Molecular Crystals and Liquid Crystals

ISSN: 1542-1406 (Print) 1563-5287 (Online) Journal homepage: http://www.tandfonline.com/loi/gmcl20

Mixtures of Thermotropic Mesogens as Components of Model DPPC Membranes: Effects of Intermolecular Interactions on Phase Transitions

L. N. Lisetski, A. O. Krasnikova & S. I. Torgova

To cite this article: L. N. Lisetski, A. O. Krasnikova & S. I. Torgova (2015) Mixtures of Thermotropic Mesogens as Components of Model DPPC Membranes: Effects of Intermolecular Interactions on Phase Transitions, Molecular Crystals and Liquid Crystals, 623:1, 113-118, DOI: 10.1080/15421406.2015.1017263

To link to this article: http://dx.doi.org/10.1080/15421406.2015.1017263

Published online: 21 Dec 2015.

Mol. Cryst. Liq. Cryst., Vol. 623: pp. 113–118, 2015

ISSN: 1542-1406 print/1563-5287 online
DOI: 10.1080/15421406.2015.1017263

Mixtures of Thermotropic Mesogens as Components of Model DPPC Membranes: Effects of Intermolecular Interactions on Phase Transitions

L. N. LISETSKI,[1,*] A. O. KRASNIKOVA,[1] AND S. I. TORGOVA[2]

[1]Institute for Scintillation Materials, STC "Institute for Single Crystals" of National Academy of Sciences of Ukraine, Kharkov, Ukraine
[2]P.N.Lebedev Physical Institute of Russian Academy of Sciences, Moscow, Russia

Thermotropic mesogens of different chemical nature - 4-pentyl-4′-cyanobiphenyl (5CB), azoxy nematic ZhK-440, and cholesteryl oleyl carbonate (COC) were introduced as dopants to hydrated DPPC, with their effects on phase transitions recorded by DSC. When mesogen pairs (5CB + ZhK-440 and 5CB + COC) were added at constant total concentration, dependence of transition temperature to L_α *phase on 5CB concentration was linear for COC and nonlinear for ZhK-440, with effects of cyanobiphenyl-azoxybenzene charge transfer complexes manifested in both types of mesophases. Such dual doping of hydrated DPPC allows modeling of drug-membrane interactions in the case of joint application of different drugs.*

Keywords Differential scanning calorimetry; intermolecular interaction; liquid crystal mixtures; lyotropic mesophases; phase transitions; phospholipid model membranes

1. Introduction

For most practical applications, liquid crystals (LC) are commonly used in the form of mixtures composed of several mesogenic components, which can also include nonmesogenic dopants. For each specific application, the composition of LC mixtures is optimized to ensure, in general, a required combination of optical, viscoelastic, dielectric, and other properties in a broad (or specified) temperature range. The stability and performance characteristics of a LC mixture are related to its homogeneity at the molecular level—the effects of differences in molecular structure of the components and possible specific intermolecular interactions should be as weak as possible. In this case, the LC mixture characteristics (nematic to isotropic transition temperature, dielectric anisotropy, etc.) are essentially linear with the component concentration.

However, certain important cases can be noted when there are strong specific interactions between molecules of different components in the LC mixture. One of the

*Address correspondence to L. N. Lisetski, Institute for Scintillation Materials, STC "Institute for Single Crystals" of National Academy of Sciences of Ukraine, 60 Lenin Ave., 61001 Kharkov, Ukraine. E-mail: lisetski@isma.kharkov.ua

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/gmcl.

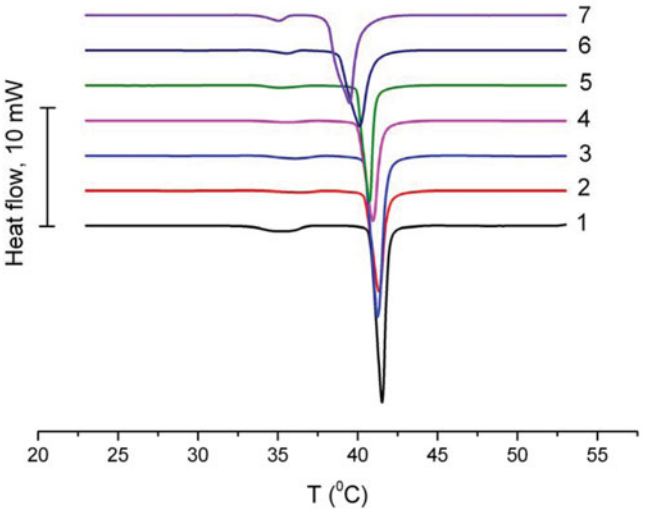

Figure 1. DSC thermograms illustrating the effect of thermotropic LC dopants on transitions gel–ripple phase–Lα phase of hydrated DPPC (1:1) : 1—no dopant, 2—5% ZhK-440, 3—4% ZhK-440 + 1% 5CB, 4—3% ZhK-440 +2% 5CB, 5—2% ZhK-440 +1% 5CB, 6—1% ZhK-440 +4% 5CB, 7—5% 5CB. Dopant concentrations are given in mass % with respect to dry DPPC. Heating rate—2 K/min, heat flow values normalized to sample mass of 25 mg.

most significant examples is interaction between nematic cyanobiphenyls and azoxy compounds, resulting in formation of charge-transfer complexes [1], which can lead, e.g., to induced smectic phases [2]. A different situation has been observed in mixtures of cyanobiphenyls and benzylideneanilines, where similar effects on the phase states are due not to any complex formation on the chemical level, but just to the factors of molecular packing [3]. Formation of effective supramolecular structures can be assumed for certain mixtures of cyanobiphenyls and cholesterol esters, where both mesophase stability and optical properties are also strongly determined by molecular packing [4, 5].

Similar phenomena can be also observed in LC systems of a different type—lyotropic phases of hydrated phospholipids, with their multibilayer structure generally considered as a physical model of cell membranes [6]. For this purpose, the most widely used is hydrated DPPC (L-α-dipalmitoyl-phosphatidylcholine), which undergoes clear and well-reproducible LC phase transitions in physiological temperature range. The sequence of LC phases in hydrated DPPC is $L_{\beta'} \rightarrow P_{\beta'} \rightarrow L_{\alpha}$ (often described as 'gel $\rightarrow$ ripple phase $\rightarrow$ LC phase'), with mesomorphic phase transitions at $\sim$36°C (pre-transition, T_p) and $\sim$42°C (main phase transition, T_m), [7–9]. The structures of lyotropic DPPC phases are very similar to thermotropic smectic A (L_{α}) or smectic H ($L_{\beta'}$). Addition of biologically relevant substances (e.g., drugs) to hydrated DPPC affects LC phase transitions similarly to the effects of nonmesogenic dopants on phase transitions in thermotropic LC—generally, the transition temperature T_m is lowered, and the differential scanning calorimetry (DSC) peak is smeared; an increase in T_m would suggest some kind of specific interactions in the system. Thus, studies of the effects of various chemical substances on LC phase transitions of DPPC membranes have become a widely used tool in modern studies of 'drug-membrane interactions' [10–12].

In particular, when two different dopants are introduced into the liquid crystal phase of hydrated DPPC (modeling the joint use of two different drugs that could interact when incorporated into a phospholipid membrane), their joint effect on T_m can be essentially nonadditive. Such behavior was observed in [13, 14], where introduction of either decamethoxinum (antimicrobial drug) or 2,5-dihydroxybenzoic acid (DHB) led to significant lowering of T_m, while their joint introduction (in the same total concentration) caused just DSC peak smearing, without noticeable effects on T_m. This suggested some kind of intermolecular complexing between decamethoxinum and DHB, which, in its effect on LC phase transition temperatures, is similar to interaction of cyanobiphenyls and azoxy compounds in the nematic phase [1, 2]. Further examples of such 'drug—drug' interactions in model DPPC membranes were reported in a recent paper [15]. To complete the analogies and connections between hydrated DPPC and conventional thermotropic LC phases, one could note studies on interaction between hydrated DPPC and 5CB [16], as well as on hydrated phosphatydil cholines containing azobenzene groups [17] or doped by azobenzene compounds [18].

Thus, the present study was aimed at 'bridging the gap' between conventional nematic LC mixtures with interacting components and LC phases of hydrated phospholipids with interacting dopants. We used LC phases of hydrated DPPC doped with pairs of mesogenic compounds—4-pentyl-4′-cyanobiphenyl (5CB) + a mixture of azoxy nematics (ZhK-440), and 5CB + cholesteryl oleyl carbonate (COC)—a cholesterol ester (which can also be considered as a component of phospholipid cell membranes). The anticipated specific interactions between the molecules of these mesogenic substances were expected to be manifested in differential scanning calorimetry (DSC) peaks of 'double-doped' hydrated DPPC.

2. Materials and Methods

The liquid crystalline lamellar lyotropic L_α phase was formed in water dispersions (50:50) of dipalmitoylphosphatidylcholine (DPPC) obtained from Alexis Biochemicals, Switzerland. As dopants, we used a standard nematic 5CB (4-*n*-pentyl-4′-cyanobiphenyl) of 99.5% purity obtained from Chemical Reagents Plant, Ukraine, a photoactive nematic ZhK-440 (4-*n*-butyl-4′-methoxyazoxybenzene + 4-*n*-butyl-4′-heptanoyl-azoxybenzene in 2:1 ratio), obtained from NIOPIK, Russia, and additionally purified by column chromatography on silicagel using a mixture of petroleum ether and benzene as the eluent with subsequent recrystallization from hexane at −20°C, and cholesteryl oleyl carbonate (COC) obtained from Aldrich, USA. The sample preparation included mixing the dopants with DPPC in appropriate ratios, solving the mixture in chloroform/ethanol (2:1), evaporation of the solvent in a 'Concentrator plus' device, Eppendorf, Germany, adding the required quantity of water, and storing for several days at 4°C. Differential scanning calorimetry (DSC) studies were carried out using a Mettler DSC1 calorimeter (Switzerland). DSC thermograms were obtained on heating and cooling at 2 K/min. The phase transition parameters of model lipid membranes were determined using the original Mettler 'Star^e SW 11.00' software.

In the samples studied, the doped DPPC to water ratio was 50:50, the total amount of the introduced dopants was 5% (mass) with respect to DPPC, and the ratio of 5CB and ZhK-440 (or 5CB and COC) was varied from 0 to 100%. Thus, the mixtures of 5CB and ZhK-440 could be considered as a quasi-binary system in DPPC. This approach is essentially similar to that used in [1] for the binary systems of 5CB and dialkylazoxybenzenes.

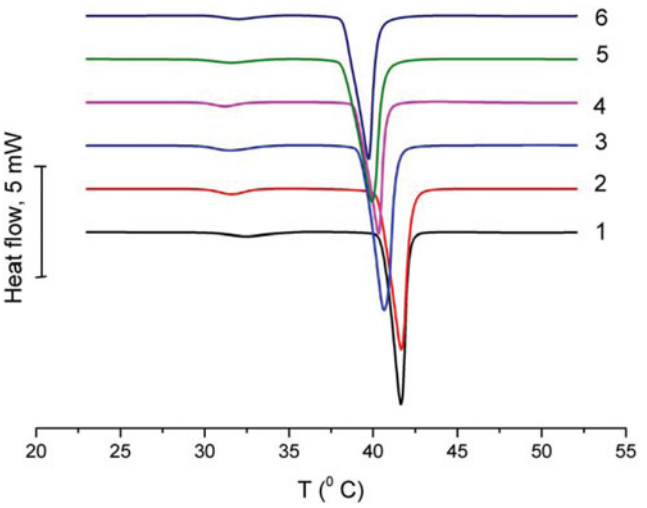

Figure 2. DSC thermograms illustrating the effect of thermotropic LC dopants on transitions gel–ripple phase–L_α phase of hydrated DPPC (1:1) : 1—no dopant, 2—5% COC, 3—3.5% COC + 1.5% 5CB, 4—1.5% COC + 3.5% 5CB, 5—0.5% COC + 4.5% 5CB, 6—5% 5CB. Dopant concentrations are given in mass % with respect to dry DPPC. Heating rate—2 K/min, heat flow values normalized to sample mass of 25 mg.

3. Results and Discussion

Figures 1 and 2 show DSC thermograms of the hydrated DPPC—undoped and doped with 5CB + ZhK-440 and 5CB + COC mixtures, with 5CB gradually substituting for ZhK-440 or COC in the series of plots. In both cases, T_m (the temperature of transition to Lα phase) is only slightly lowered upon addition of pure ZhK-440 or COC, while introduction of 5CB lowers T_m of hydrated DPPC by about 2°C, with intermediate values of T_m obtained for the mixed systems. All thermograms show clear and well-defined T_m peaks, with small pre-transition T_p peaks persisting in the mixed systems. This suggested that the samples were sufficiently homogeneous to provide reliable data on phase transition temperatures.

The plots of T_m as function of concentration of 5CB in mixed 5CB + ZhK-440 and 5CB + COC dopants are shown in Fig. 3. With COC, T_m is linear with 5CB concentration in this quasi-binary system, suggesting that eventual specific interactions are negligible. Really, the effects of steric factors and supra-molecular packing, which manifest themselves in the 5CB+COC thermotropic mixture [5], could not be expected to contribute in the system where 5CB and COC molecules are randomly distributed in the large volume of hydrated DPPC. On the contrary, the charge transfer complexes of cyanobiphenyl and azoxybenzene molecules formed in the 5CB+ZhK-440 mixture [1] persist in the hydrated phospholipid medium, remaining intact as supramolecular units. Hence the nonadditive behavior of T_m in Fig. 3. The negative sign of the observed deviation from linearity can be easily explained, e.g., by assuming that certain fraction of the complexes formed do not penetrate to the lipid bilayer, remaining in the water phase; thus, the effect of 5CB+ZhK-440 on T_m depression is weaker than the effect of 5CB+COC. Thus, the nature of interaction between molecules of different components of a liquid crystal mixture is basically similar both in conventional thermotropic systems and in hydrated phospholipid media.

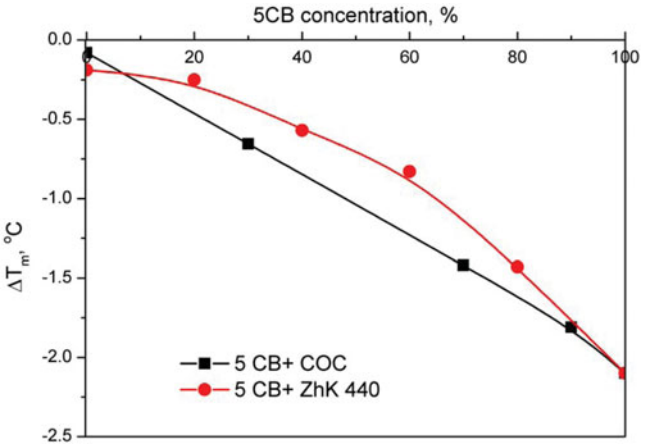

Figure 3. Changes in the transition temperature to L_α phase of hydrated DPPC (1:1) upon introduction of 5CB + COC and 5CB + ZhK-440 mixtures as function of 5CB concentration in the dopant mixture. Total content of the dopants in all cases is 5% with respect to dry DPPC.

Turning back to the results of [13–15], we can argue that effects of interactions between the drugs of different chemical nature introduced into lyotropic lamellar structures of hydrated DPPC are similar to the interaction effects between different mesogens, either introduced into the same DPPC system or studied as a thermotropic liquid crystal mixture. We can assume that such dual doping of hydrated DPPC can be used for modeling the processes of drug–membrane interactions in the case of joint application of different drugs, thus bridging the gap between studies of drugs in phospholipid membranes and studies of intermolecular interactions in thermotropic liquid crystal mixtures.

References

[1] Waclawek, W., Dabrowski, R., & Domagala, A. (1982). *Mol. Cryst. Liq. Cryst.*, *84*, 255.
[2] Heppke, G., & Richter, E. J. (1978). *Z. Naturforsch.*, *33a*, 185.
[3] Lisetski, L. N., Sidletski, O. Ts., Moshel, N. V., Malikov, V. Ya., & Stadnik, P. E. (2001). *Mol. Cryst. Liq. Cryst.*, *361*, 181.
[4] Yu, L. J., & Labes, M. M. (1979). *Mol. Cryst. Liq. Cryst.*, *54*, 1.
[5] Lebovka, N. I., Lisetski, L. N., Nesterenko, M. I., Panikarskaya, V. D., Kasian, N. A., Minenko, S. S., & Soskin, M. S. (2013). *Liq. Cryst.*, *40*, 968.
[6] Papahadjopoulos, D., & Miller, N., (1967). *Biochim. Biophys. Acta*, *135*, 624.
[7] Nagle, J. F., & Tristram-Nagle, S., (2000). *Biochim. Biophys. Acta*, *1469*, 159.
[8] Wack, D. C., & Webb, W. W. (1989). *Phys. Rev. A*, *40*, 2712.
[9] Pikin, S. A., Kharakoz, D. P., Tiktopulo, L. I., & Pikina, E. S. (2005). *Cryst. Rep.*, *50*, 308.
[10] Seydel, J. K., & Wiese, M. (2002). *Drug-Membrane Interactions: Analysis, Drug Distribution, Modeling* , Wiley-VCH Verlag GmbH&Co. KGaA.
[11] Peetla, C., Stine, A., & Labhasetwar, V. (2009). *Mol. Pharm.*, *6*, 1264.
[12] Pignatello, R., Musumeci, T., Basile, L., Carbone, C., & Puglisi, G. (2011). *J. Pharm. Bioallied Sci.*, *3*, 4.
[13] Vashchenko, O., Pashynska, V., Kosevich, M., Panikarska, V., & Lisetski, L. (2011). *Mol. Cryst. Liq. Cryst.*, *507*, 55.
[14] Vashchenko, O. V., Pashinskaya, V. A., Kosevich, M. V., Panikarskaya, V. D., & Lisetski, L. N. (2010). *Biopolymers Cell*, *26*, 472.

[15] Kasian, N. A., Pashynska, V. A., Vashchenko, O. V., Krasnikova, A. O., Gömöry, A., Kosevich, M. V., & Lisetski, L. N. (2014). *Mol. BioSyst.*, *10*, 3155.
[16] Lockwood, N. A., Meli, M.-V., Surjosantoso, A., Kim, E. B., de Pablo, J. J., & Abbott, N. L. (2007). *Liq. Cryst.*, *34*, 1387.
[17] Song, X., Perlstein, J., & Whitten, D. G. (1995). *J. Am. Chem. Soc.*, *117*, 7816.
[18] Liu, T., Bao, C., Wang, H., Lin, Y., Jia, H., & Zhu, L. (2013). *Chem.Commun.*, *49*, 10311.