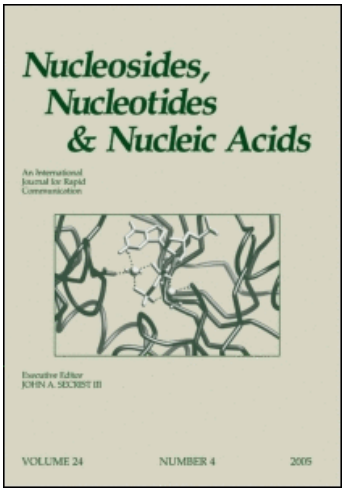

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Synthesis of [5'-Phosphoryl-N(α)]-oligonucleotidyl-peptides

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SYNTHESIS OF [5'-PHOSPHORYL-N(α)]-OLIGONUCLEOTIDYL-PEPTIDES

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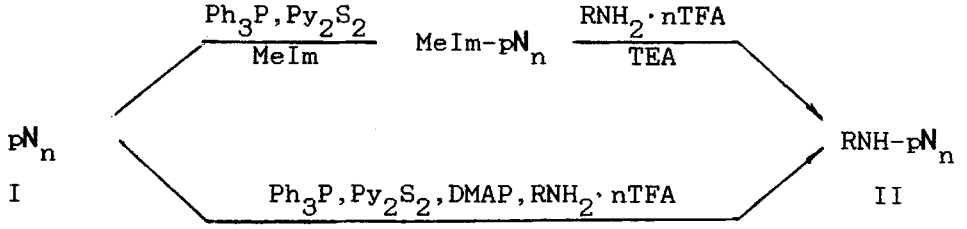
ABSTRACT. An effective method for the synthesis of oligonucleotidyl-peptides via formation of a phosphoroamide bond between deblocked oligonuleotide and amino group of N-terminal amino acid was proposed.

To study structure and properties of covalently bound nucleotide-peptide complexes, nucleotidyl-peptides are used as model systems. The suggested method for covalent binding of deblocked oligonucleotides to the N-terminal amino group of peptides proved to be rather effective.

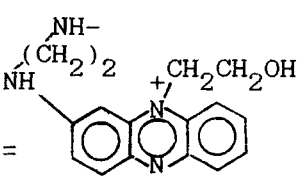
The reactions between an oligonucleotide (10^{-4}-10^{-3} M) and a peptide (2.5×10^{-2}M) were carried out in ahydrous DMSO and DMF by triphenylphosphine (Ph_3P, 0.4 M) and



δ=0.2 ppm (Ia) δ=5.14 ppm (IIa)

a) pN_n=pT(Ac) RNH_2= PRV-OMe
b) pN_n=pCCCC RNH_2= PRV-OMe
c) pN_n=pTCAATC RNH_2=LRLRLRGNH$_2$
d) pN_n=pTCAATCpPhn RNH_2=LRLRLRGNH$_2$
e) pN_n=pCGTCCTCpPhn RNH_2=LRLRLRGNH$_2$

Phn-=



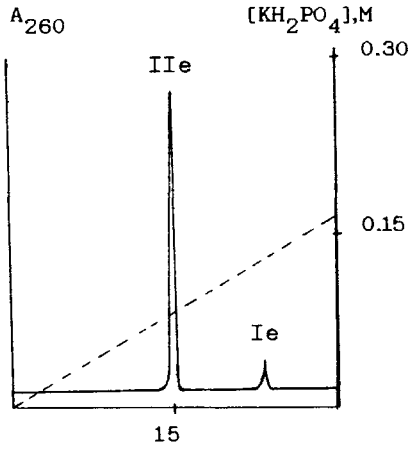


Fig.1.IEC of the reaction mixture containing IIe on a Polysyl CA 80 column.

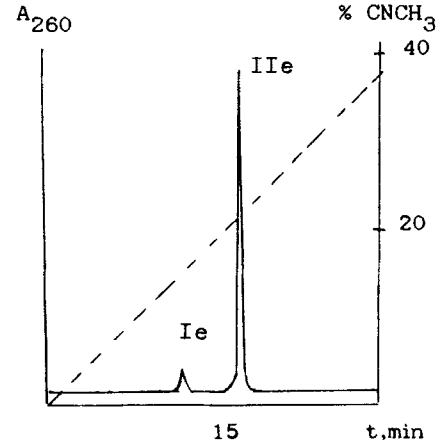


Fig.2.RPC of the reaction mixture containing IIe on a Lichrosorb RP 18 column.

2,2'-dipyridyldisulfide (Py_2S_2, 0,4 M) in the presence of nucleophilic catalysts (1 M): 4-N'-N'-dimethylaminopyridine (DMAP) or 1-methylimidazole (MeIm).

According to the SCHEME the terminal phosphate of oligonucleotide must be activated prior to the addition of the peptide and TEA (0.2 M) . In the case of DMAP, all componets are mixed simultaneously and TEA is not added . All products were HPLC-purified with the yield of 70-80%.

The oligonucleotide-peptides bearing hydrophobic residues eluted from the column before the initial oligonucleotide (FIG.1) during IEC and after the initial oligonucleotide in RPC (FIG.2). The oligonucleotide-peptides are hydrolysed to yield parent oligonucleotides under conditions of phosphoroamide bond hydrolysis (20°C, 14 hr, pH 1).

The obtained results prove that oligonucleotidyl-peptides, including those bearing arginine residue,may be synthesized by our method to give a high yield.