Electronic States of a Lipid Membrane Reinforced with Siloxane Bond*

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We investigate the electronic states of a simple model of a lipid bilayer membrane with a siloxane-bond-reinforced surface using first-principles calculations based on density functional theory. Our model is a simple representation of a cerasome, a material that has proved promising as a drug delivery medium. Analyzing the electronic density of states reveals that there is a mid-gap state originating from the Si–C antibonding state. The existence of an antibonding state at mid-gap indicates that we can selectively excite an electron to this state and thus break up the siloxane network. [DOI: 10.1380/ejssnt.2014.112]

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I. INTRODUCTION

Drug therapy usually produces undesirable side effects, because the effects of a drug spread out over healthy tissues or organs as well. When we can deliver the drug directly to the diseased area, the side effects are minimized. Recently, drug delivery systems (DDSs) have attracted much interest [1]. The construction of a DDS requires the technology to encapsulate a drug and release it around the diseased area. Lipid bilayer vesicles, so-called liposomes, are typical DDS materials. Much research has been devoted to determining the basic properties of liposomes as well as expanding their commercial applications. However, liposomes are not very stable because all the lipids are connected via van der Waals interactions. As a result of this low stability, liposomes cannot reach the diseased area intact. Kikuchi and his coworkers overcame this problem by hybridizing ceramics and liposome technologies. Cerasomes, i.e., liposomes featuring surfaces reinforced with a siloxane bond network, have been developed [2, 3]. It has been shown that a cerasome can encapsulate a drug and is much more stable than a liposome [4]. Thus, cerasomes are promising materials for DDS. However, the improvement in stability is accompanied by a difficulty in opening the capsule. Breaking the chemical bonds of a cerasome surface requires information about its microstructure and electronic states, but the microscopic properties of cerasomes remain unclear.

II. MODEL AND METHODS

In the present study, we use the PHASE code [5], a program package for performing first-principles total energy calculations based on density functional theory (DFT) and the ultrasoft pseudopotential scheme. We use the generalized gradient approximation for the exchange-correlation term [6]. The cutoff energies for the wave function and charge density are 15 Ryd and 60 Ryd, respectively [7].

To model the cerasome, we adopt [3-((N,N-dihexadecylamino)-succinylamino)propyl]triethoxysilane (Fig. 1) from among a variety of cerasome lipids [8]. The smallest diameter of the cerasome is about 50 nm, which is too large to treat whole vesicles in a conventional DFT calculation. In this study, we focus on the electronic states of the surface. Although the cerasome has a vesicular structure, at the microscopic scale, we can approximate it by a membrane. With the membrane model, we can use periodic boundary conditions that would allow us to perform calculations using a unit cell containing only hundreds of atoms. The interaction between bilayers in the cerasome involves van der Waals forces that play no important role in the surface state. We approximate the bilayer membrane by a monolayer membrane. Since we have no information about the microscopic surface structures of the cerasome, we need to make an assumption as to the lipid structure. As there are three Si–O– bonds in the inorganic part of the lipid, we assume a honeycomb structure that exhibits close-packing with three coordination sites in a two-dimensional lattice. There is little electronic interaction between the surface siloxane bond and hydrocarbon tail, which act as the hydrophobic components of the membrane. To reduce the calculation cost, we approximate the hydrocarbon tail by CH₃, the smallest possible hydrocarbon group.

Figure 2 illustrates the membrane model used in this study after geometrical optimization. The angle between axes a and b is 120° in the honeycomb structure. The lengths of axes a and b are both 1.084 nm. To determine the size of the unit cell, we calculate the total energies using several lengths for axes a and b. We adopt the

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FIG. 1: Chemical structure of a cerasome lipid.

This study constructs a simple model of the cerasome and investigates its electronic states.
III. RESULTS AND DISCUSSION

Before calculating the electronic states of the membrane model, we calculate that of a single lipid molecule. Figure 3 illustrates the molecule used in this study. All atomic coordinates are determined from a snapshot geometry in the classical molecular dynamics calculation. Figure 4(a) shows the electronic density of states (DOS) of the molecule. Clearly, the HOMO-LUMO gap is 4.1 eV. We next calculate the electronic states of the membrane model, whose DOS is shown in Fig. 4(b). The band gap, 2.8 eV, is narrower than the HOMO-LUMO gap of the molecule. This shows that the bands originating from HOMO and LUMO are broadening with the siloxane bond network. The most important difference from the DOS of the molecule is the presence of mid-gap states around 1.3 eV. To determine the cause of the mid-gap states, we calculate the partial charge density with the energy window ranging from 1.09 eV to 1.36 eV. Figure 5 shows the calculated partial charge. We can easily see that there are nodes between Si and C atoms. The nodes of the partial charge indicate that the mid-gap states are composed of anti-bonding states of Si–C bonds that connect the inorganic siloxane network to the organic parts of the lipid. The reason why anti-bonding states of Si–C are redshifted from unoccupied bands and emerged in the mid-gap of the membrane model presumably has to do with the surface geometry of the model. The average bond angle of Si–O–Si bonds in the membrane model is 140°. This is wider than the corresponding average bond angle of Si–O–C bonds in the lipid molecule, 108°. These results show that the Si–O bonds are flattened $sp$- or $sp^2$-like in the membrane, but tetracoordinated $sp^3$-like in the molecule. When the Si–O bond becomes a multiple bond, the oxygen deprives the Si–C bond of an electron because the multiple bond needs more electrons than the $sp^3$ single bond. Thus, the Si–C bonding state becomes unstable, causing a redshift in the antibonding states. This is the mechanism for the emergence of mid-gap states in the membrane model.

As mentioned above, the mid-gap states are antibond-
ing states. This means that if we can excite an electron to the mid-gap states, there is a possibility of breaking the siloxane network and hence the membrane itself.

We have assumed a perfect siloxane network; however, there are many O$^-$ and OH groups on the surface of an actual cerasome. The influence of these groups may not be small; thus, a more realistic model is necessary. Nevertheless, we can expect that the mid-gap states revealed in this study will remain valid for the cerasome because as in the present model, there are three coordinated siloxane networks in a cerasome.

IV. CONCLUSION

A simple model of a cerasome, a lipid bilayer vesicle reinforced with siloxane bonds, is constructed. The electronic states of the model are investigated using DFT calculations. Comparing the electronic DOS of the membrane model with that of the molecule reveals that there are mid-gap states in the membrane model that are not in the molecule. These mid-gap states are caused by antibonding states of Si–C bonds that connect the siloxane network and the organic parts of the lipid.

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[5] See the website of Center for Research on Innovative Simulation Software, Institute of Industrial Science, the University of Tokyo: http://www.ciss.iis.u-tokyo.ac.jp/
[7] The cutoff energies seem small for C, N and O atoms. We have checked the DOS of the molecule using a cutoff energy of 25 Ryd for the wavefunction. We found a slight difference between the shapes of DOS obtained using 15 Ryd and 25 Ryd and concluded that we can discuss the electronic state with the present cutoff energy in this study.