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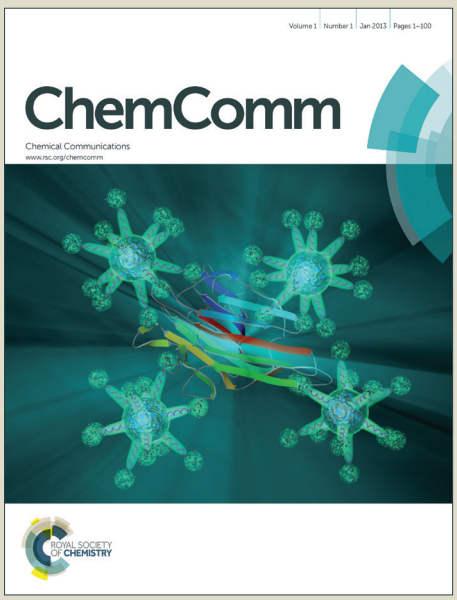

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Self-assembly induced solubilization of drug-like molecules in nanostructured ionic liquids†

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Here we report a novel self-assembly induced solubilization strategy with nanostructured ionic liquids as solvents. Highly ordered mesoscopic structures featuring the solute as a key component, such as liquid crystals, were formed via self-assembly in nanostructured long-chain carboxylate ionic liquids, resulting in extremely high solubilities for sparingly soluble drug molecules.

Dissolution is a fundamental process that is vital for chemistry and biological science. Unfortunately, many drug molecules exhibit poor solubility due to their large molecular weight and structural complexity,[1] which leads to low bioavailability[1,2] and substantially hinders the development of efficient separation methods and drug delivery systems.[3] Drug molecules typically possess multiple structural segments with different physicochemical properties (e.g., both hydrogen-bonding (H-bond) and hydrophobic segments) and strong intermolecular interactions (crystal packing). Therefore, drug molecules are difficult to solvate with water or common organic solvents.[1b,4] To date, a wide variety of solubilization strategies in addition to molecular modification[5] have been developed to improve their solubility, and these strategies include using mixed solvents with tunable physicochemical properties,[6] constructing micelles and microemulsions,[7] adding buffer media as a cosolvent,[8] and employing deep eutectic solvents with tailored structures[9]. Ionic liquids (ILs) have also been investigated as a type of designable solvent with enhanced solubility for drug-like molecules compared to molecular solvents[10] due to their multiple solvation interactions.[11] These approaches can be primarily classified as a "solvation method" that relies on modifying the physicochemical properties of the medium to enhance the interactions between the solute molecules and the solvents in the local solvation shell surrounding the solutes. Although substantial progress has been made, the solubility of relatively large molecules with both H-bond and hydrophobic segments is still limited. Therefore, novel solubilization strategies are still required.

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Recently, nanostructurally organized ILs have received considerable attention due to their distinct mesoscopic order at room temperature.[12] For ILs with long alkyl chains, mesoscopic structural heterogeneities were observed due to the respective aggregation of the neutral alkyl tails and the charged head groups/counter ions into segregated mesoscopic nonpolar and polar nanodomains.[13] The unusual nanostructure in the ILs represents one of their most peculiar properties and has stimulated many studies with applications to ion conductors with nano-ion channels, separation, synthesis, electrochemistry, and photochemistry.[14]

Herein, we report a novel and versatile approach, which is refer to as a self-assembly induced (SAI) solubilization strategy with nanostructured ILs, for the dissolution of sparingly soluble drug-like molecules with both H-bond and hydrophobic segments. First, the drug-like molecules formed an amphiphilic complex with nanostructured ILs via H-bond interactions, and then, the complex undergoes secondary self-assembly in the nanostructured ILs to form a highly ordered aggregation structure, such as a liquid crystal (LC) at room temperature (Fig. 1c). With this strategy, the enhancement of solubilization could transcend the limit of the conventional interaction-adjustment mode, which resulted in extremely high solubilities of various drug-like molecules being achieved. For example, the molar solubilities (solubility defined as the mole ratio of solute to solvent) of cholesterol and stigmasterol were as high as to 0.91 and 0.93 at 50°C, which are 5~8000-fold larger than its solubilities in organic solvents, micelles, microemulsions, and common ILs. In addition, in SAI solubilization strategy, only LCC IL is required and the solute contributes to the construction of mesoscopic structures, which is different from the micelle and microemulsion methods that consist of solvent and surfactant and dissolve solute in their pseudophase (e.g., solubilization of lipophilic molecule in oil-in-water microemulsion).

A class of long-chain carboxylate ILs (LCC-ILs) with a tetrabutylphosphonium cation ($[P_{4444}][C_nH_{2n+1}COO]$, n= 7, 9, 11, 13, and 15, molecular structures see Figs. 1c and S1) was designed for the solubilization of drug molecules. The LCC-ILs were prepared via neutralization of a tetrabutylphosphonium hydroxide aqueous solution with fatty acids.[15] The LCC-ILs prepared in this work are all transparent liquids at room temperature with their glass transition

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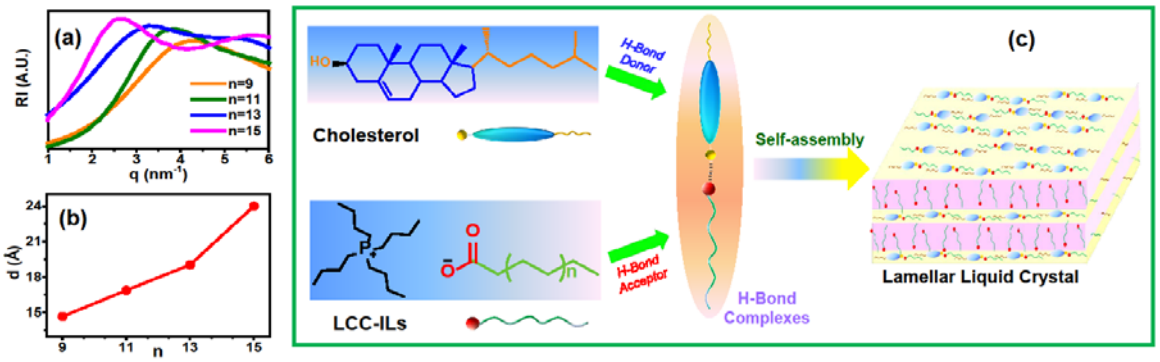

Fig.1 (a) SAXS patterns of $[P_{4444}][C_nH_{2n+1}COO]$ (n= 9, 11, 13, 15) at room temperature; (b) The spatial correlation size (D) as a function of carbon number n; (c) Schematic diagram of self-assembly induced solubilization process in nanostructured IL and the chemical structures of cholesterol and $[P_{4444}][C_nH_{2n+1}COO]$

temperature or melting point below -40°C. However, LCC-ILs (n= 1, 3, and 5) with short chain carboxylate anions were solid at 25°C, indicating the key role of long alkyl chains on their liquid behavior. It is important to note that nanoscale organizations were observed in these LCC-ILs using small angle X-ray scattering (SAXS). As shown in Fig. 1a, obvious low-Q diffraction peaks were detected in $[P_{4444}][C_nH_{2n+1}COO]$ with n= 9, 11, 13, and 15, indicating the existence of nanoscale segregation of the alkyl tails in these ILs. The spatial correlation size (D) corresponding to the low-Q peak position (Q_{max}) ($D = 2\pi/Q_{max}$) is also reported in Fig. 1b. The D value of $[P_{4444}][C_nH_{2n+1}COO]$ with n= 9, 11, 13, and 15 ranges from 14 to 25 Å, indicating that the long-range order in the LCC-ILs is on the nanometer scale. In addition, the D value is dependent on the alkyl chain length of the carboxylate anion, and this value increases with an increase in the carbon number of the anion. Therefore, the degree of order of these nanostructured ILs is also substantially dependent on the length of the alkyl chain in the anion. In addition, the LCC-ILs exhibit very strong H-bond basicity (the ability of H-bond acceptor), and their Kamlet-Taft parameters (β) are as high as 1.60 and considered to be the highest level among reported solvents,[16] which is crucial for the solubilization processes due to significant role that H-bond interactions play in self-assembly.

The dissolution ability of these nanostructured LCC-ILs was evaluated using cholesterol as a typical solute. As "the most highly decorated small molecule in biology",[17] a detailed understanding of the dissolution behavior of cholesterol molecules in solvents is important. In conventional organic solvents and water, the molar solubility of cholesterol is low (e.g., approximately 0.000001-0.03, Fig. 2a).[18] The solubility of cholesterol in micelle and microemulsion is relatively high compared to pure solvents but still limited (0.05-18%, mass fraction),[19] because the solubility in microemulsion is strongly relied on the capacity of their oil core. It is important to note that the nanostructured LCC-ILs exhibited excellent dissolution ability for cholesterol, and their solubilities were as high as 0.40-0.90 at 50°C which was 30~8000-fold larger than those of organic solvents and common ILs (Fig. 2a). To the best of our knowledge, this value represents the highest solubility reported for cholesterol.[10c,18,19] As shown in Fig. 2b, the solubility of cholesterol generally increased as the length of anionic alkyl chain increased, and it is important to note that $[P_{4444}][C_{11}H_{23}COO]$ could be regarded as a watershed solvent that exhibits a major leap in solubility, indicating the importance of the long alkyl chain in the dissolution. In addition, the solubility of cholesterol in LCC-IL increased with increasing temperature from 25 to 50°C (Fig. 2b).

The nanostructured LCC-ILs also exhibited excellent dissolu for a wide range of sparingly soluble drugs with various molecular structures (e.g., in $[P_{4444}][C_{15}H_{31}COO]$ at 25°C, naproxen 1.27, acid 0.095, hydrocortisone 0.22, stigmasterol 0.42, vitamin D_3 0.87, and indomethacin 0.72, detailed data see Fig. S3). The solubilit each compound is the highest level reported in the literature.[20] contrast, the solubility of these drugs in water is less than 0.00001 (their solubilities in ethanol, DMSO and 1-octanol were listed Table S1). Our work showed that drug molecules with both stron H-bond donor (e.g., hydroxyl and carboxyl group) and hydrophobic segment (e.g., steroid-ring, phenyl, and multi-heterocyclic ring), in-

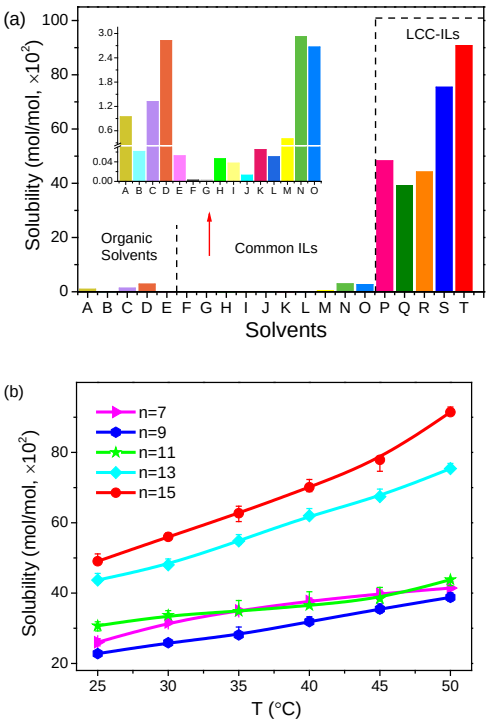

Fig. 2 (a) Molar solubility of cholesterol in organic solvents, common ILs and LC ILs at 50°C: A. ethanol B. DMSO C. n-hexane D. ethyl acetate E. acetonitrile F [BMim]BF_4 G. [BMim]PF_6 H. [BMim]Tf_2N I. [BPy]Tf_2N J. [EMim]$EtOSO_3$ [BMim]HSO_4 L. [BMim]CF_3SO_3 M. [BMim]$[CH_3COO]$ N. [OMim]Br O. [OMim]PF_6 $[P_{4444}][C_7H_{15}COO]$ Q. $[P_{4444}][C_9H_{19}COO]$ R. $[P_{4444}][C_{11}H_{23}COO]$ S. $P_{4444}][C_{13}H_{27}COO]$ $[P_{4444}][C_{15}H_{31}COO]$ (Full names of ILs and their structures see Fig. S2); (b) Mol solubility of cholesterol in LCC-ILs as a function of temperature.

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-cluding sterols, phenylpropanoids, and arylpropionic acid derivatives, generally have very high solubility in LCC-ILs.

We found that LCC-ILs were miscible with water due to their amphiphilic properties. The solubilities of seven drug molecules in water/$[P_{4444}][C_{15}H_{31}COO]$ and phosphate-buffered saline (PBS) /$[P_{4444}][C_{15}H_{31}COO]$ mixtures at 35°C were measured and results were shown in Fig. S4. The aqueous solution of LLC-IL also exhibited good dissolution for those drug molecules and their solubilities increased with the increasing of IL concentration. The solubilities of drugs in PBS system were slightly lower than those in water system, which was ascribed to the salt effect of PBS. Although the drug solubility in LCC-IL aqueous solution decreases compared to pure LCC-IL system, it is still 2~35-fold higher than in common microemulsion at similar condition (Table S2) and is 2-4 order of magnitude larger than in pure water even at low IL concentration.

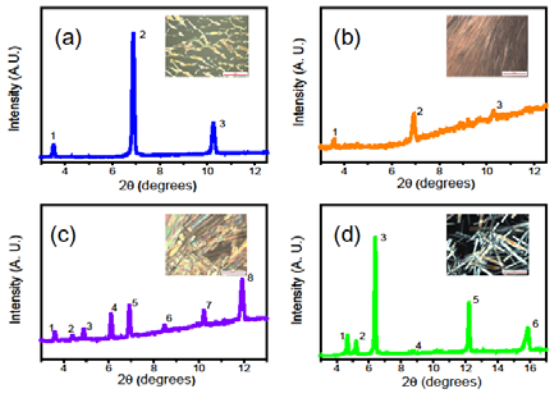

Fig. 3 POM images and WAXD patterns of the LCC-IL/cholesterol samples at 40 °C. (a) $[P_{4444}][C_{15}H_{31}COO]$/cholesterol (3/2, mol/mol); (b) $[P_{4444}][C_{13}H_{27}COO]$ /cholesterol (2/1); (c) $[P_{4444}][C_{11}H_{23}COO]$/cholesterol (5/2); (d) $[P_{4444}][C_9H_{19}COO]$ /cholesterol (2/1). The scale bar is 100μm.

Polarized optical microscopy (POM) and wide angle X-ray diffraction (WAXD) were employed to gain insight into the dissolution mechanism. The mixtures of $[P_{4444}][C_nH_{2n+1}COO]$ and cholesterol were isotropic, and no LC texture was detected when the concentration of cholesterol in the LCC-ILs was less than approximately 0.13 (Fig. S5). With increasing cholesterol concentration, optical defect textures were observed, indicating the formation of a LC phase. As shown in Fig. 3, a typical silk-shaped texture was detected in the $[P_{4444}][C_{15}H_{31}COO]$/cholesterol system (Fig. 3a), and a raft-shaped texture was observed in the $[P_{4444}][C_{11}H_{23}COO]$/cholesterol system (Fig. 3c). The WAXD patterns also strongly support the presence of a LC structure. When $n\leq12$, more than 4 diffraction peaks were observed in the WAXD patterns (Figs. 3c, 3d and S6), where the q ratios ($q= 4\pi\sin\theta/\lambda$) were $\sqrt{2} : \sqrt{3} : \sqrt{4} : \sqrt{7} : \sqrt{8} : \sqrt{11} : \sqrt{18} : \sqrt{22}$, $\sqrt{2} : \sqrt{3} : \sqrt{4} : \sqrt{8} : \sqrt{10} : \sqrt{14}$ and $\sqrt{3} : \sqrt{4} : \sqrt{6} : \sqrt{12}$ for n= 11, 9 and 7 respectively, suggesting a ragged mesophase between a lamellar and cubic phase[21]. While the carbon number of the anion increase to 13 or 15, three distinct Bragg peaks appeared with a diffraction vector ratio of $q_1 : q_2 : q_3 = 1: 2 : 3$ (Figs. 3a and 3b), indicating that the lamellar phase existed in the n= 13 or 15 system[21], and the order degree of the mesophase improved compared to that of the n<13 system. In addition, strong H-bond interactions between the hydroxyl group of cholesterol and the LCC-ILs were observed by infrared (IR) spectroscopy and ^{1}H NMR (Fig. S7 and S8). After mixing $[P_{4444}][C_{15}H_{31}COO]$ with cholesterol, a wide peak located at 3160 cm^{-1} appeared in the spectrum, and this peak was due to the hydroxyl stretching of the H-bonded cholesterol (Fig. S7). In addition, a remarkable shift in the α-H of cholesterol was detected in this sample (Fig. S8). In addition, the lamellar LC structures were also observed in the $[P_{4444}][C_{15}H_{31}COO]$ /stigmasterol and $[P_{4444}][C_{15}H_{31}COO]$/vitamin D_3 systems (Figs. S9 and S10).

According to the aforementioned analysis, we speculate that the LCC-ILs and cholesterol form an amphiphilic complex via H-bond interactions between the hydroxyl group of cholesterol and the carboxylic group in the ILs. Then, the complex undergoes secondary self-assembly induced by van der Waals interactions between the long alkyl chains in the anions to form LC structures. Both nanoscale segregation of alkyl tails and strong H-bond interactions play crucial roles in these dissolution processes. In comparison to the molar solubility of cholesterol in LCC-ILs at 50°C, the solubility of cholesterol in $[BMim][CH_3COO]$ (0.013) in the absence of nanoscale segregation is low even though these ILs have similar H-bond basicity, indicating the crucial role of alkyl segregation in the dissolution. The solubilities of cholesterol in 1-octyl-3-methylimidazolium hexafluorophosphate ($[OMim]PF_6$) and 1-octyl-3-methylimidazolium bromide ([OMim]Br), which exhibit nanoscale segregation of the alkyl tails[22] with weak or moderate H-bond basicity, are also very low (0.027 and 0.029, respectively). Therefore, a strong H-bond interaction is also a key factor in the ultra-high solubility. Davis et al.[10c] has reported a better solubility of cholesterol in a low-melting point hydrophobic IL (0.30, mass fraction) than those in conventional solvents and common ILs, but the solubility in LCC-ILs (0.91) reported here is significantly higher than their result, which further demonstrates the superiority of the SAI solubilization strategy.

In addition to the ultra-high solubility, the self-assembly induced solubilization strategy using nanostructured ILs has two distinctive features. First, differing from the classic microemulsion solubilization method that consists of surfactants, solvents, and other excipients,[7] only one LCC-IL was employed in this strategy due to the unique properties of these nanostructured ILs including the wide liquid range and self-assembly mesoscopic structure. Secondly, the SAI solubilization strategy is highly reversible. Although drug molecules are easily dissolved in LCC-ILs and the LC structure is very stable under ambient conditions, 98.3% cholesterol, 98.2% stigmasterol, and 96.7% vitamin D_3 were precipitated from the LCC-ILs by simply adding some anti-solvents, such as acetonitrile (Fig. S10). This phenomenon confirms that the SAI solubilization strategy is a physical dissolution process based on reversible H-bond self-assembly rather than covalent modification. This reversibility is very important for potential application of LCC-ILs in separation and drug delivery systems. Up to date, several IL-based methods have been developed for drug formula and drug delivery[5c,7c,10d,23] and here we discuss the possibility of SAI solubilization strategy for drug-related application. However, the toxicity of LCC-ILs was unexplored and should be carefully evaluated before designing IL-based drug delivery materials into practical application.

In summary, we proposed a novel SAI solubilization strategy with nanostructured ILs as solvents. The drug-like molecules undergo

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dual self-assembly in the LCC-ILs to form highly ordered mesoscopic structures at room temperature. This strategy resulted in extremely high solubilities for various drug-like molecules, and the enhancement in solubility could transcend the limit of the conventional interaction-adjustment mode. The solubilities of typical drug-like molecules, such as cholesterol, naproxen, indomethacin, and stigmasterol, were as high as 0.51, 1.27, 0.72 and 0.43, respectively at 25°C, which significantly larger than those in water, conventional molecular solvents, and common ILs. Our work shows that both mesoscopic aggregation and H-bond interactions play pivotal roles in the self-assembly induced dissolution behavior. Based on its excellent performance and unique chemistry, we believe that the SAI solubilization strategy will inspire more application of nanostructured ILs for advanced separation and novel drug delivery systems.

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