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Electron transport in DNA initiated by diaminonaphthalene donors alternatively bound by non-covalent and covalent association†

Neil P. Campbell[a] and Steven E. Rokita*[a,b]

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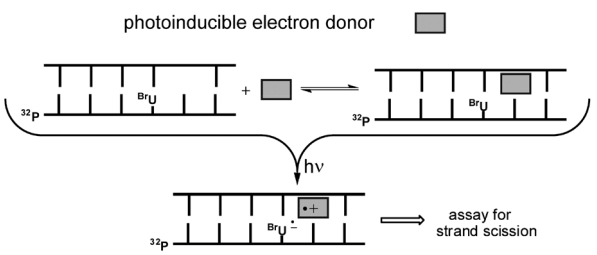
Covalent conjugation is typically used to fix a potential charge donor to a chosen site for studying either hole or excess electron transport in duplex DNA. A model system based on oligonucleotides containing an abasic site and ^{Br}dU was previously developed to provide a rapid method of screening new donors without the need of synthetic chemistry. While this strategy is effective for discovering important lead compounds, it is not appropriate for establishing extensive correlations between molecular structure and donor efficiency as demonstrated with a series of closely related electron donors based on diaminonaphthalene. The non-covalent system accurately identified the ability of the donors to reduce a distal ^{Br}dU in DNA, but their varying efficiencies were not recapitulated when attached covalently to an equivalent sequence of DNA. Reduction within the covalent system was not sensitive to the strong donor potentials as consistent with charge recombination dominating the net migration of charge.

Introduction

The ability of DNA to transport charge is subject to intense study from perspectives of physics, chemistry and biology due to its broad implications in fields ranging from sensors[1–4] and nanoelectronics[5–7] to DNA damage and skin cancer.[8–10] The parameters affecting hole transport initiated by one electron oxidation of DNA have been explored in greatest detail, but interest in the complementary process of excess electron transport (EET) that is initiated by one electron reduction of DNA is rapidly developing as well.[11–15] These processes share a sensitivity to the nucleotide sequence and helical structure that separate the initial charge donor and its ultimate acceptor.[11–15] Both ground- and excited-state properties of the charge donor also contribute greatly to the efficiency of charge transport since photoexcitation is typically used to trigger the single electron reaction with DNA. Aromatic stacking is essential for transport,[16–19] and the reducing/oxidizing power of the donor can dramatically influence initial electron injection into DNA and subsequent partitioning between back electron transfer and migration to a distal acceptor.[20–24]

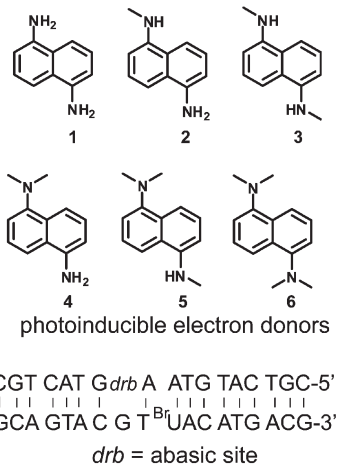
A wide variety of aromatic compounds and transition metal complexes have been examined for their ability to donate charge to duplex DNA. Most typically, these rely on covalent attachment to fix their location at a chosen position within the helix. Strategies for this vary, but all require at least a moderate commitment to synthetic chemistry. Our laboratory had developed a functional screen for EET that could be used to evaluate a range of donors prior to their covalent attachment.[25] This system is based on duplex DNA containing an abasic site and ^{Br}dU (Scheme 1). The abasic site provides a unique environment for the donor to associate and stack within the duplex. For example, naphthalene derivatives related to those described in this report may not bind or intercalate into a canonical duplex of DNA but will still associate selectively to



Scheme 1 A functional assay to screen potential electron donors for associating with DNA and initiating EET as detected by strand scission generated by single electron reduction of ^{Br}dU.

[a]*Department of Chemistry and Biochemistry, University of Maryland, College Park, MD 20742, USA*
[b]*Department of Chemistry, Johns Hopkins University, 3400 N. Charles St., Baltimore, MD 21218, USA. E-mail: rokita@jhu.edu; Fax: +1-410-516-8420; Tel: +1-410-516-5793*

†Electronic supplementary information (ESI) available: Initial rates of DNA strand scission as a measure of EET, chromatographic separation of the conjugate products **ODN3** and **ODN4**, MALDI-TOF analysis of oligonucleotide conjugates, electrophoretic separation and detection of scission products induced by EET within DNA containing electron donors attached covalently. See DOI: 10.1039/c3ob42433b



Scheme 2 Structure of electron donors and DNA used in the screen for EET supported by non-covalent association.

an abasic site.[26] The ^{Br}dU serves as a potent trap for EET and ultimately induces strand scission that can easily be quantified.[27–30] Only internal electron transfer within individual duplexes has been detected under these conditions since EET is insensitive to reagents that quench solvated electrons.[29] Similarly, only donors that can bind and stack into DNA promote the characteristic strand scission associated with single-electron reduction of ^{Br}dU.[25] An equivalent duplex lacking an abasic site remained inert in the presence of donors.

The non-methylated parent diaminonaphthalene (**1**, Scheme 2) represents a strong excited-state donor that supported efficient EET in the screen above.[25] In contrast, the *N*,*N*,*N*′,*N*′-tetramethylated derivative (**6**) offered a more moderate donor potential and induced EET less efficiently. Since both donors were expected to bind with similar affinity to the abasic site of DNA, donor strength appeared likely to influence the net transport of an electron to ^{Br}dU. However, this initial correlation is not supported by more extensive analysis presented below.

Results and discussion

Our original interest in EET derived from its contribution to thymine–thymine dimer repair catalyzed by DNA photolyase.[31] A successful and influential model system of this enzyme based on aniline illustrated the utility of aromatic amines as photoexcited electron donors.[32] The activity screen outlined in Scheme 1 was then used to identify aromatic amines that may be applied more broadly to EET in duplex DNA. The same strategy has now been used to evaluate the role of photoexcited potential in the differential efficiencies of EET induced by donors **1–6**. This opportunity became available after synthesis and characterization of the full series of methylated diaminonaphthalenes.[33] These derivatives provided a range of potentials with minimal variation in structure. Interestingly, compensatory effects in the photochemical properties of these donors clustered their excited-state potentials around −3.22 V and −2.99 V (*vs.* SCE).

Previous studies on EET involving oligonucleotide conjugates of donor **6** demonstrated only mild sensitivity to ambient concentrations of molecular oxygen.[29] While optimizing conditions to measure the activity of the diffusible donors, a similar analysis was repeated for donor **1** since it had expressed maximal activity in our original trial.[25] Oligonucleotides **ODN1** and **ODN2** were annealed to create the duplex with an abasic site for donor binding and a ^{Br}dU for trapping migration of the excess electron (Scheme 1). Gel electrophoresis was used to separate the products of **ODN2** scission induced by one electron reduction of ^{Br}dU and subsequent piperidine treatment. The 5′-[^{32}P] label allowed for identification and quantitation of the 5′-fragments (Fig. 1). The ^{Br}dU residue is mildly sensitive to basic conditions and yielded a

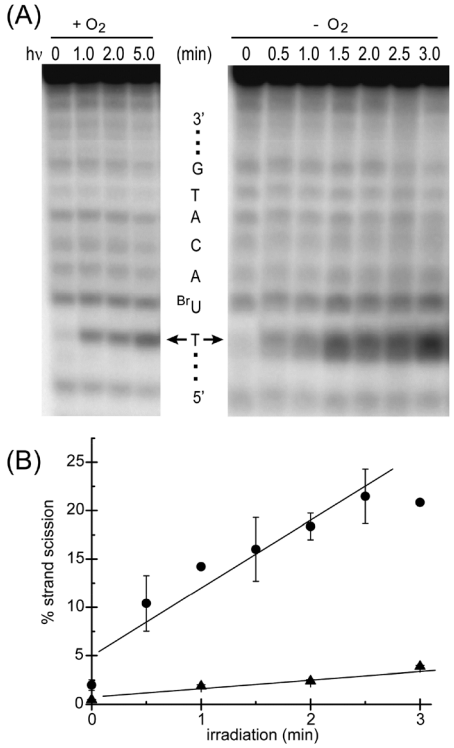


Fig. 1 EET induced between by a diffusible donor and a ^{Br}dU acceptor within duplex DNA containing an abasic site. (A) DNA (**ODN1**/**ODN2**) and diaminonaphthalene (**1**, 1 mM) were irradiated for the indicated time (λ > 335 nm) under aerobic and anaerobic conditions alternatively and then treated with hot piperidine to induce strand scission at the residue (T) on the 5′-side of ^{Br}dU after its capture of an electron. Products were separated by gel electrophoresis and detected by phosphoimagery. (B) The fraction of the 5′ scission product formed under aerobic (▲) and anaerobic (●) conditions was quantified relative to total DNA. The error represents the spread of duplicate measurements, and linear best fits were used to estimate the initial rate of the collective processes controlling electron injection, migration and capture.[35] The background level of strand scission induced by piperidine treatment is indicated by the value measured at t_o. This was not subtracted from the yield of scission as evident by the non-zero interceptions.

low background level of strand scission after incubation with piperidine. However, only scission at the T residue positioned directly to the 5′-side of ^{Br}dU demonstrated the expected dependence on photo-induced EET.[27–29] The efficiency of this process in the presence of **1** was dramatically suppressed by the ambient concentration of molecular oxygen. This sensitivity is likely due to the presence of excess donor that may readily react with the oxygen during irradiation. Such an excess was necessary to detect EET as determined previously from a limited study on the concentration dependencies of **1** and **6**.[25] Under these conditions, only a small fraction of the donor could be protected from reaction by stacking into the abasic site provided by the **ODN1**/**ODN2** duplex. In contrast, the donor–oligonucleotide conjugates examined previously were used in near stoichiometric concentrations and provided protection to most all of the available donor. The susceptibility of the non-conjugated donors **1–6** to molecular oxygen was also evident when attempting experiments based on fluorescence as well.[34] Consequently, further investigations were conducted under anaerobic conditions to focus attention on the donors' ability to inject electrons into duplex DNA and drive reduction of ^{Br}dU from a distal site.

Strand scission of **ODN2** within a duplex with **ODN1** was monitored over short irradiation time to compare the maximum activity of donors **1–6** and to minimize their inevitable degradation under extended exposure to UV light (λ > 335 nm). Even the related oligonucleotide conjugates of **6** investigated previously were sensitive to prolonged irradiation.[25] Initial rates[35] were estimated by linear fit of the data including, but not forced through, the background level measured prior to irradiation (Fig. 1 and S1, ESI†). From this analysis, donor **1** again demonstrated much greater activity (>10-fold) than donor **6** (Table 1). Additionally, the most strongly reducing excited-state donors (**1**, **2** and **3**) supported the most efficient EET as indicated by single electron reduction of ^{Br}dU within the duplex. The rate induced by **1** may be inflated by the low background of strand scission at t_o since exclusion of its value from the linear fit yielded a rate of 4.4 ± 0.6 (% min^{-1}) that is very similar to those induced by **2** and **3**. The diaminonaphthalene derivative **4** belongs to the group of weaker excited-state donors including **6**. Consistent with the original trend, these express diminished abilities to induce EET. Only donor **5** deviated from the relationship established by the other closely related derivatives. Although the surprisingly efficient induction of EET by **5** may represent a unique exception, it could alternatively suggest that the prior correlation between donor strength and EET detected in this screen was serendipitous.

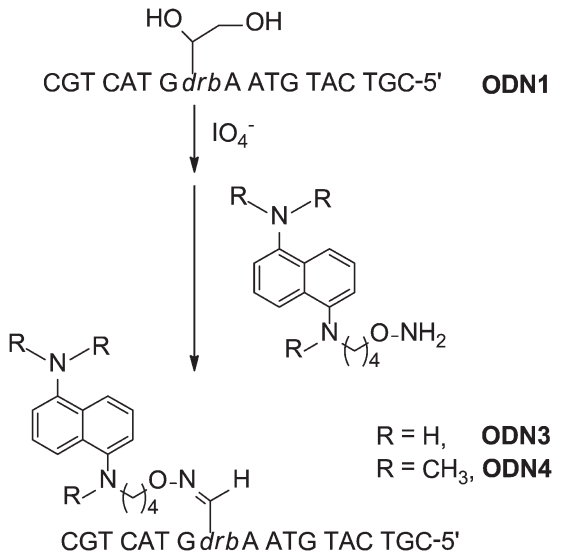
Driving force potential likely affects individual steps of electron hopping between proximal donor–acceptor pairs,[36,37] but the overall efficiency of charge transport from the initial donor to distal acceptor is the sum of many diverse and competing processes including excitation and relaxation of the chromophore, separation and recombination of charge and subsequent hopping of an electron through arrays of nucleobases in both strands of duplex DNA.[11,38] A diffusible donor present in excess over its DNA contributes further variables into this complex array of processes but at least the observed efficiencies of EET are not a function of the differing extinction coefficients of the donors (**1–6**).[33] The high concentration of donors (1 mM) used in the screen was sufficient to absorb all incident photons used to excite them. The varying efficiencies may instead have reflected the chemistry of the donors when free of duplex DNA and their ability to repopulate the abasic site. Similarities in the structures of **1–6** might suggest that binding affinities for the abasic site of **ODN1**/**ODN2** would be equally similar. However, their orientations within the abasic site could still differ and strongly influence the complex balance of competing processes that contribute to EET. Rather than exploring the intricacies of these variables, evaluation of the non-conjugated system was placed in context by direct comparison to an equivalent conjugated system. Many of the uncertainties associated with non-covalent assembly are removed after the donor is covalently tethered to the DNA and used in near stoichiometric quantities as common in most all other studies on EET.

To compare the efficiencies of EET in such a covalent system, the *N*-(4-aminooxybutyl) analogues of **2** and **6** were prepared and coupled to a unique aldehyde formed in DNA after periodate oxidation of a protected deoxyribose derivative using standard protocols (Scheme 3).[25] The two conjugates (**ODN3** and **ODN4**, respectively) were purified by reverse-phase chromatography and confirmed by MALDI-TOF analysis (Fig. S2 and S3, ESI†). These oligonucleotides were then annealed with the same complementary sequence and electron trap used in the screen above (**ODN2**). Again, samples were irradiated (λ > 335 nm) and monitored over time for strand scission (Fig. S4, ESI†). Use of the donor conjugates at concentrations almost stoichiometric to their complementary strand (1.3 : 1) appeared to equalize their efficiency for EET that previously had differed by ~10-fold in the non-conjugated system. The initial rates measured for **ODN3**/**ODN2** and **ODN4**/**ODN2** were nearly identical (0.8 ± 0.1% min^{-1} and 0.6 ± 0.06% min^{-1}, respectively) (Fig. 2). Not surprisingly, the efficiencies of both were much greater per mole when linked to the DNA and used in μM concentrations rather than the mM concentrations of **1–6**. The lack of difference in EET efficiencies for the conjugated donors also indicates that the values summarized in Table 1 are

Table 1 E_{ox}, E^*_{ox} and efficiency of ^{Br}dU reduction by EET in duplex DNA for diffusible electron donors **1–6**

Donor	E_{ox} [a] (V)	E^*_{ox} [a] (V)	Rate[b] (% min^{-1})
1	0.250	−3.24	7.0 ± 1.0
2	0.220	−3.24	4.6 ± 0.5
3	0.208	−3.18	4.2 ± 0.3
4	0.380	−3.01	0.8 ± 0.1
5	0.350	−2.98	4.0 ± 0.5
6	0.400	−2.99	0.5 ± 0.1

[a] Potential *vs.* SCE measured previously.[33] [b] Initial rate of strand scission induced after electron capture by ^{Br}dU and subsequent piperidine treatment (see Fig. 1 and S1, ESI).[35]



Scheme 3 Conjugation of donors to DNA.

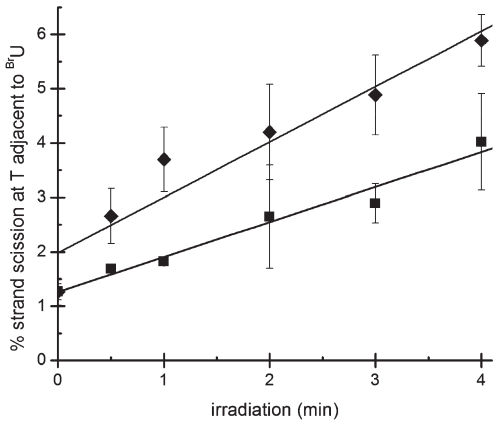


Fig. 2 EET induced between covalently bound donors and a ^{Br}dU acceptor within duplex DNA. DNA alternatively containing the conjugate of donor **2** (**ODN3**/**ODN2**, ◆) and its methylated derivative **6** (**ODN4**/**ODN2**, ■) was irradiated (λ > 335 nm) for the indicated times and monitored after piperidine treatment by gel electrophoresis and phosphoimage analysis as described in Fig. 1 (see Fig. S4, ESI†). Initial rates were calculated from the linear fit of strand scission (% *vs.* total).[35] Each experiment was repeated at least twice, and error bars represent the range of the data.

influenced by processes independent of the donor–DNA complex. Duplex DNA containing an abasic site to accommodate excited-state donors and a trap to detect charge transport continues to offer a convenient method for screening a wide range of candidates for later covalent coupling to oligonucleotides. This approach readily differentiates between active and inactive compounds[25] but is not appropriate for correlating chemical and physical properties to relative efficiencies of charge transport. Too many additional variables are introduced by the excess donor used to saturate the abasic site of the non-conjugated system. Similar efficiencies of EET induced by the two conjugated diaminonaphthalenes likely reflect a common determinant controlling their activity. Their excited-state potential is sufficiently potent for donation of an electron to any of the nucleobases. This in turn allows for minimal separation of initial charges and rapid recombination. Migration of a charge away from its site of entry in DNA is thus infrequent relative to its primary injection unless a system is designed to enhance separation of the initial charges.[39–42]

Materials and methods

General

Reagents were purchased from Fisher Scientific or Aldrich at enzymatic grade or better and used without further purification unless otherwise specified. The diaminonaphthalenes and the protected derivative of *N*-(4-aminooxybutyl)-1,5-diaminonaphthalene (**7**) were prepared as described previously.[25,33] All aqueous solutions were prepared with distilled deionized water (Barnstead NANOpure II purifier, >17.8 MΩ). Oligonucleotides were purchased from IDT DNA (Coralville, IA) and TriLink Biotechnologies (San Diego, CA) with standard desalting. γ-[^{32}P]-ATP and T4 polynucleotide kinase were used to label **ODN2** using standard conditions, and excess ATP was removed by a P6 Micro Bio-Spin column (Biorad, Hercules, CA).

Protected derivative of *N*,*N*,*N*′-trimethyl-1,5-diaminonaphthalene (8)

N-(4-Aminooxybutyl)-1,5-diaminonaphthalene protected with a norbornene-2,3-dicarboximide group[25] (430 mg, 1.10 mmol) was combined with Na_2CO_3 (369 mg, 4.40 mmol), methanol (12 mL), water (6 mL) and THF (6 mL) in a round bottom flask equipped with a magnetic stir bar and nitrogen inlet. Dimethyl sulfate (417 μL, 4.40 mmol) was then added and the mixture was stirred at room temperature overnight under nitrogen. The reaction was treated with 1 M NaOH to a pH > 11 and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness to yield the desired material (381 mg, 80%) as a light purple solid. ^{1}H NMR ($CDCl_3$) δ 7.95 (t, 2H, J = 8 Hz), 7.37–7.42 (m, 2H), 7.11 (d, 1H, J = 7 Hz), 7.07 (d, 1H, J = 7 Hz), 6.14 (t, 2H, J = 2 Hz), 3.96 (t, 2H, J = 6 Hz), 3.41 (s, 2H), 3.10–3.17 (m, 4H), 2.89 (s, 6H), 2.84 (s, 3H), 1.44–1.77 (m, 6H) and consistent with published values.[25]

Deprotection of the diaminonaphthalene derivatives prior to DNA conjugation

The norbornene-2,3-dicarboximide group was removed by refluxing the protected derivatives (**7** and **8**) with hydrazine hydrate (20% v/v) in 95% ethanol for 30 min as described previously.[43] *N*-(4-Aminooxybutyl)-1,5-diaminonaphthalene (**9**): ^{1}H NMR ($CDCl_3$) δ 7.14 (m, 4H), 6.75 (dd, 1H, J = 2,5 Hz), 6.58 (d, 1H, J = 8 Hz), 4.26 (b), 3.72 (t, 2H, J = 6), 3.27 (t, 2H, J = 7 Hz), 3.30 (m, 2H), 2.75 (m, 2H). ESI MS m/z calc. for $C_{14}H_{19}N_3O$ (M + H) 246.1528, found 246.1393. *N*-(4-Aminooxybutyl)-*N*,*N*′,*N*′-trimethyl-1,5-diaminonaphthalene (**10**): ^{1}H NMR

($CDCl_3$) δ 7.95 (t, 2H, J = 8 Hz), 7.37–7.42 (m, 2H), 7.11 (d, 1H, J = 7 Hz), 7.09 (d, 1H, J = 7 Hz), 6.14 (t, 2H, J = 2 Hz), 3.95–3.98 (m, 2H), 3.42 (m, 2H), 3.11–3.16 (m, 4H), 2.90 (s, 6H), 2.84 (s, 3H). ESI MS m/z calc. for $C_{17}N_{25}H_3O$ (M + H) 288.2086, found 288.2196.

Preparation of oligonucleotide conjugates

An abasic site within the appropriate oligonucleotide was generated from its precursor using periodate and then coupled with the hydroxylamine-linked electron donors as described previously.[29] The desired conjugates **ODN3** and **ODN4** were purified by reverse-phase (C18) HPLC with a gradient of 10% acetonitrile in 50 mM triethylamine acetate (pH 5.0) to 30% acetonitrile in 35 mM triethylamine acetate over 15 min followed by an increase to 90% acetonitrile over another 10 min (1 mL min^{-1}) (Fig. S2, ESI†). MALDI-TOF of conjugate **ODN3** calc m/z 5605, found 5606. MALDI-TOF of conjugate **ODN4** calc m/z 5648, found 5648 (see also, Fig. S3†).

Initiation and characterization of excess electron transport in DNA

Duplex DNA containing the abasic site was annealed after combining [^{32}P]-labeled ^{Br}dU-containing **ODN2** (1.5 μM, 90 μCi per sample) and **ODN1** (2.0 μM) in 100 mM NaCl and 10 mM sodium phosphate pH 7. This solution was heated to 90 °C for 3 minutes and then allowed to cool to room temperature over more than three hours. The indicated electron donors (**1–6**, 1.0 mM) were then added to the DNA solution and allowed to equilibrate at 4 °C for a minimum of one hour. Aliquots of 25 μL were removed for irradiation (1000 W Xe arc lamp) through the open top of a 1.5 mL disposable centrifuge tube that was held in an aluminum cooling block (10 °C) covered with a 335 nm cutoff glass filter (WG335, Schott). Unless indicated, samples were maintained under anaerobic conditions within a sealed glove bag. The glove bag was purged and filled with nitrogen a minimum of five times. After irradiation, samples were suspended in a 10% v/v solution of piperidine (30 μL), heated for 30 min at 90 °C, and dried under reduced pressure. The resulting residue was again resuspended in 30 μL water and dried under reduced pressure three additional times to remove all residual piperidine. Finally, samples were dissolved in loading solution (5 μL, 8 M urea, 40% sucrose, 0.05% bromophenol blue, 0.05% xylene cyanol in standard Tris/borate/EDTA buffer) and loaded onto a 20% denaturing polyacrylamide gel that had been prerun for 30 min. Products were separated by electrophoresis, detected by phosphoimagery and quantified with ImageQuant 5.2 software. Initial rates were determined by linear best fits using Origin (Microcal ver. 6.0). Data points without error bars were measured only once.

Duplex DNA containing the donor conjugates was treated as described above after annealing **ODN3** and **ODN4** (2.0 μM) alternatively with **ODN2** (1.5 μM, 45 μCi per sample) in 10 mM sodium phosphate (pH 7.0) and 100 mM NaCl by heating to 90 °C and slowly cooling to ambient temperature over 3 h.

Acknowledgements

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