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Microscopic and macroscopic anisotropy in supramolecular hydrogels of histidine-based surfactants

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ABSTRACT

The synthesis of novel histidine-based surfactants and their self-assembling properties into anisotropic microscopic and macroscopic spaces are reported. Below pH 8, surfactant molecules self-assemble into micelles whereas hydrogelation occurs above pH 8 even at very low concentrations (0.3%w/v). Structure, size, and morphology of the fiber-like lamellar aggregates were determined by SAXS and WAXS measurements, polarized optical microscopy, transmission and scanning electron microscopy, and linear and circular dichroism.

Soft materials known as hydrogels have gathered recently much attention, owing to their unique properties and versatile applications in many areas, from applied chemistry to biomedicine. In this respect, a major challenge is the development of biocompatible and/or biodegradable low molecular weight hydrogelators with well-defined chemical structures and predictable properties, as compared to polymers. To this end, amphiphilic molecules, namely surfactants, appear as suitable candidates since they form well-characterized supramolecular structures. Appropriately grafted with amino acid moieties they are able to form stimuli sensitive hydrogels.

The design of chiral low molecular weight gelators (LMWGs) with chirality transcribed to the supramolecular architectures is of particular interest due to the promising features and practical applications in the field of nanomaterials, tissue engineering, drug carriers, molecular recognition, or microfluidic devices.[1]

Amino acid derivatives could provide such optical activity due to their intrinsic chirality. They have already been used successfully as building blocks for hydrogels, based on weak, non-covalent interactions such as hydrogen bonding, π–π stacking and the hydrophobic effect: compounds based on phenylalanine,[2] valine, isoleucine, lysine,[3] cystine,[4] L-alanine,[5] have already been reported. Furthermore, some surfactants such as amphiphiles,[6] bola-amphiphiles,[7] and gemini amphiphiles,[8] can be used as gelators to form supramolecular hydrogels.

In this work, our interests focus on supramolecular hydrogels of L-histidine amphiphilic pseudo-peptide which involves discrete chiral molecular components with a well-defined chemical structure. The presence of biocompatible and biodegradable moieties makes them suitable for biological applications. A triblock pseudo-peptidic amphiphile (alkyl-polyethylenoxide-aminoacid, $C_{14}H_{29}$-$(EO)_3$-AA_3), designated as **GlyGlyHisEO$_3$C$_{14}$**, was synthesized and characterized. The morphology of supramolecular hydrogels induced by this LMWG **GlyGlyHisEO$_3$C$_{14}$** was investigated by using microscopy techniques. Both linear dichroism (LD) and circular dichroism (CD) were used to investigate the gel formation and the interactions between the gel and amino acids, suited for chiral discrimination within induced chiral spaces.

The triblock (hydrophobic–hydrophilic–peptidic) gelator investigated in this work was synthesized step-by-step, similarly to a peptide coupling. The reaction route is outlined in Scheme 1. In the first step, 2,2′-(ethylenedeoxy)bis(ethyleneamine) was monoprotected by tritylation. The monoprotection was easily realized by using a large excess of diamine which can be removed at the end of the reaction by a simple extraction with an aqueous phase. The alkyl group is then grafted by amidation of the tetradecanoic acid using the peptide coupling method. Similarly, the amino acids are successively introduced by using BOP coupling reagent. Then, the Boc protective group was removed with gaseous HCl in a mixture of Et_2O and THF. The resulting products are obtained in good to excellent yields.

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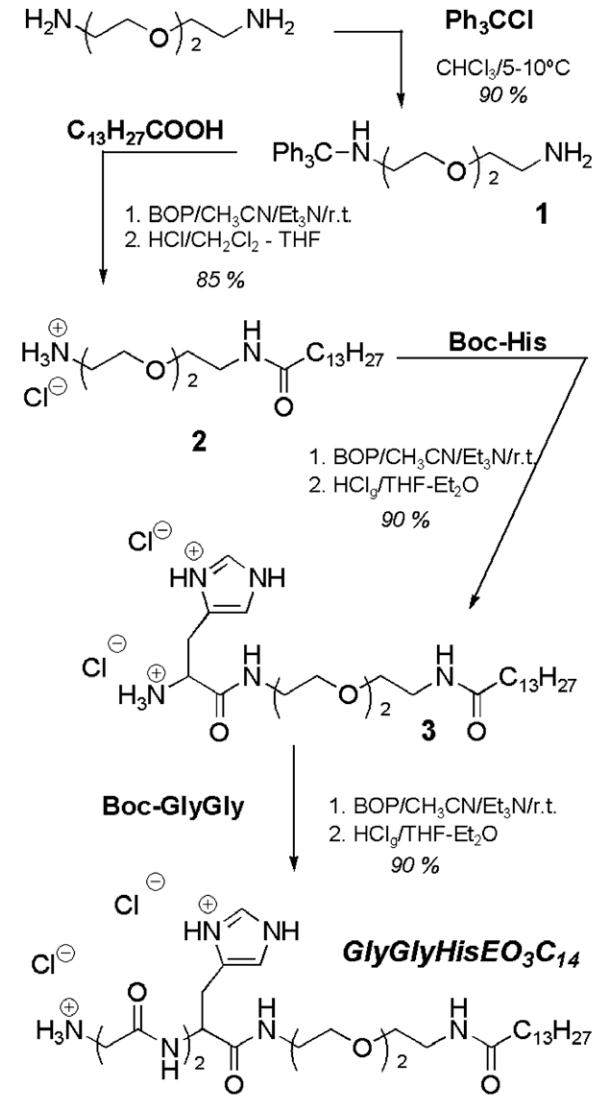

Scheme 1. Synthetic scheme of the gelator.

Amide moieties were chosen as block links since they are stable at pH 8–10 solutions and they posses both hydrogen donor and acceptor properties, with respect to the ester group.

GlyGlyHisEO$_3$C$_{14}$ was obtained as a chloride salt. At pH 2, micellar phases are formed whereas hydrogelation occurs upon increasing the pH in the range of 8–10 for a minimal gelator concentration of 0.3%w/v. The hydrogel is sensitive to external stimuli such as variations of temperature and pH (Fig. 1). Up to 6 mg/mL the melting temperature (T_{dgel}) was very sensitive to the concentration, and remains constant at 37 °C for higher concentrations. Another remarkable feature of many supramolecular gels is their thixotropy. When the **GlyGlyHisEO$_3$C$_{14}$** hydrogel was mechanically stirred or sonicated a viscous liquid was formed, which turned into a gel spontaneously after some time. This process could be repeated several times (Table 1).

The structure of the gel was studied by simultaneous small and wide-angle X-ray scattering (SAXS and WAXS) measurements (Fig. 2). At low concentrations of the gelator (6%w/v) only the scattering profile was observed. However, when the concentration of the gelating compound was increased to 50%w/v, a clear Bragg reflection appeared in the low-angle region indicating a periodicity distance of 6.4 nm, accompanied by a chain order peak in the wide-angle regime, with a characteristic distance of d = 4.2 Å (data not shown), suggesting thus the presence of a L_β lamellar phase. Upon slow heating from 35 to 40 °C it undergoes a phase transition to a new, poorly ordered such as disk phase, showing only a broad diffraction peak, with a correlation distance of about 43 Å. The phase transition temperature was in agreement with the previously observed data by the dropping ball method.

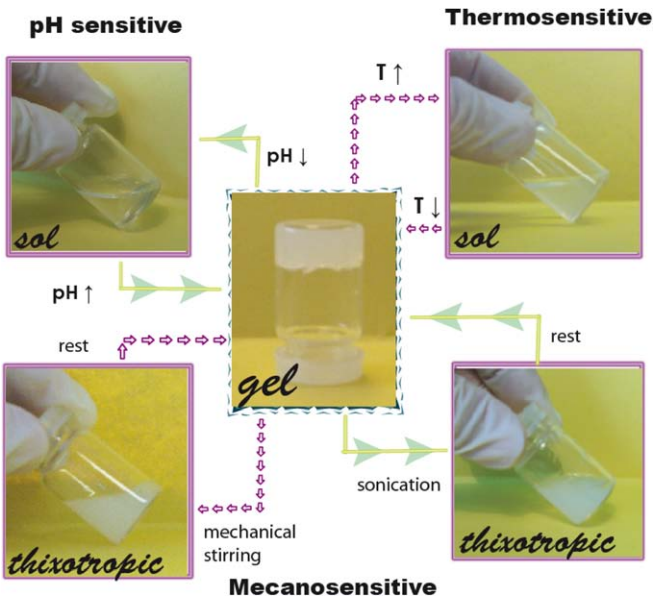

Figure 1. Stimuli sensitive behavior of **GlyGlyHisEO$_3$C$_{14}$** supramolecular hydrogel.

Table 1
Gelification temperatures T_{gel} and melting temperatures T_{dgel}

	Gly-Gly-His-EO$_3$-C$_{14}$		
Concn (g/L)	1	3	6
T_{gel} (°C)	08	10	13
T_{dgel} (°C)	11	24	37

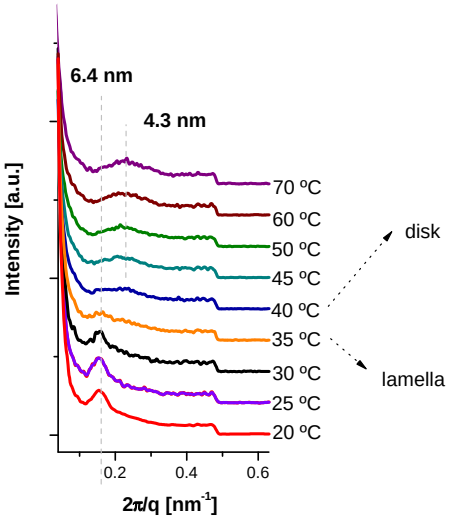

Figure 2. SAXS profile of concentrated gel of **GlyGlyHisEO$_3$C$_{14}$** at different temperatures (where q is the scattering vector).

Considering the chiral structure of L-**GlyGlyHisEO$_3$C$_{14}$**, it seems natural to use circular dichroism spectroscopy in order to investigate the supramolecular architectures originating from the chiral monomer during self-assembly.[9] However, the simultaneous measurement of the LD/CD spectra gives clear evidence for the macroscopic anisotropy of the gel sample, thus making the observed CD spectra unexploitable. As shown in Figure 3, a peak appeared in the amide-absorption region (220–225 nm), due to the π–π^* transition of spatially organized CONH groups within homochiral assemblies.[10] With an increase in the temperature, the intensity of this peak decreases suggesting that the LD signal observed is due to a macroscopically ordered arrangement of the monomer through week non-covalent interactions within the hydrogel. Indeed, H-bonding between neighboring amides plays a major role in the construction of the hydrogel network and therefore these transitions are extremely sensitive to the temperature. The intensity of the LD signal decreased drastically upon heating from 35 to 40 °C which corresponds to the transition temperature from gel to solution, also observed by other techniques such as X-ray measurements or the visual T_{gel} determination method described above.

Moreover, polarized optical microscopy (POM) used for the hydrogels reveals the presence of anisotropic fibers (Fig. 4). Deeper insights on the morphology of these fibers were recorded by TEM. The micrographs show bundles containing thin (less than 100 nm) aligned fibers that form the gel. The fibers are hundreds of micrometers long but less than 1 μm wide, and the water is trapped in the interstitial spaces.

Upon drying, these fibers aggregate to form larger fiber bundles as shown in Figure 5. These aligned fibers posses a standard lamella structure, as one can observe from the cross-section of an individual fiber.

Due to the chiral nature of the elementary constituent of the gel, as well as the high anisotropy of the self-assembled aggregates, one can imagine the use of this medium for selective detection and separation of chiral species. To do so, a hydrophobic amino acid, phenylalanine, was chosen as model for chiral discrimination of hydrophobic molecules. Indeed, at the gelating pH weak non-covalent interactions between the two components might exist, that is, electrostatic interactions between the carboxylate (COO^-) of the amino acid and the ammonium group (NH_3^+) of the gelator as well as π-stacking between the phenyl moiety of Phe and the imidazole group of the gelator, respectively. Consequently, LD spectra of the hydrogel were registered for mixtures with enantiomerically pure L-Phe and racemic L,D-Phe (Fig. 6). As shown below, no significant changes were induced by L-Phe, whereas the racemic mixture produced a significant decrease in the dicroic signal, probably because the D-Phe disrupts the interactions between the gelator molecules. Although additional work is needed to extend this study to other optically active mixtures, the chiral bilayers of **GlyGlyHisEO$_3$C$_{14}$** seem to be responsible for the formation of oriented interstitial spaces able to discriminate between enantiomers in racemic mixtures.

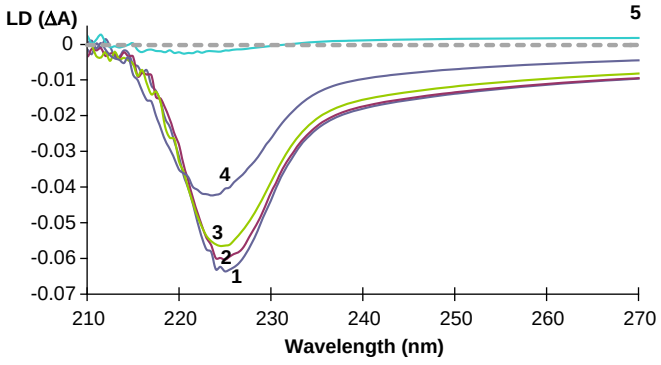

Figure 3. LD spectra of **GlyGlyHisEO$_3$C$_{14}$** hydrogels (pH 8) at various temperatures (**1**–**5** correspond to 20 °C, 25 °C, 30 °C, 35 °C, and 40 °C, respectively).

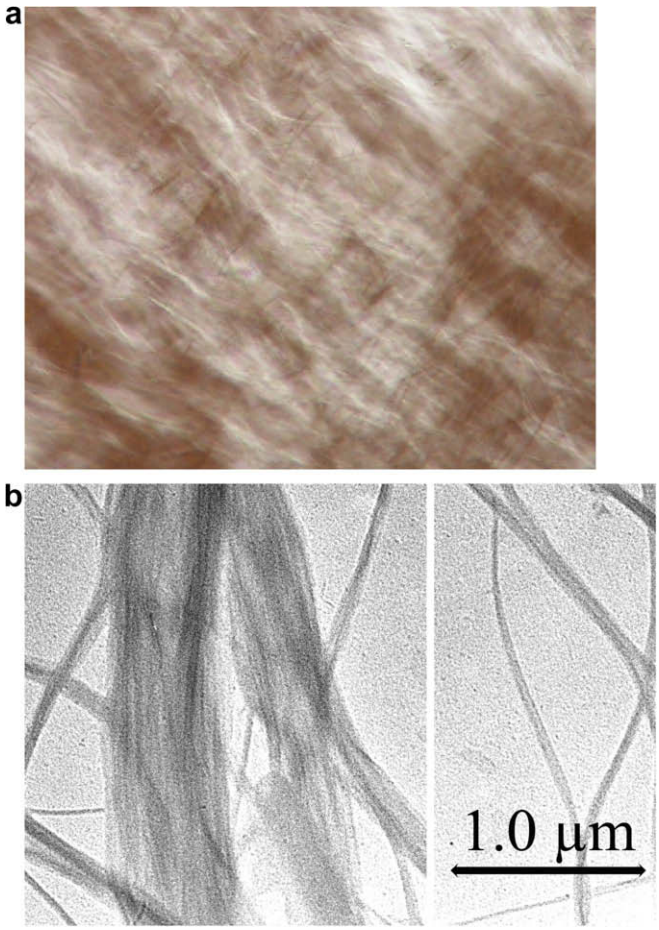

Figure 4. (a) POM of **GlyGlyHisEO$_3$C$_{14}$** hydrogel 50 % (w/v) and (b) TEM images of 0.3% (w/v) hydrogels of **GlyGlyHisEO$_3$C$_{14}$** indicating fiber bundles.

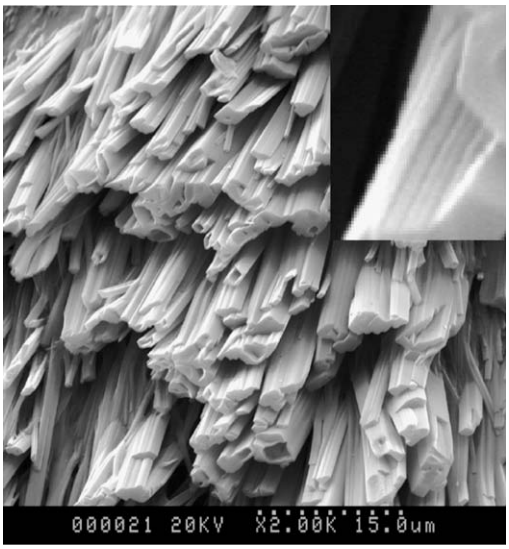

Figure 5. SEM micrographs of **GlyGlyHisEO$_3$C$_{14}$** hydrogels after drying (the inset is magnified 10 times).

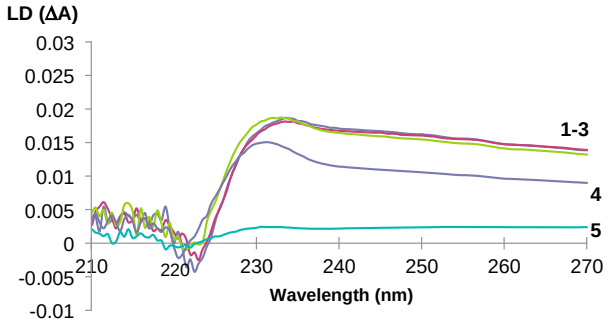

Figure 6. LD spectra of **GlyGlyHisEO$_3$C$_{14}$** hydrogels with D,L-Phe (pH 8) at various temperatures (**1**–**5** correspond to 20 °C, 25 °C, 30 °C, 35 °C, and 40 °C, respectively).

In summary, we assessed the gelation properties of a new LMWG based on a (L)-Gly-Gly-His peptidic moiety. This compound functions as an amphiphilic hydrogelator (pH 7–8) able to interact selectively with D,L-phenylalanine, through weak, non-covalent interactions, creating thereby highly anisotropic supramolecular hydrogels at both microscopic and macroscopic levels. This constitutes an interesting way to organize 'soft spaces' and to align molecules and supramolecular architectures through molecularly controlled self-assembly, in other words by decreasing the entropy of the system by structural tailoring. Therefore, these chiral hydrogels could potentially serve as general matrices to host various chiral compounds, either hydrophobic or hydrophilic, and to be used as an enantiomeric sensor or separation device for a range of chiral molecules.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.093.

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