Effect of 2′-5′ Phosphodiesters on DNA Transesterification by Vaccinia Topoisomerase*

Berit O. Krogh‡, Christopher D. Claeboe§, Sidney M. Hecht§, and Stewart Shuman‡¶

Vaccinia topoisomerase forms a covalent DNA-(3′-phosphotyrosyl)-enzyme intermediate at a pentapyrimidine target site 5′-CCCTT↓ in duplex DNA. By introducing single 2′-5′ phosphodiesters in lieu of a standard 3′-5′ phosphodiester linkage, we illuminate the contributions of phosphodiester connectivity to DNA transesterification. We find that the DNA cleavage reaction was slowed by more than six orders of magnitude when a 2′-5′ linkage was present at the scissile phosphodiester (CCCTT↓p↓p↓p↓p↓). Thus, vaccinia topoisomerase is unable to form a DNA-(2′-phosphotyrosyl)-enzyme intermediate. We hypothesize that the altered geometry of the 2′-5′ phosphodiester limits the ability of the tyrosine nucleophile to attain a requisite, presumably apical orientation with respect to the 5′-OH leaving group. A 2′-5′ phosphodiester located to the 3′ side of the cleavage step (CCCTT↓p↓p↓p↓p↓N) reduced the rate of transesterification by a factor of 500. In contrast, 2′-5′ phosphodiesters at four other sites in the scissile strand (TpCGCCCTTp↓ ATP↓pC) and five positions in the nonscissile strand (3′-GGGApApTpApA) had no effect on transesterification rate. The DNAs containing 2′-5′ phosphodiesters were protected from digestion by exonuclease III. We found that exonuclease III was consistently arrested at positions 1 and 2 nucleotides prior to the encounter of its active site with the modified 2′-5′ phosphodiester and that the 2′-5′ linkage itself was poorly hydrolyzed by exonuclease III.

Type IB topoisomerases modulate the topological state of DNA by cleaving and rejoining one strand of the DNA duplex. Cleavage is a transesterification reaction in which the scissile Np↓N phosphodiester is attacked by a tyrosine of the enzyme, resulting in the formation of a DNA-(3′-phosphotyrosyl)-enzyme intermediate and the expulsion of a DNA strand having a 5′-OH terminus. In the religation step, the DNA 5′-OH group attacks the covalent intermediate resulting in expulsion of the active site tyrosine and restoration of the DNA phosphodiester backbone. Vaccinia topoisomerase is a prototype of the type IB topoisomerase family (1). The poxvirus enzyme is distinguished from the nuclear topoisomerase I by its compact size (314 amino acids) and its site-specificity in DNA transesterification. Vaccinia topoisomerase binds and cleaves duplex DNA at a pentapyrimidine motif sequence 5′-TCCTCC↓.

Received for publication, March 14, 2001
Published, JBC Papers in Press, April 3, 2001, DOI 10.1074/jbc.M102312200

* This work was supported by National Institutes of Health Grants GM46330 (to S. S.) and CA78415 (to S. M. H.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “in press” to indicate this fact.

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THE JOURNAL OF BIOLOGICAL CHEMISTRY Vol. 276, No. 24, Issue of June 15, pp. 20907–20912, 2001
Printed in U.S.A.
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Type IB topoisomerases functionally relevant phosphates were initially identified by studying the effects of phosphate ethylation on topoisomerase binding (9). Ethylation of the +1, +2, +3, and +4 phosphates on the scissile strand (positions CpCpTpTp↓ within the pentamer motif) and the +3, +4, and +5 phosphates on the nonscissile strand (3′-GpGpGpA↓) interfered with topoisomerase-DNA complex formation. The relevant topoisomerase-phosphate contacts are arrayed across the minor groove of the DNA helix (9). Phosphate ethylation is a relatively crude modification interference method, insofar as it simultaneously eliminates the negative charge on the phosphate and introduces a bulky aliphatic group. Subsequent studies of the catalytic contributions of individual phosphates have entailed less drastic modifications, for example replacing the standard 3′-5′ phosphodiester by a 3′-OH/5′-PO4 nick (13). This modification interrupts the DNA backbone and introduces additional negative charge (net charge of about −1.5 at pH 7.0 at the nick versus −1.0 for the phosphodiester) but adds only minimal bulk (one extra oxygen). A 3′-OH/5′-PO4 nick in lieu of the scissile phosphodiester abolished transesterification by the TP↓ nucleotide (defined as the +1 nucleotide) is linked to Tyr-274 of the enzyme.

The stereochemical outcome of the net cleavage-religation reaction of vaccinia topoisomerase is a retention of configuration at the scissile phosphodiester. This suggests that the component cleavage and religation reactions entail in-line SN2-type displacements in which the attacking nucleophile is apical to the leaving group and each transesterification results in an inversion of configuration (2). Four conserved amino acid side chains of vaccinia topoisomerase (Arg-130, Lys-167, Arg-223, and His-265) are required for catalysis (3–5). Mutational and structural data suggest that the two arginines and the histidine interact directly with the scissile phosphodiester and enhance catalysis by stabilizing the developing negative charge on a pentacoordinate phosphorane transition state (2–7). Lys-167 serves as a general acid catalyst during the cleavage reaction, donating a proton to expel the 5′-OH leaving group (8).

Type IB topoisomerases engage the DNA target site circumferentially, forming a C-shaped clamp around the duplex (6, 7, 9). The DNA moieties that contribute to target site recognition and enable catalysis by vaccinia topoisomerase have been examined using synthetic substrates containing a single CCCCT site. Modification interference, modification protection, base and sugar analog substitution, and UV cross-linking experiments indicate that vaccinia topoisomerase makes contact with specific bases and phosphates of DNA in the vicinity of the CCCCT element (9–12). For example, dimethyl sulfate protection and interference experiments revealed interactions with the three guanine bases of the pentamer motif complementary strand (3′-GGGAA) (10), and permanganate oxidation interference highlighted a functional interaction with the +2 T base of the scissile strand (CCCTT) (12).

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vaccinia topoisomerase, but did not affect the noncovalent binding of topoisomerase to the nicked DNA (13). This result indicated that vaccinia topoisomerase is an obligate nucleotidyl-3’-phosphotransferase that cannot transsterify to a 5’ phosphomonoester. Placement of a 3’-OH/5’-PO4 nick at position +2 (CCCTTPpT) slowed the rate of transsterification by a factor of 500. A “missing phosphate” analysis of the DNA target site entailed replacement of phosphodiester with a 3’-OH/5’-OH nick, a maneuver that eliminates one negative charge along with potential hydrogen bonding interactions between the topoisomerase and the nonbridging phosphate oxygens. This interference method revealed a contribution of the −1 phosphate of the scissile strand (CCCTpT), which enhances the rate of transsterification by a factor of 40 (13).

Here we present a more subtle modification interference analysis in which we investigate the positional effects of introducing single 2’-5’ phosphodiester modifications. In the absence of significant substitution for the scissile phosphodiester at positions 8, 1, 2, 4, and 3 were adsorbed onto nicked DNA by amphotericin B and then purified by high-performance liquid chromatography. The post-nicked DNA was then hybridized to complementary 60-mer DNAs.

**RESULTS**

**Effects of Single 2’-5’ Phosphodiester Modifications within the Scissile CCCTT Strand**—A series of 18-mer scissile strands containing a single 2’-5’ phosphodiester at positions +8, +2, +1, −1, −2, and −3 were used. A 5’-32P-labeled and annealed to an unlabeled 30-mer strand to form a “suicide” substrate for vaccinia topoisomerase (Fig. 1). Cleavage results in covalent attachment of a 5’-32P-labeled 12-mer (5’-pCCGTGGCTGCCCTTp) to the enzyme via Tyr-274. The unlabeled 6-mer leaving strand 5’-pGATCC dissociates spontaneously from the protein-DNA complex. Loss of the leaving strand drives the reaction toward the covalent state.

The reaction of topoisomerase with the imidate control substrate contained an end point of 90% covalent adduct formation, and the reaction was completed within 20 s (Fig. 1). The extent of transesterification at 5 s was 80% of the end point value. From this datum, we calculated a single-turnover cleavage rate constant of 0.3 s−1 (Table I). Introduction of a 2’-5’ phosphodiester at positions +8, +2, −2, or −3 had no significant effect on the reaction end point or the cleavage rate con-
substantially, the rate of cleavage by a factor of 4 (Table II). Other modifications of the nonscissile strand did not have a significant impact on cleavage of the −1 modified 18-mer.

Effects of Combining Scissile Strand 2′-5′ Modifications with Nonscissile Strand 2′-5′ Modifications—A series of doubly modified substrates containing one 2′-5′ phosphodiester in the scissile strand and one 2′-5′ phosphodiester in the nonscissile strand was prepared by annealing the modified 32P-labeled 18-mer strands to each of the modified unlabeled 30-mer strands. The substrate combinations and the results of the analysis of transesterification kinetics are shown in Table II.

We found that the modifications of the −3 and −2 positions of the scissile strand, which by themselves had no deleterious effect on transesterification, also had no significant effect on the rate of cleavage when combined with any of the five singly substituted complementary strands. (Our operational definition of a significant effect is one that elicits at least a 4-fold change in )

| Position of 2′-5′ modification | Kinetic data | % cleavage |
|-------------------------------|-------------|-----------|
| 18-mer | 30-mer | $k_{obs}$ (s$^{-1}$) |
| none | none | 0.30 | 90 |
| +2P | − | 0.93 | 81 |
| −2P | +2P | 0.36 | 87 |
| −1P | +2P | 0.00062 | 87 |
| +2P | − | $<1 \times 10^{-7}$ | |
| +2P | +2P | 0.23 | 88 |
| none | none | 0.31 | 93 |
| − | none | 0.44 | 84 |
| − | −1P | 0.33 | 84 |
| +1P | +1P | 0.41 | 88 |
| +1P | +2P | 0.26 | 85 |
| +1P | +3P | 0.35 | 87 |

a Significant rate decrement.

We found that the modifications of the −3 and −2 positions of the scissile strand, which by themselves had no deleterious effect on transesterification, also had no significant effect on the rate of cleavage when combined with any of the five singly substituted complementary strands. (Our operational definition of a significant effect is one that elicits at least a 4-fold change in $k_{obs}$.) In contrast, the +2 modification of the scissile strand, which also had no deleterious effect per se, was inhibitory when combined with 2′-5′ phosphodiester modifications on the complementary strand that were also benign by themselves (Table II). A hierarchy of synergetic effects was evident, whereby “cross-strand” combination with a 2′-5′ phosphodiester at position +2 on the nonscissile strand elicited a 100-fold decrement in cleavage rate ($k_{obs} = 0.002$ s$^{-1}$), combination with modifications at −1 ($k_{obs} = 0.02$ s$^{-1}$) or +3 ($k_{obs} = 0.013$ s$^{-1}$) resulted in an order of magnitude rate decrement, and combination with a 2′-5′ linkage at +1 slowed cleavage by a factor of 4 ($k_{obs} = 0.051$ s$^{-1}$).

The already severe negative effect of the 2′-5′ phosphodiester at position −1 of the scissile strand ($k_{obs} = 6.2 \times 10^{-4}$ s$^{-1}$) was exacerbated by a factor of 8 in combination with 2′-5′ phosphodiester at positions −1 or +2 on the complementary strand ($k_{obs} = 7.5 \times 10^{-5}$ s$^{-1}$) (Table II). Other modifications of the nonscissile strand did not have a significant impact on cleavage of the −1 modified 18-mer.

Effects of 2′-5′ Phosphodiester Modifications on Exonuclease III—E. coli exonuclease III catalyzes unidirectional digestion of duplex DNA from the 3′-end to liberate 5′ dNMP products. The phosphodiesterase activity of exonuclease III is impeded by chemical modifications of the phosphate backbone (20, 21), including the 2′-5′ phosphodiester modification studied here (14, 15). To confirm the incorporation of the 2′-5′ phosphodiester during chemical synthesis of the topoisomerase substrate strands and further explore the effects of this modification on the phosphodiesterase activity of exonuclease III, we annealed the 5′-32P-labeled 30-mers containing the complement of the topoisomerase cleavage site to a complementary 60-mer strand and incubated the duplexes with exonuclease III. The 5′-labeled digestion products were resolved by denaturing gel electrophoresis (Fig. 3). All of the unmodified 30-mer was converted after 15–30 min to 5′-labeled species 8–10 nucleotides in length. A ladder of partially digested strands was evident at 5 min. Introduction of a 2′-5′ phosphodiester at position −2 resulted in a kinetic roadblock to exonuclease III digestion located 1 nucleotide 3′ of the site of the modification (−A−pGpT). The paused species persisted at 30 min and was only slowly converted to a species arrested at the site of modification (−A2−pGpA). There was almost no digestion of the 32P-labeled DNA past this point. Changing the position of the 2′-5′
phosphodiester modification elicited a corresponding shift in the site of the impediment to exonuclease III digestion (Fig. 3). In the case of the +1 phosphate modification, the progress of exonuclease III was arrested after 5 min at points 1 and 2 nucleotides 3’ of the modified phosphate. After 15 and 30 min, the major products were arrested at the site of modification and 1 nucleotide upstream and only a minority of the DNA strands were degraded past the modified phosphodiester. The upstream block to digestion was apparent, but less pronounced, on the −1 phosphate-modified strand, so that most of the DNA was digested up to the site of the +1 phosphodiester and no further (Fig. 3).

The 5’-32P-labeled 18-mers containing the CCCTT topoisomerase cleavage site were also annealed to a complementary 60-mer strand and digested with exonuclease III (Fig. 4). Here again, the 2’-5’ modifications arrest exonuclease III at sites 1 and 2 nucleotides 3’ of the modified phosphodiester and, as the reaction proceeds, at the modified phosphodiester itself. These results indicate that exonuclease III can sense the conformation of the DNA backbone in advance of the position of its active site.

**DISCUSSION**

**Conformational Requirements at the Scissile Phosphodiester**

**Differ between Poxvirus and Cellular Type IB Topoisomerases**—The rate of DNA transesterification by vaccinia topoisomerase was reduced by more than six orders of magnitude by a 2’-5’ linkage at the scissile phosphodiester (CCCTT<sub>2</sub><sup>p</sup> N<sub>p</sub>). Thus, vaccinia topoisomerase is essentially unable to form a DNA-(2’-phosphotyrosyl)-enzyme intermediate. The 2’-5’ modification is relatively subtle because it does not alter the charge on the scissile phosphate or introduce bulk. We hypothesize that the altered geometry of the 2’-5’ phosphodiester limits the ability of the nucleophile Tyr-274 to attain its requisite apical orientation with respect to the 5’-OH leaving group. Additional perturbations of contacts of the phosphate oxygens with the catalytic Arg-130, Arg-223, His-265, and Lys-167 side chains in the ground state or the transition state may also contribute to the inability of the poxvirus enzyme to cleave the 2’-5’ phosphodiester.

Arslan et al. (14, 15) showed that mammalian topoisomerase I is quite capable of cleaving a 2’-5’ phosphodiester to form a DNA-(2’-phosphotyrosyl)-enzyme intermediate, although the extent of the reaction at the modified phosphodiester was reduced because the enzyme was diverted to an alternative (unmodified) cleavage site 2 nucleotides upstream. Apparently, the active site of the mammalian type IB topoisomerase is better able to accommodate the altered geometry of a 2’-5’ phosphodiester. Note that the mammalian enzyme is also much less fastidious than the vaccinia topoisomerase with respect to the nucleotide sequence at the cleavage site. The cellular and poxvirus topoisomerases have a common fold and the same constellation of catalytic side chains (6, 7), but the structural nuances that account for the greater stringency of the poxvirus topoisomerase active site are entirely uncharted.

**Interference Effects at the Phosphodiester Immediately 3’ and 5’ of the Cleavage Site**—A 2’-5’ modification of the −1 phosphate (CCCTTp N<sup>2</sup><sub>p</sub>) reduced the rate of transesterification by vaccinia topoisomerase by a factor of 500. This effect was an order of magnitude more deleterious than simply rerouting the enzyme to a 3’-OH/5’-OH nick (13). We infer that the 2’-5’ modification interference is not caused solely by a perturbation of functional contacts between the topoisomerase and the −1 phosphate. Rather, we invoke an additional effect of the unconventional 2’-5’ linkage on the conformation of either the adjacent −2 nucleoside (CCCTTp N<sup>2</sup><sub>p</sub>) or the −1 nucleoside (CCCTTp N<sup>A</sup><sub>p</sub>) or both. Note that removal of the −1 phosphate plus the −2T nucleoside reduces the cleavage rate by three orders of magnitude (13), which is similar to the effect elicited by the 2’-5’ modifi-
cation of the −1 phosphate. It is also conceivable that a 2′-5′ modification of the −1 phosphate affects the conformation of the adjacent (unmodified) scissile phosphodiester in such a way as to make it unfavorable for transesterification chemistry. Mammalian topoisomerase I also displays profound interference of cleavage by 2′-5′ phosphodiester immediately 3′ of the cleavage site (14, 15).

A 2′-5′ modification of the +2 phosphate (CCCT <sup>2</sup>p <sup>7</sup>T <sup>1</sup>N) had no effect on vaccinia topoisomerase. This result was remarkable, given that the introduction of a 3′-OH/5′-PO<sub>4</sub> nick at the +2 position slowed the rate of cleavage by a factor of 500 (13). Thus, a modification that preserves the electrostatics on the +2 phosphate and the continuity of the backbone is benign compared to one that breaks the backbone and imposes an extra negative charge. Covalent intermediate formation was also suppressed by introduction of a single 2′-O-methyl moiety on the +2 sugar (10). Apparently, the combination of a 2′-OMe with the standard 3′-5′ phosphodiester was more detrimental than substitution of the 2′ carbon (as a phosphate ester) in the context of a 3′ deoxy sugar. In the crystal structure of vaccinia topoisomerase, the side chains of Arg-84, Ser-268, and Ser-270 coordinate a sulfate
proposed to correspond to the +2 phosphate of the scissile strand (6). In the mammalian topoisomerase-DNA crystal (7), the +2 phosphate interacts with Lys-433, which is the mammalian counterpart of vaccinia Arg-84. Mammalian topoisomerase I is also unaffected by a 2'-5' linkage immediately 5' of the cleavage site. Thus, the relevant contacts to the +2 phosphate appear not to be disrupted by the 2'-5' phosphodiester.

Cross-strand 2'-5' Modification Interference—Single modifications at five phosphodiesters on the nonscissile strand had no significant effect on transesterification by vaccinia topoisomerase. However, some of the nonscissile strand modifications were inhibitory in concert with a 2'-5' phosphodiester at positions +2 or −1 on the scissile strand. Indeed, modification of the −1 or +2 phosphodiesters of the nonscissile strand elicited 10-fold synergistic effects in combination with scissile strands containing either +2 or −1 phosphate modifications. The most severe synergistic effect (100-fold) was observed with 2'-5' modifications at the +2 positions of both DNA strands. Insofar as the observed negative cross-strand effects involve phosphates located on opposite faces of the B-form DNA duplex, a simple interpretation of the data is that certain local distortions of the duplex in the vicinity of the scissile phosphate adversely affect the transesterification reaction.

2'-5' Phosphodiester Effects on Exonuclease III—Exonuclease III employs a one-step in-line mechanism in which an activated water attacks the scissile phosphodiester (which is coordinated to an essential divalent cation) and expels the 3'-O-phosphate. This result implies that exonuclease III surveys or senses the phosphate backbone in advance of the active site.

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J. Biol. Chem. 2001, 276:20907-20912.
doi: 10.1074/jbc.M102312200 originally published online April 3, 2001

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