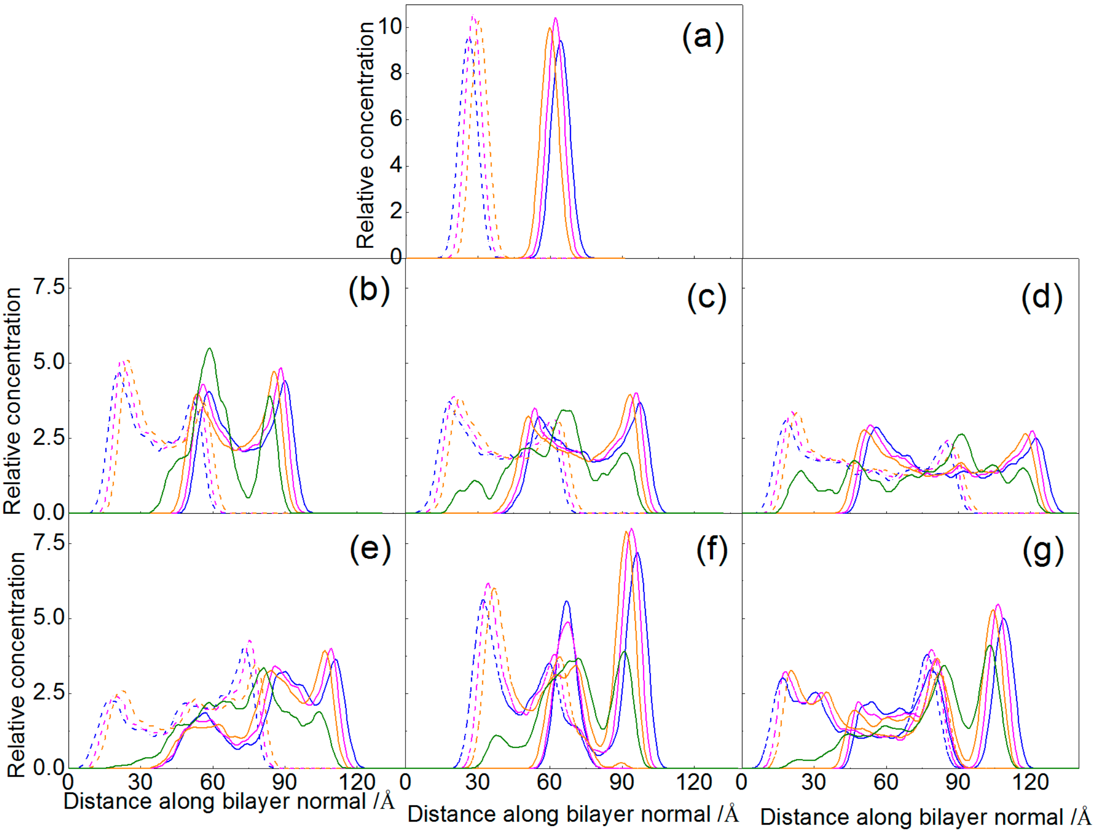
Supplementary Information

Figure S1. Relative concentration profiles for systems with different borneol concentration, 0% (**a**); 3.31% (**b**); 7.64% (**c**); 16.42% (**d**); 21.89% (**e**); 32.83% (**f**); 54.59% (**g**). In all plots, blue, pink, and orange lines represent profiles of NC, PO, and GL beads in DPPC (1,2-dipalmitoylsn-glycero-3-phosphatidylcholine) bilayer, while green lines represent the BO beads of borneol. The solid and dash lines denote opposite sides of the bilayer.



Rotational Time Correlation Function (RTCF) is not only a dynamic quantity depended on a time delay, *t*, but also an equilibrium property, obtained by the averaging of an equilibrium vector in phase space. It is often used to evaluate if the systems have reached equilibrium within simulation times and it can be calculated with the following formula:

$$M(t) = \frac{3}{2}\langle(\hat{u}(t_0)\cdot\hat{u}(t_0+t)^2\rangle - \frac{1}{2} \tag{1}$$

where *u*(*t*) is the unit direction vectors of time *t*. It can be seen from Figure S2, all systems have reached equilibrium within simulation times.

Figure S2. RTCF of C3–C4 vectors in DPPC bilayer (**a**) and APL (**b**) of systems with different borneol concentration.

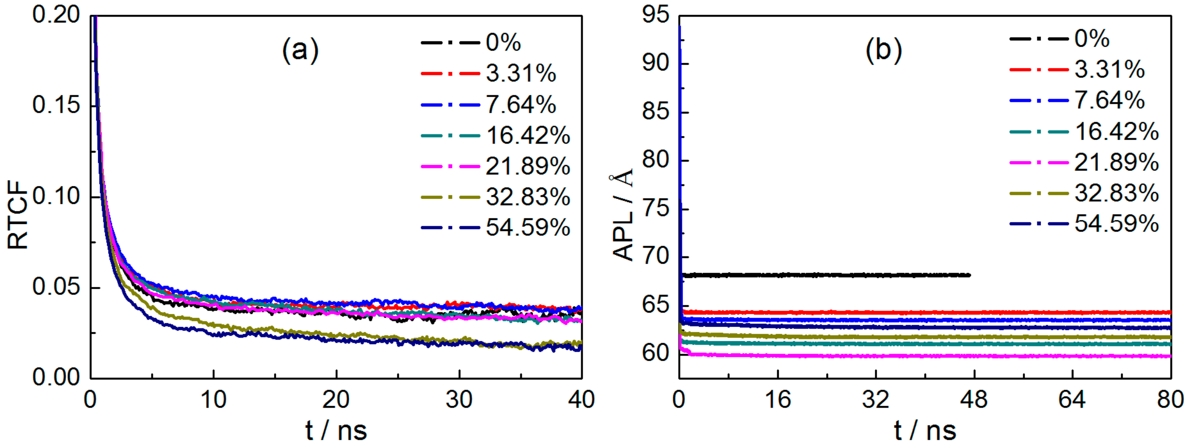


Figure S3. Final snapshots of all systems: 0% (**a**); 3.31% (**b**); 7.64% (**c**); 16.42% (**d**); 21.89% (**e**); 32.83% (**f**); 54.59% (**g**). The green dots represent the carbon beads in CG borneol, the purple dots represent the PO (namely the CG site represents the phosphate groups in DPPC molecule), the pink dots represent the carbon beads in DPPC, the blue dots represent CG waters, the orange dots represent the GL beads (namely the glyceryl groups) of DPPC and red dots represent BO (the hydroxyl groups) beads of borneol. The DPPC lipid tails and beads in borneol except BO were not shown and water beads in non-bilayer structures within the bilayer interior were highlight in 21.89%, 32.83% and 54.59% final configurations for the sake of brevity.

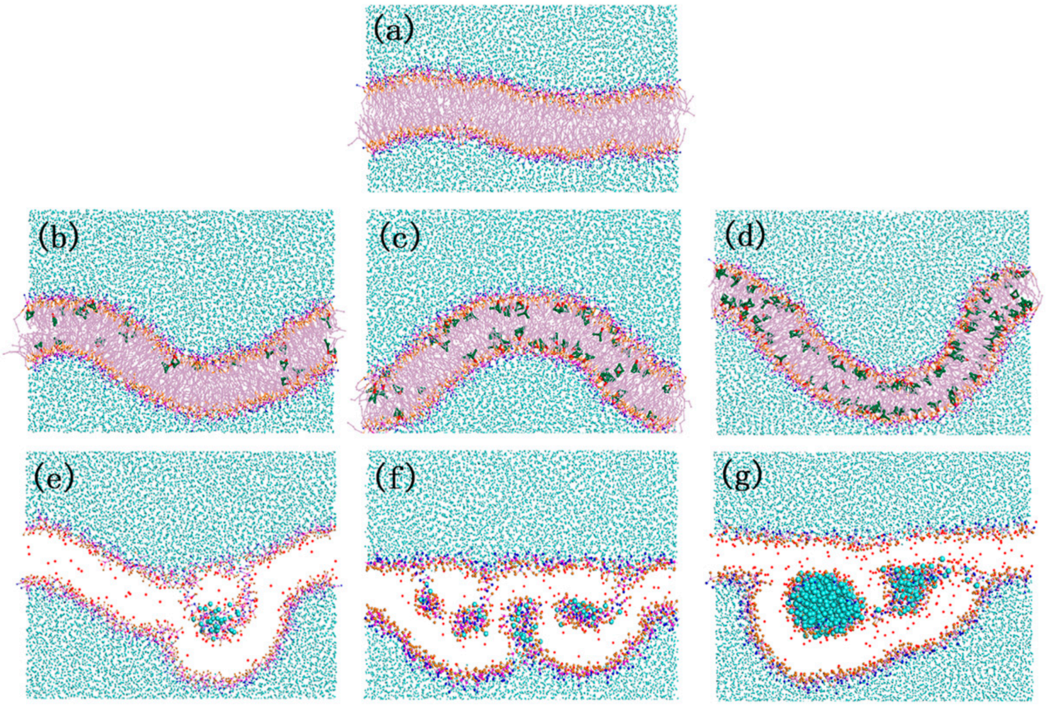


Figure S4. Formation of inverted micelle-like structures within the bilayer interior for system with 54.59% borneol: (**a**) 0 ps; (**b**) 4840 ps; (**c**) 14,680 ps; and (**d**) 80,000 ps. The green dots represent the carbon beads in CG borneol, the purple dots represent the PO (namely the CG site represents the phosphate groups in DPPC molecule), the pink dots represent the carbon beads in DPPC, the blue dots represent CG waters, the orange dots represent the GL beads (namely the glyceryl groups) of DPPC and red dots represent BO (the hydroxyl groups) beads of borneol. The carbon beads of DPPC lipid tails and borneol were not shown for the sake of brevity, and the BO beads of borneol were represented by red dots.

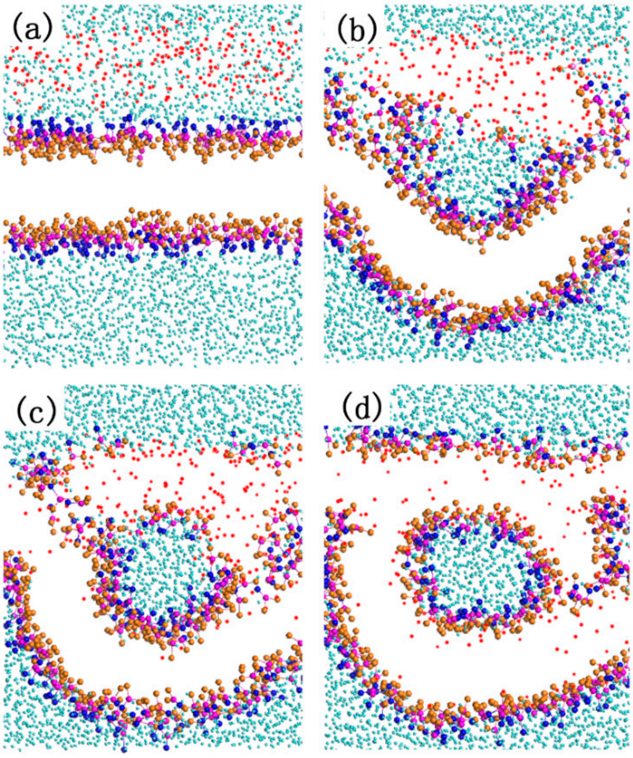


Figure S5. Aggregation of borneol molecules in system with borneol concentration at 16.42%. The green dots represent the carbon beads in CG borneol, the purple dots represent the PO (namely the CG site represents the phosphate groups in DPPC molecule), the pink dots represent the carbon beads in DPPC, the blue dots represent CG waters, the orange dots represent the GL beads (namely the glyceryl groups) of DPPC and red dots represent BO (the hydroxyl groups) beads of borneol.

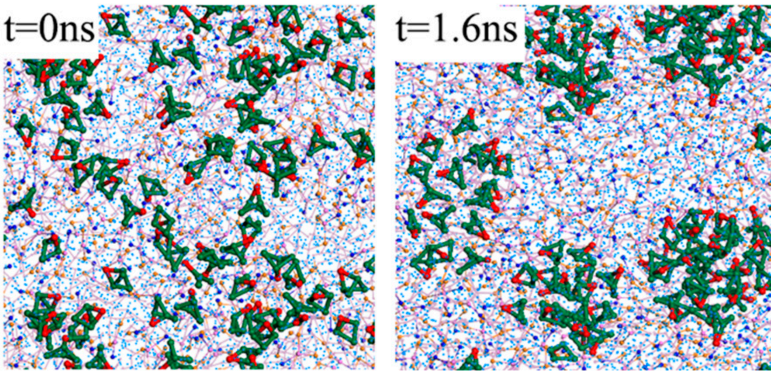


Figure S6. Relative concentration profiles of DPPC bilayer system with 32.83% borneol at different temperature: 285 K (**a**); 305 K (**b**); 325 K (**c**); and 345 K (**d**). In all plots, blue, pink, and orange lines represent profiles of NC, PO, and GL beads in DPPC bilayers, while green lines represent the BO beads of borneol. The solid and dash lines denote opposite sides of the bilayer.

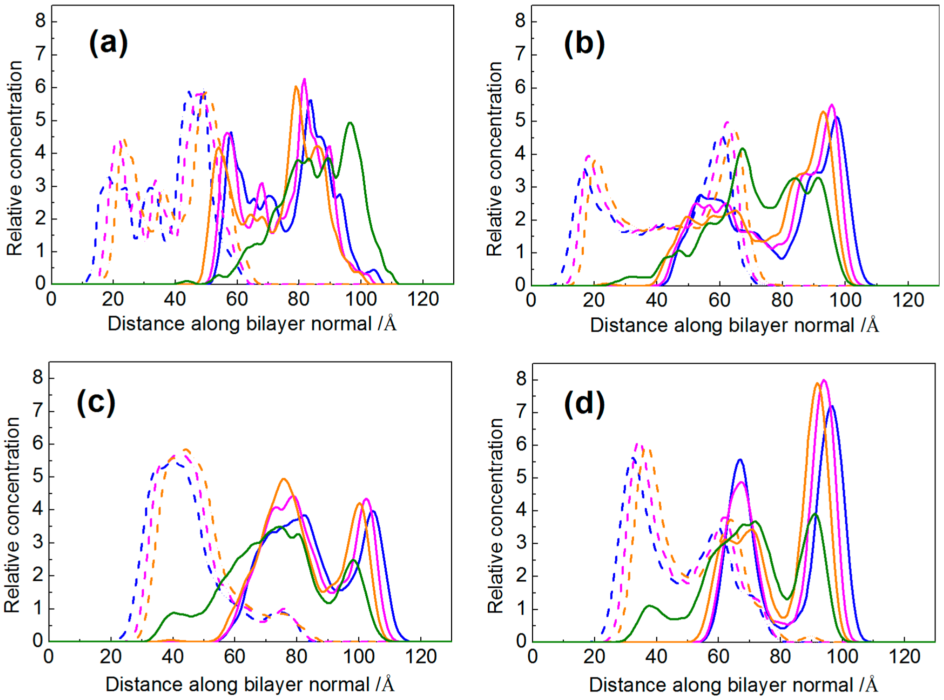


Figure S7. RDFs of system with 32.83% borneol at different temperature: 285 K (**a**); 305 K (**b**); 325 K (**c**); 345 K (**d**). In all plots, blue, pink, and orange lines represent profiles of NC–BO, PO–BO, and GL–BO beads. The solid and dash lines denote opposite sides of the bilayer and data of $r > 12$ Å were not shown for the sake of brevity

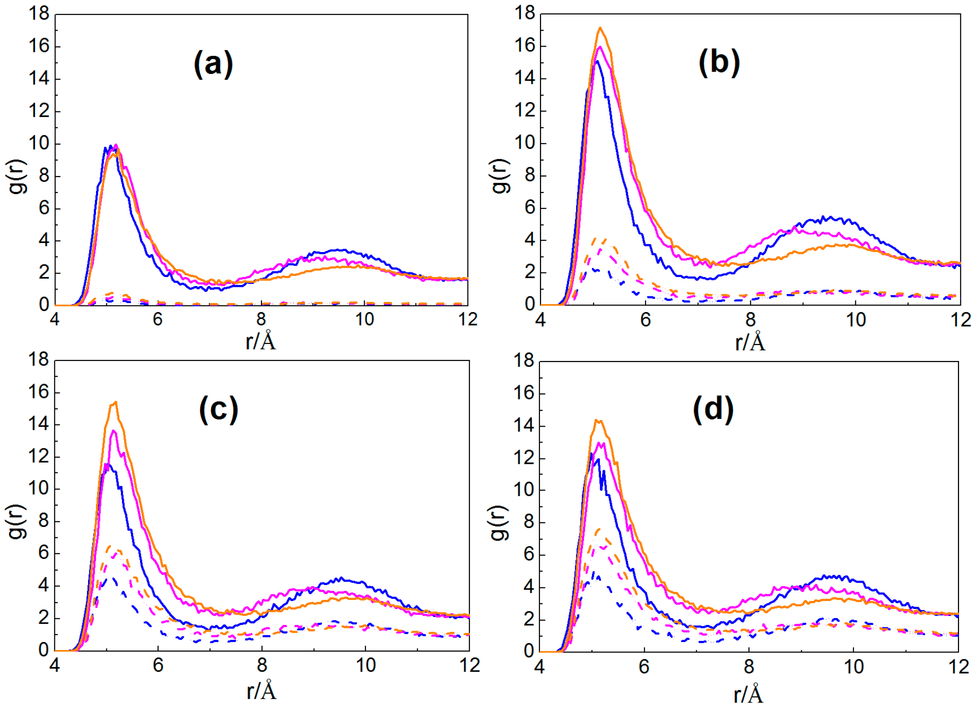


Figure S8. MSD of BO (**1**) and C4 (**2**) beads in systems with 7.64% (**a**) and 32.83% (**b**) borneol at different temperature: 285 K (black line); 305 K (red line); 325 K (blue line); 345 K (green line).

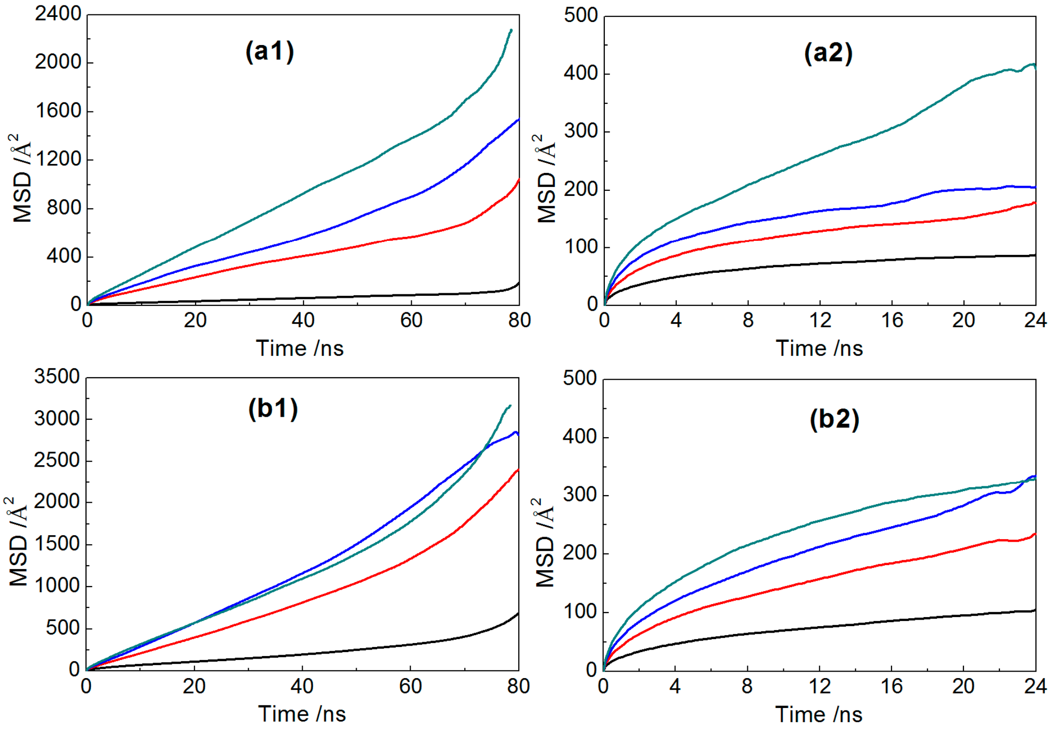
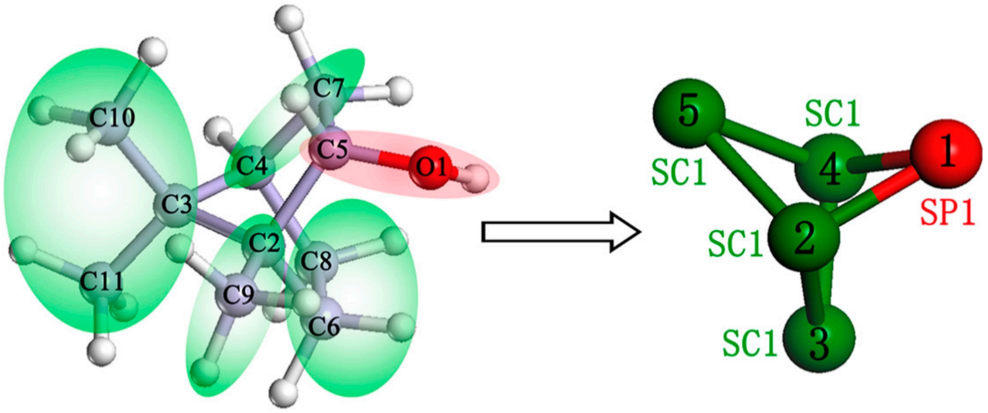


Figure S9. Atom-to-bead mapping scheme of borneol. Black bold letters were number of atoms (or beads), the green and red letters were Martini bead type of coarse-grain (CG) sites.



The Martini force field parameter for DPPC was obtained from Marrink's study. Because no Martini force field parameter for borneol had been reported before, we parameterized it using method provided in Martini website.

According to the coarse-grained mapping rule of Martini force field, in order to preserve the geometry of small ring compounds, a 2 or 3 to 1 mapping procedure is adopted and a special particle set, labeled "S", was used to model ring structures. Figure S9 and Table S1 shows the detailed mapping and parameterizing scheme of borneol molecule. As shown in Figure S9, borneol molecule was mapped to five coarse-grain (CG) sites (including four SC1 beads and one SP1 beads).

In order to obtain the structural properties of borneol at atomistic level, such as bonds, angle and dihedrals, simulations based on COMPASS atomistic force field were carried out using Discover module in Materials Studio software package. The initial configuration used in this simulation was built by putting 100 borneol molecules in aqueous randomly. Then the structural properties of borneol were analyzed, and the results were used to parameterize Martini borneol. Considered the thermodynamic properties of the CG model, the partitioning free energy between water and octanol was calculated for Martini borneol. Both water and octanol phase consisted of 3764 CG sites, with about 0.01 mole fraction of the solvents replaced by borneol molecules. All these simulations were performed under NPT ensemble. Temperature was controlled at 298 K by berendsen thermostat [39] with a time constant of 0.1 ps and pressure was coupled isotropically by berendsen barostat [39] with a time constant of 0.1 ps and reference pressure of 1 bar. Three dimensional periodic boundary conditions were applied. For atomistic simulations, both the coulomb and the van der Waals interactions were controlled with atom based method, both of the cutoff was set to 14 Å. For coarse-grained simulations, the coulomb interactions were controlled with Ewald method [40,41], while the van der Waals interactions were controlled with group based cutoff method [42], both of the cutoff was set to 15.5 Å. The partitioning free energy is obtained from the equilibrium densities of borneol in the water and octanol phase according to formula 1, and the lipo-hydro partition coefficient log$P$ was also calculated according to formula 2.

$$\Delta G^{part} = kT \ln\left(\frac{\rho_{oil}}{\rho_{wat}}\right) \tag{2}$$

$$\log P = \log\left(\frac{C_{oil}}{C_{wat}}\right) \tag{3}$$

The final parameters of Martini borneol was given in Table S1. Both the structural and thermodynamic properties of parameterized Martini borneol were analyzed and compared with atomistic results (see Figure S10 and Table S2). In Figure S10a, the first peak of angle distribution profile represents angle 4–5–2 (namely angle C2–C3–C4 in atomistic borneol), and another peak represents angle 1–2–3 (angle C5–C2–C6) and 1–4–3 (angle C7–C4–C8). In Figure S10b, we plotted the distribution of dihedral 5–2–3–4 (namely C3–C2–C6–C8 in atomistic borneol) and 5–4–1–2 (dihedral C3–C4–C7–C5). All these angles and dihedrals were critical in preserving the three-dimensional configurations and keeping the ring structure rigid. Finally, the bonds distribution in S10c covered all the C–C bonds in backbone of borneol molecule. It can be seen that our martini model of borneol could mimic the atomistic borneol well.

Table S1. Overview of the borneol CG topology.

Beads	Type
1	SP1
2	SC1
3	SC1
4	SC1
5	SC1

Table S1. *Cont.*

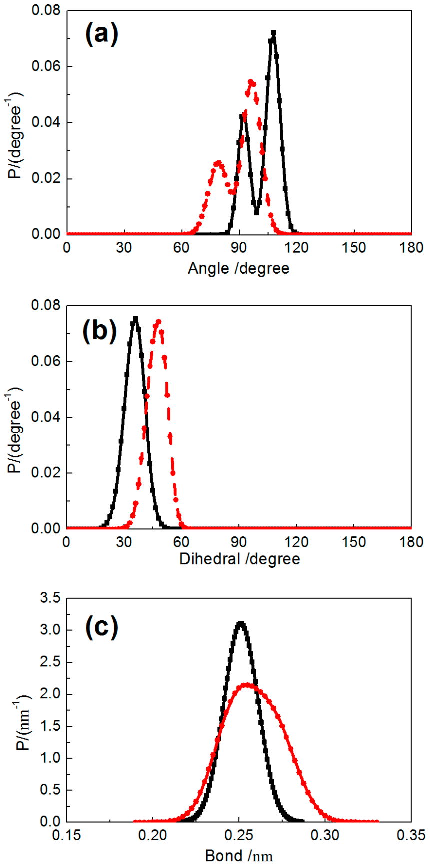
Bonds (*i*, *j*)	**Length (nm)**	**K_{bond} (kJ·mol^{-1}·nm^{-2})**
1, 2	0.25	20,000
1, 4	0.26	20,000
2, 3	0.26	20,000
2, 5	0.25	20,000
3, 4	0.23	20,000
4, 5	0.25	20,000
Angles (*i*, *j*, *k*)	**Angle (deg)**	**K_{angle} (kJ·mol^{-1})**
1, 2, 3	107.527	200
1, 4, 3	106.523	200
4, 5, 2	93.000	200
Dihedrals (*i*, *j*, *k*, *l*)	**Angle (deg)**	**$K_{dihedral}$ (kJ·mol^{-1}·rad^{-2})**
5, 2, 3, 4	37.675	300
5, 4, 1, 2	36.025	300

Table S2. Thermodynamic properties of borneol.

Thermodynamic Properties	**COMPASS**	**Martini**	**Predicted ***
log$P$	2.71 ± 0.25	3.23 ± 0.05	2.55 ± 0.25
ΔG^{part} (kJ)	3.12×10^{-23}	3.03×10^{-23}	2.42×10^{-23}

* Obtained from ACD/labs.

Figure S10. The angle (**a**); dihedral (**b**) and bong (**c**) distribution of both atomistic COMPASS (solid) and coarse-grained Martini (dash) force field.



Considered the cost of computation, before performing the systematic studies, we have taken the DPPC bilayer system with 21.89% borneol molecules as an example to select the reasonable simulation time, which could reduce as much cost as possible in the case of keep the simulation quality. In this pre-experiment study, 180 ns molecular dynamics simulation was performed. Snapshots at different simulation time were shown in Figure S11. We can found that the system did not change significantly after 80 ns. APL and RTCF were also analyzed and shown in Figure S12. It can be seen that the system have reached equilibrium within 80 ns. Thus we took 80 ns as a reasonable simulation end.

Figure S11. Snapshots of pre-experiment at different simulation time. The green dots represent the carbon beads in CG borneol, the purple dots represent the PO (namely the CG site represents the phosphate groups in DPPC molecule), the pink dots represent the carbon beads in DPPC, the blue dots represent CG waters, the orange dots represent the GL beads (namely the glyceryl groups) of DPPC and red dots represent BO (the hydroxyl groups) beads of borneol.

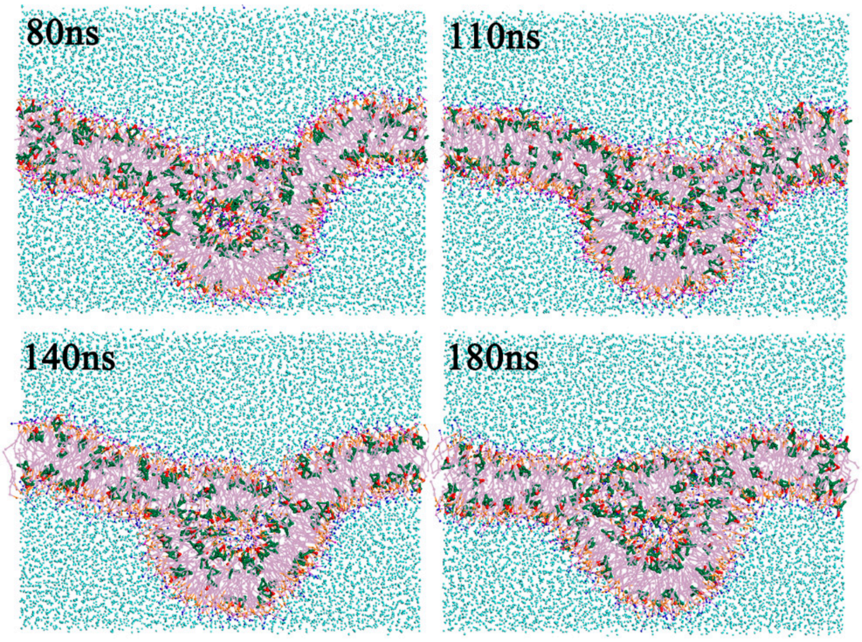


Figure S12. RTCF of C3–C4 vectors (**a**) and APL (**b**) in systems with 21.89% borneol.

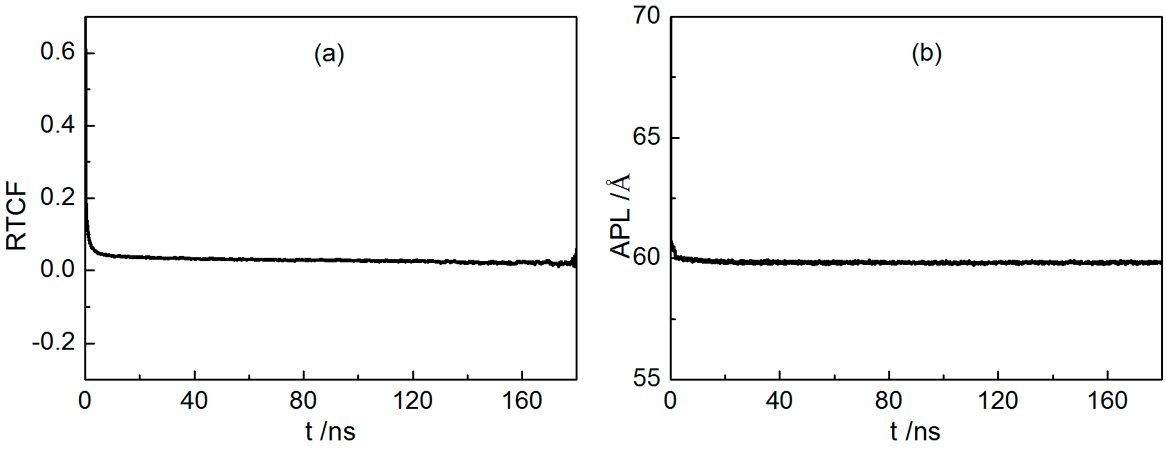


Figure S13. The APL (**a**) and bilayer thickness (**b**) of pure DPPC bilayer in different temperature.