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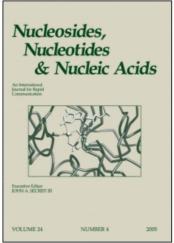
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Three-phase - Synthesis of Oligonucleotides

Hartmut Seliger^a; Kailash Chand Gupta^a Univ. Ulm, Ulm, F.R. Genmany

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"THREE-PHASE" - SYNTHESIS OF OLIGONUCLEOTIDES

Hartmut Seliger * and Kailash Chand Gupta Univ.Ulm, Sektion Polymere, Oberer Eselsberg, D7900 Ulm, F.R.Germany

SUMMARY: Stable reagents were made from nucleoside-phosphorochloridites and polymeric sec. amines. Treatment of these with tetrazole/CH₃CN 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 reactivity 1. For this reason we prepared polymeric reagents from 5'-DMTrdN-P(OCH₃)Cl (N = common nucleosides) and polystyrene or silicagel containing $(C_2H_5)NH$ - or piperazino groups. When samples of these were treated with tetrazole + acetonitrile, and the solutions syringed 2 to support-bound nucleosides, detritylation yield monitoring and dinucleotide workup indicated near-quantitative internucleotide bond formation. Subsequently, the tetrazole/CH2CN solution generated from DMTrdT-reagent was fed into an automatic synthesizer and used for the preparation of $dA(T)_A$ and $d(T)_8$: yields 77% resp. 68% after C_{18} -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 species 3, which is now further investigated.

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