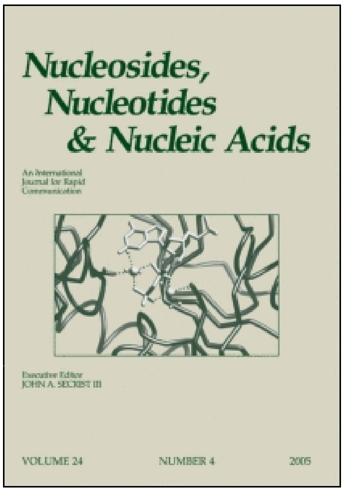

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DNA Apurinic Sites: Synthesis of a Model Compound and Study of its Reactivity with 3-Aminocarbazole

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DNA APURINIC SITES : SYNTHESIS OF A MODEL COMPOUND AND STUDY OF ITS REACTIVITY WITH 3-AMINOCARBAZOLE

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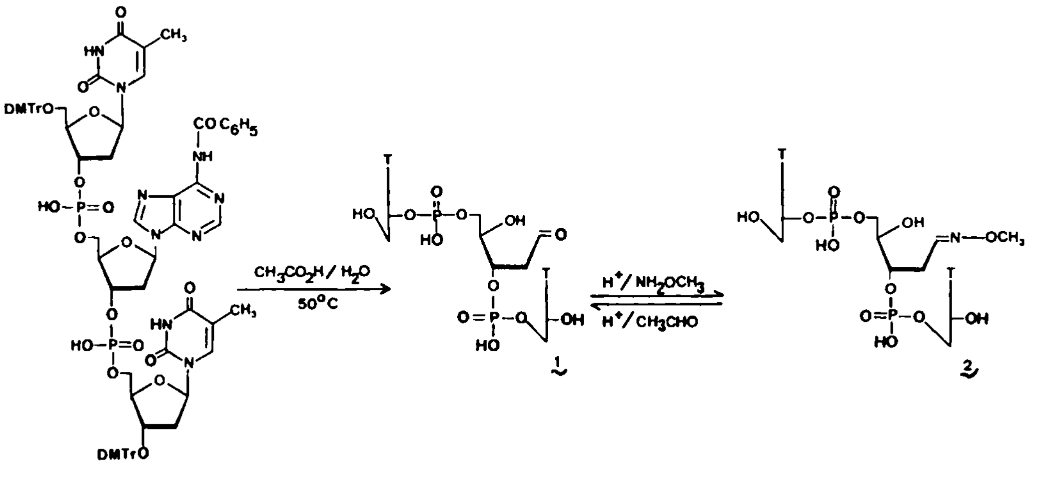
Summary The mechanism of breakage of apurinic DNA with 3-aminocarbazole was determinated on a short oligonucleotide model. The results founded contrast with those reported in the literature.[1]

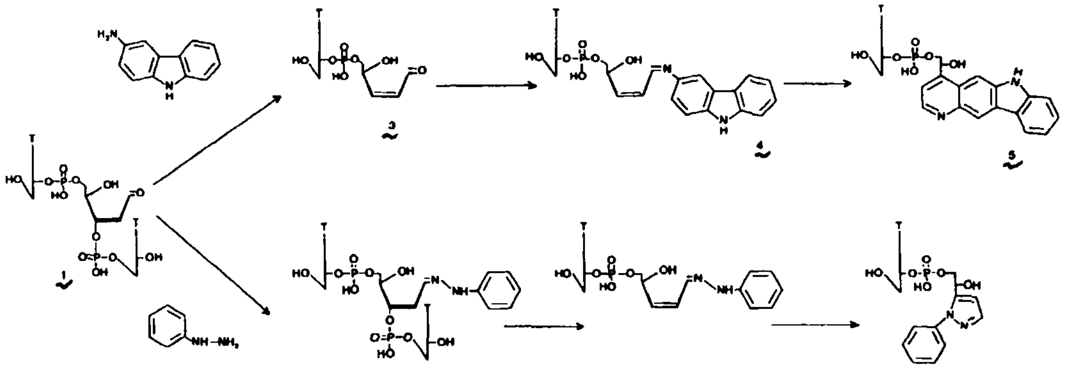
Using the phosphotriester approach in solution the fully-protected trinucleotide diphosphate TpApT was synthesized. Subsequent phosphate deprotection and careful acidic treatment which removed the trityl protection and cleaved the purine glycosidic bond gave the desired apurinic model 1. Direct attemps to purify 1 were unsuccessful due to degradation.



DMTr: 4,4'-dimethoxytrityl

Treatment of the crude compound with methoxyamine[2] gave a stable adduct 2 which was then easily purified by preparative HPLC. Upon treatment of the methyloxime derivative 2 with acetaldehyde in acidic medium, the pure AP site 1 was obtained.

Analysis of the reaction between the model 1 and 3-aminocarbazole revealed a two step reaction : (1) formation of an α,β-unsaturated aldehyde 3 resulting from β-elimination of 5'-phosphate thymidine and caracterized by its UV spectrum (maximum 222 nm); (2) subsequent formation of an α,β-unsaturated Schiff base 4. This second intermediate appears to incorporate aminocarbazole moiety on the basis of the UV absorption at 305 and 366 nm. Attempts to isolate 4 failed since it undergoes facile cyclisation to the (6H) pyrido [3,2-b] carbazole derivative 5 caracterized with (FAB) mass spectrometry and high resolution ^{1}H-NMR spectroscopy.



These results contrast with those found in case of phenylhydrazine where β-elimination occurred after phenylhydrazone formation. In this case intermediates were caracterized by their UV spectra based on the literature.[1]

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1. Coombs, M.M., and Livingston, D.C., *Biochim. Biophys. Acta*, 1969, *174*, 161-173.
2. Liuzzi, M., and Talpaert-Borlé, M., *J. Biol. Chem.*, 1985, *260*, 5252-5258.