Columnarly Assembled Liquid-Crystalline Peptidic Macrocycles Unidirectionally Orientable over a Large Area by an Electric Field

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S *Supporting Information*

ABSTRACT: Being inspired by naturally occurring peptidic macrocycles, we developed liquid-crystalline (LC) compounds **1** and **2** that are capable of self-assembling into hexagonal columnar mesophases over a wide temperature range that includes room temperature. Their bowl-shaped macrocyclic cores are conformationally robust because of the presence of internal H-bonds, while the columnar assembly is ensured by intermolecular H-bonding interactions involving the exocyclic amide units. When an electric field was applied to their LC films from a direction orthogonal to the film plane, the columns were oriented homeotropically over a large area.

Membranes with unidirectionally oriented nanopores have attracted long-term attention in various aspects of biological and nonbiological permeation phenomena. In particular, nanoporous organic membranes, which can dynamically change their pore orientation in response to physical stimuli, not only are interesting in relation to biomembranes[1a] but also have the potential for application to separation technologies.[1b] Since liquid-crystalline (LC) molecules are dynamic and possibly can change their orientation in response to an electric field (E-field),[2,3] several LC materials with columnarly assembled macrocyclic cores have been developed.[4] To date, however, no such macrocyclic LC molecule has been claimed to be E-field-responsive. For the realization of E-field-responsive nanoporous assemblies, we considered that a conformationally rigid, non-planar macrocycle capable of exerting a large dipole moment might be a promising structural motif.

Here we report that peptidic macrocycles **1** and **2** (Figure 1) self-assemble into columnar LC mesophases over a rather wide temperature range that includes room temperature. Furthermore, unprecedentedly, their columns can be oriented uniformly over a large area upon application of an E-field. By coincidence, we were fascinated by the structures of a series of naturally occurring peptidic macrocycles isolated from the marine organism *Lissoclinum*.[5−7] With the help of internal H-bonds,[8] these macrocyclic peptides adopt a highly robust, bowl-shaped conformation capable of exerting a large dipole moment. Being inspired by such structural features, we developed compounds **1** and **2** (Figure 1), whose macrocyclic cores bear branched paraffinic wedges attached via polar amide spacers. We expected that these exocyclic amide groups in **1** and **2** might selectively form intermolecular H-bonds, ensuring the columnar assembly of their macrocyclic cores.

For the syntheses of **1** and **2**,[9] L-glutamate-containing cyclic peptide precursors were prepared according to methods similar to those reported previously,[10] and a gallate-based branched paraffinic wedge was attached to each glutamate unit. Compounds **1** and **2** thus obtained were unambiguously characterized by their ^1H and ^{13}C NMR spectra and MALDI−TOF mass spectra (Figures S1−S4 in the Supporting Information).[9] Compound **1** in C_6D_{12} (2.4 mM) displayed broad ^1H NMR signals at 25 °C. However, when the sample was heated to 70 °C, the spectrum was entirely sharpened (Figure 2a), and two amide NH signals appeared at 8.48 and 7.06 ppm. By reference to reported examples,[8] the former NH signal was assigned to the endocyclic amide protons (NH^{endo}) that are H-bonded to the nitrogen atoms of the proximal thiazole units within the macrocycle. Hence, the latter NH signal is most likely due to the exocyclic amide protons (NH^{exo}). Upon 20-fold dilution of the sample solution with C_6D_{12}, the signal due to the intramolecularly H-bonded amide NH^{endo}, as expected, did not shift at all (Figure 2a). In contrast, the NH^{exo} signal displayed a 0.36 ppm upfield shift (Figure 2a). The contrasting behaviors thus observed upon dilution indicate that the exocyclic amide groups are H-bonded without interference by the endocyclic amide units. It is also noteworthy that the amide NH^{endo} signal remained intact upon the addition of a strongly H-bonding acceptor such as dimethyl sulfoxide (DMSO) [0.05% (v/v)], whereas that of NH^{exo} displayed a 0.21 ppm downfield shift (Figure S5a).[9] The high stability of the internal H-bonds suggests that the bowl-shaped macrocyclic core of **1** is conformationally robust. Substantially identical ^1H NMR spectral profiles were observed for **2** upon dilution with C_6D_{12} (Figure 2b) and addition of DMSO (Figure S5b).[9]

Differential scanning calorimetry (DSC) analysis of **1** on second heating showed an LC mesophase over the temperature range from −12 to 77 °C (Figure S6a).[9] Polarized optical microscopy (POM) at 75 °C displayed a fan texture, which is characteristic of hexagonal columnar (Col_h) LC materials (Figure S7a).[9] X-ray diffraction (XRD) analysis of **1** at the same temperature showed diffraction peaks with *d* spacings of 35.2, 20.6, and 17.6 Å, which were indexed as the (100), (110), and (200) diffractions of a Col_h assembly with an intercolumnar distance of 40.6 Å (Figure 2c). Likewise, compound **2** self-assembled into a columnar LC material. Notably, the temperature
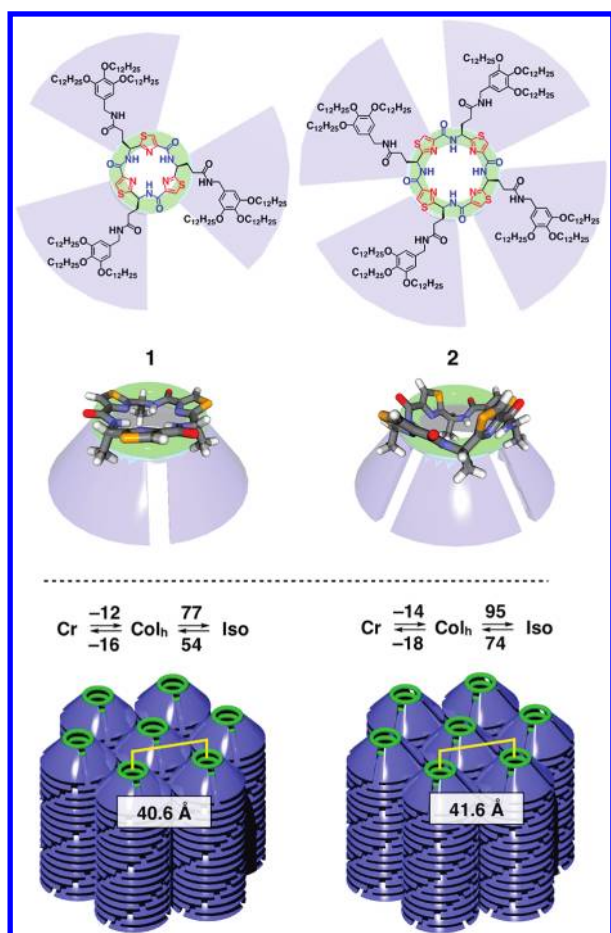

Figure 1. Molecular structures and phase transition diagrams (temperatures in °C) of LC macrocyclic oligopeptide derivatives **1** and **2**. Their core units are bowl-shaped (see the schematic illustrations) and self-assemble columnarly with a hexagonal geometry (numerical values represent intercolumnar distances). The estimated pore diameters for **1** and **2** are 4.0 and 5.7 Å, respectively.

range of its LC mesophase (−14 to 95 °C; Figure S6b)[9] was wider than that of **1**. POM and XRD profiles indicated that the LC material from **2** adopts a Col_h geometry (Figure S7b and Figure 2d).[9] As expected, its intercolumnar distance (41.6 Å) was larger than that of **1** (Figure 2d). On the basis of these dimensional aspects, the molecular models shown in Figure 1 are expected for the columnarly assembled **1** and **2**, wherein the branched paraffinic wedges that wrap around the stacked columns most likely adopt a fan shape.

We confirmed that the columnar assembly of **1** and **2** is indeed ensured by intermolecular H-bonding interactions involving their exocyclic amide groups (Figure 2a,b). For example, in FT-IR spectroscopy at 25 °C, compound **2** showed stretching vibrations due to amide CO (overlapped CO^{endo} and CO^{exo}), NH^{exo}, and NH^{endo} at 1663, 3316, and 3390 cm^{-1}, respectively, which are typical of those of H-bonded amide groups. When **2** was heated to allow its LC-to-isotropic (Iso) phase transition, the vibrational band due to NH^{exo} shifted discontinuously toward higher wavenumber, indicating that the H-bonds were weakened upon heating. In sharp contrast, the vibrational band due to NH^{endo} remained intact during the phase transition (Figure 2f). Thus, not only in solution (see above) but also in the LC state, the endocyclic amide groups of **2** did not hamper the H-bonding
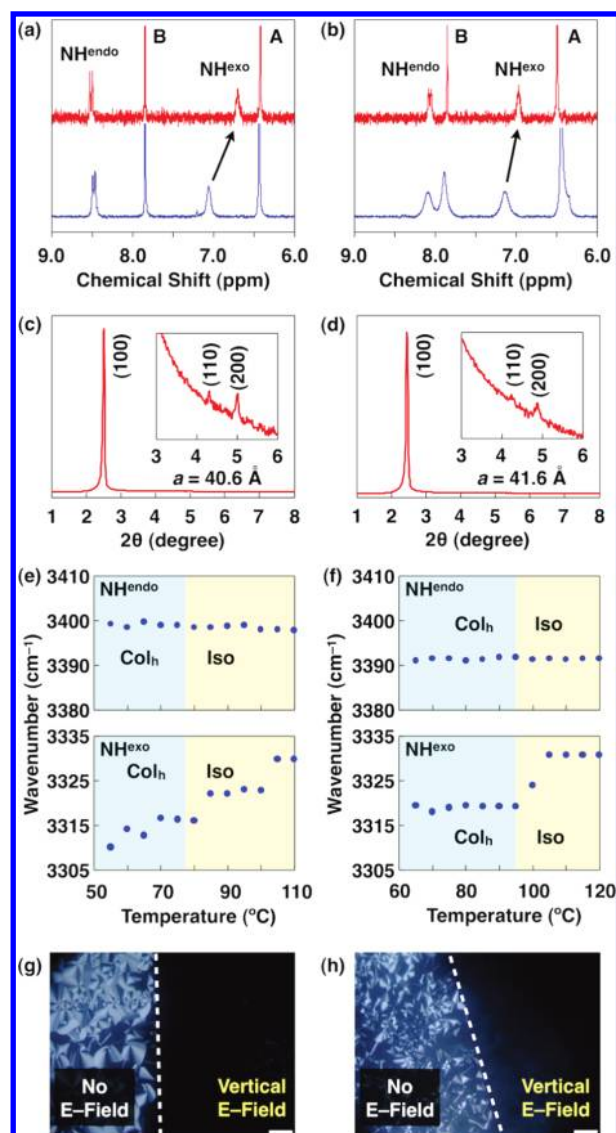

Figure 2. (a, b) ^1H NMR spectra of (a) **1** and (b) **2** at 70 °C in C_6D_{12} at 2.4 mM (blue) and 0.12 mM (red). Signals A and B represent phenyl and thiazole protons, respectively. (c, d) XRD patterns of (c) **1** at 75 °C and (d) **2** at 93 °C. (e, f) Wavenumbers (cm^{-1}) of the NH^{endo} and NH^{exo} stretching vibrations in the FT-IR spectral profiles of (e) **1** on heating from 50 to 110 °C and (f) **2** on heating from 60 to 120 °C. (g, h) POM images of (g) **1** at 75 °C and (h) **2** at 93 °C, sandwiched by glass plates (5 μm separation) partially coated with ITO electrodes. A rectangular-shaped 1.0 Hz AC voltage (120 V peak-to-peak) was applied to the samples. Scale bars represent 200 μm.

interactions of the exocyclic amide units. Although the spectral change profile of **1** associated with the LC-to-Iso phase transition was similar to that of **2**, the band shift of NH^{exo} was not as explicit as that of **2** (Figure 2e). This observation is in accord with the fact that the clearing temperature of the LC mesophase of **1** (Figure 1) was lower than that of **2** (see above).

Quite interestingly, we found that upon application of an E-field, the LC columns of both **1** and **2** undergo large-area unidirectional orientation (Figure 2g,h). For investigating the E-field responsiveness, we prepared a sandwich-type cell with two parallel-oriented glass plates (5 μm separation) partially coated with indium tin oxide (ITO) electrodes. Next, a 1 Hz square-wave

AC voltage (120 V peak-to-peak) was applied to film samples of these molecules during incubation in the cell at a temperature just below the LC-to-Iso phase transition. At 75 °C, the film sample of **1**, for example, started to lose its characteristic birefringent texture in the E-field-exposed area sandwiched by the ITO electrodes (Figure 2g). In 3 h, this area became entirely nonbirefringent, indicating that the LC columns of **1** were oriented homeotropically relative to the electrodes.[11] In contrast, other areas without the E-field (i.e., sandwiched by an ITO electrode and a glass plate) remained birefringent. Meanwhile, heating the LC sample of **1** to induce its LC-to-Iso phase transition followed by cooling to 75 °C without the E-field resulted in the development of a birefringent texture over the entire sample. All of these observations demonstrate that the homeotropic orientation of the columns was driven by application of the E-field. It is also noteworthy that even after the E-field was switched off, the large-area unidirectional columnar orientation was maintained throughout an observation period of half a year. The same was true for LC compound **2** (Figure 2h). As for the origin of the observed E-field responsiveness, we consider that compounds **1** and **2** interact with the applied E-field in a dipolar fashion. It should be noted that these compounds carry not only multiple amide units but also bowl-shaped cores that are capable of exerting a large dipole moment.

In conclusion, we have developed peptides **1** and **2** as the first E-field-orientable macrocyclic LC molecules that self-assemble into columnar structures. Upon application of an E-field, the LC columns are oriented homeotropically over a large area. Furthermore, as long as the materials are kept in their LC mesophase temperature range, this large-area unidirectional orientation, once developed, is maintained even without the E-field. If freestanding membranes are available from these oriented LC films, one can envisage selective transport of molecules and ions across the membranes.[1] Hence, the design of cross-linkable versions of these molecules is one of the interesting challenges worthy of further investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Synthesis and characterization details and POM, XRD, DSC, and FT-IR spectral data for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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(11) In conformity with the homeotropic columnar orientation, the E-field-exposed area was birefringent when the film sample was viewed at a tilt angle of 45°.