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Biomimetic Synthesis and Properties of Polyprenoid

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This chapter is dedicated to the memory of Marie-Claire Dillenseger and Pr Guy Ourisson.

1. Introduction

The polyprenoids, which represent the largest family of natural products in the living world, are biogenic compounds that derive from the assemblage and modification of five-carbon isoprene units. Some polyprenoids, such as cholesterol in animals, phytosterols in plants or hopanoids and α,ω -dihydroxylated carotenoids in Bacteria (Fig. 1), are of paramount importance in biological membranes, where they act as reinforcers (Ourisson & Nakatani, 1994). Without these reinforcers, the self-organization of phospholipid molecules would not resist from shear stresses.

Membranes of Bacteria and Eukarya are formed by the self-assembly of amphiphilic phospholipids whose polar head-groups are linked to two fatty acid chains by ester bonds. The molecular dimensions of cholesterol, phytosterols and hopanoids approach closely those of hydrophobic parts of phospholipid molecules in their stretched form, and their hydrophobic tails are localized in the middle of the membrane (Yamamoto et al., 1993). Thus, these terpenoids reinforce the lipid bilayer by cooperative attractive van der Waals forces and modulate membrane rigidity and fluidity (Milon, Lazrak et al., 1986). In some Bacteria, carotenoids reinforce membrane by crossing both halves of the bilayer (Milon, Wolff et al., 1986).

Archaea, the third major kingdom of living organisms, possess structurally unique lipids: their polar head groups are linked to polyprenyl chains by ether bonds, in contrast to the ester bonds and n-acyl chains in Eucarya and Procarya. These ether linkages, which are chemically stable, enable these organisms containing membranes to survive under extreme conditions of pH, temperature, pressure and salt concentration (Chong, 2010; Koga et al., 1993). Another striking feature of some archaeal lipids is the presence of 72-membered rings (Eguchi et al., 2000).

Apart from this maintenance of the membrane integrity, membrane terpenoids fulfill many other functions. Dolichol phosphates are widely present in membranes and are involved in the N-glycosylation of proteins. Ubiquinones, which are composed of a 1,4-benzoquinone

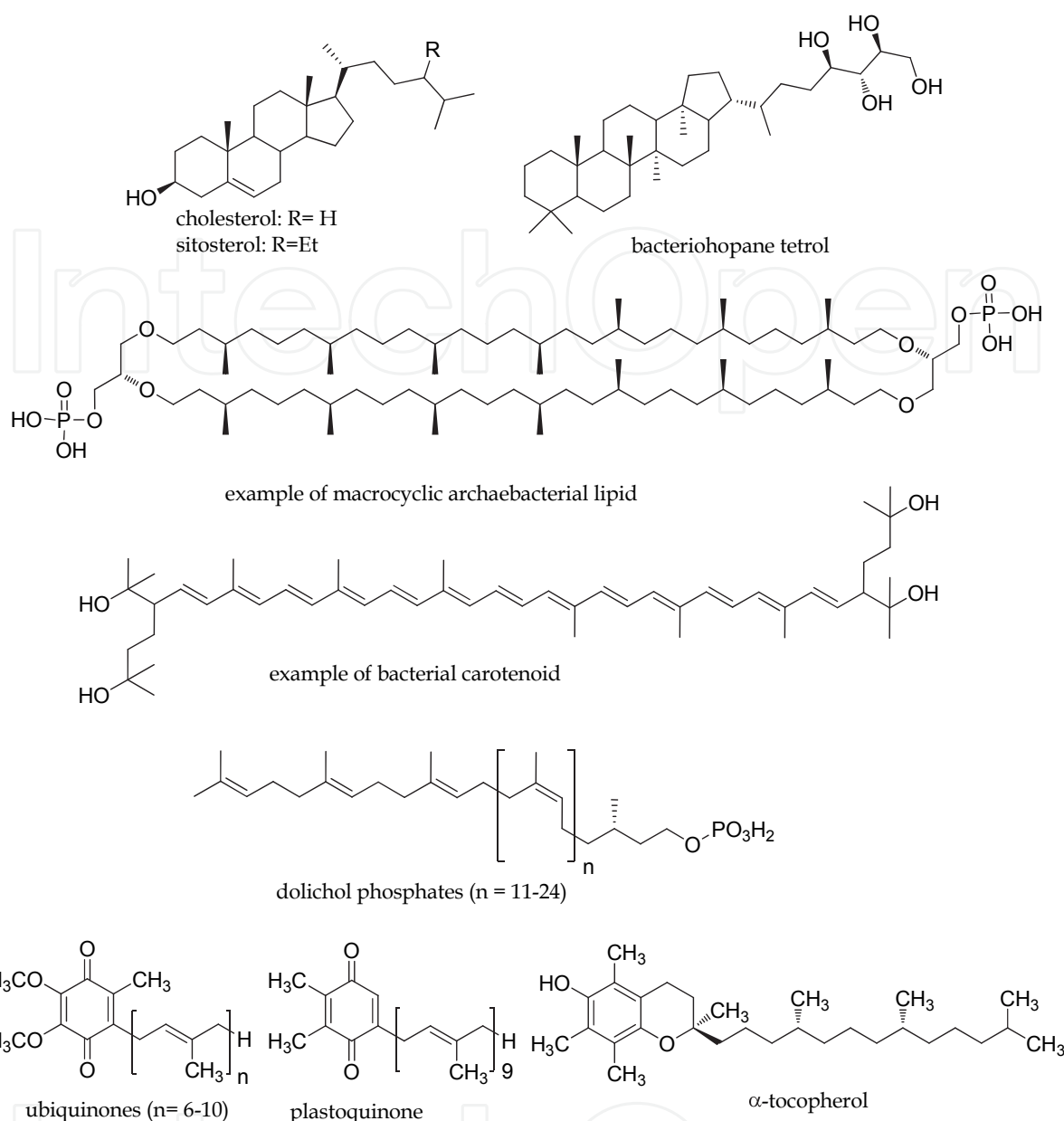


Fig. 1. Representative examples of natural polyprenoids.

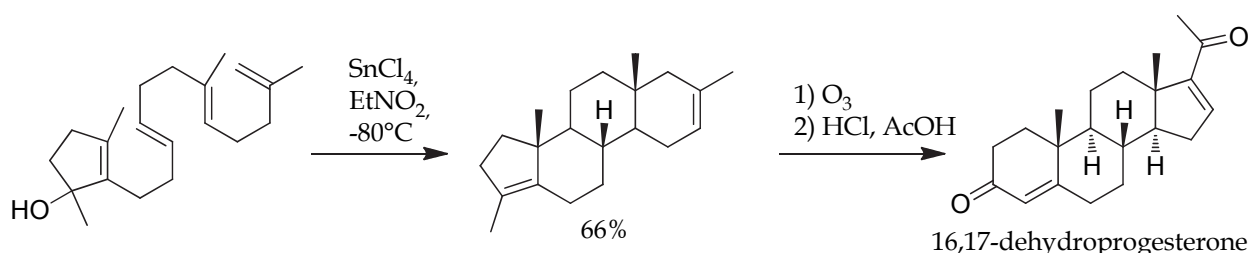
moiety linked to a polyprenyl chain, play a critical role in the electron transport within the inner membrane of mitochondria. In their reduced form, ubiquinones, and tocopherol (which has a similar structure) function act as antioxidants, preventing lipid peroxidation (Burton, 1994; Kawamukai, 2002). Plastoquinone, another coenzyme that belongs to the family of quinines conjugated to a polyprenyl chain, is deeply involved in the transfer of electrons in photosynthesis and in the scavenging of reactive oxygen species in chloroplasts (Ke, 2001; Mubarakshina & Ivanov, 2010). Carotenoids, which contain a conjugated polyene chain that strongly absorbs light in the visible regions, play a critical role in photosynthesis, where they participate in the energy-transfer process and prevent the formation of toxic singlet oxygen (Demmig-Adams et al., 1996). Another polyenic polyprenoid, retinal binds covalently to sensory rhodopsin in animals or bacteriorhodopsin in *Halobacterium*. Absorption of photons induces a photoisomerisation of this pigment that is at the core of the

process of vision and ion transport across the bacterial membrane. Beyond their localization in biological membranes, terpenoids play diverse biological roles, in particular as hormones in animals (steroids hormones, vitamin D and retinoic acid) and plants (gibberellins, abscisic acid) (Bohlmann & Keeling, 2008).

In this chapter, we will provide an update of some recent advances in biomimetic synthesis and properties of terpenoids with a focus on illustrative examples which may inspire future directions of research.

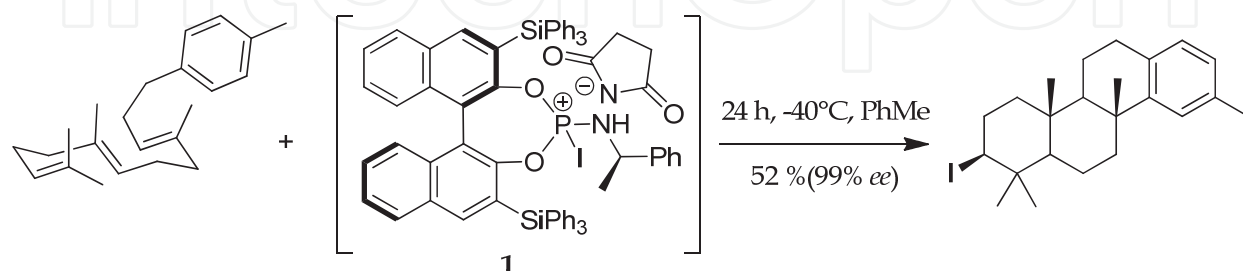
2. Recent progress in the biomimetic synthesis of polyprenoids

The discovery by the teams of Bloch and Woodward (Woodward & Bloch, 1953) that the open-chain polyene, squalene, is the key biogenetic precursor of lanosterol, together with the theoretical concepts of Stork and Eschenmoser (Eschenmoser et al., 1955; Stadler et al., 1957; Stork & Burgstahler, 1955) regarding the mechanism of the polycyclization of squalene to give polycyclic triterpenoids in the late 50s, pave the road for what remains one of the most elegant synthesis in organic chemistry: the biomimetic carbocyclization of polyprenoids. In 1968, Johnson and collaborators achieved the first synthesis of a polyprenoid in a biomimetic fashion (Scheme 1) (Johnson et al., 1968). This achievement stimulated further studies, which have been presented in an excellent review in 2005 (Yoder & Johnston, 2005). In this section, we will present more recent studies that highlight the efficiency and elegance of this approach.



Scheme 1. First biomimetic polycyclization of a polyprenoid (Johnson and coll., 1968).

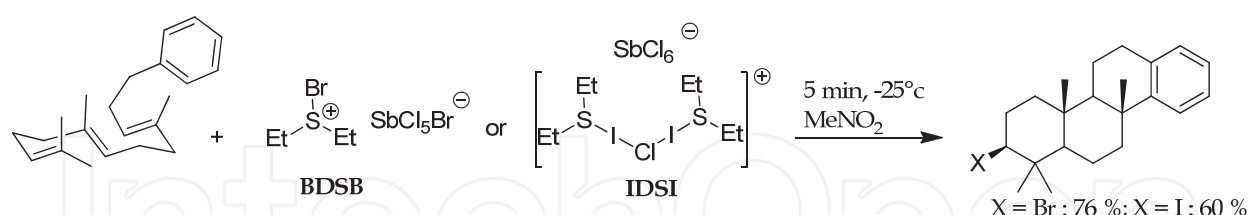
While the use of halogenating agents to initiate polyene cyclizations used to be sluggish, Ishihara and coworkers developed in 2007 the first enantioselective and high-yielding polycyclisation induced by a halogen atom using the chiral phosphoramidite **1** combined with NIS (or NBS) (Scheme 2) (Sakakura et al., 2007).



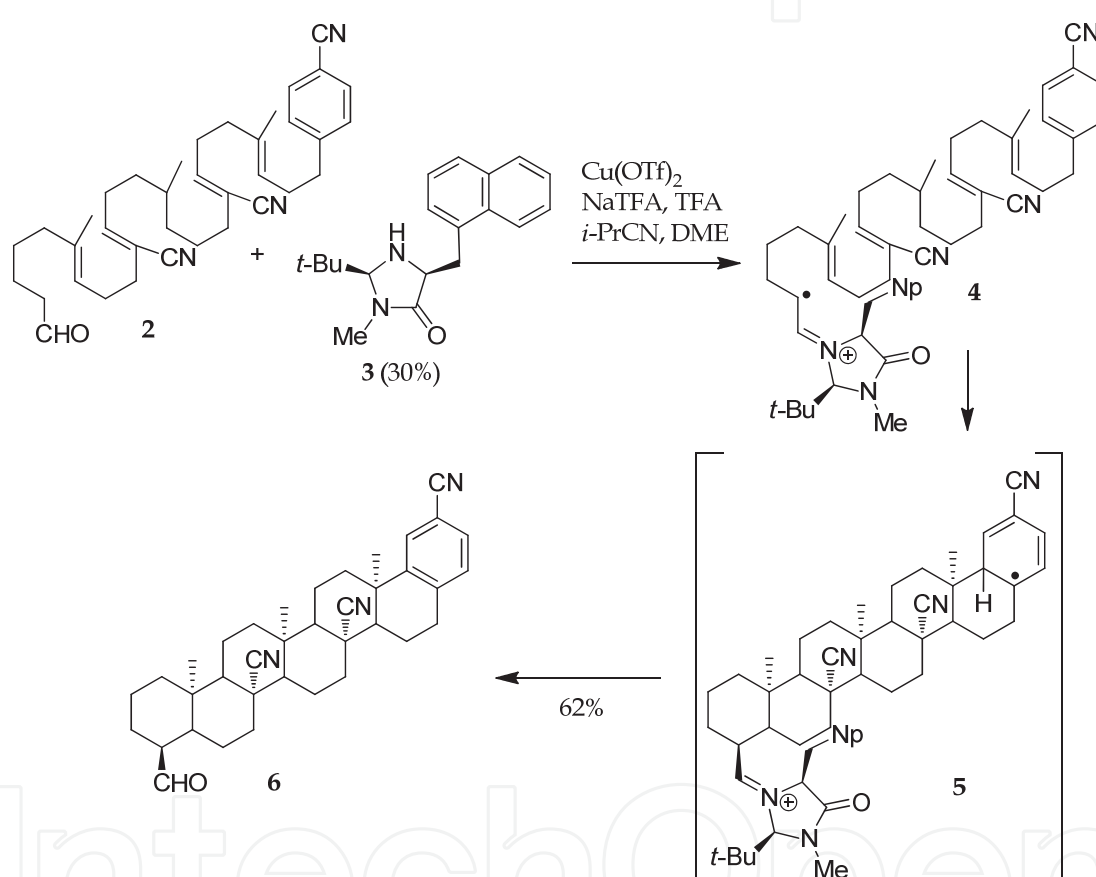
Scheme 2. Enantioselective polycyclization induced by a chiral source of iodonium.

In 2010, Snyder and coworkers developed BDSB and IDSI as simple and convenient reagents for the direct synthesis of a diverse range of halogenated polycyclic terpenoids via cation- π

cyclizations (Scheme 3) (Snyder et al., 2010). The efficiency of approach was demonstrated through the formal synthesis of several complex natural polycyclic polyterpenoids.



Scheme 3. Halonium-induced polycyclization.

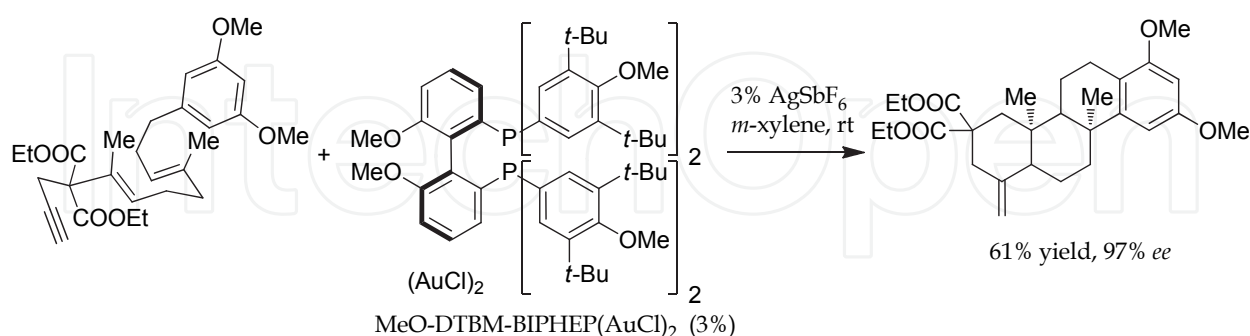


Scheme 4. Organocatalyzed enantioselective polycyclization.

The recent blossom of organocatalysis has already impacted the biomimetic cyclisation of polyprenoids. MacMillan and co-workers used their organo-SOMO catalysis strategy to induce a powerful cascade reaction via a single electron transfer catalyzed by the imidazolidinone **3** (Scheme 4) (Rendler & MacMillan, 2010). Condensation of aldehyde **2** with **3** afforded the imino radical intermediate **4** upon oxidation with $\text{Cu}(\text{OTf})_2$. This radical engaged in a series of 6-endotrig radical cyclizations to give the cyclohexadienyl radical **5** that upon a second oxidation and liberation of the catalyst afforded the pentacyclization product **6** in 62% yield.

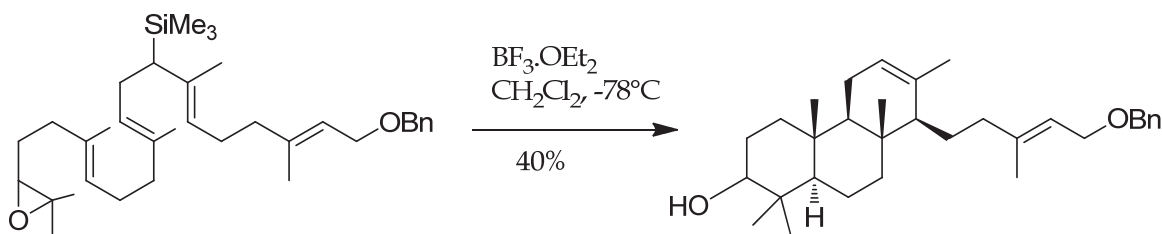
During the last decade, the use of gold catalysts emerged as important tools in organic synthesis due to their carbophilic π -acid character that renders possible the generation of

impressive structural complexity in an atom economic manner. This chemistry is well depicted in the recent report of Toste and colleagues of an efficient enantioselective polycyclization reaction initiated by the activation of a terminal alkyne (Scheme 5) (Sethofer et al., 2010).



Scheme 5. Gold(I)-catalyzed enantioselective polycyclization.

To investigate the membrane reinforcing effects of tricyclopolyprenols on polyprenyl phosphates vesicles as a model of “primitive” membranes (*vide infra*), we developed a biomimetic cyclization controlled by an allylsilane (Ribeiro et al., 2007). Allylsilanes had previously been used to terminate the polycyclizations of polyprenoids, but as far as we know, our approach was the first one to involve an allylsilane that is not located at the extremity of the polyenic chain (Scheme 6). This strategy allowed us to synthesize enough material for extensive biophysical studies.



Scheme 6. Cyclization of an epoxypolyprenoid controlled by an internal allylsilane.



Scheme 7. Biomimetic condensation of isopentenol 7 with prenol 8 induced by montmorillonite K10.

While the biomimetic cyclisation of polyprenoids has been explored for almost half a century, the biomimetic synthesis of polyprenols from C5 alcohols has been scarcely examined (Désaubry et al., 2003). We showed that a clay, montmorillonite K-10 mediates the condensation of isopentenol 7 with prenol 8 to generate a mixture of isomeric diprenols 9 (Scheme 7), supporting the hypothesis that polyprenol may have been formed in prebiotic conditions, and possibly constitute primitive membranes (Ourisson & Nakatani, 1999). These steps could be repeated, and lead from C10 to C15, then C20 polyprenols.

3. Biomimetic systems of photosynthesis

The synthesis of biomimetic nanoscale devices has been of paramount importance to better understand the intimate process of photosynthesis (Gust et al., 2001). This photoinduced electron transfer involves light harvesting and funneling, charge separation and migration, coupled to a slow charge recombination. Artificial reaction centers are composed of a carotenoid (as an electron donor chromophore that absorbs visible light) conjugated to an electron acceptor moiety (such as fullerene or a quinone) through a porphyrin that controls the electron transfer and prevents the photophysical pathways that depopulate excited states. Moore, Gust and collaborators designed in 1997 a superb example of such biomimetic device, which was composed of a carotenoid conjugated to a quinone through a porphyrin (Fig. 2) (Steinberg-Yfrach et al., 1997).

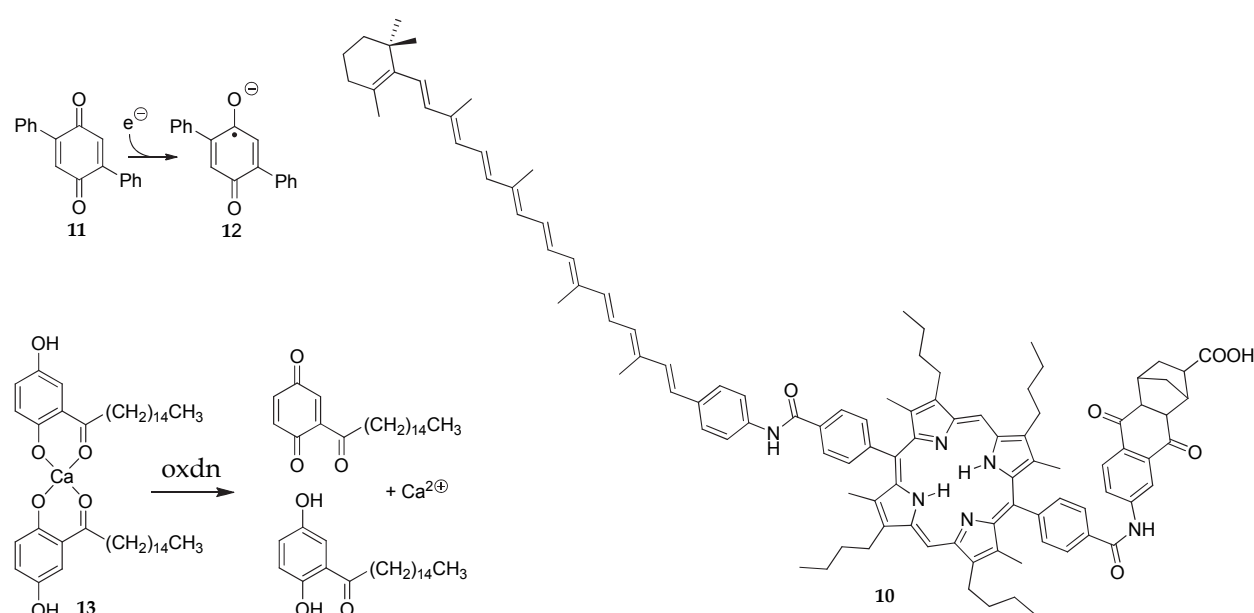


Fig. 2. Artificial reaction center composed of carotenoid conjugated to a quinone through a porphyrin unit.

This triad 10 can be inserted in the membrane of a liposome to act as light-driven proton pump in presence of the quinone 11 as a surrogate for the electron carrier NADPH in photosynthesis. Absorption of light leads to the formation of the diradical carotenoid $^{+}$ -porphyrin-quinone $^{-}$, which reduces 11 into a semiquinone anion 12 that can be protonated and cross the membrane. Once inside the liposome, 12 reduces the carotenoid radical cation, which terminates the redox loop, resulting in a pH gradient between the inside and outside of the liposome.

Next, the same team complexified further this system by embedding in the membrane the enzyme F_0 - F_1 ATP synthase, which uses the proton-motive force to generate ATP from ADP and inorganic phosphate (Steinberg-Yfrach et al., 1998). This “semi-biomimetic” system that combines an enzyme with a fully artificial synthetic membrane could efficiently synthesize ATP. This type of approach cannot economically compete with commercial silicon solar cells, but beautifully unravels the elegance of photosynthesis process designed by Nature. These authors pursued their work by combining their photosynthetic triad 10 with a lipophilic Ca^{2+} -binding shuttle 13 to induce a membrane potential and a light-driven

transmembrane transport of Ca^{2+} (Bennett et al., 2002). The triad 10 was vectorially imbedded in the membrane of a liposome, with the naphtoquinone part toward the external surface and the carotenoid moiety inside the hydrophobic part of the membrane. Light absorption induced charge separation to form a carotenoid radical cation that oxidized complex 13 to release Ca^{2+} inside the liposome.

4. Development of polyprenoid-based gene delivery systems

Beyond its critical use as a tool in research, the delivery of nucleic acids into cells represents a lot of hope to treat incurable genetic diseases and some cancers. The most widely used approach is the formulation of DNA into condensed particles by using cationic lipids or cationic polymers (Mintzer & Simanek, 2009). These particles can cross the cell membrane and carry the DNA into the cytoplasm where it migrates into the nucleus to induce expression of the transgene. This technology represents an intense field of research, and over the last two decades the physicochemical properties of cholesterol and archeal lipids have been exploited to design new tools for gene transfection.

The rigidity of cholesterol improves the stability of cationic lipids-DNA complexes. The efficiency of this class of lipids has been demonstrated with the polyamine conjugate GL67 (Fig. 3) that efficiently transferred the gene of CFTR into the lungs of cystic fibrosis patients, and alleviated the burden of their ailment (Alton et al., 1999).

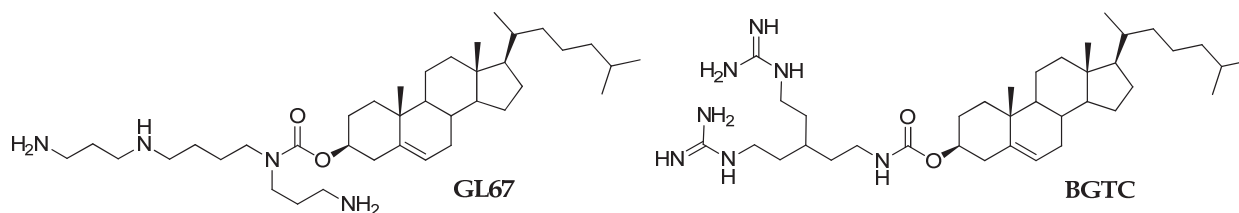


Fig. 3. Structure of the cationic cholesterol conjugates GL67 and BGTC.

The replacement of the amines by guanidines led to the design of a new class of cationic cholesterol derivatives, such as bis(guanidinium)-tren-cholesterol (BGTC) that efficiently delivery genes to the airway epithelium of mice and sheeps *in vivo* (Luton et al., 2004; Vigneron et al., 1996). However, this vector has not been examined in clinical trials yet.

The unique physical characteristics of archael lipids allow to the formation of extremely stable membrane that can resists to shear, thermal, osmotic and pH stresses. These features have been exploited in the design of gene delivery systems with enhanced stability. The most promising vectors are di- and tetraether-type archael derivatives conjugated to a poly(ethylene glycol) (PEG) chain and folic acid (FA) (Fig. 4) (Laine et al., 2008). The PEG moiety was introduced to reduce the interactions with blood proteins, while the folate moiety allowed the targeting of tumor cells overexpressing the folate receptor. The FA-PEG570-diether combined with cationic lipid demonstrated an *in vitro* transfection efficiency that was much superior to that of Lipofectamine, which is the standard transfected agent the most widely used. Future development of these promising gene carriers for treatment of cancers are still in progress.

The success of gene delivery of nucleic acids in animal model has triggered clinical studies that begin to display promising results.

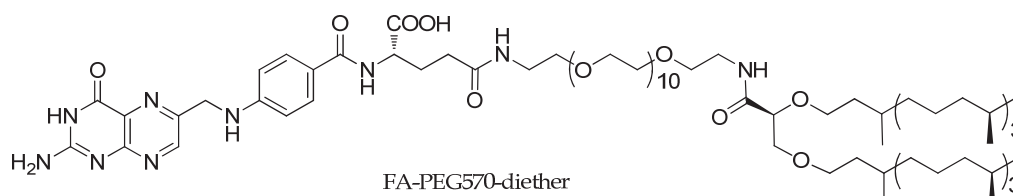


Fig. 4. Structure of folic acid conjugated to a diether-type archaeal lipid.

Albeit this methodology needs further improvement, the design of new vectors based on the cholesterol and archaeal lipids is expected to provide new opportunities to overcome the critical limitations of current gene delivery systems, such as low efficiency of transfection *in vivo*, potential toxicity and acute immune response.

5. Biomimetic cell membranes

Terpenoids are universal membrane constituents and are essential to reinforce the membranes of all living organisms (Rohmer et al., 1979). Long term investigation of Guy Ourisson and Yoichi Nakatani on polyprenoids in the fossil record and membrane reinforcers has prompted them to propose a phylogenetic classification of membrane terpenoids (Fig. 5) (Ourisson & Nakatani, 1994).

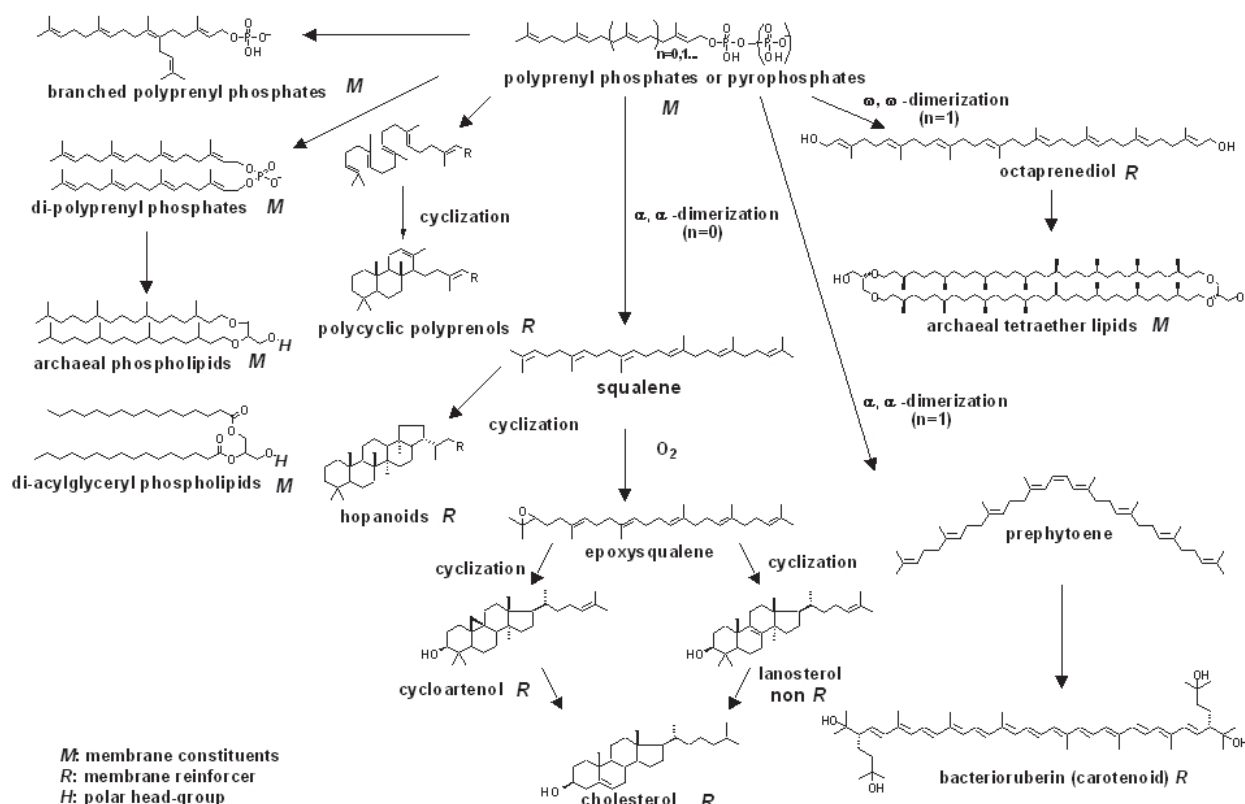


Fig. 5. Hypothetical evolution of membrane polyprenoids (modified from Ourisson & Nakatani, 1994).

From a retrograde analysis, they have proposed that polyphenyl phosphates might be even more primitive membrane constituents than archeal membrane lipids. And they have postulated that primitive membranes could have been more readily formed from the

simplest possible terpenoids, the acyclic polyprenols, linked to an appropriate and simple polar head-group like a phosphate anion (Ourisson & Nakatani, 1999). The polyprenyl chains of archaea are biosynthesized by C5 increments, and the chemistry involved in these elongation steps are simple alkylations of double bonds (Porter & Sandra, 1981). They postulated that the simplest possible polar head is a phosphate, as in many other biochemical reactions, because of its universal presence in the head groups of membrane lipids (Westheimer, 1987).

Based on these observations, our group has synthesized phosphate esters containing 1 or 2 polyprenyl chains and has demonstrated, by using fluorescence microscopy, that these lipids do form spontaneously vesicles in water in a wide pH range, when the chain contains 15 to 30 C-atoms (Pozzi et al., 1996; Birault et al., 1996; Streiff et al., 2007). The monolayer properties of some polyprenyl phosphates were also investigated at the air-water interface (Ariga et al., 2005). In brief, single-chain polyprenyl phosphates occupy now a central position in the postulated phylogenetic sequence of membrane terpenoids. To mimic a possible primitive system of vesicles, we hypothesized that these membranes could be formed by a mixture of polyprenyl phosphates and their corresponding alcohols. They are indeed formed spontaneously by hydration of a lipid film. At first, we showed that single-chain polyprenyl phosphates form stable vesicles at pH 2-9. We, then, observed that addition of free polyprenols increases the stability of vesicles at higher pH. This observation is in good agreement with the model of Israelachvili *et al.* that predicts vesicle formation in function of the ratio of the hydrophilic and hydrophobic volume (Israelachvili et al., 1977).

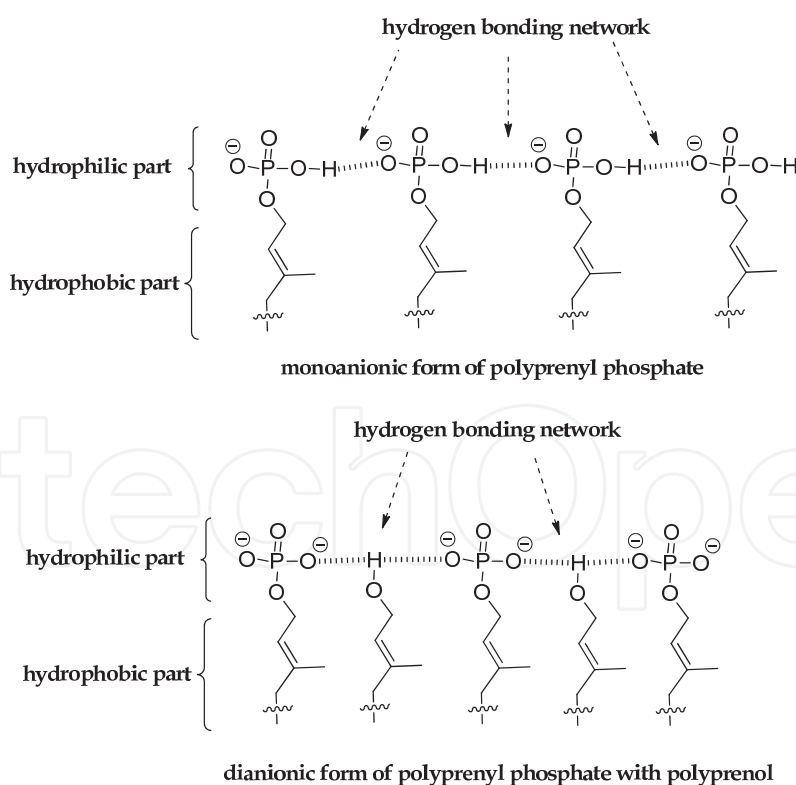


Fig. 6. Hydrogen bonding network at the phosphate head group.

Indeed, the addition of alcohol increases the hydrophobic volume of the membrane and therefore stabilizes the vesicles at higher pH. Moreover, the intermolecular hydrogen bonding network between the head group area of polyprenyl phosphate and the polyprenyl

alcohol contributes also to the stabilization of the vesicles at basic pH (Fig. 6) (Apel et al., 2002; Walde et al., 1997).

Consistently, we observed that the addition of the free polyprenol decreases the water permeability of polyprenyl phosphate vesicles. A very extensive study on the water permeability of membrane made of geranylgeranyl phosphate with polyprenyl alcohols bearing different structural parameters (chain length, degree of unsaturation and cycle) provided the evidence that the efficiency of the reinforcement is dependent on the structure of the polyprenols (Fig. 7) (Ribeiro et al., 2007; Streiff et al., 2007).

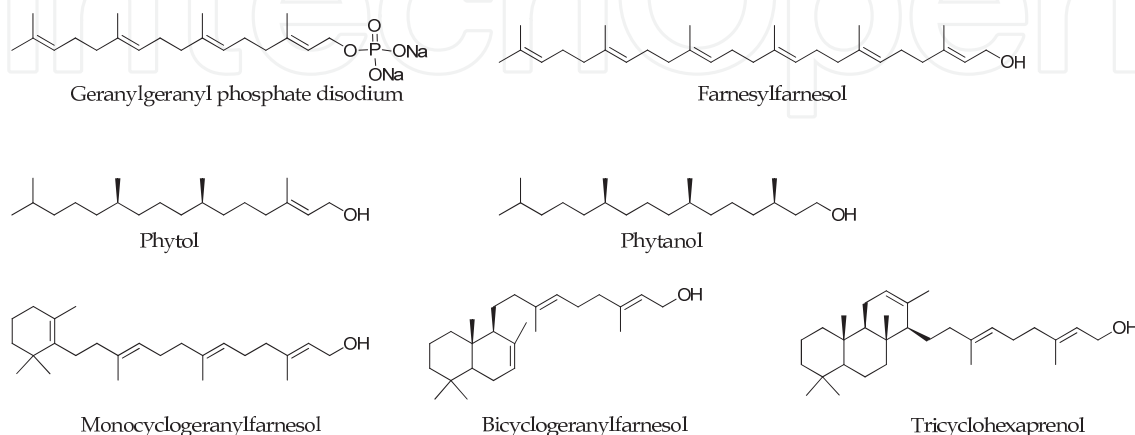


Fig. 7. Structure of geranylgeranyl phosphate and polyprenols.

The incorporation of farnesylfarnesol to membrane made of geranylgeranyl phosphate does stabilize it against water permeability. Probably, farnesylfarnesol bearing a longer chain than the geranylgeranyl phosphate penetrates to the opposite leaflet in an interdigitated manner (Fig. 8) (Slater, 2005). The additional van der Waals interaction may contribute to stabilize the membrane.

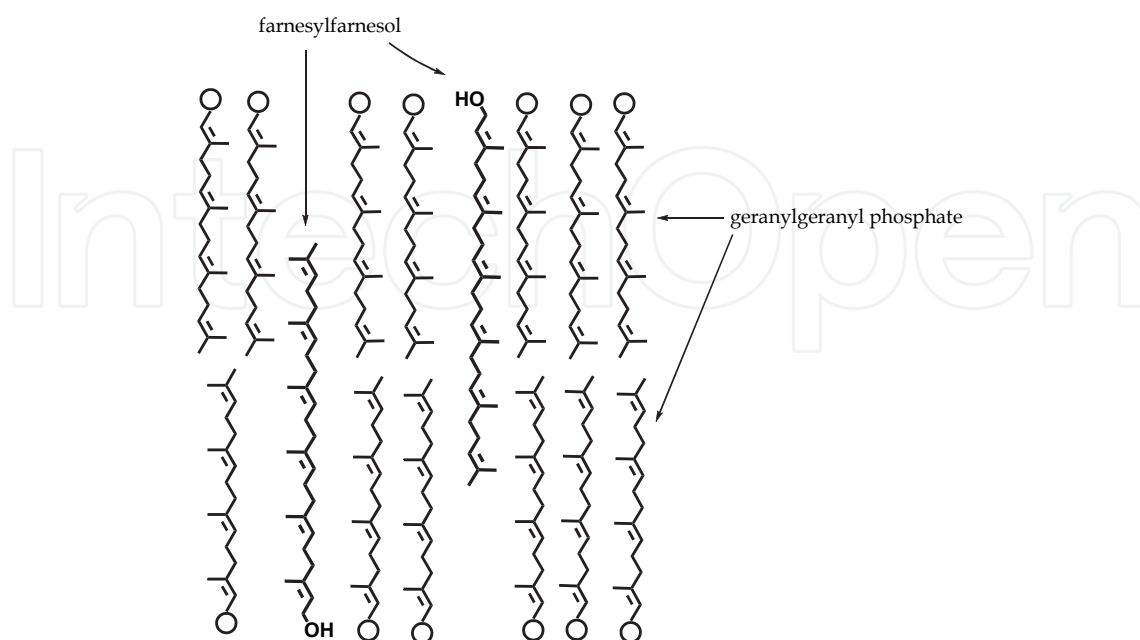


Fig. 8. Interdigitation of farnesylfarnesol in membrane made of geranylgeranyl phosphate.

The incorporation of molecules through the two leaflets of a membrane bilayer was also observed in the case of α,ω -dihydroxylated carotenoids, and it highly stabilized the membrane (Milon, Wolff et al., 1986). In the case of cyclic polyprenyl alcohol, our group has demonstrated that only the alcohol fitting the size of geranylgeranyl phosphate stabilizes the membrane against water permeability. Thus, monocyclogeranylfarnesol, bicyclogeranylfarnesol and tricyclohexaprenol reinforce efficiently the membrane made of geranylgeranyl phosphate. However, the number of rings has no significant effect on the water permeability, while the chain length is the critical parameter of system consisting of polyprenylphosphate/polycyclopolyprenol. The suitable size of polycyclopolyprenols for an optimal reinforcing effect against water permeability might be important for the enhancement of van der Waals interactions and the compactness of the membrane. This observation is in good accordance with cholesterol, the reinforcer of animal membrane, which size is similar to that of mammal lipid membrane. Interestingly, tricyclohexaprenol may be the biogenic precursor of tricyclohexaprenane found in organic fossils (Ourisson & Albrecht, 1992). It is supposed that tricyclohexaprenol may exist in living cells and its function would be a reinforcer of membrane. The presence of unsaturated polyprenyl alcohol, such as phytol or phytanol, also reinforces membrane against water permeability. All these data reproduce the mechanism of membrane reinforcement found in nature. We also demonstrated by ^{31}P -NMR that the asymmetry of the membrane in small vesicles implies a difference of the ionization state of the phosphate head group between the outer and inner membrane surface. This vectorial property may be a factor leading to “self-complexification” of these primitive vesicles (Lee et al., 2002).

Furthermore, Guy Ourisson and Yoichi Nakatani postulated that the highly branched isoprenoid alkanes and alkenes, which are distributed widely and abundantly in many types of sediment, may have been derived from branched polyprenyl phosphates potentially present in the biomembranes of some primitive organisms (Robson and Rowland, 1986; Rospondek et al., 1997). These polyprenyl-branched polyprenyl phosphates could result from a simple alkylation of non-substituted polyprenyl phosphates.

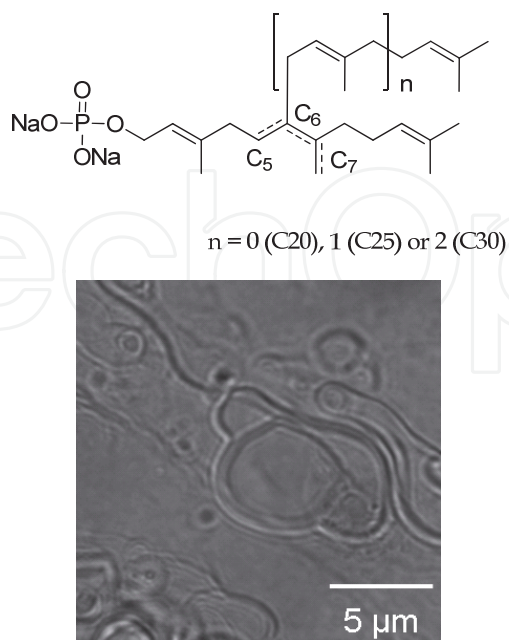


Fig. 9. Structure of synthesized branched polyprenyl phosphate and example of formed vesicle ($n=1$, pH 7).

The recent isolation of the branched isoprenoid hydrocarbons from diatoms also suggests that the corresponding alcohols or phosphates may still exist on Earth (Belt et al., 2000; Damsté et al., 2004). A series of 2- or 6-(poly)prenyl-substituted polyprenyl phosphates have been synthesized by Nagano *et al.* (Nagano et al., 1999; Takajo et al., 2001), and we found that these higher branched polyprenyl phosphates form vesicles in water in a physiological pH domain (Ghosh et al., 2000; Gotoh et al., 2006) (Fig. 9). Moreover, we have demonstrated that vesicle formation and robustness of the membrane against water permeability depend on different structural parameters such as substituted-chain length and the position of the double bonds. The branched polyprenyl phosphate C25 ($n=1$) has the optimal length to form robust vesicles. Comparison of water permeability between the branched polyprenyl phosphate C25 and geranylgeranyl phosphate showed that the substituted lipid C25 has a clear advantage against mechanical stress. Therefore, these results may imply that polyprenyl substitution could be one step of the evolution of biomembranes, by a simple alkylation of non substituted polyprenyl phosphates.

As a following study, we aimed to find out how “primitive” membranes made of single-chain lipids could have evolved towards a cell-wall-like structure (Fig. 10) (Ghosh et al., 2000; Gotoh et al., 2006). We have demonstrated that phytol-labeled polysaccharide pullulans coat giant vesicles made up of single-chain polyprenyl phosphates or of double-chain phospholipids present in Archea and Eukarya.

In these cases, phytol plays the role of an anchor inserted into the outer layer of vesicles. We have also shown that the same polysaccharide labeled with cholesterol similarly covers the outside of vesicles made of Eukaryotic lipids (Ueda et al., 1998). These results indicate the criteria for efficient insertion of a lipophilic anchor into a bilayer: a nearly identical structure of the bilayer phospholipids and the anchoring chains of the polysaccharide is required, or else the fit must be closely adapted, as in the case of cholesterol and *n*-acyl lipids (similar cross-sections and lengths). This would provide a mechanism for selecting membrane constituents during the course of biomembrane evolution.

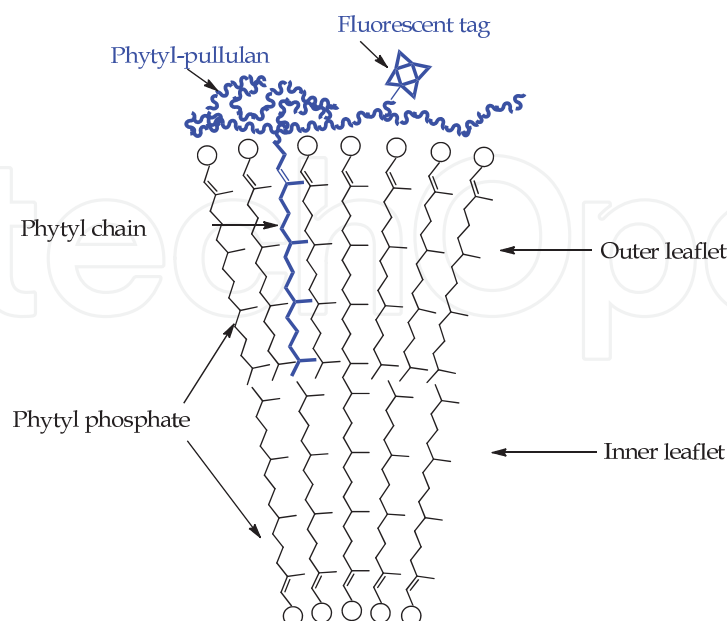


Fig. 10. Coating vesicle surface with a fluorescent conjugate of phytol with a polysaccharide, pullulan (modified from Ghosh et al., 2000).

During the evolution process, cell membranes have acquired several biological functions to communicate with the external world. In a recent work, we have observed the binding of the lectins to the polysaccharide on the surface of vesicles made of double-chain lipids (Gotoh et al., 2007). This shows that giant vesicles, coated by “hydrophobized” pullulan, can act as high affinity ligands for glucose-binding lectins. However, vesicles made of “primitive” single-chain lipids, coated by phytyl-pullulan, are not stable in the presence of these lectins. Our findings, thus, show a clear advantage of double-chain lipid vesicles over the single-chain variants. This might rationalize the selection of double-chain over single-chain lipids during the evolution of membrane complexity.

As a final step of development of biomimetic vesicle to proto-cell, encapsulation of biomolecules, such as DNAs, RNAs, proteins, etc., might have been indispensable. In collaboration with Yoshikawa's group, we have demonstrated that giant DNAs can be efficiently entrapped within microscopically observable cell-sized “primitive” giant vesicles prepared by a “natural” swelling method (Fig. 11) (Nomura et al., 2001).

We have also verified that encapsulated T7 DNA molecules are transcribed into RNAs inside such giant vesicles (Tsumoto et al., 2001). Moreover, we showed that compartmentalization had dramatic effects: 1) gene expression takes place more efficiently inside vesicles than outside, and 2) vesicles can protect internal gene products from attack by an external proteinase, indicating that a compartmentalization with a lipid boundary between the inner space and the outer environment is probably advantageous for life (Nomura et al., 2003). These studies on transcription and translation within vesicles, and on “primitive” membranes lipids should contribute to a better understanding of the development of biomimetic vesicles to proto-cells.

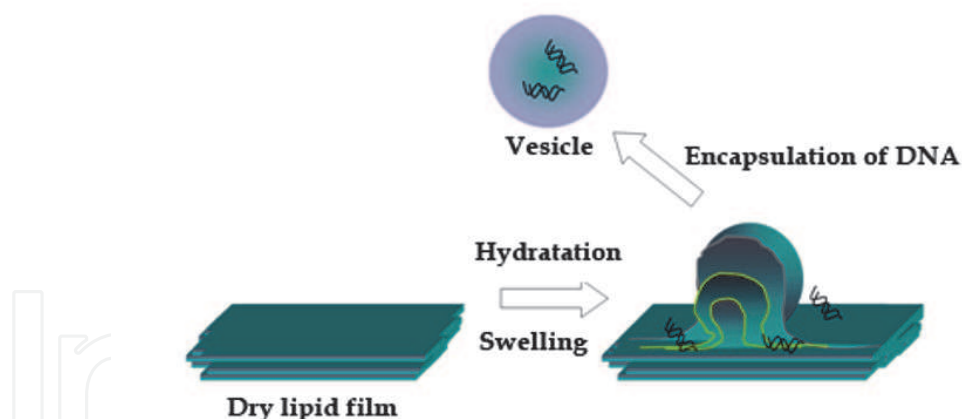


Fig. 11. Encapsulation of DNA by natural swelling (modified from Nakatani & Ourisson, 2005).

6. Conclusion

Due to their diversity of structure, physical and biological functions, polyprenoids constitute a large pool of building blocks that have been inspiring chemists in three different manners: (i) in the design of polyene cyclisations reactions to synthesize complex natural products, (ii) in the elaboration of speculative scenarios on the origin of Life, which currently escape from direct experimental demonstrations, and (iii) in the creation of self-assembling molecular structures that mimic some key features of living organisms; the most

spectacular example being the liposome-based system developed by Moore, Gust, and their co-workers that uses sunlight to accumulate protons inside the liposome, as it is in the chloroplast (Steinberg-Yfrach et al., 1997). We have demonstrated that polyprenylphosphates, which we had postulated "primitive" membrane constituents, form vesicles in water and polyprenyl alcohols reinforce the membrane. We have also shown that self-organization of polyprenylphosphates in water into closed vesicles, leads automatically to self-complexification into "proto-cells" (Ourisson & Nakatani, 2006). This academic demonstration that a synthetic system may emulate a complex natural molecular process did not find any application yet. However, in another field, gene therapy, polyprenoids-based vectors may find soon some clinical applications with an economic viability. These achievements illustrate well Genrich Altshuller's statement that "In nature there are lots of hidden patents" (Altshuller, 1997). In the future, the combination of polyprenoids to synthetic molecules, macromolecules or engineered biopolymers may result in the development of sophisticated systems containing multiple components. Such synthetic systems will take advantage of the physicochemical properties of polyprenoids as membrane reinforcers or electron transporters to efficiently fulfill their function.

7. Acknowledgment

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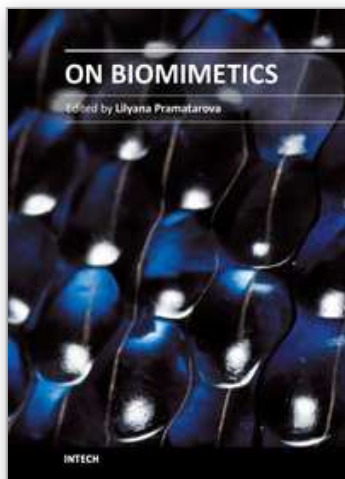
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Bio-mimicry is fundamental idea – How to mimic the Nature™ by various methodologies as well as new ideas or suggestions on the creation of novel materials and functions. This book comprises seven sections on various perspectives of bio-mimicry in our life; Section 1 gives an overview of modeling of biomimetic materials; Section 2 presents a processing and design of biomaterials; Section 3 presents various aspects of design and application of biomimetic polymers and composites are discussed; Section 4 presents a general characterization of biomaterials; Section 5 proposes new examples for biomimetic systems; Section 6 summarizes chapters, concerning cells behavior through mimicry; Section 7 presents various applications of biomimetic materials are presented. Aimed at physicists, chemists and biologists interested in biomineralization, biochemistry, kinetics, solution chemistry. This book is also relevant to engineers and doctors interested in research and construction of biomimetic systems.

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