University of Groningen

DNA-surfactant complexes

Liu, Kai; Zheng, Lifei; Ma, Chao; Goestl, Robert; Herrmann, Andreas

Published in:
Chemical Society Reviews

DOI:
[10.1039/c7cs00165g](https://doi.org/10.1039/c7cs00165g)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Liu, K., Zheng, L., Ma, C., Goestl, R., & Herrmann, A. (2017). DNA-surfactant complexes: self-assembly properties and applications. *Chemical Society Reviews*, 46(16), 5147-5172.
<https://doi.org/10.1039/c7cs00165g>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Cite this: *Chem. Soc. Rev.*, 2017, 46, 5147

DNA–surfactant complexes: self-assembly properties and applications

Kai Liu,^a Lifei Zheng,^b Chao Ma,^b Robert Göstl^{*c} and Andreas Herrmann^{†‡*b}

Over the last few years, DNA–surfactant complexes have gained traction as unique and powerful materials for potential applications ranging from optoelectronics to biomedicine because they self-assemble with outstanding flexibility spanning packing modes from ordered lamellar, hexagonal and cubic structures to disordered isotropic phases. These materials consist of a DNA backbone from which the surfactants protrude as non-covalently bound side chains. Their formation is electrostatically driven and they form bulk films, lyotropic as well as thermotropic liquid crystals and hydrogels. This structural versatility and their easy-to-tune properties render them ideal candidates for assembly in bulk films, for example granting directional conductivity along the DNA backbone, for dye dispersion minimizing fluorescence quenching allowing applications in lasing and nonlinear optics or as electron blocking and hole transporting layers, such as in LEDs or photovoltaic cells, owing to their extraordinary dielectric properties. However, they do not only act as host materials but also function as a chromophore itself. They can be employed within electrochromic DNA–surfactant liquid crystal displays exhibiting remarkable absorptivity in the visible range whose volatility can be controlled by the external temperature. Concomitantly, applications in the biological field based on DNA–surfactant bulk films, liquid crystals and hydrogels are rendered possible by their excellent gene and drug delivery capabilities. Beyond the mere exploitation of their material properties, DNA–surfactant complexes proved outstandingly useful for synthetic chemistry purposes when employed as scaffolds for DNA-templated reactions, nucleic acid modifications or polymerizations. These promising examples are by far not exhaustive but foreshadow their potential applications in yet unexplored fields. Here, we will give an insight into the peculiarities and perspectives of each material and are confident to inspire future developments and applications employing this emerging substance class.

Received 3rd March 2017

DOI: 10.1039/c7cs00165g

rsc.li/chem-soc-rev

1. Introduction

In recent years, the electrostatic interaction of surfactants (or lipids) and oppositely charged polymers has been the subject of extensive studies.^{1–6} Although complex formation between double stranded (ds) and single stranded (ss) DNA and cationic surfactants (or lipids) allows access to unique composite features, the interaction between biological macromolecules and surfactants has received only little attention when compared

to the efforts undertaken with fully synthetic polymers. Complexation of DNA and surfactants, for example, leads to spontaneous formation of highly organized assemblies induced by their molecular shape and weak intermolecular interactions, such as van der Waals and dipolar forces.^{7–10} The inherent structural flexibility of these complexes can lead to a variety of scientific and technological pursuits. On the one hand, gene delivery approaches have exploited lyotropic liquid crystal formation between cationic lipids and DNA.^{11,12} These promising complexes are easy to mass-produce and less immunogenic than viral vectors with comparable function. On the other hand, the investigation of DNA function in a water-free environment expands the use of DNA outside of the conditions traditionally dictated by nature particularly benefiting the many technologies that are incompatible with aqueous systems, such as high- and low-temperature applications.¹³ Introducing phase changes by temperature is achieved by employing DNA–surfactant solvent-free liquid crystalline materials^{14,15} allowing the development of flexible and printable DNA electronic components where water

^a State Key Laboratory of Rare Earth Resource Utilization, Changchun Institute of Applied Chemistry of Chinese Academy of Sciences, 130022, Changchun, China

^b Zernike Institute for Advanced Materials, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands. E-mail: a.herrmann@rug.nl

^c DWI – Leibniz Institute for Interactive Materials, Forckenbeckstr. 50, 52056 Aachen, Germany. E-mail: goestl@dwI.rwth-aachen.de

[†] Present address: DWI – Leibniz Institute for Interactive Materials, Forckenbeckstr. 50, 52056 Aachen, Germany.

[‡] Present address: Institute of Technical and Macromolecular Chemistry, RWTH Aachen University, Worringergweg 2, 52074, Aachen, Germany.

is detrimental for device performance. From a fundamental perspective, solvent-free DNA-surfactant liquid crystals enable the manipulation of ordering and fluidity possibly altering or creating new ensemble properties, such as improved mechanical behaviour significantly distinct from DNA lyotropic liquid crystals or dissolved DNA systems. Moreover, research examining the solvent-free and solid-state properties of DNA-surfactant films is also gaining momentum, owing to its relevance to biomaterials-inspired drug delivery.¹³ Concomitantly, dried bulk films are characterized by lower nuclease degradation, fewer barriers to long term storage, and allow localized delivery by direct implantation in combination with controlled release and dosage adjustment. Meanwhile, DNA-surfactant films are starting to reveal their importance beyond bioengineering and medical applications in the fields of nano- and optoelectronics.^{16,17} While additionally most investigations of DNA-based chemical/enzyme reactions are currently limited to aqueous environments, neutralization of the charge on the DNA by surfactants provides a hydrophobic coating that can shuttle DNA into an organic phase.¹⁸ This allows the exploitation of DNA-surfactant complexes as versatile and general scaffolds for DNA functionalization in the organic phase.

In this review, we outline seminal and recent research in this exciting field introducing DNA and its properties, while specifically focusing on the self-assembly behaviours of DNA-surfactant and DNA-lipid complexes and eventually discussing advantages and disadvantages of these complexes in various applications from biomedicine to bioelectronics.

2. Overview of DNA-surfactant complexes

2.1 DNA

The existence of deoxyribonucleic acid (DNA), nowadays known to carry the hereditary information of all living cells, was uncovered by Miescher in 1869.¹⁹ Almost a century later, in 1953, Watson and Crick succeeded in elucidating the double-stranded helical structure of DNA.²⁰ Today we know that DNA is a stable polymeric biomacromolecule, consisting of 2'-deoxyribose, phosphate groups, and nitrogenous heterocyclic nucleobases, which are linked together linearly. In nature, four nucleobases are present in DNA; the pyrimidines adenine (A) and guanine (G) and the purines thymine (T) and cytosine (C). Each polynucleotide is characterized by a specific nucleobase sequence, conventionally written in the direction from the 5'-end to the 3'-end of the sugar phosphodiester backbone. In the double-stranded state, they pair in two by the natural Watson-Crick pairing G:C and A:T (Fig. 1a), and form the hydrophobic centre of the helix. DNA exhibits a highly hydrophilic surface due to the negatively charged phosphate groups rendering DNA soluble in water and buffered aqueous solutions. In the most common structure of DNA, the B-form,²¹ the bases are generally oriented perpendicular to the macromolecular axis with a helix periodicity of *ca.* 10 base pairs, equivalent to approximately 3.4 nm, while the diameter of the bare DNA is *ca.* 2 nm. Double-stranded DNA is characterized by a distinct melting point at which one

Fig. 1 Representation of DNA helix, building blocks and DNA nanoobjects. (a) Structure of B-type DNA duplex,²⁴ A-T and G-C base-pairs and structures of the four nucleosides, deoxyadenosine, deoxythymidine, deoxycytidine and deoxyguanosine. (b) DNA oligonucleotides with programmed sequences self-assemble into 2D and 3D wireframe structures like a cube.²⁵ Adapted with permission from ref. 24, Copyright 2011 Royal Society of Chemistry and ref. 25, Copyright 2003 Macmillan Publishers Ltd.

double-strand separates into two single strands – a phenomenon that is highly dependent on the GC content,²² the number of base pairs and therefore on the length of the DNA strands as well as the surrounding buffer and salt concentrations. Therefore, DNA strands have extraordinary specificity, as they can recognize and bind to complementary partner strands in very dilute solutions. This specific binding of DNA is a result of a combination of diverse forces such as electrostatic repulsion of the charged hydrophilic phosphate backbone, van der Waals forces and base stacking or π - π interactions in the hydrophobic core and hydrogen bonding between nucleobases.

Nowadays, oligonucleotides (short DNA strands) can be routinely fabricated by employing automated synthesizers using phosphoramidite building blocks²³ with lengths larger than 100 nucleotides (100 mers) of a defined nucleotide sequence. Moreover, solid phase synthesis technology is suitable to incorporate unnatural monomers as well and hence the development of synthesis and modification procedures²⁴ contributed significantly to the understanding of the physical properties and biological function of DNA. At the same time, synthetic DNA has played an important role in nanotechnology. For example, folding DNA strands into well-defined structures of different geometries was pioneered by Seeman.²⁵ In an early study, branched DNA molecules were employed to form specific motifs (small building units with specific sticky ends) that could further self-assemble into 2D and 3D structures (Fig. 1b). These properties render DNA a very appealing material for use in various fields,^{26–33} including drug and gene delivery, molecular computing, biosensors, and even photoelectric and micro-electronic devices.

2.2 Ionic self-assembly of DNA-surfactant complexes

Self-assembling hierarchical and supramolecular materials have attracted considerable attention among researchers interested in obtaining architectures with novel properties and functions.^{34–37} Generally, functional and structural properties of self-assembled structures are altered by controlling intermolecular forces for non-covalent tethering, *e.g.* the manipulation of π - π interactions, van der Waals forces, ionic forces or hydrogen bonding. In this vein, an ionic self-assembly strategy driven by Coulomb forces was recently introduced to produce supramolecular materials.^{38,39} Specifically, the addition of charged surfactants to oppositely charged poly- and oligoelectrolytic species yielded nanostructured bulk materials in a cooperative process. The modular assembly strategy allows introducing organic and inorganic electrolytes of varying size, charge, molecular weight and functionality into hybrid architectures.^{40–42}

As for any other surfactant-polyelectrolyte pair,^{43,44} the complexation of cationic surfactants and DNA occurs at a very low concentration (the critical aggregation concentration), which is usually a few orders of magnitude lower than the critical micelle concentration of the surfactant. This can be attributed primarily to the strong electrostatic interactions between the surfactant and the phosphate groups of DNA.^{45,46} As shown in Fig. 2, the binding between the surfactant and DNA follows a two-step process: first, binding of a surfactant molecule to an isolated phosphate site on the DNA strand and secondly, a

Fig. 2 The cooperative binding of DNA and surfactants by electrostatic interaction.⁵⁰ The interactions of surfactants (depicted as micelle) and the helical DNA result in rod-like (right) or spherical structures (left). Adapted with permission from ref. 50, Copyright 2000 Royal Society of Chemistry.

highly cooperative binding event enabled by the hydrophobic interactions between the alkyl chains of the surfactant.⁴⁷ The phase diagrams of DNA-cationic surfactant systems show a strong associative behavior.⁴⁸ The phase separation starts at very low concentration of DNA or the surfactant and is enhanced as the alkyl chain length of the surfactant increases. Consequently, different kinds of soft matter aggregates,⁴⁹ such as viscous liquids, gels, liquid crystalline phases and precipitates, may form at or above the critical aggregation concentration, depending on the DNA concentration and other properties of the system (such as salinity, hydrophobicity as well as backbone rigidity of DNA, and tail length as well as head-group structure of the surfactant).⁵⁰

The interactions of cationic surfactants with DNA have been studied extensively and changes of the hydrophobic moiety of the surfactants affect their complexation with DNA considerably. The surfactant cetyltrimethylammonium bromide (C16, CTAB), for example, binds more readily to DNA than dodecyltrimethylammonium bromide (C12, DTAB),⁴⁸ leading to formation of a precipitate at lower concentrations for CTAB than for DTAB. The interactions of surfactants with DNA can also be tuned efficiently by controlling the head-group structure.^{51,52} For instance, negatively charged and non-ionic surfactants will not associate directly with DNA. Moreover, it has been observed that increasing the hydrophobicity of the surfactant⁵³ by, for example, addition of an aromatic ring between the head group and the tail results in an effect similar to increasing the surfactant chain length. Modifications of the head group through the introduction of a hydroxyl substituent can lead

to other, more subtle changes in the interactions between DNA and the surfactant.⁵⁴ Counterions in the form of salts can also be added causing complicated, either stronger or weaker, effects on the phase behaviour depending on the experimental conditions. Generally, oppositely charged macro-ions in solution attract each other and tend to form a bound complex. When separated, each macro-ion is surrounded by a diffuse layer of spatially confined counterions. Upon approach, the fixed macro-ion charges partially, and sometimes fully, neutralize each other, releasing mobile counterions into the bulk solution, thereby increasing their translational entropy. This scenario suggests that macro-ion association in solution is an entropically driven process and cannot readily be described by the Coulomb-interaction of two isolated charges.⁵⁵ Therefore, the actual contribution of the counterion entropy to the free energy of association, and hence the self-assembly process, depends on the detailed geometries and charge distributions of the separated and bound macro-ions.^{55–58}

3. Lyotropic liquid crystals of DNA–surfactant and DNA–lipid complexes

The lyotropic liquid crystalline (LLC) behaviours of DNA–surfactant and DNA–lipid complexes in aqueous solution have been investigated very thoroughly. The earliest structure presented, known as the bead-on-a-string structure, consists of liposomes attached to DNA strands.^{59,60} Electron microscopy studies revealed a variety of features including oligo lamellar⁶⁰ and tube-like structures, indicating lipid bilayer-covered DNA.^{61,62}

Detailed X-ray diffraction investigations have been carried out on complexes of dsDNA and mixtures of cationic lipids,^{63–65} such as DOTAP (dioleoyltrimethylammonium propane) or DMTAP (dimyristoyltrimethylammonium propane) and neutral lipids, such as DOPC (dioleoyl phosphatidylcholine) or DOPE (dioleoyl-phosphatidylethanolamine), unravelling the structural consequences of the phase transitions: in aqueous solution, the complexes exhibit optically birefringent LLC phases originating from a multi-lamellar structure with alternating lipid bilayer and DNA monolayers (Fig. 3a). There are no trans-bilayer positional correlations of the DNA strands when the bilayers are in the L_α fluid phase and the DNA chains confined between the bilayers form a 2D smectic phase.⁶⁶ However, at low temperatures, when the bilayers are in the L_β phase and hence more rigid,⁶⁷ positional correlations develop across the bilayers and a 2D rectangular lattice of dsDNA emerges. Concomitantly, replacing the neutral lipid DOPC with cosurfactant DOPE in the complex⁶⁸ changes the mesophase from a multi-lamellar structure (L_α) (Fig. 3a) into an inverted hexagonal (H_{II}) liquid-crystalline phase induced by DOPE's negative curvature (Fig. 3b). In addition, a similar structural transition to the hexagonal (H_I) phase was achieved as a function of increasing ratio of hexanol (a membrane-soluble cosurfactant) to DOPC reducing the membrane bending rigidity.

In the Safinya group, a new type of highly charged (>16 charges), multivalent cationic lipid with a dendritic head group

Fig. 3 Schematic representation of four representative LLC structures of dsDNA–lipid complexes. (a) Structure of the lamellar phase (L_α) with alternating lipid bilayers and DNA monolayers.⁶⁸ (b) Structure of the inverted hexagonal phase (H_{II}), composed of DNA inserted within inverse lipid tubules, which are arranged in a hexagonal lattice.⁶⁸ (c) Structure of the hexagonal phase (H_I), where the large dendritic cationic lipid head group leads to the formation of rod-like lipid micelles arranged on a hexagonal lattice with DNA inserted within the interstices with honeycomb symmetry.⁶⁹ (d) Structure of the double gyroid cubic phase (Q_{II}) in water.⁷³ It consists of two intertwined but not interpenetrating water channels (blue and orange) that are separated by a lipid bilayer (grey) surface. Adapted with permission from ref. 68, Copyright 1998 The American Association for the Advancement of Science, ref. 69, Copyright 2006 American Chemical Society, and ref. 73, Copyright 2013 Royal Society of Chemistry.

(MVLBG2) was synthesized for the study of DNA–lipid self-assembly.⁶⁹ Complexes of dsDNA with mixtures of MVLBG2 and DOPC exhibit novel dual lattice structures. In the H_I phase, DNA rods surround the hexagonally arranged tubular lipid micelles forming a three-dimensional continuous substructure with honeycomb symmetry (Fig. 3c). Furthermore, a series of multivalent lipids with dendritic head groups from MVLG2 (4+), MVLG33 (8+), MVLBiG1 (8+), to MVLBiG2 (16+) were used to investigate the influence of the head group charge on the DNA–lipid structures.⁷⁰ It was found that the lamellar phase, hexagonal phase (H_I) and disordered hexagonal phase of DNA–lipid complexes coexisted with hexagonally ordered dsDNA bundles at different molar ratios of dendritic lipids and DOPC. Interestingly, the study revealed that the formed LLC structures of DNA–lipid complexes are responsive to environmental changes when a multivalent lipid with a disulfide bond is introduced.⁷¹ In a reducing environment the disulfide bridges are cleaved to thiols allowing the rearrangement from the lamellar (L_α) structure into a loosely organized phase including a separated phase of DNA bundles.

Recently, very short dsDNA strands with non-pairing overhanging end groups were complexed with DOTAP and DOPC.⁷² The interplay of shape anisotropy and DNA end-to-end

interactions for short dsDNA with single-stranded oligothymine (T) overhangs causes nematic ordering while the 11 base pair (bp) DNA rods with 5 and 10 T overhangs remain in an isotropic phase. When the overhangs are decreased to 2 T, a 2D columnar nematic phase with finite-length columns forms. Additionally, the complexation of 5 bp short dsDNA with dTdT overhangs, glycerol monooleate (GMO) and DOTAP resulted in a gyroid cubic structure (Fig. 3d).⁷³ The change of the DNA end structure ("sticky" overhangs, no overhang (blunt) and "non-sticky" overhangs) allows phase transition between the gyroid cubic structure and the hexagonal phase. These results offer new possibilities for the design of LLC stacking of anisotropic rods in lipid-based complexes.

Besides DNA complexes based on cationic lipids,¹² zwitterionic lipids have been employed to confine DNA into a multilamellar LLC phase^{74,75} yielding DNA–DNA in-plane correlation depending on the preparation conditions. Dawson and Rädler further investigated the self-assembly behaviour of DNA–zwitterionic lipid complexes in the presence of divalent cations (Ca^{2+})⁷⁶ finding that a dsDNA–dipalmitoyl phosphatidylcholine–calcium complex exhibits a rectangular columnar phase (Fig. 4a),⁷⁷ which had been observed in cationic DNA–DMPC–DMTAP complexes previously.⁶⁷ When a gemini lipid was introduced into the DNA–DMPC complex, Caminiti and co-workers discovered dsDNA trans-bilayer ordering in the rectangular columnar phase.⁷⁸ Increasing the temperature results in rearrangement of this highly ordered LLC phase into a simple rectangular phase dissipating this trans-bilayer structure (Fig. 4b).

Fig. 4 Schematic representation of the rectangular columnar phase of dsDNA–lipid complexes. (a) Arrangement of DNA in a complex composed of DNA, zwitterionic lipid and calcium ions (Ca atoms not shown) in which a rectangular columnar phase of DNA was present.⁷⁷ (b) The structure evolution of the DNA ordering within a DNA–gemini lipid–DMPC complex as a function of temperature.⁷⁸ At low temperature, DNA arranged into a centred rectangular columnar phase between interdigitated lipid bilayers (i). With increasing temperature, DNA formed a simple rectangular DNA lattice (ii). At higher temperature, the trans-bilayer coupling disappeared and only a lamellar phase with in-plane DNA–DNA positional correlation was observed (iii). Adapted with permission from ref. 77 and 78, Copyright 2004 and 2007 American Chemical Society.

Furthermore, a series of nucleolipids derived from nucleobases have been synthesized to be combined with DNA.^{79–81} Besides electrostatic and hydrophobic interactions in this type of DNA–lipid complexes, additional hydrogen bonding and π – π stacking capabilities were introduced to further modulate the interactions between DNA and the synthetic lipid. For instance, uridine-based nucleolipids including DOTAU (*N*–[5′-(2′,3′-dioleoyl)-uridine]-*N*′, *N*′, *N*′-trimethylammonium tosylate) and DOUPC (*O*-ethyl-dioleoylphosphatidylcholinium-uridine) were complexed with DNA and the obtained DNA–lipid LLC samples arrange into L_α phases.^{82,83} SAXS analysis indicated that the DNA(polyA)–DOTAU complexes exhibit a more compact layer structure than DNA(polyA)–DOTAP due to tighter association between the uracil base of DOTAU and adenine of the DNA(polyA) strand. Additionally, neutral and anionic nucleolipids have been developed for the formation of DNA–lipid complexes, where the driving forces are phosphate–sugar and nucleobase–nucleobase interactions.^{84–87}

Apart from these complexes, there have been many structural studies involving nucleic acids combined with other alkylmethylammonium bromides, including dodecyltrimethylammonium bromide (DTAB), cetyltrimethylammonium bromide (CTAB), didodecyltrimethylammonium bromide (DDAB), dioctadecyltrimethylammonium bromide (DIAB), decyltrimethylammonium bromide (ETAB), tetradecyltrimethylammonium bromide (TTAB) and some gemini bis(quaternary ammonium) surfactants.^{88–92} In 1992, Minsky and co-workers systematically investigated DNA packing within DNA–surfactant complexes by X-ray scattering.⁹³ A regular 2D hexagonal packing (H_I) of dsDNA–TTAB and dsDNA–CTAB was proposed, where DNA is interspersed between surfactant aggregates. Mel'nikov *et al.* confirmed the 2D hexagonal structure for DNA–CTAB complexes⁹⁴ based on the first two diffraction peaks, which have a spacing ratio of $1/3^{1/2}$. A multilamellar structure was also determined by small-angle X-ray scattering (SAXS) in DNA–DIAB complexes.^{65,94} Based on these experimentally observed structures, a number of theoretical calculations have investigated the interactions and structures of the DNA–surfactant complexes in more detail.^{95–100}

The addition of a co-surfactant, such as hexanol, to a CTAB solution is known to alter the phase structure by decreasing the spontaneous curvature of the surfactant aggregates transforming them from cylinders to bilayers.¹⁰⁰ Moreover, short-chain alcohols substantially lower the bending rigidity of bilayers¹⁰¹ indicating that co-surfactants significantly influence the structure of these complexes. Alongside, re-entrant phase transitions and the formation of two hexagonal structures H_I and H_{II} driven by variations in the DNA and hexanol concentrations in CTAB–DNA–hexanol complexes were observed.^{102,103} When mixing sodium 3-hydroxy-2-naphthoate (SHN) in the dsDNA–CTAB system, the DNA–CTAB–SHN complexes exhibit a hexagonal phase at low SHN concentration, whereas at high SHN concentrations the complex transitions into a lamellar structure with intercalated DNA sublayers.¹⁰⁴

The Chu group used different cationic surfactants (CTAB or DDAB) and the zwitterionic surfactant 1-palmitoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (PHGPC) with DNA to study the self-assembly properties.¹⁰⁵ The complexes of dsDNA and

double-tail DDAB formed a bilayered lamellar structure, whereas the complexes between dsDNA and single-tail CTAB preferred a structure of 2D hexagonal closed-packed cylinders. The ssDNA-CTAB complex forms a cubic structure due to the different stiffness of dsDNA and ssDNA. The addition of PHGPC to the dsDNA-CTAB induced a structural transition from a 2D hexagonal to a multi-bilayered lamellar structure. In the DNA sublayers, the DNA-DNA spacing depends on the ratios of CTAB to PHGPC and CTAB to DNA, respectively.

Recently, Lindman and co-workers investigated the self-assembly behaviour of a ternary system, which included dsDNA-DTAB, water, and a non-ionic surfactant (dodecyl tetraethylene glycol, $C_{12}EO_4$; or dodecyl octaethylene glycol, $C_{12}EO_8$).¹⁰⁶ The supramolecular assemblies evolve from a 2D hexagonal structure to a lamellar phase as the concentration of the non-ionic surfactant is increased. In the lamellar phases, short $C_{12}EO_4$ separates in the DTAB layer. Thereby, the DTAB head group interacts with the dsDNA while the $C_{12}EO_4$ head group protrudes into the aqueous reservoirs (Fig. 5a). However, when $C_{12}EO_8$ with a longer non-ionic head group is incorporated into the ternary system, a fully swollen mesophase of $C_{12}EO_8$ coexists, wherein the ethylene oxide moieties are present within the DNA-DTAB layers (Fig. 5b). Lindman and co-workers also reported that the DNA-DTAB complex can form various LLC phases in the

presence of lecithin.^{107,108} With lecithin as the co-surfactant a lamellar phase, a reverse hexagonal phase, and a bi-continuous cubic phase were developed (Fig. 5c). However, when the volume of the hydrophobic part of the surfactant was increased by changing single-chained DTAB with a double-chained DDAB, the dsDNA-DDAB-lecithin complex formed only the lamellar and hexagonal phases.¹⁰⁹ This indicates that DNA-surfactant systems can be tuned into different self-assembled LLCs by varying the hydrophobicity of the surfactant or by adding a co-surfactant.

4. Thermotropic liquid crystals of DNA-surfactant complexes

In addition to the study of LLC behaviours of DNA-surfactant complexes in solutions, solvent-free thermotropic liquid crystal-line (TLC) structures were recently investigated in our own group.^{14,15} Complexation of nucleic acids with cationic surfactants containing two long aliphatic chains followed by dehydration was shown to be a generally applicable scheme for the production of DNA-surfactant TLCs.¹⁴ For example, an oligonucleotide (22 mer ssDNA) and the cationic surfactant dimethyldioctylammonium bromide (DOAB) were complexed in a simple procedure, including

Fig. 5 LLC behaviour of dsDNA-surfactant complexes in the presence of a co-surfactant. Schematic depictions of the intercalated lamellar structures of the DNA-DTAB- $C_{12}EO_4$ complex (a) and the DNA-DTAB- $C_{12}EO_8$ complex (b) in aqueous solution.¹⁰⁶ In a, $C_{12}EO_4$ units (green) are penetrated in the DNA (blue) sublayer. In b, all $C_{12}EO_8$ units are incorporated into the DNA-DTAB lamellar layers. (c) Schematic illustration of the transformation of the LLC structures found in the DNA-DTAB-lecithin system.¹⁰⁸ Adapted with permission from ref. 106, Copyright 2009 American Chemical Society and ref. 108, Copyright 2011 Royal Society of Chemistry.

a final lyophilisation step to remove any excess water. The solvent-free ssDNA–DOAB complex was birefringent, viscous and did not solidify at room temperature. Investigation of the thermal properties indicated the presence of a TLC phase between -7 and 41 °C. The typical focal-conic textures characteristic of smectic order were observed on cooling from isotropic to the mesophase and SAXS measurements indicated long-range ordered smectic layers of the ssDNA–DOAB TLC. In this lamellar phase, ssDNA sublayers are alternately intercalated between aliphatic hydrocarbon sublayers (Fig. 6a). Each repeating layer consists of a cationic surfactant bilayer that electrostatically interacts with an anionic oligonucleotide sublayer. Within the ssDNA sublayer, the oligonucleotide chains of ssDNA were randomly packed within the sublayer without any positional or orientational order. Freeze-fracture transmission electron microscopy (FF-TEM) neatly visualizes the topography of the TLC lamellar structure revealing long-range ordering between the flat and smooth layer surfaces of the ssDNA–DOAB TLC separated by distinct and continuous steps (Fig. 6b). In addition, TLCs from ssRNA–DOAB were fabricated following the same complexation procedure.¹⁴

The lengths of the ssDNA and surfactant's alkyl chains are extremely important in tuning the TLC physical properties of the complexes.¹⁵ To elucidate this effect, a series of TLC materials were prepared by electrostatic complexation of single-stranded oligonucleotides (6 mer, 14 mer, 22 mer, and 50 mer) with a single type of cationic surfactant (dioctyldimethylammonium bromide (DOAB), didecyldimethylammonium bromide (DEAB) and didodecyldimethylammonium bromide (DDAB)) or with a two-component mixture of surfactants (DOAB + DEAB, DOAB + DDAB, and DEAB + DDAB). SAXS measurements indicate characteristic long-range ordered lamellar structures with sharp first-order reflection peaks and the following harmonics. Employing surfactants bearing longer alkyl chains clearly leads to a

modulation in the TLC layer spacing as expressed through a shift of the first-order reflections. In the ssDNA–DDAB complex, an isotropic–smectic-modulated smectic phase (Sm_{mod}) sequence was found. While at higher temperatures the SAXS data revealed a normal smectic phase, cooling below 50 °C gave rise to a subsidiary satellite peak close to the smectic layer reflection peaks indicating additional periodicity perpendicular to the layer normal (Fig. 6c). This feature was identified as an in-plane layer undulation, which can be clearly confirmed by FF-TEM. Modulated crests and troughs are aligned alternatively on the fractured surfaces and propagate along different layers without disruption of the smectic lamellar structure (Fig. 6d). The binary (or ternary) DNA–surfactant complexes are proven to be thermally stable over a wide range of temperatures until decomposition sets in at about 200 °C. The phase transition temperatures for these complexes can be controlled over an extremely broad range yielding fluid DNA at temperatures as low as -20 °C, allowing the transition from crystalline to liquid crystalline up to 65 °C and from liquid crystalline to isotropic between 41 °C and 130 °C. Notably, we found a correlation between the phase-transition temperatures and the length of the surfactant alkyl chains. When the aliphatic chain length of the surfactant was increased in the binary (or ternary) complexes, the melting and clearing points were generally increased. Moreover and as confirmed by rheology measurements, the viscosity of the ssDNA–surfactant TLCs increases with the alkyl chain lengths of the surfactants. These new solvent-free ssDNA–surfactant TLCs have negligible volatility, exhibit high DNA content and are thermally stable up to 200 °C rendering them suitable for a variety of technological applications incompatible with aqueous systems, such as those relying on comparably high and low temperatures.

5. Bulk film materials of DNA–surfactant complexes

In addition to self-assembly in soft phases, such as the liquid crystals described earlier, DNA–surfactant complexes can be aligned in bulk films fabricated by casting the materials from organic solvents. In that respect, Okahata and co-workers developed an oriented DNA–surfactant film consisting of cationic surfactant *N,N,N*-trimethyl-*N*-(3,6,9,12-tetraoxadocosyl)ammonium bromide mixed with dsDNA.¹¹⁰ Following their protocol, freeze-dried poly-ion complex precipitates can be obtained that are soluble in organic solvents, such as chloroform, benzene or ethanol, but not in aqueous buffered solution. A free-standing water-insoluble DNA film was prepared by drop-casting and was stretched to produce oriented dsDNA strands with their axes aligned along the stretching direction (Fig. 7a). The alignment was verified by X-ray diffraction measurements. Upon stretching in addition to the circular reflection at 41 Å, diffractions on the equator of 41 Å and on the meridian of 3.4 Å were observed. Heeger and co-workers¹¹¹ obtained comparable results fortifying the notion of parallelly aligned DNA strands to the stretching direction of the film and the base pair stacking perpendicularly to

Fig. 6 TLC behaviour of ssDNA–surfactant complexes.¹⁵ (a) Proposed lamellar structure of DNA–surfactant TLC. The lamellar bilayer structure consists of a sublayer of ssDNA and an interdigitated sublayer of the surfactants. (b) Lamellar structure fractures visualized by FF-TEM. (c) Proposed modulated lamellar structure of ssDNA–surfactant TLC and (d) the corresponding FF-TEM image. Adapted with permission from ref. 15. Copyright 2015 John Wiley & Sons, Inc.

the DNA strand direction even further. When the stretched film was dried, only the diffraction peaks on the equator at 41 Å were retained, but no diffraction on the meridian for the base pairs. This suggests that the orientation of the base pairs does not remain perpendicular to the stretching direction although the DNA strands stay aligned. Additionally, a comparable procedure was reported for the production of aligned RNA-surfactant films.¹¹² Okahata and co-workers introduced the Langmuir-Blodgett (LB) method to align a dye-intercalated dsDNA-surfactant complex.^{113,114} Employing this procedure, DNA strands are either

uniformly oriented by vertical dipping or randomly oriented by horizontal lifting of the substrate.

Recently, Wu and co-workers reported the self-organization of DNA into honeycomb structures on solid substrates by simple solution casting of a dsDNA-ditetradecyldimethylammonium (DTDA) complex at high relative humidity (Fig. 7b).¹¹⁵ The honeycomb structure results from self-assembly of the complex due to condensation of water droplets in a particular pattern at the interface of the film and surrounding air. The morphology of the microporous structures can be adjusted by slightly

Fig. 7 Self-assembly of DNA-surfactant complexes in bulk films. (a) Schematic diagram of a stretchable DNA-surfactant film with aligned DNA helices.^{110,112} The film was cast on a Teflon plate, and the solvent was evaporated slowly under saturated vapour at room temperature (i). The as-cast film (ii), the stretched film of the DNA-lipid complex in water moisture and its DNA packing (iii), and the stretched DNA-lipid film in the dry state (iv) are shown. The DNA strands in as-cast films were found to align with respect to each other in both wet and dry states as the film was stretched. (b) Honeycomb-patterned DNA-surfactant films cast on a glass substrate under a moist airflow.¹¹⁵ Characterization of the microstructure via SEM (i and ii) and AFM (iii-v). (c) Schematic structure of a DNA-DDAB film indicating the structural change that takes place upon wetting and drying the film.¹¹⁹ Adapted with permission from ref. 110, 115 and 119, Copyright 1996 and 2009 American Chemical Society and ref. 112, Copyright 2002 John Wiley & Sons, Inc.

changing the concentration of the DNA-complex solution. Notably, the choice of solvent for film casting has a significant effect on the regularity of the honeycomb structure owing to differences in evaporation rates. These self-organizing honeycomb structures are promising architectures for potential applications in biosensors, optical and optoelectronic devices.^{115–118}

In addition to their static properties, the response of DNA-surfactant complex films to humidity and temperature has been investigated thoroughly. In that respect, the Tirrell group discovered that a film composed of DNA and the cationic surfactant DDAB exhibits structural switching between dsDNA-DDAB in the solvated state and ssDNA-DDAB in the dry state (Fig. 7c).¹¹⁹ Generally, the double-stranded structure of DNA is prevalent in aqueous media primarily because the hydrophobic core consisting of π -stacked bases is stabilized by hydrogen bonds overcoming the repulsion of the charged phosphate groups in the DNA backbone.¹²⁰ However, when the aqueous environment is exchanged for a less polar solvent, such as isopropanol, the H-bond interactions between the nucleobases weaken leading to a comparatively destabilized double helix. A similar process is responsible for the separation of the dsDNA into two single strands upon complexation with DDAB in a dry film: the cationic surfactant DDAB is bound to the DNA through electrostatic interactions and is thus forced to undergo a structural transition exposing the hydrophobic bases to the tails of the surfactant. This process disrupts the surfactant bilayer with interdigitated alkyl chains and causes the formation of a surfactant monolayer (Fig. 7c). In this arrangement, the hydrophilic head group of the surfactant monolayer interacts with the phosphate backbone of the DNA while the surfactant alkyl chains bind to the bases of the ssDNA. Once the DNA-DDAB film is hydrated at a relative humidity level of at least 60%, the two complementary DNA strands hybridize quickly and structural reorganization is observed.¹²¹ In addition, the melting temperature of DNA complexed in the wet film is slightly lower and spans a wider temperature range than that of pristine DNA in solution, presumably due to the presence of DDAB.

6. Applications of DNA-surfactant complexes

To date, self-assembled DNA-lipid complexes have been mainly investigated in bulk films and as liquid crystals. In both states the respective materials exhibit well-defined structures, high structural stability and easy processability thereby allowing diverse potential applications ranging from optoelectronics to biomedicine and therapeutics.

6.1 Bulk film materials and applications based on DNA-surfactant complexes

6.1.1 Electrical conductivity of bulk DNA-surfactant complex films. There is considerable interest in using DNA as a building block for molecular electronics and computation.^{122–126} Although it is experimentally proven that pristine DNA is an insulator,^{127,128} DNA's complementary strand recognition and helical structure are

outstandingly useful as a 1D matrix material to study anisotropic charge transport. To this effect, Okahata and co-workers have investigated the anisotropic conductivity of DNA-surfactant films prepared by mechanical stretching to align the dsDNA strands.^{110,112–114} When a 2000 bp DNA film was put on a comb-shaped electrode with the DNA helices aligned perpendicular to the Au electrodes, a large current was observed with a conductivity in the range of 10^{-5} S cm⁻¹ (Fig. 8a).^{129,130} In stark contrast, when the film was placed with DNA strands aligned parallel to the two electrodes, electrical conductivity was several orders of magnitude lower with only 10^{-9} S cm⁻¹. Non-stretched DNA films (dsDNA strands oriented randomly in the film plane) exhibited a conductivity of 10^{-7} – 10^{-8} S cm⁻¹. These measurements hint towards the notion that DNA films conduct current more efficiently along the DNA helical axis than in a perpendicular orientation. It should be noted that the internal charge transport might be caused by ion movement within the DNA-surfactant complex, where the transport efficiency is related to the DNA helical structure and orientation.¹³¹

When longer DNA (30 000 bp, *ca.* 10 mm length) was employed in measurements with DNA aligned perpendicularly to the electrodes, the stretched DNA film yielded large ohmic currents (0–0.7 mA) that increased linearly with an increase of the applied voltage in the range of ± 0.5 V. The conductivity was calculated to be in the range of 10^{-3} S cm⁻¹ (Fig. 8b).¹³² In contrast, DNA films prepared from short DNA molecules (500 bp, *ca.* 0.2 mm length) resulted in comparably small conductivities around 10^{-6} S cm⁻¹. Additionally, temperature-dependent conductance experiments of the DNA-surfactant films revealed that above 60 °C the conductivity drastically decreased by several orders of magnitude, though reversible upon cooling. The thermal conductivity characteristics can be explained by reversible changes in the intramolecular stacking of nucleobases within the double stranded DNA of the aligned films. Similar anisotropic conductivity was observed for DNA films prepared by the LB method, in which 200 mer dsDNA-surfactant monolayers were deposited on the same comb-shaped electrode by vertical dipping.¹³³ The electric current along the DNA strands was *ca.* 300 times larger than that in the cast-stretched film. A possible explanation for this phenomenon is that an improved contact between electrodes and films is warranted by this method of preparation: DNA strands were directly deposited on Au electrodes when using the LB method, while the DNA-surfactant cast film was mechanically pressed on the electrode surface.

Beyond the mere directionality of conductivity, photo-induced electron transfer mediated by intercalated dye molecules within the double helix of aligned DNA films was investigated.^{127,134} Acridine orange intercalated between base-pairs and aligned perpendicularly to DNA strands in the film gave rise to a large photocurrent when DNA strands were again aligned perpendicularly to the two electrodes (Fig. 8c). Photocurrents increased linearly with increasing voltage indicating that the photogenerated electrons pass through stacked base-pairs of the aligned DNA strands in the film.

6.1.2 Optical properties of bulk DNA-surfactant complex films. Besides their electrical properties, the optical and optoelectronic properties of DNA-surfactant films are also

Fig. 8 Anisotropic electric conductivity of oriented DNA-surfactant films. (a) Dark currents for aligned 2000 bp DNA-surfactant films on comb-type electrodes at 25 °C.¹²⁹ DNA double helices in the film were orientated perpendicular to the two electrodes and were measured under ambient conditions (i), the same film measured in a vacuum (ii), and DNA strands in the film were placed parallel to the electrodes both in a vacuum and under ambient conditions (iii). (b) Direct currents of aligned DNA films on a comb-type electrode at 25 °C in a dry box.¹³² (i) The film prepared from long DNA (10 mm, 30 000 bp) and (ii) from short DNA (0.2 mm, 500 bp). In both films the DNA was aligned perpendicularly to the two electrodes. (c) Photoinduced currents for aligned DNA films in which acridine orange intercalates between base-pairs.¹²⁹ (i) At 0.01 V, (ii) 0.05 V, and (iii) 0.1 V applied voltage on comb electrodes with DNA strands aligned perpendicularly to the two electrodes. (iv) DNA strands in the film oriented parallel to the two electrodes at 0.1 V. Pulsed light above 380 nm was irradiated from a 150 W xenon lamp at 25 °C. Adapted with permission from ref. 129, Copyright 1998 American Chemical Society and ref. 132, Copyright 2001 Royal Society of Chemistry.

important for their application. The optical properties of DNA-surfactant films are mainly dependent on parameters, such as the type of surfactant, the length of the DNA or the amount of incorporated dyes. DNA films generated from quaternary ammonium-based surfactants, particularly cetyltrimethylammonium chloride (CTMA), exhibit high transmission in the near infrared and visible region of the spectrum.^{135,136} The refractive indices of these thin films vary broadly with wavelength but remain constant in the range of 1000–1250 nm (slightly > 1.526) rendering them low-loss optical materials.¹³⁷ The films are thermostable up to temperatures of 200 °C while retaining an electrical resistance of 10–105 GΩ suggesting that DNA-CTMA is an appealing candidate for optical waveguides and optical cladding in nonlinear electro-optic modulators. Furthermore, Ogata and co-workers prepared a series of dye doped DNA-surfactant films (Fig. 9a),¹³⁸ which exhibit high transparency from 300 to about 1000 nm with good processability for multilayer integration into large-area optoelectronic devices. Interestingly, these films were also found to be thermo-extensive, *i.e.* they elongate upon heating, over a temperature range of 100 to 148 °C.

In regard to fundamental photophysical behaviour, DNA-surfactant complexes were used to prevent decreasing fluorescence with increasing dye concentration attributed to various effects summarized as concentration quenching. By utilizing DNA-surfactant complexes as a matrix to separate dye molecules, the formation of dye aggregates and excitation deactivation by collisions are largely inhibited warranting high fluorescence efficiencies even at high dye concentrations.^{136,139,140} For example, the fluorescent dye 4-[4-(dimethylamino)styryl]-1-dodecyl pyridinium bromide (DMASDPB) was doped into a DNA-CTMA complex.¹³⁶

While fluorescence intensity still decreased with increasing dye concentration, a significantly higher emission was recorded when blended in the DNA-CTMA complex as compared to blending in a poly(methyl methacrylate) (PMMA) matrix. This effect was even more pronounced employing rare earth (Eu) complexes leading to an emission intensity amplification of two orders of magnitude. Additionally, relaxation times in the DNA-CTMA film were found to be twice as long as compared to PMMA films, suggesting a peculiar structural confinement of the dye in the DNA-CTMA matrix.

In turn, Choi and co-workers investigated the absorption and fluorescence characteristics of DNA-CTMA and PMMA thin films doped with (*E*)-2-(2-(4-(diethylamino)styryl)-4H-pyran-4-ylidene)malononitrile (DCM).¹³⁹ Notably, they found that the fluorescence intensity of the DCM-doped DNA increases up to a dopant concentration of 10 wt%, while in PMMA the photoluminescence intensity diminishes already at only 3 wt% of the dopant. Moreover, and in stark contrast to the PMMA blend, the emission maximum did not undergo a bathochromic shift characteristic of aggregate formation with increasing dye concentration while blended in DNA-CTMA. Together, these results clearly indicate that DNA accommodates and separates the DCM molecules more efficiently than PMMA.

Moreover, the conjugated polymer poly(fluorenevinylene) containing alkyl chains with terminal quaternary ammonium groups (Q) was complexed with DNA to prevent aggregation of the π -conjugated system.¹⁴⁰ Due to efficient compartmentalisation leading to reduced conformational relaxation and thus reduced excitation deactivation, the fluorescence lifetime of Q was considerably increased from the picosecond to the nanosecond range. Owing to their steric restrictions, DNA-surfactant complexes can

Fig. 9 Optical properties of DNA-surfactant bulk films. (a) Photographs of a series of DNA-surfactant films and functional-dye-doped DNA-surfactant films.¹³⁸ (b) Photoluminescence spectra of the ternary Cz-DNA-PVP film bearing 11.4 wt% PVP and its mixtures with DCM dye.¹⁴² (i) Cz-DNA-PVP (PVP, 11.4 wt%), (ii) Cz-DNA-PVP (PVP, 11.4 wt%) doped with 0.3 wt% DCM, (iii) Cz-DNA-PVP (PVP, 11.4 wt%) doped with 5.0 wt% DCM, (iv) Cz-DNA-PVP (PVP, 4.2 wt%) doped with 5.0 wt% DCM, and (v) Cz-DNA-PVP (PVP, 11.4 wt%) doped with 5.0 wt% DCM. Tuneable colours from blue, orange to red were achieved, indicating cascade energy transfer from the Cz moieties to the DCM molecules through the PVP units. CTMA: cetyltrimethylammonium, CP: cetylpyridinium, BDMA: benzyldimethylcetylammmonium, DMSDBP: 4-[4-(dimethylamino)styryl]-1-dodecyl pyridinium bromide, Cz: carbazole, PVP: pyrenylvinylene-phenylene, DCM: (E)-2-(2-(4-(diethylamino)styryl)-4H-pyran-4-ylidene)malononitrile. Adapted with permission from ref. 138, Copyright 2001 American Chemical Society and ref. 142, Copyright 2009 John Wiley & Sons, Inc.

furthermore be used as effective scaffolds for fluorescence resonance energy transfer (FRET).^{141,142} Choi and co-workers prepared a DNA complex accommodating two different fluorophores in the surfactant side chains – carbazole (Cz) and pyrenylvinylene-phenylene (PVP). They found that an inclusion of only 2.2 wt% PVP in the ternary complex suffices to induce excitation transfer to the Cz moiety. This is a remarkable improvement when compared to the simple solution host-guest system of the two dyes, which does not yield any recordable energy transfer below 11.4 wt% PVP.¹⁴² More interestingly, when DCM was doped into the Cz-DNA-PVP complexes, tuneable emission colours from blue over orange to red can be realized due to cascade energy transfer from the Cz to the DCM moieties through PVP as the transmitter unit (Fig. 9b).

Concomitantly, dye-doped DNA-surfactant complexes have been studied for applications in lasing. Ogata and co-workers reported a DNA-CTMA film blended with Rhodamine 6G that was pumped by a nanosecond 532 nm laser beam.¹⁴³ Though it was not clear whether the dye was completely intercalated or groove-bound, light amplification as well as linewidth narrowing were observed over a certain threshold energy. Following up on this idea, the Grote group created distributed feedback (DFB) lasing structures that consist of a grating etched into an SiO₂-Si wafer substrate with a DNA-CTMA/sulforhodamine 640 (SRh) dye layer.¹⁴⁴ They found that both the output energy and the line-width of the emission peaks of the DFB structure are considerably more responsive to changes in the pumping energy than the planar structure implying improved lasing capabilities of the dye in DNA as compared to the reference PMMA sample. Lopez and co-workers studied the optical gains of lasing in dsDNA-CTMA/DCM composites.¹⁴⁵

The optimal amplification density was observed at ≈ 2.5 wt% of DCM while excitation quenching occurred at higher concentrations. Amplified spontaneous emission (ASE) and lasing in a two-layer system composed of a DNA-CTMA/Rhodamine 6G layer superimposed on a periodic surface relief grating structure were investigated and compared.¹⁴⁶ The signal intensity of the emitted light increased considerably faster than the ASE. These studies indicate that DNA intercalation and minor groove binding of fluorescent dyes are efficient supramolecular structures for potential lasing applications.

Due to the versatility and easy processability of DNA-surfactant complexes, their nonlinear optical properties have been investigated for use in optical communication systems. Grote and co-workers succeeded in preparing a DNA-CTMA thin film containing a DR1 chromophore on indium tin oxide-coated glass. An electro-optic coefficient of 2.13 pm V^{-1} at $\lambda = 633 \text{ nm}$, which is comparable to the value for a PMMA film with the same concentration of DR1, was achieved.¹³⁶ In nonlinear optics, second- and third-harmonics were generated in ternary DNA-surfactant complexes.¹⁴⁷ It was found that the second-harmonic generation signals were very weak, due to the absence of any orientation of the dye molecules owing to the DNA double-helical structure. The third-order nonlinear susceptibility values are increased compared to a cured epoxy resin matrix, which can be attributed to the better dispersion of the dye molecules in the DNA-surfactant matrices implying that the intercalation of dye molecules into DNA-surfactant complexes promotes charge migration and nonlinear optical activities.¹⁴⁸ Besides, nonlinear optics can be utilized to study the electronic, vibrational, electrostatic and chiral characteristics of DNA at surfaces, interfaces and in its native state.¹⁴⁹ An understanding

of these properties is crucial for tracking DNA recognition events in real time and for learning about specific molecular kinetics.

6.1.3 Optoelectronics with bulk DNA-surfactant complex films. Organic light-emitting diodes (OLEDs) containing DNA-surfactant complexes have been fabricated, which led to significant enhancement of luminance and device efficiency over conventional device structures.^{150–153} A DNA-CTMA complex shows a large band gap (4.7 eV) and a high dielectric constant, which may function as an electron blocking layer (EBL) in OLEDs.¹⁶ Significantly enhanced electroluminescence (EL) is obtained by fabricating green- (Alq₃, tris-8-hydroxyquinoline aluminum) and blue-emitting ((NPD, *N,N*-bisnaphthalene-1-yl)-*N,N*-bisphenylbenzidine) OLEDs with a DNA-CTMA complex as EBL (Fig. 10a). The luminous performances of the blue and green OLEDs with and without the DNA-CTMA electron-blocking layer are compared in Fig. 10b. The energy level diagram in Fig. 10b intuitively confirms that DNA-CTMA acts as an EBL in the device. Similarly impressive results have been reported in quantum dot-LEDs (QD-LEDs),¹⁵⁴ where the dsDNA-CTMA complex acts as a combined hole

transporting and electron-blocking layer (HTL/EBL). In that device arrangement, a high external quantum efficiency ($\approx 4\%$), high brightness ($\approx 6580 \text{ cd m}^{-2}$), low turn-on voltage ($\approx 2.6 \text{ V}$) and significantly improved colour purity were achieved for QD-LEDs. Concomitantly, the material combination of DNA with Cz-modified CTMA was utilized as a host for a phosphorescent material (Ir(Cz-ppy)₃) in OLEDs.¹⁵⁵ Efficient energy transfer from the DNA-Cz host to the metal-to-ligand charge transfer (MLCT) band of Ir(Cz-ppy)₃ was observed leading to significantly improved OLED efficiency when the electron transport compound PBD (5,4-*tert*-butylphenyl-1,3,4-oxadiazole) was co-doped into the phosphorescent light-emitting layer. The maximum luminance was raised from 244 cd m^{-2} to 1135 cd m^{-2} , and the maximum luminous efficiencies were up to 3.41 cd A^{-1} .

Kobayashi and co-workers produced an even more sophisticated, colour-tuneable OLED device composed of a DNA/polyaniline/Ru(bpy)₃²⁺ complex.¹⁷ In this device, red-emitting DNA/polyaniline/Ru(bpy)₃²⁺ acts as the hole transporting layer while green-emitting Alq₃ was chosen as the electron transporting layer (Fig. 10c). With

Fig. 10 OLED studies involving DNA-surfactant complexes. (a) DNA-CTMA complex working as an electron blocking layer (EBL) in OLEDs increases device luminous efficiency and luminance as evidenced by photographs of electroluminescence emission.¹⁶ (i) Green Alq₃ baseline OLED at 25 V (707 mA cm^{-2} , 590 cd m^{-2} , 0.35 cd A^{-1}). (ii) Green Alq₃ OLED with DNA-CTMA EBL at 25 V (308 mA cm^{-2} , 21100 cd m^{-2} , 6.56 cd A^{-1}). (iii) Blue NPD baseline OLED at 20 V (460 mA cm^{-2} , 700 cd m^{-2} , 0.14 cd A^{-1}). (iv) Blue NPD OLED with DNA-CTMA EBL at 20 V (200 mA cm^{-2} , 1500 cd m^{-2} , 0.76 cd A^{-1}). (b) Luminance vs. current density plot in green Alq₃ and blue NPD EL devices with and without DNA-CTMA EBL. The inset shows an energy level diagram in a green-emitting OLED structure with DNA-CTMA EBL. (c) Current density vs. voltage relationship and photographs of an OLED prepared from a DNA/polyaniline/Ru(bpy)₃²⁺ complex as the hole transporting layer and Alq₃ as the electron transporting layer, with inset showing the OLED structure.¹⁷ The luminescence colour changed dramatically with increasing voltage above the bias voltage of 5 V. (d) The corresponding EL spectra and the International Commission on Illumination emission coordinates at various voltages. Adapted with permission from ref. 16 and 17, Copyright 2006 and 2010 AIP Publishing LLC.

increasing electric field the colours of the emitted light changed from green (5 V) over yellow (14 V) and orange (16 V) to red (18 V). The corresponding EL spectra and the International Commission on Illumination emission coordinates at various voltages are shown in Fig. 10d. In-depth experiments indicated that the shift in the carrier recombination region is responsible for the observed effects as it increases with the applied voltage: at low voltage, the hole mobility of the DNA/polyaniline/Ru(bpy)₃²⁺ complex layer was superior to the electron mobility of the Alq₃ layer and thus recombination occurred mainly in the Alq₃ layer. As the voltage and hence the electric field increase, the electron mobility of the Alq₃ layer likewise increases rapidly and the electrons can move through the interface and recombine with the holes in the DNA complex layer. This results in a continuous shift in the recombination region from the Alq₃ layer to the DNA/polyaniline/Ru(bpy)₃²⁺ complex layer allowing multi-colour emission in this OLED structure.

Furthermore, Sotzing and co-workers reported electrospun DNA-CTMA nanofibers doped with the dye coumarin 102 as a FRET-donor and 4-(4-dimethylaminostyryl)-1-dodecylpyridinium bromide as a FRET-acceptor.¹⁵⁶ Efficient energy transfer between both components was observed, even at low loading levels of the FRET-acceptor. The emission wavelength was controlled by varying the donor-acceptor ratio shifting the fluorescence from blue over orange to pure white. Moreover, solid-state LEDs were coated with white-light-emitting DNA-CTMA-based nanofibers. By changing the total dye loading from 1.33 to 10% in the DNA-CTMA matrix, the LED colour temperature could successfully be tuned from cool white to warm white.

Simplistically, OLED devices can be regarded as inverse Grätzel cells which enable the photovoltaic process, *i.e.* the transformation of light energy into electric energy. Therefore, it is expected that DNA-surfactant complex-containing photovoltaic devices might have comparably favourable properties as their OLED counterparts. For example, double-stranded calf-thymus DNA and the nucleobase adenine were employed as hole transporting materials in a dye sensitized nanocrystalline TiO₂ solar cell.¹⁵⁷ The short circuit currents were found to be two and four times larger for calf-thymus DNA and adenine cells, respectively, compared to their non-DNA containing counterparts. Notably, the stability of adenine-based devices was found to be higher than those prepared from calf-thymus DNA as double strands tend to degrade under prolonged light exposure. Concomitantly, Jin and co-workers reported a solar cell in which a DNA-CTMA complex was employed as a hole injection layer to replace the commonly used PEDOT:PSS.¹⁵⁸ These solar cells exhibited rectifying behaviour in the dark and solar energy conversion occurred under illumination by a 300 W projector lamp. However, further characterization of such devices is necessary to confirm the utility of DNA-CTMA as a hole injection layer in organic solar cells.

In this section, we showed that DNA-surfactant complexes gain more and more importance for incorporation into optoelectronic devices including OLEDs and solar cells due to their favourable material properties,^{150,151,153} such as good temperature stability, a wide HOMO/LUMO band-gap, low optical absorption, low optical scattering losses and mechanical robustness.

Notably, DNA molecules are subjected to enormous electrical fields.^{159,160} However, DNA-surfactant complexes are polyelectrolytes, which might be sensitive to external electric fields. The DNA-surfactant complexes are thus likely to undergo internal structure changes or degradation due to cleavage of the electrostatic bonds between DNA and the surfactant. These processes may even lead to their migration in the devices and hence diverse problems in terms of long-term stability still need to be resolved. It is thus thinkable that research efforts will be directed to evaluate and better understand material properties of various DNA-surfactant complexes in devices ultimately leading to improved performance in their desired applications.

6.1.4 Drug and gene delivery with bulk DNA-surfactant complex films. Beyond potential bioelectronic and optical applications, DNA-surfactant complexes are successfully employed for drug and gene delivery. Bulk DNA-surfactant complexes are characterized by long term *in vivo* stability of the DNA component and subsequently can recover biological activity once wetted.¹³ These materials contain a high local concentration of the therapeutic nucleic acid agent and hence the study of bulk DNA-surfactant structures is developing into an exciting field for drug and gene delivery applications. Tirrell and co-workers recently simulated a drug release system by employing an ethidium bromide-labelled DNA-DDAB film.¹²¹ When exposed to a buffer solution, such as PBS, electrostatic screening of the DNA-complex' charges led to disassembly of the film in a layer-by-layer fashion releasing ethidium bromide. It is thus reasonable to expect the film to disassemble easily *in vivo* and to act as a drug delivery vehicle or DNA depot.

Similarly to ethidium bromide, anticancer drug molecules, such as daunorubicin and doxorubicin, also intercalate into DNA inhibiting the enzyme topoisomerase II and prevent the DNA from duplication in fast-replicating cells.¹⁶¹ These drugs are potentially useful in DNA-surfactant films as they could be incorporated into the complex and then locally elute after implantation upon film degradation, either through nuclease action or ion replacement. In this fashion, a drug delivery system was realized by blending the DNA-surfactant complex with poly(lactide-*co*-glycolide) and the drug daunorubicin.¹⁶² The complex was obtained by casting a film from DMSO/CHCl₃ solution and subsequent incubation into an aqueous solution of daunorubicin with drug loading being controlled by immersion time. The pharmaceutically active payload was released from the films after introduction into PBS and the release rate was dependent on the chemical structure of the surfactants. These results clearly indicate that a film of the three components – DNA, surfactant and PLGA – is a promising matrix for anti-cancer drug delivery.

In addition, cationic polymers have been used to complex DNA for drug and gene delivery applications, including local gene delivery to cells and vascular delivery from stent coatings.^{163–165} Venkatraman and co-workers reported the release and transfection efficiencies of plasmid DNA-lipofectamine complex films.¹⁶⁶ The release was observed to be comparably slow but could be accelerated considerably by the addition of gelatine creating

pores in the polymer film. Alongside, it was found that transfection of the released plasmid DNA was more efficient than that of naked DNA presumably owing to the more compact form of the DNA-lipofectamine complex.

Layer-by-layer (LBL) deposition of polyelectrolytes is a convenient and well-established method for the incorporation of natural and synthetic polyelectrolytes into thin nanostructured assemblies¹⁶⁷ and hence an ideal method to generate thin DNA-polymer films.¹⁶⁸ In this regard, multi-layered polyelectrolyte films fabricated from plasmid DNA and a polycation were utilized to achieve localized transfection of cells without the aid of a secondary transfection agent.¹⁶³ Though the specific mechanisms through which cells interact with these materials and internalize incorporated DNA remain to be elucidated, it was deemed possible that the employed polycationic polymer contributes considerably to the condensation, internalization and expression of plasmid DNA.

Overall, materials bearing surface-tethered DNA complexes represent an attractive framework for the local or non-invasive delivery of DNA from the surfaces of implants or biomedical devices. Various cationic polymers, such as poly(lysine), poly(histidine), polyethyleneimine and poly(amidoamine), can be employed to form complexes with DNA for use in gene delivery applications.^{169–171} In that way, major improvements to transfection efficiency and sustained delivery could be realised.^{172–175} However, for an eventual breakthrough in clinical applications the major barriers for cell transfection, including endosomal escape and penetration into the nucleus, still need to be overcome by clever molecular design and synthesis.

6.2 Soft phase materials and applications based on DNA-surfactant complexes

6.2.1 Lyotropic liquid crystals and gene delivery based on DNA-surfactant complexes. In Sections 2 and 3, it was shown that DNA-surfactant complexes spontaneously assemble into distinct lyotropic liquid crystalline phases whose nanoscale structures can be probed with various techniques including synchrotron X-ray diffraction spectroscopy as performed by the group of Safinya and others. As shown in Fig. 3, the prevalent lamellar phases stem from dsDNA that is sandwiched between cationic membranes (L_α),⁶⁸ the inverted hexagonal phase with DNA encapsulated within inverse lipid tubes (H_{II})⁶⁸ and the more recently discovered H_I phase⁶⁹ with hexagonally arranged rod-like micelles surrounded by DNA chains, which form a continuous substructure with honeycomb symmetry. These liquid crystalline phases play a particularly important role for applications in gene delivery and gene silencing as well as for ongoing clinical gene therapy efforts worldwide. As synthetic non-viral delivery systems, DNA-surfactant complexes initially have been investigated for gene transfection by Felgner and co-workers.⁶⁰ They discovered that transfection efficiencies (TEs) employing these materials are significantly higher than those for other chemical delivery systems, such as anionic liposomes with encapsulated DNA, calcium phosphate precipitation or polycationic reagents (DEAE-dextran or polylysine).

Alongside, Safinya and co-workers undertook elegant efforts developing new DNA-surfactant complexes for gene therapy studies, in particular to understand the correlation between the transfection mechanism and internal DNA-surfactant structural characteristics for improving TE.^{176–180} In a series of comprehensive studies, the TE was indeed found to be structure dependent. Notably, it was found that the membrane charge density (σ_M) is a universal parameter, which is predictive of the TE in lamellar DNA-surfactant complexes.^{181,182} For this study, a series of multivalent surfactants (MVLs) were synthesized allowing the systematic variation of the charge from MVL²⁺ to MVL⁵⁺. The complexation between DNA, cationic MVLs and neutral DOPC led to the formation of lamellar structures (L_α). In the mesophases, the membrane charge density was varied by changing the amount of neutral DOPC while keeping the amount of DNA and cationic MVLs per sample constant.

As shown in Fig. 11a, the universal TE curve of lamellar complexes exhibits three well-defined regimes. Regime I (dark grey), corresponding to low σ_M , features an exponential increase in efficiency over three orders of magnitude. Regime III (light grey), corresponding to high σ_M , is characterized by a decrease in efficiency with increasing σ_M suggesting that electrostatic interactions impede successful DNA delivery by lamellar DNA-surfactant complexes. These two effects antagonize each other in intermediate characteristic regime II (white) as the region of optimal charge density exhibiting the highest TE. This characteristic identifies σ_M as a universal parameter, *i.e.* a predictor of TE, for transfection by lamellar DNA-surfactant complexes.¹⁸¹

The TE data in combination with results obtained from confocal microscopy for low and high TE complexes interacting with cells¹⁸² suggest a model of cellular uptake of lamellar complexes depicted schematically in Fig. 11b. An increase in σ_M (regime I) enhances fusion between the cationic membranes of lamellar complexes (trapped in endosomes) and anionic endosomal membranes facilitating the release of complexes to the cell cytoplasm. However, a very large σ_M (regime III) inhibits cationic membranes from efficiently releasing anionic DNA upon cell entry after endosomal escape giving rise to the optimal σ_M (regime II) observed in experiments.¹⁸¹ In contrast, the inverted hexagonal phase of a DNA-DOTAP-DOPE complex⁶⁸ exhibits high TE even at low σ_M (independent of σ_M) due to its distinct mechanism of cellular entry relying on the fusogenic properties of DOPE.^{182,183} This has rendered DOPE a popular choice as a co-surfactant for DNA complexes. In addition, other hexagonal mesophases (H_I and disordered H_I) of DNA-MVLBG2-DOPC complexes showed enhanced transfection efficiency deviating from the universal bell curve observed for lamellar complexes (Fig. 11a).^{69,70} This suggests a new, yet still unclear mechanism of action for these dendritic DNA-surfactant complexes.

Recently, the Safinya group investigated the effect of cholesterol and steroids on the TE of the lamellar DNA-DOTAP-DOPC complex.¹⁸⁴ Addition of cholesterol with 15 mol% yielded 10-fold TE improvement and similarly other steroids with alkyl tails also strongly enhanced TE. However, charge density variation does not cause these improvements. In fact, the reduction of the

Fig. 11 Gene transfection applications based on liquid crystals being composed of DNA-surfactant complexes. (a) Transfection efficiency (TE) as a function of the membrane charge density σ_M for lamellar DNA-surfactant complexes.¹⁸¹ TE data for the hexagonal complex (open circles) deviate from the universal curve, indicative of a different transfection mechanism for the inverted hexagonal mesophase. (b) Model of cellular uptake of the lamellar DNA-surfactant liquid crystals.¹⁸¹ Complexes adhere to cells due to electrostatics (i) and enter through endocytosis (ii and iii). Low σ_M complexes remain trapped in the endosome (iv). High σ_M complexes escape the endosome (v) where released DNA may form aggregates with cationic biomolecules (vi) or the complexes are less able to dissociate and less DNA is available (vii). (c) Double gyroid DNA-lipid cubic phases containing two (green and orange) water channels.²⁰² A lipid bilayer surface (grey) separates the two intertwined but independent water channels. (d) Total specific gene knockdown (KT, black lines and symbols) and nonspecific gene knockdown (KNS, red lines and symbols) for siRNA-DOTAP-GMO complexes (squares) and siRNA-DOTAP-DOPC complexes (circles) as a function of mole fraction of neutral surfactants (Φ_{NL}).²⁰² (e) Schematic phase diagrams showing different self-assembled DNA-tobramycin-surfactant liquid crystalline structures observed as a function of tobramycin-to-DNA charge ratio (T/D) and lipid-to-DNA charge ratio (L/D) for the hexagonal DNA-tobramycin bundles, lamellar DNA-DOTAP-DOPE-tobramycin (i) and inverse hexagonal phase DNA-DOTAP-DOPE with free tobramycin (ii), assuming a fixed DNA concentration.²⁰⁴ Dashed lines show approximate boundaries between single phase regions and the shaded coexistence region where both tobramycin-DNA close-packed bundles (DNA-tobramycin bundle) and the DNA-DOTAP-DOPE complexes are observed. Tobramycin is represented as a red 'C' shape in the models. Adapted with permission from ref. 181, Copyright 2005 John Wiley & Sons, Inc. and ref. 202 and 204 Copyright 2009 and 2010 American Chemical Society.

membrane's hydration repulsion layer – having its origin in the replacement of DOPC by cholesterol – promotes fusion between cationic membranes of DNA-lipid complexes and anionic endosomal membranes, thus facilitating release of complexes and enhancing TE.

To decrease DNA-lipid toxicity, a series of degradable multi-valent lipids with a disulfide bond were investigated for their potential in gene delivery.^{71,185} The initially formed lamellar phase of DNA-lipid complexes completely disappears when reducing agents, such as DTT or glutathione, are added. These complexes exhibit reduced cytotoxicity and comparable TE to those of non-degradable analogs.¹⁸⁵ Additionally, the synthesized nucleolipids including DOTAU and DOUPC have shown

low toxicity and their efficiencies in *in vitro* transfection assays yield promising results.^{82,83}

To date, synthetic lipid vectors with high transfection efficiencies have been available for *in vitro* applications, but they are not yet successful *in vivo*.^{186–188} The low TE efficiency of lipid vectors *in vivo* is due to the numerous biological and physico-chemical barriers. In order to stabilize DNA-lipid complexes sterically for *in vivo* gene therapy, poly(ethylene glycol) (PEG) modified lipids can be introduced.^{189–195} However, gene delivery efficiency was strongly reduced, likely due to the weakened electrostatic binding of DNA-lipid complexes to cells leading to reduced cellular uptake. To address these issues, an acid-labile PEG-lipid was designed to lose its PEG chains at the pH of late endosomes,

which showed enhanced TE.¹⁹² This result was ascribed to efficient endosomal escape enabled by the acid-labile PEG-lipid shedding its PEG chains in the low pH environment of late endosomes thus effectively strengthening the electrostatic interactions that promote fusion of the membranes of the complex and endosomes. In these systems, RGD-peptide-grafted PEG-lipids were also used for cell attachment and uptake investigations.^{193–195} The RGD-tagged DNA complexes exhibited strongly increased cellular attachment and uptake. The TE of RGD-tagged DNA-DOTAP-DOPC-PEG2000 increased by about an order of magnitude between the complexes with low and high membrane charge density confirming that the TE of RGD-tagged DNA-lipid complexes is improved by high σ_M . Additionally, Rab11-GFP and a Lysotracker were used to simultaneously colocalize DNA-PEG-lipids with recycling endosome (Rab11) and late endosome/lysosome (Rab7/Lysotracker) pathways.¹⁷⁵ The results suggested that the increased σ_M makes stronger electrostatic attractions between DNA-lipid complexes and endosome luminal membranes, thus leading to enhanced late endosome/lysosome pathway selection and higher TE. The decreased σ_M would enhance the recycling endosome pathway for DNA-lipid complexes and lower TE.

It was discovered that cytoplasmic delivery of exogenous small interfering RNA (siRNA) can induce gene silencing^{196,197} as part of the RNA interference pathway inducing major research efforts towards their advancement.^{198–202} However, to date the limiting step in realizing the full potential of the gene silencing technology has been the development of efficient chemical carriers for siRNA. To tackle this issue, a series of siRNA-surfactant complexes (siRNA-DOTAP/DOPE, siRNA-DOTAP/DOPC, siRNA-MVL5/DOPC) were fabricated that exhibited lamellar and inverted hexagonal mesophases.²⁰¹ It was found that inverted hexagonal siRNA-DOTAP/DOPE features high toxicity and much lower target-specific gene silencing than the investigated lamellar siRNA complexes. This may result from an excessive fusion of DOPE containing complexes with the cell membrane, possibly creating pores and leading to membrane instability. Notably, the siRNA complex combined with pentavalent surfactant MVL5 exhibited lower toxicity and superior silencing efficiency when compared to monovalent DOTAP.

More recently, a new double-gyroid cubic mesophase was discovered,²⁰² in which cationic DOTAP and non-ionic glycerol monooleate (GMO) were combined with siRNA. Fig. 11c shows a schematic representation of the unit cell of an inverse bi-continuous cubic phase (Q_{II}) containing siRNA. This phase is composed of a bilayer surface that divides two intertwined but independent water channels (hosting the siRNA molecules). As anticipated, these complexes allow high levels of sequence-specific gene knockdown in the regime of low charge density where lamellar complexes are considerably less efficient. The investigated mesophase was found to be highly efficient in cytoplasmic delivery of siRNA-surfactant complexes yielding sequence-specific gene silencing while warranting low cytotoxicity (Fig. 11d). Due to the low charge density of the cubic phase membranes, these results were accompanied by virtually no negative consequences for cell viability and plasma membrane integrity. This significant

discovery is consistent with the aforementioned hypothesis²⁰³ that the tendency of cubic phase forming lipids for pore formation leads to membrane fusion of the gyroid siRNA-surfactant complex and endosomal membranes upon endocytosis. Pores, in turn, allow for efficient cytoplasmic siRNA delivery leading to gene silencing.

Beyond the applications in gene delivery and gene silencing, DNA-surfactant liquid crystals bear enhanced antimicrobial properties for cystic fibrosis (CF).²⁰⁴ Tobramycin is an aminoglycoside antibiotic commonly administered to CF patients *via* inhalation and can induce DNA to pack into hexagonal aggregates. Therefore, it would be unavailable for interaction with bacteria in the DNA-containing CF airway surface liquid. Wong and co-workers found that interactions between DNA and tobramycin can be significantly modified by the presence of mixtures of surfactants (DOTAP + DOPE) realizing various phase transitions, *i.e.* hexagonal packed DNA-tobramycin, lamellar structured DNA-DOTAP-DOPE-tobramycin and inverse hexagonal DNA-DOTAP-DOPE with free tobramycin (Fig. 11e). In these phases, DNA is rendered available for cellular interaction and hence tobramycin's antimicrobial activity is recovered suggesting that optimized cationic amphiphile surfactant solutions have the potential to enhance antimicrobial function in highly infected environments that contain increased concentrations of anionic inflammatory polymers (like DNA bundles).²⁰⁴

The presented examples clearly demonstrate that liquid crystals of DNA-surfactant complexes exhibit several outstanding features for interaction with cells and therapeutics: they are comparably safe for use in human as no viral genes are present to cause disease, lack proteins rendering the synthetic vector non-immunogenic and are found to be significantly less cytotoxic than other DNA complexes combined with quaternary ammonium surfactants. Beyond these advantages and in stark contrast to genetically engineered viral vectors, these synthetic vectors show enormous potential for transferring and expressing large pieces of DNA ($> 10^6$ base pairs) into cells.^{205,206} However, delivery efficiencies of these liquid crystalline complexes remain low compared to those of engineered viral vectors and it is hence necessary to further develop a comprehensive understanding of the interactions of DNA-surfactant complexes with cell membranes and other components, such as the cytoskeleton network leading to cytosol delivery of complexes followed by DNA release and gene expression.

6.2.2 Thermotropic liquid crystals and electrochromic properties based on DNA-surfactant complexes. As discussed in Section 4, we reported new types of thermotropic LCs based on ssDNA-surfactant complexes that can be obtained by a simple and general preparation method.^{13,14} Phase transition temperatures from the isotropic liquid phase to the LC phase as well as the crystalline phase can be modulated conveniently over a broad temperature range by controlling the average length of the cationic surfactant complexed to the negatively charged single-stranded nucleic acid molecule allowing application under a wide range of non-natural conditions. Very recently, we enhanced this concept by developing ssDNA-surfactant TLCs that can undergo phase-dependent electrochromism (Fig. 12).²⁰⁷

In the liquid crystalline and isotropic phases, electric field-induced colouration and bleaching can be switched on a second timescale. However, transition to the smectic liquid crystalline phase allows a remarkable optical memory of the written state lacking colour decay for multiple hours in the absence of an applied voltage. These notable results imply that the volatility of an optoelectronic state can be controlled simply by undergoing a phase transition employing the DNA-surfactant TLC material.

An application of double potential steps of 0 V and 4 V causes the DNA-surfactant TLC to reversibly change colour between transparent and magenta in the isotropic liquid phase (Fig. 12c). By investigating the redox behaviour of the TLC complexes, the origin of the colouration could be pinpointed to the formation of nucleobase radical cations. When the electrochromic switching time of these TLC materials is correlated with the length of the employed DNA, it becomes obvious that the rate of DNA oxidation is limited by the rate of mass transport. Hereafter, cooling the ssDNA-surfactant liquid to the smectic TLC phase while an applied voltage of 4 V is maintained, conserves the

magenta colour (Fig. 12a and b) with the coloured state even temporarily preserved after returning to 0 V and completely bleached within 24 h (Fig. 12d). Further cooling of the ssDNA-TLC material in the coloured state induces phase transition from the LC to the crystalline phase extending the persistence time of the magenta state even more at 0 V (Fig. 12d). The complete recovery of the colourless state in the crystalline phase was observed within about 30 h. Polarized optical microscopy revealed that reorientation of the oxidized DNA-surfactant smectic layers occurred when a voltage was applied during the phase transition process from isotropic to LC (Fig. 12a and b). Due to the formed parallel alignment of the oxidized ssDNA-surfactant complex, the surfactant sublayers may act as an insulating barrier preventing electron hopping. Therefore, the reduction process of ssDNA radical cations might be decelerated.

Besides regarding the decolouration process as visual clock function, the electrochromic DNA-surfactant TLC devices also exhibit the feature of a ceiling temperature indicator. These possibilities render this type of TLC material an optimal and cheap candidate for the development of smart tag applications

Fig. 12 Electrochromism of ssDNA-surfactant TLCs.²⁰⁷ (a and b) The study of electrochromic behaviour utilizing polarization optical microscopy. Scale bar is 100 μm . (c) Strong absorption bands in the ultraviolet-visible absorption spectrum of the ssDNA-surfactant TLC isotropic liquid appeared in the region of 350 to 600 nm under an applied voltage (black curve) and disappeared shortly after the voltage was removed (red curve). (d) Decay kinetics of the coloured state in different phases. Adapted from ref. 207. Licensed under CC BY 2016 Springer Nature.

for packaging of perishable food or temperature sensitive medical products and drugs.

6.2.3 Hydrogels and release properties based on DNA-surfactant complexes. A general understanding of the interactions between DNA and oppositely-charged surfactants, particularly their phase behaviour, establishes a foundation for the development of novel DNA-based materials. Beyond the already covered bulk DNA-surfactant films and soft-matter liquid crystals, DNA-surfactant hydrogels have been developed based on associative phase separation and interfacial diffusion.²⁰⁸ For the preparation of this type of structures, DNA solutions are added dropwise *via* a needle to gently agitated surfactant solutions.^{209,210} Under the right set of conditions, droplets from DNA solutions instantaneously gel into discrete particles upon contact with the surfactant solution. This fabrication process is facile, efficient and forgoes the addition of any cross-linker or organic solvent improving it significantly as compared to the procedures traditionally employed to fabricate DNA hydrogels.^{211,212} The driving force for this strong association is the electrostatic interaction between the two components and the entropic increase when the respective counter-ions are released.²¹³ The association strength is tuned by varying the chemical structure of the cationic surfactant and allows control over the spatial homogeneity of the gelation process yielding either a homogeneous DNA matrix or different DNA reservoir devices. This enables various applications for the controlled encapsulation and release of ssDNA and dsDNA.

For example, Lindman and co-workers reported on the formation of DNA hydrogel particles by mixing solutions of DNA (either ssDNA or dsDNA) with solutions of the cationic surfactant CTAB.²¹⁴ The size of the resulting DNA-CTAB gel particles varied between 1 and 2 mm yielding loading efficiencies of >99% for dsDNA-CTAB and ssDNA-CTAB. Further studies explored the effect of ionic strength on the release of DNA from these gel particles. Total release of DNA was obtained when dsDNA-CTAB hydrogels were placed in aqueous solutions containing high salt concentrations. Interestingly, a lower percentage of DNA release was observed for ssDNA-CTAB gels. This striking difference suggests that the surfactant-DNA interaction is much stronger in the case of ssDNA than for dsDNA. Concomitantly, scanning electron microscopy images indicate that dsDNA-CTAB hydrogels exhibit higher porosity, which is consistent with the higher degree of swelling being reached compared to hydrogels containing ssDNA-CTAB. In order to investigate the influence of the surfactant structure on the formation of hydrogel particles and their release properties, double chain surfactant DDAB was combined with DNA and compared with single chain surfactant DTAB complexes.²¹⁵ DNA-DTAB gel particles exhibited a rapid DNA release dissolving readily in the medium on the timescale of multiple hours. In stark contrast, DNA-DDAB hydrogels yielded an initial burst release independent of the secondary structure of the nucleic acid over 1 d. Hereafter, a linear cumulative release could be monitored until the end of the experiment (62 d). Even after this prolonged exposition time, the amounts of released DNA from dsDNA-DDAB and ssDNA-DDAB were not quantitative but only 63% and 34%, respectively.

Furthermore, the effect of different counter-ions on the formation of the DNA-surfactant hydrogel particles was examined.²¹⁶ In particular, single chain surfactant dodecyltrimethylammonium with different counter-ions (HSO_4^- , CF_3SO_3^- , Cl^- and Br^-) was complexed with DNA. These studies revealed that the degree of counter-ion dissociation from the surfactant micelles and the polar/hydrophobic character of the counter-ion are important for controlling DNA entrapment, swelling/shrinking behaviour and DNA release kinetics of the DNA hydrogels. Moreover, these gel particles were assessed for haemolysis revealing that with increasing DNA-surfactant interaction, haemolysis and DNA release kinetics are impeded.

In conclusion, these DNA-surfactant hydrogels represent a conceptually new design of non-viral vectors for the delivery of therapeutic DNA. The colloidal carrier protects nucleic acid molecules from deleterious degradation and may provide therapeutically advantageous sustained release of payload. Although these carriers may offer various advantages over conventional gene-delivery systems, their toxicity may be significant due to the presence of cationic surfactants. Hence, a continuous effort focused on improving safety, feasibility and efficacy of colloidal carriers will be the challenging goal to bring these materials further towards clinical application.

6.3 Applications in synthetic chemistry with DNA-surfactant complexes

DNA-surfactant complexes are soluble in organic solvents,^{110,217–220} such as chloroform, toluene, *N,N*-dimethylformamide (DMF) and methanol rendering them versatile and broadly applicable scaffolds for DNA-templated organic synthesis, DNA functionalization and DNA polymerization in the organic phase. Exemplarily, Liu and Rozenman found that DNA-templated amine acylation can be carried out efficiently and sequence-specifically in organic solvents in the presence of CTAB.²²¹ Employing the same surfactant to shuttle DNA into DMF overcomes the solubility difference of hydrophilic DNA and hydrophobic molecules efficiently yielding amphiphilic DNA-lipid conjugates.²²²

In a previous work, we reported an organic-phase coupling strategy for nucleic acid modification by using a hydrophobic ssDNA-surfactant complex as a reactive scaffold.¹⁸ A remarkable range of amphiphile-DNA structures (DNA-pyrene-, DNA-triphenylphosphine- and DNA-hydrocarbon conjugates as well as DNA block copolymers) could be obtained employing the general synthetic protocol depicted in Fig. 13a, which relies on acylation reactions at the DNA terminus. The homogeneous amine acylation reaction between a ssDNA-DDAB complex and the hydrophobic moieties was carried out in an organic solvent (DMF or THF). Afterwards, the reaction mixture was treated with highly concentrated NaCl solution to release ssDNA conjugates from the DDAB shell. Further characterization confirmed that the desired products were obtained without by-product formation. In particular, the efficiencies of coupling large hydrophobic polymer moieties to ssDNA were comparable to or even higher than those from the solid-phase and other heterogeneous solution grafting approaches.^{223–229} This “ssDNA-surfactant” strategy requires neither the purchase and maintenance of an in-house DNA

synthesizer nor the use of sophisticated and expensive reagents greatly reducing the cost of synthesizing “difficult” DNA amphiphiles. Therefore, the ssDNA–surfactant complex offers a new platform to functionalize DNA with various, previously inaccessible hydrophobic adducts in a facile and efficient way.

We then extended the scope of our “DNA–surfactant” approach by introducing site-specific modifications at nucleobases within a fully deprotected ssDNA molecule employing the

palladium-catalysed Sonogashira–Hagihara coupling reaction,¹⁸ which previously had only been realized by reactions on protected on-column oligonucleotides.^{230,231} In the strategy we developed (Fig. 13b), ssDNA–surfactant complexes were first prepared and lyophilized and then allowed to react with ethynylpyrene in the presence of $\text{Pd}(\text{PPh}_3)_4$ and CuI in DMF under inert conditions. After cation exchange with sodium chloride, the final crude products were purified by reverse phase HPLC. Further analysis

Fig. 13 ssDNA–surfactant complex as a reactive scaffold for nucleic acid modification and polymerization in the organic phase.¹⁸ This strategy can overcome the solvent incompatibility of hydrophilic DNA and hydrophobic moieties during conjugation. (a) Scheme of the organic-phase synthesis of terminal functionalized ssDNA, nucleic acid amphiphiles and ssDNA block copolymers employing amine acylation reaction. (b) Site-specific functionalization of ssDNA nucleobases by Pd-catalysed Sonogashira–Hagihara reaction. (c) Synthesis of ssDNA side-chain homopolymers from ssDNA–norbornene–DDAB complex macromonomers by ring-opening metathesis polymerization. Adapted with permission from ref. 18, Copyright 2014 American Chemical Society.

showed that the desired products were obtained with coupling efficiencies higher than 50%. This indicated that fully deprotected oligonucleotides can be effectively and precisely functionalized under Sonogashira-Hagihara conditions on the scaffold provided by the lipophilic ssDNA-surfactant complex.

Furthermore, our DNA-surfactant strategy was applied for the generation of a new type of ssDNA brush (*i.e.* DNA side chain homopolymers) by ring-opening metathesis polymerization (Fig. 13c).¹⁸ For this purpose, norbornene modified ssDNA macromonomers were synthesized after which the ssDNA was complexed with DDAB by electrostatic interaction. The polymerization was carried out using Grubbs-type carbene catalysts in organic solvents (THF or CHCl₃). Polyacrylamide gel electrophoresis (PAGE) analysis of the crude products revealed multiple distinct bands that formed a ladder-like pattern, indicating the formation of high molecular weight ssDNA species. ssDNA brushes with different degrees of polymerization showed distinct differences in electrophoretic mobility. Therefore, they could be separated conveniently employing PAGE. Mass spectrometry revealed that each band on the PAGE corresponded to a single side-chain DNA brush indicating the monodispersity of the purified products. While statistical copolymers exhibiting DNA

side chains were known to the literature,^{232–234} our products are moreover the first example of homopolymer ssDNA brushes rendering the polymerization of norbornene functionalized ssDNA-surfactant complex macromonomers ideal for the fabrication of novel ssDNA side chain architectures with high ssDNA grafting density.

Generally, DNA-surfactant complexes are fabricated by the introduction of hydrophilic surfactants into the aqueous phase that are just hydrophobic enough to cause DNA aggregation.²³⁵ Due to this solubility requirement, the pool of surfactants available for the formation of DNA-surfactant complexes is rather limited. To tackle this issue, we recently presented a ligand exchange method to prepare DNA-surfactant complexes with a broad range of surfactants regardless of their solubility properties (Fig. 14a).²³⁶ In the first step of this protocol, water-soluble cationic surfactant 4-(hexyloxy)anilinium (ANI) is employed to prepare the respective DNA-ANI complex. This complex precipitates out of aqueous solution and is collected by centrifugation. Afterwards, water-insoluble dodecylammonium (DA) is introduced into the DNA-ANI system while dissolved in organic solvent yielding a DNA-DA complex after dialysis. We postulate that the substitution of the aniline for the primary

Fig. 14 Preparation of ssDNA-surfactant complexes employing water-insoluble surfactants.²³⁶ (a) Two-step process for the formation of ssDNA-surfactant complexes with amine surfactants. (b) Molecular structure of terthiophene carrying an amine group for complexation with ssDNA. (c) Construction of a non-covalent light harvesting system based on a chromophore labelled ssDNA-pyrene surfactant complex. Adapted with permission from ref. 236, Copyright 2015 American Chemical Society.

amine is the result of a proton transfer between the two surfactants participating in the exchange following a simple acid–base reaction mechanism where the conjugate acid of aniline protonates the respective alkyl amine. Other alkyl amines, including octadecylamine, dioctadecylamine and trioctylamine, are consequently also compatible with this two-step ligand exchange method (Fig. 14a). Circular dichroism (CD) measurements show that the double strand helical structure in the DNA–amine surfactant complexes is retained.

Beyond alkyl amines, we employed our method to encapsulate DNA using terthiophene conjugated amine surfactant (Fig. 14b). The CD data suggest that the terthiophene molecules assemble in a right-handed helix because of complexation with the DNA molecule.^{237,238} We further explored this strategy to construct a light harvesting system (Fig. 14c). Using the ANI substitution method, chromophore (490LS, ATTOTEC) labelled DNA was complexed with a pyrene-modified amine surfactant. We successfully showed that within the DNA–surfactant complex, energy transfer from pyrene to the chromophore occurs.

Since the two-step exchange protocol does not rely on coprecipitation of DNA with the selected surfactant in an aqueous solvent, we also investigated the lower size limits of small ligands that keep DNA soluble in the organic phase. In this case, triethylammonium was used to replace ANI in the organic phase and solubilize salmon testes DNA (2000 bp) in organic solvent. NMR spectroscopy clearly indicated that the molecular ratio of DNA pentose to triethylammonium approximated 1 : 1 confirming that one phosphate group was complexed by one cationic ligand and that the ligand exchange proceeded to completion. Reducing the steric hindrance of the surfactant shell around the DNA in that manner could have a significant impact on the efficiency of DNA functionalization^{18,221,222} as well as DNA-mediated catalysis in the organic phase.²³⁹ Beyond that, this novel approach for functionalization of DNA by surfactant exchange in organic solvents may be beneficial in expanding the scope of DNA-based nano- and biotechnologies.

7. Summary and outlook

The ionic self-assembly of DNA–surfactant complexes is an exciting area of nucleic acid research and has received increasing attention in recent years. The driving force for this ‘bottom-up’ self-assembly process is the electrostatic interaction between anionic DNA and cationic surfactants. As summarized in Fig. 15, the organization of DNA–surfactant complexes into bulk films, lyotropic liquid crystals, thermotropic liquid crystals and hydrogels results in striking applications in electronics, optics and optoelectronics, gene therapy, drug delivery and synthetic chemistry. Various notable applications and devices could already be realized, amongst them ordered films of aligned DNA exhibiting high electronic conductivity, a DNA–surfactant matrix enhancing fluorescence efficiency of dispersed dyes or bulk DNA–surfactant films employed as components in biological OLEDs and photovoltaic cells with improved performance. However, the sensitivity of the DNA–surfactant complex to light and electric fields still

Fig. 15 Summary of DNA–surfactant complexes forming different types of materials. Bulk films could be fabricated conveniently by casting the complexes from organic medium.¹¹² Packing modes of lyotropic^{68,69,73} and thermotropic¹⁵ liquid crystalline mesophases are strongly dependent on the DNA chains, head group charge and chain length of chosen surfactants, counterions and the presence of other polyelectrolytes. DNA–surfactant hydrogel²¹³ particles are fabricated easily and efficiently without adding any kind of cross-linker or organic solvent. Adapted with permission from ref. 68, Copyright 1998 The American Association for the Advancement of Science, ref. 69, Copyright 2006 American Chemical Society, and ref. 73, Copyright 2013 Royal Society of Chemistry, ref. 15 and 112, Copyright 2002 and 2015 John Wiley & Sons, Inc., and ref. 213 copyright 2014 Elsevier.

requires improvement as it may impair long-term device stability. Moreover, residual water molecules within the ionic DNA–surfactant materials could negatively influence the device performance under ambient conditions. Controlling the amount of water molecules attached to the DNA chains thus appears to be a critical factor for obtaining stable devices. Notably, the biological activity of DNA–surfactant bulk films can be recovered once wetted rendering them potentially suitable for gene therapy and drug release by direct implantation *in vivo* in combination with controlled delivery and dosage adjustment.

Beyond bulk applications, soft-phase materials of DNA–surfactant complexes, including liquid crystals and hydrogels, have been developed and investigated. These materials are of particular interest for gene therapy as their gene transfection and silencing properties are comparably safe and non-toxic when compared to viral vectors. A preliminary understanding of the delivery mechanism at the individual complex level has been achieved by a combination of structural analysis and fluorescence microscopy. However, a comprehensive understanding of the nature of the interactions of DNA–surfactant complexes with cell membranes and events leading to release of active nucleic acids within the cell cytoplasm is urgently needed for successful transfection applications. Their transfection efficiency and the onset of toxicity with increasing cationic surfactant/nucleic acid ratios need to be improved in order to compete with viral vectors. A continuous search to understand the role of amphiphilic surfactants, salts and other polyelectrolytes in DNA–surfactant assembly behaviour is imperative to enhance delivery efficiencies within current gene therapy trials and other drug delivery systems.

Alongside, the recently developed thermotropic liquid crystals of DNA-surfactant complexes provide a hydrophobic environment and lack high dielectric water content offering opportunities for the development of flexible and printable DNA electronic components. These solvent-free materials allow the manipulation of ordering and fluidity, and may exhibit novel ensemble optoelectronic properties. Phase-dependent electrochromism based on this new type of material has been developed allowing control over the volatility of optoelectronic states simply by changing the phase of the DNA-surfactant TLCs. Due to their high thermal stability, these types of soft DNA-surfactant materials are moreover suitable for a broad range of new fields of application differing from the current pursuit in aqueous solutions. For example, they may act as a fluid depot for cargo storage and a directly injectable scaffold for drug delivery. As chemically modified oligonucleotides, they might be used as reactive inks to functionalize biochips. Such TLC materials can be processed easily, which offers opportunities for the development of solvent-free catalysts. Moreover, DNA-surfactant complexes can be applied as a simple, generic strategy for overcoming incompatibilities in solubility in the production of functionalized DNA molecules like DNA amphiphiles, DNA block copolymers and side-chain DNA brushes. These achievements may greatly accelerate the exploration of potential DNA applications in bio- and nanotechnology and thus render DNA-surfactant complexes a promising prospect for the resolution of unanswered questions at the interface of biology, nanotechnology and materials science.

Competing financial interest

The authors declare no competing financial interest.

Acknowledgements

This research was supported by the European Union (European Research Council Advanced Grant and STREP project MICREA-GENTS), the Netherlands Organization for Scientific Research (NWO-Vici, NWO-Echo), the Zernike Institute for Advanced Materials, the start-up supports from Changchun Institute of Applied Chemistry, and the National Thousand Talents Program for Distinguished Young Scholars.

References

- 1 E. D. Goddard and K. P. Ananthapadmanabhan, *Interactions of Surfactants with Polymers and Proteins*, CRC Press, 1992.
- 2 M. Antonietti, J. Conrad and A. Thunemann, *Macromolecules*, 1994, **27**, 6007–6011.
- 3 O. Ikkala and G. T. Brinke, *Chem. Commun.*, 2004, 2131–2137.
- 4 C. K. Ober and G. Wegner, *Adv. Mater.*, 1997, **9**, 17–31.
- 5 J. Ruokolainen, G. T. Brinke and O. Ikkala, *Adv. Mater.*, 1999, **11**, 777–780.
- 6 W. J. MacKnight, E. A. Ponomarenko and D. A. Tirrell, *Acc. Chem. Res.*, 1998, **31**, 781–788.
- 7 S. Zhou and B. Chu, *Adv. Mater.*, 2000, **12**, 545–556.
- 8 M. Rosa, R. Dias, M. D. G. Miguel and B. Lindman, *Biomacromolecules*, 2005, **6**, 2164–2171.
- 9 D. Langevin, *Adv. Colloid Interface Sci.*, 2009, **147–148**, 170–177.
- 10 B. Lindman, *Colloid Polym. Sci.*, 2016, **294**, 1687–1703.
- 11 D. Luo and W. M. Saltzman, *Nat. Biotechnol.*, 2000, **18**, 33–37.
- 12 C. R. Safinya, J. Deek, R. Beck, J. B. Jonesa, C. Leal, K. K. Ewert and Y. Li, *Liq. Cryst.*, 2013, **40**, 1748–1758.
- 13 S. Gajria, T. Neumann and M. Tirrell, *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.*, 2011, **3**, 479–500.
- 14 K. Liu, D. Chen, A. Marcozzi, L. Zheng, J. Su, D. Pesce, W. Zajaczkowski, A. Kolbe, W. Pisula, K. Müllen, N. A. Clark and A. Herrmann, *Proc. Natl. Acad. Sci. U. S. A.*, 2014, **111**, 18596–18600.
- 15 K. Liu, M. Shuai, D. Chen, M. Tuchband, J. Y. Gerasimov, J. Su, Q. Liu, W. Zajaczkowski, W. Pisula, K. Müllen, N. A. Clark and A. Herrmann, *Chem. – Eur. J.*, 2015, **21**, 4898–4903.
- 16 J. A. Hagen, W. Li, A. J. Steckl and J. G. Grote, *Appl. Phys. Lett.*, 2006, **88**, 171109.
- 17 K. Nakamura, T. Ishikawa, D. Nishioka, T. Ushikubo and N. Kobayashi, *Appl. Phys. Lett.*, 2010, **97**, 193301.
- 18 K. Liu, L. Zheng, Q. Liu, J. W. de Vries, J. Y. Gerasimov and A. Herrmann, *J. Am. Chem. Soc.*, 2014, **136**, 14255–14262.
- 19 R. Dahm, *Dev. Biol.*, 2005, **278**, 274–288.
- 20 J. D. Watson and F. H. C. Crick, *Nature*, 1953, **171**, 737–738.
- 21 X. J. Lu and W. K. Olson, *Nucleic Acids Res.*, 2003, **31**, 5108–5121.
- 22 E. Yeramian, *Gene*, 2000, **255**, 139–150.
- 23 S. L. Beaucage and M. H. Caruthers, *Tetrahedron Lett.*, 1981, **22**, 1859–1862.
- 24 T. J. Bandy, A. Brewer, J. R. Burns, G. Marth, T. Nguyen and E. Stulz, *Chem. Soc. Rev.*, 2011, **40**, 138–148.
- 25 N. C. Seeman, *Nature*, 2003, **421**, 427–431.
- 26 D. Yang, M. J. Campolongo, T. N. Nhi Tran, R. C. H. Ruiz, J. S. Kahn and D. Luo, *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.*, 2010, **2**, 648–669.
- 27 Y. Dong, Z. Yang and D. Liu, *Acc. Chem. Res.*, 2014, **47**, 1853–1860.
- 28 F. Wang, X. Liu and I. Willner, *Angew. Chem., Int. Ed.*, 2015, **54**, 1098–1129.
- 29 A. V. Pinheiro, D. Han, W. M. Shih and H. Yan, *Nat. Nanotechnol.*, 2011, **6**, 763–772.
- 30 M. Kwak and A. Herrmann, *Chem. Soc. Rev.*, 2011, **40**, 5745–5755.
- 31 J. W. de Vries, F. Zhang and A. Herrmann, *J. Controlled Release*, 2013, **172**, 467–483.
- 32 M. Kwak and A. Herrmann, *Angew. Chem., Int. Ed.*, 2010, **49**, 8574–8587.
- 33 T. Schnitzler and A. Herrmann, *Acc. Chem. Res.*, 2012, **45**, 1419–1430.
- 34 T. Kato, N. Mizoshita and K. Kishimoto, *Angew. Chem., Int. Ed.*, 2006, **45**, 38–68.
- 35 C. K. McLaughlin, G. D. Hamblin and H. F. Sleiman, *Chem. Soc. Rev.*, 2011, **40**, 5647–5656.

- 36 O. Ikkala and G. ten Brinke, *Science*, 2002, **295**, 2407–2409.
- 37 N. Houbenov, J. S. Haataja, H. Iatrou, N. Hadjichristidis, J. Ruokolainen, C. F. J. Faul and O. Ikkala, *Angew. Chem., Int. Ed.*, 2011, **50**, 2516–2520.
- 38 K. P. Sharma, A. M. Collins, A. W. Perriman and S. Mann, *Adv. Mater.*, 2013, **25**, 2005–2010.
- 39 C. F. J. Faul and M. Antonietti, *Adv. Mater.*, 2003, **15**, 673–683.
- 40 C. F. J. Faul, *Mol. Cryst. Liq. Cryst.*, 2006, **450**, 255–265.
- 41 C. F. J. Faul, *Acc. Chem. Res.*, 2014, **47**, 3428–3438.
- 42 K. Thalberg, B. Lindman and G. Karlstrom, *J. Phys. Chem.*, 1991, **95**, 3370–3376.
- 43 K. Hayakawa, J. P. Santerre and J. C. T. Kwak, *Biophys. Chem.*, 1983, **17**, 175–260.
- 44 B. Lindman, F. Antunes, S. Aidarova, M. Miguel and T. Nylander, *Colloid J.*, 2014, **76**, 585–594.
- 45 *DNA Interactions with Polymers and Surfactants*, ed. R. Dias and B. Lindman, John Wiley & Sons, Hoboken 2008.
- 46 V. A. Izumrudov, M. V. Zhiryakova and A. A. Goulko, *Langmuir*, 2002, **18**, 10348–10356.
- 47 C. H. Spink and J. B. Chaires, *J. Am. Chem. Soc.*, 1997, **119**, 10920–10928.
- 48 R. Dias, S. Mel'nikov, B. Lindman and M. G. Miguel, *Langmuir*, 2000, **16**, 9577–9583.
- 49 L. Piculell and B. Lindman, *Adv. Colloid Interface Sci.*, 1992, **41**, 149–178.
- 50 P. Smith, R. M. Lynden-Bell and W. Smith, *Phys. Chem. Chem. Phys.*, 2000, **2**, 1305–1310.
- 51 V. Jadhav, S. Maiti, A. Dasgupta, P. K. Das, R. S. Dias, M. G. Miguel and B. Lindman, *Biomacromolecules*, 2008, **9**, 1852–1859.
- 52 R. S. Dias, L. M. Magno, A. J. M. Valente, D. Das, P. K. Das, S. Maiti, M. G. Miguel and B. Lindman, *J. Phys. Chem. B*, 2008, **112**, 14446–14452.
- 53 L. Goracci, R. Germani, G. Savelli and D. M. Bassani, *ChemBioChem*, 2005, **6**, 197–203.
- 54 A. Dasgupta, P. K. Das, R. S. Dias, M. G. Miguel, B. Lindman, V. M. Jadhav, M. Gnanamani and S. Maiti, *J. Phys. Chem. B*, 2007, **111**, 8502.
- 55 M. T. Record, C. F. Anderson and T. M. Lohman, *Q. Rev. Biophys.*, 1978, **11**, 103–178.
- 56 K. A. Sharp, R. A. Friedman, V. Misra, J. Hecht and B. Honig, *Biopolymers*, 1995, **36**, 245–262.
- 57 S. A. Palkar and A. M. Lenhoff, *J. Colloid Interface Sci.*, 1994, **165**, 177–194.
- 58 M. C. Morán, T. Alonso, F. S. Lima, M. P. Vinardell, M. G. Miguel and B. Lindman, *Soft Matter*, 2012, **8**, 3200–3211.
- 59 P. L. Felgner and G. Rhodes, *Nature*, 1991, **349**, 351–352.
- 60 P. L. Felgner, T. R. Gadek, M. Holm, R. Roman, H. W. Chan, M. Wenz, J. P. Northrop, G. M. Ringold and M. Danielsen, *Proc. Natl. Acad. Sci. U. S. A.*, 1987, **84**, 7413–7417.
- 61 J. Gustafsson, G. Arvidson, G. Karlsson and M. Almgren, *Biochim. Biophys. Acta*, 1995, **1235**, 305–312.
- 62 F. L. Sorgi and L. Huang, *FEBS Lett.*, 1994, **356**, 361–366.
- 63 J. O. Rädler, I. Koltover, T. Salditt and C. R. Safinya, *Science*, 1997, **275**, 810–814.
- 64 T. Salditt, I. Koltover, J. O. Rädler and C. R. Safinya, *Phys. Rev. Lett.*, 1997, **79**, 2582–2585.
- 65 D. D. Lasic, H. Strey, M. C. A. Stuart, R. Podgornik and P. M. Frederik, *J. Am. Chem. Soc.*, 1997, **119**, 832–833.
- 66 T. Salditt, I. Koltover, J. O. Rädler and C. R. Safinya, *Phys. Rev. E: Stat. Phys., Plasmas, Fluids, Relat. Interdiscip. Top.*, 1998, **58**, 889–904.
- 67 F. Artzner, R. Zantl, G. Rapp and J. O. Rädler, *Phys. Rev. Lett.*, 1998, **81**, 5015–5018.
- 68 I. Koltover, T. Salditt, J. O. Rädler and C. R. Safinya, *Science*, 1998, **281**, 78–81.
- 69 K. K. Ewert, H. M. Evans, A. Zidovska, N. F. Boussein, A. Ahmad and C. R. Safinya, *J. Am. Chem. Soc.*, 2006, **128**, 3998–4006.
- 70 A. Zidovska, H. M. Evans, K. K. Ewert, J. Quispe, B. Carragher, C. S. Potter and C. R. Safinya, *J. Phys. Chem. B*, 2009, **113**, 3694–3703.
- 71 R. S. Shirazi, K. K. Ewert, B. F. B. Silva, C. Leal, Y. Li and C. R. Safinya, *Langmuir*, 2012, **28**, 10495–10503.
- 72 N. F. Boussein, C. Leal, C. S. Mcallister, K. K. Ewert, Y. Li, C. E. Samuel and C. R. Safinya, *J. Am. Chem. Soc.*, 2011, **133**, 7585–7595.
- 73 C. Leal, K. K. Ewert, N. F. Boussein, R. S. Shirazi, Y. Li and C. R. Safinya, *Soft Matter*, 2013, **9**, 795–804.
- 74 T. Pott, A. Colin, L. Navailles and D. Roux, *Interface Sci.*, 2003, **11**, 249–257.
- 75 T. Pott and D. Roux, *FEBS Lett.*, 2002, **511**, 150–154.
- 76 J. J. McManus, J. O. Rädler and K. A. Dawson, *Langmuir*, 2003, **19**, 9630–9637.
- 77 J. J. McManus, J. O. Rädler and K. A. Dawson, *J. Am. Chem. Soc.*, 2004, **126**, 15966–15967.
- 78 G. Caracciolo, D. Pozzi, R. Caminiti, G. Mancini, P. Luciani and H. Amenitsch, *J. Am. Chem. Soc.*, 2007, **129**, 10092–10093.
- 79 A. Gissot, M. Camplo, M. W. Grinstaff and P. Barthélémy, *Org. Biomol. Chem.*, 2008, **6**, 1324–1333.
- 80 P. Barthélémy and M. Camplo, *MRS Bull.*, 2005, **30**, 647–653.
- 81 P. Barthélémy, S. J. Lee and M. Grinstaff, *Pure Appl. Chem.*, 2005, **77**, 2133–2148.
- 82 P. Chabaud, M. Camplo, D. Payet, G. Serin, L. Moreau, P. Barthélémy and M. W. Grinstaff, *Bioconjugate Chem.*, 2006, **17**, 466–472.
- 83 L. Moreau, P. Barthélémy, Y. Li, D. Luo, C. A. H. Pratac and M. W. Grinstaff, *Mol. BioSyst.*, 2005, **1**, 260–264.
- 84 J. Arigon, C. A. Prata, M. W. Grinstaff and P. Barthélémy, *Bioconjugate Chem.*, 2005, **16**, 864–872.
- 85 P. Barthélémy, C. A. Prata, S. F. Filocamo, C. E. Immoos, B. W. Maynor, S. A. Hashmi, S. J. Lee and M. W. Grinstaff, *Chem. Commun.*, 2005, 1261–1263.
- 86 M. Banchelli, D. Berti and P. Baglioni, *Angew. Chem., Int. Ed.*, 2007, **46**, 3070–3073.
- 87 S. Milani, F. B. Bombelli, D. Berti and P. Baglioni, *J. Am. Chem. Soc.*, 2007, **129**, 11664–11665.

- 88 A. Bilalov, U. Olssona and B. Lindman, *Soft Matter*, 2012, **8**, 11022–11033.
- 89 D. Uhríková, G. Rapp and P. Balgavý, *Bioelectrochemistry*, 2002, **58**, 87–95.
- 90 D. McLoughlin, M. Impérator-Clerc and D. Langevin, *ChemPhysChem*, 2004, **5**, 1619–1623.
- 91 X. Zhao, Y. Shang, J. Hu, H. Liu and Y. Hu, *Biophys. Chem.*, 2008, **138**, 144–149.
- 92 Q. Chen, X. Kang, R. Li, X. Du, Y. Shang, H. Liu and Y. Hu, *Langmuir*, 2012, **28**, 3429–3438.
- 93 R. Ghirlando, E. J. Wachtel, T. Arad and A. Minsky, *Biochemistry*, 1992, **31**, 7110–7119.
- 94 S. M. Mel'nikov, V. G. Sergeyev, K. Yoshikawa, H. Takahashi and I. Hatta, *J. Chem. Phys.*, 1997, **107**, 6917–6924.
- 95 D. Harries, S. May, W. M. Gelbart and A. Ben-Shaul, *Biophys. J.*, 1998, **75**, 159–173.
- 96 L. Goluboric and M. Gloubovic, *Phys. Rev. Lett.*, 1998, **80**, 4341–4344.
- 97 S. O'Hern, T. C. Lubensky and J. Toner, *Phys. Rev. Lett.*, 1999, **83**, 2745–2748.
- 98 N. Dan, *Biochim. Biophys. Acta*, 1998, **1369**, 34–38.
- 99 S. May, D. Harries and A. Ben-Shaul, *Biophys. J.*, 2000, **78**, 1681–1697.
- 100 P. Ekwall, L. Mandell and K. Fontell, *J. Colloid Interface Sci.*, 1969, **29**, 639–646.
- 101 C. R. Safinya, E. B. Sirota, D. Roux and G. S. Smith, *Phys. Rev. Lett.*, 1989, **62**, 1134–1137.
- 102 R. Krishnaswamy, V. A. Raghunathan and A. K. Sood, *Phys. Rev. E: Stat., Nonlinear, Soft Matter Phys.*, 2004, **69**, 031905.
- 103 R. Krishnaswamy, G. Pabst, M. Rappolt, V. A. Raghunathan and A. K. Sood, *Phys. Rev. E: Stat., Nonlinear, Soft Matter Phys.*, 2006, **73**, 031904.
- 104 R. Krishnaswamy, P. Mitra, V. A. Raghunathan and A. K. Sood, *Europhys. Lett.*, 2003, **62**, 357–362.
- 105 S. Zhou, D. Liang, C. Burger, F. Yeh and B. Chu, *Biomacromolecules*, 2004, **5**, 1256–1261.
- 106 C. Leal, A. Bilalov and B. Lindman, *J. Phys. Chem. B*, 2009, **113**, 9909–9914.
- 107 A. Bilalov, U. Olsson and B. Lindman, *Soft Matter*, 2009, **5**, 3827–3830.
- 108 A. Bilalov, U. Olsson and B. Lindman, *Soft Matter*, 2011, **7**, 730–742.
- 109 A. Krivtsov, A. Bilalov, U. Olsson and B. Lindman, *Langmuir*, 2012, **28**, 13698–13704.
- 110 K. Tanaka and Y. Okahata, *J. Am. Chem. Soc.*, 1996, **118**, 10679–10683.
- 111 C. Yang, D. Moses and A. J. Heeger, *Adv. Mater.*, 2003, **15**, 1364–1367.
- 112 Y. Hoshino, S. Tajima, H. Nakayama and Y. Okahata, *Macromol. Rapid Commun.*, 2002, **23**, 253–255.
- 113 Y. Okahata, T. Kobayashi and K. Tanaka, *Langmuir*, 1996, **12**, 1326–1330.
- 114 Y. Okahata and K. Tanaka, *Thin Solid Films*, 1996, **284–285**, 6–8.
- 115 H. Sun, W. Li and L. Wu, *Langmuir*, 2009, **25**, 10466–10472.
- 116 S. May and A. Ben-Shaul, *Biophys. J.*, 1997, **73**, 2427–2440.
- 117 M. H. Stenzel, *Aust. J. Chem.*, 2002, **55**, 239–243.
- 118 B. Martin, M. Sainlos, A. Aissaoui, N. Oudrhiri, M. Hauchecorne, J. P. Vigneron, J. M. Lehn and P. Lehn, *Curr. Pharm. Des.*, 2005, **11**, 375–394.
- 119 T. Neumann, S. Gajria, M. Tirrell and L. Jaeger, *J. Am. Chem. Soc.*, 2009, **131**, 3440–3441.
- 120 O. Sinanoglu and S. Abdunur, *Photochem. Photobiol.*, 1964, **3**, 333–342.
- 121 T. Neumann, S. Gajria, N. F. Boussein, L. Jaeger and M. Tirrell, *J. Am. Chem. Soc.*, 2010, **132**, 7025–7037.
- 122 T. Omabegho, R. Sha and N. C. Seeman, *Science*, 2009, **324**, 67–71.
- 123 C. J. Murphy, M. R. Arkin, Y. Jenkins, N. D. Ghatlia, S. H. Bossmann, N. J. Turro and J. K. Barton, *Science*, 1993, **262**, 1025–1029.
- 124 E. Braun, Y. Eichen, U. Sivan and G. Ben-Yoseph, *Nature*, 1998, **391**, 775–778.
- 125 D. Porath, A. Bezryadin, S. de Vries and C. Dekker, *Nature*, 2000, **403**, 635–638.
- 126 D. Porath, G. Cuniberti and R. Di Felice, *Top. Curr. Chem.*, 2004, **237**, 183–227.
- 127 P. J. de Pablo, F. Moreno-Herrero, J. Colchero, J. Gómez Herrero, P. Herrero, A. M. Baró, P. Ordejón, J. M. Soler and E. Artacho, *Phys. Rev. Lett.*, 2000, **85**, 4992–4995.
- 128 A. J. Storm, J. van Noort, S. de Vries and C. Dekker, *Appl. Phys. Lett.*, 2001, **79**, 3881–3883.
- 129 Y. Okahata, T. Kobayashi, K. Tanaka and M. Shimomura, *J. Am. Chem. Soc.*, 1998, **120**, 6165–6166.
- 130 Y. Okahata, T. Kobayashi, H. Nakayama and K. Tanakat, *Supramol. Sci.*, 1998, **5**, 317–320.
- 131 C. Li, E. A. Hemmig, J. Kong, J. Yoo, S. Hernández-Ainsa, U. F. Keyser and A. Aksimentiev, *ACS Nano*, 2015, **9**, 1420–1433.
- 132 H. Nakayama, H. Ohnobe and Y. Okahata, *Chem. Commun.*, 2001, 2300–2301.
- 133 Y. Okahata and H. Nakayama, *Proc. Jpn. Acad.*, 2000, **76**, 145–150.
- 134 Y. Okahata and T. Kawasaki, *Top. Curr. Chem.*, 2005, **260**, 57–75.
- 135 J. Mysliwiec, A. Kochalska and A. Miniewicz, *Appl. Opt.*, 2008, **47**, 1902–1906.
- 136 J. G. Grote, J. A. Hagen, J. S. Zetts, R. L. Nelson, D. E. Diggs, M. O. Stone, P. P. Yaney, E. Heckman, C. Zhang, W. H. Steier, A. K. Y. Jen, L. R. Dalton, N. Ogata, M. J. Curley, S. J. Clarson and F. K. Hopkins, *J. Phys. Chem. B*, 2004, **108**, 8584–8591.
- 137 J. G. Grote, D. E. Diggs, R. L. Nelson, J. S. Zetts, F. K. Hopkins, N. Ogata, J. A. Hagen, E. Heckman, P. P. Yaney, M. O. Stone and L. R. Dalton, *Mol. Cryst. Liq. Cryst.*, 2005, **426**, 3–17.
- 138 L. Wang, J. Yoshida, N. Ogata, S. Sasaki and T. Kajiyama, *Chem. Mater.*, 2001, **13**, 1273–1281.
- 139 J. E. Lee, E. D. Do, U. R. Lee, M. J. Cho, K. H. Kim, J. I. Jin, D. H. Shin, S. H. Choi and D. H. Choi, *Polymer*, 2008, **49**, 5417–5423.
- 140 Y. J. Yu, Y. W. Kwon, K. N. Kim, E. D. Do, D. H. Choi, J. I. Jin, H. W. Shin, Y. R. Kim, I. J. Kang and J. A. Mikroyannidis, *Macromol. Res.*, 2009, **17**, 245–249.

- 141 B. Liu, B. S. Gaylord, S. Wang and G. C. Bazan, *J. Am. Chem. Soc.*, 2003, **125**, 6705–6714.
- 142 U. R. Lee, J. E. Lee, M. J. Cho, K. H. Kim, Y. W. Kwon, J. I. Jin and D. H. Choi, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 5416–5425.
- 143 Y. Kawabe, L. Wang, S. Horinouchi and N. Ogata, *Adv. Mater.*, 2000, **12**, 1281–1283.
- 144 Z. Yu, W. Li, J. A. Hagen, Y. Zhou, D. Klotzkin, J. G. Grote and A. J. Steckl, *Appl. Opt.*, 2007, **46**, 1507–1513.
- 145 M. Leonetti, R. Sapienza, M. Ibisate, C. Conti and C. Lopez, *Opt. Lett.*, 2009, **34**, 3764–3766.
- 146 J. Mysliwiec, L. Sznitko, A. Sobolewska, S. Bartkiewicz and A. Miniewicz, *Appl. Phys. Lett.*, 2010, **96**, 141106.
- 147 B. Sahraoui, M. Pranaitis, D. Gindre, J. Niziol and V. Kazukauskas, *J. Appl. Phys.*, 2011, **110**, 083117.
- 148 B. Derkowska, O. Krupka, V. Smokal and B. Sahraoui, *Opt. Mater.*, 2011, **33**, 1429–1433.
- 149 S. R. Walter and F. M. Geiger, *J. Phys. Chem. Lett.*, 2010, **1**, 9–15.
- 150 T. Singh, N. Sariciftci and J. Grote, *Adv. Polym. Sci.*, 2010, **223**, 189–212.
- 151 Y.-W. Kwon, D. H. Choi and J.-I. Jin, *Polym. J.*, 2012, **44**, 1191–1208.
- 152 A. J. Steckl, H. Spaeth, H. You, E. Gomez and J. Grote, *Opt. Photonics News*, 2011, **22**, 34–39.
- 153 E. F. Gomez, V. Venkatraman, J. G. Grote and A. J. Steckl, *Adv. Mater.*, 2015, **27**, 7552–7562.
- 154 Q. Sun, G. Subramanyam, L. Dai, M. Check, A. Campbell, R. Naik, J. Grote and Y. Wang, *ACS Nano*, 2009, **3**, 737–743.
- 155 M. J. Cho, U. R. Lee, Y. S. Kim, J. Shin, Y. M. Kim, Y. W. Park, B. K. Ju, J. I. Jin and D. H. Choi, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 1913–1918.
- 156 Y. Ner, J. G. Grote, J. A. Stuart and G. A. Sotzing, *Angew. Chem., Int. Ed.*, 2009, **48**, 5134–5138.
- 157 A. Bandyopadhyay, A. K. Ray and A. K. Sharma, *J. Appl. Phys.*, 2007, **102**, 064508.
- 158 V. Kolachure and M. H. C. Jin, Proceedings of the 33rd IEEE Photovoltaic Specialists Conference, San Diego, 2008.
- 159 S. Garaj, W. Hubbard, A. Reina, J. Kong, D. Branton and J. A. Golovchenko, *Nature*, 2010, **467**, 190–194.
- 160 S. van Dorp, U. F. Keyser, N. H. Dekker, C. Dekker and S. G. Lemay, *Nat. Phys.*, 2009, **5**, 347–351.
- 161 A. Bodley, L. F. Liu, M. Israel, R. Seshadri, Y. Koseki, F. C. Giuliani, S. Kirschenbaum, R. Silber and M. Potmesil, *Cancer Res.*, 1989, **49**, 5969–5978.
- 162 T. Fukushima, M. Kawaguchi, T. Hayakawa, S. Takeda, Y. Inoue, J. Ohno and K. Taniguchi, *Dent. Mater. J.*, 2007, **26**, 854–860.
- 163 C. M. Jewell, J. Zhang, N. J. Fredin and D. M. Lynn, *J. Controlled Release*, 2005, **106**, 214–223.
- 164 J. Zhang and D. M. Lynn, *Adv. Mater.*, 2007, **19**, 4218–4223.
- 165 J. Blacklock, Y. Z. You, Q. H. Zhou, G. Mao and D. Oupick, *Biomaterials*, 2009, **30**, 939–950.
- 166 Y. Ramgopal, D. Mondal, S. S. Venkatraman and W. T. Godbey, *J. Biomed. Mater. Res., Part B*, 2008, **85**, 496–503.
- 167 A. Kolbe, L. L. del Mercato, A. Z. Abbasi, P. Rivera Gil, S. J. Gorzini, W. H. C. Huibers, A. Poolman, W. J. Parak and A. Herrmann, *Macromol. Rapid Commun.*, 2011, **32**, 186–190.
- 168 Y. Lvov, G. Decher and G. Sukhorukov, *Macromolecules*, 1993, **26**, 5396–5399.
- 169 T. Segura and L. D. Shea, *Bioconjugate Chem.*, 2002, **13**, 621–629.
- 170 T. Segura, M. J. Volk and L. D. Shea, *J. Controlled Release*, 2003, **93**, 69–84.
- 171 P. Midoux, C. Pichon, J. J. Yaouanc and P. A. Jaffès, *Br. J. Pharmacol.*, 2009, **157**, 166–178.
- 172 G. Iacomino, G. Picariello, F. Sbrana, A. Di Luccia, R. Raiteri and L. D'Agostino, *Biomacromolecules*, 2011, **12**, 1178–1186.
- 173 E. V. B. van Gaal, R. S. Oosting, W. E. Hennink, D. J. A. Crommelin and E. Mastrobattista, *Int. J. Pharm.*, 2010, **390**, 76–83.
- 174 J. C. Rea, R. F. Gibly, A. E. Barron and L. D. Shea, *Acta Biomater.*, 2009, **5**, 903–912.
- 175 J. C. Rea, A. E. Barron and L. D. Shea, *J. Pharm. Sci.*, 2008, **97**, 4794–4806.
- 176 K. K. Ewert, A. Ahmad, H. M. Evans and C. R. Safinya, *Expert Opin. Biol. Ther.*, 2005, **5**, 33–53.
- 177 S. Chesnoy and L. Huang, *Annu. Rev. Biophys. Biomol. Struct.*, 2000, **29**, 27–47.
- 178 K. K. Ewert, A. Zidovska, A. Ahmad, N. F. Boussein, H. M. Evans, C. S. McAllister, C. E. Samuel and C. R. Safinya, *Top. Curr. Chem.*, 2010, **296**, 191–226.
- 179 C. R. Safinya, K. K. Ewert and C. Leal, *Liq. Cryst.*, 2011, **38**, 1715–1723.
- 180 *Gene Therapy Protocols*, ed. J. Le Doux, Humana Press, Totowa, 3rd edn, 2008.
- 181 A. Ahmad, H. M. Evans, K. Ewert, C. X. George, C. E. Samuel and C. R. Safinya, *J. Gene Med.*, 2005, **7**, 739–748.
- 182 A. J. Lin, N. L. Slack, A. Ahmad, C. X. George, C. E. Samuel and C. R. Safinya, *Biophys. J.*, 2003, **84**, 3307–3316.
- 183 *Pharmaceutical Perspectives of Nucleic Acid Based Therapeutics*, ed. R. I. Mahato and S. W. Kim, Taylor and Francis, London, 2002.
- 184 A. Zidovska, H. M. Evans, A. Ahmad, K. K. Ewert and C. R. Safinya, *J. Phys. Chem. B*, 2009, **113**, 5208–5216.
- 185 R. S. Shirazi, K. K. Ewert, C. Leal, R. N. Majzoub, N. F. Boussein and C. R. Safinya, *Biochim. Biophys. Acta*, 2011, **1808**, 2156–2166.
- 186 V. P. Torchilin, T. S. Levchenko, R. Rammohan, N. Volodina, B. Papahadjopoulos-Sternberg and G. G. M. D'Souza, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 1972–1977.
- 187 T. Gjetting, N. S. Arildsen, C. L. Christensen, T. T. Poulsen, J. A. Roth and V. N. Handlos, *Int. J. Nanomed.*, 2010, **9**, 371–383.
- 188 M. Bunuales, N. Duzgunes, S. Zalba, M. J. Garrido and I. Larduya, *Nanomedicine*, 2011, **6**, 89–98.
- 189 A. Martin-Herranz, A. Ahmad, H. M. Evans, K. Ewert, U. Schulze and C. R. Safinya, *Biophys. J.*, 2004, **86**, 1160–1168.
- 190 B. F. B. Silva, R. N. Majzoub, C. Chan, Y. Li, U. Olsson and C. R. Safinya, *Biochim. Biophys. Acta*, 2014, **1838**, 398–412.
- 191 R. N. Majzoub, K. K. Ewert, E. L. Jacovetty, B. Carragher, C. S. Potter, Y. Li and C. R. Safinya, *Langmuir*, 2015, **31**, 7073–7083.

- 192 C. Chan, R. N. Majzoub, R. S. Shirazi, K. K. Ewert, Y. Chen, K. S. Liang and C. R. Safinya, *Biomaterials*, 2014, **33**, 4928–4935.
- 193 R. N. Majzoub, C. L. Chan, B. F. B. Silva, K. K. Ewert, K. S. Liang, E. L. Jacovetty, B. Carragher, C. S. Potter and C. R. Safinya, *Biomaterials*, 2014, **35**, 4996–5005.
- 194 K. K. Ewert, V. R. Kotamraju, R. N. Majzoub, V. M. Steffes, E. A. Wonder, T. Teesalu, E. Ruoslahti and C. R. Safinya, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 1618–1623.
- 195 R. M. Majzoub, E. A. Wonder, K. K. Ewert, V. R. Kotamraju, T. Teesalu and C. R. Safinya, *J. Phys. Chem. B*, 2016, **120**, 6439–6453.
- 196 S. M. Elbashir, J. Harborth, W. Lendeckel, A. Yalcin, K. Weber and T. Tuschl, *Nature*, 2001, **411**, 494–498.
- 197 N. J. Caplen, S. Parrish, F. Imani, A. Fire and R. A. Morgan, *Proc. Natl. Acad. Sci. U. S. A.*, 2001, **98**, 9742–9747.
- 198 T. C. Karagiannis and A. El-Osta, *Cancer Gene Ther.*, 2005, **12**, 787–795.
- 199 M. Sioud, *Trends Pharm. Sci.*, 2004, **25**, 22–28.
- 200 C. R. Safinya, K. K. Ewert, R. N. Majzoub and C. Leal, *New J. Chem.*, 2014, **38**, 5164–5172.
- 201 N. F. Bouxsein, C. S. McAllister, K. K. Ewert, C. E. Samuel and C. R. Safinya, *Biochemistry*, 2007, **46**, 4785–4792.
- 202 C. Leal, N. F. Bouxsein, K. K. Ewert and C. R. Safinya, *J. Am. Chem. Soc.*, 2010, **132**, 16841–16847.
- 203 D. P. Siegel, *Biophys. J.*, 1999, **76**, 291–313.
- 204 K. R. P. Drew, L. K. Sanders, Z. W. Culumber, O. Zribi and G. C. Wong, *J. Am. Chem. Soc.*, 2009, **131**, 486–493.
- 205 J. J. Harrington, G. Van Bokkelen, R. W. Mays, K. Gustashaw and H. F. Williard, *Nat. Genet.*, 1997, **15**, 345–355.
- 206 W. Roush, *Science*, 1997, **276**, 1192–1193.
- 207 K. Liu, J. Varghese, J. Y. Gerasimov, A. O. Polyakov, M. Shuai, J. Su, D. Chen, W. Zajackowski, A. Marcozzi, W. Pisula, B. Noheda, T. T. M. Palstra, N. A. Clark and A. Herrmann, *Nat. Commun.*, 2016, **7**, 11476.
- 208 *Cross-Linked DNA Gels and Gels Particles*, ed. R. S. Dias and B. Lindman, Wiley Interscience, New York, 2008.
- 209 M. C. Morán, F. R. Baptista, A. Ramalho, M. G. Miguel and B. Lindman, *Soft Matter*, 2009, **5**, 2538–2542.
- 210 M. C. Morán, M. R. Infante, M. G. Miguel, B. Lindman and R. Pons, *Langmuir*, 2010, **26**, 10606–10613.
- 211 D. Costa, A. J. Valente, M. G. Miguel and J. Queiroz, *Adv. Colloid Interface Sci.*, 2014, **205**, 257–264.
- 212 D. Costa, M. G. Miguel and B. Lindman, *Adv. Colloid Interface Sci.*, 2010, **158**, 21–31.
- 213 M. C. Morán, M. P. Vinardell, M. R. Infante, M. G. Miguel and B. Lindman, *Adv. Colloid Interface Sci.*, 2014, **205**, 240–256.
- 214 M. C. Morán, M. G. Miguel and B. Lindman, *Biomacromolecules*, 2007, **8**, 3886–3892.
- 215 M. C. Morán, M. G. Miguel and B. Lindman, *Soft Matter*, 2011, **7**, 2001–2010.
- 216 M. C. Morán, T. Alonso, F. S. Lima, M. P. Vinardell, M. G. Miguel and B. Lindman, *Soft Matter*, 2012, **8**, 3200–3211.
- 217 L. E. Bromberg and A. M. Klibanov, *Proc. Natl. Acad. Sci. U. S. A.*, 1994, **91**, 143–147.
- 218 S. M. Mel'nikov, V. G. Sergeyev and K. Yoshikawa, *J. Am. Chem. Soc.*, 1995, **117**, 2401–2408.
- 219 V. G. Sergeyev, S. V. Mikhailenko, O. A. Pyshkina, I. V. Yaminsky and K. Yoshikawa, *J. Am. Chem. Soc.*, 1999, **121**, 1780–1785.
- 220 V. G. Sergeyev and V. A. Kabanov, *Langmuir*, 1999, **15**, 4434–4440.
- 221 M. M. Rozenman and D. R. Liu, *ChemBioChem*, 2006, **7**, 253–256.
- 222 T. R. Pearce, B. Waybrant and E. Kokkoli, *Chem. Commun.*, 2014, **50**, 210–212.
- 223 M. Lemaitre, B. Bayard and B. Lebleu, *Proc. Natl. Acad. Sci. U. S. A.*, 1987, **84**, 648–652.
- 224 Z. Li, Y. Zhang, P. Fullhart and C. A. Mirkin, *Nano Lett.*, 2004, **4**, 1055–1058.
- 225 F. E. Alemdaroglu, K. Ding, R. Berger and A. Herrmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 4206–4210.
- 226 M. P. Chien, A. M. Rush, M. P. Thompson and N. C. Gianneschi, *Angew. Chem., Int. Ed.*, 2010, **49**, 5076–5080.
- 227 F. Teixeira Jr., P. Rigler and C. Vebert-Nardin, *Chem. Commun.*, 2007, 1130–1132.
- 228 C. J. Yang, M. Pinto, K. Schanze and W. Tan, *Angew. Chem., Int. Ed.*, 2005, **44**, 2572–2576.
- 229 J. Jeong and T. Park, *Bioconjugate Chem.*, 2001, **12**, 917–923.
- 230 V. V. Filichev and E. B. Pedersen, *J. Am. Chem. Soc.*, 2005, **127**, 14849–14858.
- 231 S. I. Khan and M. W. Grinstaff, *J. Am. Chem. Soc.*, 1999, **121**, 4704–4705.
- 232 M. Murata, W. Kaku, T. Anada, Y. Sato, T. Kano, M. Maeda and Y. Katayama, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3967–3970.
- 233 P. Chen, C. Li, D. Liu and Z. Li, *Macromolecules*, 2012, **45**, 9579–9584.
- 234 K. J. Watson, S. J. Park, J. H. Im, S. T. Nguyen and C. Mirkin, *J. Am. Chem. Soc.*, 2001, **123**, 5592–5593.
- 235 D. Matulis, L. Rouzina and V. A. Bloomfield, *J. Am. Chem. Soc.*, 2002, **124**, 7331–7342.
- 236 W. Chen, J. Y. Gerasimov, P. Zhao, K. Liu and A. Herrmann, *J. Am. Chem. Soc.*, 2015, **137**, 12884–12889.
- 237 P. G. A. Janssen, A. R. Carretero, D. G. Rodríguez, E. W. Meijer and A. P. H. J. Schenning, *Angew. Chem., Int. Ed.*, 2009, **48**, 8103–8106.
- 238 P. G. A. Janssen, N. Meeuwenoord, G. Marel, S. J. Farouji, P. Schoot, M. Surin, Z. Tomovic, E. W. Meijer and A. P. H. J. Schenning, *Chem. Commun.*, 2010, **46**, 109–111.
- 239 R. P. Megens and G. Roelfes, *Org. Biomol. Chem.*, 2010, **8**, 1387–1393.