
**Supramolecular Chemistry**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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**To cite this Article** Mukai, Masaru , Maruo, Kohei , Kikuchi, Jun-ichi , Sasaki, Yoshihiro , Hiyama, Satoshi , Moritani, Yuki and Suda, Tatsuya(2009) 'Propagation and amplification of molecular information using a photoresponsive molecular switch', Supramolecular Chemistry, 21: 3, 284 — 291
**To link to this Article: DOI:** 10.1080/10610270802468439
**URL:** http://dx.doi.org/10.1080/10610270802468439

*Supramolecular Chemistry*
Vol. 21, Nos. 3–4, April–June 2009, 284–291

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# Propagation and amplification of molecular information using a photoresponsive molecular switch

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(*Received 11 July 2008; final version received 8 September 2008*)

Molecular communication is a bio-inspired communication paradigm using molecules as information carriers. The molecular communication system includes propagation of information carrier molecules between a molecular sender and a molecular receiver and followed by amplification of the information at the receiver. In this article, we built an example molecular communication system using a gemini peptide lipid as a molecular switch. The molecular switch embedded in the lipid bilayer membranes exhibited photoresponsive recognition behaviour towards metal ions, such as $Cu^{2+}$ and $Zn^{2+}$, to control propagation of molecular capsules formed by small liposomes to a giant liposomal receiver. In addition, the molecular switch acted as an artificial receptor in the receiver, receiving a photonic signal to communicate with an enzyme as a signal amplifier by using $Cu^{2+}$ ion as a mediator between the receptor and the amplifier.

**Keywords:** molecular communication; liposomal membrane; photoresponsive molecular switch; gemini peptide lipid; enzyme



## Introduction

In biological system, cell membranes play pivotal roles as platforms for systematic transformation of materials, energy and information. In order to simulate such biological functions, lipid bilayer vesicles formed by phospholipids or synthetic lipids have been widely employed as cell membrane models (*1–8*). While some biologically important events such as material transport, catalysis and energy conversion have been successfully simulated in the liposomal membranes (*9–14*), there have been few reports using lipid membranes as platforms for information processing.

Recently, we coined a word 'molecular communication', which is a new communication paradigm using molecules as information carriers (*15*). Information and communication technology highly developed in the last century now supports our daily life; however, there is growing interest to seek a novel communication technology that complements the present communication technology using electrons and photons as information carriers. The molecular communication inspired by the biological information processing would be one of the candidates. In general, the molecular communication system includes propagation of information carrier molecules between a molecular sender and a molecular receiver and followed by amplification of the information at the receiver.

In this article, we built an example molecular communication system using the liposomal membranes. The present system is composed of two processes: propagation of molecular capsules to a molecular receiver and amplification of molecular information at the receiver (Figure 1). The molecular capsules that carry information molecules were formed by small liposomal membranes. On the other hand, a giant liposome was employed as the molecular receiver. In order to realise selective propagation of the molecular capsules to the receiver, a gemini peptide lipid (**1**) was used as a photoresponsive molecular switch (Chart 1). When the molecular switch was embedded in both the molecular capsules and the receiver, the propagation of the molecular capsules to the receiver was controlled by photonic signals in the presence of transition metal ions. The molecular switch in the receiver also acted as an artificial receptor, which tunes the activity of an enzyme as a chemical signal amplifier, by using $Cu^{2+}$ ion as a mediator between the receptor and the amplifier.

## Experimental section

### *General*

A gemini peptide lipid having an azobenzene moiety and L-histidyl residues (**1**) was synthesised by following the previously reported procedure (*16*).

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ISSN 1061-0278 print/ISSN 1029-0478 online

DOI: 10.1080/10610270802468439
http://www.informaworld.com

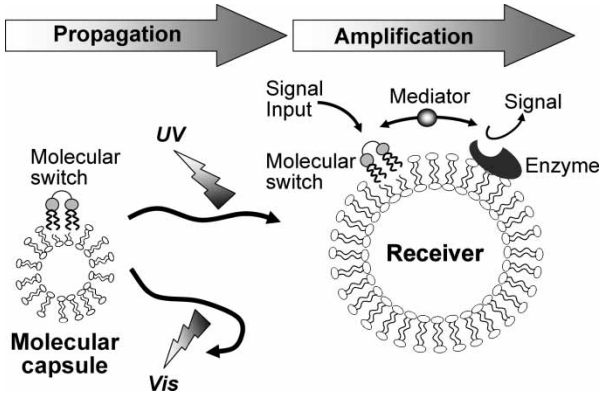


Figure 1. Molecular communication system composed of propagation of molecular information to a molecular receiver and amplification of the information at the receiver.

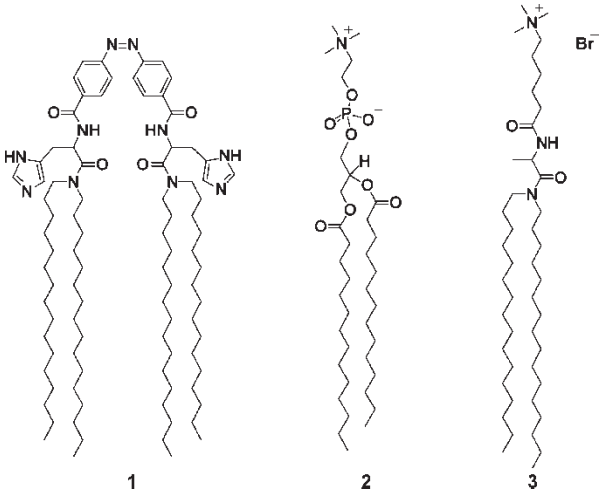


Chart 1. Structural formula of gemini peptide lipid (**1**), phospholipid (**2**) and peptide lipid (**3**).

Dimyristoylphosphatidylcholine (**2**) was obtained from NOF Corporation (Tokyo, Japan), as a guaranteed reagent and used without further purification. A cationic peptide lipid, *N*,*N*-dihexadecyl-$N^{\alpha}$-[6-(trimethylammonio)hexanoyl]-L-alaninamide bromide (**3**), was prepared according to the literature (*17*). Preparation of the reference compounds for **1**, a non-gemini peptide lipid having an L-histidyl residue (**4**) and a gemini peptide lipid having an azobenzene moiety and L-alanyl residues (**5**) was performed in a manner according to the synthesis of **1**. Synthesis of a gemini peptide lipid having an oligo(ethylene oxide) moiety and L-histidyl residues (**6**) was reported elsewhere (*18*).

The following compounds were commercially available as guaranteed reagents and used without further purification: L-lactate dehydrogenase (LDH) from pig heart (Boehringer Mannheim GmbH, Mannheim, Germany); β-nicotinamide adenine dinucleotide disodium salt (NADH) (Sigma-Aldrich Co., St Louis, MO, USA); sodium pyruvate (Wako Pure Chemical Industries, Ltd, Osaka, Japan); and copper(II) perchlorate hexahydrate (Kanto Chemical Co., Inc., Tokyo, Japan).

Photoisomerisation of the azobenzene moiety in the gemini peptide lipid was performed by irradiation with a Ushio SX-UID500X Xe lamp (500 W). Toshiba UV-D33S, UV-D36S and UV-29 bandpass filters and Asahi Techno Glass L-42 and Y-43 filters were used for UV and visible light irradiation, respectively.

### *Preparation of liposomes*

Small liposomes employed in this study were prepared according to the established protocol as follows. A mixture of lipids containing 0.5 mmol $dm^{-3}$ of phospholipid **2** or 1.0 mmol $dm^{-3}$ of peptide lipid **3** including 0.05 mmol $dm^{-3}$ of gemini peptide lipid **1** was dissolved in chloroform. The solvent was evaporated under nitrogen gas flow and the residual trace solvent was completely removed *in vacuo*. Hydration of the thin film obtained on the wall of a vial was performed at 40°C with an appropriate amount of pure water or 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulphonate (HEPES) buffer (10 mmol $dm^{-3}$, pH 7.0). Multi-walled bilayer vesicles were formed upon vortex mixing of the aqueous dispersion. The corresponding small liposomes were prepared by sonication of the dispersion sample with a cup-type sonicator above the phase transition temperature for 20 min at a 30 W power.

Giant liposomes were prepared by the gentle hydration of a lipid film. A chloroform solution of appropriate amounts of lipid mixture was dried under vacuum for 3 h to obtain the thin film. The film was hydrated with water at 40°C for 2 h. The liposome suspension was incubated at 25°C for an hour prior to microscopic observation. The concentrations of the phospholipid and the gemini peptide lipid were set to 0.5 and 0.05 mmol $dm^{-3}$, respectively. Microscopic observation was carried out using an Olympus IX71 epifluorescence microscope, and the images were recorded using an Olympus DP70 colour CCD camera.

### *Measurements*

Electronic absorption spectra were taken on a Shimadzu UV-2400 spectrophotometer (Shimadzu, Kyoto, Japan). Circular dichroism (CD) spectra were recorded on a JASCO J-820 spectropolarimeter (Jasco, Easton, MD, USA). Hydrodynamic diameter ($D_{hy}$) of the liposomes was measured by a Photal DLS-6000 dynamic light-scattering (DLS) spectrophotometer equipped with a He–Ne laser at 633 nm. Time course of the light scattering from the sample was analysed by the cumulant method at an angle of 90° from the incident light.

### *Enzyme assay*

Enzymatic activity of LDH in an aqueous HEPES buffer ($10\,mmol\,dm^{-3}$, pH 7.0) was determined at 30°C using sodium pyruvate as the substrate. The assay sample solution ($1\,cm^{-3}$) was prepared by mixing LDH ($2.8\,nmol\,dm^{-3}$) and β-NADH ($0.25\,mmol\,dm^{-3}$) with liposomal membrane formed by peptide lipid **3** ($1.0\,mmol\,dm^{-3}$) and molecular switch **1** ($0.050\,mmol\,dm^{-3}$) in the presence and absence of an appropriate concentration of metal ions. The reaction was started upon addition of the pyruvate ($0.50\,mmol\,dm^{-3}$). The catalytic activity of LDH in the reduction of pyruvate to L-lactate was evaluated spectrophotometrically by following a consumption rate of β-NADH. For the determination of the concentration of β-NADH, a value of $6220\,dm^3\,mol^{-1}\,cm^{-1}$ was used as the molar extinction coefficient at 340 nm.

## Results and discussion

### *Design of molecular communication system*

Figure 1 depicts a molecular communication system that we consider in the initial phase of our research. The system is constituted in a combination of two processes, i.e. propagation of a molecular capsule with molecular information to a molecular receiver and amplification of the information at the receiver. We employed small liposomes in a diameter range of 100–200 nm as the molecular capsules, since they encapsulate various information molecules in the inner aqueous compartment or in the hydrophobic lipid membrane domain depending on their hydrophilicity. As a molecular receiver, we chose a giant liposome in the cell size. In order to achieve selective propagation of a molecular capsule to a molecular receiver, molecular switch **1** being capable of assembling liposomal membranes through photoresponsive molecular recognition was embedded in both the molecular capsule and the receiver.

Molecular design of the molecular switch was inspired by naturally occurring gemini lipid, cardiolipin, having a unique dimeric lipid structure and interesting biological functions (*19*, *20*). Although much attention has been focused on physicochemical properties of synthetic gemini surfactants connecting two surfactant molecules via a spacer group (*21–24*), there are few reports on the synthetic gemini lipids with two double-chain segments like the cardiolipin. The molecular switch **1** is composed of three parts: two hydrophobic double-chain segments as hydrophobic anchors to the lipid membrane; two chiral histidyl residues as metal-binding sites; and an azobenzene spacer unit as a photoresponsive part. We have recently clarified that $Cu^{2+}$-binding affinity of *cis*-**1** embedded in a liposomal membrane was much higher than that of the corresponding *trans*-form to give a photoresponsive assembling system of small liposomes (*16*). We observed the liposomal assembly by means of freeze-fracture replica TEM and dynamic light-scattering measurements; however, fluorescence microscopy was unable to apply to visualise such assembly due to fluorescence quenching by $Cu^{2+}$ ions. In the present work, $Cu^{2+}$ ions were replaced by $Zn^{2+}$ ions to visualise the photoresponsive dynamic propagation behaviour of molecular capsules to a molecular receiver.

As for amplification of molecular information at a molecular receiver, we employed an artificial signal transduction system composed of a set of an artificial receptor, an enzyme and a mediator between them. We have previously shown that catalytic activity of lactate dehydrogenase bound on a liposomal membrane was switched by an external signal input to an artificial receptor embedded in the membrane in the presence of $Cu^{2+}$ ion as a mediator (*25–33*). Here, we chose the molecular switch **1** as an artificial receptor in the receiver. Thus, in the present signalling system, the enzymatic activity as a chemical signal output would be switched by photonic signal input into the receptor, while the previous receptors recognise chemical species as an input signal.

### *Propagation of molecular information using a photoresponsive molecular switch*

Photonic control of propagation behaviour of a molecular capsule to a target molecular receiver is schematically shown in Figure 2. Upon UV light irradiation, the molecular switches embedded in the molecular capsule and the receiver drastically change their conformation through photoisomerisation of the azobenzene moiety from the *trans*-form to the corresponding *cis*-form. Judging from a molecular modelling study, metal-binding affinity of *cis*-**1** is much enhanced when compared with that of the *trans*-form, since the former takes an effective intramolecular coordination geometry of two imidazolyl ligands towards one metal ion (*16*). Since $Zn^{2+}$ ion provides four coordination sites, the metal ion stabilises by forming the 1:2 complex with *cis*-**1**. Thus, the molecular capsule equipped with *cis*-**1** is capable of binding to a receiver having the same molecular switch. On the contrary, visible light irradiation converts *cis*-**1** to the corresponding *trans*-form with less metal-binding affinity to prohibit the propagation of the molecular capsule to the receiver.

The photoisomerisation behaviour of molecular switch **1** embedded in the small liposomal membrane formed by **2** was monitored by electronic absorption and CD spectroscopy at 30°C. Upon UV light irradiation, absorbance characteristic to *trans*-**1** at 333 nm was decreased with concomitant increase in absorption at 258 and 440 nm assigned to the corresponding *cis*-isomer (Figure 3(a)). A photostationary state was attained within

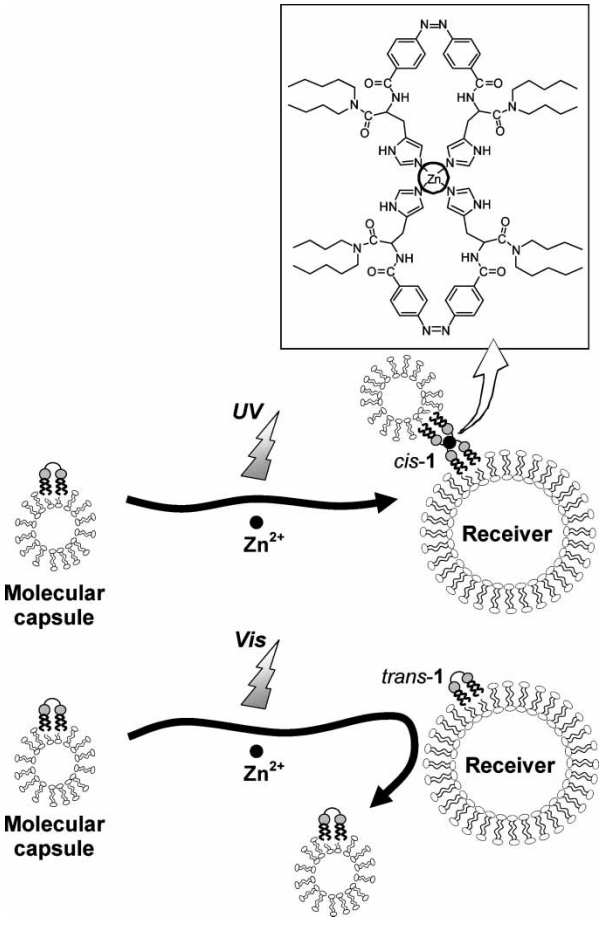


Figure 2. Photonic control of propagation of a molecular capsule to a molecular receiver by using a molecular switch **1**.

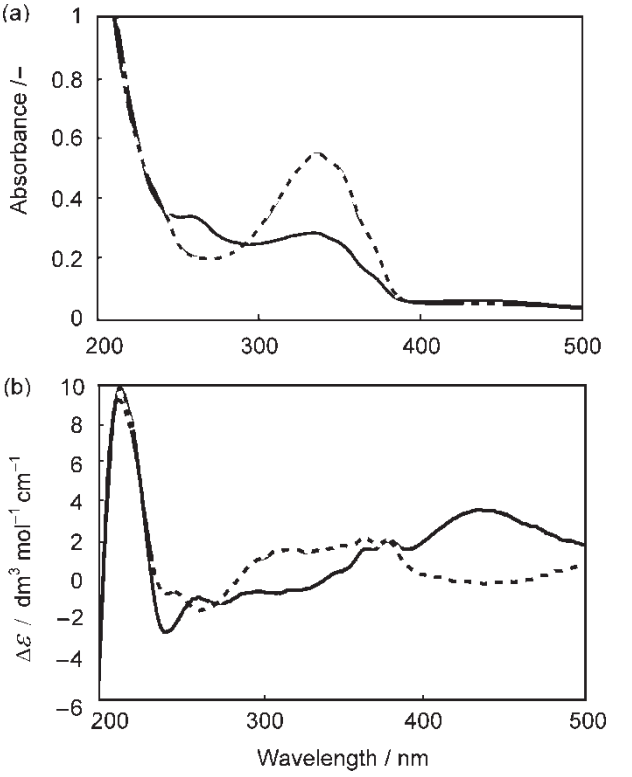


Figure 3. (a) Electronic absorption and (b) CD spectra of a gemini peptide lipid **1** embedded in liposome formed by **2** upon visible (dotted line) and UV (solid line) light irradiation at pH 9.0 and 30°C. Concentrations in mmol $dm^{-3}$: [**2**], 0.50; [**1**], 0.050.

30 min, indicating the efficient conversion from *trans*-**1** to *cis*-**1** even in the liposomal membrane. On the other hand, a backward isomerisation took place upon visible light irradiation for 2 min. Since the present molecular switch possesses chiral L-histidyl residues directly connected to the azobenzene moiety, the photoisomerisation process was also monitored by the CD spectroscopy. Induced CD spectral change characteristic to the isomerisation of *trans*-**1** to the corresponding *cis*-form was observed in a region of absorption bands of the azobenzene moiety (Figure 3(b)). In the liposomal membrane, the photoisomerisation of **1** proceeded in the liquid-crystalline state but not in the gel state below the phase transition temperature. In addition, thermal isomerisation from *cis*-**1** to *trans*-**1** was extremely slow in the liquid-crystalline state of the matrix membrane. For example, the half-life monitored by means of electronic absorption spectroscopy was 20 h in the liposome formed by **2** at 30°C. Thus, all experimental data for *cis*-**1** were taken within 30 min after its photochemical formation to exclude the influence of the thermal isomerisation.

Interaction of $Zn^{2+}$ ions with molecular switch **1** embedded in the small liposomal membrane was evaluated by CD measurements at pH 9.0 and 30°C. In general, metal–ligand interactions are much enhanced at the lipid membrane–water interface rather than in aqueous solution (*14*, *34*). The CD spectra of the molecular switch embedded in the liposome were changed significantly upon addition of $Zn^{2+}$ ions, reflecting the binding of $Zn^{2+}$ ions to the L-histidyl residues of **1**. The titration isotherms were obtained by monitoring the CD intensity at 339 and 431 nm for *cis*-**1** and *trans*-**1**, respectively (Figure 4), which were applied to determine the binding constant of $Zn^{2+}$ ions to the molecular switch. The Job-plot analyses for the liposomal system revealed that $Zn^{2+}$ ions bind to the molecular switch in a ratio of 1:2. Thus, the binding constant for the 1:2 complex of $Zn^{2+}$ ions with *cis*-**1** in the liposomes was evaluated to be $1.0 \times 10^{10}\,dm^6\,mol^{-2}$. The value is comparable to the binding constant of $Cu^{2+}$ ions with *cis*-**1**, $0.5 \times 10^{10}\,dm^6\,mol^{-2}$ (*16*). Contrastingly, the binding constant for the 1:2 complex of $Zn^{2+}$ ions with *trans*-**1** in the liposome was $9.0 \times 10^7\,dm^6\,mol^{-2}$, being much weaker than that for the corresponding *cis*-form. Accordingly, the metal–ligand interactions are effectively switched by the photoisomerisation of the molecular switch embedded in the liposomal membranes.

In order to clarify functions of the photoresponsive molecular switch for the propagation of molecular capsules,

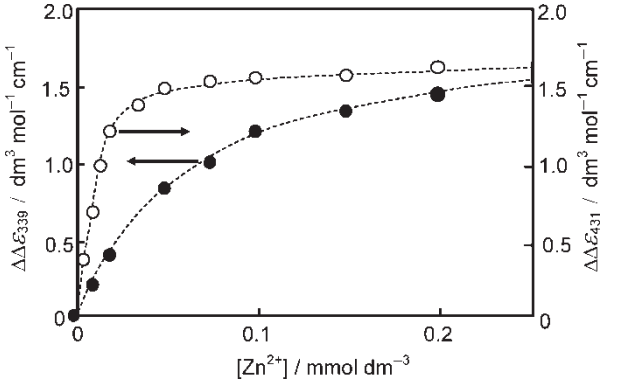


Figure 4. Changes in molar CD upon $Zn^{2+}$ titration of the *cis*-**1** (open circle) and *trans*-**1** (closed circle) at pH 9.0 and 30°C. The gemini peptide lipid **1** was embedded in liposome formed by **2**. Concentrations in mmol dm$^{-3}$: [**2**], 0.50; [**1**], 0.050.

the photoresponsive assembling behaviour of small liposomes equipped with **1** was evaluated by DLS measurements. As shown in Figure 5, hydrodynamic diameter ($D_{hy}$) of the liposomes containing *cis*-**1** with high metal-binding affinity was increased from 170 to 520 nm upon addition of $Zn^{2+}$ ions at pH 9.0 and 30°C. On the other hand, the liposomes containing *trans*-**1** with much lower metal-binding affinity kept the $D_{hy}$ value nearly constant in the presence and absence of $Zn^{2+}$ ions under similar conditions. The results clearly indicate that the difference in the metal-binding ability between *cis*-**1** and *trans*-**1** in the liposomal membrane markedly reflected on the photoresponsive assembly of liposomes.

On these grounds, the photonic control of propagation of small liposomes as molecular capsules to a giant liposome as a molecular receiver was evaluated by microscopic observations. The molecular capsules and the molecular receivers both containing molecular switch **1** were premixed and incubated in the presence of $Zn^{2+}$ ions at pH 9.0 and 30°C. Upon UV light irradiation of

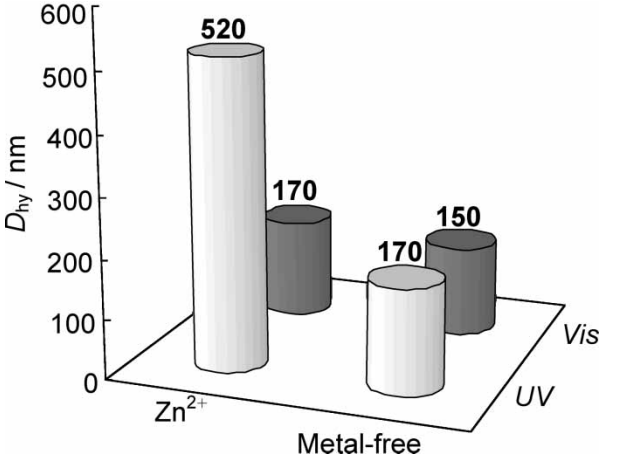


Figure 5. Effects of $Zn^{2+}$ ions and photoirradiation on the vesicular assembly as evaluated by DLS at pH 9.0 and 30°C. Concentrations in mmol dm$^{-3}$: [**2**], 0.50; [**1**], 0.050; [$Zn^{2+}$], 0.50.

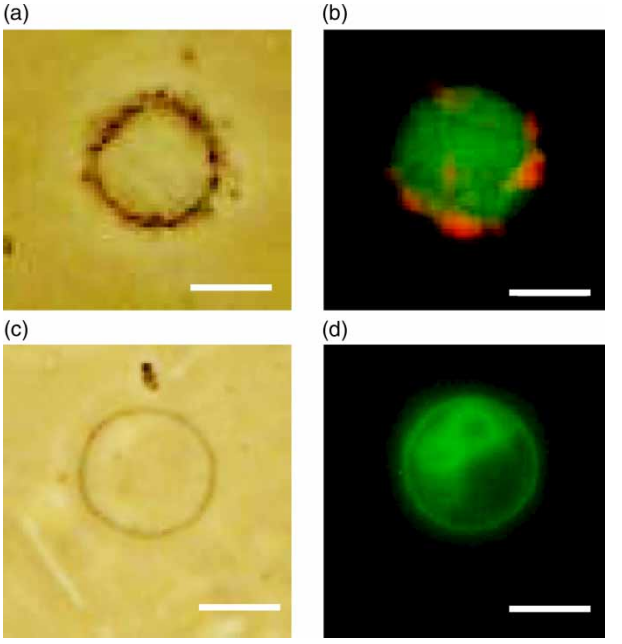


Figure 6. (a,c) Phase-contrast and (b,d) fluorescent microscopic images for mixtures of small liposomes (molecular capsules) and giant liposomes (receivers) embedding **1** in (a,b) the *cis*-form or (c,d) the *trans*-form at pH 9.0 and 30°C. Concentrations in mmol dm$^{-3}$: [**2**], 0.50; [**1**], 0.050; [$Zn^{2+}$], 0.50. Scale bar = 10 μm.

the mixture, the molecular capsules that appeared as small black dots were observed on the surface of the molecular receiver in the phase-contrast microscopic images (Figure 6(a)), whereas no molecular capsule was observed on the receiver upon visible light irradiation (Figure 6(c)). The results imply that selective propagation of the molecular capsules to the molecular receiver was attained with *cis*-**1** but not with *trans*-**1**. To confirm the photonic control of propagation behaviour, the molecular capsules and the molecular receivers were stained with a red fluorescent dye (*N*-(lissamine rhodamine B sulphonyl)-1,2-dihexadecanoyl-*sn*-glycero-3-phosphoethanolamine) and with a green fluorescent dye (*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-1,2-dihexadecanoyl-*sn*-glycero-3-phosphoethanolamine), respectively. The fluorescence microscopic observation clearly revealed that the red-labelled molecular capsules were propagated onto the green-labelled molecular receiver upon UV light irradiation, while visible light irradiation only gave the image of the green molecular receiver (Figure 6(b) and (d)).

### *Amplification of molecular information using a photoresponsive molecular switch*

Photoswitching behaviour for the amplification of molecular information at a molecular receiver is schematically shown in Figure 7. A basic framework

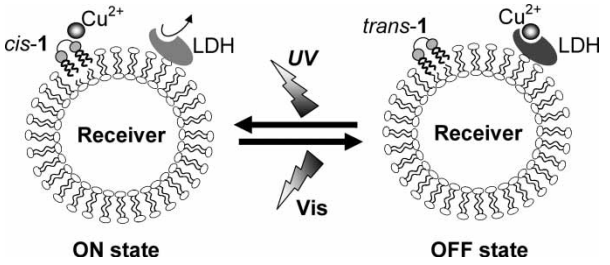


Figure 7. Photonic control of enzymatic activity at a molecular receiver by using a molecular switch **1**.

of the receiver was constructed with a bilayer vesicle of a cationic peptide lipid **3**. Photoresponsive molecular switch **1** as an artificial receptor and NADH-dependent LDH as a signal amplifier were immobilised on the receiver membrane mainly through hydrophobic and electrostatic interactions, respectively. We have previously shown that the cationic bilayer vesicle provides an effective platform for the immobilisation of LDH with keeping its catalytic activity (*35*) and that $Cu^{2+}$ ion performed as a potent competitive inhibitor for the enzyme bound on the cationic vesicle (*26*). On the other hand, the molecular switch embedded in lipid bilayer membranes drastically changes $Cu^{2+}$-binding affinity through the photoisomerisation of the azobenzene moiety. Thus, in the molecular receiver equipped with the molecular switch and the enzyme, input of a photonic signal to the molecular switch would be converted to amplified chemical signal output at the enzyme through the translocation of $Cu^{2+}$ ion as a mediator between them. In order to evaluate the signal transduction efficiency from the kinetic analysis of the enzymatic reaction with high accuracy, we employed a small bilayer vesicle with relatively low light scattering in the following measurements.

Figure 8 shows LDH activities on the molecular receiver formed by peptide lipid **3** and molecular switch **1** as a function of $Cu^{2+}$ concentration. The LDH activity was evaluated as a magnitude of the initial velocity in the presence of $Cu^{2+}$ ions relative to that of the corresponding metal-free system. The enzymatic activity on the molecular receiver containing *trans*-**1** was drastically decreased with an increase of $Cu^{2+}$ concentration, mainly reflecting binding of the metal ions to the enzyme active site, since the metal-binding ability of the molecular switch in the *trans*-form is much lower than that of the enzyme. On the other hand, the enzymatic activity on the molecular receiver containing *cis*-**1** showed higher value in a $Cu^{2+}$-concentration range less than 20 $\mu$mol dm$^{-3}$ under the present conditions, when compared with that on the molecular receiver containing *trans*-**1**. The results clearly indicate that signal amplification as an enzymatic reaction on the molecular receiver is switchable through the photoisomerisation of the molecular switch.

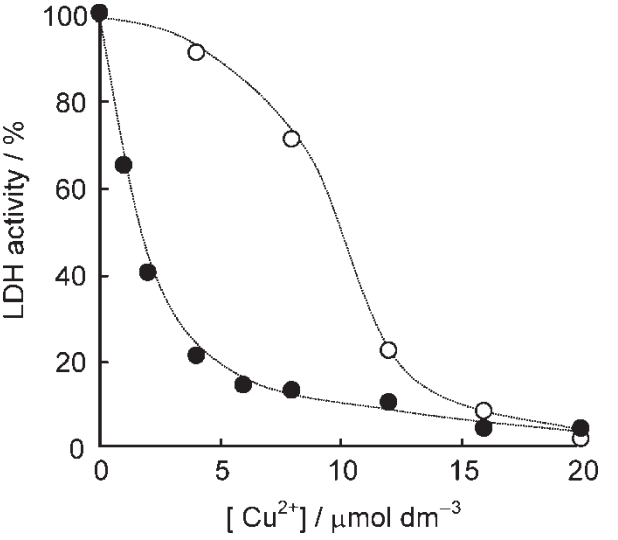


Figure 8. $Cu^{2+}$ concentration dependences of LDH activity on a liposome formed by **3** embedding **1** in the *cis*-form (open circle) or the *trans*-form (closed circle). LDH activity was evaluated as a magnitude of the initial velocity ($\nu_0$) in the presence of $Cu^{2+}$ ions relative to that of the corresponding metal-free system in an aqueous HEPES buffer (10 mmol dm$^{-3}$, pH 7.0) at 40°C. Concentrations in mmol dm$^{-3}$: [**1**], 0.050; [**3**], 1.0; [$Cu^{2+}$], $4.0 \times 10^{-3}$; [β-NADH], 0.25; [pyruvate], 0.50; [LDH], $2.8 \times 10^{-6}$.

The present molecular receiver was highly specific to metal ions as the mediator species between the molecular switch and the enzyme. LDH activities on the receiver formed by peptide lipid **3** containing molecular switch **1** in the *cis*- or *trans*-form in the presence and absence of various metal ions are listed in Table 1. Concentrations of the metal ions in Table 1 were set to 4.0 $\mu$mol dm$^{-3}$, where the magnitude of photoswitching in the enzymatic activity was a maximum under the conditions in Figure 8. While the enzymatic activity on the receiver was markedly changed from 18 to 74% through the photoisomerisation of *trans*-**1** to *cis*-**1** in the presence of $Cu^{2+}$ ions, other metal ions such as $Zn^{2+}$, $Ni^{2+}$ and $Co^{2+}$ did not perform as effective mediators between the molecular switch and the enzyme. The molecular switch has analogous binding affinity towards $Cu^{2+}$ and $Zn^{2+}$ ions, whereas the enzymatic activity was specifically inhibited by $Cu^{2+}$ but not by $Zn^{2+}$ ions. Thus, $Cu^{2+}$ ion exhibiting strong affinity towards both the molecular switch and the enzyme acts as a specific mediator in the present molecular receiver system.

In order to clarify the structural importance of the gemini peptide lipid having an azobenzene moiety and two L-histidyl residues as the photoresponsive molecular switch, molecular switch **1** was replaced by three reference lipids: non-gemini peptide lipid with an L-histidyl residue **4**; gemini peptide lipid with an azobenzene spacer unit but without two imidazolyl groups **5**; and gemini peptide lipid with two L-histidyl residues but without an azobenzene

Table 1. LDH activities in an aqueous HEPES buffer (10 mmol dm$^{-3}$, pH 7.0) at 40°C[a].

| Entry | Molecular switch | Lipid | Metal ion | $v_0$[b] ($10^{-7}$ mol dm$^{-3}$ s$^{-1}$) | Activity[c] (%) |
|---|---|---|---|---|---|
| 1 | – | – | – | 3.60 | 100 |
| 2 | – | **3** | – | 3.58 | 99 |
| 3 | *cis*-**1** | **3** | – | 2.94 | 82 |
| 4 | *trans*-**1** | **3** | – | 2.94 | 82 |
| 5 | – | – | $Cu^{2+}$ | 0.14 | 4 |
| 6 | *cis*-**1** | **3** | $Cu^{2+}$ | 2.67 | 74 |
| 7 | *trans*-**1** | **3** | $Cu^{2+}$ | 0.66 | 18 |
| 8 | – | – | $Zn^{2+}$ | 3.28 | 91 |
| 9 | *cis*-**1** | **3** | $Zn^{2+}$ | 3.09 | 86 |
| 10 | *trans*-**1** | **3** | $Zn^{2+}$ | 3.24 | 90 |
| 11 | – | – | $Ni^{2+}$ | 3.24 | 90 |
| 12 | *cis*-**1** | **3** | $Ni^{2+}$ | 3.10 | 86 |
| 13 | *trans*-**1** | **3** | $Ni^{2+}$ | 3.10 | 86 |
| 14 | – | – | $Co^{2+}$ | 3.42 | 95 |
| 15 | *cis*-**1** | **3** | $Co^{2+}$ | 3.10 | 86 |
| 16 | *trans*-**1** | **3** | $Co^{2+}$ | 3.13 | 87 |

[a]Concentrations in mmol dm$^{-3}$: [**1**], 0.05; [**3**], 1.0; [metal ion], 4.0 × $10^{-3}$; [β-NADH], 0.25; [pyruvate], 0.50; [LDH], 2.8 × $10^{-6}$.
[b]Initial velocity for the LDH-catalysed reduction of pyruvate to L-lactate was monitored spectrophotometrically by following a consumption rate of NADH. Values are accurate within ± 5%.
[c]A magnitude of $v_0$ in the presence of the molecular switch, the lipid or the metal ion to that of $v_0$ in the buffer (entry 1).



moiety **6** (Chart 2). LDH activities on the molecular receiver formed by **3** containing these molecular switch analogues were evaluated upon UV or visible light irradiation (Figure 9). The results clearly indicate that the gemini structure with both an azobenzene spacer unit and two L-histidyl residues is essential to perform as the photoresponsive molecular switch to control the enzymatic activity on the molecular receiver.

## Conclusions

It became apparent that a bio-inspired molecular communication system was constructed by using lipid bilayer membranes. The system includes two processes; that is, propagation of molecular capsules to a target molecular receiver and amplification of molecular information at the receiver. Both processes were controlled by a common photoresponsive molecular switch embedded in the lipid membranes. Thus, propagation of molecular capsules to a molecular receiver was controlled by photonic signals. In addition, signal amplification as an enzymatic reaction was effectively switched on a molecular receiver through intermolecular communication between a molecular switch and an enzyme, using a photonic stimulus and a metal ion as an input signal and a mediator, respectively. Although the present work is regarded as the initial phase of research in molecular communication, various kinds of supramolecular communication systems would be imagable on the basis of our research results. We believe that further

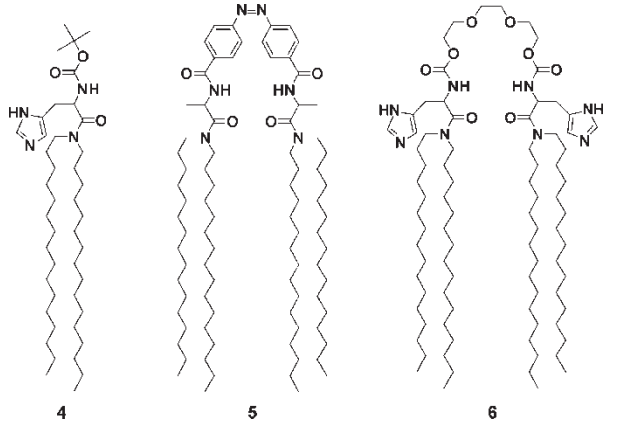


Chart 2. Structural formula of non-gemini peptide lipid (**4**) and gemini peptide lipids (**5** and **6**).

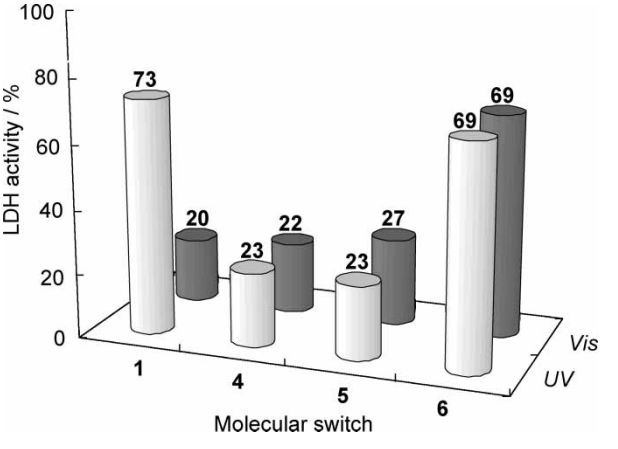


Figure 9. Photoswitching behaviour of LDH activity using various molecular switches (**1**, **4**, **5** or **6**) embedded in liposome formed by **3** upon UV or visible light irradiation in an aqueous HEPES buffer (10 mmol dm$^{-3}$, pH 7.0) at 40°C. Concentrations in mmol dm$^{-3}$: [**1**], 0.050; [**4**], 0.050; [**5**], 0.10; [**6**], 0.050; [**3**], 1.0; [$Cu^{2+}$], 4.0 × $10^{-3}$; [β-NADH], 0.25; [pyruvate], 0.50; [LDH], 2.8 × $10^{-6}$.

extensive study aiming to develop the molecular communication system will promise to open the door for an interdisciplinary area between supramolecular science and information and communication technology.

## Acknowledgements

This research was supported in part by a Grant-in-Aid for Scientific Research (KAKENHI) in Priority Areas 'System Cell Engineering by Multi-scale Manipulation' (No. 20034035) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

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