ence on metal ion, counterion, and all ligand components, and therefore would have been difficult to identify using traditional approaches. Furthermore, the screening method used in these studies should be immediately applicable to the discovery of catalysts for almost any desired reaction, and we are currently evaluating the scope of this strategy in our laboratories.

Received: October 12, 1998 [Z12524IE]
German version: *Angew. Chem.* **1999**, *111*, 987 – 991

Keywords: asymmetric catalysis · combinatorial chemistry · epoxidations · solid-phase synthesis

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[4] Experimental details for the library synthesis have been furnished as supporting information.

[5] For each metal library prepared the solution volume was chosen such that at least two equivalents of the metal source were available for complex formation.

[6] A recent advance in the screening of catalyst libraries has been the ingenious use of thermographic imaging to detect the heat generated by exothermic reactions that occur at reactive centers, thus distinguishing polymer-bound catalysts from pools of inactive structures. S. J. Taylor, J. P. Morken, *Science* **1998**, *280*, 267 – 270. See also M. T. Reetz, M. H. Becker, K. M. Kühling, A. Holzwarth, *Angew. Chem.* **1998**, *110*, 2792 – 2795; *Angew. Chem. Int. Ed. Eng.* **1998**, *37*, 2647 – 2650.

[7] Since the activity of a metal library could be a reflection of either the reaction efficiency or the number of catalysts present, all oxidants that showed detectable epoxidation activity were subjected to the deconvolution procedure outlined herein. In addition to H_2O_2(aq), anhydrous TBHP was also found to be effective, although a completely different set of active metals was obtained (which will be discussed elsewhere). No epoxidation activity was detected for oxidants such as O_2, $NaIO_4$, 4-phenylpyridine-*N*-oxide (4-PPNO), and *N*-methylmorpholine-*N*-oxide (NMO).

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[9] 1 mg library samples (equivalent to 10 copies of the full ligand set) were screened.

[10] Many other metal – ligand libraries produced a variety of non-epoxide reaction products or catalyzed the nonproductive disproportionation of H_2O_2 to O_2 and water.

[11] The facile synthesis of parallel ligand libraries was accomplished with an IRORI directed synthesis system.

[12] See supporting information.

[13] As would be expected, nearly all of the 96 $FeCl_2$ complexes provided good levels of epoxidation activity, which confirmed the validity of **18** and **19** as catalyst lead structures. However, ligands prepared with end cap **32** showed uniformly poor reactivity, which indicates that proper attachment of the pyridine ring to the peptide chain is of crucial importance.

[14] As immobilization of these catalysts to polymeric supports might influence their activity, the evaluation of soluble analogues is underway and will be reported in due course.

Long-Range Electron Transfer through DNA Films**

Shana O. Kelley, Nicole M. Jackson, Michael G. Hill,* and Jacqueline K. Barton*

The possibility of efficient DNA-mediated charge transport has been debated since the discovery of the double helix.[1, 2] Photoinduced electron transfer between reactants bound to DNA, or between bases contained within the π stack, has led to varied conclusions regarding the nature of DNA as a medium for long-range charge transport.[3–5] Consistently, however, species well stacked within the helix have exhibited remarkably fast electron transfer over long distances.[3] Indeed, the integrity of the base stack itself appears necessary for efficient long-range electron transfer, as perturbations caused by intervening mismatches or bulges greatly diminish the yields of DNA-mediated charge transport.[3, 6]

Electrochemistry has been used extensively to investigate the kinetics of electron transfer through self-assembled monolayers on solid surfaces.[7] Systems that feature redox-active head groups held at variable distances by aliphatic alkanethiols or conjugated linkers have yielded important information regarding the ability of different media to promote long-range electronic coupling. In an effort to investigate DNA-mediated electron transfer involving *ground-state* reactants, we have applied these methods to study redox-active intercalators bound at discrete sites within the individual helices of a DNA monolayer on gold.

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[**] We are grateful to the Camille and Henry Dreyfus Foundation (Faculty Start-up Grant to M.G.H.), the Research Corporation (M.G.H.), and the NIH (GM49216 to J.K.B., predoctoral traineeship to S.O.K.). In addition, we thank Dr. M. J. Allen for assistance with the AFM measurements, and Prof. F. C. Anson for helpful discussions.

  1433-7851/99/3807-0941 $ 17.50+.50/0

We have previously developed techniques for assembling DNA duplexes derivatized at the 5′ end with thiol-terminated linkers onto gold surfaces.[8, 9] Electrochemical assays, radioactive tagging experiments, and atomic force microscopy (AFM) all indicate that the duplexes form densely packed monolayers oriented in an upright position with respect to the gold.[9, 10] This contrasts the structure of monolayers formed from single-stranded oligonucleotides, where the individual DNA strands may lie flat on the gold surface.[11]

Duplex-modified electrodes exhibit very high affinities for DNA-binding substrates, and promote efficient electron transfer between the electrode and redox-active intercalators noncovalently bound to the helices.[8] However, in previous studies the exact location of the intercalators within the duplexes was not fixed, hence a systematic evaluation of the effect of distance on the rate of electron transfer through DNA could not be obtained.

To investigate charge transduction through DNA as a function of distance, we have site-specifically cross-linked a redox-active intercalator, daunomycin (DM),[12] into the DNA

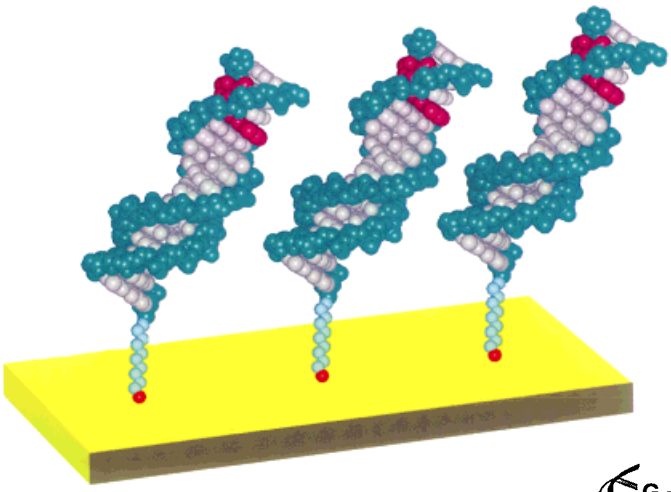

Figure 1. Schematic illustration of a gold surface modified with 15-base-pair thiol-modified duplexes, including the DM–guanine cross-link incorporated into the DNA monolayer. The sizes of all components—DNA base stack (grey), sugar–phosphate backbone (green), DM (magenta), and linker (blue; the terminal thiol is red)—are depicted relative to actual proportions. The helices shown are oriented at an angle of about 70° to the gold suface, which results in a through-space separation between DM (central plane) and the electrode of approximately 50 Å.

films (Figure 1). Daunomycin undergoes a reversible reduction[13] within the potential window of the monolayers,[8] and covalent adducts of intercalated DM cross-linked to the 2-amino group of guanine[14a] have been crystallographically characterized.[14b] The site of intercalation was controlled in the duplexes by incorporating a single guanine–cytosine (GC) base step in otherwise adenine–thymine (AT) or inosine–cytosine (IC) sequences; as DM requires the N2 atom of guanine for covalent cross-linking, the intercalator is constrained to these positions. Moving the GC step along the duplex therefore provided a systematic variation in the location of the DM-binding site relative to the thiol-terminated linker. Cross-linking DM to the DNA in solution, and then depositing the labeled duplexes onto gold, afforded a series of films in which the intercalator was linked quantitatively at a known separation from the electrode surface (Figure 2).

The AFM images of films composed of 15-base-pair DM-labeled duplexes were virtually identical to those of the unlabeled analogues,[9] revealing densely packed monolayers with heights greater than 45 Å at open circuit. Cyclic voltammograms obtained for these electrodes showed the reversible reduction of DM at -0.65 V versus SCE,[12] and possessed features characteristic of surface-bound species (e.g., linear plots of peak current versus scan rate).[15] Integration of the electrochemical signals gave surface coverages (Γ) of electroactive DM ranging from 60–75 pmol cm^{-2}; these values are in good agreement with the coverages of 15-base-pair duplexes previously measured by ^{32}P labeling.[8, 16, 17] Given the 1:1 stoichiometry of cross-linked DM to DNA (confirmed by UV/Vis spectroscopy), these data indicate that all of the bound DM is electrochemically reduced at the modified surfaces; doping the films with increasing percentages of DM-free duplexes resulted in a linear decrease in the electrochemical signals, suggesting that each of the bound intercalators is electrochemically active.

Remarkably, efficient reduction of DM was observed regardless of its position along the 15-base-pair sequence (Figure 3).[18] Not only were the intensities of the DM signals

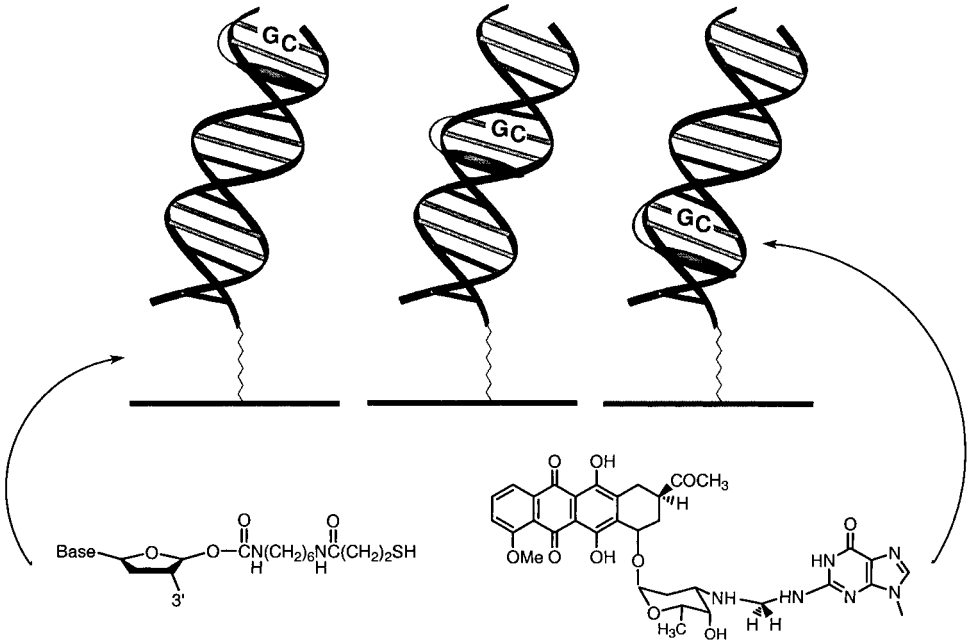

Figure 2. Schematic diagram depicting DNA duplexes used for study of distance-dependent reduction of DM. Also depicted are the DM–guanine cross-link (right) and the thiol-terminated tether which connects the duplex to the electrode surface (left). This tether provides 16 σ bonds between the electrode and the base stack.

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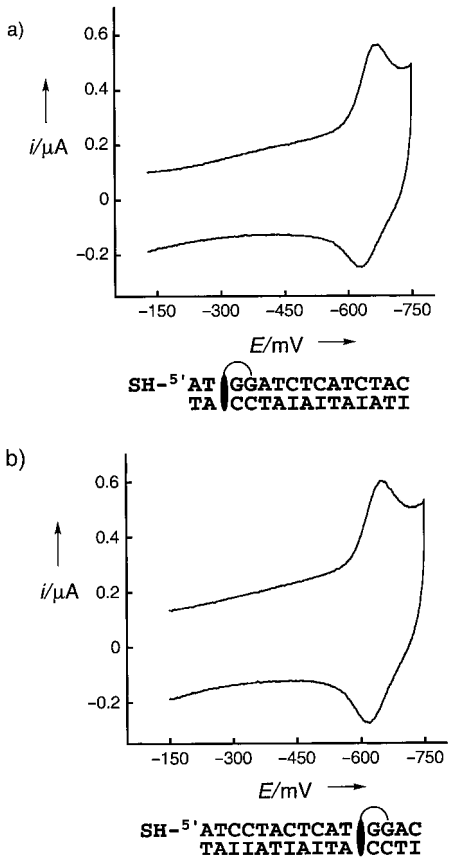

Figure 3. Cyclic voltammograms of gold electrodes modified with the DM-cross-linked thiol-terminated duplexes: a) SH-5′AT**GG**ATCTCATCTAC + inosine complement and b) SH-5′ATCCTACTCAT**GG**AC + inosine complement; where the bold **G**s represent the DM cross-linking site. For these duplexes, the surface coverage of electroactive DM, as measured by integrating the currents within these voltammograms, were 0.65×10^{-10} and 0.75×10^{-10} mol cm^{-2}. The DM:DNA stoichiometry for these same samples, measured by absorption spectroscopy, were 0.9:1 and 1.1:1, respectively. Thus, the charge does not depend on distance, but does reflect the yield of cross-linking.

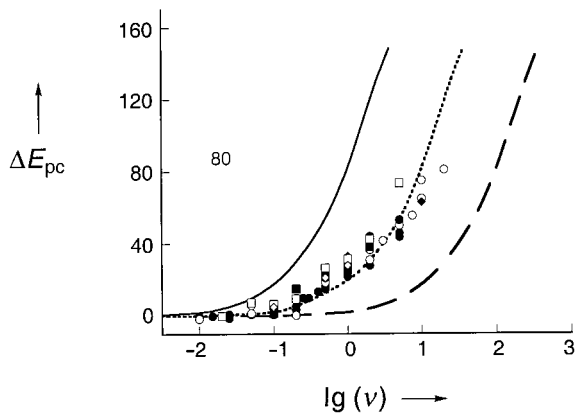

Figure 4. Plot of peak splitting ΔE_{pc} ($\Delta E_{pc} = E_{pc} - E^0$) versus lg($\nu$) ($\nu$ = scan rate). Measurements were obtained on the following sets of duplexes: (●) SH-5′AT**GG**ATCTCATCTAC (+inosine complement), (○) SH-5′ATCCTACTCAT**GG**AC (+inosine complement), (▲) SH-5′**GC**ATTATATAATTA (+complement), (□) SH-5′ATAT**GC**TATAATTA (+complement), (◆) SH-5′ATTATATA**GC**ATTA (+complement), (■) SH-5′ATTATATAATT**GC**T (+complement). For comparison, simulated curves[34] which correspond to rate constants varying by two orders of magnitude are shown: $k \approx 10^1$ s^{-1} (——), 10^2 s^{-1} (••••), 10^3 s^{-1} (– – –). IR compensation was employed at scan rates higher than 1 V s^{-1}.

the same for each of the duplexes studied, but the characteristic splittings between the cathodic and anodic waves as a function of scan rate were essentially invariant throughout the entire series (Figure 4). Clearly, within the resolution of this experiment, increasing the through-helix DM – gold separation does not substantially affect the rate of electron transfer.

If the electron transfer pathway proceeds through the double helix, these results indicate exceptionally efficient charge transport through DNA and imply that the rate-determining step may be tunneling through the σ-bonded linker. A shallow distance dependence through the π stack would be consistent with the results of photoinduced electron transfer between intercalators and other well-stacked species,[3] but is in sharp contrast to findings of analogous studies in which the reactants were not or poorly intercalated into the base stack.[4] These latter studies report values for β (the decay of electronic coupling with distance)[19] ranging from 0.6 – 1.4 Å^{-1}. It should be noted that β here reflects only an empirical evaluation of the distance dependence.[20] In our system, a β value of 1.4 Å^{-1} would imply that the rate of electron transfer should drop by more than 15 orders of magnitude between the two sequences shown in Figure 3. Similarly, if β were 0.6 Å^{-1}, these rates would differ by greater than six orders of magnitude. Such large changes are inconsistent with our data; a β value of 0.1 Å^{-1} would yield a difference in the rates for these two assemblies of only one order of magnitude, which may not be detectable by our analysis.

Could an alternative gating mechanism be responsible for the lack of distance dependence observed in these experiments? We considered dynamical processes[21] that might bring the intercalated DM into direct contact with the metal surface, as well as diffusional mechanisms in which charge might propagate laterally throughout the film from local "hot spots" (e.g., defect sites) where the DM is in close contact with the electrode. To differentiate among these possibilities, we constructed a series of films that featured intervening perturbations in the base stacks of the individual helices, but left the overall structures of the DNA monolayers preserved. A through-helix pathway would result in significantly attenuated rates of electron transfer to the DM, whereas dynamical or diffusional mechanisms would yield rates that are largely unaffected.

To accomplish this, a single site within the 15-base-pair duplex was mutated to produce a CA mismatch between the intercalated DM and the electrode surface. Although CA mismatches are known to cause only local disruptions in the DNA base stack with the bases remaining intrahelical,[22] the presence of intervening mismatches have been shown to decrease the yield of photoinduced electron transfer through DNA.[3, 23] Indeed, this one-base change switched off the electrochemical response entirely (Figure 5).[24] Significantly, sequences in which the positions of DM and the CA mismatch were reversed (such that the mismatch was located above the DM relative to the gold) showed no diminution in the electrochemical response. Moreover, AFM images of the CA-mutated sequences were indistinguishable from those of the

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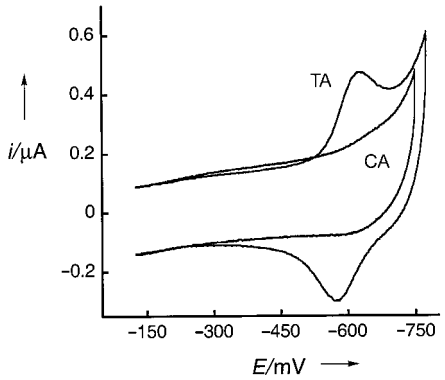

Figure 5. Cyclic voltammetry of gold electrodes modified with the DM-cross-linked thiol-terminated duplexes containing TA and CA base pairs. Sequence: SH-SH-5′ATTATATAATT**GC**T, where the complement contains either a T or a C opposite from the italicized A residue.

fully base paired analogues, revealing that the bulk structure of the DNA films was not significantly altered by the presence of the mismatch.[25]

To test for lateral charge propagation through these films, a series of monolayers were doped with increasing fractions of CA-mismatched helices. In all cases, the electrochemical signals decreased linearly with increasing percentages of mutated duplexes. This linear response indicates that electro-*inactive* intercalators (presumably those molecules bound to the mismatched duplexes) are not reduced by the electro-*active* species, and lateral charge diffusion is evidently quite slow.

The observation of an attenuated electrochemical response in the presence of a point mutation strongly implicates the stacked bases as the pathway for electron transfer. Indeed, the ability to detect such mutations may hold great promise for the development of DNA-based biosensors. Many electrochemical sensors have been developed based on hybridization-dependent responses,[26] but the sensitivity reported here to single-base mismatches provides an alternative means to detect mutations with genetic sequences. The application of this approach to non-cross-linked systems is currently underway.[27]

The nature of DNA as an electron transfer medium has been the subject of intense debate,[3–6, 28] and the extent of charge delocalization within DNA has profound biological implications.[1] Here, long-range charge transport through DNA-modified films has been demonstrated in a series of structurally characterized assemblies. The recent discovery of conductivity along the base-stacking direction of oriented DNA films,[29] and now the observation of long-range electron transfer to a ground-state intercalated species, may provide evidence that the DNA base stack exhibits "wirelike" behavior.

Experimental Section

Fabrication of DNA-modified surfaces: Gold electrodes were derivatized as previously reported.[8] The 15-base-pair oligonucleotides immobilized on a controlled pore glass resin were treated in succession with carbonyldiimidazole and 1,6-diaminohexane (1 g per 10 ml of dioxane, 30 min each) at the 5′-hydroxy terminus before cleavage from the resin.[30] After deprotection, the free amine was treated with 2-pyridyldithiopropionic acid *N*-succinimide ester to produce a disulfide.[31] The sequences were purified by reverse-phase HPLC, converted into free thiols with dithiothreitol, and repurified before hybridization to their complements. Derivatized oligonucleotides were characterized by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry and HPLC retention times. Before deposition onto gold surfaces, the presence of free thiol was confirmed using a spectroscopic assay based on dithionitrobenzene.[32]

Thiol-terminated duplexes (0.1 mM) containing an adjacent pair of guanine residues were hybridized, incubated with 0.2% formaldehyde and 0.2 mM DM in 100 mM phosphate (pH 7) for 1 h, and extracted with phenol to remove excess DM. Subsequently, samples were subjected to gel filtration chromatography and deposited on gold surfaces for 12–24 h in the presence of 100 mM $MgCl_2$. Before deposition, electrode surfaces were prepared by mechanical polishing with alumina, sonication, and oxidative etching in acid solution. The stoichiometry of the DM-cross-linking reaction was assayed by comparing the absorbance of DNA and the intercalated DM; one DM per duplex was found for all sequences studied.[33] The surface structures of the DM-labeled films were determined with AFM techniques as previously described.[9]

Electrochemical measurements: Cyclic voltammetry was carried out on 0.02-cm^2 polycrystalline gold electrodes with a Bioanalytical Systems (BAS) Model CV-50W electrochemical analyzer at $(20 \pm 2)^\circ C$ in 100 mM phosphate buffer (pH 7). A normal three-electrode configuration consisting of a modified gold-disk working electrode (≈ 0.03 cm^2), a saturated calomel reference electrode (SCE, Fisher Scientific), and a platinum wire auxiliary electrode was used. The working compartment of the electrochemical cell was separated from the reference compartment by a modified Luggin capillary. Potentials are reported versus SCE. Heterogeneous rate constants were determined as previously reported.[8, 34] Measurements were also carried out on modified gold(111) surfaces prepared either by vapor deposition of gold onto mica, or by melting the tip of a gold wire into a small ball (≈ 2 mm in diameter) with a hydrogen flame. Other than a slight narrowing of the voltammetric peak widths ($\approx 5-10$ mV), the signals were very similar for both polycrystalline and Au(111) electrodes.

Received: October 15, 1998 [Z12531IE]
German version: *Angew. Chem.* **1999**, *111*, 991–996

Keywords: biosensors · cyclic voltammetry · DNA structures · electron transfer · monolayers · thin films

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[16] Based the cross-sectional area of DNA (≈ 3 nm^2) and the geometrical area of the gold electrodes (0.03 cm^2), the maximum surface coverage of DNA is calculated as approximately 6×10^{-11} mol cm^{-2}. The Γ value for DM appears to exceed slightly the theoretical Γ value for DNA, and likely results from electrode surface roughness.
[17] To assess routinely the surface coverage of DM-derivatized DNA on gold, the electrochemical response of $[Fe(CN)_6]^{4-}$ (2 mM) was monitored. This negatively charged ion is repelled from the surface of the modified electrode by the polyanionic DNA, and exhibits essentially no response when the surface is well covered. While not a direct measure of surface coverage, this technique allows the convenient assay of individual electrodes for adequate modification. As the electrode-modification procedure did not always result in uniform surface coverages for the DM-modified duplexes, only electrodes that appeared well covered using both the integrated current of the DM reduction and the ferrocyanide test were studied.
[18] Based on molecular modeling, if DM is bound at the end of the duplex closest to the electrode (Figure 3a), the through-helix DM – electrode separation is greater than 10 Å; if the intercalator is cross-linked to the end of the duplex farthest from the electrode, the DM-electrode separation is greater than 35 Å (Figure 3b).
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[25] The AFM measurements revealed monolayer thicknesses of about 40 Å at open circuit for both CA- and TA-containing duplexes; moreover, the oxidation of ferrocyanide was similarly attenuated at both surfaces. Expected masses for DM-cross-linked DNA duplexes (accounting for the one-base change) were measured by mass spectrometry, and spectrophotometric assays revealed that the extent of cross-linking was identical in both fully paired and mismatched sequences.
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[33] For example, the oligonucleotide SH-(CH_2)CONH$(CH_2)_6$NHCO$_2$-$^{5'}$ATCCTACTCATGGAC hybridized with the inosine complement was modified with DM and analyzed by MALDI-TOF spectrometry. Mass-to-charge ratios of 5284 (calcd: 5282; DM + SH strand), 4541 (calcd: 4540; (complement), and 4742 (calcd: 4742; SH strand) were detected. These values correspond to the calculated masses for fragments expected from this duplex. UV/Vis absorption spectroscopy also revealed a duplex:DM stoichiometry of 1:1 based upon comparison of the duplex absorbance at 260 nm and the absorbance of intercalated DM at 480 nm ($\varepsilon = 7.5 \times 10^3$ M^{-1} cm^{-1}). In the presence of 100 mM phosphate and 100 mM $MgCl_2$ (pH 7), thermal denaturation studies of 5 μM duplexes (monitored by absorbance at 260 nm) revealed melting temperatures of 48 and 50 °C for the native and DM-cross-linked duplexes, respectively. A similar melting profile was obtained by monitoring hypochromicity at 482 nm for the DM duplex.
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Electron Tunneling in DNA**

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The idea that DNA is an effective medium for long-range electron tunneling is far from new.[1] Radiation biologists invoked this concept almost 40 years ago to account for the unusually high conductivity of solid DNA.[2] Later studies found that the conductivity arose from ice particles.[3] The effect has also been explained in terms of high charge mobility along the outside of the duplex.[4] Both EPR[5] and luminescence[6] results have been interpreted in terms of long-range electron tunneling whereas pulse radiolysis studies[7] indicate electron tunneling is restricted to less than five base pairs. Other investigators searched in vain for soliton effects.[8] More

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[**] This work was supported by the Royal Society of London.