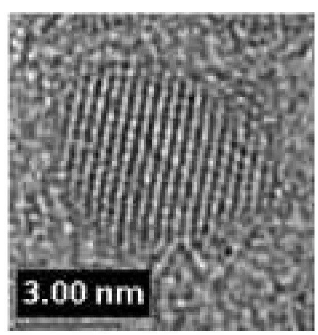
Molecular Tailoring of *Monolayer Protected Nanoparticles*

Santanu Bhattacharya
Department of Organic Chemistry
Indian Institute of Science
Bangalore 560 012, India

INDO-US WORKSHOP ON NANOTECHNOLOGY – 2004
"Issues in Interdisciplinary Research & Education", IISc, Bangalore, India

What are nanoparticles?

Any particle that has one of its dimensions in nm range, preferably 1 - 100 nm. This is the regime where the size effects on the properties is maximum.



Why nanoparticles?

- Effective control on the properties of matter
- Biological inertness of noble-metals
- Easy preparation and long-term stability
- Small size in comparison of biological cells
- Opportunity to track movement by EM

Nanoparticles assume special properties by virtue of their miniature size that distinguish them from larger particles, including changes in color as they grow smaller and smaller.

Due to their compact structure, nps emit light and can act as a fluorescent tag. This makes them highly suitable as contrast agents for MRI, in positron emission tomography (PET) for molecular imaging in patients, or as fluorsc. tracers in optical microscopy.

Nps also have advantages over conventional dyes: they fade less quickly, they are less toxic to cells and they can be used in combination to create almost an infinite number of colors.

Because of their high surface area & tunable electronic properties, nanoparticles can serve a range of roles,

from electron acceptors/donors in photonic devices – in which the energy from light is converted into electricity or

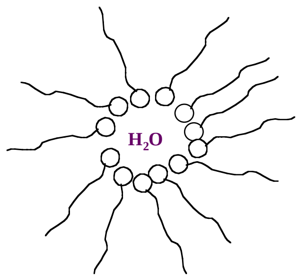
useful chemicals – to catalysts in environmental cleanups.

Functionalities known to stabilize Noble-metal nanoparticles

- **Organo-Chalcogenides : RSH, RSeH etc.**
- **Bunte Salts : $RS_2O_3^-$**
- **Citrate / ascorbate.**
- **Amines / amides : R NH_2, RNHCOR'**

Size and shape controlled synthesis of nanoparticles

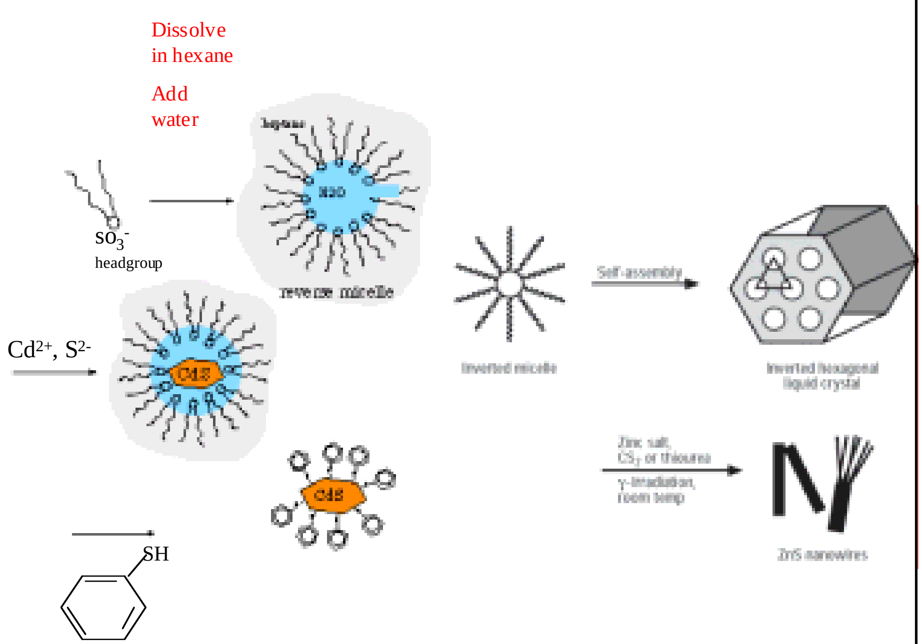
Use of reverse - micelles

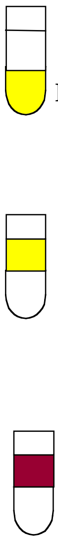


- Inner aqueous pool of nanometer size
- ‘Micellar Exchange’ rate controls size
- Shape control also possible

AOT, SDS or TOAB in hydrocarbons are frequently used surfactants for nanoparticle synthesis

Bis-(2-ethylhexyl)sulfosuccinate sodium salt (AOT)
Sodium dodecyl sulfate (SDS)
Tetraoctyl ammonium bromide (TOAB)





$HAuCl_4$ (aq.) + $Br^-N^+(Octyl)_4$ (toluene)

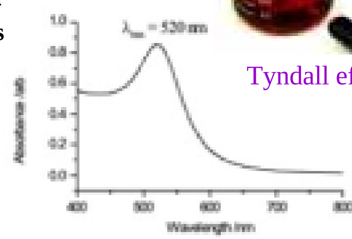
↓ **Stir**

$[AuCl_4]^-N^+(Octyl)_4$ (toluene)

↓ **Aq. $NaBH_4$ 10 X excess**

Au - nanoparticles

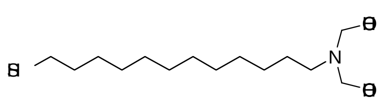
Tyndall effect

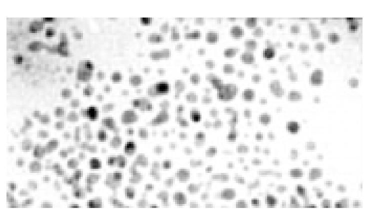


Surface plasmon band in Au-np

pH-controlled reversible assembly of Au-np stabilized by metal-chelating thiol derivative

- **Characteristic UV-vis changes in gold nanoparticles solution upon change in inter-particle distance / local dielectric constant : Opportunities for new sensors**



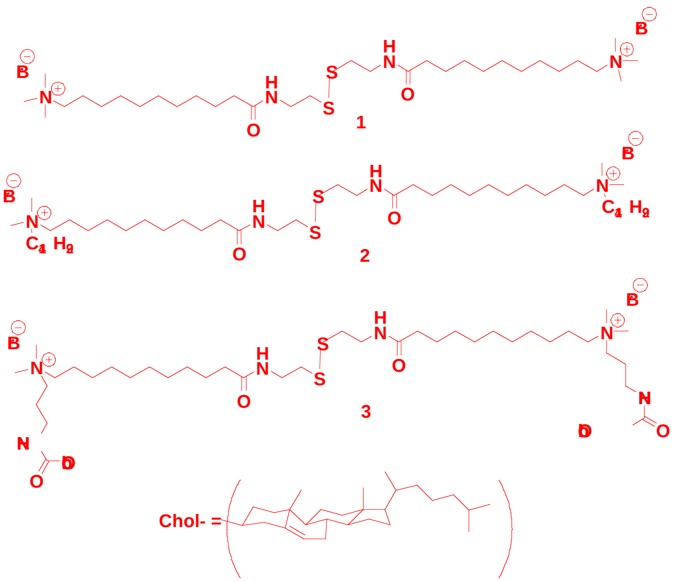


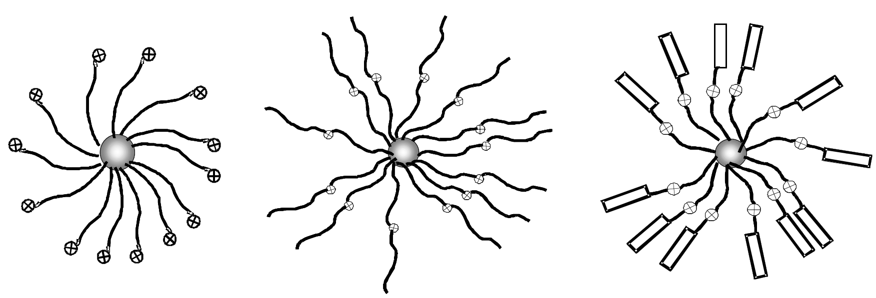
Au-np stabilized with metal-chelating ligand, at pH 12.

⇄

Dense Au-np aggregate at pH ~ 6.5.

Disulfides utilized for nanoparticle preparation



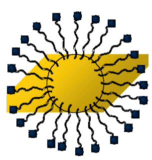


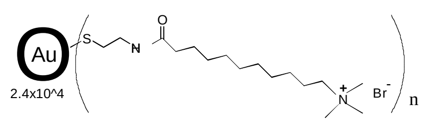
Characterization of nanoparticles

- UV-vis spectrometry, ^{1}H NMR, FT IR.
- TEM: by the bulkiness of the ligand employed.
- Particle size could be controlled by the bulkiness of the thiol
- Interaction with model biological membranes made by using

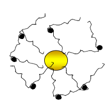
naturally occurring lipid, dipalmitoyl phosphatidylcholine vesicles.

Cationic alkanethiol-stabilized gold nanoparticles

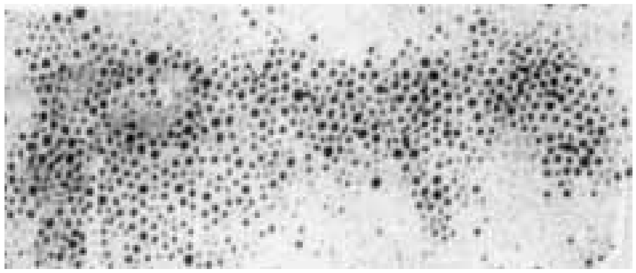




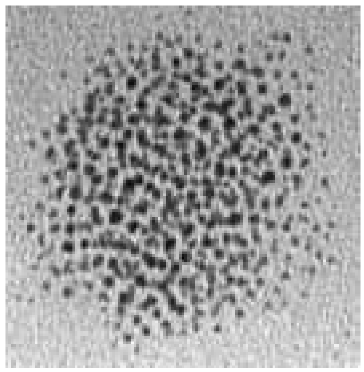
Aq. solution shows surface plasmon band λ_{max} at ~510 nm
TEM shows that particles have ~6 nm diameter



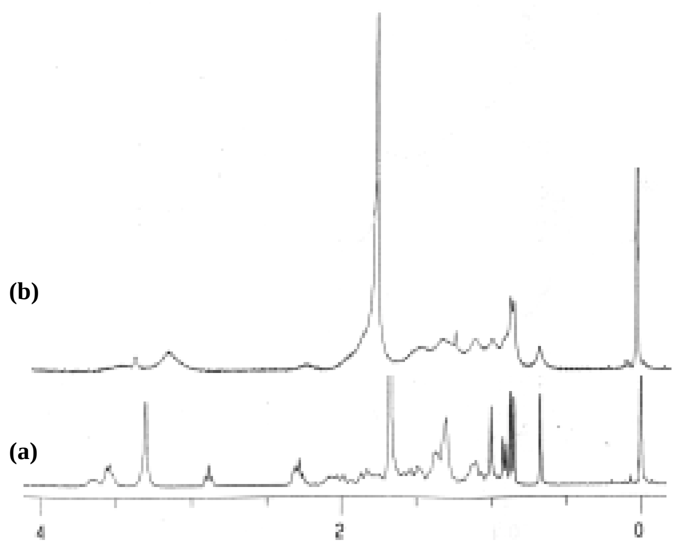
Methanolic solution shows surface plasmon band λ_{max} at ~525 nm
TEM shows that particles have ~3 nm diameter



Hydrophilic nanoparticles

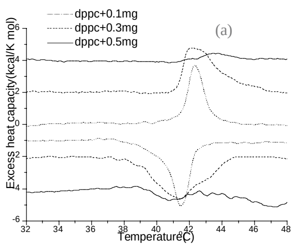


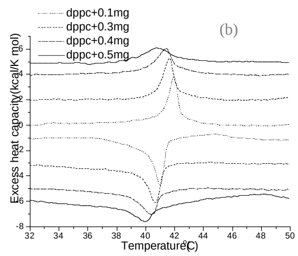
Hydrophobic nanoparticles

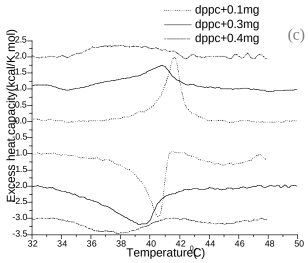


nanoparticle

[1]H-NMR spectrum of (a) cholesterol compound (b) nanoparticle synthesized using it in $CDCl_3$.



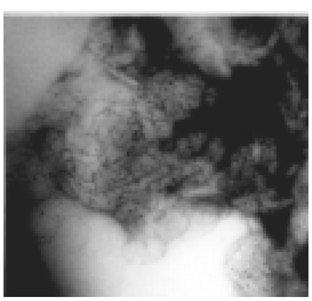




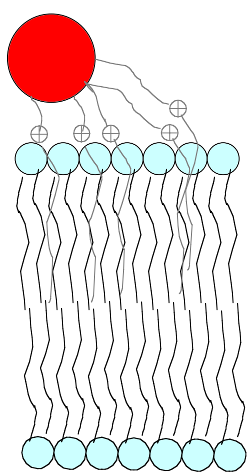
DSC thermograms of interaction DPPC vesicles with:

- Hydrophilic cationic 'single-chain' gold nanoparticles
- Hydrophobic 'double-chain' nanoparticles
- Hydrophobic 'cholesterol-containing nanoparticles

Interaction of 'double-chain' Cationic nanoparticle with DPPC membranes



TEM of negatively stained DPPC vesicles impregnated with nanoparticles



Interaction of two-chain Cationic Nanoparticles with DPPC Membranes

Effects of the nanoparticle incorporation into DPPC vesicles

• DSC results show that nanoparticles indeed interact with DPPC vesicles

• Hydrophilic nanoparticles are markedly different in their interaction with vesicles as compared to the hydrophobic particles

• The 'double chain' nanoparticle allows the vesicles to retain their sanctity up to 50 wt. % loading

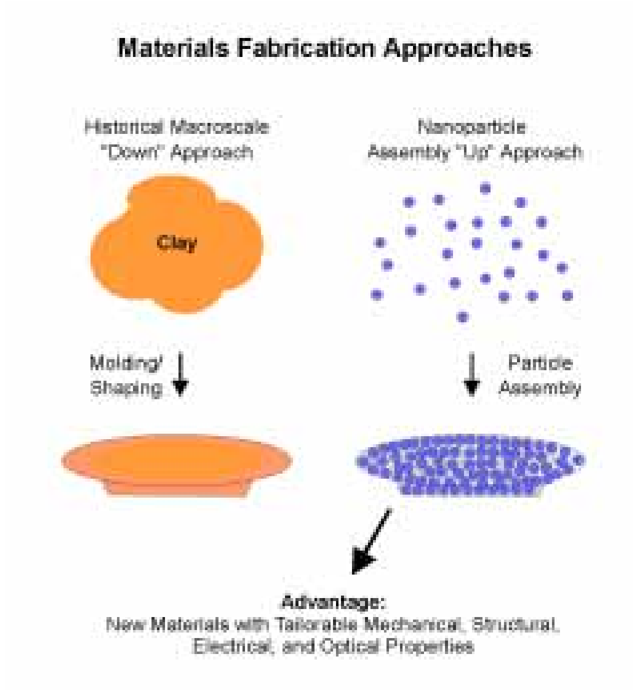
• Cholesterol-derivatized nanoparticles showed abolition of the melting transition at around 30 wt % loading

Assembling Nanoparticles

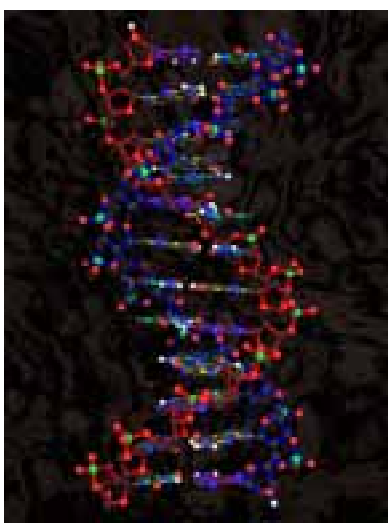
• Important in technological applications.

• The ability to assemble the 'building blocks' of bulk materials: the 'bottom-up' approach .

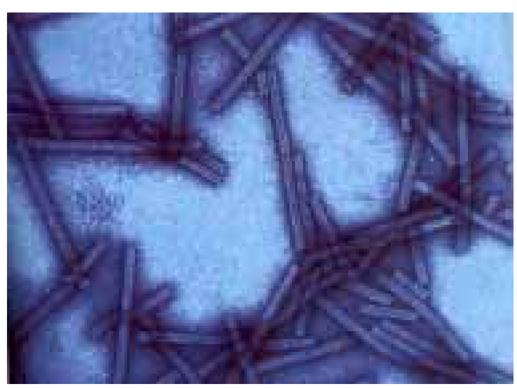
• Sensing of biological and chemical analytes using optical changes.



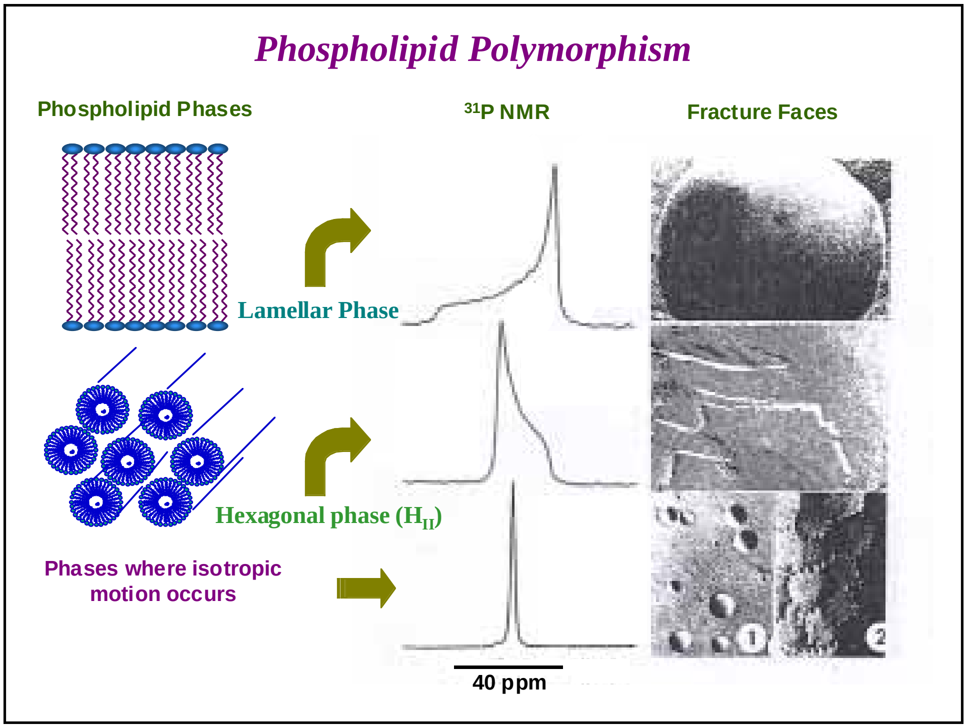
Biological templates



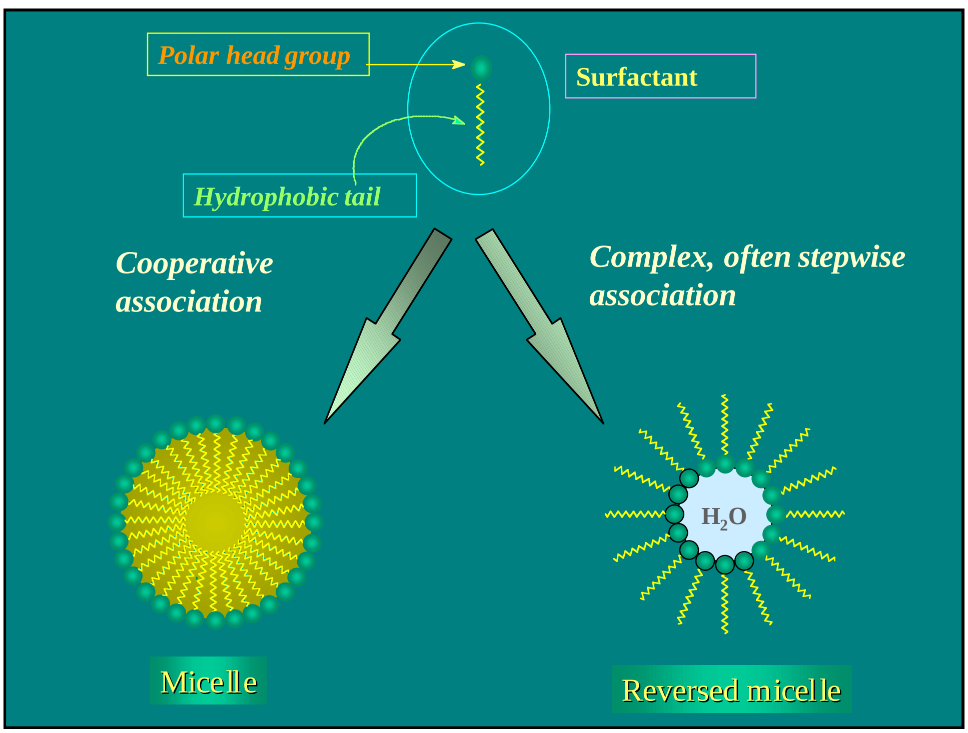
ds - DNA



Tobacco Mosaic Virus



Phospholipid Polymorphism
Phospholipid Phases
31P NMR
Fracture Faces
Lamellar Phase
Hexagonal phase (H$_{II}$)
Phases where isotropic motion occurs
40 ppm



Polar head group
Surfactant
Hydrophobic tail
Cooperative association
Complex, often stepwise association
H$_2$O
Micelle
Reversed micelle

Sodium palmitate aggregates as templates for nanoparticle assembly

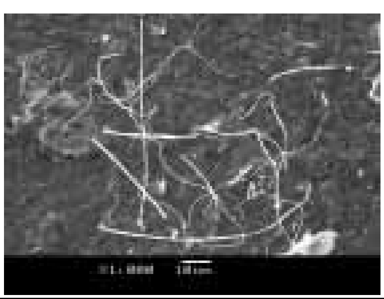
Ultramicroscope image of
Sodium palmitate jelly in water.

Can we assemble cationic Nanoparticles on these templates?

Zsigmondy, .R.; Bachmann, W.; Bachmann, v.W. *Kolloid-Zeitschift*, **1912**, *11141*, 145.

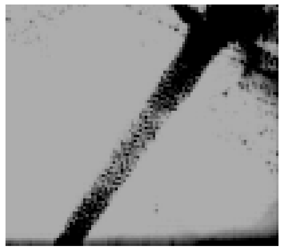
Mesostructural arrangement of nanoparticles using ion-pairing

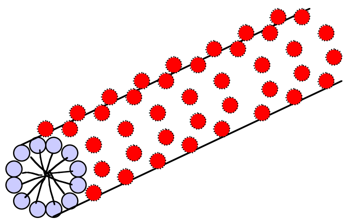
90 nm



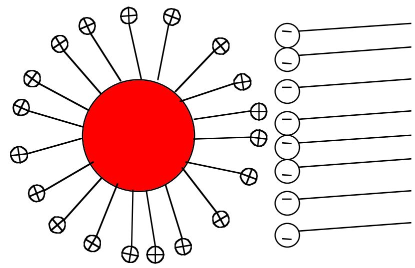
TEM and SEM images of assembly of Cationic Nanoparticles on anionic Sodium palmitate tubules

Nanoparticle Aggregation on the anionic surface of soduim palmitate aggregate





Low magnification view of the assembly of nanoparticle on the anionic fibrous aggregate



The 'molecular view' of the assembly showing ion-pairing interactions between the nanoparticle and the aggregate

---

Although nanoparticles are similar in size to proteins and DNA, man-made nanoparticles can be engineered to have specific or multiple functions.

Bioconjugated quantum dots, embedded in tiny beads made of polymer material, can be finely tuned to a myriad of different colors that can tag a multitude of different proteins or genetic sequences in a process called "multiplexing."

By chemically binding the quantum dots to particular genes and proteins, one can develop molecular nanoprobes to rapidly analyze biopsy tissue from cancer patients, to monitor the effectiveness of drug therapy, as scaffolding in tissue engineering, and as "smart bombs" to deliver controlled amounts of drugs into genetically classified tumor cells.

We have begun to develop functional nanoparticles that are linked to biological systems e.g. peptides, proteins and DNA.

In general, nanoparticles used in the Drug Delivery System are 50 to 1000 nanometers in size. Among various measures to prepare nanoparticles, one can utilize nanoparticles in the range of 20 - 100 nm with bi-layer structures comprising inner and outer cores.

They are formed by the spontaneous aggregation in aqueous media of block copolymers or lipids consisting of the molecular-level conjugation of hydrophobic and hydrophilic ends respectively.

Polymeric micelle structures are up to 100 nm in size with distinct bilayer structures comprising inner and outer cores (micellar nanoparticles). They are formed by the spontaneous aggregation in aqueous media of designer molecules. Such systems could act as stable carrier systems in the blood-stream and initial studies show that they accumulate in cancerous tissue

The micellar nanoparticles with functional groups attached on their surfaces prevent adsorption and coagulation of blood components which make them really appropriate for use as a surface coating material for medical devices.

Another promising application is the use of micellar nanoparticles bound with antibodies as the main constituent of diagnostic reagents for immunological use that are designed to react specifically with antigens to provide high sensitivity analysis.

Avoiding endothelial cells_

Micellar nanoparticles coated with hydrophilic polyethylene glycols curb non-specific interactions and absorption of drugs into endothelial cells and in turn maintain macromolecules in the blood for a long duration.

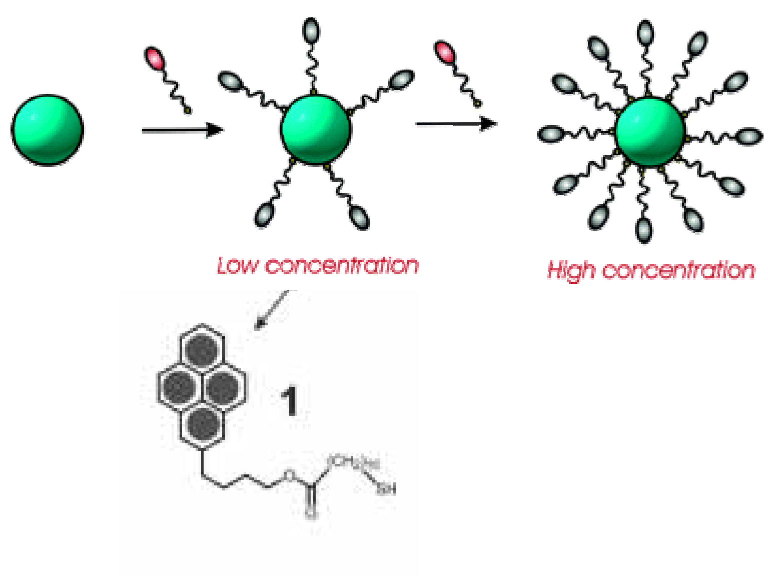
_Endothelial cells consist of basic protection cells that erode and digest pigments and particles such as old erythrocytes, cells, and bacteria. They are part of spleens, lymph vessels, liver, and lung. They remove materials that the bodies find abnormal.

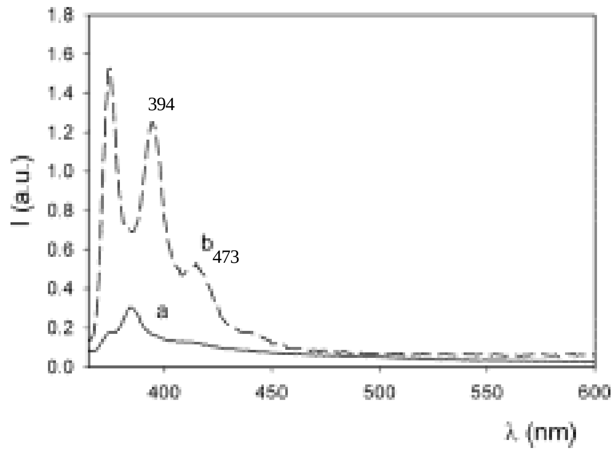
Aasheesh Srivastava

Department of Science & Technology

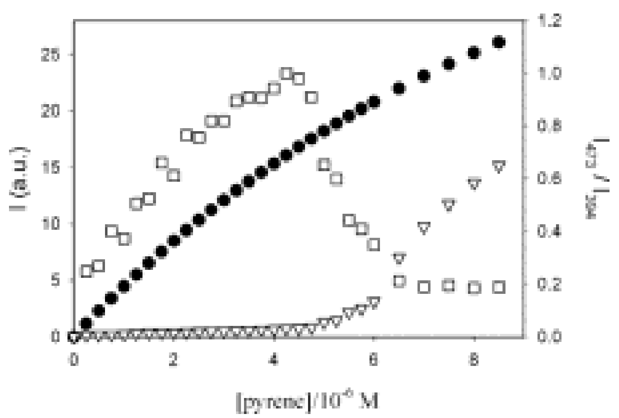
Department of Biotechnology

Modulation of the Photophysical Properties of Gold Nanoparticles by Accurate Control of the Surface Coverage

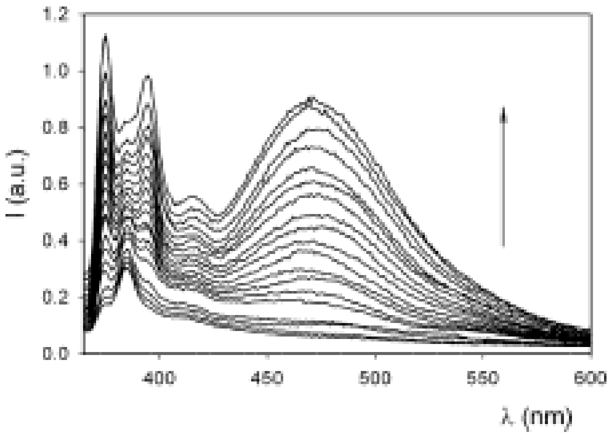




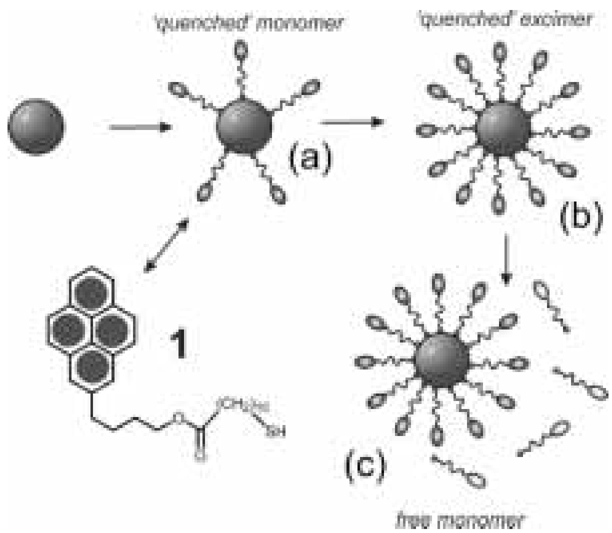
Fluorescence spectra upon excitation at 341 nm of two CH_3CN solutions of gold nanoparticles (8 _ 10^{-9} M) after the addition of the same amount of **1** (a) or 1-pyrenebutanol (b) (2.5 _ 10^{-7} M).



Changes in the F.I. at 394 nm of two CH_3CN solutions of gold nps (8 _ 10^{-9} M) during addition of **1** (∇) or 1-pyrenebutanol (◊). Ratio (□) of the intensity at 473 nm with respect to 394 nm (λ_{exc} = 341 nm) in the case of the addition of **1**.



Changes in the fluorescence spectra (λ_{exc} = 341 nm) of a solution containing gold nanoparticles (8 nM) for addition of **1**. Each curve corresponds to an additional 2.5 _ 10^{-7} M.



Simplified Representation of the Organization of the Fluorescent Thiols on the Nanoparticle Surfaces

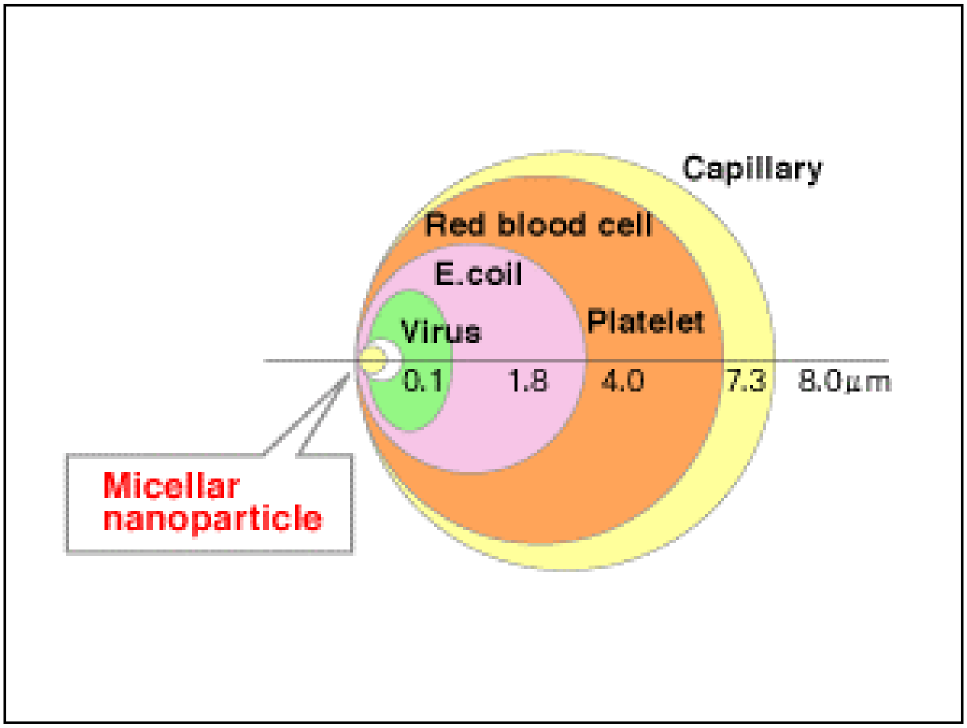
BIOLOGICAL APPLICATIONS

- **Expanding ability to characterize genetic make up will revolutionize the specificity of diagnostics and therapeutics**
- **Nanodevices can make gene sequencing more efficient**
- **Effective and less expensive health care using remote and *in-vivo* devices**
- **New formulations and routes for drug delivery, optimal drug usage**
- **More durable, rejection-resistant artificial tissues and organs**
- **Sensors for early detection and prevention**

- **Nanoparticles**

In general, nanoparticles used in the Drug Delivery System are 50 to 1000 nanometers in size. Among various measures to manufacture nanoparticles, NanoCarrier uses technology to utilize nanoparticles in the range of 20 - 100nm with bi-layer structures comprising inner and outer cores. They are formed by the spontaneous aggregation in aqueous media of block copolymers consisting of the molecular-level conjugation of hydrophobic and hydrophilic polymers respectively.
Polymeric micelle structures are several dozen nanometers in size with distinct bilayer structures comprising inner and outer cores (micellar nanoparticles). They are formed by the spontaneous aggregation in aqueous media of block copolymers consisting of the molecular-level conjugation of hydrophobic and hydrophilic polymers respectively.
Associate Professor Masayuki Yokoyama and Professor Teruo Okano of Tokyo Women's Medical University and Professor Kazunori Kataoka of the University of Tokyo were the first in the world to conceptualize and propose the development of micellar nanoparticles _often called polymeric micell_as functional particles. They demonstrated that such particles could act as stable carrier systems in the bloodstream and showed that they accumulated in cancerous tissue.
These findings sparked worldwide interest and have become the driver of growth in research into functional micellar nanoparticles. The aforementioned professors and Associate Professor Yukio Nagasaki of the Science University of Tokyo discovered that the micellar nanoparticles with functional groups introduced on their surfaces prevented adsorption and coagulation of blood components which make them particularly appropriate for use as a surface coating material for medical devices. Another promising application is the use of micellar nanoparticles bound with antibodies as the main constituent of diagnostic reagents for immunological use that are designed to react specifically with antigens to provide high sensitivity analysis. Avoiding endothelial cells_
NanoCarrier's micellar nanoparticles are coated with hydrophilic polyethylene glycols that curb non-specific interactions and absorption of drugs into endothelial cells and in turn maintain macro molecules in the blood for a long duration.

_Endothelia cells consist of basic protection cells that erode and digest pigments and particles such as old erythrocytes, cells, and bacteria. They are part of spleens, lymph vessels, liver, and lung. They remove materials that the bodies find abnormal.


Capillary
Red blood cell
E.coil
Platelet
Virus
0.1
1.8
4.0
7.3
8.0µm
Micellar
nanoparticle