The effect of metal activators on the fidelity of DNA synthesis has been examined. Using the DNA polymerase from avian myeloblastosis virus, the accuracy of Co$^{2+}$, Mn$^{2+}$, and Ni$^{2+}$-activated DNA synthesis was determined with different polynucleotide templates. With poly(dA-T) as the template, the error frequency for dCMP incorporation was 1:1400, 1:1100, and 1:600 for Mg$^{2+}$, Co$^{2+}$, and Mn$^{2+}$, respectively, at maximally activating concentrations. The error frequency was invariant with respect to [Mg$^{2+}$] but increased with greater than activating concentrations of Co$^{2+}$ and Mn$^{2+}$. This increase resulted from differential rates of complementary and noncomplementary nucleotide incorporation. The enhanced error frequency was nonspecific as it occurred with all polynucleotide templates and with all noncomplementary deoxy- and ribonucleotides which were tested. Nearest neighbor analyses of the reaction products indicated that the noncomplementary deoxynucleotides were incorporated as single base substitutions. The fidelity of Ni$^{2+}$-activated DNA synthesis was invariant with respect to [Ni$^{2+}$] and was similar to that obtained using Mg$^{2+}$. During DNA synthesis with Mn$^{2+}$, the addition of Co$^{2+}$, Mn$^{2+}$, or Ni$^{2+}$ resulted in a decrease in the fidelity of DNA synthesis. The relationship between decreases in the fidelity of DNA synthesis and metal mutagenesis, or carcinogenesis, or both, is considered.

All of the DNA polymerases which have been isolated and characterized to date require an added divalent metal cation for catalysis (1, 2). It had been considered that only Mg$^{2+}$ or Mn$^{2+}$ could fulfill this requirement. However, we have recently demonstrated that other divalent metal cations may substitute for Mg$^{2+}$ or Mn$^{2+}$ during catalysis (3). Co$^{2+}$ and Zn$^{2+}$ activated DNA synthesis with Escherichia coli DNA polymerase I. Co$^{2+}$ and Ni$^{2+}$ activated DNA synthesis with the DNA polymerases from avian myeloblastosis virus (AMV) and sea urchin nuclei. Homogeneous AMV DNA polymerase is devoid of any detectable 3' → 5' “proofreading” exonucleolytic activity (4). This has been demonstrated by the inability of the enzyme to hydrolyze mismatched terminal nucleotide even when the number of molecules of enzyme was equal to the number of initiator termini and by the ability of the enzyme to utilize mismatched termini as starting points for polymerization.

The synthesis of DNA using several divalent metal cations suggested the possibility that the fidelity of DNA synthesis may be influenced or altered by the metal activator. Using AMV DNA polymerase, we have measured the incorporation of complementary and noncomplementary nucleotides using Co$^{2+}$, Mn$^{2+}$, and Ni$^{2+}$. The results suggest that the fidelity of in vitro DNA synthesis is a function of the divalent metal cation used during catalysis. As this polymerase lacks a detectable proofreading exonuclease activity, any changes in fidelity could not be mediated by differences in the excision of noncomplementary nucleotides but must reflect alterations in base selection during catalysis.

MATERIALS AND METHODS

Enzymes — AMV DNA polymerase used in these studies was a generous gift of Dr. J. Beard, (Life Science Building, St. Petersburg, Fla.) or purified to homogeneity from isolated virions as described by Kacian and Spiegelman (5). The latter polymerase was shown to be homogeneous by isoelectric focusing in that incorporation of complementary and noncomplementary nucleotide substrates and zinc content were proportional to protein content across the peak. Upon electrophoresis in sodium dodecyl sulfate-polyacrylamide gel the enzyme displayed only two distinct protein bands of molecular weight 65,000 and 110,000 which have been designated α and β subunits, respectively. Similar results were obtained using either enzyme preparation. Spleen phosphodiesterase and micrococcal nuclease were purchased from Worthington.

Chemicals — Unlabeled deoxynucleotides were purchased from Calbiochem. Tritium-labeled and α$^{32}$P-labeled deoxynucleotides were purchased from New England Nuclear or from Amersham/Searle. The purity of the labeled deoxynucleoside triphosphates was determined by chromatography and by measuring their relative effectiveness as substrates for AMV DNA polymerase (6). Metals were purchased as chloride salts from Baker Chemical Co. and were of greater than 99.9% purity.

Poly(dA-T) was prepared by the de novo reaction using Escherichia coli DNA polymerase I (7). Maximally activated calf thymus DNA was prepared by hydrolysis with pancreatic DNase until the DNA was most efficiently utilized as a template by sea urchin nuclear DNA polymerase (8). Calf thymus DNA was obtained from Worthington and all other polymers were acquired from P-L Biochemicals.

The abbreviation used is: AMV, avian myeloblastosis virus.
DNA Polymerase Assay—The fidelity of DNA synthesis using poly(dA-T) as the template was measured in a reaction (total volume 0.05 ml) which contained 100 mM Tris/maleate (pH 7.6), 60 mM KCl, 50 mM dATP, 60 mM [α-32P]dGTP (10 to 20 dpm/pmol), 50 mM 1H[dATP (10,000 to 50,000 dpm/pmol), 1 µg of poly(dA-T), and 0.5 µg of AMV DNA polymerase. Assays were incubated for 60 min at 37°C.

The fidelity of DNA synthesis using poly(C)-oligo(dG) as the template was measured in a reaction (total volume 0.05 ml) which contained 100 mM Tris/maleate (pH 7.6), 10 mM KCl, 20 mM [α-32P]dGTP (10 to 20 dpm/pmol), 50 mM 1H[dATP (10,000 to 50,000 dpm/pmol), 1 µg of poly(C)-oligo(dG), and 0.5 µg of AMV DNA polymerase. Assays were incubated for 60 min at 37°C. Incorporation of the radioactive deoxynucleotides into an acid-insoluble precipitate was determined after repeatedly precipitating the polynucleotide product with 1.0 N perchloric acid and solubilizing with 0.2 M NaOH as previously described (9). The error frequency was defined as the ratio of the noncomplementary to the total complementary deoxynucleotide incorporated.

RESULTS

Metal Activation of DNA Synthesis—The ability of Co2+, Mn2+, and Ni2+ to substitute for Mg2+ in catalysis with AMV DNA polymerase was investigated (Fig. 1). In contrast to the broad Mg2+ optimum (3 to 50 mM) observed with activated calf thymus DNA, maximal synthesis with Co2+ was achieved at 1 mM while concentrations greater than 3 mM were markedly inhibitory. Maximum synthesis with Mn2+ was achieved at 0.6 mM; with Ni2+ maximum synthesis was achieved at 2 mM. The maximal rate of nucleotide incorporation with Mn2+, Co2+, and Ni2+ was 65, 25, and 76%, respectively, of that achieved with Mg2+. With Co2+ or Mn2+ synthesis was approximately linear for up to 60 min and was proportional to enzyme concentration (results not shown). The divalent metal cation concentration required to achieve the maximal rate of synthesis was template-dependent. With AMV DNA polymerase, a broad magnesium optimum (3 to 50 mM) observed with poly(C) as the template (5 to 50 mM) (10) or salmon sperm DNA (5 to 70 mM) (11); poly(dA-T) as the template, maximum synthesis was achieved at 2 mM Mg2+ (9).

Fidelity of DNA Synthesis with Polydeoxynucleotide Templates—The accuracy of DNA synthesis using AMV DNA polymerase and poly(dA-T) was determined using Mg2+, Co2+, or Mn2+ (Table I). At the lowest Co2+ concentration, 0.2 mM, AMV DNA polymerase incorporated one noncomplementary deoxynucleotide, (dCMP) for every 1827 complementary deoxynucleotides (dTTP) polymerized. This error frequency of 1:1827 was elevated with increasing Co2+ concentration. In the same experiment, the fidelity of Mg2+-activated DNA synthesis was 1:1680. The error frequency also varied with respect to Mn2+ concentration. At 0.2 mM Mn2+ the error frequency was 1:750. Increasing the Mn2+ concentration further elevated the error frequency. The fidelity of concurrent controls with Mg2+ was 1:1318. These results suggested that the error frequency of Co2+ or Mn2+-activated DNA synthesis was dependent on the metal cation concentration. This is in contrast to Mg2+ where the error frequency was invariant with respect to concentration (9, 10). Furthermore, the fidelity of DNA synthesis with Mn2+ was consistently lower than that using Mg2+.

The effect of Co2+ on the fidelity of DNA synthesis with poly(dA-T) as the template but using a different noncomplementary deoxynucleotide was examined (Fig. 2). Using dGTP as the noncomplementary deoxynucleotide the error frequency was also dependent on the Co2+ concentration. At the Co2+ optimum of 0.4 mM, AMV DNA polymerase incorporated one noncomplementary deoxynucleotide (dGMP) for every 579 complementary deoxynucleotides (dAMP) polymerized. At the Co2+ concentration this error frequency was elevated (1:1827). The increase in the error frequency of Co2+-activated DNA synthesis was not restricted to a specific noncomplementary deoxynucleotide. Furthermore, the increased infidelity observed at high concentrations of Co2+ appeared to primarily result from a preferential inhibition in the incorporation of the complementary nucleotide.

The requirements for the incorporation of complementary and noncomplementary deoxynucleotides with 4 mM Co2+ were identical and appeared typical for DNA synthesis (Table II). This cobalt concentration is higher than the optimum for Mg2+ (9). The cobalt concentration was 0.2 mM. MAGNIFICATION during DNA Synthesis

TABLE I

Effect of divalent cations on incorporation of complementary and noncomplementary nucleotides

The assay for complementary and noncomplementary deoxynucleotide incorporation with poly(dA-T) as a template was performed as described under "Materials and Methods." All reactions were performed in duplicate and the average values given after subtraction of incorporation in the absence of enzyme which was <0.07 and <0.018 for dTTP and dCTP, respectively.

| Divalent cation | Complementary nucleotide incorporation | Noncomplementary nucleotide incorporation | Error frequency |
|----------------|----------------------------------------|------------------------------------------|----------------|
| Mg2+ 5.0 µM  | 555 0.66 1:1680  | 180 0.33 1:1085  | 1:1560  |
| Co2+ 0.2 µM  | 201 0.22 1:1877  | 125 0.22 1:745  | 1:750  |
| Mn2+ 0.1 µM  | 106 0.28 1:1085  | 56 0.28 1:745  | 1:757  |
| Mg2+ 5.0 µM  | 185 0.28 1:1321  | 56 0.28 1:745  | 1:757  |
| Co2+ 0.5 µM  | 133 0.41 1:1647  | 65 0.41 1:1647  | 1:1647  |
| Mn2+ 0.5 µM  | 76 0.25 1:1600  | 35 0.25 1:1600  | 1:1600  |
| Mg2+ 5.0 µM  | 20 0.80 1:1200  | 10 0.80 1:1200  | 1:1200  |
| Co2+ 0.5 µM  | 19 0.68 1:1200  | 10 0.68 1:1200  | 1:1200  |
| Mn2+ 0.5 µM  | 19 0.68 1:1200  | 10 0.68 1:1200  | 1:1200  |
Metal-induced Infidelity during DNA Synthesis

Fig. 2. Fidelity of cobalt-activated DNA synthesis. The accuracy of Co²⁺-activated DNA synthesis was determined in a reaction mixture (total volume 0.05 ml) which contained the following: 100 mM Tris/maleate (pH 8.0), 50 μM dTTP, 50 μM [α-³²P]dATP (26 dpm/pmol), 50 μM [³²P]dGTP (27,000 dpm/pmol), 1 μg of poly(d(A-T)), and 1 μg of AMV DNA polymerase. The cobalt concentration in the reaction mixture was varied systematically from 0.2 to 10 mM. All assays were incubated for 60 min at 37° and were performed in duplicate. Assays were terminated and washed as described under "Materials and Methods." Incorporation in the absence of nucleotide at 5 mM Co²⁺ was 200 cpm and the efficiency of counting [³H] was 22%.

Table II

| Reaction mixture | dTMP | dGMP |
|------------------|------|------|
| Complete         | 11.00| 0.81 |
| -Co²⁺ (4 mM)     | <0.01| <0.002 |
| -AMV DNA polymerase | 0.01| <0.002 |
| -poly(d(A-T))    | 0.081| 0.017 |
| -dTTP            | <0.002|      |

Table III

Nearest neighbor analysis of product of poly[d(A-T)]/ polymerization

| Substrate | Metal | Error frequency | Radiosotope transfer following hydrolysis |
|-----------|-------|-----------------|-----------------------------------------|
| [α-³²P]dGTP | Mg²⁺ (5 mM) | 1:1072 | 99 | 1 |
| [²²P]dTTP | Co²⁺ (1 mM) | 1:1510 | 99 | 1 |

Table IV

Effect of Co²⁺ on fidelity of poly(C)-oligo(dG) polymerization

All reactions were performed in duplicate and the averages determined. Incorporation in duplicate samples varied by a maximum of 10%. Reactions without an added metal incorporated 0.06 pmol of the noncomplementary deoxynucleotide and 12 pmol of the complementary deoxynucleotide. These values were subtracted from those obtained in reactions with added Co²⁺.

Table V

| Substrate | Metal | Error frequency | Radiosotope transfer following hydrolysis |
|-----------|-------|-----------------|-----------------------------------------|
| [α-³²P]dGTP | Mg²⁺ (5 mM) | 1:1072 | 99 | 1 |
| [²²P]dTTP | Co²⁺ (1 mM) | 1:1510 | 99 | 1 |

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It has been reported that Mn²⁺-activated synthesis of any of these reaction components reduced complementary deoxynucleotide, and Ni²⁺ as the added divalent metal cation. AMV DNA polymerase, the complementary deoxynucleotide, dGMP. Thus, the experiment. The reaction requirements for DNA synthesis with Ni²⁺ as the added divalent metal ion are shown in Table VIII. Furthermore, the error frequency was invariant with respect to Ni²⁺ concentration. Furthermore, the error frequency was invariant with respect to these reaction components reduced complementary and noncomplementary deoxynucleotide incorporation to less than 14% of the incorporation with the total reaction.

The total reaction mixture (0.5 ml) contained 100 mM Tris/maleate (pH 7.6), 10 mM KCl, 20 μM [α-³²P]dATP (25,000 dpm/μmol), 20 μM [¹H]dGTP (715 dpm/μmol), 5 μg poly(C)-oligo(dG), and 2.5 μg of AMV DNA polymerase. The second product was made in an identical assay mixture which contained 20 μM dATP and 20 μM [α-³²P]dGTP (184 dpm/μmol). The isolation and hydrolysis of the product with micrococcal nuclease and spleen phosphodiesterase were performed as previously described (4). The deoxynucleoside monophosphates were separated by one-dimensional thin layer chromatography in isobutyric acid, 1 M ammonium hydroxide (5:3) (12).

Incorporation of Ribonucleotides during Co²⁺-activated DNA Synthesis. Poly(C)-oligo(dG) was used as the template primer with 5 mM Mg²⁺. Increasing concentrations of Mg²⁺ and Co²⁺ using [α-³²P]dGTP were analyzed greater than 90% of the radioactivity was recovered as dGMP. Thus, the noncomplementary nucleotide (dAMP) was present predominately as a single base substitution.

The effect of Co²⁺, Mn²⁺, and Ni²⁺ on Mg²⁺-activated DNA synthesis was investigated. Poly(C)-oligo(dG) was used as the template and the substrates were [α-³²P]dATP with either [¹H]dCTP or [¹H]dGTP. Alkaline treatment of the product of the reaction was omitted from the washing procedure.

Effect of Metal Cations on Mg²⁺-activated DNA Synthesis. The reaction mixture (total volume 0.05 ml) contained 100 mM Tris/maleate (pH 7.6), 10 mM KCl, 20 μM [α-³²P]dGTP (10 dpm/μmol), 20 μM [¹H]dATP (10 dpm/μmol), 1 μg of poly(C)-oligo(dG), and 0.5 μg of AMV DNA polymerase. Ni²⁺ was added as NiCl₂ and the final concentration is indicated. Assays were incubated at 37°C for 60 min and were performed in duplicate. All reaction mixtures were stopped and washed as described under "Materials and Methods."

Effect of cobalt on ribonucleotide incorporation

| Ribonucleotide and Metal | Complementary nucleotide | Ribonucleotide Incorporation | Error Frequency (dpm/pmol) |
|-------------------------|--------------------------|----------------------------|---------------------------|
|                         | dGTP                     |                            |                           |
| 5 mM Mg²⁺               | 312                      | 0.081                      | 1:8,852                   |
| 0.2 mM Co²⁺             | 138                      | 0.079                      | 1:1,747                   |
| 4 mM Co²⁺               | 152                      | 0.198                      | 1:768                     |

Fig. 3. Fidelity of nickel-activated DNA synthesis. The reaction mixture (total volume 0.05 ml) contained 100 mM Tris/maleate (pH 7.6), 10 mM KCl, 20 μM [α-³²P]dGTP (10 dpm/μmol), 20 μM [¹H]dATP (10 dpm/μmol), 1 μg of poly(C)-oligo(dG), and 0.5 μg of AMV DNA polymerase. Ni²⁺ was added as NiCl₂ and the final concentration is indicated. Assays were incubated at 37°C for 60 min and were performed in duplicate. All reaction mixtures were stopped and washed as described under "Materials and Methods."
The results presented in this paper suggest that (a) several metal cations may activate DNA synthesis by AMV DNA polymerase and (b) the accuracy of DNA synthesis may be dependent on the metal activator. With AMV DNA polymerase, Co\(^{2+}\), Mn\(^{2+}\), and Ni\(^{2+}\) substituted for Mg\(^{2+}\) in catalysis dependent on the metal activator. With AMV DNA polymerase and DNA template, these metal cations may activate DNA synthesis by AMV DNA polymerase to a degree that is dependent on the metal activator.

Metal-induced Infidelity during DNA Synthesis

**Table VII**

| Reaction requirements for complementary and noncomplementary nucleotide incorporation with poly(C)-oligo(dG) |
|---------------------------------------------------------------|
| The assay conditions for measuring the fidelity of DNA synthesis are given under "Materials and Methods." All reactions were performed in triplicate and the averages determined. The reaction contained 3 mM Ni\(^{2+}\) except where noted. |

| Reaction mixture          | dGMP (pmol incorporated) | dAMP (pmol incorporated) |
|---------------------------|--------------------------|--------------------------|
| Complete                  | 74                       | 0.106                    |
| -Ni\(^{2+}\)              | 0                        | <0.004                   |
| -AMV DNA polymerase       | 0.02                     | <0.004                   |
| -poly(C)-oligo(dG)        | 0.06                     | 0.015                    |
| -dGTP                     |                          | 0.009                    |

**Table VIII**

| Effect of manganese on magnesium-activated DNA synthesis |
|---------------------------------------------------------|
| The assay mixture of 0.05 ml contained 100 mM Tris/maleate (pH 7.6), 10 mM KCl, 3 mM MgCl\(_2\), 20 mM [\(\alpha^{32}\)P]dGTP (4 dpm/pmol), 20 \(\mu\)M [\(\alpha^{32}\)P]dATP (22,000 dpm/pmol), 1 \(\mu\)g of poly(C)-oligo(dG), and 0.5 \(\mu\)g of AMV DNA polymerase. The concentration of Co\(^{2+}\) in the reaction mixture was varied systematically from 0 to 6 \(\mu\)M Co\(^{2+}\). Incubations terminated at zero time without Co\(^{2+}\) incorporated 0.05 pmol of dAMP and 10 pmol of dGMP. All reactions were stopped and washed as described under "Materials and Methods." |

**Table IX**

| Effect of nickel on magnesium-activated DNA synthesis |
|------------------------------------------------------|
| The assays were performed as described in Table VIII except that a different batch of AMV DNA polymerase served as an enzyme source. |

**DISCUSSION**

The molecular mechanisms which determine the decreased fidelity of DNA synthesis with Co\(^{2+}\) or Mn\(^{2+}\) are unknown. AMV DNA polymerase lacks any detectable 3'→5' proofreading exonuclease activity (4) so that it cannot excise mismatched nucleotides incorporated during polymerization (15, 16). Therefore, increases in the error frequencies observed with Co\(^{2+}\) or Mn\(^{2+}\) could not be due to a diminished proofreading capacity. Thus, it may be reasonable to assume that the different metals substitute for Mg\(^{2+}\) at the active site on the enzyme: (a) kinetic analysis of DNA polymerization suggested that AMV DNA polymerase may contain multiple nucleotide binding sites (17). It is possible that divalent cations interact differently with each of the nucleotide binding sites. (b) Sloan et al. (18) have measured the conformation of the Mn\(^{2+}\) deoxynucleoside triphosphate complex on the active site of Escherichia coli DNA polymerase I by nuclear magnetic resonance. Their results indicate that the enzyme, in the absence of template, adjusts the conformation of the Mn\(^{2+}\)-dATP so that it is indistinguishable from that of a thymidylate unit in the Watson-Crick double helical structure of DNA. Such a present structure would facilitate complementary base-pairing. In the presence of template, changes in this conformation of the substrate when coordinated with different divalent cations might account for differences in the fidelity of DNA synthesis. In addition, changes in the error frequency at greater than activating metal concentrations could be due to binding of the metal to additional weak sites on the enzyme causing a conformational change in the enzyme structure altering the conformation at the active site. In this regard, it is of interest to note that the interaction of AMV DNA polymerase with Be\(^{2+}\) is not activating but decreases the accuracy of DNA synthesis (19).

It can be argued that the observed increase in error frequency at high metal concentrations represented the selective acid precipitation of unincorporated noncomplementary nucleotides. However, nearest neighbor analysis is based on the hydrolysis of the purified product by enzymes of known specificities. These results indicated that the noncomplementary nucleotides were incorporated in phosphodiester linkage and were predominantly distributed in the product as single base substitutions. Also, the high infidelity did not appear to result from selective interaction of metals with particular nucleotides. For example, at high Co\(^{2+}\) concentrations (5 mM) the incorporation of dGTP is markedly inhibited when it is the complementary nucleotide (Table IV, poly(C) as the template).
while it is undiminished at the same Co$^{2+}$ concentration when it is the noncomplementary nucleotide (Fig. 3), with poly[d(A-T)] as template. These considerations indicated that infidelity using Mn$^{2+}$ and Co$^{2+}$ did not result from selective binary interactions of the metal cations with specific nucleotide substrates.

Physical studies have clearly demonstrated that divalent metal cations interact with the phosphates and bases on polynucleotides (20) suggesting that they can alter base-pairing specificities. Thus, the increased infidelity observed at high concentrations (2 to 10 mm) of Mn$^{2+}$ and Co$^{2+}$ could reflect metal interaction with the template facilitating the formation of noncomplementary base pairs during polymerization. However, binding studies do not support this interpretation. Measurements of the interaction of Mn$^{2+}$ with activated DNA by electron paramagnetic resonance (21) indicate a stoichiometry of 0.36 Mn$^{2+}$ per DNA phosphorus. For each mole of activated DNA (molecular weight >70,000) there were two tight Mn$^{2+}$ binding sites and 52 weaker sites having an invariant dissociation constant of 68 μM. The $K_i$ for the inhibitory effects of Mn$^{2+}$ on the incorporation of the correct nucleotide observed in this paper is about 2 mm, a concentration at which all the metal binding sites on the template would be expected to be occupied. Thus, it is unlikely that the high infidelity observed with Mn$^{2+}$ is brought about by the interaction of metal cations with the template.

Cobalt and nickel are known carcinogens (22). Manganese is a potent mutagen (12, 23) and has been recently reported to be carcinogenic (24). It is possible that the alterations in fidelity observed with AMV DNA polymerase using Co$^{2+}$, Mn$^{2+}$, or Ni$^{2+}$ may also occur with eukaryotic DNA polymerases. Furthermore, it may be of interest to note that all of these metals alter the fidelity of DNA synthesis in the presence of saturating concentrations of Mg$^{2+}$; a situation which could occur in vivo.

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