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DNA Photonics – Photoinduced Electron Transfer in Synthetic DNA-Donor–Acceptor Systems

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Abstract: Recent experimental and theoretical results have demonstrated that structural dynamics are critical for a comprehensive mechanistic understanding of DNA charge transfer (CT). While the initial controversies regarding the long-range conductivity properties and wire-type behavior of DNA have been settled, a new field, DNA photonics, has emerged around the photophysics of nucleic acids. The contributions that can be expected from future studies in DNA photonics will be focused on the complex interactions between structural and electronic properties of DNA which are profound for biomedical applications such as DNA-targeted drug design. In this paper we report about our collaborative experimental efforts to expand the new and highly exciting field of DNA photonics. Experimental data from several different classes of functionalized DNA systems will be presented to illuminate the relationship between structural dynamics and charge injection/migration using state-of-the art femtosecond broadband spectroscopy. Our results present strong evidence for the involvement of hydrogen bond dynamics which must be considered as a specific mode of solvation dynamics inside the DNA helix.

Keywords: DNA Photonics

Torsten Fiebig, born 1969 in Bremen, Germany, obtained his PhD with Jürgen Troe at the University of Göttingen in 1996 for his work on electron transfer in covalently linked bichromophores. After a postdoctoral stay at Caltech with Ahmed Zewail during which he became familiar with the topic of charge transfer in DNA, he was appointed as a junior faculty member at the Technical University in Munich in 2000, where he started his collaboration with Hans-Achim Wagenknecht. This collaboration continued after Torsten Fiebig moved to Boston College as an assistant professor in 2003. Fiebig's research interest lies in the fundamental understanding of molecular interactions and ultrafast processes (*e.g.* energy, electron and proton transfer) in complex molecular architectures. His group is developing and applying new spectroscopic methodologies for probing real-time structural changes in biological systems. The underlying goal is to understand *molecular function* by probing *structure* and *dynamics* simultaneously.

Hans-Achim Wagenknecht was born in Pforzheim in 1968. He received the diploma in chemistry at the University of Freiburg in 1995 and a Ph.D in organic chemistry from the University of Basel in 1998. His thesis work under the direction of Professor W.-D. Woggon investigated the catalytic cycle of chloroperoxidase using synthetic porphyrin thiolate complexes as active-site analogs. Following his doctoral studies, he was a postdoctoral fellow with Professor J. K. Barton at the California Institute of Technology in Pasadena. In 2000 he started his independent research at the Technical University Munich. His habilitation on 'Investigation of Charge Transfer in DNA using Synthetically Modified Oligonucleotides' was completed in 2003. His work was supported by fellowships from the Swiss National Science Foundation, the Novartis Foundation and the DFG (Emmy-Noether). Wagenknecht received calls for professorships at the Universities of Erlan-

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CHIMIA **2007**, *61*, No. 4

gen and Regensburg. In Fall 2005, the Wagenknecht group moved to the University of Regensburg. The main research interests are the design and synthesis of fluorophore-modified DNA for the investigation of charge and energy transfer processes for applications in DNA analytics, in biotechnology, and as nanodevices. Wagenknecht's previous awards include the Award of the Dr.-Otto-Röhm-Gedächtnisstiftung (2003), the ORCHEM-Award for Organic Chemistry (2004), and the Bredereck-Award for Bioorganic Chemistry (2005).

1. Introduction

Eley and Spivey mentioned in the 1960s for the first time that DNA could provide an efficient pathway for charge transfer along the helical axis.[1] The regularly stacked one-dimensional array of aromatic DNA bases led the authors speculate about molecular-wire properties of DNA. However, at that time important questions about the mechanism, the dynamics and, most importantly, the distance dependence of DNA-mediated charge transfer could not be addressed experimentally. Since DNA could only be obtained from natural sources with mixed sequences, the proposal of charge transfer through the DNA remained highly speculative. Early experimental studies, which were limited to γ-pulse radiolysis, revealed the first information about ions and radicals inside the DNA.[2,3]

The development of automated solid-phase synthesis and DNA phosphoramidite building block chemistry gave access to desired oligonucleotides in sufficient quantities.[4,5] This development provided the basis for the preparation of structurally well-defined DNA-donor-acceptor systems for systematic studies of DNA-mediated charge transfer.[6,7] The group of Jacqueline Barton advanced the field in the 1990s with a remarkable publication on DNA-mediated electron transfer between two metallointercalators, both of them either non-covalently bound or covalently tethered to DNA.[8–10] Since then, the subject has grown to an enormous research field. Research groups of different chemistry subdisciplines, such as organic chemistry, inorganic chemistry, physical chemistry and biochemistry, as well as biologists, physicists and materials scientists are now working with DNA and have contributed significantly to this topic (Fig. 1). A fascinating and highly controversial scientific discussion was initiated. DNA was considered as a molecular wire,[11–13] or as an insulating,[14,15] semiconducting,[16] conducting,[17,18] or superconducting[19] biopolymer. Many details of the mechanism have been elucidated by now and the discussion has lost most of its controversy. Based on the experiments in the 1990s (for the oxidative mode) and in the early 2000s (for excess electron transfer) it was possible to develop a better understanding of the mechanisms and the chemistry induced by charge transfer processes in DNA.[20,21] It is now established that DNA-mediated charge transport does occur on fast timescales, following different mechanistic regimes.[22,23] Depending on the design of the DNA assay, it can yield chemical reactions over distances in the nanometer range.

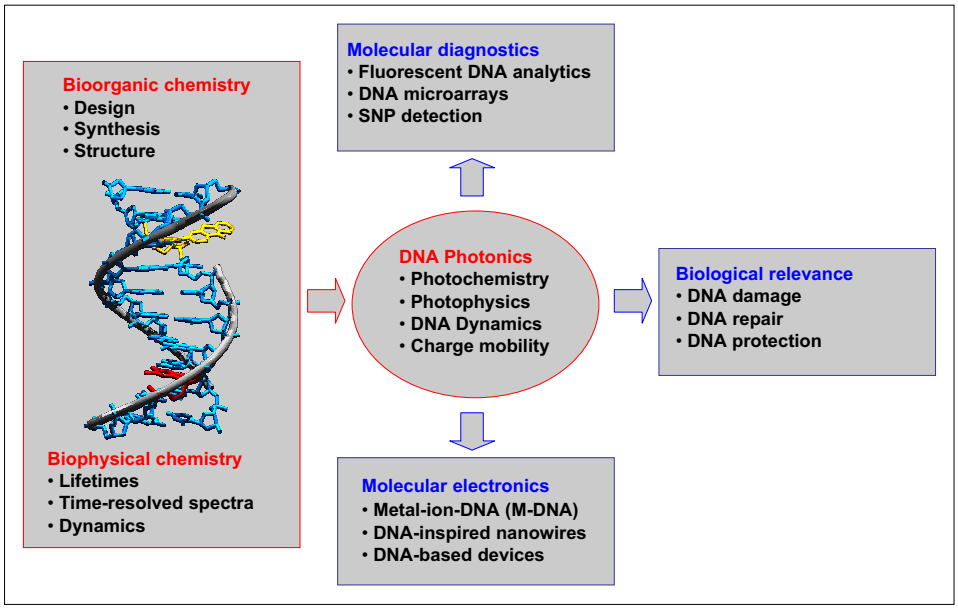

Fig. 1. Interdisciplinary nature of the studies of charge transfer processes in DNA

While the initial controversy regarding the long-range conductivity properties and 'wire-type-behavior' of DNA has been settled, a new and broader scientific field, ***DNA photonics***, has emerged around the photophysics of nucleic acids with respect to potential applications.[24] The development of chromophore-labeled nucleic acids is a research topic of increasing interest with important applications in nanobiotechnology.[25]

2. Preparation of Modified DNA for Studies of Photoinduced Charge Transfer

In order to study photoinduced charge transfer processes through the DNA, it is necessary to modify oligonucleotides with suitable photochemically activatable compounds.[6] We focused on well-characterized organic chromophores as charge donors, *e.g.* ethidium, pyrene, phenothiazine. These organic chromophores can be synthetically incorporated into oligonucleotides by two principally different structural approaches:[26–31]

i) Chromophores as DNA base attachments
ii) Chromophores as artificial DNA base or base pair surrogates.

DNA base modifications can be introduced *via* the automated solid-phase methodology by using the corresponding synthetic DNA building blocks (Fig. 2). In the first steps, the charge donor is synthetically attached to natural DNA bases, *e.g.* by palladium-catalyzed cross-coupling methodologies.[28] The halogenated nucleoside precursor and the boronic acid of the chromophore can be prepared according to standard procedures. Subsequently, the 4,4'-dimethoxytrityl group is introduced to the 5'-hydroxy group of the 2'-deoxyribose moiety, and the phosphoramidite group to the 3'-hydroxy group in order to yield the fully protected DNA building block.

Alternatively to the synthetic building block strategy, DNA modifications can be introduced by solid-phase methods which are applied during or after the complete automated solid-phase synthesis. Most of these so-called postsynthetic methods have molecular probes attached to the 5'-terminal hydroxy group and rely on an amide bond formation between the carboxylate group as part of the charge donor and the amino group as part of a linker or a modified DNA base in the oligonucleotide.[6] In our group, a fast and versatile synthetic approach is applied for the preparation of modified oligonucleotides in which the chromophore is attached to the DNA base *via* an acetylene bridge (Fig. 3).[29–32] One possibility for this methodology is the application of commercially available phosphoramidites that carry a halogen as a reactive group on the DNA base. The automated DNA synthesis is interrupted after the incorporation of this special phosphoramidite, then the Sonogashira-type cross-coupling procedure with the chromophore is performed and subsequently the automated DNA synthesis is continued to the full oligonucleotide. Finally, the

CHIMIA **2007**, *61*, No. 4

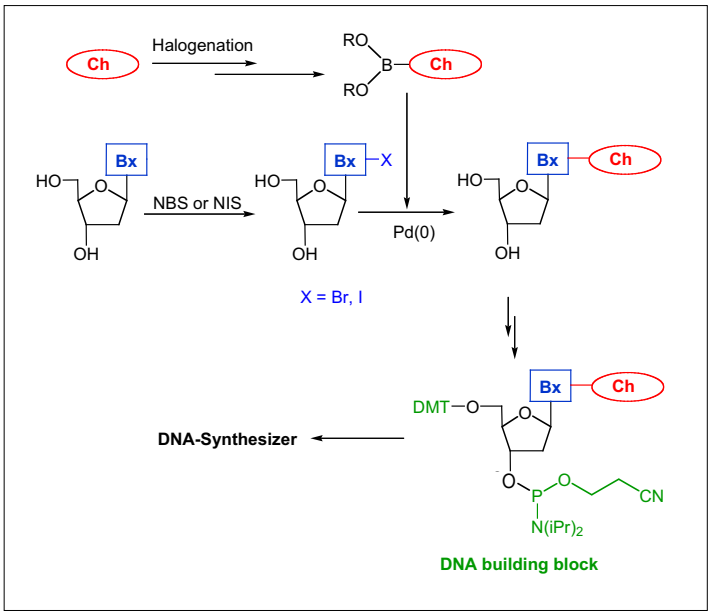

Fig. 2. Principal synthetic route for the modification of DNA bases in oligonucleotides by organic chromophores using the building block strategy (Bx = base, Ch = chromophore)

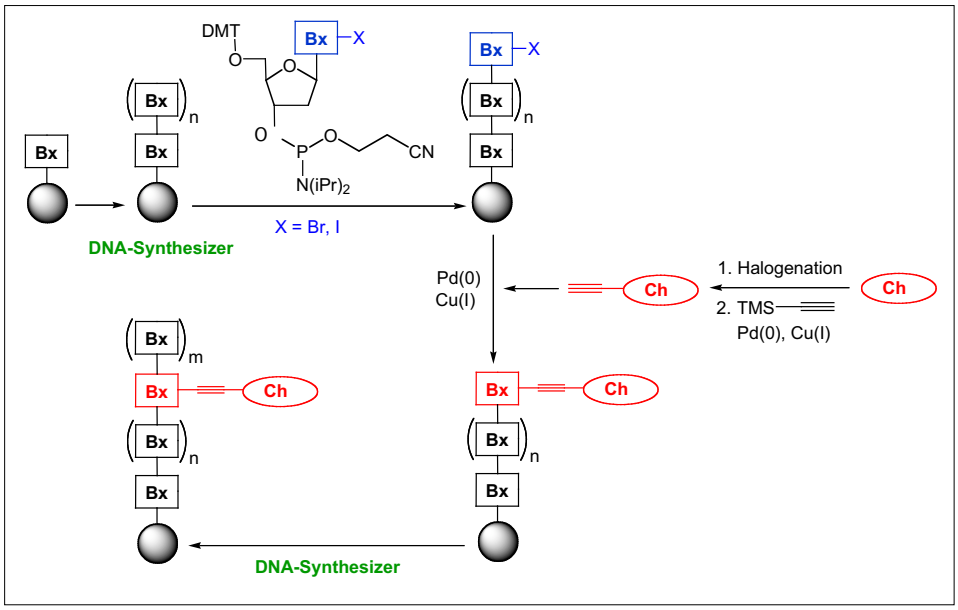

Fig. 3. Synthetic semi-automated solid-phase strategies for the chromophore modifications in DNA (Bx = base, Ch = chromophore)

oligonucleotide is cleaved off the beads and purified by HPLC, gel electrophoresis or capillary electrophoresis. Using this methodology, the preparation of the corresponding water-sensitive phosphoramidite, which represents in a lot of cases a synthetic bottleneck, can be avoided. The modification protocol is versatile and can be applied to oligonucleotides of different lengths and/or different base sequence compositions.

For DNA base surrogates the corresponding artificial nucleoside needs to be synthesized starting from a reactive precursor of the 2'-deoxyribofuranose moiety. There is a large number of recently reported syntheses of chromophores as DNA base substitutes, *e.g.* coumarines,[33] flavine derivatives[34] and thiazole orange derivatives.[35,36] Additionally, a variety of phosphoramidites as DNA building blocks for the introduction of fluorophores to DNA is commercially available, *e.g.* acridine derivatives.[37] Clearly, the synthetic protocols for this kind of DNA modifications do not follow a principle strategy which can be applied in a versatile fashion, as is the case for the DNA base modifications mentioned in the previous paragraphs. It is important to point out, that for the synthetic incorporation of ethidium,[30,31] indole[38] and perylene bismide[39] that have been performed in our group, the 2'-deoxyribose moiety had to be replaced by a 2-amino-1,3-propandiol as an acyclic phosphodiester bridge. This makes clear that this type of DNA-chromophore modification represents the most time-consuming option, and a lot of synthetic research efforts need to be invested in order to develop a reliable synthetic procedure for the routine synthesis of chromophore-modified DNA.

3. Femtosecond Broadband Pump-Probe Spectroscopy

Real-time information about the dynamics of photoinduced charge transfer processes can be obtained from optical pump-probe experiments using ultrashort laser pulses. Fig. 4 illustrates the basic layout of this technique. After a pump pulse has optically excited a certain volume in the sample cell, a second laser pulse (probe pulse) detects the pump-induced change in absorbance. The arrival of the probe pulse can be controlled through a variable delay line that determines the optical path length of the probe pulse before being split into two pulses (signal and reference) and focused into the sample.

After passing through the sample both signal and reference are spectrally dispersed and simultaneously detected on a CCD sensor. Compared with the conventional (two-color) pump-probe technique, broadband pump-probe spectroscopy can (in principle) capture and resolve reactant, intermediate and product states simultaneously. By measuring the pump-probe spectra as a function of time one not only obtains 'kinetic traces at multiple wavelengths' but moreover the complex spectral evolution which includes detailed information about spectral shifts, lineshapes and linewidths can be followed.[40] There are up to three contributions to the pump-probe spectra. Depending on the spectral range of interest one can observe i) induced transient absorption of excited states, ii) stimulated emission from excited states, and iii) ground state bleaching. Although the separation of these contributions is not always straightforward one can apply different methods to simplify the interpretation of pump-probe spectra. In fact, in many cases ii) and iii) can be accounted for by using steady state fluorescence and absorption data, or simply by selecting a wavelength range where these contributions are not significant.

One of the central elements of the broadband pump-probe setup is the white light (WL) continuum used for probing. WL generation occurs when ultrashort laser pulses propagate through optically transparent solid media with certain symmetry properties.[41–43] Several nonlinear optical processes contribute to this phenomenon. The core of current theoretical models is the

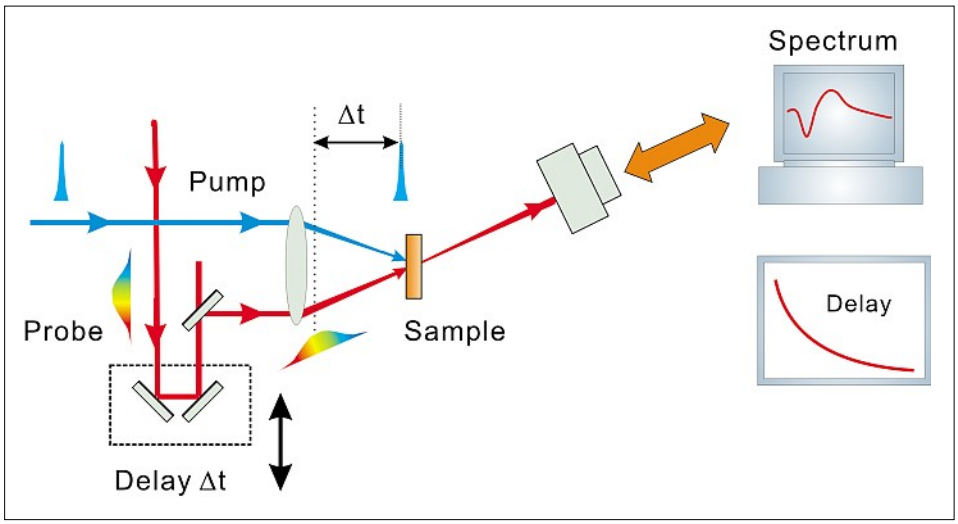

Fig. 4. Schematic layout of a broadband pump-probe setup

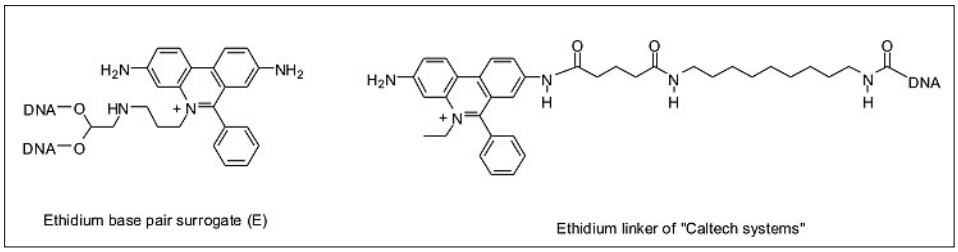

Fig. 5. Comparison of two ethidium-linker systems. Left: the new ethidium base pair surrogate; Right: the long, flexible intercalator system studied at Caltech ('Caltech system').[46]

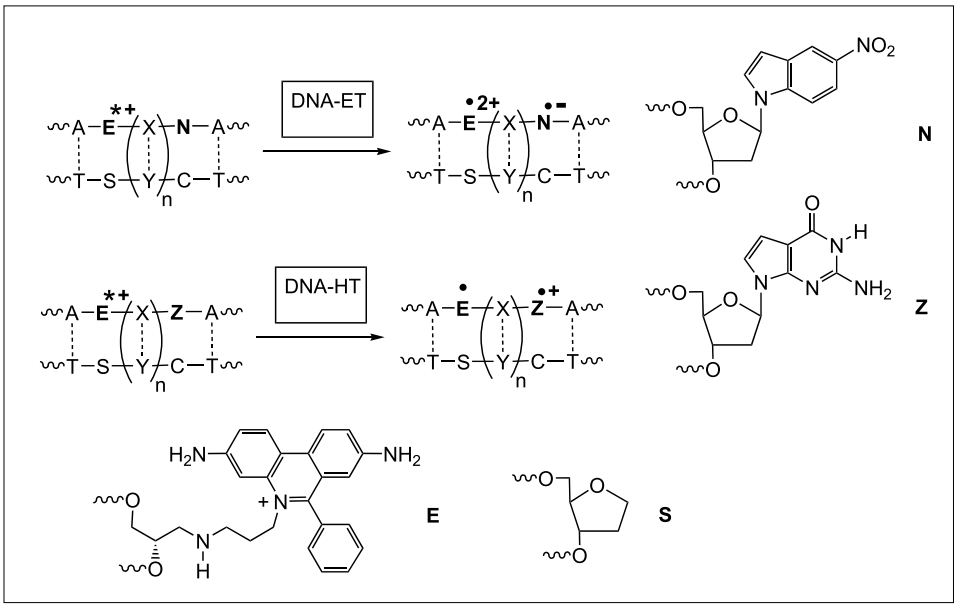

Fig. 6. DNA system for the direct spectroscopic comparison of oxidative hole transfer in E/Z-modified DNA and reductive electron transfer in E/N-modified DNA (n = 1–3)

formation of an 'optical shock wave'[44,45] that interacts with a low-density electron-hole plasma, generated in the medium by multiphoton ionization. The complex interplay between the shock wave and the plasma leads to a sharp steepening (and shortening) of the laser pulse in the time domain and thus to substantial broadening in the frequency domain (uncertainty principle).

4. Conformational Dynamics and Base Pair Motions in DNA Charge Transfer

4.1. *Ethidium-modified DNA Assemblies*

In 1999 Wan *et al.* reported the first time-resolved measurements on a DNA-intercalated chromophore that served as a hole donor after photoexcitation.[46] The intercalator, ethidium (E), was covalently bound to the sugar phosphate backbone using a molecular linker that controlled the distance between the intercalation site and the hole acceptor (7-deazaguanine, Z).

Fig. 5 compares the ethidium base surrogate used by Wagenknecht and Fiebig[47] ('surrogate system'), with the one synthesized by Barton *et al.*[46] ('Caltech system'). In both systems, ethidium is covalently linked to the DNA backbone, however, in the Caltech system, the ethidium is attached to the 5' terminal hydroxyl group of one of the DNA strand. Due to the flexibility of the alkyl chain, ethidium can intercalate into the base stack without significant restraints of its orientational motion.[48] In contrast, the present DNA duplexes contain ethidium that is inserted (not intercalated) as a base pair analog into the base stack. The sugar moiety of natural nucleosides was replaced by an acyclic linker system which is tethered to the N-5 position of the phenanthridinium heterocycle.[30,31] Hence, it is considerably more rigid and the ethidium lacks the conformational freedom that is characteristic for the Caltech system. Whereas the base stack has to locally unwind to accommodate the intercalator in the Caltech systems, the surrogate system contains an abasic site analog (S) on the counter strand, allowing ethidium to be inserted into the stack without structural distortions.

In the E/Z systems the emission of photoexcited ethidium is quenched as a result of a hole transfer ($E(Z^{\bullet+}/Z = 1.0$ V[49]). For reductive electron transfer, 5-nitroindole (N) is an ideal electron acceptor because of its suitable reduction potential ($E(N/N^{\bullet-}) = -0.3$ V[50]). Due to the favorable reduction potential of ethidium, ethidium-modified DNA has been mostly employed to investigate oxidative hole transfer. DNA–acceptor conjugates where ethidium serves as electron donor had not been reported until recently. The comparison of DNA-mediated electron (ET) and hole transfer (HT), initiated by photoexcited ethidium is particularly relevant because of the structural similarities between the redox constituents (Fig. 6).

We have combined femtosecond pump-probe and nanosecond fluorescence lifetime measurements to extract kinetic data that covered a broad spectrum of timescales, ranging from picoseconds to several hundred nanoseconds. Redox inert duplexes (in which Z and N were replaced by G) served as reference systems. In the DNA duplexes, where the charge acceptor (N or Z) is separated from ethidium by a single base pair, charge transfer takes place as indicated by a rapid transient decay component of 50 ps (22%) for ET, or 150 ps (27%) for HT, respectively. The relatively small amplitudes of the picosecond time components reflect

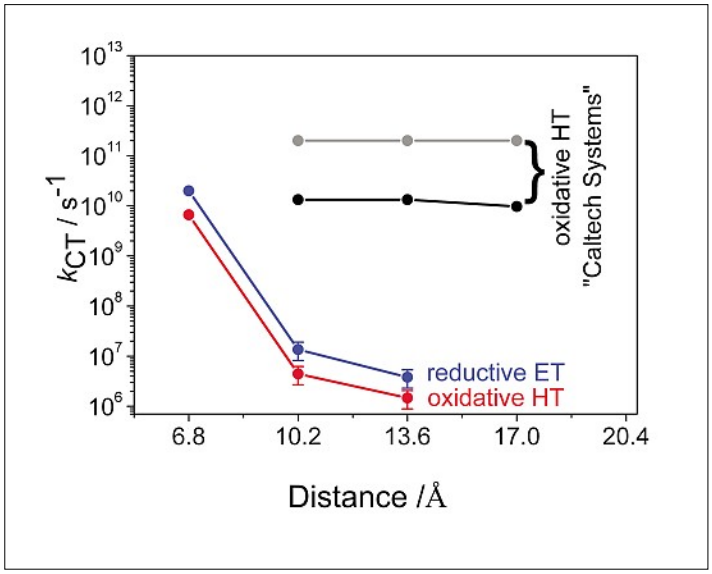

Fig. 7. Charge transfer rate distance dependencies for our system (blue: ET, red: HT) in comparison with those in Caltech systems (black, gray; rates found in ref.[46]). Copyright 2006, National Academy of Sciences, USA.

the fractions of reactive molecules with favorable, well-stacked structures already present in the ground state. For the DNA assemblies bearing 5-nitroindole or 7-deazaguanine separated by more than one base pair, no ultrafast dynamics are observed in the pump-probe spectra. However, the lack of a short-time decay in these DNA conjugates does not necessarily equate to the absence of charge transfer. Fluorescence quenching and fluorescence lifetime measurements confirmed that slower charge transfer (on the nanosecond to microsecond timescale, see Fig. 7) takes place in these systems.

The difference for HT rates across distances larger than one base pair is astoundingly dramatic (4–5 orders of magnitude). It is obvious that ethidium, when rigidly inserted as a base pair surrogate, does not facilitate long-range ultrafast charge transfer. Remarkably, this finding is true for both types of charge transfer, reductive ET and oxidative HT. The fact that HT and ET across a single base pair occur on the timescale of 100 ps proves that the inserted ethidium exhibits strong electronic coupling to adjacent bases within the stack. The stark contrast in the distance dependence of the Caltech and the surrogate ethidium systems must therefore be attributed to their inherently different dynamical properties. In the surrogate system, nuclear motions are largely inhibited due to the short linker and the tight insertion mode. Thus 'conformational sampling' of the accessible configurational space is disabled. In contrast, in the loosely tethered intercalator system nuclear motions and conformational sampling are favorable and warrant high charge transfer rates, even across a distance of several base pairs. The results underline the importance of conformational gating for facilitating efficient charge transfer in DNA over long distances. The fact that both electron and hole transfer are characterized by similar rates and distance dependencies, suggest that conformational sampling may be a generic prerequisite for any electronic transfer process through π-stacked nucleic acids.

Recently, Wagenknecht *et al.* employed the ethidium/DNA/7-deazaguanine system (with two intervening base pairs) as an assay to detect DNA base mismatches and abasic sites.[51] By using the charge transfer process in addition to the emission properties of photoexcited ethidium, the detection of single base mismatches does not rely solely on the small differences in the hybridization energies between matched and mismatched duplexes. In fact, the presence of a single base mismatch (or an abasic site) between ethidium and 7-deazaguanine yields enhanced fluorescence quenching compared to the matched duplexes. This observation is entirely consistent with the concept of conformational gating as a prerequisite for long-distance charge transfer: Mismatches or abasic sites lead to local unwinding of the duplex and create locally reduced rigidity. As a result, enhanced base-pair motions facilitate long-range charge transfer more efficiently.

4.2. *Investigation of Reductive Electron Transfer in Pyrene- and Phenothiazine-modified DNA*

As already pointed out in the previous section, DNA-mediated charge transfer processes can be divided into oxidative (electron) hole transfer or reductive (excess) electron transfer processes. HT has a significant relevance for oxidative DNA damage which may result in mutagenesis, apoptosis, or cancer.[52–54] Nearly all publications until the year 2000 focused on this mode of charge transfer.[20,21] Hence, the underlying mechanism for HT has been elucidated more satisfactorily than the mechanism for ET. Motivated by potential applications in biotechnology and DNA-based electronic nanodevices[25] involving excess electron transfer, reductive ET was under investigation extensively over the last five years.[7,20,21,55] ET processes are also relevant for the design of electrochemical DNA chips for sensitive detection of single base mutations.[56] A new but related area of research is moving away from the pure biological view on DNA towards DNA-inspired architecture that features important additional properties. Most recently, a chain of up to 10 metal ions could be incorporated into the middle of the base stack of such a DNA architecture.[57,58]

In recent studies, we have applied pyrene-modified nucleosides as electron donors. The locally excited state of pyrene (Py*) can act as a precursor state for electron transfer to adjacent pyrimidine bases. Based on the redox potential ($Py^{\bullet+}$/Py=1.5 V *vs.* NHE) and the singlet energy of pyrene (E_{00}=3.25 eV),[59] the driving force of the electron transfer was estimated to be 50–150 mV, using the reduction potentials of –1.8 V and –1.9 V for the pyrimidine pairs $C^{\bullet-}$/C and $T^{\bullet-}$/T, respectively. These values have been derived from charge transfer studies with photoexcited 2-aminopurine.[60] We prepared Py-dU and 5-(pyren-1-yl)-2'-deoxycytidine (Py-dC) by Suzuki-Miyaura-type cross coupling reactions.[28] By comparing Py-dC and Py-dU spectroscopically in aqueous solution as nucleoside models for electron transfer in DNA we were able to obtain the information that a small energy difference exists between $U^{\bullet-}$ and $C^{\bullet-}$.[61] Most importantly, we detected a difference in the basicity of the generated pyrimidine radical anions that was originally mentioned by Steenken. [62] Our studies revealed that intramolecular electron transfer and protonation in Py-dU occurs much faster (4.7 ps) in comparison to Py-dC (40 ps), however, the cytosine radical anion $C^{\bullet-}$ is being protonated on a picosecond timescale. These results suggest a) that protonation of the cytosine radical anion $C^{\bullet-}$ may also occur in DNA, and b) that protonation potentially interferes with electron hopping over C–G base pairs. Hence, we proposed that only the thymine radical anion $T^{\bullet-}$ but not the cytosine radical anion $C^{\bullet-}$ can participate as an intermediate charge carrier for excess electron migration in DNA.

We incorporated Py-dU into DNA duplexes (Fig. 8) and studied the electron transfer processes using a combination of different techniques, comprising mainly steady-state fluorescence spectroscopy, time-resolved laser spectroscopy, and

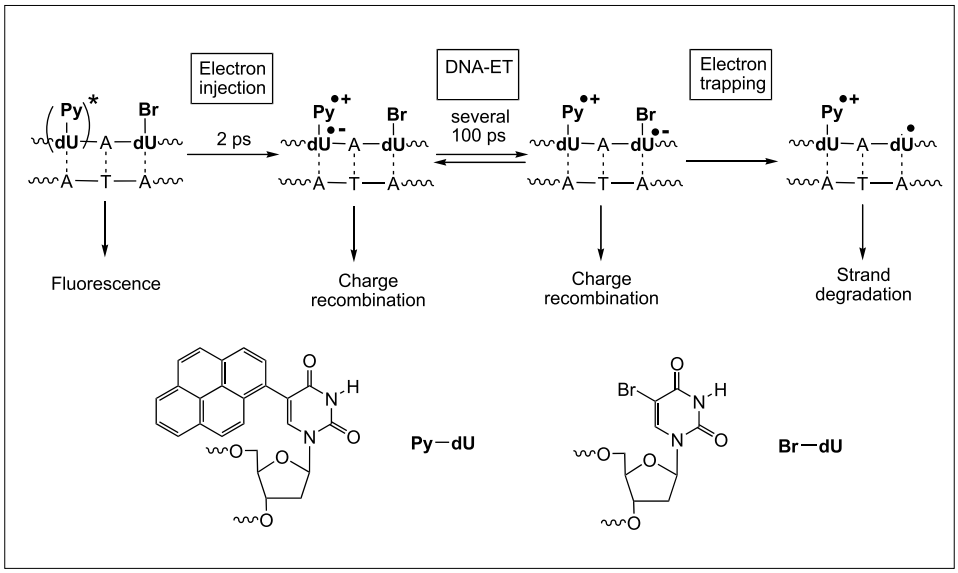

Fig. 8. Photoinduced electron transfer in DNA between Py-dU as the electron donor and Br-dU as the kinetic electron trap

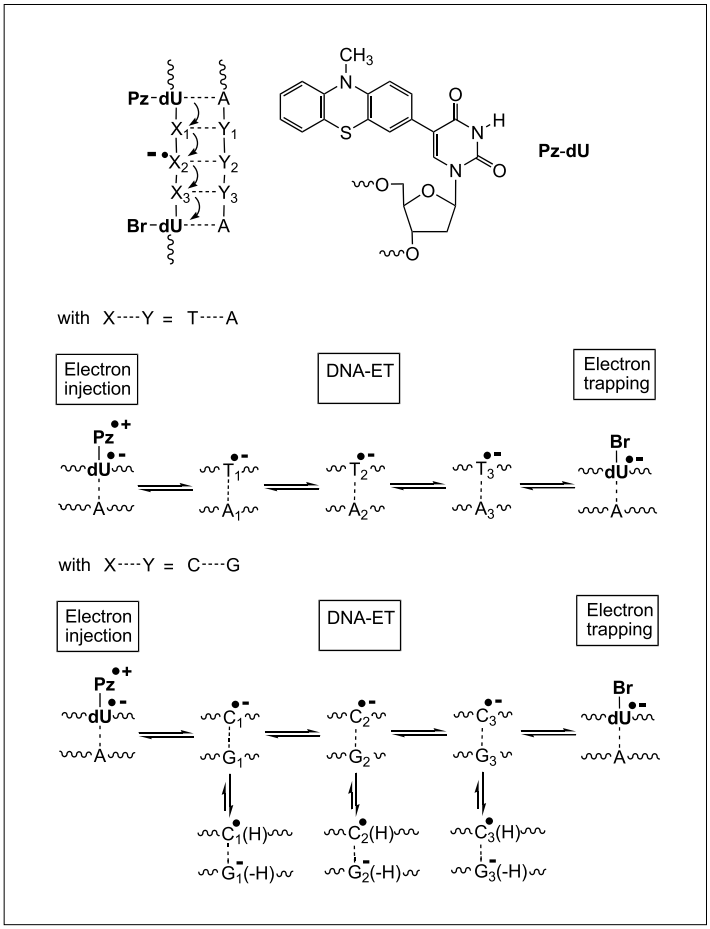

Fig. 9. Photoinduced electron transfer in DNA with Pz-dU as the electron donor and Br-dU as the electron acceptor

chemical probing by 5-bromo-2'-deoxyuridine (Br-dU).[26,63,64] It is known that Br-dU represents a kinetic electron trap since it undergoes a chemical modification after its one-electron reduction which can be analyzed by piperidine-induced strand cleavage and has been applied to quantify the efficiency of DNA-mediated electron transfer processes.[65,66]

The femtosecond time-resolved pump-probe spectra showed strong evidence for an involvement of base stacking fluctuations and hydrogen bonding interactions inside the DNA helix that accompanies and influences the electron transfer dynamics.[64] The wide range of reactivities and rate constant are indicative of a manifold of conformational states in DNA at room temperature. The electron injection process into the duplexes shows only minor variations because it occurs between the covalently connected Py and dU moieties. However, the subsequently formed charge-separated state $Py^{\bullet+}$-$dU^{\bullet-}$ exhibits strong kinetic dispersion in its lifetimes which is consistent with multi-conformational DNA. Furthermore, our results indicate that the electron shift to the Br-dU acceptor occurs on the timescale of several hundred picoseconds, therefore competing with charge recombination in these duplexes. It is reasonable to assume that subsequent migration steps will be faster since the Coulomb interaction between the excess electron and $Py^{\bullet+}$ decreases drastically with distance. Hence, the several hundred picosecond timescale provides a lower limit for the rate of reductive electron transport between single bases in DNA.

Alternatively to pyrene, phenothiazine (Pz) was used as the photochemical electron donor since the reduction potential of Pz in the excited state ($E(Pz^{\bullet+}/Pz^*)$ = –2.0 V) is ~200 mV stronger compared to pyrene.[67] We synthesized the Pz-modified uridine (Pz-dU) and incorporated it into oligonucleotides together with Br-dU group two, three or four base pairs away from the Pz-dU group (Fig. 9).[27] The intervening base pairs were chosen to be either T–A or C–G. Remarkably, the DNA duplexes with the intervening T–A base pairs show a significantly higher cleavage efficiency compared to the DNA duplexes with the intervening C–G base pairs. It becomes clear that in our assay, T–A base pairs transport electrons more efficiently than C–G base pairs. This further supports our proposal (as mentioned above) that the cytosine radical anion $C^{\bullet-}$ plays only a minor role as an intermediate electron carrier compared to the thymine radical anion $T^{\bullet-}$.

5. Final Conclusions and Outlook

Over the past decade many conflicting reports on the electronic conduction properties of DNA have appeared in the literature. Many of these conflicts have arisen because inherently different molecular systems (chromophores, sequences, surrounding media, temperature, *etc.*) were unjustifiably compared with one another. The few examples presented here reflect the complexity of electronic and structural interactions that dictate electronic transfer processes in DNA. Unraveling the details of these interactions will undoubtedly result in a better understanding of DNA photonics. Future studies using new spectroscopic techniques that are sensitive to both the structural and the dynamical evolution of complex molecules will strongly assist these efforts.

A unique structural feature of the DNA base stack is the hydrogen bond interface between the complementary strands. Because of the quasi-quantum nature of the hydrogen atom and the directionality of the hydrogen bond, this structural element is pivotal for DNA-mediated charge transfer. We have demonstrated that proton rearrangement in the hydrogen bond networks can influence the energetics of radical ions in DNA which may facilitate transport over long distances.

Finally, the importance of hydrogen bonding for DNA photonics is not limited to charge transfer reactions involving DNA radical ions. A significant involvement of hydrogen bonding modes has also been proposed for excited state dynamics of DNA bases.[68] However, there have been very few attempts to tackle this important topic experimentally. Addressing the influence of hydrogen bond rearrangements on photoinduced dynamics in DNA will be a major experimental challenge in the future.

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