PERSPECTIVE

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Electrontransfer through DNA and metal-containing DNA

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DNA is currently explored as a new material for functional, molecular nano-architectures. In this respect, one major question is to transform DNA into a conducting material which has the potential for self-assembly into electronically active networks. The article covers recent insight into how DNA transports positive (holes) and negative (excess electrons) charges. It was found that holes move through DNA over significant distances using a G- and to a lesser extent also A-based hopping mechanism. EPR studies and recent investigations with model systems show that excess electrons can also hop through the duplex. The second part of the article describes how DNA is currently modified, particularly coated with metals, in order to increase the conductivity.

1 Introduction

Today strong efforts are under way to create DNA-inspired electronically active materials with self-organization properties.[1–3] The hope is that such a novel material may self assemble into complex conductive nano-wire networks,[4] which may have a fascinating technological potential. In this context, the question of how electrons travel through DNA is of fundamental importance. Investigation of how charges move through DNA and studies of how such a charge movement can be accelerated[5] or manipulated is in consequence a very timely research topic.[6,7] In this review we cover recent aspects of hole and excess electron transfer through DNA. We describe briefly the various approaches taken to increase the conductivity of DNA, *e.g.* by metallization of the DNA double strand. For a more detailed description of metallized DNA we refer the reader to an excellent review article written by Richter.[8]

This perspective is divided into two parts. In the first part, we describe briefly the transport of a positive charge, **a hole**, through DNA. We cover mostly recent results, which explain how a negative charge, an excess electron, moves through the DNA duplex. In order to distinguish this electron transfer from the hole transfer process, we call the transport of an electron through DNA: **excess electron transfer**. The last part of the article describes attempts to incorporate metals into the double helix or to metallize DNA with the intention to create DNA-based nano-wires.

Thomas Carell

Thomas Carell has been a full Professor of Organic Chemistry in the Department of Chemistry at the Philipps-University Marburg since 2000. Research in the group headed by Professor Carell is structured around biological chemistry and bio-inspired nano-materials with unusual optical and electronic properties. Thomas Carell (b. 1966) studied chemistry at the University of Munster and Heidelberg and received his diploma in 1993 from the University of Munster. He earned his doctoral degree (Dr. rer. nat.) in 1995 from the University of Heidelberg. After postdoctoral studies at the Massachusetts Institute of Technology, Cambridge (MIT), he moved to the ETH Zurich (Switzerland) as a research associate. He obtained his habilitation in 1999. In 2000 he joined the faculty of the Department of Chemistry at the Philipps-University Marburg as a full professor. He received the Kekule-Scholarship (1990), the Feodor-Lynen Fellowship (1993), the Liebig-Fellowship (1995), the Siemens Award (1995), the ADUC Award (1998), the Dozenten-Scholarship (1999), GDCh award for Medicinal Chemistry (1999) and the Novartis Young Investigator Award (2003). Since 2000 he has been a member of the Young Academy and was the Ginsberg lecturer at the Technion (Israel) in 2002.

Christoph Behrens

Christoph Behrens was born 1974 in Frankfurt/Main. He studied Chemistry at the University of Marburg. He performed his diploma studies in 2000 in the group of Professor G. Boche. He finished his PhD thesis in the group of Professor Carell working on excess electron transfer. In June 2003 he joined the group of Professor C.-H. Wong at the Scripps Institute/La Jolla.

Johannes Gierlich

Johannes Gierlich was born 1977 in Ludwigshafen/Rhein. He studied Chemistry in Marburg from 1998. After one semester at Auckland University/NZ he joined the group of Profesor Carell in November 2002. He has finished his diploma thesis and is currently working on his PhD thesis.

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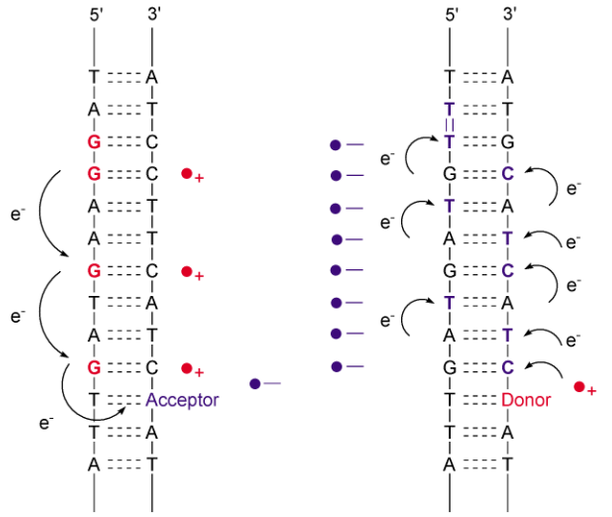


Fig. 1 Comparison of hole hopping process through DNA (left) and of a putative excess electron hopping (right) mechanism.

2 Electron transfer in non-metal-containing DNA

2.1 Hole and excess electron transfer through DNA

First insights into how DNA might transport charges along the helix axis came from studies about the transfer of a positive charge – **a hole** – through the DNA double helix. This charge transfer is, not only from a material science point-of-view, but also biologically of fundamental importance.[9,10] Hole transfer is directly involved in DNA-damage formation and the distance over which holes can move in DNA therefore determines at which positions in the genome oxidative DNA lesions may cluster.[11] It was found that single electron oxidation of DNA, which can be viewed as a hole injection process, yields initially a guanine radical cation in close vicinity to the injection site, because guanine is the nucleobase with the lowest oxidation potential.[12,13] Many detailed investigations[14,15] over the past decade showed that the initially formed guanine radical cation is able to participate in a long range charge delocalisation process (Fig. 1), which allows the radical cation to move through DNA over distances that can exceed 200 Å (20 nm).[10,16–18] This long range delocalization process was found to involve the movement of the positive charge between guanines in the duplex. The positive charge virtually hops through DNA by using guanines as stepping stones (Fig. 1).[19,20] This fact determines that the hole transfer efficiency depends critically on the amount of guanines in the DNA duplex and their distances to each other. Although the long range hopping process is now well accepted, some mechanistic details are still under intensive investigation and certain observations are still controversially debated.[21,22]

In contrast to our rather deep understanding of hole movement through DNA, little is known about the transfer of a negative charge, an excess electron, through the DNA duplex (Fig. 1).[23,24] If an electron donor or an electrode onto which DNA is grafted, injects electrons into the duplex, it is currently not clear how the injected excess electrons distribute in the DNA duplex.

We do not know if these negative charges move through DNA and if yes over what distance they may travel and how the base sequence modulates such a hypothetical excess electron transfer. These questions are however directly linked to the current efforts of creating DNA-inspired materials for nanoelectronic applications.[25]

If we consider that the pyrimidine nucleobases possess the lowest reduction potential (Table 1), we can postulate that they may function as the required stepping stones during the excess electron transfer reaction. Since every base pair contains either a cytosine or a thymine, one can in principle imagine a sequence independent hopping of excess electrons through DNA as depicted in Fig. 1. Giese *et al.* was the first to suggest such a process.[26]

Table 1 Reduction potentials of some nucleobases[a]

Base	Reduction potential/V		
	E(Red)[b]	*E*(Red)[c]	*E*(Red)[d]
dG	−2.76		
dA	−2.45		
dC	−2.23	−1.09	−2.1 (DMC)
dT	−2.14	−1.10	−2.1 (DMT)
U	−2.04	−1.05	−2.1 (DMU)
T=T			−2.2 (DMTD)

[a] DMC = Dimethylcytosine, DMT = Dimethylthymine, DMU = Dimethyluridine, DMTD = Dimethylthymine-dimer. [b] Polarographic potentials in DMF *versus* NHE.[12] [c] Data from pulse radiolysis experiments in water at pH = 8.5 against NHE.[40] [d] Data from fluorescence quenching experiments in acetonitrile against SCE.[37,38]

Table 2 pK_a-values of the reduced nucleobases[39,41]

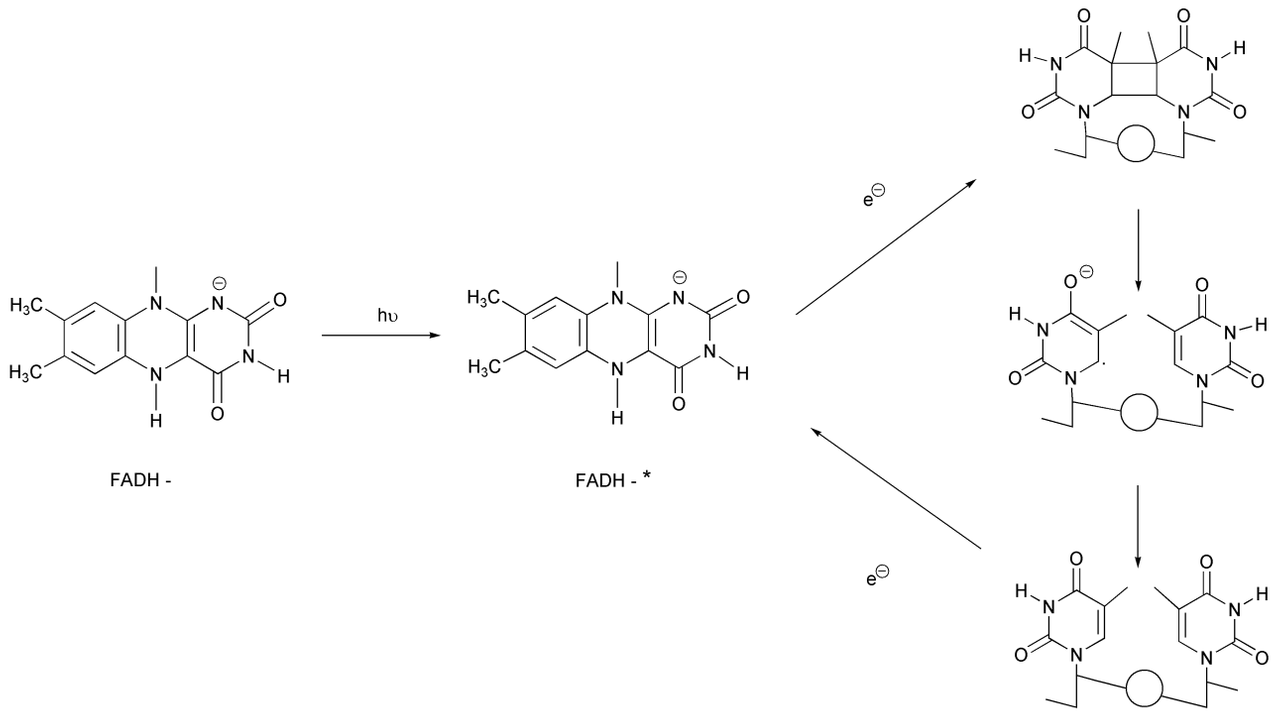
Equilibrium	pK_a
$TH^{\bullet} \rightleftharpoons T^{\bullet -} + H^+$	6.9
$TH^+ \rightleftharpoons T + H^+$	−5
$AH \rightleftharpoons A^- + H^+$	>14
$CH \rightleftharpoons C^{\bullet -} + H^+$	13
$CH^+ \rightleftharpoons C + H^+$	4.3
$GH \rightleftharpoons G^- + H^+$	9.5

Insight into the excess electron transfer capabilities of DNA was recently gained with the help of defined, synthetic donor–DNA-acceptor systems.[27] The obtained results together with data from extensive EPR-measurements, provide information into how DNA mediates excess electron transfer.[15,28,29]

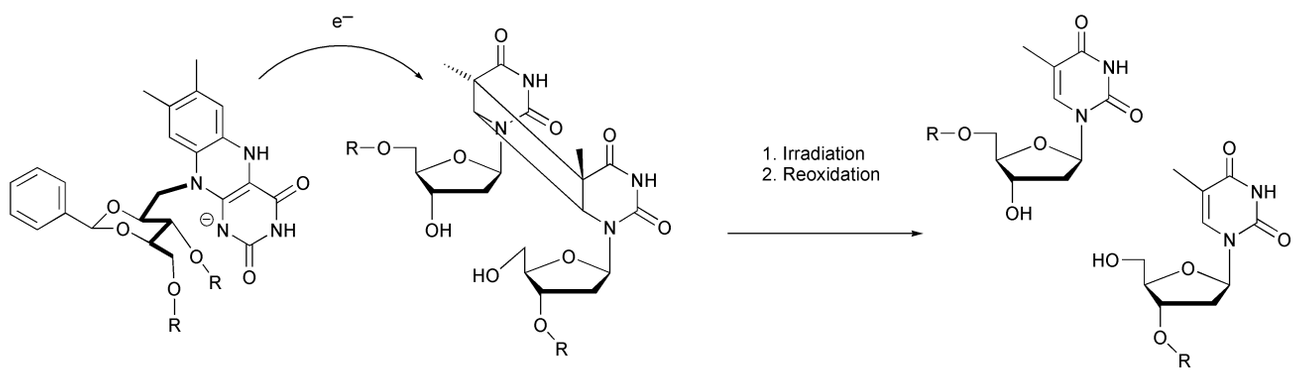
2.2 Excess electron transfer through DNA in nature

Electron donation to nucleobases (reduction) is not only of fundamental importance in material science, but also biologically interesting. Electron injection into DNA is performed by enzymes called DNA photolyase.[30] This protein is needed in many organisms for the efficient repair of UV-induced lesions in DNA.[31,32] UV-irradiation of cells induces the formation of a number of cyclobutane-type photoproducts, which are highly mutagenic and responsible for UV-induced cell death.[33] These lesions are repaired (split) by electron injection from a light excited, reduced and deprotonated flavin coenzyme ($FADH^-$*) inside the protein. Upon single electron reduction, the dimer (–T=T–) spontaneously cleaves back into the two monomers (repair: –T=T– ⟶ –T T–) as shown in Scheme 1.

This photolyase mechanism has been exploited for the design of model DNA strands, which allow the excess electron transfer capabilities of DNA to be deciphered.[34,35] This was possible because single electron reduction of the T=T-dimer and of all other nucleobases by the $FADH^-$* is a thermodynamic favorable process. The reduction potential of the reduced and deprotonated $FADH^-$* in its photoexcited state is believed to be around $E_{red*} = -2.6$ V against NHE,[36–38] which is negative enough to reduce all nucleobases including the T=T dimer as evident from the reduction potentials listed in Table 1. The reduction potentials show that thymine is the nucleobase, which is most easily reduced. An important issue in a protic solvent like water is, however, also the pK_a-values of the nucleobase radical anions, because proton transfer will have a strong effect on the reduction potentials. Table 2 lists the pK_a-values of some nucleobase radicals.[39] The thymine radical anion has a rather neutral pK_a of about 7. Rapid protonation of the cytosine radical anion (pK_a = 13) is, however, a strongly exothermic process, which may interrupt any excess electron transfer through DNA.



Scheme 1 Depiction of the repair mechanism employed by DNA photolyases for the repair of mutagenic UV-induced genome lesion.



Scheme 2 Depiction of the flavin induced cleavage of a T=T, which gives rise to a DNA strand break.

2.3 Excess electron transfer in donor-DNA-acceptor model systems

In order to study electron transfer through defined DNA strands, we prepared DNA double strands, which contain a special T=T lesion and a flavin donor site specifically incorporated into DNA. The dimer possesses an open backbone inducing an easily detectable strand break upon single electron reduction followed by cycloreversion. By systematically increasing the distance between the flavin donor and this T=T acceptor we could determine over what distance an extra electron is able to move through DNA. The chemistry that was used to investigate this electron transfer event is depicted in Scheme 2. The DNA double strands **1a**–**h**, prepared for the study are shown in Fig. 2. In these double strands, the distance between the flavin donor and the dimer acceptor was systematically increased from 3.4 Å to about 30 Å using additional A:T base pairs between the redox partners. For the measurement, solutions (pH = 7.4) containing the DNA strands were irradiated (360 nm) under anaerobic conditions, after reduction of the flavin with sodium dithionite.[34] HPLC analysis of samples removed from the assay solution after defined time intervals allowed the amount of dimer splitting to be quantified which was dependent on the irradiation time.

Since efficient repair (splitting) of the dimer was even observed in the double strands **1g** and **1h**, the experiments showed that an excess electron can efficiently travel over a distance of about 30 Å.[27] The rather small decrease of the repair efficiency with increasing distance indicated furthermore, that the excess electron does not travel directly from the flavin to the dimer employing a Marcus mechanism,[42,43] but hops using the intermediate A:T base pairs as temporary charge carriers. This result is in good agreement with data obtained from γ-radiolysis and EPR experiments.[15,28,29,44]

Based on the result that electrons hop through DNA over significant distances, the next scientific milestones will now be to analyze how the sequence of the DNA influences the transfer efficiency. Double strands with G:C base pairs inserted between the dimer and the flavin are currently under preparation and will be investigated. Analysis of the repair yields in such double strands will hopefully reveal further insights into how DNA mediates an excess electron transfer. Another important aspect is to clarify the kinetics of the excess electron transfer through DNA. Short time spectroscopic experiments by Lewis and Wasielewski with stilbenediether donor-bridged DNA hairpins suggest that excess electrons move more slowly through the duplex compared to electron holes and that in consequence the excess electron transfer is likely to be restricted to shorter distances.[45]

However, by clever design, novel DNA structures may be found which allow efficient transport of excess electrons through DNA. Along this line, one approach is to change one

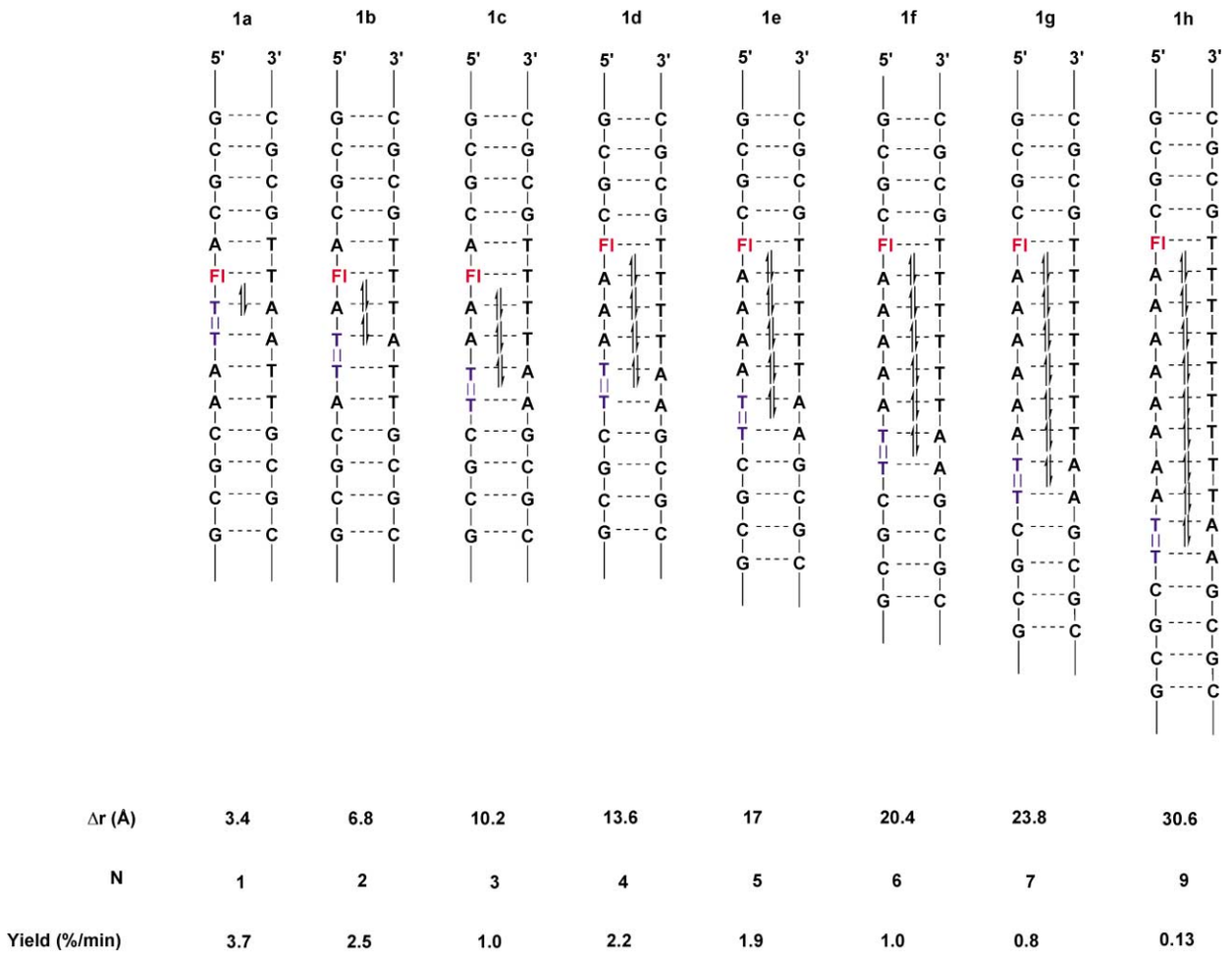


Fig. 2 Depiction of the DNA double strands containing the flavin and the dimer T=T at systematically increased distances.[27]

of the bases in the canonical base pair T:A into an organic molecule that is able to switch reversibly and easily between various redox states. Such a molecule could again be the flavin, which is used by nature as an essential ingredient in coenzymes like FAD, where it is responsible for the shuttling of electrons between proteins.[46,47] Flavin was selected by nature for electron transport because it is able to exist in a fully reduced, in a semi-reduced (radical) and in a fully oxidized redox state as shown in Fig. 3a. More importantly, the molecule features a hydrogen bonding pattern similar to thymine and hence may be able to participate in a hydrogen bonded base pair with the nucleobase A (Fig. 3b).[35] However, flavin is just too large to base pair with adenine in a B-conformational double helix structure. Instead a more linear pairing system must be devised to be able to accommodate the much larger flavin:A base pair. Such a linear pairing system could be the pyranosyl pairing system (Fig. 3b), which was developed by the group of Eschenmoser[48] and is a superb pairing system for the preparation of DNA-inspired materials. Fig. 3b depicts the discussed theoretical flavin:A base pair,[49] and the pyranosyl pairing system. Fig. 3c shows a model structure obtained for a putative pyranosyl duplex with six envisioned consecutive flavin:A base pairs.[50]

3 Excess electron transfer in metal-containing DNA-materials

3.1 Metals inside the duplex

In order to create DNA-inspired materials with strongly enhanced conducting properties, the development of metal containing DNA double strands, which contain the metal ions stacked on top of each other in the middle of the double helix is a new and highly exciting research direction. The groups of Schultz[52,53] and Shionoya[54] have pioneered over the last few years the development of base pairs, which are held together not by hydrogen bonds but by metal coordination forces.

The Shionoya group have synthesized a large variety of base pairs **1**–**5**, depicted in Fig. 4a, which are able to coordinate ions of Cu, Ag, B, Pd, Cd and Zn. Incorporation of these base pairs into a standard DNA double helix seems to be possible and depending on the metal, the base pairs contribute to the stability of the duplex. Very recently a DNA double strand was prepared containing more than one metal containing base pair in an array (Fig. 4b).[58] EPR- and CD-studies show that the metals indeed interact with each other, which led the authors to suggest that a metal containing "DNA" duplex is formed containing the metals stacking on top of each other inside the duplex.

In a similar direction, Schultz and Romesberg[52,53] prepared the metal coordinating base pairs **6**–**8** (Fig. 5) able to complex ions of Ag and Cu. The Tor[59] group is experimenting with the bipy-containing nucleobase **9** allowing also complexation of Cu ions. Again incorporation of these metal chelating base pairs provided DNA-inspired duplexes, the stability of which is influenced by the presence of the corresponding metal ion indicating that the metal is indeed complexed by the base pair in the DNA duplex.

3.2 Metals complexed by the DNA duplex (*M*-DNA)

Besides attempts to assemble DNA-like materials with a metal core, metals can also be attached to the outside of the DNA double strand in the grooves. This metal coordination allows in principle the creation of nano-wires with increased electron

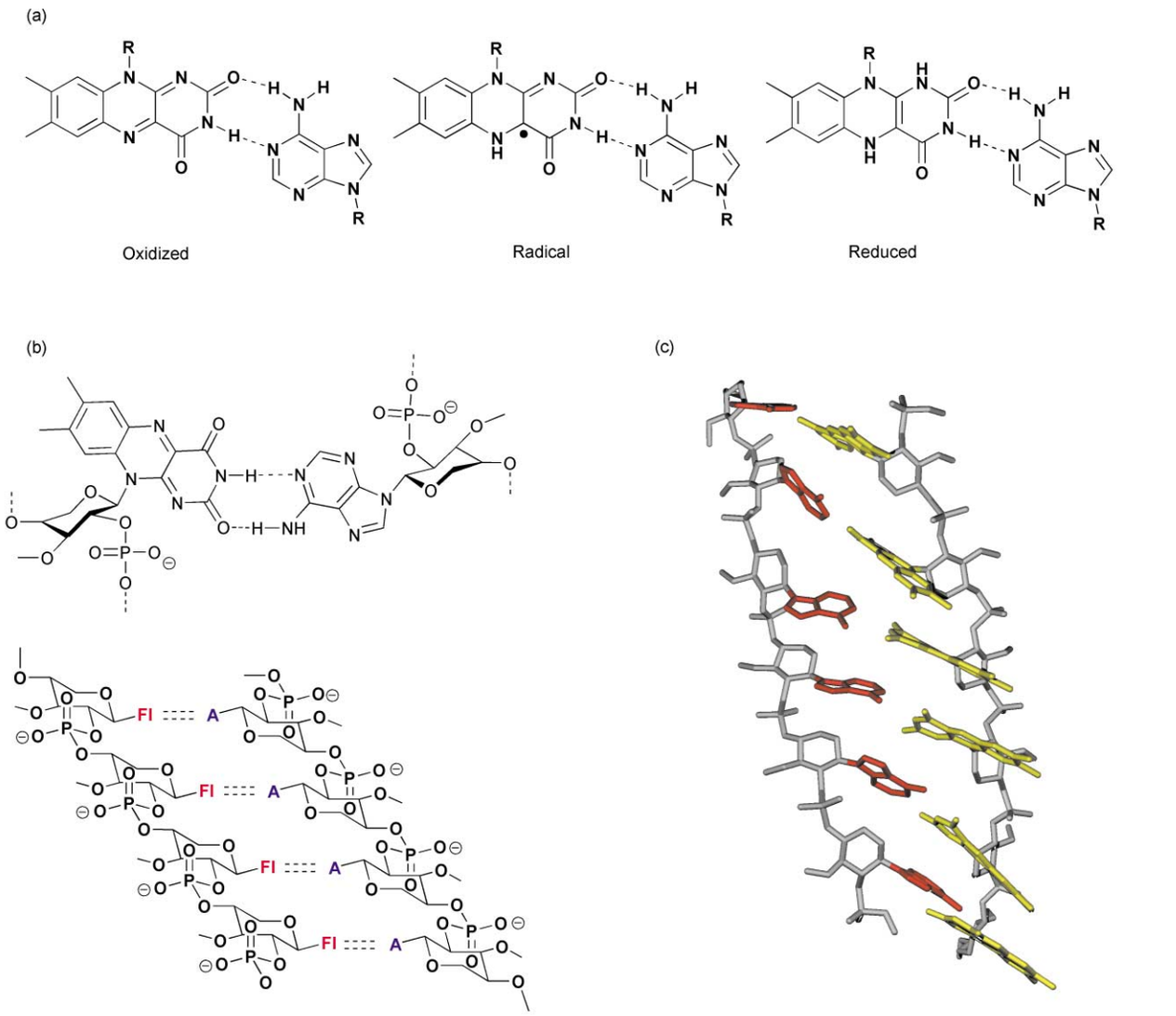


Fig. 3 The flavin:A base pair with the flavin in three different redox states (a). Depiction of the envisioned flavin:A pairing system (b), together with a schematic view of the 3′-methyl-xylopyranose (p-mXNA) double strand and a modeling study of a putative homo-flavin:A(p-mXNA) double helix (c).[51]

conductivity. The general approach to create *M*-DNA exploits that DNA is a polyelectrolyte with a polyanionic sugar-phosphate backbone. This is able to complex positively charged metal ions. *M*-DNA is simply formed upon addition of bivalent metals like Zn^{2+}, Co^{2+}, Ni^{2+} or Hg^{2+} to DNA. The exact position of the metals is currently not clear. They might be located in the grooves of the DNA double strand, but it is also possible that they replace a H-bonding proton inside the strand. Lee *et al.*[60–62] reported that a DNA strand modified with a fluorescein and a rhodamine shows a strong fluorescence decrease of the fluorescein upon *M*-DNA formation with Zn^{2+}. The author suggested that the effect could be caused by a fast electron transfer over a distance of 150 Å. Direct atomic force microscope (AFM) investigations, however, of *M*-DNA showed that the DNA has a strongly reduced length but failed to detect any increased conductivity.[63] Even though evidence for an improved electron transfer is still rather weak *M*-DNA holds great promise as a new material for the preparation of self-assembling electronic circuits.

Whereas *M*-DNA is a DNA double stranded structure complexed with bivalent metals, other approaches to increase the conductivity of DNA are directed toward full metallization of long DNA strands. In the past few years novel procedures have been developed, which allow full coating of the DNA-double helix with metals like Pd, Pt, Au, Ag and even with semiconducting CdS.[64]

3.3 Metals coating the duplex

Coating of a DNA wire with Ag^0 allows to date preparation of the most advanced metal wires templated by a DNA double strand. This was recently achieved by Braun *et al.* (Fig. 6).[4] The group bridged two nano-electrodes with a single 16 μm long λ-DNA double strand and exchanged the Na^+ ions at the sugar-phosphate backbone by Ag^+-ions.[65] The ion exchange was monitored by the quenching of the fluorescence of appropriately fluorescence labeled DNA by the Ag^+ ions. The Ag^+-coated DNA was subsequently reduced using either light or a basic hydroquinone solution to give nanometer-sized metallic Ag grains deposited on the DNA. Exposing the DNA-containing nano-structure to a solution of acidic hydroquinone and Ag^+ under low-light conditions allowed the development of a process similar to classical black-and-white photography but now on the DNA wire. The few Ag^0 atoms at the DNA strand catalyze the deposition of further Ag^0 along the DNA duplex forming a completely Ag-covered DNA wire, able to conduct electricity. Typical wires have a length of about 12 μm and a width of about 100 nm with 30–50 nm size metal grains deposited along the DNA backbone. The silver-coated DNA wires had a resistance of several MΩ over a length of about 15 μm. The DNA-construct featured an ohmic behaviour with a non-conducting gap for small voltages. In a similar approach Au-grains could be deposited on Ag-labeled λ-DNA, yielding

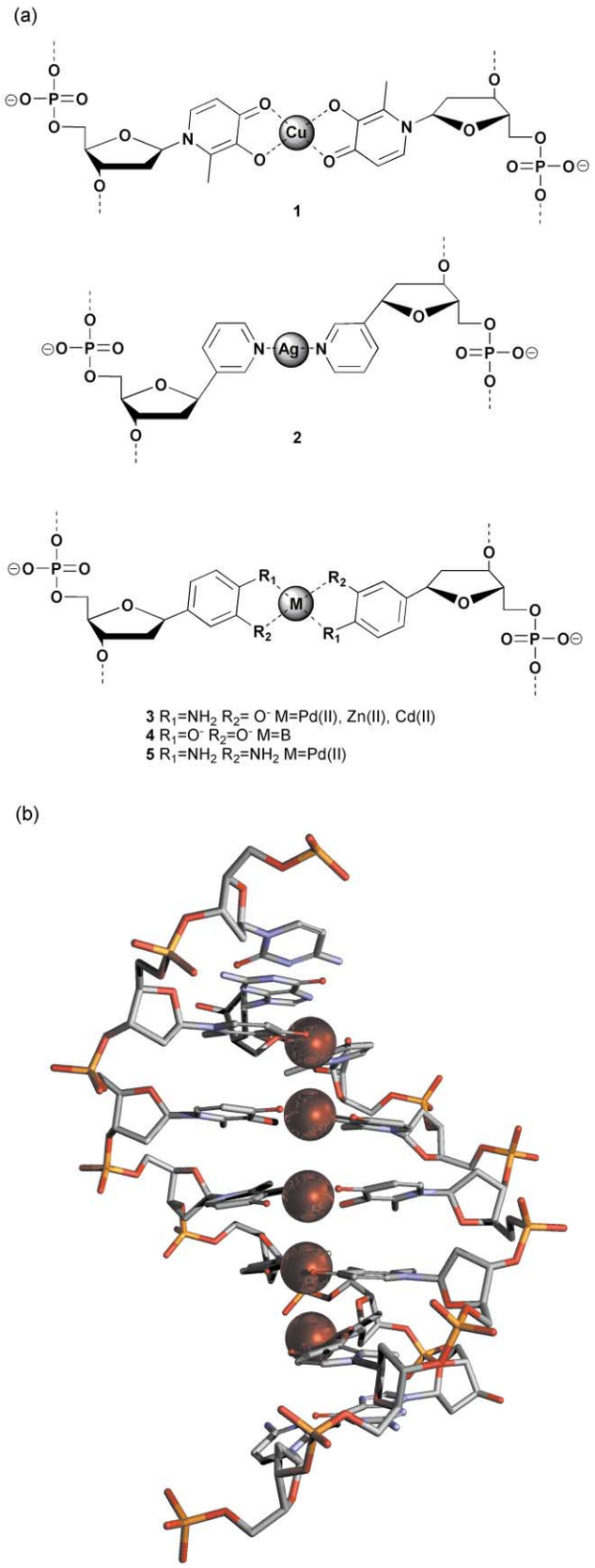


Fig. 4 a) Metal chelating base pairs **1**–**5** prepared by the group of Shionoya[54–57] and b) depiction of how the authors envision the structure of a DNA duplex made up of five consecutive metal chelating base pairs **1**.[58]

DNA strands with a resistance of only about 25 Ω up to currents of 200 nA over a length of a few micrometers. This corresponds to a conductance of *ca.* 7×10^4 S cm^{-1}, which is one seventh of polycrystalline gold. It is now clear that DNA can be used to template, at least in principle, complex electronically conducting nano-structures.[66]

Controlled assembly of the conducting nano-wires requires sequence specific metallization of the DNA strand, which can be viewed as lithography on a single DNA molecule. Keren polymerased several RecA proteins on a single-stranded DNA molecule.[66] The formed multimeric DNA–RecA complex bound to the complementary sequence in λ-DNA in a strand invasion process. In the complexed region, Ag-seeds were unable to bind, preventing gold-coating (by addition of $KAuCl_4$ followed by reduction with hydroquinone) in the protected area. This method allowed for the first time construction of a continuous gold wire with a defined gap. Removal of the RecA protein gave an intact DNA duplex, which can be utilized for further constructive operations.

An even more controlled way for the defined coating of DNA with gold are two new methods developed by Willner[67] (Fig. 7) and more recently Yonezawa.[68] The Willner group attached a single psoralene-unit to a gold cluster. Addition of the modified clusters to double helical DNA caused intercalation of the flat-psoralene ring into the duplex. Irradiation of the formed complex induced a [2 + 2] cycloaddition reaction between the psoralene and the thymines in DNA, which allowed to label AT rich sequences specifically with Au-clusters to give defined Au-nano-particle wires. The Yonezawa group stabilized Au-particles with thiocholinbromide thereby creating cationic Au-clusters able to adsorb on the negative backbone of λ-DNA. In this approach the adsorbed metastable Au clusters fused over time spontaneously to give metallized DNA-Au wires.

Next to the coating of DNA with Au and Ag, deposition of Pd-grain on DNA was used to prepare conducting DNA-wires.[69,70] Richter *et al.* complexed λ-DNA first with Pd^{2+} and secondly reduced the Pd^{2+} with a solution containing sodium citrate, lactic acid and methylamine borane, which leads to the formation of nanoscale Pd clusters on the DNA template. These clusters established at the end of the developing process a quasi-continuous Pd-grain coat around the DNA. The group could create 5 μm long DNA wires coated with 20–40 nm size Pd-cluster aggregates. The 60 nm wide DNA wires showed ohmic transport of electrons with an overall resistance of <1 kΩ for a total length of 6 μm. This corresponds to an upper conductivity of 2×10^4 S cm^{-1}, which is only five times smaller compared to bulk palladium.[8] These Pd wires and the Ag/Au nano-cluster covered DNA double strands provide clear evidence that DNA can be used to assemble nano-structures with moderate conducting properties. Other nano-structures containing Pt-covered DNA[71] or DNA-CdS-networks,[72] broadens the potential of these new bio/inorganic composite materials and extend their applicability even into the field of photoelectronics.

Even though it may be a long way until such nano-structures will become a part in nano-electronic tools the first steps to use DNA for the construction of electronic circuits and photoelectronic devices is made.[66]

4 Conclusion

From detailed model studies we can learn how DNA transports excess electrons and we can start to deduce how the DNA molecule has to be chemically modified in order to increase the electron transfer efficiency. Truly conducting DNA will clearly require the preparation of largely modified DNA strands in which the DNA may act only as a template. The current attempts to create DNA inspired materials, which can self assemble into defined two- and three-dimensional arrays, and which possess either a metallic coat or a metallic interior are at the moment the most promising approaches. Clearly, conductivity data obtained so far open up a new promising and highly exciting scientific research field.

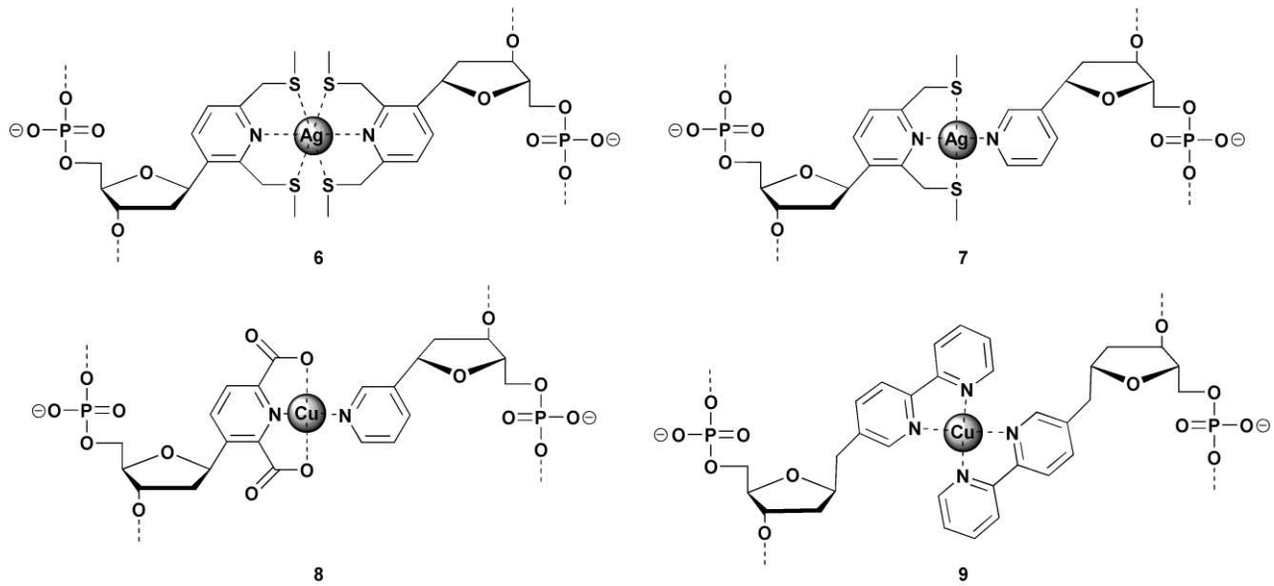


Fig. 5 Metal chelating base pairs **6**–**9** prepared by Schultz, Romesberg[52,53] and Tor.[59]

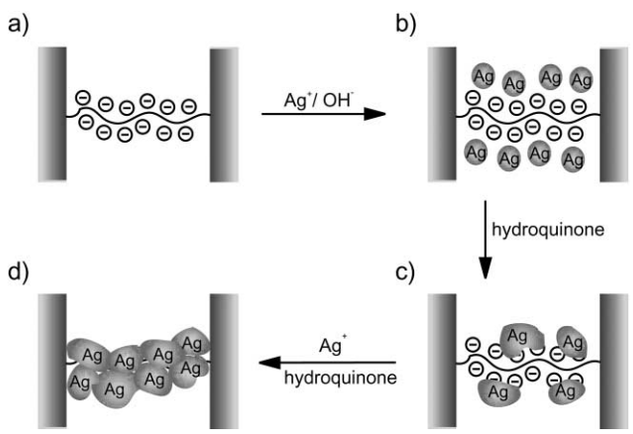


Fig. 6 Black-and-white photography on a DNA double helix. a) DNA between two nano- electrodes, b) Na^+/Ag^+ ion exchange, c) reduction to form nanometer-size Ag grains on the DNA, d) development process.[65]

We hope that in the future such materials can be used to self assemble into complex functional networks with defined electrical properties. If this becomes true, then chemistry and in particular supramolecular chemistry will start to contribute to the advances in nano-electronics in the often quoted bottom-up approach. We come closer to the dream of many chemists to develop DNA-containing molecules into the "silicon of the nano-world". For the reader interested in a more detailed inside into the fascinating world of DNA based materials we recommend two excellent recent reviews written by Richter[8] and Willner.[73]

Acknowledgements

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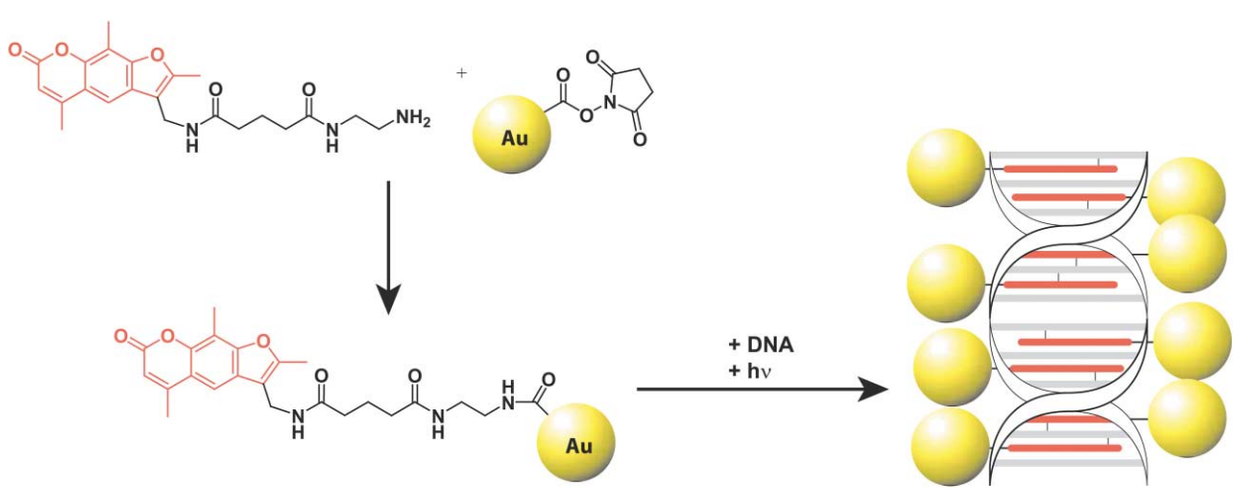

Fig. 7 Depiction of the psoralene-modified gold nano-particles and synthesis of a DNA wire.

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