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Solid Phase Synthesis of DNA Under a Non-Depurinating Condition with a Base Labile 5'-Protecting Group (Fmoc) Using Phosphiteamidite Approach

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SOLID PHASE SYNTHESIS OF DNA UNDER A NON-DEPURINATING CONDITION WITH A BASE
LABILE 5'-PROTECTING GROUP (Fmoc) USING PHOSPHITEAMIDITE APPROACH

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Summary: 5'-Fmoc protected 2'-deoxynucleoside building blocks have been employed in DNA synthesis in order to remedy the depurination problem.

One disadvantage of the methods^{1,2} used today in the synthesis of DNA is the depurination encountered during the removal of the 5'-DMTr group from N⁶-protected deoxyadenosine blocks. Several attempts have been made to prevent this by either altering the acidic conditions employed³ or by varying the N⁶ protecting group⁴. Other authors have modified the trityl group⁵ or used p-phenylazophenylloxycarbonyl⁶ which could be removed under basic hydrolytic conditions.

We have previously shown that the 9-fluorenylmethoxycarbonyl (Fmoc)⁷ group could be used in oligodeoxynucleotide synthesis, by synthesizing a T₂₄ fragment. We now wish to report that the Fmoc group can also be employed in the phosphiteamidite approach² on solid phase constituting a DNA synthesis strategy fully based on non-acidic reaction conditions. The 5'-Fmoc protected nucleosides were prepared in 60-80% yields by treatment with Fmoc-Cl (1.3 equiv. dissolved in dry acetonitrile 10 ml/mmol) of the nucleosides in dry pyridine (10 ml/mmol). These 5'-Fmoc protected nucleosides were then converted to their corresponding phosphiteamidites following standard methods², except that THF was used as solvent and that only two equiv. of base were used. The reaction was worked up as usual⁸, and the phosphiteamidites were purified by silica gel chromatography using CH₂Cl₂:EtOAc:pyridine (2:2:1, v/v/v) for separation. The ³¹P-NMR spectra of the crude and purified amidites are shown in Fig. 1. It was found that the 5'-Fmoc group could be cleaved by treatment with DBU (30 equiv.) in

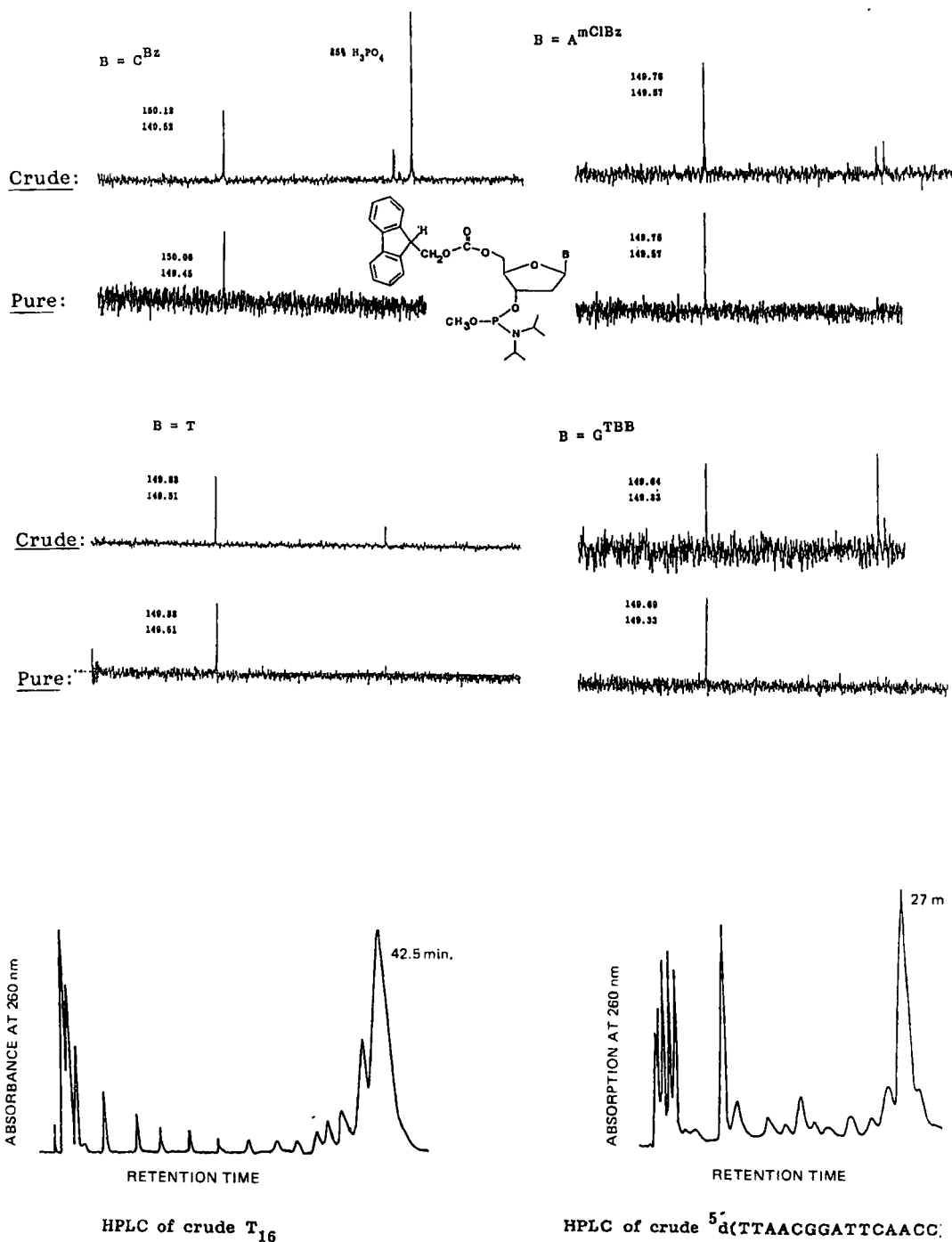


Fig. 2

dry acetonitrile within 18 seconds at 20 °C. Under these conditions there was approximately 1% cleavage of the support. To demonstrate the usefulness of this technique we have synthesized⁸ T₁₆ and a mixed sequence 5'd(TTAACGGATTCAACC)³'. Fig. 2 shows the Hplc⁹ elution profiles of the crude mixtures after deprotection². They were also subsequently characterized by ³²P-labelling and electrophoresis. We believe that this method offers a potential solution to the problem of depurination although the stability of the support requires some improvement.

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