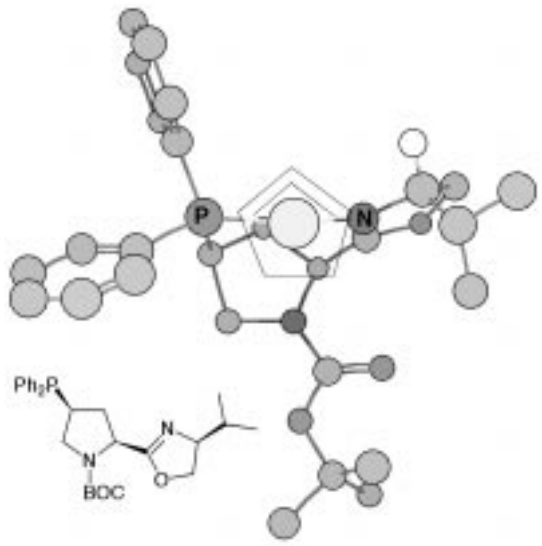

Figure 1. Model of the metal complex with an allyl group attached.

Experimental Section

Procedure for π-allyl alkylation: The phosphanyldihydrooxazole ligand was mixed with $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ in degassed solvent, followed by addition of the cyclic allylic acetate. To this mixture a solution containing dimethyl malonate (3 equiv), tetrabutylammonium fluoride (TBAF) (3 equiv) and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (3 equiv) was added slowly through a addition funnel (30 min). After the reaction was complete, water was added to quench the reaction and the organic solvent was removed by evaporation. The water layer was then extracted with diethyl ether twice and the ether solution was washed with saturated $NaHCO_3$, brine, and dried over Na_2SO_4. Evaporation of solvent gave a residue that was chromatographed by using EtOAc/*n*-hexanes (10/90, v/v) as an eluant to afford a colorless oil.

The enantiomeric purity was determined by integration of the NMR signals of the methyl residues on the dimethyl malonate, upon titration with europium chiral shift reagent $[Eu(hfbc)_3]$.

The ligand with the opposite configuration can be synthesized from D-hydroxyproline, which is accessible from L-hydroxyproline.[30]

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DNA Responds to Ionizing Radiation as an Insulator, Not as a "Molecular Wire"**

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The understanding of electron and hole transfer in DNA is critical to predicting the biological consequences of exposure to ionizing radiation. These processes are biologically relevant since about 50 % of the consequential damage is produced by direct-type events,[1] that is, from one-electron loss (holes) and one-electron gain directly by the DNA[2] or by fast transfer of holes and electrons to the DNA from adjacent solvent.[3] Transfer processes are chemically relevant since the distribu-

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tion of damage confronting the DNA repair enzymes is dependent on electron transfer events occurring within a fraction of a second following energy deposition. Over the past four decades, scientists working on the radiation physics and chemistry of DNA have given considerable attention to the question of DNA conductivity. This body of literature provides rather strong evidence, further discussed below, that the DNA polymer behaves as an insulator and not as a "molecular wire".

The possibility that DNA might possess properties of a molecular wire has been raised in recent years by a series of experiments using photochemistry to initiate and detect electron transfer. In 1993 Murphy et al. concluded that electron transfer was long range (>4.0 nm) and fast ($>10^9\ s^{-1}$).[14] In this and subsequent work (see reference [4] for a review), it was concluded that the dependence of the electron transfer rate on distance is relatively shallow; that is, the exponential factor β[5] is approximately $0.2\ Å^{-1}$. The extremely small value of β was attributed to high electron and hole mobility through the "π-ways" of stacked bases. Other laboratories using photochemistry concluded that the value of β is much larger. For electron transfer, Meade and co-workers obtained $\beta \approx 1.0\ Å^{-1}$,[6] and for hole transfer Lewis et al. obtained $\beta \approx 0.6\ Å^{-1}$.[7] Thus, there is a debate with regard to range, rate, and mechanism of electron transfer in DNA.[8–11]

Relatively absent from this debate has been discussion of earlier findings largely from the radiation research community, findings which are difficult to reconcile with unusually fast electron transfer rates over long distances (i.e., a β value an order of magnitude smaller than $1.0\ Å^{-1}$). The absence is, in part, due to concern over the possibility that the mechanism of electron transfer through DNA might depend on the means by which electrons or holes are created. Chemistry initiated by electronic excitation often differs from that initiated by ionization. In the case of DNA conductivity, while there are indeed different artifacts that affect interpretation, electron and hole mobility through extended stacks of bases should be independent of the source of the electron and hole. The finding that electrons and holes migrate through the stacked bases of duplex DNA is not under debate; this was established decades ago.[12, 13]

Here we show that DNA at 4 K is an extraordinarily efficient trap for both holes and electrons. Since the yield of trapped holes and electrons depends on the competition between electron–hole recombination and trapping reactions, the yield must also depend on electron transfer rate and distance. If the rate over long distances is fast, the yields of trapped radicals are small. This situation is analogous to that employed by Murphy et al., where a decreased yield in fluorescence was used to deduce a fast rate of electron transfer over a (presumably) known distance.[14] Because their study lacks direct evidence of electron transfer, it is difficult to rule out other explanations.[15, 16] What is needed are better defined samples. This shortcoming is overcome in the work presented here by employing crystalline deoxyoligonucleotides whose structures are known to angstrom resolution.

Crystals of the oligodeoxyneuclotides d(CTCGAG) and d(CCCTAGGG) were grown following published procedures.[17, 18] The crystals were verified to conform to the published structures using a MSC R-Axis II X-ray detector with a cooling device that maintained the crystals at 77 K. Crystalline samples were irradiated at 4 K by 70-keV X-rays,[19] and EPR spectra recorded at the same temperature. Examples of first-derivative spectra are provided in Figure 1. To our knowledge, these are the first published EPR spectra of drug-free single crystals of oligonucleotide DNA. The qualitative features of the spectra are consistent with a radical population dominated by one-electron-reduced cytosine and one-electron -oxidized guanine.[20, 21] Here we focus on the total yield of trapped radicals in DNA.

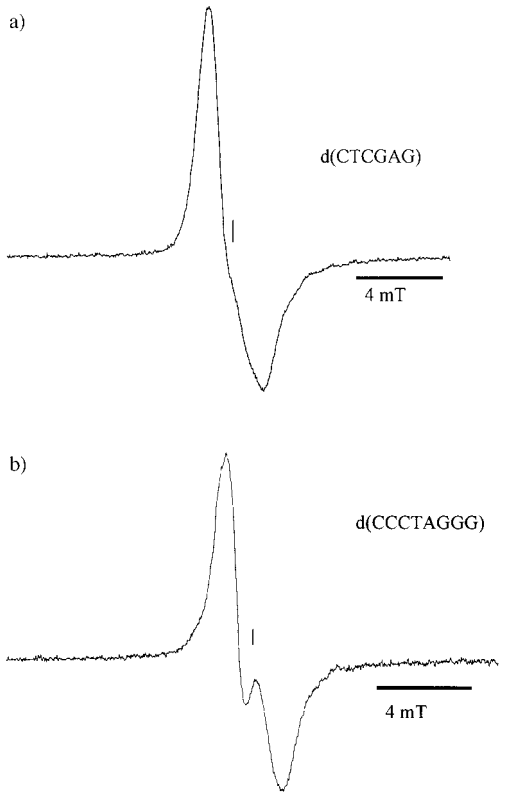

Figure 1. Single-scan 20-mT Q-band EPR spectrum of a) a single crystal of d(CTCGAG) taken at 4 K after a 12-kGy dose (crystal orientation undetermined) and b) a single crystal of d(CCCTAGGG) taken at 4 K after a 20-kGy dose (orientation is B_0 parallel to the crystallographic a axis). The position of $g = 2.0023$ is indicated by the vertical line.

The free radical yields were calculated from the initial slope of the dose-response curves (the presaturation linear region, dose <5 kGy) that are presented in Figures 2 and 3. To measure the concentration of free radicals trapped by DNA, the intensity of each spectrum was compared to the intensity of a ruby standard.[19]

The yield of the d(CTCGAG) system was obtained from six different single-crystal or polycrystalline samples weighing from 28 to 209 μg. The oligonucleotide molecules stack pseudo-continuously in an end-to-end fashion, maintaining π-bond overlap. The duplex is in a B-form conformation. The measured free radical yield (FRY) is $G(\mathrm{fr}) = 0.75 \pm 0.14$ μmol of free radicals per Joule of absorbed energy (fr = free radical). The yield of the d(CCCTAGGG) system was

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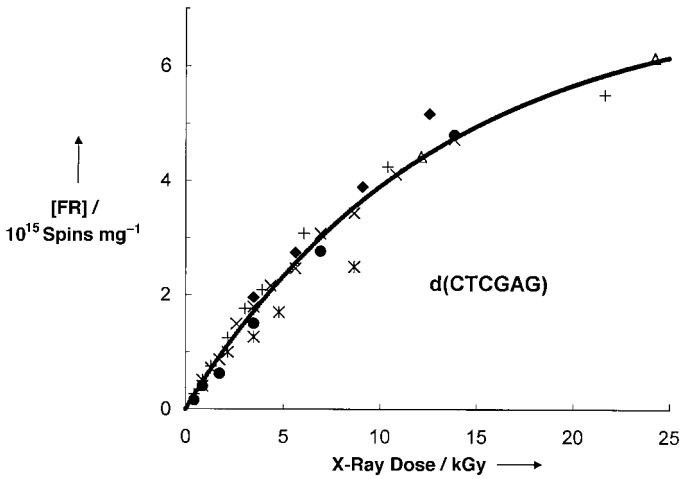

Figure 2. Plot of the free radical concentration versus the X-ray dose for six different crystalline samples of d(CTCGAG) irradiated and measured at 4 K. The solid curve represents the least-squares fit by the equation $C = C_i(1 - e^{-\sigma D})$, where C is the free radical concentration at dose D, C_i is the concentration at dose saturation, and σ is the cross-section for radical destruction; $C_i = 7.2 \times 10^{18}$ fr g^{-1} and $\sigma = 0.078$ kGy^{-1}. From this we conclude that the maximum trapping capacity of d(CTCGAG) at high doses is 7.2×10^{18} fr g^{-1}.

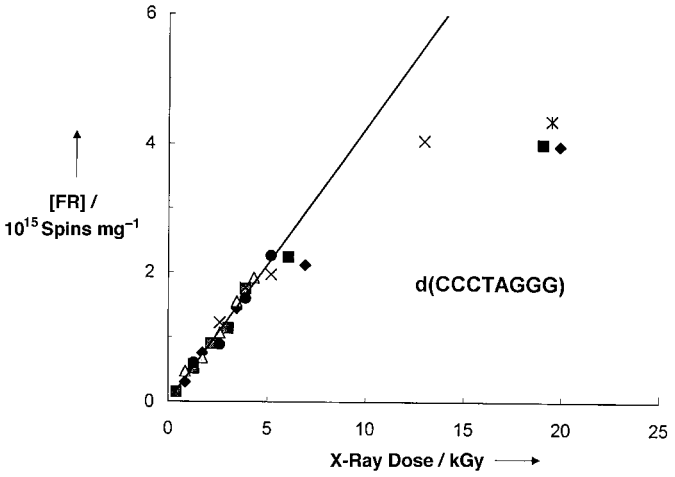

Figure 3. Plot of the free radical concentration versus the X-ray dose for six different crystalline samples of d(CCCTAGGG) irradiated and measured at 4 K. The linear region of the data below 5 kGy has been fitted with a least-squares curve. From the slope of this line we may determine the free radical yield of the d(CCCTAGGG) crystal samples. The same fitting procedure was followed in determining the free radical yield of the d(CTCGAG) samples.

determined from six different crystalline or polycrystalline samples weighing between 71 and 230 μg. The terminal base pair of one helix contacts the sugar phosphate backbone of its lattice neighbor; there is no continuity in base stacking between adjacent octamers. The duplex is A-form, and the resultant yield is $G(\mathrm{fr}) = 0.70 \pm 0.04$ μmol J^{-1}. The G(fr) values are revealing in three ways: 1) the absolute magnitude is large, 2) the magnitude for a given crystal type is independent of crystal size, and 3) the two different types of crystals give values of the same magnitude.

The measured yield of trapped radicals in crystalline DNA corresponds to about 60% ($\approx$0.7/1.2) of the radicals initially formed by the radiation (the initial radical yield of liquid water, which has a stopping power comparable to that of DNA,[22] is $G(\mathrm{fr}) = 1.2$ μmol J^{-1} [23]). This is an exceptionally high yield given that a large fraction of the initial radicals must be lost by geminate ion recombination. Furthermore, high yields can only occur if the conductivity of the DNA crystals is *very* low. In a conductor, there are effectively no barriers to prevent the electrons and holes from combining. For example, it is well known that a three-dimensional conductor like metallic copper has a radical yield of zero. A solid with two-dimensional conductivity provides a matrix that could trap one electron or hole per conducting plane. To provide a comparison with a two-dimensional conductor, we measured G(fr) for graphite at 4 K by using a 0.5-mm pencil lead with a room-temperature conductivity of 1 S cm^{-1}. The G(fr) value of graphite (< 0.005 μmol J^{-1}) is too small to detect in the presence of the quartz sample holder.

In sharp contrast, crystals of α-methylmannoside (a lattice of sugar molecules that is an insulator) give a yield of 0.5 μmol J^{-1} at 4 K. As shown in Table 1, this is comparable to DNA irradiated in the form of films, powders, and crystals. Also, given the large body of work on electron transfer in proteins (see for example reference [24]), we measured the free radical yield of lysozyme crystals at 4 K. The G(fr) value of lysozyme (0.57 ± 0.03 μmol J^{-1}) shows that the probability of electron–hole combination within this protein lattice is essentially the same as observed for DNA. The range of electrons and holes in lysozyme crystals, therefore, is comparable to the range in DNA.

Table 1. Free radical yields at 4 K of various materials exposed to ionizing radiation, and comparison of DNA samples against known conductors and insulators.

Material	Form	Yield [μmol J^{-1}]
copper	wire	0
graphite rod	pressed powder	< 0.005
α-methylmannoside	crystalline	0.44 ± 0.03[a]
lysozyme	crystalline	0.57 ± 9.04[a]
calf thymus DNA	film	0.4–0.5[b]
calf thymus DNA	lyophilized powder	0.5–0.6[b]
d(CCCTAGGG)	crystalline	0.70 ± 0.04[a]
d(CTCGAG)	crystalline	0.75 ± 0.14[a]
d(CGATCG):anthracycline	crystalline	0.24 ± 0.03[a]

[a] Quoted errors are relative errors; absolute errors are higher ($\pm 25\%$).[46]
[b] Hydration state of 16 waters per nucleotide.[46]

If π-ways in DNA exist, the d(CTCGAG) hexamer crystal is optimized to detect them. Assuming base stacking continuity results in electrical continuity, the hexamer crystal would be unable to trap more than two free radicals per continuous duplex column (i.e., one electron or hole per "strand"). Since each strand of stacked bases extends the length of the crystal, strand length depends on crystal size and shape. Assuming one radical per strand of stacked bases in a cubic crystal containing 100 μg of d(CTCGAG),[25] the calculated free radical concentration is less than 10^{15} fr g^{-1}. Observed concentrations exceed this value by more than three orders of magnitude. The maximum measured concentration at free radical saturation is 7.2×10^{18} fr g^{-1}. Each strand of approximately 10^6 bases traps, on average, around 6000 free

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radicals. Viewed another way, the free radical density at dose saturation, assuming uniform trapping across the entire crystal, is about one free radical per 57 bp, a through-base-stack distance of 17 nm. Since energy deposition is not uniform,[26] the mean interradical distance is smaller.

The high density of holes and electrons trapped by d(CTCGAG) at dose saturation is compelling evidence that no conductive states exist in the B-form helix. Indeed, if electron or hole transfer is long-range, then the FRY in d(CTCGAG) crystals should depend on crystal size. Reducing the size of a cubic crystal by 10-fold should increase the FRY by a factor of 2.154. Variations in crystal size, from less than 10 μg to greater than 100 μg, give FRYs within the observed standard deviation of ±20%, further indicating that the range at 4 K is limited.

A comparison between the two crystals provides an estimate of the electron range. The largest run of stacked bases in d(CCCATGGG) is 8 bp, and yet G(fr) is the same as for d(CTCGAG), where base stacking is continuous. This observation of limited range is consistent with a number of studies that indicate the mean range of a thermalized electron through DNA is short. EPR measurements at 4–77 K have provided evidence that the range of thermalized electrons and holes in DNA is at least 2 bp[19] with a mean between 3–11 bp.[27, 28]

Further support of a short range comes from EPR measurements on single crystals of a hexamer anthracycline complex.[19] The complex contains two intercalated anthracyclines per d(CGATCG) with intercalation occurring between each of the tandem CG base pairs. Base stacking is continuous through the crystal.[29] It is known from single-crystal EPR that holes and electrons trap only at anthracycline. No DNA-centered radicals are observed. This is expected given the redox properties of anthracycline, which make it the deepest trapping site for both electrons and holes. It also proves that holes migrate through the stacked bases. We have measured the FRY of these crystals at 4 K and find that $G(\mathrm{fr}) = 0.27 \pm 0.03$ μmol J^{-1}.[30] Thus, the high density of anthracycline traps does not increase yields. This can be understood if pure duplex DNA contains, inherently, a high density of traps such that the range of thermalized electrons and holes is limited to very short distances.

If DNA had a metallike band structure, one should expect an increased conductivity at low temperatures. This phenomenon has not been observed: in fact, the opposite is true. To date, we have measured G(fr) values and temperature effects on 12 different types of crystals, representing a wide range of conformation, packing, and sequence. We have observed that G(fr) of crystalline DNA irradiated at 4 K and annealed to 240 K has 20–40% of the yield obtained at 4 K.[31, 32] The EPR spectrum qualitatively changes in a manner consistent with an initial set of radicals that are shallowly trapped, accompanied by reversible protonation/deprotonation. These low-temperature radicals convert into a set of more deeply trapped species at higher temperatures, and these are typically irreversibly protonated/deprotonated.[33] A minimum and maximum distance for the thermally activated migration has been estimated. The minimum is about 2 nm based on the absence of spectral features due to radical pairs.[27] The maximum is on the order of 20 nm based on the free radical concentration remaining after annealing at 240 K. Both boundaries are compatible with the results of Razskazovskii et al.[28] With track structure calculations (currently underway), it should be possible to determine the distribution of migration distances from our measurements on crystalline DNA. As with other EPR studies that show a decrease in radical concentration upon annealing,[34–36] there is no doubt that electron transfer occurs through the stacked bases of duplex DNA and that electrons migrate by thermally activated hopping.

The migration of charge through DNA is supported by experiments with solid-state EPR,[33] pulse radiolysis,[37] and product analysis.[38, 39] In a paper by Razskazovskii et al., it is concluded that the mean distance of electron migration at 77 K is 11 bp and that above 150 K thermally activated migration extends to 30 bp or more.[28] Their results are consistent with a base-to-base hopping mechanism.

Our observations on crystalline DNA are well explained by a model in which the migration of electrons and holes is propagated primarily by hopping between shallow traps. At temperatures less than 80 K, the deepest electron trap is cytosine (C),[20, 40] where the rate of proton transfer from N1 of guanine (G) to N3 of $C^{\bullet -}$ (forming $C(N3+H)^{\bullet}$)[41] competes effectively with the rate of electron transfer.[42] Likewise, the deepest hole trap is guanine,[20, 43] where proton transfer away from N1 of $G^{\bullet +}$ to N3 of C (forming $G(N1-H)^{\bullet}$)[44] competes with hole transfer.[45] Steenken has written an excellent review of the role of proton transfer in moderating electron transfer.[42] Proton transfer separates the charge from the unpaired electron, leaving a neutral radical on one strand and a diamagnetic ion on the conjugate base of the opposing strand and reduces the probability of electrons and holes combining.

In conclusion, crystalline oligodeoxynucleotides serve as well-defined samples that give improved precision in the measurement of free radical yields. Increased length of base stacking beyond eight base pairs has no effect on free radical yields, and the yields are markedly high (0.7 μmol J^{-1}). The high yields coupled with the absence of a dependence on long-range base stacking supports the conclusion that the range of holes and electrons at 4 K is short (2–8 bp). It follows that DNA is effectively an insulator.

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A Rational Approach to Selective Recognition of NH_4^+ over K^+ **

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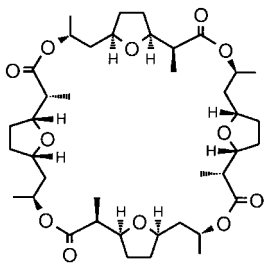
Over the past several decades there has been considerable interest in developing receptors for NH_4^+. Such receptors are desirable as sensors in clinical analysis and in environmental chemistry.[1] For example, concentrations of urea or creatinine in biological samples can be determined indirectly by measuring the amount of NH_4^+ released upon enzyme-catalyzed hydrolysis of the substrates. These receptors are also useful for determining the concentrations of NH_4^+ or ammonia in drinking water and in the air. One of the most effective NH_4^+ receptors is nonactin (**1**), a natural antibiotic agent that is currently used commercially in ion-selective electrodes (ISE).[1, 2] However, a serious drawback of nonactin is that it binds only about ten times more tightly to NH_4^+ than to K^+. Similarly, crown ethers show little or no selectivity for binding NH_4^+ over K^+.[3] Here we report a rationally designed receptor (**2**) that is highly selective for binding NH_4^+ over K^+.



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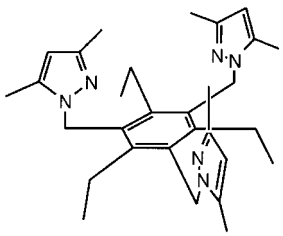

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