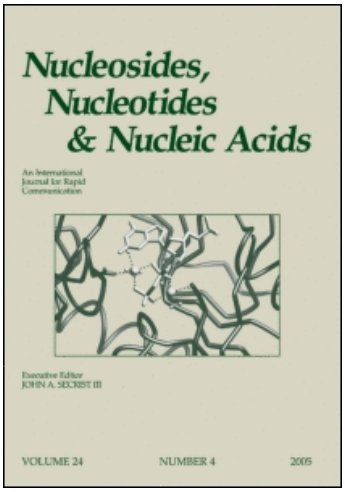

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Depurination As a Yield Decreasing Mechanism in Oligodeoxynucleotide Synthesis

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To cite this Article Efcavitch, J. William and Heiner, Cheryl(1985) 'Depurination As a Yield Decreasing Mechanism in Oligodeoxynucleotide Synthesis', Nucleosides, Nucleotides and Nucleic Acids, 4: 1, 267
To link to this Article: DOI: 10.1080/07328318508077883
URL: http://dx.doi.org/10.1080/07328318508077883

NUCLEOSIDES & NUCLEOTIDES, 4(1&2), 267 (1985)

DEPURINATION AS A YIELD DECREASING MECHANISM IN OLIGODEOXYNUCLEOTIDE SYNTHESIS

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The synthesis in our laboratory of very long (80-106 bases) oligodeoxynucleotides using the phosphite method of Matteucci and Caruthers[1] in an automated DNA synthesizer indicates the true efficiency of this multiple step process. The coupling efficiency as measured by trityl cation release is 99.5-99.8%. However the yield obtained is still below the theoretical yield calculated from the above efficiency. We have attempted to elucidate yield decreasing mechanisms in long oligodeoxynucleotide synthesis. Crude reaction mixtures of phosphate-deblocked oligonucleotides which had no 5'-trityl group and which were examined immediately after cleavage from the support show one major species by high resolution PAGE. Harsher hydrolysis generates a new pattern of products superimposed upon the initial ladder representing cleavage at purine residues internal to the full length oligonucleotide. In many cases the cleavage ladder is significantly more intense than the coupling ladder. Hydrolysis at apurinic sites in ammonium hydroxide at 55° C is apparently quantitative. The implications of this study are that internal depurination does not interfere with chain propagation but directly reduces the isolated yield. The efficiency of the phosphite coupling, oxidation, demethylation, and base deprotection are not the yield limiting steps. Synthesis of even longer fragments may be achievable with a reduction in the depurination of the propagating chain. More significantly, compounds isolated after proper hydrolysis will not contain any apurinic sites making these compounds suitable for biological use.

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 0732-8311/85/0401-0267$3.50/0