A comparison of *straight*- and *branch*-chained lipid bilayers for static and dynamic properties: A molecular dynamics study

W. Shinoda[*1], M. Mikami[*2], T. Baba[**3], and M. Hato[**4]

[*]RICS and SYNAF, AIST, Central 2, Umezono 1-1-1, Tsukuba 305-8568, Japan
[1] w.shinoda@aist.go.jp, [2] mikami.masuhiro@aist.go.jp
[**]NRI, AIST, Central 5, Higashi 1-1-1, Tsukuba 305-8565, Japan
[3] t-baba@aist.go.jp, [4] m.hato@aist.go.jp

ABSTRACT

A bilayer composed of branch-chained lipid molecules is generally believed to have high bilayer stability and low ion leakage. To understand how the chain branching affects the bilayer properties on the molecular level, two molecular dynamics simulations of lipid bilayers have been undertaken in the isothermal-isobaric ensemble. The first simulation was carried out on the straight-chained DPPC bilayer, the second on the branch-chained DPhPC. The detailed analyses on the chain conformation revealed that the segmental order of branched chains was lower than that of straight chains. As for the intermolecular packing order in the bilayer plane, however, a relatively neat lipid arrangement was observed for the branch-chained DPhPC bilayer. A significant lowering in the chain mobility was observed as a result of chain branching. The high bilayer stability of the branch-chained DPhPC bilayer would arise from the low chain mobility and the neat lateral arrangement of the lipid in the bilayer.

Keywords: molecular dynamics, lipid bilayers, branched chain, bilayer stability, permeability

1 INTRODUCTION

In general, a bilayer composed of branch-chained lipid molecules is believed to have high bilayer stability and low ion leakage. Some of us have synthesized a novel, branch-chained glycolipid to develop a stable bilayer matrix for membrane proteins,[1] and the bilayer was actually shown to have low proton permeability.[2] It has not been well understood, however, how the branched chain does affect the bilayer properties on the molecular level. In this study, to understand the effect of the chain branching on the structure and dynamics of bilayers, two molecular dynamics (MD) simulations have been undertaken in the isothermal-isobaric ensemble. The first simulation was carried out on the straight-chained dipalmitoyl phosphatidylcholine (DPPC) bilayer, the second on the branch-chained diphytanoyl phosphatidylcholine (DPhPC).

2 CALCULATIONS

Each bilayer system consisted of 72 lipid and 2,088 water molecules as shown in Fig.1. The lipid molecules were modeled by the CHARMM force field (PARM27) [3]

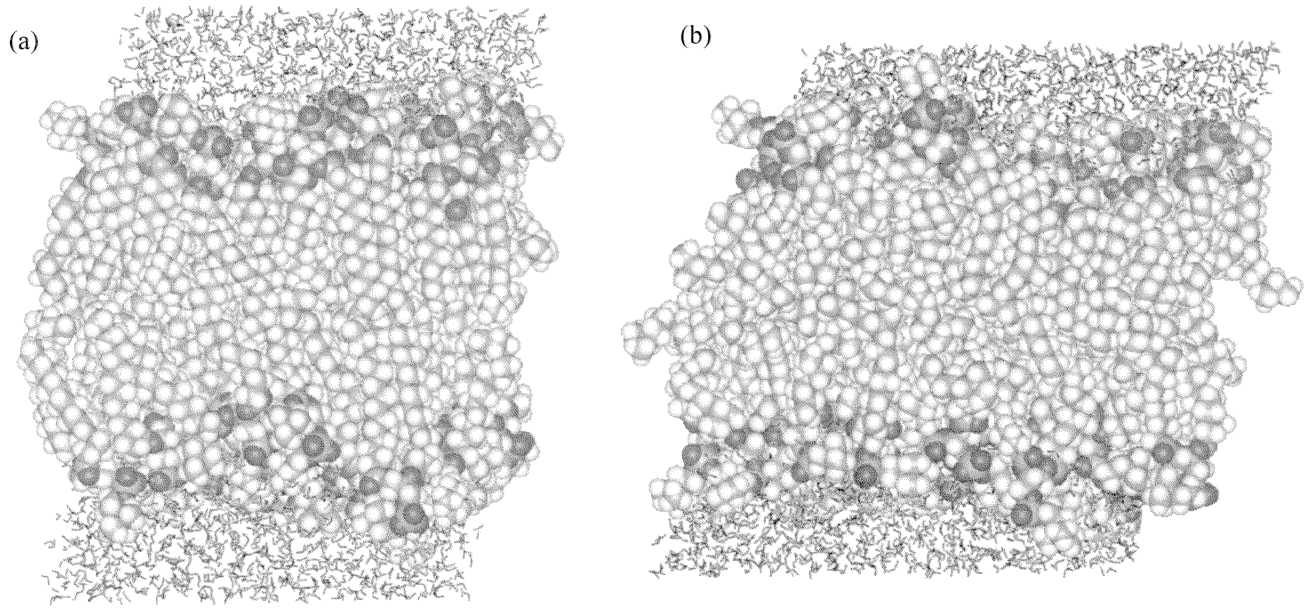

Figure 1: Snapshots of the calculated (a) DPPC and (b) DPhPC bilayer systems. Sphere : lipid and line : water.

with the modified TIP3P water.[4] The Lennard-Jones interactions were truncated between 10 and 12Å with a smooth switching of the potential. Electrostatic interactions were calculated with the Ewald method. [5] To generate the isothermal-isobaric (NPT) ensemble, the fully flexible cell was employed as the barostat, and the Nosé-Hoover chain (length = 5) was used as the thermostat.[6] 2.5ns-NPT-MD simulation (1ns for equilibration) has been carried out for each system at the same thermodynamic condition; P=0.1MPa and T=323K (in the liquid crystal phase). All bond length relevant to hydrogen atoms were fixed by using the SHAKE/RATTLE/ROLL algorithm[6]. This allowed us to use the time step of 2fs. MD simulations and all analyses have been carried out on a 16-nodes AlphaStation XP1000(600MHz) using the MD simulation tool "MPDyn",[7] in which parallel directives were implemented using public domain Message Passing Interface (MPI).

3 RESULTS

The average molecular surface areas per lipid determined using the last 1.5ns trajectories were 62.0Å^2 in DPPC and 76.8 Å^2 in DPhPC membranes, both of which were in good agreement with those obtained by experimental measurements.[8,9] While the difference of the molecular area between DPPC and DPhPC was as large as about 15Å^2, the peak to peak distance of the electron density profile (membrane thickness) did not show significant change (39.6Å in DPPC, 38.2Å in DPhPC membrane). The analyses on the orientational distribution of the hydrophobic chains revealed that the chain orientation parallel to the bilayer normal was most probable both for the DPPC and DPhPC molecules, whereas the distribution was broader for the latter. Husslein *et al.* reported that the bimodal distribution of chain orientation was observed in their MD of DPhPC bilayer, and their second peak was found at the 90 degree to the bilayer normal.[10] However, we observed a single peak in the distribution of the chain orientation for both bilayer systems. In Fig. 2, distributions of angle between two chains in a lipid molecule were plotted for both DPPC and DPhPC molecules. The chain vector was defined as one connecting from the carbonyl carbon (C1) and the tail carbon(C15). Although the two chains in a lipid were most probably parallel to each other in both bilayers, the distribution of DPhPC is significantly broader than that of DPPC. The broadening may be responsible for the larger molecular area of DPhPC.

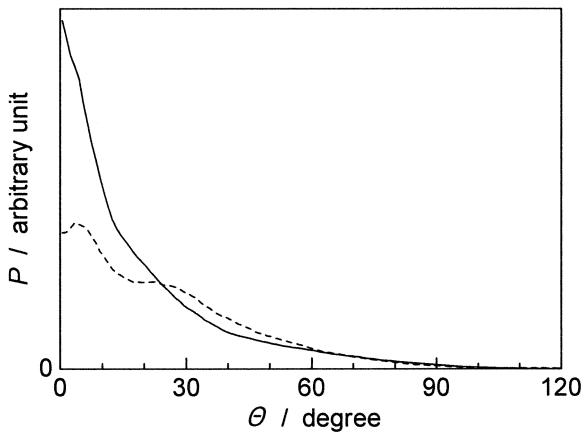

Figure 2: Distribution of the angle between two chains in a lipid molecule. Solid line : DPPC and dashed line : DPhPC.

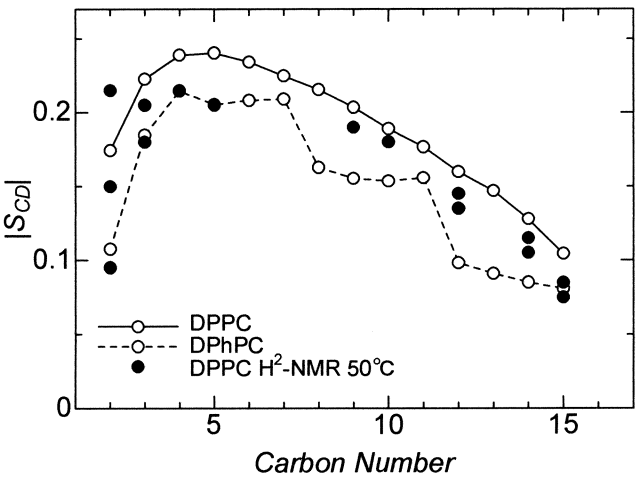

Figure 3: Order parameter profiles along the main chain of the lipid.

The order parameter, S_{CD}, was calculated and plotted as a function of carbon number in Fig. 3. The order

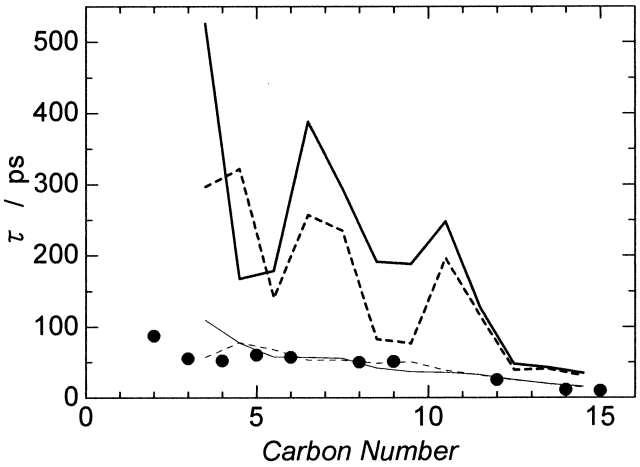

Figure 4: Relaxation time of the correlation function, $C(t)$. Thin dashed line : *sn*-1 chain of DPPC, thin solid line : *sn*-2 chain of DPPC, thick dashed line : *sn*-1 chain of DPhPC, thick solid line : *sn*-2 chain of DPhPC, and solid circle : NMR CD relaxation time of DPPC[11].

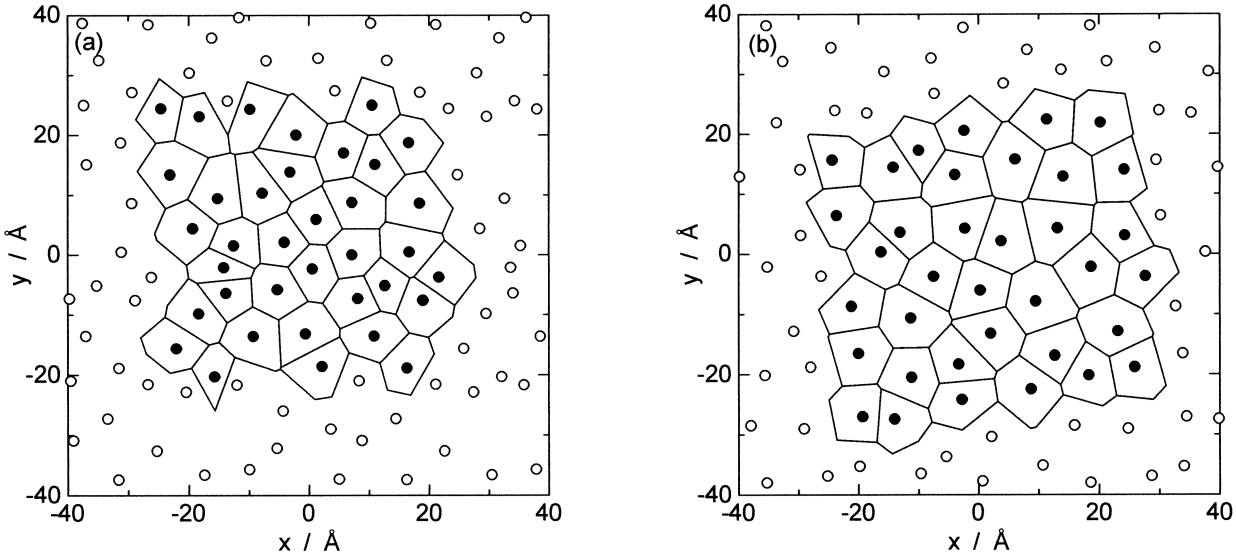

Figure 5: Two-dimensional Voronoi tessellation for *x-y* projection of the centers of mass (dots) of the lipid molecules in the upper half of the bilayer. (a) DPPC and (b) DPhPC bilayer systems.

parameter profile obtained from NMR measurement [11] was also plotted for DPPC. The calculated order parameter profile satisfactorily reproduced the experimental one. DPhPC molecules showed a stepwise variation at the positions where the branch methyl groups located (3, 7, 11, 15). The characteristic stepwise profile was also reported by the previous MD study.[10] The stepwise profile must be closely related with the fact that the *gauche* conformers were relatively probable in the vicinity of the *tert*-methyl groups. DPhPC showed slightly lower order parameters over the chain.

In order to assess the mobility of chains, we have investigated the rate of *gauche-trans* isomerization of the dihedrals in chains. We used the state function, [12]

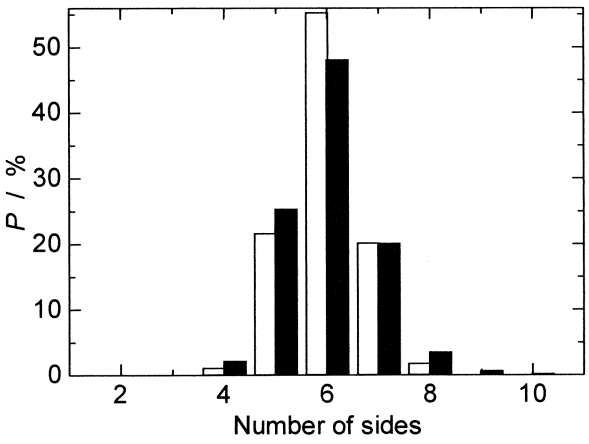

Figure 6: Distribution of the number of sides of the Voronoi polygon. Closed : DPPC and Open : DPhPC.

$$S(t,\phi)=\begin{cases}0 & (\phi<(2/3)\pi,\ \textit{gauche}\ \text{state})\\ 1 & (\phi\geq(2/3)\pi,\ \textit{trans}\ \text{state})\end{cases},$$

to estimate the isomerization rate. This function describes the state of the dihedral angle ϕ at time t. The relaxation time of the correlation function,

$$C(t)=\frac{\langle\delta S(t)\cdot\delta S(0)\rangle}{\langle\delta S^2\rangle},$$

gives a measure of the net isomerization rate, where

$$\delta S(t)=S(t)-\langle S\rangle.$$

The correlation functions showed approximately exponential decay. The relaxation time was estimated by the numerical integration of the correlation function, and a correction was made by fitting the tail region of the correlation function to a single exponential one. The calculated relaxation times of the function, $C(t)$, were plotted in Fig. 4 as a function of carbon number. It was clearly shown that the branched chain was less mobile than the straight one; for the middle part of the chains, the relaxation time of the correlation function of DPhPC was approximately five times longer than that of DPPC. NMR relaxation time of segmental CD vectors due to the torsion dynamics of DPPC [13] was also plotted in Fig. 4. The calculated relaxation time was comparable to the experimental one. DPhPC showed the peaks at the *tert*-carbon in the relaxation time profile. This indicated low mobility of *tert*-carbon. The same trend was observed experimentally.[14]

In order to analyze the lateral packing of the lipid molecules in a bilayer plane, 2-dimensional Voronoi analyses for the center of mass of lipids [15] have been undertaken. In Fig. 5, snapshots of lipid centers of mass

projected on the *x-y* plane (the bilayer plane) were shown for DPPC and DPhPC bilayers, respectively. A glance of Fig. 5 revealed that DPhPC molecule aligned in a relatively ordered arrangement in the layer plane, compared with DPPC molecule. To evaluate the order of the packing quantitatively, the distribution of the number of sides of a Voronoi polygon was calculated (Fig. 6). If the lipid molecules form an ideal-hexagonal packing in the bilayer plane, all the side number is 6. The broadening of the distribution demonstrates a disorder from the hexagonal arrangement. In Fig. 6, the narrower distribution was observed for the DPhPC bilayer, showing that relatively neat arrangement of lipid molecules was plausible as a result of chain branching.

4 CONCLUSIONS

We have investigated the effect of chain branching on the structure and dynamics of lipid bilayers by using MD simulations. From a comparison between DPPC and DPhPC bilayers, we observed that, though branched-chains have less ordered segments, the branch-chained DPhPC molecules formed a rather neat arrangement in the bilayer plane, and the chain dynamics was much slower than that of the straight-chained DPPC. The high bilayer stability of the branch-chained DPhPC bilayer would arise from the low chain mobility and the neat lateral packing of the lipid in the bilayer.

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