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Supramolecular liquid crystallinity as a mechanism of supramolecular polymerization

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Two types of supramolecular self-assembling polymers should be distinguished: the open type characterized by units with binding sites exposed to the surface and thus capable of extended growth (e.g. some synthetic and natural supramolecular polymers), and the closed type with binding sites internally compensated yielding well defined oligomeric complexes (e.g. DNA, collagen, haemoglobin). The growth of the open assemblies may be defined as a supramolecular polymerization. Both types form corresponding supramolecular liquid crystalline (SLC) phases, but the behaviour of the closed-type SLC is generally indistinguishable from that of liquid crystals formed by molecularly dispersed units. Quite different is the case of the open-type SLC when the anisotropic forces stabilizing the nematic phase interact with the contact forces that promote the growth of the assembly. In this case a cooperative enhancement of growth occurs simultaneously with the formation of the ordered phase. The theoretical basis for the growth coupled to orientation mechanism, laid down to explain the formation of linear micelle aggregates, may apply to most types of supramolecular polymerization. Outstanding resulting expectations are a large degree of supramolecular polymerization, orientation, superimposition of other growth mechanisms, dampened polydispersity and termination steps.

1. Introduction

It was probably Lehn [1] who was the first to refer to a supramolecular liquid crystal (SLC) as a system formed by units capable of self-assembly into long supramolecular particles forming liquid crystalline solutions or melts. He described supramolecular polymers based on rigid anthracene segments terminated by either uracil or pyridine residues (cf. figure 1) characterized by triply H-bonded joints and reported to display lyotropic mesophases. Other polymers based on less rigid units capable of main chain multifunctional hydrogen bonding instead showed thermotropic behaviour [2]. Lehn suggestively referred to the SLC as a 'macroscopic expression of molecular recognition'. The purpose of this note is to analyse critically, in terms of existing theory, the implications that supramolecular liquid crystallinity has in the assembly of linear functional structures of both biological and synthetic origin.

2. Definitions

Consistently with the above description of the SLC, it is appropriate to define a liquid crystal formed by unassociated (molecularly dispersed) units as a *molecular liquid crystal* (MLC). To be sure, MLCs include a supramolecular component in the form of soft [3] or hard [4, 5] anisotropic attractive interactions known to

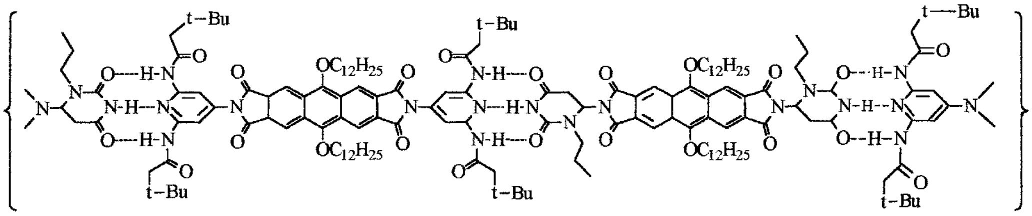

Figure 1. A rigid synthetic supramolecular polymer of the open type based on anthracene segments terminated by uracil or pyridine residues. The chain has a structure of the AABBAA…type stabilized by a system of triple H-bonds. Cooperativity occurs within each triplet of H-bonds, but does not affect binding of successive units.

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be the prevailing stabilizing forces for thermotropic and lyotropic systems, respectively [6] (see figure 2A). For the SLC, however, the *contact* attractions which stabilize the assembly (see figure 2C) and originate from the more familiar supramolecular interactions (H-bonds, charge transfer, amphiphilic, segregation…) [7, 8], also need consideration.

Two types of supramolecular assembly, both capable of forming liquid crystalline phases, need to be defined. The first case (see figure 2B) is that of stable or *closed* assemblies which have internally compensated, strong contact interactions, but have no or only weak residual attractive interactions over the particle surface. Examples are DNA [9], scleroglucan [10], and some synthetic polymers [11, 12] such as poly(*p*-benzamide) [11], forming assemblies which have a discrete number of units (respectively 2,3,7). No further association–dissociation equilibria accompany the isotropic–liquid crystalline transitions for these assemblies. Their liquid crystalline behaviour, known before the current emphasis on supramolecular polymers, is properly described in terms of MLC theory using the geometrical parameters of the assembled particle without a need to account otherwise for contact interactions.

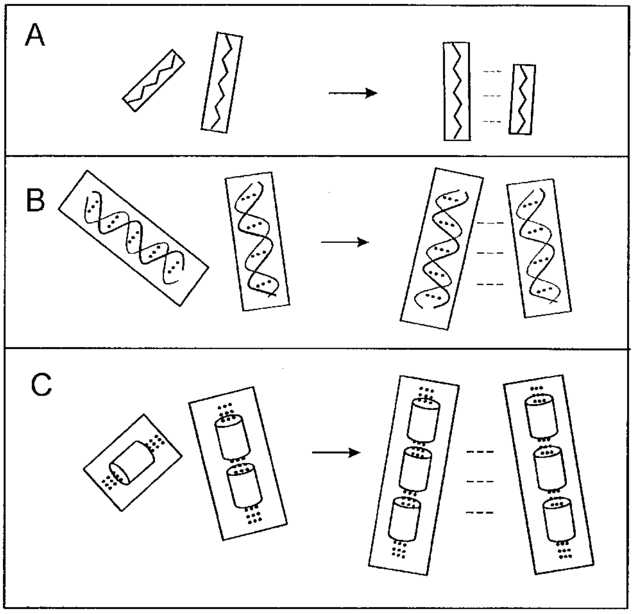

Figure 2. The transition from the disordered isotropic state (left) to the oriented, nematic state (right) for A: molecularly dispersed polymers, B: supramolecular polymers of the closed type, C: linear supramolecular assemblies of the open type. --- represents the anisotropic attractive interactions that stabilize the nematic phase; ··· represents the contact interactions that stabilize the assembly. The two types of interactions are uncoupled for the closed type (B) supramolecular liquid crystal. Coupling of the two interactions for the open type SIC (C) causes growth simultaneously with orientation.

The distinctive features of the SLC become evident when association–dissociation equilibria, or alterations in the shape and organization of the assembled particle, occur during mesophase formation. Representative of this type of system is the case of the supramolecular polymer in figure 1, or the case of micelles [13] (see figure 2C). In these instances, the supramolecular assembly may be defined as of the *open* type and a detailed consideration of the coupling between contact and soft/hard anisotropic attractions becomes necessary.

Irrespective of the formation of a liquid crystalline phase, an open supramolecular polymer is capable of indefinite growth, a process which can be defined as a *supramolecular polymerization* and may produce not only linear sequences (as in figure 1) but also planar or three-dimensional structures.

Linear supramolecular polymerization, which will alone be considered here, is vastly different from conventional *molecular polymerization* due to the different strength of the main chain bonds and the type of repeating units (complex, even polymeric units for the former, low molecular weight bifunctional residues for the latter, see figure 3). Nevertheless, some concepts and questions which are relevant in molecular polymerization need to be considered also in its supramolecular counterpart. In particular: how large will the supramolecular polymer grow, how wide will its polydispersity be, will there be a termination step, and what will the polymerization mechanism be?

3. Polymerization mechanisms

To shed light on the above questions, recourse can be made to existing theory describing the coupling between linear growth and an Onsager-type nematic order which was first presented by Gerbart *et al.* [14] to interpret the assembly of micelles into linear particles. The theory predicted that unlimited linear growth, accompanied by extreme fractionation, was cooperatively triggered at the onset of the isotropic to nematic transition. The mechanism was revised by Odijk [15, 16] who recognized that the partial flexibility of the linear assembly decouples its growth in the nematic phase. Further analysis by van der Schoot [17] focused on the effect of flexibility on the interplay between growth and orientation. Hentschke

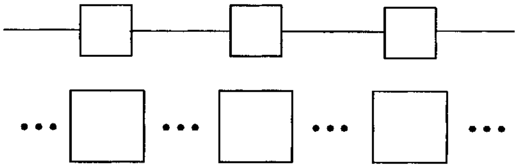

Figure 3. Scheme for molecular (small units, strong covalent bonds) and for supramolecular (large units, weak secondary bonds) polymerizations.

[18] expanded the theory including columnar ordering, and used it for interpreting the phase diagram [19] of a discotic amphiphile.

These theories retain the characteristic components of the free energy density of a lyotropic MLC (F_{ster}, F_{E}, F_{el} representing, respectively, the hard and soft interactions and the flexibility of the molecular chain). Adding an F_{intra} term to account for the internal stabilization of the assembled particle, the free energy of the micellar or amphiphilic nematic can thus be approximated as [15–19]:

$$F^{\mathrm{S}} = F^{\mathrm{S}}_{\mathrm{ster}} + F^{\mathrm{S}}_{\mathrm{E}} + F^{\mathrm{S}}_{\mathrm{el}} + F^{\mathrm{S}}_{\mathrm{intra}}. \qquad (1)$$

Detailed calculations provide the analytical dependence for the increase of the length of the aggregate with the contact energy. At a critical volume fraction v^* of free units, liquid crystalline order occurs simultaneously with a sudden growth to a limit controlled by the extent of semiflexibility.

Semiflexibility in the isotropic state is characterized by the ratio L_{i}/q of the length L_{i} attained by the particle just before the nematic transition occurs to its persistence length q, (both quantities are normalized by the chain diameter). In the nematic state, the onset of semiflexibility is instead related to the ratio L_{N}/λ of the growth length L_{N} to its deflection length λ. The latter is smaller than the persistence length (15, 18):

$$\lambda \approx q/\alpha \qquad (2)$$

where α, which is larger than unity and increases with concentration, is a parameter inversely related to the width of the angular distribution of tangent vectors along the contour of the aggregate which is deflected toward the director of the nematic field [15–19].

The author of this note has already suggested [20] that the above theory does not need to be restricted to amphiphilic compounds and may indeed represent a general approach to the supramolecular assembly of open linear systems, both synthetic (e.g. figure 1) and natural systems. It seems appropriate, however, to clarify how the above mechanism of growth coupled to orientation relates to the generally accepted growth mechanisms described in the literature for open assemblies.

The latter mechanisms typically involve: (i) the identification of the chemical groups responsible for supramolecular recognition of the basic units, and (ii) the description of their linear growth in terms of successive binding steps with or without intra-particle cooperative effects. In terms of multistage open association theory (MSOA), if all accretive steps (units→dimers→oligomers…) are treated as independent events characterized by identical equilibrium constants K, one obtains the following dependence of the average molecular mass $\langle M \rangle$ of the assembly upon the concentration C of free basic units having molecular mass M_0 [20–22]:

$$C \approx (M_0/KN_{\mathrm{A}})(\langle M \rangle/2M_0)^2 \qquad (3)$$

N_{A} being the Avogadro number. The value of K controls the extent of growth. If each unit recognizes and binds to the next through a contact standard free energy change of $\approx 34\,\mathrm{kJ\,mol^{-1}}$ (a strong H-bond), equation (3) predicts that growth is severely limited. At the relatively large concentration of $0.01\,\mathrm{g\,ml^{-1}}$ of basic units, the average $\langle M \rangle$ corresponds to trimers, and there is a size distribution (even in molecular polycondensation the relatively low values of K are known to preclude the attainment of large $\langle M \rangle$ under equilibrium conditions).

Multiple interactions and cooperative effects are known to occur in several biological assemblies and would amount to larger association constants. For instance, during the first stage of fibrin polymerization, trombin uncovers two (A type [23]) binding sites on the central domain of fibrinogen. To these sites, two terminal domains of two similar units may bind causing linear, cooperative growth (figure 4) [23, 24]. It is to be noted that the diagram in figure 4 conforms to the cooperative growth model due to Oosawa and based on the occurrence of a repeating 'nucleus' composed of three or four monomers [25]. It was suggested that Oosawa's theory explains the formation of the long linear assemblies (in the μm range) formed during the G→F transformation in actin. This model for intraparticle cooperative growth cannot however be applied to supramolecular polymers characterized by a simple head-to-tail sequence of repeating units.

Alternative growth mechanisms that naturally account for large values of $\langle M \rangle$, for length termination steps and for sharp distributions are also known. These are however restricted to the occurrence of a polynucleotide template. Tobacco mosaic virus, for instance, has a cylindrical geometry with length = 300 nm, diameter = 18 nm, and a centre hole with diameter = 4 nm. The hole hosts a single RNA molecule, while 2130 identical proteins ($M_0 \approx 20\,000$) form the outer layer helicoidal assembly having 16.3 units per turn. The system can be disassembled and reassembled *in vitro* with or without RNA. However, without RNA it reassembles into

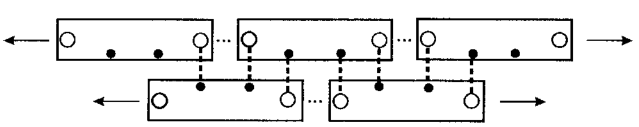

Figure 4. Scheme for the assembly of fibrinogen residues during the early conversion to linear fibrin filaments. To the A sites (●) uncovered by trombin on the central domain of each residue, two terminal sites (○) of two similar residues bind with strong interactions [23]. A weaker terminal-to-terminal attraction was also recently discovered [24]. Cooperative growth ensues.

polydisperse stacks of disks each composed of 17 units [26]. Two assembling mechanisms can therefore be suggested. The helical arrangement, the cut-off length and the lack of polydispersity are controlled by self-assembly over the RNA template. However, the lateral and longitudinal distribution of interacting sites on the protein units, as well as their shape, are designed for the self-assembly of the cylindrical outer layer.

4. Features of growth coupled to orientation

At variance with the above cases, no specific knowledge of the chemistry of the binding sites and of intra-particle cooperative effects is essential to the mechanism of growth coupled to orientation. The latter relies only on a cooperative effect resulting from a generic interplay between inter- and intra-particle interactions, modulated by a geometrical parameter related to the persistence length. It is therefore a general mechanism of a fundamental character and the analysis of its expected features can thus be schematized.

4.1. *Assembly size*

The persistence lengths of linear micelles and protein assemblies attain values above the 20 μm range [15, 27, 28]. Deflection lengths, equation (2), can thus attain dimensions in the order of 1 μm. When these values are compared with the largest persistence lengths reported [29] for molecular polymers (10–100 nm) it appears that assemblies growing at the critical volume fraction can easily reach dimensions one order of magnitude larger than molecules known to form molecular liquid crystals [29]. The theory [15–19] predicts that the critical volume fraction will be in the accessible range provided the flexibility of the assembly is not too large, in which case the nematic phase may be suppressed. The evaluation of the persistence length for supramolecular polymers is a subject that needs extensive investigation. Large persistence lengths are to be expected for assemblies based on units that are intrinsically rigid and are coupled by strong multifunctional contacts capable of cooperative interactions (in the case of figure 1, the three hydrogen bond scheme has a localized cooperativity, while the scheme in figure 4 shows a cooperativity favouring the addition of neighbouring units).

4.2. *Orientation*

As it polymerizes, the supramolecular polymer also attains a high degree of orientational order due to the simultaneous formation of the SLC. Order parameters have been shown to increase with the persistence length of the assembly [17].

4.3. *Superimposition of growth mechanisms*

A superimposition occurs between growth according to the MSOA theory and growth coupled to orientation. The point is illustrated in figure 5 schematizing the expected variation of the length of the growing assembly as a function of the concentration of free units. The growth curves shown in the range $v < v^*$ correspond to increasing values of the association constant in equation (3). Even if an assembly can grow to a considerable size ($L < q$) by virtue of the association constants, eventually a further sudden increase of length is observed when the SLC appears at v^*.

4.4. *Polydispersity*

While according to MSOA theory a size distribution must occur, a tendency to dampen polydispersity can be read into the theory of growth coupled to orientation. Pending a detailed theoretical assessment of the actual distribution [30], a main factor to be considered is that the parameters that limit growth, persistence or deflection lengths, do not exhibit a size distribution (as is known to be the case for the mean dimensions of a gaussian chain). A general feature of excluded volume treatments that applies to both MLCs and SLCs is that the critical volume fraction is inversely related to the axial ratio of the particle. Therefore, the particle which grows when the concentration is increased up to the critical value v^* is necessarily the one with the largest possible axial ratio which, for semiflexible chains, is expressed in terms of the persistence length [6]. While the latter does not depend upon concentration, the deflection length, equation (2), does; this suggests that a decrease of length may occur at $v > v^*$.

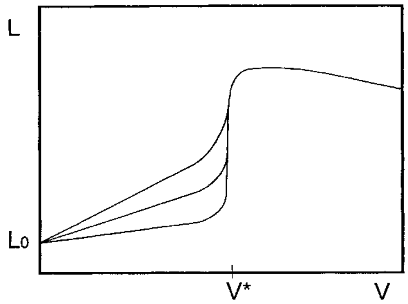

Figure 5. Scheme for the variation of the length L of a supramolecular assembly with the volume fraction of free units v having initial length L_0. When $v < v^*$ growth is described by the MSOA theory, equation (3), three curves for increasing values of the binding constant being represented. At the critical volume fraction v^* sudden growth occurs simultaneously with the formation of the nematic phase.

4.5. *Termination step*

Growth coupled orientation no longer occurs when the growing chain attains the limit of the persistence length. The latter may therefore be regarded as the termination step in supramolecular polymerization. In molecular polymerization or, in some supramolecular polymerizations of biological polymers, length control is instead achieved by the addition of a non-growing unit or a suitable template.

5. Experimental verification and outlook

Further theoretical elaboration, as well as experimental verification of the mechanism of growth coupled to orientation is clearly needed. So far only a few experiments can be cited in support of this mechanism. The linear assembly of cylindrical micelles forming a nematic phase has been characterized and found to be consistent with theory [15–19]. Hentschke *et al.* [19] reported the phase diagram of the discotic amphiphile 2,3,6,7,10,11-hexa-(1,4,7-trioxaoctyl)triphenylene in D_2O. The nematic phase formed at an amphiphile volume fraction $\approx 20\%$ at $T \approx 10°C$. Details of the phase diagram were in line with theory.

A most exciting example is the association of α- and β-tubulin molecules into microtubules that grow to a size visible under the polarizing microscope. The supramolecular polymerization is triggered by the GTP → GDP reaction that uncovers sites on β-tubulin to which complementary sites on α-tubulin may bind. The reverse reaction causes the depolymerization of a microtubule and the system acts as a biological oscillator that assists processes such as cell division and motility. Hitt *et al.* [27] have shown that liquid crystallinity may be detected in tubulin solutions in synchronism with the assembly–disassembly process. At the time the experiments were made, the mechanism of growth coupled to orientation was not widely known and it was assumed that growth progressed by cooperative association until an axial ratio large enough to carry the system into the mesophase was reached. However, the results of Hitt *et al.* are in line with the possibility that once β-tubulin is activated by the GTP → GDP reaction, polymerization and liquid crystallinity are the simultaneous manifestation of growth coupled to orientation.

Although, as shown above for tubulin, one of the functional characteristics of supramolecular polymers is their ability to undergo dynamic association–dissociation processes, the possibility of stabilizing supramolecular polymers by the *subsequent* formation of chemical bonds also exists [31]. In this way it becomes possible to stabilize extremely complex, functional structures that would have been practically impossible to assemble by ordinary syntheses. Nature has also adopted the strategy of self-assembly followed by the superimposition of chemical bonds in the case of some large structures such as, for instance, the keratin fibre [8].

Finally, it is of interest to note that another type of coupling between orientation and a supramolecular effect has been theoretically discussed. The formation of the H-bonding scheme that stabilizes the α-helical conformation of molecular polymers was in fact shown to be enhanced by the simultaneous formation of the mesophase [32, 33].

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