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Self-Assembly of Viruses as Models for the Design of new Macromolecular and supramolecular architectures

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SELF-ASSEMBLY OF VIRUSES AS MODELS FOR THE DESIGN OF NEW MACROMOLECULAR AND SUPRAMOLECULAR ARCHITECTURES

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ABSTRACT

This paper reviews the principles of self-assembly of rodlike viruses, such as tobacco mosaic virus (TMV), and discusses with selected examples the strategy used in our laboratory to produce synthetic systems which self-assemble via related principles.

INTRODUCTION

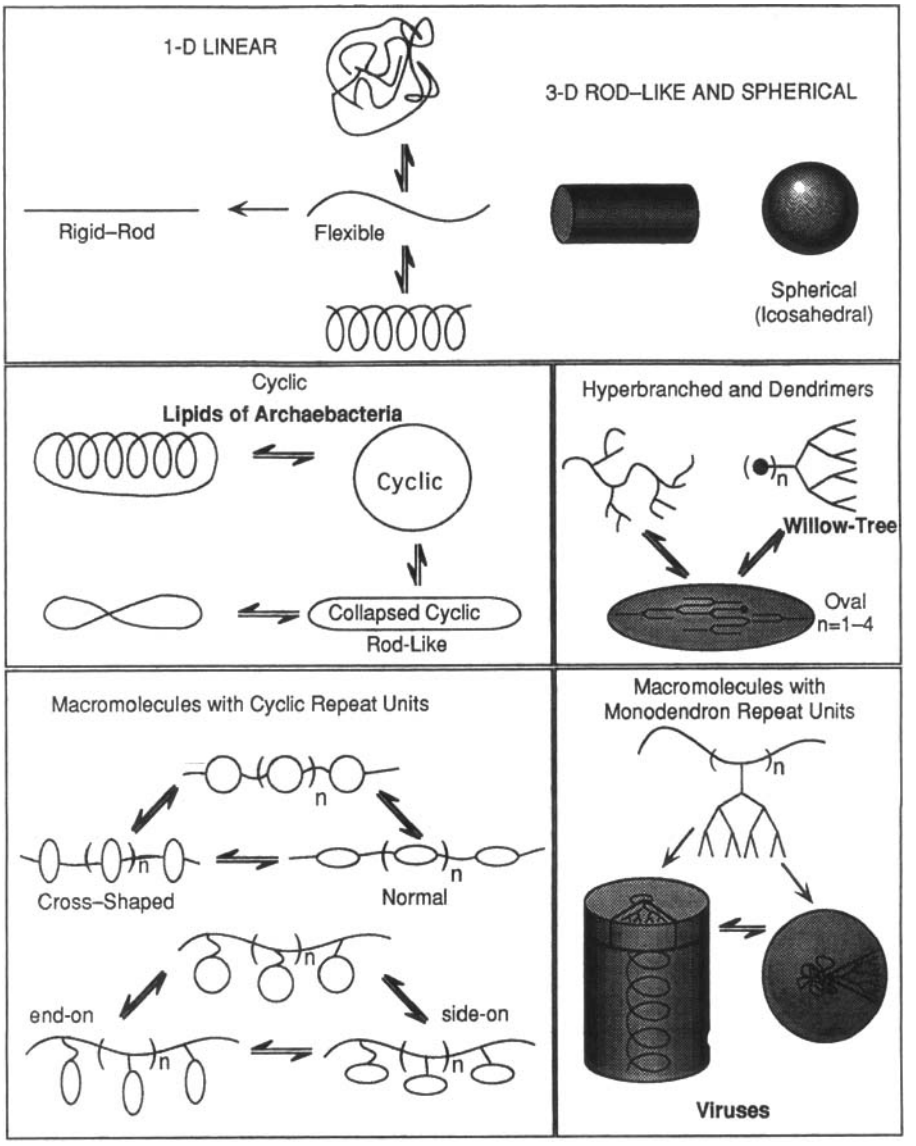
We are using Nature as a model to design novel molecular, macromolecular, and supramolecular systems with complex architecture which self-assemble into well defined 3-dimensional shapes. Complex molecular, macromolecular, and supramolecular architectures are abundant in Nature since they are responsible for the production of structural natural materials, and for the generation of some of the most efficient mechanisms of storage and transfer of energy and information (i.e., DNA, lipids, polysaccharides, proteins, and some complex systems which are based on them such as viruses, collagen, etc.).

Very little is presently understood about the molecular design and the influence of architecture on the mechanism of supramolecular shape formation and the properties of complex synthetic systems. For example, only a few primitive mechanisms are presently used to change the conformation of a linear polymer from statistical random-coil to extended (i.e., increased rigidity, helicity, and liquid

crystallinity). Our present efforts are directed to the molecular design, elaboration of synthetic methods, synthesis and characterization of well-defined and/or monodisperse linear, cyclic, branched, hyperbranched, and dendrimeric (macro)molecules with different rigidities and multiple preferred conformers, which form thermotropic and lyotropic liquid crystalline (LC) phases. These (macro)molecules are subsequently used as building blocks for the construction of even more complex macromolecular and supramolecular systems. For several reasons we have directed our present efforts to the design of systems which exhibit, besides crystalline and isotropic, also LC phases. Their synthesis is more challenging than that of amorphous compounds. Simultaneously, this additional complexity recompenses, since it provides a fast access to the determination of the "shape" of the resulted molecular, macromolecular, or supramolecular architecture with the aid of liquid crystallinity. Therefore, the final shapes we are aiming to are 1-dimensional rigid-rod, 3-dimensional rodlike, or tubular and spherical or icosahedral. 3-Dimensional rod and spherical shapes, as well as their distorted versions, can generate almost all assemblies encountered as ordered soft phases of block copolymers and as thermotropic, lyotropic, and amphotropic LC phases generated by synthetic and biological systems. Most of the complex natural systems, such as lipids, proteins and polypeptides, nucleic acids, viruses, and various mixed systems, also exhibit, for reasons which are not yet well known, liquid crystallinity. *Liquid crystals stand between the isotropic liquid phase and the strongly organized solid state. Life stands between complete disorder, which is death, and complete rigidity, which is death again.* This provides the driving force, at least for us, to devote a large research effort to the elaboration of molecular, macromolecular, and supramolecular liquid crystals with complex architecture by using Nature as a model.

Scheme 1 summarizes various research efforts which we are actively pursing in our laboratory. They range from the elaboration of synthetic methods for the preparation of poly(*p*-phenylene)s to be used as a model for the 1-dimensional linear rigid rod polymers [1–5], to the molecular design and the investigation of chain conformation in linear flexible polymers based on conformationally flexible mesogens [6–8]. *The macrocyclic lipids of archaebacteria membranes* were used as a model to discover that macrocyclic liquid crystals provide the most suitable molecular architecture which yields calamitic LC phases via their collapsed supramolecular quasi-rigid-rod structure [9–13]. These smart macrocyclic mesogens were used to design main chain and side chain liquid crystalline polymers (LCPs) with repeat units which know how to change their configuration from *side*-on to *end*-on in side chain polymers, and from *normal* to *cross*-shaped in main chain polymers [14]. Finally, we have used the *willow-tree* as a model to produce both hyperbranched polymers [15, 16] and dendrimers [17, 18] which collapse into rodlike shapes which generate calamitic LC phases.

The goal of this presentation is restricted to a brief discussion of our research on the use of rodlike viruses as a model for the self-assembly of 3-dimensional rod-shaped or tubular supramolecular architectures. A combination of molecular, macromolecular, and supramolecular [19] chemistry is used in these investigations. Viruses [20] are rod or spherical-shape self-assembled systems which represent some of the most challenging models Nature has provided us with to learn from. Tobacco mosaic virus (TMV) is the best understood rod-shaped virus [21] (Fig. 1). Viruses are the best examples of *exact* self-assembly. At the other extreme are micelles [22]



SCHEME 1. Well-defined shapes from complex molecular, macromolecular, and supramolecular architectures using Nature as the model.

which represent the most primitive models of self-assembly. This paper will discuss some of our recent efforts *on learning from the self-assembly of rod-shaped viruses, such as TMV*. Some brief definitions and the research strategy employed in these investigations will be described before a few selected examples will be discussed.

DEFINITIONS

Exo-receptors are bodies of similar size and shape or large external surfaces. *Exo*-recognition occurs by *surface-to-surface interaction* and, therefore, requires a

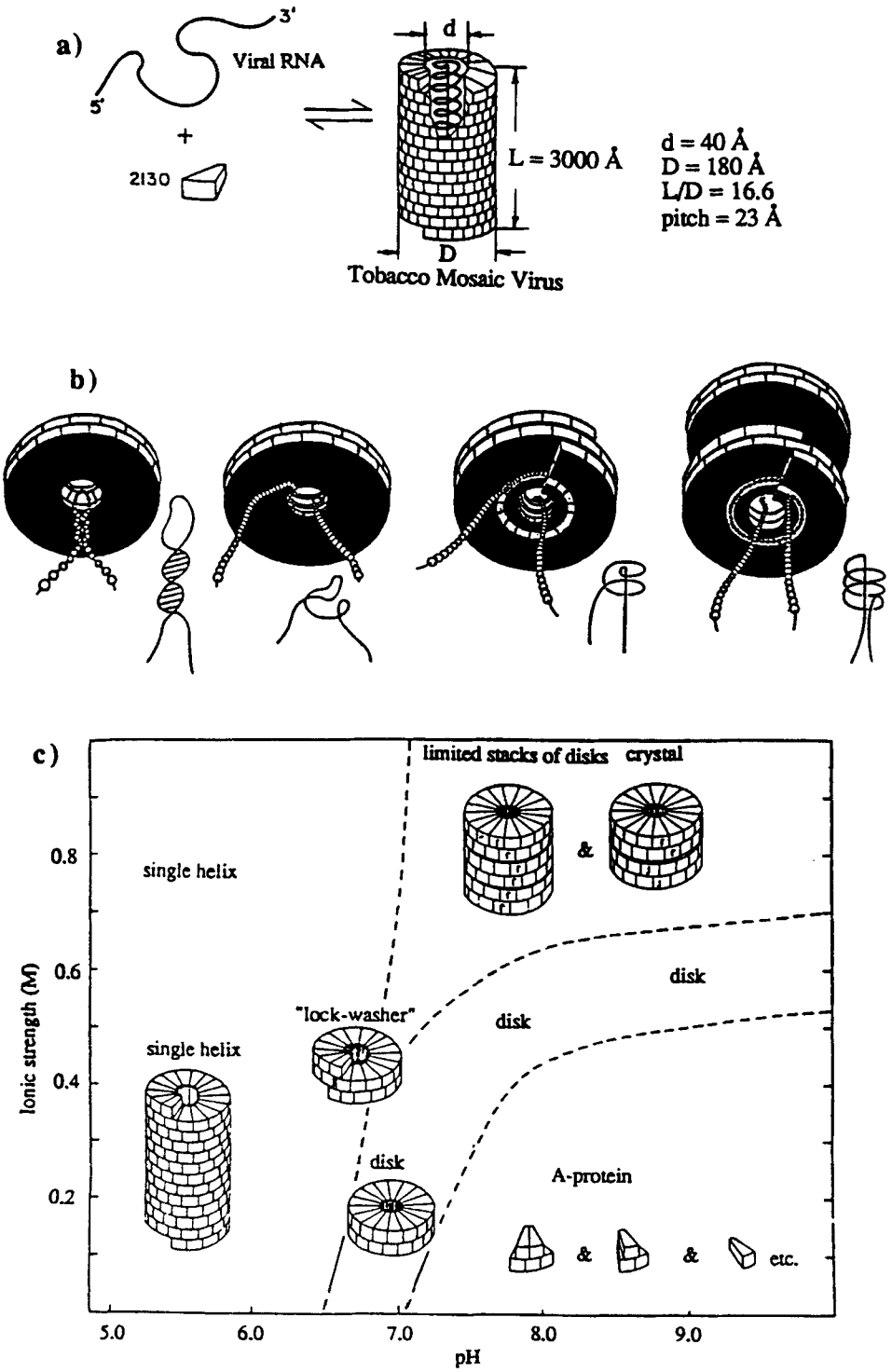


FIG. 1. The assembly of the tobacco mosaic virus: (a) from its constituent protein subunits and viral RNA into a cylindrically shaped tubular supramolecule; (b) the threading of the RNA in a hairpin conformation into a double layered disk of protein subunits initiating the change to a lock-washer conformation; (c) the dependence of the self-assembly of the protein subunits on pH (adapted from Refs. 21, 25, 30a, 32b, and 32c).

large enough contact area and a sufficient number of interactions as well as *geometrical* and *site complementarity* between surfaces. *Protein–protein* interactions, like for example at the *antibody–antigen* interface, function via these principles. Consequently, *exo*-recognition includes recognition between bodies of similar size as well as recognition at interfaces with monolayers, membranes, etc. *Endo*-receptors are *convergent cavities* such as crown-ethers, etc. Biological examples are the active sites of enzymes where a small substrate binds inside a cavity of a large protein molecule. An elegant description of *endo-* and *exo*-recognition processes was provided by Lehn [19, 23]. The construction of building blocks of well-defined shapes, i.e., *exo*-receptors, is a less developed area of chemistry than that of convergent cavities, i.e., *endo*-receptors. A very important lesson from biology is that of *quasi-equivalent* building blocks. *Quasi-equivalent* building blocks are chemically identical subunits which *self-control* their shape by switching between different conformational states [24].

Self-assembly is a *thermodynamically controlled process* in which molecular building blocks having all information required for self-assembly present in their components generate spontaneously a well-defined supramolecular architecture. Well-defined supramolecular architectures, in turn, may yield *supramolecular assemblies*. For example, rod-shaped supramolecular architectures such as those of viruses form *liquid crystalline assemblies*. Since the formation of a liquid crystalline (LC) phase is a *thermodynamically controlled process*, we are concerned with the self-assembly of those supramolecular shapes which at least in the first instance form a LC assembly. This assures that the formation of the supramolecular architecture takes place via a thermodynamically controlled self-assembling process. During the preorganization process an *extremely large entropy loss* should be balanced by an *exoenthalpic process*.

Both *endo-* and *exo*-receptors function via a delicate combination of very specific non-binding interactions, such as *electrostatic, H-bonding, hydrophobic, dipole–dipole*, etc. Even if each of these processes can *dominate* a certain self-assembling process, in most cases they are *complimentary* in function. The main role of the *endo*-receptor is to generate a very specific exoenthalpic interaction. However, in the case of the self-assembly of supramolecular architectures, the role of the *exo*-receptor is, besides that of providing a very specific exoenthalpic interaction, *to determine the 3-dimensional shape of the supramolecular architecture.*

An instructive way to envision the role of *endo-* and *exo*-receptors in the self-assembly is by comparing it with the role of the *bricks* and *cement* in construction. The *brick* plays the role of the *exo*-receptor and primarily determines the *shape* of the construction derived from it. However, the *size* of the brick and the *smoothness* of its surface determines the *strength* of the construction. Additional *strength* is provided by the cement which has a similar role with that of the *endo*-receptor.

STRATEGY

In the case of the self-assembly of TMV (Fig. 1), 2130 taper-shaped proteins (*exo*-receptors) self-assemble into a helical rod-shaped architecture with exact length and diameter [21, 25–27]. The taper shape of the protein (*exo*-receptor) is responsible for the rodlike shape of the self-assembled architecture. The electrostatic interac-

tions provided by the *endo*-receptor of the protein can be manipulated via pH and ionic strength or can be *templated* to a single chain of RNA [28]. More details of this mechanism of self-assembly are of no interest at the present stage. The *preorganization* process of this self-assembly consists of the generation of a disk based on 17 molecules of taper-shaped proteins.

Design

The synthetic strategy employed for the preparation of taper-shaped *exo*-receptors is based on the design of various monodendrons [29–32] via a convergent [33] synthetic approach. The first part of our research strategy consists in the *design* of building blocks which contain both a tapered *exo*-receptor and an *endo*-receptor, i.e., they are twin receptors. These building blocks should self-assemble first into supramolecular dislike shapes which in turn should aggregate into tubular supramolecular architectures. Tubular architectures are known to generate hexagonal columnar (Φ_h) liquid crystalline assemblies.

Characterization

We are exploiting the Φ_h liquid crystalline phase for three different purposes. First, it produces a very quick access to the shape of the supramolecular architecture generated from the self-assembly process. A thermotropic Φ_h phase can be recognized in a few minutes on a thermal optical polarized microscope. Second, it provides a mechanism to produce a thermodynamically controlled self-assembling process. Third, it generates a tool to determine the size of the supramolecular tubular architecture and, through it, provides access to the structural details of the column and the mechanism of self-assembly. A very fast access to the selection of a suitable tapered *exo*-receptor is obtained by replacing the *endo*-receptor of the building block with a polymerizable group. If the resulting oligomers and polymers generate a tubular supramolecular architecture which produces a Φ_h LC phase, it means that the tapered group is suitable for further experiments and its polymerizable group can be replaced with an *endo*-receptor. The evolution of the self-assembling process under different conditions can be estimated and analyzed by comparing the thermodynamic parameters of the Φ_h phase generated from supramolecular columns with established theoretical [34] and experimental [35] dependencies of various parameters of thermodynamically controlled phase transitions versus degree of polymerization (i.e., first-order transition temperatures, their corresponding enthalpy and entropy changes, and glass transition temperature versus degree of polymerization).

Assess Stabilities of the Supramolecular Columns

Almost identical supramolecular tubular architectures can be obtained from building blocks containing *exo*- and *endo*-receptors, or only tapered *exo*-receptors attached to polymer backbones. In the first case the *supramolecular* backbone has a *noncovalent* nature while in the second case it has a *covalent* nature. Therefore, the stabilities of various *supramolecular* backbones generated, for example, predominantly via H-bonding or electrostatic interactions, can be compared between themselves and also with that of a *covalent* backbone. At this point we should make the

clarification that the structure of a polymer containing tapered side groups which forms a *tubular shape* rather than a *statistical random-coil conformation* should also be considered a *supramolecular architecture*. In this particular case, the shape of the *exo*-receptor is responsible for the ultimate nonrandom coil shape adopted by this macromolecule. It is even more important at this point to realize that most probably, by analogy with the case of TMV [21, 25–27], polymers which penetrate through the center of a supramolecular column generated from their own tapered side groups either should have a rigid helical chain conformation that favors the assembly of its own tapered side groups into the tubular structure or, alternatively, the assembly of the tapered side groups into the tubular architecture will induce a helical chain conformation if the configurational restrictions and the flexibility of the backbone will allow it.

We will exemplify with some selected examples the principles of self-assembly summarized above. Tapered side groups containing *endo*-receptors such as crown ethers, oligooxyethylenes, and polymethacrylate backbone attached to the oligooxyethylene segment will be used for this purpose. Then we will demonstrate that the self-assembly of the least efficient tapered side-groups is enhanced by their attachment to a suitable rigid-helical chain conformation. Finally, we will provide an example in which the self-assembly of the tapered side groups of a conformationally flexible chain induces a flexible helical conformation of their own backbone.

SELF-ASSEMBLY OF 12-ABG AND 12-AG TAPERED GROUPS CONTAINING CROWN ETHERS

Figure 2 illustrates the self assembly of **12-ABG-B15C5** via complexation with MSO_3CF_3, where M is Na and K [30c, 32]. The plot in Fig. 2(b) presents the dependence of the hexagonal columnar (Φ_h)-isotropic ($T_{\Phi h\text{-}i}$) and glass transition temperatures as a function of the ratio of MSO_3CF_3/crown ether (mol/mol). The mechanism of this self-assembling process is also illustrated in Fig. 2. A very small amount of complexed metal salt overcomes the entropy loss required for the transition from a single taper-shaped molecule to a supramolecular column. This plot (Fig. 2b) can be considered a solid-state titration curve which follows the same trend as that of the dependence of the isotropization temperature versus degree of polymerization [34, 35]. This dependence suggests that during the complexation process a supramolecular backbone is generated and that its "degree of polymerization" increases with the increase of the amount of salt complexed. Alternatively, we can assume that the "persistence length" of this supramolecular column increases with the increase of the amount of salt complexed. This increase reaches a plateau at KSO_3CF_3/**12-ABG-B15C5** = 1.0 (mol/mol), while in the case of the complexes with $NaSO_3CF_3$ it continues to increase until it decomposes. This plateau is similar to that observed during the polymerization process and, therefore, it demonstrates that self-assembly can be compared with a conventional polymerization process.

Figure 3 summarizes the series of experiments which illustrate the dependence between the thermal stability and the diameter of a supramolecular column obtained from **12-ABG** and **12-AG** *exo*-receptors attached to **B15C5** [30c] and **15C5** [30d], respectively. The content of this figure is self-explanatory and is in line with that of the brick concept explained in the Definitions Section. For the same crown ether,

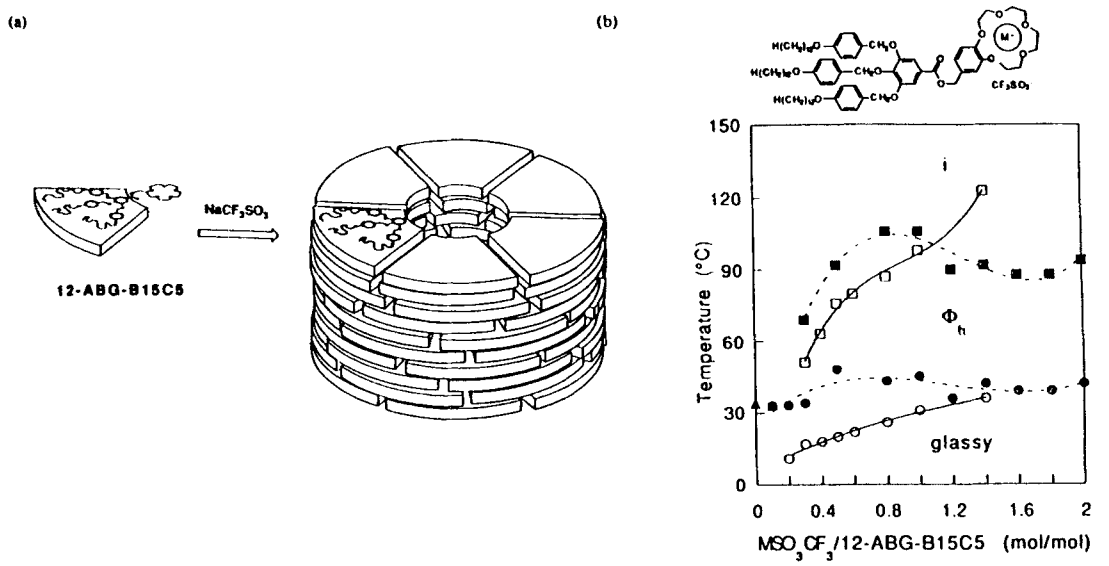


FIG. 2. (a) Schematic representation of the self-assembly of tapered structural units into tubular architectures exhibiting Φ_h mesophases. (b) The dependence of the phase transition temperatures of the complexes of **12-ABG-B15C5** with MSO_3CF_3 on the MSO_3CF_3/**12-ABG-B15C5** molar ratio. M = Na^+: (○) T_g; (□) $T_{i\text{-}\Phi h}$. M = K^+: (●) T_g; (■) $T_{i\text{-}\Phi h}$. All data were obtained from the cooling DSC scan at 20°C·min^{-1}.

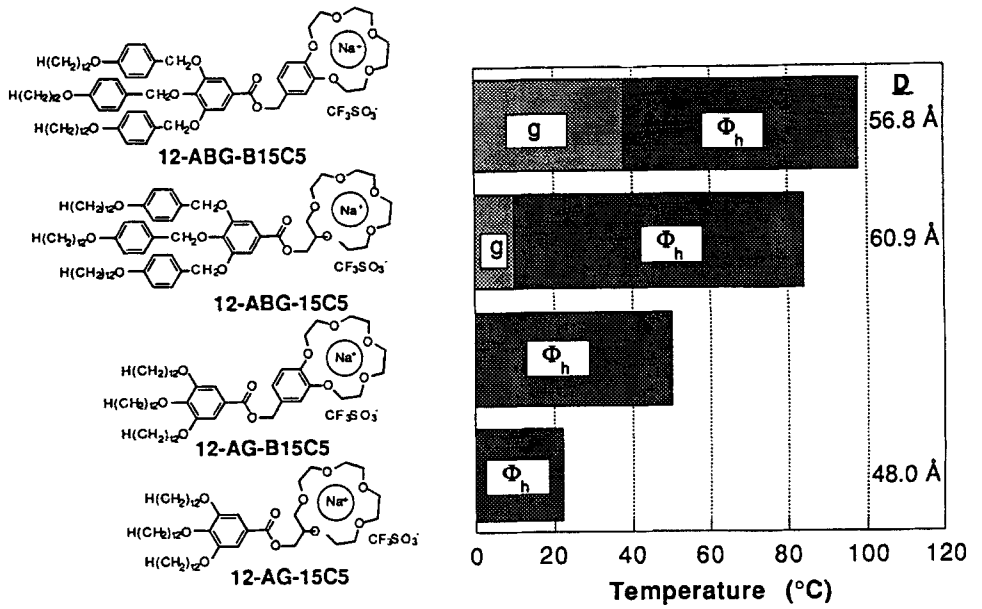


FIG. 3. Thermal transitions of the complexes with $NaSO_3CF_3$ of various tapered building blocks derived from crown ethers and the corresponding diameters, D, of the resulting tubular architectures. Data are obtained from the cooling scan at 20°C·min^{-1}.

the wider tapered group **12-ABG** provides a more suitable supramolecular architecture than that generated from **12-AG**. For the same reasons, **B15C5** attached to the same tapered side group, i.e., **12-ABG** versus **12-AG**, always creates a more stable supramolecular architecture than that generated by **15C5** attached to the same tapered groups.

SELF-ASSEMBLY OF 12-ABG, 12-ANG, AND 12-AG TAPERED GROUPS CONTAINING OLIGOOXYETHYLENIC SEGMENTS (nEO, n = 1–4) AND OF THE CORRESPONDING POLYMETHACRYLATES (12-ABG-nEO-PMA, 12-ANG-nEO-PMA AND 12-AG-nEO-PMA)

12-ABG-nEO-OH [30c] with $n = 1$ to 4 self-assembles into columnar architectures without the help of metal salt complexation. The replacement of the $-OH$ group of this series of tapered building blocks with $-OCH_3$ makes these molecules act like the corresponding **12-AG-B15C5** and **12-ABG-15C5**. However, the replacement of $-OH$ with a polymethacrylate backbone (i.e., **12-ABG-nEO-PMA**) produces supramolecular columns. As expected, the replacement of **ABG** from **12-ABG-nEO-OH** with **AG** yields **12-AG-nEO-OH** [30g] which does not self-assemble into supramolecular columns without complexation with metal salts. However, the corresponding polymers **12-AG-nEO-PMA** generate supramolecular columns.

Figure 4 compares the thermal stability (Fig. 4a) and the diameter (Fig. 4b) of the supramolecular columns generated from these systems and also from **12-ANG-nEO-OH** and **12-ANG-nEO-PMA** with $n = 4$. These results follow the same pattern as the one described in Fig. 3 for the cases of **12-ABG-B15C5**, **12-ABG-15C5**, **12-AG-B15C5**, and **12-AG-15C5**. A more detailed discussion of this behavior is available in the original publications [30]. A detailed investigation by x-ray diffraction experiments of the tubular supramolecular architecture generated from **12-ABG-nEO-PMA** suggests that during this self-assembling process a helical chain conformation is induced in the flexible backbone [31].

EVIDENCE FOR A BUILT-IN ERROR-CHECKING SYSTEM VIA CO-ASSEMBLY

Co-assembly experiments were performed on binary mixtures of **12-ABG-nEO-PMA** with different n, mixtures of **12-ABG-nEO-OH** with different n, mixtures of **12-ABG-n-EO-PMA** with **12-ABG-nEO-OH**, and of **12-ABG-nEO-OH** with **12-ABG-B15C5** [30h]. Since **12-ABG-nEO-PMA** self-assemble into individual columns with different diameters, only those columns which have very similar diameters, for example, based on $n = 3$ and 4 but not those based on $n = 1$ and 4, generate miscible polymers. This is due to the fact that miscibility of these polymers is determined by the ability of their supramolecular column to pack, i.e., be isomorphic, within the same hexagonal structure. However, **12-ABG-nEO-OHs** co-assemble within the same column due to the H-bonding interacting *endo*-receptors and therefore are miscible over their entire range of compositions. A small amount of **12-ABG-nEO-OH** mixes within the column of **12-ABG-nEO-PMA**, and this amount can be enhanced via complexation with a metal salt (Fig. 5). However,

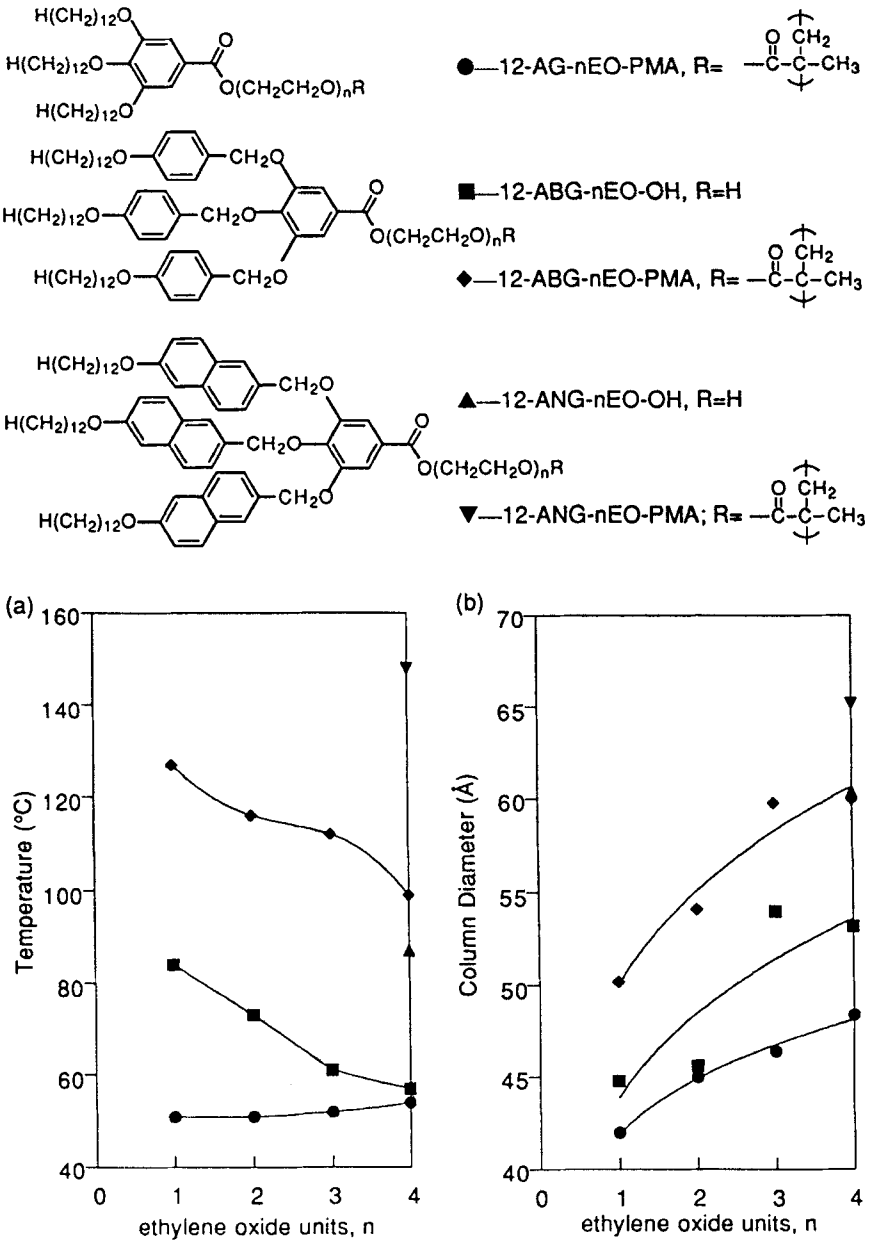


FIG. 4. The dependence of (a) the isotropization temperature and (b) the column radius on the number, n, of oligooxyethylenic units in the core of the assembly.

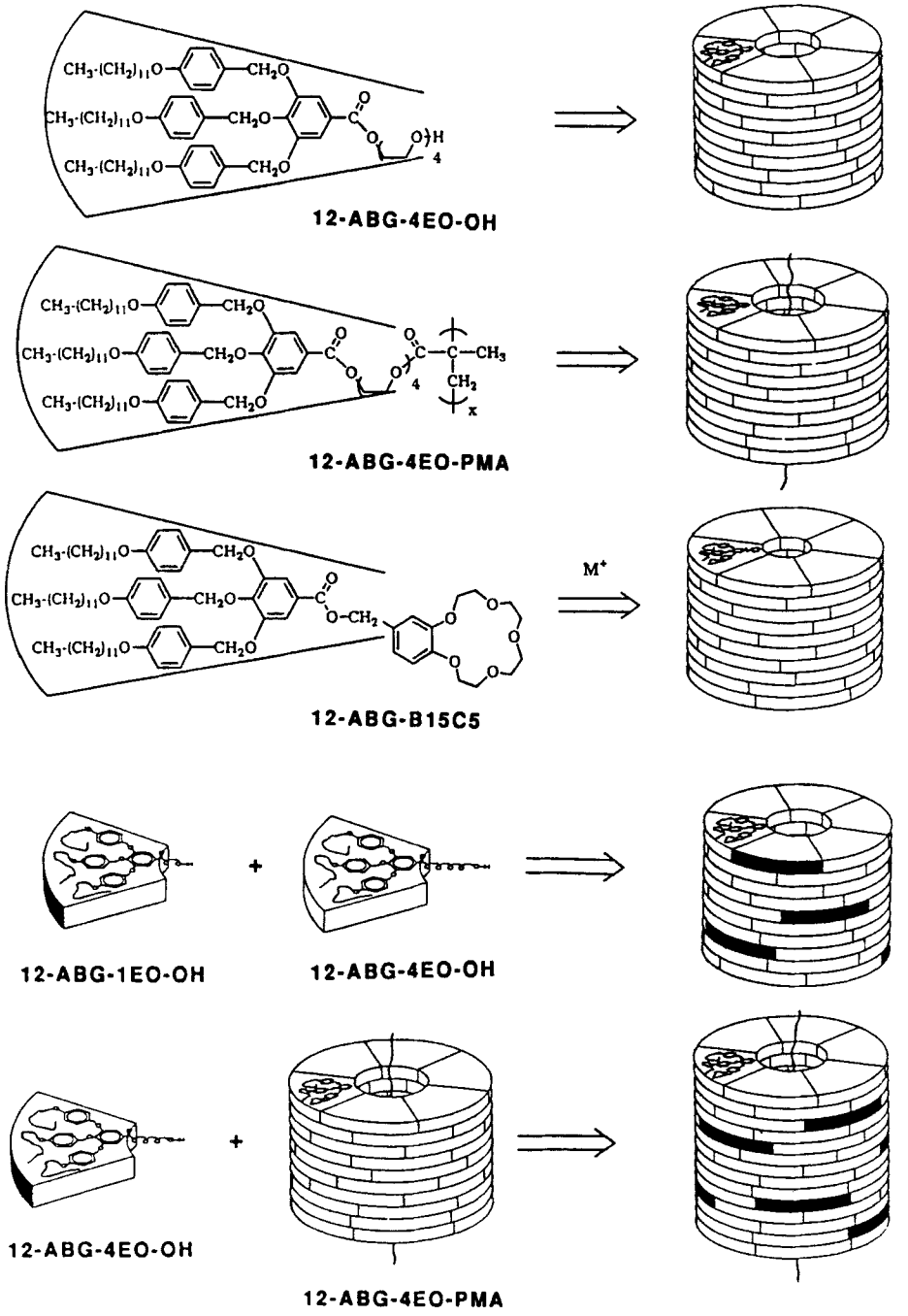


FIG. 5. Evidence for a built-in error-checking system via co-assembly of various binary combinations of **12-ABG-nEO-OH**, **12-ABG-nEO-PMA**, and **12-ABG-B15C5**.

12-ABG-nEO-OH and **12-ABG-B15C5** do not mix even in the presence of salts. Instead, each of these two components self-assembles into individual columns which are not isomorphic in their Φ_h phase. This is due to the difference between the complexation selectivity of the **B15C5** versus that of **nEO**. The former, being larger, consumes all the salt and generates columns exclusively based on **12-ABG-B15C5**. Only after this process is over is the column from **12-ABG-nEO-OH** formed. These experiments demonstrate that these self-assembling systems act like they have a built-in error-checking system which, in the examples described, is generated via their *endo*-receptor. Similar systems can also be generated via their *exo*-receptor.

EVIDENCE FOR HELICAL-CHAIN CONFORMATION FAVORING THE ASSEMBLY OF ITS 12-AG TAPERED SIDE GROUPS

The experiments described so far have demonstrated that **12-AG** tapered groups are the least efficient in this self-assembly process. The same experiments have suggested that in the case of flexible chain conformations of atactic polymers the tapered side groups should pay for the entropic penalty required to distort the chain conformation from a random coil to a helical one. Therefore, if a rigid helical chain which fits the packing requirements of the **12-AG** side groups into a supramolecular column replaces the flexible chain, the assembly process would have to be favored. Modeling experiments have shown that a *threo*-diisotactic poly(maleimide) containing **12-AG** side groups would have to contribute to the elucidation of this problem. *N*-Phenylmaleimide yields a 3/1 helical chain conformation regardless of the polymerization mechanism (radical or anionic) and also can be polymerized by a living anionic mechanism [36]. Figure 6 illustrates the synthesis of the

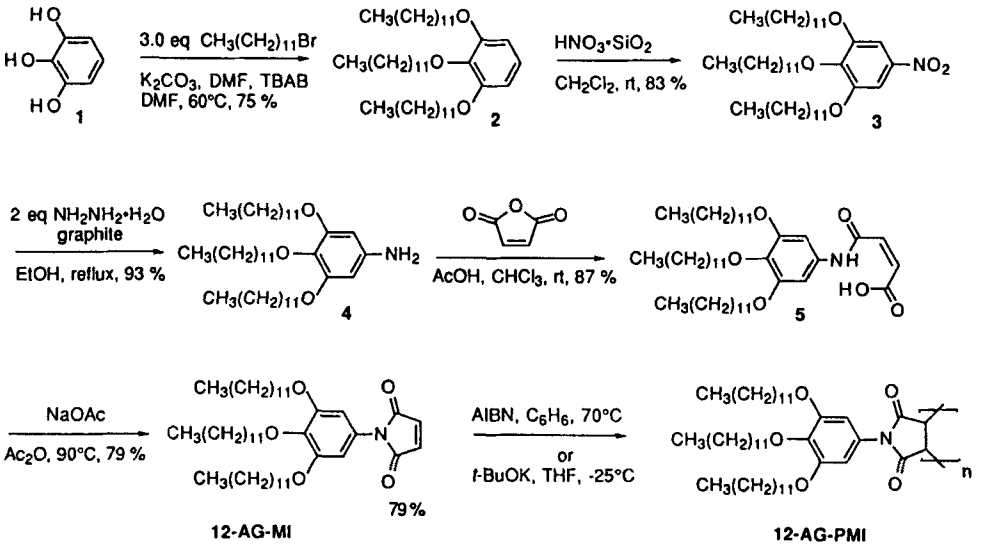


FIG. 6. Synthesis of **12-AG-MI** and of **12-AG-PMI** with *threo*-diisotactic chain conformation.

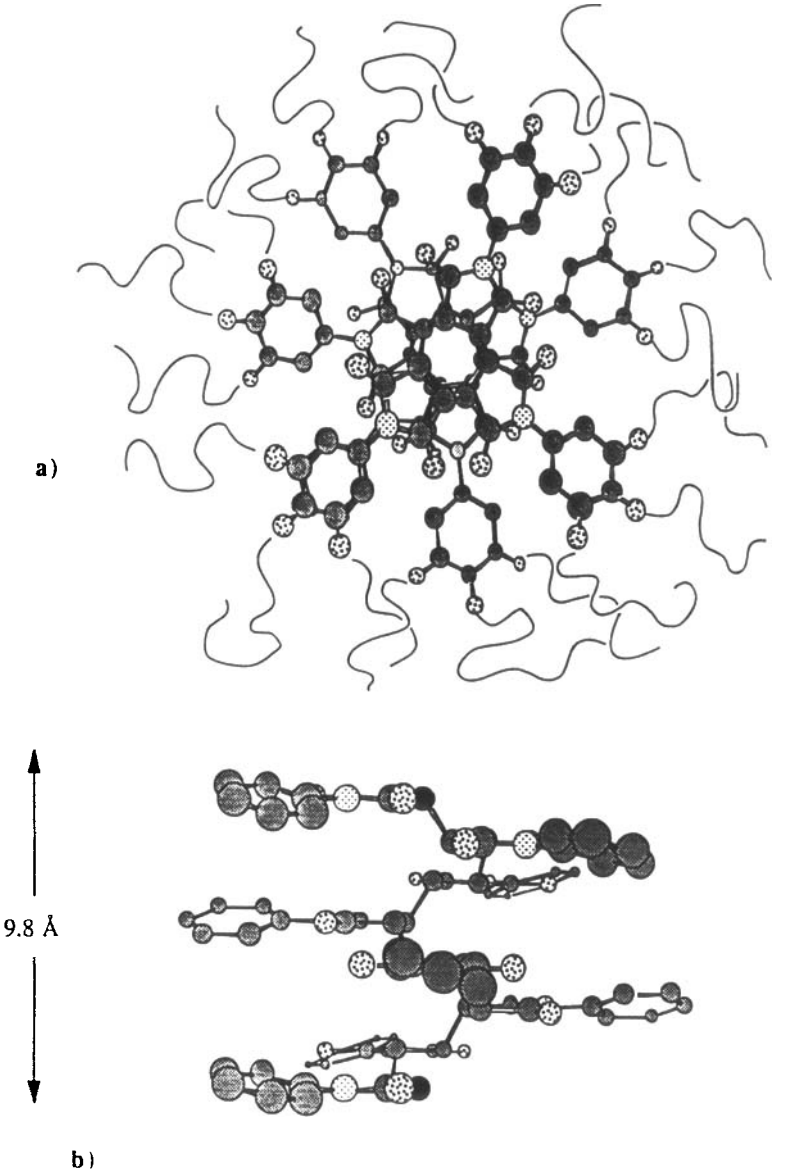


FIG. 7. Molecular model of a single chain of **12-AG-PMI** in (a) the top view of the *threo*-diisotactic 7/2 helical chain conformation and (b) the side view of the *threo*-diisotactic 7/2 helical conformation. In the top view the alkyl tails are schematically represented. In the side view hydrogens, lone pairs, and alkyloxy tails have been hidden for clarity.

12-AG-MI monomer and its polymerization [36]. As expected, the resulting polymer **12-AG-PMI** exhibits a Φ_h phase, and its structure, based on a 7/2 helical chain conformation, is outlined in Fig. 7. The stability of this Φ_h phase is higher than the decomposition temperature of **12-AG-PMI**. These series of experiments support the idea that a helical-chain conformation favors the assembly of their **12-AG** tapered side groups into a columnar architecture.

FLEXIBLE CHAIN CONFORMATION INDUCED VIA ASSEMBLY OF ITS 12-AG SIDE GROUPS

It has been suggested that poly{*exo,exo*-5,6-bis(disubstituted)-7-oxabicyclo-[2.2.1]hept-2-ene} derivatives have the ability to form a helical structure in solution with all the tetrahydrofuran oxygens facing into the interior of the helix [37]. Although a recent publication demonstrated that the above polymers adopt a coil conformation in solution [38], this does not demonstrate that they do not have the ability to form helical structures as originally suggested [37].

Figure 8 describes the synthesis of *exo,exo*-5,6-bis[3,4,5-tris(*n*-dodecan-1-yloxy)benzoate]-7-oxabicyclo[2.2.1]hept-2-ene (**12-AG-OBH**) and its polymerization by ring-opening metathesis to the polymer **12-AG-POBH** containing 37.3%

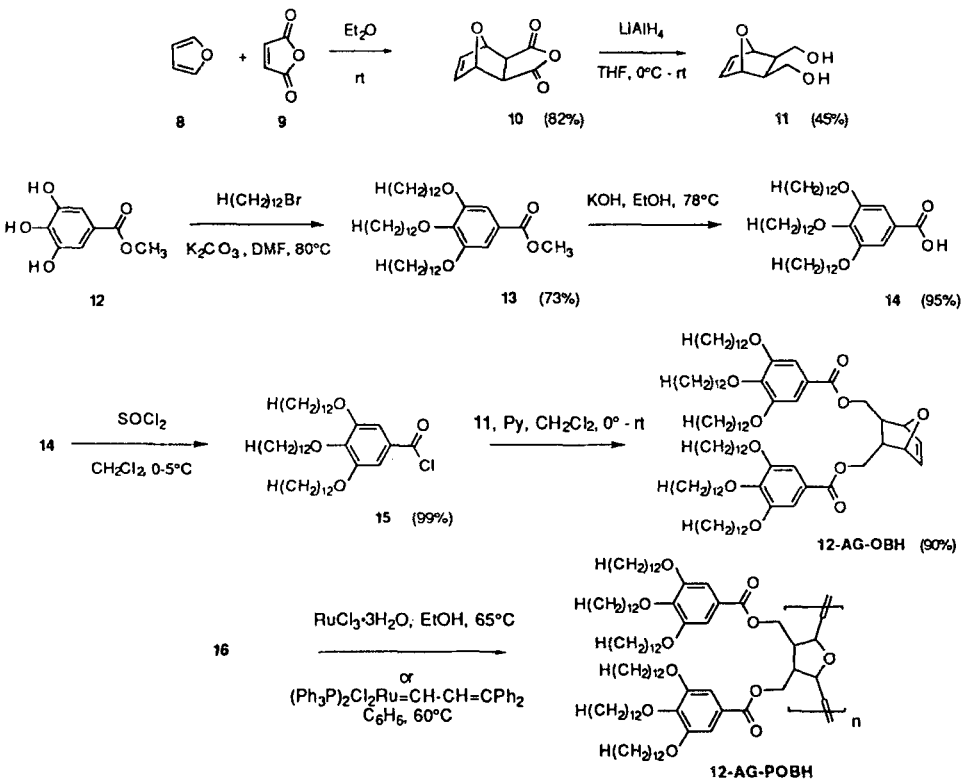


FIG. 8. Synthesis of **12-AG-OBH** and of **12-AG-POBH**.

cis and 62.7% *trans* repeat units. This polymer does display a Φ_h phase, and its characterization by x-ray diffraction experiments demonstrates that the most probable chain conformation is the 3/1 helical structure outlined in Fig. 9. This experiment demonstrates that the assembly of the two **12-AG** tapered side groups of **12-AG-POBH** into supramolecular columns induces the 3/1 helical chain conformation of its own backbone [36].

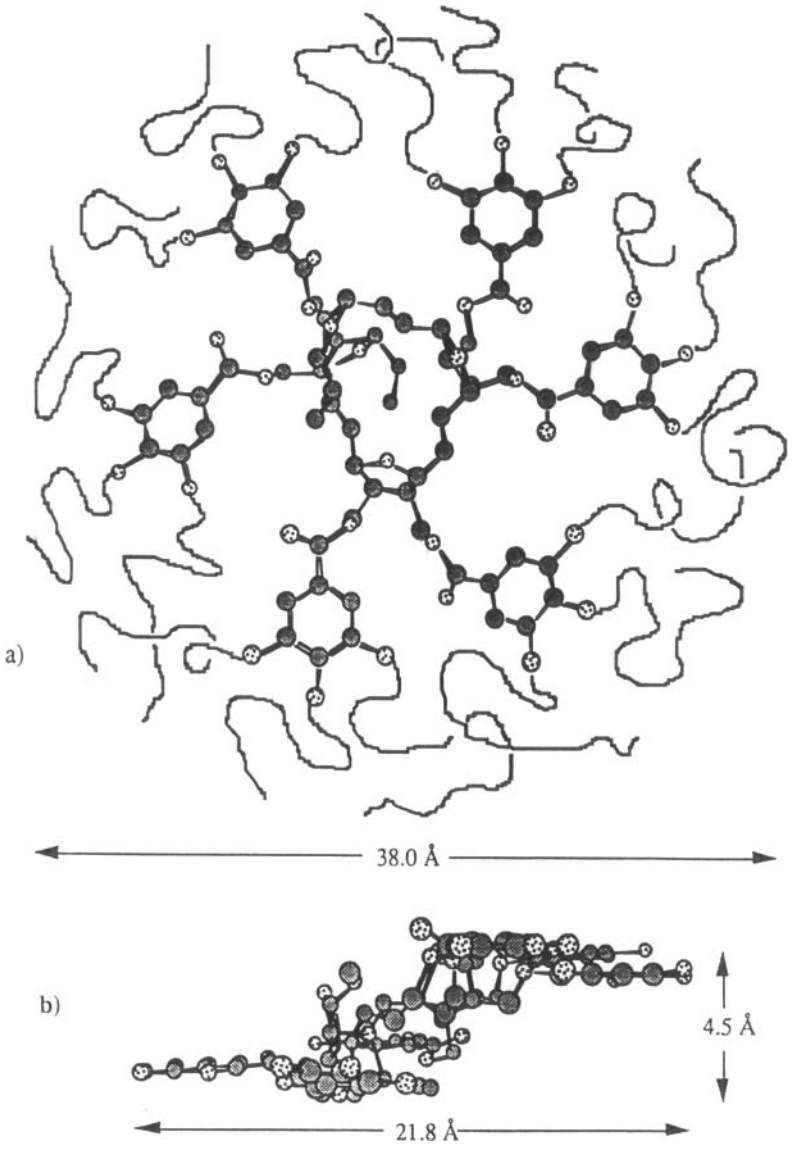


FIG. 9. Molecular model of a single chain of **12-AG-POBH** in (a) the top view of the 3/1 helical chain conformation and (b) the side view of the 3/1 helical conformation. In the top view the alkyl tails are schematically represented. In the side view hydrogens, lone pairs, and alkyloxy tails have been hidden for clarity.

CONCLUSIONS

The very few experiments summarized in this paper demonstrate the rich variety of lessons which synthetic chemists can learn from Nature. 3-Dimensional tubular structures, which exist in the solid-state and melt phases, can be tailor-made with diameters between 20 and 70 Å via principles which we learned from viruses. Deleting the **nEO** group of **12-ABG-nEO-PMA** of Fig. 4 yields a 3-dimensional tubular structure from a single chain polymer which is also stable in dilute solution. This polymer has a persistence length higher than that of the 1-dimensional rigid-rod poly(*p*-phenylene)s. This preliminary result demonstrates that, as predicted theoretically [39] and demonstrated by TMV [40], a *truly rigid-rod polymer cannot be made by a 1-dimensional chain* but by a 3-dimensional supramolecular tubular structure which is much less prone to bending fluctuations than the 1-dimensional poly(*p*-phenylene). Thus, for the first time, through our work on poly(*p*-phenylene)s [1-5, 41] and on supramolecular tubular shapes, we provided access to 1-dimensional rigid-rod and 3-dimensional rodlike systems. Presently these supramolecular tubes are being exploited for the molecular design of a new generation of membranes [42]. However, in the near future we foresee that noncovalent binding of ionic natural and synthetic polymers in the center of our supramolecular columns will find biomedical uses. Research on spherical supramolecular assemblies will be reported shortly.

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