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Supramolecular Hybrid Organic-Inorganic Multicomponent Architectures in Solution and on Surface

Presentata dal Dott. Omar Pandoli

Coordinatore Dottorato — **Prof. Maurizio Recanatini**

Relatore — **Prof. Gian Piero Spada**

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Contents

Abstract

Supramolecular architectures can be built-up from a single molecular component (building block) to obtain a complex of organic or inorganic interactions creating a new emergent condensed phase of matter, such as gels, liquid crystals and solid crystal. Further the generation of multicomponent supramolecular hybrid architecture, a mix of organic and inorganic components, increases the complexity of the condensed aggregate with functional properties useful for important areas of research, like material science, medicine and nanotechnology.

One may design a molecule storing a recognition pattern and programming a informed self-organization process enables to grow-up into a hierarchical architecture. From a molecular level to a supramolecular level, in a bottom-up fashion, it is possible to create a new emergent structure-function, where the system, as a whole, is open to its own environment to exchange energy, matter and information. “The emergent property of the whole assembly is superior to the sum of a singles parts”.

In this thesis I present new architectures and functional materials built through the self-assembly of guanosine, in the absence or in the presence of a cation, in solution and on the surface.

By appropriate manipulation of intermolecular non-covalent interactions the spatial (structural) and temporal (dynamic) features of these supramolecular architectures are controlled.

Guanosine **G7** (5',3'-di-decanoil-deoxi-guanosine) is able to interconvert reversibly between a supramolecular polymer and a discrete octameric species by dynamic cation binding and release.

Guanosine **G16** (2',3'-O-Isopropylidene-5'-O-decylguanosine) shows selectivity binding from a mix of different cation's nature.

Remarkably, reversibility, selectivity, adaptability and serendipity are mutual features to appreciate the creativity of a molecular self-organization complex system into a multilevel-scale hierarchical growth.

The creativity - in general sense, the creation of a new thing, a new thinking, a new functionality or a new structure - emerges from a contamination process of different disciplines such as biology, chemistry, physics, architecture, design, philosophy and science of complexity.

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Alle Donne della mia Famiglia

Filomena

Natalina

Angelica

Giorgia

Dalila

e

In memoria

Di mia Nonna

1. Self-organization into biological chemistry

> *Self-organization is the driving force that led up to the evolution of the biological world from inanimate matter*
>
> *Manfred Eigen*

1.1 Introduction

What is the difference between the organic chemistry and the biological chemistry?

Ilya Prigonie in a conference regard the issue of the time answered:

> *"the difference between the organic chemistry and the biological chemistry is that into biological chemistry molecules, such as DNA , are molecules that are a history, and that, with their structure they speak to us about the past in which they were constituted. They are fossils, or some history testimonials, while an organic molecule created today is a testimonial of the present and it hasn't had a historic evolution."*

The Nobel Laureate Price Giulio Natta tried to understand how the irreversibility of the ambient is fixed on the molecular order of a polimer. When we look a snow crystal, we can observe the structure and guess in which atmospheric condition it has been formed: if it was a cold atmosphere, or more less saturated and so on. One day, looking a molecule of the life, a DNA or a polimer, we could understand in what geological or biological circumstances these molecules have been formed.

The second question is: *how is it possible to impress the time and the external ambient conditions into matter?*

1.2 Thesis organisation

This thesis is organized into five chapters. Chapter 1 gives insight into the self-organization in biological chemistry and gives an introduction to practical notion of complexity and self-organization of living-system. Basic consideration of the Prigonie's dissipation structure are presented. All living system are considered open system enable to exchange energy, matter and information with their environment. On Prigonie's theory a non-equilibrium process of a open-system is connected spatially and temporally to their surrounding. In the end of chapter 1, the bases of the eastern thought useful to understand the nature of the matter and the cycle process of the *Dao* are presented.

Chapter 2 highlights the goals of supramolecular chemistry which gains the progressive control over the complex spatial (structural) and temporal (dynamic) features of matter through self-organization. Self-organization offers the full range of self-processes that

determines the internal build-up, the functional integration and the operation of the entities (building blocks) as well as its external connections to the environment.

Chapter 3 discusses how the guanosine derivatives have been used for the non-covalent synthesis of new nanostructures and biomaterials in solution and at surface. Strategies to build functional materials utilising both monotopic guanosine or ditopic guanosine derivatives are shown.

Chapter 4 describes the core of my PhD's work.

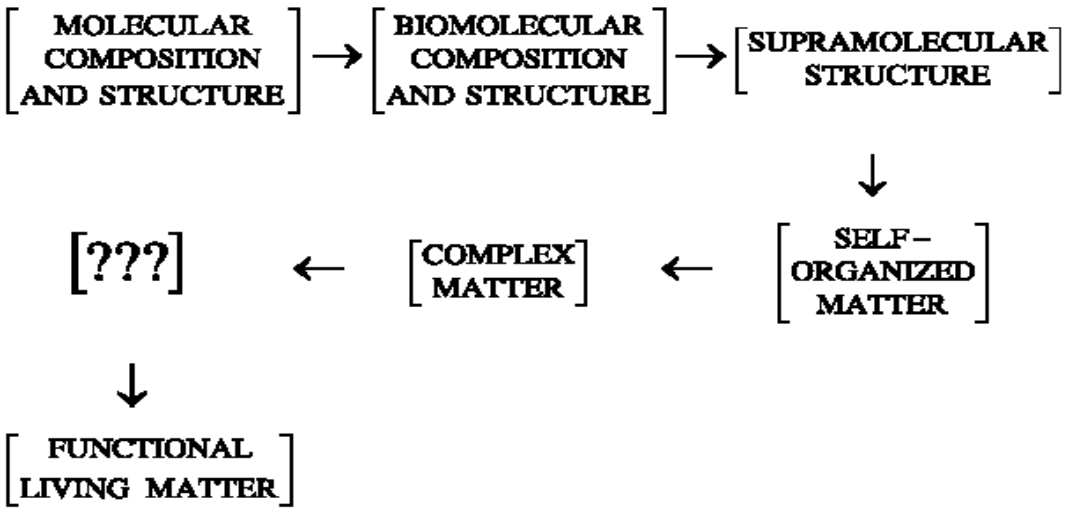
Chapter 5 describes future directions in this field of the supramolecular basic research.

1.3 How does life process work?

In 2006 a fascinating review[1] summarizes the scientific issues of the operational and mechanistic description of life, the conditions and constraints of prebiotic chemistry, together with bottom-up molecular fabrication and biomolecular nanofabrication and top-down miniaturization approaches to the origin of terrestrial life. From this lecture a lot of questions are still open about the central role of the molecular self-organization processes for the constitution of the complex biological matter.

Since Schrodinger (1944) asked the question, "*What is life?"*, the advancement of this provocative, scientific–intellectual challenge has acted as an inspiration to generations of scientists and scholars. Schrodinger (1944) asked himself if the life is based on the laws of physics, because the construction and function of living matter requires a new level of description. This hypothesis was transcended by the seminal work of Crick & Watson on the structure of DNA, which established the structure–function relations in biology. Research on the primary processes in bacterial and plant photosynthesis[2a] extended the traditional notion of the structure–function relationship. Dynamic information (in this case, the ultrafast picosecond electron transfer dynamics in the photosynthetic reaction centre) surpasses and complements structural information,[2b] providing the structure–dynamics–function relations for central biological processes, which ensure life on Earth.

The description of functional living matter requires a holistic (collective) conceptual framework[3], with some of its cornerstones being: (i) the ideas of the biologists Onsager & Morowitz[4] on complex matter, (ii) the implementation of the concepts of molecular information at the molecular and supramolecular level.[5,6,7,] and (iii) the central role of self-organization (self-assembly), which leads to the evolution of a 'complex biological matter'.[5,6,7,8,9,10] A heuristic, highly speculative, partial scheme for the emergence of living matter in the 'parameter space' of increasing complexity could be as shown in Scheme 1.



Scheme 1.1 (Adapted from reference 1)

The attributes marked by [???] are unknown, being the most fascinating. The question 'What is life?' is not only an extremely difficult question,[4,7,9,11,12,13] but also perhaps not the right question.[5,14] It is a popular game in this field to provide robust counter examples, which reveal failures in operational definitions.[4,7,8,14,] Sagan[15](1998) catalogues a list of failed attempts, including physiological, metabolic, biochemical, genetic and thermodynamic definitions of life, all of which face problems.[7,14] For example, a biochemical definition does not exclude enzymes (which are biologically functional but not living systems), while a thermodynamic definition does not exclude mineral crystals (which create and sustain local order and may reproduce). To address the question 'What is life?', one does not require a definition, but requires a scientific theory. [14] A pedagogical example [14] alludes to a much simpler question, *'What is water?'*, which Leonardo da Vinci (1513) faced when he attempted to characterize liquid water in terms of its phenomenological properties. This question could only be answered in the twentieth century with the establishment of the proper molecular composition and the structure of the H_2O molecule, together with the globally condensed phase properties of the liquid, e.g. H-bonding, local order, radial and angular distribution, solvation, structure breaking, nuclear dynamics, phase transitions and response, providing a conceptual framework of an appropriate scientific theory. Regarding the conceptual framework that will provide answers to the question, 'What is life?', Onsager & Morowitz[4] (1978), Eigen[5] (1971), Yates[6] (1987) and Lehn[7] (2003), among others, made important contributions, which will start to address the significant questions regarding the emergence and function of complex biological living matter.

A notable attempt to provide a unified description of living matter was provided by the

Onsager–Morowitz definition[4]: *'Life is that property of matter that results in the cycling of bioelements in aqueous solution, ultimately driven by radiant energy to attain maximum complexity'.*This definition implies that coupled cycles involving homogeneous and/or heterogeneous chemical reactions of bioelements (i.e. prebiotic material, building blocks of biomolecules and functional biomolecular structures) in water, which are driven by the acquisition and disposal of radiant energy, result in the organization of complex matter (with 'maximum complexity' presumably referring to information content). Of course, there is a ubiquity of complex matter (with complexity characterized by spatial, energetic and temporal structures)[16] that is not alive. It appears that the Onsager–Morowitz definition bypasses the characterization of complex biological matter and how it differs from complex chemical matter. Eigen [5] addressed the basic differences between a chemically coupled system and a living system with an abundance of chemical reactions in terms of information storage, retrieval and processing. According to Eigen[5], all reactions in a living system follow a controlled programme operated from an information centre, whose aim is the self-reproduction of the programme itself. The three essential characteristics of all living systems yet known [3,5] are self-reproduction (without which information would be lost), mutations (which allow evolution) and metabolism (which allows an optimal choice of a system for a certain function). Eigen[5], Yates[6] , Lehn[7] and Heckl[8] advanced and developed the concept of self-organization (self-assembly) and proposed that it resulted in the evolution of biological complex matter, which rests on the elements, as follows:

(i) Molecular structure formation of (living and non-living) matter is driven by molecular interactions and operates on a huge diversity of possible structural combinations.

(ii) Prior to the biological evolution, the chemical evolution took place, performing a selection on molecular diversity, leading to the embedment of structural information in chemical entities.

(iii) The implementation of the concepts of molecular information pertains to information storage at the molecular level and the retrieval, transfer and processing of information at the supramolecular level.

(iv) The formation of supramolecular structures is induced by molecular recognition (based on non-covalent intermolecular interactions, e.g. H-bonding, van der Waals interactions, charge transfer in donor–acceptor sequences and interactions in ion coordination sites). This includes self-organization, which allows adaptation and design at the supramolecular level.

(v) Self-organization involves selection in addition to design at the supramolecular level, and may allow the 'target driven selection of the fittest' [7,] leading to biologically active substances.

The arsenal of self-organization of complex biological matter driven by information acquisition, storage, retrieval and transfer, which allows selection, adaptation, self-reproduction, evolution and metabolism[5,6,7] may constitute many of the missing links (marked by [???]) in scheme 1. In particular, the mechanistic aspects of information-driven self-organization and its implications remain to be elucidated and will be subjected to intensive and extensive experimental and theoretical scrutiny in the future. Some significant issues involve the inclusion of dissipative non-equilibrium processes in living systems[17] (see section 1.6) and the 'transition' from programmed and instructed self-organized systems to 'learning' systems, which can be trained.[7]

1.4 Where can we recognise the life in a system?

To answer this question Capra[18] help us to understand, from a strictly scientific perspective, the life as a biological phenomenon. If Schrodinger's question was "What is life?", Capra rephrased the question as:

"What are the defining characteristics of living systems?"

When we look at the enormous variety of living organisms-animals, plants, people, microorganisms we immediately make an important discovery: all biological life consists of cells. Without cells, there is no life on this Earth. This may not always have been so but today we can say confidently that all life involves cells.

This discovery allows us to adopt a strategy that is typical of the scientific method. To identify the defining characteristics of life, we look for and then study the simplest system that displays these characteristics. This reductionist strategy has proved very effective in science, but no one have to fall into the trap of thinking that complex entities are nothing but the sum of their simpler parts.

Since we know that all living organisms are either single cells or multicellular, we know that the simplest living system is the cell! More precisely, it is a bacterial cell. We know today that all higher forms of life have evolved from bacterial cells. The simplest of these belong to a family of tiny spherical bacteria known as mycoplasm, with diameters less than a thousandth of a millimeter and genomes consisting of a single closed loop of double-stranded DNA.[4] Yet even in these minimal cells, *a complex network of metabolic processes** is ceaselessly at work transporting nutrients in and waste out of the cell, and continually using food molecules to build proteins and other cell components (*Metabolism, from the Greek metabole ("change"), is the sum of biochemical processes involved in life).

Although mycoplasm are minimal cells in terms of their internal simplicity, they can only

survive in a precise and rather complex chemical environment. As biologist Harold Morowitz pointed out, this means that we need to distinguish between two kinds of cellular simplicity. Internal simplicity means that the biochemistry of the organism's internal environment is simple, while ecological simplicity means that the organism makes few chemical demands on its external environment.

From the ecological point of view, the simplest bacteria are the cyanobacteria, the ancestors of blue-green algae, which are also among the oldest bacteria, their chemical traces being present in the earliest fossils. Some of these blue-green bacteria are able to build up their organic compounds entirely from carbon dioxide, water, nitrogen and pure minerals. Interestingly, their great ecological simplicity seems to require a certain amount of internal biochemical complexity.

1.4.1 The Ecological Perspective

The relationship between internal and ecological simplicity is still poorly understood, partly because most biologists are not used to the ecological perspective. As Morowitz explains:

> *Sustained life is a property of an ecological system rather than a single organism or species. Traditional biology has tended to concentrate attention on individual organisms rather than on the biological continuum. The origin of life is thus looked for as a unique event in which an organism arises from the surrounding milieu. A more ecologically balanced point of view would examine the proto-ecological cycles and subsequent chemical systems that must have developed and flourished while objects resembling organisms appeared.*[4]

No individual organism can exist in isolation. Animals depend on the photosynthesis of plants for their energy needs; plants depend on the carbon dioxide produced by animals, as well as on the nitrogen fixed by the bacteria at their roots; and together plants, animals and microorganisms regulate the entire biosphere and maintain the conditions conducive to life. According to the Gaia theory of James Lovelock and Lynn Margulis,[19,20] the evolution of the first living organisms proceded with the transformation of the planetary surface from an inorganic environment to a self-regulating biosphere. "In that sense," wrote Harold Morowitz, *"life is a property of planets rather than of individual organisms."*[4]

1.4.2 Life Defined in Terms of DNA

How does a bacterial cell work? What are its defining characteristics? When we look at a

cell under an electron microscope, we notice that its metabolic processes involve special macromolecules-very large molecules consisting of long chains of hundreds of atoms. Two kinds of these macromolecules are found in all cells: proteins and nucleic acids (DNA and RNA).

In the bacterial cell, there are essentially two types of proteins-enzymes, which act as catalysts of various metabolic processes, and structural proteins, which are part of the cell structure. In higher organisms, there are also many other types of proteins with specialized functions, such as the antibodies of the immune system or the hormones.

Since most metabolic processes are catalyzed by enzymes and enzymes are specified by genes, the cellular processes are genetically controlled, which gives them great stability. The RNA molecules serve as messengers, delivering coded information for the synthesis of enzymes from the DNA, thus establishing the critical link between the cell's genetic and metabolic features.

DNA is also responsible for the cell's self-replication, which is a crucial characteristic of life. Without it, any accidentally formed structures would have decayed and disappeared, and life could never have evolved. This overriding importance of DNA might suggest that it should be identified as the single defining characteristic of life. We might simply say: *"Living systems are chemical systems that contain DNA."*

The problem with this definition is that dead cells also contain DNA. Indeed, DNA molecules may be preserved for hundreds, even thousands, of years after the organism dies. A spectacular example of such a case was reported a few years ago, when scientists in Germany succeeded in identifying the precise gene sequence in DNA from a Neanderthal skull-bones that had been dead for over 100,000 years![21] Thus, the presence of DNA alone is not sufficient to define life. At the very least, our definition would have to be modified to: *"Living systems are chemical systems that contain DNA, and which are not dead."* But then we would be saying, essentially, "a living system is a system that is alive"-a mere tautology.

This little exercise shows us that the molecular structures of the cell are not sufficient for the definition of life. We also need to describe the cell's metabolic processes, in other words, the patterns of relationships between the macromolecules. In this approach, we focus on the cell as a whole rather than on its parts. According to the biochemist Pier Luigi Luisi, whose special field of research is molecular evolution and the origin of life, these two approaches, the "DNA-centered" view and the "cell-centered" view, represent two main philosophical and experimental streams in life sciences today.[22]

1.4.3 Membranes-The Foundation of Cellular Identity

Now if we look at the cell as a whole, a cell is characterized, first of all, by a boundary (the cell membrane) which discriminates between the system (the "self,") and its environment. Within this boundary, there is a network of chemical reactions (the cell's metabolism) by which the system sustains itself.

Most cells have other boundaries besides membranes, such as rigid cell walls or capsules. These are common features in many kinds of cells, but only membranes are a universal feature of cellular life. Since its beginning, life on Earth has been associated with water. Bacteria move in water, and the metabolism inside their membranes takes place in a watery environment. In such fluid surroundings, a cell could never persist as a distinct entity without a physical barrier against free diffusion. The existence of membranes is therefore an essential condition for cellular life. Membranes are not only a universal characteristic of life, but also display the same type of structure throughout the living world. We shall see that the molecular details of this universal membrane structure hold important clues about the origin of life.

A membrane is very different from a cell wall. Whereas cell walls are rigid structures, membranes are always active, opening and closing continually, keeping certain substances out and letting others in. The cell's metabolic reactions involve a variety of ions, and the membrane, by being semipermeable, controls their proportions and keeps them in balance. Another critical activity of the membrane is to continually pump out excessive calcium waste, so that the calcium remaining within the cell is kept at the precise, very low level required for its metabolic functions. All these activities help to maintain the cell as a distinct entity and protect it from harmful environmental influences. Indeed, the first thing a bacterium does when it is attacked by another organism is to make membranes.[23]

At the cellular level, the cell membrane plays a important role. It regulates molecular compositions and, in doing so, maintains the cellular identity.

1.4.4 Self-generation

The cell membrane is the first defining characteristic of cellular life. *The second characteristic is the nature of the metabolism that takes place within the cell boundary*. In the words of the microbiologist Lynn Margulis:

> *"Metabolism, the incessant chemistry of self-maintenance, is an essential feature of life ... Through ceaseless metabolism, through chemical and energy flow, life continuously produces, repairs, and perpetuates itself. Only cells, and organisms composed of cells,*

metabolize. "[23]

When we take a closer look at the processes of metabolism, we notice that they form a chemical network. This is another fundamental feature of life. As ecosystems are understood in terms of food webs (networks of organisms), so organisms are viewed as networks of cells, organs and organ systems, and cells as networks of molecules. One of the key insights of the systems approach has been the realization that the network is a pattern that is common to all life. *Wherever we see life, we see networks.*

The metabolic network of a cell involves very special dynamics that differ strikingly from the cell's nonliving environment. Taking in nutrients from the outside world, the cell sustains itself by means of a network of chemical reactions that take place inside the boundary and produce all of the cell's components, including those of the boundary itself.

The function of each component in this network is to transform or replace other components, so that the entire network continually generates itself. *This is the key to the systemic definition of life: living networks continually create, or re-create, themselves by transforming or replacing their components*. In this way they undergo continual structural changes while preserving their web like patterns of organization.

T*he dynamic of self-generation was identified as a key characteristic of life* by biologists Humberto Maturana and Francisco Varela, who gave it the name *"autopoiesis"* (literally, "self-making").[3,20] The concept of autopoiesis combines the two defining characteristics of cellular life mentioned above, the physical boundary and the metabolic network. Unlike the surfaces of crystals or large molecules, the boundary of an autopoietic system is chemically distinct from the rest of the system, and it participates in metabolic processes by assembling itself and by selectively filtering incoming and outgoing molecules.[22]

The definition of a living system as an autopoietic network means that the phenomenon of life has to be understood as a property of the system as a whole. In the words of Pier Luigi Luisi,

> *"Life cannot be ascribed to any single molecular component (not even DNA or RNA!) but only to the entire bounded metabolic network."*

Autopoiesis provides a clear and powerful criterion for distinguishing between living and nonliving systems. For example, it tells us that viruses are not alive, because they lack their own metabolism. Outside living cells, viruses are inert molecular structures consisting of proteins and nucleic acids. A virus is essentially a chemical message that needs the metabolism of a living host cell to produce new virus particles, according to the instructions encoded in its DNA or RNA. The new particles are not built within the boundary of the virus

itself, but outside in the host cell.

Similarly, a robot that assembles other robots out of parts that are built by some other machines cannot be considered living. In recent years, it has often been suggested that computers and other automata may constitute future life-forms. However, unless they were able to synthesize their components from "food molecules" in their environment, they could not be considered to be alive according to our definition of life.[4]

1.4.5 The Cellular Network

As soon as we begin to describe the metabolic network of a cell in detail, we see that it is very complex indeed, even for the simplest bacteria. Most metabolic processes are facilitated (catalyzed) by enzymes and receive energy through special phosphate molecules known as ATP. The enzymes alone form an intricate network of catalytic reactions, and the ATP molecules form a corresponding energy network.[20]Through the messenger RNA, both of these networks are linked to the genome (the cell's DNA molecules), which is itself a complex interconnected web, rich in feedback loops, in which genes directly and indirectly regulate each other's activity.

Biological forms and functions are not simply determined by a genetic blueprint, but are emergent properties of the entire epigenetic* network. *(From the Greek epi "above" or "beside"). To understand their emergence, we need to understand not only the genetic structures and the cell's biochemistry, but also the complex dynamics that unfold when the epigenetic network encounters the physical and chemical constraints of its environment. According to nonlinear dynamics, the new mathematics of complexity (see section 1.5), this encounter will result in a limited number of possible functions and forms, described mathematically by attractors: complex geometric patterns that represent the system's dynamic properties.[20]

Biologist Brian Goodwin and mathematician Ian Stewart have taken important steps in using nonlinear dynamics to explain the emergence of biological form.[24,25] According to Stewart, this will be one of the most fruitful areas of science in the years to come:

> *I predict-and I am by no means alone-that one of the most exciting growth areas of twenty-first-century science will be biomathematics. The next century will witness an explosion of new mathematical concepts, of new kinds of mathematics, brought into being by the need to understand the patterns of the living world.* [25]

This view is quite different from the genetic determinism that is still very widespread among molecular biologists, biotechnology companies and in the popular scientific press.

Most people tend to believe that biological form is determined by a genetic blueprint, and that all the information about cellular processes is passed on to the next generation through the DNA when a cell divides and its DNA replicates. This is not at all what happens.

When a cell reproduces, it passes on not only its genes, but also its membranes, enzymes, organelles-in short, the whole cellular network. The new cell is not produced from naked DNA, but from an unbroken continuation of the entire autopoietic network. Naked DNA is never passed on, because genes can only function when they are embedded in the epigenetic network. Thus life has unfolded for over three billion years in an uninterrupted process, without ever breaking the basic pattern of its self-generating networks.

1.4.6 Emergence of New Order

The theory of autopoiesis identifies the pattern of self-generating networks as a defining characteristic of life, but it does not provide a detailed description of the physics and chemistry that are involved in these networks. As we have seen, such a description is crucial to understanding the emergence of biological forms and functions.

The starting point for this is the observation that all cellular structures exist far from thermodynamic equilibrium and would soon decay toward the equilibrium state (in other words, the cell would die) if the cellular metabolism did not use a continual flow of energy to restore structures as fast as they are decaying. This means that we need to describe the cell as an open system. Living systems are organizationally closed (they are autopoietic networks) but materially and energetically open. They need to feed on continual flows of matter and energy from their environment to stay alive. Conversely, cells, like all living organisms, continually produce waste, and this flow-through of matter (food and waste) establishes their place in the food web. In the words of Lynn Margulis:

> *"The cell has an automatic relationship with somebody else. It leaks something, and somebody else will eat it."*[23]

Detailed studies of the flow of matter and energy through complex systems have resulted in the theory of dissipative structures developed by Ilya Prigogine and his collaborators (see section 1.6).[20] *A dissipative structure*, as described by Prigogine, *is an open system that maintains itself in a state far from equilibrium, yet is nevertheless stable: the same overall structure is maintained in spite of an ongoing flow and change of components.* Prigogine chose the term "dissipative structures" to emphasize this close interplay between structure on the one hand and flow and change (or dissipation) on the other.

The dynamics of these dissipative structures specifically include the spontaneous

emergence of new forms of order. When the flow of energy increases, the system may encounter a point of instability, known as a "bifurcation point," at which it can branch off into an entirely new state where new structures and new forms of order may emerge.

This spontaneous emergence of order at critical points of instability is one of the most important concepts of the new understanding of life. It is technically known as self-organization and is often referred to simply as "emergence." It has been recognized as the dynamic origin of development, learning and evolution. In other words, creativity (the generation of new forms) is a key property of all living systems. And since emergence is an integral part of the dynamics of open systems, we reach the important conclusion that open systems develop and evolve. Life constantly reaches out into novelty.

The theory of dissipative structures, formulated in terms of nonlinear dynamics, explains not only the spontaneous emergence of order, but also helps us to define complexity.[26] Whereas traditionally the study of complexity has been a study of complex structures, *the focus is now shifting from the structures to the processes of their emergence.* For example, instead of defining the complexity of an organism in terms of the number of its different cell types, as biologists often do, we can define it as the number of bifurcations the embryo goes through in the organism's development. Accordingly, Brian Goodwin speaks of "morphological complexity."

1.4.7 Pre biotic Evolution

Now we can summarize the defining characteristics of living systems that we have identified in our discussion of cellular life. *We have learned that a cell is a membrane-bounded, self-generating, organizationally closed metabolic network; that it is materially and energetically open, using a constant flow of matter and energy to produce, repair and perpetuate itself; and that it operates far from equilibrium, where new structures and new forms of order may spontaneously emerge, thus leading to development and evolution.* These characteristics are described by two different theories, representing two different perspectives on life: the theory of autopoiesis and the theory of dissipative structures.

When we try to integrate these two theories, we discover that there is a certain mismatch. While all autopoietic systems are dissipative structures, not all dissipative structures are autopoietic systems. Ilya Prigogine developed his theory from the study of complex thermal systems and chemical cycles that exist far from equilibrium, even though he was motivated to do so by a keen interest in the nature of life.[20]

Dissipative structures, then, are not necessarily living systems, but since emergence is an

integral part of their dynamics, all dissipative structures have the potential to evolve. In other words, there is a "prebiotic" evolution: an evolution of inanimate matter that must have begun some time before the emergence of living cells. This view is widely accepted among scientists today.

The first comprehensive version of the idea that living matter originated from inanimate matter by a continuous evolutionary process was introduced into science by the Russian biochemist Alexander Oparin in his classic book Origin of Life, published in 1929.[27] Oparin called it "molecular evolution," and today it is commonly referred to as *"prebiotic evolution."* In the words of Pier Luigi Luisi:

> *"Starting from small molecules, compounds with increasing molecular complexity and with emergent novel properties would have evolved, until the most extraordinary of emergent properties-life itself-originated."*[22]

Although the idea of prebiotic evolution is now widely accepted, there is no consensus among scientists about the details of this process. Several scenarios have been proposed, but none have been demonstrated. One scenario begins with catalytic cycles and "hypercycles" (cycles of multiple feedback loops) formed by enzymes, which are capable of self-replication and evolution.[20] A different scenario is based on the recent discovery that certain kinds of RNA can also act as enzymes, i.e. as catalysts of metabolic processes. This catalytic ability of RNA, which is now well established, makes it possible to imagine an evolutionary stage in which two functions that are crucial to the living cell (information transfer and catalytic activities) were combined in a single type of molecule. Scientists have called this hypothetical stage the "RNA world."[28]

In the evolutionary scenario of the RNA world[29] the RNA molecules would first perform the catalytic activities necessary to assemble copies of themselves and would then begin to synthesize proteins, including enzymes. These newly built enzymes would be much more effective catalysts than their RNA counterparts and would eventually dominate. Finally, DNA would appear on the scene as the ultimate carrier of genetic information, with the added ability to correct transcription errors because of its double-stranded structure. At this stage, RNA would be relegated to the intermediary role it has today, displaced by DNA for more effective information storage and by protein enzymes for more effective catalysis.

1.4.8 Minimal Life

So for the question: is there a way to define minimal features of living systems that may have existed in the past, irrespective of what has subsequently evolved? Here the answer is

given by Luisi:

> *It is clear that the process leading to life is a continuum process, and this makes an unequivocal definition of life very difficult. In fact, there are obviously many places in Oparin's pathway where the marker "minimal life" could arbitrarily be placed: at the level of self replication; at the stage where self-replication was ... accompanied by chemical evolution; at the point in time when proteins and nucleic acids began to interact; when a genetic code was formed,or when the first cell was formed.* [30]

Luisi comes to the conclusion that different definitions of minimal life, although equally justifiable, may be more or less meaningful depending on the purpose for which they are used.

If the basic idea of prebiotic evolution is correct, it should be possible, in principle, to demonstrate it in the laboratory. The challenge for scientists working in this field is to build life from molecules or, at least, to reconstruct different evolutionary steps in various prebiotic scenarios. Since there is no fossil record of evolving prebiotic systems from the time when the first rocks were formed on Earth to the emergence of the first cell, chemists have no helpful clues about possible intermediate structures, and their challenge might seem overwhelming.

Nevertheless, significant progress has been made recently, and we should also remember that this field is still very young. Systematic research into the origin of life has not been pursued for more than forty or fifty years, but even though the detailed ideas about prebiotic evolution are still very speculative, most biologists and biochemists do not doubt that life originated on Earth as the result of a sequence of chemical events, subject to the laws of physics and chemistry and to the nonlinear dynamics of complex systems.

This point is argued eloquently and in impressive detail by Harold Morowitz in a wonderful little book, *Beginnings of Cellular Life.* [4]

1.4.9 The Elements of Life

The basic elements of the chemistry of life are its atoms, molecules and chemical processes, or "metabolic pathways." In his detailed discussion of these elements, Morowitz shows beautifully that the roots of life reach deep into basic physics and chemistry.

We can start from the observation that multiple chemical bonds are essential to the formation of complex biochemical structures, and that carbon (C), nitrogen (N) and oxygen (O) are the only atoms that regularly form multiple bonds. We know that light elements make the strongest chemical bonds. It is therefore not surprising that these three elements, together with the lightest element, hydrogen (H), are the major atoms of biological structure.

We also know that life began in water and that cellular life still functions in a watery

environment. Morowitz points out that water molecules (H_2O) are highly polar, because their electrons stay closer to the oxygen atom than to the hydrogen atoms, so that they leave an effective positive charge on the H and a negative charge on the O. This polarity is a key feature in the molecular details of biochemistry and particularly in the formation of membranes.

The last two major atoms of biological systems are phosphorus (P) and sulphur (S). These elements have unique chemical characteristics because of the great versatility of their compounds, and biochemists believe that they must have been major components of prebiotic chemistry. In particular, certain phosphates are instrumental in transforming and distributing chemical energy, which was as critical in prebiotic evolution as it is today in all cellular metabolism.

Moving on from atoms to molecules, there is a universal set of small organic molecules that is used by all cells as food for their metabolism. Although animals ingest many large and complex molecules, they are always broken down into small components before they enter into the metabolic processes of the cells. Moreover, the total number of different food molecules is not more than a few hundred, which is remarkable in view of the fact that an enormous number of small compounds can be made from the atoms of C, H, N, O, P and S. The universality and small number of types of atoms and molecules in contemporary living cells is a strong indication of their common evolutionary origin in the first protocells, and this hypothesis is strengthened further when we turn to the metabolic pathways that constitute the basic chemistry of life. Once more, we face the same phenomenon. In the words of Morowitz:

> *"Amid the enormous diversity of biological types, including millions of recognizable species, the variety of biochemical pathways is small, restricted, and universally distributed."*[4]

It is very likely that the core of this metabolic network, or "metabolic chart," represents a primordial biochemistry that holds important clues about the origin of life.

1.4.10 Bubbles of Minimal Life

As shown, the careful observation and analysis of the basic elements of life strongly suggests that cellular life is rooted in a universal physics and biochemistry, which existed long before the evolution of living cells. We now turn to the second line of investigation presented by Harold Morowitz. *How could matter have organized itself within the constraints of that primordial physics and biochemistry, without any extra ingredients, so as to evolve into the complex molecules from which life emerged?*

The idea that small molecules in a primordial "chemical soup" should assemble spontaneously into structures of ever-increasing complexity runs against all conventional experience with simple chemical systems. Many scientists have therefore argued that the odds of such a prebiotic evolution are vanishingly small; or, alternatively, that there must have been an extraordinary triggering event, such as a seeding of the Earth with macromolecules by meteorites.

Today, the starting position for resolving this puzzle is radically different. *Scientists working in this field have come to recognize that the flaw of the conventional argument lies in the idea that life must have emerged out of a primordial chemical soup through a progressive increase in molecular complexity.* The new thinking, as Morowitz emphasizes repeatedly, begins from the hypothesis that very early on, before the increase of molecular complexity, certain molecules assembled into primitive membranes that spontaneously formed closed bubbles (vesicles), and that the evolution of molecular complexity took place inside these bubbles, rather than in a structureless chemical soup. With the formation of vesicles two different environments (an outside and an inside) were established, in which compositional differences could develop.

As Morowitz shows, the internal volume of a vesicle provides a closed microenvironment in which directed chemical reactions can occur which means that molecules that are normally rare may be formed in great quantities. These molecules include in particular the building blocks of the membrane itself, which become incorporated into the existing membrane, so that the whole membrane area increases. At some point in this growth process the stabilizing forces are no longer able to maintain the membrane's integrity, and the vesicle breaks up into two or more smaller bubbles.

T*hese processes of growth and replication will occur only if there is a flow of energy and matter through the membrane.* Morowitz describes plausibly how this might have happened.[4] The vesicle membranes are semipermeable, and thus various small molecules can enter the bubbles or be incorporated into the membrane. Among those will be chromophores, molecules that absorb sunlight. Their presence creates electric potentials across the membrane, and thus the vesicle becomes a device that converts light energy into electric potential energy. Once this system of energy conversion is in place, it becomes possible for a continuous flow of energy to drive the chemical processes inside the vesicle. Eventually, a further refinement of this energy scenario takes place when the chemical reactions in the bubbles produce phosphates, which are very effective in the transformation and distribution of chemical energy.

Morowitz also points out that the flow of energy and matter is necessary not only for the growth and replication of vesicles, but also for the mere persistence of stable structures. *Since all such structures arise from chance events in the chemical domain and are subject to thermal decay, they are by their very nature not in equilibrium and can only be preserved through continual processing of matter and energy*.[4] At this point it becomes evident that two defining characteristics of cellular life are manifest in rudimentary form in these primitive membrane bounded bubbles. The vesicles are open systems, subject to continual flows of energy and matter, while their interiors are relatively closed spaces in which networks of chemical reactions are likely to develop.

We can recognize these two properties as the roots of living networks and their dissipative structures.

The next stage is to set up for prebiotic evolution. In a large population of vesicles there will be many differences in their chemical properties and structural components. If these differences persist when the bubbles divide, we can speak of a pregenetic memory and of species of vesicles, and since these species will compete for energy and various molecules from their environment, *a kind of darwinian dynamic of competition and natural selection will take place, in which molecular accidents may be amplified and selected for their "evolutionary" advantages.* In addition, different types of vesicles will occasionally fuse, which may result in synergies of advantageous chemical properties, foreshadowing the phenomenon of symbiogenesis (the creation of new forms of life through the symbiosis of the organisms) in biological evolution.

Thus we see that a variety of purely physical and chemical mechanisms provides the membrane-bounded vesicles with the potential to evolve through natural selection into complex, self-producing structures without enzymes or genes in these early stages. [4]

1.4.11 Catalysts and Complexity

With the help of catalytic reactions, beneficial chance events would have been enhanced considerably, and thus a fully darwinian mode of competition would have developed, constantly pushing the protocells toward increasing complexity, further from equilibrium and closer to life. Once this happens, the entire nonlinear dynamics of networks come into play. This includes in particular the spontaneous emergence of new forms of order, as demonstrated by Ilya Prigogine and Manfred Eigen, two Nobel laureates in chemistry who pioneered the study of self-organizing chemical systems.[17,5]

The final step in the emergence of life from protocells was the evolution of proteins,

nucleic acids and the genetic code. At present, the details of this stage are still quite mysterious, but we need to remember that the evolution of catalytic networks within the closed spaces of the protocells created a new type of network chemistry that is still very poorly understood. We can expect that the application of nonlinear dynamics to these complex chemical networks, as well as the "explosion of new mathematical concepts" predicted by Ian Stewart, will shed considerable light on the last phase of prebiotic evolution. Harold Morowitz points out that the analysis of the chemical pathways from small molecules to amino acids reveals an extraordinary set of correlations that seem to suggest a "deep network logic" in the development of the genetic code.[4]

Another interesting discovery is that chemical networks in closed spaces that are subject to continual flows of energy develop processes surprisingly like those of ecosystems. For example, significant features of biological photosynthesis and the ecological carbon cycle have been shown to emerge in laboratory systems. The cycling of matter seems to be a general feature of chemical networks that are kept far from equilibrium by a constant flux of energy.

Morowitz concludes

> *"An abiding message is the necessity of understanding the complex network of organic reactions containing intermediates that are catalytic for other reactions ... If we better understood how to deal with chemical networks, many other problems in prebiotic chemistry would become appreciably simpler."*[4]

When more biochemists become interested in nonlinear dynamics, it is likely that the new "biomathematics" envisaged by Stewart will include a proper theory of chemical networks, and that this new theory will finally reveal the secrets of the last stage in the emergence of life.

1.4.12 What Is Life?

Now, let us return to the question posed at the beginning of this chapter: What are the defining characteristics of living systems? Focusing on bacteria as the simplest living systems, we characterize a living cell as a membrane-bounded, self-generating, organizationally closed metabolic network. This network involves several types of highly complex macromolecules: structural proteins; enzymes, which act as catalysts of metabolic processes; RNA, the messengers carrying genetic information; and DNA, which stores the genetic information and is responsible for the cell self-replication.

We also learned that the cellular network is materially and energetically open, using a

constant flow of matter and energy to produce, repair and perpetuate itself; and that it operates far from equilibrium, where new structures and new forms of order may spontaneously emerge, thus leading to development and evolution.

Finally, we have seen that a prebiotic form of evolution, involving membrane-enclosed bubbles of "minimal life," began long before the emergence of the first living cell; and that the roots of life reach deep into the basic physics and chemistry of these protocells.

1.5 Systems between complexity and creativity

> *Uncertainty and subjectivity should no longer be viewed negatively, as the loss of the absolute order of mechanicism, but positively, as factors of creativity, adaptation and evolution.*
>
> *Carlos Gershenson " Complexity and Philosophy"*[31]

It is interesting to note that "complexity" is derived etymologically from the Latin verb *complecti* ("to twine together") and the nom *complexus* ("network"). This issue is argued eloquently by Carlos Gersheson and co-worker which I shall follow closely in this section.[31]

The science of complexity is based on a new way of thinking that stands in sharp contrast to the philosophy underlying Newtonian science, which is based on reductionism, determinism, and objective knowledge. Determinism was challenged by quantum mechanics and chaos theory. Systems theory replaced reductionism by a scientifically based holism. Cybernetics and postmodern social science showed that knowledge is intrinsically subjective. These developments are being integrated under the header of "complexity science". Its central paradigm is the multi-agent system. Agents are intrinsically subjective and uncertain about their environment and future, but out of their local interactions, a global organization emerges. Together with the theories of self-organization and biological evolution, they moreover made us aware that regularity or organization is not given, but emerges dynamically out of a tangle of conflicting forces and random fluctuations, a process aptly summarized as "order out of chaos" (Prigogine & Stengers, 1984).[17]

Complexity is perhaps the most essential characteristic of our present society. As technological and economic advances make production, transport and communication ever more efficient, we interact with ever more people, organizations, systems and objects. And as this network of interactions grows and spreads around the globe, the different economic, social, technological and ecological systems that we are part of become ever more interdependent. The result is an ever more complex "system of systems" where a change in

any component may affect virtually any other component, and that in a mostly unpredictable manner.

The traditional scientific method, which is based on analysis, isolation, and the gathering of *complete* information about a phenomenon, is incapable to deal with such complex interdependencies. The emerging science of complexity[32,33,34] offers the promise of an alternative methodology that would be able tackle such problems. However, such an approach needs solid foundations, that is, a clear understanding and definition of the underlying concepts and principles.[35]

Research on complexity may be traced back to the study of the general system theory[36], cybernetics[37] and informatics, and their application in solving practical problems such as system engineering, system analysis and management science.

1.5.1 Holism and emergence

The first challenges to reductionism and its denial of creative change appeared in the beginning of the twentieth century in the work of process philosophers, such as Bergson, Teilhard, Whitehead, and in particular Smuts[38] (1926), who coined the word *holism* which he defined as the tendency of a whole to be greater than the sum of its parts. This raises the question what precisely it is that the whole has more.

In present terminology, we would say that a whole has *emergent* properties, i.e. properties that cannot be reduced to the properties of the parts. For example, kitchen salt (NaCl) is edible, forms crystals and has a salty taste. These properties are completely different from the properties of its chemical components, sodium (Na) which is a violently reactive, soft metal, and chlorine (Cl), which is a poisonous gas. Similarly, a musical piece has the properties of rhythm, melody and harmony, which are absent in the individual notes that constitute the piece. In fact, on closer scrutiny practically all of the properties that matter to us in everyday-life, such as beauty, life, status, intelligence, turn out to be emergent. Therefore, it is surprising that science has ignored emergence and holism for so long. One reason is that the Newtonian approach was so successful compared to its nonscientific predecessors that it seemed that its strategy of reductionism would sooner or later overcome all remaining obstacles. Another reason is that the alternative, holism or emergentism, seemed to lack any serious scientific foundation, referring more to mystical traditions than to mathematical or experimental methods.

1.5.2 General Systems Theory

This changed with the formulation of systems theory by Ludwig von Bertalanffy[36] (1973). The biologist von Bertalanffy was well-versed in the mathematical models used to describe physical systems, but noted that living systems, unlike their mechanical counterparts studied by Newtonian science, are intrinsically *open*: they have to interact with their environment, absorbing and releasing matter and energy in order to stay alive. One reason Newtonian models were so successful in predicting was because they only considered systems, such as the planetary system, that are essentially closed. Open systems, on the other hand, depend on an environment much larger and more complex than the system itself, so that its effect can never be truly controlled or predicted. The idea of open system immediately suggests a number of fundamental concepts that help us to give holism a more precise foundation. First, each system has an *environment*, from which it is separated by a *boundary*. This boundary gives the system its own *identity*, separating it from other systems. Matter, energy and information are exchanged across that boundary. Incoming streams determine the system's *input*, outgoing streams its *output*. This provides us with a simple way to connect or *couple* different systems: it suffices that the output of one system be used as input by another system. A group of systems coupled via different input-output relations forms a *network*. If this network functions in a sufficiently coherent manner, we will consider it as a system in its own right, a *supersystem*, that contains the initial systems as its *subsystems*.

From the point of view of the new system, a subsystem or component should be seen not as an independent element, but as a particular type of *relation* mapping input onto output. This transformation or processing can be seen as the function that this subsystem performs within the larger whole. Its internal structure or substance can be considered wholly irrelevant to the way it performs that function.

Every system contains subsystems, while being contained in one or more supersystems. Thus, it forms part of a *hierarchy* which extends upwards towards ever larger wholes, and downwards towards ever smaller parts[39]. For example, a human individual belongs to the supersystem "society" while having different organs and physiological circuits as its subsystems. Systems theory considers both directions, the downward direction of reduction or analysis, and the upward direction of holism or emergence, as equally important for understanding the true nature of the system. It does not deny the utility of the analytical method, but complements it by adding the integrative method, which considers the system in the broader context of its relations with other systems together with which it forms a

supersystem. Also the concept of emergent property receives a more solid definition via the ideas of *constraint* and *downward causation*.[40] Systems that through their coupling form a supersystem are constrained: they can no longer act as if they are independent from the others; the supersystem imposes a certain coherence or coordination on its components. This means that not only is the behaviour of the whole determined by the properties of its parts ("upwards causation"), but the behaviour of the parts is to some degree constrained by the properties of the whole ("downward causation"). For example, the behaviour of an individual is controlled not only by the neurophysiology of her brain, but by the rules of the society to which she belongs. Because of the dependencies between components, the properties of these components can no longer vary independently: they have to obey certain relationships. This makes much of the individual properties irrelevant, while shifting the focus to the state of their relationship, which will now define a new type of "emergent" property. For example, a sodium atom that gets bonded to a chlorine atom, forming a salt molecule, loses its ability to react with other atoms, such as oxygen, but acquires the ability to align itself into a crystalline structure with other salt molecules.

1.5.3 Complexity Science

In the 1980's, a new approach emerged which is usually labelled as *complex adaptive systems*[41] or, more generally, *complexity science.*[42] Although its origins are largely independent from systems science and cybernetics, complexity science offers the promise to extend and integrate their ideas, and thus develop a radical, yet workable alternative to the Newtonian paradigm. The roots of the complexity movement are diverse, including:

• non-linear dynamics and statistical mechanics—two offshoots from Newtonian mechanics—which noted that the modelling of more complex systems required new mathematical tools that can deal with randomness and chaos;

• computer science, which allowed the simulation of systems too large or too complex to model mathematically;

• biological evolution, which explains the appearances of complex forms through the intrinsically unpredictable mechanism of blind variation and natural selection;

• the application of these methods to describe social systems in the broad sense, such as stock markets, the Internet or insect societies, where there is no predefined order, although there are emergent structures.

What distinguishes complexity science is its focus on phenomena that are characterized neither by order, nor by disorder, but that are situated somewhere in between, in the zone that

is commonly (though perhaps misleadingly) called the *edge of chaos.*[43] Ordered systems, such as a crystal, are characterized by the fact that their components obey strict rules or constraints that specify how each component depends on the others. Disordered systems, such as a gas, consist of components that are independent, acting without any constraint. Order is simple to model, since we can predict everything once we know the initial conditions and the constraints. Disorder too is simple in a sense: while we cannot predict the behaviour of individual components, statistical independence means that we can accurately predict their *average* behaviour, which for large numbers of components is practically equal to their overall behaviour. In a truly complex system, on the other hand, components are to some degree independent, and thus autonomous in their behaviour, while undergoing various direct and indirect interactions. This makes the global behaviour of the system very difficult to predict, although it is not random.

1.5.4 Multi-agent systems

This brings us to the most important conceptual tool introduced by complexity science: the *complex adaptive system,* as defined by Holland (1996)[41], which is presently more commonly denoted as a *multi-agent system*. The basic components of a complex adaptive system are called *agents*. They are typically conceived as "black box" systems, meaning that we know the rules that govern their individual behaviour, but we do not care about their internal structure. The rules they follow can be very simple or relatively complex; they can be deterministic or probabilistic. Intuitively, agents can be conceived as autonomous individuals who try to achieve some personal goal or value ("utility" or "fitness") by acting upon their environment—which includes other agents. But an agent does not need to exhibit intelligence or any specifically "mental" quality, since agents can represent systems as diverse as people, ants, cells or *molecules*.

In that respect, complexity science has assimilated the lessons from cybernetics, refusing to draw any a priori boundary between mind and matter. From evolutionary theory, complexity science has learned that agents typically are ignorant about their wider environment or the long-term effects of their actions: they reach their goals basically by trial-and-error, which is equivalent to *blind variation* followed by the *natural selection* of the agents, actions or rules for action that best achieve fitness. Another way to describe this short-sightedness is by noting that agents are intrinsically egocentric or *selfish*: they only care about their own goal or fitness, initially ignoring other agents. Only at a later stage may they "get to know" their neighbours well enough to develop some form of cooperation.[44] But even when the agents are

intelligent and knowledgeable enough to select apparently rational or cooperative actions, they—like us—are intrinsically *uncertain* about the remote effects of their actions. This limited range of rational anticipation is reflected at the deepest level by the principle of *locality*: agents only interact with (and thus get the chance to "know") a small number of other agents which form their local neighbourhood. Yet, in the longer term these local actions typically have global consequences, affecting the complex system as a whole. Such global effects are by definition unexpected at the agent level, and in that sense *emergent*: they could not have been inferred from the local rules (properties) that determine the agents' behaviour. For us as outside observers, such emergent properties do not necessarily come as a surprise: if the interactions between the agents are sufficiently regular or homogeneous, as in the interactions between molecules in a crystal or a gas, we may be able to predict the resulting global configuration. But in the more general cases, it is impossible to extrapolate from the local to the global level. This may be better understood through the following observations.

First, agents' goals are intrinsically independent, and therefore often in conflict: the action that seems to most directly lead to A's goal, may hinder B in achieving its goal, and will therefore be actively resisted by B. This is most obvious in economies and ecosystems, where individuals and organisms are always to some degree competing for resources. Eating a zebra may be an obvious solution to the lion's problem of hunger, but that action will be resisted by the zebra. Increasing the price may be the most obvious way for a producer to increase profit, but that will be resisted by the clients switching to other suppliers. Such inherent conflicts imply that there is no "global optimum" for the system to settle in, i.e. an equilibrium state that maximally satisfies *all* agents' goals. Instead, agents will *co-evolve*: they constantly adapt to the changes made by other agents, but through this modify the others' environment, thus forcing them to adapt as well.[45] This results in an on-going process of mutual adaptation, which in biology is elegantly expressed by metaphors such as an "arms race" or the "Red Queen principle".

Second, since actions are local, their effects can only propagate step by step to more remote agents, thus diffusing across the whole network formed by the agents and their relationships of interaction. The same action will in general have multiple effects in different parts of the network at different times. Some of those causal chains will close in on themselves, feeding back into the conditions that started the chain. This makes the system intrinsically *non-linear*. This means that there is no proportionality between cause and effect. On the one hand, small fluctuations may be amplified to large, global effects by positive feedback or "autocatalysis". On the other hand, feedback can also be negative, so that large

perturbations are suppressed, possibly resulting in the stabilisation of a global configuration.

1.5.5 Creative evolution

The combination of these different effects leads to a global evolution that is not only unpredictable, but truly creative, producing emergent organization and innovative solutions to global and local problems. When we focus on the complex system in itself, we can call the process *self-organization*: the system spontaneously arranges its components and their interactions into a sustainable, global structure that tries to maximize overall fitness, without need for an external or internal designer or controller.[45,46] When we focus on the relation between the system and the environment, we may call it *adaptation*[41]: whatever the pressures imposed by the environment, the system will adjust its structure in order to cope with them. Of course, there is no guarantee of success: given the intrinsic sensitivity and unpredictability of the system, failures and catastrophes can (and do) happen, often when we do not expect them. But in the long term, on-going self-organization and adaptation appear to be the rule rather than the exception. As such, the complexity paradigm answers a fundamental philosophical question that was left open by earlier approaches: *what is the origin of the order, organization and apparent intelligence thatwe see around us?*[35]

Newtonian and systems science had eluded that question by considering that order as pre-existing. Earlier, pre-scientific philosophies had tackled the question by postulating a supernatural Creator. Darwin's theory of evolution through natural selection had provided a partial answer, which moreover remained restricted to biological systems, and thus is considered unsatisfactory by many. The co-evolution of many, interacting agents, on the other hand, seems able to explain the emergence of organization in any domain or context: physical, chemical, biological, psychological or social. While it is difficult to imagine the limitless ramifications of such a process without the support of complex computer simulations or mathematical models, the basic principle is simple: each agent through trial-and-error tries to achieve a situation that maximises its fitness within the environment. However, because the agent cannot foresee all the consequences, actions will generally collide with the actions of other agents, thus reaping a less than optimal result. This pressures the agent to try out different action patterns, until one is found that reduces the friction with neighbouring agents' activities, and increases their synergy. This creates a small, relatively stable "community" of mutually adapted agents within the larger collective. Neighbouring agents too will try to adapt to the regime of activity within the community so that the community grows. The larger it becomes, the stronger influences or "selectively pressures" on the remaining agents, so that

eventually the whole collective will be assimilated into the new, organized regime. Whenever the organization encounters a problem (loss of fitness), whether because of internal tensions or because of perturbations from the outside, a new adaptation process will be triggered in the place where the problem is experienced, propagating as far as necessary to absorb all the negative effects.

In such an organized collective, individual agents or agent communities will typically specialise in a particular activity (e.g. processing a particular type of resource) that complements the activities of the other agents. As such, agents or communities can be seen to fulfil a certain function or role within the global system, acting like functional subsystems. Thus, complex adaptive systems may come to resemble the supersystems studied by systems theory. Such a supersystem can be seen as an agent at a higher level, and the interaction of several such "superagents" may recursively produce systems at an ever higher hierarchical level.[46] However, the organization of such a complex system is not frozen, but flexible, and the same agent may now seem to participate in one function, then in another. In some cases, like in multicellular organisms, the functional differentiation appears pretty stable. In others, like in our present society or in the brain, agents regularly switch roles. But the difference is merely one of degree, as all complex systems created through self-organization and evolution are intrinsically adaptive, since they cannot rely on a fixed plan or blueprint to tell them how they should behave. This makes a naturally evolved organization, such as the brain, much more *robust* than an organization that has been consciously designed, such as a computer. The intrinsic uncertainty, which appeared like a weakness, actually turns out to be a strength, since it forces the system to have sufficient reserves or redundancy and to constantly try out new things so as to be prepared for any eventuality.

1.5.6 Multi-scale nature of complex systems

The barriers between the traditional disciplines will dissolve to yield a somewhat unified knowledge base, in which the natural and social sciences and humanities all contribute equally.[47] In response to this tendency, research strategies in various fields are changing. For instance, the biological sciences used to aim at reducing biological phenomena into the behaviour of molecules in the 20th century, but will now pay attention to system biology in the 21st century,[48] and the chemical sciences are shifting from looking at covalent bonds to understanding non-covalent intermolecular forces, leading to the appearance of supramolecular chemistry.[7]

The variety of complex systems could be classified into three categories:

- complex systems from natural evolution such as life, landscape and natural phenomena;
- complex systems in society such as cognition, physiology, ecology, economy;
- complex systems in engineering created by human activities such as fluid flow, chemical process, network, trafic system, etc.

The diversity of complex systems is a challenge for complexity science, calling for understanding the intrinsic nature of each system, though, on the other hand, the common nature of complex systems gives rise to the opportunity of unifying the different disciplines and fields. That is each discipline will benefit from the development of complexity science as a whole, while at the same time, knowledge from different disciplines become the very basis of complexity science itself. Extracting common scientific problems and deducing common knowledge from these problems should be the strategy for studying complex systems.

Complex systems are characterized by hierarchical multi-scale nature with respect not only to space but also to time, showing dissipative structures (see section 1.6) induced by inherent non-linear and non-equilibrium interactions and stabilized by exchanging energy, matter and information with their surroundings. Understanding the hierarchical multi-scale nature of complex systems is the focus of complexity science.

A representative chemical system is shown in Figure 1.1 ranging from molecular scale through factory scales to the whole ecological system scale. First, we can see the hierarchical nature of the global complex system, that is, a molecular system, studied by chemists and physicists, within a reactor system, studied by engineers, within an ecological system studied by ecologists, each of which is, however, also a multi-scale complex system.

Obviously, all these three levels of the chemical system are characterized again by their own multi-scale structures: molecular system consisting of atoms, molecules and assemblies; reactor system showing the multi-scale nature of particle (or droplet or bubble) scale, aggregate scale and apparatus scale; ecological system including process apparatus, factory, and environment. These three systems behave mostly independently, but subject, to some extent, to the constraints of the others.

Speaking broadly, the hierarchical multi-scale structures are an inherent nature of the universe, as outlined in Scheme 1.2. Elementary particles were organized into more than 100 kinds of atoms as listed in the element periodic table.

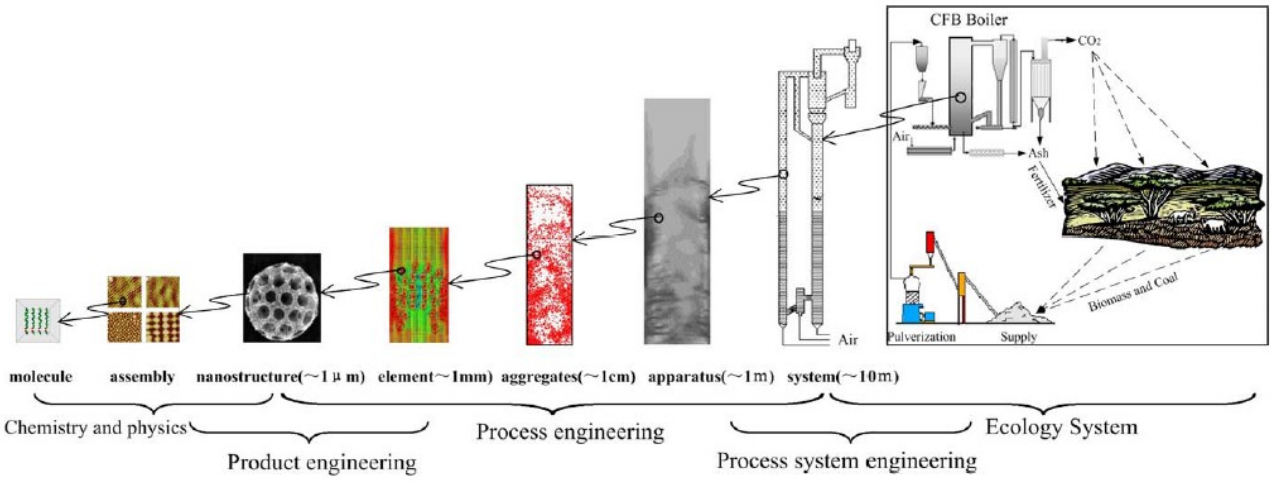
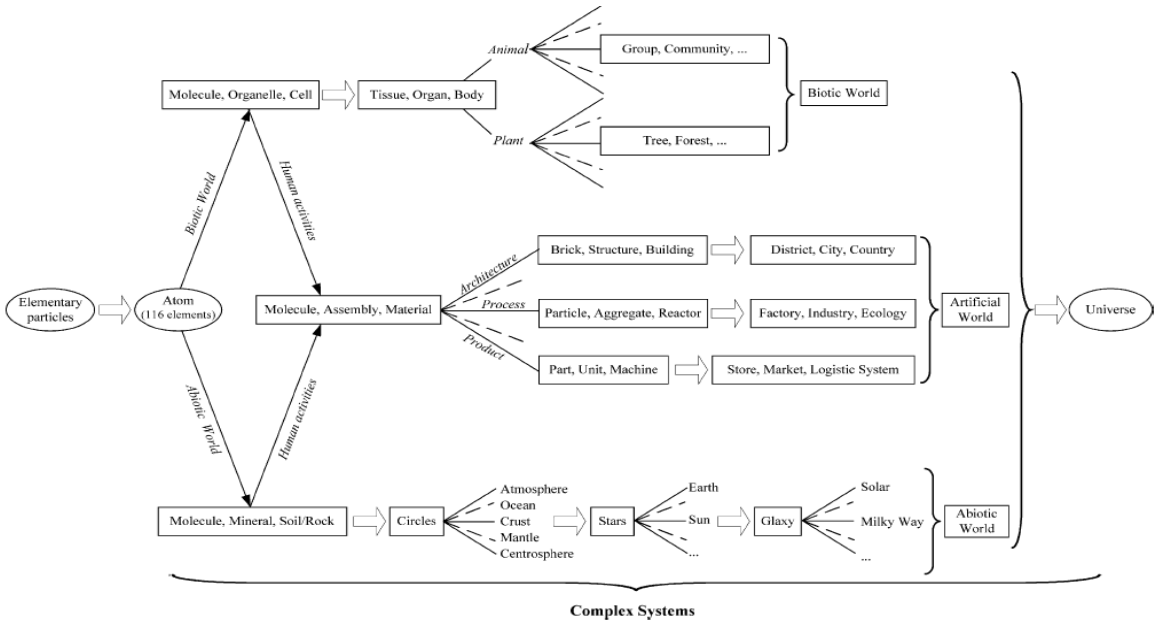


Figure 1.1 *Spatio-temporal multi-scale structures in chemical process.(Adapted from reference 49)*

Starting with these atoms, biotic and abiotic worlds were formed and evolved, each with bifurcations during evolution such as animal and plant the biotic world, and land, ocean and atmosphere for the abiotic world in nature. Further bifurcation led to the biodiversity for life and to different landscapes in nature. On the other hand, the activities of the human being created various industries, agricultures and buildings, which also show bifurcations in different engineering fields. Therefore, the biotic, abiotic and artificial worlds are all characterized by the hierarchical multi-scale nature, and start with chemical elements, and finally emerge into the whole ecological system and the universe. Reductionism was effective for the two ends of the hierarchy, but insuficient for understanding the hierarchical multi-scale "tree" between them. Complexity science is therefore generated to unify the understandings on these bifurcations of hierarchical multi-scale phenomena, and to correlate these phenomena to microscopic elementary particles and to the megascopic universe. This is the big challenge for the science and engineering of the 21st century.



Scheme 1.2 *Hierarchy, diversity and multi-scale nature of complex systems.(Adapted from reference 49)*

1.6 The dissipative structures

Ilya Prigonie, the Nobel Laureate in chemistry in 1977, was influenced by the Schrodinger's book "*What is life*?"[50] and by Jacques Monod's book "*Le hasard et la nécesité; essai sur la philosophie naturelle de la biologie moderne*".[51]

In the former, Schrodinger tried to understand the structures of the biomolecules and he said: "there must have been something into life's mechanism that prevent the degradation of the life, there must have been a irreversible phenomenon". In 1945 Prigonie had the intuition that the irreversible phenomenona may be the source of the biological organization and since that idea never let him. He had the idea that is the function that creates the structure.[52] For instance a town lives only because there are exchanges of matter and energy that operate with the country in the surrounding. In this example, it is the function, the flow of matter and energy is obviously a situation of non-equilibrium, that determines the structure.

About the second book, Prigonie did not agree with Monod because he put the life outside the concept of the matter, an event had to chaos. On the contrary, for Prigonie life is the realm of the non-linear, the life is the realm of the autonomy of the time, the realm of the multiplicity of the structures. He said: "The life is characterized for this instability that permit us to see the birth and the death of the structures into geological time".

Before explaining the new Prigonie perspective, I will recall some definitions about the

thermodinamics. A thermodynamic system, originally called a working substance, is defined as that part of the universe that is under consideration. A real or imaginary boundary separates the system from the rest of the universe, which is referred to as the environment or surroundings (sometimes called a reservoir.) A useful classification of thermodynamic systems is based on the nature of the boundary and the quantities flowing through it, such as matter, energy, work, heat, and entropy. A system can be anything, for example a piston, a solution in a test tube, a living organism, a planet, etc.

Thermodynamics is basically concerned with the flow and balance of energy and matter in a thermodynamic system. Three types of thermodynamic systems are distinguished depending on the kinds of interaction and energy exchange taking place between the system and its surrounding environment:

1. Isolated systems are completely isolated in every way from their environment. They do not exchange heat, work or matter with their environment. An example of an isolated system would be an insulated rigid container, such as an insulated gas cylinder.

2. Closed systems are able to exchange energy (heat and work) but not matter with their environment. A greenhouse is an example of a closed system exchanging heat but not work with its environment. Whether a system exchanges heat, work or both is usually thought of as a property of its boundary.

3. Open systems: exchanging energy (heat and work) and matter with their environment. A boundary allowing matter exchange is called permeable. The ocean, an organism or a single cell would be an example of an open system.

Really, a system can never be absolutely isolated from its environment, because there is always at least some slight coupling, even if only via minimal gravitational attraction.

It is a fact that, for isolated systems, as time goes by, internal differences in the system tend to became flat. Pressures and temperatures tend to equalize, as do density differences. A system in which all these equalizing processes have gone practically to completion, is considered to be in a state of thermodynamic equilibrium, it is a systems in equilibrium. Its thermodynamic properties are, by definition, unchanging in time. Systems in equilibrium are much simpler and easier to understand than systems which are not in equilibrium. Often, when analysing a thermodynamic process, it can be assumed that each intermediate state in the process is at equilibrium. This will also considerably simplify the situation. Thermodynamic processes which develop so slowly as to allow each intermediate step to be an equilibrium state are said to be reversible processes.

In open systems, matter, energy and entropy may flow in and out of the system boundaries.

Given a system, a portion of the space, the second law of thermodynamics says that there is a function, the entropy, that we can separate in two components: a entropic flow coming from the external word (d_eS) and an internal production of entropy (d_iS) of the considered system.

This production of internal entropy is for irreversible phenomenons ever positive or equal to zero. All the chemical reactions are irreversibles, all the biological phenomenons irreversibles.

But what is the irreversibility? For many scientists the irreversibility is equivalent to dissipation, disorder, but in this case, if it would be true, each structure would gained from a strong faith against the second law, so either for the life and for the universe. Prigonie points out the concept that the production of entropy holds ever two elements: an creator element of disorder, but also a creator element of order. The two elements are always bound.

It is possible to explain it with a simple example. In two boxes connected each other we put a mix of two gases, hydrogen H_2 and nitrogen N_2, if the internal temperature of the system is homogeneous T_0 , the same will be for the distribution of the two gases. But if we heat the two boxes with different temperatures T_1 and T_2, we create an heterogeneous distribution: from one side hydrogen, to the other nitrogen.

Therefore, the system subjected a thermal constrain, it is evident the dissipation an increase of entropy, but also a phenomenon ordered. This phenomenona is called antidiffusion (Figure 1.2).

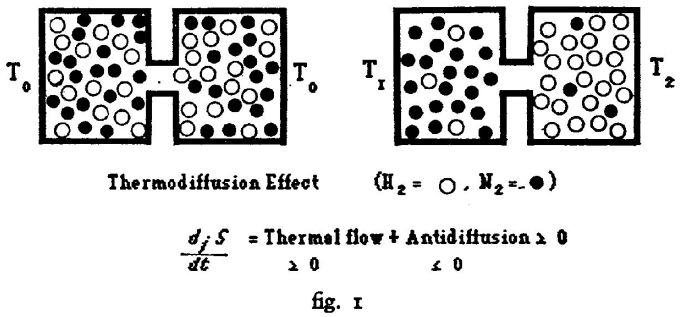


Figure 1.2
Antidiffusion phenomena.

Here order and disorder appear in the same time. Stafford Beer (1966)[53] noted a subtle but very important issue: what under some circumstances can be seen as organization, under others can be seen as disorder, depending on the purpose of the system. He illustrates this idea with the following example: when ice cream is taken from a freezer, and put at room temperature, we can say that the ice cream disorganizes, since it loses its purpose of having an icy consistency. But from a physical point of view, it becomes more ordered by achieving equilibrium with the room, as it had done with the freezer. Again, the purpose of the system is not an objective property of the system, but something set by an observer.

The second law of thermodynamics states that in an isolated system, entropy can only increase, not decrease. Such systems evolve to their state of maximum entropy, or thermodynamic equilibrium. Therefore, physical self-organizing systems cannot be isolated: they require a constant input of matter or energy with low entropy, getting rid of the internally generated entropy through the output of heat ("dissipation"). This allows them to produce "dissipative structures" which maintain far from thermodynamic equilibrium (Nicolis and Prigogine, 1977)[17]. Prigonie said:

> *"Life is a clear example of order far from thermodynamic equilibrium. Into the universe the order floats into a disorder sea"*

According to the theory of dissipative structure, an open system has a capability to continuously import free energy from the environment and, at the same time, export entropy. As a consequence, the entropy of an open system can either be maintained at the same level or decreased (negative entropy), unlike the entropy of an isolated system (i.e. one that is completely sealed off from its environment), which tends to increase toward a maximum at thermodynamic equilibrium. This phenomenon can be represented in quantitative terms as follows.[17] According to the second law of thermodynamics, in any open system, change in entropy dS in a certain time interval consists of entropy production due to an irreversible process in the system (an internal component) d_iS and entropy flow due to exchange with the environment (an external component) d_eS. Thus, a change in entropy in a certain time interval can be represented as $dS = d_eS + d_iS$ (where $d_iS > 0$). However, unlike d_iS, the external component (d_eS) can be either positive or negative. Therefore, if d_eS is negative and as numerically large as, or larger than, d_iS, the total entropy may either be stationary ($dS = 0$) or decrease ($dS < 0$).

In the former case, we can say that the internal production of entropy and entropy exported to the environment are in balance. In the second case we have a system with a higher exportation of the entropy to the environment. An open system in a dissipative structure sense can be viewed as shown in Figure 1.3.

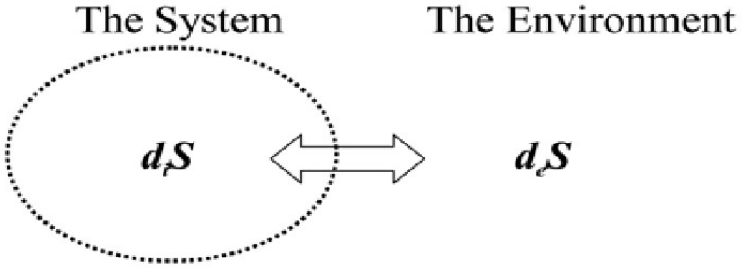


Figure 1.3 *An open system's entropy production and dissipation.*

It can be concluded that order in an open system can be maintained only in a non-equilibrium condition. In other words, an open system needs to maintain an exchange of energy and resources with the environment in order to be able to continuously renew itself.

This phenomenon needs a change of paradigma, because in classical thought the order is associated to the equilibrium (e.i. crystal) and the disorder at non-equilibrium (e.i. turbulence). Today we know that it is inexact: the turbulence is a phenomenon highly structured, in which million and million of particles are running after in a movement extremely coherent. That is the same for other phenomenons, such as the chemistry watch that is a oscillating reaction. These are phenomenons ordered that translate the establishment of a coherence between the molecules. Today the experiences in the laboratories show that the domain of non-equilibrium stabilizes new interactions of long range: the universe of the non-equilibrium is a universe coherence. That represents a new sight in contraposition of the old thought.

Here the most prominent example of dissipative structure in a physical system is convection in a liquid. If cooking oil is heated in a shallow pan, the following macroscopic changes occur: At the beginning, while the temperature of liquid is relatively uniform, heat is transmitted through the body of liquid by means of conduction in which the molecules' heat energy (molecular vibration) is transmitted to neighbouring molecules via collision without major change of position. We can say that the system is still in a thermodynamic equilibrium. Then, as the pan is heated further, the temperature gradient between the upper and lower portion of the oil becomes more pronounced and thermal non-equilibrium increases. At a certain temperature gradient, convection starts and heat is then transferred by the bulk movement of molecules. Evidently, however, the surrounding environment at first suppresses the smaller convection streams, but beyond a certain temperature gradient, the fluctuations are reinforced rather than suppressed. The system moves into a dynamic regime, switching from conduction to convection, and a new macroscopic order called “Benard's cells” (i.e. a pattern of regular hexagonal cells that appear on the surface of liquid) emerges, caused by a macroscopic fluctuation and stabilised by an exchange of energy with the environment. Such a structure is called a hydrodynamic dissipative structure, and is a version of spatial structure.

In the Bernard's instability, we can see the formation of whirls, coherence phenomenons enable to transmit the heat more efficiently than the only thermal conduction. This is an example of bifurcation that determines the appearance of new structures, the structures of the non-equilibrium, or so-called the dissipative structures. The non-equilibrium consists the excellence domain of the multiplicity of the solutions.

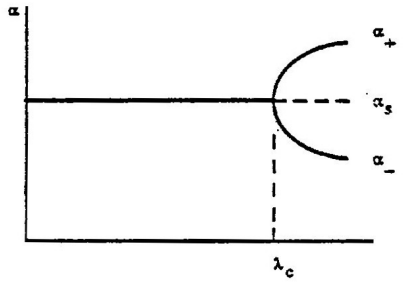


Figure 1.4 *Bifurcation point: Concentration of specie α in function of a parameter λ. For values of λ lower than the threshould λc only one solution α_s exists. Over the threshould, this solution becomes unstable and appear new solutions.*

The figure 1.4 shows the variations of the concentrations of one component for a chemistry reaction versus the equilibrium state. What is the mechanism to appear a new structure?
This is possible only with a mechanism of the amplification of the fluctuations. In a chemistry reaction, we now that there are fluctuations in any time. Without doubts, for a state close to the equilibrium or in equilibrium, this case isn't significant: the fluctuations death and the ambient come back toward a homogeneous state. But far from the equilibrium can be possible the opposite: instead to see a return toward the initial state, we sight an amplification of the fluctuations, and this amplification bring a new situation that open a series of different possibilities that the physics starts today to explore.

However, the theory of dissipative structure has the potential to be applied to systems beyond those of concern to physical-chemistry science. Prigogine saw the world-system, or human society, as a dissipative structure because it was both far-from-equilibrium and non-linear: Life is only possible in open systems exchanging matter, energy and information with the outside world. It is also clear that a society is a non-linear system; what one person does influences the action of others. Thus non-linearity increases with the size of the society. Our present society is already full of possible bifurcations.[54]

1.7 The holistic view of the eastern thought

Schrödinger (1945), who called himself a Vedantist, was deeply influenced by eastern philosophy. Schrödinger wrote:

> *From the early great Upanishads the recognition ATHMAN=BRAHMAN (the personal self equals the omnipresent, all-comprehending eternal self) was in Indian thought considered, far from being blasphemous, to represent the quintessence of deepest insight into the happenings of the world.*

In 1975 Fritjof Capra, in the Book "*The Tao of Physics. An Exploration of the Parallels Between Modern Physics and eastern Mysticism*"[55] explores the relationship between the underlying concepts of modern physics and the basic ideas Eastern mysticism. In 1990 Shimizu[56] said that the principle of self-organisation enables the connection of oriental thoughts to western thoughts. Referring specifically to Chinese philosophy, in 1998 Jones and Culliney[57] asserted that the roots of the essential ideas of the science of complexity/chaos are found within the social ordering principle of *li* (organisation or rites/decorum) in Confucius's Analects.

During the sixty century B.C., the two sides of Chinese philosophy developed into distinct philosophical schools: Confucianism and Taoism.

Confucianism was the philosophy of social organization, of common sense and practical knowledge. It provided Chinese society with a system of education and with strict conventions of social etiquette. One of its main, purposes was to form an ethical basis for the traditional Chinese family system with its complex structure and its rituals of ancestor worship. Taoism, on the other hand, was concern, primarily with the observation of nature and the discovery of its *Way*, or *Tao*. Human happiness, according to the Taoist, is achieved when men follow the natural order, acting spontaneously and trusting their intuitive knowledge.

These two trends of thought represent opposite poles in Chinese philosophy, but in China they were always seen as poles of one and the same human nature, and thus as complementary. Confucianism was generally emphasized in education of children who had to learn the rules and conventions necessary for life in society, whereas Taoism use be pursued by older people in order to regain and develop the original spontaneity which had been destroyed by social conventions.

The Chinese, like the Indians, believed that there is an ultimate reality which underlines and unifies the multiple things and event we observe:

> *"There are three terms: complete, all-embracing, the whole. these names are different, but the reality sought in theme is the same: referring to One thing"*

They called this reality the *Tao,* which originally meant "The Way". It is the way, or process, of the universe, the order of nature. The *Tao* is the cosmic process in which all things are involved; the world is seen as a continuos flow and change. The Chinese non only believed that the flow and change were essential features of nature, but also that there are constant patterns in these changes, to be observed by man. The sage recognizes these patterns and directs his actions according to them. In this way, he becomes "One with the Tao", living

in harmony with nature and succeeding in everything he undertakes. In the words of Huai Nan Tzu, a philosopher of the second century B.C.:

> *He who conforms to the course of the Tao, following the natural process of Heaven and Earth, finds it easy to manage the whole word.*[55]

The idea of cyclic pattern in the motion of the *Tao* was given a definite structure by the introduction of the polar opposites *yin* and *yang*. They are the two poles which set the limits for the cycles of change:

> *The yang having reached its climax retreats in favour of the yin; the yin having reached its climax retreats in favour of the yang.*[55]

In the Chinese view, all manifestation of the *Tao* are generated by the dynamic interplay of these two polar forces. The dynamic character of *yin* and *yang* is illustrated by the ancient Chinese symbol called *T'ai-chi T'u*, or "Diagramma of the Supreme Ultimate" (Figure 1.5).

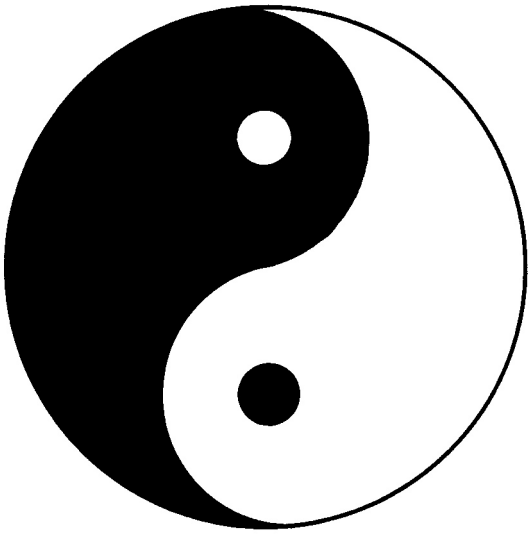


Figure 1.5 *The Tao*

This diagram is a symmetric arrangement of the dark *yin* and the bright *yang*, but the symmetry is not static. It is rotational symmetry suggesting, very forcefully. a continuous cyclic movement:

> *The yang returns cyclically to its beginning, the yin attains its maximum and gives place to the yang.*[55]

The two dots in the diagram symbolize the idea that each time one of the two forces reaches its extreme, it contains in itself already the seed of its opposite.

Both the modern physicist and the Eastern mystic have realized that all phenomena in this world of change and transformation are dynamically interrelated. Hindus and Buddhists see

this interrelation as a cosmic law, the law of *karma*, but they are generally not concerned with any specific patterns in the universal network of events. Chinese philosophy, on the other hand, which also emphasizes movement and change, has developed the notion of dynamic patterns which are continually formed and dissolved again in the cosmic flow of the *Tao.* In the *I Ching*, or Book of Changes, these patterns have been elaborated into a system of archetypal symbols, the so-called hexagrams.

The basic ordering principle of the patterns in the *I Ching* is the interplay of the polar opposite *yin* and *yang*. The *yang* is represented by a solid line, the *yin* by a broken line, and the whole system of hexagrams is built up naturally from these two lines. By combining them in pairs, four configurations are obtained, (Figure 1.6)

Figure 1.6 *The yin and yang representation*

and by adding a third line to each of these, eight "trigrams" are generated (Figure 1.7).

Figure 1.7 *Representation of eight trigrams*

In order to increase the number of possible combinations further, the eight trigrams were combined in pairs by placing one above the other. In this way, sixty-four hexagrams were obtained, each consisting of six solid or broken lines. The hexagrams were arranged in several regular patterns, among which the two illustrated in Figure 1.8 were the most common; a square of eight times eight hexagrams, and a circular sequence.

In the *I Ching*, the trigrams and hexagrams represent the patterns of the *Tao* which are generated by the dynamic interplay of the *yin* and the *yang*, and are reflected in all cosmic and human situations. These situations, therefore, are not seen as static but rather as stages in a continuous flow and change.

This is the basic idea of the Book of Changes which is expressed in is very title. All things and situations in the world are subject to change and transformation, and so are their images, the trigrams and hexagrams. They are in a state of continual transition; one changing into another, solid lines pushing outwards and breaking in two, broken lines pushing inwards and

growing together.

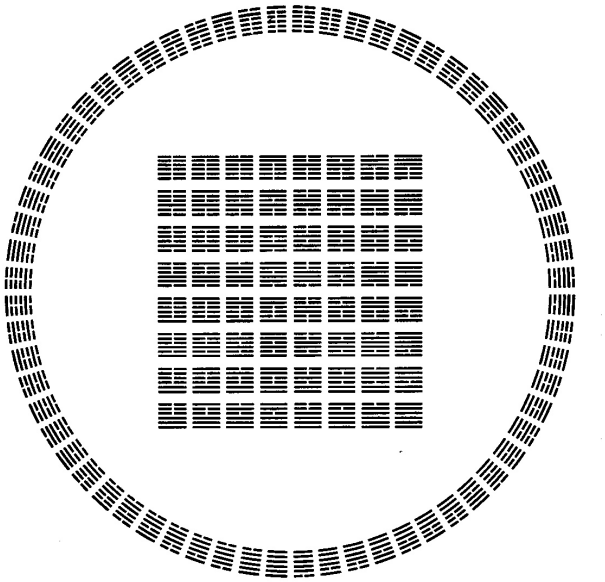


Figure 1.8 *Two regular arrangements of the 64 hexagrams.*

In the Chinese view. all things and phenomena around us arise out of the patterns of changes and are represented by the various lines of the trigrams and hexagrams. Thus the things in the physical world are not seen as static, independent objects, but merely as transitional stages in the cosmic process which is the *Tao*:

The Tao is changes and movements.

The ceaseless transformation of all things and situation is the essential message of the Book of Changes:

The Changes is a book
From which one may not hold aloof.
Its Tao is forever changing-
Alteration, movement without rest,
Flowing through the six empty places,
Rising and sinking without fixed law,
Firm and yielding transform each other.
They cannot be confined within a tule,
It is only change that is at work here.

Capra into the "*The Tao of Physics*"'s epilogue wrote:[55] "In contrast to the mystic, the physicist begins his enquiry into the essential nature of things by studying the material world. Penetrating into ever deeper realms of matter, he has become aware of the essential unity of all things and events. More than that, he has also learnt that he himself and his consciousness

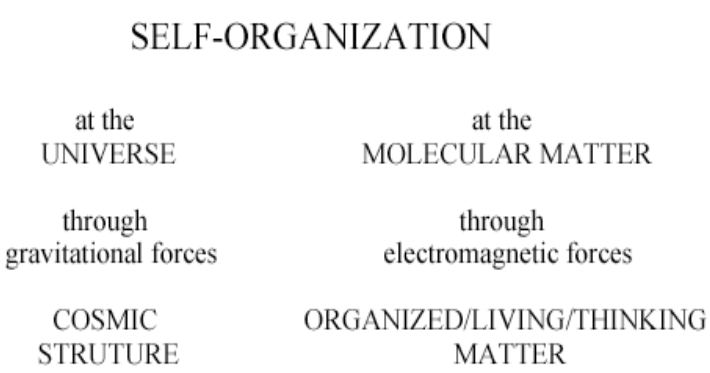
are an integral part of this unity. Thus the mystic and the physicist arrive at the same conclusion; one starting from the inner realm, the other from the outer world. The harmony between their views confirms the ancient Indian wisdom that BRAHMAN, the ultimate reality without, is identical to ATMAN, the reality within."

1.8 Conclusion

> *The goal is to progressively discover, understand, and implement the rules that govern the evolution of matter from inanimate to animate and beyond, in order to ultimately acquire the ability to create new forms of complex matter.* *J. M. Lehn*

'In the beginning was the Big Bang, and physics reigned. Then chemistry came along at milder temperatures; particles formed atoms; these united to give more and more complex molecules, which in turn associated into organized aggregates and membranes, defining primitive cells out of which life emerged'(Lehn 1995)[7]. From divided to condensed, organized, living, and up to thinking matter, the universe has evolved towards a progressive complexification of matter, through a process of selforganization[5,6] under the pressure of information. Lehn to understand the hierarchical multi-scale of the nature drew a parallel between structure formation on the grand scale of the universe and at the level of molecular matter (Scheme 1.3). Self-organization of the universe results from the operation of gravitational forces on initial inhomogeneities in density or in expansion rate at very early times.[58] Self-organization of molecular matter, non-living and living[5,6], may be considered to result from electromagnetic forces generating and operating on an infinite diversity of possible structural combinations. Cosmic self-organization is thus due to gravitation, and molecular self-organization to electromagnetic interaction.

Before biological evolution, spontaneous chemical evolution took place, operating selection on molecular structural diversity through the implementation of molecular information carried by electromagnetic interactions. Chemistry has developed from mastering the combination and recombination of atoms into increasingly complex molecules to the harnessing of intermolecular forces for the generation of informed supramolecular systems and processes.



Scheme 1.3 *Self-organization at the scale of the universe and of molecular matter. The gravitational interaction acts between all particles, but is so weak it cannot be detected experimentally. In the macroscopic world, however, the huge number of particles making up massive bodies combine their gravitational interaction to produce the force of gravity which is the dominating force in the universe at large. Electromagnetic interactions take place between all charged particles. They are responsible for the chemical processes, and the formation of all atomic and molecular structures. the strong interactions hold the protons and neutrons together in the atomic nucleus. They constitute the nuclear force, by far the strongest of all forces in nature. Electrons, for example, are bond to the atomic nuclei by electromagnetic force with energies of about ten units (called electron volts), whereas the nuclear force hold protons and neutrons together with energies of about the million units!*

Chemistry, as the science of the structure and transformation of matter, has a major role to play in this context and is at the core of the biological world, the highest level of complex matter as we know it.

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2. The supramolecular chemistry as a science of informed matter

> *Supramolecular chemistry has grown in importance because it goes beyond the molecule — the focus of classical chemistry. It also offers a fresh interface with biological and materials science.*
>
> *Gautam R. Desiraju*

2.1 Introduction

Gautam R. Desiraju has authored of two book "*Crystal Engineering: The Design of Organic Solids*" and "*The Weak Hydrogen Bond in Structural Chemistry and Biology*".[1a.] He said that for a long time chemists tried to understand nature at a level that was purely molecular — they considered only structures and functions involving strong covalent bonds, but some of the most important biological phenomena do not involve making and breaking covalent bonds — the linkages that connect atoms to form molecules. Instead, biological structures are usually made from loose aggregates that are held together by weak, non-covalent interactions. Because of their dynamic nature, these interactions are responsible for most of the processes occurring in living systems.[1b]

Chemists have been slow to recognise the enormous variety — in terms of structure, properties and functions — offered by this more relaxed approach to making chemical compounds. The slow shift towards this new approach began in 1894, when Emil Fischer proposed that an enzyme interacts with its substrate as a key does with its lock [2]. This elegant mechanism contains the two main tenets of what would become a new subject, *supramolecular chemistry*.[3,4] These two principles are *molecular recognition* and *supramolecular function*. Molecular recognition is implicit in the lock-and-key model — provided both the geometry and the non-covalent interactions are compatible between the interacting partners, you get recognition. Such highly specific interactions also lead to useful supramolecular functions. For example, it is important that an enzyme works only on the appropriate substrate. A key without its own lock or a lock without its own key is quite useless.

The initial motivation behind supramolecular chemistry was to design chemical systems that mimic biological processes. The rise of the supramolecular approach was aided by observations of stable compounds that did not involve covalent bonds. Early examples of these 'addition products' include donor–acceptor complexes and clathrate compounds (Figure 2.1b). Some donor–acceptor complexes do not involve normal covalent bonding. Instead, they

are held together by one molecule donating electrons, or perhaps sharing a hydrogen atom, with another.

A classic example of a donor–acceptor complex is formed by silver ions (Ag^+) and ethene ($CH_2{=}CH_2$), in which the ethene donates some electrons from its double bond to Ag^+ (Figure 2.1a). The interaction is not so strong that it leads to a covalent bond, but it is strong enough to form a stable complex.

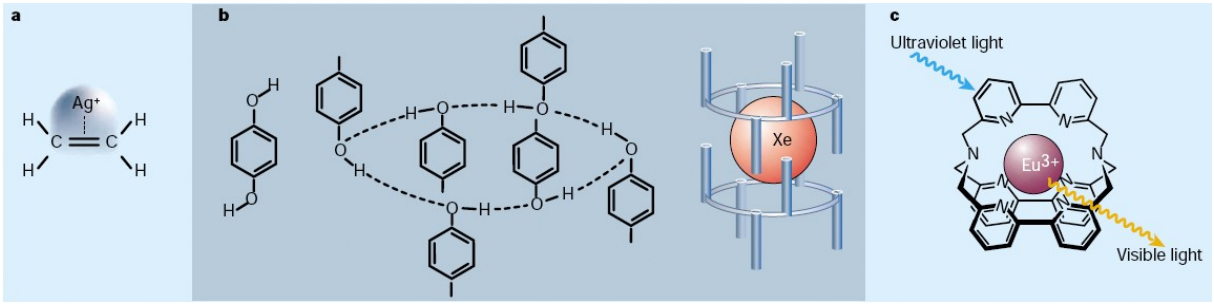


Figure 2.1 *Supramolecular structures formed by intermolecular interactions. a, A donor–acceptor complex involving silver and ethene. b, Hydroquinone molecules assemble into a clathrate using hydrogen bonds. This means they can form solid-state host–guest complexes in which the hydroquinone network is the host and the guest is a small molecule, such as the xenon atom shown. c, A cryptand contains a spherical internal cavity studded with donor sites, suitable for enclosing a metal ion. Ultraviolet light absorbed by the cryptand shown here excites the metal ion, Eu(III), which then emits radiation at longer (visible) wavelengths. (Adapted from reference 1b)*

Back in 1948, H. M. Powell[5] described a series of what he called clathrates — derived from the Latin *clathratus*, meaning 'enclosed by the bars of a grating'. These inclusion compounds are formed when small molecules, such as methanol, hydrogen sulphide or sulphur dioxide, are completely enclosed in cavities formed by a host compound, such as the quinol network (Figure 2.1b). Powell's work was the beginning of what would eventually become a major part of supramolecular chemistry — the design of host cages that allow the selective inclusion and expulsion of guest molecules. One of the oldest uses of clathrates is in crude oil refining, in which undesirable paraffins are removed from gasoline by trapping in clathrate lattices.

The early clathrates were discovered by *chance*, but rational design has led to enhanced properties. For example, a host matrix made from a copper-based polymer material absorbs and releases methane. This organic–inorganic hybrid competes with porous zeolites in its absorptive capacity, and could offer new applications for clathrates, such as the purification of drugs and trapping and storage of toxic materials.[6]

Chemists could not understand these inclusion compounds in terms of normal covalent bonding, and they were often relegated to the fringes of chemistry. But with the discovery of useful properties, chemists had to take these compounds seriously — the citadel of the

isolated molecule was vulnerable after all.

Friedrich Wöhler's synthesis of urea in 1828, the first laboratory synthesis of a naturally occurring compound, symbolized the end of the vitalistic approach to chemistry — the idea that living organisms differ from non-living substances because they possess a 'vital force'. But with the arrival of Emil Fischer and supramolecular chemistry, chemists are now more than ever concerned with the transition from chemistry to biology.

How do life processes work?

The fantastic levels of specificity achieved by biological machines may be reduced to weak interactions, to chemical recognition and function, and inexorably down to physics itself. Yet, a reductionist approach is simplistic beyond the extreme. A scientifically more acceptable view of vitalism is that living and non-living matter differ not in content but rather in *organizational complexity* — and our understanding of this theme may well turn out to be the biggest breakthrough in supramolecular science.

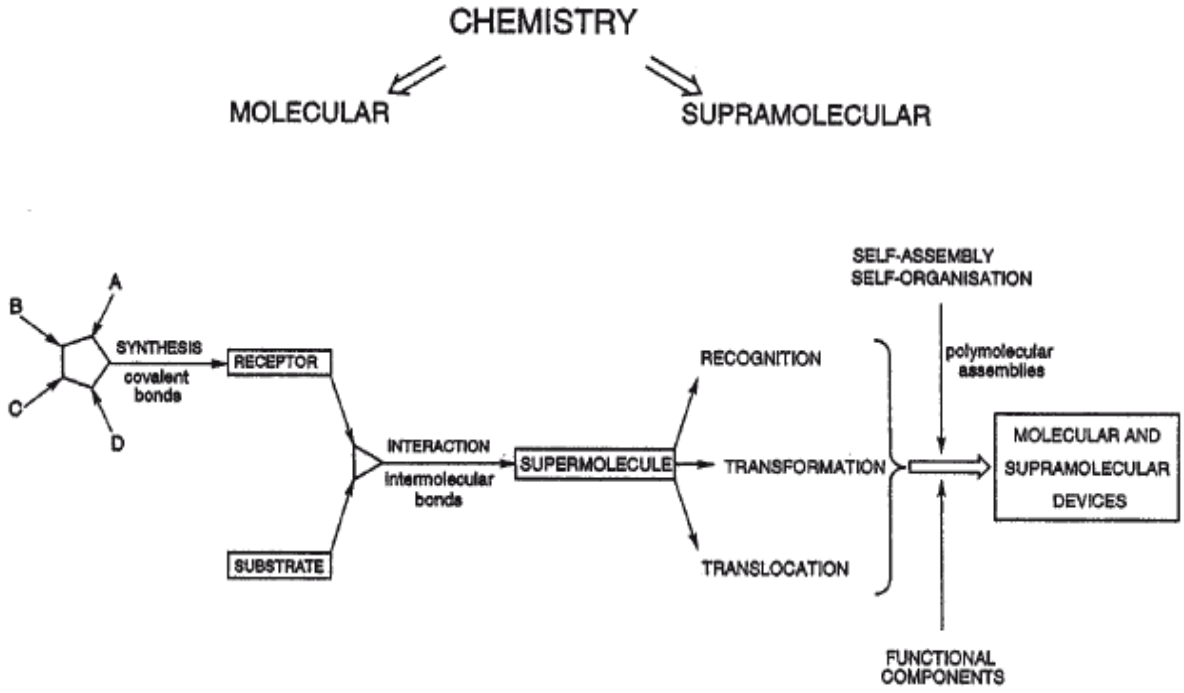
The term supramolecular chemistry was coined in 1969 by Jean-Marie Lehn in his study of inclusion compounds and cryptands (Figure 2.1c)[3]. The award of the 1987 Nobel Prize in Chemistry to Charles Pedersen, Donald Cram and Lehn signified the formal arrival of the subject on the chemical scene. Lehn defined s*upramolecular chemistry* as *"the chemistry of the intermolecular bond"*. Just as molecules are built by connecting atoms with covalent bonds, supramolecular compounds are built by linking molecules with intermolecular interactions. Supramolecular structures are the result of not only additive but also cooperative interactions, and their properties generally follow from their supramolecular character. So even with the clathrates, *their whole is more than the sum of their parts.*

These properties are important in both materials science (magnetism, conductivity, sensors, nonlinear optics) and biology (receptor–protein binding, drug design, protein folding)[3].

In any supramolecular assembly, a large number of intermolecular interactions is possible — but only a few are actually observed. The weakness of these interactions makes it difficult to predict supramolecular structures and means that, in solution, supramolecular structures are not always stable over time. But this flexibility also means that they are frequently favoured in important mechanisms, notably in biological reactions and in crystallization processes, where the ability to form short-lived transition states and to perform trial-and-error correction easily is essential.

2.2 From molecular to supramolecular chemistry

Over the last 150 years, molecular chemistry has developed a very powerful arsenal of procedures for making or breaking covalent bonds between atoms in a controlled and precise fashion and has implemented them for constructing ever more sophisticated novel molecules and materials, presenting a range of original properties of broad interest for basic and applied science. Beyond molecular chemistry based on the covalent bond, supramolecular chemistry aims at developing highly complex chemical systems from components interacting via non-covalent intermolecular forces (Scheme 2.1). It has over the last 40 years or so grown into a major field of investigation and has fuelled numerous developments at its interfaces with biology and physics, leading to the emergence and progressive establishment of supramolecular science and technology.[3,7]



Scheme 2.1 *From molecular to supramolecular chemistry: molecules, supermolecules, molecular and supramolecular devices. (Adapted from reference 11)*

Supramolecular chemistry has paved the way for the implementation of the concept of *molecular information* in chemistry, with the aim of gaining progressive control over the spatial (structural) and temporal (dynamic) features of matter and over its complexification through *self-organization*[3,8-10]. By appropriate manipulation of intermolecular non-covalent interactions, it explored the storage of information at the molecular level in the structural (geometrical and electronic) features of the molecules and its retrieval, transfer, and

processing at the supramolecular level via interactional algorithms operating through molecular recognition events based on well-defined interaction patterns (hydrogen bonding arrays, sequences of donor and acceptor groups, Van der Waals shapes, ion coordination sites, etc). This involved the design and investigation of more or less strictly preorganized molecular receptors of numerous types, capable of binding specific substrates with high efficiency and selectivity, i.e. through processes of high information content. Such developments lead to perceiving chemistry as an *information science*[11], *the science of informed matter*, involving an ever clearer perception, deeper analysis, and more deliberate application of the information paradigm in the elaboration and transformation of matter, thus tracing the path from merely condensed matter to more and more highly organized matter towards systems of increasing complexity. In chemistry, as in other areas, the language of information is extending that of constitution, structure, and transformation as the field develops towards more and more complex architectures and behaviours. It will influence profoundly our perception of chemistry, how we think about it, and how we perform it.

Three main themes line the development of supramolecular chemistry. The first one, *molecular recognition*, relies on design and preorganization and implements information storage and processing. The second, the investigation of *self-organization and self-processes* in general, relies on design; it implements programming and programmed systems. The third, *emerging phase*, introduces adaptation and evolution, based on self-organization through selection in addition to design, and implements chemical diversity and 'informed' dynamics.9

2.3 Molecular recognition via base-pairing and self-organization

Beyond molecular chemistry, supramolecular chemistry aims at constructing highly complex, functional chemical systems from components held together by intermolecular forces. Numerous molecular receptors capable of selectively binding specific substrates *via* non-covalent interactions have been developed; because it is generally reversible and under thermodynamic control, it naturally includes proof-reading to remove errors. They perform *molecular recognition* which rests on the *molecular information* stored in the interacting species.

The control provided by recognition processes allows the development of *functional molecular* and *supramolecular devices*, defined as structurally organised and functionally integrated systems built from suitably designed molecular components performing a given action (*e.g.* photoactive, electroactive, ionoactive, *etc.*) and endowed with the structural features required for assembly into an organised supramolecular architecture. Thus emerged

the areas of *supramolecular photonics, electronics, ionics* [12-21]

Suitably modified receptors act as carriers for the selective transport of various types of substrates through artificial or biological membranes. Again, many further developments may be envisaged, concerning for instance the construction of selective membrane sensors or the transport of drugs through biological barriers which may include designing artificial vectors for gene therapy and targeting if suitable target-selective recognition groups are introduced.

Recognition, reactivity, and transport represent the three basic functional features of supramolecular species (Scheme 2.1).

One the most enchanting examples in nature is the recognition processe in DNA and RNA systems that define the feature of double helical systems. They also play a critical role in stabilizing other higher-order structures, such as hairpin loops, and thus in the broadest sense can be considered as key requisites to the successful translation and replication of genetic information (Figure 2.2). The formation of duplex DNA from its single stranded constituents is a result of a set of intermolecular forces, including aromatic π-stacking, van der Waals forces, and hydrophobic effects.[22] However, the high fidelity observed in the pairing of complementary DNA sequences is largely due to the unique molecular recognition capability of naturally occurring nucleic acid bases (nucleobases) via Watson–Crick pairing and hydrogen-bonding interactions.[23-24] Related interactions also play a critical role in stabilizing higher-order RNA structures, such as hairpin loops, whereas so-called Hoogsteen base-pairing is important in the formation of triple helix DNA and so-called G-quartets. Thus, in the broadest sense, hydrogen-bonding interactions involving base-pairs must be considered as playing a salient role in such critical areas as genetic coding, biological information storage, and protein synthesis.

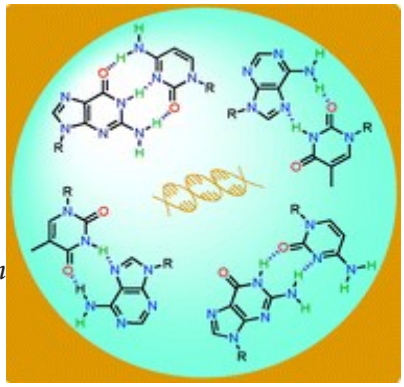


Figure 2.2 *Versatile hydrogen-bonding motifs through nucleobase-pairing. (Adapted from reference 25)*

The Sessler's group and others have been to go beyond the natural realm and to use complementary nucleobase-pairing to construct novel supramolecular assemblies (dimers, trimers, tetramer, macrocycles. polimers and helices) with possible applications in materials chemistry and nanotechnology.[25]

The different possibilities of interactions through self-recognition with different informations stored into covalent-bond structures offer huge combinations to building up self-assemblies structures. In the following figures we present a summary of the various modes of hydrogen-bonding between nucleic acids. The Watson–Crick motif (Figure 2.3), found in a range of DNA- and RNA-containing structures, is the most widely recognized hydrogen-bonding interaction in Nature. This canonical motif is defined by the pairing of guanosine with cytidine and adenosine with either thymidine or uridine. The guanosine–cytidine (GC) couple ($K_a \approx 10^3$–10^5 M^{-1} in $CDCl_3$)[26] is stabilized by a three-point hydrogen-bonding interaction, while the adenosine–thymidine (AT or AU) grouping (K_a 10^2 M^{-1} in $CDCl_3$)[27] contains a two-point hydrogen-bonding mode. Thus, based solely on the strength of association, the GC couple represents a stronger base-pairing motif. It is therefore more attractive for incorporation as a recognition subunit into new structures. For this reason, GC binding interactions have been widely used by Sessler's group. However, there are many examples where the AT (or AU) Watson–Crick motif has been used with good effect to stabilize a number of elegant supramolecular structures.

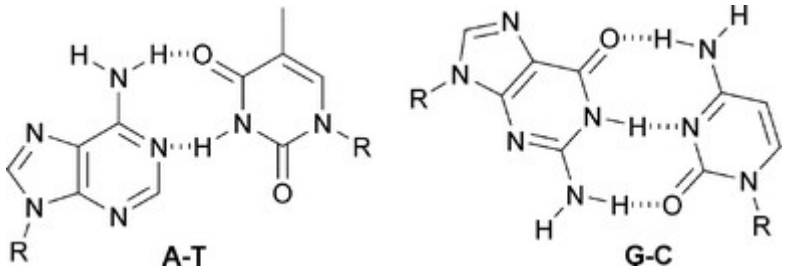


Figure 2.3 *The canonical Watson–Crick hydrogen-bonding motifs. (Adapted from reference25)*

Even though the Watson–Crick mode of bonding is prevalent in natural systems, other hydrogen-bonding motifs are available and expand the possibility for the creation of different structural networks.[28] For example, special attention needs to be paid to the Hoogsteen[29] mode of bonding synthetic self-assembled ensembles (Figure 2.4). Along with Hoogsteen interactions, other non-traditional base-pairs are found extensively in various DNA and RNA structures (Figure 2.4). In addition, these modes are also present in protein–DNA and drug–DNA interactions. Other base-pairing motifs include the wobble (mismatched) form, reverse Hoogsteen and reverse wobble. The various reverse modes are defined by a trans or antiparallel conformation of the two sugar moieties, here indicated with R.[28] Due to nucleobase tautomerization and ionization, other dimeric interactions have also been observed

but are far less common. Because many pairing modes are possible, trimers and high-order assemblies can be formed from nucleobases. Further, the aforementioned binding modes can be used in conjunction with other intermolecular forces to prepare synthetic molecular cages and supramolecular polymers.

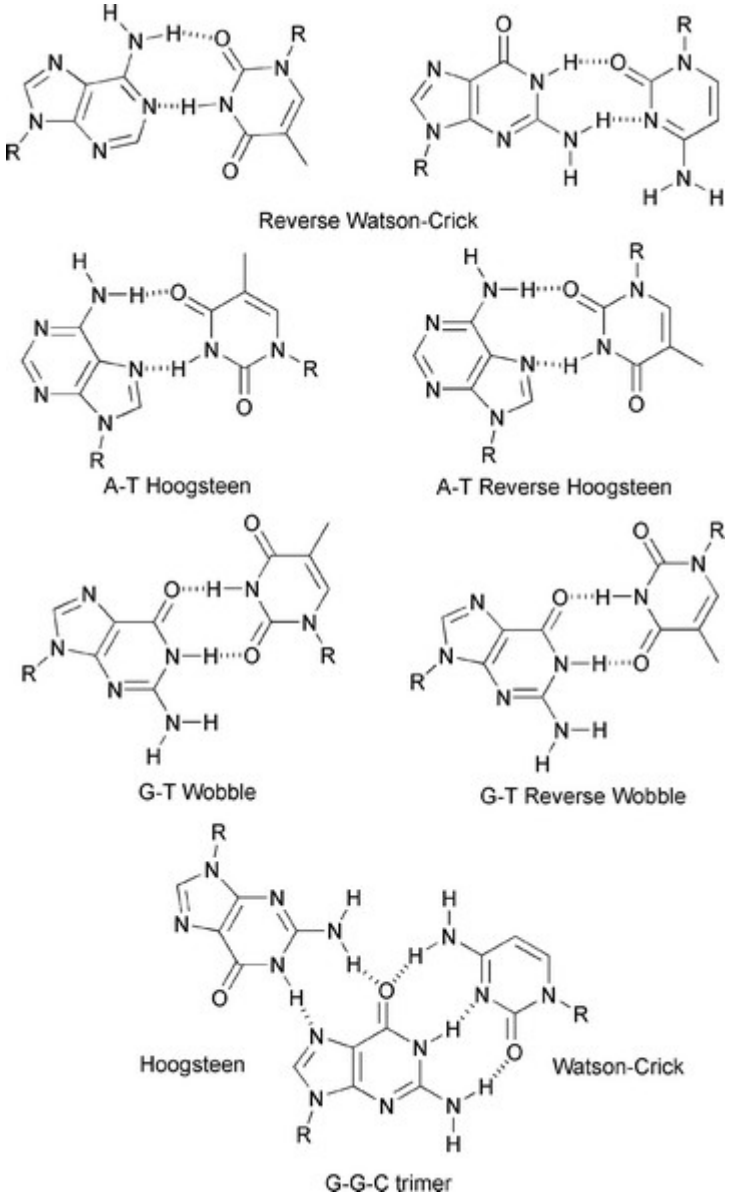


Figure 2.4 *Non-traditional base-pairing motifs. (Adapted from reference 25)*

The first efforts by Sessler's group were focused on the preparation of dimeric systems as a means of enhancing the recognition efficacy of traditional, single base-pairing modes. Towards this end, a duplex containing two sets of **G1C** base-pairing motifs was constructed (Figure 2.5).[30] Unfortunately, however, spectroscopic dilution studies performed in DMSO (a competitive solvent) revealed a rather low association constant (K_a = 6.8 M^{-1}). The low

binding affinity was attributed to the use of a system that was inherently too flexible, as well as the use of a highly competitive solvent. Therefore, subsequent design generations[31,32] encompassed enhanced rigidity, as well as substituents that would impart increased solubility in non-competitive apolar solvents.

G1C

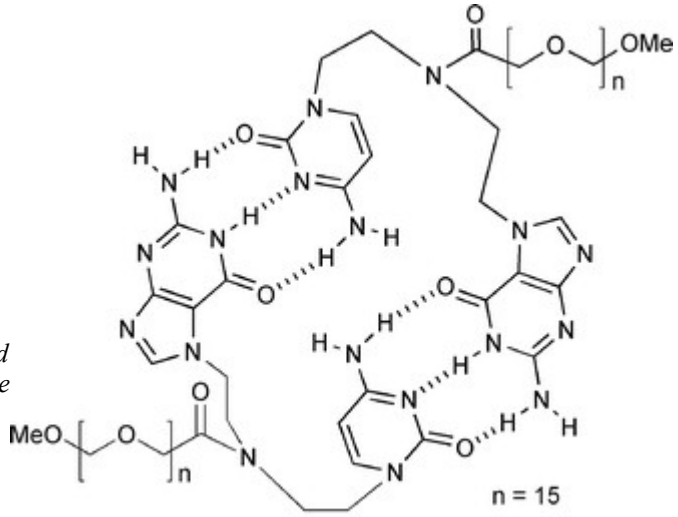


Figure 2.5 *Flexible dimeric ensemble based on* ***G1C*** *coupling. (Adapted from reference 25)*

For this reason Sessler and co-worker developed a new compoud, which is built up from a doubly functionalized anthracene monomer **G1G** (Figure 2.6), is also stabilized via four-point hydrogen-bonding interactions.[33] In this case, the paired ensemble contains four modified guanine subunits, with the net result that a very stable supramolecular structure is generated. In fact, neither dilution to the point that the complex signals could not be distinguished using ^{1}H NMR spectroscopy, nor an increase in temperature led to a detectable decrease in stability.

G1G

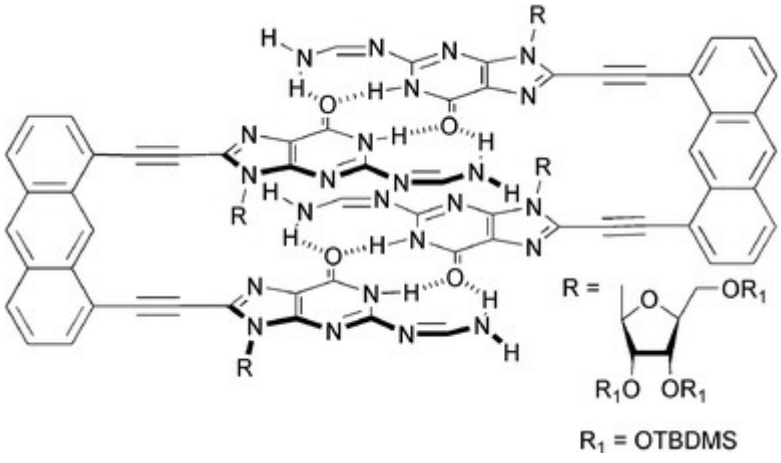


Figure 2.6 *Guanosine ditopic* ***G1G*** *stabilized via multiple four-point hydrogen-bonding interactions. (Adapted from reference 25)*

The construction of such dimeric ensembles, based on enhancing traditional nucleobase

hydrogen-bonding modes, presents researchers with an effective tool to increase association constants and to enhance the stability of self-assembled architectures. Thus, with these dimeric systems in hand, it became apparent that further functionalization could lead to the construction of more complex systems such as supramolecular polymeric arrays, high-order self-assemblies, molecular boxes or capsule systems. Such systems, in turn, are of interest because they could provide a novel means of studying energy and electron transfer in non-covalently bound ensembles.

For istance, an exciting area that has benefited from base-pairing derived ensemble formation is non-covalent energy and electron transfer model generation. Energy and electron transfer events take place in many natural processes such as photosynthesis and phosphorylation. Photosynthetic processes in bacteria occur in membrane-bound protein pigments at a reaction center, while green plant antenna proteins funnel light energy into reaction centers.[34] Once in the reaction center, an electron transfer reaction occurs, producing a charge separated radical–ion pair (CSRP) that is used to drive further chemical reactions. The ability to understand this process has intrigued chemists for quite some time.[35] In this context, Sessler and colleagues came to appreciate that non-covalent model systems might have an important role to play. In particular, they could provide important insights into how various factors, such as driving force, hydrogen-bonding pathways, and inter-chromophore orientations can influence electron and energy transfer rates and thus regulate, in a general sense, biological charge separation processes. The ability of *nucleobase-derived molecular recognition* was elected to pursue such an approach to the construction of the requisite non-covalent model systems. The first contribution from Sessler's group has been reviewed to the early 1990s.[36,37] Until now the goal of Sessler's group was to improve the lifetime of the photoinduced charge separated state changing the flexibility of the assembly system or changing the moieties appended to the nucleobases. The first generation of new electron donor–acceptor systems based on the GC base-pairing (Figure 2.7), incorporated a zinc-porphyrin appended to guanine and a quinone appended to cytosine.[13] Due to the large degree of flexibility inherent in ensemble **1**, a more rigid system, specifically ensemble **2**, was synthesized.[38] Then other effort to improve further the lifetime of the CSRP, a new donor–acceptor system, ensemble **4** (Figure 2.7), was synthesized recently from the same reserch group.[39-40] A cytidine-functionalized zinc-porphyrin was used as the photodonor, while a fullerene (C60) bearing a guanosine recognition unit was used as the electron acceptor.

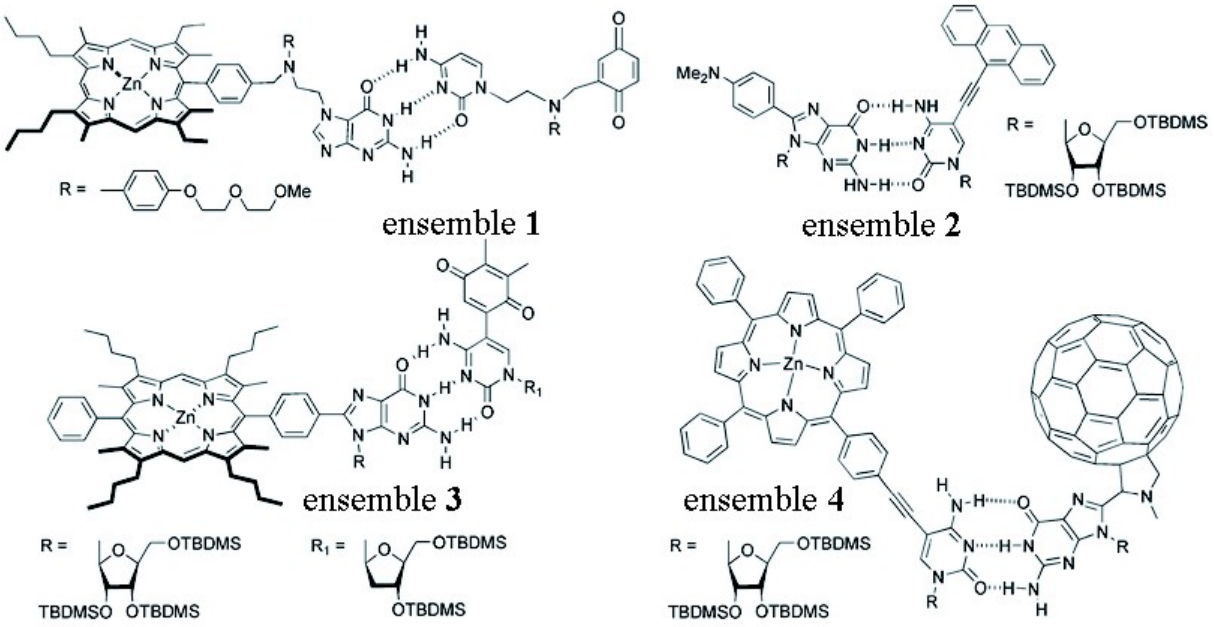


Figure 2.7 *Non-covalent energy and electron transfer model systems developed in the Sessler group. The flexible first generation ensemble* ***1*** *was followed by the more rigid second generation ensembles* ***2*** *and* ***3*** *Also shown is ensemble 4****,*** *which displays improved charge separation characteristics as the result of incorporating a fullerene acceptor subunit. (Adapted from reference 25)*

The supramolecular chemistry of functionalized nucleobases is not limited to the formation of simple dimeric ensembles. Indeed, considerable recent effort has focused on the development of higher-ordered self-assembled systems. For example, the fact that guanine contains functionality that allows it to support both Watson–Crick and Hoogsteen-type interactions makes it an ideal candidate for preparation of higher-order assemblies. In fact, in Nature guanine supports a set of self-assembled structures, including ribbons and G-quartets, polimers and helices. (See chapter 3.2).[41-44]

Given the importance of guanine dimers and homooligomers, it is not surprising that considerable attention has been devoted to the synthesis of higher-order assemblies based on mixed base-pairing interactions (i.e., hetero-pairing). Sessler and coworkers have synthesized a guanosine–cytidine dinucleoside **G2C** that self-associates into a cyclic trimer in organic solvents. They used the potent **G2C** hydrogen-bonding motif to direct assembly formation. An ethylene bridge separates the guanosine and cytidine moieties in **G2C** and preorganizes these groups for formation of the macrocycle via three GC basepairs. This well-defined supramolecular structure may find use in the construction of self-assembled dendrimers and other nanostructures. The ability of such mixed binding motifs to stabilize cyclic ensemble **5** is illustrated in figure 2.8.[45]

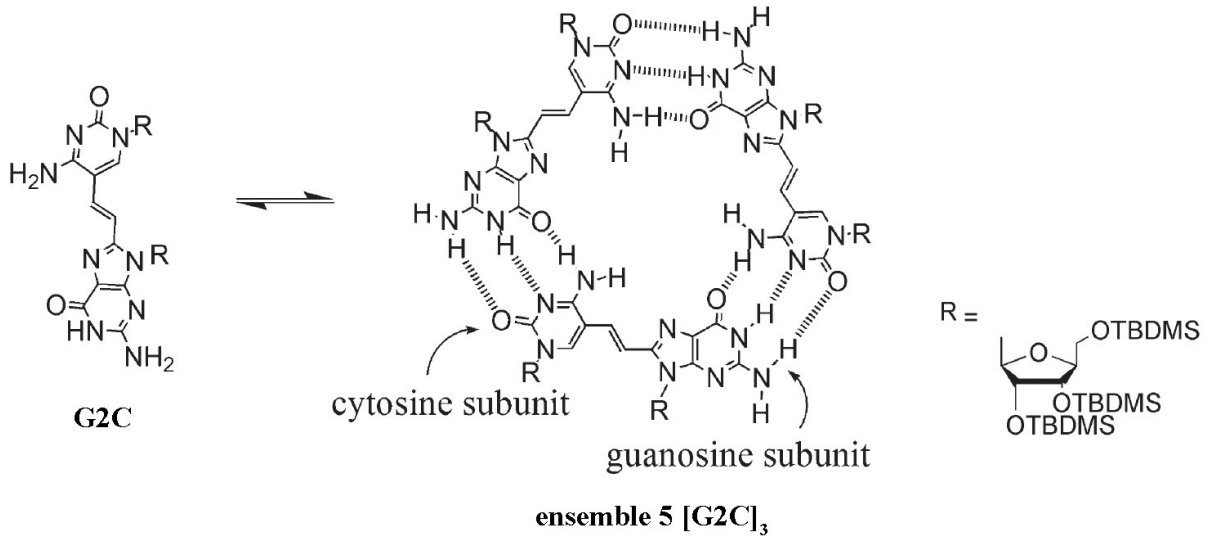


Figure 2.8 *Self-assembly of lipophilic dinucleoside* ***G2C*** *into cyclotrimer* ***[G2C]***$_3$ *(Adapted from reference 25)*

The fact that guanine contains functionality that allows it to support both Watson–Crick and Hoogsteen-type interactions makes it an ideal candidate for preparation of higher-order assemblies. In figure 2.9 is illustrated a ensemble **6** named G-quartet where the planar supramolecular structure is constituted for a hydrogen Hoogsteen-bonded network (see section 3.2).

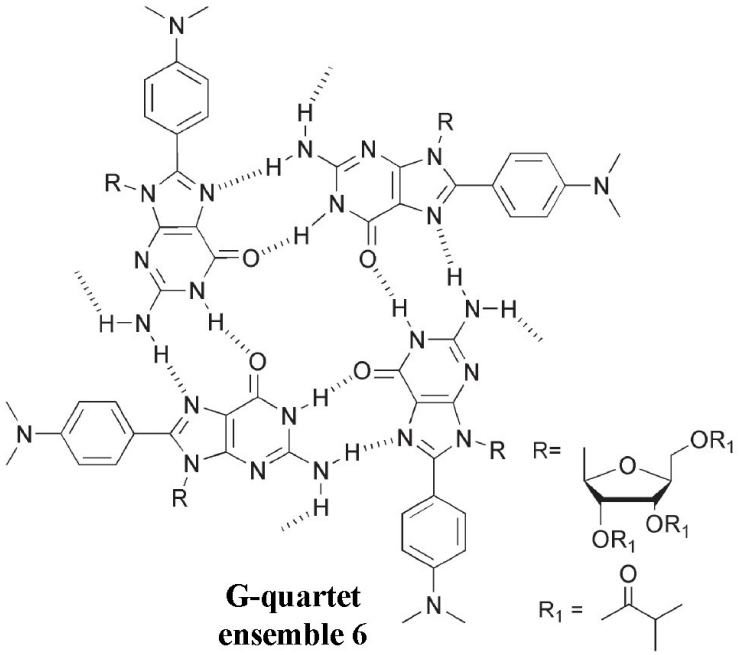


Figure 2.9 *The Hoogsteen-type interactions stabilize a tetrameric self-assembled G-quartet. (Adapted from reference 25)*

In these examples Sessler and co-worker have demonstrated the possibility to achieve optimal molecular recognition rests on the derivation of nucleobase-pairing presenting complementarity in geometry and interactions, through correct construction of one (or both) of the interacting species. Beyond mastering such preorganisation and taking advantage of it, supramolecular chemistry has been actively exploring the design of *systems undergoing self-organisation*, i.e. systems capable of spontaneously generating well-defined, organised supramolecular architectures by self-assembly from their components.[3,10,22, 46-52]

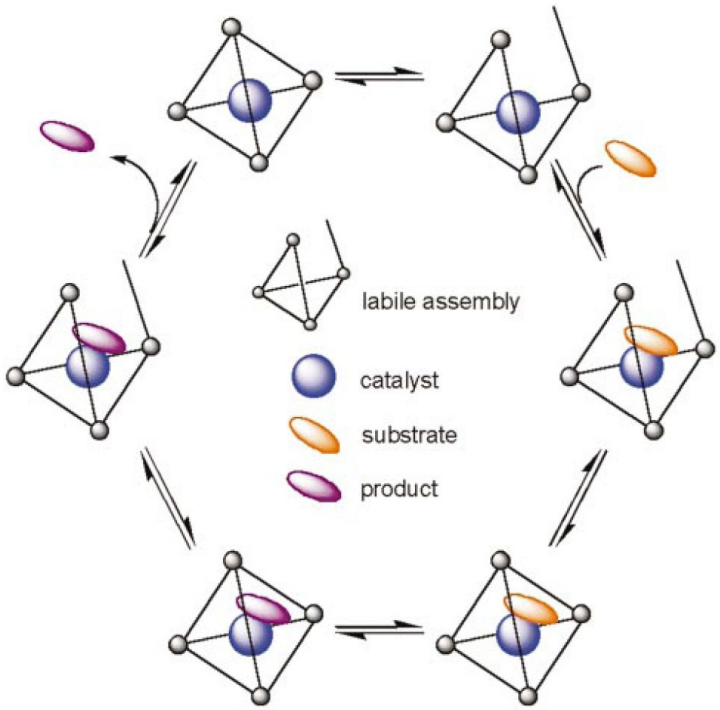
Molecular recognition-directed self-organization, making use of hydrogen bonding, donor–acceptor, and metal coordination interactions for controlling the processes and holding the components together, has given access to a range of supramolecular entities of truly impressive architectural complexity, which otherwise would have been too difficult to construct [3, 7, 13] as well as interlocked mechanically linked compounds.[53]

A *self-organization process* may be considered to involve three main stages: (i) molecular recognition for the selective binding of the basic components; (ii) growth through sequential and eventually hierarchical binding of multiple components in the correct relative disposition; it may present cooperativity and nonlinear behavior; and (iii) termination of the process, requiring a built-in feature, a stop signal, that specifies the end point and signifies that the process has reached completion. These "*self-processes"* directed via the molecular information stored in the covalent framework of the components and read out at the supramolecular level through specific interaction/recognition patterns, may be defined *processing algorithms*. They thus represent the operation of *programmed chemical systems*,[3,46,47] and are of major interest for supramolecular science, engineering and biological evolution. For the formers fields they give access to advanced functional supramolecular materials, such as supramolecular polymers,[54-57] liquid crystals and lipid vesicles[58-60] as well as solid-state assemblies;[61,62] instead for the study of biological evolution these processes represent progressive steps in the control of the self-organization of large and complex supramolecular architectures through natural-molecular programming.[11]

J. M Lehn defined that *self-organisation is the fundamental process that has led to the generation of complex matter, from particles to the thinking organism, in the course of the evolution of the universe. From divided to condensed and on to organized, living and thinking matter, the path is toward an increase in complexity through self-organization.*

In this way, unravelling the mechanisms of the self-organisation of matter offers a most challenging task to chemistry.[9] Moreover, the controlled self-organization of functional systems displaying reactivity and catalysis is crucial for the development of chemical systems

of both structural and reactional complexity. Chemically reactive self-organized entities are formed when the assembling brings together components bearing reactive functional groups. Through the appropriate disposition of specific subunits, they may be amenable to performing efficient and selective reactions and catalysis[22-63] (Scheme 2.2), and in particular result in replication and self-replication processes.[64] It has played a key role in biological evolution[8] and presents a major challenge to supramolecular chemistry.



Scheme 2.2 *Representation of chemical catalysis within a labile assembly. The scheme demonstrates the intertwing of dinamic events and illustrate the critical balance of competing reaction. (Adapted from reference 63)*

Self-organization is the driving force that led up to the evolution of the biological world from inanimate matter[8]. The inclusion of dissipative, non-equilibrium processes, as present in the living world, constitutes a major goal and challenge for the future.[11]

2.4 Dinamics chemical processes (Reversibility, Cooperativity and Flexibility)

Supramolecular chemistry has, from the start, been defined in its structural and bonding features as chemistry beyond the molecule, its entities being constituted of molecular components held together by non-covalent interactions.[7,10,65] The third feature defining its essence, resides in its *dynamic nature*, that was always implicit and operating in all processes investigated, but has been explicitly taken advantage and implemented only in more recent years. Indeed, supramolecular chemistry is intrinsically a *dynamic chemistry* in view of the lability of the non-covalent interactions connecting the molecular components of a

supramolecular entity. The resulting ability of supramolecular species to reversibly dissociate and associate, deconstruct and reconstruct allows them to incorporate, decorporate and rearrange their molecular components. This dynamic character is essential as the supramolecular entities are synthesised or, better, synthesize themselves by self-assembly from their molecular components through more or less rapid exploration of the structure/energy surface. It is thus at the basis of the generation of the highly complex architectures held together by hydrogen bonding, donor–acceptor interactions or metal ion coordination, reported by numerous laboratories.

Detailed understanding of the *dynamic processes* becomes crucial to use supramolecular assemblies to influence reaction chemistry, selectively encapsulate small molecules, or create new nanodevices. Increasingly, the focus is on application of these molecules to other chemistry problems: selective substrate binding, trapping reactive intermediates or protecting unstable species, and influencing reaction chemistry within assembly cavities.

Design of assemblies for specific applications may require full understanding and control of the solution dynamic behavior exhibited by these systems. The mechanisms of formation or ligand exchange for mononuclear metal–ligand complexes are well understood, with individual reaction types categorized and described.[66] In contrast, the description of the dynamic exchange and rearrangements of metal–ligand assemblies presents new challenges in coordination chemistry, will have important impact in the development of supramolecular chemistry, and ultimately may allow for predictable incorporation of desired properties and functionality within complex assemblies.

One of the limiting factors in the study of supramolecular assemblies is their characterization. Rigorous identification of the structures themselves can be difficult because of their large size and extended connectivity.[67] Therefore, study of their dynamic behavior can prove particularly challenging.

In certain metallo-supramolecular systems, the addition of an external agent or a change in solution conditions (photochemically or electrochemically active triggers may also be considered)[68,69] prompts the conversion of one structure to another.

Ghoussoub and Lehn[70] described a dynamic sol–gel interconversion by reversible cation binding and release in G-quartet-based supramolecular polymers. In this system, they described: 1) the formation of gels of supramolecular polymers based on G4 cores consisting of G-quartets - hydrogen bonded supramolecular macrocycles stabilized by binding of metal ions such as K^+, formed from linear ditopic monomers bearing two terminal guanine groups G2G (Figure 2.10); 2) the effect of chemical and physical parameters on these gels; 3) the

regulation of gel formation through reversible sol–gel interconversion via cation K^+ complexation and release by a cryptand [2.2.2] undergoing protonation/deprotonation (Figure 2.10).

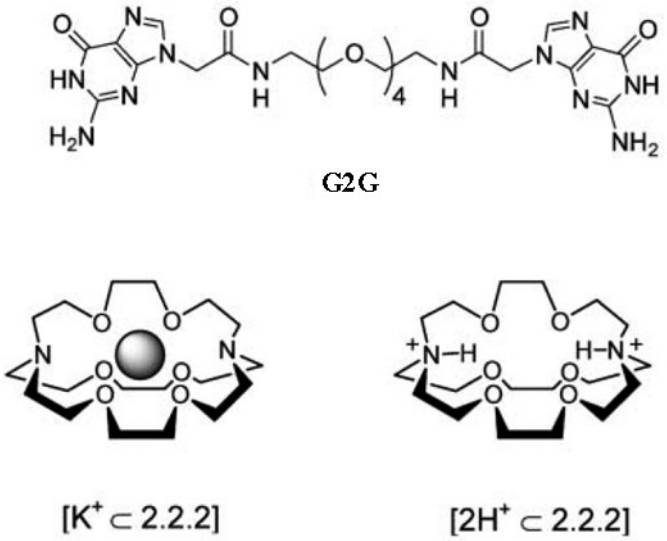


Figure 2.10 *Bis-guanine monomer* ***G2G.*** *The bound K^+ ion into the complexe [K^+ ⊂ 2.2.2] may be released by protonation of the bridgehead nitrogens to give [$2H^+$ ⊂ 2.2.2]. (Adapted from reference 68)*

The gelation properties of **G2G** may be attributed to the formation of extended supramolecular polymeric assemblies based on the formation of hydrogen bonded G-quartet macrocycles stabilized by binding of K^+ cations.[43,71] and presenting probably multiple cross-linking interconnections. The networks formed may be considered to encompass the various superstructures resulting from a combination of a chain of G_4 units interconnected in a double-linear fashion and of a fully cross-linked array (Figure 2.11).

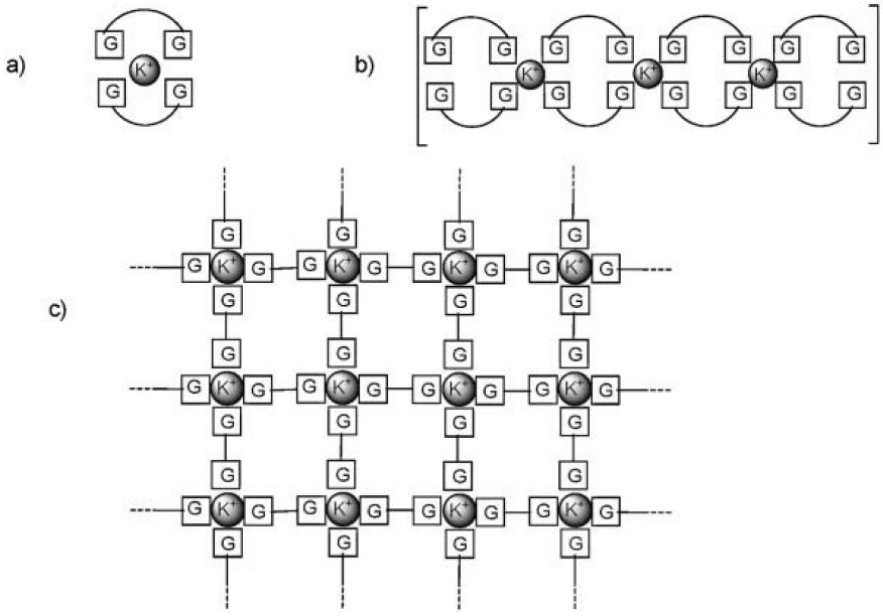


Figure 2.11
Possible supramolecular entities formed by ***G2G*** *through association into G-quartets stabilized by K^+ binding:*
*(a) internally-bridged [(**G2G**)$_2$ K^+] assembly;*
(b) linear chain of doubly-bridged G_4 units;
(c) fully cross-linked regular array of G_4 units. (Adapted from reference 68)

The reversible gel-sol interconversion may be achieved by sequential sequestering and release of the core-stabilizing metal ions, by means of a competing ligand, whose cation binding properties may be modulated by external triggers such as protonation/deprotonation (Figure 2.12). The present system described from Ghoussoub and Lehn represents a class of *supramolecular dynamers*,[72] dynamic polymers of supramolecular nature, whose polyassociation may be controlled by external parameters.

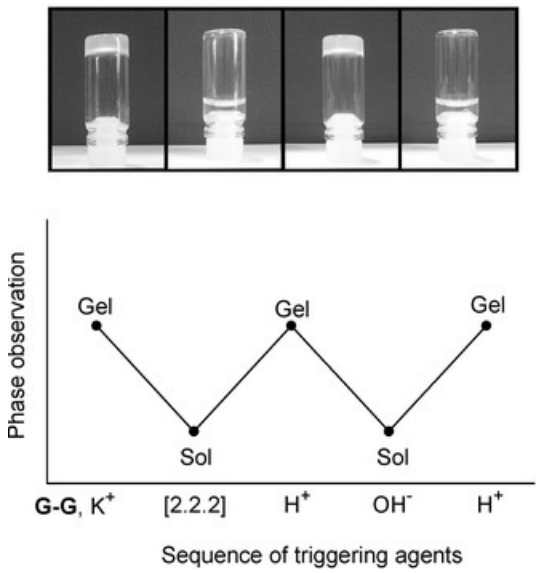


Figure 2.12 *(Top) Visual observation of the reversible gel–sol interconversion of the hydrogel formed by a sample of* ***G2G*** *(10 mM) in 100 mM (10 eq.) KCl. From left to right: initial sample; addition of 10 eq. cryptand [2.2.2]; addition of 10 eq. HCl; addition of 10 eq. NaOH; all samples at room temperature (22 °C).*
(Bottom) Schematic representation of the modulation of the gel–sol status induced by the sequence of triggering agents. (Adapted from reference 68)

Ghoussoub and Lehn were able to control the mesoscale dynamic sol-gel interconversion, i.e., from a disordered guanine solution to gel-forming ordered G-quartet architectures, through reversible cation binding and release.[68] However, a great challenge remains to control the switching between two or more highly ordered guanine-based.

In section 4.2 we described a tunable interconversion between discrete supramolecular assemblies from a lipophilic guanosine, i.e., G-ribbons and G-quartet columns, fueled by cation complexation and release.[73]

Supramolecular chemists are gaining new insight into the motion of supramolecular assemblies. Raymond and co-worker into brief perspective intitled "*Supramolecular assembly dynamics"* inquired: *What do they do and how do they do it?*[63a]

Understanding this dynamic process is sure to shape the design and the application of the assembly chemistry. It must be remembered that the *reversibility, cooperativity and flexibility*

of supramolecular components are essential to their efficient self-asembly also impart dynamic solution properties.63,[74-76] Harnessing the full functionality of these nanostructures will require control over their intricate molecular dynamics.

2.5 From supramolecular chemistry to dynamic combinatorial chemistry (DCC)

> *The spontaneous but controlled generation of complex supramolecular entities by means of suitable components and interactions amounts to performing self-organisation by design.*
>
> *J. M. Lehn*

Until now we have considered two of three overlapping phases in the development of supramolecular chemistry. The first is that of molecular recognition relies on design and preorganization and implements information storage and processing. The second concerns self-assembly and self-organization, i.e., self-processes in general; it relies on design and implements programming and programmed systems. The third, emerging phase, introduces adaptation and evolution; it relies on self-organization through selection in addition to design, and implements chemical diversity and ‘‘informed’’dynamics.

In this section we summarize some experiments by using guanine derivatives reported from Davis, Lehn and Balasubramanian that describe a new branch of the supramolecular chemistry: the “Dynamic Combinatorial Chemistry” (DCC) defined as a combinatorial chemistry under thermodynamic control; where in a dynamic combinatorial library (DCL), all constituents are in equilibrium. This requires the interconversion of library members into one another through a reversible chemical process, which can involve covalent bonds or noncovalent interactions including metal-ligand coordination and metal-dipol interactions. An extensive review was published by Sander and Otto where they shown all the powerfull application of this methodology.[77]

The unique advantage of dynamic combinatorial chemistry over traditional combinatorial chemistry is the fact that library members that engage in noncovalent interactions are favored over their less strongly interacting counterparts. This makes DCLs attractive tools to screen for compounds that play a role in molecular recognition of some kind. At present, the main applications are in (i) identification of the most stable structure in mixtures of structures with different conformational properties (foldamers) (Figure 2.13a),[79-85] (ii) selection of aggregates between library members that can take place through intermolecular noncovalent interactions (Figure 2.13b),[86-92] it has real potential for the discovery of self-assembling molecules including interlocked architectures and new soft materials, (iii) selection of a host or receptor

by a guest (Figure 2.13c),[93-98] (iv) selection of a guest or ligand by a host (Figure 2.13d).[86-87,99-104]

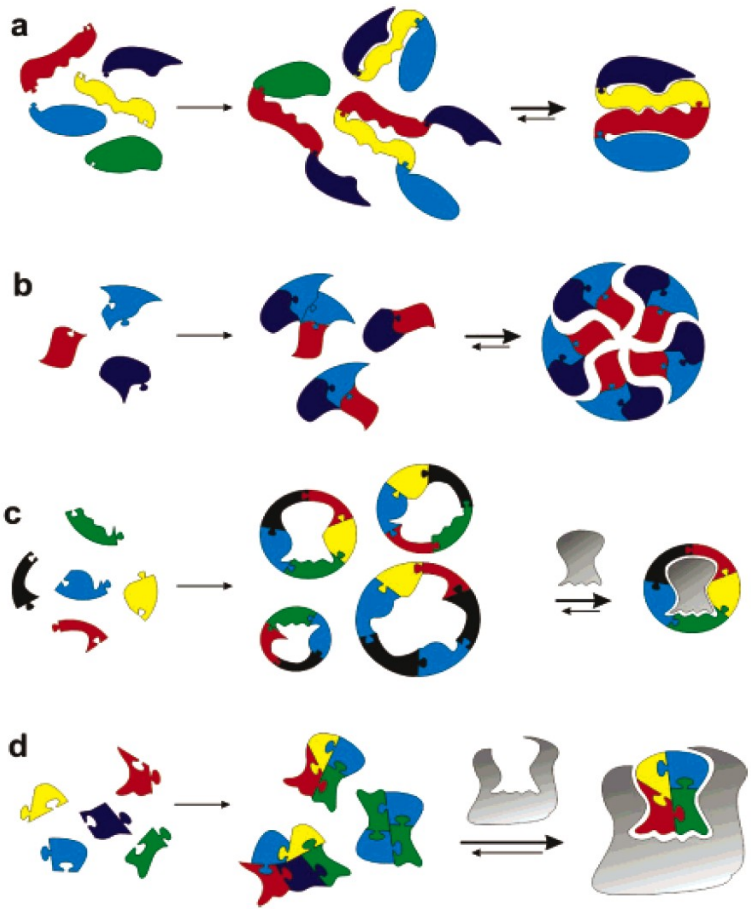


Figure 2.13 *Different ways of selecting specific members of a dynamic combinatorial library on the basis of noncovalent interactions: (a) selection of foldamers driven by internal noncovalent interactions; (b) selection of self-assembling molecules on the basis of noncovalent interactions between different library members; c) selection of a host by a separately introduced guest; (d) selection of a guest by a separately introduced host. (Adapted from reference 77)*

In 2005 Lehn and Sreenivasachary described a G-quartet system in which the formation of a supramolecular hydrogel drives the selection of the components that form the constituent leading to the most stable gel. It embodies a *process of self-organization by selection* under the pressure of gelation. It presents triple process dynamics, two at the supramolecular level and a third one of covalent dynamic nature, which involves *selection by covalent self-assembly* of the component that generates the hydrogel of highest cohesive strength.[105]

The system brings together several features of particular interest, namely (i) self-organization and dynamics at both the supramolecular and molecular levels; (ii) generation of dynamic hydrogels; (iii) *dynamic selection* of the optimal components; (iv) implementation of biochemical components; and (v) *adaptive behavior* in response to external factors.

These dynamic hydrogels were formed by covalent modification of the sugar sidechains that extend from stacked G-quartets. Reaction of hydrogel A formed from 5'-hydrazido **G 1** with a mixture of aldehydes produced a family of acylhydrazones self-assembled to form gel B (Figure 2.14). This dynamic combinatorial library of G-quartet acylhydrazones selected the aldehyde that lead to the most stable gel.

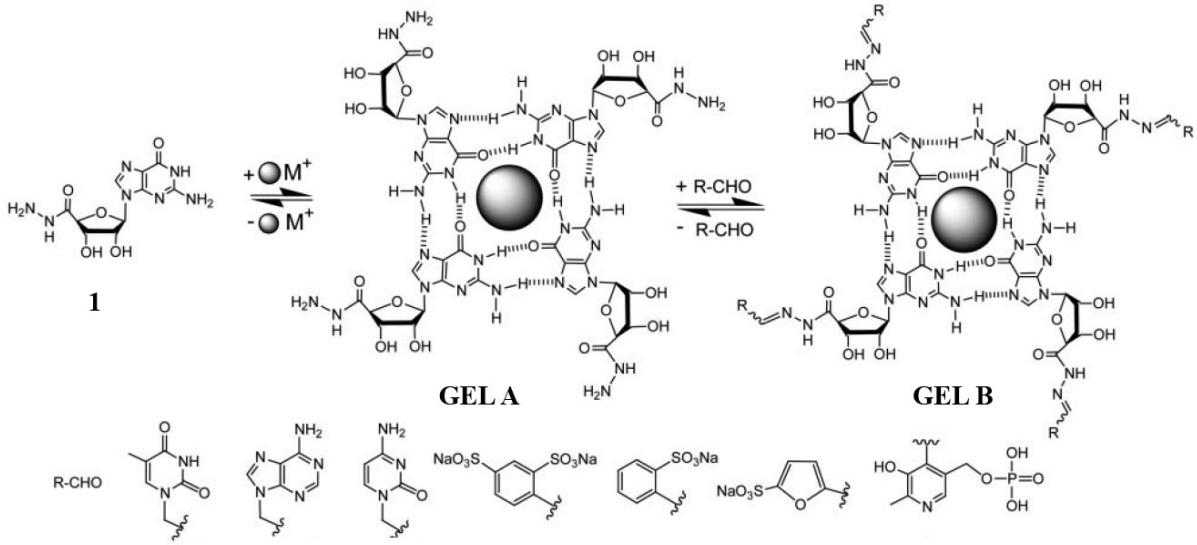


Figure 2.14 *Dynamic hydrogels using a G-quartet assembly by condensation with various aldehydes. (Adapted from reference 105)*

The G-quartet system wherein component selection from a DCL is driven by the physical properties of the product. They shown that **guanosine hydrazide 1** formed thermally reversible gels at moderate pH in the presence of both Na^+ and K^+. These gels presumably are formed by the stacking and interlocking of G-quartets. The 5'-hydrazide in the G-quartet gels A was reacted with a library of aldehydes to form acylhydrazone bonds, allowing the authors to study the effects of sidechain modification on gel properties B. While addition of some aldehydes destroyed the hydrogels, other aldehydes formed acylhydrazone gels that were stronger than the parent gel formed from **hydrazide G 1.** These findings prompted Lehn and Sreenivasachary to determine whether the thermodynamic stability of the gel phase might actually drive the component selection in their DCL. Thus, a mixture composed of 4 acylhydrazones (A-D in Figure 2.15), formed from reaction of **aldehydes 2** and **4** with **hydrazides G 1** and **serine 2**, was generated under conditions where the 5-acylhydrazones could equilibrate by undergoing reversible bond cleavage and reformation. The product mixture, measured by ^1H NMR, was sensitive to temperature. At 80 °C, above the gel transition temperature, the distribution of products was statistical, indicating that the 4 acylhydrazones (A–D) were of similar stability. Between 25–55 °C, acylhydrazone B, in its

gel-state, and C in solution were favored over acylhydrazones A and D. In this case, self-assembly of **G hydrazide 1** was driven by selection of the components that gave the most stable hydrogels B.

The stability of the G-quartet hydrogel altered the dynamic equilibrium of acylhydrazones and directed reaction of the **G hydrazide 1** with **aldehyde 2**. Lehn explained that the process amounts to gelation-driven self-organization with component selection and amplification based on G-quartet formation and reversible covalent connections. This DCC approach may well have broad applications in medicinal chemistry and material science.

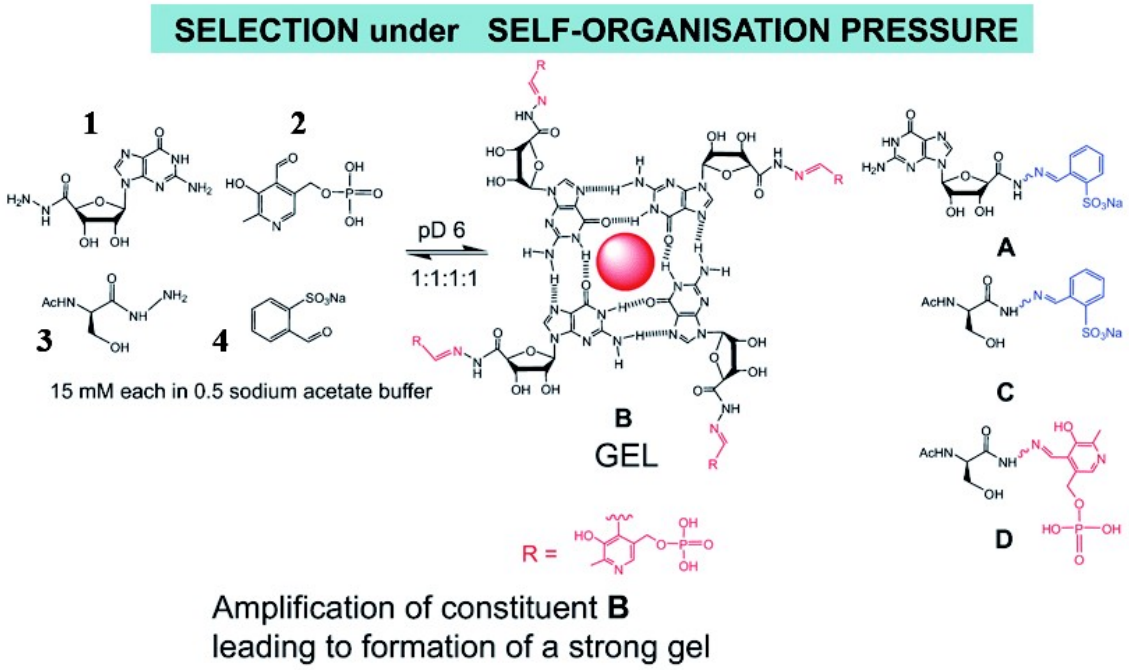


Figure 2.15 *Generation of a dynamic library of acylhydrazones C, D and of the acylhydrazone G-quartets A and B from hydrazides **1**, **3** and aldehydes **2** and **4**.*

A simple and fashion example of selective activity (self-sorting) is shown from lipophilic guanosine derivatives that spontaneously form macrocycles that act as receptors for alkali and Ba^{2+} cations in organic solvents.[106]

The Davis's original intent was to determine if guanosine **G 5** and iso-Guanosine **isoG 6** would form a Watson–Crick base pair (Figure 2.16).[107] In the process, they found that **G 5** and **isoG 6** self-associate in a cation-dependent process to give hydrogen-bonded macrocycles in organic solvents. Crystal structures show that **G 5** forms assemblies based on hydrogen-bonded tetramers (G-quartets),[108,109] and **isoG 6** gives hydrogen-bonded pentamers (Figure 2.17).[110] The G-quartet is a well-known motif in nucleotide and DNA structure,[111,112] while a pentaplex has been formed from isoG-oligonucleotides and Cs^{+}.[113] These different self-assembled units can be ascribed to the orientation of the nucleobase's hydrogen bonding

groups (Figure 2.17).[110,113] For **G 5**, the donor and acceptor sites are located 90° relative to each other, an orientation that is optimal for formation of a cyclic tetramer. The angle between **isoG**'s hydrogen bonding donor and acceptor groups is close to 110°, favoring a cyclic pentamer. In these systems, a cation is almost always required to stabilize the hydrogen-bonded macrocycles.[114] With regard to the alkali ions, the G-quartet from **G 5** is moderately selective for binding K^+ over Na^+ and Rb^+. In contrast, the expanded **isoG** pentamer is highly selective for binding the larger Cs^+ ion,[110] although **isoG 6** will complex all of the alkali cations. The larger size of the **isoG 6** pentamer, relative to the **G 5** quartet, also explains the different ion binding selectivity shown by these derivatives. **IsoG 6** is selective for coordinating the largest alkali cation, Cs^+ (r = 1.67 Å), whereas G-quartets are K^+ selective (r = 1.33 Å).[113]

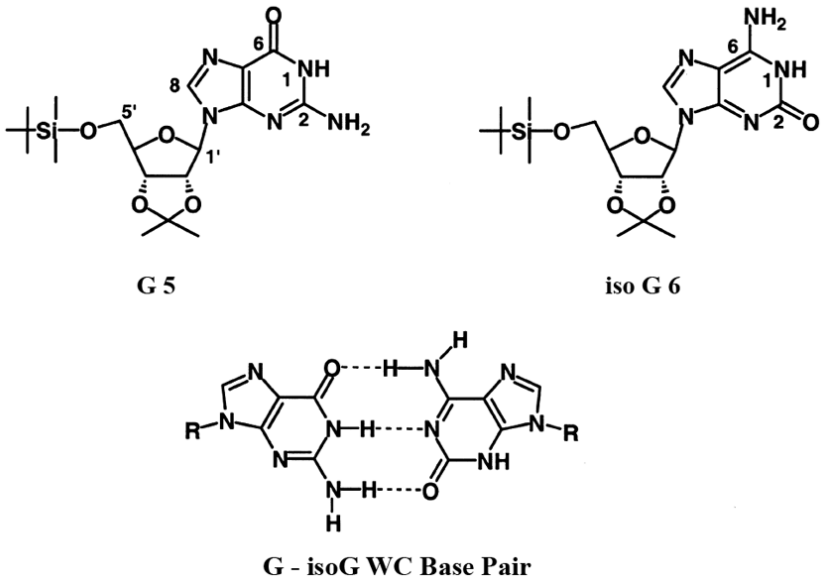


Figure 2.16 *Chemical structure of* ***G5***, ***isoG6*** *and relative interaction Watson–Crick base pair.*

IsoG 6 is an isomer of guanosine, differ only in the transposition of an oxygen and nitrogen atom, this simple positional change in molecular structure leads to significant differences in the supramolecular organization and cation selectivity for the two assemblies. Both **G 5** and **isoG 6** can further aggregate by cation-stabilized stacking of hydrogen-bonded layers. Thus, **G 5** forms a hexadecamer composed of four stacked G-quartets,[108,109] while **isoG 6** gives a sandwich decamer [**isoG 6**]$_{10}$·M^+ (Figure 2.18).[109,110]

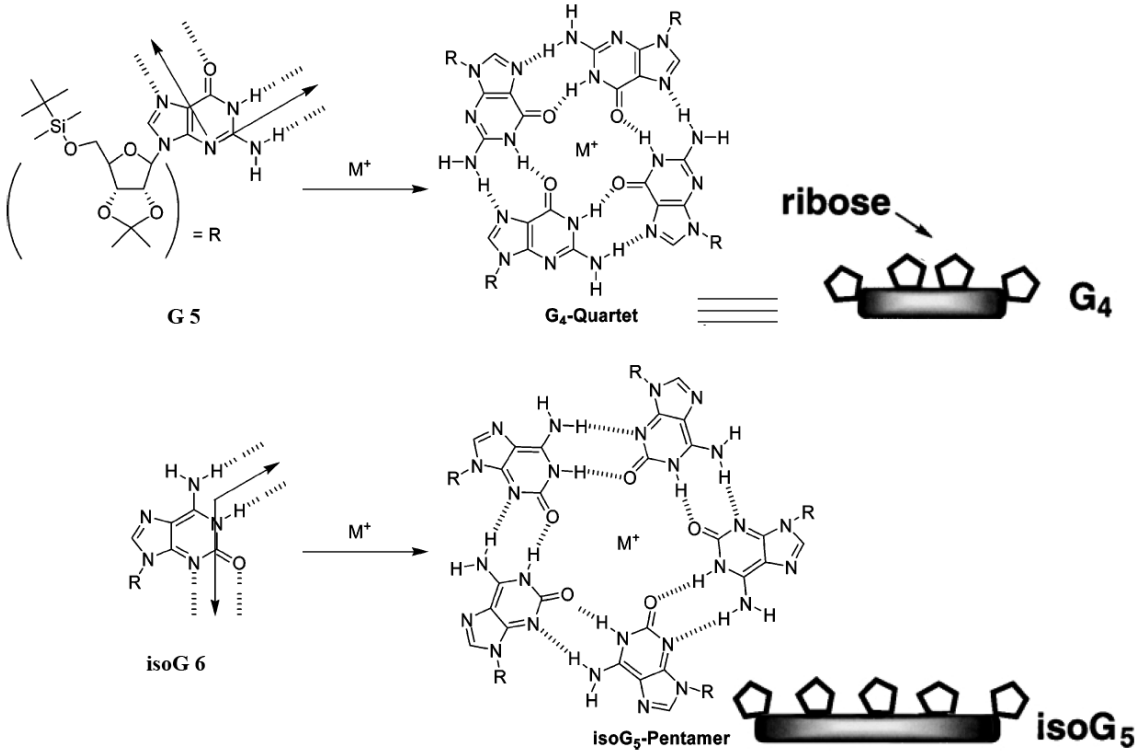


Figure 2.17 *DCLs of macrocycles using hydrogen-bonding and metal-ligand interactions. Lipophilic nucleosides* ***G 5*** *and* ***isoG 6*** *self-associate in the presence of cations to give G4-quartets or isoG$_5$-pentamers. The orientation of the nucleoside's hydrogen bond donor and acceptor groups determines assembly size.*
(Adapted from reference 4)

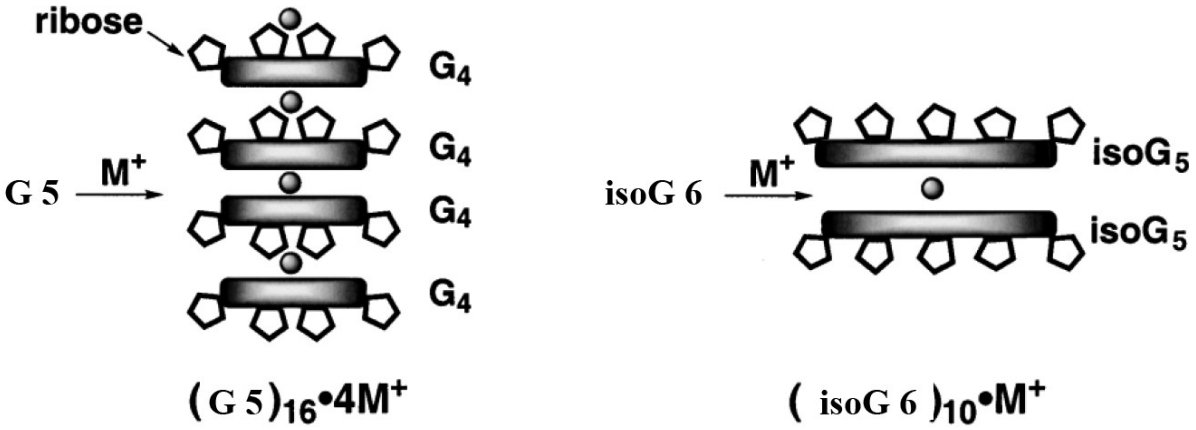


Figure 2.18 *The G4-quartets and isoG5-pentamers stack in the presence of cations.* ***G 5*** *binds metal cations to give a hexadecamer composed of four G4-quartets.* ***IsoG 6*** *binds metal cations to form a sandwich decamer.*

Davis and colleagues conducted a *self-sorting study* in CD_2Cl_2 to illustrate how the cation dictates the self-assembly patterns for **G 5** and **isoG 6**.[106] An equimolar mixture of the two isomers in CD_2Cl_2 , in the absence of cations, formed a mix of hydrogen-bonded species. Addition of Ba^{2+} to this mixture gave quantitative formation of two discrete hydrogen-bonded

complexes, four G tetramers stacking around two Ba^{2+} ions, $(G)_{16}Ba^{2+}$, and a sandwich complex of two isoG pentamers around a Ba^{2+} ion, $(isoG)_{10}Ba^{2+}$, were formed. (Figure 2.19).

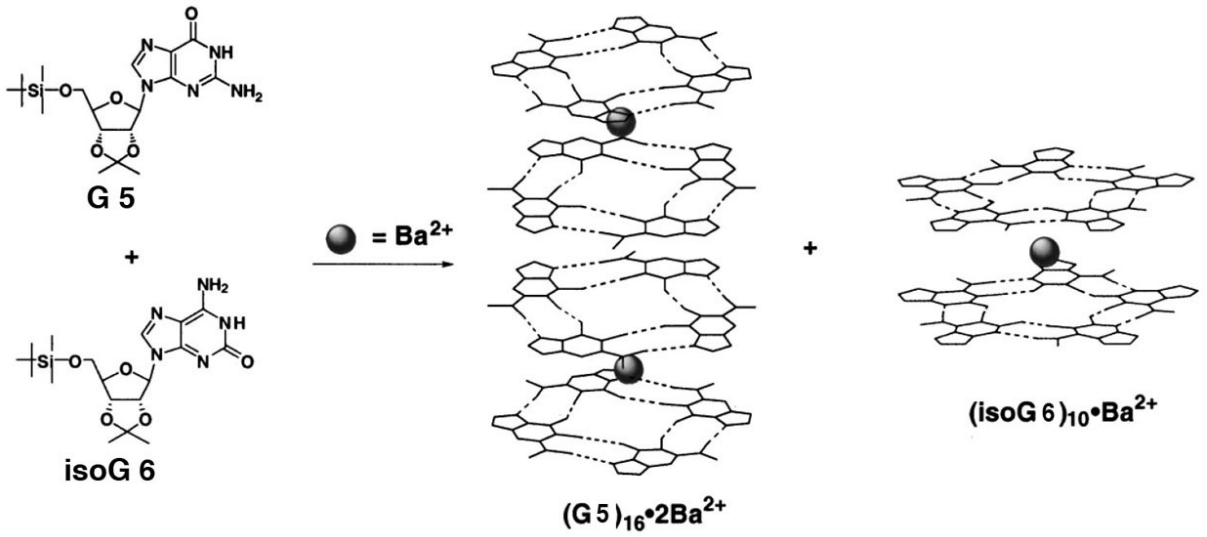


Figure 2.19 *The isomers* ***G 5*** *and* ***isoG 6*** *'self-sort' in the presence of barium picrate to give discrete complexes.*

Before doing the mixing experiment with the isomeric nucleosides and metal cation, Davis first characterized the structures of individual assemblies formed by **G 5** and **isoG 6** in the presence of Ba^{2+} picrate. Proton NMR showed that **G 5** extracts Ba^{2+} picrate from water into CD_2Cl_2 to give a hydrogen-bonded complex with 8 equiv. of nucleoside bound to each Ba^{2+}: an hexadecamer in CD_2Cl_2 solution (Figure 2.20 D).[109] A crystal structure of $[\mathbf{G\ 5}]_{16}{\cdot}2[BaPic_2]$ confirmed that 16 units of **G 5** associate around two Ba^{2+} cations to form a G-quadruplex with four stacked G-quartets.[109] NMR integration also showed that **isoG 6** extracts Ba^{2+} picrate from water into CD_2Cl_2 to give a complex with a 5:1 nucleoside–picrate stoichiometry (Figure 2.20 E), consistent with a decamer, $[\mathbf{isoG\ 6}]_{10}{\cdot}[BaPic_2]$.

Davis next used an equimolar mixture of **G 5** and **isoG 6** to extract Ba^{2+} picrate from water into CD_2Cl_2 (Figure 2.20 F). After the extraction, only ^1H NMR signals for the two separate complexes, $[\mathbf{G\ 5}]_{16}{\cdot}2Ba^{2+}$ and $[\mathbf{isoG\ 6}]_{10}{\cdot}Ba^{2+}$, were present. The spectrum in figure 2.20 F is essentially a composite of spectra obtained from the individual nucleoside complexes (Figure 2.20 D and E). In figure 2.20 F, there was no NMR evidence for cross-association of these two isomers in the presence of Ba^{2+} picrate.

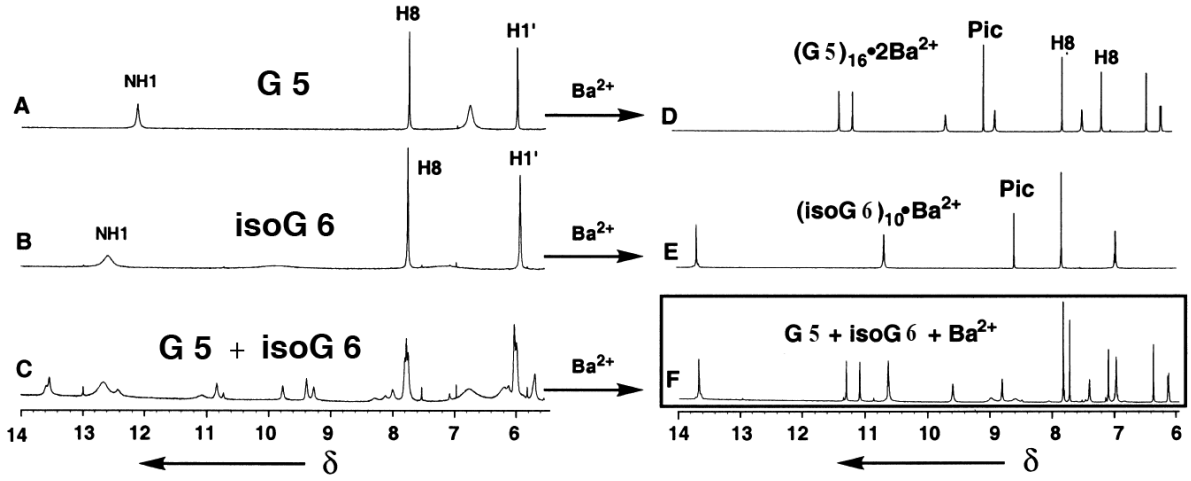


Figure 2.20 *A series of 1H NMR spectra in CD_2Cl_2 at room temperature showing the region from δ 14.0–6.0 ppm. (A) Recrystallized* ***G 5*** *(11 mM); (B) recrystallized* ***isoG 6*** *(11 mM); (C) an equimolar mixture of* ***G 5****(5.5 mM) and* ***isoG 6*** *(5.5 mM) 1 day after mixing; (D) recrystallized* ***[G 5]***$_{16}2Ba^{2+}$ *hexadecamer; (E) recrystallized* ***[isoG 6]***$_{10}Ba^{2+}$ *decamer; (F) an equimolar mixture of* ***G 5*** *(5.5 mM) and* ***isoG 6*** *(5.5 mM) after extraction of* $Ba^{2+}(Pic)_2$ *from water.*

These experiments demonstrated the cation's dynamic central role in expressing the hydrogen-bonding and base-stacking information embedded in the nucleoside monomers.[106] Both **G 5** and **isoG 6** self-associate essentially quantitatively upon addition of Ba^{2+} picrate. The two isomers, each with its own unique hydrogen bonding pattern, are completely sorted into structures composed of G-quartets and isoG pentamers, provided a Ba^{2+} cation is available to direct self-recognition.

This self-sorting illustrated that a cation is needed to template formation of distinct assemblies in solution from this mixture of nucleosides. This experiment was a prime example of the equilibrium shifting that characterizes *dynamic non-covalent chemistry*.

The folding of G-rich peptide oligonucleotides into PNA quadruplex structures in DCLs was reported recently by the Balasubramanian group.[115] PNA was chosen rather than DNA because it is easier to functionalize with amino acids. The tetranucleotides TTTT and TGGG were functionalized with amino acid sequences at both termini in order to provide good solubility, flexibility, and a thiol group for the exchange reaction (Figure 2.21).

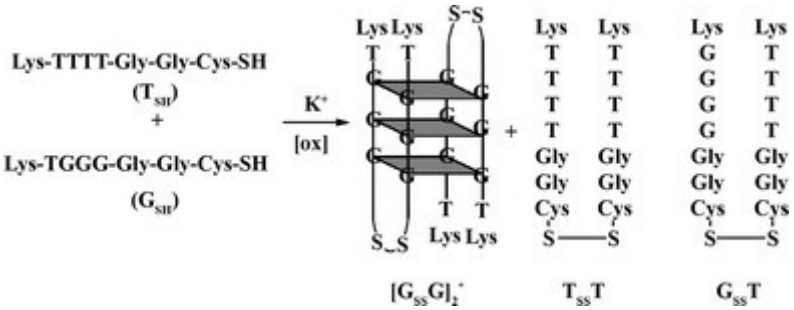


Figure 2.21 *Oxidation of the PNA strands TSH and GSH provides disulfides. In the presence of K^+,* ***$G_{SS}G$*** *is amplified. (Adapted from reference 115)*

Upon oxidation under kinetic control, the dimers **$T_{SS}T$**, **$G_{SS}T$**, and **$G_{SS}G$** were formed in an essentially statistical ratio. However, under thermodynamic control, and in the presence of potassium ions, self-sorting occurred, and a dimerization of $G_{SS}G$ was observed. MS, UV-vis melting experiments, and D/H-exchange NMR studies confirmed that an intermolecular complex of two **$G_{SS}G$** entities was formed. Similarly, when potassium was replaced by sodium or lithium, less or no self-sorting was observed, and DCLs equilibrated at temperatures above the quadruplex melting temperature did not show any amplification. The authors also demonstrated that nucleobase recognition occurs prior to disulfide formation. Formation of **$G_{SS}G$** disulfide depended strongly on the template, being most effective with K^+, the cation that can best stabilize a G-quadruplex.

Another DCC strategy has been used to produce small molecule ligands that bind to DNA G-quadruplexes (Figure 2.22). Previous studies have shown that (i) acridone ligands (A) stack on the terminal G-quartet of a G-quadruplex and that (ii) various peptides (P) interact with the grooves formed by the tetraplex backbone. Balasubramanian and colleagues used a disulfide exchange reaction, with glutathione disulfide and a G-quadruplex template, to identify novel G-quadruplex binders that combine both the acridone and peptide recognition units.[116] Disulfide exchange can be carried out in water under reversible conditions at moderate pH, but the reaction is quenched with acid to determine the composition of products. Using an oligonucleotide of sequence 5-biotin(GTTAGG)5, that contains the human telomere sequence, as a template, Balasubramanian showed a 400% increase in formation of a heterodimeric disulfide **AssP**, a compound containing the acridone (**A 15**) and peptide (**P 16**) domains (Figure 2.22). In addition, the authors discovered that a peptide dimer **PssP** was formed in 5-fold greater amount in the presence of the G-quadruplex. This study established that the DCC approach could identify new G-quadruplex ligands, a potentially important endeavor in the search for potent telomerase inhibitors.

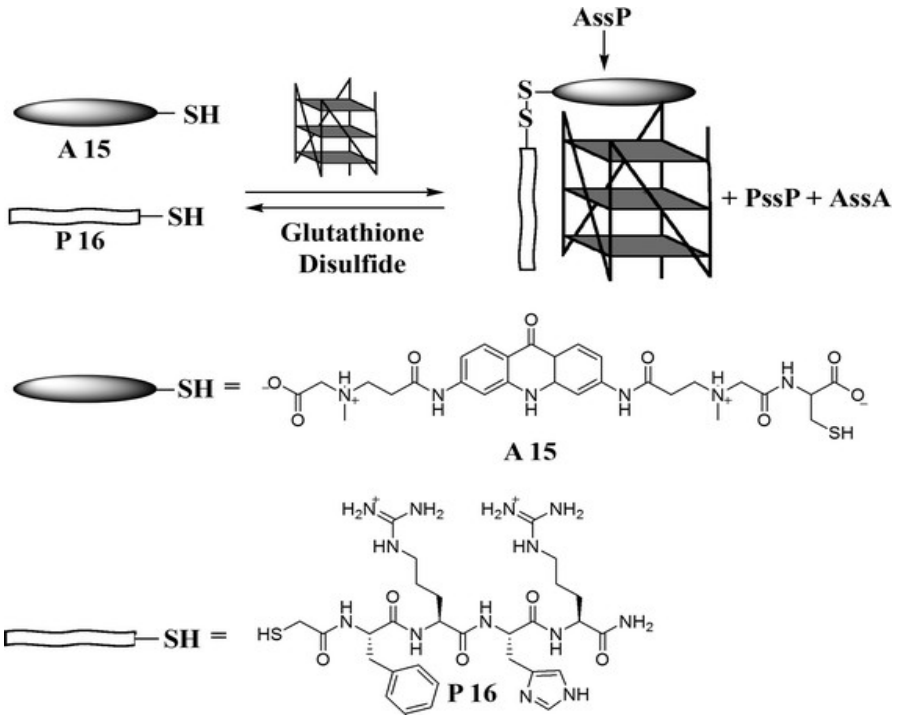


Figure 2.22 *The **AssP** disulfide product is amplified in the presence of a G-quadruplex template. (Adapted from reference 116)*

The basic feature of DCC is its dynamic character that allows for generation of constitutional molecular and supramolecular diversity on which to operate selection in response to the pressure of chemical or physical internal or external factors, thus enabling adaptive chemistry.

Implementation of DCC may be considered from three points of view:

1. the exploration of synthetic systems directed at revealing the basic features of dynamic covalent or non-covalent chemistry;
2. the development of dynamic materials;
3. the application to the search for bioactive substances.

2.6 Conclusion

Whereas molecular preorganization relies entirely on design, supramolecular self-organization introduces in addition the possibility to let the system build up by selection.

Self-organization by design has been pursued with the goal to achieve full control over the output supramolecular entity by means of correctly instructed components, specific interaction algorithms, and (as much as possible) strict programming. Design is knowledge-based and has an explicit information content.

Self-organization by selection requires dynamic diversity (constitutional and or morphological) on which to operate. This is made possible by the implementation of Dynamic Chemistry responding to the pressure of either internal or external factors. Selection has an implicit information content. It is also truly a supramolecular process, because it occurs in relation to interactions with surroundings (which may be either the medium or a more or less distant part of a folded macromolecule). The introduction of the selection paradigm into (supramolecular) chemistry brings about a fundamental change in ways, means, and outlook. Of course, the question is not to replace the deliberately planned linear process of design by a multisection trial-and-error process of selection. *Design and selection are not mutually exclusive but are complementary for reaching systems of higher complexity through self-organization.* The ultimate goal is to merge design and selection in self-organization to perform self-design, where function-driven selection among suitably instructed dynamic species generates the optimal organized and functional entity.

The combination of the features of supramolecular systems - information and programmability, dynamics and reversibility, constitution and diversity - leads toward the emergence of adaptive evolutive chemistry.[15]

Implementing both design and selection, *self-organization offers adjustability* (through self-correction, self-healing under internal dynamics); *adjustability leads to adaptation* (through reorganization under interaction with environmental effectors); *adaptation becomes evolution*, when acquired features are conserved and passed on.

Adaptation is illustrated by functionally driven optimization through selection from pools of dynamically interconverting supramolecular species. Evolutive chemical systems suppose multiple dynamic processes with sequential selection acquisition fixation steps and undergo progressive change of internal structure under the pressure of environmental factors. But the world of selection is a brutal world, where only the fittest survives.

Jean Marie Lehn affirmed:

> *Beyond programmed systems and in line with an evolutive chemistry, the next step in complexity consists in the design of chemical ''learning''systems, systems that are not just instructed but can be trained.*[117]
>
> *The incorporation of the arrow of time, time irreversibility, leads to self-organization in nonequilibrium, dissipative systems through irreversible processes.*[8] *It implies the passage from closed systems to open and coupled systems that are connected spatially and temporally to their surroundings.*[118]

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3. Self-assembling of Guanine Nucleoside derivatives: serendipity or programmed system?

In scientific research, "chance favours the prepared mind"
Louis Pasteur

3.1 Introduction

Fritjof Capra, the bestselling author of "The Tao of Physics", into a second book entitled *"The Hidden Connection"*[1] introduces a new unified framework for the understanding of biological and social phenomena, a framework that enables us to adopt a systemic approach to some of the critical issues of our time. He make a deep analysis of living systems in terms of four interconnected perspectives - form, matter, process, and meaning – it makes possible to apply a unified understanding of life to phenomena in the realm of matter, as well as to phenomena in the realm of meaning. For example, he shown that metabolic networks in biological systems correspond to networks of communications in social systems; chemical processes producing material structures correspond to thinking processes producing semantic structures; and flows of energy and matter correspond to flows of information and ideas.

A central insight of this unified systemic understanding of life is that its basic pattern of organization is the network. At all levels of life - from the metabolic networks inside cells to the food webs of ecosystems and the networks of communications in human societies - the components of living systems are interlinked in network fashion.

Another interesting different point of view for our society is the design of the urban society. It will be shown in an exhibition and workshop during the manifestation of Torino 2008 "The World Design Capital".[2] In this case the object of the discussion will be central into flexibility to design in a fast-changing society: labyrinths of roads, agglomerations of buildings and mazes of relations.

In 2050 over 90% of the world's population will live in cities, places that already today are characterised by growing complexity (see section 1.5). *The urban panorama is a system of close-knit connections between material objects and immaterial factors produced by man*. An often chaotic space, that conditions, restrains and sometimes paralyses movement, considerably reducing the space of individuals' movements. Too often, in fact the structure and products used every day are characterised by rigidity and poor adaptability. In this scenario, flexibility becomes a need and a response at the same time.

Flexibility as a need to break down walls, to leave well-trodden paths, to step away from pre-packaged solutions. Flexibility as a response: an attitude that allows individuals to react to

a context that changes at ever-increasing speed and produces unexpected results, sometimes with an explosive impact.

If the designers and architects question themselves about *bond between flexibility and design*, where flexibility is intended as the ease with which a system or components of it can be modified and adapted for use in different applications or setting to the ones for which they were originally designed, and in the same place, as the diverse ways of designing the world and society starting from a concept of adaptability, from the perspective of transforming town and city environments into more elastic place, durable but also welcoming and changeable spaces, thereby, the chemists may have to work to design cleaver and informed molecules to build up beautiful molecular and supramolecular architectures with activity-structure changeable and adaptable to the surrounding environment to exchange matter, energy and information.

How it is possible to create new functionality for objects, materials and machines ?

The concepts described in the previous sections (i.e. reversibility, flexibility, adaptability and cooperative process) probably they are not sufficient to understand the "magic" development of the Nature world and its living organisms. But a new concept can be introduce to highlight the *creativity of the Nature*, the Serendipity:

> *Serendipity conceals within it all the madness of a creator,*
> *the force of things to choose their destiny and the work of chance.*

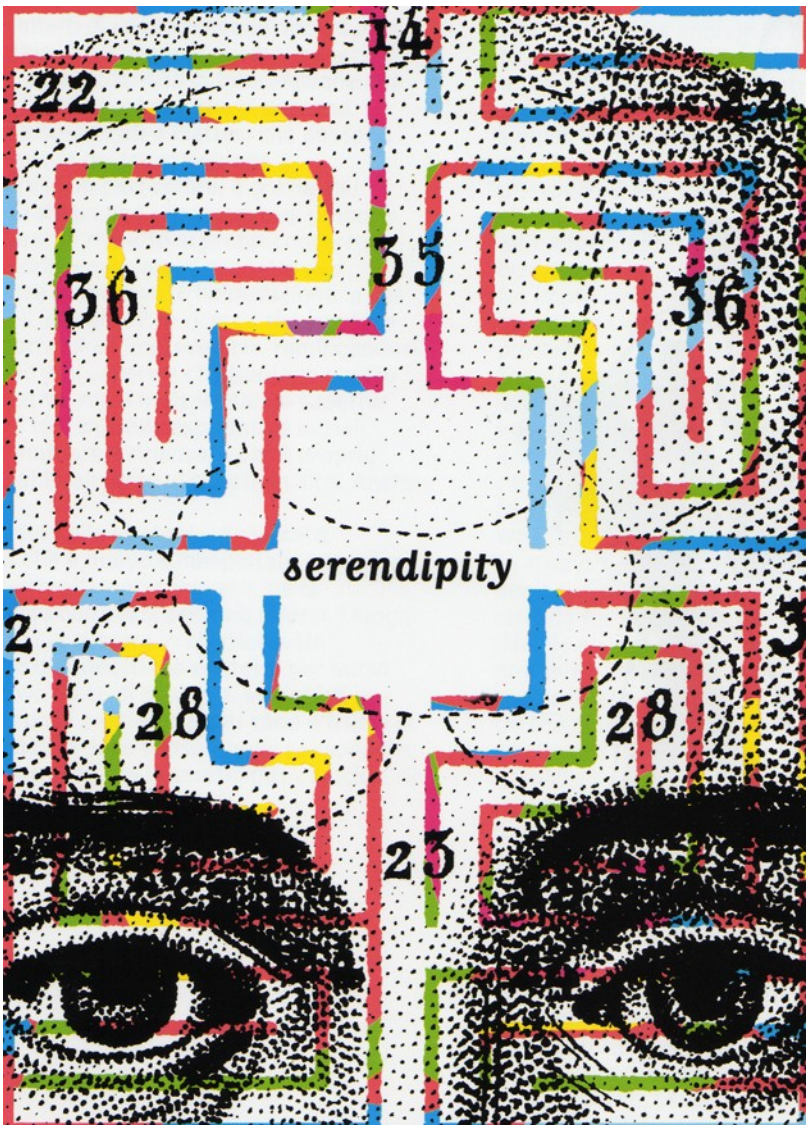
The world "Serendipity" was introduced in 1700 by Horace Walpole. In a letter to an acquaintance, he commented on a Persian legend in which *"the travellers were always making discoveries, by accidents and sagacity, of things which they were not in quest of"*. After that, the word " Serendipity" was used in many field, often with a wide range of meanings, to that in 2004 it was defined as "one of ten English words that were hardest to translate".

"*Serendipity*" seems to play an important role in the world of science. Many discoveries have been attributed to this *"accidental sagacity"*. For example, the discovery of polythylene by the German chemist Hans von Pechmann in 1989 happened by chance as he was studying the reactivity of diazomethane. Spencer Silver, a chemist from 3M, was discouraged because a new adhesive he had developed was too weak for any kind of application; only by pure chance, many years later, while a secretary was throwing out the pages covered with that useless glue, did he realise that such a luck of sticking power could have a great advantage:

and so the POST-IT® was born.

After these examples, Vincenzo Balzani remind us, as scientists, a fundamental thing:

> *we shouldn't keep our gaze fixed too hard on the objective we set ourselves at the start of our research. Better to look at a broader context and try to adapt to the road that lies ahead. Also because deviations often take us further away from what we believe to be our "main road". This is true of everyday life in which we often discover, by chance and to our great surprise, lots of wonderful things that we weren't looking for and that we didn't even believe existed.*



Evangelia Kranioti

Serendipity nasconde in sè tutta la follia di un creatore,
la forza degli oggetti di scegliere il loro destino e l'intervento del caso.

3.2 Supramolecular architectures generated by self-assembly of guanosine derivatives in solution and on the surface

In 1987, the pioneering work of Donald J. Cram,[3] Jean-Marie Lehn [4] (who coined the term 'Supramolecular Chemistry') and Charles J. Pedersen[5] was recognised by the award of the Nobel Prize in Chemistry ''for their development and use of molecules with structure specific interactions of high selectivity''

Giovanni Gottarelli and Gian Piero Spada in 18 years of intensive and successful research started at the end of the '80s from the fortuitous observation of a lyotropic behavior exhibited by a guanylic nucleotide in water, discovered several guanosine derivatives which self-assemble in different architectures (discs, ribbons, helices in figure 3.1) depending on their structure and environment. In 2004 in a published article entitled "*The Disclosure of the Stepwise Supramolecular Organization of Guanosine Derivatives: Serendipity or Programmed Design?"*[5] they described their scientific story starting from the study of several dinucleoside phospates produced from their collegue Anna Garbesi.

In 2007 Jeff Davis and Gian Piero Spada[6] for the twentieth anniversary[7] of the special event, "the birth of Supramolecular chemistry", described the supramolecular recognition of self-assembling guanosine derivatives. In the present year many supramolecular chemists in the world are continuing to design other fashion molecular and supramolecular structures miming the living systems of the Nature.

3.2.1 Self-organization of guanosine derivatives in solution

Guanosine analogs, with their self-complementary hydrogen-bonding edges and aromatic surfaces, are programmed to self-associate. Guanine has two hydrogen bond acceptors (N7 and O6) on its Hoogsteen face and two hydrogen bond donors (N1 amide and N2 amino) on its Watson–Crick face (Figure 2.3 and Figure 2.4).

For guanosine and 2'-deoxyguanosine derivatives (Figure 3.2), there are several potential points for modification that may bring to discover new potential molecular and supramolecular structures: 2', 3', and 5' positions of the ribose and C8, N2, and N3 of the guanine base. In many cases, base modification introduces new properties and flexibilities that might not be possible for the unmodified guanine.

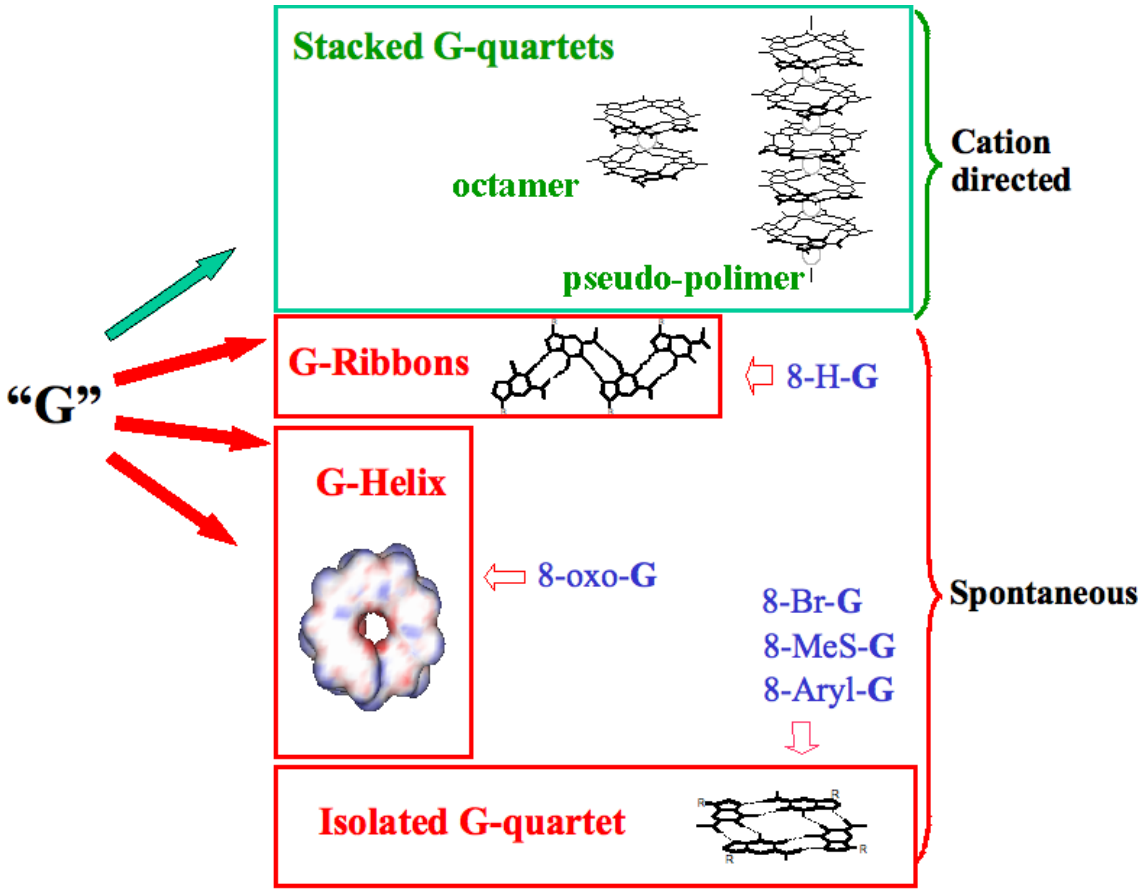


Figure 3.1 *Depending on the conditions, guanosine derivatives can self-associate in different architectures in solution and at surface. These ordered structures can be used, in different manner, such as ion-selective membrane channels, self-assembled nanowires and either as scaffolds for photo- or electroactive moieties for the fabrication of molecular electronic devices, or for the construction of scaffold for protein surface recognition.*

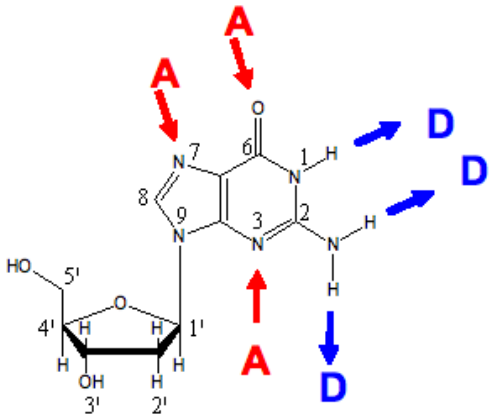


Figure 3.2 *Chemical structure of 2'-deoxyguanosine* ***dG*** *with its self-complementary donor and acceptor groups.*

For example, Gottarelli, Spada and co-workers[8-11] found that 2'-deoxyguanosine derivatives self-assemble in solution, in G-quartet templated by alkaly cation (Figure 3.4), while, without ions self-assemble in ribbons (Figure 3.7) and a new 8-oxoguanosines self-assemble into helical architectures (Figure 3.8).

Sessler and co-workers[7,12] reported that a C8-modified guanosine nucleoside forms a G-quartet in the absence of templating metal ions, it forms a so-called empty G-quartet (Figure 3.10). Rivera[13] and colleagues reported that a C8-aryl-substituted guanosine derivatives can form G-quartets with the presence of a metal ions (Figure 3.11). Wu[14] recently demonstrated that a N2-modified guanosine derivative can form discrete G-octamers (Figure 3.12). Araki[15] and Yoshikama introduced nonpolar and flexible alkylsilyl groups into 2'-deoxyguanosine to obtain efficient organogelators for alkanes, which gels' basic structure is a sheetlike assembly with anti-parallel G ribbons as shown in figure 4.8. Other experiments, at surface, confirmed the self-organization of guanosine-based molecules and its possible application in materials science and nanotechnology (See section 3.2.2).

In 1995, Gottarelli, Spada and colleagues reported that 3',5'-didecanoyl-2'-deoxy-guanosine **dG7** extracts K^+ picrate from water into $CDCl_3$ to give a discrete octamer [**dG 7**]$_8$·K^+ Pic.[8] The K^+ cation was essential for formation of this lipophilic octamer structure obtained by a stacking of two planar G-quartets (Figure 3.3). The G-quartet is constituted for a hydrogen Hoogsteen-bonded network, while, the main forces to ensemble two quartets are the ion-carbonyl interactions and the π– π interactions between stacked G-quartets.

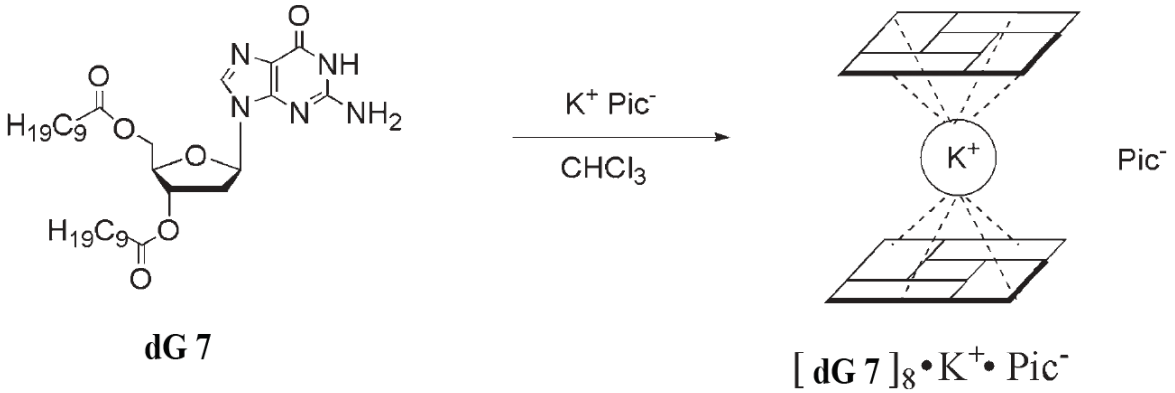


Figure 3.3 *Lipophilic [**d7**]$_8$·K^+ octamer formed by extraction of K^+ picrate from water. The dash line represent the ion-carbonyl interaction.*

The role of cation templating is not only to stabilize two sandwiched G-quartets by coordination of eight carbonyl oxygen atoms, but with more potassium picrate, the G-quadruplex or pseudo-polimers, a long columnar structure, can be formed by the vertical stacking of several G-quartets spaced by a single metal cation. In the octamer and pseudo-polimers, the quartets are not staked in register, but rotated by ca. 30° (Figure 3.4). As for DNA, in the crystal and in solution they present a helical structure sinister as shown with a model and a CD spectrum in Figure 3.5. The sugar moieties transfer their chirality to the supramolecular structure in a very efficient way, even if the nucleosides are not covalently

bonded. In section 3.2.2 we will see how Barboiu reached a polymer helical structure, left and right-handed, without any chiral moieties in the molecular information process to build up the supramolecular assemblie.[16]

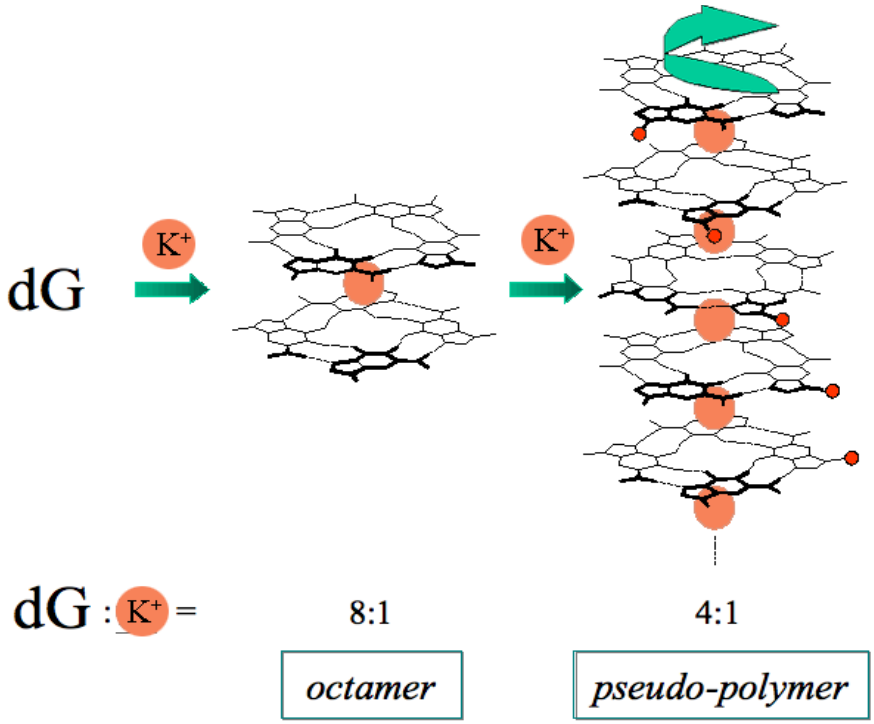


Figure 3.4 *The cation-directed self-assembly of Lipophilic dG derivatives for octamer and pseudo-polimer structures.*

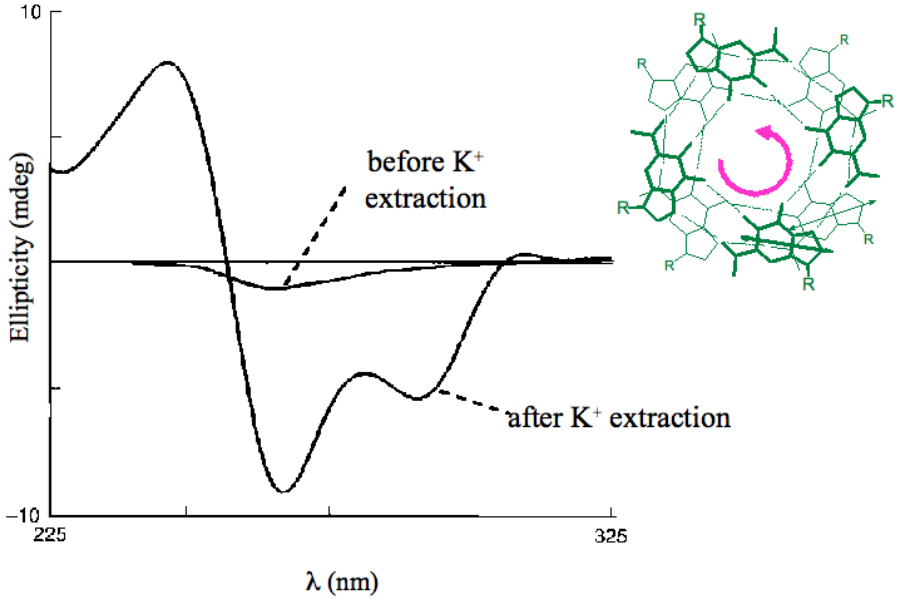


Figure 3.5
CD spectrum of a pseudo-polimer structure whit a negative skew angle between the quartets. Although the CD spectrum of ***dG7*** *in the region of the intense π- π transitions of the guanine chromophore at ca. 260 nm is monosignate and weak (band before K^+ extraction), the stabilization of stacked G-quartet-based structures induced by the K^+ ion introduces a negative exciton signal (band after K+ extraction). The adjacent quartets are, in fact, rotated by a well-defined angle:[5] this causes the interaction between the transition moments located in the different G-quartets originating the bisignate couplet.*

The G-quadruplex, with a chiral twisted supramolecular architecture, represents a nice example of a dynamic supramolecular system where guanine and guanosine molecules are used. It plays a very important role in biology, particularly in nucleic acid telomers, for the potential interest in cancer therapy, of inhibition of telomerase,[17] and in the study of proteins that bind to G-Quadruplexs (Figure 3.6).[18,19]

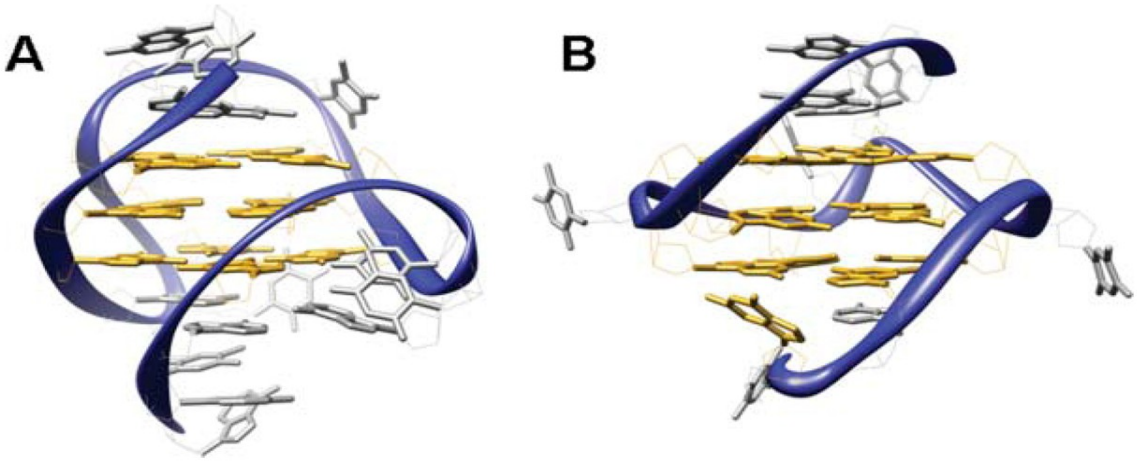


Figure 3.6 *Example of quadruplex-polymorphism: NMR structures of quadruplexes from the human telomeric sequence (guanines in gold). (Adapted from reference 20)*

Without templating cations, **dG 7** organizes into two different hydrogen-bonded ribbons.[9] Changing the sugar substituents or the solvent it is possible to modulate the ribbon's hydrogen-bonding pattern (giving ribbon A or B as in Figure 3.7). As described in Section 3.2.2, these ribbons have applications in the molecular electronics field.[21]

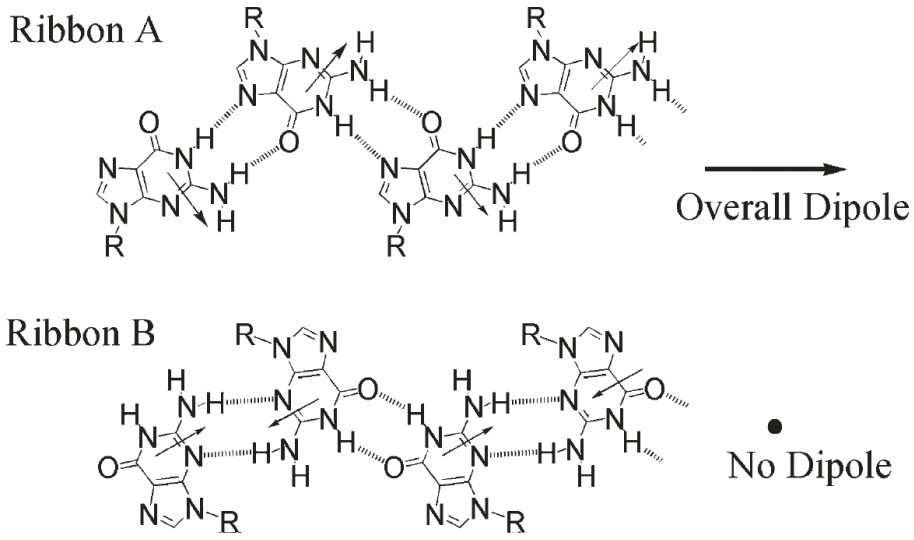
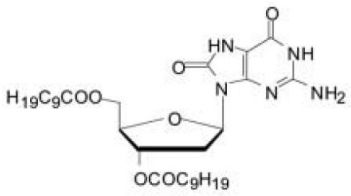


Figure 3.7 *Two different H-bonded ribbons formed by self-assembly of lipophilic* ***dG 7*** *in absence of cations. Ribbon A has a net dipole, whereas ribbon B contains no dipole.*

Recently, Gottarelli, Spada and colleagues described another unique structure obtained

upon self-assembly of a lipophilic nucleoside.[11] 8-oxoG **8** formes a hydrogen-bonded helix in organic solvents (Figure 3.8 5). This self-assembly pattern for 8-oxoG **8** is very different from the hydrogen-bonded ribbons formed by **dG 7**.

8



8-oxoG

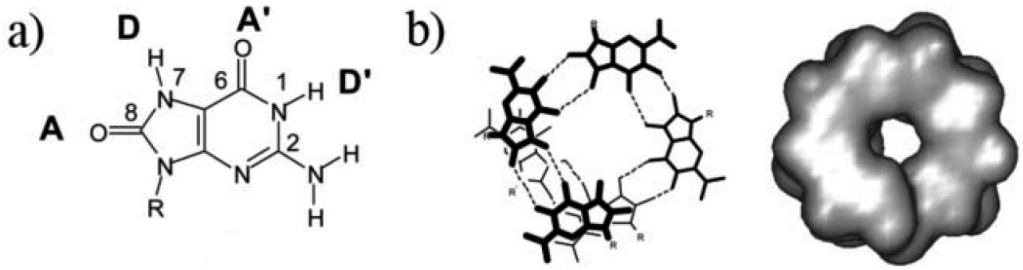


Figure 3.8 *a) Chemical structure of 8-Oxoguanine **8** and b) 8-oxoG-helical structure. (Adapted from reference 11)*

In the absence of the appropriate templating cation, guanosine analogues usually form hydrogen-bonded dimers or ribbons. But, not always. Sessler and colleagues synthesized a G analog **9** that self-associates into an empty G-quartet without the assistance of a cation template.[12] Guanosine can be found in both *syn* and *anti* conformation (Figure 3.9) therefore an attachment of a dimethylaniline moiety to the guanine C8 position gives a conformationally constrained nucleoside that adopts a *syn* glycosidic bond conformer in the solid state and in solution. This *syn* conformation prevents the nucleoside from forming the type B hydrogen-bonded ribbon and ensures G-quartet formation (Figure 3.10). This study showed how synthetic chemistry could be used to produce unnatural nucleobases for the *non-covalent synthesis* of stable supramolecular assemblies. The use of the basic design of a covalent strucuture to build discrete assemblies is clearly important in supramolecular chemistry and nanoscience.

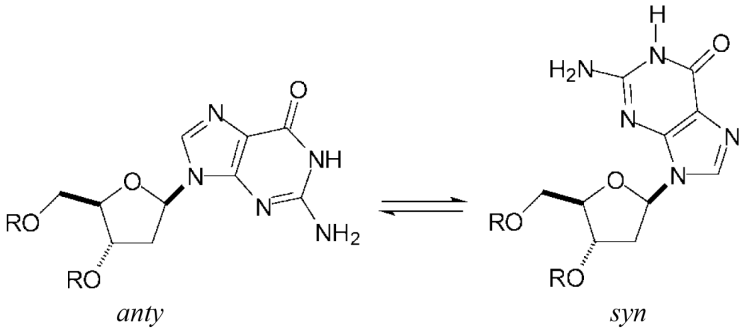


Figure 3.9
The anti and syn conformations of a guanosine derivative C8 unsubstituted.

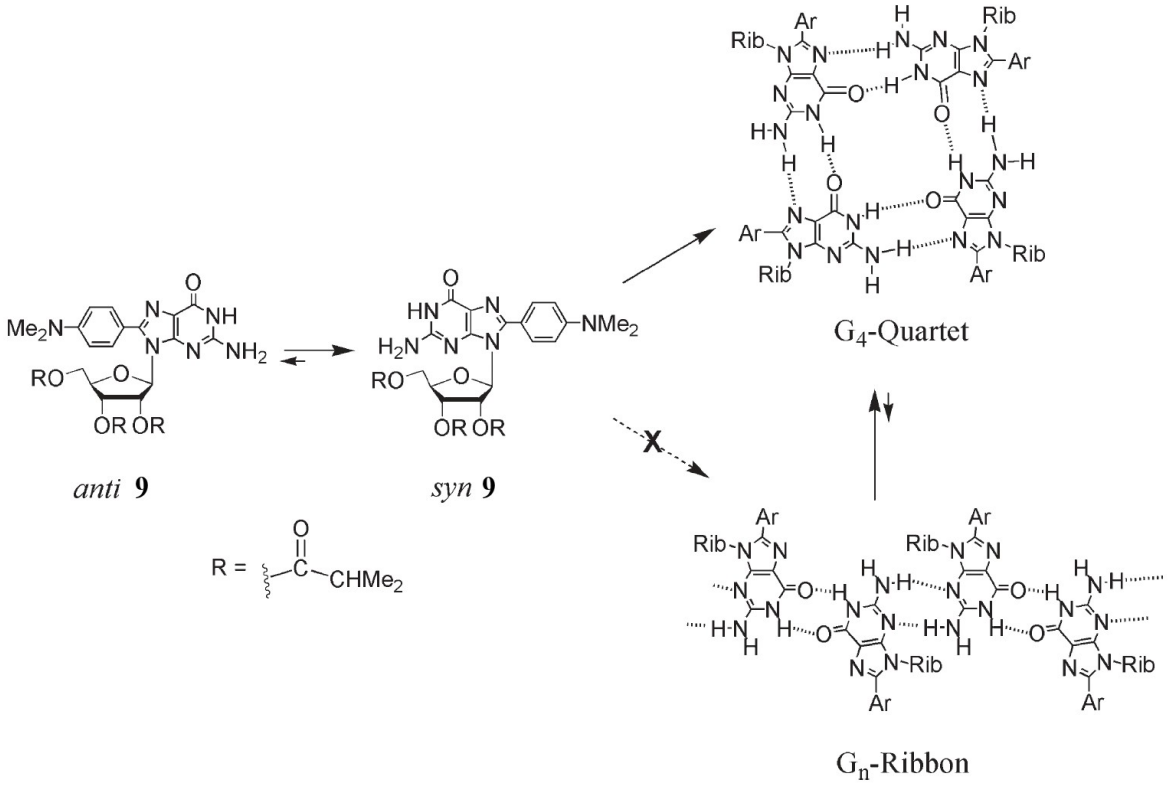


Figure 3.10 *Conformationally constrained* ***G 9*** *forms a G-quartet without a cation.(Adapted from reference 12)*

Rivera and co-workers have demonstrated the stabilization of G-quartets starting from 8-aryl-dG analogues such as **dG 10**.[13] By adding a hydrogen-bond acceptor to the C8 position, they succeeded in involving the exocyclic N2 amino hydrogen that does not normally participate in G-quartet hydrogen bonding (Figure 3.11).

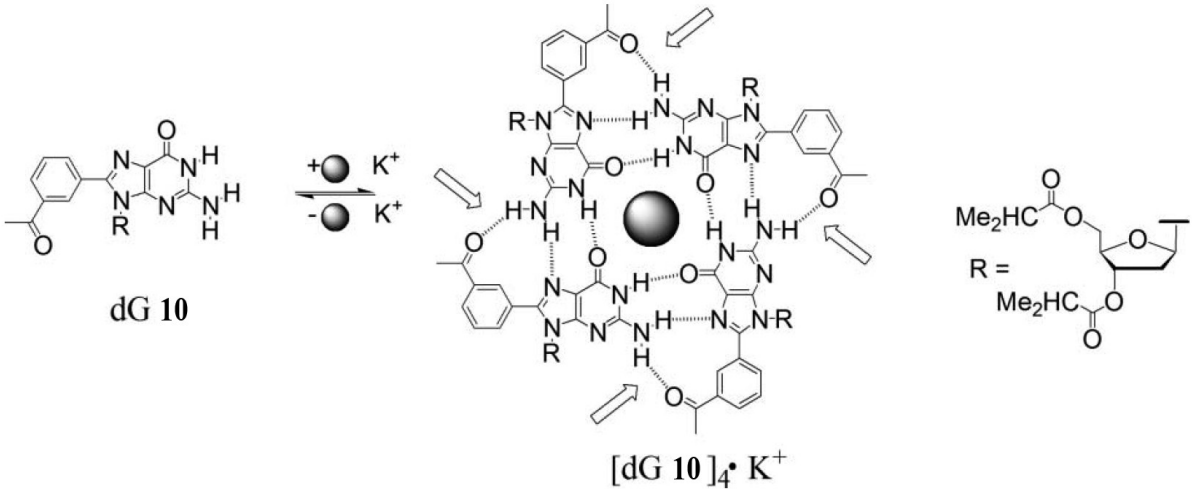


Figure 3.11 *A G-quartet formed from* ***dG 10****, a modified nucleobase with an expanded Hoogsteen hydrogen bonding face. (Adapted from reference 13)*

Variable temperature and dilution NMR experiments on the G-quadruplex [**dG 10**]$_{16}$·3K$^+$ showed increased stability when compared with assemblies formed from unsubstituted G derivatives. Rivera proposed that the stability of G-quartets formed from this 8-aryl-dG analog **10** was due to three factors. First, C8 substitution forces **dG 10** into the *syn* glycosidic conformation, prohibiting formation of hydrogen bonded ribbons. Second, the additional aromatic rings attached to C8 provide a larger surface for stronger π– π interactions between stacked G-quartets. Finally, the C8 substituent in **dG 10** enables four additional hydrogen bonds per G-quartet, as illustrated in Figure 3.11.

Wu and co-worker found that N2-modified guanosine derivatives, 2-N-(4-n-butylphenyl)-2,3,5-O-triacetylguanosine (**G 11**) and 2-N-(4-pyrenylphenyl)-2,3,5-O-triacetylguanosine (**G 12**), self-associate into discrete octamers that contain two G-quartets and a central ion (Figure 3.12). In each octamer, all eight guanosine molecules are in a *syn* conformation and the two G-quartets are stacked in a tail-to-tail fashion.[14] (See next section for head and tail conformation assignment)

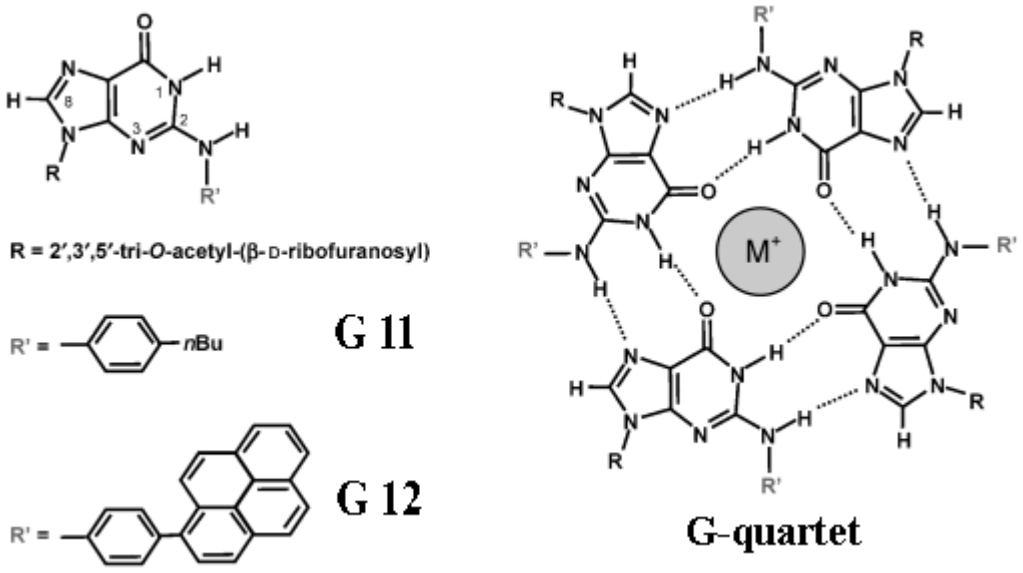


Figure 3.12 *Chemical structure of* ***G 11*** *,* ***G 12*** *and G-quartet structure.(Adapted from reference 14)*

On the basis of NMR spectroscopic evidence, they hypothesized that the stacking interaction between the N2-side arms (phenyl in **G 11** and pyrenyl in **G 12**) can considerably stabilized the octamer structure (Figure 3.13).

In a G-octamer, the main forces to hold two G-quartets together are the ion-carbonyl interactions and the π- π stacking between the guanine bases. It is plausible that the additional π- π stacking between the N2 side-arms in both **G 11** and **G 12** octamers further stabilizes these octamer structures.

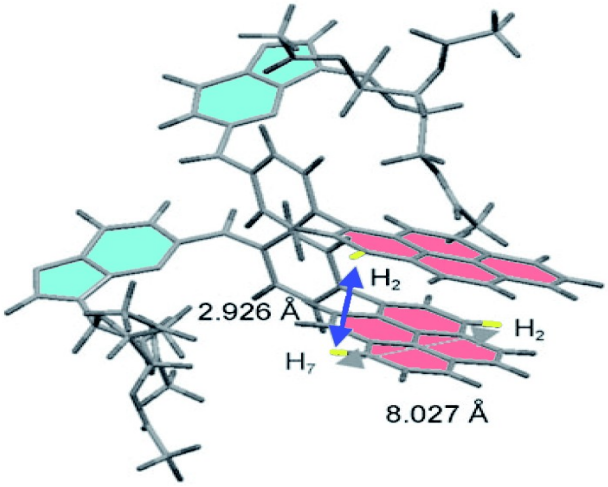


Figure 3.13
*Part of the **G 12** octamer model (Green) that shows the stacking between two pyrenyl groups (Magenta). Noe cross peaks are observed between H_7 and H_2 of the pyrenyl group. As shown, the distance between H_2 and H_7 within the same pyrenyl ring is approximately 8.027 Å. This distance is generally too long to generate any NOE effect. On the other hand, the **G 12** octamer model suggests that the distance between H_2 and H_7 from two different G-quartets (interquartet) is about 2.926 Å.*

Wu and colleagues suggested to design new N2-modified guanosine derivatives in which the π- π stacking between the N2 groups can be optimized. It might be possible that such a π-π stacking between N2 groups would provide a strong enough attraction to hold the two G-quartets so that the central cation becomes unnecessary, this would give rise to an empty G-octamer.

3.2.2 Self-organization of guanine and guanosine derivatives on the solid surface

The knowledge of the interactions between biologically active molecules, such as proteins, nucleic acids, etc., and solid surfaces is relevant to the preparation of biocompatible material, and biosensors, with application in supramolecular chemistry, biomedicine, drug screening, molecular electronics and optoelectronic.

Purine and pyrimidine bases are aromatic planar heterocycles which contain both proton acceptor and proton donor groups and hydrogen bonding interactions between them facilitates molecular recognition during biological information processing.

On flat uncharged surfaces, the bases are planar-arranged like jigsaw puzzle pieces on a table: hydrogen bonds between the bases can be likened to the interlocking features of the jigsaw puzzle which specify the matching rules between adjacent pieces (Figure 3.14).[21] The resulting structures are monolayers which are formed spontaneously by molecular self-assembly and they have been investigated with a molecular and sub-molecular resolution by scanning probe microscopy (SPM).[22] One of the most fundamental tasks is to determine the molecular packing structure of the films and study the transformation of the structure as a function of the substrate potential and chemical composition of organic solution. Monolayer

organic films prepared by Langmuir-Blodgett (L-B) and self-assembly techniques shown in figure 3.15, have been intensively studied.[23]

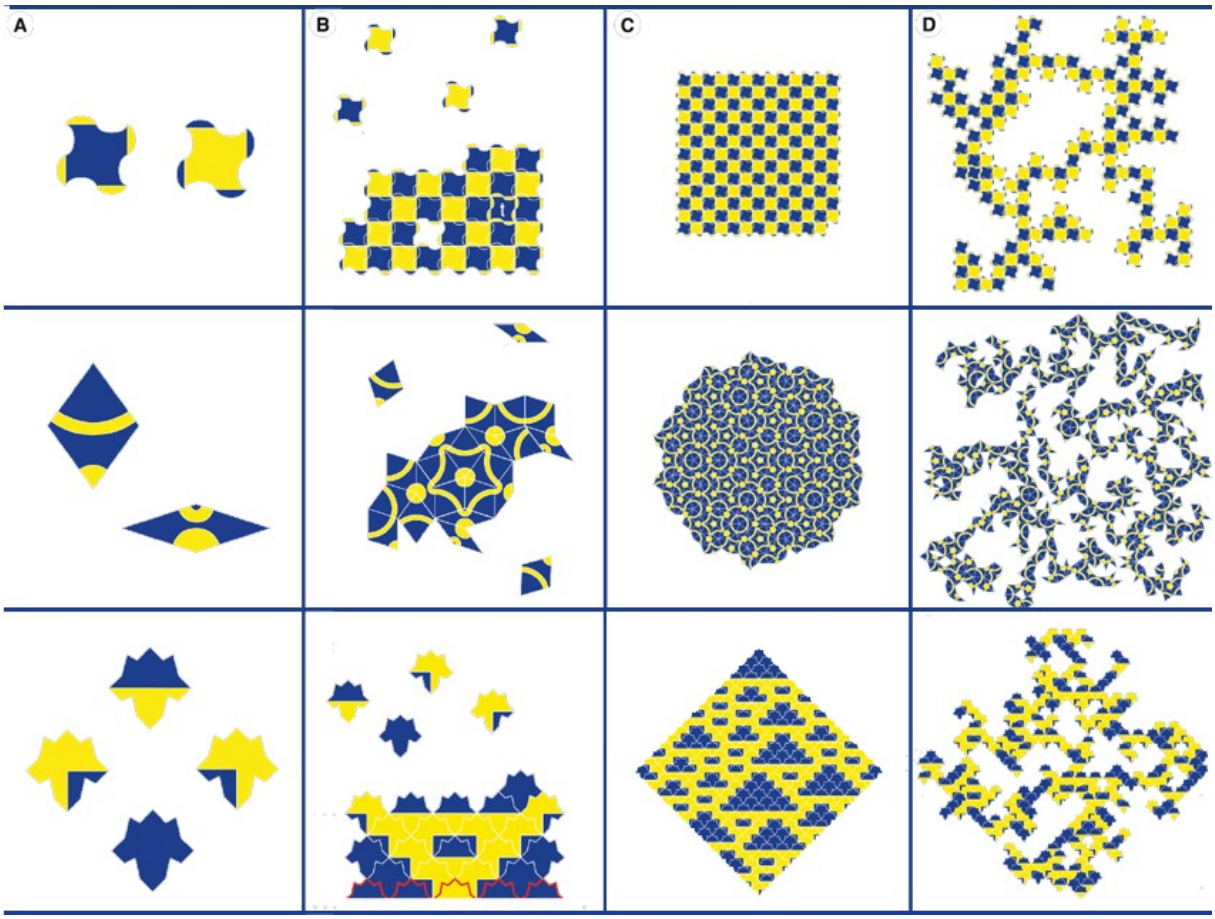


Figure 3.14 *Tiles, and structures formed by simulation. A tiling is an arrangement of tiles (shapes) that covers the plane. Tiles, matching rules, and the tilings are abstract mathematical objects but their geometrical natures suggest physical analogues. Real objects (e.g., atoms) may be thought of as tiles, binding interactions (e.g., chemical bonds) as matching rules, and self-assembled structures (e.g., molecules) as partial tilings. (Adapted from reference 21)*

Molecular nano-structures are attractive in such diverse fields because of the tunability of the properties of these materials by selectively modifying specific functional groups while leaving the rest of the molecule unchanged. Immobilisation on a surface is required for many of the applications that these molecules are directed towards. Therefore, to achieve a suitable organisation one must consider not only interactions between the organic molecules themselves, but also those between organic molecules and the surface. When the monolayers of guanosine formed from solutions have crystalline characteristics the SPM images can be interpreted also in terms of the geometrical placement of planar arranged molecules that interact laterally by intermolecular hydrogen bonding.

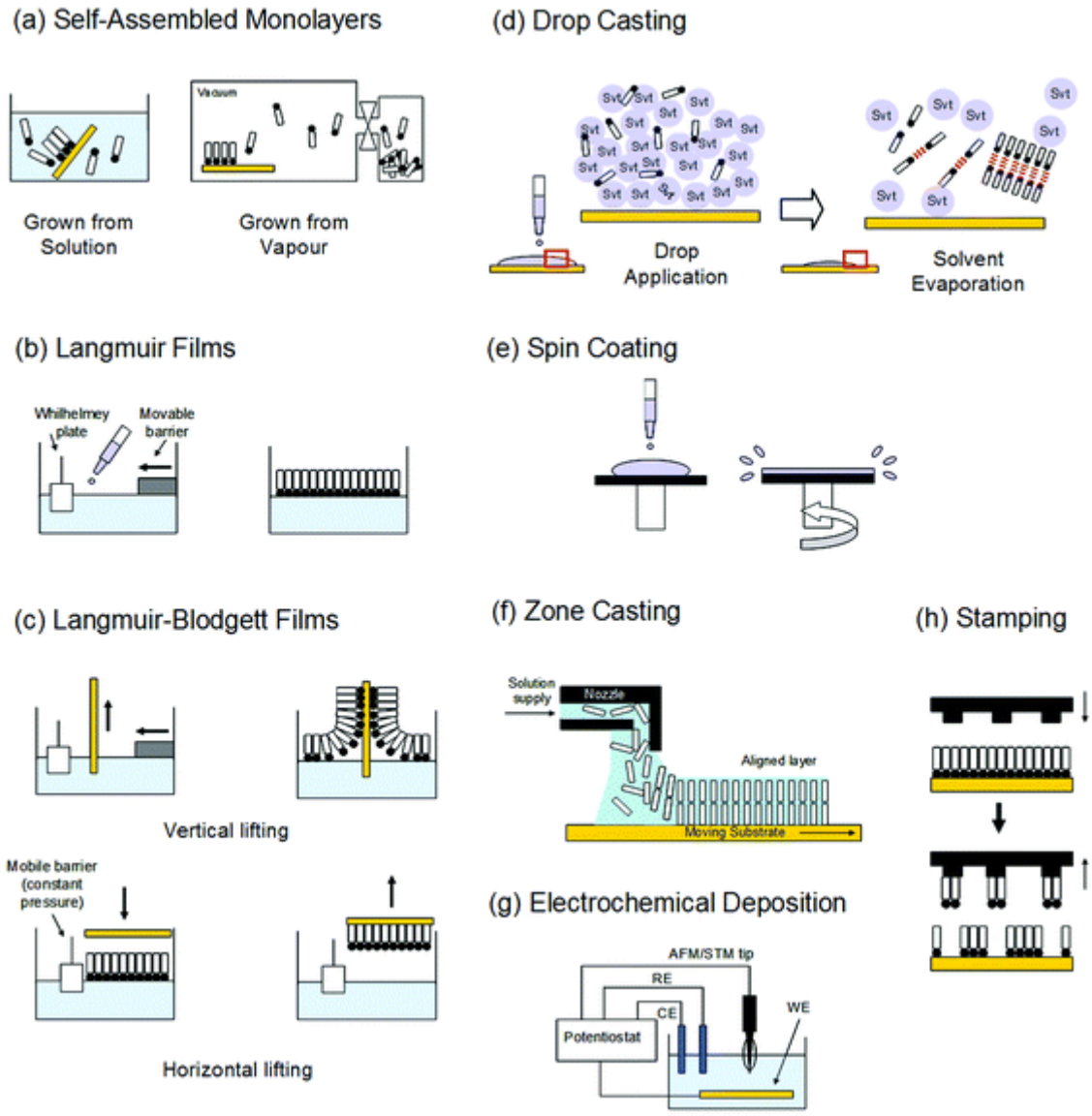


Figure 3.15
Overview of the various preparation routes for the deposition of molecular nano-structures on surfaces. a) Growth of SAMs can be done either in solution or in vacuum. b) Langmuir films are formed by spreading amphiphilic molecules on a liquid surface. c) LB films are prepared by transferring Langmuir films onto a solid substrate.
(d) Generation of nano-structures as a result of combined self-assembly and dewetting when a drop-casted solution is evaporated on a surface.
(e) In spin-coating, a residual layer remains on the substrate owing to surface tension when an excess of a solution is placed on the surface and then rotated at high speed. (f) Oriented, anisotropic layers of soluble molecular materials are prepared by zone casting which consist of casting a suitable solution, continuously supplied by a nozzle, onto a moving substrate. (g) Crystalline mono- and multilayer films can be grown on a substrate by electrochemical deposition. The sample is the working electrode (WE). The reference electrode (RE) and the counter electrode (CE) ensure the control over electrochemical processes within the cell and at the working electrode surface. This process and the resulting structures can be studied at the nano-scale if the cell is integrated in an AFM/STM microscope. (h) Schematic representation of the procedure for patterning a pre-formed SAM using stamps.(Adapted from reference 23)

Construction of surface architectures via controllable self-assembly processes is a challenging goal, which can lead to a broad range of applications in nanoscale molecular

electronic devices and surface coatings in bio-compatible materials. Promising candidates for such exploration are guanine **G** and its derivatives. They are unique among the DNA constituents for their property to form highly stable supramolecular structures, which are stabilized by Watson-Crick binding and or Hoogsteen binding.[24]Guanine is also distinctive among the DNA-bases for its low ionization potential, due to which it plays a key role in electrical conductivity of DNA-based materials. [25-28]

Recently, Besenbacher, Otero and colleagues showed that guanine **G 13** (Figure 3.16) is able to adopt a kinetically stable empty G-quartet when placed on a gold surface (Figure 3.17 and 3.18).[29] In the case of **G 13**, the available N9-H and the neighboring N3 positions may be crucial for stabilizing the network of connected G-quartets.

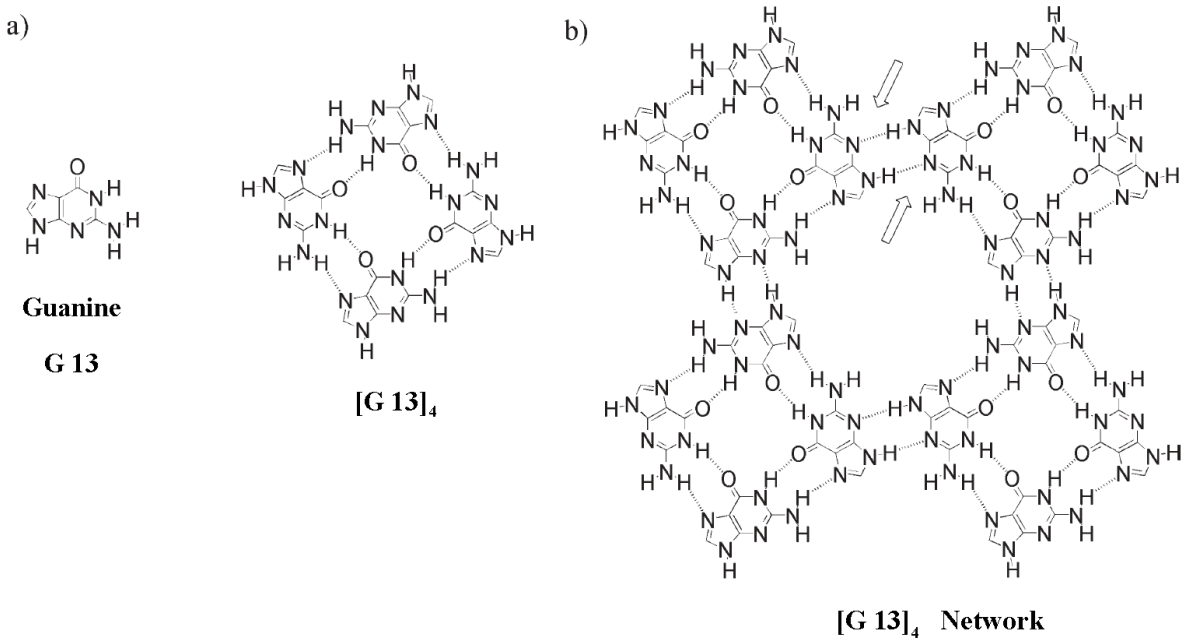


Figure 3.16 *(a) Chemical structure of an empty G-quartet formed by guanine* ***G 13****. (b) A hydrogen bound network of empty G-quartets. Each G-quartet can form up to eight additional hydrogen bonds with neighboring G-quartets (arrows). (See reference 29)*

STM images recorded at 150-170 K shown that guanine molecules evaporated onto Au(111) under ultrahigh vacuum (UHV) condition, self-assembled into well-ordered islands with irregular shapes (Figure 3.17 a). Figure 3.17 b shows a closer view of the self-assembled G-network structure, whose lattice parameter is 1.5±0.1 nm. The STM results demonstrated that each unit cell is composed of four molecules (Figure 3.17 c).

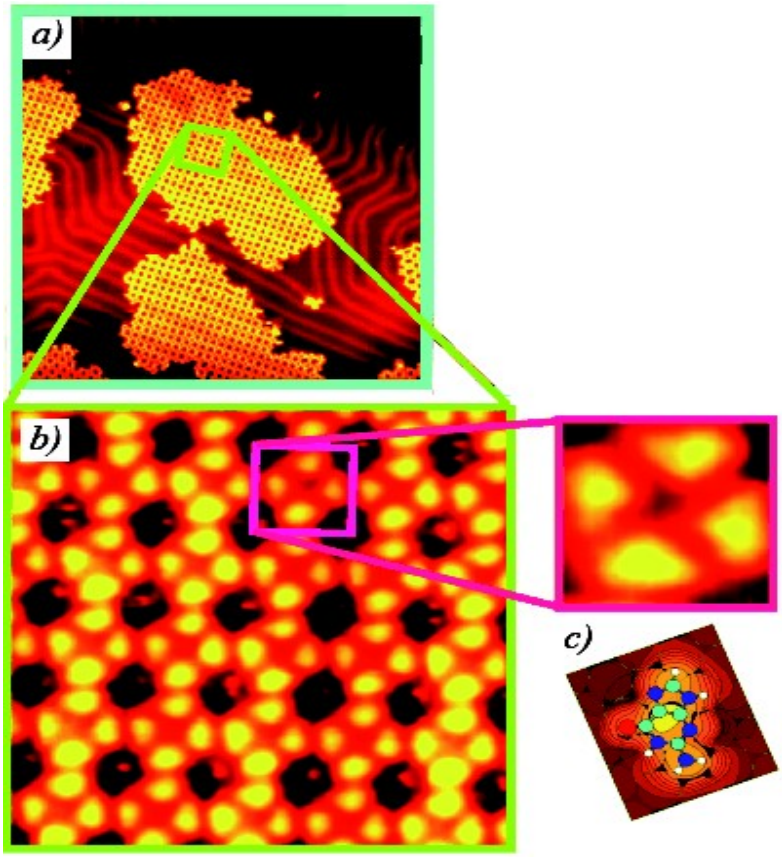


Figure 3.17
a) STM image (100×100 nm^2) of several self-assembled G islands on Au(111);
b) STM image (8×8 nm^2) showing that the G network has an almost square geometry in which the lattice parameter is 1.5 nm, and the unit cell is composed of four guanine molecules;
c) higher magnification (1.5×1.5 nm^2) of image b) showing a high-resolution image of the unit cell. Guanine molecules appear as triangular protrusions, in good agreement with theoretical calculations for guanine adsorbed flat onto Au(111) terraces. (Adapted from reference 29)

In figure 3.18 is shown a clear superimposition of the G-quartet structure determined by X-ray crystallography on G-quadruplex DNA crystals and the STM images reported before, a good correspondence has been observed between the former and the unit cell of G network proposed by Otero.[29]

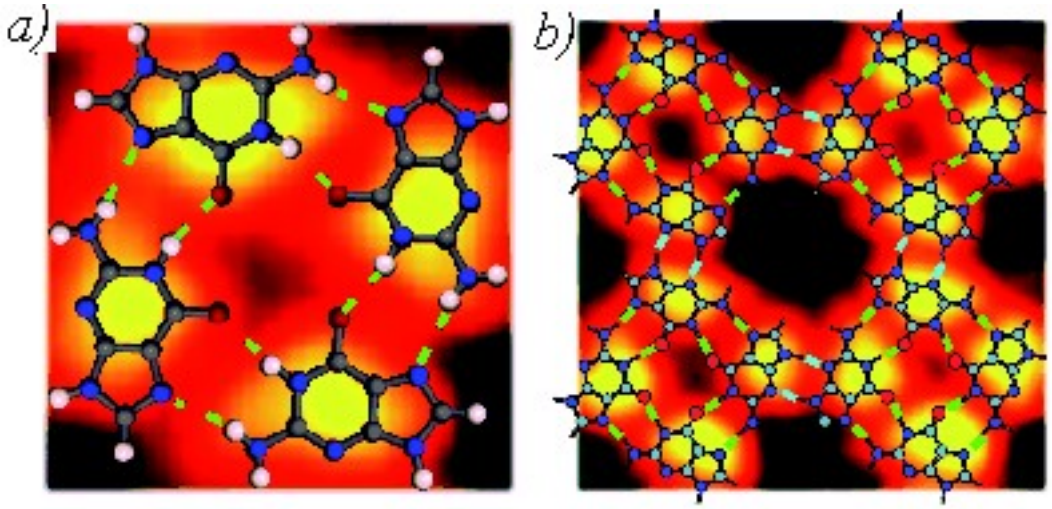


Figure 3.18 *a) Comparison of a high-resolution STM image of the G-quartet unit cell with the Hoogsteen-bonded G-quartet structure determined by X-ray crystallography; b) comparison of an STM image of several G-quartet unit cells with the relaxed structure obtained by DFT calculations. The lateral interaction between G quartets occurs by eight new hydrogen bonds between the peripheral N3 and N9 atoms of neighboring guanine molecules. Intraquartet hydrogen bonds are shown in green; interquartet hydrogen bonds, in blue.*

Otero also discovered that the G-quartet network is not the only H-bonded network that guanine adopts when deposited onto Au(111). By annealing the sample at 400 K, the G network changed irreversibly to another structure, depicted in Figure 3.19 and no trace of the G-quartet structure was found after annealing. The high-temperature network is composed of antiparallel molecular type-A ribbons (Figure 3.19 b). These ribbons are well-known motifs for self-assemblies of guanosine derivatives in solution and in crystal state.[30,31]

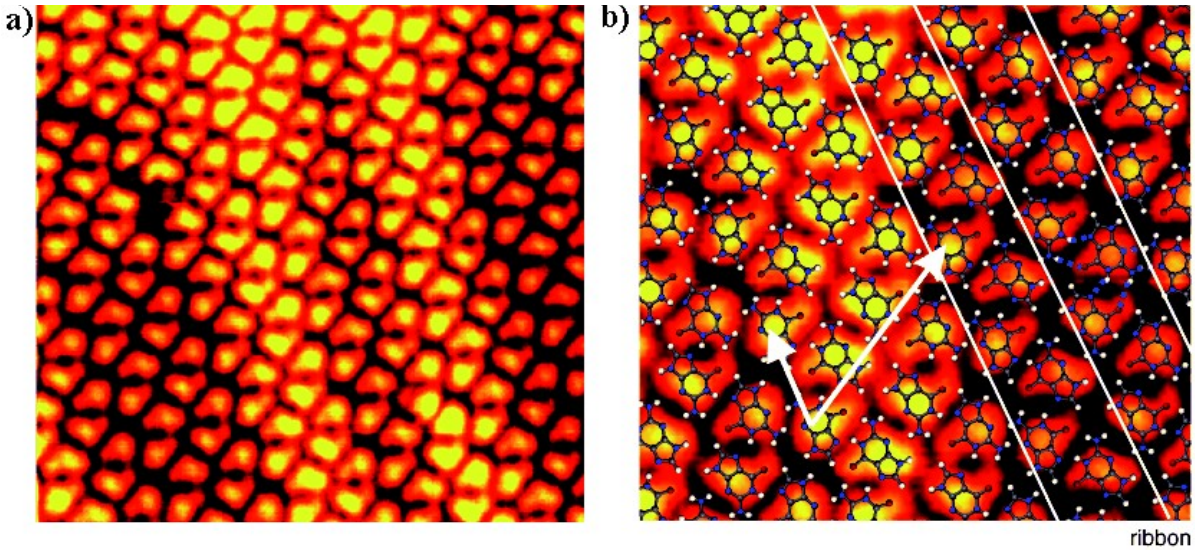
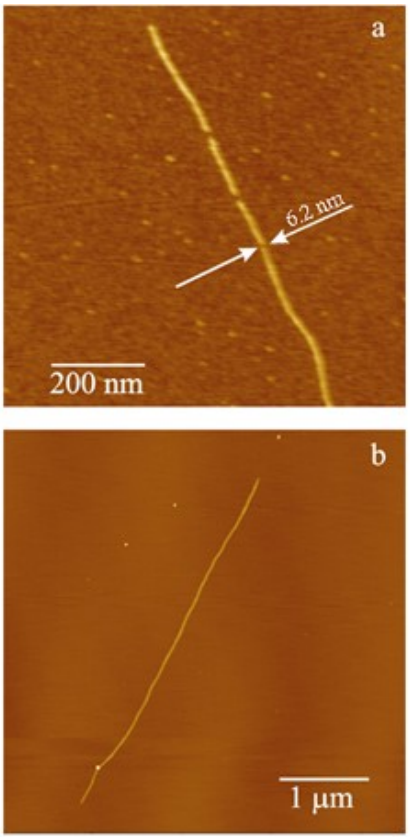


Figure 3.19 *a) STM image (10×10 nm²) of the high-temperature phase of guanine on Au(111); b) model for the H-bonded network that corresponds to the high-temperature phase of guanine on Au(111) with unit vectors displayed. The local environment of each guanine molecule within this network is similar to that within the G-quartet network, in that each molecule is coordinated by six hydrogen bonds to three nearest neighbors. Ribbon patterns are indicated.(Adapted from reference 29)*

Therefore, although the G-quartet network is stable at room temperature, it does not correspond to the most stable arrangement of guanine molecules on the Au(111) surface. This suggests that the preference for the G-quartet network for depositions carried out at room temperature is a phenomenon governed by kinetics rather than thermodynamics. Otero therefore raised the question: why do guanine molecules assemble exclusively into the G-quartet structure when deposited at room temperature, and what is the reason behind the stability of the metastable G-quartet network?

Gottarelli, Spada and Samorì reported the self-assembling of **dG 14** by drop-casting onto mica substrate under ambient temperature condition (Figure 3.20 and 3.21).[10] The scanning force microscopy image shown a dried nano-ribbon formed from self-assembly of **dG 14**. These nano-structures are remarkably straight and exhibit a length of up to 8 μm. Their heights and width are constant for well-defined ribbons segments, but not for the whole sample. The width of the ribbon, around 6.2 nm, is consistent with its proposed supramolecular structure in Figure 3.22.



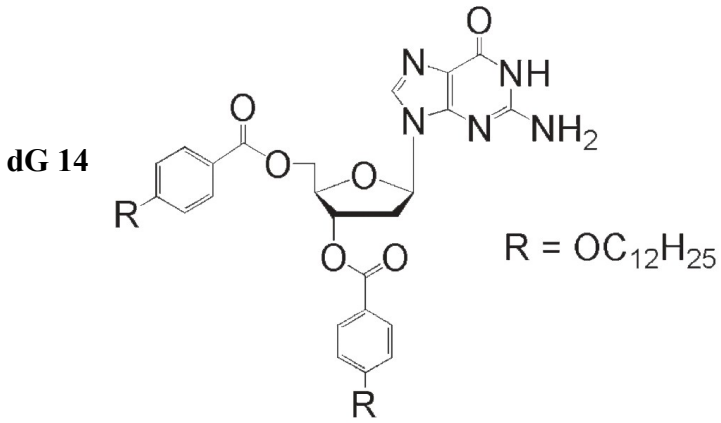


Figure 3.20 *Chemical structure of* ***dG 14.***

Figure 3.21 *SFM tapping mode height images of* ***dG 14*** *cast on freshly cleaved, washed mica substrate. a) Ribbon with a width from 6.1 nm and 6,7 nm and thicknesses from 0.95nm to 1.1 nm. b) Single dry nanoribbon with length of 8 µm.(Adapted from reference 10)*

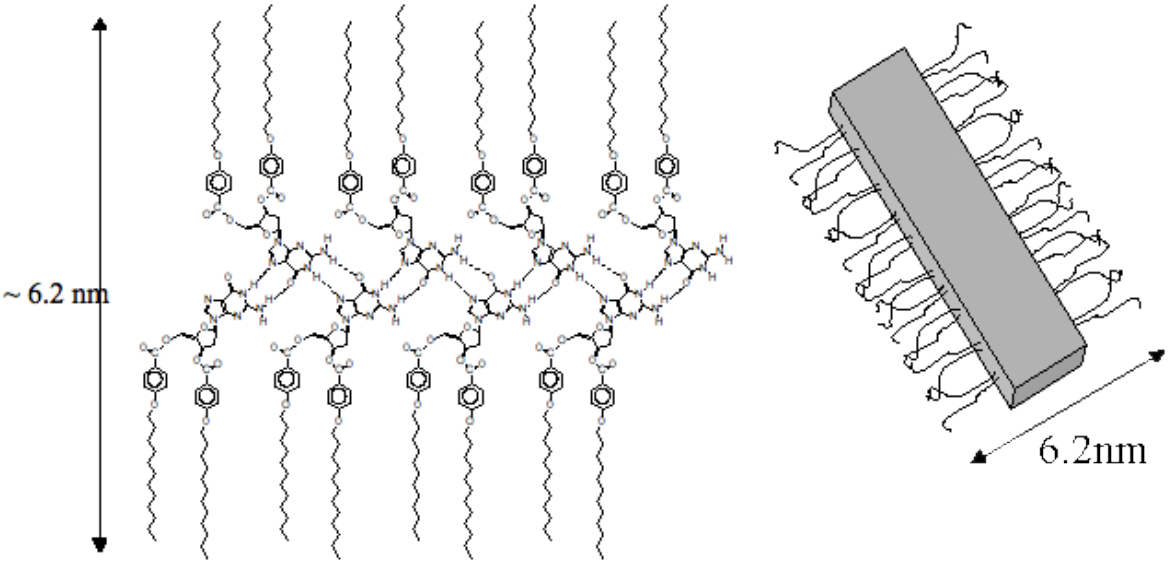


Figure 3.22 *Molecular arrangement of* ***dG 14*** *in the dry ribbons visualized with SFM.*

Gottarelli, Spada and Rinaldi have proposed the use of nanoribbons formed from **dG 14** guanine units in the design of molecular electronic nanodevices.[32-34] Self-assembled nanoribbons obtained from drop casting were used to interconnect gold nanoelectrodes fabricated by electron beam lithography (Figure 3.23). The typical length of the oriented arrays of ribbons (a nanocrystal) was reported to be approximately 100 nm.

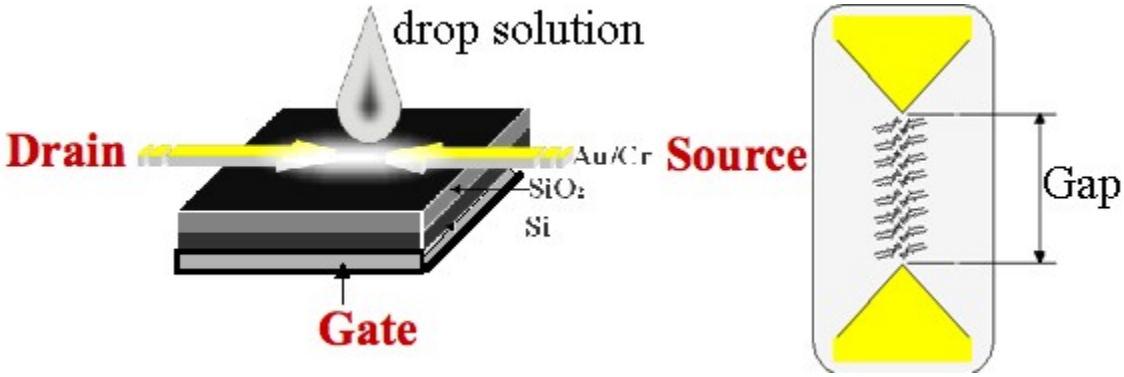


Figure 3.23 *The preparation of the nanodevice. (Adapted from reference 32)*

For a contact gap of 60 nm or less only one nanocrystal of the **dG 14** assembly is probed. Under these conditions the plot of current intensity vs. voltage (I–V) shows a clear diode-like behavior (Figure 3.24 a), with currents on the order of μA for positive bias and nA for negative bias. This rectifying feature points out the existence of the strong dipole in each nanocrystal that originates from the dipole of the guanine units ordered in the ribbon-like structure of type A (Figure 3.7). If a three-terminal device is prepared, the system behaves as a Field Effect Transistor when the guanosine nanoribbons are used to interconnect the drain and source terminals.[33]

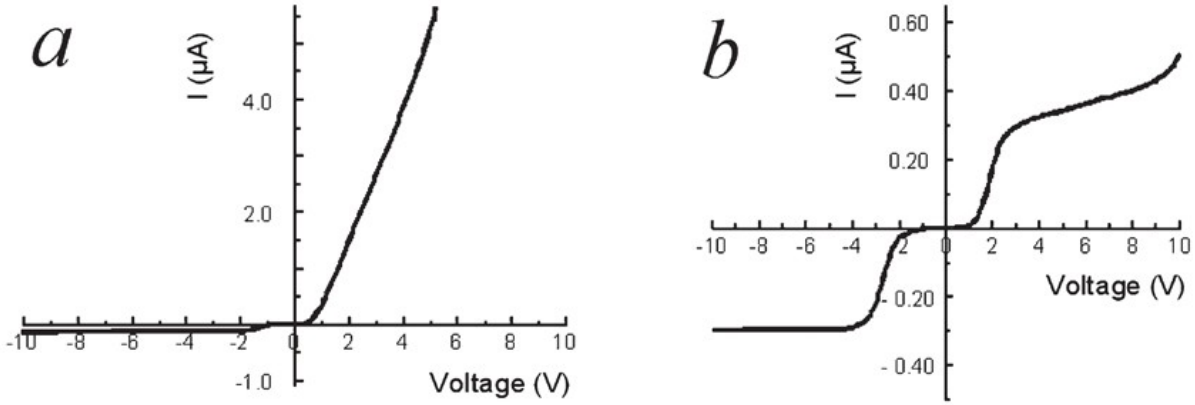


Figure 3.24 *Current intensity vs. voltage (I–V) plot for nanoribbons of* ***dG 14*** *in 60 (a) and 120 nm (b) contact gap devices. (Adapted from references 33,34)*

A major challenge is to orient this material between the electrodes. In fact, with the drop casting procedure, there is no control on the orientation of the nanocrystals with respect to the nanocontacts. Some devices rectify in one direction, others in the opposite direction, and other devices do not rectify at all. The situation changes dramatically in the 120 nm device (Figure 3.24 b). In this case, a few nanocrystals of self-assembled **dG 14** are probed by the electrodes

and the total dipole of the sample between the electrodes averages to zero because the nanocrystals are randomly oriented. The I–V plot is non-linear and symmetric with a zero-current region between –2 V and +2 V. At higher bias, the current increase at sub-μA levels is typical of a metal–semiconductor–metal device. An interesting property of this 120 nm device is its high photo-responsivity, as the current increases from sub-μA level in the dark to sub-mA levels under illumination of a few mW of power.[34]

Rowan and co-worker[35-36] reported a self-assembly on the surface of a ditopic monomers guanine **G2$_n$G**, consisting of a linear alkyl chains with guanine peptide nucleic acid (PNA) end group could result in the formation molecular-sized bands on HOPG when adsorbed from a water/DMSO solution (Figure 3.25).

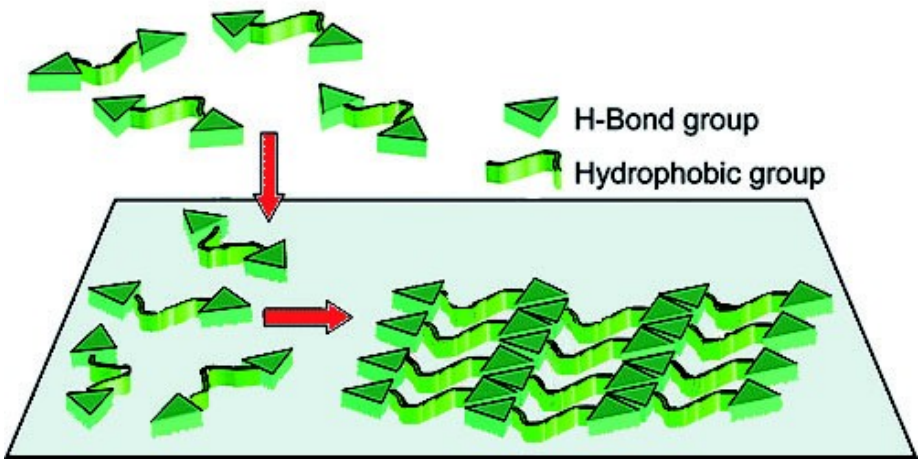


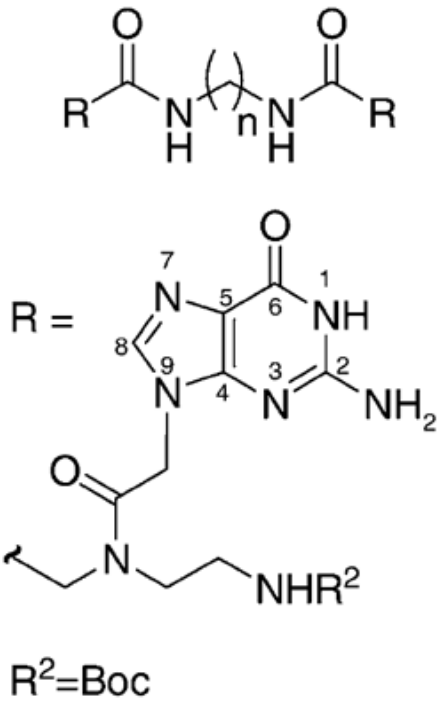
Figure 3.25 *Picture model of a self-assembling at surface of a ditopic monomer* ***G-spacer-G.*** *Guanine end groups with h-bond group are depicted as triangular shape. The ditopic monomers are initially in solution followed by adsorption and assembly to form linear band structures via hydrogen bonding network.*

These model ditopic monomers comprise three components, (1) a hydrocarbon core with *n* (= 8, 10, 12, 18) methylene groups, to enhance adsorption onto a hydrophobic surface in the presence of an aqueous medium, (2) the guanine end groups, to facilitate adsorbate-adsorbate interactions through hydrogen bonding, and (3) peptide nucleic acid (PNA) chains primarily used to link the hydrocarbon cores and the guanine moieties (Figure 3.26).[36]

All the monomers drop-casting on the the surface were absorbed and the images of the covered surface were capture using a fluid tapping AFM setup at ambient temperature (Figure 3.27 a-d). The images captured show that there are molecular-sized bands on HOPG dependent on the length of the hydrocarbon core in the assembling monomers. For example, **G2$_8$G**, **G2$_{10}$G**, **G2$_{12}$G**, and **G2$_{18}$G** had band-widths of 3.2 ± 0.1, 3.5 ± 0.1, 3.8 ± 0.1, and 4.8 ± 0.1 nm, respectively . The dark bands in the AFM phase images correspond to the hydrocarbon segments and the lighter bands correspond to the PNA-bpc-nucleobase

segments.

Now if the guanine end groups have the importance to self-associate and to obtain the desirable tunable molecular-sized bands, the Rowan's group inquired: how does the guanine self-assemble on the surface?



G2$_n$G

Figure 3.26 *Chemical structure of* ***G2nG****.*

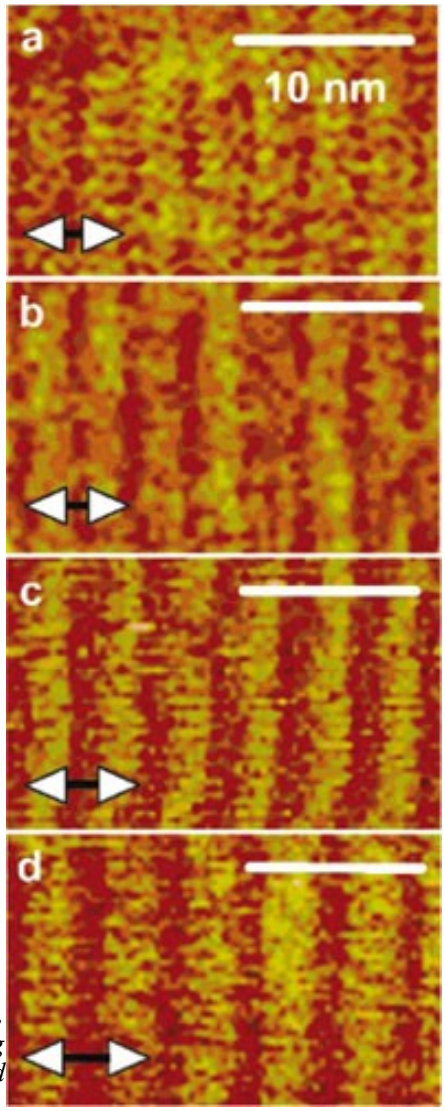


Figure 3.27 *AFM phase images of (a)* ***G2$_8$G****, (b)* ***G2$_{10}$G****, (c)* ***G2$_{12}$G****, and (d)* ***G2$_{18}$G*** *molecular-sized bands on HOPG. Band spacing increases with increasing length of the hydrocarbon core.(Adapted from reference 36)*

How described above and shown in figure 3.7, the guanine motifs can self-organize in two different ribbon-like A and B structures. Rowan d proposed another possible ribbon-like structure with a different hydrogen bonding network. This new scheme named double-stranded assembly and shown in figure 3.28d matches well the width of the observed bands on HOPG and the width of modeled bands in energy-minimized models.

All the models of the **G2$_n$G** assemblies using this double-stranded guanine motif showed lower modeled energies than the models using the motifs proposed from Spada and Gottarelli. In this case probably the PNA-Boc groups within the **G2$_n$G** assemblies sterically hinder the formation of the guanine motif shown in figure 3.26 above.

This centrosymmetric double-stranded motif is composed of guanine dimers formed through the Watson-Crick faces of two guanine moieties. This dimeric motif is extended into a tape through additional nucleobase hydrogen bonding through the N2-H and N7 on the Hoogsteen face of adjacent guanine dimer moieties. While two of the exo-amino hydrogens are in close proximity (* in Figure 3.28 d), modeling indicates that these atoms are separated by 3 Å with no Van der Waals overlap.

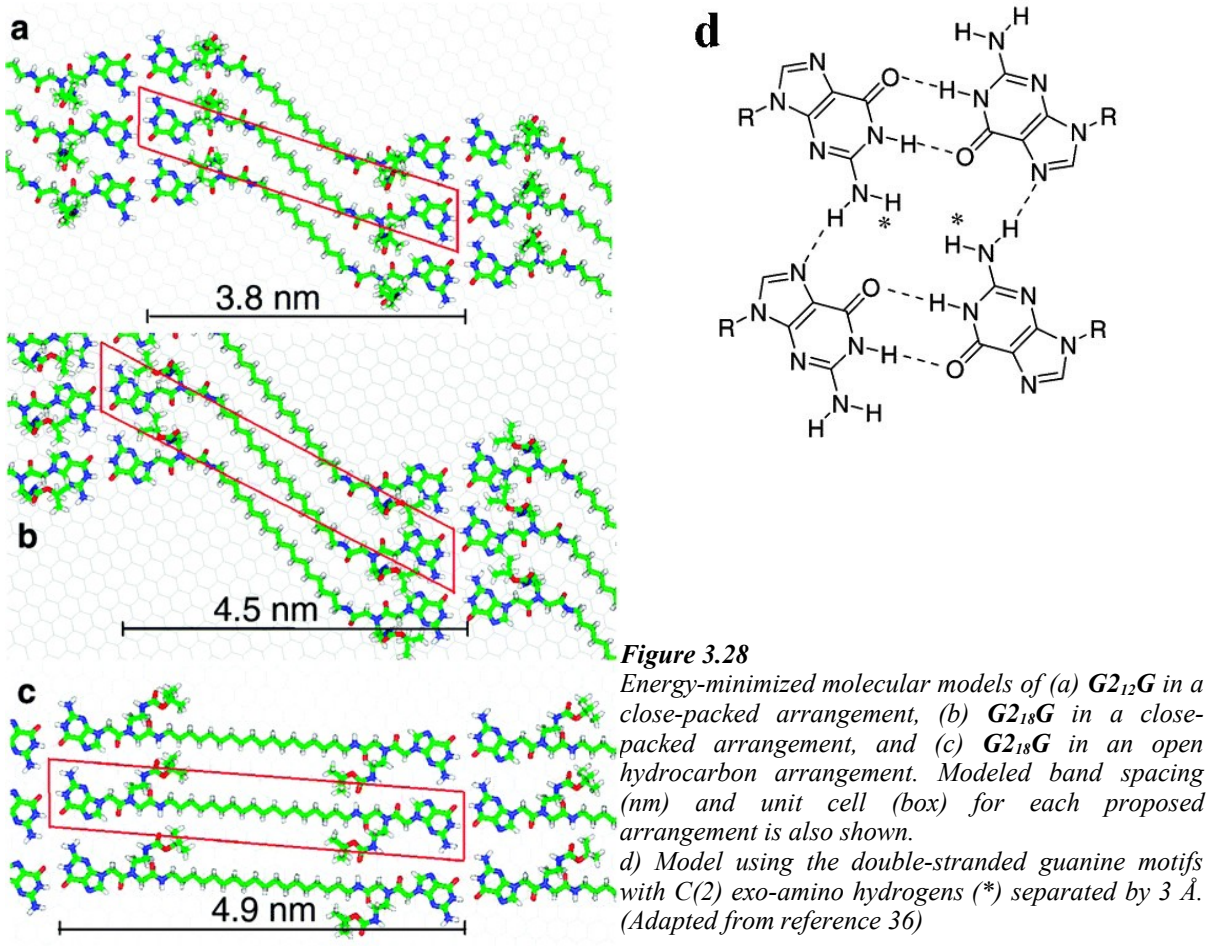


Figure 3.28
*Energy-minimized molecular models of (a) **G2$_{12}$G** in a close-packed arrangement, (b) **G2$_{18}$G** in a close-packed arrangement, and (c) **G2$_{18}$G** in an open hydrocarbon arrangement. Modeled band spacing (nm) and unit cell (box) for each proposed arrangement is also shown.*
d) Model using the double-stranded guanine motifs with C(2) exo-amino hydrogens (*) separated by 3 Å. (Adapted from reference 36)

In all **G2$_n$G** models the hydrocarbons are close packed, presumably to maximize packing efficiencies (not all the model are shown in figure 3.28). Interestingly, the molecular model of **G2$_{18}$G** assemblies with close-packed alkyl chains (Figure 3.28b) suggested a band spacing of 4.5 nm, which is significantly less than the observed 4.8 ± 0.1 nm by AFM. Rowan did not have a clear explanation for this change in hydrocarbon arrangement; although (Figure 3.28c), it seems that the Boc groups play an important role. In the open arrangement of **G2$_{18}$G** the Boc group is adsorbed onto the graphite surface, and there appears to be hydrogen bonding between the amide N-H and carbamate C=O of adjacent molecules. In the more close-packed

arrangement (Figure 3.28 b) the Boc groups sit on top of the molecules, and there is no amide-carbamate hydrogen bonding.

To examine the effect that the PNA linker group has on the assembly of these systems, Rowan and colleagues have designed and synthesized a new monomer **G3G** (Figure 3.29a), similar to the molecular design of **G1G** in Figure 2.10, which is simply a ditopic guanine endcapped dodecane with no PNA linker groups.

Like **G2$_n$G**, **G3G** assembled into epitaxially aligned molecular-sized bands with a molecular-sized banding spacings of 2.5 ± 0.1 nm (Figure 3.29b). Molecular modeling was again used to help understand the arrangement of the molecules within these molecular-sized band assemblies. Assemblies of **G3G** were modeled using all three surface guanine motifs outlined in Figure 3.7 and Figure 3.28d. A model using the guanine motif by Spada had bands that matched the 2.5 nm band spacing, while a model using the double-stranded guanine motif (Figure 3.28d) had modeled band widths that matched 3.4 nm band spacing observed only in little domains not shown in figure 3.28b.

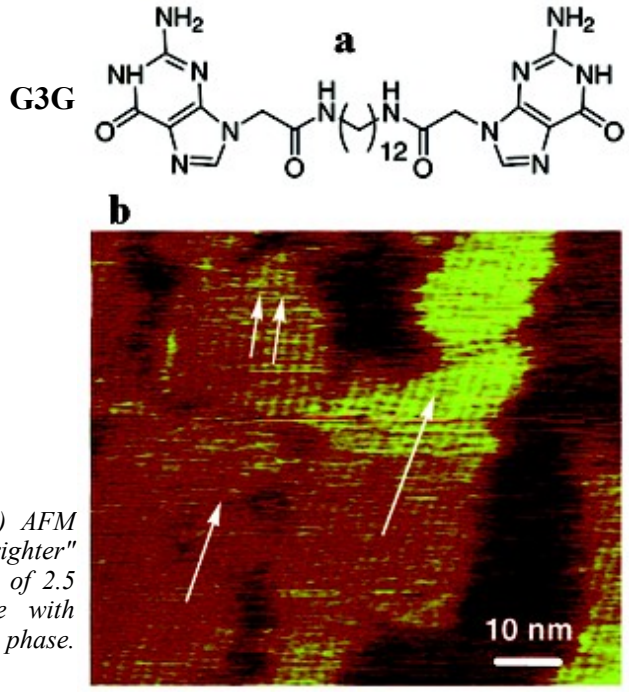


Figure 3.29 *(a) Chemical structure of **G3G**. (b) AFM phase image of multiple domains of **G3G** ("brighter" areas) forming molecular-sized bands with widths of 2.5 nm. (arrows). Surface coverage is incomplete with surrounding "darker" regions having an amorphous phase. (Adapted from reference 36)*

The Rowan's experiments suggest that the PNA linker in **G2$_n$G** hinders the formation of the guanine tape in Figure 3.7, presumably on account of steric repulsions, thus only allowing the system to assemble through one guanine motif, namely the double-stranded assembly.

Moreover, the assemblies are composed of bands with widths that can be systematically varied by simply changing the length of the core hydrocarbon unit. Furthermore, this concept has been extended into using these assemblies as scaffolds to supramolecularly graft

hydrophilic groups onto HOPG (see section 3.3). This is an important consideration if regular repeatable banding structures are targeted for the surface scaffolds, either to control a second molecular layer deposition in the space, or to storage information above the surface, or to direct a bio-mineralization from organic matrix as happen in Nature. Supramolecular chemistry at the interface plays a defining role in the "bottom-up" approach to nanoarchitectures which have a myriad of potential technological applications in areas such as nanoelectronics, biological coatings, and catalytic processes.[37,38]

3.3 Guanosine derivatives as versatile scaffolds to control self-organization materials

The relative orientation of molecules in a material can influence very dramatically the property (their optical, magnetic or electronic characteristics). This statement holds for bulk materials as well as for nanostructures (objects such as monolayers, nanowires, nano-dots and other aggregates with at least one dimension less than 100 nm). It is in the latter area that great activity and excitement are presente since the 1990's, because of the potential of molecular systems in the emerging nanoscience and nanotecnology. It is hoped that the bottom-up approach inherent to the use of molecular systems will lead to the fabrication of devices on scales unreachable through exclusive use of current top-down techniques,[39] but also that molecular materials have unique properties compared with their oxide and related counterparts.[40]

To exploit the self-assembly – the aggregation of disordered molecules into an ordered structure under equilibrium conditions – many functional molecules have been employed as the building blocks for nanostructures with different properties, then the guanosine derivatives will be used as a representative examples to demonstrate the general principles applicable for scaffolding nanostructured materials.

As mentioned above, Rowan and co-worker have shown that to design new solid-liquid interfacial (surface) assemblies (see section 3.2.2), both surface-adsorbate and adsorbate-adsorbate interactions need to be taken into account.[35] For instance, designing the correct interactions between a molecule and a surface can be critical in creating ordered surface assemblies. Thus, designing the appropriate surface-adsorbate interactions can be a powerful tool in controlling the nature of the molecular surface assembly. They reported a study of an assembling supramolecular polymers, derived from low-molecular weight nucleobase-endcapped monomers on a surface as a way to organize functional groups at the nanoscale

and as such act as molecular-scale surface scaffolds (Figure 3.30).[36]

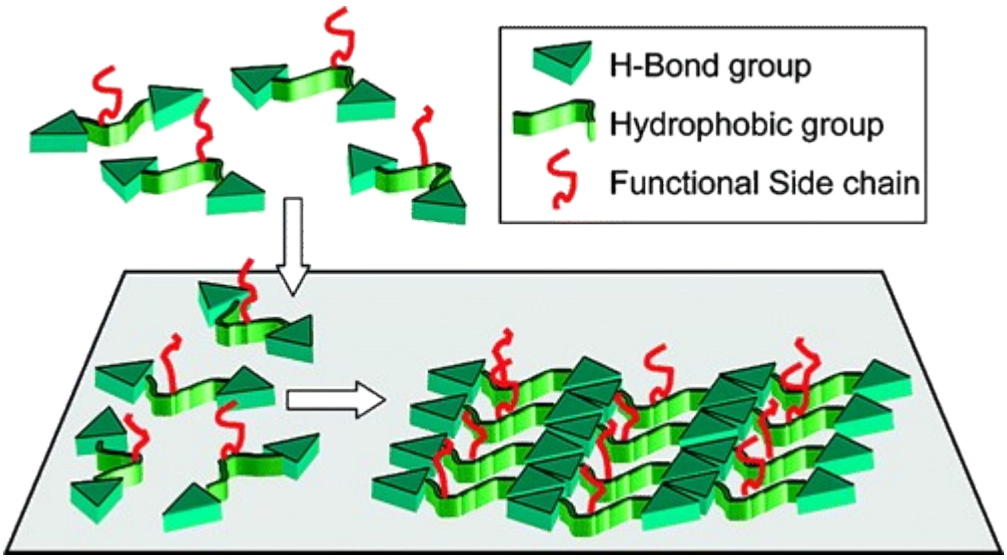
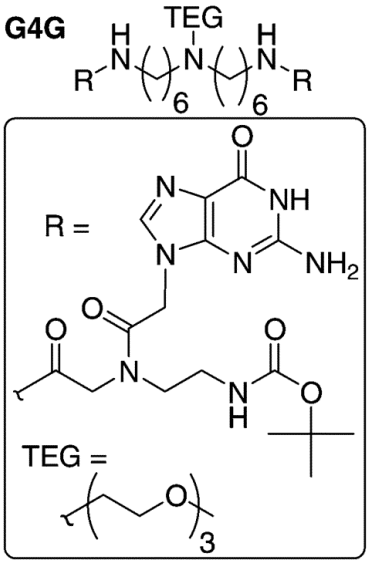


Figure 3.30 *Concept of organized functional groups arranged through surface supramolecular polymerization. Monomers are initially in solution followed by adsorption and assembly to form linear band structures that present side groups in an ordered array on a hydrophobic surface.*

In medicine, specifically in implanted devices, the thromboresistance of biomaterial coatings is determined by interactions with plasma proteins and platelets.[41] In the blood the platelets act indirectly as a marker for plasma protein adsorption and are a critical step in surface-induced thrombosis. So, it is crucial to prevent thrombosis the creation of hydrated layer[42] at the surface which acts to reduce non-specific protein adsorption, protein denaturation, and platelet adhesion. For this goal it has been proposed that chemical groups that mimic the hydrated layer will improve thromboresistance and blood bio-compatibility.

The Rowan's group has shown that using triethylene glycol monomethyl ether (TEG) groups attached to ditopic monomers **G4G** (Figure 3.31),[36] the supramolecular scaffold-organized TEG surfaces exhibited reduced protein absorption and platelet adhesion. The short-chain TEG was chosen to demonstrate the concept of the scaffold coating in part for ease of synthesis. In their proof-of-concept design, TEG is anchored from a tertiary amine that is located at the center of the hydrocarbon core that is flanked by two guanine PNA-Boc groups.

AFM fluid tapping mode images showed **G4G** adsorbed on HOPG with molecular-sized bands of width 3.8 ± 0.1 nm that are similar in width to the molecular-sized bands observed with **G2$_{12}$G** (Figure 3.32 a,b).



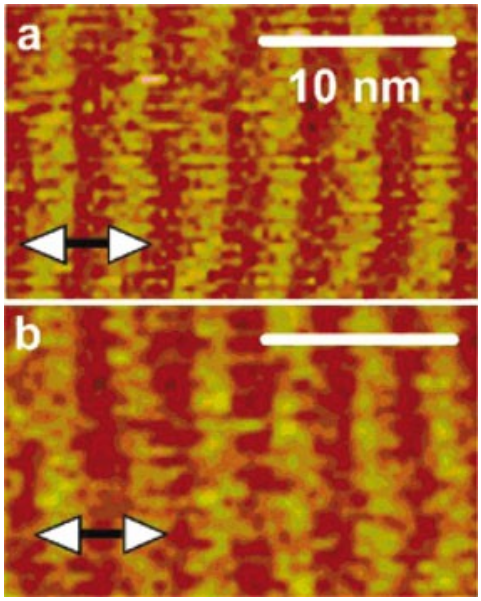


Figure 3.31 *(Left) Chemical structure of* ***G4G****.*
Figure 3.32 *(Right) Comparison of the AFM phase images of (a)* ***G2$_{12}$G****, forming 3.8 nm bands, and (b)* ***G4G****, forming 3.8 nm bands. The 3.8 nm widths of both these assemblies suggests the molecules in both assemblies are arranging similarly.(Adapted from reference 36)*

Molecular modeling of **G4G** (Figure 3.33 b) using a double-stranded motif and a close-packed arrangement similar to **G2$_{12}$G** shows modeled bands of 3.9 nm that match the observed band spacing. However, by adding an attachment point (the tertiary nitrogen) for the TEG, the number of core atoms between guanine PNA moieties changes from being even in **G2$_{12}$G** to being odd in **G4G**. As a result, the molecules close pack in a slightly different arrangement compared to **G2$_{12}$G** (Figure 3.28 a,b). In this case, a pseudo-centrosymmetric assembly is predicted for the **G4G**, in which adjacent double-stranded guanine motifs run antiparallel with respect to each other, whereas in **G2$_{12}$G** they run parallel.

Modeling also suggests that the TEG groups are not large enough to completely cover the hydrophobic scaffold coating. Calculations from the models suggest a density of 0.32 TEG groups/nm^2. In any case, initial studies to probe the biological effect of the current assembly were performed using static platelet adhesion.

These Rowan's grafted assemblies have been shown to be stable at biologically relevant temperatures and have even shown the ability to influence biological processes, namely static platelet adhesion.

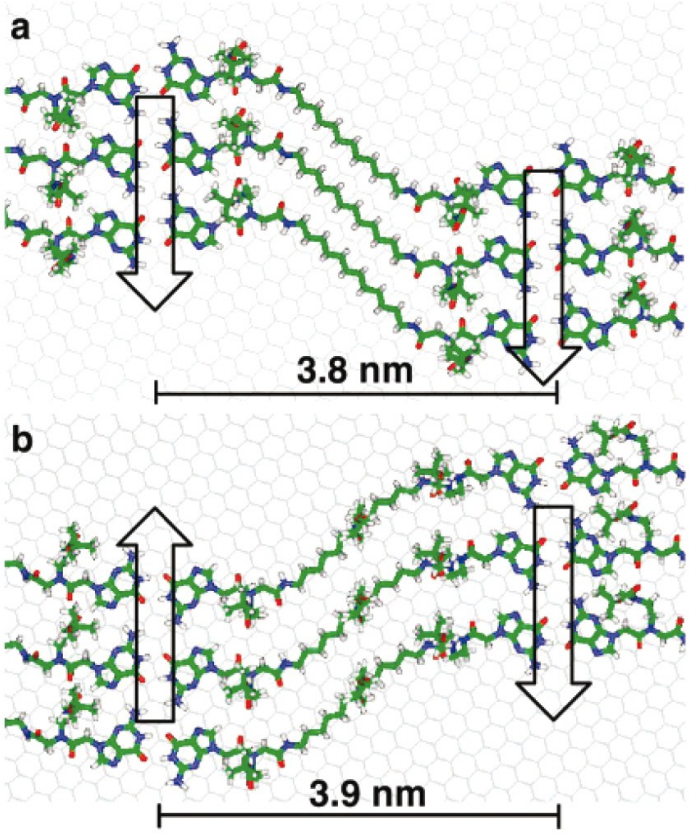


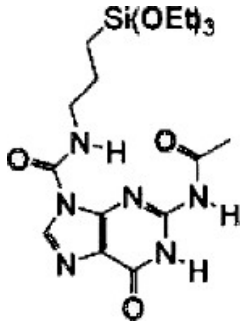
Figure 3.33
*Energy-minimized molecular models of (a) **G2$_{12}$G**, and (b) **G4G** with modeled bands that match the observed band spacings. Change in number of core atoms changes packing arrangement of molecules so that adjacent guanine motifs run parallel in (a) and antiparallel in (b).*

Rowan and colleagues affirm that this concept of using the surface assemblies as scaffolds is potentially a very versatile one in which a wide range of biologically active (or other functionalities) can be envisaged, opening the door to systematic, facile functionalization of a surface using a simple dip-coating process.

For other utility, Barboiu and colleagues have reported a long-range amplification of the G-quadruplex supramolecular chirality into hybrid organic–inorganic twisted nanorods, followed by transcription into inorganic silica microsprings by using the sol–gel process.[16] In this case they have shown a new way of embedding supramolecular chirality in materials, a process of interest for the development of a supramolecular approach to nanoscience and nanotechnology.

They have shown that from a molecular building block, as a guaninesiloxane **Gsi 15** (Figure 3.34) precursor of the achiral G-quartet and the chiral supramolecular G-quadruplex is possible to transcribe the supramolecular chirality of a dynamic supramolecular architecture and to transfer the supramolecular chirality of the G-quadruplex at the nanometric and micrometric scale with the creation of nanosized hybrid or microsized organic-inorganic superstructures, respectively. For all of these reasons, the guanine building block has been used as a molecular precursor to conceive hybrid chiral materials at the nanometric and

micrometric scales.



Gsi 15

Figure 3.34 *Chemical structure of* ***Gsi 15.***

The main strategy consisted of generating (amplifying) dynamic supramolecular G-quartets and G-quadruplexes by K^+ ion templating, from a dynamic pool of supramolecular dimeric, oligomeric ribbon-type, or cyclic supramolecular architectures (Figure 3.35). The G-quadruplex architectures are then fixed in a hybrid organic–inorganic material by using a sol–gel transcription process, followed by a second inorganic transcription in silica, that is, calcination.

The **GSi 15** derivative was prepared to have two structural features:[43] 1) molecular-recognition binding sites for the G-quartet formation were encoded in the guanine molecule and 2) the triethoxysilane groups were covalently bonded to the guanine moiety, thereby allowing the self-organized dynamic superstructures present in solution to be transcribed (frozen) by the sol–gel process into a solid hybrid material (Figure 3.35 b and c).

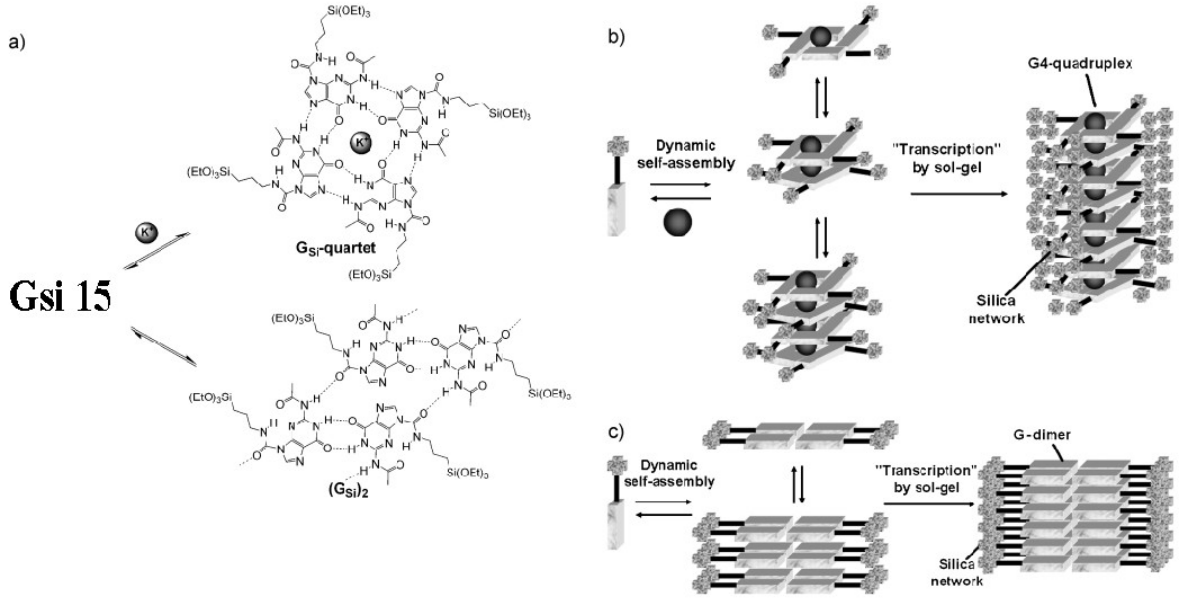


Figure 3.35 *a) The cation-templated hierarchic self-assembly of guanine alkoxysilane* ***GSi 15*** *gives the G-quartet. b,c) Representations of the transcription of the G-quadruplex into solid hybrid materials by a sol–gel process b) in the presence and c) in the absence of templating K^+ ions. (Adapted from reference 16)*

Impressive Scanning electron microscopy (SEM) revealed that the G-quadruplex hybrid material has a twisted hexagonal rodlike morphology (with a hexagonal cross-section), of 350–850 nm in outer diameter and around 2 μm in length. Owing to the lack of molecular chirality in the organic precursor, both left and right-handed supramolecular packings are formed and then frozen in twisted hexagonal rods, as shown in Figure 3.36 a. Remarkably, these resulting hybrid structures are hexagonally twisted, presumably from being templated by the chiral hexagonal packing of the G-quadruplexes (Figure 3.36 b,c).

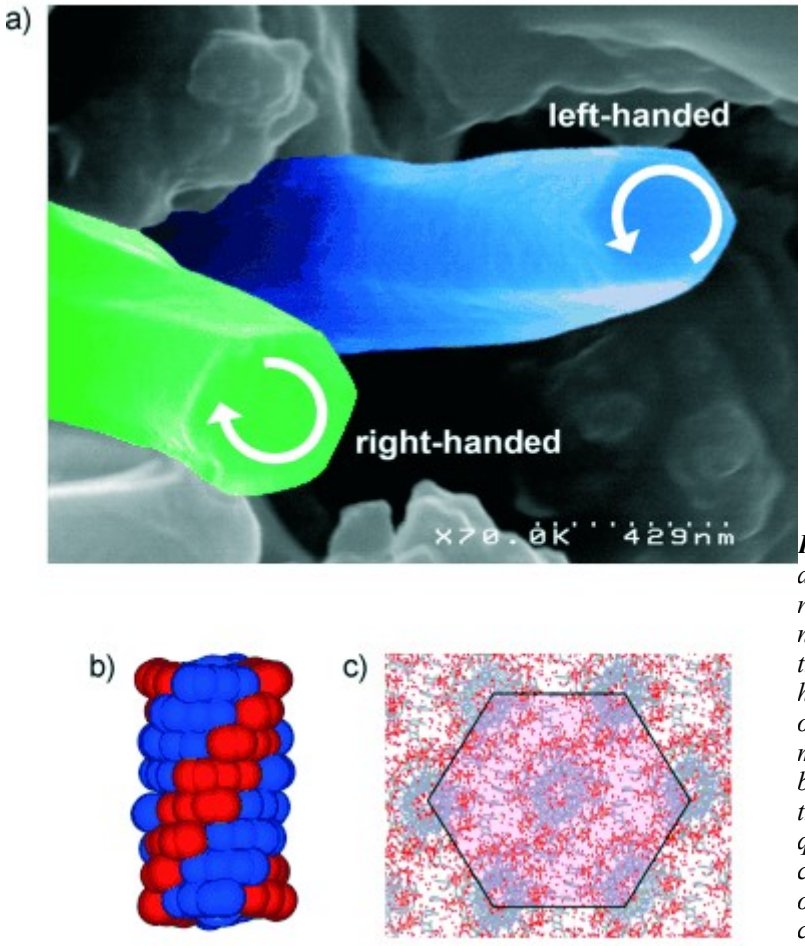


Figure 3.36
a) SEM image of the left- and right-handed twisted hexagonal nanorods resulting from sol–gel transcription of the chiral hexagonal G-quadruplex into the organic–inorganic hybrid material.
b) Space filling representation of the crystal structure of the G-quadruplex.
c) Hexagonal crystal packing observed in the published crystallographic data. (Adapted from reference 16)

Upon calcination of the G-quartet hybrid at 400°C, a helical silica material was formed and three kinds of morphologies can be recognized. In Figure 3.37 is possible to note, a) helical nanofibers with a thickness of 250 nm; b) helical nanobundles formed from individual nanofibers; c) silica microsprings, with an outer diameter of 2–8 μm, an inner diameter of 1–4 μm, and a helical pitch of 1.2–3.8 μm.

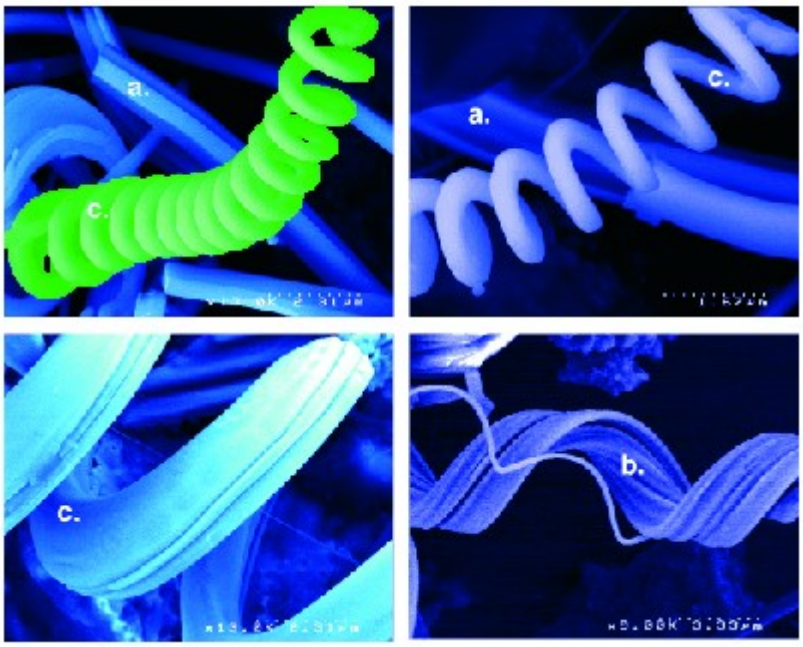


Figure 3.37 *SEM images of silica*
a) nanofibers,
b) nanobundles, and
c) microsprings resulting from calcination of the hybrid nanorods. (Adapted from reference 16)

However, Borboiu affirmed that the *"dynamic communication"* between the supramolecular self-assembly of nucleobases and the polymerization processes, which kinetically and stereochemically might communicate, is not so trivial. Similar "communication processes" have been identified in DNA transcription into inorganic materials.[44]

In another interesting work, Barboiu and colleagues have proposed a synthetic route for preparing self-organized ion-channel systems that have been "frozen" in a polymeric matrix.[45] They reported an example of a long-range amplification of G-quadruplex self-organization into macroscopic polymeric functional films. They used a ditopic bisiminoboronate-guanosine **G5G** as molecular precursors to obtain a G-quartet polymeric membrane materials at the macroscopic scale, and then by K^+ ion templating self-assembled into G-quartet-type supramolecular superstructures (Figure 3.38).

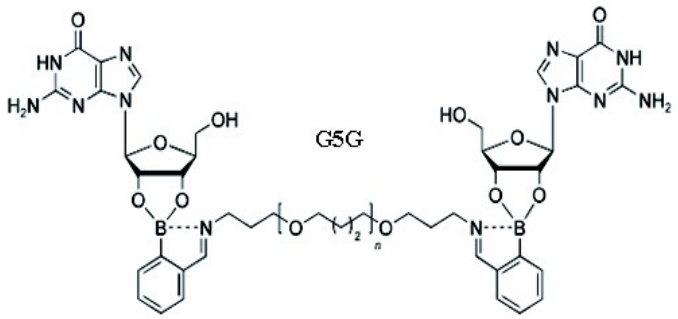


Figure 3.38 *Chemical structure of* ***G5G****.*

In this case the **G5G** derivative was prepared to have two structural features: a) two guanine end groups that encoded the recognised informations; b) a hydrofobic alkyl chain to link the two guanine and cross link the supramolecular structures G-quartets. The **G5G** can self-associate in two type networks to form a polymeric membrane films in the absence (**M_0**) and presence of templating K^+ ions (**M_{G4}**) (Figure 3.39).

The Borboiu's idea was to fix a "frozen" G-quadruplexes self-correlate with a directional order generating an anisotropic mesophases interconnected by condensed hydrophobic bridges. Then, this anisotropic characteristic could be studied to understand wheter the G-quadruplex ordered membrane films contributes to the fast electron/proton transfer by the formation of directional conduction pathways. So that, mixed cationic Na^+/K^+ or selective K^+ transport was probed to better understand the diffusional ion exchanges along "fixed" G-quadruplex polymeric pathways.

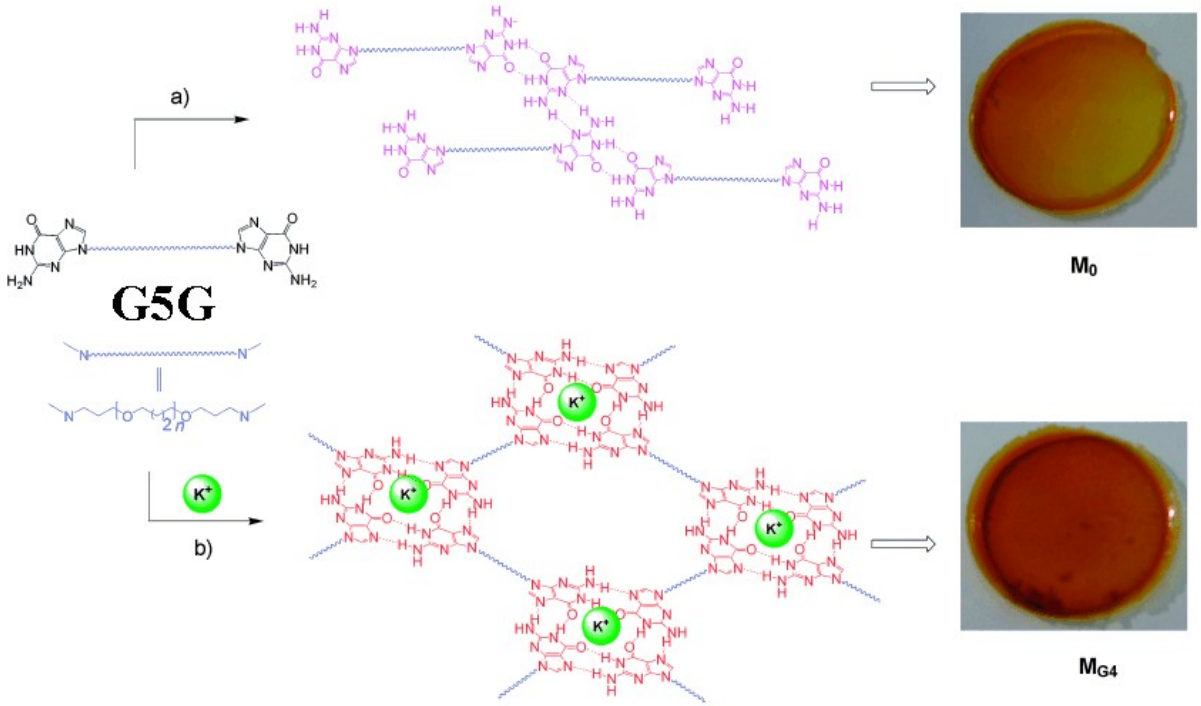


Figure 3.39 *The cation-templated hierarchical self-assembly of **G5G** gives networks in solid, self-supporting, polymeric membrane films in the a) absence (**M_0**) and b) presence of templating K^+ ions (**M_{G4}**). (Adapted from reference 45)*

The competitive transport of Na^+ and K^+ cations across membrane **M_{G4}** according to the solution–diffusion mechanism [46] and against its thermodynamic gradient, was evaluated under passive transport conditions. Figure 3.40 shows the concentration versus time transport profiles of Na^+ and K^+ ions. The feed phase was filled with an equimolar solution of NaCl/KCl, while the strip phase was distilled water. The G-quartet membrane **M_{G4}** presents a

nonlinear saturation behavior of the transport profile of Na^+ and K^+ ions, which indicates a strong affinity of the membrane towards the solutes.[46] They first noted an initiation step where the membrane functions like a "sponge" for the K^+ ions, while the smallest Na^+ ions are transported faster through the membrane.

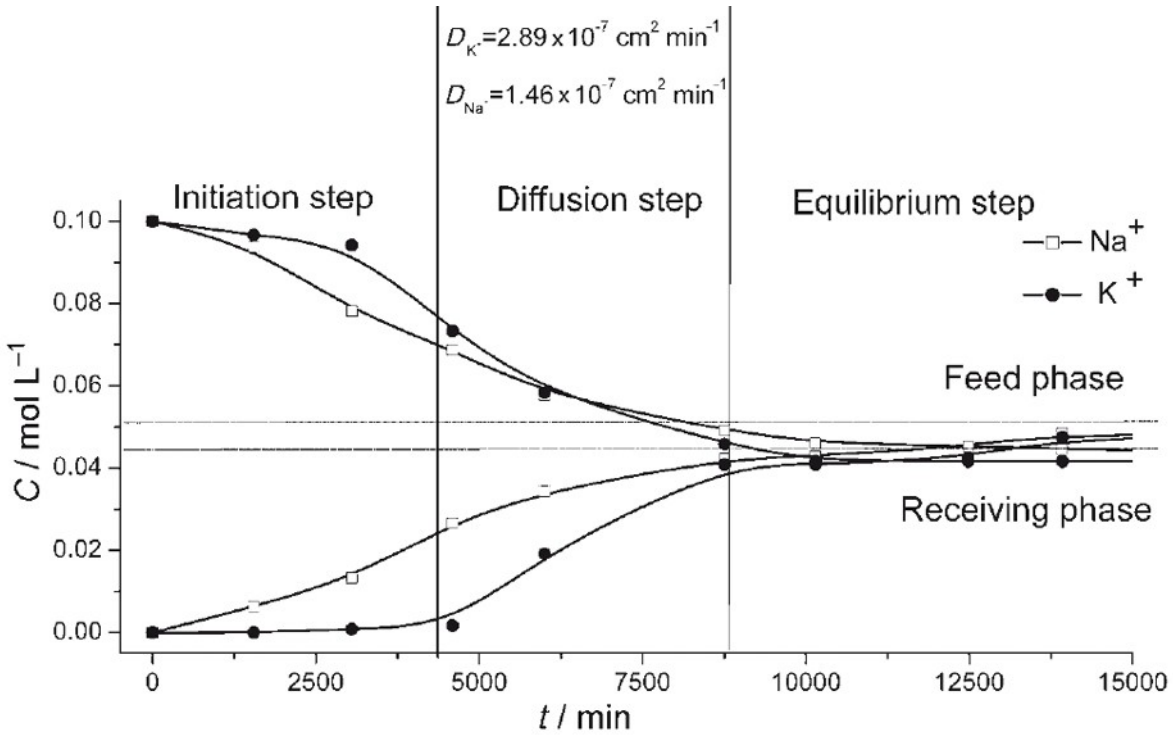


Figure 3.40 *Transport profiles of Na^+ and K^+ ions through the $\mathbf{M}_{G4}$ membrane, shown as concentration in the feed, the membrane,and the receiving phase versus time. (Adapted from reference 45)*

Into initiation step the, probably, mixed cationic Na^+/K^+ G-quadruplexes are formed along ion exchange pathways.[47] Certainly, a substantial contribution to this phenomenon arises from the high affinity of G-quartets for K^+ ions, which may stay within the hydrophilic G-quadruplex pathways. After this initiation step, in a second diffusion step the K^+ ions are transported twice as fast as Na^+ ions. This apparent selectivity is consistent with the development of K^+- conducting pathways along membrane-spanning K^+-filled oligomers. Finally, the system reaches the equilibrium step.

The Barboiu's results give an example of the long-range amplification of G-quadruplex self-organization into macroscopic polymeric functional films. Mixed cationic $Na^{+/}K^+$ or selective K^+ transport enabled us to better understand the diffusional ion exchanges along "fixed" G-quadruplex polymeric pathways.

In 2000 Jeff Davis[48] obtained a good crystal of the 5'-*t*-butyldimethylsilyl-2',3'-isopropylidene guanosine **G 5**: the x-ray structure confirmed that, in the hexadecamer structure the picrate anion is not passive; it contributes to keep together the complex structure by means of hydrogen-bonds with the exocyclic NH of two different quartets (Figure 3.41 a and b). The binding contribution of the picrate anion was evident also from an ESI-MS study.[48]

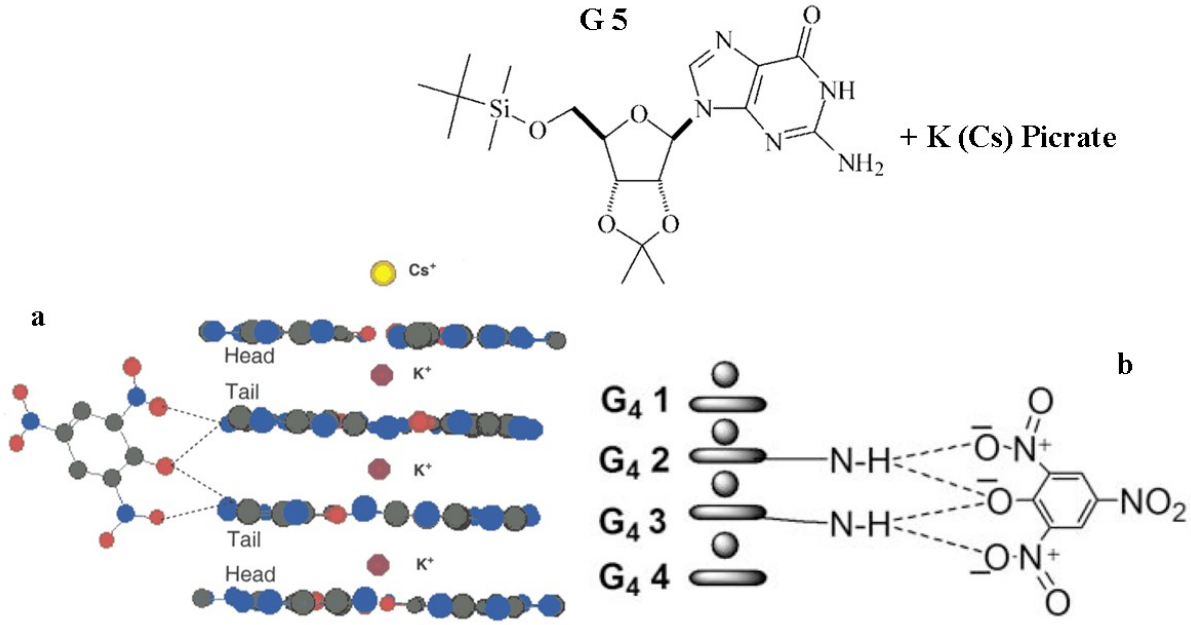


Figure 3.41 *Chemical structure of* ***G 5****, a) The single crystal X-ray structure shows that cation-templated self-assembly of 16 equiv. of* ***G 5*** *gives a lipophilic G-quadruplex* $[\mathbf{G\ 5}]_{16}\ 3K^{+}/Cs^{+}4Pic^{-}$ *b) Model of the interaction between the anion picrate and the two inner G-quartet. (Adapted from references 48)*

In the same period Shi, Davis[49] and co-worker demonstrated that lipophilic guanosine **G 5** undergoes cation-templated self-assembly to form a discrete hexadecamer in the solid-state, in solution and in the gas phase. The template cations, such as Na^{+}, K^{+} and Ba^{2+}, are located along the central axis of the cylindrical complex, sandwiched between G-quartet layers. Furthermore, four picrate anions are bounded to the surface of the G-quadruplex through hydrogen bonds.

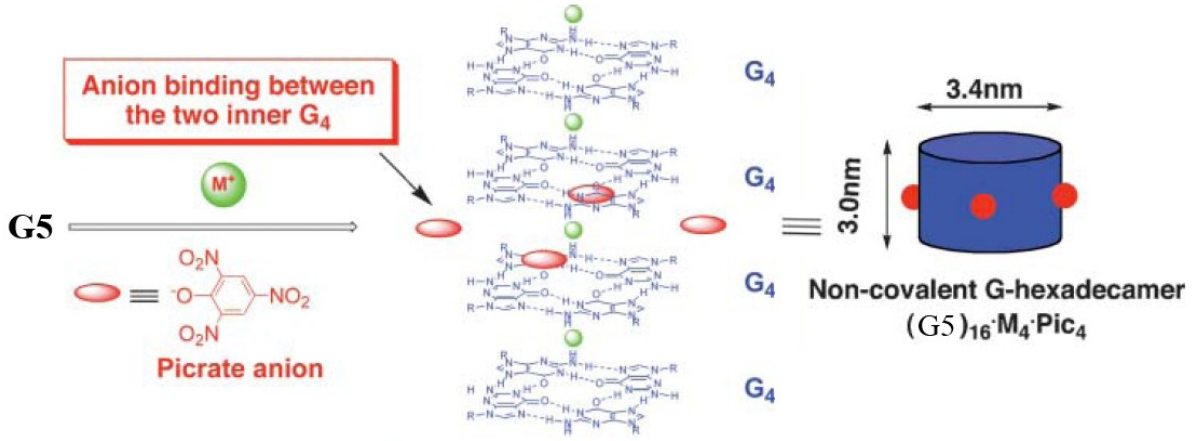


Figure 3.42 *Chemical structure of* ***G 5****, chemical structure of hexadecamer cation-anion templated. (Adapted from refernce 50)*

In the crystal structure of the G-hexadecamer similar in figure 3.42, picrate anions coordinate with the exocyclic amino group of the central two G-quartets through the anion's phenolate oxygen and the two nitro groups at the ortho positions. The para position, which is solvent-exposed from the G-quadruplex, provided an ideal synthetic handle for the extension of the supermolecule without disturbing the G-quartet's key non-covalent interactions. For this reason, in 2008, Wu[50] and colleague designed and synthesized the 2,2,6,6-tetranitrobiphenolate (TNBP) dianion as a bridging anion that could be used to tether individual G-hexadecamers (Figure 3.43).

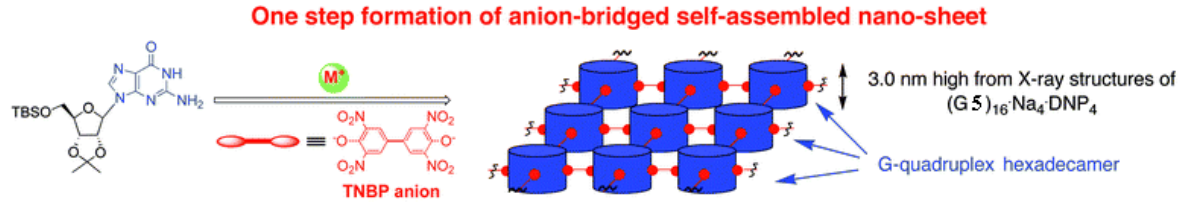
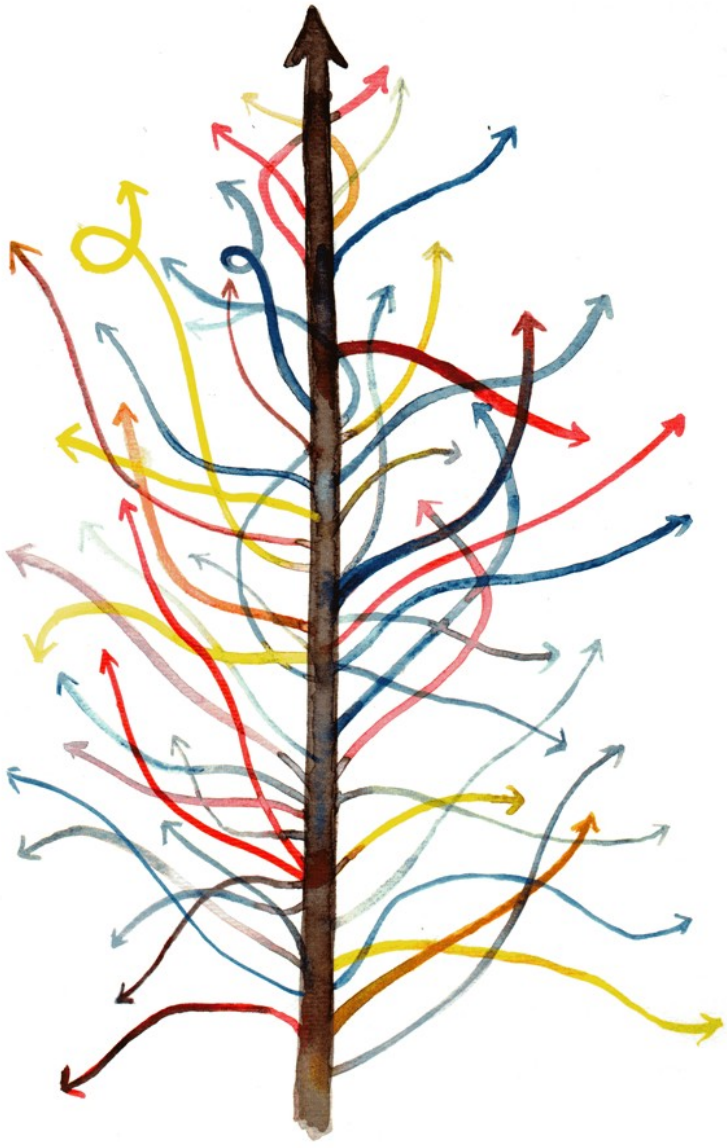


Figure 3.43 *Schematic illustration of the nanosheet of the* ***(G 5)****$_{16}$·Na^{+}_{4}·$TNBP^{2-}_{2}$ complex. (Adapted from reference 50)*

The structure has been characterized by solution NMR, solid-state NMR, powder XRD and AFM and all the information supported a novel non-covalent polymeric nano-sheet produced through small molecule self-assembly in a single step. In this case the covalently-linked dianion $TNBP^{2-}$ promotes the formation of a non-covalent polymer by cross-linking lipophilic G-quadruplexes wich may provide unique properties as a novel nanosheet material.

3.4 Conclusion

In several examples exposed in this chapter, guanosine derivatives, either in solution or on the surface, are able to self-associate in different supramolecular structures depending on their function and external ambient. The recognition pattern stored into covalent molecular structure drives the informed self-organization program to obtain huge diversity of possible structural combinations. The serendipity is a characteristic property for a complex chemical matter that represents a creative force to generate new form, process and functionality of matter.



LaurenceDuthoit

Tree of serendipity

The branches of the tree, its beauty and equilibrium come from the little chance events of life, that make it more poetic and joyful

3.5 References

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4.0 Multicomponents supramolecular hybrid architectures in solution and on the surface.

> *The essence of supramolecular chemistry is that the structure and properties of the higher-level entities (supermolecules, crystals) cannot be predicted directly or immediately from those of the lower-level entities (molecules).* *G.R. Desiraju*

4.1 Introduction

Into chapter 1 I gave a basic notion of the self-organization's principles in biological systems underling the point of view of the biology chemistry, the complexity science and the holistic eastern thought.

Into chapter 2 I presented an introduction to the supramolecular chemistry and how the combination of the system's features (information and programmability, dynamics and reversibility, constitution and diversity) can be trained toward the emergence of a adaptative/evolutive chemistry.

Into chapter 3 I showed as the molecular recognition pattern of the guanosine derivatives can be used to induce and control self-organization in 1D, 2D and 3D to perform supramolecules self-assembled, sush as wires, layers, film, membranes, geles and liquid crystals, in solution, at solid-liquid interface and in the solid state.

Now after that we present a noncovalent synthesis relies on self-assembly of multiple components into discrete supramolecules, such as ribbon, octamer and hexadecamer.

We show a dynamic process to organise and disorganise the highly ordered supramolecular structures between ribbons and octamer (Section 4.2).

We show how a little modification of the concentration in a system can emerge a new structure and co-evolving from dimers to ordered nanoribbons in solution and at surface (Section 4.3).

Then we show how the introduction of a new element can destroy a complex system to obtain a new highly multi-hierarchical system of complex interactions (Section 4.4).

The final dates produced in collaboration with Rolic Technology L.t.d. are closed to confident relationship (Section 4.5).

4.2 Reversible interconversion between a supramolecular polymer and a discrete octameric species from a guanosine derivative by dynamic cation binding and release

Reversibility is a hallmark of supramolecular chemistry.[1] By exploiting the information stored in the molecule, in particular, its preprogrammed propensity to undergo self-recognition and self-association pathways, in combination with the reversibility of its self-assembly under external stimuli such as temperature or chemical environment, it is possible to implement molecule-sized prototypes of dynamic chemical devices.[2] Besides the fundamental interest in controlling motions on the nanoscale, these device prototypes can be important for future data storage.[3]

As described in section 2.4 Ghoussoub and Lehn were able to control the mesoscale dynamic sol-gel interconversion, i.e., from a disordered guanine solution to gel-forming ordered G-quartet architectures, through reversible cation binding and release.[16] However, a great challenge remains to control the switching between two or more highly ordered guanine-based.

We report here on the tunable interconversion between discrete supramolecular assemblies from a lipophilic guanosine, i.e., G-ribbons and G-quartet columns, fueled by cation complexation and release (Figure 4.1 and 4.2).

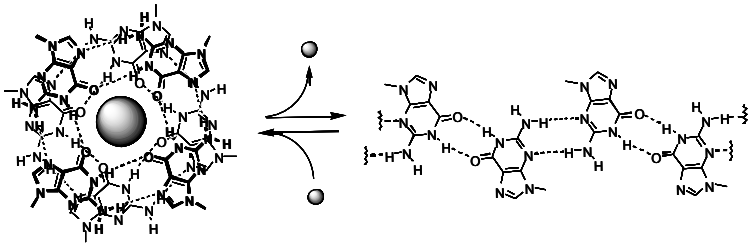


Figure 4.1 *Reversible interconversion of the supramolecular assemblies of guanine moieties fueled by cation complexation and release: the metal templated octamer and G-ribbon.*

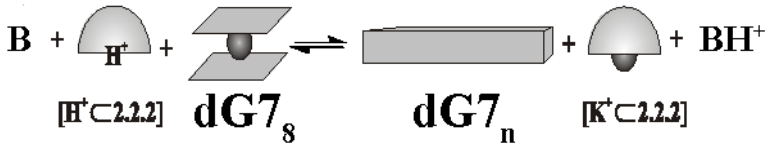


Figure 4.2 *Schematic representation for a tuneable supramolecular system: the metal templated octame* $K^{+}dG7_{8}$*, and G-ribbon* $dG7_{n}$*.*

The G-quartet structures are harnessed by the presence of a coordinated potassium cation: this offers the possibility of triggering a reversible ribbon-quartet interconversion by

controlled sequential addition and removal of K^+. The cryptand [2.2.2] offers an efficient complexation of K^+ to yield the cryptate $[K^+ \subset 2.2.2]$.[17] Upon protonation of one of the bridgehead nitrogens, the bound K^+ can be released, leading to the formation of $[H^+ \subset 2.2.2]$ (Figure 4.3). Such an approach was proven to be successful to trigger the reversible conversion between a coiled and stretched conformation in an oligomeric pyridine-pyrimidine derivative (Figure 4.4).[18]

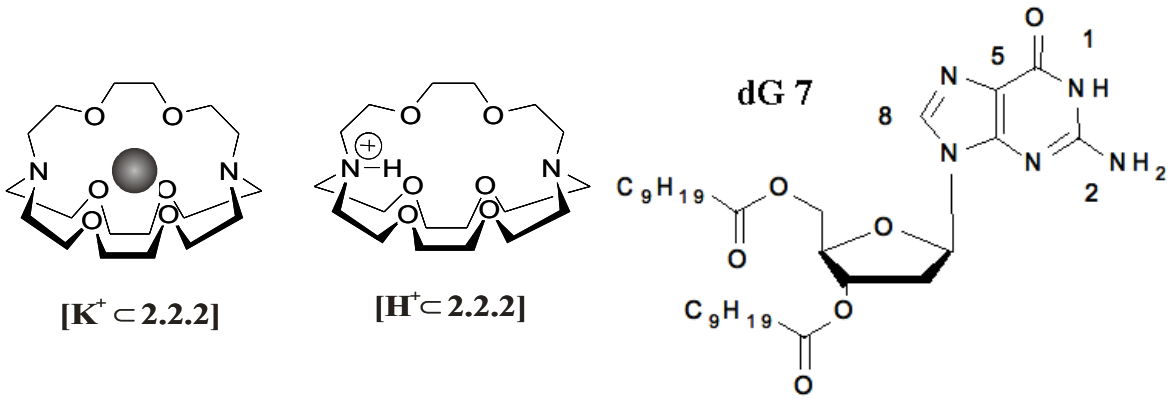


Figure 4.3 *[2.2.2] (1,10-diaza-4,7,13,16,21,24-hexaoxabicyclo-[8.8.8]hexacosan) with potassium K^+ and H^+ and Guanosine derivative (di-decanoil deoxi-Guanosine)* ***dG 7***

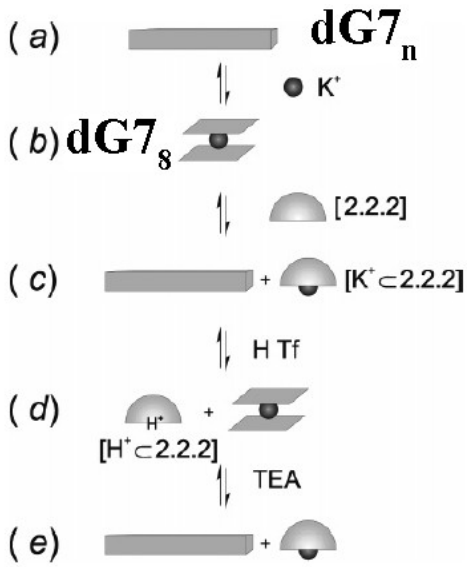


Figure 4.4 *The stepwise reversible interconversion between the ribbon* ***dG7n*** *and the octamer* ***K⁺ dG7₈***.

The addition (Figure 4.4) of 1/8 equiv of potassium picrate to a chloroform solution of the guanosine derivative **dG7** transforms the supramolecular ribbon[8] $\mathbf{dG7_n}$ into the octameric complex $\mathbf{K^+dG7_8}$[5] (see experimental section). Upon subsequent addition to $\mathbf{K^+dG7_8}$ of 2.5 equiv of [2.2.2], the potassium complex reverts to the original G-ribbon $\mathbf{dG7_n}$ (because of the small difference between the stability constants of $[K^+ \subset 2.2.2]$ and $\mathbf{K^+dG7_8}$, the conversion from $\mathbf{K^+dG7_8}$ to $\mathbf{dG7_n}$ requires an excess of cryptand). Upon addition of 1 equiv of trifluoromethanesulfonic acid (HTf), K^+ is released from the cryptate and the octameric

complex $\mathbf{K^+dG7_8}$ is regenerated. In contrast to Lehn et al.,[16,18] who obtained the release of K^+ by protonation of both the nitrogen atoms of the cryptand, we added only 1 equiv of acid. In fact, upon addition of more than 1 equiv, the octameric species $\mathbf{K^+dG7_8}$ is no longer the most abundant self-assembled species in solution, as revealed by CD and ^{1}H NMR spectroscopies. Adding there after 1 equiv of triethylamine (TEA) deprotonates [$H^+ \subset$ 2.2.2]; the free cryptand recaptures K^+, and the G-ribbon $\mathbf{dG7_n}$ is formed again. The interconversion may be repeated by sequential addition of acid and base. The cycle was repeated three times without apparent degradation of the system; however, the salt formation prevents the possibility of an indefinite repetition of the switching.

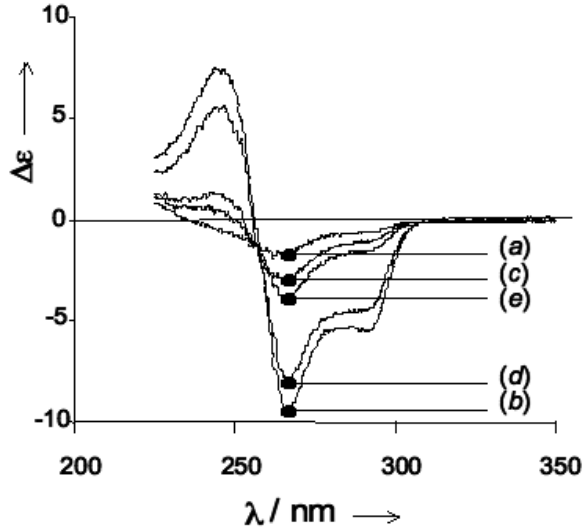


Figure 4.5 *Observation of the reversible ribbon-octamer interconversion in a solution of* ***dG7*** *(13.5 mM) in $CDCl_3$ (path length = 0.01 cm) by CD spectroscopy. (a) Initial sample (**dG7$_n$**); (b) after addition of 1.7 mM potassium picrate (**K$^+$dG7$_8$**); (c) after addition of 4.2 mM cryptand [2.2.2] (**dG7$_n$**); (d) after addition of 4.2 mM HTF (**K$^+$dG7$_8$**); and (e) after addition of 4.2 mM Et_3N (**dG7$_n$**).*

Circular dichroism (CD) and ^{1}H NMR can both be exploited to monitor the ribbon-octamer $\mathbf{dG7_n} >> \mathbf{K^+dG7_8}$ interconversion. In fact, CD spectroscopy has been successfully used to study the cation-directed assembly of homoguanylic and guanosine-rich oligonucleotides,[19] as well as that of lipophilic guanosines.[20] Although the CD spectrum of $\mathbf{dG7_n}$ in the region of the intense π- π transitions of the guanine chromophore at ca. 260 nm is monosignate and weak (Figure 4.5, trace a), the stabilization of stacked G-quartet-based structures induced by the K^+ ion introduces a negative exciton signal (Figure 4.5, trace b). The adjacent quartets are, in fact, rotated by a well-defined angle:[5] this causes the interaction between the transition moments located in the different G-quartets originating the bisignate couplet.[21]

^{1}H NMR spectroscopy has been employed to characterize the assembled species in chloroform solutions of **dG7n.**[5,6,8,10,20] Although the species $\mathbf{dG7_n}$ exhibits one set of signals,[10,23] the complex $\mathbf{K^+dG7_8}$ shows two sets of signals in a 1:1 ratio:[5,20] one set corresponds to molecules belonging to one quartet, and the other corresponds to molecules of the other, nonequivalent, quartet.

In particular, the region between 5 and 13 ppm, corresponding to the H(1), H(8), and NH(2)signals, represents an unambiguous signature of the ribbon-octamer conversion: the broad H(8) and H(1) signals at 7.9 and 12.1 ppm, respectively, in **dG7n** (Figure 4.6, trace a) are replaced by two sharp H(8) signals (in an approximate 1:1 ratio) at 7.4 and 8.0 ppm and by two sharp H(1) resonances at 12.1 ppm when the supramolecular complex $\mathbf{K^+dG7_8}$ is the dominant species (Figure 4.6, trace b). As observed also by CD spectroscopy, the sequential addition of cryptand, acid, and base (Figure 4.6, traces c-e) allows the switching between the two signatures of the ribbon and the octamer.[24]

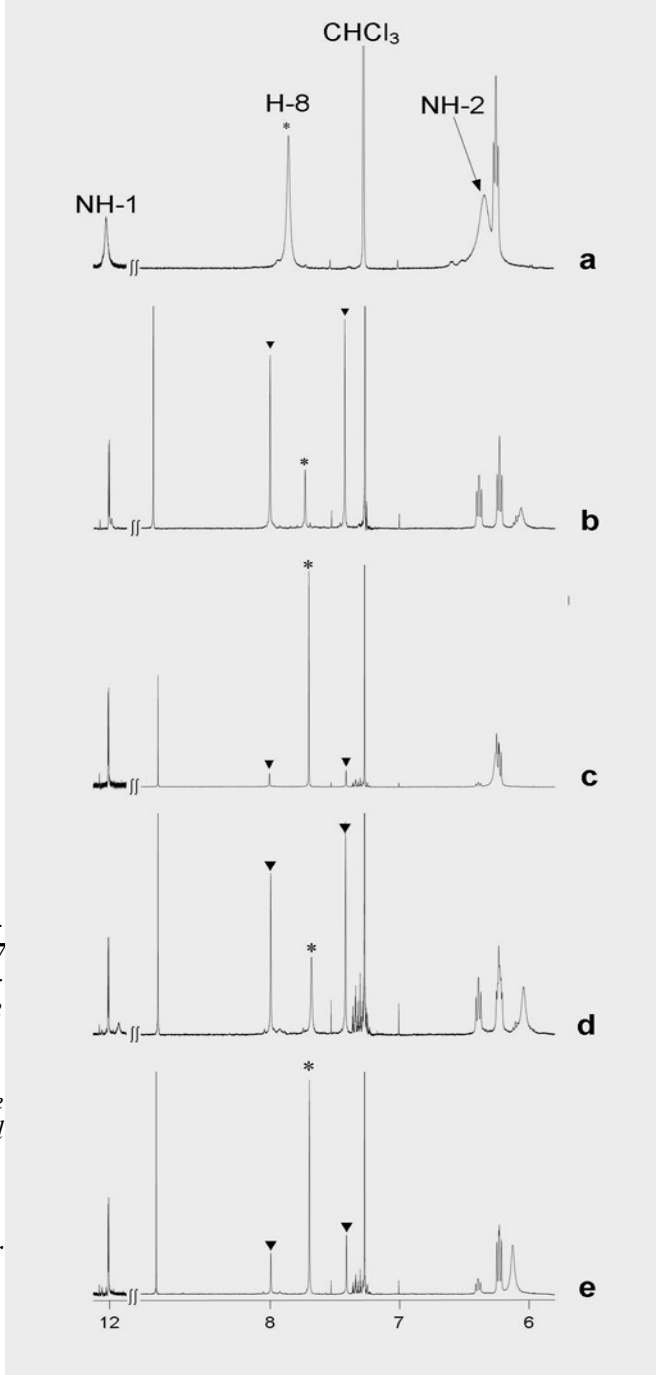


Figure 4.6 *Observation of the reversible ribbon-octamer interconversion in a solution of* ***dG7*** *(13.5 mM) in $CDCl_3$ by ^1H NMR spectroscopy; only the downfield portion of the spectra (5-13 ppm) is shown.*
(a) Initial sample (dG7n);
(b) after addition of 1.7 mM potassium picrate ***(K^+dG7_8)****; (c) after addition of 4.2 mM cryptand [2.2.2]* ***($dG7_n$)****;*
(d) after addition of 4.2 mM HTF ***(K^+dG7_8)****; and*
(e) after addition of 4.2 mM Et_3N ***($dG7_n$)****;*
The stars and triangles mark the H(8) signals for the ribbon and octamer species, respectively.

In summary, we have shown the ionic modulation of the reversible interconversion between two highly ordered supramolecular motifs of a guanosine derivative. This supramolecular dynamer can be of importance as a model system to mimic the formation-annihilation of G-quartet-based architectures, which might be of biological significance, in the frame of nucleic acid telomerase.

Experimental section: the guanosine derivative **dG7** was synthesized according to the procedure reported in ref 10. A 13.5 mM deuteriochloroform solution of **dG7** was prepared and left to stand for a week at +4 °C (solution a). On this solution, both CD (Jasco J710, path length = 0.01 cm) and ^{1}H NMR (Varian 400 MHz) spectra were recorded (curves a in Figures 5 and 6) at room temperature. A volume of solution a was shaken at 20 °C with an equal volume of a 1.68 mM aqueous solution of potassium picrate; the two phases were kept in contact at +4 °C for 2 days; afterwards, the organic phase was recovered (solution b) and CD and ^{1}H NMR spectra were recorded (curves b, Figures 5 and 6). A portion of 7 mL of solution b was added to 11.0 mg (0.029 mmol) of **[2.2.2]** (1,10-diaza-4,7,13,16,21,24-hexaoxabicyclo-[8.8.8]hexacosan, Aldrich), and the system was stirred overnight at room temperature (solution c): CD and ^{1}H NMR spectra were then recorded (curves c, Figures 5 and 6). An aliquot of 6 mL of solution c was added to 3.73 mg (0.025 mmol) of trifluoromethanesulfonic acid (Aldrich) and stirred for 1 h (solution d). CD and ^{1}H NMR spectra were recorded (curves d, Figures 5 and 6). A portion of 300 μL (0.021 mmol) of a 70 mM deuteriochloroform solution of triethylamine (redistilled from CaH_2) was added to 5 mL of solution d and stirred for 1 h: CD and ^{1}H NMR spectra were recorded (curves e, Figures 5 and 6). Upon addition of the acid, the equilibration between the two self-assembled species required ca. 30 min, whereas after addition of the base, it takes ca. 20 min.

4.3 Self-assembly of an alkylated guanosine derivative into ordered supramolecular nanoribbons in solution and on solid surfaces

We report on the synthesis and self-assembly of a guanosine derivative bearing an alkyloxy **G16** side group under different environmental conditions. This derivative was found to spontaneously form ordered supramolecular nanoribbons in which the individual nucleobases are interacting through H-bonds. In toluene and chloroform solutions the formation of gel-like liquid-crystalline phases was observed. Sub-molecularly resolved scanning tunneling microscopic imaging of monolayers physisorbed at the graphite-solution interface revealed

highly ordered two-dimensional networks. The recorded intramolecular contrast can be ascribed to the electronic properties of the different moieties composing the molecule, as proven by quantum-chemical calculations. This self-assembly behavior is in excellent agreement with that of 5'-*O*-acylated guanosines, which are also characterized by a self-assembled motif of guanosines that resembles parallel ribbons. Therefore, for guanosine derivatives (without sterically demanding groups on the guanine base) the formation of supramolecular nanoribbons in solution, in the solid state, and on flat surfaces is universal. This result is truly important in view of the electronic properties of these supramolecular anisotropic architectures and thus for potential applications in the fields of nano- and opto-electronics.

G16

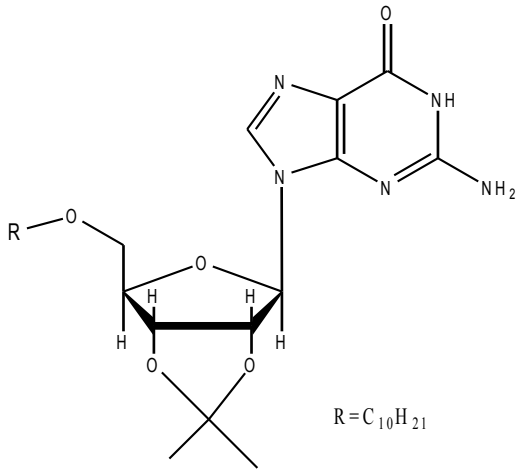


Figure 4.7 *Chemical structure of* ***G16****.*

Araki and Yoshikawa recently introduced nonpolar and flexible alkylsilyl groups into 2'-deoxyguanosine to obtain efficient organogelators for alkanes.[9] From an in-depth structural analysis, they concluded that in these gels the basic structure is a sheetlike assembly: the supramolecular structure consists of anti-parallel G ribbons like in Figure 4.8 linked through two additional inter-tape hydrogen bonds between NH(2) and N(3) of the two guanines belonging to adjacent ribbons. Upon heating, a gel-to-liquid-crystal phase transition is observed and has been ascribed to the selective cleavage of the inter-tape H-bonds.

In our attempts to find general strategies to form guanosine nanoribbons, we never observed this sheet-like architecture for 5'-*O* acylated guanosines. To verify the universality of the tendency for guanosine derivatives to form ribbonlike motifs irrespective of the nature of the 5'-*O* substitution, we prepared the *O*-alkylated guanosine **G16**. Our specific goal was to find out if the carbonyl group in the 5'-*O*-acylated derivative, which is known to interact through an intra-ribbon H-bond with NH(2), was essential for the formation of nanoribbons. It

is worth stressing that the strongly anisotropic quasi-1D nanoribbons were found to possess interesting physicochemical properties,[12-13,25-26] while the 2D sheetlike assemblies can be expected to hold different yet more modest properties for applications in (opto)electronics.

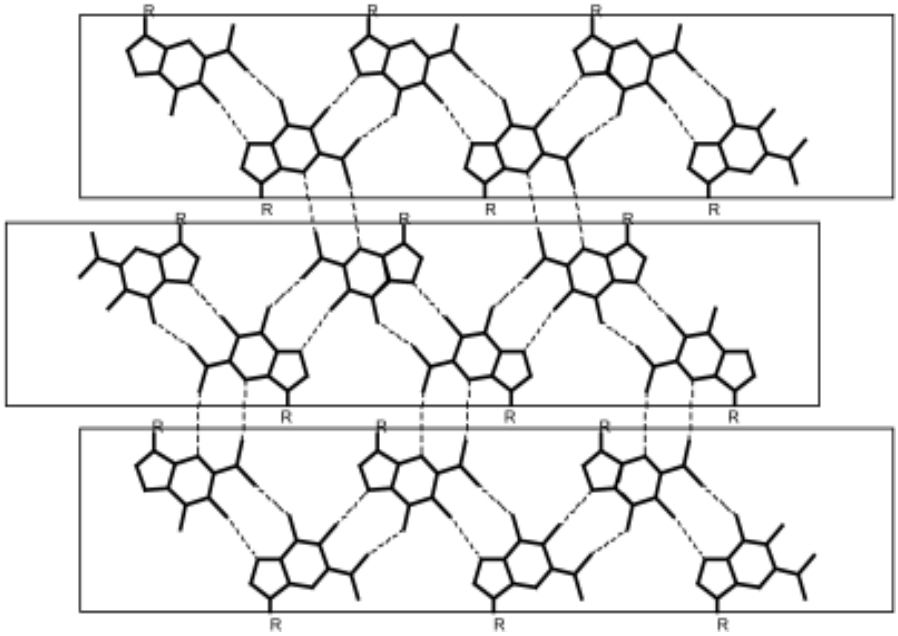


Figure 4.8 *Two-dimensional H-bonded sheet of guanine moieties. The boxes highlight the individual guanine ribbons connected by H-bonds between NH(2) and N(3) of two facing guanines belonging to adjacent ribbons. (Adapted from reference 27)*

In light of this, it is of paramount importance to find universal strategies to form functional nanoribbons from different guanosine derivatives in order to control and improve the properties of the supramolecular arrangements. We report here on the synthesis, solution characterization, and self-assembly of **G 16.**

Small-angle X-ray diffraction characterization made it possible to study the structure in the liquid-crystalline phases, scanning tunneling microscopy investigations, corroborated by quantum chemical calculation, were employed to unveil the structural and electronic properties of the self-assembled species on graphite.

Results and Discussion. Self-assembly in solution: The supramolecular behavior of compound **G16** was studied by NMR spectroscopy. Spectra were recorded at room temperature in $CDCl_3$ and $[D_6]DMSO/CDCl_3$ 3:1 solutions with concentrations ranging from 8×10^{-3} to 7×10^{-2}M. Signals (Table 4.1) were assigned on the basis of 2D COSY and NOESY experiments.

Table 4.1 *^{1}H NMR (400 MHz) chemical shifts (ppm) for solutions of* ***G16*** *at RT. Assignments were made on the basis of COSY and NOESY spectra.*

c **(solvent)**	**NH(1)**	**H(8)**	**NH(2)**	**H(1')**	**H(2')**	**H(3')**	**H(4')**	**H(5'/5'')[a]**	**OCH_2**	**isopropylidene CH_3[a]**
8×10^{-3} M ($CDCl_3$)	12.02	7.76	6.01	6.02	5.15	4.92	4.43	3.64-3.57	3.43	1.62-1.39
3×10^{-2} M ($CDCl_3$)	12.02	7.76	6.25	6.02	5.18	4.92	4.42	3.62-3.57	3.43	1.62-1.39
7×10^{-2} M ($CDCl_3$)	12.02	7.77	6.28	6.02	5.18	4.92	4.42	3.63-3.57	3.43	1.62-1.39
5×10^{-2} M ([D_6]DMSO/$CDCl_3$)	10.64	7.73	6.17	5.91	5.03	4.90	4.27	3.55-3.48	3.35	1.49-1.28

[a] Diastereotopic protons have not been assigned.

Modest line broadening was observed upon increasing the concentration in $CDCl_3$. The proton spectrum in [D_6]DMSO/$CDCl_3$ shows the NH(1) signal at δ =10.64 ppm. This signal shifts to δ =12.02 ppm in pure $CDCl_3$ solutions and is unaffected when the concentration is increased from 8×10^{-3} to 7×10^{-2} M. The NH(2) signal appears as a broad singlet at δ =6.17 and 6.01 ppm in [D_6]DMSO/$CDCl_3$ and in the most diluted $CDCl_3$ solution, respectively, and shifts slightly downfield with increasing concentration in chloroform (δ =6.28 ppm for the 7×10^{-2} M solution). The NH(1) group therefore always seems to be hydrogen-bonded in chloroform, while the NH(2) is eventually hydrogen-bonded only at higher concentration. While NOESY spectra recorded for the most dilute solutions in $CDCl_3$ and in DMSO show cross peaks with phases opposite to the diagonal, solutions above 3×10^{-2} M exhibit cross peaks with the same phase as the diagonal. Therefore, in the lower concentration range in chloroform the aggregates are still in the fast-tumbling regime[28] and no extensive hydrogen bonding seems to occur. Given that the molecular weight of **G 16** is 463, and considering the downfield shift observed for the NH(1) proton in $CDCl_3$ relative to the signal in DMSO, we can conclude that the compound exists as a dimer in dilute chloroform solution, as observed before[8] for a similar compound. At higher concentrations the scenario is markedly different:

with increasing concentration we observed the formation of supramolecular oligomeric/polymeric aggregates with higher "molecular" weight and slower tumbling rates, as evidenced by negative cross peaks in the NOESY spectra.

Information on the structure of supramolecular aggregates can be gathered from a closer inspection of NOESY and ROESY spectra. In Figure 4.9 the NOESY spectrum of a 7×10^{-2} M solution of **G16** in $CDCl_3$ (mixing time 100 ms) is reported. The spectrum shows cross peaks (boxed) between NH(1) and H(8) and between NH(2) and H(8) signals. These signals are characteristic of the ribbon-like supramolecular arrangement shown in Figure 3.7 A.[8] It is noteworthy that cross peaks between NH(2) and H(2') or H(1') signals are very weak and cross peaks between isopropylidene CH_3 and NH(2) signals are absent. These last interactions would be expected both if the supramolecular structure were of the type depicted in Figure 3.7 B or in the case of a sheetlike assembly analogous to the one described by Araki and co-workers (Figure 4.8). It should be pointed out that proton spectra did not change with time and that NOESY spectra were recorded on aged samples in wet $CDCl_3$: under these same conditions, the analogous didecanoyl ester derivative[8] self-assembles through the hydrogen-bond network shown in Figure 3.7 B.

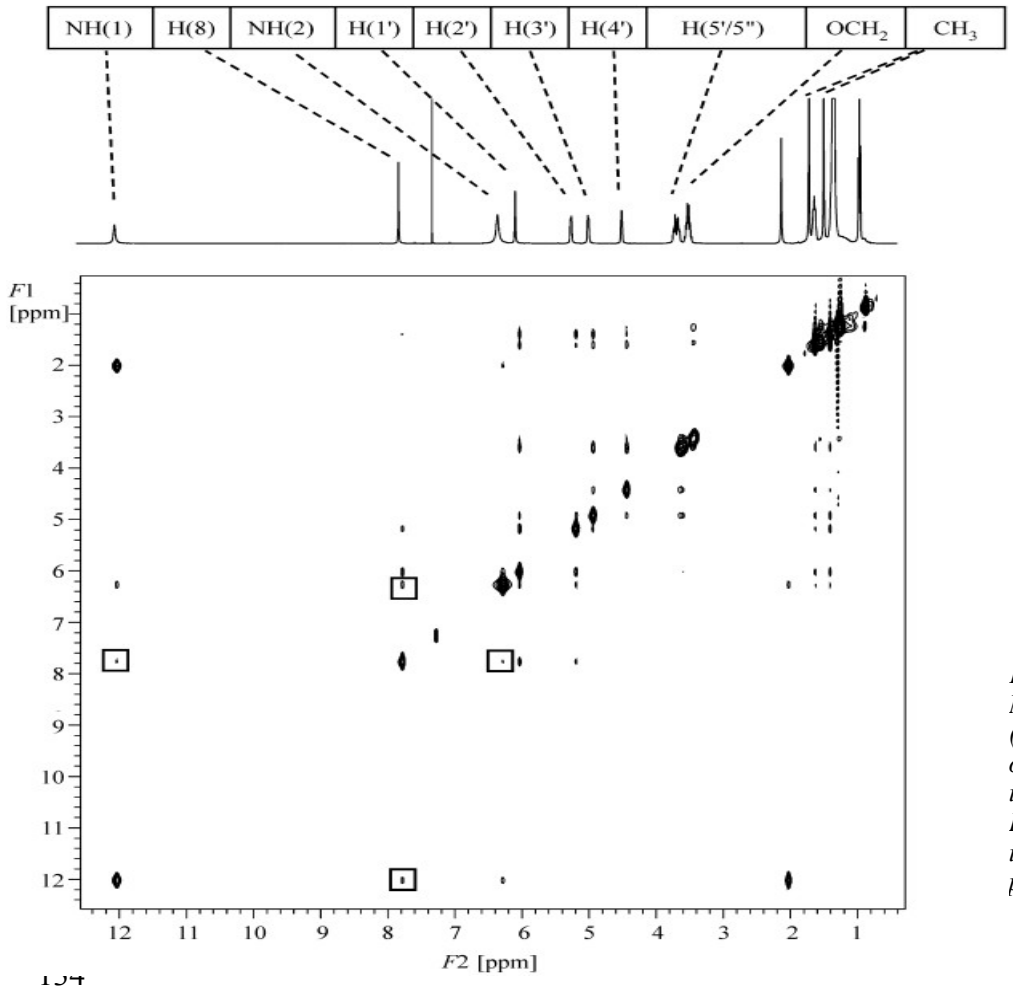


Figure 4.9 *NOESY spectrum (mixing time 100 ms) of 7×10-2 M* ***G16*** *in $CDCl_3$ at RT. Relevant intermolecular cross-peaks are boxed.*

The CD spectrum of **G16** in chloroform shows (Figure 4.10 a) weak signals in the 300-220 nm wavelength region corresponding to the low-energy transitions of the guanine chromophore. This behavior is in agreement with previous reports on ribbon-forming guanosines[29] in contrast with helix-forming guanosines, which give relatively intense CD, as reported for 8-oxoguanosine derivatives.[21a,30]

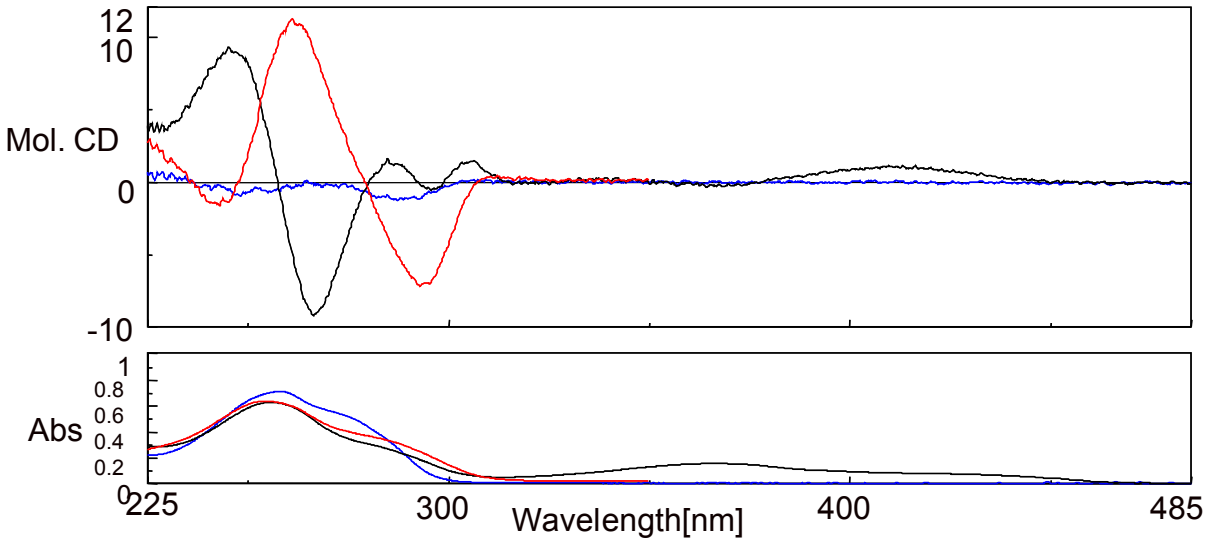


Figure 4.10 *CD-UV spectrum for the compound* ***G16*** *in $CHCl_3$: a) without ions in ribbon structures (blu line), b) presence of Kpicrate (dark line) and c) in presence of KI in solid-liquid extraction (red line).*

The liquid-crystalline phase: Compound **G16** exhibits lyotropic liquid-crystalline properties in organic solvents. Polarized optical microscopy (POM) reveals the presence of a birefringent fluid phase at *c*>2.5 % (*w*/*w*) in toluene and chloroform (Figure 4.11).

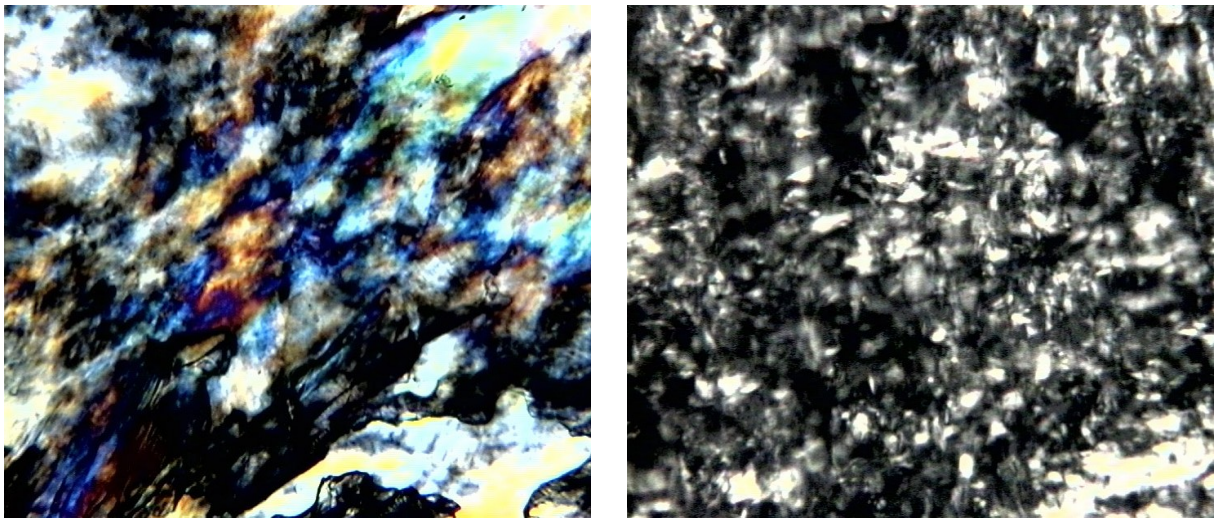


Figure 4.11 *Polarized optical microscopy images of 7% (w/w) solutions of* ***G16*** *in toluene (left) and chloroform (right). Magnification 100X.*

X-Ray diffraction experiments confirm the existence of a liquid-crystalline order. Compound **G16** was investigated in toluene and in chloroform at different concentrations and in the form of a dry film produced by drop-casting chloroform solutions. While diffraction spectra in chloroform solutions were very low in intensity (due to chloroform absorption), one or two intense peaks in the low-angle region and a large band in the high-angle region were detected in toluene solutions.

Better-resolved X-ray diffraction profiles were obtained at concentrations higher than 50 % (*w*/*w*) or by using the dry film cast from chloroform solution. In particular, the low-angle diffraction region is characterized by a series of broad peaks that can be indexed according to a 2D rectangular lattice of *p2mm* symmetry.[31] From the Bragg spacings $Q_{h,k}$, the unit cell dimensions *a* and *b* have been derived using Equation (1), in which *h* and *k* are the Miller indices of the observed Bragg reflections. The unit cell parameters show a dependence on concentration (see Table 4.2), while a rather small unit cell has been derived for the dry film.

$$Q_{h,k} = 2\pi((h/a)^2 + (k/b)^2)^{0,5} \qquad (1)$$

Table 4.2 *Low-angle X-ray diffraction results. A and b are the parameters of the 2D rectangular unit cell, c is the weight of* ***G16*** *over the total weight of the sample,* S_{core} *is the cross-sectional area of the central core of the ribbon (see text).*

***a* [Å, ±0.5]**	***b* [Å, ±0.5]**	***c* [*w*/*w*, ±5 %]**	$\boldsymbol{S_{core}}$ **[Å^2, ±10 %]**
25.9	9.8	1.0	78.0
28.7	10.0	0.9	79.4
32.0	11.5	0.75	84.9
36.7	11.7	0.6	79.9
38.0	12.0	0.5	70.1
40.2	-[a]	0.4	-
43.5	-[a]	0.3	-
44.6	-[a]	0.2	-
46.1	-[a]	0.1	-

[a] Only one peak is detected at low concentration, therefore the b parameter cannot be determined.

The high-angle diffraction region is characterized by two bands, the first rather narrow and centered at about Q=(5.46 Å)$^{-1}$, while the second is very large and centered at Q=(4.5 Å)$^{-1}$. Both peak positions are insensitive to the toluene concentration.

The X-ray diffraction profiles are thus consistent with the presence of a liquid-crystalline phase:[32] the low-angle peaks suggest a 2D rectangular packing of aggregates, whose distance depends on the amount of solvent. According to the symmetry group, two aggregates are present in the unit cell (see Figure 4.12). On the other hand, the high-angle large band indicates the disordered conformation of the hydrocarbon chains (eventually dissolved in the solvent), while the narrow band provides evidence for an intra-aggregate characteristic repeat distance of 5.5 Å.

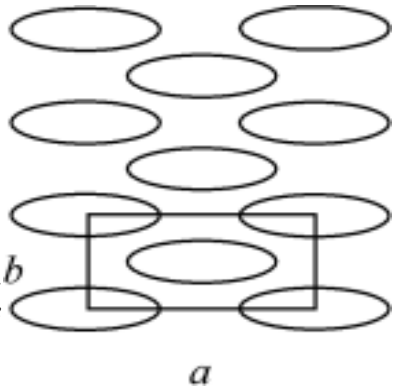


Figure 4.12 *Geometrical model for the 2D-rectangular phase. The cross section of the aggregates is represented as an elipsoid.*

From the unit cell parameters, the cross-sectional area S_{core} of the central core of the aggregates can be determined, assuming that they are infinite in length and that the unit cell can be divided into two regions, one holding the guanosine residues and the other the alkyl chains together with the organic solvent.[29] The relation between S_{core} and the 2D rectangular unit cell surface is given in Equation (2),[32] in which $c_{v,G}$ is the volume concentration of the guanosine residue inside the unit cell volume.

$$2\, S_{core} = a\ b\ c_{v,G} \qquad (2)$$

In the special case when the solvent is absent, $c_{v,G}$ corresponds to the volume fraction of the guanosine residue (V_G=470 Å^3) with respect to the molecular volume (V=770 Å^3) calculated from standard atomic dimensions. A cross-section of about 80 Å^2 has been calculated (see Table 4.2), independent of the toluene concentration. The cross-sectional area of the guanosine core of the ribbon calculated from molecular models is indeed around 70 Å^2, very similar to the experimentally derived values.

According to our previous results,[29] the observed data and the behavior detected as a

function of concentration are consistent with the occurrence of a phase in which the structure elements are ribbons, infinite in length and parallel to each other, packed in a 2D-rectangular lattice. The ribbons contain the guanine residues in the extended hydrogen-bonded configuration, while the alkyl chains, together with the organic solvent in which they are dissolved, fill the lateral gap between the ribbons. The diffuse band observed at Q=(4.5 Å)$^{-1}$ is characteristic of liquid paraffins, and indicates a disordered (liquid-like) organization within the hydrocarbon region.[29,30]As the solvent is expected to scatter in the same Q region, no detailed information on the hydrocarbon conformation can be derived. On the basis of the ribbon structures reported in Figure 3.7, the peak centered at Q = (5.5 Å)$^{-1}$ could be related to the guanosine repeat distance within the ribbon.

Self-assembly at the solid-liquid interface: Given the interesting results obtained on the self-assembly of **G16** in solution as observed with indirect methods, we extended our studies to STM to provide mapping in real space. In fact, STM imaging offers sub-molecularly resolved imaging of the local density of states (LDOS) of a molecular adsorbate at the surface.[33] The high resolution that can be achieved by STM enables discrimination between different chemical functionalities adsorbed at surfaces.[34] STM was successfully employed in an ultra-high vacuum environment to investigate guanine-based architectures in which single units are interacting through H-bonds to form quadruplexes on Au(111), which were found to be stabilized by resonance-assisted hydrogen bonding.[35] The unique versatility of STM enables the in situ exploration of the self-assembly of an organic molecule at the interface between its own solution in a poorly polar solvent and a solid conductive substrate.[36]

Figure 4.13 displays a high-resolution STM image of **G16** self-assembled at the graphite-solution interface. This STM current image reveals a 2D crystalline lamellar structure with a rectangular periodic motif. The determined cell parameters are a=2.20±0.20, b=1.43±0.15 nm, α=83±4°.

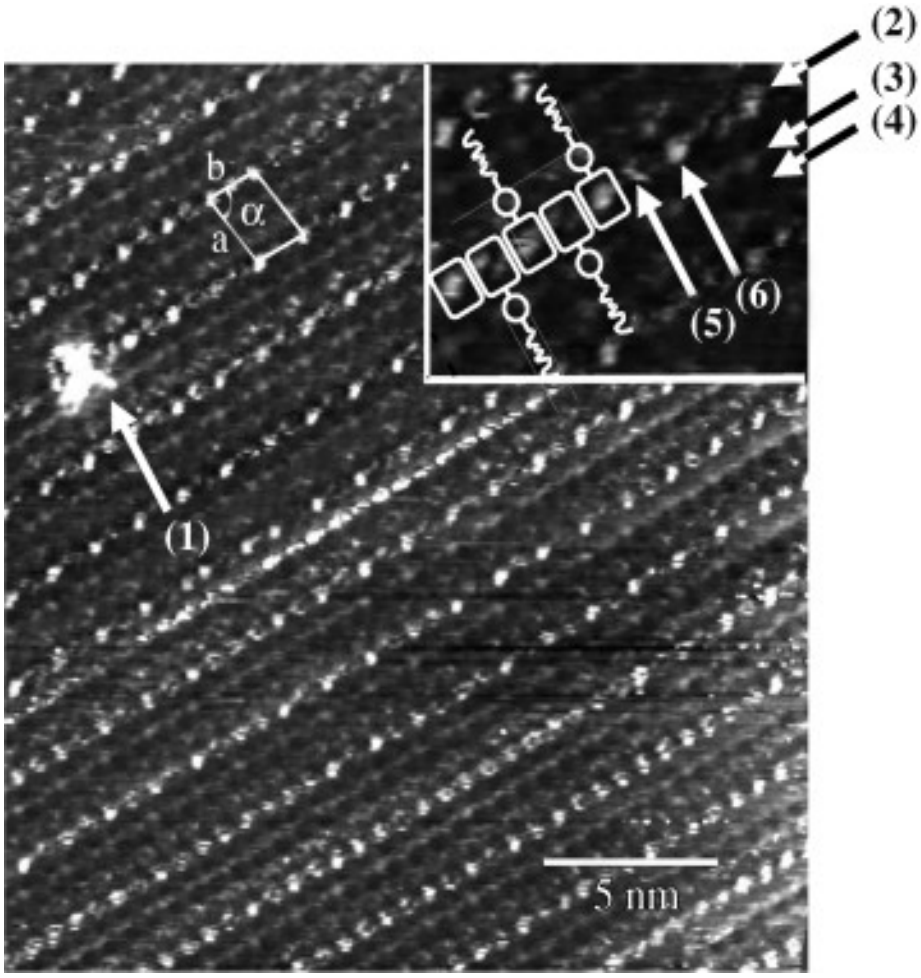


Figure 4.13 *STM current image of* ***G16*** *at the graphite-solution interface using trichlorobenzene as the solvent. Bias voltage (Ut)=400 mV and average tunneling current (It)=30 pA. Arrow 1 marks a defect probably due to a disordered cluster adsorbed on the self-assembled monolayer. Inset (top, right) shows the zoom-in highlighting the three different types of contrast in a row: guanine core (arrow 2), ribose (arrow 3) and aliphatic tails (arrow 4). Two adjacent guanines, linked by H-bonds, appear with different contrasts as marked by arrows 5 and 6. A cartoon of the H-bonded network is shown in the inset: the rectangles represent the guanine bases, the circles stand for the sugars, and the aliphatic tails are sketched with lines.*

Assuming resonant tunneling between the frontier orbitals of the moieties at surfaces and the Fermi level of the substrate as the dominant mechanism for contrast formation in STM measurements, the probability for electrons to tunnel from occupied states of the substrate to the unoccupied states of the adsorbates depends on the energy gap between them. In view of this we have performed quantum-chemical calculations to estimate the energy of the frontier orbitals of the moieties composing our molecular system, that is, the highest occupied (HOMO) and the lowest unoccupied molecular orbitals (LUMO), and we have compared them with the Fermi level of the graphite substrate. The results are summarized in Figure 4.14. Because the experimental results were obtained in the condensed phase, for the interpretation of the STM contrasts they have to be considered only for the trend in the energy

differences of the levels.

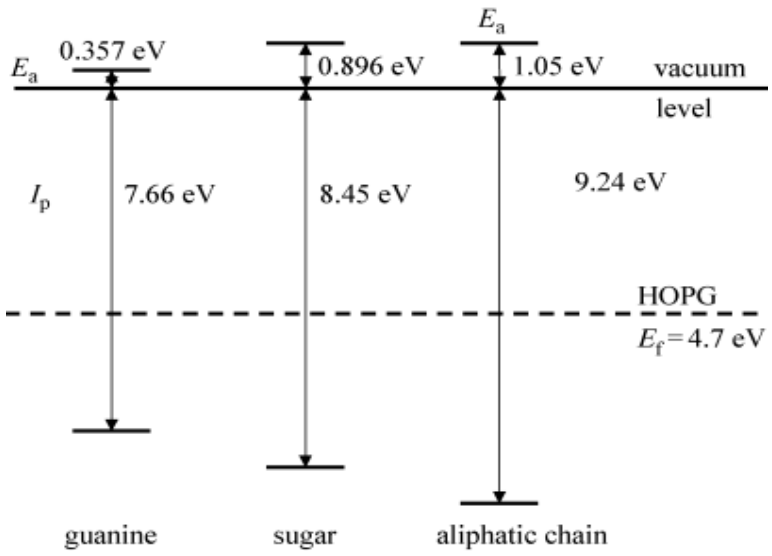


Figure 4.14 *Scheme of the adiabatic electron affinities (Ea) and ionization potentials (Ip) for guanine, sugar, and aliphatic chain ($C_{10}H_{22}$) in vacuo, as calculated from energy differences between the optimized structures of neutral and charged systems at the B3LYP/6-311+G*//B3LYP/6-31G* level of theory.*

In our current STM image, the brightest spots, which are marked with arrow 2 in the inset in Figure 4.13, can be attributed to the guanine cores, since the energy difference between their HOMO and the Fermi level of the graphite substrate is rather small.[37] Spots with a lower brightness, indicated with arrow 3, can be ascribed to the ribose, while the darker part of the image (arrow 4) can be attributed to the aliphatic side chains, which have not been resolved, probably owing to their high conformational mobility on a time scale faster than the STM imaging. Therefore the detailed analysis assisted by quantum-chemical calculations made it possible to discriminate different moieties composing **G 16**.

A careful inspection reveals that the contrast of two adjacent guanines linked by H-bonding is different (see, for example, those marked by arrows 5 and 6 in Figure 4.13; this can be explained in view of a different packing in the *X*,*Y* with respect to the HOPG lattice underneath. The value of the cell parameter *a*, which roughly amounts to half of the estimated ribbon width, suggests that the alkyl tails in two adjacent H-bonded ribbons are interdigitated. Given the STM resolution obtained, and in view of the pretty similar size of the unit cell that can be expected for the two nanoribbons depicted in Figures 3.7 A and B, taking into account the estimated unit cell and relative error bar, we are unable to unambiguously ascribe the supramolecular motif shown in Figure 4.13 to either one or the other nanoribbon-type.

On a larger scale, a monolayer of **G16** is polycrystalline (Figure 4.15). Up to seven

domains with a diameter of a few tens of nanometers are observed. The orientation of most of the lamellae is symmetry-equivalent with respect to the crystalline substrate lattice. The high-resolution imaging achieved in the polycrystalline structure made it possible to record two different kinds of defects on the nanometer length scale. The first kind of defect consists of empty domains in which the molecules are not adsorbed at surfaces; an example of missing molecules is indicated by a grey arrow. Such defects get recovered on the time scale of a few minutes. The second kind of defect is found at the domain boundaries, which have a fuzzy character and surround some crystals (marked with white arrows). At these frontiers the molecules are more loosely packed.

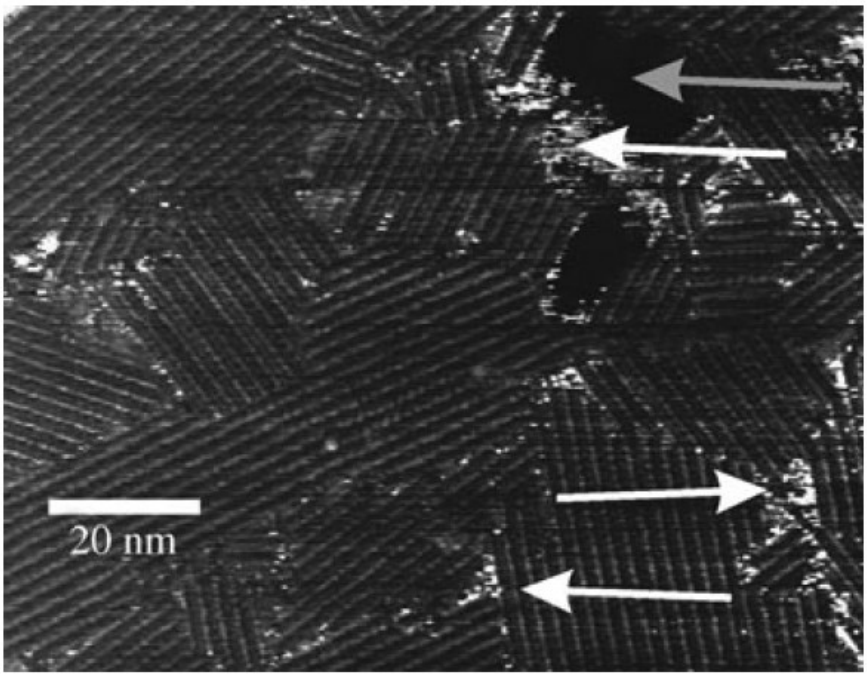


Figure 4.15 *Current STM survey image of self-assembled architecture of* ***G16*** *recorded at the solid-liquid interface on HOPG.* U_t*=290 mV and average* I_t*=200 pA.*

In summary, in our attempt to find general strategies to form functional nanoribbons from guanosine derivatives, we have prepared *O*-alkylated guanosine, which is an extension of the well-known 5'-*O*-acylated guanosines. Our specific goal was to find out if the carbonyl group, existing in the 5'-*O*-acylated derivative, which is known to interact through an intra-ribbon H-bond with NH(2), was essential for the formation of nanoribbons. We have thus synthesized and studied the self-assembly of **G16** under different environmental conditions. NMR, X-ray, and STM measurements revealed that **G16** self-assembles into highly ordered nanoribbons in which the single nucleosides are held together by H-bonds. This self-assembly behavior appears to be universal, as it is in line with many other guanosine derivatives, and in particular with that of 5'-*O*-acylated guanosines, revealing that the presence of the carbonyl

unit in the 5'-*O*-acylated derivative is not a prerequisite for the formation of the nanoribbon. The self-assembled motif observed for **G16** conveys parallel ribbons, most probably with parallel dipoles. This result is very important in view of the well-known physico-chemical properties of these quasi-1D nanostructures, and in particular for their use in (opto)electronics.

Experimental section: 2',3'-O-Isopropylidene-5'-O-decylguanosine.

2',3'-O-Isopropylideneguanosine (Sigma) (0.4 g, 1.2 mmol) was dried in vacuo over P_2O_5 for 2 h at 50 °C and suspended in anhydrous THF (10 mL). NaH (0.058 g, 2.4 mmol) and 1-bromodecane (1.24 mL, 6 mmol) were added. The mixture was heated at reflux overnight, then cooled to room temperature. The solvent was removed and the residual solid was taken up in dichloromethane, washed with water, dried over $MgSO_4$, concentrated in vacuo, and applied to a silica gel column using 94:6 dichloromethane/methanol as the eluent. The product was recrystallized from ethanol to afford a white solid (0.26 g, 48 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ =0.86 (t, 3 H; CH_3), 1.25 (m, 14 H; CH_2), 1.39 (s, 3 H; CH_3), 1.53 (m, 2 H; OC-H_2CH_2), 1.61 (s, 3 H; CH_3), 3.43 (m, 2 H; O-CH_2), 3.55-3.64 (m, 2 H; H5'-H5"), 4.42 (m, 1 H; H4'), 4.92 (m, 1 H; H3'), 5.17 (m, 1 H; H_2'), 6.00 (d, 1 H; H1'), 6.28 (s, 2 H; NH_2), 7.76 (s, 1 H; H8), 12.02 ppm (s, 1 H; NH); ^{13}C NMR (300 MHz, [D_6]DMSO): δ =13.93 (CH_3), 22.07 (CH_2), 25.21 (CH_3), 25.53 (CH_2), 26.98 (CH_3), 28.68 (CH_2), 28.30 (CH_2), 28.93 (CH_2), 28.97 (CH_2), 28.99 (CH_2), 31.28 (CH2), 70.23 (CH_2), 70.61 (CH_2), 81.44 (CH), 83.68 (CH), 84.99 (CH), 88.56 (CH), 113.01 (C), 116.76 (C), 135.69 (CH), 150.67 (C), 153.64 (C), 156.68 ppm (C); elemental analysis calcd (%) for $C_{23}H_{37}N_5O_5$: C 59.59, H 8.04, N 15.11; found: C 59.16, H 7.71, N 15.48.

CD spectra were recorded with a JASCO J-710 spectropolarimeter using cells of the appropriate path length. NMR spectra were recorded with Varian Mercury instruments at 300 or 400 MHz.

X-ray diffraction experiments were performed using a Philips PW1830 X-ray generator equipped with a Guinier-type focusing camera operating in a vacuum: a bent quartz crystal monochromator was used to select the $Cu_{K\alpha 1}$ radiation (λ=1.54 Å). The investigated Q range ($Q=(4\pi\sin\theta)/\lambda$, where 2θ is the full scattering angle) was between 0.068 and 2.3 $Å^{-1}$. Diffraction patterns were recorded on a stack of two Kodak DEF-392 films: film densities were measured using a digital scanner.

STM experiments were carried out at ambient pressure and room temperature at the solid-liquid interface. Almost saturated solutions in 1,2,4-trichlorobenzene (Aldrich) were applied

to the basal plane of the highly oriented pyrolytic graphite (HOPG) substrate (Advanced Ceramics, ZYH grade). Mechanically cut Pt/Ir (80 %/20 %) tips were employed. The STM images of the molecules were recorded in current mode with scan rates of about 20-50 line s^{-1}. The measurements were carried out using a picoAmp-Nanoscope IIIa Multimode set-up (Digital Instruments, Santa Barbara, CA) using a positive tip bias. The high-resolution image was corrected for thermal drift with respect to the HOPG lattice.

Adiabatic electronic affinities and ionization potentials for the molecules were evaluated as differences between the total energies of the optimized neutral and the corresponding optimized ions. The total energies and equilibrium geometries for the neutral and ionic species were obtained from full density functional optimizations at the 6-31g* level (B3LYP/6-31g*) using the Gaussian 03 program. Single-point energies at B3LYP/6-311g*//B3LYP/6-31g* were carried out to determine more accurate energy values.[38]

4.4 Cation-Templated self-assembly of a lipophilic alkoxy guanosine: solution structure of a $Ag^{+}G_8$ octamer or $Ag^{+}G_{16}$ hexadecamer?

The lipophilic nucleoside 5'-deciloxy-2',3'-isopropylideneguanosine **G16**, extracts potassium and silver salts from water into organic solvent (Figure 4.16). It is known that the K^+ extraction drives the self-association of guanosine derivatives to give a G-quartets staked structures: octamer, hexadecamer or polimeric columar species.[39] Previous studies revealed that the 5'-decanoyl-2',3'-isopropylideneguanosine derivative forms an octameric supramolecular complex, $(G)_8$-K^+, formed by coordination of a single K^+ ion by eight monomers in a symmetric tail-to-tail (or head-to-head) staking of two planar G-quartets. The unique difference between, **G16** and 5'-decanoyl-2',3'-isopropylideneguanosine, is in the moiety in 5' position: an ester group in the 5'-*O*-acylated derivative and an ether group in the *O*-alkylated guanosine **G16**. This structural modification determines a huge difference in the hierarchical self-assembling in different ambient condition. Using divalent instead of monovalent cations brings to different self-assembling processes.[40] Moreover the idea to use the transition metal instead of the alkali metal ions, is based on the different oxidation states, coordination geometry as well as photochemical and magnetic properties. The design and preparation of coordination polymers (which may be viewed as metallo-organic framework MOFs) may be an important area of research in material science, medicine, and chemical technology.[41] One may design coordination polymers by matching the coordination demandes of the linkings metal with those of the bridging organic ligand.

Supramolecular polymer chemistry is a branch of material science which is developing through the combination of polymer chemistry with supramolecular chemistry. The supramolecular polymer is generated by self-assembly of complementary monomeric compounds. [42]

Constituents of the chain are linked through reversible connections enabling the polymer to grow, shorten, rearrange and adapt. This class of compounds is defined as 'dynamic combinatorial materials' [43] and is currently drawing a great deal of attention. The first aim of supramolecular polymer chemistry is to allow predictable control over the polymer structure or, more precisely, over the packing arrangement of the polymeric entities in the solid state and also the structure of the infinite array itself.

The principles and strategy for the engineering of these polymers are based on two general concepts: supramolecular interactions and supramolecular synthons introduced by Desiraju in 1995.[44] Fundamental to such an approach is the need for interactions between molecular building blocks that are sufficiently reliable to permit some degree of predictability and control over the formation of supramolecular assemblies and networks. The term supramolecular synthon, is often applied to structural units comprising weaker, and thus inherently flexible, non-covalent linkages.

Coordination polymers based on Ag(I) cations are attracting a great deal of attention primarily because they are readily available.[45] Indeed, due to the high lability of the bond Ag-"donor atom" the process of the formation of the coordination polymer is totally reversible. The resulting Ag(I) coordination polymers can generally be crystallised allowing investigation by single-crystal X-ray diffraction. The coordination sphere of Ag(I) is similarly very flexible and can adopt coordination numbers between two and six and various geometries (linear, trigonal, tetrahedral, trigonal-pyramidal and octahedral). The structural flexibility of these complexes is essential for the investigation of non-covalent interactions, as even weak intermolecular forces significantly affect the geometry and topology of the Ag(I) coordination polymers in the solid state.

In this work we describe a CD and NMR study supporting by a molecular modelling of a possible "octamer" $(\mathbf{G16})_8$-K^+ or "hexadecamer" $(\mathbf{G16})_{16}$–xAg^+ in $CDCl_3$.

Result and discussion: The CD spectrum of **G16** in chloroform at RT ($1x10^{-2}$ M) in absence of ions shows a monosignate and weak signals in the 300-200 nm wavelength region corresponding to the intense π- π transitions of the guanine chromophore at ca. 260 nm (Figure 4.16a, trace green). This behavior is in agreement with previous reports on ribbon-

forming guanosines (Figure 4.10 a).

The addition of a excess of solid potassium picrate to a chloroform solution of the guanosine derivative **G16** transforms the supramolecular ribbon **G16$_n$** into the supramolecular complex with a bisignate CD signal. The stabilization of stacked G-quartet-based structures induced by the K^+ ion introduces a negative exciton signal (Figure 4.16b, trace blue). The adjacent quartets are, in fact, rotated by a well-defined angle:[5] this causes the interaction between the transition moments located in the different G-quartets originating the bisignate couplet.[21] The presence of achiral picrate chromophore enganged to the supramolecular structure is confirmed by the induced positive signal at ca. 420 nm. This suggests a cooperative behaviour for the stabilization of the staked G-quartets.[46]

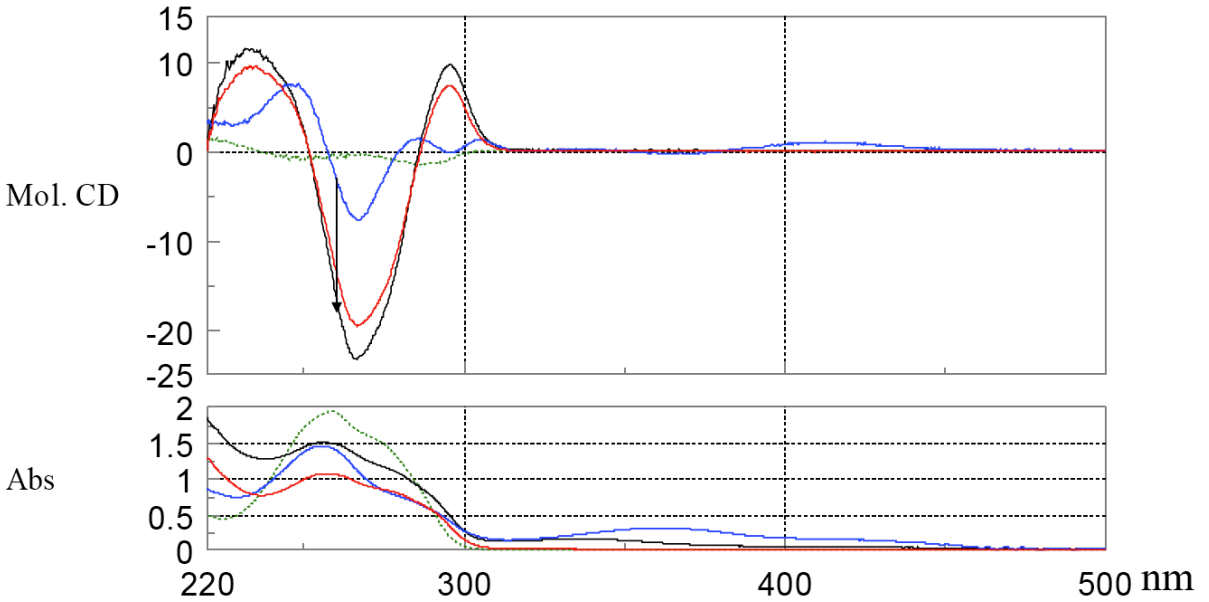


Figure 4.16 *CD spectrum of* ***G16*** *in $CDCl_3$ 1x10^{-2}M at RT a) green monosignate and weak signal in absence of ions in the 300-200 nm wavelength region; b) blue CD spectrum after solid-liquid extraction of potassium picrate shows a bisignate signal centred at 260 nm with a induced positive weak signal by picrate chromophores; c) red CD signal after a solid-liquid extraction of $AgNO_3$ salt with a increased negative band at 265 nm; d) black CD spectrum after addition of $AgNO_3$ to the solution c) with the disappearance of the induced signal corresponding to the picrate chromophore at ca. 420 nm.*

G16 with $AgNO_3$ salt after solid-liquid extraction presents a CD spectrum (Figure 4.16c, trace red) quite different to that with Kpicrate. In this case an increasing of the negative signal centred at ca. 265 nm is evident. If we add solid $AgNO_3$ salt in excess to the solution b (blue trace), a new spectrum appears (Figure 4.16d, trace black) with a trace similar to that Figure 4.16c (red line). Also, the picrate's induced signal disappeares. This behaviour could be explained as a rearrangement into new supramolecular structure pushed by the stronger affinity/selectivity for the $AgNO_3$ ions pair.

The same behaviour is confirmed by ^{1}H NMR experiments at RT in Figure 4.17. The ^{1}H NMR spectrum (Figure 4.17 A) of **G16** in $CDCl_3$ is characteristic of the ribbon-like structure as shown in Figure 4.9. The addition of solid Kpicrate salt in excess to a $CDCl_3$ solution of **G16** causes diagnostic changes in the ^{1}H NMR spectrum (Figure 4.17 B). The region of the ^{1}H NMR spectrum between 6.5 and 12.5 ppm, which include resonances for H8 aromatic proton and the imino NH(1) proton, is used to characterize the assembled species in solution similar to the octameric structure for the **dG7** derivative.

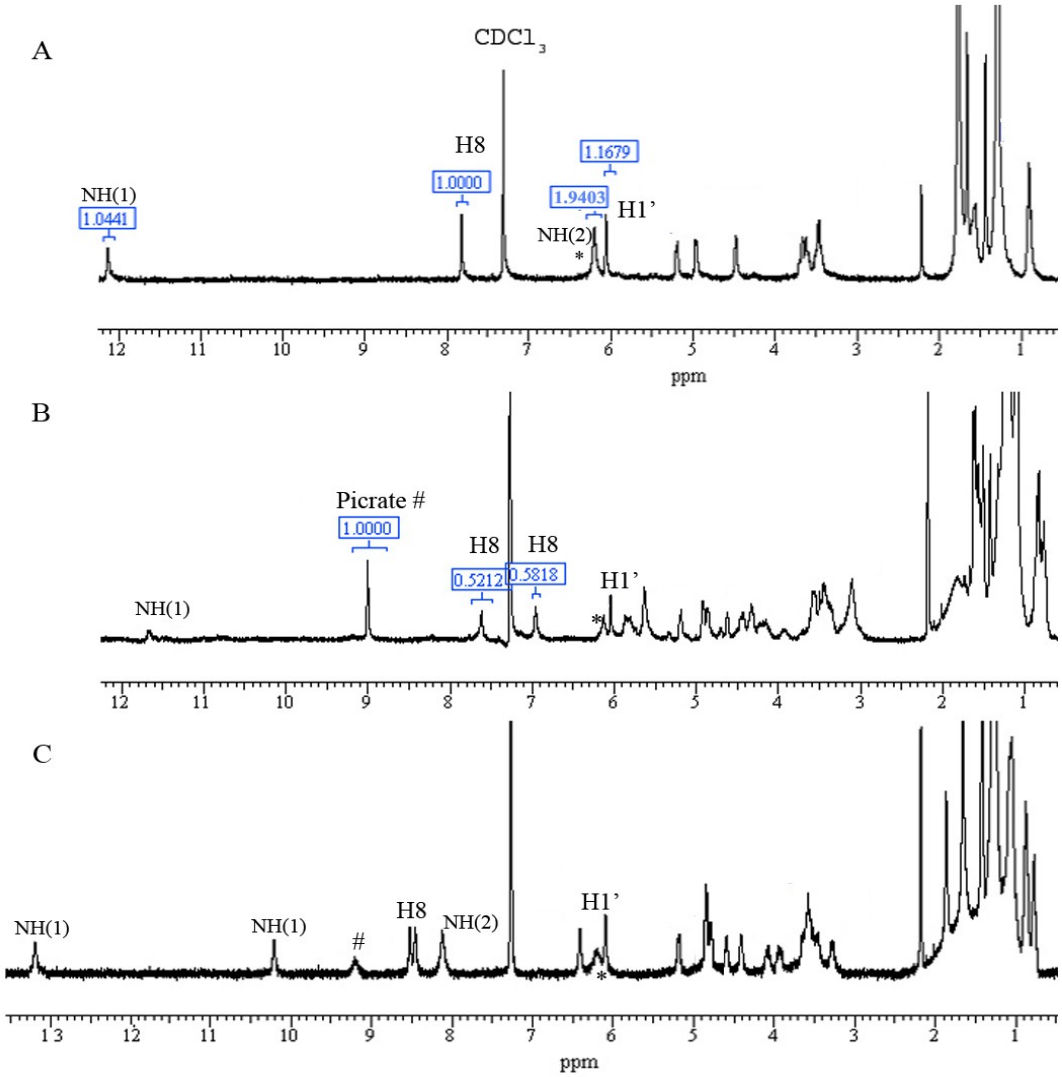


Figure 4.17 *^{1}H NMR of **G16** in $CDCl_3$ at RT ($1x10^{-2}$M) a) in absence in ions; b) in presence of Kpicrate after solid-liquid extraction and c) after addition of solid salt $AgNO_3$ into solution b).*

The picrate's signal at ca. δ=9 ppm enables the **G16** to K^+ stoichiometry to be determined by peak integration. The spectrum in Figure 4.17 b reflects the formation of an assembled species with two sets of signals with a ratio K:**G16** =1:2. The splitting of the H8 signal in two

peak centred to 7.27 ppm recall the formation of the octameric structure presented in Figure 4.6 for the **dG7**. Upon addition of $AgNO_3$ to solution B, a new specie appears with two new sets of signals and the picrate's signal decreases. This behaviour is in agreement with CD experiments (Figure 4.16) and confirms the desplacement of Kpicrate operated by $AgNO_3$.

Using different Ag salts, such as AgI, $AgBF_4$, Ag cycloesilbutirrate, Ag paratoluensulfonate and KNO_3 we have never seen similar strong competition and transformation of a single new supramolecular structure in solution. Instead, Davis a co-worker reported that **G5** self-assembles with a 1:1 mixture of Ba^{2+} and Sr^{2+} salts to give a statistical (1:1:2) mixture of hexadecameric G-quadruplexes $(G5)_{16}{\cdot}2Ba^{2+}{\cdot}4A^-$ and $(G5)_{16}{\cdot}2Sr^{2+}{\cdot}4A^-$, and a mixed hexadecamer $(G5)_8{\cdot}Ba^{2+}{\cdot}(G5)_8{\cdot}Sr^{2+}{\cdot}4A^-$.[40]

For a deep analysis and to confirm the double sets of signals generated using $AgNO_3$ additional ^1H NMR (600 MHz) experiments have been performed (Figure 4.18). The double set of signal can be attributed either an octamer or a hexadecamer in asymmetric conformation. Assignment of the correct one is not so easy.

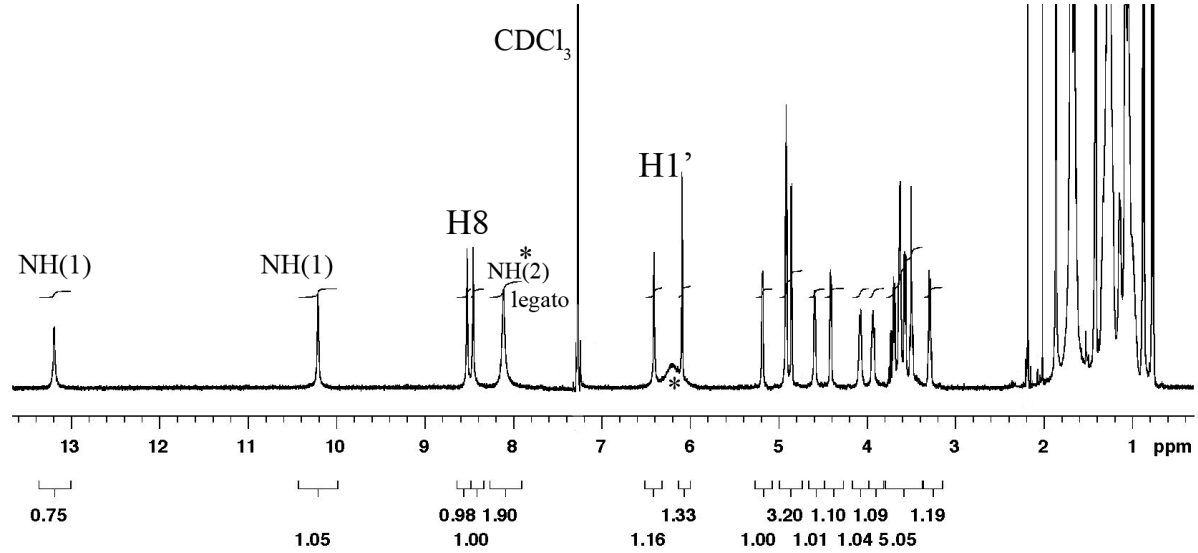


Figure 4.18 *^1H NMR (600 MHz) of **G16** in $CDCl_3$ ($1x10^{-2}M$) with $AgNO_3$ after solid-liquid extraction.*

Our previous experiments suggested a shift from octameric structure (in presence of potassium ions) toward an hexadecameric structure after addition of $AgNO_3$. This is justified from a staking of two octameric structures, each of them formed by coordination of a single Ag^+ ion by eight **G16** monomers. The nature of the anion in Ag^+ does not permit us the prediction of the stoichiometry of the supramolecular arrangement and to understand if the hexadecamer is staked by π-π interaction between two octamers or by interposition of another silver cation. Only the huge splitting of NH(1) proton signals with a significant downfield

chemical shift for one of the two aromatic amino protons ($\Delta\delta$ > 3ppm), give us the opportunity to suppose a hexadecameric structure with different solvent-exposed NH(1) protons. This supposition is related to the Rivera's work that deeply justify the hexadecameric structure with the same information.[47]

The ^{1}H NMR spectrum of **G16** with $AgNO_3$ solid in excess after a solid-liquid extraction in $CDCl_3$ has two sets of signals in a 1:1 ratio (Figure 4.18 and 4.19).

The region between 3 and 7 ppm, that includes resonances for alifatic protons of the ribose ring, was assigned by a 2D COSY and NOE experiment. The ^{1}H NMR chemical shifts for the exchangeable and nonexchangeable protons of **G16** with $AgNO_3$ in $CDCl_3$ at RT are listed in table 4.3. As described below, one set of NMR signals corresponds to a **G16** nucleoside with an *anti* conformation about the C(1')-N(9) glycosidic bond, whereas the other set of signals is due to 50% of the **G16** adopting a *syn* conformation (Figure 4.21).

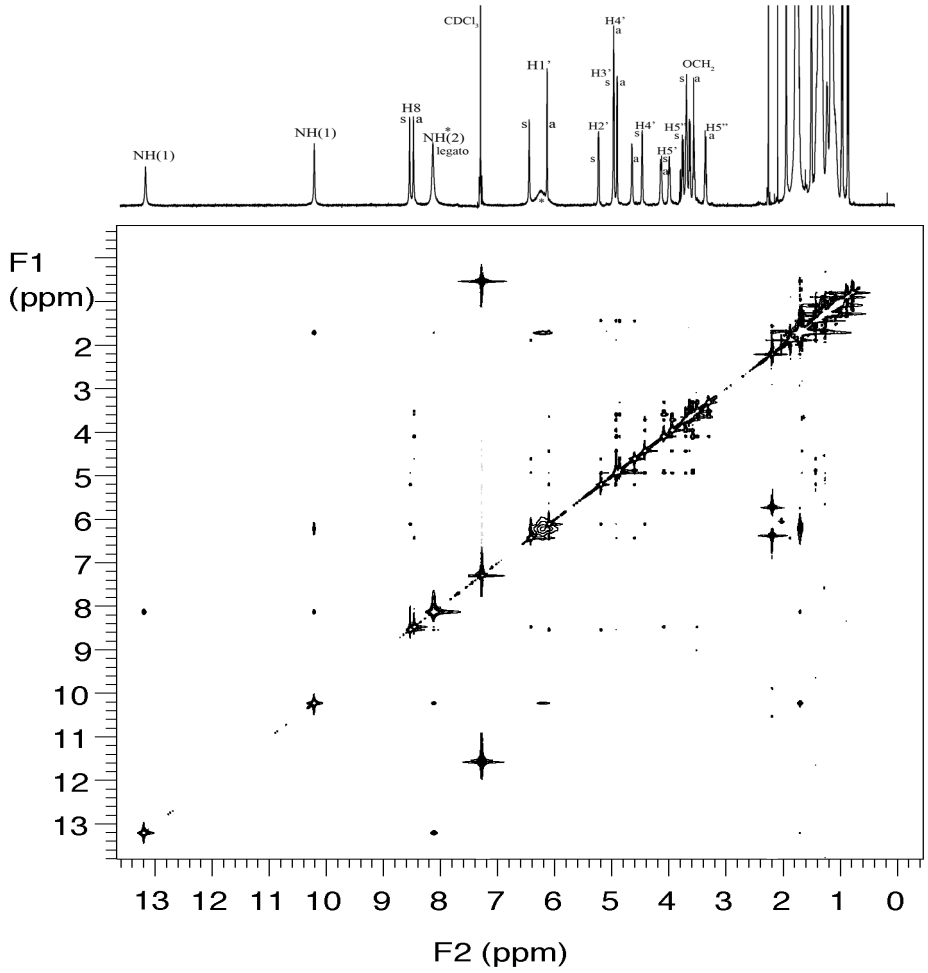


Figure 4.19 *2D NOESY spectrum 600 MHz) of G16 in $CDCl_3$ ($1x10^{-2}$M) with $AgNO_3$ after solid-liquid extraction.*

Table 4.3 *1H NMR (600 MHz) chemical shifts for* ***G16*** *with AGNO3 in CDCl3 at RT*

^{1}H	NH(1)	NH(1)	NH(2_A)	NH(2_B)	H8	H1'	H2'	H3'	H4'	H5'	H5''
Syn	13,10	10,10	8,10	5,20	8,55	6,10	5,20	4,90	4,40	3,90	3,70
Anti					8,45	6,40	4,60	4,80	4,90	4,10	4,80

Assignment of anti and syn G16: The 2D NOESY spectrum (Figure 4.19 and 4.20) has two sets of signals in a 1:1 ratio that do not interconvert on the NMR time scale. The separate signals are due to two distinct conformations about the C(1')-N(9) glycosidic bond.

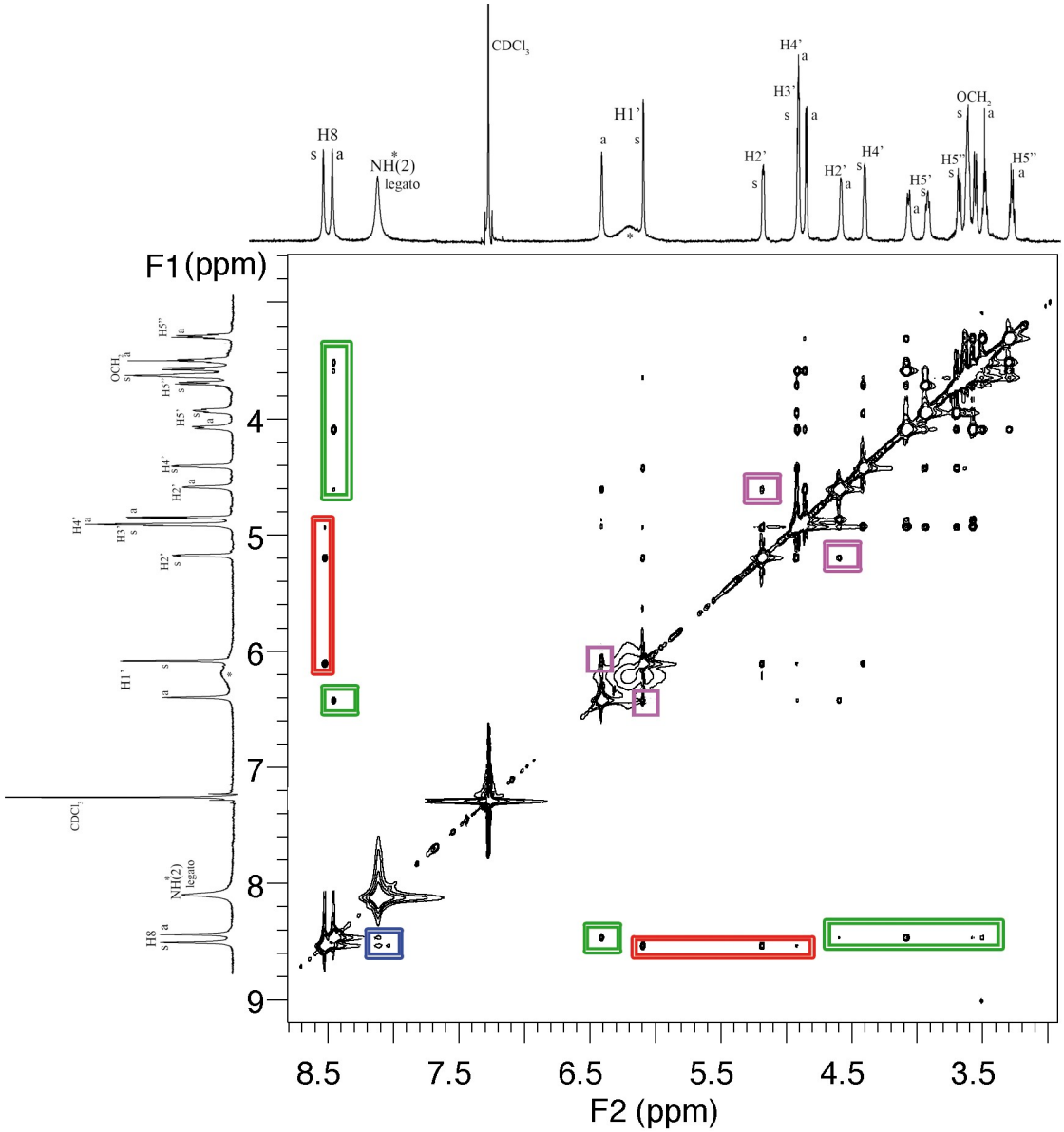


Figure 4.20 *2D NOESY spectrum zoom of the figure 4.19. Traces red highlight the NOEs cross peak for the syn conformer; traces green highlight the NOEs cross peak for the anti conformer; traces blue highlight the NOEs cross peak for the H-bonds intraquartets interaction and traces purple highlight the NOEs cross peak for the interquartets interactions. Relevant intermolecular cross-peaks are boxed.*

One species is an *anti* conformer, while the other species adopts a *syn* conformation as shown in Figure 4.21.

The presence of rigid anti and syn conformers of **G16** is remarkable. Rotation about the C(1')-N(9) glycosidic bond of nucleosides is typically fast on the NMR time scale, and the observed ^{1}H NMR signals are time averages of rapidly equilibrating anti and syn rotamers.[48] Moreover, the syn conformer is usually only predominant in purines with C(8) substituents that are large or capable of intramolecular hydrogen bonding.[48] Ag^{+} is supposed templates and stabilizes both the structure of the octamer or the hexadecamer in $CDCl_3$.

The ^{1}H-^{1}H NOE cross-peak intensities can defined glycosidic bond configuration. The H8, H1', H2', H3' and H5' regions of the NOESY spectrum, shown in Figure 4.20, clearly distinguish the two H8 resonances. The *syn* conformer (H8= δ 8,55 ppm) has strong H8-H1' and H8-H2' NOEs and a medium strength H8-H3' NOE, while the *anti* conformer (H8= δ 8,40 ppm) has strong H8-H1', H8-H5', H8-H5" and H8-OCH_2 NOE cross-peaks and a weak H8-H2' NOE cross-peak. These interactions are highlighted in Figure 4.20 for the two conformers. In Figure 4.21 is shown the two conformers in equilibrium.

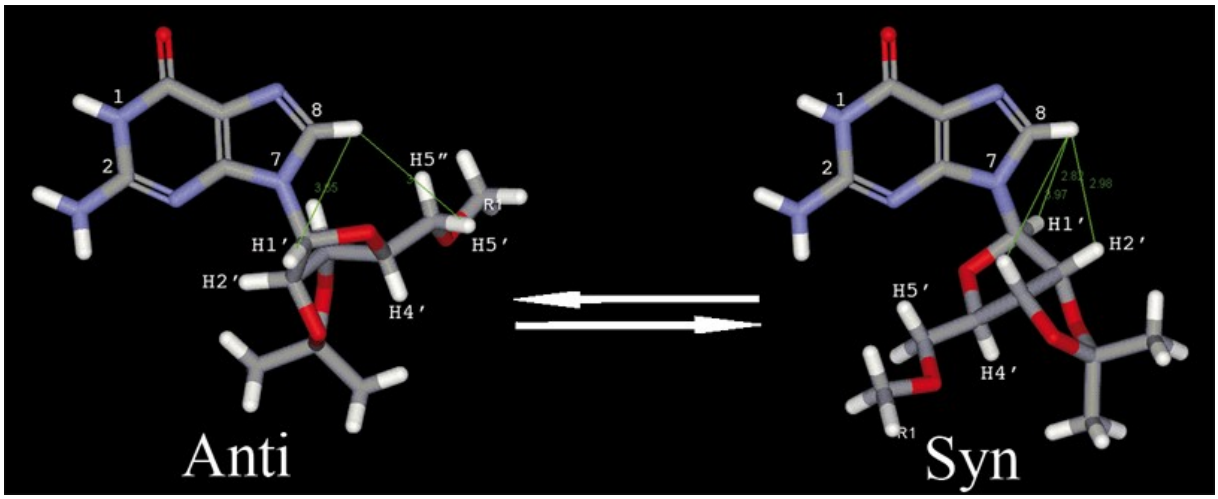


Figure 4.21 G16 *in anti and syn equilibrium conformation.*

The ^{1}H-^{1}H NOE cross-peak intensities can also define the intraquartets interactions (inside the G-quartets) and interquartet interactions (between two staked G-quartet). The former information evidences the Hoosteen H-bonds network for the formation of a planar G-quartets; the latter permits to have evidence of the superimposition of two planar G-quartet that have interactions close each other 3-3,4 Å, well within ^{1}H-^{1}H NOE range.

Both H8, *syn* and *anti,* have NOEs cross-peaks with exocyclic amino protons (NH(2) = δ 8,15 ppm) that evidence the formation of the Hoosteen H-bonding network for a planar G-

quartet arrangement (see trace blue in Figure 4.20), while no one interaction appears for the amino proton NH(2) = δ 5,20 ppm. The large difference for the amino proton's shifts (Δδ = 2,90 ppm) indicates that one of the amino protons in each pair is in hydrogen bond, while the other is solvent-exposed (Figure 4.22).[49] The downfield-shifted resonances at δ 8,15 ppm were assigned as the hydrogen-bonded amino protons ($NH2_A$), and the upfield-shifted resonances at δ 5,20 ppm were assigned as the non-hydrogenbonded amino protons ($NH2_B$).

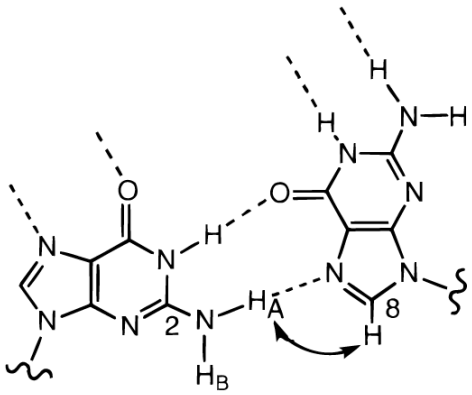


Figure 4.22 *The intraquartet $NH2_A$-H8 NOE in a G-quartet base-pair. (Adapted from reference 51)*

Moreover, the *syn* conformer (H1'= δ 6,10 ppm) has a strong NOE cross-peak with the *anty* conformer (H1'= δ 6,40ppm), while a weak NOE cross-peak appears between H2' *syn* and H2' *anty*. These NOE cross peaks could be attributed to the interquartets for the formation of a octameric structure. But before, we have to consider that with a 1:1 ratio of *anti* **G16** and *syn* **G16**, there are many possible arrangements of the two isopropylideneguanosine rotamers within the octamer. Alternative arrangements include: two stacked tetramers with alternating *syn* and *anti* **G16** residues (the alternating structure in Figure 4.23a); two stacked tetramers both containing a *syn-syn anti- anti* **G16** arrangement (the adjacent structure in Figure 4.23b) and an all-*anti* **G16** tetramer stacked on an all-*syn* **G16** tetramer (Figure 4.23c). In addition, the two tetramers can be arranged in four different relative orientations, either head-to-tail, tail-to-head, tail-to-tail or head-to-head (Figure 4.24).[50] The last two structural possibilities were dismissed on the basis of symmetry that only have one set of ^{1}H NMR signals.

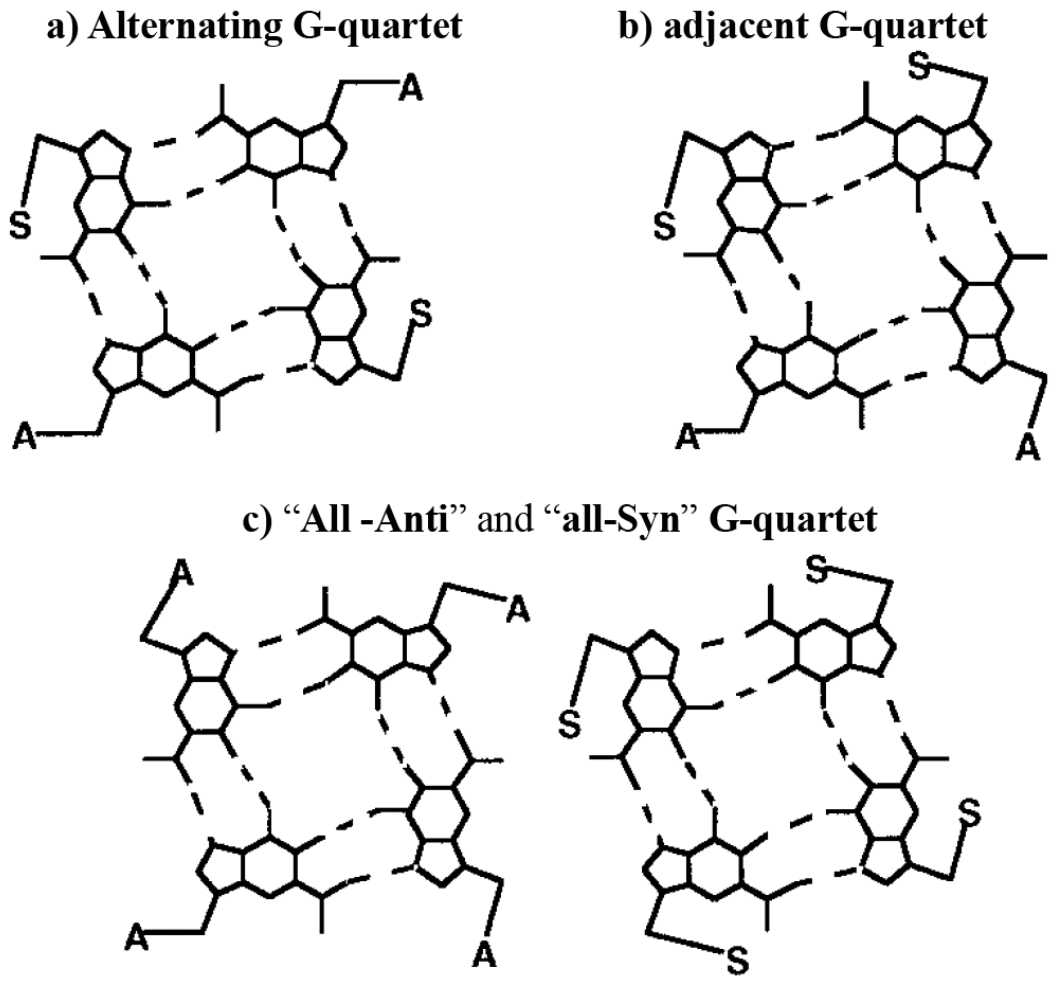


Figure 4.23 *(A) alternating G-quartet structure, syn-anti-syn-anti; (B) adjacent G-quartet structure, syn-syn-anti-anti; and (C) combination of all-syn and all-anti G-quartet structures. (Adapted from reference 51)*

The NOE cross peaks can evidence interactions between protons not more far than 4-5 Å. This limit of NOE permits us to exclude a NOE cross-peak between H1' and H2' protons of the same quartet in any of the proposed "alternating or adjacent" G-quartet given that each ribose ring is into the vertices of the planar quartet with dimensions of 10-11 Å for side. So that, the $H1'_{syn}$-$H1'_{anty}$ and the $H2'_{syn}$-$H2'_{anty}$ interactions can't be of the same G-quartet but only for two distinct quartets with the formation of a octamer or hexadecamer. The experiments made at RT does not discriminate the diagnostic NOE cross-peak between H8 and $NH(2_A)$, as reported by Gottarelli and Spada.[51] In their paper they were able to discriminate a well definite octamer with a all-*anti* and all-*syn* G-quartets. So that we can only propose for the **G16**-quartet a molecular modelling with the same model proposed by Gottarelli and Spada for the **dG7**-octamer: an all-*syn* quartet stacked above the all-*anti* quartet.[51] In principle, the all-anti **G16-**quartet and all-*syn* **G16-**quartets in $(\mathbf{G16})_8$-Ag^+ can be arranged in four possible relative

orientations, either head-to-tail, tail-to-tail, tail-to-head, or head-to-head.[50] Each of these arrangements should give rise to two sets of NMR signals for each resonance. Two of them and cartoon representation is shown in Figure 4.24.

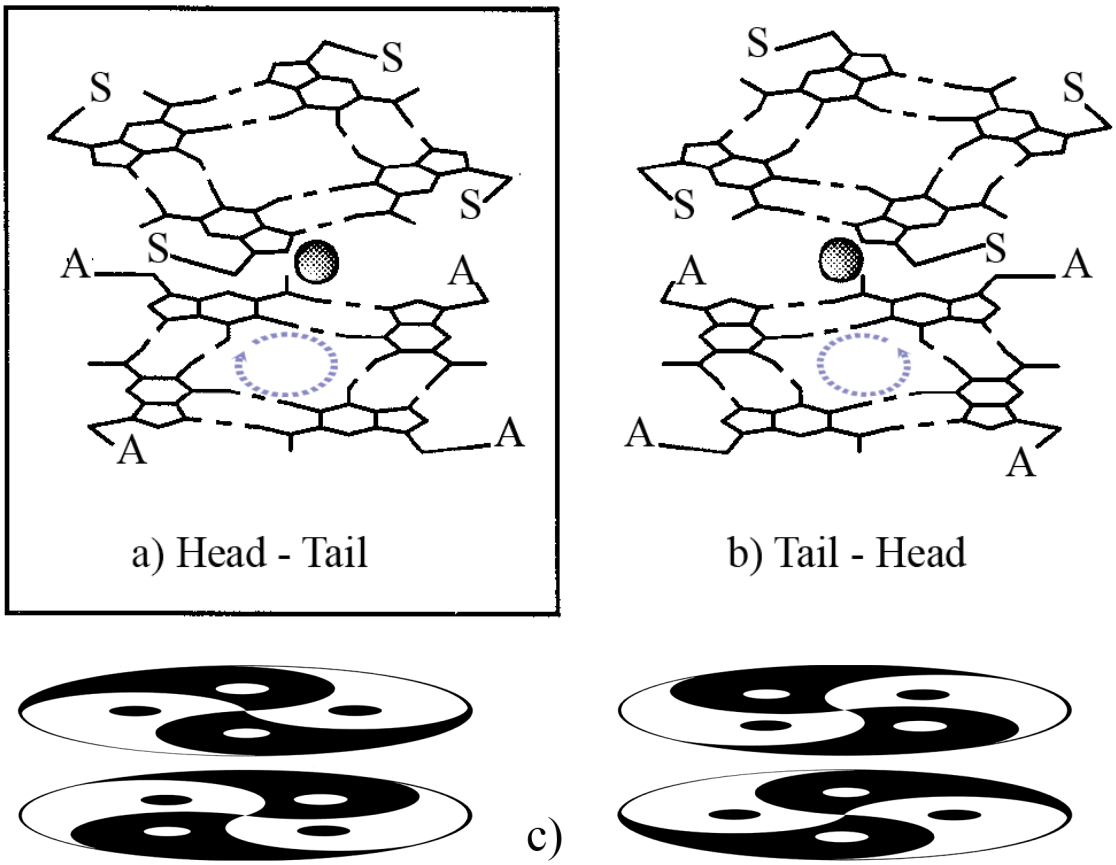


Figure 4.24 *Definition of the "head" and "tail" sides of a G-quartet is as defined by Feigon.[50] The head, relative to the central Ag^+, has a clockwise rotation of the N-H···O=C hydrogen-bonding pattern (i.e., from the donors to the acceptors), whereas the tail has a counterclockwise rotation. The two possible arrangements of* ***(G16)***$_8$*-Ag^+ containing all-anti and all-syn G-quartets are represented in a) Head-Tail and b) Tail-Head conformation associated to a cartoon representation. (Adapted from reference51)*

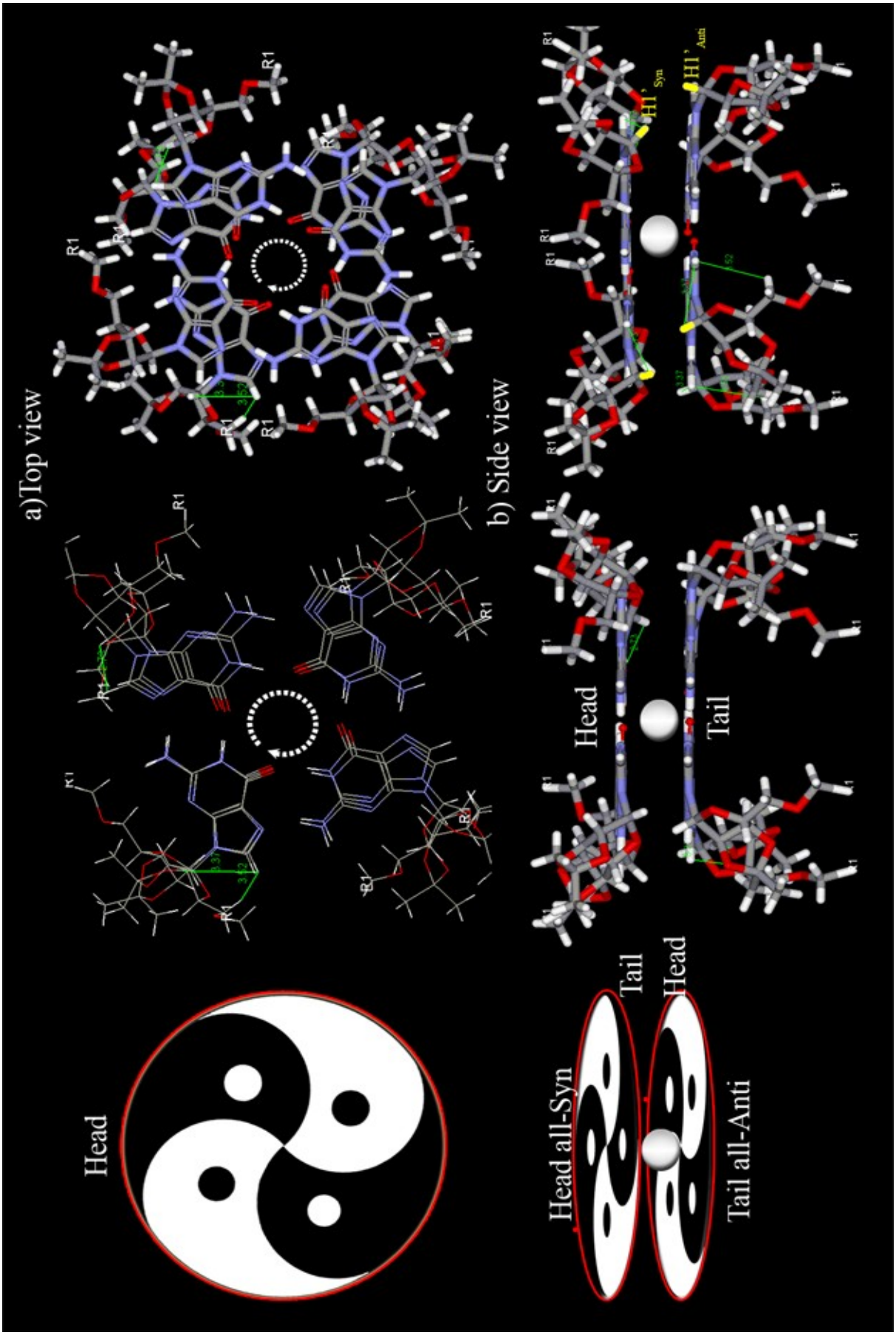
Molecular modelling of **G16**-quartet in all-*syn* conformation revealed that the "tail" is less crowed than its "head" because of the conformation around the glicosidic bond. Instead, molecular modelling experiment of **G16**-quartet in all-*anti* conformation revealed that "head" is less crowed that its "tail" (Figure 4.25b side view). This sterical conformation of the distinct planar **G16**-quartet could prevent the formation of a octamer for a staking of two quartets in Tail-Head fashion for evident sterical hiedrance. The other two conformation Head-Head and Tail-Tail are also forbid for the missing of the interquartet interaction indicated from the 2D NOESY experiments.

How explained before, the 2D NOESY experiments revealed a H1'*syn*-H1'*anti* NOE cross-peak that indicated an interquartet interaction. Such modelling experiments show an Ag-templated octamer in a "Head-to-Tail" orientation originated by staking between a **G16**-all-*anti* -quartet's *"head-face"* and *a* ***G16****-all-syn* -quartet's *"tail face"* (Figure 4.25b, side view). In this unique model the H1' protons of each **G16**-quartet, in all-*syn* and all-*anti* conformation, can expose face-to-face the two H1' protons (*syn* and *anti*) with an average distance of 3,10 Å, well within the NOE range (Figure 4.25b and 4.26)

This octameric architecture presents two different solvent-exposed faces: a head all-*syn* and a tail all-*anti* (Figure 4.25b). The head *all-syn* (on top) presents the ribose rings deviated outside from the G-quartet plane, while the tail *all-anty* (on bottom) has the ribose rings almost vertical respect to the G-quartet plane. This arrangement probably permits a hierarchical self-assembly for another staking of a second octamer above the **G16**-all-*syn*-quartet (Figure 4.26). The supramolecular synthesis of an hexadecamer could justifies the splitting of the NH(1) proton with $\Delta\delta > 3$ppm, where the inner NH(1) proton signals have a significant downfield chemical shift over 13ppm (Figure 4.18). This chemical shift value have never been seen for an octameric structure.

Corroborated by Molecular Modelling one possibility for the π-π staking between two octamers is that the all-*syn* "Head-faces" could be rotated to each other to minimize the steric clashes between the sugar in the upper and lower octamer. In this condition an hexadecamer architecture is shown by a molecular modelling in Figure 4.26.

Figure 4.25 *Top view for* ***G16****-quartets staking in octameric structure not rotated each other (left side), and G16-quartets twisted approximately 30° relative each other (right side). In wellon are highligthed the two protons syn and anti and a cartoon represents the conformation G-quartet.*


a)Top view
b) Side view
Head
Head all-Syn
Tail
Head
Tail all-Anti
Head
Tail
H1'Syn
H1'Anti
R1

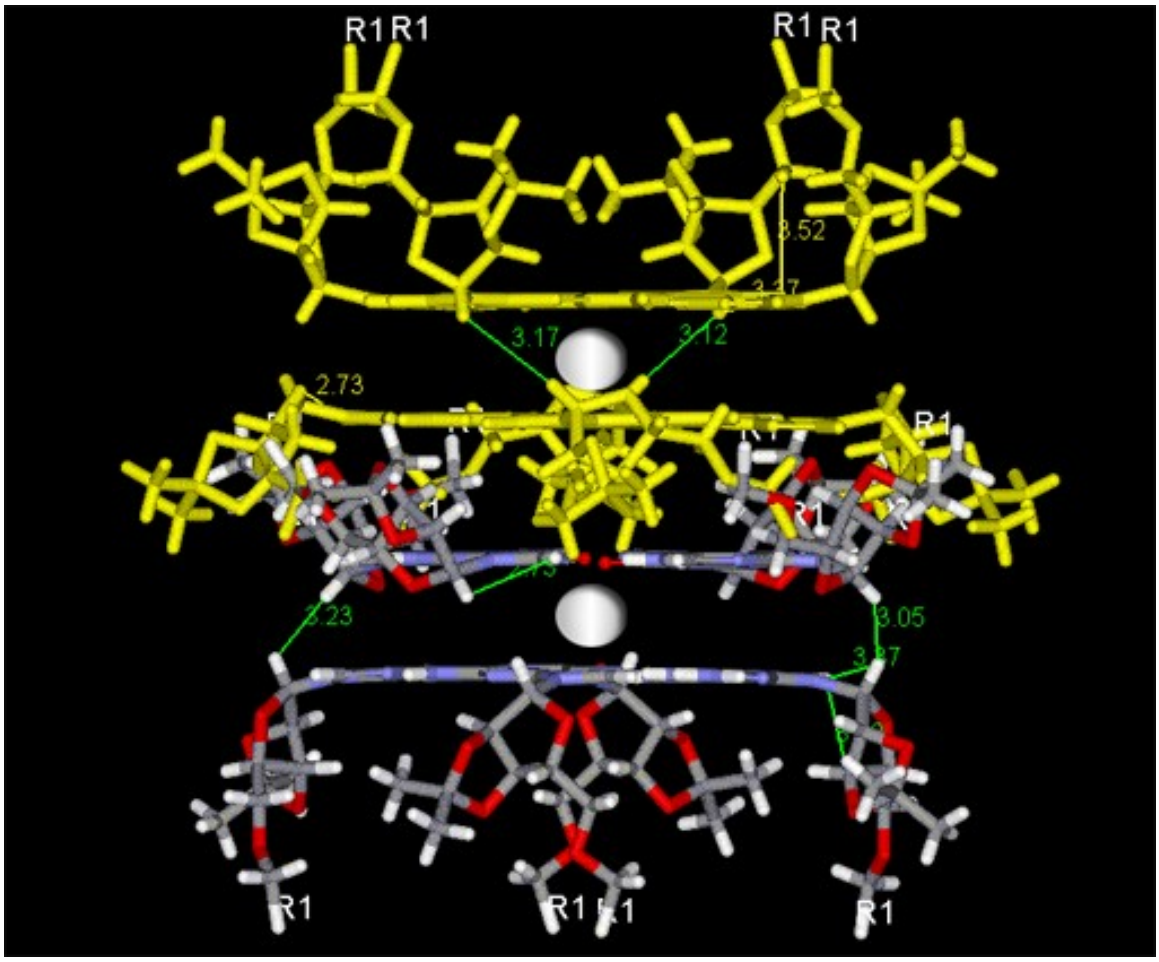


Figure 4.26 *Molecular modelling for an hexadecamer architecture. The second upper octamer in yellon is twisted with a rotation of 45° relative the first lower octamer .*

In summary, we have shown how the addition of silver ions can destroy a well ordered supramolecular structure (octamer formed by potassium ions) to obtain a new highly multi-hierarchical system of complex interactions (hexadecamer formed by silver ions). The characterization of other structures formed in different ambient conditions is continuing in our laboratory.

Experimental section: 2',3'-O-Isopropylidene-5'-O-decylguanosine.

2',3'-O-Isopropylideneguanosine (Sigma) (0.4 g, 1.2 mmol) was dried in vacuo over P_2O_5 for 2 h at 50 °C and suspended in anhydrous THF (10 mL). NaH (0.058 g, 2.4 mmol) and 1-bromodecane (1.24 mL, 6 mmol) were added. The mixture was heated at reflux overnight, then cooled to room temperature. The solvent was removed and the residual solid was taken up in dichloromethane, washed with water, dried over $MgSO_4$, concentrated in vacuo, and

applied to a silica gel column using 94:6 dichloromethane/methanol as the eluent. The product was recrystallized from ethanol to afford a white solid (0.26 g, 48 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ =0.86 (t, 3 H; CH_3), 1.25 (m, 14 H; CH_2), 1.39 (s, 3 H; CH_3), 1.53 (m, 2 H; OC-H_2CH_2), 1.61 (s, 3 H; CH_3), 3.43 (m, 2 H; O-CH_2), 3.55-3.64 (m, 2 H; H5'-H5"), 4.42 (m, 1 H; H4'), 4.92 (m, 1 H; H3'), 5.17 (m, 1 H; H_2'), 6.00 (d, 1 H; H1'), 6.28 (s, 2 H; NH_2), 7.76 (s, 1 H; H8), 12.02 ppm (s, 1 H; NH);

CD spectra were recorded with a JASCO J-710 spectropolarimeter using cells of the appropriate path length. NMR spectra were recorded with Varian Mercury instruments at 300 or 400 Mhz.

Molecular Modeling simulations were performed using the Software DS Viewer Pro 5.0 package from Accelrys.

4.5 Colaboration activity with Rolic Technology Ltd

Subject Research Project : *Development of polymerisable chiral dopant for liquid crystal prepolymers (LCPs) and their for the preparation of cholesteric thin films.*

Project duration: October 1st, 2005 to September 30, 2006

Project manager: Prof. Gian Piero Spada (University of Bologna)
Prof. Zoubair M. Cherkaoui (Rolic Technologies Ltd)
from 3rd August, 2005 to 19 Dicember 2005)
Dr. J-F Eckert (Rolic Technologies Ltd)
from 19 Dicember to 30 September 2006)

All the information and results relating to the Research Project are confidentials and not published.

4.6 Conclusion

Mimicking nature, hierarchical self-assembly[52] provides a tool for bottom-up nanoconstruction of sophisticated functional architectures[53] as for the unraveling of complex biological arrangements and processes, [54,55] paving the way towards their potential application in the realms of nanotechnology[56] and nanomedicine.[57] Self-assembly is an intrinsic property

of DNA nucleosides.[54] Learning to precisely control nucleoside self-assembly represents a powerful way of constructing a wealth of complex architectures and nanostructured materials, as well as devices with pre-programmed (dynamics) functions.[58] Ultimately, one might foresee their use as components for bio-hybrid electronics,[59] such as transistors. Lipophilic guanosine nucleosides can undergo different self-assembly pathways, depending on the experimental conditions (Figure 3.2). The presence of monovalent and divalent cations can template the formation of G-quadruplex-based octamers or columnar aggregates, depending on the concentration of the ion and nucleobase, both for organic- soluble[6,39,51,60] and water-soluble derivatives.[61] These G quadruplexes are of great interest because they hold potential in anticancer drug design as they can act as enzyme telo- merase inhibitors.[62]

In the absence of metal templates, guanosines without a C(8) substituent self-assemble, both in solution and in the solid state, into ribbon-like architectures with an anti orientation of the base around the glycosidic bond.[39,8,27,29] These ribbon structures are interesting as they are the building blocks for newlyotropic mesophases formed in organic solvents.[29,63] In the solid state the ribbons, by bridging gold electrodes, are photoconductive.[25] More interestingly, these ribbons also display rectifying properties.[26] A field-effect transistor based on this supramolecular structure has recently been described (Figure 3.23). [13]

4.7 References

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22. The recovery of the signals of the initial spectrum $\mathbf{dG7}_n$ and of $\mathbf{K^+dG7_8}$ is not complete for the existence of multiple equilibria after acid/base addition.
23. The chemical shift of H(2) at 6.3 ppm is indicative of the existence of a supramolecular ribbon-like architecture in solution (see ref 10) involving the H(2) protons.
24. The NMR signals of the ribbons (in particular, those of H(8) and NH(2)) in the

presence of cryptate (traces c and e of Figure 4) are sharper as compared to those of the starting spectrum (trace a of Figure 4). This could reflect the differences in the bulk properties of the system (e.g., polarity) and/or the size (and polidispersity) of the ribbon after addition of cosolutes (cryptand, acid, and base).

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5.0 Future directions

New metal-organic frameworks (MOFs) have attracted wide interest because they provide a novel route towards porous materials that may find applications in molecular recognition, catalysis, gas storage and separation.[1] The so-called rational design principle—synthesis of materials with predictable structures and properties—will be explored using appropriate Guanosine with organic molecular moieties connected to metal nodes to control pore size and functionality of open coordination networks.[2,3]

Moreover, the basic research to study the non-covalent weak interactions is paramount important for understanding the dynamic nature of all the supramolecular phenomena presents in the living and non-living systems.

In light of this, the basic research of the self-organization is running in four directions. In each of them the self-organization process is implicit into the transformation, replication and self-maintaining of live or alive matter. It is involved in the Prigonie's dissipative structure, in the Maturana and Varela's autopoietic system, in the hierarchical complex matter and in the interlocking webs of life. As shown a “re-active” system is opened to its own environment exchanging matter, energy and information through different communication channels.

Self-organization involves two complementary phenomena, such as pre-organization and re-cognition, these self-processes with high selectivity and affinity operate for a new whole system with emergent properties, like a simple key-lock system where receptor and substrate are complementary subunities with a winning structure-function well defined.

We remember that a emergent property is superior than of the sum of the singles parts. For this concept, “smart” complex matter presents an higher emergent property than the sum of the single molecular constituents. Therefore a multi-scale system, either at molecular level or supramolecular level, in response to the environment's input achieve a set of conditions and constrains (adaptative and cooperative) with its neighbours leading up to a balanced eco-system from organic chemistry to biological chemistry.

In this contest basic supramoelcular research, an excellent interface between material science and information science studies: i) molecular recogniton and pre-organization manipulating the molecular information storage; ii) self-assembly and self-organization read-out at supramolecular level and iii) outlooks a progress emerging of creative condensed phase by a adaptative “soft” chemistry.

In the holistic view, all living system are open-system. They must die (a bifurcation as sudden deviation) and re-born (re-organize) into a cycle of birth and death. So that “smart”

supramolecular matter, which features depend on molecular information, is by nature a *"dynamic informed" complex matter* that evolves by communication processes reaching a *"biological" complex matter* connected spatially and temporally to their surrounding (or web of life).

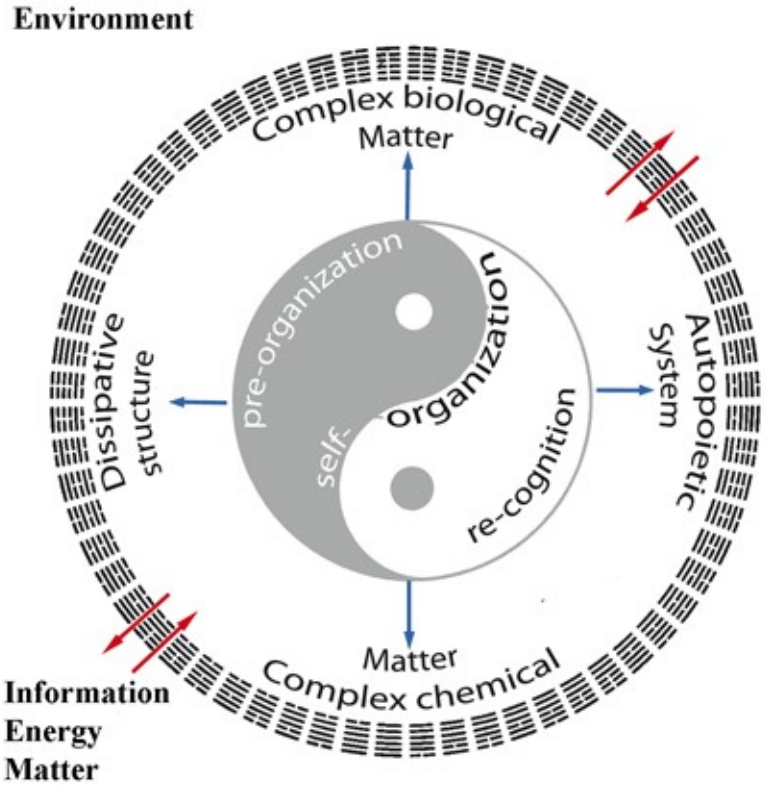


Figure 5.1 *A hierarchical system governed by self-processes depending on the exchanges with its own environment. With another point of view the principal characteristic of the Dao is the cyclic nature of its ceaseless motion and change. The Book of Changes "Yi jing" also reflects the ceaseless transformation of all things and situations. The transformation of yin into yang and yang to yin shows a process of evolution.*

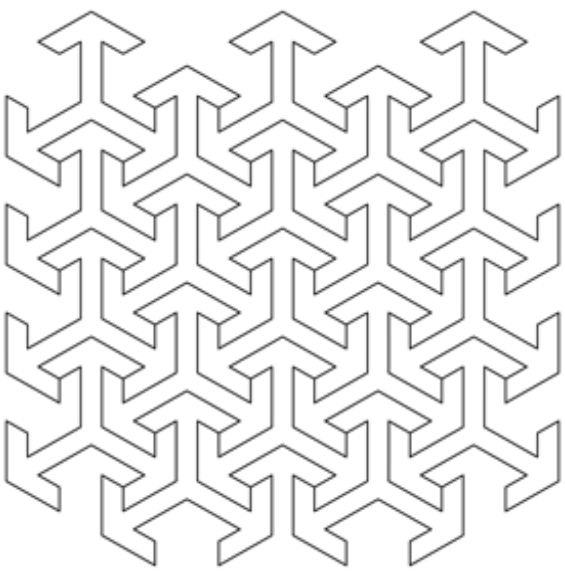
5.1 Arabian geometric patterns: images for graphic resource, inspiration and funny design

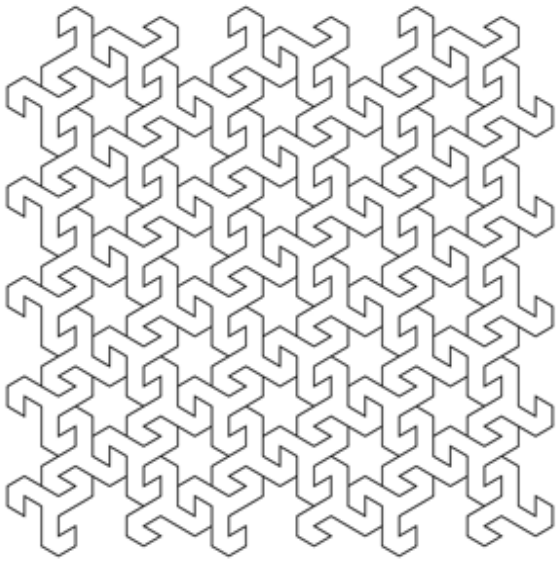
The cultures of the Middle East that embraced Islam have always shown a passion for geometrical design. More than five thousand years ago, at Warka in Mesopotamia – the land between the Tigris and Euphrates – complex geometrical mosaics, based upon equilateral triangles, were part of the architectural vocabulary.

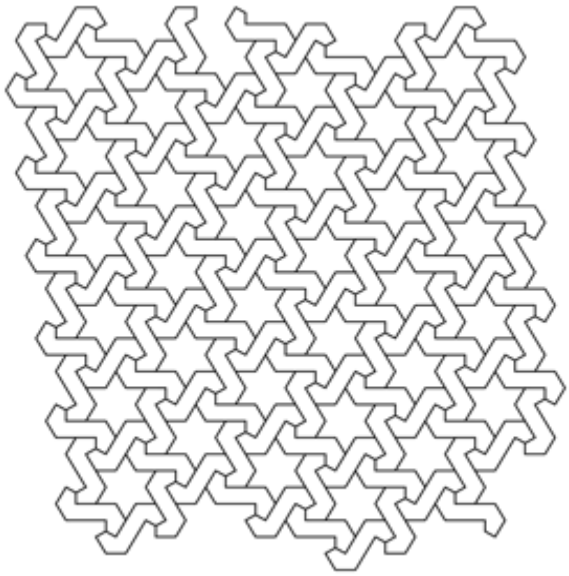
It has often been said that Islamic geometrical design was developed in response to a Qur'ranic objection to the representation of living creatures. Despite the preference for geometrical decoration in the Islamic world, Persia, Mughal India and Turkey produced

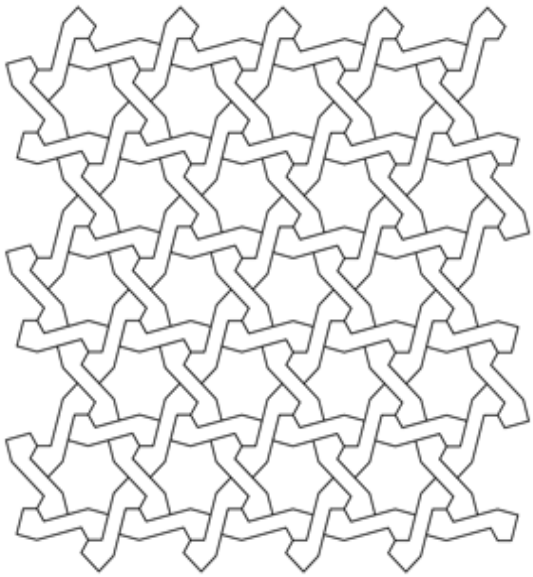
sophisticated figurative works of art, including portraits. What is significant, however, is that geometry and the making of mathematical instruments acquired Greek learning and preserved it – when scientific knowledge was at low ebb in the west.

The designs that I propose in this thesis'last part are only few geometric patterns that were originally recorded in the 1870s, primarily from Egypt ian, Persian and Syrian sources, by Jules Bourgoin.[4] The designs are interlocking, so it is possible to create larger patterns by repeating the components. The follows image can be used as a graphic resource and for inspiration to create molecular layers with a well defined geometry depending on the pattern recognition stored into molecular level. Other Arabian geometric patterns are stored in high resolution on CD-ROM.









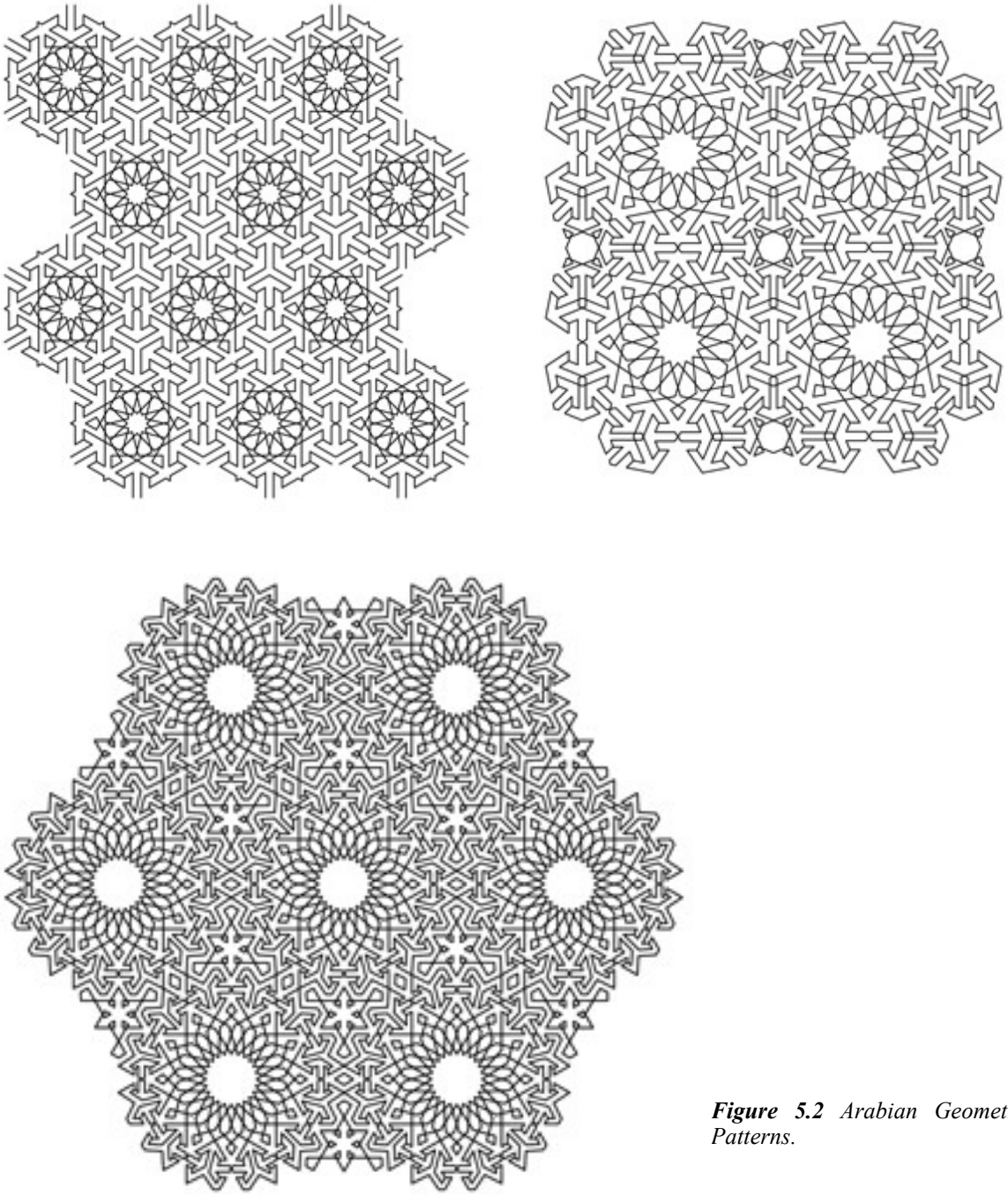


Figure 5.2 *Arabian Geometric Patterns.*

5.2 References

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5.6 Curriculum Vitae

Nome / Cognome	**Omar Pandoli**
Indirizzo	E. Alessandrini, 9 64026 Roseto degli Abruzzi (TE)
Telefono	+390858941593 Cellulare +3933337672496
E-mail	omar.pandoli2@unibo.it
Cittadinanza	Italiana
Data di nascita	3 GIU. 77
Sesso	Maschile
Settore professionale	**Chimica supramolecolare, nanotecnologie, scienze dei materiali, trasferimento tecnologico, scuola, animazione scientifica**
Istruzione e formazione	
Data	**1 GEN. 05 - 31 DIC. 07**
Titolo della qualifica rilasciata	PhD in Scienze Chimiche presso l'Università degli Studi di Bologna
Principali tematiche	Attività di ricerca finalizzata allo sviluppo professionale nella ricerca scientifica nell'ambito del piano di formazione dal titolo "Studio di architetture supramolecolari ibride organiche-inorganiche in soluzione e su superfici solide"
	14 MAR. 03
	Laurea presso l'Università degli studi di Bologna
	Sintesi e studio di nuovi materiali organici foto-responsivi
	110/110 con lode
Esperienza professionale	
Date	**01 NOV. 06 – 31 OTT. 07**
Lavoro o posizione ricoperti	Assegnista di ricerca
Principali attività e responsabilità	Funzionalizzazione di derivati della guanosina con gruppi foto ed elettroattivi e caratterizzazione delle loro architetture supramolecolari
Datore di lavoro	Dipartimento di Chimica Fisica ed Inorganica dell'Università di Bologna
	23 OTT. 07 - 15 DIC. 07

Insegnante

Insegnamento della materia "Scienze dell'Alimentazione"

I.P.S.S.A.R. "B. Scappi" Castel San Pietro Terme (BO)

15 FEB. 06 - 10 GIU. 06

Insegnante

Insegnamento della materia "Chimica e Laboratorio"

Liceo Artistico "F. Marchetti", Bologna

10 GEN. 06 - 12 GEN. 06

Animatore scientifico

Animazione scientifica nell'ambito della manifestazione "Scienza in Piazza "di Casalecchio di Reno, Bologna

Fondazione Golinelli, Bologna

01 OTT. 05 - 30 SET. 06

Collaborazione scientifica per una ricerca applicata industriale

Sintesi e caratterizzazione di dopanti chirali di cristalli liquidi termotropici per la preparazione di film sottili colesterici

Rolic Technologies L.t.d. Basilea, Svizzera

01 LUG. 04 – 31 GIU. 05

Assegnista di ricerca

Sintesi e caratterizzazione di architetture supramolecolari partendo da guanosine derivatizzate

Dipartimento di Chimica Organica "A.Mangini" dell'Università di Bologna

01 OTT. 03 - 30 MAR. 04

Borsista per una ricerca di base nell'ambito delle scienze dei materiali

Sintesi e caratterizzazione di nuove molecole organiche per applicazioni opto-elettroniche (NLO)

Departamento de Quimica Organica , Facultad de Ciencias, Universidad de Zaragozza, Spagna

1 APR. 03 - 30 SET. 03

Borsa di ricerca per idee imprenditoriali innovative e ad alto contenuto di conoscenza

Progetto GOLDFISH- Produzione di filetti di trota addizionati con omega-3

Consorzio SPINNER (Servizi per la Promozione dell'Innovazione e della Ricerca dell'Emilia Romagna)

Collaborazioni

Date **01 NOV. 06 - 01 FEB. 07**

Lavoro o posizione ricoperti Borsista Marco Polo

Principali attività e responsabilità Caratterizzazione di materiali organici nanostrutturati su superfici inorganiche

Datore di lavoro Nanochimie lab. Institut de Science et d'Ingenierie Supramoleculaires (ISIS), Universitè Louis Pasteur, Francia

2004-2005

Collaboratore scientifico

Caratterizzazione di auto-assemblaggi supramolecolari su superfici inorganiche partendo da guanosine lipofile

Nanochemistry Lab., CNR-ISOF, Bologna

15 MAG 05– 25 MAG 05

Collaboratore scientifico

Studio di proprietà foto-elettro conduttive di polimeri supramolecolari organici

National Nanotechnology Lab (NNL) Distretto Tecnologico ISUFI, Lecce

Pubblicazioni scientifiche

G.Gottarelli, , S. Pieraccini, O. Pandoli, S. Masiero, R. Labruto and G. P. Spada
"The control of the cholesteric pitch by some azo photochemical chiral switch",**Chem. Eur. J. 2004, 10, 5632-39**

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