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DETERMINATION OF THE SPATIAL STRUCTURE OF A DNA DUPLEX WITH A NON-COMPLEMENTARY CU PAIR BY NMR SPECTROSCOPY*

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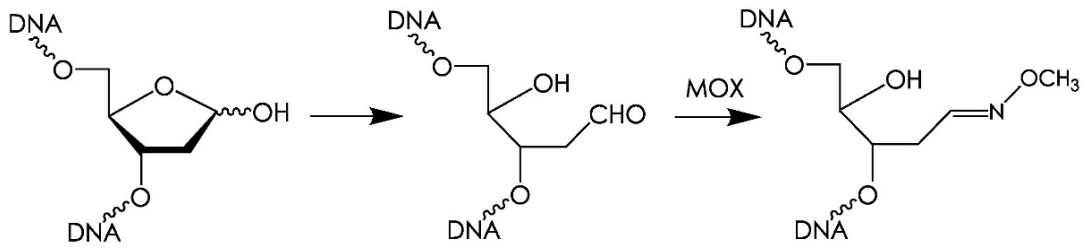
Abstract

DNA molecules are constantly being damaged. In human cells the amount of damage can reach several thousand per cell per day. This damage includes changes in the chemical structure of DNA, chain breakage or the presence of incorrect bases or their fragments. However, cells have repair systems to help repair these damages. The study of processes modeling DNA repair is an urgent task, since DNA damage is the cause of many diseases. DNA structures with AP sites can be used to develop drugs to treat tumors and other conditions.

In this study, we focused on the structural characteristics of a DNA duplex containing a methoxyamine AP site (see Figure). This site is of particular interest due to its potential as an antitumor agent that is currently undergoing clinical trials. Methoxyamine is known to cause specific DNA damage by forming adducts, which leads to changes in the structure of DNA that can affect its stability and functionality. Understanding these modifications is crucial for evaluating the therapeutic efficacy and safety of methoxyamine in clinical settings.



Methoxyamine derivative of the AP site

To gain insight into the structural dynamics of DNA modified with methoxyamine, we use a duplex containing an irregular CU pair as a reference model. This CU pair serves as a valuable tool for understanding how non-canonical base pairs affect the overall stability and conformation of DNA. By examining the duplex of the CU pair, we can establish a model for comparing the structural effects caused by the modification of methoxyamine.

Nuclear magnetic resonance (NMR) spectroscopy was used in this study mainly because of its ability to provide detailed information about the structure and dynamics of nucleic acids in solution. NMR allows us to observe the conformational states of the DNA duplex, especially in the presence of non-canonical base pairs such as CU pairs. This method is especially useful for studying dynamic processes such as the rapid exchange between different structural forms, which is crucial for understanding how DNA reacts to damage and modification.

The work investigated the NMR spectra of the duplex in the H_2O + D_2O system. From the temperature dependence of the spectra, it can be concluded that the C-G pairs located between the terminal pairs and AT pairs are sufficiently strong, which indicates the formation of stable B-type helices in these fragments. Some signals, especially those associated with CU and nearby base pairs, become narrower with increasing temperature, indicating the presence of rapid exchange between structures due to the process occurring in the central region, which contains a non-complementary CU base pair.

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