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Interfacial energy consideration in the organization of a quantum dot–lipid mixed system

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Abstract

We propose a theoretical model for a quantum dot (QD)–lipid mixed system based on a simple geometrical assumption for a single-component lipid (DOPC) monolayer deformation profile. In this system, there are two possible states: a quantum dot–liposome complex (QLC) state where QDs are incorporated into the lipid bilayer of the liposome, and a quantum dot–micelle complex (QMC) state where an individual QD is covered by a lipid monolayer. In this model, the elastic deformation energy of the QLC is smaller (larger) than that of the QMC for the QD size smaller (larger) than a certain critical size. Therefore, the QLC is a more stable state than the QMC for the QD size smaller than a certain critical size. The prediction shown in this model is very consistent with our recent experimental results. To our knowledge, this is the first theoretical model that predicts the size dependence of the stability of the QD in the lipid bilayer.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Instead of complex biomembranes which have components of diverse phospholipids, proteins and cholesterols, liposomes, which have much less components, have attracted a great deal of attention as bio-mimic systems because of their simplicity. Furthermore, researchers have conducted extensive studies of liposomes for cosmetic, medical and pharmaceutical applications to increase the efficiency and stability of liposomes in living organisms [1]. In the case of drug delivery research [2], liposomes with some biomolecules for specific binding are typically labeled by fluorescent probes in order to monitor whether they are effectively bound to their destinations or not [3]. Recently, quantum dots (QDs) have been preferred to organic fluorescent dyes for visualizing a target because of their prominent optical properties such as emission peak shifts through size tuning and the feasibility of simple modifications of the chemical properties of the QD surface [4]. Interesting experimental results about the bioconjugation of QDs with phospholipids in aqueous environments forming quantum dot–micelle complexes (QMC) [5] or quantum dot–liposome complexes (QLC) [6] have been reported. In the QLC state, QD is incorporated into the lipid bilayer of a liposome, and in the QMC state, QD is covered by a lipid monolayer. The interplay between QDs and phospholipids in aqueous solutions is mainly driven by the strong hydrophobic interaction between lipid hydrocarbon chains and trioctylphosphine oxide (TOPO) on QDs. Recently, we verified experimentally that in the QLC state the incorporation of QDs into the lipid bilayer of liposomes, as shown in figure 1(a), is dependent on the relative QD size with respect to the lipid bilayer thickness [7]. Figure 1(b) is the confocal image of the QLCs, which clearly shows the fluorescent signal emitted from the QDs confined in the lipid bilayer of giant liposomes. Being motivated by these experimental results, we propose a theoretical model explaining the QD size dependence in terms of the elastic deformation energy of the lipid bilayer.

Many theoretical models have been developed to explain the interaction between the amphiphilic membrane proteins and the surrounding lipid molecules [8]. The hydrophobic part of the integral protein is mostly longer or shorter than the length of the hydrophobic region in the membrane, which is called hydrophobic mismatch. In order to avoid the exposure of the excess hydrophobic part to water or to suppress the formation of voids inside the membrane, the monolayer deformation and the conformational change of lipid

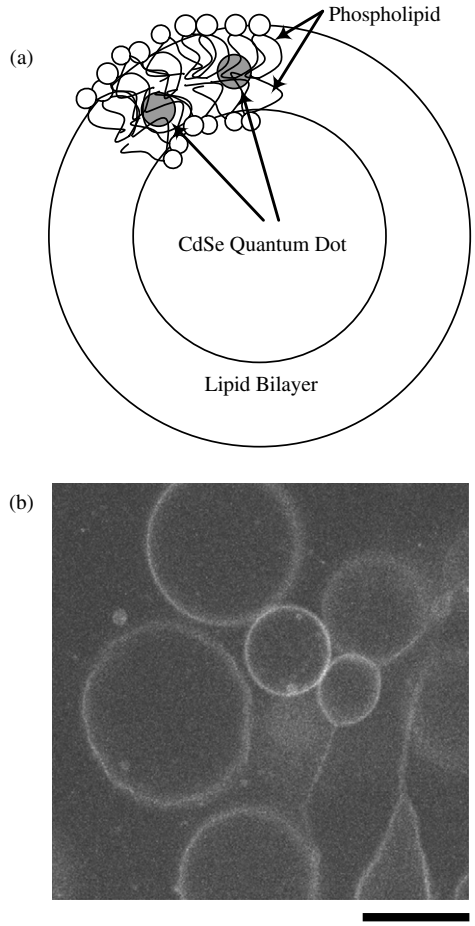

Figure 1. (a) A schematic diagram of QD–liposome complex (QLC). QDs are incorporated into the lipid bilayer of a liposome. This is an exaggerated picture compared with the real size ratio of a QD to a giant liposome. (b) The confocal fluorescent cross-sectional image of giant QLC prepared from the mixture of asolectin lipids and green-emitting CdSe QDs by the electroformation method. A clear fluorescent signal is emitted from the perimeter of giant liposomes. The scale bar is 50 μm.

hydrocarbon chains take place in the vicinity of the protein. In the QD–lipid mixed system, the hydrophobic mismatch between the QDs and the lipid aggregated structure (bilayer or micelle) is not expected because the surface chemical property of pure QDs is not amphiphilic but purely hydrophobic due to the presence of TOPO molecules. However, since the hydrophobic QD surface must be completely covered by the lipid monolayer in order to avoid the high energy penalty caused by exposure of the hydrophobic part to water, monolayer bending and the conformational change of lipid hydrocarbon chains such as stretching, compression and tilting are inevitable.

The detailed experimental data about the hydrocarbon chain structures around QDs, which is the crucial information in modeling, has not been reported yet due to the difficulties in detecting and analyzing nanostructures in fluid environments within a several nanometer resolution. Therefore, in this work, we made five assumptions as follows. (i) The QD is approximated as a hydrophobic hard spherical particle with a radius of R_{QD}. (ii) The lipid bilayer of a liposome is assumed

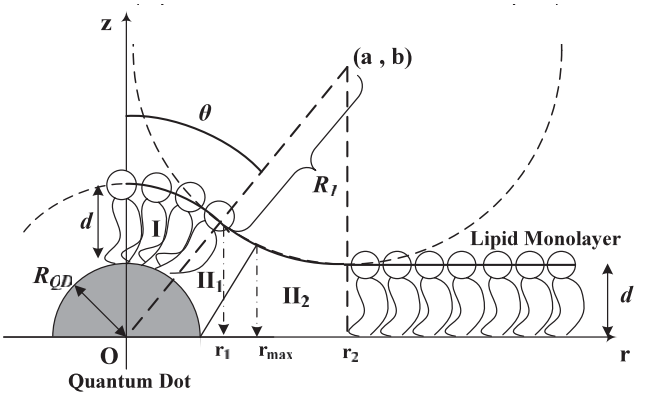

Figure 2. A model for the deformation of the lipid monolayer interface around the QD in the QLC state. In regime I ($0 \leqslant r \leqslant r_1$, where r is the coordinate of the monolayer interface), most hydrocarbon chains keep their lipid monolayer thickness d without any stretching or compression. The local curvature is a constant, $R_{\mathrm{QD}} + d$. In contrast, in regime II ($r_1 \leqslant r \leqslant r_2$), the chains are a little stretched from d to remove the void formation around the quantum dot. Regime II is divided into two local regimes II_1 ($r_1 \leqslant r \leqslant r_{\mathrm{max}}$) and II_2 ($r_{\mathrm{max}} \leqslant r \leqslant r_2$). The end of the hydrocarbon chain contacts the QD surface in regime II_1. The end of the chain in regime II_2 contacts the $z = 0$ plane. These two parts are separated by the lipid with maximally stretched hydrocarbon chains located at $r = r_{\mathrm{max}}$.

to be a planar lipid bilayer due to the large difference in size between the QD and liposome. (iii) The QD-induced lipid monolayer deformation profile is composed of two circular arcs with different radii. The boundary separating these two arcs is determined by the angle θ_{min}, which minimizes the elastic deformation energy of the QD–lipid bilayer system (this will be described in detail later). (iv) We examine whether QD can stably remain in the lipid bilayer or not by comparing the elastic deformation energy between the QLC and QMC states for different QD sizes R_{QD}. However, it is worthwhile to note that QMC is just selected as an alternative system to satisfy the above purpose, in other words, there is no possibility of transitions between these two states. (v) The number of lipid molecules required to cover up the QD hydrophobic surface in the QLC and QMC is almost the same. Through this last assumption, we can neglect the hydrophobic interaction energy between the QD and lipids in considering the elastic deformation energy of these two states.

As a result, our model predicts the dependence of the stability of the QDs in lipid bilayers on the QD size for a fixed lipid monolayer thickness. For example, QDs larger than a certain critical size cannot stay in lipid bilayers due to a high energy penalty. This prediction is consistent with our recent experimental results [7] as well as the results by Gopalakrishnan *et al* [6], where QLCs are successfully prepared with green QDs (smaller than the critical size), but not with red QDs (larger than the critical size).

2. Modeling

For a simple approach to obtain the elastic deformation energy, we assume that the inner- and outer-lipid monolayers are symmetrically deformed in the vicinity of the QD incorporated in the lipid bilayer. Figure 2 shows the cross section of

the outer monolayer surrounding a QD. The deformed lipid monolayer has an azimuthal symmetry around the z axis. The monolayer profile in this figure can be represented by two circular arcs joined continuously at an angle θ. The radius of the arc in the non-stretched monolayer (regime I) is $R_{QD}+d$, which is the radius of the two identical principal curvatures. The radius of the arc in the stretched monolayer (regime II) is $R_1=[(R_{QD}+d)\cos\theta-d]/(1-\cos\theta)$, which is the radius of the curvature in the plane of the paper. For a given radius R_{QD} and monolayer thickness d, the above elastic deformation energy can be expressed as a function of a single parameter, angle θ, which ranges from 0 to $\sin^{-1}[d/(R_{QD}+d)]$ due to the geometric constraints of the monolayer thickness and the QD size.

According to the five assumptions the lipid bilayer elastic deformation energy $\Delta E_{def,QLC}$ consists of two contributions: the monolayer bending energy ΔE_{bend} due to the change in curvature of the monolayer surrounding the QD and the stretching energy of the hydrocarbon chain $\Delta E_{stretch}$ due to the change in the monolayer thickness in order to remove the voids near the QD inside the bilayer [9]. We neglect the Gaussian curvature energy in this model:

$$\Delta E_{def,QLC}=\Delta E_{bend}+\Delta E_{stretch} \tag{1}$$

$$\Delta E_{bend}=\frac{\kappa}{2}\int_{I}\left(\frac{2}{R_{QD}+d}-\frac{1}{R_0}\right)^2 dA + \frac{\kappa}{2}\int_{II}\left(-\frac{1}{R_1}+\frac{1}{R_2}-\frac{1}{R_0}\right)^2 dA \tag{2}$$

$$\Delta E_{stretch}=\frac{K}{2}\int_{II}\left(\frac{u}{d}\right)^2 dA. \tag{3}$$

Here, κ is the bending modulus of the lipid monolayer; K, the compression–expansion modulus of the lipid monolayer; R_{QD}, the radius of QD; R_0, the radius of the monolayer spontaneous curvature; and R_1 and R_2, two radii of the principal curvatures in regime II of the stretched hydrocarbon chains. Finally, u is the extent of the stretched hydrocarbon chain from the unperturbed lipid monolayer thickness d. The first term in the bending energy corresponding to regime I can be transformed:

$$\frac{\kappa}{2}\int_{I}\left(\frac{2}{R_{QD}+d}-\frac{1}{R_0}\right)^2 dA = 2\pi\kappa(d+R_{QD})^2\left(\frac{1}{R_0}-\frac{1}{d+R_{QD}}\right)^2 - 2\pi\kappa\left(\frac{1}{R_0}-\frac{1}{d+R_{QD}}\right)^2(d+R_{QD})^2\cos\theta. \tag{4}$$

In regime II, the out-of-plane principal curvature $1/R_2$ is a function of r as $1/R_2(r)=(a-r)/(R_1 r)$. Therefore, after the integration from $r_1=a-aR_1/\sqrt{a^2+b^2}$ to $r_2=a$, the second term in the bending energy can be expressed as a function of θ only.

For the simple calculation of the stretching energy of the hydrocarbon chain, regime II is divided into two local regimes II_1 and II_2 as shown in figure 2:

$$\Delta E_{stretch}=\frac{K}{2d^2}\left(\int_{II_1}(u_1(r))^2\,dA+\int_{II_2}(u_2(r))^2\,dA\right). \tag{5}$$

The amount of stretching of the hydrocarbon chain in each part is given as follows. In regime II_1:

$$u_1(r)=\frac{1}{R_1}\left\{a\lambda+b\sqrt{R_1^2-\lambda^2}-[R_1^2+((a^2-b^2)\lambda^2+2ab\lambda\sqrt{R_1^2-\lambda^2}+R_1^2(R_{QD}^2-a^2))^{1/2}]\right\}^{1/2}-d, \tag{6}$$

and in regime II_2:

$$u_2(r)=\sqrt{\frac{b^2R_1^2}{R_1^2-\lambda^2}}-d-R_1. \tag{7}$$

Here, $\lambda\equiv a-r$. Finally, we can obtain θ_{min} which corresponds to the minimum elastic deformation energy by means of differentiation $d\Delta E_{def,QLC}/d\theta\ |_{\theta=\theta_{min}}=0$. Furthermore, we are able to check the continuity between two regimes on a monolayer deformation at $r=r_{max}=a-R_1(a-R_{QD})/\sqrt{(a-R_{QD})^2+b^2}$ with $\theta=\theta_{min}$.

Now we turn our focus to the elastic deformation energy for the QMC shown in figure 3. As far as we know, any aggregated structures made of phospholipids and QDs, except the QLC and the QMC, have not been reported yet. That is the reason we select the QMC as a comparative system to the QLC in this model. The QMC reported by Dubertret *et al* was prepared with a phospholipid composed of a large optimum headgroup area relative to a hydrocarbon chain volume. This means that the intrinsic curvature of the lipid is proper for covering a high curvature surface corresponding to the QD size in terms of the packing parameter consideration [10]. However, a several-nanometer-sized QD cannot be readily covered with phospholipids like DOPC molecules due to their intrinsic molecular structure, i.e. the double hydrocarbon chains of the phospholipids are bulkier than the single hydrocarbon chain of the surfactants [5]. According to the reported experimental data, the radii of most QDs (R_{QD} = 2–4 nm including the TOPO chain) are smaller than the minimum radius of an SUV (small unilamellar vesicle) prepared by a sonication method, which ranges from 10 to 15 nm [11]. In other words, the hydrocarbon chain must be accompanied by conformational changes such as stretching and compression during the high curvature micelle formation from DOPC lipid. Therefore, in this model we simply assume that the elastic deformation energy of the QMC is defined as the sum of a monolayer bending energy required to envelop a hydrophobic QD surface and a hydrocarbon stretching or compression energy associated with the conformational changes required to cover up a high curvature QD surface, as expressed in equation (8):

$$\Delta E_{def,QMC}=\frac{\kappa}{2}\left(\frac{2}{R_{QD}+d+u}-\frac{1}{R_0}\right)^2 4\pi(R_{QD}+d+u)^2 + \frac{K}{2}\left(\frac{u}{d}\right)^2 4\pi(R_{QD}+d+u)^2. \tag{8}$$

We consider two different cases in calculating $\Delta E_{def,QMC}$ with respect to the QD size. In the first case, the total interfacial area of the QMC is assumed to be strictly equal to the deformed interfacial area of the QLC, which acts as a constraint on the chain length of the QMC. The total interfacial area of the QMC

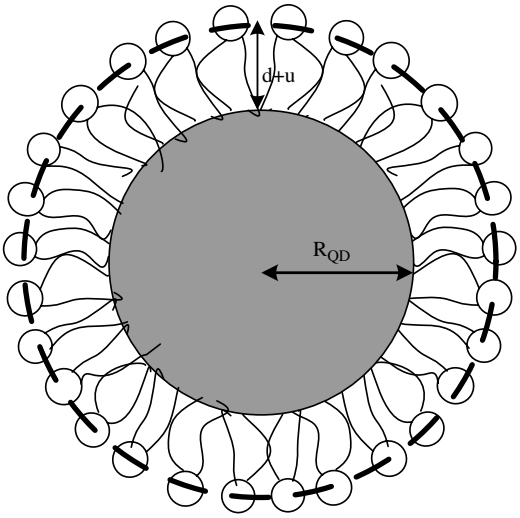

Figure 3. A schematic diagram of the QD–micelle complex (QMC). The QD is covered by a lipid monolayer with thickness $d + u$, where d is the unperturbed monolayer thickness and u is the extent of stretching or compression.

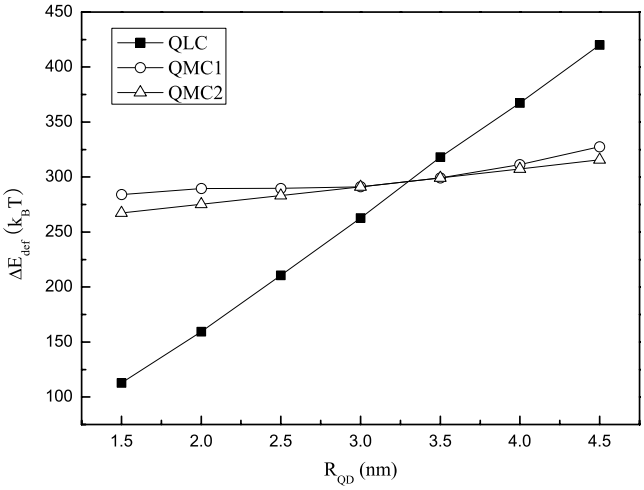

Figure 4. The elastic deformation energy of the QLC and QMC with varying QD size. The QMC energy obtained from the first and second case are denoted by QMC1 and QMC2, respectively. When the radius R_{QD} is below the critical size $R_{cr} \sim 3.25$ nm, the energy of the QLC is smaller than that of the QMC, indicating that the QD can be preferably incorporated into the lipid bilayer.

is simply expressed by $4\pi(R_{QD} + d + u)^2$, where u is the amount of stretching or compression of the hydrocarbon chain in the QMC. The deformed interfacial area of the QLC is the sum of the areas in regimes I and II as

$$\text{Deformed area of QLC} = 4\pi\left[\left(d + R_{QD}\right)^2 - {R_1}^2 + \frac{b{R_1}^2 - b\left(d + R_{QD}\right)^2}{\sqrt{a^2 + b^2}} + aR_1\,\text{Tan}^{-1}\left(\frac{a}{b}\right)\right]. \quad (9)$$

Then we obtain the elastic deformation energy of the QMC by substituting u, which is determined by equating the deformed area of the QLC with the total interfacial area of the QMC, into equation (8). In the second case, instead of imposing the above constraint on the surface area of the QMC, and thus on the chain length $(d + u)$, we allow the variation of chain length and minimize $\Delta E_{\text{def,QMC}}$. The elastic deformation energy of the QMC is obtained by substituting $u_{\min}$, which satisfies $\mathrm{d}\Delta E_{\text{def,QLC}}/\mathrm{d}u|_{u=u_{\min}} = 0$, into equation (8).

3. Results and discussion

First, we examined the dependence of the elastic deformation energy on the QD size. Figure 4 shows the total elastic deformation energies of the QLC and the QMC with respect to R_{QD}, calculated with the parameter values in table 1. The elastic deformation energy of the QMC obtained from the two cases are both plotted: the results of the first and second case are denoted by QMC1 and QMC2, respectively. Below the critical size $R_{cr} \sim 3.25$ nm, the incorporated state of the QD into the lipid bilayer (QLC) has a lower energy, and is thus more stable than the enveloped state such as the QD–phospholipid micelle (QMC). Note that the QMC energies obtained from the two different cases yield exactly the same value for R_{cr}. The green-emission QDs,

Table 1. DOPC monolayer parameters.

Parameters	Value	Unit	Reference
Bending modulus, κ	9	k_BT	[12]
Monolayer thickness, d	1.3	nm	[13]
Area stretching modulus, K	23	k_BT nm^{-2}	[14]
Monolayer spontaneous curvature $1/R_0$	$-1/16$	nm^{-1}	[15]

used by Gopalakrishnan *et al* for the successful incorporation of QDs into liposomes [6], have the size $R_{green} \sim 2.5$ nm, including the TOPO chain length 1 nm, which is well below R_{cr}. Furthermore, the fact that Gopalakrishnan *et al* failed to observe any fluorescent emission from the lipid bilayer in the case of red-emission QDs with $R_{red} \sim 4$ nm (larger than R_{cr}) is consistent with the prediction in this model. For comparison of this model with the experimental data using DMPC [6], we need the exact information about the DMPC monolayer parameters. But it is hard to find the experimental value of the monolayer's spontaneous curvature R_0 in the case of a DMPC lipid. According to our model, if the $1/R_0$ of the DMPC is a positive value close to zero, then the critical size R_{cr} is ~ 1.5 nm, which is about the core size of a green-emission QD without a TOPO chain.

Second, in order to understand the origin of the QD size dependence of state selection, we examined the area of deformation (figure 5(a)) and the energy contribution (figure 5(b)) for each of regimes I and II of the QLC. Obviously, both the area and the energy for each regime increase with the QD size. We found two interesting properties as follows. (i) When the radius of the QD is small, the energy of regime I is larger than that of regime II while the surface area of regime II is larger than that of regime I. (ii) As the radius of the QD is increased, the energy of regime II becomes larger than that of regime I even though the surface

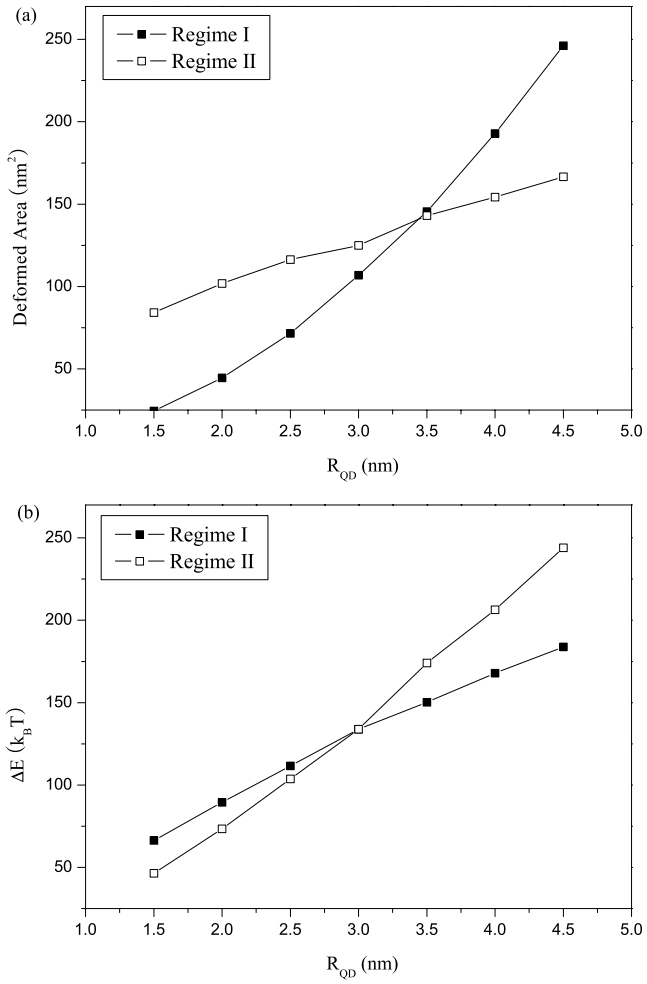

Figure 5. (a) The plot of the deformed area of the lipid monolayer as a function of the QD size in regimes I and II of the QLC. Note the rapid increase of the area of regime I with the increase of QD size. (b) The elastic deformation energy as a function of the QD size in regimes I and II. The energy in regime I is only the bending energy, and that in regime II is composed of the bending and stretching energy. Note the rapid increase of the elastic deformation energy of regime II with the increase of QD size.

area of regime II becomes smaller than that of regime I. In other words, the contribution of regime II to the total elastic deformation energy becomes much larger compared with that of regime I as the size of the QD is increased. This is mainly because the energy in regime II contains the energy of the hydrocarbon chain stretching. When the radius of the QD is small, the contribution of the stretching energy is small since the chains do not need to stretch much. In addition, the bending energy of regime II is also small because one of the principal curvatures is close to the monolayer spontaneous curvature of the lipids. To be precise, both the extent of chain stretching and the principal curvature are dependent on the area of regime II through θ. However, in the case of small QD, the dependence of chain stretching and the principal curvature on the area is negligible. Therefore, the system reduces the total elastic deformation energy by increasing the proportion of regime II which has relatively small energy. In the case of a large QD, if the surface area of regime II is large, the chains

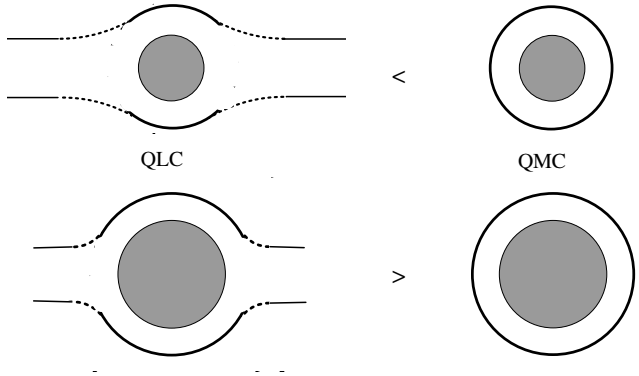

Figure 6. A schematic diagram showing the surface profile of the QLC and the QMC for the QD size smaller (upper part) and larger (lower part) than the critical QD size. The inequality indicates the magnitude of the elastic deformation energy. The dotted line in the QLC is regime II where the stretching of hydrocarbon chains occur.

must be stretched to a greater extent to avoid the formation of voids in the membrane. The total elastic deformation energy is greatly reduced by decreasing the area of regime II. Even if the spontaneous curvature in regime II becomes large, the corresponding bending energy is still smaller than the chain stretching energy.

Figure 6 shows the surface profile of the QLC and QMC states for small and large QD size and summarizes the QD size dependence of the state selection of the QD–lipid mixed system. We find that the extent of conformational change of the chain length in the QMC is almost negligible ($|u/d| \sim 0.02$). Thus, the structure of regime I in the QLC is almost identical to that of QMC (the thick lines in figure 6). As the size of the QD is increased, regime I becomes the dominant portion of the QLC, which can be understood such that the deformed part around the QD in the QLC state becomes more similar to the QMC state (see the similarity between the QLC and the QMC for the large size QD in figure 6). The only difference is in the highly stressed regime II with a large energy due to the chain stretching in a small area (the dotted portion of the QLC for the large size QD in figure 6). Therefore, when the QD size is larger than a certain value the system abandons the unfavorable regime II and selects the QMC state.

4. Summary

We suggest a theoretical model in order to explain recent experimental results for a QD–lipid mixed system by using pure geometrical assumptions for a single-component lipid monolayer deformation profile. One important advantage in the present model is that the numerical form of the elastic deformation energy can be simplified as a function of a single parameter. By calculating the elastic deformation energy of the QLC and then comparing it with that of the QMC, we find that the QLC is more stable than the QMC for a QD size smaller than a certain critical value, which depends on the type of lipids.

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References

[1] Gregoriadis G 2006 *Liposome Technology* (New York: Taylor and Francis)
[2] Allen T M and Cullis P R 2004 *Science* **303** 1818–22
[3] Michalet X, Pinaud F F, Bentolila L A, Tsay J M, Doose S, Li J J, Sundaresan G, Wu A M, Gambhir S S and Weiss S 2005 *Science* **307** 538–44
[4] Medintz I L, Uyeda H T, Goldman E R and Mattoussi H 2005 *Nat. Mater.* **4** 435–46
[5] Dubertret B, Skourides P, Norris D J, Noireaux V, Brivanlou A H and Libchaber A 2002 *Science* **298** 1759–62
[6] Gopalakrishnan G, Danelon C, Izewska P, Prummer M, Bolinger P Y, Geissbuhler I, Demurtas D, Dubochet J and Vogel H 2006 *Angew. Chem. Int. Edn* **45** 1–6
[7] Wi H S, Lee K and Pak H K 2008 submitted
[8] Nielsen C and Andersen O 2000 *Biophys. J.* **79** 2583–604
[9] Helfrich W 1973 *Z. Naturf.* C **28** 693–703
[10] Israelachvili J N 1994 *Intermolecular and Surface Forces* (New York: Academic)
[11] Watts A, Marsh D and Knowles P F 1978 *Biochemistry* **17** 1792–801
[12] Chen Z and Rand R P 1997 *Biophys. J.* **73** 267–76
[13] Benz R and Janko K 1976 *Biochim. Biophys. Acta* **455** 721–38
[14] Tristram-Nagle S, Petrache H I and Nagle J F 1998 *Biochemistry* **23** 2696–703
[15] Keller S L, Bezrukov S M, Gruner S M, Tate M W, Vodyanoy I and Parsegian V A 1993 *Biophys. J.* **65** 23–7