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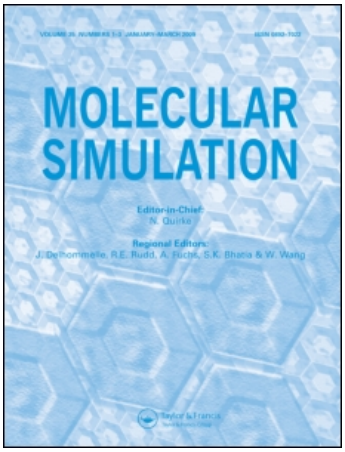


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# Simulation of self-assembly behaviour of fluorinated phospholipid molecules in aqueous solution by dissipative particle dynamics method

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In order to prepare novel biomaterials, it is essential to investigate the self-assembly behaviour of molecules containing both hydrophobic and hydrophilic groups, and to understand their structural change and morphological development. In this paper, we studied the self-assembly behaviour of fluorinated double-chain phospholipid molecules in aqueous solution at various simulation steps, concentrations, temperatures and pH values via the dissipative particle dynamics simulation method. The self-assembly behaviours of hydrogenated analogues and fluorinated single-chain phospholipids at various concentrations were also investigated for comparison. It was found that all molecules could form microsphere at low concentration, and aggregated to form various shapes with the increase of concentration. Fluorinated double-chain phospholipids were apt to form bilayer membrane more easily than hydrogenated/fluorinated single-chain phospholipids. Besides concentration, temperature and pH value of the aqueous solution also influence the self-assembly behaviour of the investigated molecules. A stable bilayer membrane could be achieved for the fluorinated double-chain phospholipids at a relatively high concentration when pH value and temperature of aqueous solution were close to physiological conditions, i.e., pH 7 and $T = 37^{\circ}C$. This work provides a direct 'observation' of self-assembly behaviour in the molecular level, which is important for the development of novel biomaterials, where surface structure is required to be well controlled.

**Keywords:** fluorinated phospholipid; dissipative particle dynamics; mesoscale simulation; self-assembly behaviour

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## 1. Introduction

Phospholipids are the main components of biological membranes, and are soluble in water. They can self-assemble into various structures such as micelle, bilayer, microsphere, ellipsoid, cylinder and so on. Among these structures, bilayer has been considered as the most important from a biological point of view [1]. The structural characteristics of these structures and the details of the phase diagrams strongly depend on the physico-chemical nature of the constituents. Therefore, understanding the relation between molecular structure and aggregation behaviour is of great importance. Fluorinated phospholipid was reported to exhibit extreme hydrophobicity, high fluidity, biological inertness and chemical stability [2]. Because of these outstanding properties, it has been applied in many fields including blood substitutes, diagnosis and drug delivery [3]. More details on fluorine-containing phospholipids regarding synthesis, applications, solution and interfacial properties have been described in the literature [4]. Phosphatidylcholine is an important type of phospholipid. The large improvement in biocompatibility of the phosphatidylcholine polymer is critical to suppress protein adsorption [5–7], and limits other biological responses such as platelet adhesive, complement activation and inflammatory [8–10]. In our previous studies, we have synthesised a series of fluorinated single-chain phospholipid polyurethanes, which displayed good biocompatibility for polyurethanes [11,12]. However, the protein adsorption could not be completely suppressed due to the absence of real phospholipid membrane formed on the polyurethane surfaces. Hence, a new phospholipid molecule with high self-assembly ability that could form biomembrane on the polyurethane surfaces should be designed and synthesised.

Computer simulation has become a useful tool to elucidate the aggregation behaviour of phospholipid, surfactant and block copolymer [6,7,13]. The simulation results provide more microscopic level information than experiment. Dissipative particle dynamics (DPD) is a coarse-grained simulation method introduced by Hoogerbrugge and Koelman [14,15]. It is based on the dynamics of soft particles, corresponding to a group of several atoms. The DPD technique has been successfully used in many areas, e.g. mesoscale chemical engineering, nanotechnology and biomedical materials and devices [16].

In this paper, a series of fluorinated double-chain phospholipids are designed for application in the synthesis of biocompatible polyurethane. Two hydrocarbon chains of phospholipid are replaced by two fluorocarbon chains, which are ended by an amino group and a $CF_3$ group, respectively. Changing the chain length will give a series of fluorinated double-chain phospholipid models.

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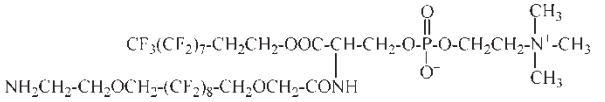


Figure 1. The structure of fluorinated double-chain phospholipid molecule.

By calculating the lowest binding energy of them with Materials Studio® 4.0 software program (Accelrys Software Inc, San Diego, CA, USA), we obtained the most stable molecular structure (Figure 1), which is of spatial helical conformation shown in Figure 2.

The self-assembly behaviour of fluorinated double-chain phospholipids in aqueous solution is simulated by DPD method, and compared with those studied on the hydrogenated analogues and fluorinated single-chain phospholipids. The self-assembly behaviour of the novel fluorinated phospholipids is investigated under various simulation steps, concentrations, temperatures and pH values of solution. The results will provide valuable structural information for the self-assembly of fluorinated phospholipids that are important for preparing phospholipid biomembrane on polymer surfaces.

## 2. Methods

### 2.1 DPD simulation theory

DPD is a mesoscale simulation method. It provides a dynamics algorithm, which incorporates hydrodynamics in studying coarse-grained systems over long length and time scales. In this method, a series of soft particles called beads that represent groups of several atoms or fluids interact with each other [17]. The force between each pair of beads comprises of a conservative force $F^{C}$, a dissipative force $F^{D}$ and a random force $F^{R}$ obeying the following equation [18]:

$$f_i = \sum_{i \neq j} \left( F_{ij}^{C} + F_{ij}^{D} + F_{ij}^{R} \right). \quad (1)$$

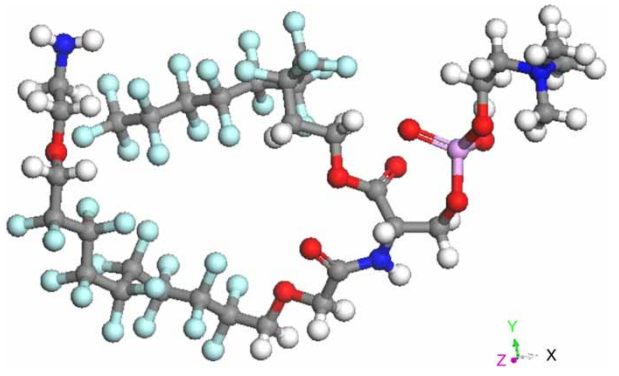

Figure 2. Stable spatial conformation of fluorinated double-chain phospholipid molecule.

Since the establishment of expression between DPD parameters and Flory–Huggins parameters $\chi_{ij}$ by Groot and co-workers [5,6], DPD simulation method has been increasingly applied to solve a wide range of problems involving complex fluids, such as diblock copolymer microphase separation [7], polymer–surfactant aggregation [8] and aggregation behaviour of fluorinated surfactant [9].

### 2.2 Simulation models and method

In these coarse-grained models shown in Figure 3, fluorinated double-chain phospholipid, hydrogenated analogue and fluorinated single-chain phospholipid are

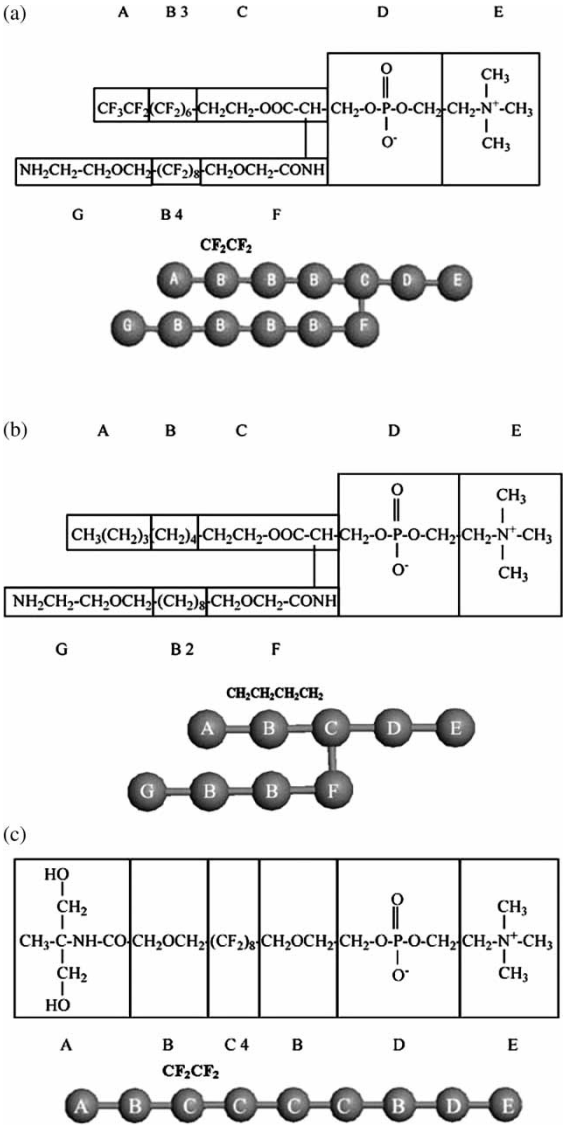


Figure 3. Molecular structures and coarse grained models: (a) fluorinated double-chain phospholipid, (b) hydrogenated analogue and (c) fluorinated single-chain phospholipid.

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Table 1. Interaction parameters $a_{ij}$ in fluorinated phospholipid system.

| | W | A | B | C | D | E | F | G |
|---|---|---|---|---|---|---|---|---|
| W | 25.00 | | | | | | | |
| A | 157.91 | 25.00 | | | | | | |
| B | 130.92 | 25.30 | 25.00 | | | | | |
| C | 82.75 | 36.40 | 32.33 | 25.00 | | | | |
| D | 122.53 | 30.91 | 28.15 | 26.35 | 25.00 | | | |
| E | 43.00 | 417.50 | 360.35 | 250.10 | 344.49 | 25.00 | | |
| F | 64.19 | 53.87 | 46.24 | 28.28 | 35.06 | 203.35 | 25.00 | |
| G | 59.27 | 52.07 | 44.78 | 28.04 | 34.46 | 188.64 | 25.00 | 25.00 |

represented by several beads. The hydrophilic head of the fluorinated double-chain phospholipid molecule consists of two hydrophilic groups (Figure 3(a)), i.e. choline group (E) and phosphate group (D) [10,19]. Ester group ($CH_2CH_2OOCCH$) is designated as C. For the two hydrophobic fluorinated chains of the molecule, one is ended by amino group and the other by $CF_3$ group. The hydrophobic chain ended by $CF_3$ is divided into four beads, including one A bead ($CF_3CF_2$) and three B beads [$(CF_2)_2$] [20,21]. The chain ended by amino group includes six beads, i.e. one G bead ($NH_2CH_2CH_2OCH_2$), four B beads and one F bead ($CH_2OCH_2CONH$). Analogously, the coarse-grained models of hydrogenated and fluorinated single-chain phospholipid molecules are detailed in Figure 3(b) and (c), respectively. In all models water molecule is treated as an individual W bead.

After building the coarse-grained models for the three phospholipid molecules, we can obtain Flory–Huggins parameters from solubility parameters [22],

$$\chi_{ij} = (\delta_i - \delta_j)^2 V_{\text{ref}}/RT, \tag{2}$$

where $R$ is gas constant, $T$ is temperature, $\delta_i$ and $\delta_j$ are the solubility parameters of a pair of interacting beads, and $V_{\text{ref}}$ is the average molar volumes of two beads, which could be calculated using discover and amorphous cell modules in Materials Studio 4.0 software with the COMPASS force field at 298 K and under atmospheric pressure.

Groot and co-workers [5,6] proposed the relationship between interaction parameter $a_{ij}$ and Flory–Huggins parameter $\chi_{ij}$:

$$a_{ij} \approx a_{ii} + 3.27\chi_{ij} \quad \rho = 3, \tag{3}$$

$$a_{ij} \approx a_{ii} + 1.45\chi_{ij} \quad \rho = 5, \tag{4}$$

where $\rho$ is the density, $a_{ii}$ is the interaction parameter between beads of the same type, and can be calculated according to Equation (5) [9].

$$a_{ii} = 75k_BT/\rho. \tag{5}$$

The bead density of the system is close to that of water with $\rho = 3$, and the cut-off radius is $r_C = k_BT = 1$. Therefore, from Equations (3) and (5), $a_{ij}$ can be obtained,

$$a_{ij} \approx 25 + 3.27\chi_{ij}. \tag{6}$$

Tables 1 and 2 list the calculated $a_{ij}$ values for the fluorinated and hydrogenated phospholipid systems, respectively.

### *2.3 Simulation condition*

All computational works were performed with the software program Materials Studio 4.0 installed on a DELL PowerEdge SC430 sever. The simulation system contained phospholipids and water in a cubic cell of size $20 \times 20 \times 20r_c^3$ with a periodic boundary condition. The total beads were 24,000 and the spring constant C was chosen as 4.0 [5]. To obtain the steady results, 100,000 DPD steps have been adopted with a time step of 0.05 ns [9].

Table 2. Interaction parameters $a_{ij}$ in hydrogenated phospholipid system.

| | W | A | B | C | D | E | F | G |
|---|---|---|---|---|---|---|---|---|
| W | 25.00 | | | | | | | |
| A | 72.31 | 25.00 | | | | | | |
| B | 74.40 | 25.06 | 25.00 | | | | | |
| C | 82.75 | 25.29 | 25.64 | 25.00 | | | | |
| D | 122.53 | 25.22 | 25.03 | 26.35 | 25.00 | | | |
| E | 43.00 | 224.61 | 230.41 | 250.10 | 344.49 | 25.00 | | |
| F | 64.19 | 29.85 | 31.05 | 28.28 | 35.06 | 203.35 | 25.00 | |
| G | 59.27 | 29.42 | 30.51 | 28.04 | 34.46 | 188.64 | 25.00 | 25.00 |

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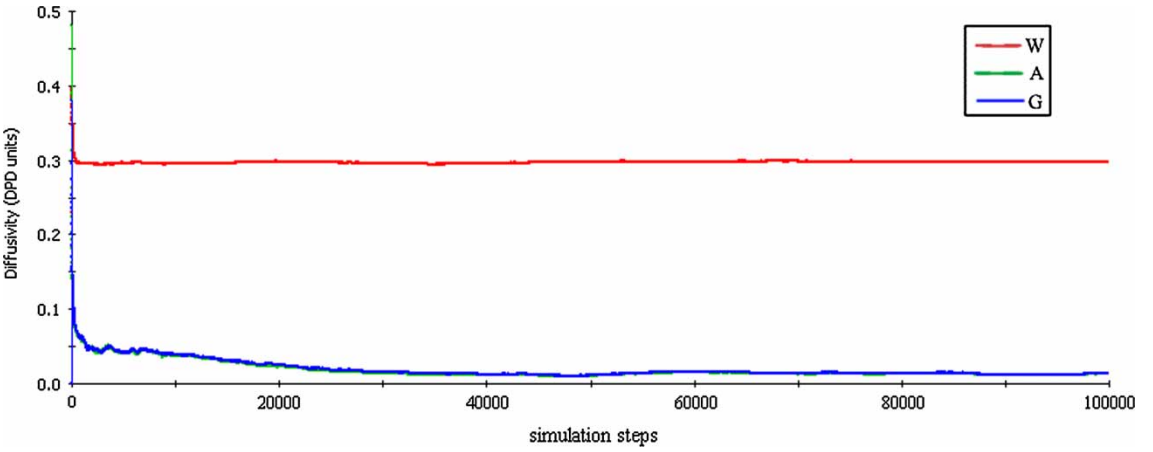


Figure 4. Diffusivity plot of 5% fluorinated double-chain phospholipid system with the simulation steps: red, green and blue curves represent results of water W, hydrophobic tail groups A and G, respectively.

## 3. Results and discussions

### *3.1 Effect of simulation steps on the self-assembly behaviour*

The simulation results of diffusivity for 5% fluorinated double-chain phospholipid system are plotted versus simulation steps in Figure 4. The profiles of hydrophobic groups A and G almost overlapped, and they reached steady state at 30,000 steps, while it took only several hundred steps for water bead to obtain the same state. Considering the DPD simulation quality and computation cost, 100,000 steps are sufficient for the simulation.

Figure 5 illustrates the self-assembly behaviour of the fluorinated double-chain phospholipids in aqueous solution with the increasing simulation steps when the molar fraction of phospholipids is 5%. In the figure, red, green, white and blue beads represent the hydrophilic head

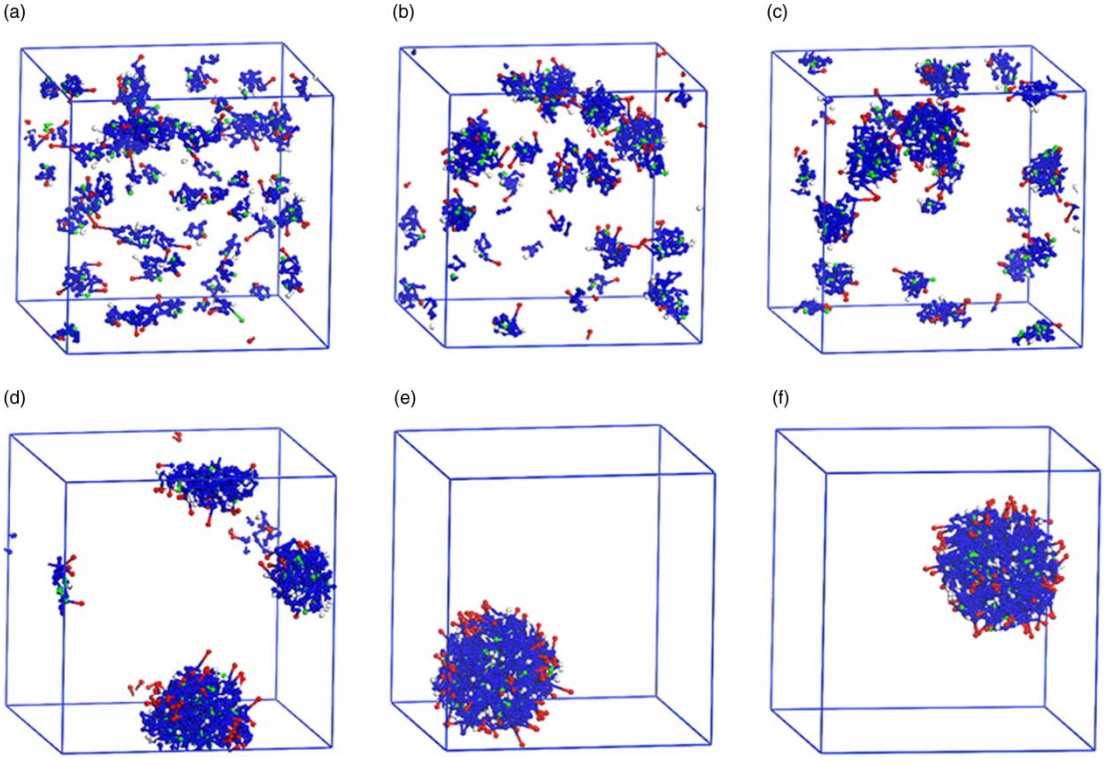


Figure 5. Dependence of aggregation evolution of fluorinated double-chain phospholipid on the simulation steps: (a) 100 steps, (b) 1000 steps, (c) 3000 steps, (d) 20,000 steps, (e) 60,000 steps and (f) 10,0000 steps (A, green; E, red; G, white; others, blue).

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group E, the hydrophobic tail group A, the other hydrophobic tail group G, and the left groups, respectively [20,21]. In order to observe the aggregation behaviour clearly, the water beads are not shown in the figure. Shown in Figure 5(a), except that a few phospholipid molecules tended to aggregate, most of them were disordered in aqueous solution at the beginning (100 simulation steps). At the step of 1000, phospholipid molecules began to aggregate and form small micelles in different sizes (Figure 5(b)). These small micelles gradually grew to big micelles with the simulation steps increased to 20,000 (Figure 5(c),(d)). Finally, only one big microsphere was observed at 60,000 steps (Figure 5(e)), and the self-assembly form remained unchanged with the simulation steps further increased to 100,000, indicating that this system reached a dynamic equilibrium. Phospholipids are weak surfactants and have a very low critical micelle concentration (CMC) value because of their two long hydrophobic chains (for instance, CMC of dipalmitoyl phosphatidylcholine in aqueous solution at 25°C was reported to be $4.7 \times 10^{-10}$ mol/l [23]). These results suggest that the CMC of fluorinated phospholipid is far lower than the simulated concentration, and phospholipids are able to aggregate into micelles observed in our simulation. Furthermore, Figure 6 shows a section view of phospholipid microsphere simulated at 100,000 steps. It was apparent that the hydrophilic heads distributed on the surface of the microsphere, while the hydrophobic tails were almost in the inner of the microsphere. Such distribution appears to result in a more stable microsphere.

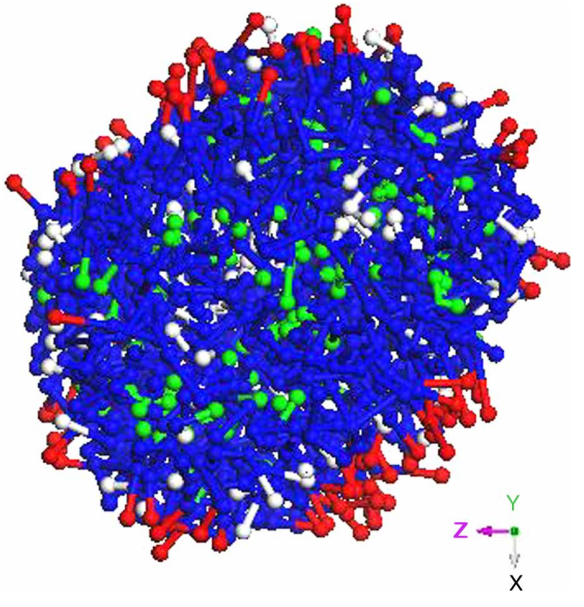


Figure 6. Section view of fluorinated double-chain phospholipid microsphere at concentration 5%.

### *3.2 Effect of concentration on the self-assembly behaviour*

The self-assembly behaviours of fluorinated phospholipids and hydrogenated counterparts in aqueous solution at various concentrations are shown in Figure 7. The concentrations used in the simulation are a molar fraction of phospholipids. As can be seen from Figure 7(a),(b), all fluorinated and hydrogenated phospholipid molecules could aggregate into microsphere at the concentrations of 5 and 10%. Moreover, the microsphere formed at 10% was larger than that at 5%. This is ascribed to the fact that the separated oil phases are easier to collide and join together when the phospholipid content is high [24]. However, the aggregated shapes showed interesting differences between fluorinated and hydrogenated phospholipids with the concentration increased to 15%. Both fluorinated double-chain and fluorinated single-chain phospholipids aggregated into ellipsoid, while hydrogenated analogues grew to microsphere. With the further increase of phospholipid content, cylindrical and lamellar structures were observed (Figure 7(d)). These result from the increasingly higher density of polar groups distributed in the external surfaces of microspheres, rendering stronger interactions among microspheres. Some of phospholipids aggregated to minimise the outer surface of microspheres, and made the whole system more stable [25]. At the concentrations of 20%, the fluorinated double-chain phospholipids formed bilayer, while the aggregate morphologies of hydrogenated and fluorinated single-chain phospholipids were of cylindrical structures (Figure 7(d)). The above observations reveal that the concentration levels of phospholipids play an important role in their self-assembly behaviour and fluorinated double-chain phospholipids are apt to form bilayer membrane more easily than hydrogenated/fluorinated single-chain phospholipids.

To further understand the bilayer membrane structure of fluorinated double-chain phospholipids, we investigated the density profile in the bilayer direction and the corresponding snapshot. Figure 8 shows the density profile and the snapshot of the resulting bilayer at a concentration of 20%. As observed from Figure 8(b), the hydrophobic tails were located in the inner of the bilayer, which was reflected in the curve (Figure 8(a)). Both hydrophobic tail groups A and B had two peaks around the bilayer mid plane, and a minimum at the mid plane (Figure 8(a)). The hydrophilic head group E was more hydrated. It exhibited two peaks at the interface of the bilayer, which pointed to water. The curve representing the other hydrophilic tail group G was almost constant across the hydrophobic region of the bilayer due to the linkage between G and the hydrophobic B bead. The density of water decreased rapidly to around one in the hydrophobic region (Figure 8(a)). It was clear that water penetrated to the

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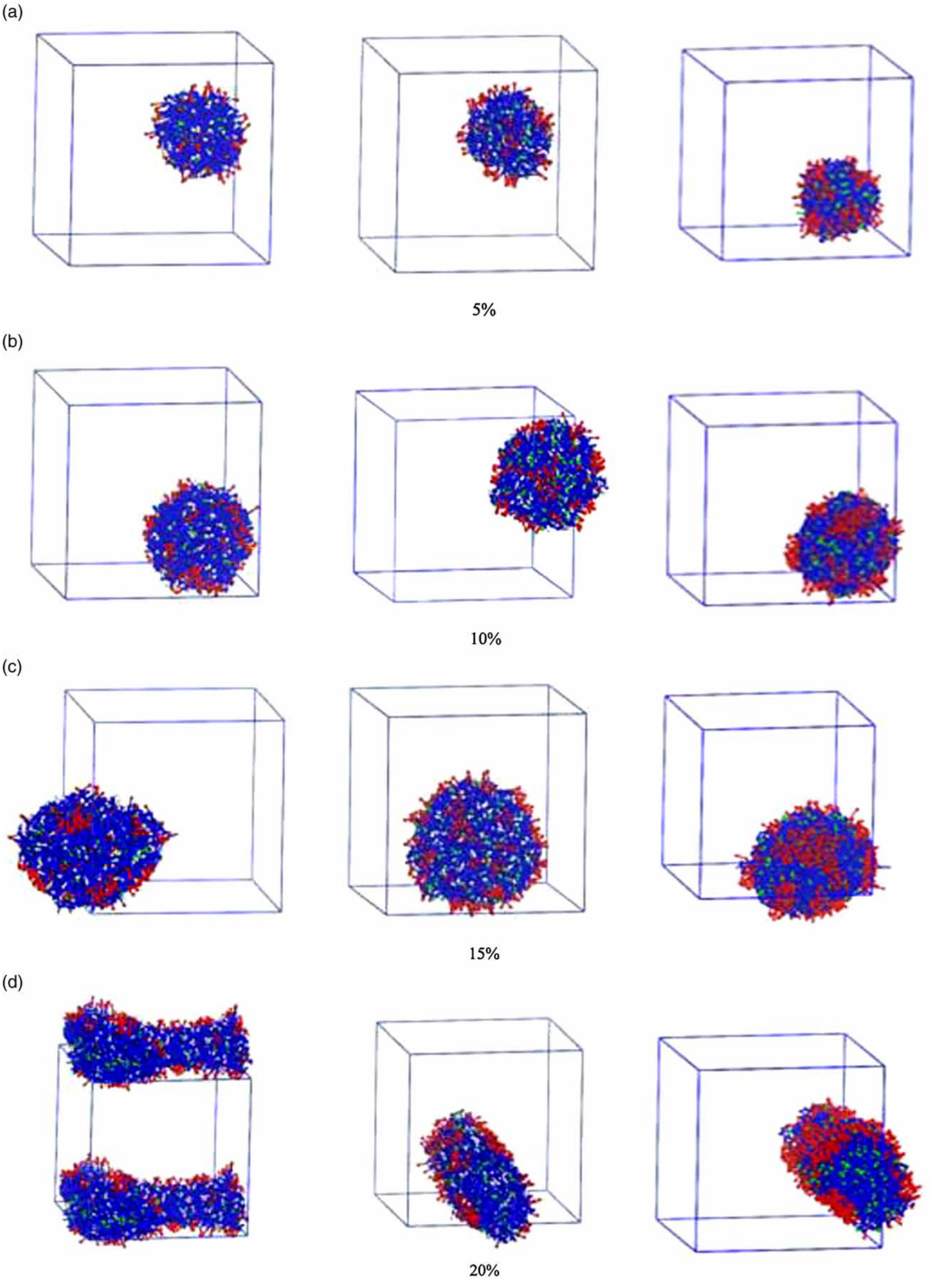


Figure 7. Self-assembly behaviours of fluorinated double-chain phospholipids (left column of figures), hydrogenated ones (middle column of figures) and fluorinated single-chain phospholipids (right column of figures) at different concentrations: (a) 5, (b) 10, (c) 15 and (d) 20%.

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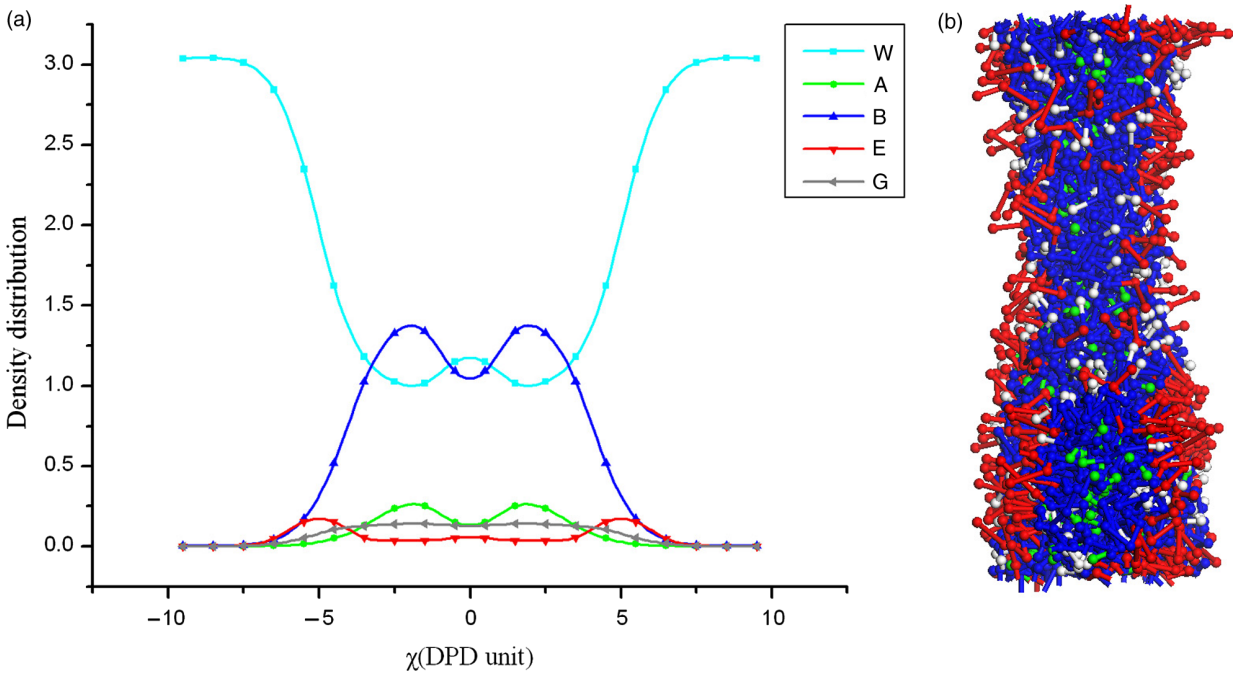


Figure 8. (a) Density profile and (b) snapshot of the bilayer at the concentration of 20% (in the density profile, W, Cyan; A, green; B, blue; E, red; G, grey, other beads were omitted).

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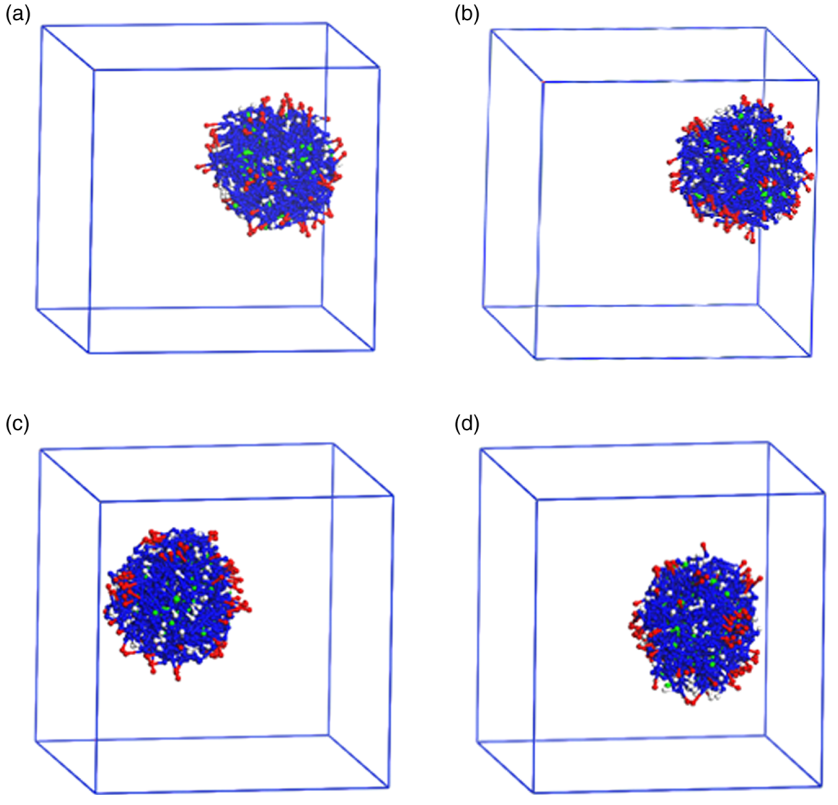


Figure 9. Self-assembly behaviour of fluorinated double-chain phospholipids at various temperatures and at concentration 5%: (a) 298 K, (b) 310 K, (c) 323 K and (d) 353 K.

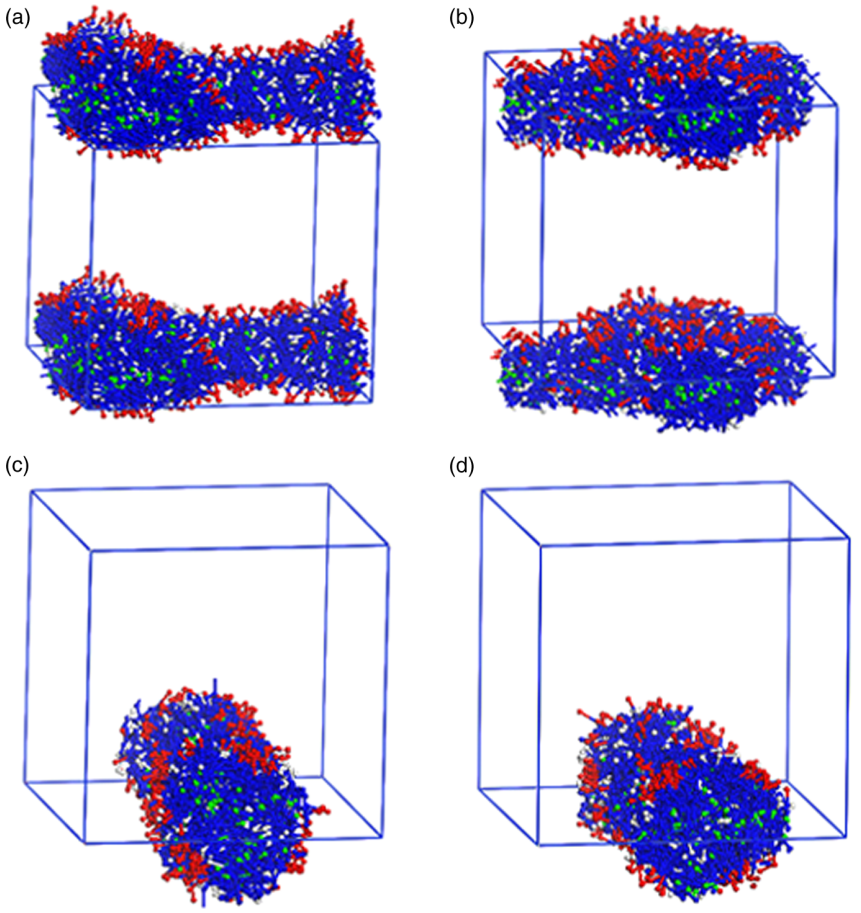


Figure 10. Self-assembly behaviour of fluorinated double-chain phospholipids at various temperatures and at concentration 20%: (a) 298 K, (b) 310 K, (c) 323 K and (d) 353 K.

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whole aggregate because of the hydrogen bonds between the amino groups of G beads and water.

For the fluorinated double-chain phospholipids, the low polarisability of fluorine resulted in low van der Waals interactions between fluorinated chains [4] and consequently enhanced hydrophobicity. The perfluorinated chains exhibited both hydrophobic and lipophobic properties [4,26]. These strong hydrophobicity and low van der Waals interactions increased the tendency of fluorinated phospholipids to self-assemble in aqueous solution, which were able to aggregate more easily and stably compared with the corresponding hydrogenated ones [9]. The reasons for the formation of fluorinated double-chain phospholipid bilayer might be attributed to the hydrogen bonds between hydrophilic chains and water, as well as between water and water of the hydrated layer [27]. In our previous studies [11,12], we did not observe that the fluorinated single-chain phospholipid could form biomembrane structure on polyurethane surfaces, even though the concentration of the phospholipid was very high. This is in agreement with the simulation results.

### *3.3 Effect of solution temperature on the self-assembly behaviour*

The effect of temperature on the self-assembly behaviour of the fluorinated double-chain phospholipids in aqueous solution was also investigated. Figure 9 shows the self-assembly behaviour of fluorinated double-chain phospholipids at different temperatures when the concentration is 5%. The fluorinated phospholipid molecules could form microsphere at temperatures from 298 to 353 K. It appears that temperature has little impact on the self-assembly behaviour when the concentration is relatively low.

However, when the phospholipid concentration is increased, change of temperature leads to different aggregate morphologies. Figure 10 exhibits the self-assembly behaviour of the fluorinated double-chain phospholipids under various temperatures at the concentration of 20%. Fluorinated phospholipid molecules formed bilayer membrane at the relatively low temperatures of 298 and 310 K. With temperature increased to 323 or 353 K, bilayer membrane of fluorinated phospholipids changed to cylindrical shape. At the relatively low temperatures, fluorinated phospholipids display remarkable

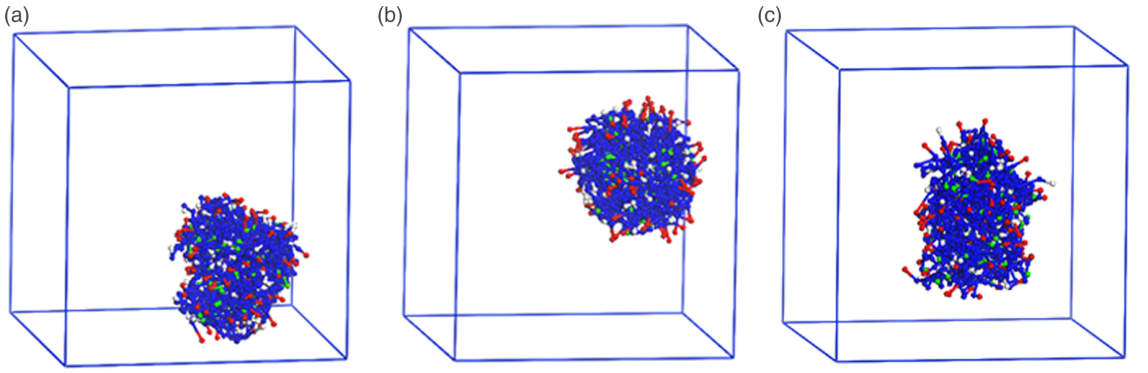


Figure 11. Self-assembly behaviour of fluorinated double-chain phospholipids at 5% aqueous solution and various pH values: (a) pH 1, (b) pH 7 and (c) pH 13.

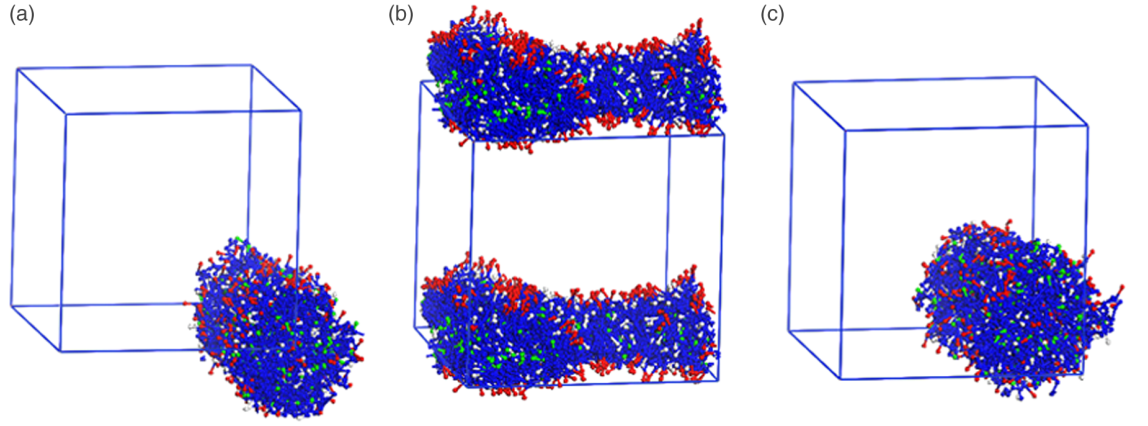


Figure 12. Self-assembly behaviour of fluorinated double-chain phospholipids at 20% aqueous solution and various pH values: (a) pH 1, (b) pH 7 and (c) pH 13.

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long-term stability because their hydrophobic interactions are sufficient to maintain a stable bilayer structure in water [25,28]. However, when temperature is further increased and exceeds the phase transition one [29], bilayer structure becomes unstable due to the change of group interactions, and molecules tend to aggregate to a different stable structure, e.g. cylinder. The simulation results demonstrate that the fluorinated phospholipids can form stable bilayer membrane at the relatively high concentration under physiological temperature condition.

### *3.4 Effect of pH value on the self-assembly behaviour*

We also investigated the effect of pH value of the aqueous solution on the self-assembly behaviour of the fluorinated phospholipids. The simulation results at concentrations of 5 and 20% are displayed in Figures 11 and 12, respectively. It is clear that the pH value of system has significant impact on the self-assembly behaviour of phospholipids. At a low concentration (Figure 11), fluorinated phospholipid molecules formed microsphere at pH 7, and changed to microsphere with a gap at pH 1 and rod at pH 13. While at high concentration (Figure 12), they formed bilayer at pH 7, and cylinder at both pH 1 and 13. The results indicate that the self-assembly behaviour of fluorinated phospholipids can be made tunable by adjusting the pH values.

## 4. Conclusions

In summary, the results presented show that DPD is a powerful tool to understand the self-assembly behaviour of phospholipids under the influence of structure and concentration of phospholipids, temperature and pH value of aqueous solution. The DPD simulation results reveal that the self-assembly morphologies of the novel fluorinated double-chain phospholipids, hydrogenated analogues and fluorinated single-chain phospholipids are strongly dependent on the concentration, temperature and pH value of aqueous solution. The fluorinated double-chain phospholipids could form bilayer membrane more easily than the hydrogenated and fluorinated single-chain

ones. A stable bilayer membrane of fluorinated double-chain phopholipids was obtained at a relatively high concentration and under physiological condition. This study provides useful information for the self-assembly of the fluorinated phospholipids, which will be helpful for preparing phospholipid biomembrane on polymer surfaces.

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