Supramolecular Architecture

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Amplification and Transcription of the Dynamic Supramolecular Chirality of the Guanine Quadruplex**

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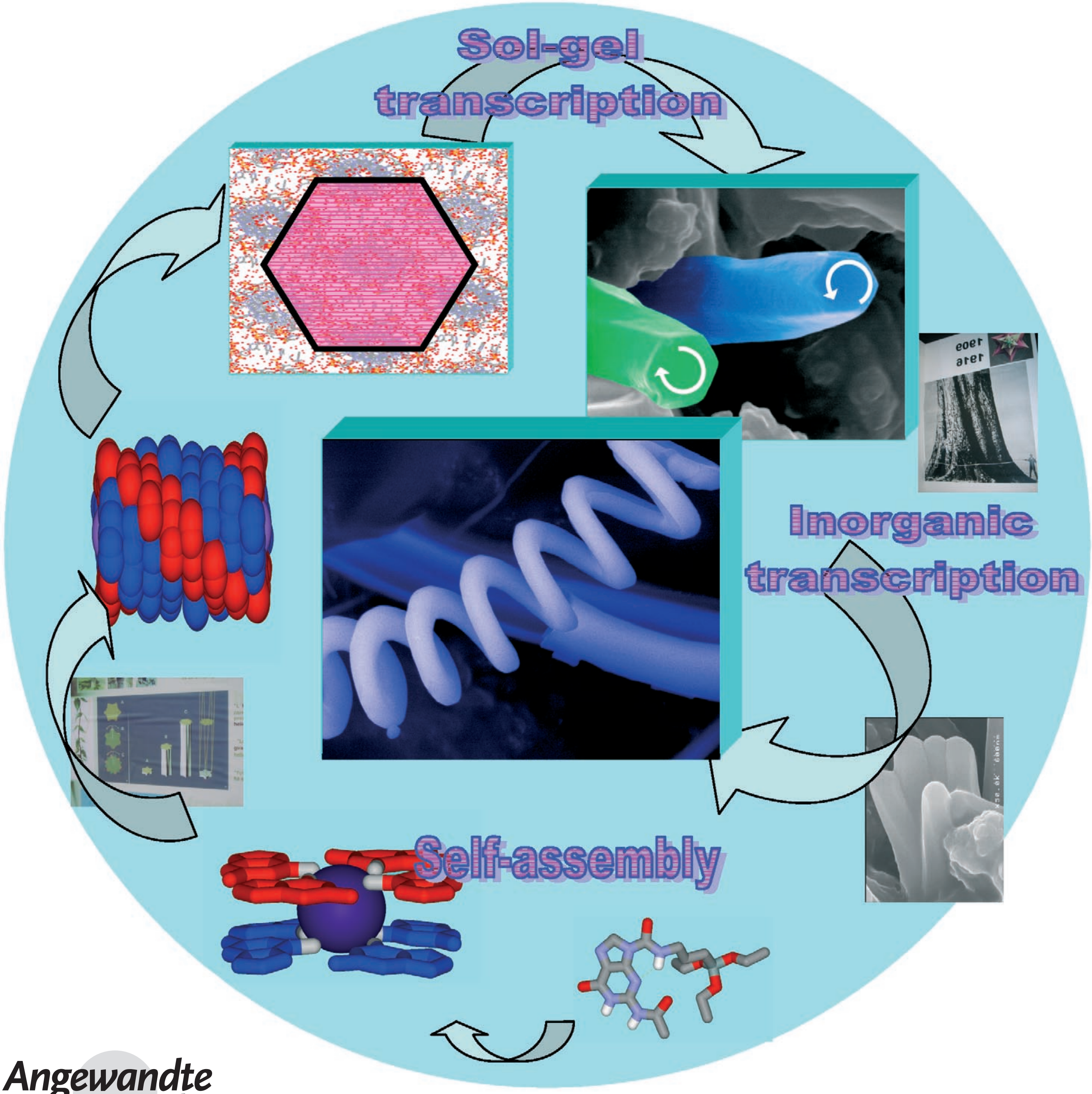

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The implementation of supramolecular chemistry in materials science has led to the development of supramolecular materials where the molecular components are held together by sets of noncovalent interactions.[1–4] Molecular chirality may be used as a means to assemble molecules[5,6] and macromolecules[7–11] into supramolecular structures with dissymmetric shapes.[3,4] The supramolecular chirality, which results from both the properties and the way in which the molecular components associate, is by constitution dynamic and, therefore, examples of the large-scale transcription of such "virtual" chirality remain rare. Only a few reports describe the formation of artificial chiral supramolecular architectures from achiral templates such as molecular surfactants,[12–14] polymers,[15–17] or DNA.[18]

In this context, in the last few decades, the supramolecular macrocycle of four guanine (G) building blocks[19,20] and the similar folic acid quartet[21] have been proposed as powerful scaffolds for building synthetic supramolecular ion channels. The G-quartet, the hydrogen-bonded macrocycle formed by the self-assembly of guanosine, is stabilized by alkali cations.[19] The role of cation templating is to stabilize, by coordination to the eight carbonyl oxygen atoms of two sandwiched G-quartets, the G-quadruplex, the columnar device formed by the vertical stacking of four G-quartets. The G-quadruplex, with a chiral twisted supramolecular architecture, represents a nice example of a dynamic supramolecular system when guanine and guanosine molecules are used. It plays a very important role in biology, particularly in nucleic acid telomers of potential interest in cancer therapy.[19]

Only very recently, a successful new strategy involving a reversible polymerization process was described by Davis and co-workers to generate a rich array of interconverting ion-channel conductance states of a functional unimolecular G-quadruplex in a phospholipid membrane.[20] Polymeric guanosine hydrogels that can be reversibly interconverted between gel and sol states may by used for the synthesis of adaptative functional nanostructures.[22]

Many research groups have demonstrated that functional self-organization can be readily transcribed into hybrid nanostructures by using the sol–gel process.[23] Accordingly, we have reported a synthetic route for preparing self-organized ion-channel systems that have been "frozen" in a polymeric matrix, as a straightforward approach for the design of a novel class of solid hybrid membranes.[24]

For all of these reasons, in this study, the guanine building block is used as a molecular precursor to conceive hybrid chiral materials at the nanometric and micrometric scales. Our efforts involve the synthesis and self-assembly of a guaninesiloxane monomer, $\mathbf{G_{Si}}$, in the G-quartet and G-quadruplex supramolecular hybrid architectures. The main strategy consists 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 1).[19] 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. A sol–gel sample without potassium triflate, resulting in the formation of a layered structure with the guanine moieties regularly packed by H-bonding and stacking interactions, was prepared as a reference, under the same reaction conditions (Figure 1).

The $\mathbf{G_{Si}}$ derivative that was prepared for the studies described here[25] is based on two structural features: 1) molecular-recognition binding sites for the G-quartet formation are encoded in the guanine molecule and 2) the triethoxysilane groups are 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.

3-Isocyanatopropyltriethoxysilane was treated with N2-acetylguanine (dimethylsulfoxide, room temperature) to afford, after crystallization, $\mathbf{G_{Si}}$ as a white powder.[26] The generation of the G-quadruplex hybrid material can be achieved by mixing the $\mathbf{G_{Si}}$ derivative with potassium triflate in acetone and then performing the sol–gel process at room temperature with benzylamine as a catalyst. We also carried out sol–gel polymerization in the absence of K^+ ion templating; this resulted in the formation of a G-dimer hybrid material. Both hybrid materials were then calcinated at 400 °C in order to transcribe their superstructural features into the inorganic silica replica materials.

FTIR and NMR spectroscopic analyses of the products indicate the formation of a self-organized organic–inorganic network. The FTIR spectrum of the hybrid materials shows the appearance of broad vibrations of $\nu_{\text{Si-O-Si}} = 900\text{–}1200\ \text{cm}^{-1}$, instead of the vibrations of $\nu_{\text{Si-OEt}} = 950$, 1070, and 1100 cm^{-1} that were initially observed for the molecular precursor $\mathbf{G_{Si}}$. Evidence for H-bonding and K^+ complexation was obtained from the vibration shift of the C=O bonds, detected after the hydrolysis–condensation reactions: the $\nu_{\text{C=O}}$ band shifts from 1737 to 1699 cm^{-1}. This demonstrates that the self-organization is preserved in the hybrid materials throughout the sol–gel polymerization process. The ^{29}Si MAS NMR spectroscopy results are in agreement at this stage for both hybrid materials (which are prepared by using the same sol–gel conditions), with a partially condensated hybrid material (61.3 %), with only a low percentage of cross-linked T3 [C–Si(OSi)$_3$] (8 %) units and mostly composed of T1 [C–Si(OSi)(OH)$_2$] (24 %) and T2 [C–Si(OSi)$_2$(OH)] (68 %) units, showing a predominantly 2D arrangement. This indicates that the different self-

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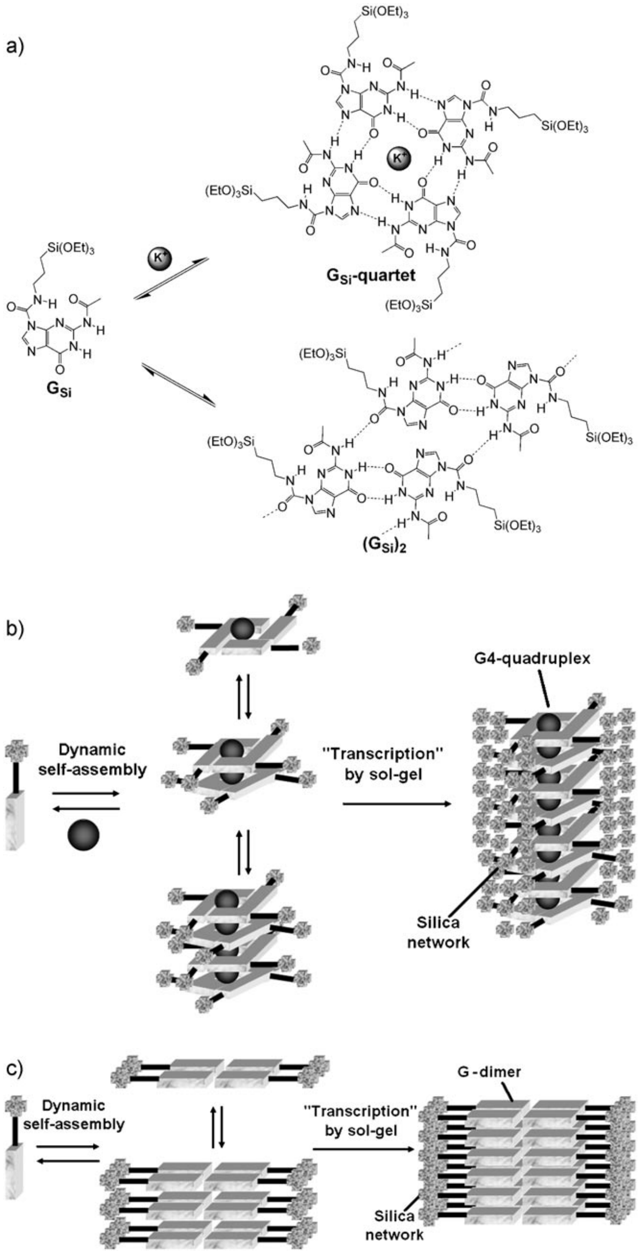

Figure 1. a) The cation-templated hierarchic self-assembly of guanine alkoxysilane gives the G-quartet. b,c) Representations of the transcription of the G-quadruplex into solid hybrid materials by a sol–gel process b) in the presence and c) in the absence of templating K$^+$ ions.

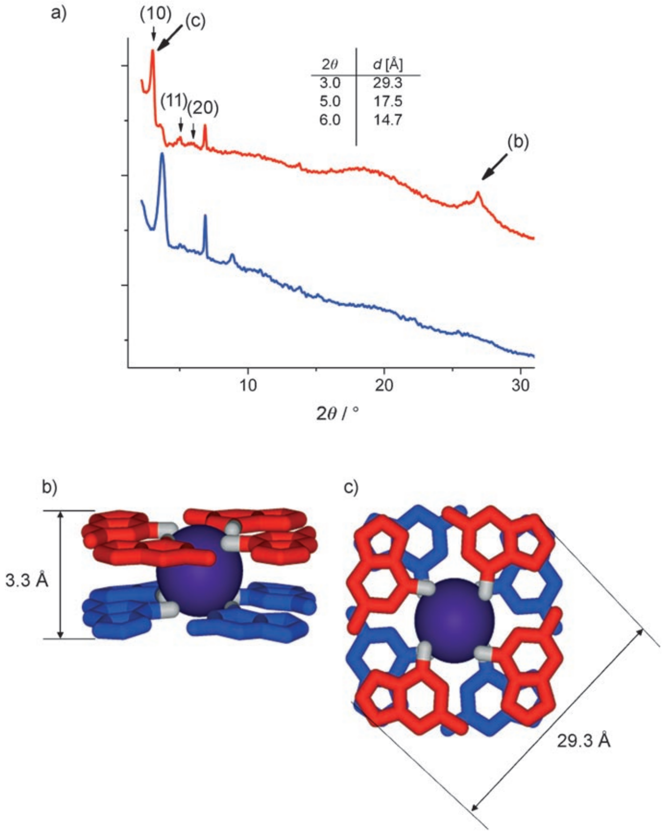

Figure 2. a) XRD patterns of nontemplated (blue) and K$^+$-templated (red) hybrid materials before calcination. b) Stick representation of the π–π stacking between planar G-quartets. c) Top view, in stick representation, from the crystallographic data.[27] (The K$^+$ ions are shown as spheres.)

assembly processes that occur in the presence or absence of the K$^+$ templating ions do not influence the hydrolysis–condensation reactions of the alkoxysilane groups during the sol–gel process.

Further insights on the structure and morphology of the hybrid materials were obtained by X-ray powder diffraction (XRPD). Figure 2a shows the XRPD pattern of the G-dimer hybrid material (blue). The Bragg diffraction peak at $2\theta = 3.5°$ corresponds to a characteristic distance $d = 25.2$ Å, compatible with the length of the $(\mathbf{G_{Si}})_2$ dimer, whereas the peak at $2\theta = 6.9°$ corresponds to a distance $d = 12.8$ Å, which is the monomeric length. In the G-dimer hybrid lattice, the $(\mathbf{G_{Si}})_2$ units pack into parallel ribbons of H-bonded dimers (Figure 1c). The XRPD pattern of the G-quadruplex hybrid (red) presents three well-resolved peaks in the range 2.5–6.5°, which can be indexed as the (10), (11), and (20) Bragg reflections, based on a two-dimensional hexagonal *p6mm* unit cell with $a = 33.9$ Å (Figure 2a); this result indicates that this hybrid material has a highly ordered hexagonal structure. The Bragg diffraction peak at $2\theta = 3.0°$ corresponds to a characteristic distance $d = 29.4$ Å, compatible with the diameter of the G-quartet superstructure. In the wide-angle region, an additional peak appears at $2\theta = 26.7°$, which corresponds to a distance $d = 3.3$ Å and is representative for the π–π stacking distance between two planar G-quartets (Figure 2b).

Scanning electron microscopy (SEM) reveals 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 seen in Figure 3a. Remarkably, these resulting hybrid structures are hexagonally twisted, presumably from being templated by the chiral hexagonal packing of the G-quadruplexes (Figure 3b,c).

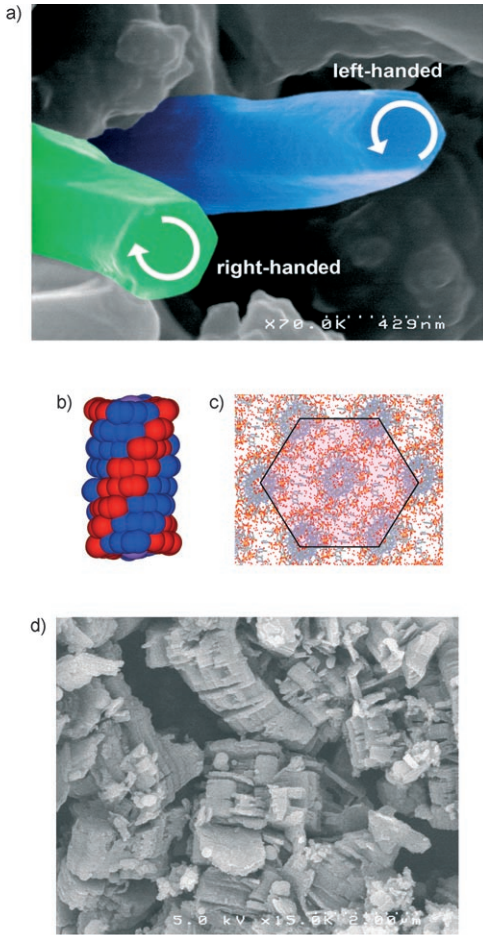

Figure 3. a) SEM image of the left- and right-handed twisted hexagonal nanorods resulting from sol–gel transcription of the chiral hexagonal G-quadruplex into the organic–inorganic hybrid material. b) Space-filling representation of the crystal structure of the G-quadruplex. c) Hexagonal crystal packing observed in the published crystallographic data.[27] d) SEM image of the G-dimer hybrid in the absence of any K$^+$ salt.

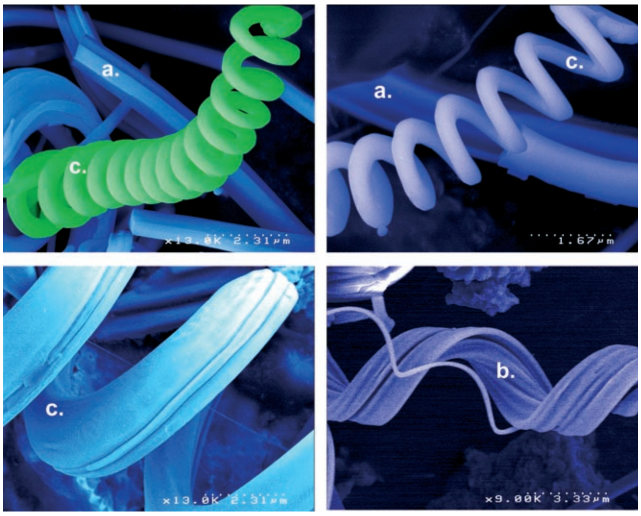

Figure 4. SEM images of silica a) nanofibers, b) nanobundles, and c) microsprings resulting from calcination of the hybrid nanorods.

Upon calcination of the G-quartet hybrid at 400 °C, a helical silica material is formed (Figure 4) and three kinds of morphologies can be recognized. Firstly, helical nanofibers with a thickness of 250 nm are observed. Secondly, helical nanobundles formed from individual nanofibers are found. The third morphology is the most interesting one: 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. Once again, the generated inorganic helix entities are observed to have distinguishable left or right chirality without inflection points. As expected, for the G-dimer hybrid prepared in the absence of any K$^+$ salt, the corresponding calcinated material is present in a less-ordered structure, as shown by SEM analysis (Figure 3 d).

The present results show the long-range amplification of the G-quadruplex supramolecular chirality into hybrid organic–inorganic twisted nanorods, followed by transcription into inorganic silica microsprings. We believe that, in the first sol–gel step, the polycondensation reactions of the inorganic alkoxysilane network take place around the tubular twisted superstructure of the G-quadruplex. In this way, the dynamic G-quadruplex is fixed in a covalently bonded siloxane network and a structural (constitutional) memory of the G-quadruplex is transcribed into the hybrid materials. These fixed (“frozen”) objects are chiral and self-correlate with a hexagonal order, as proven by XRPD experiments, to generate anisotropic mesophases interconnected through condensed siloxane bridges. These rodlike phases might have different dimensional features, depending on the concentration, sol–gel time, etc. We obtained a hybrid material featuring a twisted hexagonal rodlike morphology of about 2 μm in length and 350–850 nm in diameter by the sol–gel process. The mixture of these entities contains left- and right-twisted nanorods, as a result of the nonpreferential dissymmetric orientation of the G-quartets. The structures are chiral and no inversion centers have been observed within the same entity. Amazingly, these materials are, at the nanometric or micrometric scale, topologically analogous to the G-quadruplex supramolecular counterpart. Similar “communication processes” have been identified in DNA transcription into inorganic materials.[18]

After the sol–gel process, the preformed helical silica network probably has embedded enough chiral information to be irreversibly amplified (reinforced) during the calcination process, when almost total condensation of the Si–OH bonds occurs. By calcination of the hybrid material, the templating twisted G-quadruplex architectures are eliminated and inorganic silica anisotropic nanofibers, nanobundles, and microsprings are obtained. They present the same helical topology, without inversion inside the helix. These objects have a different helical pitch, which strongly depends on self-correlation between the hexagonal twisted mesophase domains at the nanometric level.

The assembly behavior of the G-quadruplex[19] and the transcription of structural information into polymeric,[2,4,5] hybrid,[18,24] and inorganic materials[23] have been amply described before. However, multicomponent chiral self-assembly of the dynamic G-quadruplex is difficult to preserve along long distances when guanine and guanosine molecules are used.

Our findings show a new way to transcribe the supramolecular chirality of a dynamic supramolecular architecture; the transfer of the supramolecular chirality of the G-quadruplex at the nanometric and micrometric scale is reported, with the creation of nanosized hybrid or microsized inorganic superstructures, respectively. Moreover, we obtain chiral materials by using an achiral guaninesiloxane, $\mathbf{G_{Si}}$, as a precursor of the achiral G-quartet and the chiral supramolecular G-quadruplex. Figure 2a represents the first picture of the dynamic G-quadruplex transcribed at the nanometric level; it opens the door to a new materials world paralleling that of biology. Finally, our results show a new way of embedding supramolecular chirality in materials, a process of interest for the development of a supramolecular approach to nanoscience and nanotechnology in working toward systems of increasing functional complexity.

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