

Controlling Thread Assemblies of Pharmaceutical Compounds in Liquid Crystal Phase by Using Functionalized Nanotopography

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Received May 23, 2009. Revised Manuscript Received March 5, 2010

The ability to control the organization of molecules in different aggregates is important for the fundamental understanding of polymorphism and for engineering desired pharmaceutical properties of drug molecules such as bioavailability, stability, and non-toxicity. Here, we describe the control of the molecular assembly of two hydrated molecules in liquid crystal phases (so-called chromonic liquid crystals) uniformly over long distances. The two molecules include an antiallergy drug, disodium cromoglycate (5'DSCG), and a dye molecule, Sunset Yellow (SY dye). The surfaces consist of self-assembled monolayers (SAMs) of functionalized alkanethiols supported on gold films that were prepared by deposition of gold onto glass slides at an incident angle oblique from the surface normal of the glass slides. Hydrated molecular threads of 5'DSCG and SY dye aligned parallel to the surface of the SAMs and uniformly over the large surface area. The azimuthal direction of the uniform alignment was either parallel or perpendicular to the direction of gold deposition depending on whether the total number of skeletal atoms (non-hydrogen), p , is odd or even in the SAMs composed of a variety of functional groups, including methyl, hydroxyl, or tri(ethylene glycol). When two SAMs differing in one methylene unit ($-\text{CH}_2-$) in the aliphatic chains (for example, $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ and $\text{HS}(\text{CH}_2)_{12}(\text{OCH}_2\text{CH}_2)_3\text{OH}$) were supported on each gold film of the optical cell, the odd–even effect creates a twisted assembly of the molecular hydrates between the surfaces. Considering the high percentage of water in the hydrate studied (~ 70 to 88 wt %), this surface approach has the potential to provide a powerful way to influence the molecular arrangement in general for other solvates or hydrates.

1. Introduction

Molecules can form many phases and a wide range of structures of crystals or solvates (in the case of water–hydrates), affording the terms polymorphs^{1–7} or pseudo-polymorphs,^{1,3,4,8–13} respectively. One elaborate classification of phases suggests the existence of glass, crystal, condensation crystals (fully or partially conformationally

disordered and mobile crystals with positional and orientational order), plastic crystals (positionally ordered crystal with local rotational disorder and mobility), liquid crystals (orientationally ordered mobile liquids), and liquid (or melt).^{14,15} Molecular assembly can also be classified in a 2-dimensional map with one axis indicating the increase in molecular order and the other in molecular motion.¹⁶ The understanding of how such diverse assemblies so readily emerge is far from complete, yet the ability to organize molecules in crystals,^{17–20} solvates,^{1,3,5,6,21,22} or aggregates^{23,24} is critically important for obtaining

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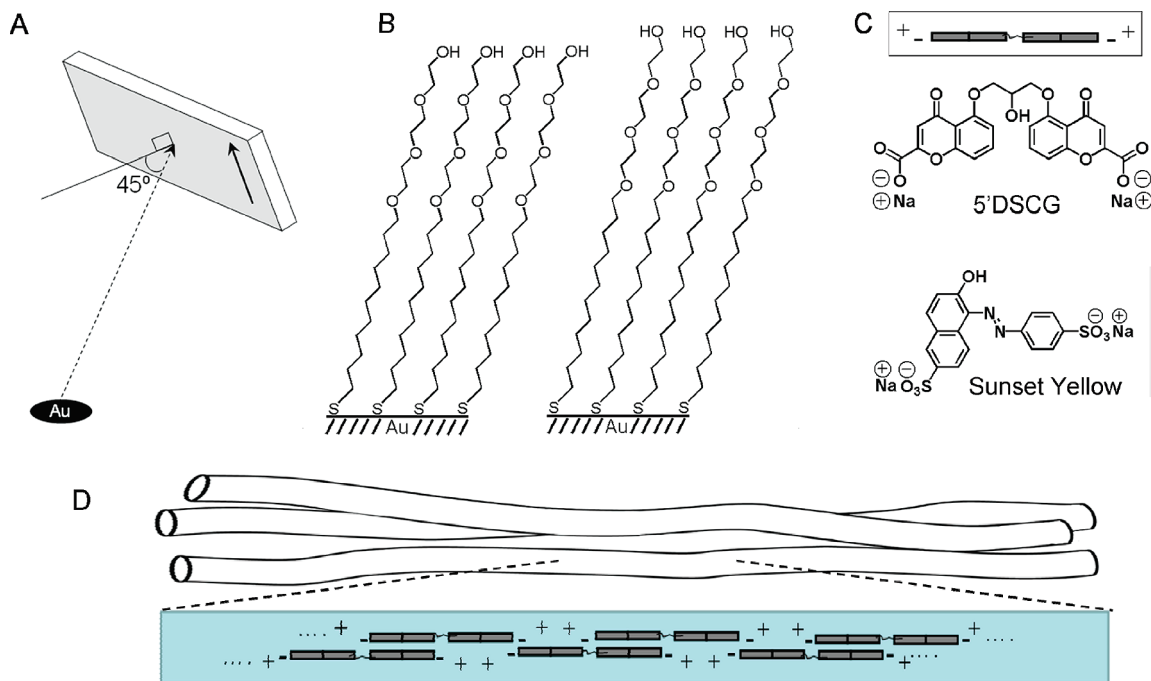


Figure 1. (A) Vapor deposition of gold atoms on glass slide at an oblique angle of incidence from the surface normal. Solid arrow indicates direction of gold deposition projected onto the glass slide. (B) Scheme of SAMs formed by $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ and $\text{HS}(\text{CH}_2)_{12}(\text{OCH}_2\text{CH}_2)_3\text{OH}$. (C) Molecular structures and schematic representation of 5'DSCG and Sunset Yellow dye. (D) Thread model for the assembly of nonamphiphilic molecules that form liquid crystal phases in water. Each thread consists of noncovalent polymer of nonamphiphilic molecules connected by salt bridges that are positioned on the aromatic ring of another nonamphiphilic molecule.³⁵

desired properties of pharmaceutical compounds, including solubility, bioavailability/bioequivalence, chemical stability, and in some cases, non-toxicity.²⁵ In this work, we present the control of hydrated molecules in a liquid crystal phase over thousands of micrometers that consists of more than 1.62×10^{16} molecules²⁶ by using self-assembled monolayers of functionalized alkanethiols on gold films that have an anisotropic topography at the nanometer-scale.²⁷ We also demonstrate the control of the x - y orientation (azimuthal direction) of the molecular assembly either parallel or perpendicular to the anisotropic features of the gold topography by changing the number of methylene units in the alkanethiols that form the monolayers on gold films. This method enables the creation of a twisted assembly of threads of hydrates.

While molecules can form novel assemblies,^{28–34} assembly of entirely water-soluble small molecules in water without precipitation or crystallization is entropically challenging. In a recent study, we revealed that an unusual nonamphiphilic lyotropic liquid crystal phase formed by a small nonamphiphilic dichromonyl organic molecule of pharmaceutical interest is, in fact, a form of polymorph.³⁵ Disodium cromoglycate (5'DSCG), an anti-inflammatory drug reported in the 1960s,^{36,37} forms highly birefringent phases (so-called chromonic liquid crystals), when dissolved in water at concentrations ranging from 12 wt % to 21 wt % at room temperature.^{38–40} Because the molecules are not amphiphilic, these birefringent phases form a unique class of nonamphiphilic lyotropic liquid crystals. The molecular organization in this hydrated liquid crystal has been controversial.^{41–45}

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In that recent study, we also showed that 5'DSCG molecules in the liquid crystal phase form solvated threads linked by stabilized salt bridges that are positioned on top of the desolvating aromatic rings (Figure 1).³⁵ This assembly structure resembles wormlike micelles,^{46–52} and is grossly different from the stacking models proposed since its discovery. In addition, we discovered that the formation of this class of liquid crystals is extremely sensitive to the details of molecular structure and can result in different pseudopolymorphs depending on isothermal aging or rapid cooling of the same sample.³⁵

Controlled nucleation and crystal growth of organic^{53,54} and inorganic crystals⁵⁵ and drug polymorphs^{54,56–58} by self-assembled monolayers on isotropic metal surfaces has been reported. For thermotropic liquid crystals,^{59–62} as well as a lyotropic liquid crystal in water,⁶³ Abbott and co-workers have demonstrated planar, uniform orientation by using self-assembled monolayers of alkanethiols on anisotropic gold films that are prepared by depositing gold atoms at a fixed angle of incidence from the normal of the surface onto a glass substrate. Furthermore, the azimuthal direction of the liquid crystal alignment can be switched between perpendicular and parallel to the direction of the gold deposition by changing the number of methylene units between odd and even in the alkanethiols of the monolayers, respectively.^{61,64} Whereas these past examples focused mainly on thermotropic liquid crystals composed of neat organic oil, this work explores the influence of surfaces on the molecular arrangement in hydrates (with content of water up to 88 wt %) that form

liquid crystal phases. Figure 1A shows a schematic representation of an oblique deposition of gold atoms onto a glass slide. Gold films prepared by this oblique deposition possess an anisotropic topography at nanometer-scale, the roughness of which exhibits a statistical corrugation with ~ 20 – 40 nm in wavelength and ~ 1 – 2 nm in amplitude.²⁷ Two hydrates of nonamphiphilic molecules, 5'DSCG and Sunset Yellow dye, were studied in this work (Figure 1C). This class of liquid crystals consists of thread-like assembly of molecules linked by salt bridges stabilized by stacking on aromatic rings (Figure 1D).³⁵ We explored the effect of both hydrophobic and hydrophilic SAMs formed by alkanethiols including $\text{HS}(\text{CH}_2)_k\text{CH}_3$, $k = 14, 15$; $\text{HS}(\text{CH}_2)_m\text{OH}$, $m = 8, 11, 16$; $\text{HS}(\text{CH}_2)_n(\text{OCH}_2\text{CH}_2)_3\text{OH}$, $n = 9$ – 13 (For example, see Figure 1B).

2. Experimental Section

Chemicals. Disodium cromoglycate (5'DSCG) was purchased from MP Biomedicals (Solon, OH). Sunset Yellow dye was purchased from Aldrich (Milwaukee, WI). Synthesis of the tri(ethylene glycol)-terminated SAMs $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ and $\text{HS}(\text{CH}_2)_{12}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ has been described in detail previously.^{65,66} All aqueous solutions of liquid crystals were prepared with deionized water with a resistivity of $18.2 \text{ M}\Omega \text{ cm}$ (Milli-Q system, Millipore, Bedford, MA). Ethanol (99.98%) was obtained from Pharmco (Brookfield, CT).

Glass Substrates. Substrates used for gold films were Fisher's Finest premium microscope slides from Fischer Scientific (Pittsburgh, PA). Prior to gold deposition, glass slides were cleaned with Piranha solution. **Warning!** Piranha solution is extremely corrosive and can potentially detonate when mixed with significant amounts of oxidizable materials. It is advised to neutralize the Piranha solution with sodium hydroxide after use. Slides were soaked in a Piranha solution (7 parts concentrated sulfuric acid and 3 parts hydrogen peroxide solution) at 70°C for 45 min. After cooling, piranha solution was poured off, and slides were rinsed sequentially 20 times with deionized water, 10 times with ethanol, and 10 times with methanol. The cleaned slides were dried with a stream of nitrogen and kept in 100°C oven overnight.

Deposition of Gold Films. Deposition of gold films was done as previously reported.⁶⁴ Semitransparent gold films were deposited onto the glass substrates using an electron beam evaporation system (Thermionics, Port Townsend, WA). Titanium ($\sim 70 \text{ \AA}$) was deposited initially to enhance the adhesion of gold. Gold film ($\sim 280 \text{ \AA}$) was deposited with angles of incidence of either 0° or 45° with respect to the surface normal of the glass slide which was held on a stationary holder.⁵⁹ Pressure was maintained no higher than 2×10^{-6} Torr throughout the deposition.

Preparation of SAMs on Obliquely Deposited Gold Films. Gold films deposited on microscope glass slides were cut into strips ($\sim 8 \text{ mm} \times 2.5 \text{ cm}$) along the direction of gold deposition. (Figure 1A) The strips were rinsed with ethanol (200 proof) and dried with a stream of nitrogen gas. Gold films were immersed in ethanolic solutions containing 2 mM of alkanethiols for 12 h.

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Optical Cells and Birefringence Characterization. Aqueous solutions of 12 wt % 5'DSCG and 30 wt % Sunset Yellow dye were prepared and aged in vials for 12 h to allow complete dissolution. Optical cells were prepared by assembling two gold films as a sandwich with a sheet of Saran wrap (average thickness $\sim 13\ \mu\text{m}$) as spacer. The sheet of Saran wrap was punctured with a hole puncher to create a well to accommodate liquid crystal samples. After being subjected to vortex mixing, the LC sample was loaded into the well formed by the punctured Saran wrap, which was placed on top of one of the SAMs (supported by the gold films). The liquid crystal sample was immediately covered with the other SAM and secured with four binder clips on all sides. Samples were viewed and recorded between either crossed or parallel polars using an Olympus BX51 polarizing microscope. Luminosity was quantified using Adobe Photoshop CS2.

Preparation of Wedge Cell. A wedge cell was prepared similar to the optical cell described above, except that an additional strip of Saran wrap was placed in between the two SAMs at one end of the optical cell such that the optical cell had a spacer thickness of $\sim 26\ \mu\text{m}$ on one end and $\sim 13\ \mu\text{m}$ on the other. A drop containing 28 μL of a liquid crystal sample (12 wt % 5'DSCG or 30 wt % Sunset Yellow dye) was applied to the well. Binder clips were used to secure the two ends of the cell. The birefringence of the sample in the punctured hole was observed between crossed polars with the direction of the gold deposition perpendicular to the long axis of the quarter-wave plate (QWP). The shift in the interference color (red-to-blue or blue-to-red) as the QWP was inserted into the optical path was recorded for determining the azimuthal direction of the alignment of liquid crystals.⁶⁷

3. Results and Discussions

3.1. Uniform Planar Alignment of Hydrated Molecules in LC Phase on SAMs $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ Supported by Obliquely Deposited Gold Films. We examined the influence of SAMs of tri(ethylene glycol)-terminated alkanethiols on aligning molecular threads of liquid crystal phases consisting of 12 wt % 5'DSCG in water. Figure 2 shows the optical images of the same liquid crystals sandwiched between different surfaces under cross polars. The samples were rotated between the crossed polars, and images were taken at orientations with the direction of gold deposition oriented at 0° , 45° , and 90° relative to one of the polars. The optical textures of hydrated 5'DSCG sandwiched between plain glass slides with a spacer of $\sim 13\ \mu\text{m}$ exhibited colorful textures with defects (result not shown). On naked gold films that were obliquely deposited at 45° , liquid crystal formed by 5'DSCG also produced colorful birefringence (Figure 2A). These results suggest that the orientation of the threads in the liquid crystal is random on these surfaces. Figure 2B shows optical images of the hydrated 5'DSCG between two SAMs of $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ supported by gold films deposited perpendicular to the surface (i.e., at an angle of incidence of 0° from the normal of the surface). Because of the lack of self-shadowing,⁶⁴ the magnitude of anisotropy in the surface topography of the gold film deposited at normal incidence is minimal compared to gold deposited at any oblique

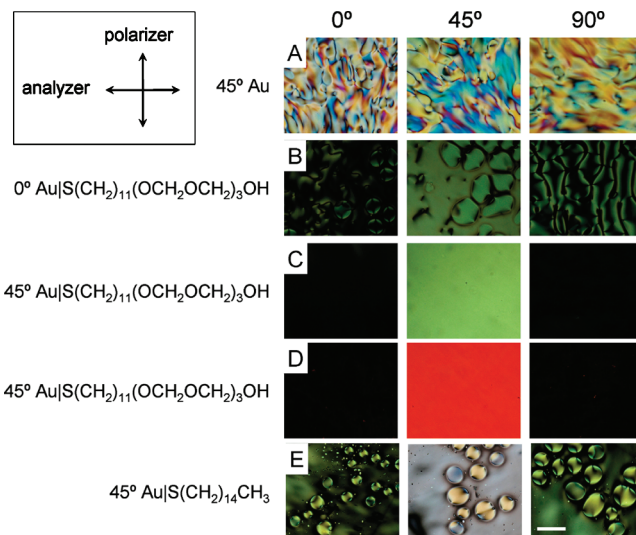


Figure 2. Optical textures of nonamphiphilic liquid crystals of 12 wt % 5'DSCG (A–C, E) or 30 wt % SY dye (D) in water between crossed polarizers at ambient temperatures. The angles of gold deposition and the types of SAMs on the gold films are shown on the left of the micrographs. Orientations of the crossed polarizers (inset), and the angle between the direction of gold deposition in the samples and one of the polarizers are shown above the micrographs. Scale bar = 95 μm .

angle from surface normal. On this surface, the optical texture of hydrated 5'DSCG was relatively more uniform than that on bare gold films, but still contained many defects.

Figure 2C shows the optical images of 5'DSCG sandwiched between gold films deposited at an angle of incidence of 45° from the surface normal supporting the same SAMs of $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$. On these obliquely deposited gold films, which possess an anisotropic nanotopography,²⁷ the liquid crystal (hydrated 5'DSCG) exhibited uniform alignment over large areas. A strong modulation in the intensity of transmitted light was observed when the sample was rotated every 45° with respect to either one of the crossed polarizers, and with a maximum extinction of light intensity when the direction of gold deposition is either parallel or perpendicular to one of the crossed polars (Figure 3A). This result indicates that the threads of hydrated 5'DSCG assumed a uniform planar orientation on the surface (Figure 3B). The azimuthal direction, which is parallel to the direction of gold deposition, was determined by using wedge cells and asymmetric LC cells (see below).

Many water-soluble dye molecules are reported to form an assembly in water.^{46,68–74} Among these nonamphiphilic

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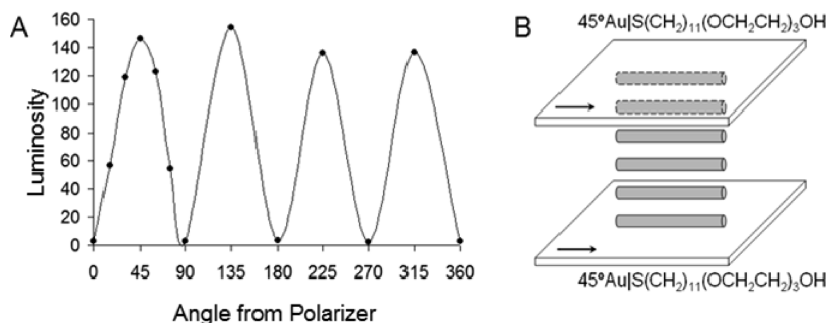


Figure 3. (A) Intensity of transmitted light through hydrated 5'DSCG (12 wt % in water) as a function of sample orientations (the angle between the direction of gold deposition and one of the crossed polarizers). The surfaces of the liquid crystal cell consist of SAMs of $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ supported on gold films obliquely deposited at 45°. (B) Schematic representation of uniform alignment of threads of the hydrates (see Figure 1) on SAMs supported by gold films deposited at 45° from the surface normal of the glass slides. The arrows indicate the direction of gold deposition projected onto the surface. The azimuthal direction is determined by using wedge cells and asymmetric LC cells.

molecules, 30 wt % Sunset Yellow dye (SY dye) in water also forms a liquid crystal phase with considerable birefringence (about 200 times lower than that of 5'DSCG).⁶⁸ Figure 2D shows optical images of SY dye (30 wt % in water) sandwiched between obliquely deposited gold films supporting $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$. Uniform alignment for this liquid crystal was also observed. Because the SY dye was red in color,⁷⁵ the liquid crystal exhibited a uniform red color when the sample (the direction of gold deposition on the gold film) is oriented 45° to either one of the crossed polars.

Interestingly, the liquid crystal of hydrated 5'DSCG exhibited more uniform alignment with defects on hydrophobic surfaces (SAM of $\text{HS}(\text{CH}_2)_{14}\text{CH}_3$) supported by nanostructured gold films (obliquely deposited at 45°) than on naked gold films that were obliquely deposited at 45° from the normal of glass surfaces. However, the sample is less prone to develop defects on the hydrophilic, tri-(ethylene glycol)-terminated monolayers than on methyl-terminated monolayers (Figure 2E). Together these results suggest that SAMs on obliquely deposited gold films have the potential for controlling the molecular assembly in hydrates or solvates.

3.2. Determination of the *x-y* Orientation (Azimuthal Direction) of Threads Formed by Hydrated 5'DSCG Relative to the Direction of Gold Deposition of Obliquely Deposited Gold Films. The results in Figure 2C show uniform alignment of the molecular threads on SAMs supported by nanostructured gold films, but not the azimuthal direction of the threads relative to the direction of gold deposition. To determine the azimuthal alignment of the hydrated 5'DSCG on the SAMs formed from $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$, a wedge shaped LC cell was prepared by inserting an additional spacer at one end to make the spacer thickness $\sim 26\ \mu\text{m}$ on one end, and $\sim 13\ \mu\text{m}$ on the other end.⁷⁶ When the wedge-shaped cell was oriented with the direction of minimum roughness

parallel to the long axis of the quarter wave plate (QWP), a "rainbow" of interference colors was generated in the sample.⁶⁷ Upon insertion of the QWP, a red-to-blue shift in the interference color was observed on the wedged LC cell composed of two SAMs of $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ supported on gold films obliquely deposited at 45° (See Supporting Information). This red-to-blue shift indicates that, on SAMs of $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$, threads of hydrated 5'DSCG align parallel to the direction of gold deposition. Conducting the same experiment using SAMs of $\text{HS}(\text{CH}_2)_{12}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ afforded a blue-to-red shift. These results suggest that while $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ aligns liquid crystals parallel to the direction of gold deposition, $\text{HS}(\text{CH}_2)_{12}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ aligns liquid crystals perpendicular to gold deposition. We determined the azimuthal directions of hydrates (both 5'DSCG and SY dye) on other SAMs (see below).

3.3. Odd–Even Effect of SAMs on the Azimuthal Direction of LC Orientation. Next, we prepared asymmetric LC cells with one gold film supporting SAM of $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ and the other of $\text{HS}(\text{CH}_2)_{12}(\text{OCH}_2\text{CH}_2)_3\text{OH}$ to further confirm the odd–even effect from the SAMs on the azimuthal alignment of liquid crystal phase of hydrates. Figure 4 shows the liquid crystal images of hydrated 5'DSCG (Figure 4A) and SY dye (Figure 4B) in this asymmetric LC cell. In contrast to the LC cell composed of the same SAMs on both surfaces, the samples exhibited bright images when viewed between crossed polarizers, and maximum light extinction when viewed between parallel polarizers. This result suggests that a 90° twist distortion of the director of the threads from the two surfaces was generated. Such twisted orientation of the liquid crystals sandwiched between the two SAMs differing in one methylene unit in length confirms that the odd–even effect exists for hydrated molecular threads, even when the sample contains a large content of water (88 wt %). On tri(ethylene glycol)-terminated SAMs supported by obliquely deposited gold films, we found that monolayers with odd number of skeletal atoms (total number of carbon and oxygen atoms) aligned the threads of both hydrated 5'DSCG and Sunset Yellow dye parallel to the direction of gold deposition, but monolayers with even numbers of skeletal

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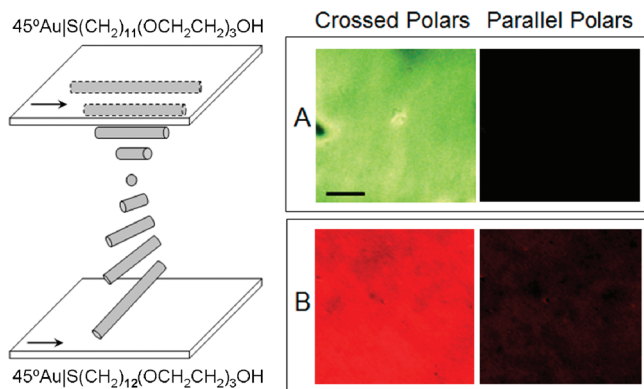


Figure 4. Optical images (between crossed and parallel polarizers) of (A) 12 wt % of 5'DSCG (B) 30 wt % of SY dye in water sandwiched between obliquely deposited gold films with one surface supporting HS(CH₂)₁₁-(OCH₂CH₂)₃OH and the other HS(CH₂)₁₂(OCH₂CH₂)₃OH. Scale bar = 152 μ m. A schematic representation showing the 90° twist distortion in the threads of the hydrates in the liquid crystal phase (see Figure 1), and the azimuthal direction of the threads on each surface is shown to the left. The arrows indicate the direction of gold deposition projected onto the surfaces.

Table 1. Azimuthal Directions of Uniform Planar Alignment of 5'DSCG and Sunset Yellow Dye^a Hydrates on SAMs Supported on Nanostructured Gold Films

SAMs	azimuthal direction ^b	<i>p</i> ^c	odd/even
HS(CH ₂) ₁₄ CH ₃	perpendicular ^e	15	odd
HS(CH ₂) ₁₅ CH ₃	parallel ^e	16	even
HS(CH ₂) ₈ OH	parallel ^e	9	odd
HS(CH ₂) ₁₁ OH	perpendicular ^d	12	even
HS(CH ₂) ₁₆ OH	parallel ^d	17	odd
HS(CH ₂) ₉ (OCH ₂ CH ₂) ₃ OH	parallel ^d	19	odd
HS(CH ₂) ₁₀ (OCH ₂ CH ₂) ₃ OH	perpendicular ^e	20	even
HS(CH ₂) ₁₁ (OCH ₂ CH ₂) ₃ OH	parallel ^d	21	odd
HS(CH ₂) ₁₂ (OCH ₂ CH ₂) ₃ OH	perpendicular ^d	22	even
HS(CH ₂) ₁₃ (OCH ₂ CH ₂) ₃ OH	parallel ^e	23	odd

^a The azimuthal direction of hydrated threads of 5'DSCG and Sunset Yellow dye are the same on all SAMs (see the Supporting Information).

^b Azimuthal direction of liquid crystal with respect to the direction of gold deposition projected onto the surface (gold was deposited at an incident angle of 45° normal of the surface of the glass slide). ^c *p*: Total number of skeletal, non-hydrogen atoms (carbon and oxygen atoms) in the alkanethiols. ^d Determined by the shift in the interference colors of wedge cells upon the insertion of the quarter wave plate. ^e Determined by the liquid crystal birefringence in asymmetric optical cells having the SAM of interest and a reference SAM with known azimuthal alignment (see Supporting Information).

atoms aligned the hydrates perpendicular to the gold deposition. The same trend of odd–even effect was also observed for hydroxyl-terminated SAMs, but a reversed trend was observed for methyl-terminated SAMs (Table 1). Whereas an odd number of skeletal atoms (sum of carbon and oxygen atoms) in tri(ethylene glycol)- and hydroxyl-terminated monolayers supported an azimuthal direction of liquid crystal parallel to gold deposition, an even number (sum of carbon atoms) in methyl-terminated monolayers supported the same azimuthal direction of liquid crystal alignment (Table 1).

We note that the two orthogonal directions of liquid crystal orientation can be engineered to exist on the same surface by using microcontact printing, which creates patterns of a methyl-terminated monolayer surrounded

by a monolayer with a different (any kind) functional group (see Supporting Information). This odd–even effect provides a powerful and potentially general method to create twisted assemblies of hydrates or solvates. This result also suggests that the mesoscopic assembly of the molecular assembly can be controlled rationally by engineering the surfaces and interfacial microenvironments, whereas the molecular organization in the threads is governed by the molecular structures and interactions (salt bridges templated by aromatics).

To explore the generality for this odd–even effect, we synthesized three more tri(ethylene glycol)-terminated alkanethiols HS(CH₂)_{*n*}(OCH₂CH₂)₃OH, where *n* = 9, 10, and 13, and used three hydroxyl-terminated alkanethiols HS(CH₂)_{*m*}OH, where *m* = 8, 11, 16. We synthesized these series of tri(ethylene glycol)-terminated alkanethiols having different methylene units by a common route shown in Scheme 1. Briefly, a diacid, for example HOOC(CH₂)₁₁COOH, was esterified in the presence of thionyl chloride to yield the diester, CH₃OOC-(CH₂)₁₁COOCH₃, which was reduced by lithium aluminum hydride to give the diol, HO(CH₂)₁₃OH. Halogenation of the diol using triphenyl phosphine and bromine gave the dibromo alkane, Br(CH₂)₁₃Br. Elimination of HBr from dibromo alkane in solvent hexamethylene phosphoramidate (HMPA) under vacuum distillation gave the ω -bromo-1-alkene, CH₂=CH(CH₂)₁₁Br. Heating 13-bromo-1-tridecene in tri(ethylene glycol) with 1 equiv of NaOH (50% in water) afforded the tri(ethylene glycol)-terminated alkene, CH₂=CH(CH₂)₁₁(OCH₂CH₂)₃-OH. The olefin was converted to the corresponding thioester under photolytic conditions in the presence of thiolacetic acid and AIBN to afford the desired CH₃COS-(CH₂)₁₃(OCH₂CH₂)₃OH. Hydrolysis of the thioester by reflux in acidic conditions gave the product HS(CH₂)₁₃-(OCH₂CH₂)₃OH (see Supporting Information for details).

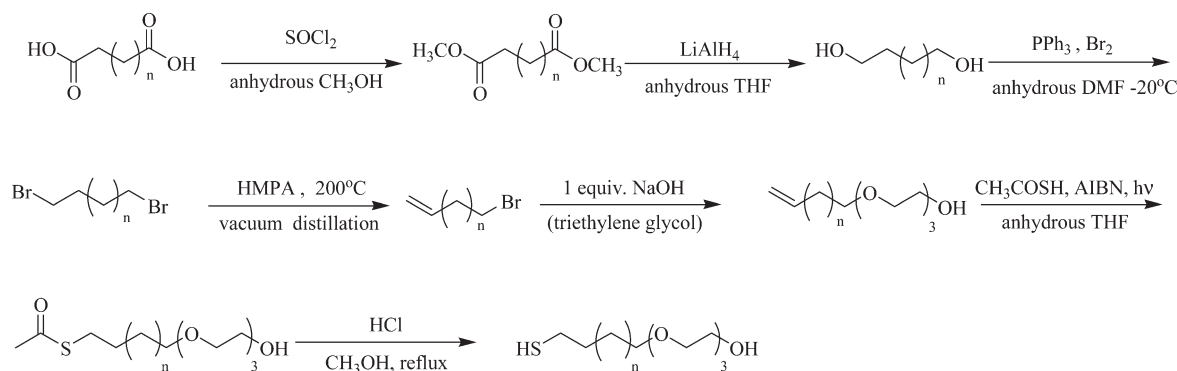
On all SAMs supported by obliquely deposited gold films (methyl-, hydroxyl-, and tri(ethylene glycol)-terminated surfaces), we observed a consistent odd–even effect on the azimuthal direction of the alignment for liquid crystals of both the hydrates of 5'DSCG and Sunset Yellow dye (Table 1). We note that both liquid crystals exhibited the same azimuthal alignment for all SAMs supported by obliquely deposited gold films.

The classical odd–even effect was often observed in the oscillation of the melting or boiling point of molecules with odd and even methylene units.^{75,77} In the case of *n*-alkyl carboxylic acids, this phenomenon was explained based on the alternating crystal densities as the number of methylene units alternate between odd and even.⁷⁸ For our case, the odd–even effect is originated from the terminal group on surfaces being oriented differently for SAMs of alkanethiols having odd or even numbers of methylene groups. Because the S–C bond of alkanethiolates

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Scheme 1



are tilted by about 30° with respect to the surface normal of gold films,^{79,80} and because the two-dimensional crystalline nature of this class of SAMs, the terminal bond (either C–C or C–O) is tilted away from normal for odd-numbered alkanethiols, and is oriented almost normal to the surface for the even-numbered alkanethiols. Forces such as elastic and flexoelectric effects, and specific molecular interactions,⁶² may contribute to the 90° switch in azimuthal orientations.⁸¹ The odd–even effect on azimuthal direction of thermotropic liquid crystal (such as *n*-(4-methoxybenzylidene)-4-butylaniline (MBBA) and 4'-cyano-4-*n*-pentylbiphenyl (5CB)) exhibited on methyl-terminated monolayers is not definitely understood.⁸² For results in this work, however, we believe that liquid crystal alignments are likely governed by an anisotropic dispersion force because of the preferred orientation of terminal groups on the surface.⁸³ As the terminal bonds (C–C or C–O) are oriented in a preferred direction, the polarization of terminal groups likely will occur in a preferred direction. This organization of terminal groups on the surface resembles the preferred orientation of molecules in a thermotropic liquid crystal, which is generally believed to be caused by dispersion forces. For these reasons, we believe that the surface of the monolayer on obliquely deposited gold films presents a structure similar to a layer of liquid crystals, which influence the orientation of actual liquid crystal in contact with the surface. Interestingly, the C–O terminal bonds on the tri(ethylene glycol)- and hydroxyl-terminated monolayer gave rise to an exact opposite pattern of odd–even effect as that afforded by the C–C terminal bonds on methyl-terminated monolayers (Table 1). This observation is consistent with the grossly different polarizabilities between the C–O and the C–C bond, which influence the LC orientation differently.

We note that odd–even effect for all SAMs studied in this work is also observed for thermotropic liquid crystal 5CB (See Supporting Information). Interestingly, the

same odd–even effect is observed for 5CB and non-amphiphilic liquid crystals (5'DSCG and SY dye) on both methyl- and tri(ethylene glycol)-terminated monolayers supported by obliquely deposited gold films. Because lyotropic liquid crystals formed by these hydrates and thermotropic liquid crystal are grossly different in molecular structure, functional groups, and physical properties, the common factor for influencing the liquid crystal orientation appears to be dispersion forces, which are ubiquitous in all systems. Furthermore, because oligo-(ethylene glycol) is water-soluble and tri(ethylene glycol)-terminated monolayers have low contact angles, these SAMs on gold films are likely hydrated. The existence of an odd–even effect for such hydrophilic surface on an aqueous solution-based liquid crystal phase suggests that the surface influence on the liquid crystal may “transmit” through the water molecules in the solvent. Furthermore, 5'DSCG and SY dye have different molecular structure, but liquid crystals formed by either molecule exhibited the same azimuthal direction on the same SAMs. These observations are consistent with the notion that the surface influence on the LC orientation is likely due primarily to anisotropic dispersion forces at the interface.

Few examples of uniform alignments have been demonstrated for lyotropic liquid crystal materials composed of either amphiphilic⁶³ or nonamphiphilic molecules.^{84,85} For example, planar uniform alignment of this nonamphiphilic liquid crystal (12 wt % of 5'DSCG) can be obtained by use of magnetic fields,⁸⁶ electric fields,⁸⁴ or by rubbing polymer coated surfaces with felt.⁸⁷ While control and understanding are relatively well established for aligning conventional thermotropic and lyotropic liquid crystals, the orientation and alignment of nonamphiphilic lyotropic liquid crystals is not well understood. One major difficulty is that the proposed stacking assembly for 5'DSCG, generally accepted since its discovery, represented essentially a

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discotic smectic phase, not a nematic phase.^{41–44,88} However, birefringence observed in this liquid crystal (12 wt % 5'DSCG) shows strong characteristics of a nematic phase. It is puzzling how a discotic smectic phase can be oriented to afford a planar uniform alignment characteristic of a nematic phase: if the columns of molecules stack face down vertically onto the surface, the boundary of the columns will create defects even when the *x*-*y* orientation of the face of the aromatic rings are oriented in a preferred direction; if the columns stack side-ways on the surface, then the alignment should represent a homeotropic orientation, which would afford a low birefringence. We note that homeotropic alignment of 5'DSCG liquid crystals has not been observed despite efforts from our group and others.⁸⁹ On the basis of our thread model, this difficulty can be readily explained by the non-uniformity of the termini of the threads, which consist of mismatched aromatic groups with charges (Figure 1D). We believed that surfaces presenting functional groups with a similar offset arrangement as the termini of the threads may orient the threads vertically—a homeotropic alignment for the threads.

In addition to the above rationale, it is also difficult to imagine how column stacking from smectic liquid crystals can afford a 90° twist of molecular assembly without defects (Figure 4). Because of the twist grain boundary effect,^{90,91} some types of defects are inevitable under twist influences for smectic liquid crystals. The assembly of molecular threads, however, can readily afford defect-free birefringence of a twisted nematic phase.

Controlled alignment of liquid crystal on surfaces is useful for a variety of applications, including liquid crystal displays,⁹² light valves,^{92,93} and sensors for chemical or biological analytes.^{94–96} For these purposes, many mechanisms have been explored for aligning thermotropic liquid crystals by using electric^{93,97} and magnetic fields⁹⁸ and anisotropic surface features.⁶¹ In contrast to conventional liquid crystals (either thermotropic or lyotropic), dichromonyl molecules are highly biocompatible,^{99,100} and thus may have potential for applications such as in situ biosensors that depend on real time protein binding events. Here, we believe that

combining the surface chemistry with nanostructured topography, such as nanopatterns prepared by lithography methods,¹⁰¹ can be used to study and control molecular arrangement in hydrates or solvates.

4. Conclusions

This work demonstrates a powerful influence on the molecular arrangement in hydrates over long distances by using surfaces composed of functionalized self-assembled monolayers on gold films that have an anisotropic topography at nanometer-scale. Whereas SAMs formed by HS(CH₂)_{odd}(OCH₂CH₂)₃OH on gold film align the molecular threads of 5'DSCG or Sunset Yellow dye in the direction parallel to gold deposition, SAMs formed by HS(CH₂)_{even}(OCH₂CH₂)₃OH align the molecular threads perpendicular to gold deposition. Because of this odd–even effect, a twisted organization of molecules in the hydrates was achieved by using surfaces composed of SAMs of certain alkanethiols having odd or even number of methylene units. As the primary molecular forces that drive the uniform alignment of the molecular threads are likely dispersion forces, we believe this surface control has the potential for controlling the molecular assembly in a wide range of phases. Furthermore, molecular assembly can be used as template for synthesis of materials with pores and structural hierarchy.^{102–104} We believe that controlling these novel liquid crystal phases composed of nonamphiphilic molecules will offer a new system for amphiphile-free templated synthesis of biocompatible materials.

Acknowledgment. We thank the Chemistry Department of SU, Syracuse Center of Excellence for CARTI award supported by the U.S. Environmental Protection Agency (Grant X-83232501-0), NSF-CMMI (Grant 0727491), and NSF-CAREER (Grant 0845686) for financial support. We also thank Professor Arindam Chakraborty for fruitful discussion. K.A. Simon was supported by a fellowship from Syracuse Biomaterials Institute.

Supporting Information Available: Direct determination of azimuthal direction of molecular threads of 5'DSCG on SAMs of HS(CH₂)₉(OCH₂CH₂)₃OH, HS(CH₂)₁₁(OCH₂CH₂)₃OH, HS(CH₂)₁₂(OCH₂CH₂)₃OH, HS(CH₂)₁₁OH, and HS(CH₂)₁₆OH by the shift in the interference colors of wedge cells upon the insertion of the quarter wave plate; inferred determination of azimuthal direction of molecular threads of 5'DSCG on SAMs of HS(CH₂)₈OH, HS(CH₂)₁₀(OCH₂CH₂)₃OH, and HS(CH₂)₁₃(OCH₂CH₂)₃OH by liquid crystal birefringence in asymmetric optical cells under crossed and parallel polarizers; patterning two orthogonal orientations of molecular threads on the same surface by microcontact printing; syntheses, ¹H NMR, ¹³C-NMR, HRMS characterization of tri(ethylene glycol)-terminated SAMs. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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