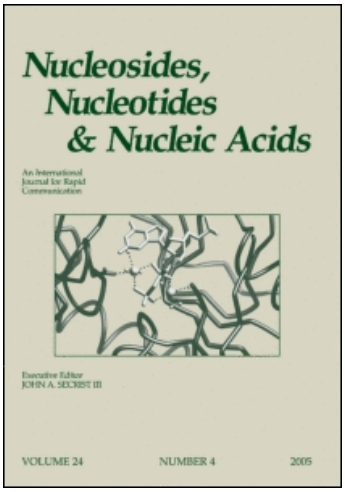

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Oligomerization Aiming at Phosphonate Analogues of Oligoadenylates

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ABSTRACT

This work deals with isopolar, phosphonate-based nucleotide analogues containing a bridging *P-C* bond instead of the ester *P-O* linkage. Specifically, starting from activated derivatives **1**, **2**, and **3**, a simple process for preparation of mixtures of short oligomers and their analyses were elaborated.

Key Words: DDC-induced oligomerization; Phosphonate 5′-nucleotides; Spontaneous formation of isopolar phosphonate internucleotide linkage; Cyclic oligoadenylates; Uranyl ions; Hybridization.

RESULTS AND DISCUSSION

Based on experiences of our laboratory with preparation of diverse phosphonate analogues of NMP,[1–3] following structure types **1**, **2**, **3** were chosen for preliminary condensation experiments.

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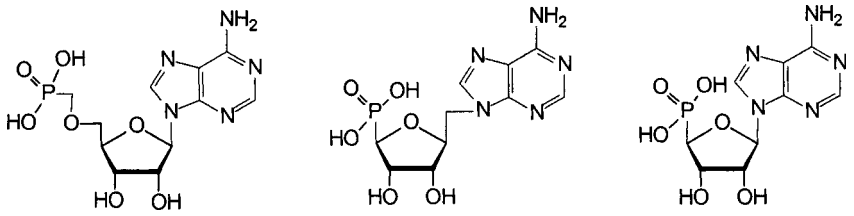

1 2 3

For spontaneous polycondensation, two approaches were worked out, i.e., modified polycondensation procedure of activated nucleotides under uranyl ion catalysis[4] in aqueous medium and DCC-induced polycondensation under anhydrous conditions.

Initially, the former method, originally worked out for phosphoro-imidazolides, was not applicable to phosphonates, due to instability of phosphonoimidazolides in aqueous solution. Hydrolysis into nucleoside-5′-phosphonates prevailed over polycondensation, however, increasing pH from 7.2 to 10, appropriately influenced the competitive reaction pathway and partially solved the problem. Typical uranyl ion-catalyzed reaction mixture consisted of 20 mM nucleoside-5′-phosphonoimidazolide in 200 mM imidazole/water pH 9.8 (0.45 mL) containing 1 mM $UO_2(NO_3)_2.6H_2O$. Oligonucleotides resulting from this condensation were predominantly linear chains up to tetramers and hexamers composed of structure types **1** and **2**, respectively. The condensation of nucleoside-4′-phosphonate **3** failed, probably due to steric reasons. Generally, comparing to described polycondensation of nucleoside-5′-phosphoroimidazolide[4] resulting predominantly in 2′–5′ linked linear oligonucleotides, the presented experiments gave rise to shorter chains with lesser regioselectivity of the internucleotide bonds.

Alternatively, DCC-induced polycondensation under anhydrous conditions resulted in cyclic oligomers, namely composed of the structure type **1**. Enhanced flexibility of **1** as the result of the presence of an *extra* methylene group at the 5′-end of the molecule, enabled growth of both cyclic and linear forms. Typical DCC-induced reaction mixture consisted of 0.1 M nucleoside-5′-phosphonate and 1 M-DCC in dry DMF (0.5 mL).

Easy access to a mixture of short oligomers would not be meaningful without similarly simple method for identification of the products. Analysis of individual oligomers inside the mixtures, didn't give the distinct structural answer, nevertheless certain evaluation was feasible.

Combining analytical data, i.e., molecular mass of individual components (LCMS), resistance towards $NaIO_4$ oxidation (distinguishing linear from cyclic oligomers on the base of cis-diol oxidative cleavage), characteristic RP-HPLC mobility (reflecting m/z order of products) or CZE mobility (reflecting charge), led to the basic image concerning the length and type of products. Specifically, e.g., DCC polycondensation product characterized by $t_R = 13.42$ (RP-HPLC), $t_m = 10.76$ (CZE; typical for compounds bearing two negative charges), dimer molecular ion mass 684.11 (LCMS) and resistance towards oxidation, is very probably cyclic dimer (see Table 1).

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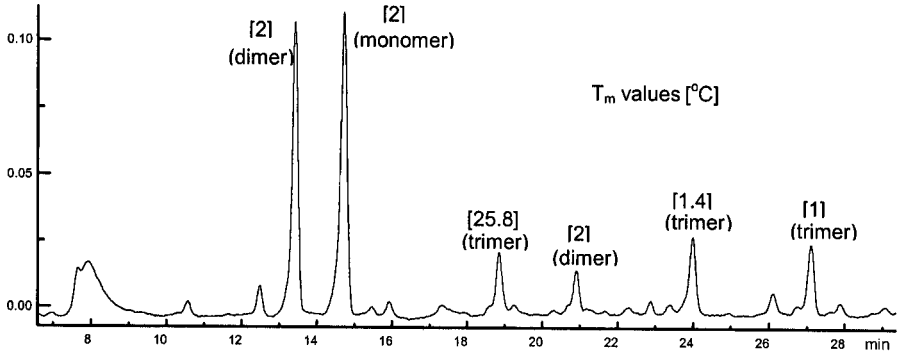
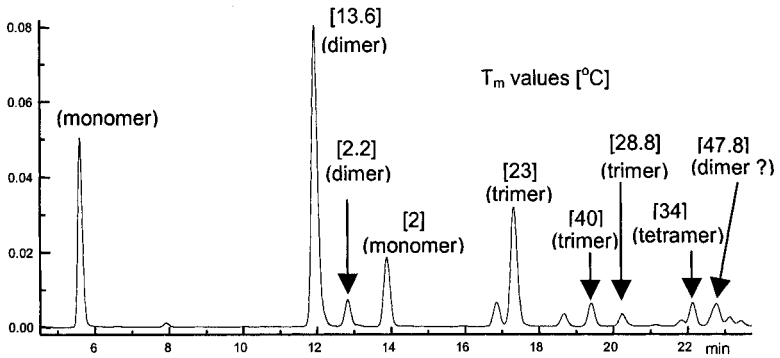
Table 1. DCC-induced polycondensation of monomer type 1.

HPLC [t_R]	Yield [%]	LCMS	Oxidation	Results
7.92	11.55	no signal	yes	monomer
12.49	1.91	687.11	yes	linear dimer
13.42	17.96	687.11	no	cyclic dimer
14.72	21.08	no signal	no	cyclic monomer
18.85	4.60	1030.16	no	cyclic trimer
20.90	3.34	687.14	no	cyclic dimer
23.99	5.98	1030.13	no	cyclic trimer
26.12	1.92	1373.18	no	cyclic tetramer
27.11	5.11	1030.12	no	cyclic trimer



Cyclic products type **1**: DCC-induced polycondensation



Linear and cyclic products type **1**: uranyl ion-induced polycondensation

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Finally, some oligomers were characterized by T_m values of their complexes with polyU. Supposedly, cyclic oligomers of structure type **1** didn't form stable complexes (if any), although, parent linear oligomers formed very stable complexes with relatively high T_m values (see chromatograms).

Exemplified polycondensation reactions do not represent general access to phosphonate homo-oligonucleotide analogues. The success of condensation is tightly borne both on the structure of monomer and parent oligomer product. Nevertheless, preliminary results showed that control of polycondensation reaction is possible, within one structure type at least; and that easy access to diverse phosphonate analogues of oligonucleotides would facilitate rough orientation in their properties.

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