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SUPRAMOLECULAR ASSEMBLIES WITH DNA*

(Special Topic Article)

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*This paper highlights and contextualizes research findings presented at an IUPAC-sponsored workshop entitled DNA Supramolecular Assemblies, held in Avignon, France on 5–6 May 2004. Special topic coverage in *Pure and Applied Chemistry* aims to highlight topical themes and offer critical insight into new and emerging concepts in chemical sciences.

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Abstract: Information storage in chemical and biological systems involves recognition processes occurring at the molecular and macromolecular level. The implementation of a "code" can consist of multiple noncovalent interactions, which include hydrogen bonds, π-stacking, hydrophobic interactions, and appropriate molecular and supramolecular architectures. With the double-helical DNA structure stabilized by Watson–Crick hydrogen bond base-pairing and aryl π–π stacking interactions, nature provides to scientists an example of one of the most sophisticated supramolecular systems. Molecular organization using these types of processes has become a very powerful strategy for the construction of well-defined nanostructures. Self-assemblies using noncovalent interactions have been designed to build fibers, membranes, two-dimensional monolayers, hydro, organo gels, etc. This paper highlights the research presented at the workshop entitled DNA Supramolecular Assemblies, which was held in Avignon, France on 5–6 May 2004. In this article, we first focus on the recent progress achieved in the design of supramolecular self-assemblies that mimic the molecular recognition functionalities found with nucleic acids. Second, we present several synthetic-DNA supramolecular assemblies currently developed to transport nucleic acids into cells. The marriage of supramolecular chemistry with nucleic acids as illustrated through examples in this article will open new avenues for designing artificial molecular devices and expand the current repertoire of supramolecular assemblies available.

Keywords: Supramolecular assemblies; DNA; amphiphiles; nucleoside; nucleic acid transport; nucleoside-based lipids.

INTRODUCTION

Supramolecular assemblies represent a vast and diverse set of structures ranging in size from nanometer to millimeter and include systems that are purely aesthetic in design to those that perform functions. The intermolecular forces that drive formation and stabilization of such structures include hydrogen bonding, electrostatic, and hydrophobic forces. In fact, it is often more than one type of noncovalent interaction that is responsible for assembly structure and function. An elegant biological example of intermolecular forces in a supramolecular assembly is found in DNA. The double-stranded helical structure of DNA is a consequence of multiple, discreet Watson–Crick hydrogen bonding and π–π stacking forces between the four bases adenine, cytosine, guanine, and thymine. A second and widely found example of a self-organized structure is observed in cells, where phosphocholine lipids align to form bilayer membranes. Adaptation of these intermolecular force principles to the design and synthesis of new supramolecular structures has led to their use in fields from mechanical engineering to medicine. These supramolecular assemblies include those that are purely synthetic to those that are a hybrid and contain both synthetic and natural components.

Molecular recognition plays a key role in the formation of supramolecular assemblies. Within this framework, the process called "self-organization", in which amphiphilic molecules assemble to form spherical droplets or other aggregates in aqueous solution, is of widespread interest. In these organized supramolecular systems, at least two distinct phenomena can be distinguished. The polar moiety belonging to the amphiphilic molecule establishes interactions with water and will tend to stabilize the

system, while the hydrophobic portions will maximize their interactions and displace water. The entire self-organization process has both enthalpically (hydrophobic chain alignment) and entropically (release of water to the surroundings) favorable energy terms. Understanding the intricate details of the self-assembly mechanism has brought about innovation and applications of supramolecular assemblies (fibers, membranes, hydrogels, organogels, etc.) to new levels [1–3]. We are particularly interested in self-assemblies and supramolecular systems involving DNA and RNA. Today, such systems provide opportunities to further characterize the relationships between molecular structure and assembly properties, to mimic natural systems for fundamental studies, to build biological sensors, and to create novel therapeutics.

This special topic article highlights the research presented at the workshop entitled DNA Supramolecular Assemblies, which was held in Avignon, France on 5–6 May 2004. First, we will focus on the recent progress achieved in the synthesis of supramolecular self-assemblies that mimic the molecular recognition functionalities found with nucleic acids. This section includes hybrid molecules bearing both nucleic acid and amphiphilic moieties. Second, we present several synthetic systems currently developed to transport nucleic acids into cells using a synthetic-DNA supramolecular assembly. These results emphasize the importance of designing chemical systems that possess sites for multiple forms of molecular recognition and provide further motivation for the study and applications of DNA supramolecular assemblies.

SUPRAMOLECULAR SELF-ASSEMBLIES THAT MIMIC THE MOLECULAR RECOGNITION FUNCTIONALITIES

One example of recognition found in nature is the base–base pairing of nucleic acids. This recognition of complementary nucleic bases inspires chemists to mimic these interactions using synthetic systems [4–6]. These concepts of molecular recognition were first used to create a stabilized supramolecular film at the air/water interface almost 15 years ago [7]. This initial report led to extensive research in this field [8]. Interestingly, it was found that amphiphiles featuring a nucleobase could also bind complementary bases at the air/water interface either when solubilized in the aqueous phase or within an organized Langmuir film. In parallel research activities, it was known that monomeric nucleic acids could not form hydrogen-bonded complementary pairs in water due to the strong competitive binding of water molecules [9]. Nevertheless, it was shown that this limitation could be overcome by the use of amphiphilic molecules and the formation of hydrophilic and hydrophobic domains. In recent years, we have witnessed the development of research efforts focused on molecular recognition at supramolecular object interfaces. Thus, by combining the assembly properties of lipids with nucleotide structures, amphiphile based-nucleosides, often referred under the names of nucleoamphiphiles or nucleolipids, have been investigated [10–12]. Complementary binding of nucleobases have been studied in micelles [13], vesicles [14], and monolayers [15,16].

Supramolecular architectures are widely used to study the role of molecular recognition in nucleolipid amphiphiles. Some of these investigations showed that chemical recognition of the bases occurs in a supramolecular structure without covalent bonds among the mononucleotides and in spherical bilayer lipidic structures. In this section, we present (1) the self-aggregation of phosphatidylnucleoside lipids and nucleoside-based amphiphiles, (2) the molecular features that influence supramolecular assemblies of peptide nucleic acids (PNAs), (3) the polymerization of nucleotide in vesicles, (4) the condensation of DNA in lipid microcompartments, and (5) the structure of dendrimer-like DNA nanomaterials.

Phosphatidyl diacylglycerol nucleoside-based lipids

The plenary lecture of Piero Baglioni from the University of Florence, Italy, reviewed the progress achieved in the formation of supramolecular self-assemblies [17], which are able to mimic the molec-

ular recognition functionalities typical of DNA and RNA. Baglioni explained that, in nature, the transmission of the biological information is realized through molecular recognition. This fundamental phenomenon is achieved in water using multiple noncovalent interactions such as hydrogen bonds and stacking interactions in conjunction with the appropriate molecular and supramolecular architectures. Several examples of phospholipid self-assembled systems decorated by DNA/RNA functionalities were presented. Most of the supramolecular structures described were based on self-assembly of double-chain phospholipids. In 1981, Rosenthal et al. reported the first synthesis of an isosteric analog of a nucleoside diphosphate coenzyme. Because liponucleotide coenzymes are obligatory intermediates in the biosynthesis of important phospholipids (phosphatidyl group donor), such as phosphatidyl diacylglycerol or phosphatidylserine, a stable potential inhibitor of this biosynthesis pathway was synthesized [18]. A family of phosphatidyl diacylglycerol nucleoside-based lipids was also investigated by Shuto et al. in 1987 [19]. These compounds, which are based on a nucleotide structure functionalized on the ribose 5' position, were judiciously prepared by using an enzymatic modification that allows the coupling reaction of a nucleoside on the polar head of a phospholipid. The resulting amphiphilic molecules possess a polar head bearing a nucleotide and diacylglycerol hydrophobic moieties. An example of a phosphatidylnucleoside structure is presented in Fig. 1. Numerous studies with these amphiphiles demonstrate that the presence of a molecular recognition group (i.e., base) dictates the phase behavior of nucleolipids. While the most important molecular information comes from the polar head, it has been also observed that self-organization can be changed by altering the alkyl chains linked to the glycerol backbone. Head–head interactions producing DNA and RNA-like recognition processes were observed as a consequence of the self-aggregation of phosphatidylnucleoside lipids. Indeed, despite the aqueous environment, base–base stacking and hydrogen-bonding interactions were identified in lamellar vesicles and in micellar aggregates. Recently, this topic was extensively reviewed by Berti and Baglioni [20,21].

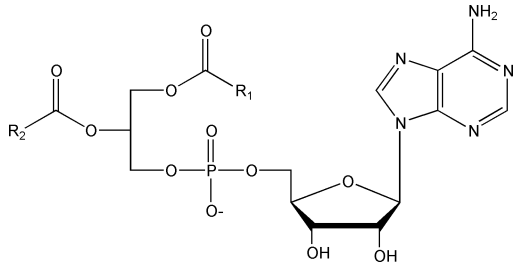
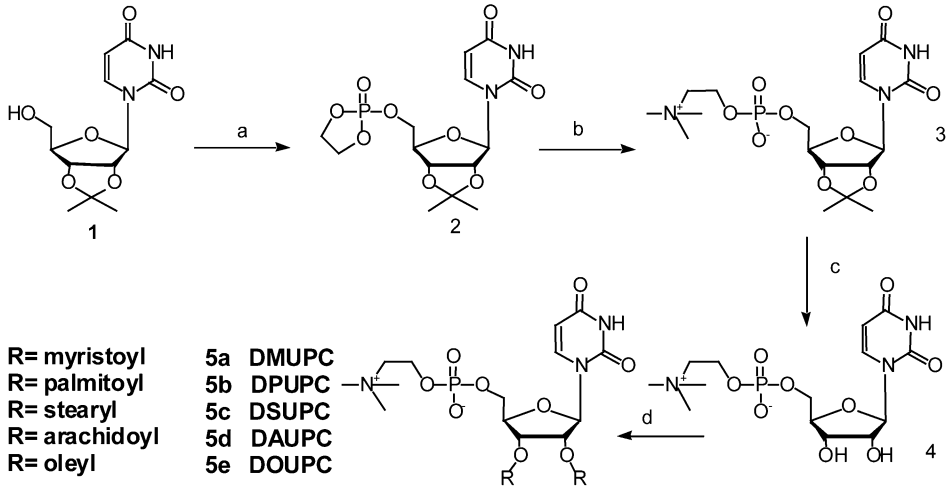


Fig. 1 Example of a phosphatidyl diacylglycerol nucleoside-based lipid derived from adenosine. Adapted from ref. [20].

Supramolecular assemblies of nucleoside-based amphiphiles

Numerous examples of natural and synthetic nucleoside-based amphiphile derivatives featuring a nucleoside or nucleotide functionalized on the ribose 5' position have been reported. As we have seen with phosphatidyl diacylglycerol nucleoside-based lipids, most of the investigations indicated that the interfacial orientation of nucleolipids provides a suitable environment for base–base pairing. For example, in a study involving micelles, it was observed that base–base interactions through stacking and hydrogen bonding are present at the micellar surface [22]. Note that this paper reports for the first time direct evidence of Watson–Crick Hoogsten molecular recognition between the complementary adenosine and uridine dioctylphosphatidyl derivatives in micellar systems. Before these investigations, the orientation and recognition of nucleoside-based amphiphiles in model membranes were achieved on structurally simple derivatives [7]. In that case, instead of grafting the amphiphilic part on the 5' ribose position, hydrophobic moieties were attached either directly to the base or through a 3-oxobutylic acid

linker. Nucleo-amphiphiles with fatty esters on the 5' and 4' positions were also prepared, and their molecular recognition capabilities were studied [16]. Surprisingly, the substitution of the 2' and 3' nucleoside ribose positions by fatty moieties has been explored only recently. Since 2002, the groups of Barthélémy and Grinstaff have been designing novel amphiphilic structures derived from nucleobases [23]. Their investigations focused on the structure and self-organization relationships—specifically, how changes in the molecular structure affect the physiochemical properties and assembly architecture. Thus, to better understand the chemical structural parameters that dictate self-assembly, the molecular structures of conventional lipids were modified via incorporation of additional molecular recognition features that can π-stack and hydrogen bond. In their design, they use ribose as a scaffold for the construction of the nucleolipid structures. This synthetic approach enables the preparation of a large variety of nonionic [24], anionic [25], cationic [26], and zwitterionic [27,28] amphiphiles. As an example, the synthesis of zwitterionic nucleoside phosphocholine amphiphiles derived from uridine is shown in Scheme 1. This four-step strategy affords the phosphocholine uridine amphiphiles **5a** through **5e**.



Scheme 1 Synthetic scheme for zwitterionic nucleoside-based amphiphiles.

Barthélémy et al. reported that these nucleolipids possess unique properties [25,28,29] such as the formation of aggregates including vesicles and fibers. Additionally, this group can prepare hydrogels and organogels (Fig. 2). The first supramolecular systems obtained are promising in many aspects and could lead to new types of materials for transport of biomacromolecules (DNA, RNA, *si*RNA) [29,30].

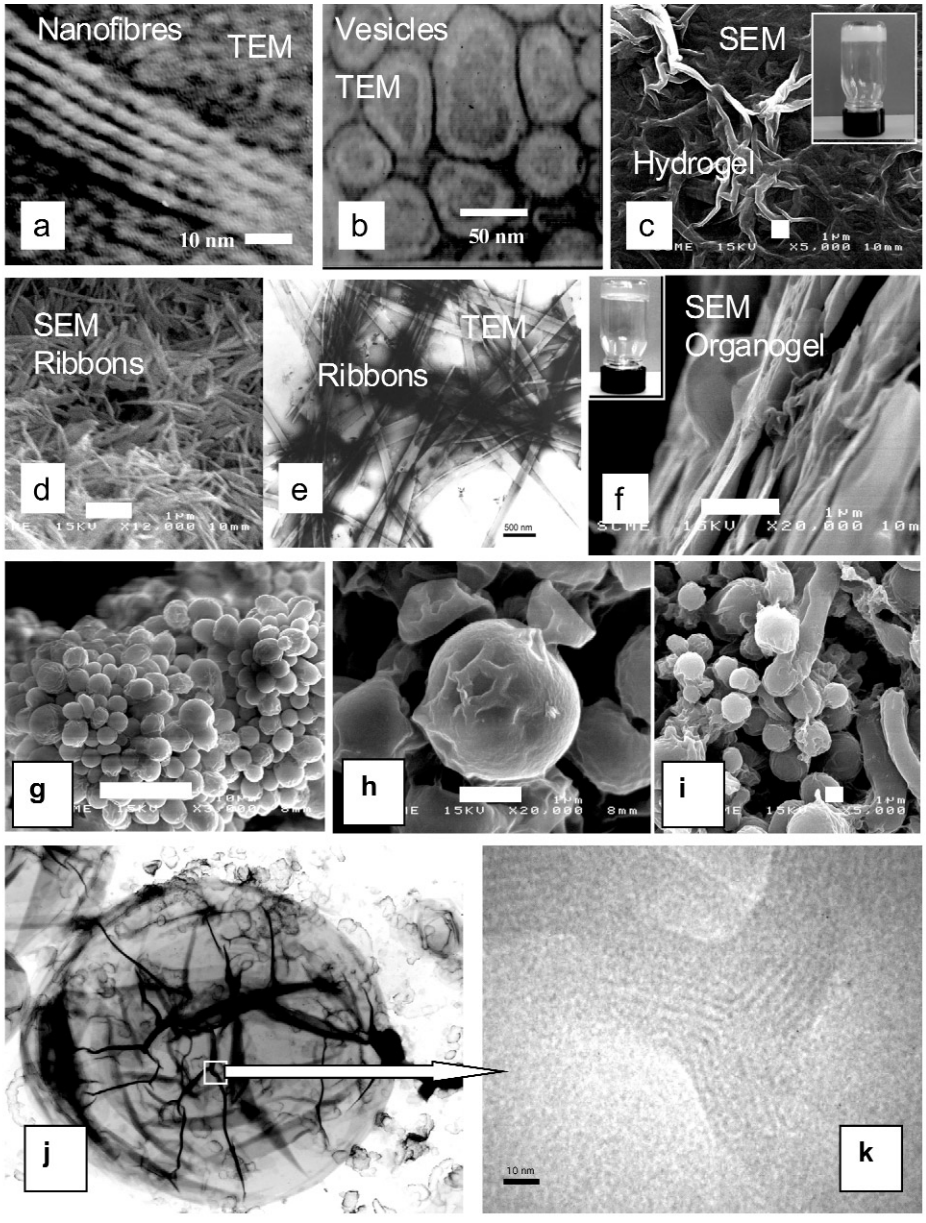


Fig. 2 Examples of electron microscopy images (TEM and SEM) showing nucleolipid self-assemblies: (a) nanofibers; (b) vesicles; (c) microfibers network; (d,e) ribbons networks; (f) lamellar phase in an organic medium; (g–j) microcapsules containing salts; (k) same microcapsules at the nanoscale fibers network.

Molecular design of peptide nucleic acids that influence supramolecular assemblies

PNAs, which mimic the molecular recognition functionalities found in DNA, are of widespread interest for numerous biochemical and biomedical applications [31]. PNAs are synthetic and achiral DNA mimics, in which the nucleic acid bases are attached to an achiral peptide backbone (see Fig. 3) [32]. Because of their high binding affinity to complementary DNA and RNA, this class of molecules has been often used as a probe in detection devices. Structures of PNA-DNA and PNA-RNA duplexes have

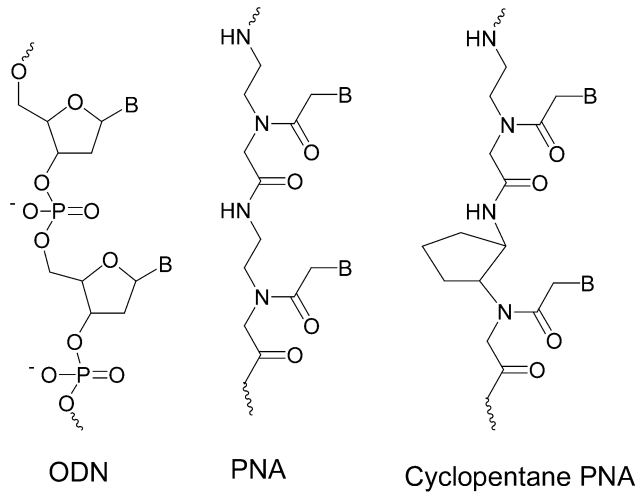


Fig. 3 Structures of ODN, PNA, and cyclopentane PNA (B = A, C, G, or T). The incorporation of a cyclopentane ring restricts the highly flexible backbone conformation of a PNA.

been intensively studied and characterized. In order to increase the PNA binding affinity for complementary oligonucleotides, and consequently improve their use for antisense properties or in a detection device, numerous PNA backbone modifications have been investigated during the last decade. Recently, Appella's group reported a novel modified PNA for detection purposes [33]. To enhance the oligonucleotide binding affinity, the authors introduced a *trans*-1,2-cyclopentane diamine into the PNA backbone. Such a molecular alteration influences the PNA-DNA supramolecular assemblies and induces a significant improvement in the binding properties of the resulting PNA to DNA and RNA. In his workshop presentation, Daniel Appella demonstrated that the sensitivity of these new PNA structures to binding DNA/RNA was improved by three orders of magnitude [34]. This work illustrates that chemical tuning of polynucleotide analogs can efficiently lead to useful applications in the development of DNA detection assays.

Polymerization of nucleotides in vesicles

It is well known that self-assemblies such as lipid vesicles can be used as drug delivery systems, but this type of aggregate is also under investigation as a nano- or micrometer-sized reaction chamber. In these experiments, the chemical substrates or reagents must enter the vesicle and undergo a chemical transformation. Thus, the permeability properties of the bilayer play a crucial role. Peter Walde from the Department of Materials at ETH Zurich described artificial systems that are capable of substrate transformation [35]. Several examples of chemical reactions were presented. In a recent and elegant study [36], Walde et al. demonstrated that nucleotide uptake by lipid vesicles is enhanced in the presence of sodium cholate. Furthermore, polynucleotide phosphorylase (PNPase), which is known to catalyze the synthesis of polynucleotide, was able to catalyze the polymerization of adenosine diphosphate (ADP) inside the vesicles. These experiments show that vesicles containing enzyme can be considered as nano- or microreactor for the production of nucleic acids. A schematic representation describing the ADP-uptake and polymerization is shown in Fig. 4.

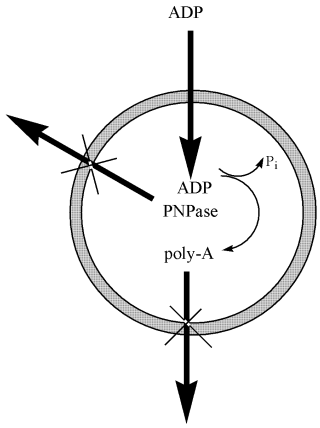


Fig. 4 Drawing showing the ADP uptake with vesicles containing the PNPase. Adapted from ref. [36].

Condensed DNA in lipid microcompartments

Nature provides numerous efficient systems capable of condensing DNA. For example, biological compartments such as the nucleus of eukaryotic cells or viruses are known to entrap high concentrations of nucleic acids. Among the numerous self-assemblies available, a recent study indicates that reverse micelles can provide an efficient environment capable of condensing DNA. This interesting study showing condensed DNA in lipid microcompartments was presented by Pasquale Stano, a collaborator of Pier Luigi Luisi (formerly at ETH Zurich), now at the Universita di Roma 3 in Rome [37]. The solubilization of DNA in the water pool provides information on the nature of the interactions of the DNA/lipid in a restricted compartment. Importantly, these investigations indicated that collapsed forms of DNA can be obtained in relatively simple systems such as reverse micelles. The DNA concentrations entrapped in these model supramolecular assemblies are similar to those found in biological systems.

Anisotropic dendrimer-like DNA

Beside the amphiphilic structures that mimic the molar recognition of nucleic acids, it is worthy to note that DNA molecules themselves possess many desirable chemical and physical properties as a polymeric material. Dan Luo and his group at Cornell University synthesized a branched Y-shaped DNA (Y-DNA), which was then assembled in a controlled fashion to form highly branched DNA materials (termed "dendrimer-like DNA") [38]. These unusual self-assembled DNA molecules can be either isotropic or anisotropic, providing the ability to link substrates, including proteins and inorganic particles. Moreover, the preparation of new DNA materials of defined composition and structure provides significant opportunities in the drug delivery, detection, and nanotechnology fields.

NUCLEIC ACID TRANSPORT

The transfer of DNA or RNA through biological membranes is a key step in the delivery of therapeutic or new genes to a host [39–41]. It has been known for some time that viruses can very efficiently transport nucleic acids across the cell membrane, however, their use as gene vectors is limited because of safety risks associated with their clinical application [42]. Consequently, there have been significant efforts to develop other transfection approaches, including the design, synthesis, and evaluation of nonviral gene-delivery systems (e.g., cationic lipids, polymers, and dendrimers) [43–49]. Since the discovery of *N*-[1-(2,3-dioleyloxy)propyl]-*N*,*N*,*N*-trimethylammonium chloride (DOTMA) as a cationic

transfecting agent [50], many cationic lipids have been explored for delivery of plasmid DNA [51,52]. The rationale for developing nonviral carriers, such as formulations based on synthetically prepared cationic lipids, stems from the need to improve the transfection activity and decrease the cytotoxicity. For this reason, numerous structural parameters have been altered and, today, a few cationic lipids are commercially available and used in the clinical setting [53]. In the second part of this special topic article, we shall present several recent examples involving supramolecular assemblies as a tool for nucleic acid transport. After a brief presentation of synthetic vectors, several aspects of the physicochemical properties and intracellular pathway of nonviral vectors complexes will be described. We will also present several approaches that aim to tune the physicochemical properties and biological activity of these synthetic vectors, including nanometric DNA particles coated with folic acid, cell-targeting systems, cationic fluorinated vectors, substrate-mediated DNA delivery, and charge-reversal amphiphilic vectors.

Nonviral gene delivery using synthetic vectors

Several structural parameters of nonviral self-assembling gene delivery systems have been explored, including altering the size and charge of the cationic polar head and the type of amphiphilic structure (e.g., bola amphiphile vs. linear polymer) [54]. Importantly, these vectors have also been evaluated and studied in terms of their biodegradability properties, nucleic acid release profiles, and targeting characteristics. Daniel Scherman's plenary lecture in Avignon underlined the different parameters that must be taken into account when cationic lipids/DNA complexes are prepared for transfection [55]. According to Scherman, efficient and successful nonviral gene transfer needs the optimization of the following steps: "preparation, purification and formulation of the therapeutic DNA and synthetic vector, plasmid administration, plasmid access to target cells, intracellular penetration, and then nuclear localization". His group has undertaken numerous studies on nonviral gene delivery, including (1) the development of plasmid DNA labeling systems by photoactivation, which can be used to conduct intracellular trafficking studies [56] and (2) the design of cationic lipids for a modulated release of DNA. The latter is based on the degradation of lipids during or after penetration into the cell. These strategies can improve DNA trafficking to the nucleus and increase transgenic expression [57].

Physicochemical properties and intracellular pathway of nonviral vectors

The mechanism(s) of DNA delivery with cationic synthetic vectors is complicated and not completely understood. However, the predominant mechanism appears to be endocytosis, which is common to cationic liposomes [58]. A proposed pathway involving nonviral vectors is shown schematically in Fig. 5, where the synthetic vector-DNA assembly is formed, transported across the cell membrane via endocytosis, the DNA is released from the endosome, enters the nucleus, and, finally, transcription. In this context, the structure of the cationic liposomes/DNA assembly, which enters the cell, has a significant impact on the efficiency of DNA delivery. Consequently, during the last 10 years, many groups have studied the physicochemical properties of cationic lipid/DNA complexes in an effort to determine which parameters are key for successful gene transfection. For example, it has been observed that the charge ratio of system (i.e., the positive charges of the vector to nucleic acid negative charges) plays a determinant role in the gene delivery. The optimal charge ratio for in vitro experiments is frequently greater than one, whereas the most efficient ratio tends to be closer to one for in vivo delivery systems [59,60]. Further contributions to this area reported by Lin et al. indicate that the membrane charge density, σ_M, of the cationic lipid-carrier (i.e., the average charge per unit area of the membrane) is a key universal parameter that controls the transfection efficiency of lamellar LC_α complexes in cell [61]. The stability of the synthetic vector-DNA assembly is also an important parameter for efficient gene delivery into cells. Indeed, this stability must be high enough to avoid the degradation when entering the plasma membrane, but low enough to allow the DNA dissociation and delivery, which is required for the internalization into the nucleus. Mély et al. have designed nonviral vectors that combine the favor-

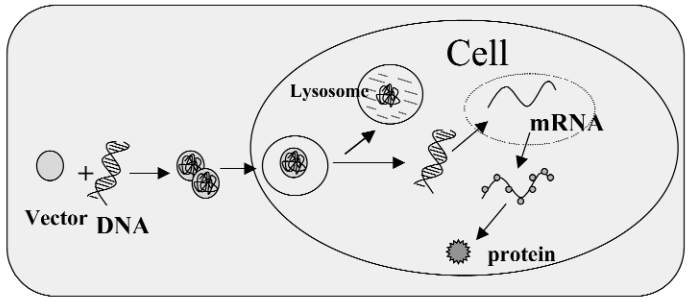


Fig. 5 The proposed pathway for DNA delivery using synthetic vectors, which includes: DNA-synthetic vector complexation, endocytosis, endosomal escape, nucleus entry, and, finally, transcription. Not drawn to scale.

able features of cationic surfactants and cationic lipids [62]. Yves Mely's presentation in Avignon focused on DNA/surfactant/lipids ternary complexes [63]. These small, homogeneous complexes were found to form packed lamellar structures differing from the usual lipoplex multilamellar organizations. Their high transfection efficiency was attributed to their internal structure, which prevents their dissociation by serum proteins. Such results nicely illustrate the importance of the physicochemical properties on the performance of the synthetic vector-DNA assemblies.

Directed assembly of DNA nanoparticles coated with folic acid

The size of the synthetic vector-DNA assembly has an impact on the intracellular trafficking, but also on the diffusion to the cells. Zuber et al. have recently reported a method for the monomolecular condensation of DNA that affords a monodisperse and stable population of particles. The technique developed relies on the condensation of DNA by cationic cysteine-based amphiphiles. The authors demonstrated that a synthetic DNA supramolecular assembly can be synthesized for gene delivery with specific diffusion and cell-recognition properties. Gene delivery with DNA nanoparticles coated with folic acid was the subject of the lecture given by Guy Zuber [64]. Such stable particles are able to enter cells via the folic acid receptor, indicating that the recognition of specific cells such as cancer cells can be realized for efficient plasmid transfection (Fig. 6) [65]. Likewise, Veronique Montero's communication further emphasized that a cell-targeting strategy for nonviral vectors can be achieved by linking specific ligands to liposome surface. Montero proposed bi-functional amphiphiles possessing sugar moieties as a tool to target the lectins present in breast cancer [66]. DNA could be entrapped in such chemical vectors and delivered in the expected cells.

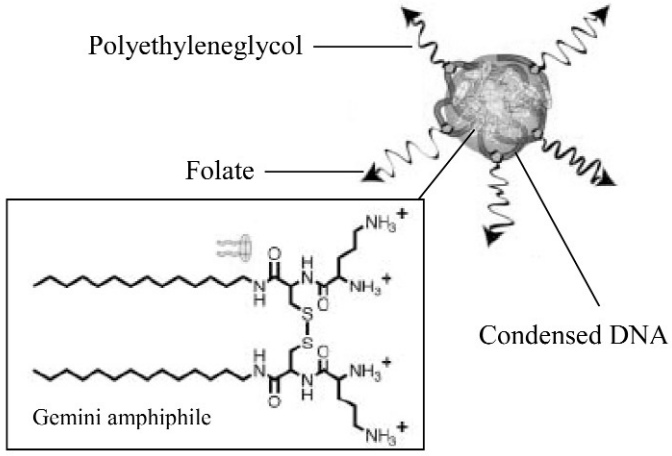


Fig. 6 Schematic representation of a nanometric DNA particle. The gemini amphiphile results from the oxidation of cationic cystein detergent. Particles are coated with a polyethyleneglycol–folate envelope. Adapted from ref. [65].

Cationic fluorinated vectors

Regarding the architecture of synthetic vectors, the composition and structure of hydrophobic chains have been altered to improve gene delivery efficiency. Of the varied modifications reported to date, the use of fluorinated hydrocarbon chains represents a novel approach. Fluorinated lipoplexes or assemblies prepared from DNA and highly fluorinated cationic and/or helper amphiphile lipids have been reported and studied by Pierre Vierling as transfection reagents [67]. Several examples of fluorinated structure and their corresponding analogs are presented in Fig. 7. The communication on fluorinated lipids, presented by Pierre Vierling in Avignon, highlighted the usefulness of fluorinated amphiphiles for nucleic acid transport [68]. The fluorinated amphiphiles described are efficient synthetic gene carriers and represent an alternative approach to the use of hydrocarbon analogs. Their noticeable transfection efficacy is attributed to the unique lipophobic and hydrophobic character of the fluorinated amphiphiles. Indeed, these features of the fluorinated assemblies prevent DNA degradation, compared to the hydrocarbon vector analog, as well as interactions with other lipophilic biomolecules [69].

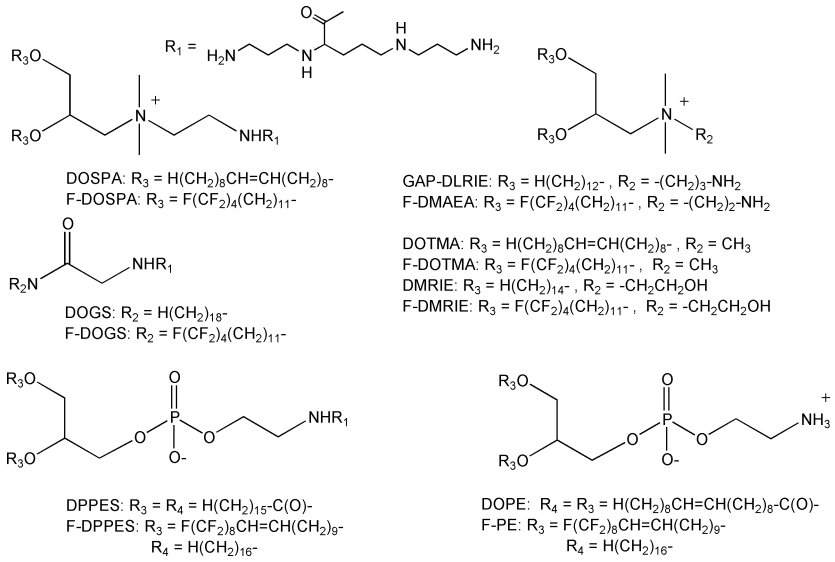


Fig. 7 Examples of structures and common names of the fluorinated and their corresponding conventional cationic and helper. Adapted from ref. [67].

DNA delivery: Vector and substrate

Different strategies involving nonviral vectors can be combined to overcome the barriers to effective gene transfer. The local DNA concentration in the cell microenvironment is known to effect gene transfer. In a recent study, Shea and his group at Northwestern University described a novel approach based on polymeric structures attached to a surface [70]. Indeed, the DNA delivery system developed combines two strategies in which cationic polymer/DNA complexes are immobilized to biomaterial surfaces that support cell adhesion placing DNA in close proximity to the cell. This substrate-mediated DNA delivery system offers a new way for DNA transport. Such a concept could find applications in many fields where localized gene delivery is important [71].

Charge-reversal amphiphiles for gene delivery

Cell entry of lipoplexes is a necessary step in the gene delivery pathway, but it is not the rate-determining step. In other words, not all of the nucleic acid that enters the cell arrives at the nucleus and is transcribed. Recently, Zabner et al. reported that the amount of gene expression was significantly lower than that of the level of endocytosis [72]. These results clearly indicate that the escape of nucleic acids from the endosome is one of the limiting factors in gene delivery. Consequently, significant amounts of the delivered nucleic acid is unable to escape from the endosomal compartments into the cytoplasm after entry. Grinstaff et al. have proposed the use of a functional synthetic vector system to overcome the DNA release barrier [73]. They synthesized an amphiphile that undergoes an electrostatic transition intracellularly from cationic to anionic (Fig. 8). This charge-reversal or -switchable amphiphile performs two roles: first, it binds and then releases DNA, and second, as an anionic multicharged amphiphile, it destabilizes membrane bilayers. Studies demonstrating the charge-reversal amphiphile concept were pedagogically presented by Mark W. Grinstaff [74]. High transfection efficiency was observed using these synthetic carriers compared to synthetic vectors such as DOTAP and Transfast.

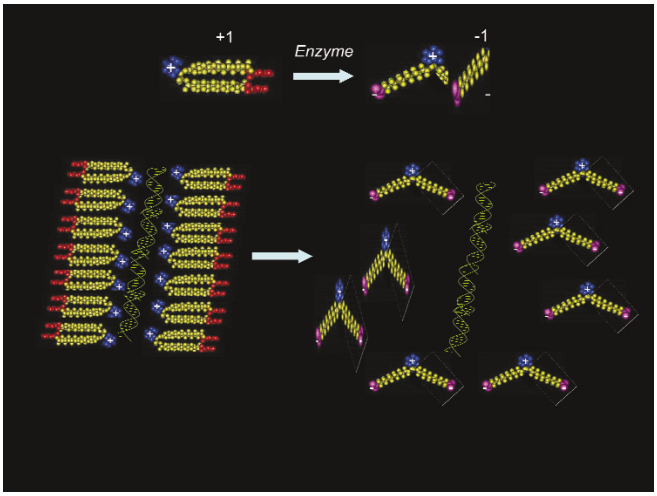


Fig. 8 Charge-reversal approach. Adapted from ref. [74].

CONCLUSION

In 2003, the scientific community celebrated the 50th anniversary of the elucidation by James Watson and Francis Crick of the structure of DNA as a double helix, using the X-ray fiber diffraction patterns obtained by Franklin, Wilkins, and their associates [75]. Based on this discovery and the chemical evidence on base complementary of Chargaff [76], it became clear that that information could be passed from one generation to the next via a semiconservative replication process. Since 1953, basic and applied research has led to numerous applications involving DNA including, for example, the possibility to modify or alter the genetic code of a living cell. In parallel to these research activities, the last 30 years have also seen another research breakthrough—supramolecular chemistry. The preparation of supramolecular structures resulting from the self-organization of molecules has provided the scientific community an additional approach to the preparation of complex structures. By mimicking and manipulating the molecular interactions found in natural supramolecular systems (DNA, lipidic bilayers, proteins, etc.) chemists have designed and synthesized a wide range of supramolecular assemblies. In a recent review [77], Jean Marie Lehn wrote that "The generation of a given superstructure through self-organization results, in its simplest form, from the operation of a single-code assembly program". It is clear that molecular information is one of the most important key parameters to be used in the design of novel complex systems. Importantly, such information or code can be used to create supramolecular architectures that are pleasing to the eye or those that are functional (e.g., vectors for transfection). The marriage of supramolecular chemistry with nucleic acids as illustrated through examples in this article will open new avenues for determining the relationships between molecular structure and properties and self-assembly. Indeed, the reliable prediction of supramolecular architectures involving noncovalent bonds remains one of the most difficult challenges in the field. Our ability to manipulate these systems for specific basic studies or applications (e.g., in medical, biotechnology, defense industries), at a level of control that is realized today with covalent chemistry, will enable the preparation of supramolecular assemblies of even greater complexity.

ACKNOWLEDGMENTS

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