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Three-phase - Synthesis of Oligonucleotides

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"THREE-PHASE" - SYNTHESIS OF OLIGONUCLEOTIDES

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SUMMARY: Stable reagents were made from nucleoside-phosphorochloridites and polymeric sec. amines. Treatment of these with tetrazole/ CH_3CN and transfer of the resulting solution to immobilized oligonucleotide gave 95% chain elongation.

While phosphoramidite reagents are most valuable for oligonucleotide synthesis, their design is still a compromise between stability and reactivity¹. For this reason we prepared polymeric reagents from 5'-DMTrdN-P(OCH₃)Cl (N = common nucleosides) and polystyrene or silicagel containing (C₂H₅)NH- or piperazino groups. When samples of these were treated with tetrazole + acetonitrile, and the solutions syringed² to support-bound nucleosides, detritylation yield monitoring and dinucleotide workup indicated near-quantitative internucleotide bond formation. Subsequently, the tetrazole/ CH_3CN solution generated from DMTrdT-reagent was fed into an automatic synthesizer and used for the preparation of dA(T)₄ and d(T)₈ : yields 77% resp. 68% after C₁₈-HPLC workup² (ca. 95% per cycle). In addition to demonstrating the preparative applicability and stability (>1 year) of polymeric phosphoramidites, our studies shed light on the mechanistic role of tetrazole, which may obviously act not only through proton transfer, but also, by nucleophilic attack, generate an active species³, which is now further investigated.

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3. A tetrazolide intermediate has been proposed e.g. by T.M. Cao et al., *Tetrahedron Lett.* 24, 1019 (1983).