Enhancing Liquid-Crystalline Order and Fluidity of a Hydrophobic Host with Trace Hydrophilic Solvent

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Abstract. An impurity usually degrades the crystalline order of the host material. Here we investigate an intriguing counterexample where an impurity strongly enhances the ordering of a thermotropic liquid crystal while increasing its fluidity. At 5 wt%, glycerol enhances the smectic layering of the hydrophobic host itraconazole by reducing the random molecular offsets in each layer, creating more compact layers with nearly zero thermal expansion. We attribute glycerol's effect to its cross-linking of itraconazole by hydrogen bonds within a monolayer. This system suggests the intriguing prospect of enhancing the structural order of a hydrophobic thermotropic liquid crystal with a small dose of protic solvent. This effect is potentially related to the dual role of glycerol in a bio-protective glass, namely, plasticizer for global mobility and anti-plasticizer for local mobility.

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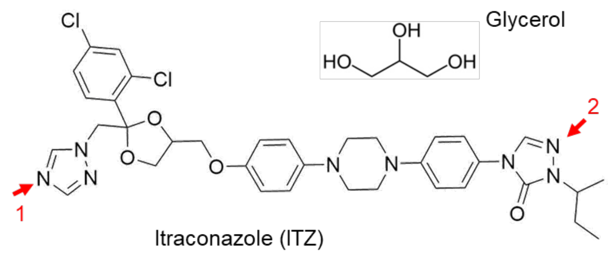
Introduction

A liquid crystal (LC) has liquid-like fluidity and crystal-like anisotropy, a combination of properties that enables many applications of LCs as displays, sensors, and anisotropic solvents.[1] For glass-forming LCs,[2,3,4,5] it is possible to create solid materials whose structures are formed in the fluid state and then frozen in the glassy state,[6] and through vapor deposition, to manipulate mesoscopic ordering at the deposition interface to create oriented anisotropic glasses.[7]

LC formation is a process of spontaneous self-assembly and it is not surprising that an impurity typically frustrates the process. For the well-studied thermotropic system 8CB, non-mesogenic solvents[8] and nanoparticles[9,10] reduce the stable temperature range of the smectic phase. In this context, the glycerol-itraconazole (ITZ) system is a remarkable counterexample with potential applications. ITZ (Scheme 1) is a WHO Essential Medicine for treating fungal infections. Because of its low aqueous solubility, ITZ is formulated as an amorphous or reduced-crystallinity solid to enhance its bioavailability. ITZ is a thermotropic LC with a nematic and a smectic phase,[11,12] and the addition of glycerol strongly alters its phase behavior.[13,14] At 5 wt%, glycerol lowers the energy of the smectic phase relative to the isotropic phase by a factor of 20 in comparison with the amount in pure ITZ.[13] A similar stabilizing effect seems to occur when ITZ is exposed to water vapor.[15] In contrast to these protic solvents, other non-mesogenic dopants show no stabilizing effect, including structurally similar antifungals[16] and polymers.[17]



Scheme 1. Molecular structures of itraconazole (ITZ) and glycerol. Arrows 1 and 2 indicate the preferred hydrogen-bond acceptors based on crystal structures.

The ordering effect of glycerol on ITZ differs from the classic lyotropic LC phenomenon where a non-mesogenic amphiphile becomes a LC upon hydration.[18,19] The glycerol-ITZ case is different because ITZ is non-amphiphilic and is already a thermotropic LC. Understanding this system could help broaden the application of dopants in controlling LC structures and their fluidity.

Here we report extensive X-ray scattering measurements to characterize glycerol's effect on the LC structure of ITZ. We find that glycerol causes the smectic layers to be more compact with more sharply defined density modulation and that it changes the layer thermal expansion from large and positive to small and negative. This is a remarkable effect considering that glycerol increases the system's fluidity. This effect occurs because glycerol molecules reduce the random molecular offsets within a layer by cross-linking the ITZ molecules through hydrogen bonds. We discuss the application of this effect to enhance fluidity and ordering in other non-amphiphiles and relate it to glycerol's effect on bio-protective glasses.

Materials and Methods

Materials and Sample Preparation. Itraconazole (ITZ, 98% pure) was purchased from Alfa Aesar (Ward Hill, MA) and glycerol was purchased from Sigma-Aldrich (St. Louis, MO). ITZ with 5 wt% glycerol was prepared by dissolving 21.6 mg glycerol in 1 mL methanol and 410 mg ITZ in 20 mL dichloromethane.[13] The two solutions were mixed, without causing precipitation, and the combined solution was evaporated overnight in a fume hood. The resulting solid material was ground to a free-flowing powder.

Differential Scanning Calorimetry (DSC). DSC was performed with a TA Q2000 differential scanning calorimeter. A sample 3 – 6 mg in mass was sealed in an aluminum pan and heated or cooled at 10 K/min to measure the glass transition temperature and LC transition temperatures.

X-ray Scattering. X-ray scattering was performed using a Cu Kα source with two setups that covered different q ranges. In Setup 1, a Bruker D8 Discover with an Instec mK2000 heater was used to cover $q = 0.1 – 1$ Å^{-1}. In Setup 2, a Bruker D8 Venture Photon III four-circle diffractometer with an Oxford Cryostream 700 temperature controller was used to cover $q = 0.3 – 2$ Å^{-1}. Diffraction angles were calibrated with silver behenate and D-mannitol crystals measured under the same conditions. Scattering measurements were performed in transmission using samples placed in capillary tubes (Charles Supper, MA, 1.5 mm OD, 10 μm wall thickness). To prepare a sample, a solid powder in a capillary tube was melted at 453 K and the tube was flame sealed. The molten sample was cooled at a controlled rate to form a glass. In a typical measurement, a glassy sample was heated to the equilibrium liquid state and was cooled on the instrument (at 0.007 K/s) back to the glassy state. At each temperature, the sample was held for 5 minutes to equilibrate and measured for 5 or 10 minutes (exposure time). For all our samples, the two-dimensional scattering patterns were isotropic, indicating no preferred orientation of LC domains; they were integrated azimuthally using Datasqueeze, DIFFRAC.EVA, or Apex3 to yield the 1D intensity versus q profiles. The data from the two setups were combined by matching the overlapping regions.

Results

Figure 1 shows the DSC traces of pure ITZ and ITZ containing 5 wt% glycerol, hereafter referred to as G5-ITZ. We focus on this composition because it shows the largest stabilizing effect in terms of the smectic/isotropic transition enthalpy.[13] Our DSC traces agree well with those of Rams-Baron *et al.*[14] Upon cooling from the isotropic liquid, ITZ shows a transition to the nematic phase at 363 K (T_{NI}), a transition to the smectic phase at 347 K (T_{SN}), and a glass transition at 328 K (T_g).[12] The phase sequence is reversed on reheating. In the presence of 5 wt% glycerol, ITZ shows a single LC transition at 352 K from the isotropic to the smectic phase with much larger latent heat, ΔH_{SI} = 12 J/g, compared to 0.6 J/g for pure ITZ.[13] This indicates a strong energetic stabilization of the smectic phase by glycerol. This effect is remarkable since other dopants in ITZ have the opposite effect,[16,17] namely, they decrease ΔH_{SI}. Another notable effect of glycerol is that it significantly reduces the T_g of ITZ, by 2 K according to our data and 4 K according to Ref. 13. Consistent with its reduced T_g, G5-ITZ has shorter dielectric relaxation times than ITZ.[14] Thus, glycerol simultaneously stabilizes and fluidizes the smectic phase.

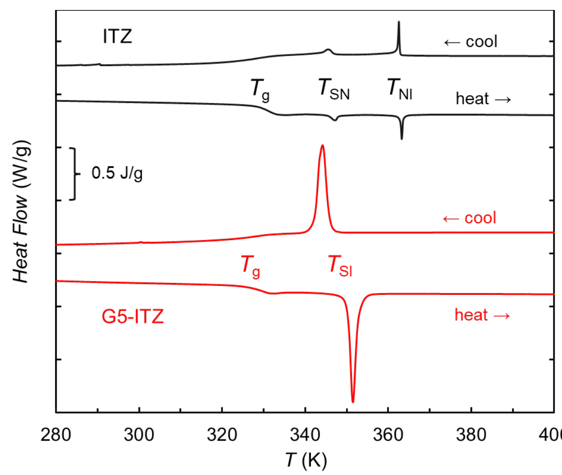


Figure 1. DSC traces of ITZ and G5-ITZ during cooling and subsequent heating at 10 K/s. The labeled transitions are: isotropic-nematic (T_{NI}), nematic-smectic (T_{SN}), isotropic-smectic (T_{SI}), and glass transition (T_g).

Effect of Glycerol on the Smectic Structure. Figure 2 shows the X-ray scattering patterns of the glasses of ITZ and G5-ITZ, both prepared by cooling from the isotropic liquid (at 0.007 K/s) and measured in the glassy state at 298 K. The sharp peaks at low q are the scattering by the smectic layers; the broad peak near 1.35 Å^{-1} is associated with the lateral packing of the rod-like molecules within a layer. Pure ITZ shows the first- and second-order smectic scattering (n = 1 and 2), with the first-order peak being stronger. G5-ITZ exhibits a different pattern where the second-order peak is the strongest and the third-order peak is observable. The relative intensities of the scattering peaks contain information on the density modulation perpendicular to the smectic layers: a sinusoidal modulation yields a single peak at n = 1 and a more sharply defined modulation yields higher-order peaks. Thus, glycerol causes the smectic layers to be more sharply defined. Later we will present a structural model to quantitatively explain the change of the scattering pattern.

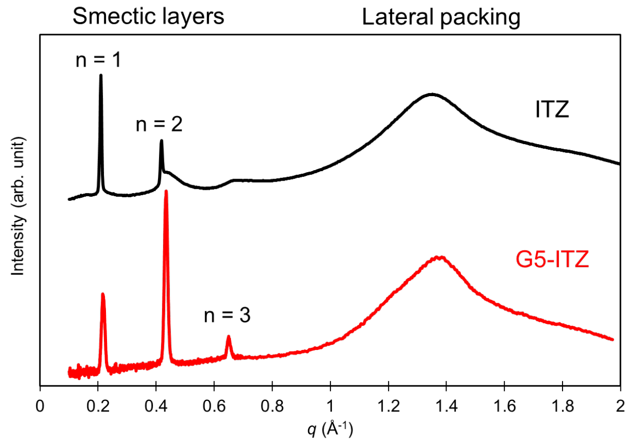


Figure 2. X-ray scattering patterns of ITZ and G5-ITZ glasses measured at 298 K. The sharp peaks at low q are the scattering by the smectic layers; the broad peak at 1.35 Å^{-1} is associated with the lateral packing of molecules in a layer.

Figure 3 shows the smectic-layer spacing L of ITZ and G5-ITZ as a function of temperature. Both were measured during cooling from the isotropic liquid at 0.007 K/s. L is given by $L = 2\pi/q_1$, where q_1 is the position of the first-order smectic scattering peak obtained by curve fitting (see Figure S1). The result for pure ITZ in the equilibrium liquid state was previously reported by Yu *et al.*[20] The break in each dataset corresponds to the glass transition (T_g). Above the break, the system is an equilibrium liquid and below the break, a glass.

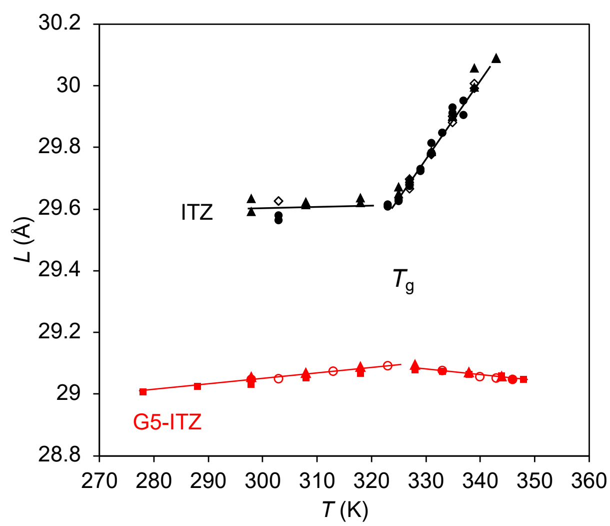


Figure 3. Smectic-layer spacing of ITZ and G5-ITZ. The different symbols of the same color represent independent measurements with different samples.

For pure ITZ in the equilibrium liquid state, L decreases rapidly with cooling, with a thermal expansion coefficient α_{Sm} of 932 (20) ppm/K. This value is surprisingly large for a molecular liquid and has been attributed to the intralayer disorder that increases with temperature (see below).[20] In the glassy state, α_{Sm} is reduced, as expected, to 42 (19) ppm/K. The doping of glycerol in ITZ significantly decreases the layer thickness L, by 3% at 340 K. In addition, glycerol changes α_{Sm} from a large positive value (932 ppm/K) to a small negative value, -81 (8) ppm/K. In the glassy state, G5-ITZ has a positive α_{Sm}, 57 (6) ppm/K, comparable to that for the pure ITZ glass.

Figure 4 shows the areas of the smectic scattering peaks A_n where n = 1, 2, and 3 as functions of temperature for ITZ and G5-ITZ. With cooling below the smectic temperature (T_{SN} for ITZ and T_{SI} for G5-ITZ), these areas increase, as expected, and the rise is significantly faster in G5-ITZ. As already seen in Figure 2, glycerol alters the orders of the scattering-peak areas: for pure ITZ, $A_1 > A_2$ and $A_3 = 0$; for G5-ITZ, $A_2 > A_1 > A_3$.

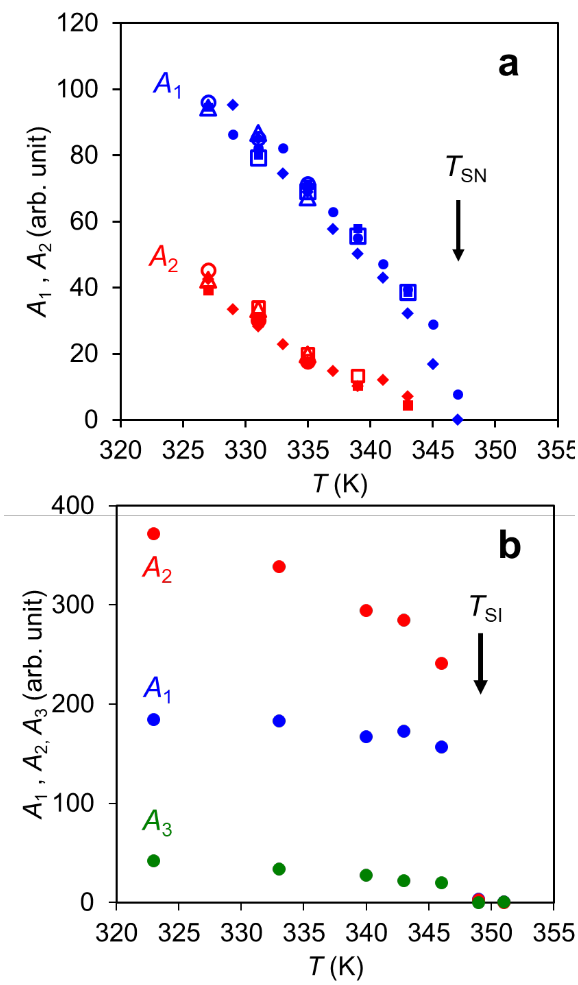


Figure 4. Areas A_n of smectic scattering peaks of (a) ITZ and (b) G5-ITZ measured during cooling from above the smectic transition temperature (T_{SN} for ITZ and T_{SI} for G5-ITZ).

To fully characterize glycerol's effect on the smectic phase of ITZ, we now turn to the lateral packing within a smectic layer. This information is obtained from the broad scattering peak at 1.35 Å^{-1} (Figure 2). Figure 5 shows the effect of glycerol on the spacing d_L of lateral packing and its correlation length ξ_L. The data were collected during cooling from the isotropic liquid. d_L and ξ_L are calculated from $d_L = 2\pi/q_L$ and $\xi_L = 2/w_L$, respectively, where q_L and w_L are the position and the full width at half maximum of the lateral-packing peak obtained by fitting the peak with a Lorentzian function (see SI). The equations to calculate d_L and ξ_L follow the fact that a Lorentzian scattering peak corresponds, through a Fourier transform, to an exponentially damped sinusoidal density modulation of wavelength $2\pi/q_L$ and decay length $2/w_L$.[21] These two parameters characterize, respectively, the lateral molecular spacing and the regularity of packing.

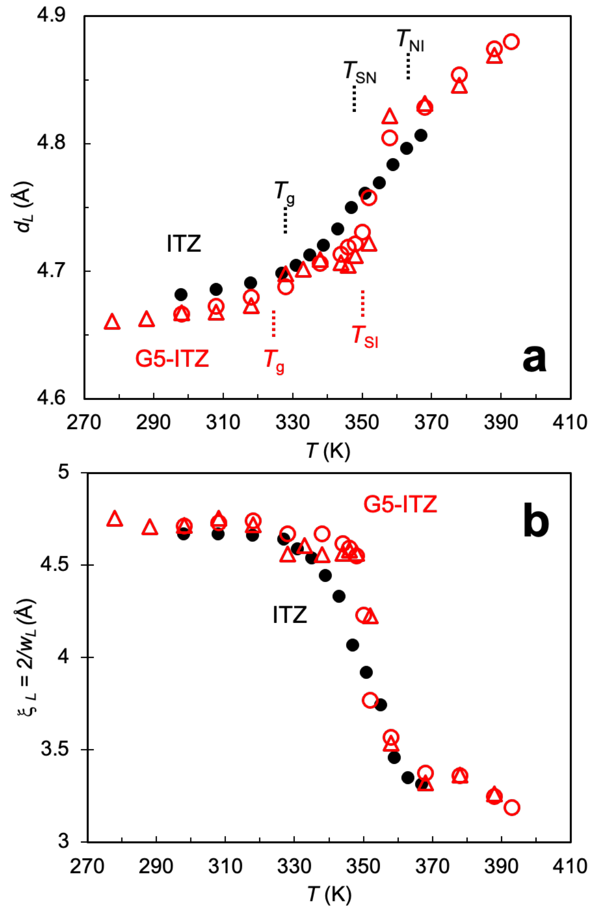


Figure 5. Spacing (a) and correlation length (b) for the lateral packing within a smectic layer of ITZ (solid circles) and G5-ITZ (open symbols) during cooling from an isotropic liquid.

Figure 5a shows that on cooling, the lateral spacing d_L decreases. For pure ITZ (solid circles), the decrease is smooth through the LC transitions at T_{NI} and T_{SN}. Further cooling to T_g and below slows down the decrease of d_L, as expected. For G5-ITZ (open symbols), above 360 K, d_L decreases linearly with cooling, and below 360 K, d_L drops sharply. This drop occurs at 10 K above the smectic transition T_{SI}, i.e., in the isotropic liquid. This indicates a strong pre-transition effect (tightening of lateral packing before the smectic phase is entered).[22] In the glassy state ($T < T_g$), G5-ITZ has smaller d_L than ITZ, indicating tighter lateral packing, and approximately the same thermal expansion coefficient. The tighter lateral packing, combined with the thinner smectic layers (Figure 3), suggests that the glycerol-doped material is denser, despite its higher fluidity indicated by lower T_g (Figure 1) and shorter relaxation time.[14] Thus glycerol is a plasticizer with respect to mobility but an "anti-plasticizer" with respect to structure. This phenomenon is analogous to glycerol's effect on a trehalose glass: at 5 wt %, glycerol is a plasticizer for global mobility and an anti-plasticizer for local mobility,[23] a connection we will discuss later.

Figure 5b shows the effect of glycerol on the lateral correlation length ξ_L. For pure ITZ, ξ_L rises as the nematic phase is entered at 360 K (T_{NI}), indicating that orientational order leads to more regular packing; the rise continues through the smectic transition at T_{SN}, and is frozen below T_g. For G5-ITZ, the ξ_L curve roughly traces that of pure ITZ, despite lacking a nematic phase. The ξ_L of G5-ITZ rises near 360 K, 10 K above the smectic transition at T_{SI}, again indicating a pre-transition effect. On entering the smectic phase at T_{SI} (near 350 K), ξ_L increases more quickly in G5-ITZ than in pure ITZ, reaching a higher value; further cooling freezes ξ_L in the glassy state at approximately the same level as in pure ITZ. Overall, the effect of glycerol on the lateral packing is more subtle than on the smectic structure, consistent with the description of a smectic LC as having crystal-like interlayer structure and liquid-like intralayer structure. Nevertheless, glycerol causes the intralayer structure to be more ordered.

Discussion

We have shown that low-concentration glycerol can significantly increase the smectic order of ITZ. At 5 wt%, glycerol increases the energetic stability of the smectic phase (Figure 1),[13] makes the smectic layers more compact and more thermally stable (Figure 3), sharpens the profile of density modulation (Figure 4), and makes intralayer packing tighter and more regular (with longer correlation length, Figure 5). Below we place the glycerol-ITZ system on McMillan's ordering diagram and propose a structural model for glycerol-doped ITZ.

McMillan's Theory. Figure 6 shows McMillan's smectic ordering diagram[22] where we indicate the proposed positions for ITZ and G5-ITZ. McMillan's mean-field theory predicts the existence of a smectic phase as a function of temperature and the driving force for smectic ordering captured by the dimensionless parameter α. At $\alpha < 1$, the smectic phase during heating first transforms to the nematic phase and then to the isotropic phase; at $\alpha > 1$, it transforms directly to the isotropic phase. In this theory, pure ITZ would have an α value slightly below 1, reflecting its smectic/nematic/isotropic phase sequence (Figure 1), and G5-ITZ would have an α value slightly above 1, thus having no nematic phase. This theory predicts a jump of the entropy of transition from ITZ to G5-ITZ, consistent with the increase of the smectic transition enthalpy ΔH_{SI} (Figure 1). Quantitatively, the predicted increase of ΔH_{SI} is significantly smaller than the observed (a factor 2 vs 20). From ITZ and G5-ITZ, the theory predicts a sharper rise of smectic order in G5-ITZ for the same undercooling below the transition temperature, in qualitative agreement with experiment (Figure 4). In this theory, α is a fitting parameter, that does not provide a molecular explanation for glycerol's stabilizing effect on the smectic phase of ITZ, a question considered below.

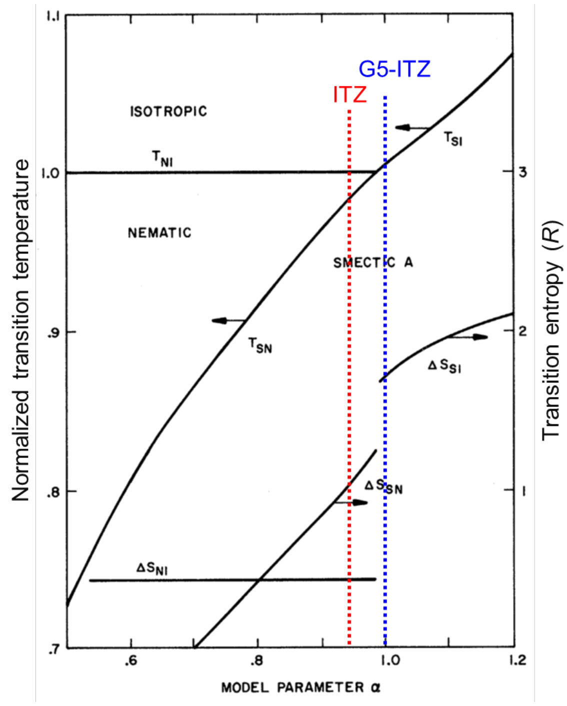


Figure 6. Ordering diagram of McMillan's theory with the proposed positions of ITZ and G5-ITZ.[22] As the driving force for smectic ordering (α) increases, the smectic phase exists up to higher temperature and has higher transition entropy. ITZ (red line) is situated to the left of the tricritical point ($\alpha = 1$) and G5-ITZ (blue line) to the right. Figure adapted with permission from Ref 22. Copyright 1971 American Physical Society.

Molecular Model for Glycerol's Stabilization of Smectic Layers. Figure 7 illustrates a structural model for the effect of glycerol on the smectic layers of ITZ. This model builds on the explanation of Yu *et al.*[20] for the unusually large thermal expansion of the smectic layers of pure ITZ. The α_{Sm} value of pure ITZ, 932 ppm/K, is anomalous since this one-dimensional expansion coefficient exceeds the typical value for the volumetric expansion α_V for molecular liquids (e.g., α_V = 750 ppm/K for *o*-terphenyl).[20] It is proposed that the rod-like molecules within a layer are randomly offset from each other along the layer normal. With heating, the random offset increases, leading to a greater increase of layer thickness than expected for normal thermal expansion. In other words, the large α_{Sm} value is the combined result of normal thermal expansion and structural change (increase of intralayer disorder). A similar situation exists for saperconazole (SAP), an analog of ITZ where the Cl atoms are replaced by F (Scheme 1). The smectic layers of SAP also have an unusually large thermal expansion coefficient, α_{Sm} = 686 (11) ppm/K,[24] which we attribute to the same effect.

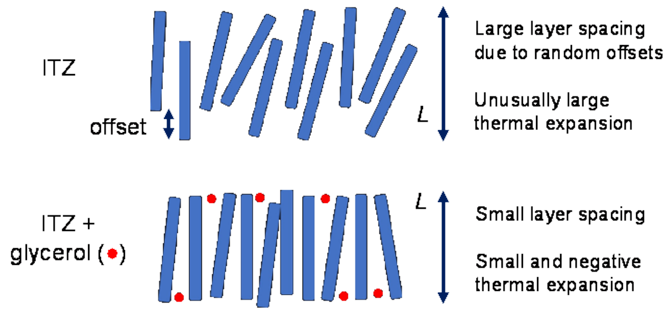


Figure 7. Models for the smectic layer of ITZ (top) and glycerol-doped ITZ (bottom).

We propose that the presence of glycerol reduces the intralayer molecular offsets in pure ITZ. This is illustrated in Figure 7 (bottom) where the red dots represent glycerol molecules. This model immediately explains the more compact smectic layers (smaller *L* in Figure 3). Since the random molecular offsets within a layer are reduced, the observed thermal expansion coefficient should be closer to that for normal thermal expansion. This explains the reduced α_{Sm} value in the presence of glycerol. This model does not immediately explain the *negative* thermal expansion of glycerol-doped ITZ, which could result from the reduction of conformational disorder and the optimization of hydrogen bonding as discussed below.

The proposed model also explains the effect of glycerol on the relative intensities of the smectic scattering peaks (Figures 2 and 4). Figure 8 shows the simulated scattering patterns for two simple molecular models for the smectic layers that have different intralayer molecular offsets (see the .cif files in the SI). In these models, the ITZ molecules have the conformation and the antiparallel arrangement observed in the crystal.[25] At present these models are intended to reproduce the sharp smectic scattering peaks, but not the broad peaks associated with amorphous packing (excluded volume effect). Because of its low concentration and low scattering density, glycerol is omitted in the models. The software Mercury was used to predict the scattering patterns. We find that the relative intensities of the smectic scattering peaks depend strongly on the intralayer molecular offset. For pure ITZ, the observed pattern is well reproduced with an offset of 4 Å (Figure 8a), though the model predicts a third peak that is absent in the experimental pattern. For G5-ITZ, the observed pattern is well reproduced by setting the intralayer molecular offset to 0. Overall, these results support the hypothesis (Figure 7) that glycerol reduces the intralayer molecular offset.

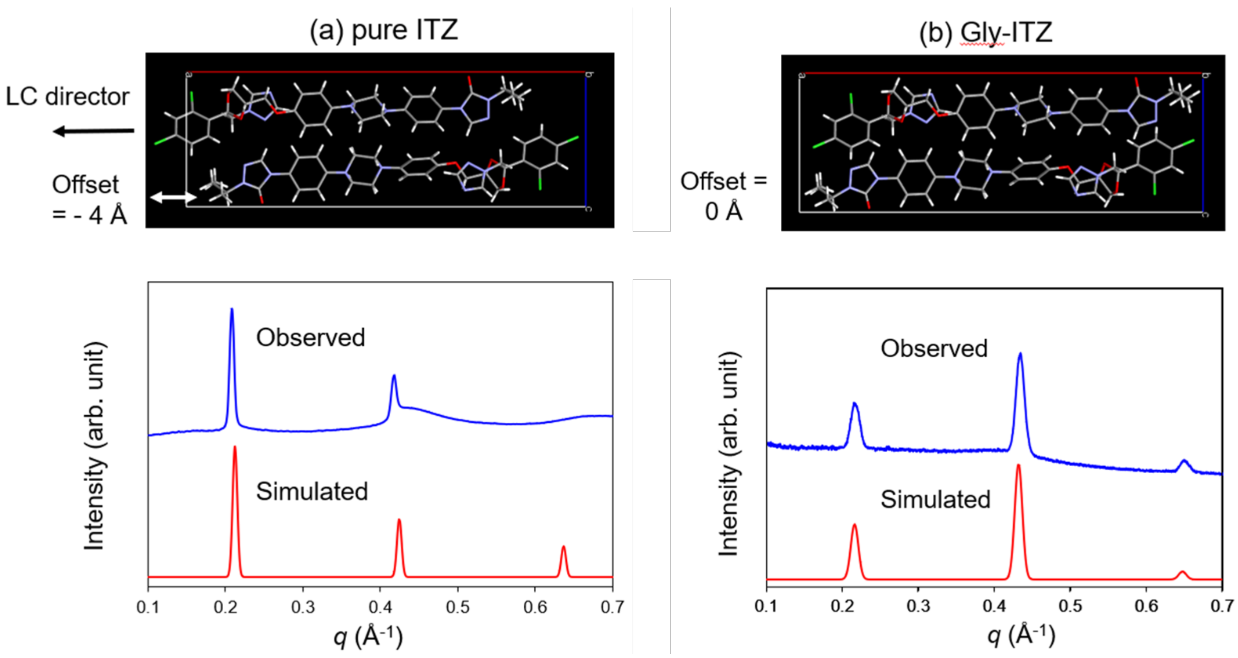


Figure 8. Molecular models for the smectic layers in (a) pure ITZ and (b) glycerol-doped ITZ and their scattering patterns. In each model the adjacent molecules are antiparallel as in the crystals of ITZ and are offset along *a* (LC director) by 4 Å in (a) and 0 in (b).

We now consider the possible sites of interaction between glycerol and ITZ. ITZ is highly hydrophobic (log P = 5.7) and it is unlikely that the polar glycerol molecules are inserted into a smectic layer between approximately parallel ITZ molecules. The fact that glycerol tightens the lateral packing of ITZ molecules (smaller d_L in Figure 5a) supports this view. We speculate that the glycerol molecules reside near the boundaries of the layers through hydrogen-bonding with the terminal groups of ITZ. While lacking hydrogen-bond donors, ITZ has several acceptors and is known to form hydrogen bonds with glycerol according to FTIR.[14] Based on crystal structures, the two preferred acceptors are located at the ends of the ITZ molecule (labeled 1 and 2 in Scheme 1). Acceptor 1 participates in the hydrogen bond between ITZ and a diacid in their co-crystal,[26] as well as the hydrogen bond between fluconazole (a similar antifungal to ITZ) and water in the monohydrate crystal.[27] In posaconazole, another ITZ-like antifungal containing a hydroxyl group (OH), Acceptor 1 is hydrogen-bonded to OH in one of the two polymorphs[28] and Acceptor 2 in the other.[29] By hydrogen-bonding to these acceptors, glycerol molecules would be placed near the boundaries of the smectic layers. This would reduce the random molecular offsets within a layer and stabilize the smectic structure. This model gives a tentative explanation for the small negative temperature slope of L for $T > T_g$ in Figure 3b: Since the optimization of hydrogen bonds may cause density to decrease, as seen in the freezing of water, the negative slope of L could reflect the ever-improving hydrogen bonding as T decreases in the equilibrium liquid state. As the system enters the glassy state ($T < T_g$), structure is frozen apart from normal thermal expansion and the temperature slope of L becomes positive. We speculate that a similar interaction occurs when nematic ITZ is exposed to moisture, causing an increase of smectic order.[15] The proposed binding sites of glycerol and water can be tested in future work by ssNMR.[30]

Conclusions

An impurity generally degrades the crystalline order of the host molecules. This is observed for many impurities doped in LCs, but the glycerol-ITZ system is a notable exception. With 5 wt% glycerol, the smectic layers of ITZ are significantly more ordered, as evidenced by lower energy (Figure 1), smaller layer spacing and virtually zero thermal expansion (Figure 3), and tighter and more regular lateral packing (Figure 5). This ordering effect occurs while the system becomes more mobile with lower T_g and shorter relaxation time. We attribute glycerol's effect to its hydrogen bonding to the terminal groups of ITZ (Figure 7), thus "crosslinking" the rod-like molecules and reducing the random molecular offsets within a layer. This model explains all the structural features observed and is supported by a simulation of the X-ray scattering patterns in which the molecular offset is varied (Figure 8).

The glycerol-ITZ system provides an intriguing demonstration that a small amount of a protic solvent can strongly enhance the energetic stability[13] and the structural order of a hydrophobic thermotropic LC. Doping a non-mesogenic solvent in a thermotropic LC typically causes a destabilizing effect.[8] There have been reports that a thermotropic LC phase can persist and even gain a larger temperature range of occurrence when doped with a solvent, [31,32,33,34] but little structural characterization as performed here is available to determine whether the solvent enhances or degrades the LC order. For imidazolium-based ionic liquid crystals, hydration can increase the stable temperature range of the smectic phase[34] and according to MD simulations, sharpen the density modulation of the smectic layers.[35] It may be fruitful to investigate these systems using the same approach to test the finding of this work. In the classic lyotropic LC phenomenon, a non-mesogenic amphiphilic host becomes a LC when mixed with water.[18,19] These systems differ from glycerol-ITZ since ITZ is not amphiphilic and is already a thermotropic LC. Furthermore, the structural unit for the smectic phase of ITZ is a monolayer, not a bilayer as in the classic lyotropic phases. This highlights a broader application of protic-solvent doping to enhance LC order and fluidity. This work has shown that to apply this approach, the host need not be amphiphilic and can be a thermotropic LC. It could be applied to a hydrophobic host like ITZ that has hydrogen-bond acceptors but is deficient in hydrogen-bond donors. By forming hydrogen bonds with a protic solvent, the host is expected to develop polar/nonpolar layering and mesoscopic order, while gaining mobility because of the low T_g of the solvent.

The dual effect of glycerol on ITZ in enhancing mobility and improving structure is reminiscent of its effect on the bio-protective glass trehalose.[23] Cicerone and Soles showed that a small dose of glycerol in trehalose simultaneously reduces the T_g and the amplitude of thermal vibrations (Debye-Waller factor) on the nanosecond timescale, with the latter effect being beneficial to the stability of the proteins embedded in the matrix.[23] Remarkably, this effect is maximal at 5 wt% glycerol, the same concentration at which glycerol has the largest stabilizing effect on smectic ITZ. By MD simulations, Dirama *et al.* showed that low-dose glycerol can strengthen the hydrogen bonds in trehalose, with the optimal concentration being 5 wt%.[36] This system differs from ours in that trehalose is hydrophilic and non-mesogenic, while ITZ is the opposite. Again, these results motivate a broader exploration of glycerol doping as a tool to increase global mobility and enhance local structure.

The glasses of ITZ exemplify hybrid materials with features between those of normal isotropic glasses and highly ordered crystals.[7] The glasses of pure ITZ[6] and other glass-forming mesogens[24,37] can be prepared to have tunable LC order. These hybrid materials combine the advantages of normal glasses (e.g., macroscopic uniformity and ease of processing in the fluid state) and of crystals (e.g., preferred molecular orientation and packing) for optimizing materials properties.[7] In this context, glycerol's striking enhancement of ITZ's LC order further broadens the spectrum of achievable structures.

Acknowledgements

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Supporting Information. Peak fitting analysis and .cif files for smectic models of G5-ITZ and ITZ.

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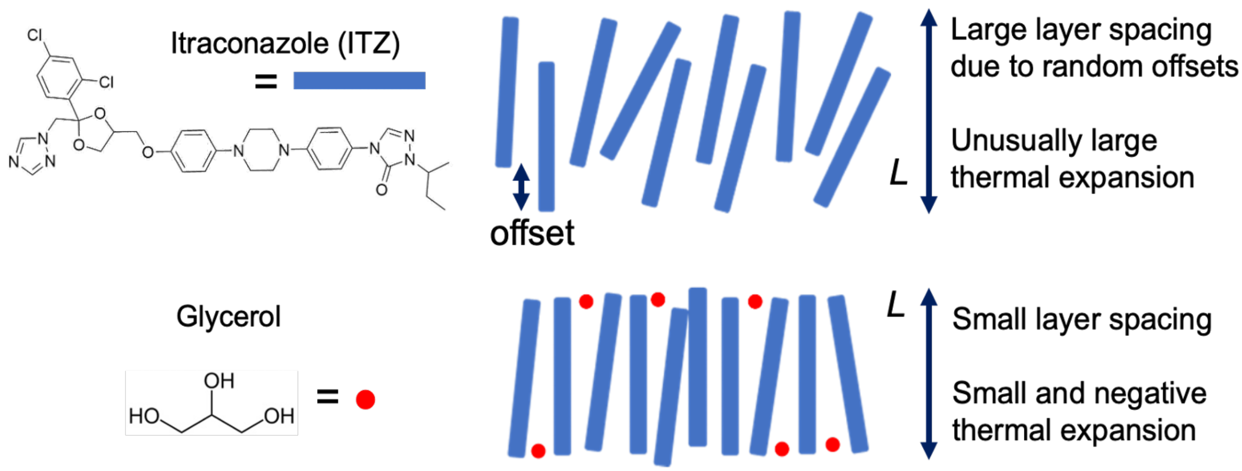

Synopsis: The smectic layers of itraconazole (ITZ) have random molecular offsets, resulting in larger layer spacing. The addition of glycerol reduces the offsets by hydrogen bonding to the terminal groups of ITZ, thus condensing layer spacing.

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