On the Mechanism of Long-Range Electron Transfer through DNA**

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Over the past years the discussion on the mechanism of long-range charge transfer through DNA has been centered around the β value in Equation (1). This equation describes the fast exponential decrease in the rate of charge transfer with increasing distance.[1] Depending on the experiment, β values of about 1.0 $Å^{-1}$ or 0.1 $Å^{-1}$ were reported.[2, 3] Such differences in β values have dramatic effects on the rate. Thus, for a charge transfer over 50 Å and a β value of 0.1 $Å^{-1}$, the rate should be nearly 20 orders of magnitude faster than for a β value of 1.0 $Å^{-1}$. It is unlikely that both β values can be realized for long-range charge transport in DNA.

Recently we proposed a hopping mechanism for the long-range charge transfer[4] in which the charge tunnels between DNA bases of similar redox potentials. Thus, long-range charge transfer in DNA consists of a series of short-range tunneling processes which can be described by Equation (1). Whereas the *positive* charge is transported by oxidation of the guanine bases (G) during hole transfer in mixed DNA sequences, the *negative* charge should be conducted by reduction of the bases thymine (T) and cytosine (C). This conclusion is derived from the redox potentials of the bases, which are different for guanine (G) and adenine (A)[5, 6] and similar for thymine (T) and cytosine (C).[6, 7] In the case that every single hopping step occurs over the same distance, the hopping mechanism is described by Equation (2).[4a, b] In sharp contrast to Equation (1), a weak distance dependence of the relative rate constants k results from Equation (2).

$$\ln k \propto -\beta \Delta r \quad (1)$$

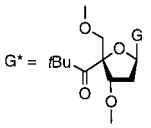
$$\ln k \propto -\eta \ln N \quad (2)$$

In Equation (2), η is a proportionality factor which in the simplest case should be about 2, and N is the number of hopping steps.[4a, b] We have now proven the validity of Equation (2) experimentally through charge-transfer reactions over 10 to 40 Å in DNA strands **1a**–**3a**.

The experiments are based on an assay in which a 4′-acylated nucleoside is incorporated into double-stranded DNA.[4a] Norrish I photocleavage and subsequent heterolysis

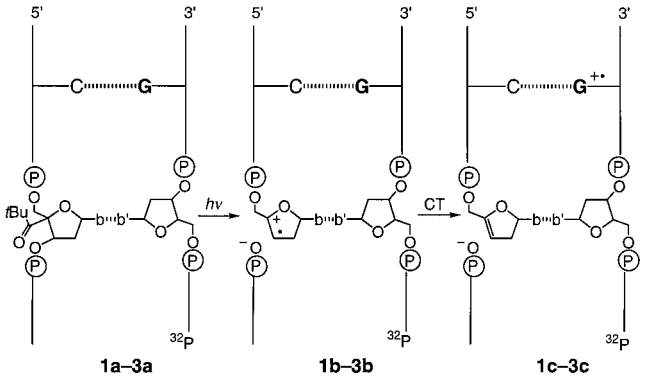
3′-CGCATTATATTATGGG **X** G_{22}CA TTATAATACGCTGCACGCA-^{32}P
5′-GCGTAATATAATACCC **Y** C G*TAATATTATGCGACGTGCGT-3′

1a–3a



	X Y
1a	TT AA
2a	TTGTT AACAA
3a	TTGTTGTTGTT AACAACAACAA

leads to the sugar radical cations **1b**–**3b**, which transfer the positive charge onto the neighboring G base of the ^{32}P-labeled complementary strand (**1c**–**3c**; Scheme 1). Starting from



Scheme 1. Generation of the guanine radical cation $G^{\bullet+}$ in the ^{32}P-labeled strands **1c**–**3c** by photolysis of the ketone unit in the modified strands **1a**–**3a**.

here the positive charge is transported through the DNA over the nucleotide pairs **XY** until it reaches a GGG unit, where it is trapped irreversibly. In competition with the charge transfer, the radical cation $G^{\bullet+}$ can be trapped with H_2O. This leads to a damaged G^{ox} position,[4a] at which the DNA is cleaved after treatment with piperidine. We have shown recently that the relative rate constant of charge transfer (k_{rel}) from $G^{\bullet+}$ over the G bridges to the GGG unit is equal to the ratio of the cleavage products GGG/G; cleavage at all G positions was taken into account.[4a]

The experiments were carried out with double-stranded 40- to 49-mers **1a**–**3a**, which have repeating AT,AT double units between the G bases.[8] Following Equation (2) the number of hopping steps N has the value of 1, 2, or 4 for the strands **1a**, **2a**, and **3a**, respectively. Two independent series of measurements were performed; the mean values are compiled in Table 1.[9]

Figure 1 shows that a plot of $\ln k_{rel}$ versus $\ln N$ yields a η value of 1.7 ± 0.2. Thus, hole transfer over 10, 20, and 40 Å is well described by a hopping model.[10] In Scheme 2 the arrows demonstrate how the charge of $G_{22}^{\bullet+}$ hops between the G bases until it reaches the GGG unit.

If Equation (1) was applied and the experimental data were fit to a straight line, a β value of 0.07 would result. This hypothetical β value implies a superexchange mechanism in

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Table 1. Experimental data for the double strands **1a**–**3a** and **4**–**6**. The oxidative damage at the G and GGG units was quantified after piperidine treatment and polyacrylamide gel electrophoresis with a phospho-imager.

DNA strand	N	Δr [Å]	GGG/G = k_{rel}
1a	1	10	8.9 ± 1.9
2a	2	20	2.8 ± 0.4
3a	4	40	0.88 ± 0.12
4	–	54	2.3 ± 0.7[4a]
5	–	54	0.04 ± 0.02
6	–	17	0.03 ± 0.015[4a]

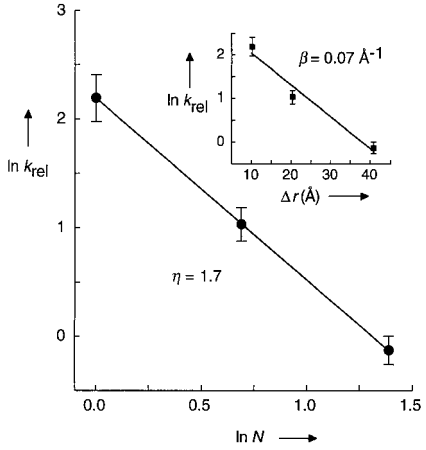
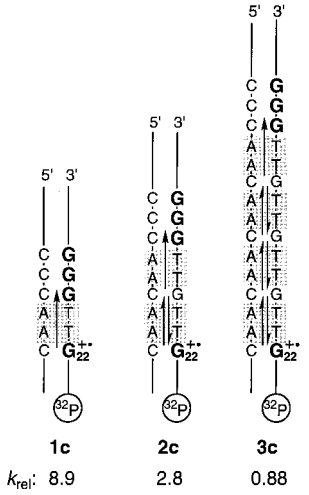
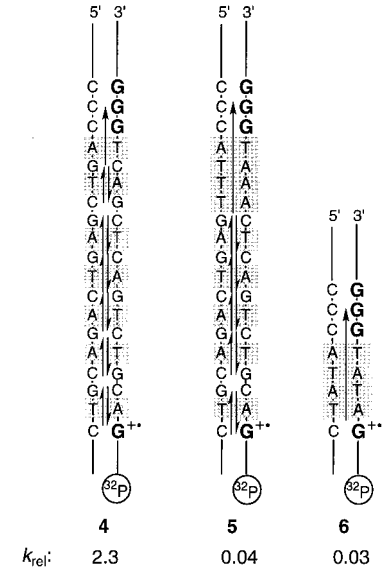


Figure 1. Dependence of the relative rate of charge transport (k_{rel}) on the number of hopping steps N and on the total distance Δr (inset).



Scheme 2. Charge transfer (indicated by the arrows) from $G_{22}^{\bullet+}$ to the GGG unit in one (**1c**), two (**2c**), or four hopping steps (**3c**).

which the distance dependence is very small. However we have shown recently that long-range charge transfer through mixed DNA strands cannot be described by this superexchange mechanism.[4a] This is also demonstrated by experiments with oligonucleotides **4** and **5**.[11] In both strands the charge was transported over 54 Å, but the transfer is 60 times faster in **4** than in **5**. Following our hopping mechanism,[4a] the rate-determining step in double strand **5** is the tunneling over a sequence of four AT base pairs. Therefore, in **5** charge transfer over 54 Å occurs at a similar rate as over 17 Å in **6** (Scheme 3).[4a]



Scheme 3. Charge transfer (indicated by the arrows) from $G^{\bullet+}$ to the GGG unit in different double strands **4**, **5**, and **6**.

Our studies show that charge transport through DNA can take place by hopping steps between bases having similar redox potentials. Since guanine (G) is the base of lowest oxidation potential in DNA, transfer of the positive charge occurs by tunneling between the guanine bases. The rate of these tunneling steps depends strongly on the distance between the neighboring G bases. Therefore, the base sequence plays a decisive role on the hole transfer. Following the hopping mechanism, transport of a negative charge takes place by reduction of thymine (T) and cytosine (C), which possess similar reduction potentials. Since one of these pyrimidine bases is present in each base pair, one can expect that electron transfer should not be dependent on the sequence.

A modification of natural DNA changes the redox potential of single bases. Following the hopping mechanism this should exert a strong influence on the efficiency of charge transfer.

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[1] Comments on charge transfer in DNA: a) D. N. Beratan, S. Priyadarshy, S. M. Risser, *Chem. Biol.* **1997**, *4*, 3; b) E. K. Wilson, *Chem. Eng. News* **1997**, *75*(8), 33; c) T. L. Netzel *J. Chem. Educ.* **1997**, *74*, 646; d) G. Taubes, *Science* **1997**, *275*, 1420; e) S. Priyadarshy, S. M. Risser, D. N. Beratan, *J. Biol. Inorg. Chem.* **1998**, *3*, 196; f) N. J. Turro, J. K. Barton, *J. Biol. Inorg. Chem.* **1998**, *3*, 201; g) T. L. Netzel, *J. Biol. Inorg. Chem.* **1998**, *3*, 210; h) F. D. Lewis, R. L. Letsinger, *J. Biol. Inorg. Chem.* **1998**, *3*, 215; i) E. S. Krider, T. J. Meade, *J. Biol. Inorg. Chem.* **1998**, *3*, 222.

[2] a) A. M. Brun, A. Harriman, *J. Am. Chem. Soc.* **1992**, *114*, 3656; b) A. M. Brun, A. Harriman, *J. Am. Chem. Soc.* **1994**, *116*, 10383; c) S. J. Atherton, P. C. Beaumont, *J. Phys. Chem.* **1995**, *99*, 12025; d) F. D. Lewis, T. Wu, Y. Zhang, R. L. Letsinger, S. R. Greenfield, M. R. Wasielewski, *Science* **1997**, *277*, 673; e) K. Fukui, K. Tanaka, *Angew. Chem.* **1998**, *110*, 167; *Angew. Chem. Int. Ed.* **1998**, *37*, 158;

f) E. Meggers, D. Kusch, M. Spichty, U. Wille, B. Giese, *Angew. Chem.* **1998**, *110*, 474; *Angew. Chem. Int. Ed.* **1998**, *37*, 460.

[3] a) C. J. Murphy, M. R. Arkin, Y. Jenkins, N. D. Ghatlia, S. H. Bossmann, N. J. Turro, J. K. Barton, *Science* **1993**, *262*, 1025; b) S. O. Kelley, R. E. Holmlin, E. D. A. Stemp, J. K. Barton, *J. Am. Chem. Soc.* **1997**, *119*, 9861.

[4] a) E. Meggers, M. E. Michel-Beyerle, B. Giese, *J. Am. Chem. Soc.* **1998**, *120*, 12950; b) J. Jortner, M. Brixon, T. Langenbacher, M. E. Michel-Beyerle, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 12759; see also: c) T. Melvin, S. Botchway, A. W. Parker, P. O. Neill, *J. Chem. Soc. Chem. Commun.* **1995**, 653; d) S. M. Gasper, G. B. Schuster, *J. Am. Chem. Soc.* **1997**, *119*, 12762.

[5] S. Steenken, S. V. Jovanovic, *J. Am. Chem. Soc.* **1997**, *119*, 617.

[6] C. A. M. Seidel, A. Schulz, M. H. M. Sauer, *J. Phys. Chem.* **1996**, *100*, 5541.

[7] S. Steenken, J. P. Telo, H. M. Novais, L. P. Candeias, *J. Am. Chem. Soc.* **1992**, *114*, 4701.

[8] In contrast to the assay that we have used previously,[4a] the experiments were carried out with 4′-pivaloyl-substituted guanosine. The synthesis of this guanosine derivative was performed in analogy to that for the modified thymidine: A. Marx, P. Erdmann, M. Senn, S. Körner, T. Jungo, M. Petretta, P. Imwinkelried, A. Dussy, K. J. Kulicke, L. Macko, M. Zehnder, B. Giese, *Helv. Chim. Acta* **1996**, *79*, 1989. Photolysis of monomeric 4′-pivaloyl-substituted guanosine that was phosphorylated at the 3′-OH position gave the enol ether in 85% yield. This shows that the charge transfer between the carbohydrate radical cation and the base G is very fast.

[9] The double strands **1a**–**3a** contained 3 ± 0.5 pmol of 4′-pivaloyl-modified strands and 1 ± 0.2 pmol of the corresponding 5′-^{32}P-labeled complementary strands. They were photolyzed for 15 min in phosphate buffer (200 μL, 20 mM, 100 mM NaCl, pH 7.0) at 15 °C with a 500-W Hg high-pressure lamp in the absence of oxygen. An aliquot of the solution was incubated for 30 min with 1M piperidine at 90 °C, then lyophilized overnight, and analyzed by denaturated polyacrylamide gel electrophoresis (1500 V, 3.5 h). The modified strands were replaced by unmodified strands in control experiments. The dried gels were autoradiographed with a phospho-imager and analyzed with the software ImageQuant. Quantification of the piperidine-induced bands was performed by substracting the intensities obtained in the control experiments from the intensities obtained with the modified double strands.

[10] Experiments with other DNA strands are under way.

[11] The measurements were carried out under the conditions described in detail in reference [4a]. The sequences of the strands correspond to those given there.

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