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GUANOSINE DERIVATIVES: SELF-ASSEMBLY AND LYOTROPIC LIQUID CRYSTAL FORMATION

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The self-assembly and lyotropic mesomorphism of guanosine derivatives are reviewed. Natural and synthetic guanosine nucleotides self-assemble into columnar aggregates based on G-quartets; at the appropriate concentrations these aggregates form, in water, lyotropic mesophases of the cholesteric and hexagonal type. Lipophilic derivatives undergo different types of self-assembly: in the presence of alkali metal ions they form, in organic solvents, columnar structures and lyomesophases similar to those observed for the hydrophilic derivatives; in the absence of ions they form instead ribbon-like aggregates which give rise to new types of lyotropic phases. The ribbon-like aggregates have interesting electrical properties.

Keywords: self-assembly; supramolecular chemistry; guanosine; columnar assembly; ribbon-like assembly

Among bases forming DNA, the guanine represents a versatile molecule that, depending on the environment, can undergo different self-assembly pathways. In this review article we describe first the behaviour of guanylic (oligo)nucleotides in water; then the self-assembly processes of lipophilic guanylic derivatives in the presence and in the absence of alkali metal ions is described.

We would like to thank all the co-workers who contributed to this work and who are individually recognised in the cited references, in particular Elisabetta Mezzina (University of Bologna), Paolo Mariani (University of Ancona), Paolo Samori and Anna Garbesi (ISOF-CNR, Bologna). A special thank to Dr. Gloria Proni (Columbia University) who handled most part of the work on alkali metal salts of guanosine derivatives when she was in our research group.

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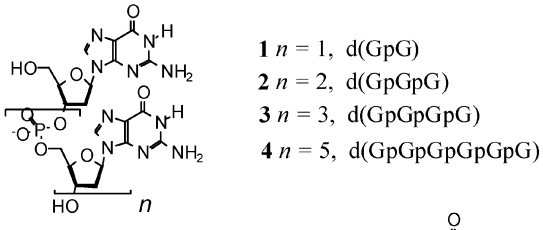
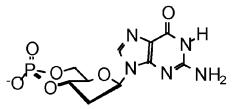
1. ALKALI METAL SALTS OF GUANOSINE DERIVATIVES

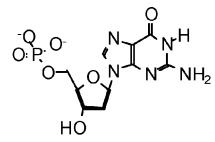
Our interest in guanosine started at the end of 80's [1] from a fortuitous observation. We found that a 5% w/w aqueous solution of 2'-deoxyguanylyl-(3'-5')-2'-deoxyguanosine **1**, sodium salt, prepared for a routine ^{1}H-NMR experiment was highly viscous and liquid crystalline. The spectrum was in fact dominated by resonance corresponding to water. If we had already been equipped with a better performing NMR spectrometer, we would have worked at much lower concentration (in isotropic solution) and the LC properties of **1** would have been unnoticed. This compound exhibits indeed a cholesteric and a hexagonal phase with the following transition concentrations (w/w at Room Temperature): Iso–2.5%–Chol–18%–Hex.



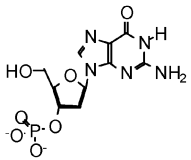
1 n = 1, d(GpG)
2 n = 2, d(GpGpG)
3 n = 3, d(GpGpGpG)
4 n = 5, d(GpGpGpGpGpG)



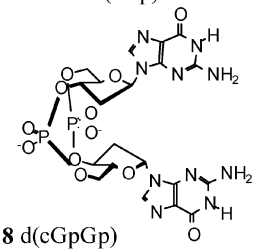
5 d(cGp)



6 d(pG)



7 d(Gp)



8 d(cGpGp)

In the following years, we described the lyomesomorphism of many guanylic nucleotides and oligonucleotides [2]. A few of them are reported above. Typically cholesteric and hexagonal phases are formed, however in a few cases only the hexagonal (e.g.: **8**) or an additional square phase (e.g.: **7**) is observed.

How can we explain the formation of aqueous lyotropic mesophases from these small molecules? It was known that several biopolymers, for example DNA [3], show LC phases in water. The formation of DNA LC has been interpreted as follows [3]: the DNA double-helix can be assimilated to a rod with a hydrophilic surface and a lipophilic core. These elongated objects are chiral and can self-correlate with a cholesteric or a hexagonal order, depending on the water content (see Fig. 1).

The optical texture of DNA mesophases are reminiscent of those observed for our guanosine derivatives. However, our guanosines are *not* polymers and their molecules are *not* long anisometric objects as DNA, therefore a different explanation of the LC formation must be invoked. Guanine is in some way peculiar. Among nucleobases, guanine possess a

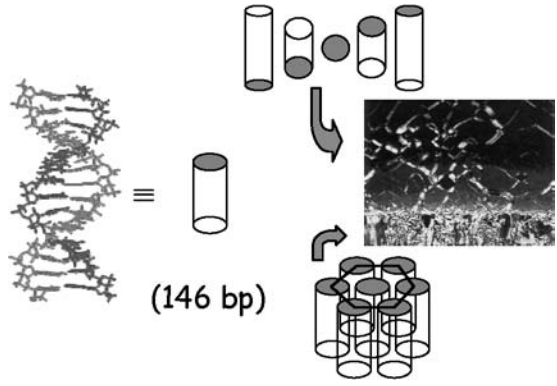


FIGURE 1 (see COLOR PLATE XVI) Lyotropic LCs from DNA fragments.

unique sequence of groups which act as donors and acceptors of H-bonds. These groups are of fundamental importance in the self recognition and self-assembly process. This process can occur through the formation of the so-called G-quartet [4] in which four guanines give rise to a cyclic H-bonded motif (Fig. 2).

This G-quartet motif has been recognised as the fundamental unit of the four-stranded helix of poly(G) [5], a polymer in which the monomeric unit is the guanosine moiety. In this structure the G-quartets are linked via the covalent phospho-sugar bridges (Fig. 3).

In spite of the absence of a sugar-phosphate backbone, also the low molecular weight guanosines **1**–**8** and related molecules self-assemble according to the G-quartet scheme [6,7]. The quartets are piled up one on

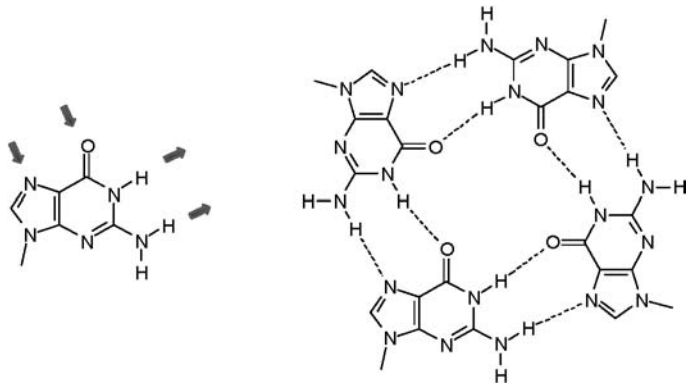


FIGURE 2 Guanine and the G-quartet.

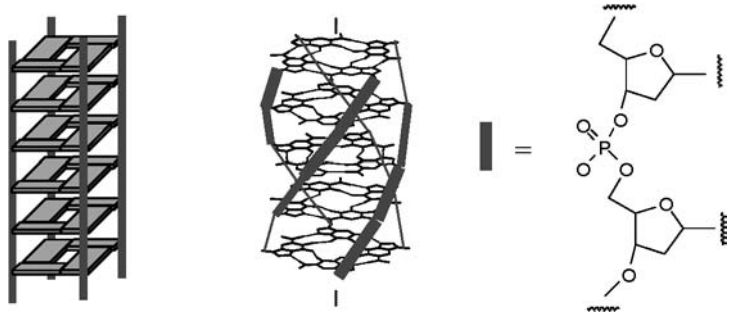


FIGURE 3 (see COLOR PLATE XVII) The four-stranded helix of poly(G).

top of the other at the van der Waals distance and the cations (the counterions) are sandwiched between them (see Fig. 4). Stacking interactions and coordination of the metal stabilise these structures also in the absence of any covalent bridges between the adjacent G-quartets. As a consequence of the intrinsic chirality of the compounds, the stacking is not in register, but each G-quarter is rotated with respect to the adjacent ones.

Depending on concentration, temperature, amount of salts eventually added, these aggregates self-correlate to originate mesophases of the cholesteric or hexagonal type. The basic structure is a chiral columnar aggregate based on G-quartets held together by non-covalent interactions.

The cholesteric phase can easily be aligned with a magnetic field to give a fingerprint or a planer texture without unwinding the cholesteric helix that is oriented parallel to the applied field (Fig. 5). This magnetic behaviour indicates that the objects composing the phase have negative diamagnetic anisotrophy, as expected for rod-like aggregates with the planes perpendicular to the long axis [7].

Low angle X-ray diffraction work confirmed the assignment of the phases evinced from optical microscopy. In particular, in the high angle

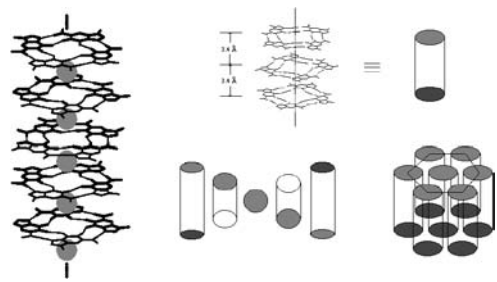


FIGURE 4 (see COLOR PLATE XVIII) Lyotropic LCs from self-assembled guanosines.

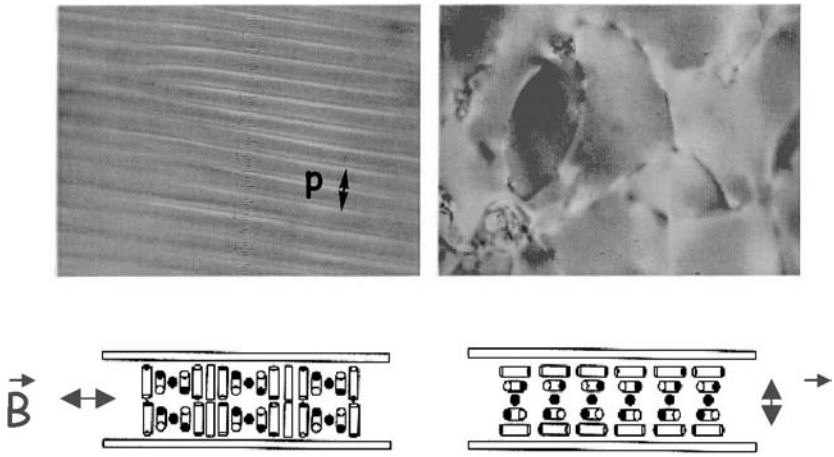


FIGURE 5 (see COLOR PLATE XIX) Fingerprint and planar textures from a cholesteric aqueous solution of 1.

region a sharp peak corresponding to the periodicity of 3.4 Å, typical of stacked aromatic systems, is present. Electron density maps have been calculated and they support the existence of a G-quartet based system [7].

At the beginning of 90's the first evidence at atomic resolution of a G-quartet and of a G-quartet based system has been reported [8]. X-ray diffraction experiments on a single crystal obtained from the tetraplex of the oligonucleotide d(TG_4T) show clearly the G-quartets, the location of the cations, and the chiral stacking of the G-quarters (see Fig. 6).

The self-assembly process of guanosine derivatives can easily and conveniently be followed by circular dichorism spectroscopy (CD). Spectra of isolated species are usually drastically different from those of the assembled species and of the cholesteric phases [9]. In Figure 7 the case of 7, whose assembly process is driven by temperature [10], is reported as an example. At 30°C the spectrum of the unassembled molecule is recorded. At lower temperature (5°C) an exciton couplet is observed in

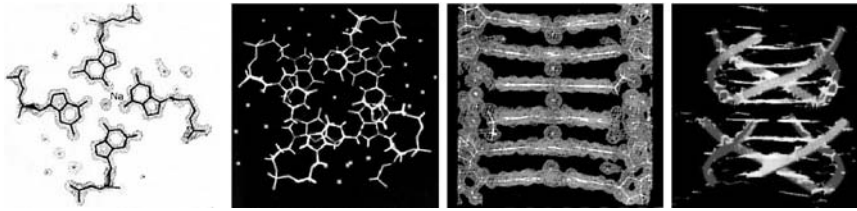


FIGURE 6 (see COLOR PLATE XX) The crystal structure of d(TG_4T)

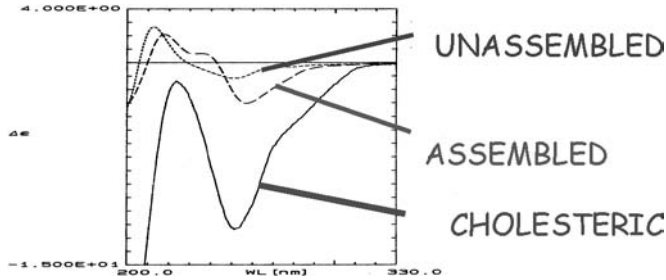


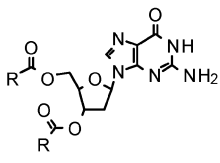
FIGURE 7 CD spectra of 7 in water (c = 4% w/w) at 30, 5, and 1°C.

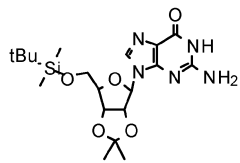
correspondence of the main absorption band of the guanine. The particular sequence of the opposite signed bands (negative-positive) can be related to a left-handed stacking of adjacent G-quartets.

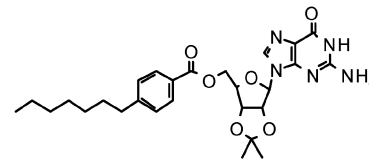
At 1°C the solution is cholesteric and a very intense signal appears: the negative sign is indicative of a left-handed phase. Therefore, from CD spectroscopy, we can determine the handedness of the chiral columnar aggregate and of the cholesteric phase.

2. SELF-ASSEMBLY OF LIPOPHILIC GUANOSINE DERIVATIVES DIRECTED BY IONS

Based on the data in aqueous solution, and in particular on the role of the cation, we investigated the behaviour in organic solvents. To study this process in organic solvents, lipophilic derivatives (Lipo-G) such as deoxyguanosine diesters **9**–**13** have been prepared.







9, R = C_9H_{19}
10, R = *p*-($C_{12}H_{25}O$)-Ph
11, R = C_2H_5

12

13

One interesting property of these Lipo-G's is that they can behave as ionophores. In classical extraction experiments, chloroform solutions of the Lipo-Gs **9** and **10** were shaken with aqueous solutions of alkali picrates (that are insoluble in chloroform); the yellow colour associated to the picrate chromophore is transferred into the organic phases (see Fig. 8) [11].

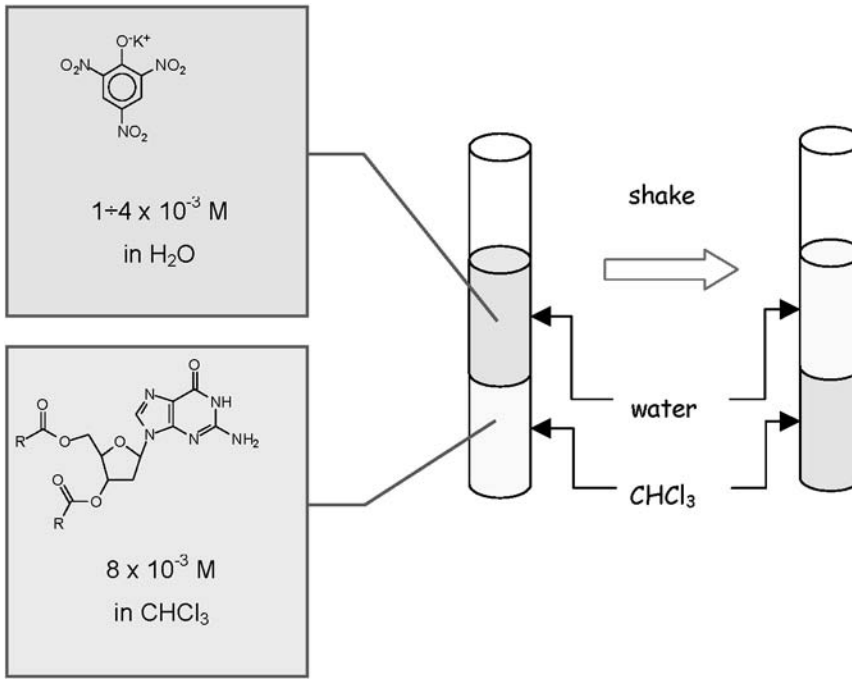


FIGURE 8 (see COLOR PLATE XXI) A typical extraction experiment.

These Lipo-Gs are therefore able to transfer the akali picrate in the organic phase! This is a quite new behaviour: in fact Lipo-Gs are "self-assembled" ionophores different from the usual covalent ionophores (like crown ethers). As already seen in hydrophilic systems, the self-assembly process can be followed by CD spectroscopy which clearly show the formation of a G-quartet stacked system.

But what is the structure of the complex formed in the organic phase? It depends on the molar ratio between Lipo-G and alkali picrate used in the extraction experiment. NMR spectroscopy allows to follow easily the assembly process by recording spectra at different [Lipo-G]/[Picrate] ratios. A part of the spectrum of Lipo-G **9** in chloroform is reported in Fig. 9; in particular, the signals of the protons H8 and H1 are evident. After extraction in a 8:1 molar ratio, the spectrum in the H8 and H1 region changes. Increasing the amount of alkali picrate (4:1 ratio or less), the NMR spectrum changes again. NMR spectra show the existence of two different complexes with different stoichiometry [11].

These results are compatible with the scheme of cation-directed self-assembly of the Lipo-G reported in Figure 10. The alkali metal ion acts as

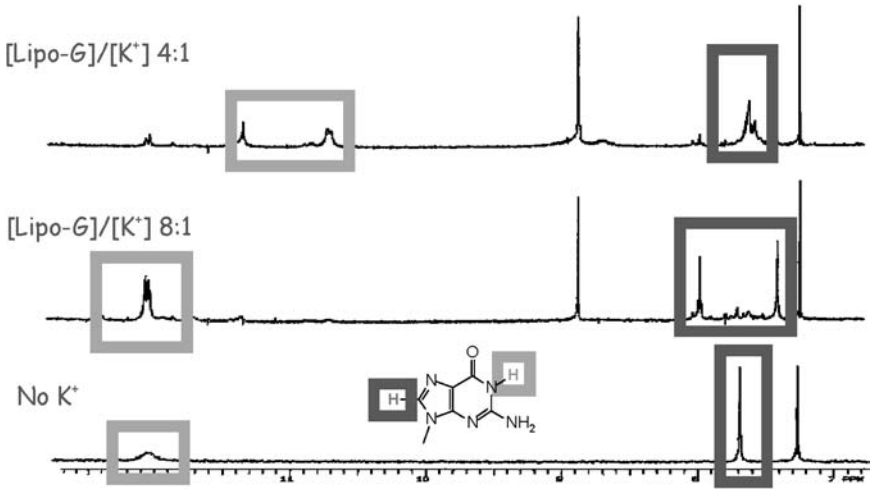


FIGURE 9 (see COLOR PLATE XXII) NMR spectra of 9 in $CDCl_3$ in the presence of different amount of potassium picrate.

cement to keep the G-quarters together. On increasing the amount of K^+ we observe first the formation of the "octamer" with two G-quartets coordinating a metal ion, and then a *pseudo*-polymeric species with a 4-to-1 stoichiometry. In particular, if the molar ratio K/Lipo-G is 1:8 or less the octamer is the most abundant species, while for higher ratio polymeric columnar aggregates (with a stoichiometry of 4:1) are progressively observed [11].

A more detailed NMR investigation has led to the resolution of the structure of the octamer formed by Lipo-Gs [12]. The NMR spectrum shows two sets of signals in a 1:1 ratio (Fig. 11). One set corresponds to quartets

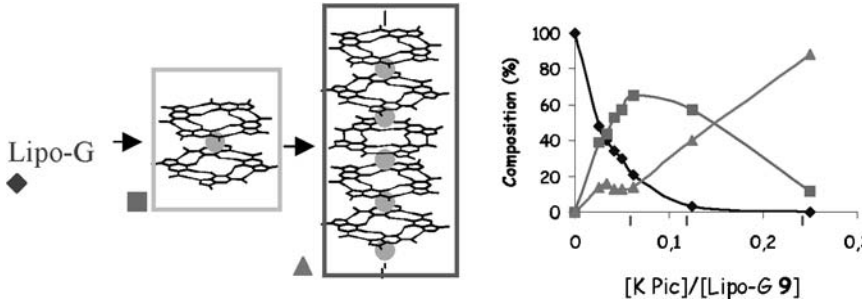


FIGURE 10 (see COLOR PLATE XXIII) The cation-directed self-assembly of Lipo-Gs.

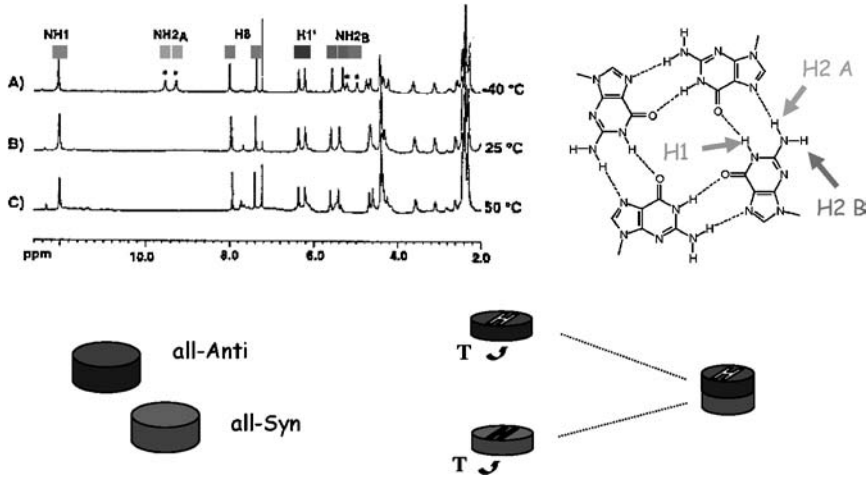


FIGURE 11 (see COLOR PLATE XXIV) NMR spectrum of 9_8KI in $CDCl_3$ and the proposed structure.

formed by guanosines in *anti* conformation and the other is due to quarters of guanosines in *syn* conformation. Even from a quick inspection of the spectrum in Figure 11 it appears that the chemical shifts of NH1 and of the two amino protons are consistent with a G-quartet based structure; in particular, the large difference in the chemical shift of the two amino protons are indicative of the fact that one is solvent exposed, while the other one is involved in a H-bond. A detailed NMR investigation lead to the most likely structure for the octamer that presents an all-*anti* tetramer stacked on top of an all-*syn* quartet in a well defined head-to-tail arrangement.

Also the *pseudo*-polymeric aggregate has been characterised in a similar way by NMR [13]. The spectrum shows three sets of signals in a 1:1:1 ratio which can be attributed to three different conformationally homogeneous G-quartets (Fig. 12). The repetition along the column of the three different quartets is unique and well defined and the stereochemical regularity of these columnar polymeric G-aggregates is amazing: the Lipo-G contains all the structural information necessary to drive the self-assembly towards this highly ordered polymeric structure.

We have already shown that Lipo-Gs are able to act as self-assembled ionophores [11]. Considering that Lipo-Gs and their assembled species are chiral, it was thought that chiral anions could possibly be enantiodiscriminated by the chiral surface of the columnar aggregates. *N*-(2,4-dinitrophenyl) derivatives of aminoacids were chosen to test the validity of this hypothesis. The initial racemic aqueous solution becomes enantioenriched after extraction [14]. A few results obtained with Lipo-G **10** are reported in

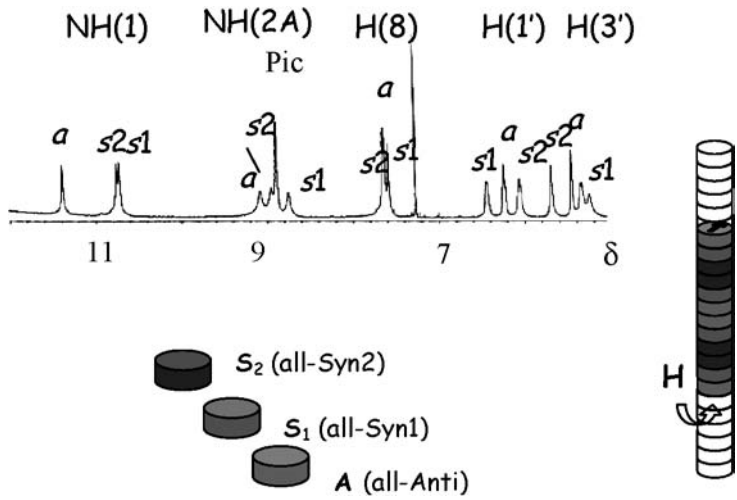


FIGURE 12 (see COLOR PLATE XXV) NMR spectrum of $\mathbf{9}_4$KPic in $CDCl_3$ and the proposed structure.

Table I. To our knowledge this is the first case of a selector that is a self-assembled species.

The first atomic resolution structure of a lipophilic columnar aggregates has been obtained from Lipo-G **12** crystallized with potassium and cesium picrate. It confirms the structure proposed in solution with co-axial chirally stacked G-quarters and metal ions sandwiched between planes [15].

When dissolved in hydrocarbon solvents, lipophilic G-quadruplexes form lyomesophases of the cholesteric (Fig. 13*a*) and hexagonal (Fig. 13*b*) type as confirmed by microscopic observations and X-ray measurements [16]. In particular X-ray diffraction confirms the columnar nature of both phases with a stacking repetition of 3.4 Å. The cholesteric phase may be aligned with magnetic fields (Fig. 13*c*,*d*) and its magnetic behaviour is analogous, as expected, to that observed for hydrophilic guanosines.

TABLE I The Enantiomeric Excesses in the Aqueous Layer after Extraction of Racemic *N*-(2,4-Dinitrophenyl)Aminoacids with Lipo-G **10**; [AA]/[Lipo-G] = 0.5

AA	ee_{aq}	Extraction Yield
Trp	0.25	0.46
Phe	0.29	0.50
Ala	0.05	0.38
Ile	0.12	0.45

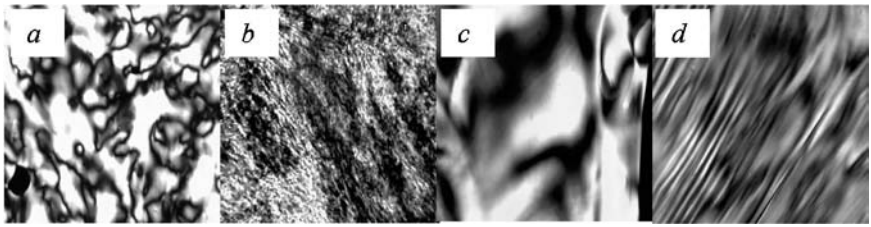


FIGURE 13 (see COLOR PLATE XXVI) Textures of 9_4KPic in heptane: *a*, *c*, *d*, c = 10%; *b*, c = 20% w/w.

3. SELF-ASSEMBLY OF LIPOPHILIC GUANOSINE DERIVATIVES NOT-MEDIATED BY IONS

If we look again at the NMR spectrum of a Lipo-G we could notice that even at relatively high duration (sub-mM) the chemical shift of NH1 is typical for a H-bonded proton. The simplest way to justify this finding is the existence of a dimeric form in which NH1 is involved in a H-bond. On increasing the concentration the NH2 signal moves downfield suggesting that also this group becomes progressively involved in H-bonding. The involvement of the NH2 protons in H-bonding at high concentration is confirmed by IR spectra: the bands corresponding to the stretching of free amino protons reduce when concentration increases. The existence of dimer, trimer and other oligomeric species (up to 13 guanines for Lipo-G 13 in the experiment shown in Fig. 14) is confirmed by ESI-MS [17].

Which is the structure of the oligomeric species? If we consider that the dimer present at low concentration has two donors and two acceptors of H-bonding the scheme of assembly sketched in Figure 15 seems probable: increasing concentration the dimeric units hold together involving amino groups and nitrogens-3 to give a ribbon-like structure.

This structure of the ribbon explains the spectroscopic behaviour as a function of concentration described before. Furthermore it is in agreement with NOE experiments (see Fig. 15) that show interactions that are absent in the dimer, namely between amino NH2 and imino NH1 protons and between amino or imino and sugar protons. These NOE interactions can be considered a signature of this self-assembled H-bonded ribbon.

The situation is indeed more complex than that described above. In fact, the NMR spectrum of fresh solution in anhydrous chloroform is different from those different above which were recorded in "standard" chloroform. In particular the H8 signal is broad in fresh solutions and moves upfield and sharpens with time. This observation suggested that freshly prepared solutions maintain a memory of the solid state in which a different structure is present [17].

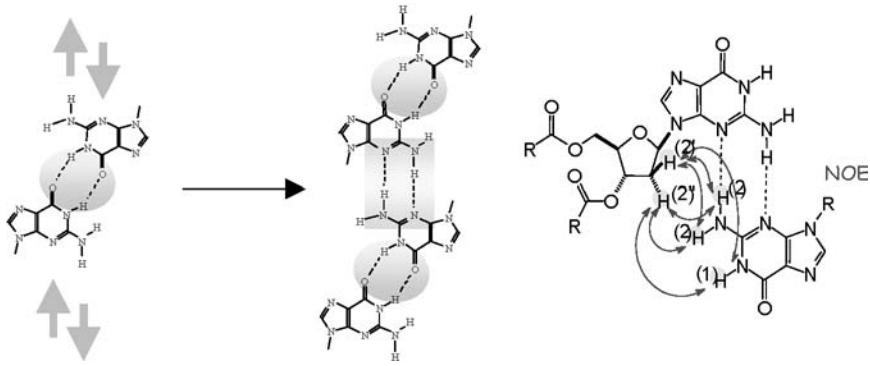


FIGURE 14 (see COLOR PLATE XXVII) ESI-MS of 13 in $CHCl_3$ (+ formic acid 10%).

NOE experiments of fresh solutions give indication of a different pattern of proximities (Fig. 16). In particular, interactions of H8 with H2 and H1 are now present and disappear with time while the interactions described in Figure 15 appear.

We propose therefore for the solid state (and the freshly prepared choloroform solution) the existence of a different type of ribbon (see Fig. 17). In chloroform solution, this ribbon I slowly transforms via internal rearrangement into the thermodynamically stable ribbon II and re-forms when solvent is removed.

Single crystal X-ray analysis of Lipo-G 11 has recently confirmed the existence of the ribbon I in the solid state [18]. Only in very few cases crystals are formed, depending on the molecular structure of the Lipo-G. More frequently (namely from 9 and 10) fibre-like solids are obtained [19] whose X-ray diffraction data are in agreement with the structure of ribbon I

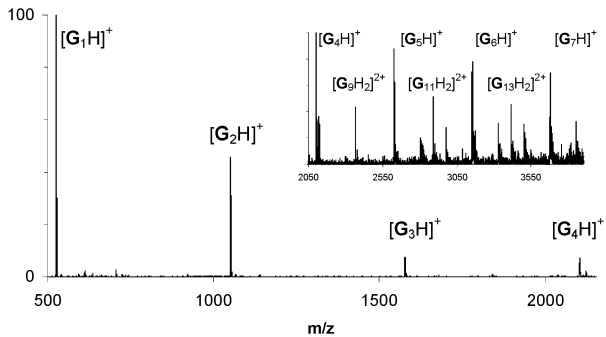


FIGURE 15 The self-assembly of Lipo-Gs in chloroform solution.

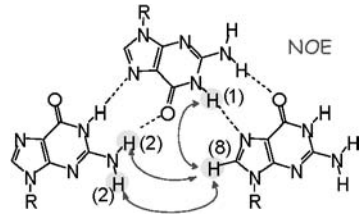


FIGURE 16 (see COLOR PLATE XXVIII) NOE interactions in freshly prepared solution of **9**.

(as confirmed by NMR spectrum recorded immediately after dissolution in chloroform).

Lipo-G compounds are able to form lyotropic mesophases in several solvents [18]. A texture of a phase obtained from **9** in hexadecane is reported in Figure 18. X-ray diffraction data are consistent with the occurrence of a phase in which the structure elements are infinite in length and are packed in a 2-D square cell with their long-axis parallel to each other.

The self-assembled G-ribbons have been "seen" with the scanning probe microscopies [17,20]. The picture in Figure 19 is a Scanning Force Microscopy (SFM) image and shows a dried nanoribbon formed on the basal plane of the substrate (mica). Its width around 6.2 nm is consistent with its proposed structure.

The picture on Figure 20 is a Scanning Tunnelling Microscopy (STM) image (at the interface graphite/solution) of closely packed arrays of

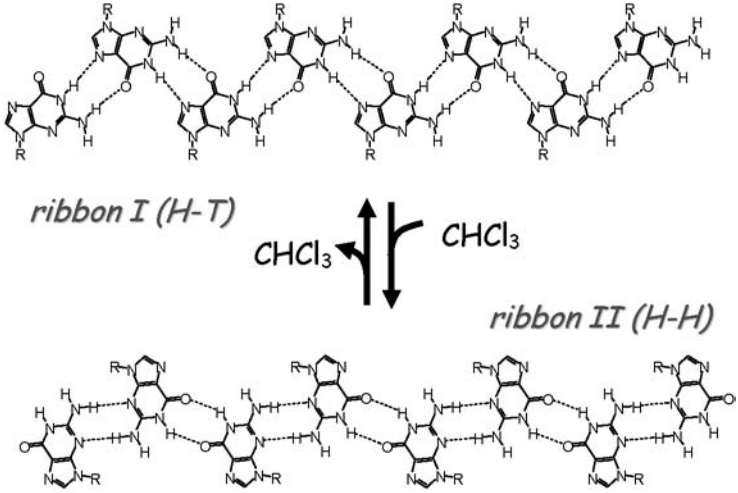


FIGURE 17 The two different modes of Lipo-G self-assembly.

FIGURE 18 (see COLOR PLATE XXIX) Optical texture of **9** in hexadecane (c = 9% w/w).

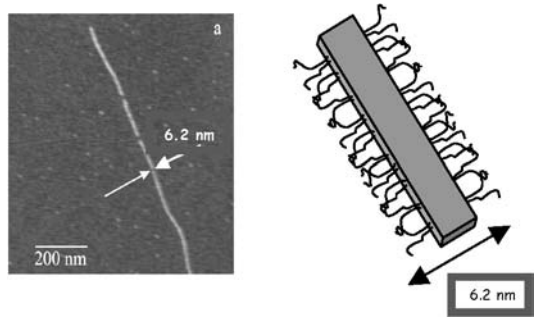


FIGURE 19 (see COLOR PLATE XXX) SFM picture of a nanoribbon of **10**.

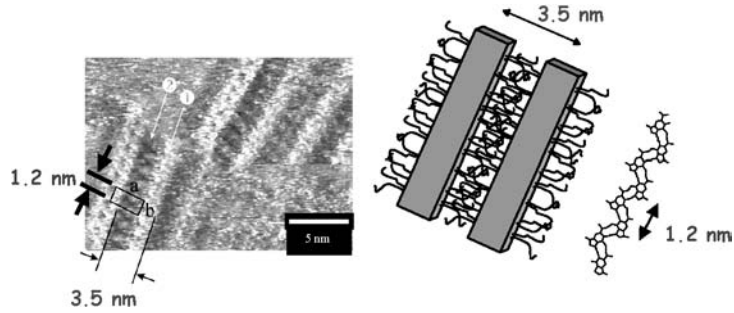


FIGURE 20 (see COLOR PLATE XXXI) STM picture of an array of nanoribbons of **10**.

H-bonded ribbons that interdigitate. The unit cell dimension b perfectly matches that of the ribbon I found in Single Crystal by X-ray.

We tired to take advantage from the self-assembly properties of guanosine derivatives in the design of molecular electronic nanodevices [21]. Self-assembled nanoribbons obtained from drop casting were used to

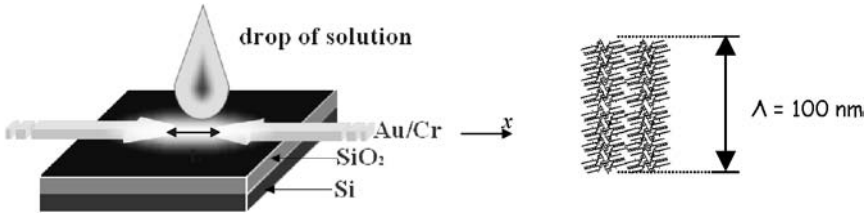


FIGURE 21 (see COLOR PLATE XXXII) The preparation of the nanodevice.

interconnect gold nanoelectrodes fabricated by electron beam lithography (Fig. 21). The formation of nanoribbons between the nanoelectrodes with different gaps were followed in loco with SFM. The typical length of the oriented arrays of ribbons (a nanocrystal) is 100 nm. The dependence Current Intensity vs Voltage is recorded.

For contact gap of 60 nm or less only one nanocrystal is probed. Under these conditions a clear diode-like behaviour is exhibited (Fig. 22*a*), with currents of the order of the μA for positive bias and nA for negative bias. This rectifying feature points out to the existence of the strong dipole in each nanocrystal: this originates from the dipole of the guanine units ordered in the ribbon-like structure of the nanocrystals.

The situation changes dramatically in the 120 nm device (Fig. 22*b*). In this case few nanocrystals 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, symmetric with a zero-current region (between −2V and +2V). At higher bias, the current increase at sub-μA levels, and the behaviour is typical of a metal-semiconductor-metal device. An interesting property of this 120 nm device is its high photoresponsivity [22]: the current increases from sub-μA level in the dark to sub-mA levels under few mW power illumination.

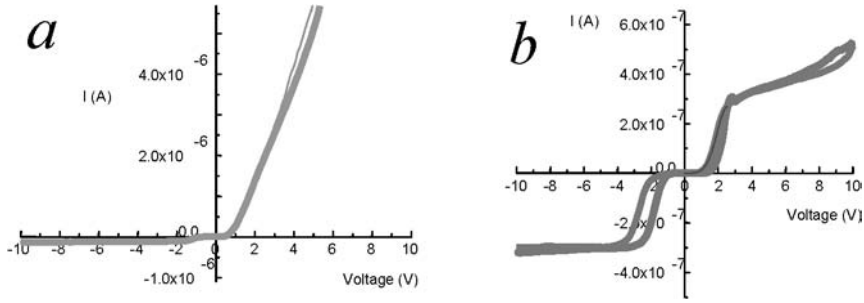


FIGURE 22 (see COLOR PLATE XXXIII) I-V plot for 60 (*a*) and 120 nm (*b*) contact gap devices.

4. CONCLUSIONS

In summary, the most striking feature of guanosine derivatives is their possibility to grow in ribbon-like and columnar structures and these different assemblies can be switched with ions. Both structures may originate partially ordered systems, including LC.

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