Acyclovir Triphosphate Is a Suicide Inactivator of the Herpes Simplex Virus DNA Polymerase*

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The triphosphate form of 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir), ACVTP, inactivates the herpes simplex virus type 1 DNA polymerase. ACVTP does not innately inactivate resting polymerase, but becomes an inactivator only while being processed as an alternative substrate. Pseudo first-order rates of inactivation were measured at varying concentrations of ACVTP and fixed concentrations of the natural substrate, deoxyguanosine triphosphate. These studies indicated that a reversible enzyme-ACVTP (Michaelis-type) complex is formed at the active site prior to inactivation. The formation of this complex was competitively retarded by deoxyguanosine triphosphate. An apparent dissociation constant (K₀) of 3.6 ± 0.2 (S.D.) nM was determined for ACVTP from this reversible complex. A second method for the estimation of the K₀ which used the extrapolated initial velocities produced a value of 5.9 ± 0.4 (S.D.) nM. The rate of conversion of the reversible complex to the inactivated complex, at saturating ACVTP, was calculated to be 0.24 min⁻¹. No reactivation of enzyme activity was detected following isolation of the inactivated complex by rapid desalting on Sephadex G-25. Under these conditions, an overall reactivation rate of 1.5 X 10⁻⁸ min⁻¹ could have been easily detected. Therefore, the overall inhibition constant must have been less than 3 pM. In contrast, when host DNA polymerase was incubated with 14 μM ACVTP, only 60% inhibition of enzyme activity was observed, but inactivation was not detected. These data indicate that ACVTP functions as a suicide inactivator of the herpes simplex virus type 1 DNA polymerase, and is only a weak reversible inhibitor of DNA polymerase α.

The nucleoside analogue 9-[(2-hydroxyethoxy)methyl]guanine, acyclovir, is a specific and potent inhibitor of herpes simplex virus replication in vivo and in vitro (1, 2). The selectivity of ACV against HSV-1, herpes simplex virus type 1 is incorporated into a DNA primer-template by this enzyme (6). Furthermore, ACVTP is not excised from the primer-template by the 3',5'-exonuclease activity associated with the HSV DNA polymerase (7) and, therefore, would be expected to prevent further chain elongation because of the absence of a 3'-hydroxyl moiety (8, 9). In this report, we show that during the process of incorporating ACVMP into DNA, HSV-1 DNA polymerase becomes inactivated. Data are presented that show that ACVTP can be classified as a suicide inactivator.

EXPERIMENTAL PROCEDURES

Materials—[8-¹⁴C]dGTP (12 Ci/mmol) and [methyl-¹⁴C]dTTP (40 Ci/mmol) were purchased from ICN Chemical and Radioisotope Division, Irvine, CA. Ultrapure deoxyinosine triphosphates were obtained from P-L Biochemicals. Their purity was confirmed to be greater than 99% by high pressure liquid chromatography. ACVTP was prepared in these laboratories as previously described by Furman et al. (6). Calf thymus DNA was obtained from Calbiochem-Behring. Bovine pancreatic DNAase I was purchased from P-L Biochemicals. DEAE-cellulose, cellulose phosphate, carboxymethyl cellulose, and DEAE-cellulose paper (DE81) were obtained from Whatman. Sephadex G-25 medium grade was purchased from Pharmacia Fine Chemicals, Piscataway, NJ.

Cells and Virus—HeLa S3 cells were grown in suspension in Joklik's modified minimal essential medium (Gibco) supplemented with 10% newborn calf serum (M. A. Bioproducts, Walkersville, MD). The KOS strain of HSV-1 was maintained by low multiplicity passage with 10% newborn calf serum (M. A. Bioproducts, Walkersville, MD). The KOS strain of HSV-1 was maintained by low multiplicity passage with 10% newborn calf serum (M. A. Bioproducts, Walkersville, MD). The KOS strain of HSV-1 was maintained by low multiplicity passage with 10% newborn calf serum (M. A. Bioproducts, Walkersville, MD).

DNA Primer-Template—Activated calf thymus DNA was prepared by the method of Schlabach et al. (11). The DNA template was purified by phenol/chloroform extraction.

Enzyme Purifications—HSV-encoded DNA polymerase was purified through phosphocellulose according to previously published methods (2, 6). Fractions containing viral polymerase activity were pooled and applied to a 1.5 X 6 cm column of native DNA cellulose previously equilibrated with Buffer A (20 mM Tris-HCl, pH 7.6, 1 mM EDTA, 1 mM dithiothreitol, 10% glycerol) (12). The column was washed with 15 ml of Buffer A containing 0.1 M NaCl and then eluted with a 30-ml linear gradient of 0.2 to 0.6 M NaCl in Buffer A. A sharp peak of DNA polymerase was detected at 0.22 M NaCl. Fractions containing enzyme activity were pooled and dialyzed for 4 h against 2 liters of Buffer A containing 80% glycerol at 4°C. Purity of each enzyme preparation was monitored by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Gels (7.5%) were prepared and developed as described by Samuel and Joklik (13). Protein was stained with silver nitrate by the method of Morrissey (14).

The HeLa cell DNA polymerase α was purified as described previously (2).

 Rapid Desalting—Five-ml plastic syringes fitted with a porous polyethylene disc were packed with 5 ml of Sephadex G-25 medium gel equilibrated with Buffer B (50 mM Tris-HCl, pH 8.5, 12 mM MgCl₂, 100 mM NH₄SO₄, and 1.2 mM dithiothreitol). One milliliter of Buffer B containing 4 μg of bovine serum albumin was then applied and the columns centrifuged at 1500 X g for about 30 s. This
step was repeated with 1 ml of Buffer B, and then with the samples as previously described (16, 17).

Enzyme Assays—DNA polymerase assays were performed according to published procedures (2, 6). Unless otherwise specified, standard HSV-1 DNA polymerase reaction mixtures (150 μl) contained Buffer B (0.1 mM each dCTP, dATP, dGTP, and \[^{3}H\]dTTP and 0.25 mg of activated calf thymus DNA/ml. Reactions were started with approximately 0.1 unit of enzyme. One unit of DNA polymerase activity is defined as the amount of enzyme which catalyzes the incorporation of 1 nmol of dTTP/h at 37 °C. Cellular DNA polymerase α was assayed as described above for HSV-1 DNA polymerase except that (NH₄)₂SO₄ was omitted, and reactions were started with 1 unit of enzyme.

Determination of Pseudo First-Order Rates of Enzyme Inactivation—The initial concentrations of dGTP were considerably higher than its Km concentration in order to support an extended period of product formation without significant depletion of dGTP. Acyclo-GTP was used at concentrations that were adequate to greatly decrease the reaction rate during this period. A file of the time, t, than its reaction was stopped at 37 °C. Cellular DNA polymerase α was present while DNA polymerase was catalyzing the incorporation of 1 nmol of dTTP/h at 37 °C. Reactions were started with 1 unit of enzyme.

Determination of functionality of enzyme and template following inhibition by ACVTP. The assay mixtures (200 μl) contained Buffer B: 0.1 mM each dATP and dCTP, 0.1 mM dGTP, 0.1 mM \[^{3}H\]TTP (350 cpm/pmol), activated calf thymus DNA template, 0.5 μg/ml ACVTP, concentration of 0.1 μg/ml, was present as indicated. After preincubating at 37 °C for 20 min, 23.5 μl of (100 mM) dGTP and either 11.5 μl of fresh enzyme, (E) (0.1 unit), or 15 μl of fresh template, (T) (to give 5 mg/ml), were added to the indicated assay mixtures. Δ, O, control reaction mixtures lacking ACVTP; ●, reaction mixtures containing ACVTP. Samples (10 μl) were removed and assayed as indicated.

Table I

| Preincubation conditions | Activity (%) |
|--------------------------|-------------|
| Complete                 | 11.9        |
| dGTP omitted             | 7.9         |
| ACVTP omitted            | 103         |
| Template omitted         | 99          |
| Enzyme omitted           | 101         |

* Standard reaction mixtures (see “Experimental Procedures”) containing HSV-1 DNA polymerase, 0.1 μM ACVTP, 0.2 μM dGTP, 100 μM dATP, and 100 μM dCTP were preincubated for 15 min at 37 °C. Following preincubation, the reaction was started by adding \[^{3}H\]dTTP (260 cpm/pmol), 1 mM dGTP, and the omission reagent.

** Remaining activity in duplicate experiments expressed as percentage of a nonpreincubated control (no ACVTP). The control value had a velocity of 2.1 pmol/min. All velocities were linear through 15 min.

** Requirements for Inactivation—Conditions for inactivation of the enzyme were evaluated by preincubation studies. Reaction mixtures lacked dTTTP and either enzyme, primer-template, dGTP, or ACVTP (Table I). Enzyme reactions were started, after a 15-min preincubation by adding \[^{3}H\]dTTP, the omitted reagent, and 1 mM dGTP. Saturating dGTP was

Fig. 2. Time-dependent progressive inhibition of the HSV-1 DNA polymerase by ACVTP. Enzyme assays were performed as described under “Experimental Procedures.” Enzyme activity was measured by following the incorporation of \[^{3}H\]dTTP (5 μCi, 1900 cpm/pmol) in the presence of the indicated concentrations of ACVTP.

Fig. 1. Time-dependent progressive inhibition of the HSV-1 DNA polymerase by ACVTP. Enzyme assays were performed as described under “Experimental Procedures.” Enzyme activity was measured by following the incorporation of \[^{3}H\]dTTP (5 μCi, 1900 cpm/pmol) in the presence of the indicated concentrations of ACVTP.
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added to block additional binding of ACVTP. When enzyme, primer-template, or ACVTP were omitted during the preincubation step no inactivation occurred. Thus, direct inactivation of either enzyme or primer-template by ACVTP did not occur, demonstrating that ACVTP would not inactivate until the enzyme began to process it as a substrate.

Characterization of the Inactivation Process—If the deceleration in the rate of [\(^3\)H]dTMP incorporation (Fig. 1) was due to a reversible inhibition by the ACVMP-bound primer-template (7), then increasing the concentration of primer-template in the reaction mixture would be expected to competitively prevent the binding of this altered primer-template and thereby retard the rate at which the inactivation occurred. It can be seen in Fig. 3 that increasing the concentration of primer-template as much as 100-fold resulted in no changes in the rate of deceleration or in the overall level of inhibition that was obtained. The calculated \( k_{\text{inact}} \) for the enzyme, in the presence of ACVTP and 30 mg/ml, 300 mg/ml, and 3000 mg/ml of primer template, was 0.11 min\(^{-1}\), 0.10 min\(^{-1}\), and 0.11 min\(^{-1}\), respectively. Therefore, it is unlikely that the deceleration of the reaction was caused by the reversible binding of ACVMP-terminated primer-template to polymerase.

The nature of this inactivation was further investigated by calculating the pseudo first-order rate constant for the decay of enzyme activity in the presence of different concentrations of ACVTP at two fixed concentrations of dGTP. The rate of deceleration was found to increase with increasing ACVTP (Fig. 1 data with 5 \( \mu \)M dGTP). When these data were replotted as the \( \ln (P_t - P) \) versus time of incubation (see "Experimental Procedures"), the resulting lines were linear for at least 3.5 half-lives and showed no lag in the onset of inhibition (Fig. 4). The pseudo first-order rate constant, \( k_{\text{inact}} \), was determined from the slope of each line. The data were then analyzed in double reciprocal form (Fig. 5), according to the method of Kitz and Wilson (18). It is evident from Fig. 5 that inactivation of the enzyme by ACVTP is competitively retarded by the natural substrate dGTP. The relationship between ACVTP and dGTP was statistically consistent (19) with the model for competitive inhibition. These plots were linear and demonstrated a positive intercept on the y axis. Therefore, it appeared that a reversible enzyme-ACVTP complex (Michaelis-type complex) is formed prior to the inactivation step. The maximal rate for the apparent inactivation of enzyme activity, i.e. the maximal rate for the conversion of the reversible complex into an irreversible complex, was calculated to be 0.24 min\(^{-1}\) (reciprocal of the y axis intercept). Furthermore, the \( K_D \), apparent dissociation constant, of the initial enzyme-ACVTP complex can be calculated from the negative reciprocal of the x axis intercept, which is equal to \( -K_D \left(1 + \frac{[S]}{K_m}\right) \). The \( K_m \) value of 0.18 \( \mu \)M (20) for dGTP was used. In two separate experiments, an average \( K_D \) value of 3.6

![Fig. 4. Semilogarithmic plot of data in Fig. 1 showing pseudo first-order inactivation of the HSV-DNA polymerase by ACVTP.](http://www.jbc.org/)

![Fig. 5. Double reciprocal plot of the pseudo first-order rate constants with varied ACVTP. The \( k_{\text{inact}} \) values were calculated from the data displayed in Fig. 4 (5 \( \mu \)M dGTP) and from comparable experiments performed at 10 \( \mu \)M dGTP.](http://www.jbc.org/)
± 0.15 (S.D.) nM was calculated from the x axis intercepts of the lines generated at both 5 and 10 μM dGTP. In addition, the initial velocities were also calculated by extrapolation and were analyzed (see “Experimental Procedures”) by the method of Dixon (21) to offer a second method to estimate $K_{D}$ (Fig. 6). Because high concentrations of both substrates and inhibitor were required for these studies, it was not possible to estimate the $K_{D}$ from the point of intersection of the two lines (i.e. [ACVTP] $\gg K_{D}$). However, $K_{D}$ values were readily calculated from the negative reciprocal of the x axis intercept, which equals $-K_{D} = \frac{1}{[S]} \frac{1}{K_{m}}$. Values of 5.7 and 5.4 nM were determined at dGTP concentrations of 5 and 10 μM, respectively. In a second experiment, values of 6.3 and 6.9 nM were obtained. Finally, experiments performed in duplicate using the DNA polymerase of the Patton strain of HSV-1 gave $K_{D}$ values of 3.4 ± 0.85 (S.D.) nM (double reciprocal inactivation plots) and 4.9 ± 1.7 (S.D.) nM (initial velocity Dixon plots).

Irreversibility of the Inactivation Reaction—HSV DNA polymerase was incubated for 20 min with activated primer-template, 1 μM ACVTP, and 10 μM each dATP, dCTP, and dTTP. Under these conditions, 85% of the enzyme was inactivated. In two other experiments, the enzyme, when incubated with activated primer-template, 1 μM ACVTP, and either 100 μM each dATP and dCTP or 100 μM each dATP, dCTP, and dTTP, was inactivated 50 and 65%, respectively. The inactivated enzyme complexes were isolated by rapid desalting through two Sephadex G-25 columns. In a mock experiment lacking inhibitor, rapid desalting resulted in the removal of 97% of nucleoside triphosphates and the recovery of 90% of the DNA polymerase. The partially inactivated complexes were incubated for 12 h at 20 °C with 1 mM dGTP to prevent the rebinding of any released ACVTP. Samples were assayed at various times during the 12 h. Both the uninhibited controls and the partially inactivated enzymes slowly lost activity with a half-time of about 30 h. However, in no case was any reversal of inactivation observed. Under these conditions, a reactivation rate of 1.5 × 10^{-3} min^{-1} could have been easily detected.

**Fig. 6.** Dixon plot of the inhibition of HSV DNA polymerase by ACVTP. The initial velocities of the reactions displayed in Fig. 4 (5 μM dGTP) and from comparable experiments performed at 10 μM dGTP, were calculated from the values of $k_{\text{inact}}$ and $P_{f}$ as described under “Experimental Procedures.” The concentrations of ACVTP and dGTP are as indicated.

To determine if ACVTP could inactivate host cell DNA polymerase $\alpha$, conditions were selected where the initial velocity was reduced 30 and 60% by 14 μM ACVTP in the presence of 5 μM dGTP and 1 μM dGTP, respectively. A gradual decay in the rate of [3H]TMP incorporation was observed with the reaction mixtures which lacked ACVTP as well as those containing ACVTP. The calculated $k_{\text{inact}}$ for the enzyme in the absence of ACVTP, at 5 μM dGTP and 1 μM dGTP, was 0.068 min^{-1} and 0.095 min^{-1}, respectively. Including ACVTP in the reaction mixture did not increase the rate of decay of enzyme activity. Similar values for the $k_{\text{inact}}$ were obtained (0.071 min^{-1} with 5 μM dGTP and 0.097 min^{-1} with 1 μM dGTP) in the presence of 14 μM ACVTP. It is, therefore, apparent that ACVTP was not able to inactivate the host cell DNA polymerase $\alpha$ under the conditions used in this study.

**DISCUSSION**

The data presented here clearly indicate that ACVTP is a suicide inactivator of HSV DNA polymerase. Certain criteria have been suggested (22–24) to distinguish suicide inactivators. 1) The initially inert inhibitor must become an inactivator during catalysis or partial catalysis by the target enzyme. 2) A reversible (Michaelis-type) complex must form at the active site prior to inactivation. 3) The loss of enzyme activity should follow pseudo first-order kinetics. The preceding results indicate that ACVTP fits these criteria for a suicide inactivator of HSV DNA polymerase.

It has been shown that ACVTP served as an alternative substrate for the HSV DNA polymerase and that the enzyme catalyzed the incorporation of ACVMP into the DNA primer-template (6, 7). The inactivation of the HSV DNA polymerase by ACVTP occurred only under conditions where the enzyme was attempting to utilize ACVTP as a substrate (partial catalysis). ACVTP was unable to inactivate either isolated enzyme or template.

The existence of a positive finite vertical intercept in the Kitz and Wilson inactivation plots (Fig. 5) demonstrated saturable reversible binding of ACVTP to the active site of the enzyme (i.e. formation of a Michaelis-type complex) prior to the inactivation of the enzyme. Inactivation of the enzyme was retarded in a competitive manner by the substrate dGTP. A $K_{D}$ value for the initial enzyme-ACVTP complex, of 3.6 ± 0.2 (S.D.) nM estimated from the Kitz and Wilson plot was in good agreement with the values obtained by plotting the extrapolated initial velocities in a Dixon plot (5.9 ± 0.4 (S.D.) nM). Furthermore, the $K_{D}$ values reported here are in agreement with values previously determined from tangential estimates of initial velocities using standard Lineweaver-Burk plots ($K_{D}$ values of 3 and 6 nM) (7, 25). Inactivation of the enzyme was by pseudo first-order decay. Furthermore, the rate of decay showed no lag at the onset of inhibition and was linear through at least 3.5 half-lives, ruling out the possibility that the enzyme was producing a diffusible inactivator. The true first-order rate of inactivation ($k_{\text{inact}}$), at saturating ACVTP, was 0.24 min^{-1}. Although it is established that this time dependence ($t_{1/2}$ of 2.9 min) is not caused by the reversible binding of ACVMP-terminated primer-template, we can only speculate about the nature of the event. It may be the result of the length of time required for the enzyme to encounter a dCMP residue in the heteropolymeric primer-template, or to partitioning, where more than one molecule of inhibitor is incorporated for each molecule of enzyme inactivated. Alternatively, this time dependence may be caused by a slow conformational rearrangement, subsequent to phos-
phodiester bond formation. There is evidence (25) that this type of isomerization may be a rate-determining step in the polymerization process catalyzed by Escherichia coli Pol I. Studies are currently underway to investigate the nature of this first-order process.

The reason that the inactive complex does not dissociate is not known. Unlike most suicide inactivators, ACVTP does not appear to contain secondary chemical groups that are latently reactive and could form an aberrant covalent bond with the enzyme. Such a covalently bonded complex was postulated for adenosine 2',3'-riboepoxide 5'-triphosphate, a suicide inactivator of DNA polymerases from several sources (26). It is more likely that the present complex is the result of the incorporated fraudulent nucleotide inducing the enzyme into a nonproductive conformation. One can envision several possible mechanisms that could result in the "freezing" of the polymerase to the ACVMP terminus. For example, the enzyme may become trapped while trying to excise the fraudulent nucleotide. The HSV DNA polymerase has an associated 3',5'-exonuclease activity (27) that appears to have proofreading capabilities (28), but cannot excise 3'-terminal ACV (7). Alternatively, the enzyme may become "locked" into place while searching for a 3'-hydroxyl group. This group, which is missing on the ACVMP molecule, is necessary for elongation and possibly translocation (29, 30).

A postulated scheme for the inactivation of the HSV DNA polymerase ACVTP is depicted by the following equation

\[
\text{Enzyme} + \text{ACVTP} \xrightarrow{k_1} \text{Enzyme-ACVTP} \xrightarrow{k_2} \text{Enzyme-ACVMP} \xrightarrow{k_3} \text{Enzyme} + \text{PP} + \text{Template}
\]

Since regeneration of the inactivated enzymatic activity following isolation of the inactivated complex was not detected, it is possible that ACVTP is an irreversible inactivator of the HSV DNA polymerase. Under the experimental conditions used, a reactivation rate \(k_{-2}\) of \(1.5 \times 10^{-8}\) min\(^{-1}\) could have been easily detected. Thus, it is concluded that the value for the overall inhibition constant, \(K_D = k_{-2} / (k_2 + k_{-2})\), must be less than 3 pM and may approach zero.

The data presented show that ACVTP functions as a suicide inactivator of the HSV DNA polymerase. Enzyme inactivation, therefore, appears to be the major mode of inhibition of HSV DNA polymerase activity and may be the mechanism by which HSV replication is inhibited by ACV. An outstanding feature of this inhibitor is the 30- to 50-fold greater affinity that the enzyme has for ACVTP compared to the natural substrate, dGTP. This preferential binding to ACVTP permits the formation of a Michaelis-type complex, even in the presence of dGTP, which is followed by enzyme inactivation. The enzyme's high affinity for ACVTP and the fact that the viral enzyme is inactivated, whereas the cellular DNA polymerase \(\alpha\) is less sensitive to inhibition by ACV and appears not to be inactivated, contribute both to the potency and to the selectivity of this antiviral agent.

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