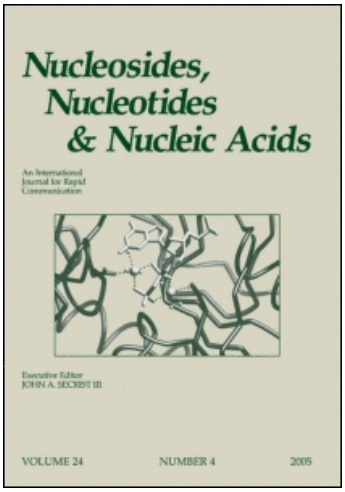

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Photoadduct Leading to Crosslinking in Ru^{II}-Derivatized Oligonucleotides

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The use of modified oligonucleotides that may recognize messenger RNA and react with the target RNA sequence is a promising strategy in the development of new drugs that control or block gene expression. [1] In this prospect we have exploited the photochemical properties of Ru(II) complexes able to form adducts with DNA.[2] Under illumination some complexes are able to abstract an electron from the guanine, the most reductive base of DNA. This process, evidenced by luminescence quenching of the metallic species, gives rise to the formation of radicals that may recombine to form a covalent bond between a guanine and one ligand of the complex.

In order to cumulate this photoreactivity with a sequence specificity, we have prepared different 17-mer duplex oligonucleotides derivatized by the $[Ru(TAP)_2dip]^{2+}$ complex.[3] Visible illumination of these duplexes induces an electron transfer with

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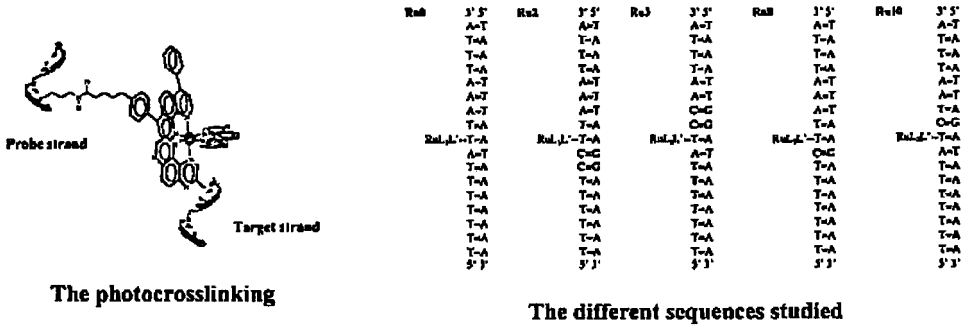

Figure 1.

formation of adducts on specific guanines on the complementary sequence. This key process leads to a crosslinking of the two strands which is easily detectable by gel electrophoresis.

As shown in the table, the photo-electron transfer, estimated by the percentage of luminescence quenching of the complex, is directly dependent on the ionisation potential (I.P.) of the involved guanines.[4] However, the amount of oligodeoxynucleotide-adduct (ODN-adduct) for each sequence is not directly correlated to the quenching process, but seems to depend on other factors such as the position of the guanines as compared to the site of tethering of the complex. For example, comparison between sequences **Ru2** and **Ru3**, or **Ru8** and **Ru10**, indicates that the yield of photo-crosslinking is higher when the guanines are in the 3′ direction on the complementary strand than in the 5′ direction as compared to the tethering site of the complex.

These results clearly show that the photocrosslinking is controlled by different factors, not only the I.P. of the reactive guanines but also geometric factors since the G located on the 3′ or 5′ side reacts differently. Moreover, the photo-crosslinked

Table 1.

Duplex	% Quenching[a]	I.P. [eV][b]	% ODN-adduct[c]	Position of G[d]
Ru0	–	–	0	–
Ru2	59 ± 2	6.32	54 ± 5	3′
Ru3	49 ± 2	6.42	17 ± 4	5′
Ru8	38 ± 2	6.55	44 ± 4	3′
Ru10	31 ± 2	6.60	16 ± 4	5′

[a]Percentage of luminescence quenching of the complex as compared to the reference sequence (**Ru0**) containng no guanine.
[b]Calculated ionisation potentials (I.P.) of the guanines present in the different sequences (4).
[c]Determined by counting the band of the ODN-adduct (photo-crosslinking) on the acrylamide gel and comparing it to the total radioactivity.
[d]Position of the guanines of the complementary strand as compared to the metal tethering site.

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duplex is not fully degraded by Exonuclease III from E.coli, a typical 3′-5′ exonuclease enzyme. The latter seems thus to be blocked by the presence of the photoadduct. These results are promising for the design of photoreactive antisense ODN′s.

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