

Research article

Synthesis of Organic Compounds and biological activity in the presence of Nano-reactors

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ABSTRACT

Nano-reactors are very small shields in nanometer dimensions with high potentials for improvement of chemical conversions with protection of catalysts against environmental impacts, as well as pent-up reactants and catalysts in small space for long time. In general, nano-reactors could be divided to two groups of natural and synthetic nano-reactors. The first group has more selective function and at the same time complicated structure; although the second group has more variety and simpler structure. In macroscopic scale, a chemical reactor is a shield enabling the reactions in certain volume. The advantage of using reactor is possibility to control reaction conditions carefully such as solvent, temperature and stirring rate. In micro and nano scale, some shields could be created isolating certain amount of reaction mixture from the mass medium. If a chemical reaction is trapped in such shield, the shield could be considered as a nano-reactor. The advantages of using the nano-reactors include more control on reaction, selectivity, and isolation of toxic and unstable materials from mass medium and reduction of toxicity of system or increase in catalyst stability and its ideality in the processes. Nano-reactors are nanometer shields, which could be prepared by various compounds including molecules, synthesis macromolecule and biologic macromolecules. In these structures, raw materials and the products are exchanged between the mass solution and nano-reactor pore. Hence, membrane permeability plays vital role in their selective function. Because of abundant advantage such as controllability of reaction and protection of catalysts against environmental impacts; types of catalyst and enzymatic reactions and preparing various nano-structures are taken in the nano-reactors.

Key words: nano-reactors, nanometer, catalysts, chemical reactor, mass medium, synthesis molecules, biologic molecules, enzymatic

INTRODUCTION

Multicomponent reactions are one-pot reactions, in which 3 or more reactants are composed in a single step, so that the products created could be a composition of important sections of all reactants; i.e. majority of atoms in the raw materials could be found in the solution. The synthesis duration is depended on the complexity of the produced molecule in each step and this is depended on number of chemical bonds during the reaction. Therefore, taking reactions creating several bonds in a single step is one of the most important challenges in synthesis with least steps. Multicomponent reactions are vital in organic chemistry and also in Medicinal Chemistry. Multicomponent reactions have many advantages including being

economic, facilitated function and vast uses compared to conventional syntheses. The reactions are useful, especially for production of various chemical complexes from drug compounds to biomolecules. Over the years, discovering new multicomponent reactions has been changed into a growing field of research, which could lead to production of new structures to discover medicines.

Designing new catalysts and discovery of their catalyst activity has led to wonderful effects in optimization of the efficiency of many organic syntheses. Development of the catalysts and replacing the toxic and unstable catalysts by them has made them environment-friendly and cost effective. Paying attention to development

of heterogenic solid acid catalysts and lack of using homogeneous acid catalysts systems is common, since the homogeneous catalysts have disadvantages such as the danger of use, corrosion, production of toxic wastes and problems with isolation. Over the years, heterogenic catalysts have been successfully used in many organic conversions and have minimized the unfavorable wastes causing environmental pollution. The catalysts are in heart of countless chemical protocols from academic research laboratories to chemical industries. Synthesis of some products such as medicines, chemicals, polymers, fuel, fibers, color, lubricants and thousands of other valuable products required for human life is impossible without catalysts. The active compounds control the mechanism of chemical conversions. Therefore, they are capable to provide favorable products economically. Through intelligent designation and use of catalysts, the construction protocols could become economic, green and sustainable more than before.

The properties and uses of organic materials with biologic activity

Types of carbon compounds in remains of a plant or animal in various steps of decomposition are called organic materials.

Organic compound refers to a kind of material and chemical compound (solid, liquid and gas) containing carbon in its molecules. The definition is not general and could not encompass all carbon-containing compounds like carbide, carbonate, cyanide and simple carbon oxides. The said compounds are in the rank of minerals, although they contain carbon.

Till early 19th century, chemicals with animal origin used to be called as organic materials and they were considered as different materials from minerals because of necessity of vital force for their production. The Vital Force Theory was rejected in 1828 by Weller by urea synthesis; although the term "organic" remained. Today, majority of materials composed of two carbon and hydrogen elements are called organic materials.

Organic materials have wide range in Organic Chemistry and are various and different. In the group of these materials, one can refer to

paraffin, oils, hydrocarbons, Olefins, acetylene, terpenes, alcohols, carboxylic acids, esters, ethers, epoxides, aldehydes, ketones, amines, amides, aromatics, organic acids, Isocyanates, products substituted from benzene, textile fibers, dyes and industrial paints.

Types of organic materials with biologic activity are divided to 3 general groups as follows:

1. Soil improvement organic materials

Soil improvement organic materials are compounds with properties of an organic compound and added to soil with the aim of improvement of the physical, chemical and biological conditions of soil. The compounds should have some conditions as follows:

- They should have the properties of organic materials in terms of raw materials and organic carbon content (organic carbon more than 10% and organic materials, more than 25%)
- The main food material content N, P₂O₅ and K₂O is usually lower than 5% in them
- In terms of degree of puberty, they could be applicable in soil or plant based on the advices presented in the brochure.
- In terms of salinity and concentration of sodium and chloride ions due to the advice of label, they could make no limitation for the plant.
- They should be free from the hazard of contamination of pathologic factors for human, livestock and plant, pesticides, harmful compounds and seed of weeds.
- The amounts of heavy elements and external materials mixed in them should be lower than the defined authorized level.

The most important types of soil improvement organic compounds could be counted as plant remains with various degrees of decay, types of composts and vermicomposts.

Organic fertilizers

Organic fertilizers refer to organic compounds with all above mentioned conditions and be also acceptable in terms of content of main nutrient elements required by the plant.

Organic growth promoters

Organic growth promoter refers to organic compounds added to soil or poured on the plants with the aim of promoting and stimulating the growth of plant. To apply the term "growth

promoter" to each organic material, its active ingredients could be considered as a criterion. The values are presented in a table for types of growth promoters in relevant section. Moreover, the following general conditions are required for organic growth promoters:

- They should be free from the hazard of contamination of pathologic factors for human, livestock and plant, pesticides, harmful compounds and seed of weeds.
- In terms of salinity and external materials, they should make no disturbance for plant growth.
- The amount of heavy elements and pollutants should be lower than the defined authorized level for them.

Types of organic growth promoters could be humic acid, fulvic acid, amino acids and seaweed extract.

The process of organic material synthesis of biologic activity in presence of nano-reactors Synthesis nano-reactors

Although protein shells are considered as natural and unique structures for catalysis of reactions

in nanometer scale, the compounds are too complicated. Synthesis molecules are simpler nano-reactors, which could be controlled easier than the natural types.

Molecular nano-reactors

Accumulation of several molecules alongside and formation of a pore to perform chemical reaction could create a molecular nano-reactor. However, in terms of structure, they could be divided to 3 groups of capsules, micelles and vesicles. The interactions causing formation of a capsule could be divided to two groups of covalent and non-covalent interactions. Cyclodextrins (CDs) as porous natural molecules could create some nano-reactors through covalent bond to other molecules, which could take various reactions selectively (figure 1-a). Calixarenes with cup-like hydrophobic pore is in this group. The molecule surrounded by hydrophilic groups is one of the molecular nano-reactors, in which various reactions such as revival of metals could be taken (figure 1- b).

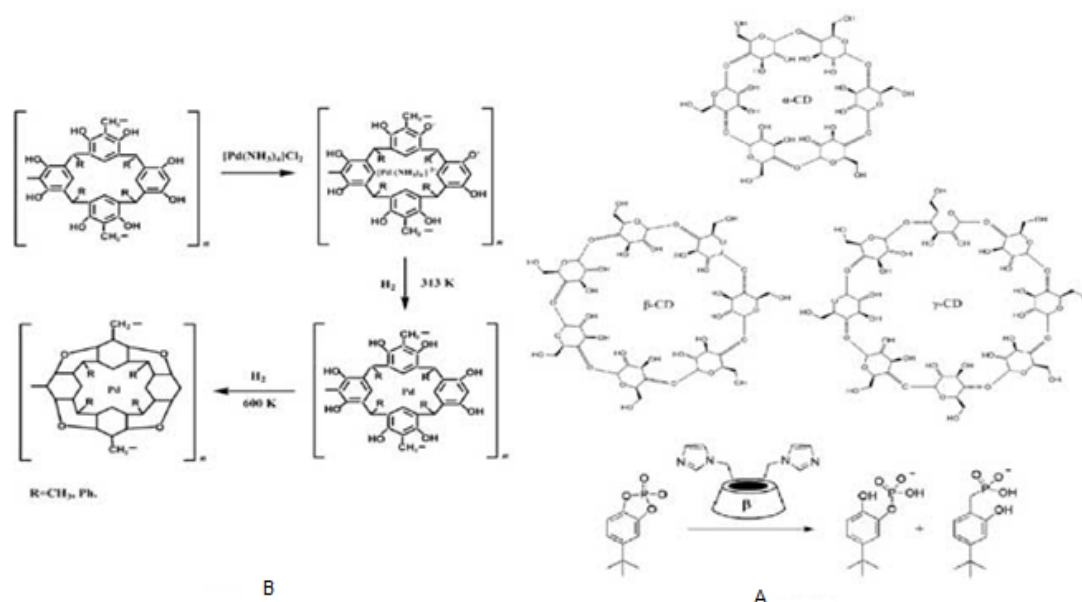


Figure 1: a) structure of types of Cyclodextrins (CDs) (upper) and cyclic phosphodiesterase ester hydrolysis reaction catalyzed by a functionalized β -Cyclodextrin (lower); b) the reactions of palladium ion reduction (II) in pore of apoly-Calixarene

As with the increase in amount and complexity of products, the design and preparation of nano-reactors based on covalent interactions becomes difficult, the production of structures with non-covalent interactions has been developed a lot over the years. The most important non-covalent interactions include hydrogen bonds and metal-ligand interactions (figure 2).

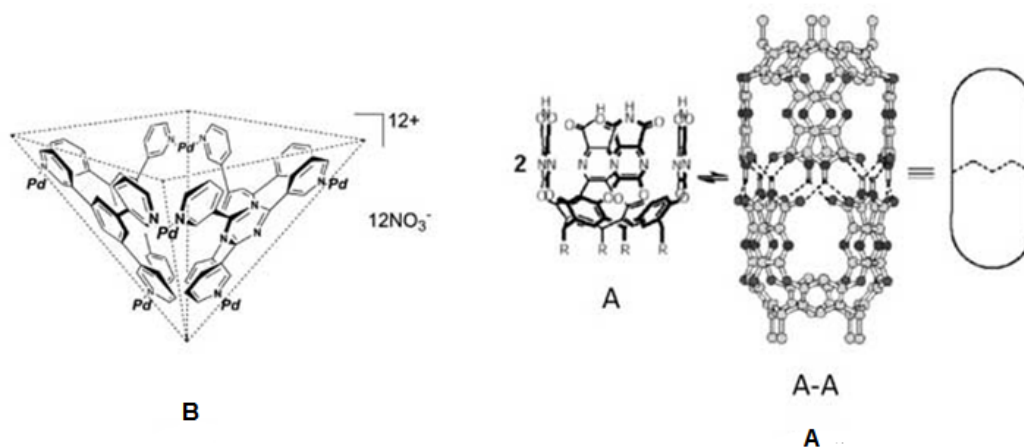


Figure 2: a) A-A capsule stabilized by 12 hydrogen bonds; b) semi-opened cage created by metal-ligand interactions

Micelles and vesicles are an accumulation of amphiphile molecules. The amphiphile molecules include a hydrophile head and a hydrophobe end. One of the most known samples could be phospholipid forming major part of cell membrane. Depending on value of an index called packing parameter, shown with (P) and defined as ($p=v/l.a$) (a is the effective level of the group placed in head of phospholipid and v and l are respectively volume and length of the hydrocarbon chain of phospholipid), accumulation of phospholipid molecules could lead to formation of micelle, reverse micelle or vesicle (figure 3). In fact, vesicle is a double-layered structure with ordered level compared to micelle. It should be noted that vesicles with phospholipid membrane are called liposome. Moreover, the term "enzymatic nano-reactors" refers to those nano-reactors containing free enzymes and the most common type could be lipid vesicle, in which the enzymes have been encapsulated. All of the structures have dimensions in nanometer scale.

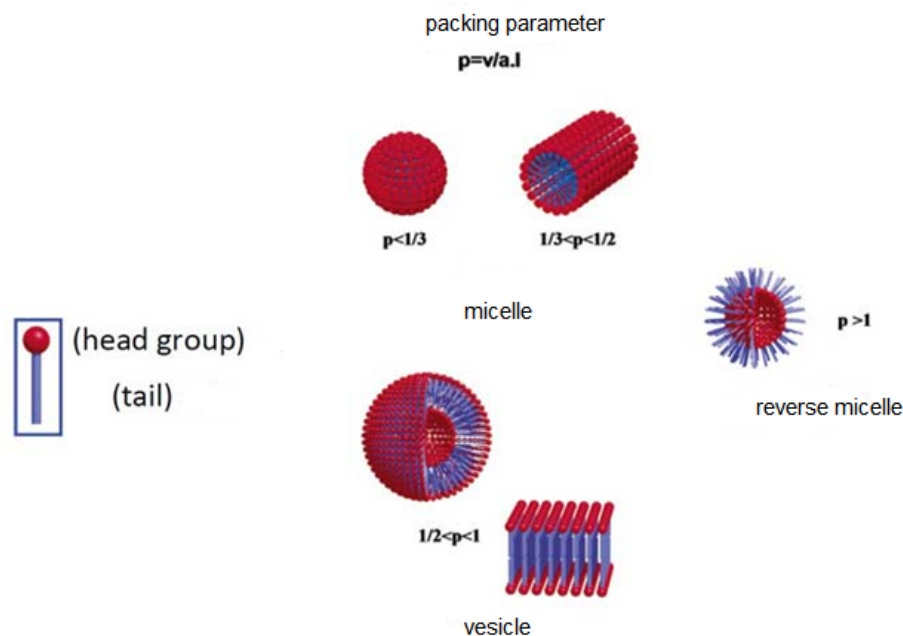


Figure 3: formation of micelle, reverse micelle and vesicle due to packing parameter




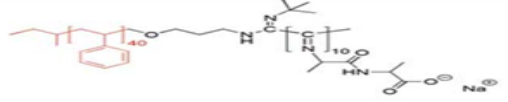



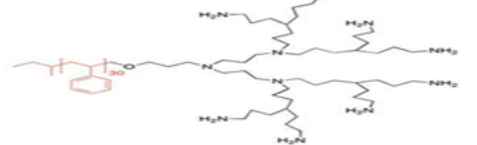
Macromolecular nano-reactors

The structural variety of polymers in terms of monomers, molecular mass, factor groups and their form had made them to be applied in various fields. In field of nano-reactor, polymers are used in form of single macromolecules with hallow inside or in form of self-assembled structures with one or more pores (like polymer micelles).

Polymersomes

If the vesicle is formed of amphiphile macromolecules (block copolymers), it could be called polymersome. Various Dib lock and triblock copolymers are used to prepare polymersomes in different sizes and thicknesses of membrane (table 1). There are various examples of using these structures as nano-reactor, in which active enzymes or metal complexes are encapsulated. To capsule the molecules inside the polymersome, several methods are available and in the simplest method, the guest molecule is added to group copolymer solution before formation of polymersome. As thickness of polymersome membrane is higher than liposomes, water penetration into their membrane is slower and to solve the problem, protein channels inside the membrane of these structures are used (figure 4).

Table 1 has presented the structure and abbreviation of some group copolymers used in creation of polymersomes (hydrophobe groups are illustrated with red color)

| abbreviation | group copolymer structure |
|---|--|
| PB-PEO |  |
| PB-PGA |  |
| PS-PAA |  |
| PS-PIAA |  |
| PPQ-PS-PPQ |  |
| PMOXA-PDMS-PMOXA |  |
| PMPS-PEO-PMPS-PEO-PMPS |  |
| PS-dendr-(NH ₂) ₃₂ |  |

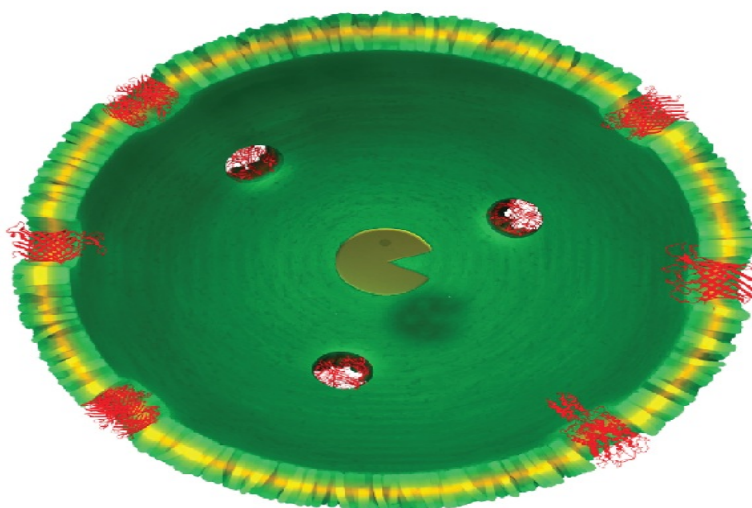


Figure 4: transect of a polymersome illustrating protein channels inside its membrane

In addition to single-enzyme reactions, multistep reactions could be also taken in the polymersomes. For example, through capsulation of glucose oxidase enzyme inside the polymersome pore, placing lipase enzyme in its membrane and covalent bond of peroxidase enzyme to its outer surface, a 3-enzyme nano-reactor could be created, which could be applied for multistep oxidation reaction of glucose derivatives.

Hydrogels

Hydrogels are water-saturated polymers with hallow spaces between their crosslinks. The hallow spaces could be used as nano-reactor for formation of core and growth of nanoparticles. For example, the compounds have been used to prepare silver nanoparticles and due to antibacterial property of silver nanoparticles; hydrogels containing these nanoparticles are used as coverage and bandage (figure 5).

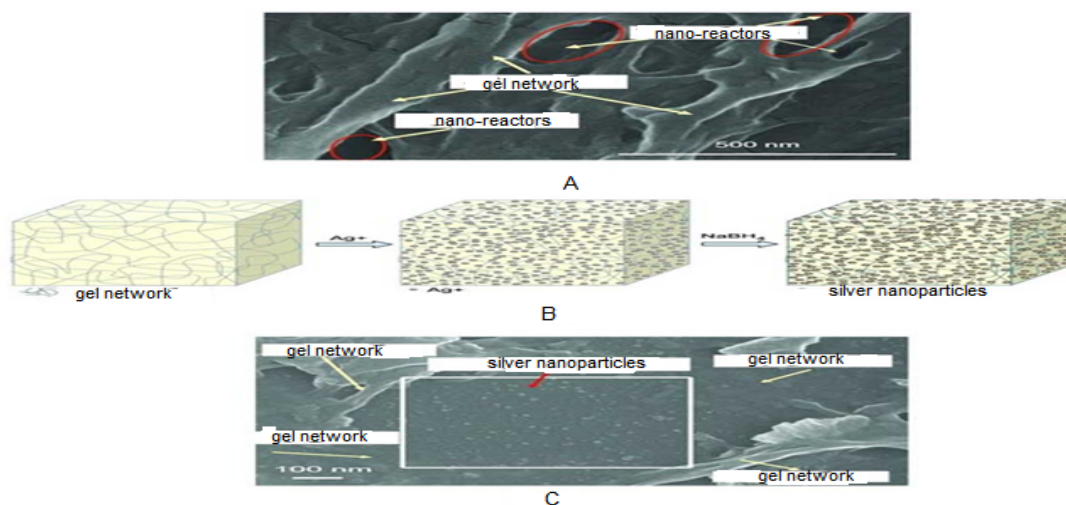


Figure 5: a) scanning electron microscopy (SEM) image of pure hydrogel; b) formation of silver nanoparticles in hydrogel network and c) SEM image of growth of silver nanoparticles in hydrogel nano-reactor

Unimolecularnano-reactors

Dendrimers are single molecules with central core with regular radial branches (figure 6-a). The use of these compounds in catalysis of reactions has been studied carefully. The place of creating covalence bond between catalyst type and dendrimer could be on the environment, in the middle or in the core of dendrimer. Over the years, the selective and sensitive dendrimers have been developed. The nano-reactors with selective and temperature sensitive branches are used as homogenous catalyst in oxidation of thiols.

Hyper branched polymers and star polymers are also placed in the group of unimolecularnano-reactors (figure 6 b and c). The macromolecular nano-reactors are considered as cost-effective corresponds of dendrimers and have the ability to capsulate the metal complexes with catalysis activity and nanoparticles through their core.

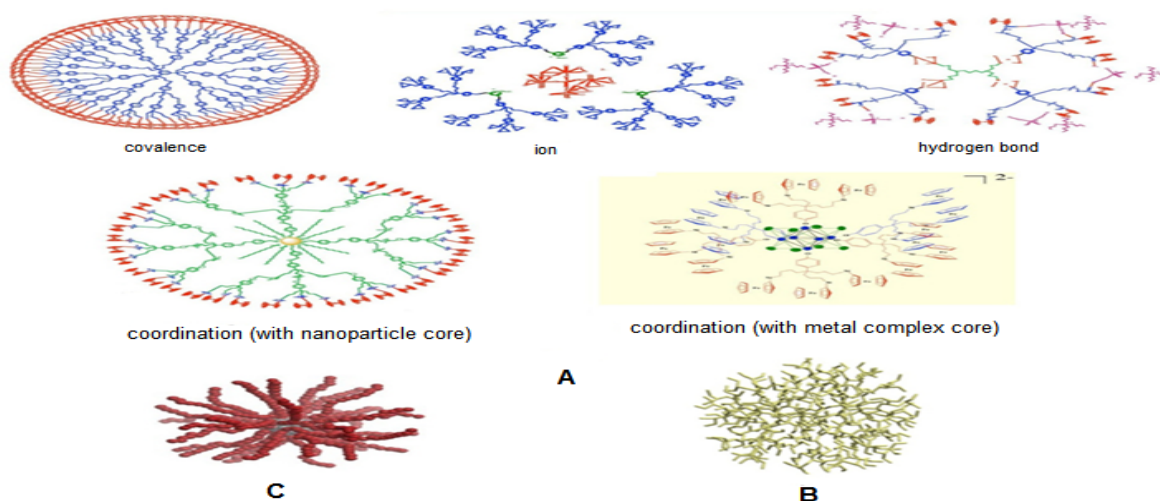


Figure 6: a) types of interactions forming dendrimers; b) hyper branched polymer and c) star polymer

Miniemulsion

Miniemulsion (also known as nano-emulsion) is a method to prepare stable droplets act as nano-reactor. In this method, the mixture of two immiscible liquids like water and oil with one or more surfactants are mixed in high speed and using various techniques such as ultra-sonication. In this state, macro-droplets with large size are broken down to nano-droplets with limited size distribution (figure 7). The size limit of these droplets is usually in range of 30-50nm and each droplet acts as an independent nano-reactor. Using this method in field of medical sciences is being developed since compounds with small sizes could be provided by means of these nano-reactors with high capacity to carry the medicine. For example, nano-reactors with droplet size of $7\pm 27\text{nm}$ have been used to prepare solid lipid nanoparticles (SLNPs).

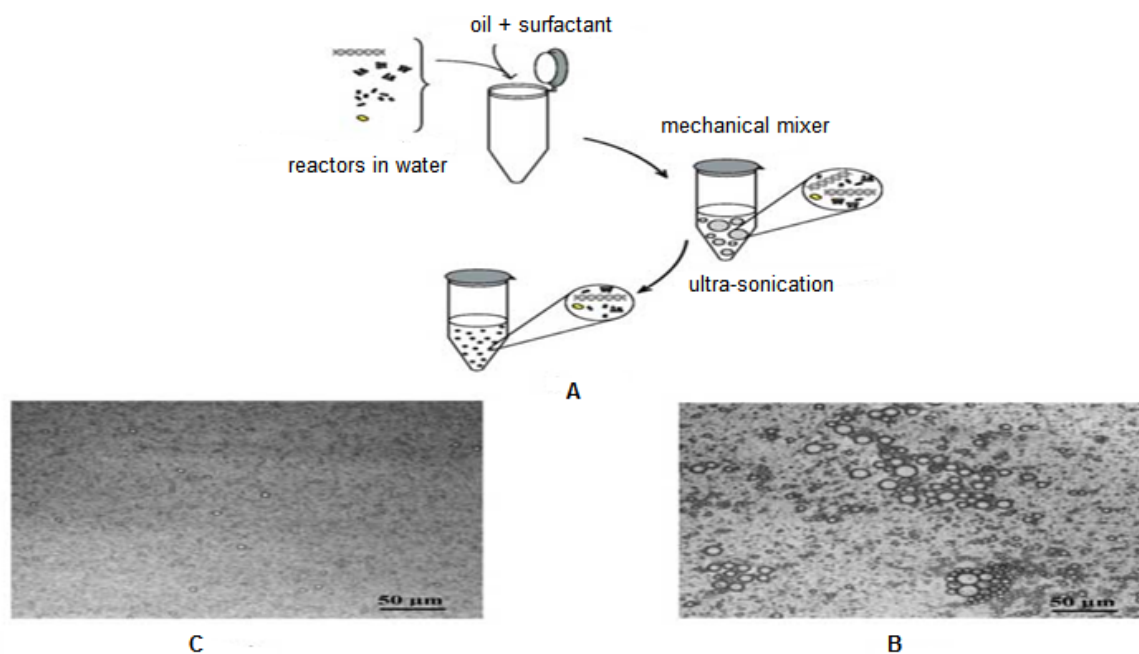


Figure 7: a) the steps of preparing miniemulsion, b) the optical microscopic image of macroemulsion and c) miniemulsion

Core-shell nanostructures

Core-shell structure has high variety and encompass from multiphase semiconductors to metal-metal oxide nanocomposites. Over the years, providing structures with variable core inside a hollow shell has been developed. If the shell is permeable against the reactors, the nanostructures of shell-core could be converted to nano-reactors with catalyst core. Among the main shell-core nano-reactors, one could refer to Pt-CoO nanostructures used to hydrogenize the ethylene. Another example is Au-TiO₂ nanocomposite with photocatalysis activity, which its activity has been stabilized with desorption or decomposition of organic molecules on the metal core under ultraviolet radiation (figure 8-a). Moreover, the shell-core structure of Au-SiO₂ has been applied as a nano-reactor for catalysis revival of 4-Nitrophenol (figure 8-b).

Porous solid materials

Porous structures of silicate and zeolite are the clearest and the most applicable compounds of this group. Zeolites are porous compounds formed mostly of Aluminosilicate. The dimensions of pores inside the silicates and zeolites vary from a few angstroms to a few nanometers. The structures have been used as nano-reactors in various processes. For example, functionalized porous silicon with Cyano group with average pore diameter of 18nm has been applied for the proteolysis process. Moreover, the zeolites containing metal complexes inside the pores with catalysis activity have been used in oxidation process, hydrogenation, isomer conversion catalyzed by acid and disproportionation reactions. Moreover, the structures have been applied to produce the nanoparticles (figure 8-c).

Nanotubes

Nanotubes are plates of atoms organized in tube form. The compounds have been formed of organic materials or minerals in terms of structure and could be prepared in single-walled or multi-walled forms. Nanotubes have high internal capacity and their outer surface could be functionalized easily. The most important compounds of this group include carbon nanotubes (CNTs) discovered in 1991 for the first time. The internal space of CNTs as nano-reactor has been used to produce types of nanostructures such as nanowires and nanoparticles (figure 8- d).

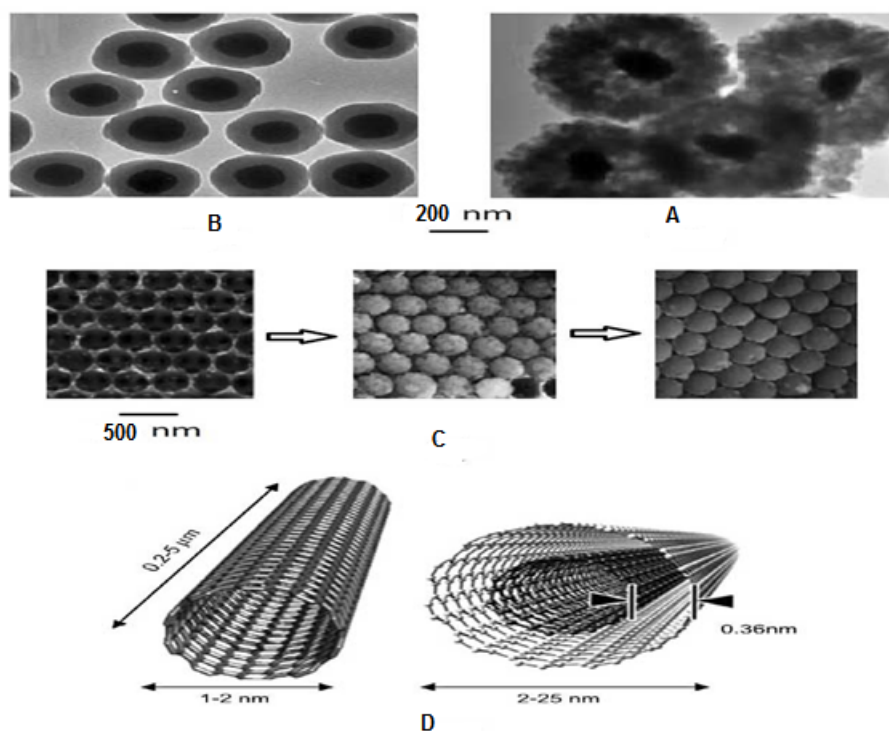


Figure 8: a) TEM image of shell-core nanoreactor Au-TiO₂ after growth of gold cores; b) TEM image of Au-SiO₂ shell-core nano-reactor and c) SEM image of growth of nanoparticles in a zeolite nano-reactor and d) single-walled and multi-walled CNTs

CONCLUSION

Nano-reactors are shields in nanometer scale, which could be gained from various compounds including molecules, synthesis macromolecules and biologic macromolecules. In these structures, the raw materials and the products are exchanged between the mass solution and nano-reactor and hence, membrane permeability could play key role in selective function of the structures. Because of abundant advantages such as controllability of the reaction and protecting catalysts against environmental impacts; types of catalyst reactions and enzyme reactions and preparing various nanostructures is done inside the nano-reactors.

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