Template Specificity of Oligonucleotides for Ribonucleic Acid Polymerase

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Recently attempts have been made to define chemically the templates used as substrates in bacterial ribonucleic acid polymerase systems and to analyze the RNA products of such systems (1-9). Enzymatically synthesized polydeoxynucleotides (2, 3, 6, 8) and polyribonucleotides (5, 7, 9, 10) permitted studies of the mechanism involved in the polynucleotide synthesis. It has been shown that an RNA polymerase preparation from Escherichia coli catalyzes the synthesis of polyadenylate dependent upon added chemically synthesized oligodeoxymidylate (1, 3, 11-13). The poly A! product has been employed in an amino acid incorporating system in vitro to direct the synthesis of polylysine (12, 13).

Our studies indicated that enzyme activities other than the template-copying activity existed in our RNA polymerase preparations. This was apparent when it was found that the chain length of the poly A was longer than that of the d(pT)12,14 used as the primer. If this system is to realize its full potential for the investigation of protein biosynthesis at the level of translation of genetic information into protein, it is desirable to produce oligoribonucleotides exactly complementary to the oligodeoxynucleotide template. We have, therefore, investigated further the template-copying activity of RNA polymerase preparations with the use of both oligodeoxynucleotides and oligoribonucleotides.

Methods were devised to suppress contaminating enzyme activities such as polynucleotide phosphorylase and poly A synthetase (4, 14-17). With our modified conditions we confirmed the template-copying activity of bacterial RNA polymerase. In addition, the use of natural and synthetic oligodeoxynucleotides gave rise to oligoribonucleotide copolymers. Analysis of chain lengths, however, still indicated the production of oligoribonucleotides longer than the oligodeoxynucleotide templates.

**EXPERIMENTAL PROCEDURE**

**Chromatographic Systems—**Nucleotide or deoxynucleotide monomers and oligomers were identified on Whatman No. 40 or Whatman DE-81 paper and were separated on a preparative scale on Whatman No. 3MM paper or on a DEAE-cellulose (carbonate form) column. Paper chromatography was carried out by the descending technique. Solvent components were as follows: Solvent A, n-propyl alcohol-concentrated NH4OH-H2O, (55:10:35, v/v); Solvent B, isobutyric acid-1.0 M NH4OH-0.1 M disodium ethylenediaminetetraacetate (1000:600:16, v/v); Solvent C, isopropyl alcohol-concentrated NH4OH-0.10 M boric acid (7:1:2, v/v); Solvent D, 0.3 M ammonium formate; Solvent E, 70% aqueous ethyl alcohol; Solvent F, 57% aqueous ethyl alcohol. Whatman No. 40 and No. 3MM were used with Solvents A, B, and C; Whatman DE-81 (DEAE-cellulose paper) with Solvent D, and Whatman 40 impregnated with ammonium sulfate according to Lane (18) with Solvents E and F.

**Oligonucleotide Preparations—**Poly A, poly U, and poly C were obtained from Miles Chemical Company, Clifton, New Jersey, as the K+ salts. The oligoribonucleotides, (pU)n, (pA)n, (pA)n, (pA)11, and (pC)n, were the generous gifts of Dr. Leon Hoppel.

The deoxyribonucleotides were purchased from Pabst Laboratories, California Corporation for Biochemical Research, and Schwarz BioResearch, Inc. The purity of each was checked before use by paper chromatography with Solvents A, B, and C. The short chain oligodeoxynucleotides, d(pA)n, d(pA)n, d(pC)n, and randomly ordered d(pT)n, were synthesized from mononucleotides according to the method of Khorana et al. (19-21). Individual oligomers were separated by column chromatography or on Whatman No. 3MM in Solvent A. The sample, d(pC)37, with chain length greater than 7, was prepared by eluting a region of a 36-hour chromatogram (Solvent A) between the heptanucleotide position and the origin. To obtain d(pT)n, a mixture of the pyridinium salts of 3'-O-acetyl dPT, dPT, and N* -anisoyl dPC in the molar ratio of 1:3:1 was polymerized and the oligomeric products were separated by column chromatography. The base ratio and average chain length of d(pT)n-2 was determined after it was hydrolyzed with snake venom phosphodiesterase (22). The products were separated by chromatography on ammonium sulfate-impregnated Whatman No. 40 paper in Solvent E (18), were eluted, and the absorbance of each was determined at its appropriate lmax, with a Zeiss spectrophotometer. Thus the molar ratio of dPT to dPC was determined to be 6:1.

Oligodeoxynucleotide fractions, d(pT)n-p, were isolated from the products of depurination of calf thymus DNA with formic acid and diphenylamine according to the method of Burton and Petersen (23). The purines were removed from the reaction products by passage, in weakly acid solution, through a column
of Dowex 50-X2 (H⁺ form). The eluate was neutralized and concentrated before the constituent oligonucleotides were separated on Whatman No. 3MM paper in Solvent A. After descending chromatography for 36 hours an ultraviolet-absorbing band 1½ inches from the origin, containing a mixture of oligo d(pTC)ₙₚ species, was eluted.

RNA Polymerase Preparations—E. coli RNA polymerase was purified 100- to 150-fold by the procedure of Chamberlin and Berg (4). Preparations H-2, BB-1, and B2A contained 1200, 1200, and 1270 units (4) per mg of protein, respectively. Preparation H-2 was dissolved in 1 × 10⁻⁵ M Tris-HCl, pH 7.8, 2 × 10⁻³ M MgCl₂, 1 × 10⁻⁵ M EDTA (disodium salt), and 1 × 10⁻² M 2-mercaptoethanol; Preparation BB-1 was dissolved in 1 × 10⁻² M Tris-HCl, pH 7.8; and Preparation B2A was dissolved in 5 × 10⁻² M Tris-acetate, pH 7.8, and 1 × 10⁻² M 2-mercaptoethanol. To obtain Preparation H-3, a solution of H-2 was diluted with an equal volume of glycerol and was dialyzed against 200 volumes of a solution containing equal volumes of 1 × 10⁻² M Tris-HCl buffer, pH 7.8, and glycerol for 18 hours with three changes of buffer (28). Thus H-3, BB-1, and B2A were magnesium-free polymerase preparations. We are grateful to Drs. P. Leder and S. Pestka for the H-2 RNA polymerase preparation and to Drs. F. Bergmann and R. Byrne for the BB-1 RNA polymerase preparation. The glycerol-free preparations were stored under liquid nitrogen whereas the glycerol-containing preparations were kept at −20°C.

The components of each reaction mixture are described in the legends of the tables. In these experiments previous reaction mixtures (12, 13) were reduced in volume to 0.05 ml to conserve materials and to allow more convenient manipulations. The purity of 14C- and 12C-nucleoside diphosphates and triphosphates was estimated by subjecting each to paper chromatography in Solvent Systems A, 13, and D. The 14C- and 12C-labeled materials were greater than 99.0/1i pure. When the &2P-ATP was contaminated with other radioactive materials, it was purified (≥98% pure) by paper chromatography with Solvent B before use.

The amount of synthesized polynucleotide was measured after precipitation at 0°C by the addition of 0.75 ml of 3% trichloroacetic acid (12) or by DEAE-cellulose paper chromatography as used by Falaschi, Adler, and Khorana (11). In the latter method 0.04 ml of the reaction mixture was directly applied to the origin of the chromatogram.

RESULTS

Oligodeoxynucleotides as Templates—Falaschi, Adler, and Khorana (11) noted that while d(pA)ₙ with n equal to and greater than 8, stimulated 14C-AMP incorporation into polymer, it did not cause poly U formation from 14C-UTP. Recently Bol lum, Groengier, and Yoneda (24) have shown that poly dA can simulate 14C-UMP incorporation into polymeric material.

With the use of our previous conditions (12, 13) we confirmed that d(pA)ₙ caused a significant incorporation of 14C AMP into poly A but also found that it stimulated 14C-UMP incorporation into polymer. Much of the 14C-AMP incorporation was present in the absence of polymer and could be inhibited by the addition of an ATP-generating system such as phosphoenolpyruvate plus phosphoenolpyruvate kinase to the system. A magnesium-free system resembling that used by Nakamoto, Fox, and Weiss (25) was used for further studies in the presence of the ATP-generating system in an attempt to suppress contaminating enzyme activities. A Mn⁺⁺ concentration curve (Fig. 1) was determined for the d(pA)ₙ stimulation of 14C-UMP incorporation.

With the use of the optimal Mn⁺⁺ concentration a variety of synthetic oligodeoxynucleotides was employed to show the template-copying activity of the RNA polymerase in a system in vitro with the results shown in Table I. The homopolymer synthesis in the absence of polymer was reduced to a low level. In Experiments 1 and 2, only one nucleoside triphosphate was added to the reaction mixture whereas in Experiment 3 both ATP and GTP were added. The presence of a second nucleoside triphosphate slightly inhibited homopolymer synthesis in the absence of polymer.

Experiments 1 and 2 showed nucleotide specificity according to complementarity with the use of d(pT)ₙ, d(pA)ₙ, and d(pC)ₙₚ as templates.

Under the conditions of Experiment 1 the presence of both d(pT)ₙ and d(pA)ₙ substantially increased the stimulation of incorporation of 14C-AMP or 14C-UMP over the sum of these incorporations resulting from the individual oligomers alone.

The results of Experiment 3 in Table I show that there was an incorporation of complementary nucleotides when oligodeoxynucleotides containing two noncomplementary base residues were added to the system, thus confirming the template-copying activity of the RNA polymerase.

Effect of Chain Length of d(pC)ₙ—An experiment to determine the minimum chain length of d(pC)ₙ required to stimulate the incorporation of 14C-GMP into polymer gave results shown in Table II. Poly C was used as a control. A significant incorporation was stimulated by d(pC)ₙ but a fraction of longer chain length, d(pC)ₙₚ, caused a more substantial incorporation. These results are similar to those of Falaschi et al. (11) who found that d(pC)ₙₚ acted as template material in an RNA polymerase system.
Table I
Specificity of nucleotide incorporation with oligodeoxynucleotide templates

In Experiment 1, the reaction mixture was similar to that described for Fig. 1 except that it contained 0.3 μmole of MnCl₂, 25 μmole of d(pC)₅, and 30 μg of H-2 RNA polymerase. The specific activities of the ³²P-ATP, ³²P-UTP, ³²P-GTP, and ³²P-CPT were 2075, 2630, 1406, and 280 cpm per μmole, respectively. The polymers added were d(pA)₁ (0.1 A₂₆₀ unit), d(pT)₅ (0.125 A₂₆₀ unit). Preincubation in the absence of polymer and enzyme, incubation of the complete system, and assay of polymeric material were the same as described for Fig. 1. The values shown for the incorporation of a ¹⁴C-nucleotide have been corrected for a zero time incorporation obtained by subtracting albumin (5 μg in 50% glycerol) for the enzyme after preincubation, and then omitting the incubation. Similar conditions were used in Experiment 2. The specific activities of ¹⁴C-UTP and ¹⁴C-CPT were different and were 2218 and 2730 cpm per μmole, respectively. The oligomer d(pC)₅ (0.086 A₂₆₀ unit) was used as the template. The conditions used in Experiment 1 were modified to obtain the results shown in Experiment 3. Differences in the reaction mixture were 0.075 μmole of phosphoenolpyruvate (Na⁺ salt) and 30 μg of H-2 RNA polymerase. Also the ¹⁴C-nucleoside triphosphate (25 μmole) was added in the presence of the specified ³²P-nucleoside triphosphate (25 μmole). The specific activities of the ³²P-ATP and ³²P-GTP were 1500 and 2500 cpm per μmole, respectively. The amounts of oligomers added were 0.086 A₂₆₀ unit of d(pT)₁₁, 0.086 A₂₆₀ unit of d(pC)₅₋₁, 0.111 A₂₆₀ units of d(pT)₅₋₁, and 0.1 A₂₆₀ units of d(pT)₅₋₁. Preincubation in the absence of enzyme and polymer was at 37°C for 10 min and incubation of the complete reaction mixture was carried out at 37°C for 20 min.

<table>
<thead>
<tr>
<th>Additions</th>
<th>³²P-AMP</th>
<th>³²P-UMP</th>
<th>³²P-GMP</th>
<th>³²P-CMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.10</td>
<td>0.10</td>
<td>0.12</td>
<td>0.30</td>
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<tr>
<td>d(pT)₁₁</td>
<td>3.43</td>
<td>0.11</td>
<td>0.10</td>
<td>0.36</td>
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<tr>
<td>d(pA)₁</td>
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<td>1.13</td>
<td>0.10</td>
<td>0.32</td>
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<tr>
<td>d(pT)₅₋₁ + d(pA)₁</td>
<td>9.22</td>
<td>2.73</td>
<td>0.10</td>
<td>0.34</td>
</tr>
<tr>
<td>Experiment 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.06</td>
<td>0.06</td>
<td>0.02</td>
<td>0.12</td>
</tr>
<tr>
<td>d(pC)₅₋₁</td>
<td>0.12</td>
<td>0.09</td>
<td>0.10</td>
<td>0.01</td>
</tr>
<tr>
<td>Experiment 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.07</td>
<td>0</td>
<td>0</td>
<td>0.53</td>
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<tr>
<td>d(pT)₁₁</td>
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<td>0.20</td>
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<td>d(pC)₅₋₁</td>
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<td>2.52</td>
<td>2.52</td>
<td>0.85</td>
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<tr>
<td>d(pT)₅₋₁</td>
<td>0.13</td>
<td>1.35</td>
<td>1.35</td>
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<tr>
<td>d(pT)₅₋₁</td>
<td>0.53</td>
<td>0.85</td>
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</table>

Analysis of RNA Product with Oligodeoxynucleotides as Templates—Nucleotide specificity of incorporation was again established with the use of the same oligodeoxynucleotides as in Experiment 3 of Table I, but under conditions where Mg⁺⁺ replaced most of the Mn⁺⁺. The reaction mixtures were set up in such a way that the labeled nucleotide incorporation could be measured and identical reaction mixtures could be worked up for the isolation of the polyribonucleotide products which were then hydrolyzed. The results are shown in Table III. The preincubation conditions and the presence of a second nucleoside triphosphate were successful in inhibiting activities other than that due to the RNA polymerase. However, a comparison of the incorporation data of Table III with that of Experiment 3...
in Table I shows that under the conditions of Table III, d(pT)23 caused much more AMP incorporation relative to GMP than it did under the former magnesium-free conditions.

The results of the nearest neighbor analysis in Table III unambiguously show the template-copying activity of the enzyme, for d32P, was transferred from α-32P-ATP to guanosine residues indicating that a ribonucleotide copolymer was produced under the direction of a deoxynucleotide copolymer. Also the results reveal that the RNA product is longer than the oligodeoxynucleotide template. The RNA product did not contain bases in the ratio expected from a faithful template copying of the oligodeoxynucleotide.

Oligoribonucleotides as Templates—As can be seen in Table IV the specificity of nucleotide incorporation was directed by complementarity with the constituents of the oligomers added to the enzyme system, thus showing that oligoribonucleotides also can serve as templates for the RNA polymerase. Experiment 1 also indicates the effect of varying the chain length of the oligoribonucleotide. The slight stimulation of 14C-AMP incorporation resulting from the addition of (pU)3 to the system was more pronounced when (pU)12 was present. Oligomers of chain length less than 8 did not stimulate 14C-AMP incorporation. The incorporation of 14C-AMP was small under the direction of (pA), but was almost comparable with that due to poly U when (pU)12 and (pA)4 were added together. This experiment was carried out at 30°C to enable double stranded species to form more easily. Also these did form was suggested strongly by the significant results. A clear stimulation of 14C-UMP incorporation by (pA)4-11 was observed but (pA)4 with chain lengths less than 8 did not act as templates. Well defined template activity was also found as shown by Experiment 2 when uridine- and cytidine-containing oligomers were used. In general the short chain oligomers were less effective than the enzymatically synthesized polymers by a factor of 10.

**Table IV**

<table>
<thead>
<tr>
<th>Additions</th>
<th>14C-CAMP mpmoles</th>
<th>14C-UMP mpmoles</th>
<th>14C-GMP mpmoles</th>
<th>14C-CMP mpmoles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experiment 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.28</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(pU)3</td>
<td>0.56</td>
<td></td>
<td></td>
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<tr>
<td>(pU)12</td>
<td>1.61</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(pU)12</td>
<td>(pA)4</td>
<td>10.17</td>
<td></td>
<td></td>
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<tr>
<td>(pA)4</td>
<td>0.46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(pA)4-11</td>
<td>0.40</td>
<td>0.91</td>
<td></td>
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</tr>
<tr>
<td>Poly U</td>
<td>10.25</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly A</td>
<td></td>
<td></td>
<td></td>
<td>13.10</td>
</tr>
<tr>
<td><strong>Experiment 2</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.05</td>
<td>0.09</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>(pU)3</td>
<td>0.29</td>
<td>0.10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(pC)3</td>
<td>0.05</td>
<td>0.08</td>
<td>1.32</td>
<td>0.04</td>
</tr>
<tr>
<td>Poly U</td>
<td>19.80</td>
<td></td>
<td></td>
<td>10.66</td>
</tr>
</tbody>
</table>

**Discussion**

The template-copying activity of RNA polymerase was studied in an attempt to determine conditions for the synthesis of a chemically defined messenger RNA which could be employed in a model cell-free system to direct polypeptide synthesis. Thus the codeword sequences of the RNA could be correlated with the amino acid residues of the polypeptide.

Bollum, Groeniger, and Yoneda (24) found that poly dA acted as a template for RNA polymerase from Azobacter vinelandii to cause the formation of poly U. We showed that a chain as short as (pA)4 could also act as a template for poly U formation. The template-copying activity of the E. coli RNA polymerase was shown by the use of chemically synthesized oligodeoxyribonucleotides. The presence of complementary oligomers such as d(pT)4 and d(pA)4 caused an increase of nucleotide incorporation (either 14C-AMP or 14C-UMP) over that resulting from the sum of the incorporations from each oligomer individually. Possible explanations of this effect are that a two-stranded complex may be a better substrate for the enzyme or is protected against nuclease degradation, or that the complementary deoxyoligomer may act as a primer for chain extension similar to that described for oligoribonucleotide primers by Niyogi and Stevens (9) in a study of polynucleotides as templates.

Our experiments revealed the presence of activities other than a template-copying activity in our RNA polymerase preparations. In early experiments a significant 14C-AMP incorporation was observed without the addition of oligonucleotide templates. The observation by Falaschi et al. (11) that d(pA)4 stimulated 14C-AMP incorporation was confirmed. A possible explanation of this effect is that d(pA)4 stimulated 14C-AMP incorporation was confirmed. A possible explanation of this chain formation is the stimulation of contaminating enzyme activity. Since various RNA polymerase preparations gave different proportions of contaminating enzyme activities such as polynucleotide phosphorylase and poly A synthetase, it appeared that these activities were not associated with the same protein as was the template-copying activity. It was possible to show that the addition of an ATP-generating system, which would convert any ADP present to ATP, could prevent polynucleotide phosphorylase action in the absence of added oligomer. Stevens and Henry (8) similarly added an ATP-generating system to their reaction mixtures when studying the RNA polymerase activity. Under these conditions residual polymer formation in the presence of the enzyme is thought to be due to a polynucleotide synthetase (15-17). An added non-
complementary nucleotide triphosphate was found to minimize the polynucleotide synthetase activity.

Since the main contaminating enzyme activities could be suppressed we did not purify the enzyme further for additional studies. Similar to the findings with oligomers containing deoxthymidine and deoxyadenosine (11, 12) d(pC), with chain length as short as 7 could act as a template. The template activity of oligodeoxynucleotides was also found under conditions in which Mn++ was largely replaced by Mg++ to make the system more easily adaptable for protein synthesis in a two-stage system similar to that used before (12, 13). Analysis of the RNA product showed that an RNA copolymer was synthesized under the direction of an oligodeoxynucleotide copolymer. However, in the presence of magnesium, as shown in Table III, there was less correlation of nucleotide incorporation with base composition of template than under the magnesium-free conditions described in Table I. When d(pTC), was used as a template, no 5P-2'(3'),5'-GDP could be detected by analysis as shown in Table III. Thus the chain length of the products could be approximated from a consideration of 5P-2'(3'),5'-ADP as the chain terminator. The chain length of the product was greater than that of the template as observed in other systems (3, 4, 11, 13) and d(pTC),, stimulated the incorporation of more 5P-AMP than expected from its base composition. This finding can be compared with the results obtained by Chamberlin and Berg (26) when studying a poly A synthetase activity associated with RNA polymerase activity. They concluded that the poly A synthesis was due to a reiterative copying process on a template by the RNA polymerase. Their conclusion suggests that the presence of GTP should inhibit this reiterative copying process. We carried out our template studies with copolymers in the presence of ATP and GTP. The observed excess of 14C-AMP incorporation may indicate that the d(pTC),, preparation contained d(pT), molecules which did not contain deoxyribose residues and were more effective templates than the copolymers. Further investigations of the accurate copying mechanism by the RNA polymerase are necessary before the system can be coupled unambiguously to an amino acid incorporating system in vitro.

We were also able to show that short chain oligoribonucleotides can act as templates in the presence of RNA polymerase and that oligomers with chain length as short as 8 monomer units had this property. This observation together with that from the studies with the oligodeoxynucleotides can be of use for the synthesis of oligoribonucleotides containing sequences difficult to synthesize chemically; templates where the chemically defined oligodeoxynucleotide or oligoribonucleotide chain is more easily obtainable can be copied by the enzyme to yield the required sequences.

The synthesis of short oligoribonucleotides of known sequence would yield possible material for the study of the polarity of reading involved in the early stages of peptide synthesis with the use of the recently described technique of Nirenberg and Leder (27).

The results in Table IV show that the tetramer (pA), was able to stimulate the incorporation of 14C-AMP directed by (pU),. Probably the stimulation occurs by priming the new chains in accord with the observations by Niyogi and Stevens (9) in a study of the effect of short complementary oligoribo-

nucleotides on the polyribonucleotide-stimulated template-copying activity of the enzyme. If short oligoribonucleotides of known sequence and not exact complementarity can be used as primers in such a reaction a synthesis of an oligoribonucleotide homopolymer containing a known sequence at one end can be effected.

**Summary**

Under conditions which inhibited contaminating enzyme activities short chain oligodeoxynucleotides and oligoribonucleotides acted as templates for ribonucleic acid polymerase and stimulated the incorporation of complementary nucleotides. The presence of two complementary oligodeoxynucleotides together resulted in greater nucleotide incorporation than the sum of the incorporations when the oligodeoxynucleotides were present individually.

A chain length of oligodeoxyctydylate (d(pC),) as small as 7 units directed 14C-guanosine monophosphate incorporation.

Synthetic and natural copolymers in the deoxy series caused the formation of ribonucleotide copolymers but chain lengths and composition of the ribonucleic acid product did not exactly reproduce the template in complementarity.

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**References**


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