Electronic Supplementary Information (ESI) for

Self-assembly Induced Solubilization of Drug-like Molecules in Nanostructured Ionic Liquids

1. Materials

Tetrabutylphonium hydroxide (40% in water) was product of TCI, octanoic acid (99%), decanoic acid (99%), dodecylic acid (98%), myristic acid (98%), palmitic acid (97%), stearic acid (98%) and cholesterol (≥95%, GC), folic acid(≥97%, HPLC), indomethacin (99%), hydrocortisone (98%) were purchased from Aladdin Reagent, 98% stigmasterol was from Xi'an Vita-Solar Biotechnology Co., Ltd, cholesterol (≥99%, GC) and DL-naproxen(≥99%) were purchased from Sigma and Xiya Reagent respectively, Vitamin D_3 (≥99%) was kindly supplied by Zhejiang Garden Biochemical High-tech Co., Ltd., China and used as received. Methanol (99.7%, HPLC), ethanol (99.7%, AR), ethyl acetate (99.5%, AR), dimethyl sulfoxide (99.0%, AR), 1-octanol (99.0%, AR), acetonitrile (99.0%, AR), sodium chloride (AR), potassium chloride (AR), disodium hydrogen phosphate (AR) and potassium dihydrogen phosphate (AR) were obtained from Sinopharm Chemical Reagent Group Co. Ltd and used without purification. The deionized water was obtained from the Wahaha Group Co. Ltd. The conventional ILs used in this study were purchased from Lanzhou Green-chem ILS, LICP, CAS, China, including 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIm][BF_4], 99%), 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIm][PF_6], 99%), 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([BMIm]Tf_2N, 99%), N-butyl pyridinium bis(trifluoromethyl sulfonyl)imide ([Bpy]Tf_2N, 99%), 1-ethyl-3- methylimidazolium ethylsulfate ([EMIm]$EtOSO_3$, 99%), 1-butyl-3-methylimidazolium hydrogen sulfate ([BMIm]HSO_4, 99%), 1-butyl-3-methylimidazolium trifluoromethansulfonate ([BMIm]CF_3SO_3, 99%), 1-butyl-3-methylimidazolium acetate ([BMIm][CH_3COO], 99%), 1-octyl-3-methylimidazolium bromide ([OMIm]Br, 99%), 1-octyl -3-methylimidazolium hexafluorophosphate ([OMIm]PF_6, 99%), with water contents of these ILs below 0.6% (mass fraction).

2. Synthesis of LCC-ILs

Ionic liquids of ([P_{4444}][$C_nH_{2n+1}COO$], n= 7, 9, 11, 13, 15) were synthesized according to the similar procedures reported in the literature.[1,2] Tetrabutylphonium hydroxide and carboxylic acid were mixed in a 100mL round-bottom flask with a molar ratio of 1:1 and then reacted at 40°C for 30 h. Then the produced ILs were distilled under a high vacuum at 55°C for 12 h to remove the water. The purity of carboxylates was ascertained by the ^{1}H NMR spectrum in $CDCl_3$.

3. Solvatochromic measurements

The Kamlet-Taft hydrogen-bond basicity β were measured by solvatochromic experiments,[3,4] using 4-nitroaniline and N,N-diethyl-4-nitroaniline as probe. Appropriate amounts of probes molecule was added into the LCC-IL sample and the IL was mixed throughly. Then the IL sample was transferred into a quartz colorimetric cell with 2mm light-path length. The maximum absorption wavelength (λ_{max}) was recorded at 25°C by UV-vis absorbtion measurements. Every sample was repeated at least five times and the average value was taken as the final one. The Kamlet-Taft parameters dipolarity/ polarizability (π*) and the hydrogen bonding basicity (β) were calculated by using equations (1) and (2),

$$\pi^* = 8.649 - 0.314\nu(1)_{max} \quad (1)$$

$$\beta = [1.035\nu(2)_{max} - \nu(1)_{max} + 2.64] / 2.80 \quad (2)$$

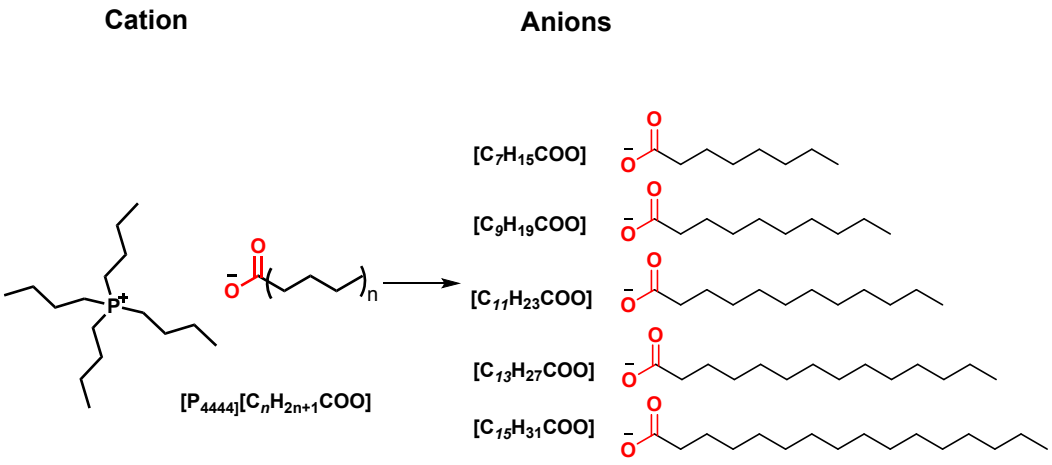
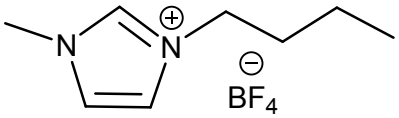
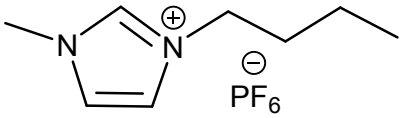


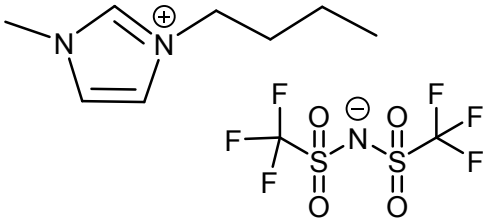
Fig. S1 Molecular structures of LCC-ILs.



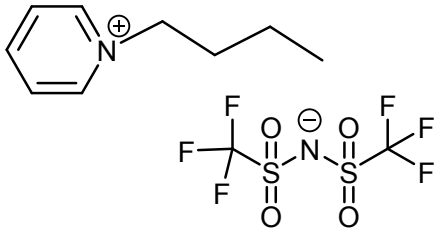
1-butyl-3-methylimidazolium
tetrafluoroborate
[BMIm]BF_4



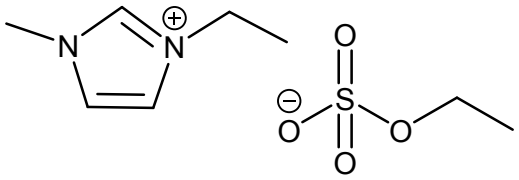
1-butyl-3-methylimidazolium
hexafluorophosphate
[BMIm]PF_6



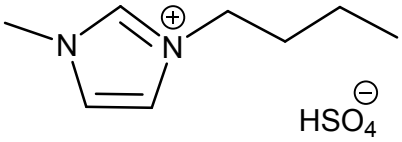
1-butyl-3-methylimidazolium
bis(trifluoromethylsulfonyl)imide
[BMIm]Tf_2N



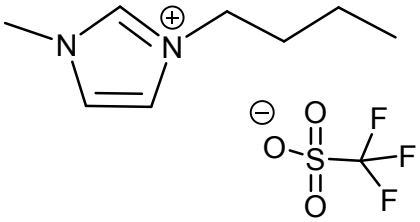
N-butyl pyridinium
bis(trifluoromethylsulfonyl)imide
[BPy]Tf_2N



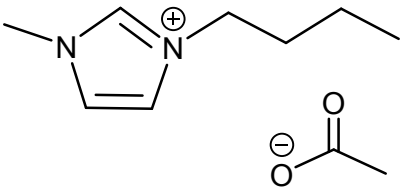
1-ethyl-3-methylimidazolium
bis(trifluoromethylsulfonyl)imide
[EMIm]$EtOSO_3$



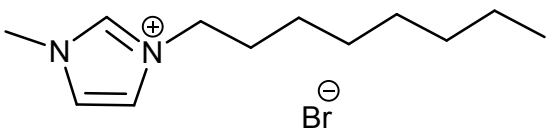
1-butyl-3-methylimidazolium
hydrogen sulfate
[BMIm]HSO_4



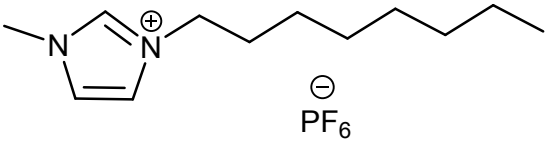
1-butyl-3-methylimidazolium
trifluoromethansulfonate
[BMIm]CF_3SO_3



1-butyl-3-methylimidazolium
acetate
[BMIm][CH_3COO]



1-octyl-3-methylimidazolium
bromide
[OMIm]Br



1-octyl-3-methylimidazolium
hexafluorophosphate
[OMIm]PF_6

Fig. S2 Structures of common ILs and the corresponding abbreviations.

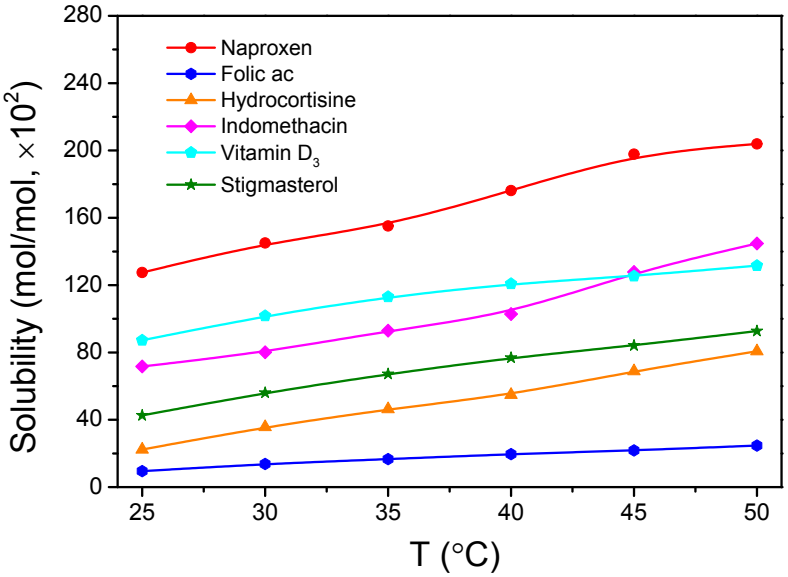


Fig. S3 Mole solubility of six poorly soluble H-bond donor drugs in $[P_{4444}][C_{15}H_{31}COO]$ as a function of temperature.

Table S1 Molar solubility of six drug-like molecules in water and organic solvents at 25°C.

Solute	Solvent			
	Water	Ethanol	DMSO	1-Octanol
Cholesterol	<0.000001[a]	0.0038[e]	0.0012[d]	0.047[i]
Naproxen	<0.000003[b]	0.015[f]	0.079[d]	0.020[i]
Folic acid	<0.000001[c]	0.00007[d]	1.26[d]	0.0095[d]
Hydrocortisone	<0.00002[c]	0.0024[g]	0.0078[d]	0.0025[j]
Indomethacin	<0.000001[c]	0.0034[h]	0.10[d]	0.0053[i]
Vitamin D_3	<0.00001[d]	0.23[d]	0.33[d]	38.18[d]
Stigmasterol	<0.00001[d]	0.0096[d]	0.0037[d]	1.89[d]

[a] Ref. 5; [b] Ref. 6; [c] Ref. 7; [d] this work; [e] Ref. 8; [f] Ref. 9; [g] Ref. 10; [h] Ref. 11; [i] Ref. 12; [j] Ref. 13

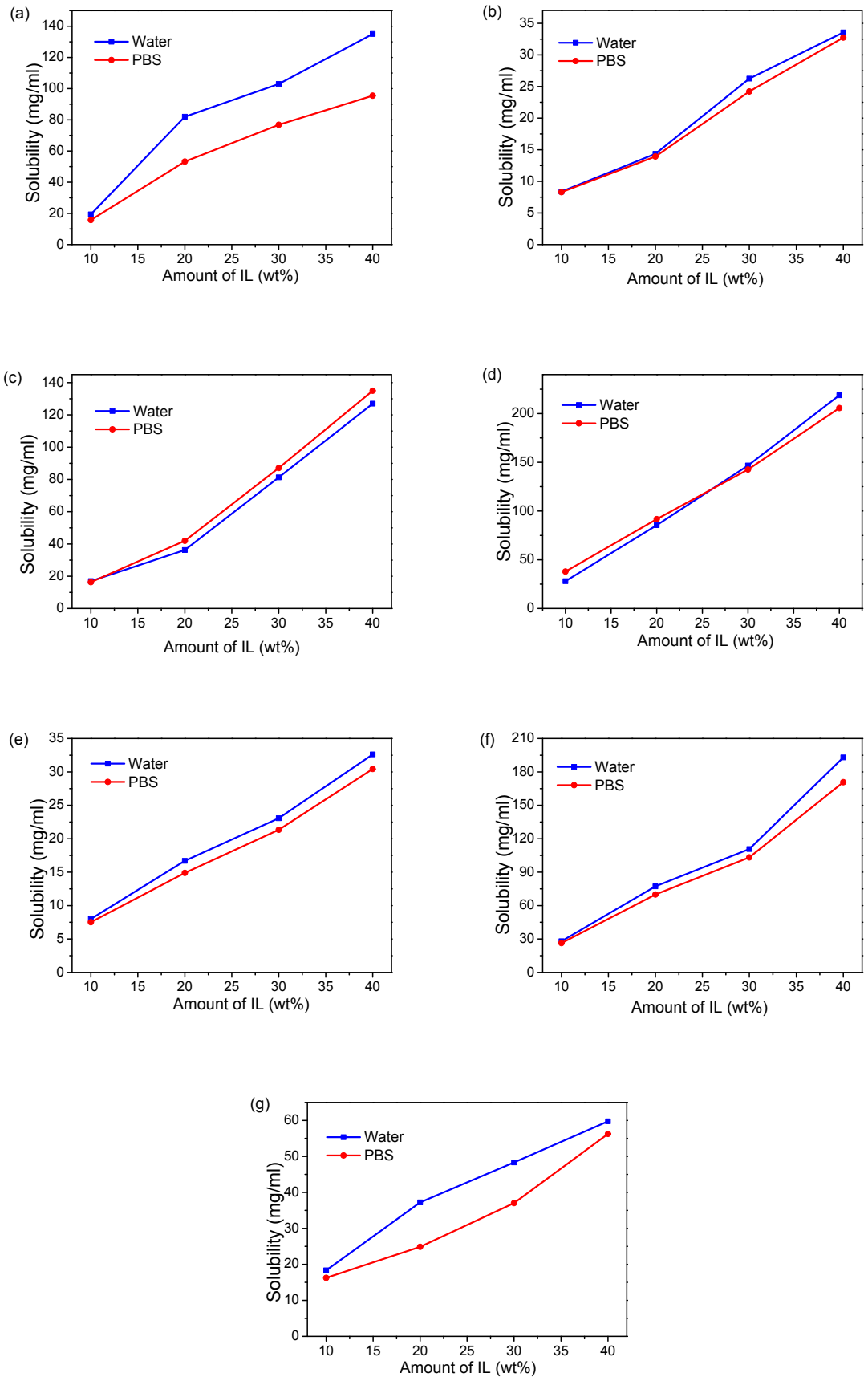


Fig. S4 Solubility (mg/ml) of drug-like molecules: a. cholesterol, b. hydrocortisone, c. naproxen, d. indomethacin, e. stigmasterol, f. vitamin D_3, g. folic acid, in water/$[P_{4444}][C_{15}H_{31}COO]$ and PBS/$[P_{4444}][C_{15}H_{31}COO]$ mixtures as a function of mass percent of $[P_{4444}][C_{15}H_{31}COO]$ at 35°C.

Table S2 Solubility of cholesterol in common microemulsion/micelle and $[P_{4444}][C_{15}H_{31}COO]$ aqueous solution.

	Common surfactant		LCC IL	
Type	Solubility	Ref.	$[P_{4444}][C_{15}H_{31}COO]$	Solubility
quillaja saponin (2.5 wt%)	0.004 wt%	14	2.5wt%	0.141 wt%
Tween 60+ethanol R-(+)-limonene+propylene glycol (30 wt%)	0.6 wt%	15	30wt%	17.04 wt%
glyceryl-1-monooctanoate (94 wt%)	18-20 wt%	16	94wt%	43.03 wt%
Sodium taurodeoxycholate (15-25mM)	0.5-0.9mM	17	15-25mM	6.94-7.40mM
sodium cholate (60mM)	3mM	18	60mM	11.77mM

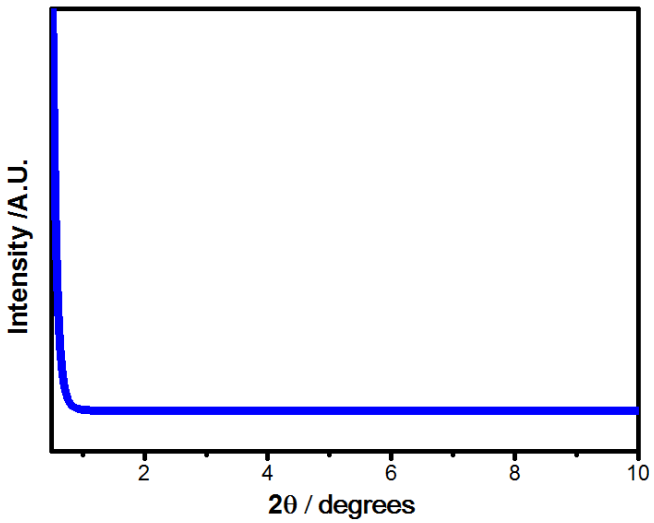


Fig. S5 WXRD pattern of $[P_{4444}][C_{15}H_{31}COO]$/Cholesterol with a molar ratio of 9 : 1 at 30°C.

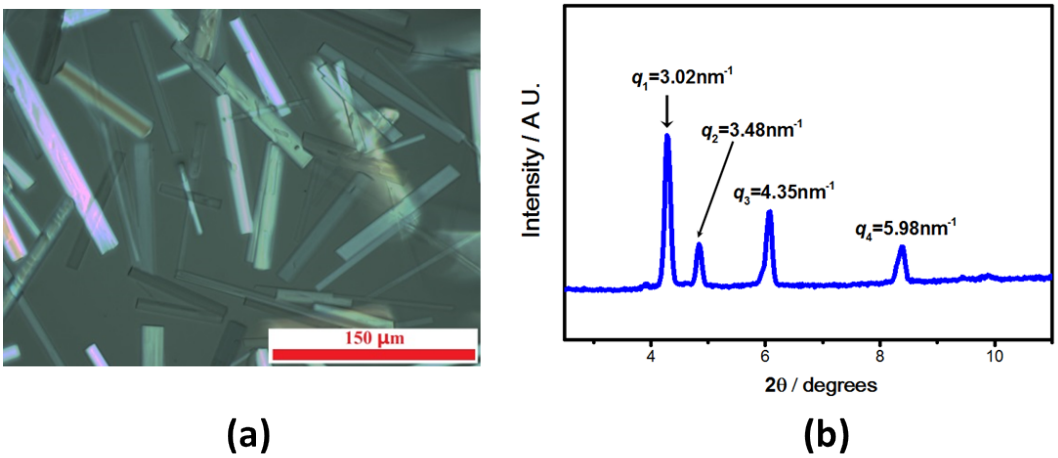


Fig. S6 POM image (a) and WXRD (b) pattern of $[P_{4444}][C_{11}H_{23}COO]$/cholesterol with a molar ratio of 1 : 4 at 40°C.

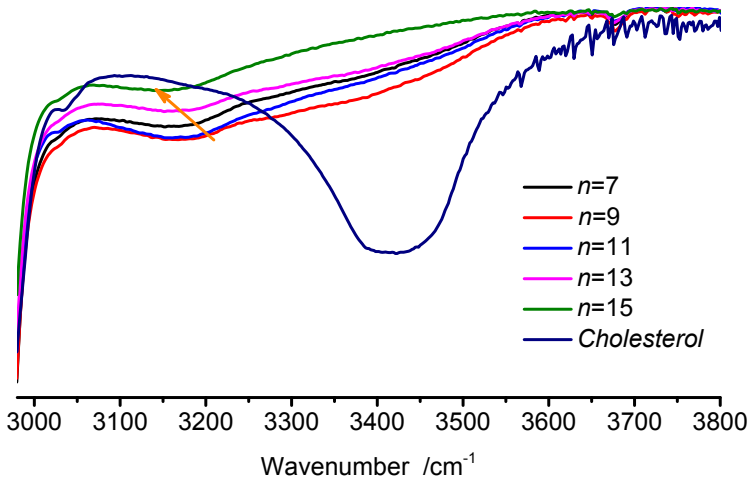


Fig. S7 IR spectrum of cholesterol and cholesterol dissolved in $[P_{4444}][C_nH_{2n+1}COO]$ (n= 7, 9, 11, 13, 15)

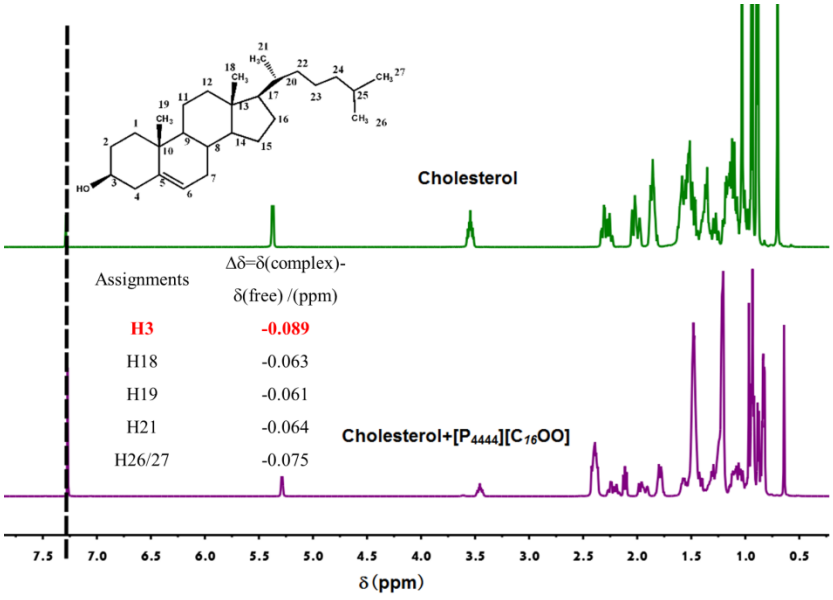


Fig. S8 ^{1}H NMR spectrum of cholesterol and $[P_{4444}][C_{15}H_{31}COO]$/cholesterol system.

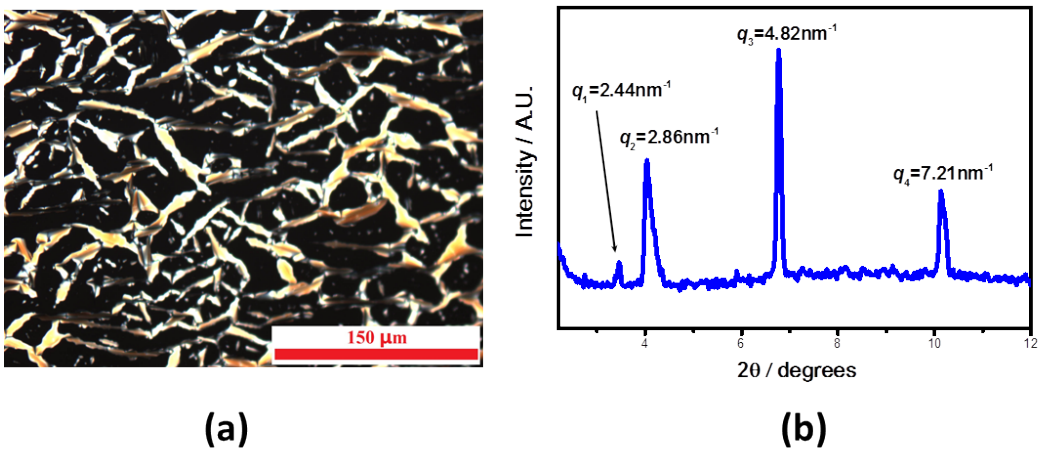


Fig. S9 POM image (a) and WXRD pattern (b) of $[P_{4444}][C_{15}H_{31}COO]$/stigmasterol with a molar ratio of 2 : 1 at 35°C. The scale bar is 150 μm.

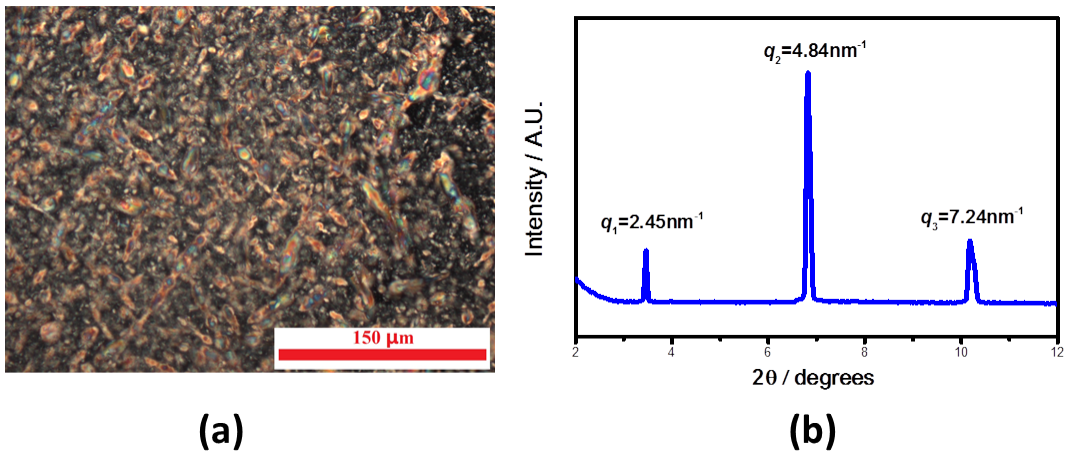


Fig. S10 POM image (a) and WXRD (b) pattern of $[P_{4444}][C_{15}H_{31}COO]$/vitamin D_3 with a molar ratio of 3 : 5 at 25°C. The scale bar is 150 μm.

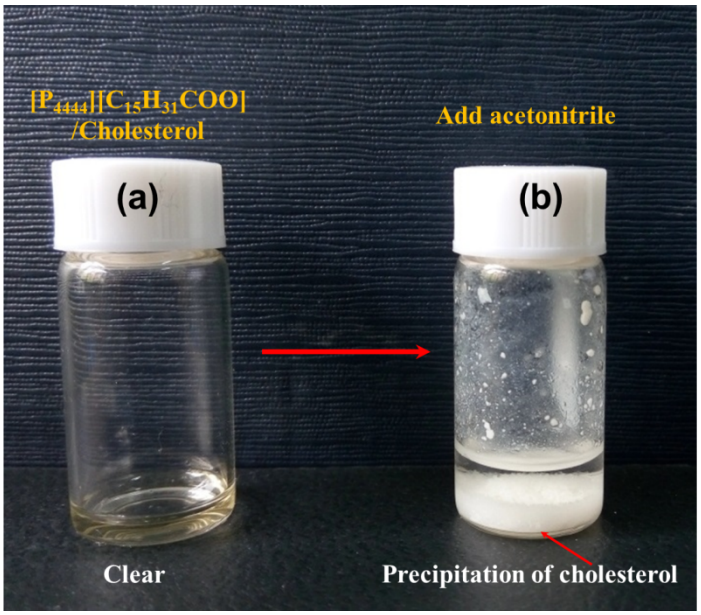


Fig. S11 Visual depiction of anti-solvents induced reversible transitions. Photograph of the $[P_{4444}][C_{15}H_{31}COO]$/cholesterol sample (a) before adding acetonitrile and (b) after adding acetonitrile.

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