographs; but detailed intensity calculations have not yet been made, and the structure cannot be considered to have been proved to be correct*." On March 6, 1953 Rosalind E. Franklin and her graduate student R. G. Gosling submitted to Acta Crystallographica two papers.[121,122] The first one reported a method to make highly oriented fibers of the sodium salt of DNA and showed the oriented diffractograms as a function of their water of hydration. At lower relative humidity (75%) a highly crystalline DNA named the A form (see Figure 1 in ref 121) was observed while at higher relative humidity (92%), a St Andrew cross diffractogram as predicted by W. Cochran, F. C. H. Crick and V. Vand[64,65] and named the B form of DNA was observed (see Figure 4 in ref 121). The following words were used by Franklin and Gosling to claim the helical structure of DNA B form: "*Here we may note that the photograph shown in Figure 4 is strongly characteristic of the type of diagram shown by Cochran, Crick & Vand in 1952 to result from a helical structure*."[65] They continue: "*The above idea seems incompatible with a structure recently proposed for DNA by Pauling & Corey (1953). These authors suggest a three helical structure in which the phosphate groups form a dense core*."[117] The final important statement of Franklin and Gosling is: "*…the transition from the crystalline to the wet state is readily and rapidly reversible, such a radical change in structure seems unlikely in the Pauling-Corey model*." On April 2, 1953 the following three papers were submitted to Nature: "Molecular Structure of Nucleic Acids" by J. D. Watson and F. H. C. Crick, "Molecular Structure of Deoxypentose Nucleic Acids" by M. H. F. Wilkins, A. R. Stokes and H. R. Wilson and "Molecular Configuration of Sodium Thymonucleate" by Rosalind E. Franklin and R. G. Gosling. They were all published back-to-back in the April 25 issue of Nature from 1953.[123–125] The Watson and Crick paper proposed the double helix of DNA and also stated: "*It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material*." Together with this sentence the Watson and Crick paper became one of the most important and influential scientific publications of the 20th century. Watson and Crick never recorded an X-ray diffractogram of DNA for their paper. They used the Rosalind Franklin Figure 4 from Franklin's publication[121] that was also incorporated in her Nature paper.[125] This X-ray diffractogram is known as "*Photo 51,*" as "*The most important photo ever taken*?" or as "*The most famous X-ray picture of the 20th century* (Figure 11c)."

Regardless of how Watson and Crick accessed this "Photo 51" from Rosalind Franklin,[126–130] together with the CCV helical diffraction theory[64,65] and the molecular models build from February to March 7, 1953 (Figure 12) Watson and Crick solved one of the most important problem of life sciences and pointed to the secret of life.

It is important to mention that Watson and Crick state at the end of their Nature paper: "*We are much indebted to Dr. Jerry Donohue* (the former student of Linus Pauling) *for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins and Dr. R. E. Franklin and their co-workers at King's College London*." Genetic implications of DNA were described soon during the same year.[131] The A structure of DNA was immediately solved and published by Franklin with Gosling[132] who knew it as a water reversible form of the B DNA form[121] and by Wilkins[120] (Figure 11). The rush to solve the structure of DNA was, most probably, instigated by the incorrect structure of DNA published by Pauling and Corey.[117] The MRC lab

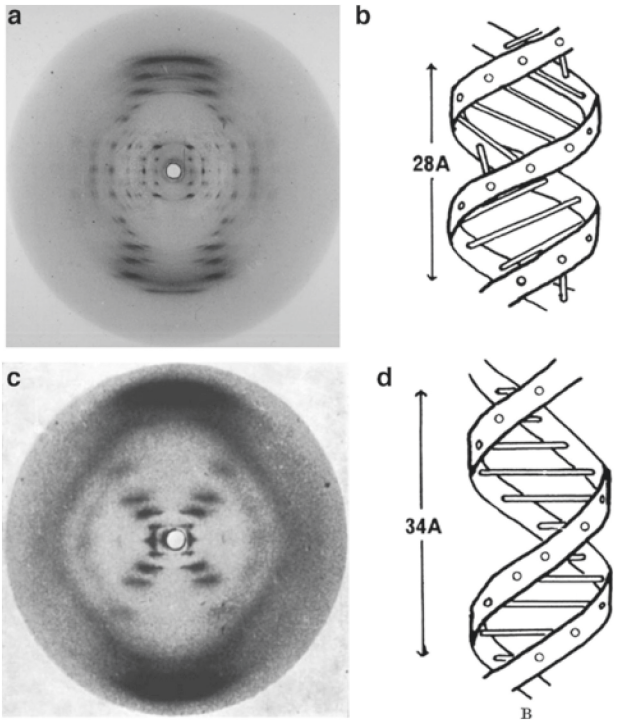

Figure 11. (a) X-ray diffraction pattern of A-DNA by Franklin and Gosling. (b) Illustration of A-DNA double helix. (c) X-ray diffraction pattern of B-DNA (photo 51) by Franklin and Gosling. (d) Illustration of B-DNA double helix by Watson and Crick. Combined and modified from references above.[121,123,125,130]

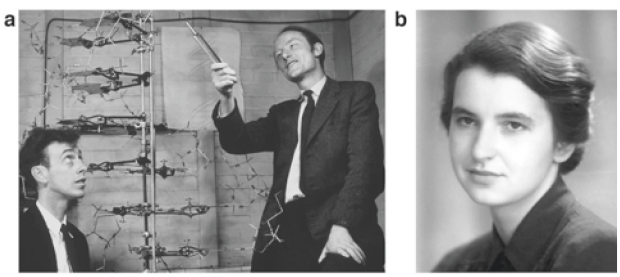

Figure 12. (a) Francis Crick and James Watson with their model of DNA double helix. (b) Rosalind Franklin.

in Cambridge knew that Pauling and Corey will correct it and they did not want to lose on the structure of DNA as they did it on the α-helix of proteins. Watson, Crick and Wilkins were awarded the Nobel Prize for Physiology or Medicine in 1962,[133–135] the same year Kendrew and Perutz received the Nobel Prize for Chemistry.[86,90] The rent to the hut (Figure 10) in which they did most of their experiments may have been rewarded by these 5 Nobel Prizes from 1962 (Figure 13). The story of The Double Helix was told by Watson in a book.[136] Rosalind Franklin died of cancer on April 16, 1958.

5. The Structure and the Mechanism of Self-Organization of Tobacco Mosaic Virus (TMV)

During mid-March 1953 Rosalind Franklin moved from King's College, London to Birkbeck College, University of

Figure 13. (a) Francis Crick (far left) and James Watson (third from right) are pictured alongside fellow Nobel Prize recipients Maurice Wilkins, John Steinbeck, Max Perutz, and John Kendrew at the Nobel Prize ceremony in 1962. (b) Max Perutz and John Kendrew with their protein models. (c) Aaron Klug.

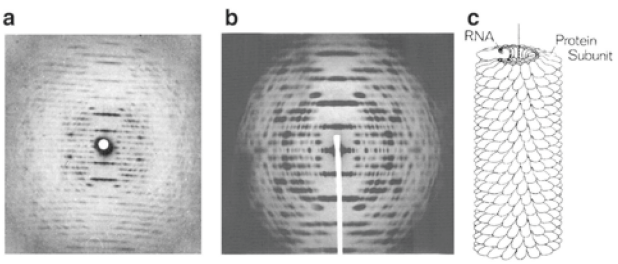

Figure 14. (a) X-ray diffraction pattern of TMV; (b) X-ray pattern of mercury isomorphically replaced TMV, both by Franklin. (c) Model of tobacco mosaic virus (TMV) by Klug.[143,149] Reproduced with permission from ref. 149. Copyright 1983, Jon Wiley & Sons.

London where she was recruited by JD Bernal who at that time was the Chair of the Department of Physics. At Birkbeck she became a senior scientist supervising her own group. John Finch, a physics student from Kings College, London joined her lab immediately followed by Kenneth Holmes, a Cambridge graduate who joined her in 1955 while Aaron Klug who just obtained his PhD from Trinity College, Cambridge with his student Finch joined her as a colleague in late 1953. The American Donald Casper joined as a postdoc in 1955. They started to work on the structure of TMV and other viruses. Although TMV was of interest to Bernal since 1936[137–141] and Watson showed that TMV is a helix in 1954[142] Franklin immediately generated TMV's best X-ray photograph and demonstrated the details of the helix, the place of RNA in its structure, its helical groove and its helical parameters by isomorphous replacement[143–148] (Figure 14). The first major international fair after WWII, Expo 56, was going to be organized in Brussels in 1958. Rosalind Franklin was invited to expose a five-foot high

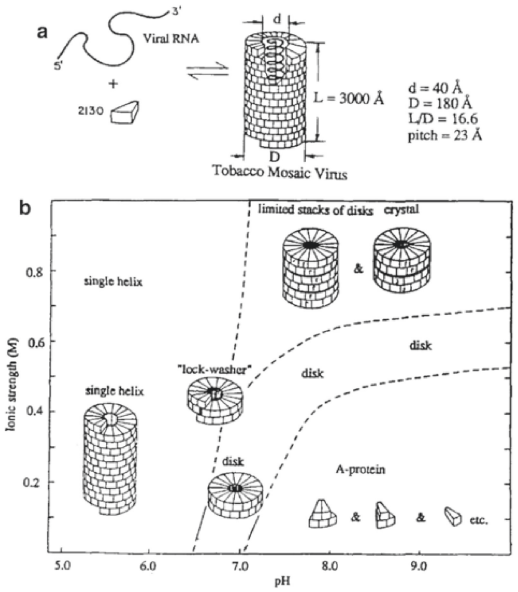

Figure 15. Phase diagram of the self-assembly of TMV by Klug.[149] Reproduced with permission from ref. 149. Copyright 1983, Jon Wiley & Sons.

model of TMV that she started working on in 1957. The "Expo 58" opened one day after she died on April 17, 1958 with her virus model in the International Science Pavilion. Aaron Klug will be awarded the Nobel Prize in 1982 for the work he started in Franklin's lab in 1953.[149–153] A schematic representation of the self-assembly of TMV from the Nobel lecture of Klug[149] is shown in Figure 15. Rosalind Franklin had seminal contributions to the 1962 Nobel Prize in Physiology and Medicine and the 1982 Nobel Prize in Chemistry, respectively, but did not share or even witness any of them.

6. From Biological to Synthetic Helical Macromolecules and their Self-Organizations

Structure determines function. Therefore, the elucidation and understanding of the hierarchical structure of biological macromolecules and of their self-organizations provides access to how they function and ultimately an entry into the "secret of life." By analogy, designing synthetic covalent and supramolecular macromolecules and the structure of their self-organizations provides access to functions displaying the same level of precision as biological functions which is one of the greatest challenges of natural sciences. In the following subchapters we will discuss synthetic macromolecules that provide similar secondary and tertiary structures with biological systems already discussed. Macromolecules that provide structures that were not yet elaborated in functions will be only very briefly mentioned.

6.1 Substituted Polyolefins, Polyacetylenes, Poly(isocyanide)s and Poly(carbodiimide)s. The first synthetic helical polymer was most probably poly(tetrafluoroethylene) or Teflon whose helical structure was determined by Bunn and Howells and reported in Nature in 1954.[154] While poly(ethylene) (PE) has a zig-zag linear conformation, the larger size of fluorine *vs* hydrogen induces a departure from the zig-zag linear conformation of PE to generate a helix. However, systematic synthesis and structural analysis of synthetic helical polymers was initiated by Ziegler-Nata or stereospecific polymerization of monosubstituted α-olefins by the Giulio Natta laboratory and published starting with the year 1955.[155–160] Karl Ziegler and Giulio Natta received the Nobel Prize in 1963 for the discovery of Ziegler-Natta or stereospecific polymerization.[159,160] A brief history of the development of Ziegler-Natta polymerization was presented in a recent perspective[16] and therefore, it will not be repeated here. The next classes of synthetic helical polymers are substituted polyacetylenes that originally were prepared also by Ziegler-Natta polymerization. Their historical development was also reported very recently.[16] The helical *cis* and *trans* stereoisomers of poly(phenylacetylene) (PPA) received the greatest and the most continuous attention since, with the exception of *cis*-cisoidal that is highly crystalline and therefore insoluble, they are soluble, can easily be functionalized and therefore, their helical conformation can be determined and monitored by a large diversity of methods including X-ray diffraction, ^{1}H and ^{13}C NMR, circular dichroism, UV-vis spectroscopy, and many others.[161–180] Methods for the living polymerization of PA and of its derivatives were elaborated and continue to be developed,[181–186] At this point this is a very active field of research in many laboratories around the world.[11,22,187–194] Polymethacylates with large substituents also adopt helical conformations[191] although they are not prepared by any stereospecific polymerization. Rigid rod-like helical polymers are also obtained from poly(isocyanide)s or poly(isonitrile)s[194–202] and from poly(carbodiimide)s.[203–212] Elegant methods for their polymerization including by living polymerizations were developed.

6.2 Self-Organizable Helical Dendronized Covalent and Supramolecular Macromolecules. A lecture and a dinner after the lecture with Aaron Klug in the fall of 1982, the day before his Nobel Prize in Chemistry was announced, provided one of us (VP) inspiration to design and investigate libraries of self-assembling dendrons and dendronized covalent and supramolecular macromolecules in order to self-organize synthetic TMV-like structures. The history of this event together with initial inspiration, failures and early successes was published by invitation.[213] This event was briefly mentioned also in some review articles.[9,10,16,17] A schematic representation of these libraries (Figure 16)[214] while their self-assembly and self-organization in a diversity of helical supramolecular columns containing a supramolecular or covalent macromolecule in their center is shown in Figure 17 together with the TMV model of Aaron Klug. A large diversity of molecular recognition processes were employed to mediate the formation of a supramolecular polymer backbone in the center of the column. They range from crown ethers, macrocyclic polyamines and oligooxyethylene podants in the presence and absence of ion pairs, hydrogen bonding and covalent polymer backbones (Figures 18, 19).[215–246]

Early review articles, written by invitation, on these early methodologies are available.[247–250] Just like in the case of TMV, the helical self-organization of the dendritic coat induces a helical conformation of the polymer backbone. All these assemblies were characterized by X-ray diffraction although they did not exhibit very high order in their X-ray photos. Numerous functions were elaborated by using their supra-

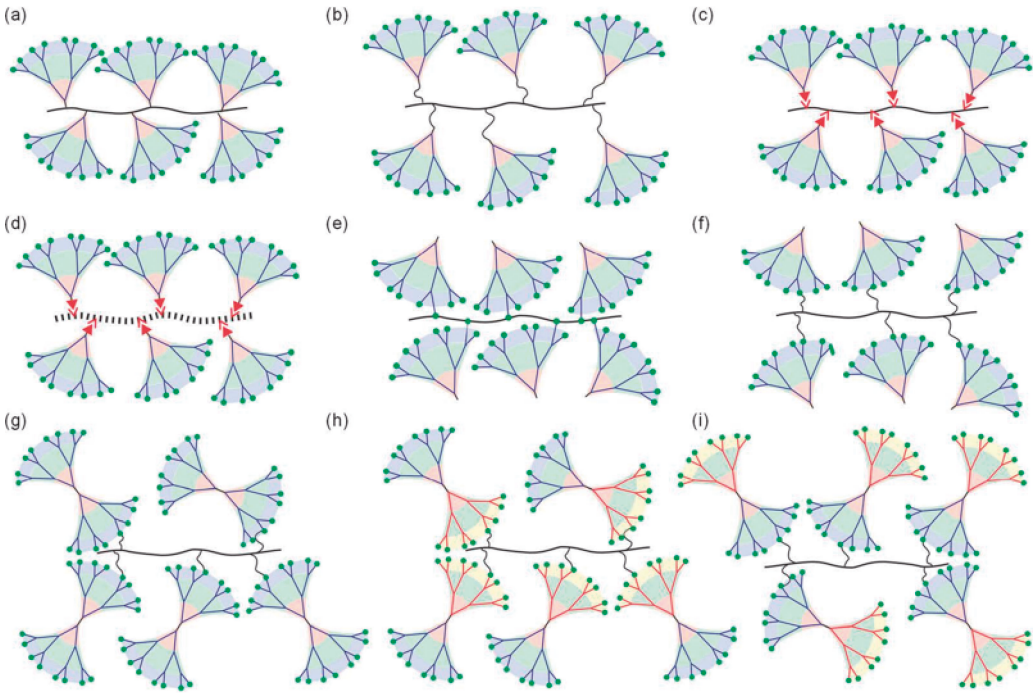

Figure 16. Self-organizable supramolecular and covalent polymers dendronized with self-assembling dendrons, twin- and Janus-dendrimers attached to their backbone from apex or periphery, directly or via a short spacer.[214] Reproduced with permission from ref. 214. Copyright 2012, American Chemical Society.

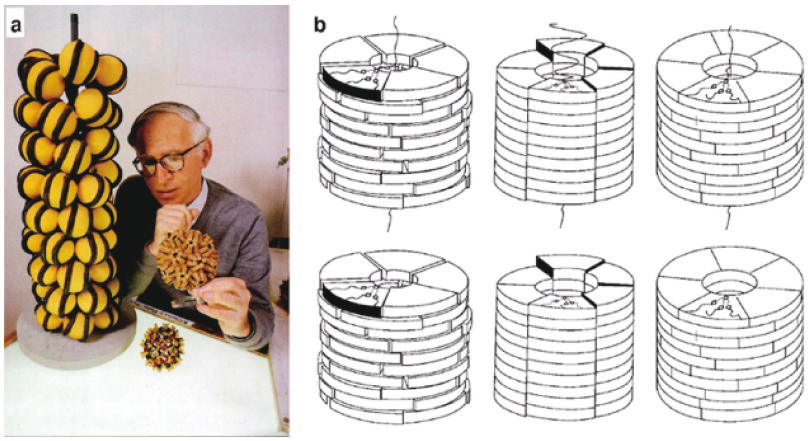

Figure 17. (a) Klug with his models of TMV and icosahedral viruses.[151] (b) Self-assembly and self-organization of dendronized supramolecular or covalent polymers in TMV-like supramolecular architectures.[9] Reproduced with permission from ref. 9. Copyright 2009, American Chemical Society.

molecular structure to design functions. Figure 18d illustrates the design of high ionic conductivity by incorporating complexes of crown ethers and oligooxyethylenes with metal salts such as alkali metal triflates.[216–224] Water separation membranes were generated *via* related principles.[251–258] For the first time a comparison of the strength of supramolecular backbones with covalent backbones was also accessed with these TMV-like assemblies.[10,216–224]

6.3 Three- and Four-Bundles of Helical Columns and Their Self-Organization into Helical Superlattices. Twin and Janus-twin self-organizable dendrimers and their corresponding dendronized polymers self-assemble and co-assemble into three- and four-bundles of helical columns that self-organize into helical hexagonal columnar superlattices.[9,10,214,259,260] This concept is illustrated in Figure 20 and although related, it differs from the classic concept of coiled-coil helical proteins where the rope or bundle architecture is mediated by hydrophobic interactions. In this particular case the bundle is connected to a covalent polymer backbone. Functions mediated by these helical self-organizations will be mentioned briefly in subchapter **6.5**.

6.4 Co-Assembly and Self-Organization of Polymers Containing Donor or Acceptor Groups with Self-Assembling Dendrons Containing Acceptor or Donor Groups into Helical Self-Repairing Electronic Columns. This TMV-mimic self-organization concept is illustrated in

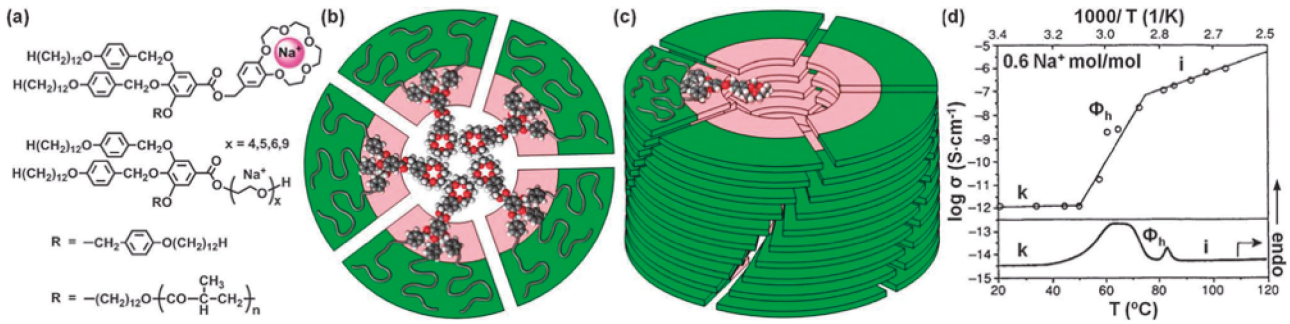

Figure 18. Helical ionic conducting columns self-organized by dendronized crown-ethers, oligooxyethylene and their polymers.[10] Reproduced with permission from ref. 10. Copyright 2016, Royal Society of Chemistry.

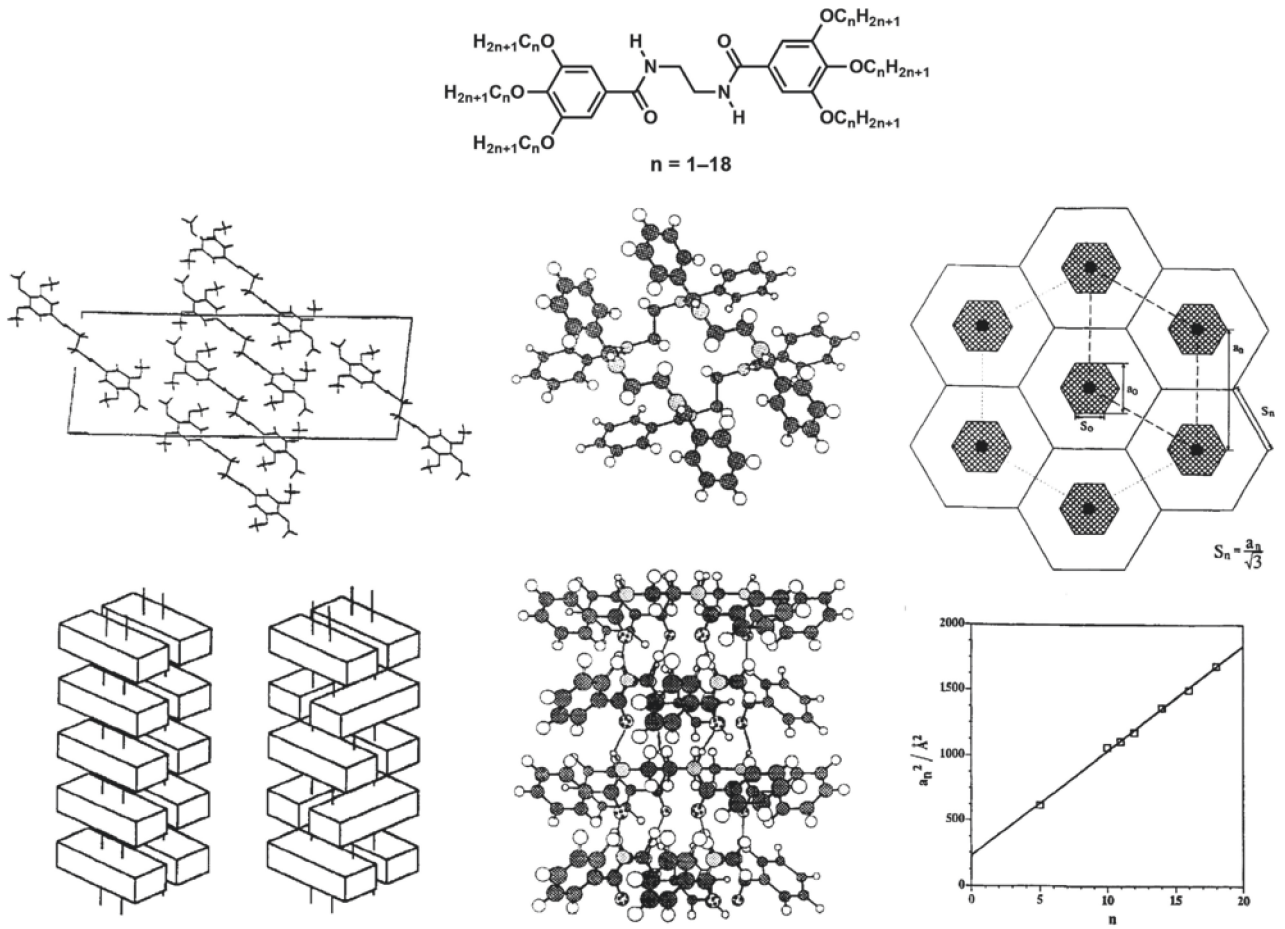

Figure 19. Self-organization of helical supramolecular polymers via H-bonding of twin tapered bisamides. Combined and rearranged from the reference above.[225]

Figure 21. Libraries of acceptor groups attached to polymers and or to self-assembling dendrons were designed to self-assemble in the absence of a complementary polymer or in the presence of a complementary polymer.[234] When co-assembly proceeds in the presence of a complementary polymer its backbone is coated with the complementary helical supramolecular dendrimer and the polymer adopts a helical conformation while being incorporated in the center of the helical column. This process resembles the mechanism of self-assembly of TMV in the presence of RNA that is schematically shown in Figure 15a. When the dendron contains acceptor groups they can also back-fold on the donor part of the dendron as shown on the right side of Figure 21. A combination of solid-state NMR and X-ray analysis demonstrated that the back-folded structural defects are self-repairing upon a simple heating and cooling process.[234,237,238] This is a very simple concept in which bioinspired order programs and self-repairs electronic functions. The charge carrier mobility of the parent donor and acceptor molecules as well as when they are attached as side groups to amorphous polymers was increased by up to 6 orders of magnitude by this hierarchical self-organization strategy.[234] A very influential paper on the increased charge carrier

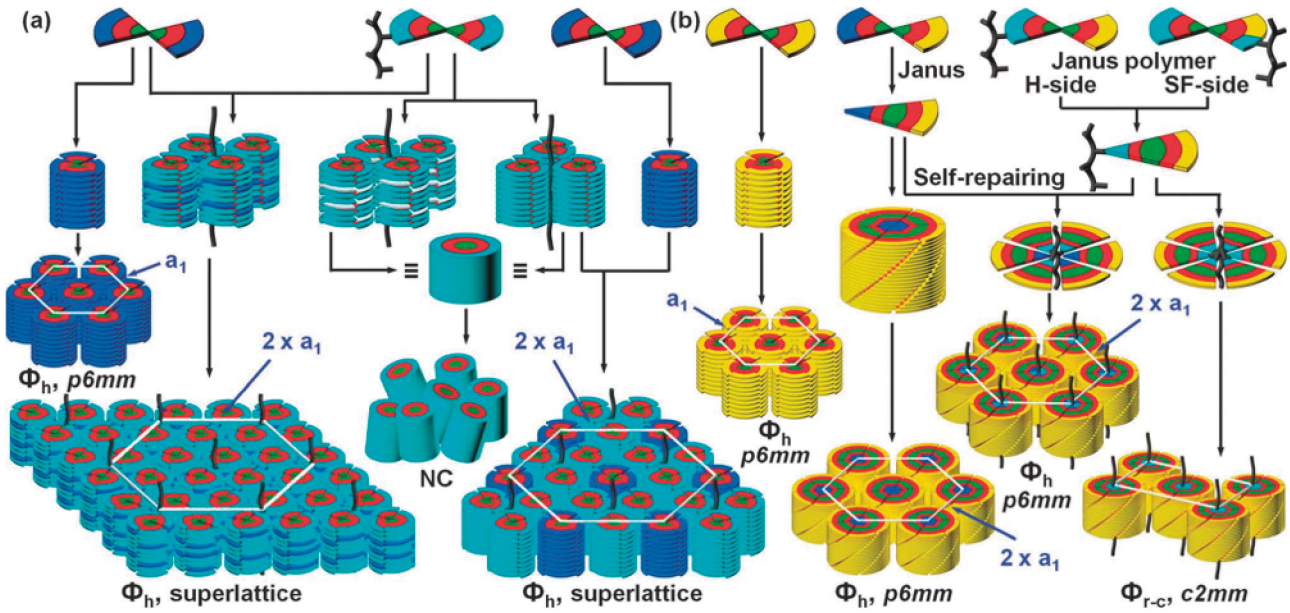

Figure 20. (a) Self-organization of twin dendrimers, twin dendronized polymers and their co-assembly with twin dendrimers and (b) Janus-dendrimers and Janus dendronized polymers into helical columnar bundles and supramolecular lattices.[214] Reproduced with permission from ref. 214. Copyright 2012, American Chemical Society.

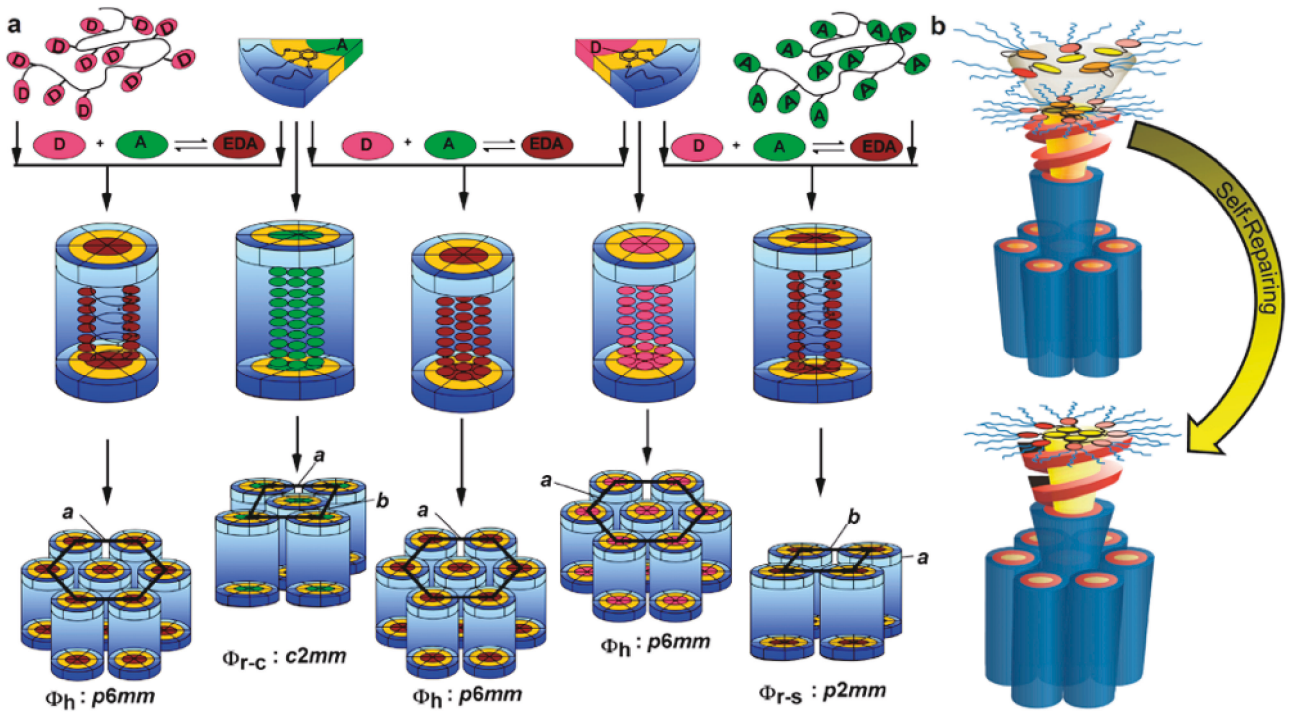

Figure 21. Self-assembly, co-assembly and self-organization of helical self-repairing electronically active periodic arrays.[234] Reproduced with permission from ref. 234. Copyright 2004, Springer Nature.

mobility, by the unrelated to TMV assembly, but instead by a highly ordered helical columnar hexagonal crystal obtained by the self-organization of the discotic molecule 2,3,6,7,10,11-hexahexylthiotriphenylene must be mentioned.[261] The corresponding molecule containing hexahexylalkoxytriphenylene does not generate the same highly ordered helical columnar hexagonal crystal and high charge carrier mobility although it exhibits macroscopic evidence of molecular chirality in the columnar mesophase.[262] Most probably, the replacement of oxygen with the larger sulfur is responsible for the induction highly ordered crystalline helicity. The co-assembly concept discussed above[234] is currently of great interest to investigate and elucidate the encapsulation and release of polymers into and from the supramolecular helical column since it resembles the encapsulation and release of RNA into viruses and into RNA based vaccines. Work on this line will be published soon.

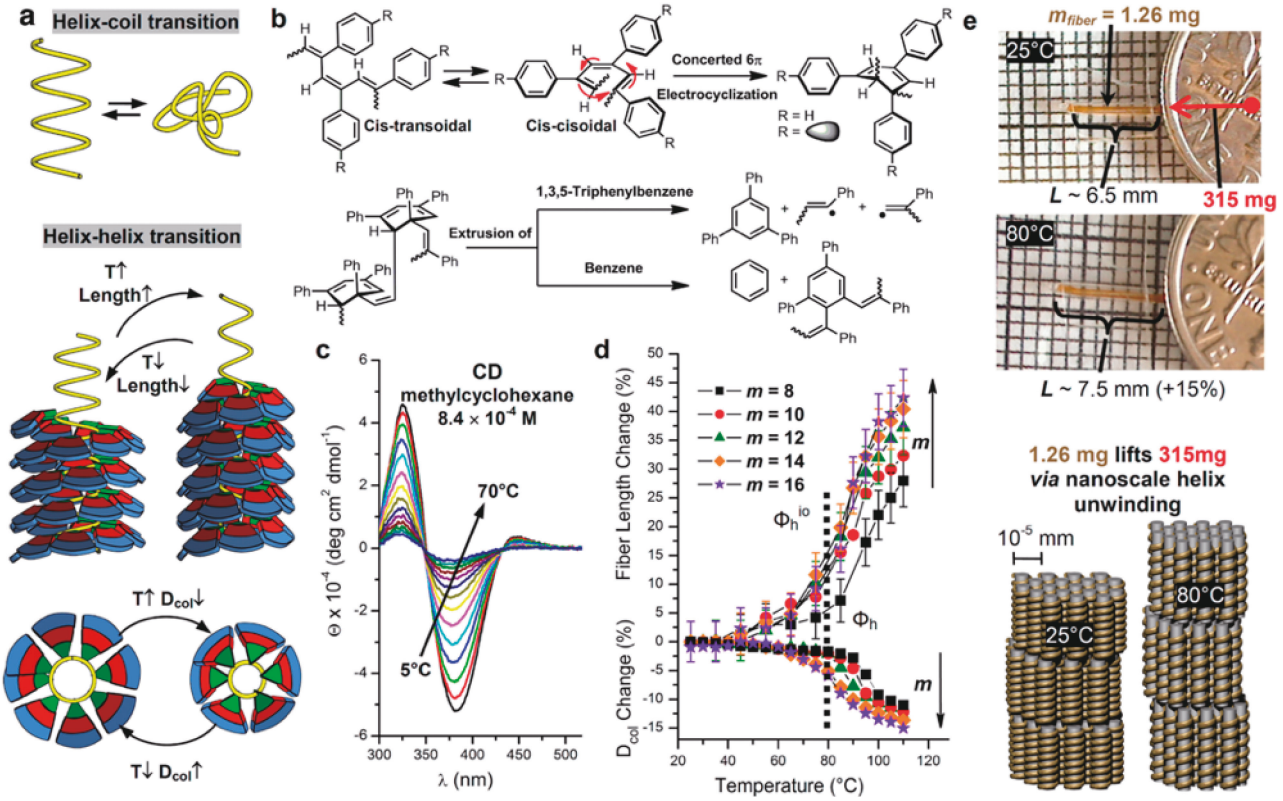

Figure 22. Irreversible intramolecular electrocyclization followed by chain cleavage of *cis*-transoidal and *cis*-cisoidal stereoisomers of PPA is eliminated by dendronizing PPA and a reversible *cis*-cisoidal to *cis*-transoidal helix-helix transition allowing the design of molecular machines is generated.[264] Reproduced with permission from ref. 264. Copyright 2005 and 2008, American Chemical Society.

6.5 An Unprecedented Thermal Reversible *Cis*-Cisoidal to Cis-Transoidal Isomerization of Helical Dendronized PPA and its Functions. Conventional helical *cis*-cisoidal and *cis*-transoidal PPA undergo a thermally induced irreversible cis-trans isomerization accompanied by intramolecular electrocyclization and chain cleavage *via* the aromatization of their intramolecular cyclohexadienic units (Figure 22).[11,165,172,194,263–266] This process occurs during a helix-coil transition of the PPA backbone as shown in Figure 22a. This irreversible electrocyclization followed by chain cleavage to release 1,3,5-trisubstituted benzene occurs both in solution and in solid state, has been recently demonstrated also by photochemical processes and can be used in the determination of the stereochemistry of PPA as well as for the preparation of membranes for separation.[176,256,257] Poly(arylacetylenes) with bulky aryl side groups do not undergo this process.[163,172,267–270] Functionalization of phenyl acetylene (PA) with a self-assembling dendron followed by stereospecific polymerization creates a *cis*-transoidal or *cis*-cisoidal PPA that is encapsulated in a rigid rod-like helical column. This rigid rod-like helical column eliminates the helix-coil transition, the cis-trans isomerization and the intramolecular electrocyclization accompanied by chain cleavage and replaces it with an unprecedented thermal reversible *cis*-cisoidal to *cis*-transoidal isomerization that is accompanied by the extension and compression of the helical column. This self-organization process changes the chemo-selectivity of the thermal induced organic reactions that occur on the native chain of cis PPA. It also provides access to a new molecular machine concept that is constructed with bundles of hexagonally packed chains of dendronized PPA (Figure 22). This molecular machine provides the first example of a molecular machine that can be interfaced with the real world.[263,264,271,272] This is a general concept that was designed and accomplished also with dendronized polymethacrylate.[259] A reversible molecular machine that increases its length on cooling and decreases it on heating was also designed with polymers dendronized with Janus dendrimers to generate helical vesicular columns.[201]

7. Quasi-Equivalent Self-Assembling Dendrons and Dendronized Polymers Self-Organize Helical Monodisperse Spheres, Quasicrystals and Frank-Kasper Phases

In order to explain the self-assembly of spherical viruses that have an icosahedral symmetry from proteins with an identical primary structure in 1962 Casper and Klug elaborated the concept of quasi-equivalence.[273–275] Purposeful switching among different conformational states exerts self-control in the construction and action of protein assemblies. Quasi-equivalence, conceived to explain icosahedral virus structures, arises by differentiation of identical proteins subunits into different conformations that conserve essential bonding specificity. A brief definition of quasi-equivalence is: "*Purposeful switching between more stable, unsociable, and less stable, associable, conformations of proteins during self-assembly of icosahedral viruses.*" Quasi-equivalence has analogy with Buckminster

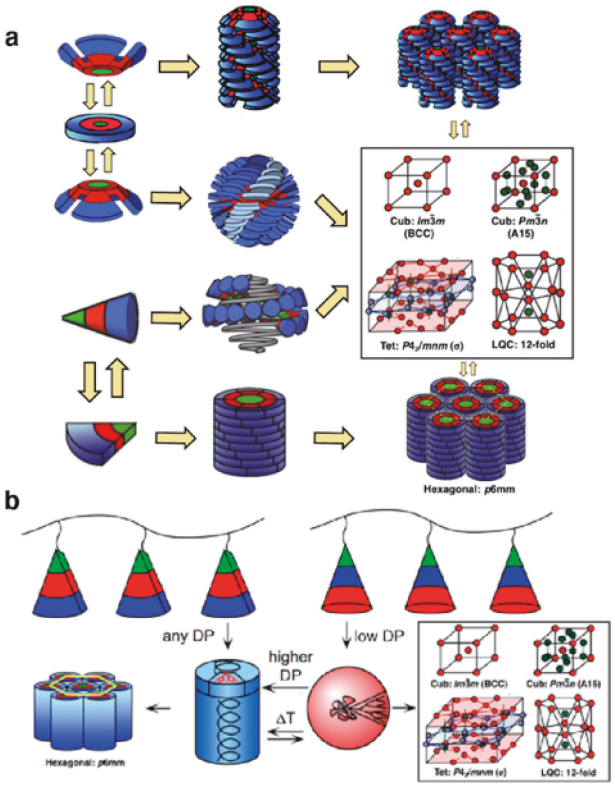

Figure 23. Quasi-equivalent conical-taper and crown-disc self-assembling dendrons, dendrimers and dendronized polymers self-assemble helical columns and helical spheres and self-organize Frank-Kasper BCC, A15, σ phases and liquid quasicrystal assemblies.[9,10,16,17]

Fuller's icosa-geodesic dome design.[276] Originally we discovered that self-assembling conical dendrons are quasi-equivalent with tapered dendrons and therefore, under a specific set of conditions they can self-organize columnar or spherical periodic arrays.[264] Libraries of self-assembling dendrons prepared by iterative synthesis were investigated to search for quasi-equivalent self-assembling dendrons *via* generation number of the dendron or dendrimer and by constitutional isomerism.[15,70,224,225,231,235,241,243,278–291] This search was many times aided by thermodynamic schemes correlating the stability of self-organizations with their morphology.[292] Subsequently, we demonstrated that self-assembling crown-shape dendrons are quasi-equivalent with disc-like dendrons and therefore, they also can self-organize either columnar or spherical periodic.[270,293–296] The quasi-equivalence of self-assembling dendrons can be mediated during their self-organization by temperature, various supramolecular interactions at their apex and in the case of self-organizable dendronized polymers by their degree of polymerization. By analogy of globular proteins spherical supramolecular dendrimers are also helical since they are generated, just like globular proteins, from short fragments of spherical columns. Therefore, both columnar and spherical assemblies generated from self-assembling dendrons and from dendronized supramolecular and covalent polymers are chiral. Most importantly the spherical dendrons self-organized in quasicrystals[297,298] and Frank-Kasper[277,299–302] phases are of identical dimensions and therefore are monodisperse. Figure 23 summarizes the concept of quasi-equivalent self-assembling dendrons and dendronized polymers self-organizing helical monodisperse spheres, quasicrystals and Frank-Kasper phases. Quasi-equivalent dendrons can be used to generate dynamic materials,[13] investigate the origins, transfer and amplification of chirality and address questions related to the origins of homochirality.[14,295a] Additional functions derived from this concept will be discussed in different subchapters.

7.1 Self-Interrupted Polymerization (SIP), Self-Accelerated Polymerization (SAP) and Self-Interrupted Living Polymerization (SILP). Conventional chain, step and living polymerization reactions rely on the reactivity of growing species being independent of their degree of polymerization.[303,304] Regardless of an electrophilic, nucleophilic or radical mechanism, conventional chain reactions are accompanied by chain transfer and termination reactions provide limited ability to predetermine the degree of polymerization and the polydispersity of the final polymer. Living polymerization reactions are free of chain transfer and termination with an ideal initiation being faster than propagation. Therefore, in living polymerizations the degree of polymerization can be predicted by the ratio between the initial concentration of the monomer to initiator. For living polymerizations, a narrow Poisson molecular distribution is obtained. Conventional polymerization of a self-assembling dendronized monomer in dilute ideal solution is accompanied by a decrease of the reactivity of the growing species to the point that when the degree of polymerization reaches the number required to form a sphere the polymerization is self-interrupted. In this polymerization that we call self-interrupted polymerization (SIP) narrow molecular weight polymers with polydispersity as narrow as in a living polymerization are obtained. SIP has been demonstrated so far with methacrylate and styrene polymerizable groups attached to a conical dendron that self-assembles in a supramolecular sphere (Figure 24).[277,305] When the same conical self-assembling dendronized monomer is polymerized in self-assembled state or even in bulk state its polymerizable groups self-assemble in a supramolecular reactor with very high concentration in its core and a spontaneous polymerization occurs leading to a mega[17] molecular weight polymer within few minutes of polymerization time (Figure 24).[277,305,306] This process is mediated both by self-assembly of a nanoreactor and by the quasi-equivalence of the conical dendron. The resulting polymers are either helical or almost extended rigid rod-like structures.[277,306] Their structure in solid state can be determined by X-ray when they are self-organized into periodic arrays or as individual assemblies and single molecules[307] as well as in periodic arrays by atomic force microscopy (AFM) (Figure 25). When the polymerization of self-assembling dendronized monomers is performed by living polymerization in dilute ideal solution, monodisperse protein-like polymers are obtained (Figure 26).[305] This is the first methodology to produce monodisperse polymers aside from iterative methods[308,309] or genetic polymerization.[310,311]

7.2 An Aquaporin (AQP) Mimic Discovered by The Self-Organization of Constitutional Isomeric Dendritic Dipeptides. Aquaporin is a transmembrane protein hydrophobic channel that transports 3×10^9 molecules of water per

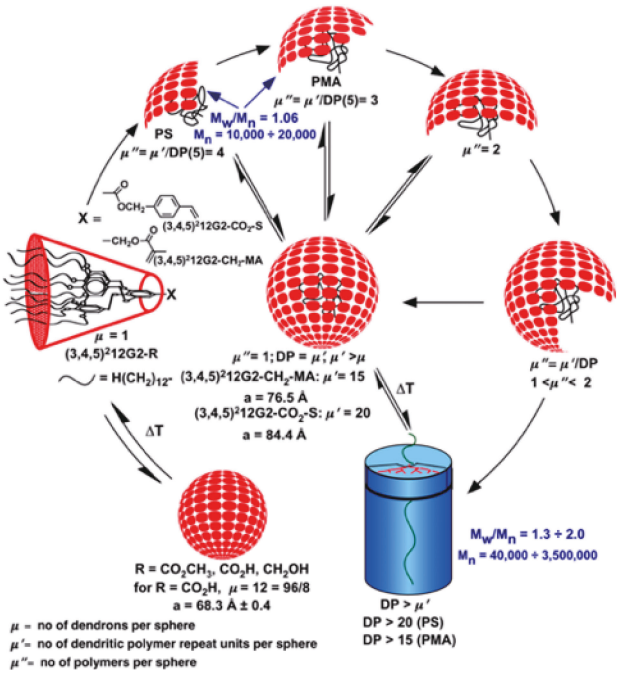

Figure 24. Conventional radical polymerizations of quasi-equivalent conical dendronized monomers and the structure and shape of the resulting polymers in dilute solution by self-interrupted polymerization (SIP) and in self-assembled stated by self-accelerated polymerization (SAP).[277] Reproduced with permission from ref. 277. Copyright 1998, Springer Nature.

second with 100% selectivity. No protons, protonated water or other species pass through this channel (Figure 27a).[312] Each of us filters several hundred liters of water per day with this channel. One of the two constitutional isomeric dendritic dipeptides shown in Figure 27b, the 3,5-disubstituted, self-organizes in a helical porous structure (Figure 27b).[239] The 3,4-constitutional isomer (Figure 27c) self-organizes in a spherical hollow sphere[287] while all other tapered dendrons form porous assemblies.[313]

The role of the protective groups of the dipeptide,[240] of the stereochemistry of the dipeptide,[314] of different pairs of amino acids forming the dendritic dipeptide,[315] of the length of the alkyl groups forming the self-assembling dendron attached to the dendritic dipeptide[241] and of the aromatic parts of the dendritic dipeptide[242,313] were investigated and the structures of the resulting porous helical structures as well as the principles of its self-organization were elucidated. Water transport by the helical porous structure via biological membranes was investigated and found to be of a selectivity close to that of natural AQP.[242] Dendritic dipeptides could be visualized with AFM on surfaces both as individual stereoisomers[307] and as their supramolecular assemblies.[239] This concept inspired other laboratories to develop very efficient membranes for water purification.[251–255] All possible stereochemical permutations of the 3,5-constitutional isomeric dendritic dipeptide were employed to investigate their role in the supramolecular polymerization and on the resulting helical porous structure in solid state by X-ray diffraction methods.[14,314] Homochiral dendritic dipeptides provide the fastest rate of self-assembly and the highest order in the crystal state followed by heterochiral and by racemic. The most interesting result of this study is that homochiral helical structures crystallize very fast, heterochiral crystallize very slow while racemic structures do not crystallize at all and form only micellar-like assemblies. This result demonstrates why homochirality is selected by biological systems.[14,314] While the handedness of a helical structure can be selected by the sergeant and soldiers and by the majority rules,[316] these rules are not used in biology since they cannot provide the high order crystal structure of biological homochiral systems discussed in the first chapters of this account.

8. Application of Helical Diffraction Theory to Self-Organizable Dendronized Supramolecular and Covalent Polymers

The extraordinary simplicity and utility of the helical diffraction theory elaborated by Cochran, Crick and Vand (CCV)[64,65] and later by Stokes[66] that explain the diffraction by a helical fiber is best described by the famous statement of Crick and Kendrew:[65,317] "*Armed with the appropriate theory it is often possible to recognize the helical nature of a fiber structure at a glance, and sometimes to specify the main parameters of the helix and its subunits with very little trouble indeed*," and also by the sentence of Crick when referring to the discovery of the double helix of DNA[318] "*….it did mean that I had the expertise at my fingertips*." Figure 28b outlines the most important parameters generated by the helical diffraction theory applied to a 5_1 single strand helix generated from atoms or atomic helix (Figure 28a) and for groups of atoms some of them being tilted as in the case of helical supramolecular dendrimers (Figure 28c).[70] The X-ray diffraction pattern of an oriented fiber of the structure from Figure 28a is illustrated in Figure 28b while the schematic pattern of the helical structure from Figure 28c is shown in Figure 28d. Both oriented fiber diffraction patterns display a St. Andrew's cross, shown in red, that is produced by the first maxima of the squared Bessel functions in the four quadrants. The St. Andrew's cross pattern indicates a long-range helical order. The angle α between the meridian and the cross and the rising slope of the helix are related to the helix radius r. The smaller the angle α is, the larger the radius r of the helix. The pitch of the helix, P, is determined by the distance between the long-range red helical features forming the cross. The atoms forming the helix in Figure 28a can be replaced with a tilted group of atoms, such as, for example, a tilted phenyl group from a dendron or dendrimer, shown in green with a red dot in Figure 28c. This group produces the diffraction feature colored in green in Figure 28d. The tilt angle of this group *vs* the helix axis (Figure 28c) is illustrated in green on the schematic of the oriented fiber X-ray pattern from Figure 28d. The diffraction features colored in blue in Figure 28b, d refer to short-range helical order. The diffraction features corresponding to the long-range stacking correlations along the helix axis are shown in yellow. The schematics from Figure 28 explain the difficulties encountered in the assignment and the determination of the helical structure when the long-range order red-marked helical features are absent due to the low resolution of a fiber X-ray diffractogram. *This explains the extraordinary signifi-*

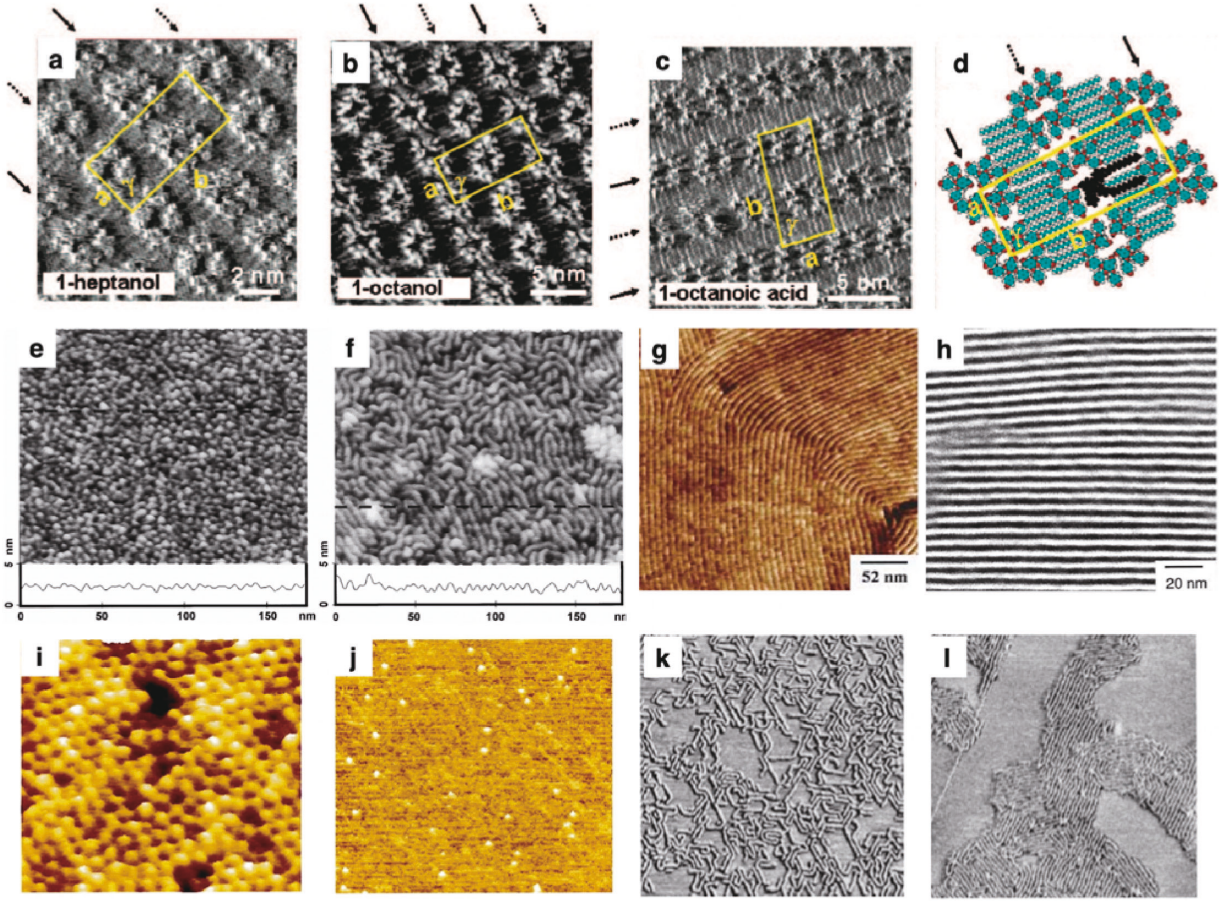

Figure 25. (a–d) STM images of monolayers of dendrimers physisorbed at the liquid-HOPG interface;[298] (e) Supramolecular helical spheres from dendronized polymers with quasi-equivalent conical dendrons at low degree of polymerization (f) and their helical columns at high degree of polymerization;[277] (g) Hollow helical colums self-organized from dendritic dipeptides;[239] (h) Supramolecular helical columns self-organized from dendronized crown ethers;[300] (i) A15 Frank-Kasper phase self-organized from single dendron-single sphere;[278] (j) the same spheres from (i) visualized as individual spheres;[278] (k) Helical columnar dendronized polymers and (l) their self-organization into columnar hexagonal arrays upon heating.[306]

cance of X-ray "photo 51" of Rosalind Franklin from Figure 10c for the determination of the double-helix of DNA and the above statement of Crick once he had solved the helical diffraction theory. Additional difficulties but also solutions to the problem are discussed in a previous publication.[70]

Today the solution to a St. Andrews oriented diffraction pattern is provided with computer generated molecular models rather than with hand build models as done by Pauling, Watson, Crick, and the other pioneers of the field (Figures 5, 9, 11, 13, 17). Also, the Cerius2 software is used to simulate the fiber X-ray diffractogram generated from models until the model fits the by simulation the experimental X-ray diffractogram. Therefore, while our laboratory transplanted the methodology used by the CVC helical diffraction theory together with the "photo 51" of Rosalind Franklin to solve the structure of DNA to related synthetic assemblies, a high-resolution X-ray diffractogram with long-range order helical features is still required for the detailed X-ray analysis of a helix. For quite a number of years before the helical diffraction theory was adopted and expanded,[70] it was already used in our laboratory to solve helical structures sometimes even by using lower-resolution oriented fiber X-ray diffractograms. Once high-resolution oriented fiber X-ray diffractograms were accessible, we discovered that columnar structures self-organized from dendronized supramolecular and covalent polymers provide a larger diversity of helical structures than proteins, nucleic acids and carbohydrates. Representative examples are shown in Figure 29.[70] In order to design new functions from helical columnar dendronized supramolecular and covalent polymers the mechanism of self-assembly of helical supramolecular dendrimers was elucidated. The schematics of these mechanisms are illustrated in Figure 30 for single stranded helical columns. A selection of the proper mechanism is required for the design of each function. For example if we want to design an electronically active supramolecular helical assembly we would select from the self-assembly models from Figure 30a, c, d, and g. If we are interested in the design of a trans-membrane protein channel-like assembly or any other kind of membrane we would select from the models illustrated in Figure 30b, e, f. If we are interested in the design of a new molecular machine based on unwinding and winding of helical structures with different pitch, we would select the model from Figure 30g.

8.1 The Hat Shaped Model Self-Organizes Helical Columns that Deracemize in Crystal State. The classic

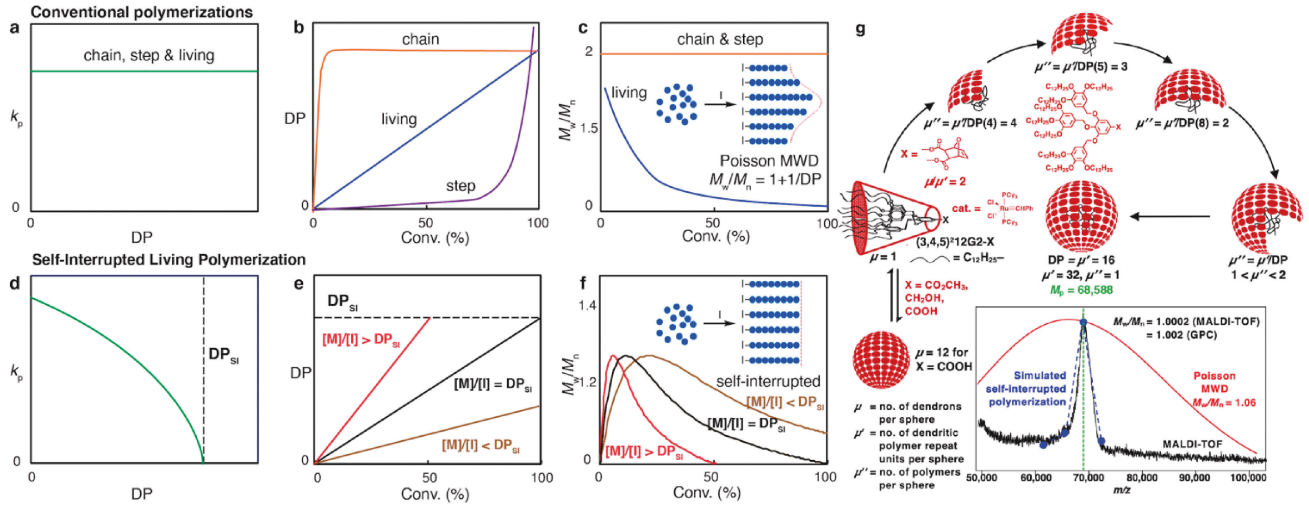

Figure 26. Self-interrupted living polymerization (SILP) provides for the first-time access to monodisperse synthetic macromolecules.[304] Reproduced with permission from ref. 304. Copyright 2020, American Chemical Society.

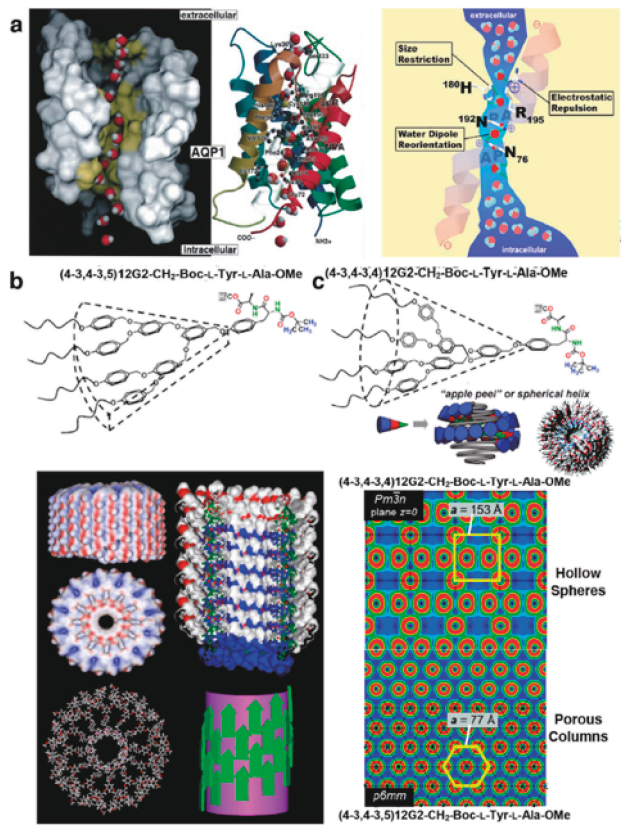

Figure 27. (a) Aquaporin (AQP) channel;[312] Self-organization of constitutional isomeric dendritic dipeptides into (b) helical porous columns[239] and (c) hollow spherical helix.[287]

experiment of Pasteur produced the first deracemization by crystallization from solution.[319] A sufficiently long-range high-order oriented fiber X-ray diffraction pattern of a helical column self-assembled from dendronized cyclotriveratrilene (CTV) (Figure 31)[320] selected from libraries of dendronized CTV[293] facilitated for the first time the complete structural analysis of a supramolecular helical column, including the detailed arrangement of its alkyl groups.

Substituted CTV are well known to self-organize helical pyramidal columns forming columnar hexagonal[293,321,322] and helical spheres.[293] Simulation of numerous columnar hexagonal periodic arrays self-organized from a diversity of helical columns was investigated. Three of these models together with their simulated oriented fiber X-ray diffractograms are shown in Figure 32. Out of them only model 3 generated from triple 12_1 helix obtained from hat-shaped columns provides a perfect match of the experimental X-ray diffractogram (compare l and m in Figure 32). The more detailed hat-shape based helical column generated from both enantiomerically pure structures are shown in Figure 33. The corresponding racemic oriented fiber X-ray diffractogram is missing the odd-number layer line reflections both in the simulated (Figure 33b) and in the experimental diffractogram. This is understandable since the unit cell of a hexagonal column consists of a single helical column or four quarters of four columns (Figures 33, 34). Therefore, the lowest free energy of a columnar hexagonal crystal lattice will generate the highest degree of crystallinity when all columns self-organizing their lattice exhibit the same helical sense. If the interaction between the hat-shaped molecules is not as strong as in the case of dendritic dipeptides that are strongly H-bonded,[239,314] deracemization will facilitate crystallization. A combination of X-ray and solid-state NMR analysis showed that at 60 °C in the crystal state the hat-conformation adopts a transient disc-like conformation that is able to exit the columns and exchange between columns (Figure 34). This mechanism provides access to deracemization in the crystal state. Analysis of the experimental oriented fiber X-ray and the transition from the racemic low order crystal to a homochiral high order crystal is illustrated in Figure 34. The odd number layer lines missing in the racemic structure appear during annealing at 60 °C for 2 hours and the racemic low columnar hexagonal crystal becomes homochiral high order crystal (Figure 34). Polymer chemists name racemic polymers atactic and homochiral poly-

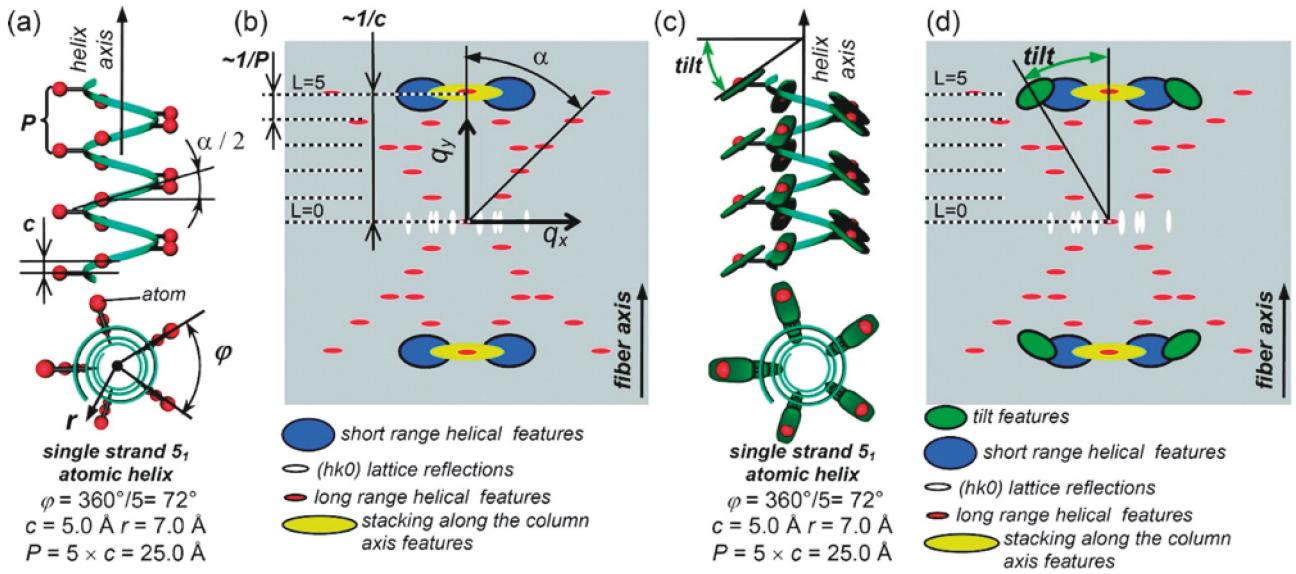

Figure 28. (a, b) Helical diffraction theory applied to a single strand 5_1 atomic helix and (c, d) to a 5_1 group of atoms some of them tilted as in dendrimers helix.[70] Reproduced with permission from ref. 70. Copyright 2008, American Chemical Society.

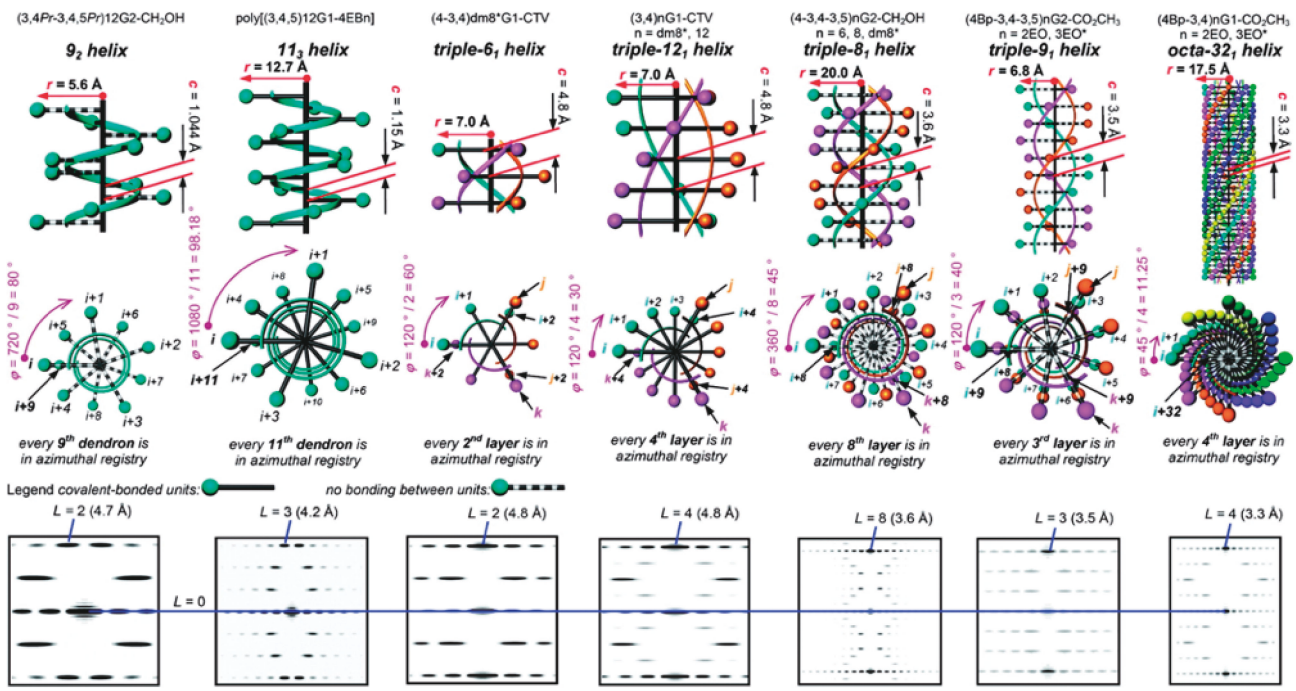

Figure 29. A library of helical structures discovered in helical dendronized supramolecular and covalent dendrimers.[70] Reproduced with permission from ref. 70. Copyright 2008, American Chemical Society.

mers isotactic while syndiotactic are heterochiral polymers (see Figure 34a). Therefore, this deracemization mechanism provides in fact a transition of an atactic dynamic supramolecular polymer into an isotactic dynamic supramolecular polymer. These dynamic supramolecular polymers behave exactly like the covalent polymers elaborated by Giulio Natta *via* stereospecific or Ziegler-Natta polymerization. The atactic or racemic is low crystallinity while the homochiral or isotactic is highly crystalline. The only difference between these dynamic supramolecular polymers and the covalent polymers is that the dynamic supramolecular polymers exhibit a reversible stereochemistry and crystallinity while the covalent do not.

8.2 The Hat Shaped Model Self-Organizes Helical Columns that Deracemize in Crystal State. The cogwheel mechanism of self-organization provides an unprecedented pathway to generate supramolecular helical structures forming highly ordered columnar hexagonal crystals, regardless of the chirality of their building blocks. According to our knowledge this mechanism is not known in biology (Figure 35).[323] It was discovered after scanning through numerous libraries of self-

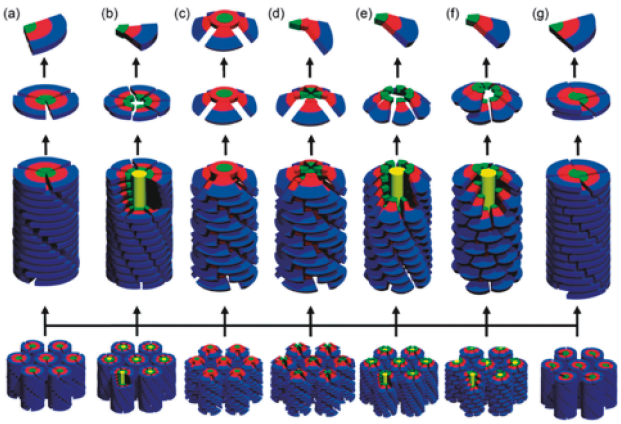

Figure 30. The mechanism of self-assembly of helical columns from self-assembling dendrimers and their self-organized columns.[70] Reproduced with permission from ref. 70. Copyright 2008, American Chemical Society.

assembling dendronized perylene bisimides (PBI).[324–328] The mechanism of self-organization was investigated both in solution and in bulk state and is illustrated in Figure 35. In the first step dimers of dendronized PBIs are assembled. The angle between the two PBIs in the dimer is 45°. Subsequently the dimers self-organize into a low ordered helical column forming

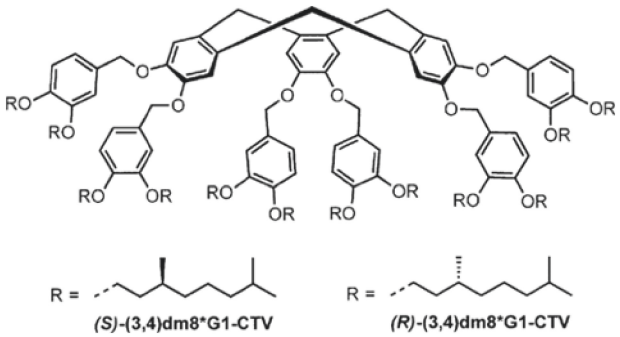

Figure 31. Helical columns self-assembled from dendronized CTV forming hat-shaped molecules.[320]

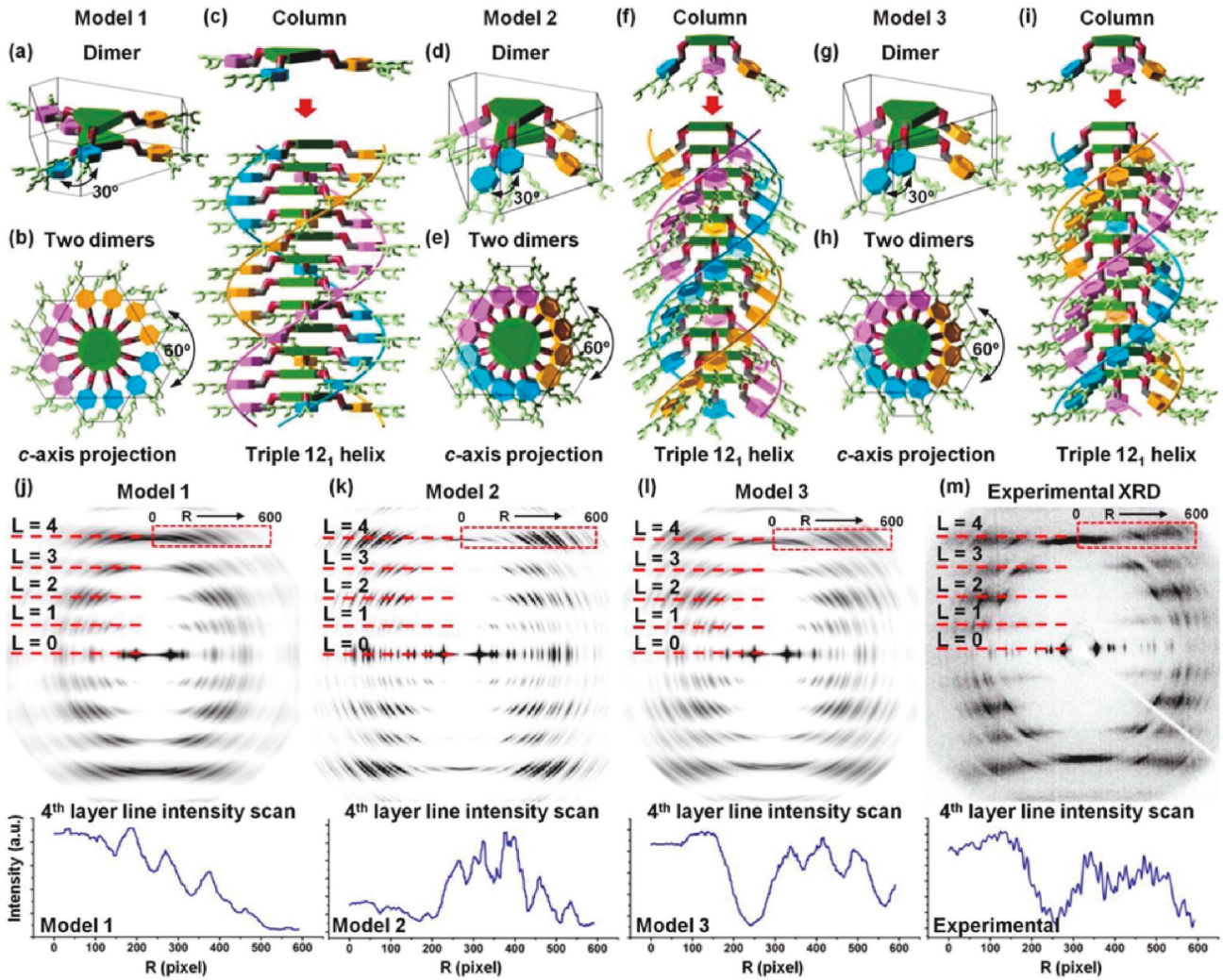

Figure 32. Elucidation of the mechanism of self-assembly and self-organization of helical columns from hat-shaped molecules via the simulation of their X-ray diffractograms with various molecular models.[320] Reproduced with permission from ref. 320. Copyright 2014, American Chemical Society.

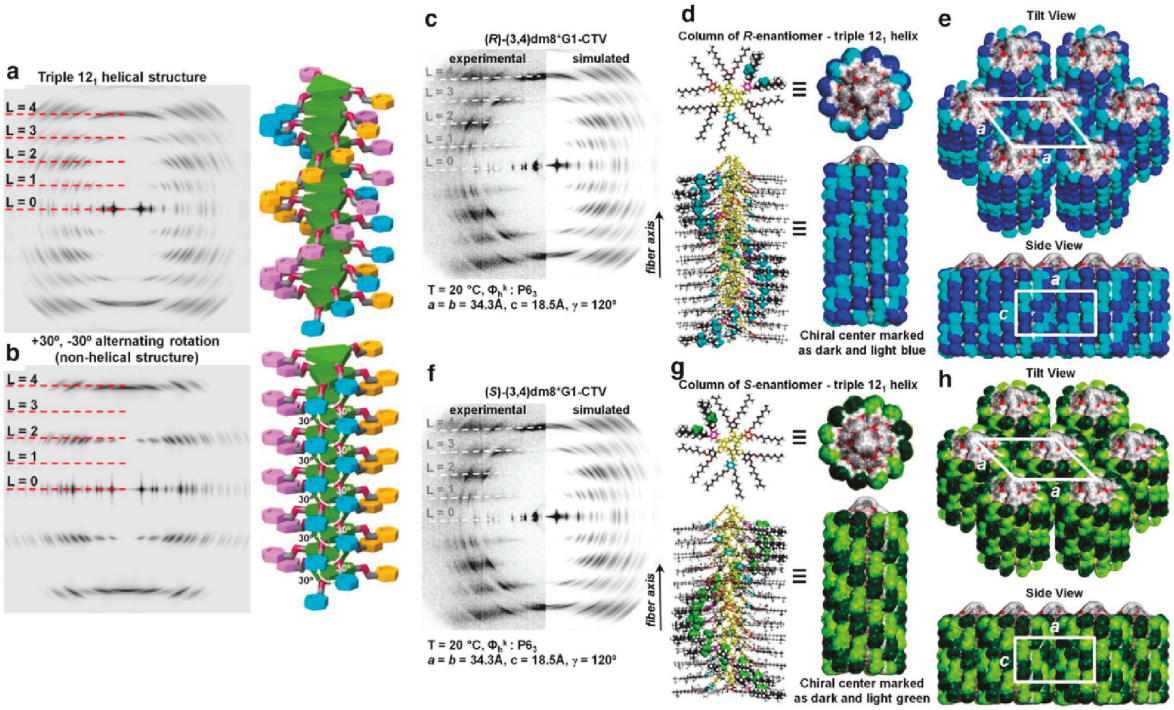

Figure 33. Simulation of the schematically illustrated homochiral (a) and racemic (b) models from the right side with the experimental X-ray helical structure of hat-shaped molecules. Helical columns and their columnar hexagonal periodic arrays self-organized from enantiomerically pure hat-shaped molecules. Simulation of their oriented fiber experimental diffractograms (c, f) by the molecular models shown (d, g) and their lattices (e, h).[320] Reproduced with permission from ref. 320. Copyright 2014, American Chemical Society.

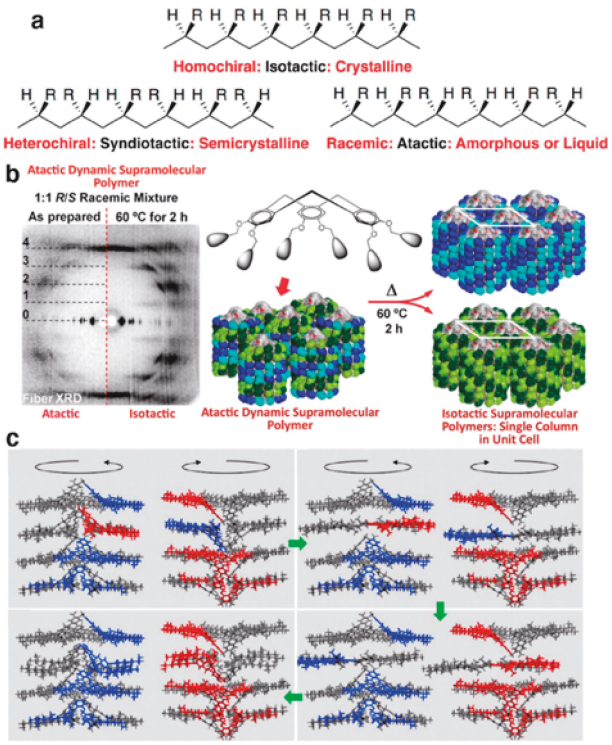

Figure 34. Homochiral dynamic supramolecular polymers by stereo-sequence rearrangement of dynamic racemic polymers in crystal state.[320] Reproduced with permission from ref. 320. Copyright 2014, American Chemical Society.

a columnar hexagonal lattice, Φ_h^{k1}, upon extremely slow cooling of 1 °C/minute the low order column, Φ_h^{k1}, rearranges into a high-order column, Φ_h^{k2}. The main difference between Φ_h^{k1} and Φ_h^{k2} consist in the fact that in Φ_h^{k1} the column is generated from dimers of PBI that are arranged of the column axis while in Φ_h^{k2} they are arranged along the column axis. In both columns there is a 90° rotation of the dimers along the column axis. Both in Φ_h^{k1} and in Φ_h^{k2} the alkyl groups of the dendron are parallel to the column axis with their two methyl groups facing the inner part of the column. The main requirement for this column is that the length of the alkyl group attached to the dendron is equal to the half pitch of the helical column. The Φ_h^{k2} phase was discovered by accident while annealing in the X-ray diffraction machine the Φ_h^{k1} phase.

Figure 36 illustrates similarities and differences between a single stranded and a double stranded supramolecular helix that is less common than a covalently linked double helix such as DNA. Without any additional explanation Figure 36 demonstrates schematically the double helix character of the cogwheel self-organization from Figure 35. Figure 37 summarizes DSC traces of the cogwheel helical self-organization generated from dendrons containing only homochiral, or racemic (left side of the column) and linear alkyl groups (right side of the Figure). The cowheel Φ_h^{k2} phase is obtained only after heating and cooling at 1 °C/minute or after annealing at 100 °C for 3 hours. The replacement of all dimethyloctyl (dm8* respectively r when it is racemic) branched alkyl groups (left side of Figure 37) with linear *n*-alkyl groups (right side of Figure 37) eliminates completely the formation of the cogwheel mecha-

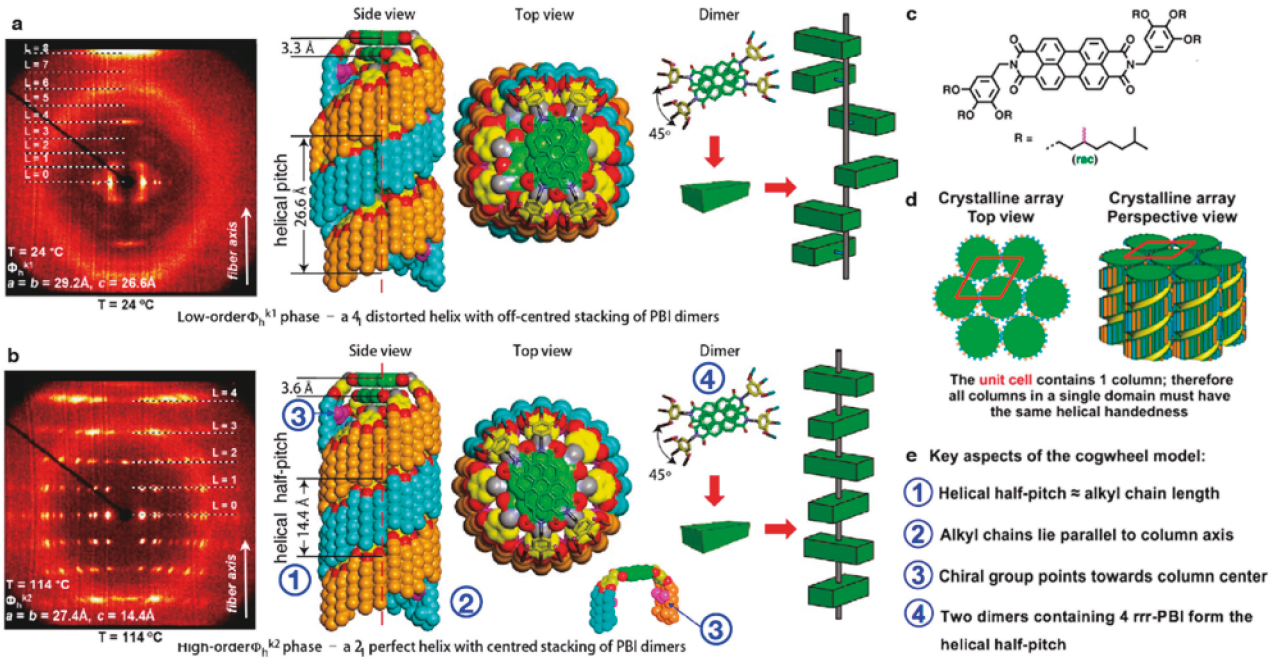

Figure 35. The cogwheel model of helical column self-organization disregards chirality.[323,327] Reproduced with permission from ref. 323, 327. Copyright 2016, Springer Nature, and 2019, American Chemical Society.

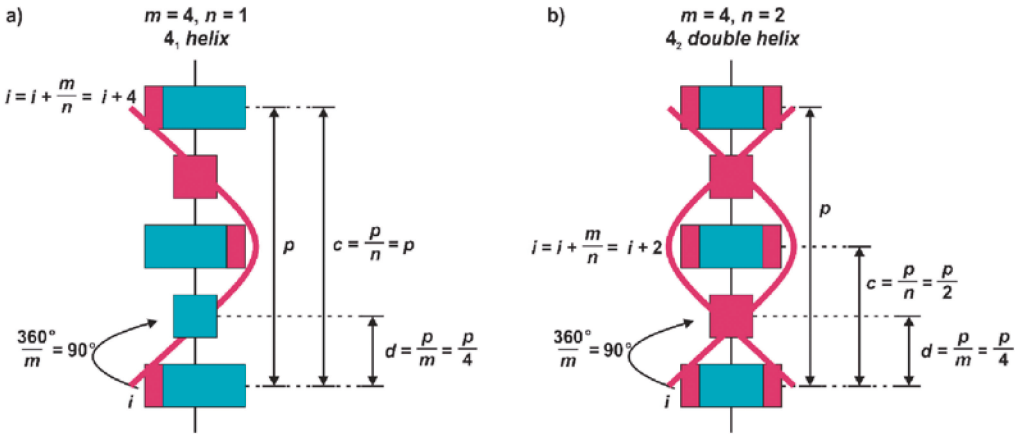

Figure 36. Comparison of supramolecular single helix (left side) with double helix (right side).[323] Reproduced with permission from ref. 323. Copyright 2016, Springer Nature.

nism of helical self-organization.[323–326] In order to potentially increase the rate of transition from the Φ_h^{k1} to the Φ_h^{k2} phase all possible compositions and sequence-defined dendrons including constitutional isomeric sequences containing hybrid branched dm8* and linear *n*-alkyl (C_nH_{2n+1}) with n = 6, 7, 8, 9 and 10 components were synthesized by iterative synthesis and the structure of the resulting supramolecular structures were investigated.[327,328] A first positive result was obtained with r8r-PBI and rr8-PBI constitutional isomers. Both of them showed the formation of the Φ_h^{k2} phase even with a rate of heating and cooling of 10 °C/min but Φ_h^{k2} was observed only on heating, the rr8-PBI exhibiting a higher enthalpy associated with the phase transition from Φ_h^{k2} to Φ_h^{k1} than its constitutional isomer r8r-PBI. This dramatic acceleration of the Φ_h^{k2} phase formation by the hybrid PBI could not have been predicted. Solid state NMR analysis demonstrated that locally increased mobility of the stereogenic center mediated by the linear *n*-alkyl neighbor facilitates the faster crystallization.[327] Surprisingly, the 9r9-PBI exhibited an extraordinary acceleration of the cogwheel Φ_h^{k2} helical self-organization to the point that Φ_h^{k2} formation is observed both on heating and on cooling with the faster rate accessible with the current instrumentation, 50 °C/minute. This extraordinary acceleration of the cogwheel Φ_h^{k2} helical self-organization was generated by the 9r9-PBI dendron sequence encoding the ideal tertiary structure of the columnar assembly (Figure 37).[328]

Figure 37 shows the perfect jacketing of the column by the alkyl groups of the 9r9-PBI sequence. This sequence matches perfectly the main requirement of the cogwheel model that demands that the length of the alkyl groups from the periphery of the column must be strictly equal to its helical half pitch (Figure 35). This cogwheel self-organization process is accom-

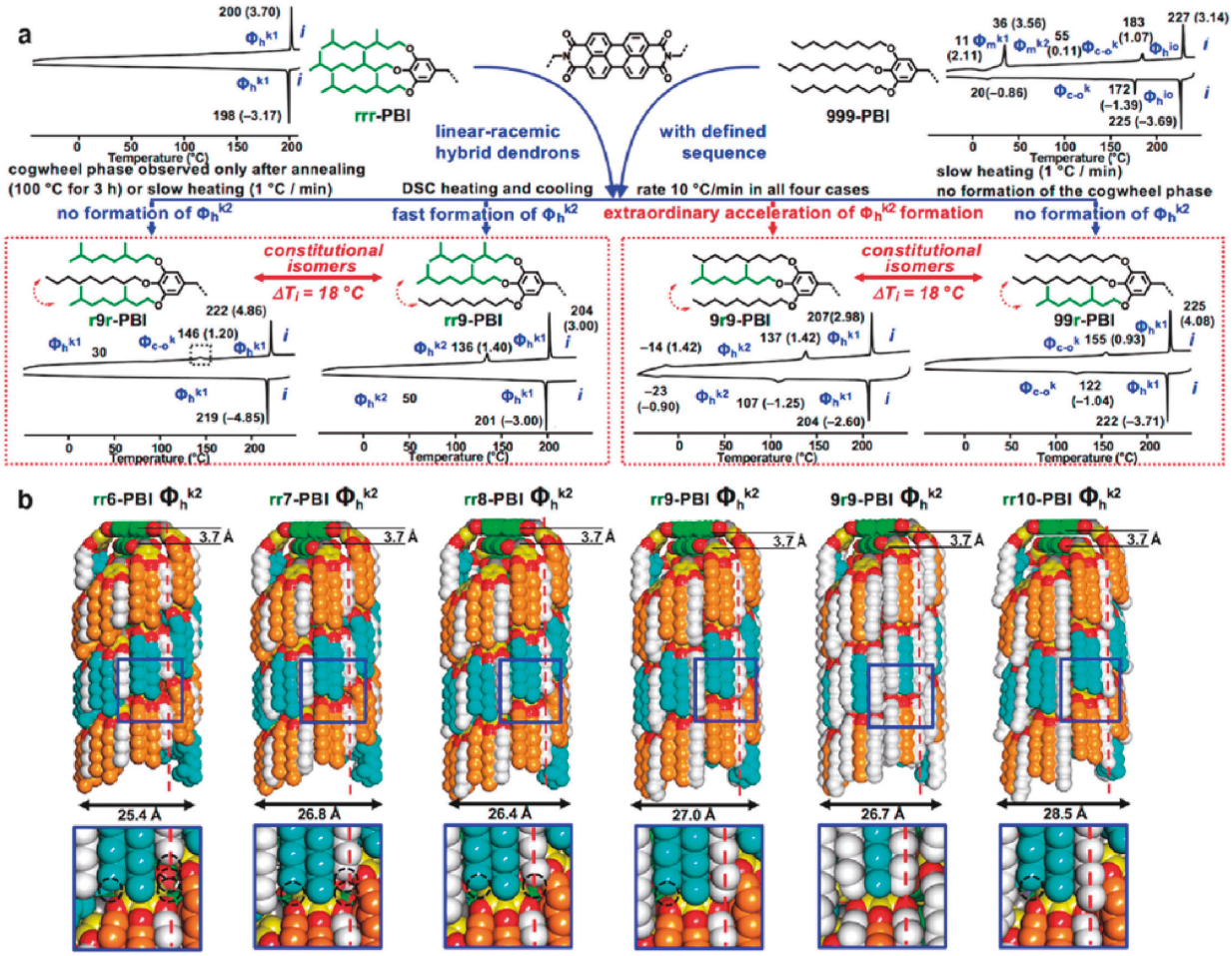

Figure 37. (a) Extraordinary acceleration of self-organization cogwheel helical columns mediated by the sequence of their self-assembling dendrons. (b) Models of cogwheels with different sequences.[328] Reproduced with permission from ref. 328. Copyright 2020, American Chemical Society.

panied by deracemization. However, the mechanism of this deracemization is not completely elucidated and therefore, it will not be discussed here. The search for new systems self-organizing *via* the cogwheel helical self-organization and elucidation of the scope and limitations of this mechanism are under investigation.[329–332]

8.3 More Complex Arrangements of Helical Columns than Biological Coiled-Coils by Supramolecular Orientational Memory (SOM) Effect. Orthogonal, tetrahedral and distorted dodecahedral arrangements of helical columnar hexagonal fragments are designed when a columnar hexagonal lattice is heated to the A15, BCC and A15 Frank-Kasper phases respectively and cooled down again to the columnar hexagonal periodic array (Figure 38).[333–335] At the transition from the columnar hexagonal to the A15 Frank-Kasper and BCC phases the supramolecular columns transform themselves into supramolecular sphere, and on cooling back, to supramolecular columns. When this sequence of phase transitions is performed with oriented fibers of supramolecular columns generated from covalent and supramolecular crown-like conformers a supramolecular orientational memory (SOM) effect occurs.

Covalent crowns mediate the self-organization of orthogonal columnar hexagonal arrays *via* the A15 Frank-Kasper phase while supramolecular crowns provide distorted dodecahedral arrangements *via* the same A15 phase. The reason for this difference is not yet exactly known and we will not speculate on its potential hypothesis here. It is however known that A15 and BCC phases generated from conical dendrons do not provide this SOM effect. An explanation for this concept was provided.[335] During cooling from the A15 and BCC phases the nucleation of the direction of formation of columns from spheres occurs on the directions of the close contact spheres from these lattices (Figure 38) and this nucleation process memorizes the orientations of the close contact spheres orientations in the columnar hexagonal arrangement of columns. These unprecedented arrangements of helical columnar hexagonal fragments are, according to the best of our knowledge, not available in biology. At the transition from columnar hexagonal columns to A15 Frank-Kasper and BCC phases and back to the columnar hexagonal array a transient architecture must consist of columns generated from helical chiral spheres. This column from helical spheres was indeed been observed for the first time as a transient structure during the SOM process[334] and subsequently as thermodynamically stable helical supramolecular columns assembled from helical chiral spheres self-organized from crown-conformers.[329,336] A half SOM

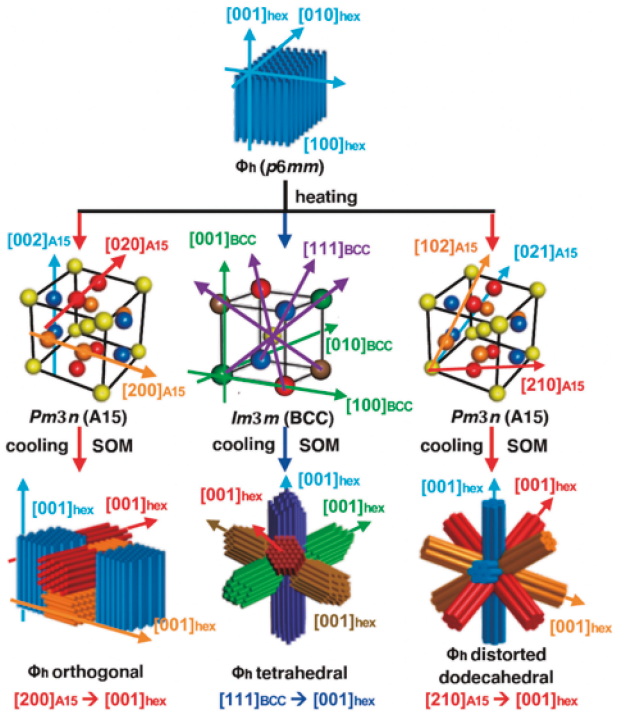

Figure 38. Orthogonal, tetrahedral and distorted dodecahedral arrangements of arrays of supramolecular helical columnar hexagonal arrays mediated by the supramolecular orientational memory effects at the transition from columnar hexagonal to Frank-Kasper phases and back to hexagonal.[333–335]

effect observed only on heating from the columnar hexagonal to the Frank-Casper phase but not on cooling was also observed.[270,286,337] One of the most surprising discoveries was that micellar-like spheres self-assembled from conical dendrons are also helical and therefore chiral.[338] A supramolecular helical chiral sphere self-assembled from 480 conical dendrons of total molar mass of 1.1×10^6 g/mol, that is in the size range of globular proteins, was recently reported.[338]

9. Will Synthetic Biology and Chemistry Ever Equal and Even Exceed the Precision and the Complexity of Biology?

We have no doubt that the answer to this question is yes. However, its time scale will depend on nothing but the dedication and the enthusiasm of the young generation of scientists and much less on the level of research funding and that of the research facilities available. With the enthusiasm of the Cavendish lab from Cambridge U, Caltech and King's College from the early 1950th the time scale of this process could be very short.

This Account is dedicated to the 70th anniversary of professor Eiichi Nakamura for his tremendous contributions to the development of the field of synthetic and supramolecular chemistry. We hope that he will like this Account as much as we liked his lectures including the one from the poster presented in Figure 39.

This work was supported by National Science Foundation Grants DMR-1807127 and DMR-1720530, the P. Roy Vagelos

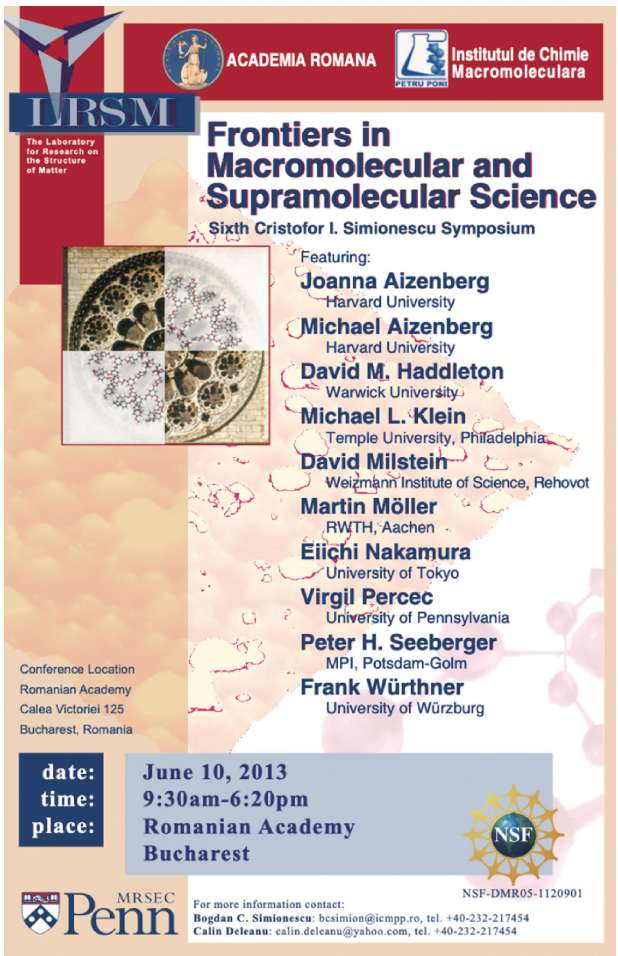

Figure 39. The poster of the Sixth Symposium Frontiers in Macromolecular and Supramolecular Science from 2013 with Professors Eiichi Nakamura and Virgil Percec as plenary speakers.

Chair at the University of Pennsylvania, and the Alexander von Humboldt Foundation.

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Dedicated to Professor Eiichi Nakamura on the occasion of his 70th birthday.

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