

Unveiling the hydrogen bonding network in liquid crystalline natural-based glycosides containing polymeric complexes: experimental and theoretical assessment.

Nurul Fadhillah Kamalul Aripin^{1,2}, Jonathan Heap³, Rafael Piñol⁴, Vijayan M. Achari^{2,5}, Alfonso Martinez-Felipe^{3,*}

¹Faculty of Chemical Engineering, Universiti Teknologi MARA, 40450 Shah Alam, Selangor Darul Ehsan, Malaysia.

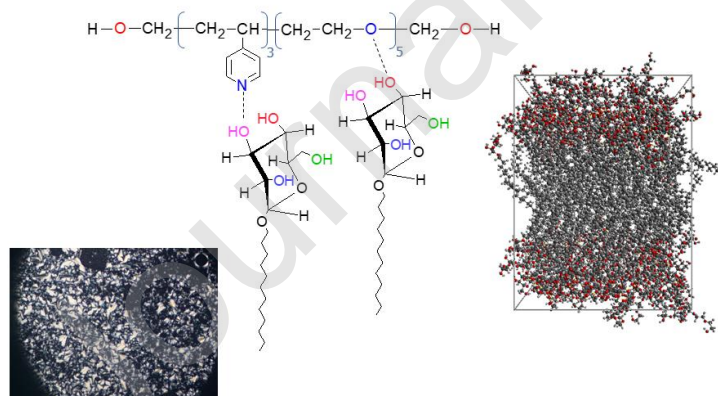
²Fundamental and Frontier Sciences in Nanostructure Self-Assembly Center, Department of Chemistry, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia.

³Chemical and Materials Engineering Group, School of Engineering, University of Aberdeen, King's College, Aberdeen AB24 3UE, Scotland, UK.

⁴Department of Condensed Matter Physics and Aragon Materials Science Institute, ICMA, University of Zaragoza- CSIC, Zaragoza, 50009 Spain.

⁵Bioinformatics Program, Institute of Biological Sciences, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia.

Graphical abstract



Abstract

In this work we present a facile and versatile strategy to prepare new amphiphilic compounds obtained from natural sources, avoiding costly covalent synthetic stages, and we introduce a

powerful methodology to describe hydrogen-bonding networks in carbohydrates liquid crystal. A series of new glycosides has been prepared by mixing a natural-based mannoside, α ManPKO, with three different polymeric substrates: poly(ethylene oxide), PEG, poly(4-vinyl pyridine), P4VP, and a block-copolymer containing PEG and P4VP segments, PEG₄₅-*b*-P4VP₁₈. The materials have been characterised by differential scanning calorimetry, polarised optical microscopy and small-angle X-ray diffraction. The resulting complexes are assembled by hydrogen-bonding and form smectic A phases, with the polymeric chains spread along the surface of the glycosides bilayers. By using Fourier-transform infrared spectroscopy, FT-IR, and molecular simulations, we have assessed the selectivity of the hydrogen bonds formed between α ManPKO and the polymeric segments. Our results suggest that the assembly of the polymeric complexes must be explained by a combination of interfacial mixing between the polymer/glycoside units at the bilayer boundaries (favoured by PEG) and the formation of strong hydrogen bonds (favoured by P4VP).

Keywords: Glycosides, supramolecular liquid crystals, hydrogen bonding, Fourier-transform infrared spectroscopy, polymeric complexes, molecular simulation.

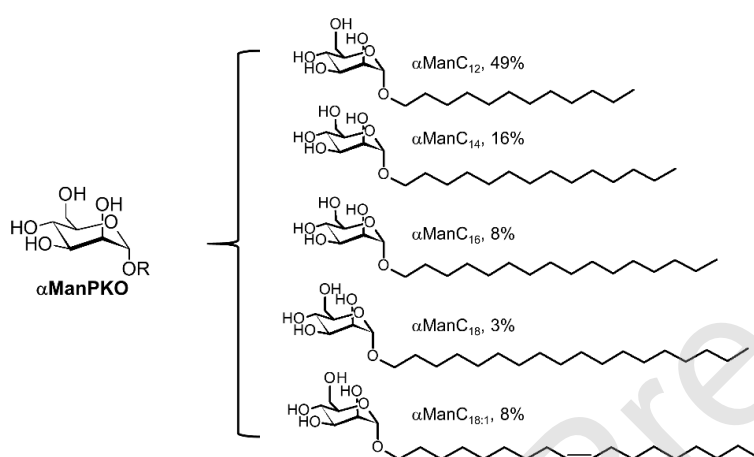
1. Introduction

Hydrogen-bonding is a versatile technique to yield new supramolecular liquid crystals^{1,2}, thanks to the directional character of the hydrogen bonds that facilitates the arrangement of anisotropic structures. The typical strength of a hydrogen bond ($1\sim 60\text{ kJ}\cdot\text{mol}^{-1}$)^{3,4} can guarantee the stability of the new materials above their processing melting points, whilst providing some degree of “softness”. Some early examples of complexes with mesogenic character include the pyridine-benzoic assemblies, reported by Kato and co-workers^{5,6}, or the seminal works by Bruce and co-workers, using alkoxy stilbazoles.⁷⁻⁹ To date, a wide range of liquid crystals continues to be prepared by hydrogen-bonding, including, chiral bent-core with supramolecular induced chirality^{10,11}, photosensitive liquid crystals^{12,13}, modular assemblies showing broad blue phases¹⁴, supramolecular dimers exhibiting the twist-bend nematic phase¹⁵⁻¹⁷, or smectic networks for selective mass and ionic transport¹⁸⁻²⁰, among many others.

Carbohydrate liquid crystals can be considered as early precedents of supramolecular mesomorphic compounds, and were already reported in the first half of the 20th century^{21,22}. More specifically, the different hydroxyl groups can form multiple hydrogen bonds between glycosides, resulting in microphase separation between polar and non-polar regions, and ultimately favouring smectic behaviour²³⁻²⁹. We note, however, that the exhibition of liquid

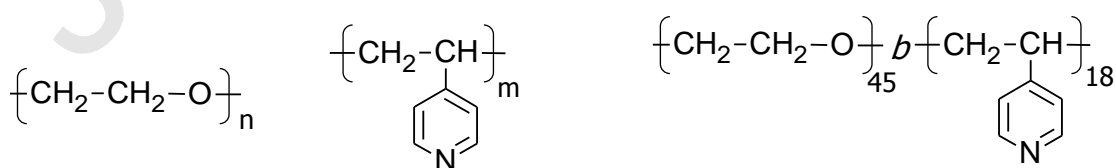
crystalline phases is not based on the formation of new “rod-like” or “disc-like” moieties by hydrogen-bonding, but instead on segregation due to the amphiphilic character of the glycosides, including hydrogen-bonding between the sugar heads. Carbohydrate liquid crystals experienced a fast development in the 1980’s and 1990’s²⁶⁻²⁸, and the mesomorphic behaviour of new glycosides continues to be the object of systematic investigation by varying their composition and stereochemistry³⁰⁻³³.

Due to its important role on the formation of liquid crystal phases, in this work we investigate with detail the hydrogen-bonding network of a natural-based glycoside, a palm kernel oil-based mannoside, α ManPKO, **1**, and its complexes with different polymeric substrates,



1, α ManPKO

The alkyl chains of α ManPKO were obtained from palm kernel oil, and then added to a mannose head by glycosidation, resulting on a mixture containing different chain lengths, and the effect of composition of **1** is currently under investigation³⁴. The formation of liquid crystalline structures and its non-toxicity, makes α ManPKO a promising candidate for drug delivery applications³⁵. α ManPKO has been complexated to three different substrates: poly(ethylene oxide), PEG, **2**; poly(4-vinyl pyridine), P4VP, **3**; and a block copolymer with both PEG and P4VP segments, PEG₄₅-*b*-P4VP₁₈, **4**,



2, PEG

3, P4VP

4, PEG₄₅-*b*-P4VP₁₈

Whilst PEG is considered as a polymer substrate of great interest for biological applications due to its bio-compatibility^{36, 37}, P4VP has been widely applied as a building block to yield supramolecular polymers^{13, 38-43}. Finally, block copolymers not only facilitate the introduction of new functionalities in different segments of the polymer chain, but they also offer further control over microphase separation by regulating their hydrophobic/hydrophilic ratios⁴⁴⁻⁴⁶.

The materials are characterised by a combination of thermal, structural, spectroscopic and modelling techniques, in order to provide relevant insights on the role of the hydrogen-bonding network to assemble liquid crystalline glycosides²³. Complexation of block-copolymers has been used for different applications and materials, including light-responsive materials studied in our lab⁴⁵. More specifically, Ikkala and co-workers have reported several examples using P4VP as a polymeric matrix; and, for selected examples, they describe the self-assembly of P4VP block copolymers complexed with cholesteryl hemisuccinate⁴⁷ and with 3-pentadecylphenol⁴⁸. These and other precedent works, however, focus on the structural and compositional analysis, whilst a detailed model of the hydrogen-bonding network is still crucial to describe and predict complexation. The assembly of glycosides, tackled in the present work, as well as other systems containing multiple and resonating hydrogen bonds⁴⁹, is particularly challenging, and requires accounting for several hydroxyl groups potentially acting as hydrogen-donors and hydrogen-acceptors. Our approach can then open new forefronts to prepare supramolecular liquid crystal polymers as drug-delivery and cosmetic formulations⁵⁰⁻⁵⁴. In the long-term, the use of amphiphilic polymers will be beneficial to provide nanocarriers stealth effects that suppress opsonisation, to reduce interactions with the reticular-endothelial system, and to ultimately prolong circulation lifetime in blood.⁵⁵⁻⁵⁷

2. Experimental section

Materials preparation

The mannoside α ManPKO, **1**, was synthesised according to the process described in detail in³⁴, and can be reviewed as electronic supplementary information (ESI, section A). D(+)-mannose monohydrate and boron trifluoride, BF₃, were purchased from Sigma Aldrich and used without further purification. The palm kernel oil, PKO, was obtained from Golden Jomalina Food Industries Sdn. Bhd. (Malaysia), and the main components after reduction were lauryl (49%), myristyl (16%) and oleyl (7%) alcohols, determined by gas chromatography-mass spectroscopy, GC-MS. The chemical structures of α ManPKO and its intermediates were assessed by ¹H-NMR spectroscopy, using a Varian NMR Systems spectrometer at 400 MHz. D(+)-mannose was

peracetylated and PKO was reduced to alcohols, followed by glycosidation with PKO, and finally deacetylation, to yield **1** ^{35, 58, 59}.

Poly(ethylene glycol), PEG, with an average molar mass of $MW=12000 \text{ g}\cdot\text{mol}^{-1}$, and poly(4-vinylpyridine), P4VP, with $MW=60000 \text{ g}\cdot\text{mol}^{-1}$, were purchased from Sigma Aldrich and used without further modification. The poly(ethylene glycol)-*b*-poly(4-vinylpyridine) block copolymer, PEG₄₅-*b*-P4VP₁₈, was synthesised at the Institute of Materials Technology of Aragon (Zaragoza, Spain) by atom transfer radical polymerisation, and details of the synthesis and characterisation are also included as ESI (section B). The average molar mass is $MW=4350 \text{ g}\cdot\text{mol}^{-1}$, and the average polymerisation degrees of each block are $n=45$ and $m=18$, verified by MALDI-TOF and ¹H-NMR.

The polymeric complexes were prepared by weighting appropriate amounts of α ManPKO, **1**, and the corresponding polymers (**2**, **3** or **4**), in a Mettler Toledo Classic Plus digital balance ($\pm 0.01 \text{ mg}$), and dissolving in dichloromethane, DCM. The resulting solutions were stirred at room temperature during 24 h, and then allowed for slow evaporation during several days, until no additional weight loss was observed. Complexation was kept to 100% (full complexation), in terms of % of equivalent glycoside units respect to polymer repeating units. Three complexes were obtained, namely, PEG• α ManPKO, P4VP• α ManPKO and PEG₄₅-*b*-P4VP₁₈• α ManPKO.

Techniques and methods

The phase behaviour of α ManPKO, **1**, and the polymeric complexes **2**, **3** and **4**, was determined by polarised optical microscopy, POM, and differential scanning calorimetry, DSC. Liquid crystalline textures were assigned by using an Olympus BX51 microscope equipped with cross-polarising filters coupled to a Mettler Toledo FP82HT hot stage. Samples were sandwiched between two glass slides, heated to their respective isotropic phases, and then cooled down to room temperature, at a rate of $10^\circ\text{C min}^{-1}$. Samples for DSC were previously dried in a vacuum oven at 50°C for at least 3 hours over phosphorus pentoxide. Around 6 mg of the samples were then placed in 40 μl -sized aluminium pans, and the heat flow measured using a Mettler Toledo differential scanning calorimeter 822e, equipped with a Haake EK90/MT intercooler. Experiments were taken in subsequent heating and cooling cycles, ranging from -40°C to above their respective clearing temperatures, at rates of $\pm 5^\circ\text{C min}^{-1}$.

The phase structures were analysed by small and wide angle X-ray diffraction, SWAXS, using a SAXess, Anton Parr, equipped with a DX-Cu 12x0.45 SERFERT X-ray tube generating $\text{CuK}\alpha$ radiation at $\lambda = 1.542 \text{ \AA}$, attached to a TCS 150 temperature controller. Samples were introduced

inside 2-cm polyimide tubes sealed with Teflon tape, and subsequently dried in a vacuum oven for at least 48 h at 30°C. Data were collected in diffraction mode and analysed with OriginPro 8 software (OriginLab). SWAXS scatterings were obtained at room temperature ($T = 30^\circ\text{C}$) and then at liquid crystalline temperature ($T = 120^\circ\text{C}$, 135°C , 140°C , for PEG• α ManPKO, PEG₄₅-*b*-P4VP₁₈• α ManPKO and P4VP• α ManPKO, respectively), after cooling from the isotropic phase. Prior to each measurement, samples were held at the corresponding temperature for five minutes, to allow for thermal equilibration.

Temperature-dependent Fourier-transform infrared spectroscopy, FT-IR, was carried out using a Thermo Nicolet NEXUS 470 main bench (Thermo Scientific), with the sample placed in a Linkam TMS93 hot stage unit for temperature control ($\pm 0.1\text{K}$). The IR data were collected in transmittance mode and analysed with OMNIC (Thermo Scientific). Samples consisted of dispersions of the complexes into dry KBr (~1% by wt. of complex), and were prepared by grinding both components into fine powder and further compression at 200 MPa for at least 10 minutes, yielding homogeneous discs of 10 mm diameter and ~1.5 mm thickness. A pristine KBr disc was also prepared and measured as the background, immediately prior to measure the samples. Discs were heated into the isotropic phase of the complexes (above 150°C), cooled down to room temperature, and the IR spectra were collected in isothermal steps, at 5°C intervals. Each measurement was taken after the temperature was stabilised for at least five minutes, to allow for thermal equilibration. Spectra were collected in the frequency range $4000/400\text{ cm}^{-1}$, with a 4 cm^{-1} resolution, and recorded as an average of 64 scans.

Simulation Procedure

Single molecular units of α ManC₁₂, α ManC_{18:1} (see chemical structure of α ManPKO, *I*), PEG, P4VP and PEG₄₅-*b*-P4VP₁₈ were modelled using Avogadro⁶⁰ and were optimised in Gaussian09⁶¹ to get a stable structure of each compound. Using *packmol*, a free modelling tool⁶², a single layer of α ManPKO containing α ManC₁₂ (80% w/w) and α ManC_{18:1} (20% w/w), was built, with 52 C₁₂ molecules and 12 C_{18:1} molecules. The single layer (64 molecules total) was replicated and arranged allowing the tail groups of the lipids pointing toward each other at the centre of the bilayer and the head groups facing opposite direction to form a single bilayer. On the top and bottom of this glycoside bilayer, 32 molecules of PEG were added to form a bilayer complex. Similarly, two other bilayer systems have been built by replacing PEG with thirty-two P4VP and seven PEG₅-*b*-P4VP₃ chains (as a PEG₄₅-*b*-P4VP₁₈ model, retaining the approximate relative

composition of the block copolymer). For comparison purposes, a single bilayer of α ManPKO is also modelled. The four systems were simulated using AMBER14⁶³, at 303 K and 1 atm.

The four glycoside lamellar systems were then equilibrated using force field parameters from *ff99SB*⁶⁴ and *GLYCAM_06j*⁶⁵, in order to model the tails and sugar head groups of the glycolipids, respectively. The *gaff*⁶⁶ force field was used to model the PEG, P4VP and PEG₄₅-*b*-P4VP₁₈ systems. A non-bond cut off of 9 Å was applied in calculating non-electrostatic interactions, and the long-range electrostatic interactions were treated using the particle mesh Ewald method⁶⁷. The SHAKE algorithm was used to constrain covalent bonds involving hydrogen. The systems were heated gradually over 2 ns from 0 to 30°C in the *NVT* ensemble, using the Andersen thermostat ($\tau_p = 0.5$ ps) and a 1 fs time step. Subsequently, the systems were equilibrated under conditions of constant pressure *NpT* by anisotropic scaling. The Berendsen algorithm was used to achieve pressure coupling, with a coupling constant of 1 ps and a compressibility of 4.5×10^{-5} bar for anisotropic coupling.

Simulations ran for a total of 350 ns, but only the last 50 ns of trajectories were used for subsequent analysis. All the coordinates were archived every 5 ps. The hydrogen bonding analysis was performed using the *cpptraj* module of AMBER, defining the O–O distance to be ≤ 4 Å and an angle cut off of 120° from linearity. The local density profiles were calculated along the bilayer normal, taking the centre of the bilayer as the origin to determine the bilayer thickness. A detailed account of the methodologies is given by Manickam Achari *et al*⁶⁸.

3. Results and discussion

Phase behaviour and structure, POM, DSC and SWAXS

The phase behaviour of α ManPKO and its complexes was assessed by polarised optical microscopy, POM, and confirmed by differential scanning calorimetry, DSC. α ManPKO forms a monotropic smectic A phase below *ca.* 146°C, assessed by the appearance of battonêtes under the polarised microscope, which further coalesce into a focal conic fan texture, in coexistence with homeotropic regions. The PEG• α ManPKO, P4VP• α ManPKO and PEG₄₅-*b*-P4VP₁₈• α ManPKO complexes, also develop battonêtes on cooling from the isotropic melt, indicating the formation of smectic A phases below $T_{SmAI} \sim 150$ °C, see **Fig. 1**. These textures flash upon pressure at high temperatures, and motions cease on cooling to room temperature. These results indicate that the mesomorphism of the glycoside is transferred to the polymer complexes, and their liquid crystal phases vitrify on cooling⁶⁹⁻⁷¹.

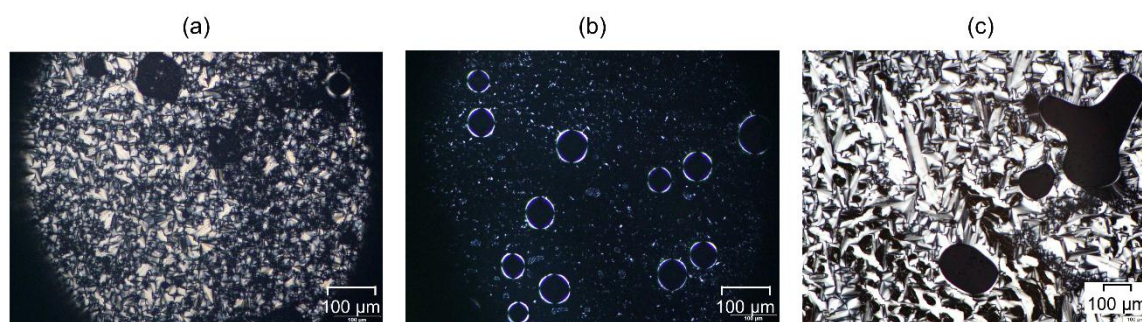


Figure 1. Polarised optical microscopy images, POM, of: (a) PEG• α ManPKO, (b) P4VP• α ManPKO and (c) PEG₄₅-*b*-P4VP₁₈• α ManPKO, showing their smectic A phases at $T \sim 130^\circ\text{C}$, evolved after cooling from their isotropic phases.

The mesomorphism of the complexes is also confirmed by our DSC observations, see **Fig. 2** and **Table 1**, even though we note that the thermal transitions associated to α ManPKO are weak and appear rather spread over the temperature axis. In **Fig. 2(a)**, the intense peak at $T_m \sim 60^\circ\text{C}$ indicates that the PEG chains also crystallise in the PEG• α ManPKO complex, whilst in **Fig. 2(b)** the glass transition of P4VP ($T_g \sim 135^\circ\text{C}$) is still visible in the complex, compare dotted and solid curves. These observations can be explained by the occurrence of phase separation between the polymer chains and the mannoside units.

Interestingly, it is also possible to detect a secondary glass transition at $T_g \sim 42^\circ\text{C}$ in the P4VP• α ManPKO curve, **Fig. 2(b)**, which could indicate certain segregation degree of the polymer chains, with some of them undergoing a plasticizing effect by the proximity of mannoside units. Another interesting phenomenon in the P4VP• α ManPKO curve is the appearance of a new melting point at $T_m \sim 13^\circ\text{C}$, which is absent in the pristine components³⁴. This temperature fits well to the melting point of dodecane and similar alkanes, and suggests that the alkyl chains of α ManPKO melt in the presence of the poly(4-vinyl pyridine) chains. The previous phase transitions of the PEG and P4VP complexes are also visible in the DSC curve of PEG₄₅-*b*-P4VP₁₈• α ManPKO, **Fig. 2(c)**, which is consistent with the occurrence of micro-segregation in block-copolymers. These transitional properties are summarised in **Fig. 2(d)**.

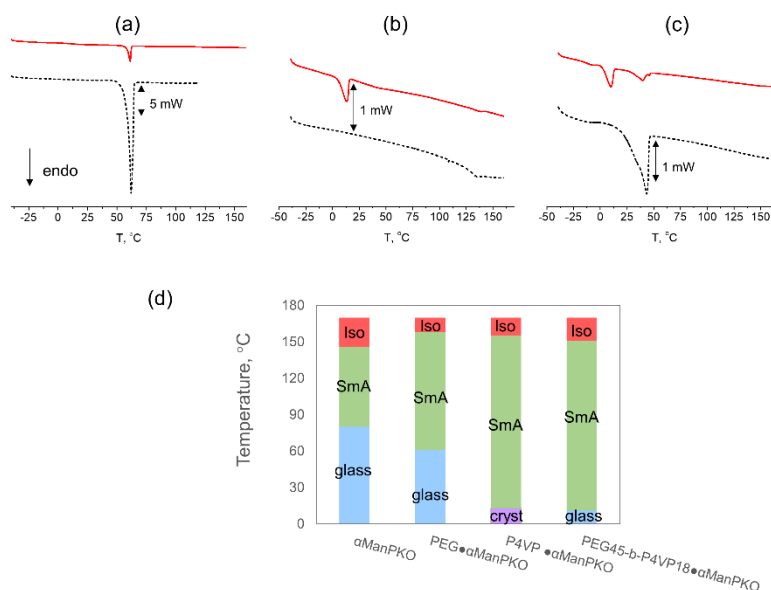


Figure 2. DSC thermograms obtained on cooling the complexes (solid curves) and the respective pristine polymers (dotted curves): (a) PEG• α ManPKO and PEG; (b) P4VP• α ManPKO and P4VP; and (c) PEG₄₅-*b*-P4VP₁₈• α ManPKO and PEG₄₅-*b*-P4VP₁₈. Y-axis: heat flow (mW), with the curves shifted arbitrarily; (d) phase diagram of the complexes.

Table 1. Thermal transitions of the complexes and pristine mannosides obtained by differential scanning calorimetry, DSC, on cooling from the isotropic phase.

Sample	T_g (°C)	T_m (°C)	ΔH_m (J·g ⁻¹)	T_{SmAI} (°C)	ΔH_{SmAI} (J·g ⁻¹)
α ManPKO	0	-	-	146	3.8
PEG	-	62	199.6	-	
P4VP	133	-	-	-	
PEG ₄₅ - <i>b</i> -P4VP ₁₈	-	43	43.6	-	
PEG• α ManPKO	13	61	13.0	158*	-
P4VP • α ManPKO	42 135	13	9.3	155*	-
PEG ₄₅ - <i>b</i> -P4VP ₁₈ • α ManPKO	-9	11 39 44	10.3 2.7 0.27	151*	-

*Clearing temperatures, T_{SmAI} , were obtained from POM.

The phase structures of the complexes are now investigated by small angle X-ray scattering, SWAXS, and for each complex we now display the corresponding scatterings in **Fig. 3**, obtained at the smectic A phase (upper) and room temperature (lower), on cooling from the isotropic melt. The results are consistent with the formation of layered smectic structures, with one strong signal at low angles (d_1) and a weaker signal ($d_2 \sim d_{1/2}$), associated to first and second order signals of the smectic layer periodicities, respectively, see **Table 2**. Samples also show broad diffuse signals at wide angles, associated to the alkyl chain distances of the α ManPKO molecules ($d_3 \sim 4.7$ - 4.9 Å). It is worth mentioning that PEG• α ManPKO exhibits two additional sharp signals overlapping the broad region, at $d_{3'} = 3.8$ Å and $d_{3''} = 4.6$ Å, indicative of partial crystallisation, which is in agreement with our DSC results in **Fig. 2(a)**.

These diffractograms are essentially identical to that of pristine α ManPKO and indicate the formation of smectic bilayers, $d_1 \sim 31$ Å, with certain degree of interdigitation of the alkyl chains (assuming an estimated averaged molecular length $d_l \sim 23$ Å and alkyl chains found in all-*trans* configuration³⁴). We note that, in the complexes, there is a slight increase in the layering spacing, which will be accounted for in terms of the molecular model developed in the next sections.

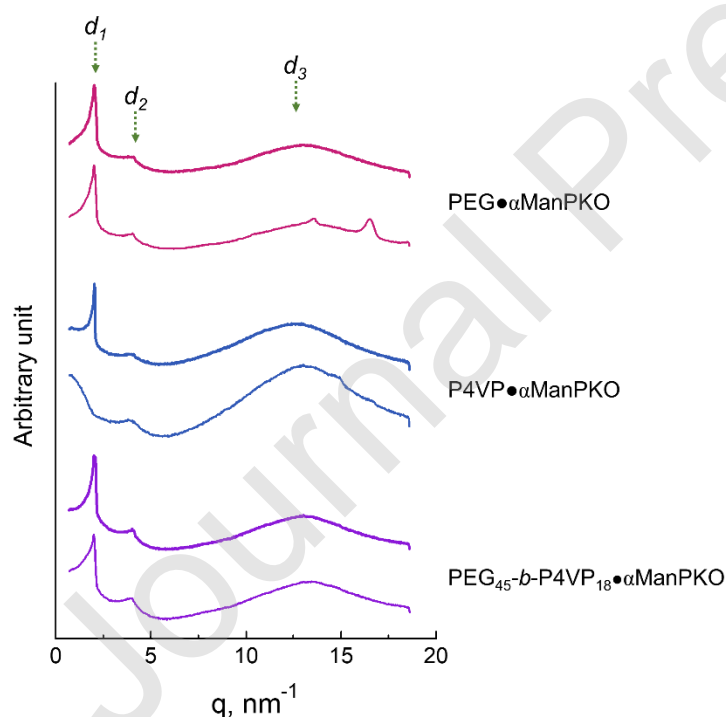


Figure 3. SWAXS scatterings of the complexes obtained in their smectic A phases (upper curves, T=140°C, 120°C and 135°C, for PEG• α ManPKO, P4VP• α ManPKO and PEG₄₅-*b*-P4VP₁₈• α ManPKO, respectively) and at room temperature (lower curves, T=25°C).

Table 2. Phase structure of the polymeric complexes and α ManPKO. Thickness of the bilayers/ d -spacings (d , Å) as obtained by small-wide angle X-ray scattering, SWAXS.

	Glass ^a			Smectic ^b		
	d_1	d_2	d_3	d_1	d_2	d_3
α ManPKO ^c	31.2	15.7	5.0	30.8	15.4	5.2
PEG● α ManPKO	31.2	15.6	3.8, 4.6	30.9	15.1	4.8
P4VP● α ManPKO	-	15.8	4.8	30.9	15.4	4.9
PEG _{45-<i>b</i>} -P4VP ₁₈ ● α ManPKO	31.3	15.6	4.7	31.2	15.6	4.8

^aT=25°C.

^bSmectic A phase scatterings of α ManPKO, PEG● α ManPKO, P4VP● α ManPKO and PEG_{45-*b*}-P4VP₁₈● α ManPKO are measured at 120°C, 120°C, 140°C and 135°C, respectively.

^cUnpublished results³⁴.

Molecular interactions, FT-IR

The specific interactions responsible for the phase behaviour of α ManPKO and its complexes are now investigated by temperature-dependent Fourier-transform infrared spectroscopy, FT-IR. **Fig. 4** displays the FT-IR spectra corresponding to α ManPKO, PEG● α ManPKO, P4VP● α ManPKO and PEG_{45-*b*}-P4VP₁₈● α ManPKO, obtained in their smectic phases, T=104°C. **Fig. 5** and **Fig. 6** highlight some specific IR vibration regions of interest.

As expected, the spectra of the complexes present several similarities, and contain different signals arising from the polymer chains and α ManPKO molecules³⁴. The C-C-O *st.* vibration regions of PEG and PEG● α ManPKO (1300 – 900 cm⁻¹) are shown with more detail in **Fig. 5(a)** and **5(b)**, respectively, where several PEG signals (broad arrows) appear overlapped with contributions from the glycoside molecules of α ManPKO, **Fig. 5(c)** (thin arrows). More specifically, the PEG● α ManPKO curve in **Fig. 5(b)** shows two maxima: at 1110 cm⁻¹, from PEG, and at 1060 cm⁻¹, from α ManPKO. We believe that the absence of step changes with temperature is caused by the inhibition of crystallisation of PEG in the KBr discs. The P4VP● α ManPKO curve in **Fig. 6(b)**, on other hand, displays blue-shifts of the 1600 cm⁻¹ peak associated to the P4VP ring vibration, **Fig. 6(a)**, which reveal the formation on cooling of new hydrogen bonds involving the pyridine ring.

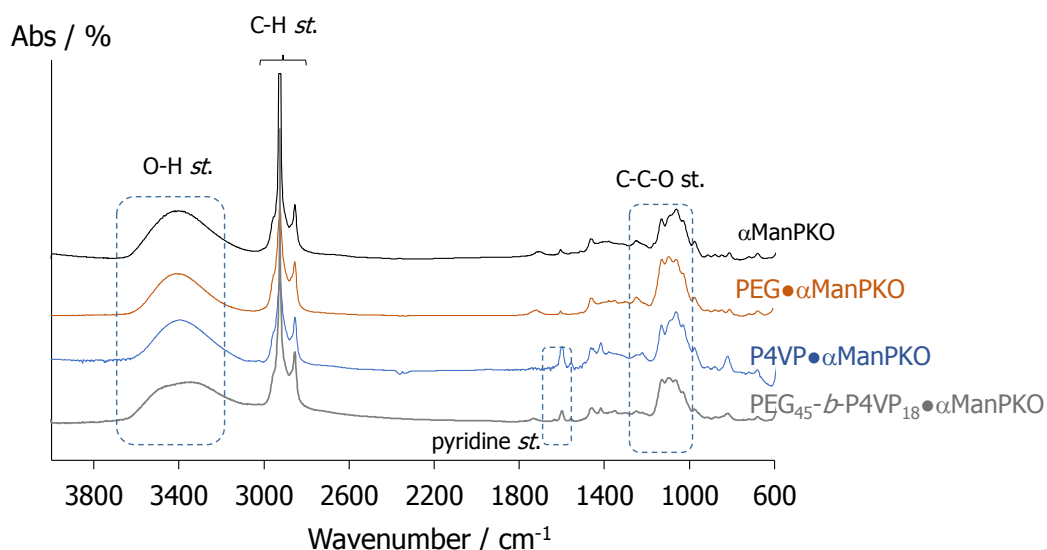


Figure 4. FT-IR spectra of the complexes and pristine α ManPKO, obtained at $T=104^{\circ}\text{C}$, highlighting some stretching, *st.*, regions of interest. Curves are shifted along the Y-axis arbitrarily.

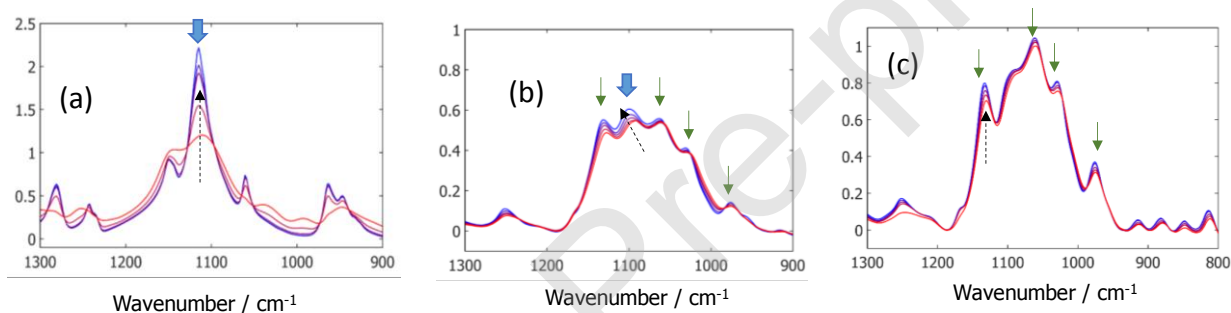


Figure 5. Temperature-dependent FT-IR spectra of (a) PEG, (b) PEG• α ManPKO and (c) α ManPKO, in the C-C-O *st.* region. Solid broad arrows indicate contributions from PEG, and solid narrow arrows, from α ManPKO. Dotted arrows indicate the direction on cooling from the isotropic phase to room temperature; Y-axes represent IR absorbance (%).

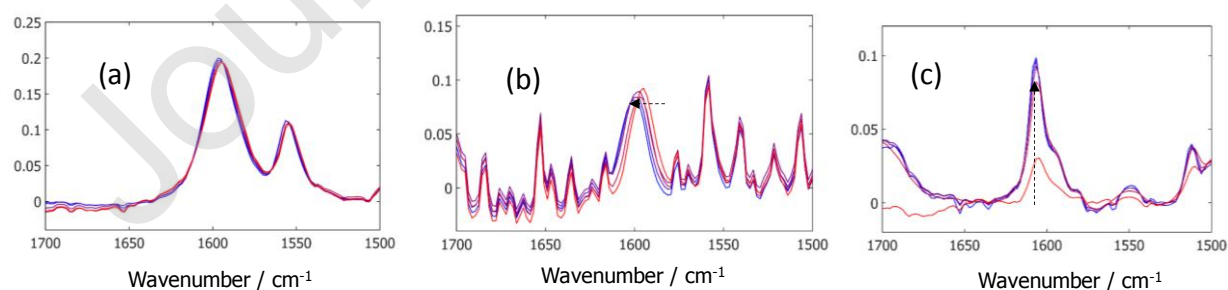


Figure 6. Temperature-dependent FT-IR spectra of (a) P4VP; (b) P4VP• α ManPKO and (c) α ManPKO. Dotted arrows indicate the direction on cooling from the isotropic phase to room temperature. Y-axes represent IR absorbance (%).

With the aim to investigate how potential interactions between the hydroxyl groups of α ManPKO and the polymer chains can contribute to assemble the new complexes, we now analyse with detail the OH stretching regions of PEG• α ManPKO and P4VP• α ManPKO in **Fig. 7(a)** and **7(b)**, respectively. The broad profiles of the OH *st.* bands, typical of sugars and glycosides, denote a distribution of hydroxyl groups found in different intermolecular environments, and the relatively low wavenumbers of the signal, $\nu \sim 3600\text{-}3000\text{ cm}^{-1}$, confirm the presence of extensive hydrogen-bonding in these complexes²³. The shift of the OH *st.* band towards lower frequencies on cooling indicates the progression to form stronger interactions within the hydrophilic domains of these complexes, due to the reconstruction of hydrogen bonds.

Fig. 7(c) displays the maxima of the OH stretching region as a function of the temperature, $\nu_{\text{OH-max}}$, and the values for PEG• α ManPKO and P4VP• α ManPKO are a few wavenumbers higher than α ManPKO (at comparable temperatures), which indicates that complexation weakens the interactions between the sugar heads of the glycoside molecules of α ManPKO. Interestingly, PEG₄₅-*b*-P4VP₁₈• α ManPKO displays the opposite trend respect to α ManPKO, suggesting the formation of stronger hydrogen bonds, and we will return to this observation later. The dynamic character of the hydrogen-bonding network can be semi-quantified by the slopes of the $\nu_{\text{OH-max}}$ graphs in **Fig. 7(c)**, also known as the wavenumber-temperature coefficients, WTC⁷². All samples under study, including the block copolymer, show similar values of WTC $\sim 0.260\text{ cm}^{-1}/\text{K}$. These also fall within the range of other sugars⁷² and glycosides²³ measured in their glassy states, but are smaller than values typically obtained in liquid crystal phases. Our results are indicative of hydrogen-bonding networks with low thermal sensitivity, in terms of Angell's strength and fragility^{73, 74}.

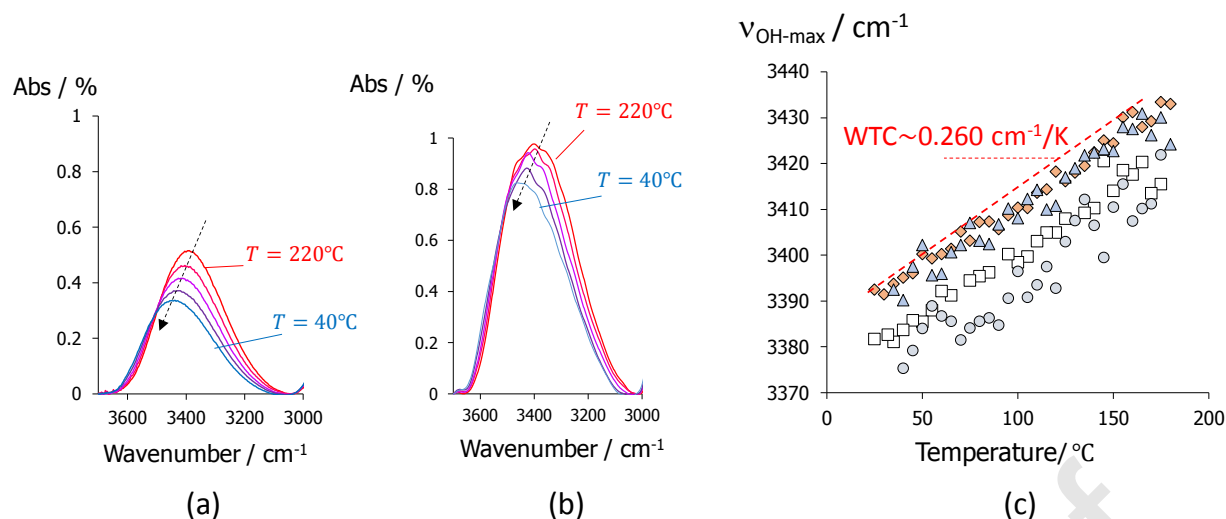


Figure 7. Temperature dependence of the IR OH stretching region corresponding to (a) PEG• α ManPKO and (b) P4VP• α ManPKO; (c) maxima of the OH stretching band frequency, $\nu_{\text{OH-max}}$, calculated for \diamond PEG• α ManPKO, \triangle P4VP• α ManPKO, \circ PEG₄₅-*b*-P4VP₁₈• α ManPKO and \square α ManPKO, as a function of the temperature. Dotted arrows indicate direction of the measurements on cooling.

Molecular Simulations

With the aim to assess the role of the intermolecular interactions on the phase structure of our complexes, studied in the previous sections, we have carried out molecular simulations on model systems. More specifically, we have modelled α ManPKO as a mixture of mannoside molecules containing $n=12$ (C12, α ManC₁₂ in *I*) and $n=18$ (C18:1 with a double bond at $n=9$, α ManC_{18:1} in *I*) alkyl chains, based on its average composition and in order to study the effect of unsaturation. This ratio was maintained in the simulations of the α ManPKO complexes, when additional PEG and P4VP segments were included, according to the *Simulation Procedure* described above in the experimental section.

The (thickness) d -spacing of the bilayer was determined by calculating the local density profile, and the area per lipid of α ManPKO was obtained by dividing the xy - plane of the bilayer with the total number of lipid present in a layer; results are shown in **Table 3**. The length of one fully stretched α ManPKO molecule with single chain C12 is about 20.2 Å, while the longer hydrocarbon chain, C18:1, extends to a maximum length of 27.5 Å (with a *trans* conformation around its double bond).⁶⁸

Snapshots of the resulting structures and conformations are displayed for PEG• α ManPKO, P4VP• α ManPKO, PEG₄₅-*b*-P4VP₁₈• α ManPKO and α ManPKO, in **Fig. 8(a)**, **8(b)**, **8(c)** and **8(d)**, respectively, and the results are in accordance with the formation of bilayers. The *d*-spacings obtained from simulations, see **Table 3**, agree with the experimental values reported above in **Table 2**. There is a slight underestimation of the layer thickness ($\leq 11.5\%$), except for P4VP• α ManPKO, which gives an excellent prediction with a positive +2.7% error. These deviations can be attributed to the length reduction of the complex used in simulation compared to the experimental conditions.

The *d*-spacing is always less than two times the fully stretched length of a single mannoside molecule, suggesting the adoption of *cis* conformers, favoured by the presence of the double bond between C₉—C₁₀ on the C18:1 chain, which induces kinks in the linear molecular structure. Nevertheless, we must consider that interdigitation of the alkyl chains affects the *d*-spacing of the bilayers, and visual inspection of **Fig. 8(c)** and **8(d)** also hints that some chains may interdigitate between the two layers. We also note that P4VP• α ManPKO shows signs of protrusion of the mannoside phase into the polymer region, see **Fig. 8(b)**. We then hypothesise that these mixing effects could be seen in the whole series if longer times were allowed, resulting in more accurate estimations of the bilayer structures.

Table 3. Calculated (modelled) thickness (*d*-spacing) of bilayers and area per lipid $A / \text{\AA}^2$.

Complexes modelled	<i>d</i> -spacing (Å)	Area per lipid, $A(\text{\AA}^2)$
PEG• α ManPKO	28.7 ± 0.8	31.7 ± 0.2
P4VP• α ManPKO	31.6 ± 0.2	24.1 ± 0.4
PEG ₄₅ - <i>b</i> -P4VP ₁₈ • α ManPKO	27.7 ± 0.6	29.9 ± 0.3
α ManPKO	29.6 ± 0.8	35.4 ± 0.5

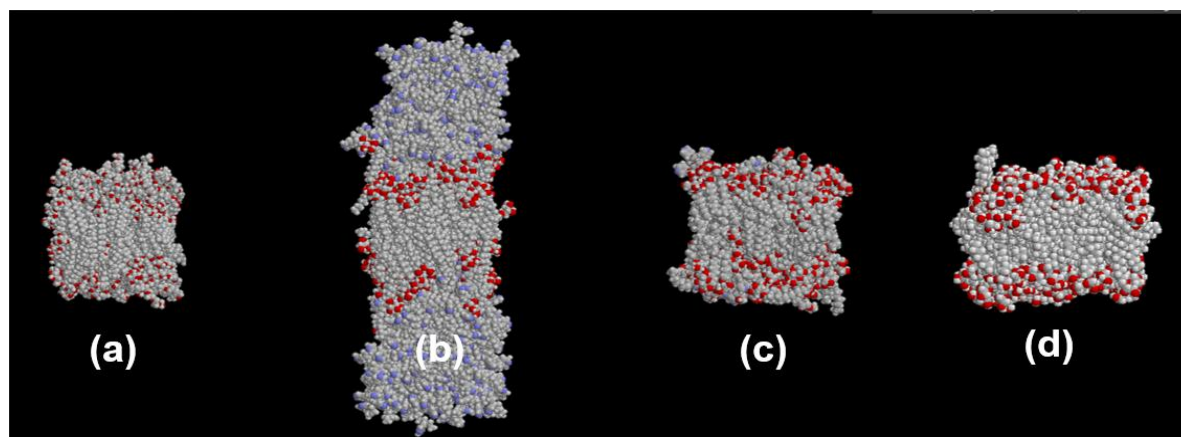


Figure 8. Snapshots of the molecular models used for (a) PEG• α ManPKO, (b) P4VP• α ManPKO, (c) PEG₄₅-*b*-P4VP₁₈• α ManPKO and (d) α ManPKO.

The FT-IR results have already evidenced the formation of specific interactions between the mannoside molecules and the respective polymer chains in the complexes, and we now quantify hydrogen-bonding *via* our molecular simulations. Based on previous findings^{34, 75}, we can rule out relevant intramolecular effects, and we then focus on intermolecular hydrogen-bonding between constituents moieties. **Fig. 9** illustrates the hydroxyl groups at the α ManPKO sugar heads capable to form hydrogen bonds, namely, O1H, O2H, O3H and O5H, and we note that these can act as both hydrogen donors and acceptors. PEG and P4VP segments contain hydrogen acceptors (oxygen and nitrogen atoms, respectively), and PEG segments also contain hydrogen donors (terminal hydroxyl groups, see **Fig. ESI7**).

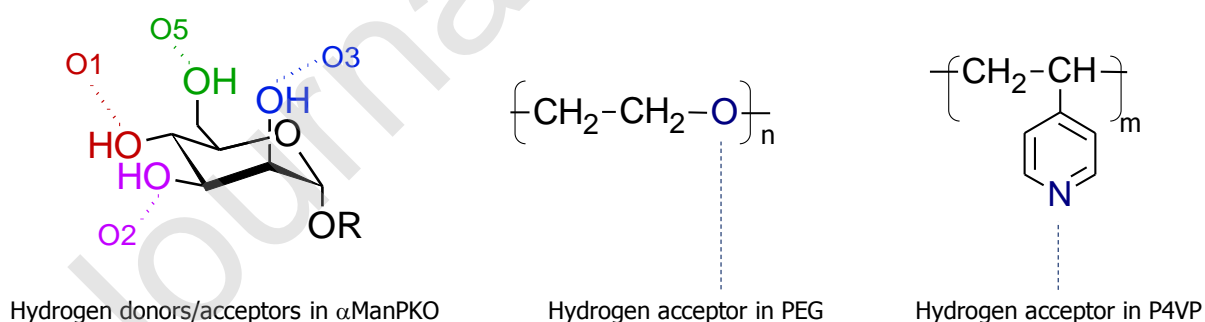


Figure 9. Labelling of the groups acting as hydrogen donors/acceptors in the complexes. We note that OH residual groups exist in both the PEG (O21, O28) and PEG₄₅-*b*-P4VP₁₈ (O201, O208) segments used during simulations, according to **Tables ESI3** and **ESI4**, and **Fig. ESI7**.

Table 4 summarises the hydrogen bonds (hits) formed in the bilayer complexes of our PEG• α ManPKO, P4VP• α ManPKO, PEG_{45-b}-P4VP₁₈• α ManPKO and α ManPKO models. The total number of hydrogen bonds between glycosides (C12 and C18:1) fall between 99 to 111 hit per-frame, with an average of 106 hit per-frame, and this indicates that the interactions between glycosides are not extensively modified by the presence and nature of polymer chains at the hydrophilic interlayer region, at least for pristine PEG and P4VP. Indeed, glycosides predominantly form hydrogen bonds *via* the equatorial O1 hydroxyl group, regardless of the presence and nature of the polymer chain.

Hydrogen-bonding between glycosides and the polymer chains does show some significant differences. In terms of overall interactions, the glycosides form more hydrogen bonds with PEG (52) than with P4VP (31), and the PEG segments preferentially form new hydrogen bonds with glycosides, rather than within other CH₂CH₂O groups in the PEG chain, see $13.92 + 2.57 > 11.18$ in **Table ESI3** (O21 and O28). By comparing the C12/C18:1-PEG and C12/C18:1-P4VP totals in **Table 4(a)** and **4(b)**, there seems to be a stronger tendency for C18:1 molecules to interact with P4VP than with PEG, and this can be also seen from **Table 4(c)** for PEG_{45-b}-P4VP₁₈• α ManPKO. These results cannot be explained, at least solely, by differences in hydrogen-bonding strength, since the v_{OH-max} (and WTC) values for PEG• α ManPKO and P4VP• α ManPKO in **Fig. 7(c)** almost overlap. Interactions must be then favoured by a stronger interfacial mixing of PEG chains and mannoside molecules at the bilayer boundaries, due to the hydrophilic nature of the PEG chains. In the case of P4VP, such interfacial interactions must be somehow hindered by the more hydrophobic nature of the pyridine ring, probably coupled with steric effects, and perhaps offset by the stereochemistry of C18:1.

Interestingly, the PEG_{45-b}-P4VP₁₈• α ManPKO model provides different tendencies for hydrogen-bonding respect to the pristine polymers, see **Table 4(c)**. As a first observation, the O2H group in the mannoside tends to form more hydrogen bonds than O1H, and P4VP is now the preferred polymer segment to interact with the glycosides, respect to PEG ($8.464 > 6.121$ in the total columns). These changes in the local distribution of hydrogen bonding could be favoured by a better interfacial mixing between polymer chains and glycosides bilayers, due to the amphiphilic character of the block-copolymer. As a result, the pyridine group of P4VP is capable to form stronger interactions with the hydroxyl groups of α ManPKO than PEG⁴, which is in excellent agreement with the shift to lower frequencies in the IR OH stretching band of PEG_{45-b}-P4VP₁₈• α ManPKO reported above in **Fig. 7(c)**.

Table 4(a). Hydrogen-bonding hits per frame, corresponding to the PEG● α ManPKO model. First molecular unit acts as donor, second as acceptor (for example, in C12 – PEG, C12 is the hydrogen donor, and the PEG unit the hydrogen acceptor). Oxygen notation according to Fig. 9 and Fig. ESI7.

	C12-C12	C12-C18:1	C18:1-C18:1	C18:1-C12	Total	C12-PEG	C18:1-PEG	Total
O1	18.14	5.59	2.81	3.54	30.07	13.07	2.87	76.08
O2	17.85	4.11	1.88	4.11	27.96	13.99	2.50	72.41
O3	17.98	2.69	2.24	3.63	26.54	10.69	2.47	66.25
O5	13.47	1.84	2.09	1.71	19.11	5.41	1.03	44.65
Total	67.44	14.23	9.02	12.99	103.68	43.16	8.87	52.03

Table 4(b). Hydrogen-bonding hits per frame corresponding to the P4VP● α ManPKO model.

	C12-C12	C12-C18:1	C18:1-C18:1	C18:1-C12	Total	C12- P4VP	C18:1-P4VP	Total
O1	18.45	7.94	0.02	6.80	33.21	6.29	4.09	10.37
O2	16.85	7.03	0.85	6.06	30.79	5.75	0.57	6.32
O3	19.20	3.58	2.86	2.30	27.94	6.38	2.76	9.14
O5	14.75	1.51	1.88	0.31	18.45	4.37	1.24	5.60
Total	69.25	20.06	5.61	15.47	110.39	22.78	8.65	31.43

Table 4(c). Hydrogen-bonding hits per frame corresponding to the PEG₄₅-*b*-P4VP₁₈● α ManPKO model.

	C12-C12	C12-C18:1	C18:1-C18:1	C18:1-C12	Total	C12-PEG	C18:1-PEG	Total	C12-P4VP	C18:1-P4VP	Total
O1	20.89	3.01	1.61	6.01	31.52	1.296	0.840	2.136	2.878	0.0004	2.878
O2	24.82	3.51	0.69	5.25	34.27	1.476	0.257	1.732	2.807	0.0000	2.807
O3	18.41	4.10	1.81	3.47	27.79	1.286	0.037	1.323	1.906	0.0000	1.906
O5	13.04	0.75	1.35	0.86	16.00	0.906	0.025	0.930	0.874	0.0000	0.874
Total	77.16	11.37	5.47	15.58	109.59	4.963	1.158	6.121	8.464	0.0004	8.464

Table 4(d). Hydrogen-bonding hits per frame corresponding to the α ManPKO model.

	C12-C12	C12-C18:1	C18:1-C18:1	C18:1-C12	Total
O1	20.41	4.82	2.26	3.89	31.38
O2	15.98	2.32	2.70	1.88	22.88
O3	18.37	3.94	2.33	2.33	26.97
O5	12.69	2.68	1.12	2.18	18.66
Total	67.45	13.76	8.41	10.28	99.90

Conclusions

We have prepared complexes of the so-called α ManPKO mannoside with different polymeric substrates, resulting in three new supramolecular polymers with smectic A mesomorphism, following a facile method to yield new formulations containing natural-based liquid crystal carbohydrates, and their lyotropic properties in water solutions are under current evaluation. The polymeric segments are located at the interface of glycoside bilayers, stabilised by specific interactions with the α ManPKO molecules.

The interfacial miscibility between the poly(ethylene oxide) segments and the mannosides promotes hydrogen-bonding in the PEG• α ManPKO complex, whilst low solubility and steric effects may restrict the interactions involving the poly(4-vinyl pyridine) chains and α ManPKO in the P4VP• α ManPKO complex. Alternatively, the amphiphilic character of the PEG₄₅-b-P4VP₁₈ block-copolymer seems to facilitate the interactions of the glycosides with the P4VP units in the PEG₄₅-b-P4VP₁₈• α ManPKO complex. Hence, it is possible to establish stronger hydrogen-bonding with the mannoside molecules, due to the high hydrogen acceptor character of the pyridine ring.

The detailed experimental/modelling analysis of the hydrogen bonds allows to discriminate interactions between different components and hydrogen acceptors and donors within sugar heads, thus opening new strategies to modify the properties of glycosides by tuning and monitoring the hydrogen-bonding network. We plan to extend this methodology to calculate the interactions using other glycosides and varying the relative block sizes, and to introduce new functionalities (such as light-responsive molecules) in different polymer blocks capable to simultaneously yield strong hydrogen bonds and favourable interfacial mixing.

Credit author statement

Nurul Fadhilah Kamalul Aripin. Conceptualization, Data curation, Data curation, Writing - original draft, Writing - review & editing, Funding acquisition.

Jonathan Heap. Experimental work, Data curation, Formal analysis.

Rafael Piñol. Experimental work, Data curation, Methodology.

Vijayan M. Achari. Data curation, Formal analysis, Writing - original draft.

Alfonso Martinez-Felipe. Conceptualization, Investigation, Writing - original draft, Writing - review & editing, Funding acquisition.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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