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The repair of psoralen monoadducts by the *Escherichia coli* UvrABC endonuclease

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ABSTRACT

We have examined the interactions of UvrABC endonuclease with DNA containing the monoadducts of 8-methoxypsoralen (8-MOP) and 4,5',8-trimethylpsoralen (TMP). The UvrA and UvrB proteins were found to form a stable complex on DNA that contains the psoralen monoadducts. Subsequent binding of UvrC protein to this complex activates the UvrABC endonuclease activity. As in the case of incision at pyrimidine dimers, a stable protein-DNA complex was observed after the incision events. For both 8-MOP and TMP, the UvrABC endonuclease incised the monoadduct-containing strand of DNA on the two sides of the monoadduct with 12 bases included between the two cuts. One incision was at the 8th phosphodiester bond on the 5' side of the modified base. The other incision was at the 5th phosphodiester bond 3' to the modified base. The UvrABC endonuclease incision data revealed that the reactivity of psoralens is 5'TpA > 5'ApT > 5'TpG.

INTRODUCTION

Nucleotide excision repair in Escherichia coli is catalyzed by a series of protein-DNA complexes (1). Using the pyrimidine dimer as a model lesion, it was demonstrated that the UvrA protein binds to UV irradiated DNA (1,2). In the presence of UvrB protein, the UvrA and UvrB proteins form a tight protein-DNA complex on the DNA, probably at the pyrimidine dimer (1). UvrC protein binds only to the UvrAB-pyrimidine dimer complex and activates the UvrABC endonuclease which cuts the damaged DNA strand on both sides of the pyrimidine dimer. One incision is made at the 8th phosphodiester bond 5' to the 5' pyrimidine of the pyrimidine dimer. The other incision is at the 5th or 6th phosphodiester bond 3' to the same 5' pyrimidine of the pyrimidine dimer (3,4). After the incision event, a stable protein-DNA complex persists on the UV damaged DNA (1) and the pyrimidine dimer containing fragment is not displaced until the arrival of the UvrD (DNA helicase II) protein and DNA polymerase I (5,6). DNA polymerase I then fills the 12 or 13 bases long gap created by the UvrABC endonuclease incisions (5,6). The continuity of the DNA strand is restored by DNA ligase (5,6).

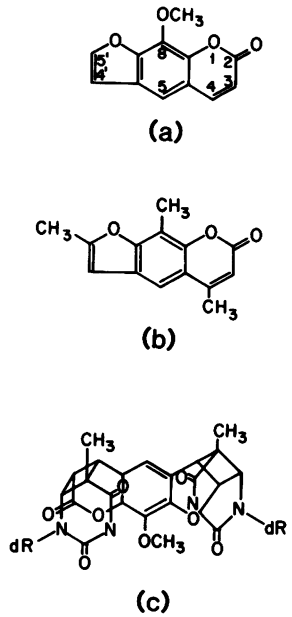

Fig. 1. The structures of (a) 8-methoxypsoralen, (b) 4,5',8-trimethopsoralen, and (c) the cis-syn-cis conformation of a thymine-8-methoxypsoralen-thymine diadduct (8).

Psoralens are a family of photoreactive furocoumarins, planar 3-ringed heterocyclic hydrocarbon compounds, which have been used to treat skin ailments such as psoriasis (7). Since 8-MOP and TMP (Fig. 1) are the two forms of psoralens whose physical and medical properties are best documented (8,9), they have been chosen for these studies. Both psoralens, when appropriately intercalated into the DNA helix and in the presence of 365nm UV light, react mainly with thymine bases to form thymine-psoralen monoadducts or thymine-

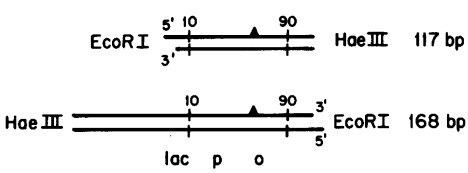

Fig. 2. Diagram of the 117 bp and 168 bp fragments containing the lac p-o region. The bases numbered 10 and 90 as in Fig. 11 are labeled on each fragment. The solid triangle on the top strand of each DNA fragment represents a psoralen monoadduct which is equally likely to form in the same DNA sequence in each DNA fragment.

psoralen-thymine interstrand DNA crosslinks (10,11). The photoreactivity of 8-MOP is highly specific for 5'TpA sequences (12). Since 8-MOP lesions are known to be repaired by the UvrABC endonuclease system in E. coli (13), and psoralen can also be used to study the repair of DNA crosslinks, we have examined the mechanism of repair of 8-MOP and TMP monoadduct lesions by UvrABC endonuclease in a way that can be directly compared with our previous studies with pyrimidine dimers. The UvrABC protein complexes during the repair of 8-MOP lesions as well as the bimodal incision of UvrABC endonuclease at 8-MOP and TMP lesions are reported.

MATERIALS AND PROCEDURES

Photoreaction of DNA with 8-MOP or TMP

8-MOP was used at a concentration of 25 μg/ml and TMP at 5 μg/ml, in a 50 μl solution of 40 μg/ml DNA, 10 mM Tris pH 7.6, 0.4 mM EDTA, 50 mM NaCl. The DNA was irradiated in a glass tube at 13J/M^2 by a 15W General Electric blacklight filtered through one inch of plain glass. The UV dose was determined by a J221 (UV Products) UV meter. After the photoreaction, the unreacted 8-MOP was removed with ethanol precipitation of the DNA followed by ethanol wash of the DNA pellet. For TMP reactions, the higher affinity of TMP for DNA requires that two chloroform extractions be included before the ethanol precipitation step to assure consistent removal of noncovalently bound

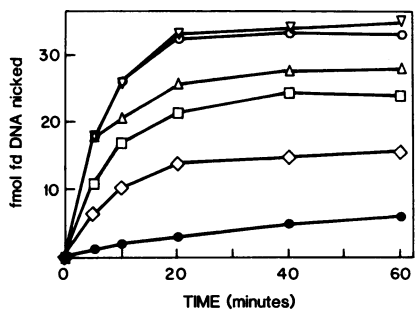

Fig. 3. 8-MOP monoadduct dependent incision of fd DNA by UvrABC endonuclease. Thirty-nine fmol of ^{3}H fd RF-I DNA-containing 0-7 psoralen monoadducts per fd molecule were incubated with 500 fmol each of UvrA and UvrB proteins and 100 fmol of UvrC protein at 37°C in a 140 μl reaction which contained 15 mM $MgSO_4$, 2 mM ATP, 85 mM KCl, 40 mM morpholinopropanesulfonate (MOPS) buffer, 1 mM dithiothreitol, pH 7.6. At each time point, the amount of nicking was measured by denaturation and renaturation of the DNA in the sample, and scoring for the nicked DNA which, being unable to renature, will bind to a nitrocellulose filter. Number of monoadducts per fd RF-I molecule: (●) 0, (◇) 0.4, (□) 0.8, (△) 1.5, (○) 4, (▽) 7.

TMP. To determine the UV dosage for forming an average of one monoadduct/fd DNA, we varied the UV dose until the complete incision by UvrABC endonuclease produced 66.7% conversion of RF-I (Replicative Form I) DNA to RF-II in the UvrABC endonuclease assay described below. To quantitate the amount of crosslink formed at each UV dose, we linearize the fd RF-I DNA, after the photoreaction, with Hpa I restriction endonuclease and score for the non-crosslinked DNA after denaturation and renaturation as in the UvrABC endonuclease assay. Only the non-crosslinked DNA will become single-stranded and bind to the nitrocellulose filter.

Preparation of UvrABC Endonuclease

The E. coli UvrA, UvrB, and UvrC proteins used in these studies were purified as described (14) and their purity, judging from SDS polyacrylamide gel electrophoresis, was better than 95%. Data in Figs. 2-5 utilized the same lots of UvrABC proteins used for the previous pyrimidine dimer studies (1) to facilitate comparison. Protein was quantitated by the method of Bradford (15) with bovine serum albumin as standard (BioRad).

The UvrABC Endonuclease Assay

The ability of UvrABC endonuclease to nick psoralen modified DNA was measured by the conversion of psoralen modified RF-I to RF-II DNA by UvrABC endonuclease (3) in a nitrocellulose filter binding assay previously described in detail (16). The assay utilizes ^{3}H-labeled fd RF-I DNA (6408 bp) at

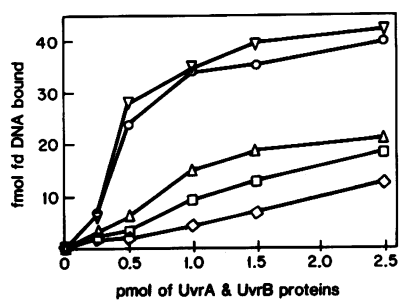

Fig. 4. Dependence of UvrAB-monoadduct protein-DNA complex formation on the amount of damage in the DNA and the amount of UvrA and B proteins. Different amounts of UvrA and UvrB proteins at a molar ratio of 1:1 were incubated for 20 minutes at 37°C with 40 fmol of fd RF-I DNA as in the nicking assay. The fd DNA contained 0 to 4 8-MOP monoadducts each. The reaction was terminated by dilution with 5 ml of 2xSSC at 4°C and kept on ice for 3 minutes before the protein bound DNA was collected by filtering through a nitrocellulose filter. The UvrAB-monoadduct complex was stable under these conditions while the UvrA-monoadduct complex was not. Number of psoralen monoadducts per fd RF-I molecule: (◇) 0, (□) 0.5, (△) 1, (○) 2, (▽) 4.

50,000cpm/μg, prepared as described (1) and scores for the first nick in the RF-I DNA.

The Protein-DNA Complex Filter Binding Assay

The formation of stable UvrABC protein-DNA complexes was measured by trapping the native protein-DNA complexes on nitrocellulose filters as described (1). The assay scores for the amount of ^{3}H-labeled DNA that is retained by the filter as a result of the DNA binding to the proteins, which in turn bind to nitrocellulose.

Analysis of UvrABC Endonuclease Incision at 8-MOP and TMP Modified DNA Fragments

A region of the lac promoter-operator region (lac p-o) about 100 basepairs (bp) long was cloned in tandom in a 285 bp EcoRI fragment that can be divided by HaeIII restriction into a 117 bp and a 168 bp DNA fragment (Fig. 2) to facilitate the ^{32}P labeling of the 5' or the 3' side of either strand of the DNA region presented in Fig. 11 (17). A more detailed explanation of the

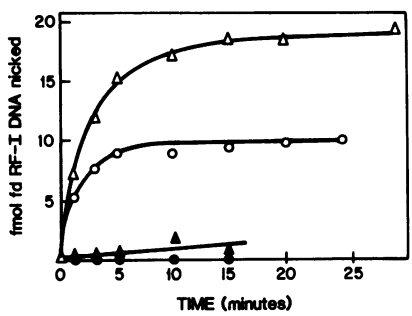

Fig. 5. Incision of preformed UvrAB-8-MOP monoadduct protein-DNA complex is not inhibited by the presence of competing DNA. Twenty fmol of ^{3}H fd RF-I DNA containing an average of four monoadducts per fd molecule were treated with 500 fmol each of UvrA and B proteins and 100 fmol of UvrC proteins in various manner as detailed below, and the nicking of the fd DNA was scored by the RF-I denaturation/renaturation assay. (△) Normal nicking of the monoadduct containing fd DNA by simultaneous addition of the UvrA, B, C proteins. (▲) The non-damage dependent nicking in the background. (●) 200-fold weight excess of pyrimidine dimer containing calf thymus double-stranded DNA over the fd DNA was added to these reactions before the addition of the UvrA, B, C proteins. (○) UvrA, B proteins were allowed 20 minutes preincubation at 37°C to form the stable UvrAB-protein-DNA complex with the monoadducts in the DNA in the assay buffer before the addition of the 200-fold weight excess of pyrimidine dimer containing calf thymus double-stranded DNA. The amount of UvrAB-protein-damaged DNA complex formed under these conditions is about 50% of the fd DNA in the assay. The incubation continued for another 5 minutes at 37°C and then UvrC protein was added to initiate the incision reaction. Samples were taken at the times indicated after the addition of the UvrC protein.

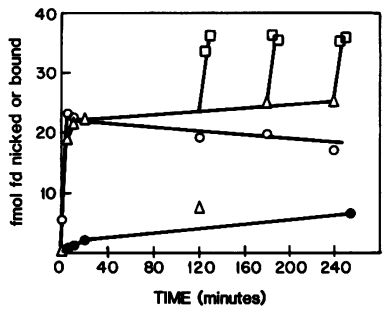

Fig. 6. Post-incision protein-DNA complex of UvrABC endonuclease with 8-MOP monoadduct-containing fd DNA. Twenty fmol of fd DNA containing four monoadducts per molecule were incubated with 500 fmol each of UvrA and UvrB proteins and 100 fmol of UvrC protein at 37°C in the nicking assay buffer. (△) An average of one monoadduct per fd molecule was incised in about 5 minutes. The incision incubation was continued for 240 minutes which is 10 times longer than necessary for all the monoadducts to be incised. That the UvrABC endonuclease was active during this period was demonstrated by its ability to rapidly act on an extra 20 fmol of labeled monoadduct containing fd DNA added at either 120, 180 or 240 minutes (□). (●) The non-damage-specific nicking of the fd DNA under the same conditions. (○) The presence of high affinity protein-DNA complex was followed by the filter binding assay. The amount of non-damage-specific binding of fd DNA in this experiment was 2 fmol.

labeling strategy was previously described (3). The analyses of the DNA sequencing gels to obtain the UvrABC endonuclease incision patterns were as described (3). The use of T_4 polynucleotide kinase to label the 5' termini and the use of Klenow fragment to label the 3' termini were as described (18).

DNA Sequencing Reactions

DNA sequencing was performed by the Maxam and Gilbert protocol for the G and G+A reactions (18) and the Rubin and Schmid (19) protocol for the pyrimidine reactions.

RESULTS AND DISCUSSION

Effect of Psoralen Lesion Density in the DNA on the Rate of UvrABC Endonuclease Incision

The rate of UvrABC endonuclease incision on 8-MOP monoadduct-containing fd DNA was roughly proportional to the monoadduct content in the DNA (Fig. 3) and reached a plateau at a damage content of about four psoralen monoadducts per fd RF-I molecule. The same dependence of the rate of incision on pyrimidine dimers content in the DNA was observed (unpublished data). The monoadduct to crosslink ratio in the fd DNA in this experiment was about 10:1 (data not shown). Processivity is not a factor in this experiment since the UvrABC endonuclease does not turn over under these conditions (1).

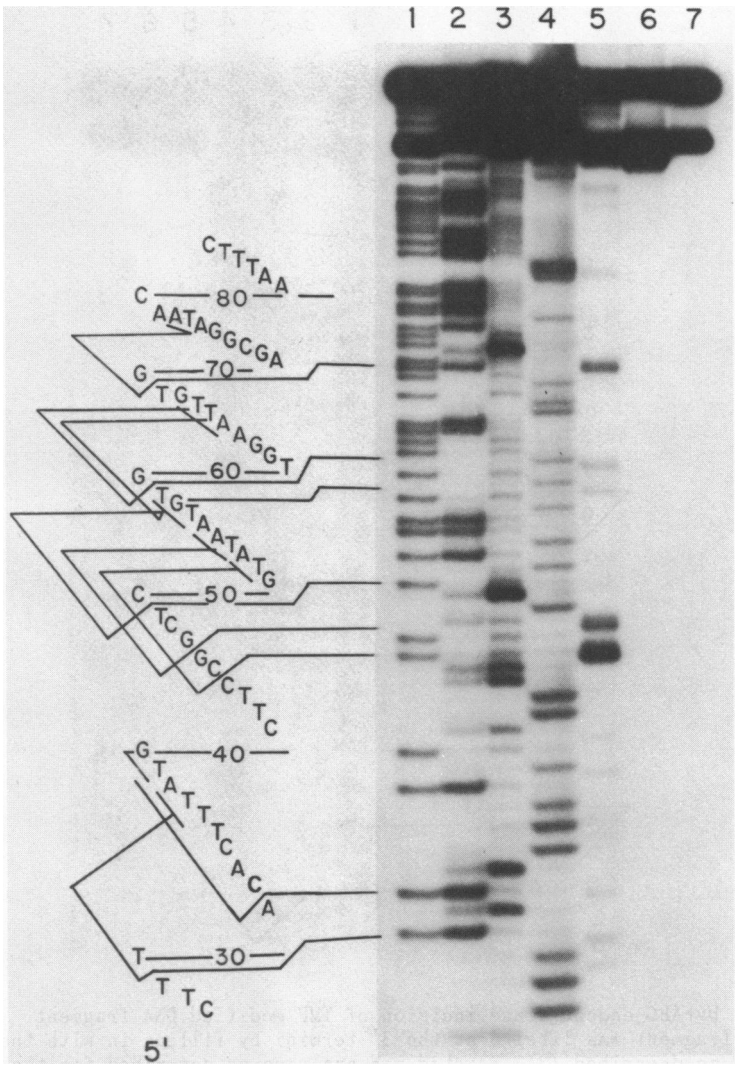

Fig. 7. UvrABC endonuclease incision of TMP modified DNA fragment. About 20 fmol of 117 bp lac p-o DNA fragment labeled at the EcoRI 5' termini with ^{32}P was treated with 530 fmol of UvrA protein, 750 fmol of UvrB protein and 263 fmol of UvrC protein under standard assay conditions for 1 hour at 37°C. The reaction was stopped by the addition of EDTA to 50 mM and incubated at 37°C for another 20 minutes. The mixture was extracted once with phenol, twice with ether, and precipitated with ethanol, washed with ethanol and dried. The dried sample was dissolved in 10 μl of tracking dye and 2 μl was loaded into a well of the DNA-sequencing gel (10% polyacrylamide, 7 M urea, ran 49°C) in Lane 5. Lanes 1,2,3,4 are DNA sequencing lanes of G, G+A, C, and T reactions, respectively. Lane 6 is a control reaction of UvrABC endonuclease digestion of the undamaged DNA fragment. Lane 7 is a control reaction of the psoralen-treated DNA without UvrABC endonuclease.

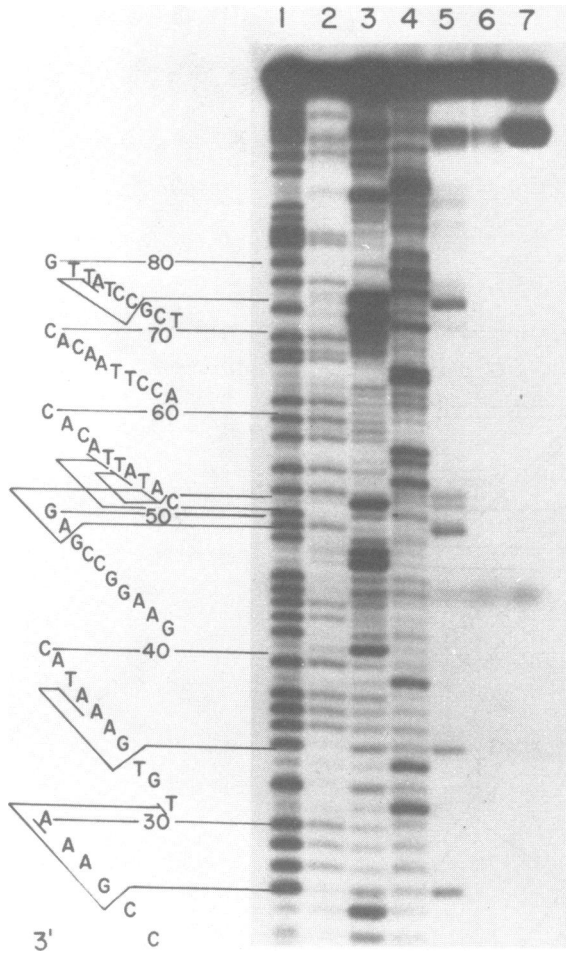

Fig. 8. UvrABC endonuclease incision of TMP modified DNA fragment. The 117 bp lac p-o fragment was labeled at the 3' termini by filling in with the Klenow fragment as described (3), reacted and analyzed as described for the experiment in Fig. 7. The labeling of the lanes is the same as in Fig. 7. The fuzzy band across lanes 5-7 near base number 43 was an artifact from our 3' labeling.

Formation of UvrAB-Monoadduct Protein-DNA Complexes on fd DNA

UvrA-UvrB proteins can form a stable protein-DNA complex on pyrimidine dimer containing DNA (1). Because this damage dependent complex is stable in 1M NaCl or 50 mM EDTA at 4°C while the protein complexes of UvrA or UvrAB on undamaged DNA are not, it is possible to remove the non-damage dependent protein-DNA complexes by terminating the binding reaction with the addition of

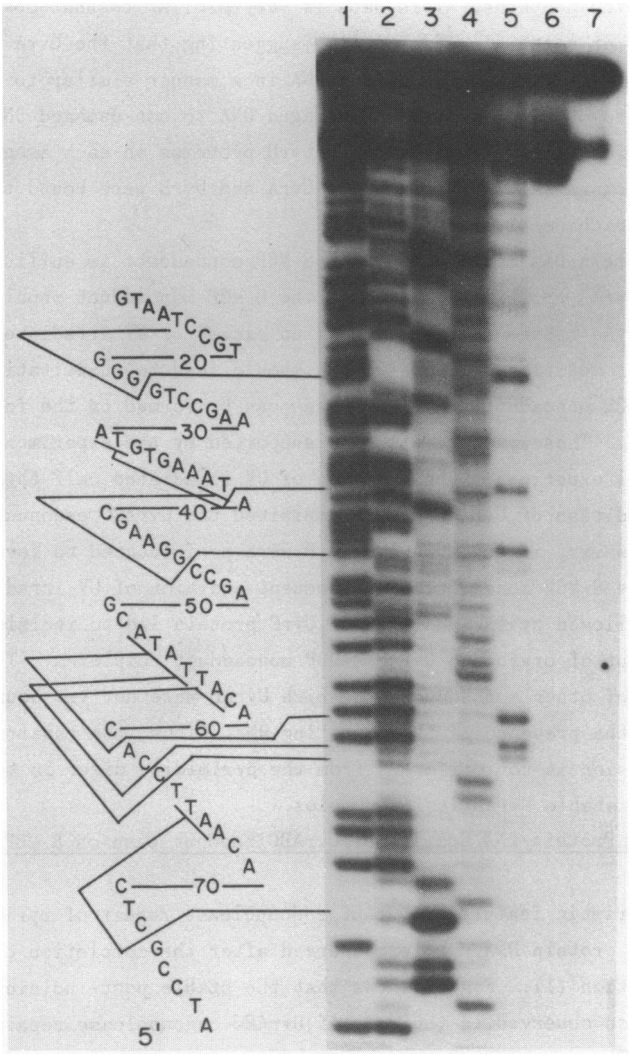

Fig. 9. UvrABC endonuclease incision of TMP modified DNA fragment. The 168 bp lac p-o fragment was labeled at the 5' termini with T_4 polynucleotide kinase as described (3), reacted and analyzed as described for the experiment in Fig. 7. The labeling of the lanes is the same as in Fig. 7.

5 ml of 2xSSC (0.3M NaCl, 0.03M trisodium citrate) at 4°C before collecting the damage-dependent complexes on the nitrocellulose filter. As seen in Fig. 4, the formation of UvrAB-monoadduct dependent protein-DNA complex was dependent on the amount of psoralen lesions on the DNA as well as the amount

of UvrA and UvrB proteins. This data is very similar to that observed for pyrimidine dimer containing fd DNA (1), suggesting that the UvrA and UvrB proteins interact with 8-MOP modified DNA in a manner similar to UV damaged DNA. The ratio of binding of 8-MOP damaged DNA to non-damaged DNA is maximal at about 500 fmol (3.75nM) of UvrA and UvrB proteins in each assay. However, the data do not reveal whether all the UvrA and UvrB were bound to the DNA and what their stoichiometry is on the DNA.

If the protein-DNA complex of UvrAB-8-MOP monoadduct is sufficiently stable, the UvrAB proteins residing on the 8-MOP monoadduct should not be displaced by the subsequent addition of an excess of UV irradiated calf-thymus DNA, and later addition of UvrC protein should lead to quantitative nicking of the UvrAB-8-MOP monoadduct complexes that can be formed on the fd DNA in the preincubation. These predictions were supported by the experiment in Fig. 5. In the control experiment, the addition of UV irradiated calf-thymus DNA before the addition of UvrA and UvrB inhibited the UvrABC endonuclease activity. However, if the UvrA and UvrB were preincubated to form a stable complex on the 8-MOP monoadducts, subsequent addition of UV irradiated calf-thymus DNA followed by the addition of UvrC protein led to incision of the expected amount of preformed UvrAB-8-MOP monoadduct complexes. Thereafter, the incision of other monoadducts to which UvrAB were not yet bound were inhibited by the presence of the competing DNA. Thus, the repair of the 8-MOP monoadduct lesion is not different from the pyrimidine dimer in terms of the nature of the stable UvrAB-lesion complex.

Post-incision Protein-DNA Complex of UvrABC Endonuclease on 8-MOP Containing fd DNA

A characteristic feature of UvrABC endonuclease repair of pyrimidine dimers is the stable protein-DNA complex observed after the completion of the incision reaction (1). Fig. 6 shows that the stable post-incision protein-DNA complex is also observed in the case of UvrABC endonuclease repair of 8-MOP monoadduct. The presence of the protein-DNA complex was followed by the protein-DNA filter binding assay. The fact that the UvrABC endonuclease remained active in the assay period was demonstrated by the rapid incision of extra monoadduct-containing fd RF-I DNA added to control samples at the second, third, or fourth hour time points. Thus, under the conditions of these experiments, the UvrABC endonuclease does not turn over *in vitro* during the repair of the psoralen monoadducts. In the case of pyrimidine dimer repair, it has been demonstrated that UvrD (DNA helicase II) and DNA polymerase I are needed for the UvrABC endonuclease to turn over *in vitro* (5,6).

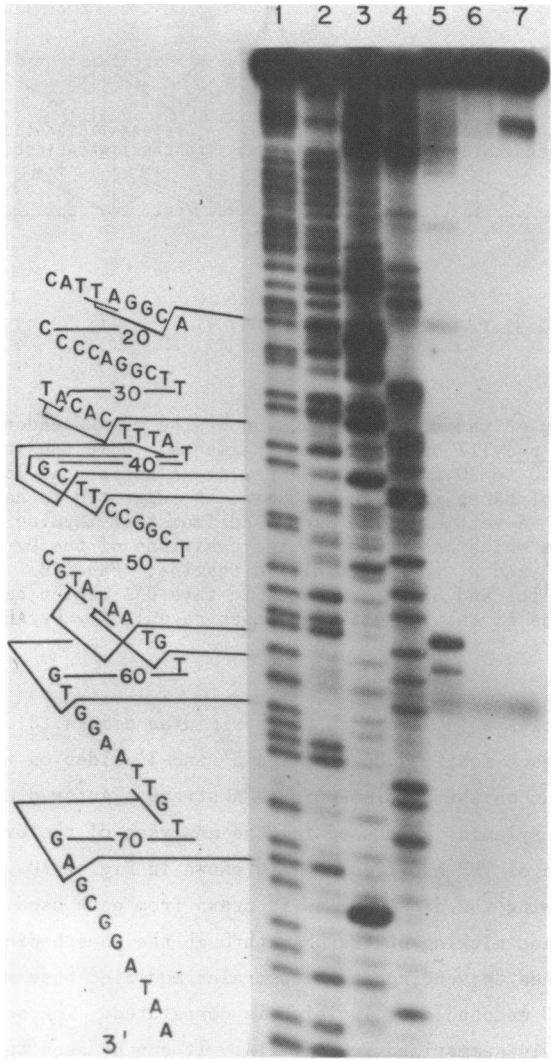

Fig. 10. UvrABC endonuclease incision of TMP modified DNA fragment. The 168 bp lac p-o fragment was labeled at the 3' termini by filling in with the Klenow fragment as described (3), reacted and analyzed as described for the experiment in Fig. 7. The labeling of the lanes is the same as in Fig. 7. The band across lanes 5-7 near base number 43 was an artifact of our 3' labeling procedure.

Pattern of UvrABC Endonuclease Incision of DNA-Containing Psoralen Monoadducts

The pattern of UvrABC endonuclease incision at TMP monoadducts was examined using the same lac p-O DNA sequence which previously facilitated the analyses

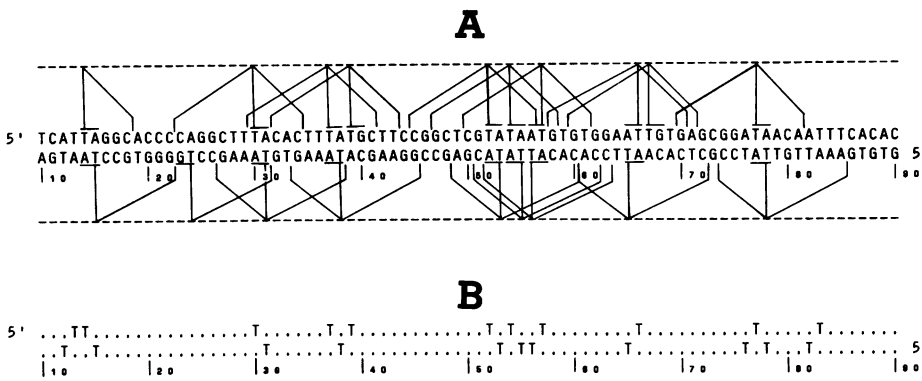

Fig. 11. Summary of the sites of incision by the UvrABC endonuclease on the TMP modified lac p-o 117 bp and 168 bp fragments. Only the incisions in the region numbered 10 to 90 are shown. Panel A: A horizontal line is drawn above or below a pair of bases in which a thymine is suggested to have formed a mono-adduct with TMP. A vertical line is traced from that thymine to the horizontal dashed line, from which one can trace the positions of the UvrABC endonuclease incisions both 5' and 3' to that modified thymine. Panel B: A presentation of the pattern of 5'TpA and 5'ApT sequences in this DNA region to show correlation with the positions of the TMP modified bases revealed by UvrABC endonuclease incision.

of UvrABC endonuclease incisions at the pyrimidine dimers (3). We examined the incision of each modified base on its 5' and 3' sides on the same DNA strand, as well as on the complementary DNA strand. Autoradiograms of the denaturing polyacrylamide gels used for the analyses of the UvrABC endonuclease incision of TMP modified DNA are shown in Fig. 7-10. To assist the readers in following the data, a line is drawn from each band produced by the UvrABC endonuclease nicking of the DNA, through the phosphodiester bond that the cut corresponds to, ending at the psoralen modified base with which the particular UvrABC endonuclease incision is correlated. The net result of the analyses for TMP is summarized in Fig. 11A. It can be seen that with only the exception of the psoralen modified thymine moiety at base number 66 of the top DNA strand, all 5' incision sites were at the 8th phosphodiester bond from the modified base. All incision sites 3' to each putative modified base were at the 5th phosphodiester bond from that base. All thymines in 5'TpA and most 5'ApT sequences have shown some reactivity with TMP and subsequent incision by UvrABC endonuclease. Fig. 11B highlights the pattern of the 5'TpA and 5'ApT sequences in this DNA fragment and the pattern is very similar to the pattern of modified bases indicated by the UvrABC endonuclease incision reactions. The relative intensities of the incision bands in the DNA sequencing gel

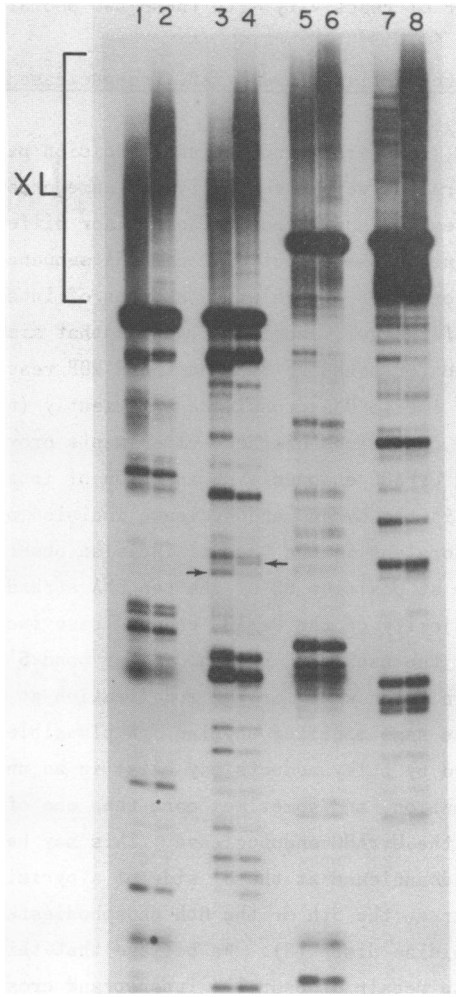

Fig. 12. Comparison of the modification of the lac p-o region by 8-MOP and TMP and the resulting UvrABC endonuclease incision patterns. The reactions of TMP and UvrABC endonuclease incision are as described in the legends to Fig. 6. The 8-MOP reactions differ in the use of 50 $\mu g/ml$ of 8-MOP in place of the TMP, and that the UV365 nm irradiation was 12,000 J/m^2. The arrows on the sides of lane 3 and 4 show the positions of the UvrABC endonuclease incisions at the 9th phosphodiester bond and the 8th phosphodiester bond from base number 66 of the top DNA strand in Fig. 11A where the thymine was modified with TMP or 8-MOP, respectively. The odd numbered lanes are UvrABC endonuclease incision of DNA modified with TMP, the even numbered lanes are UvrABC endonuclease incision of DNA modified with 8-MOP. Lanes 1-4 are the 117 bp fragments. Lanes 5-8 are the 168 bp fragments. The DNA in lanes 1,2,5,6 was labeled at the 5' end. The DNA in lanes 3,4,7,8 was labeled at the 3' end. XL indicates the region for crosslinked DNA.

suggest that the order of reactivity with these two psoralens is 5'TpA > 5'ApT > 5'TpG.

Comparison of the Photoreactivity and UvrABC Endonuclease Repair of 8-MOP and TMP

As seen in Fig. 12, the UvrABC endonuclease incision patterns of DNA damaged with both psoralens were essentially the same except for minor differences in intensities for some bands. These minor differences in intensities are probably due to the effect of local DNA sequence variations on the reactivity of each psoralen. The relative amounts of interstrand crosslinked DNA seen at the top of the gel, labeled XL, shows that similar extents of photoreaction occurred for both the TMP and the 8-MOP reactions. Since UvrABC endonuclease does not incise DNA crosslinks efficiently (unpublished data), we do not think that the conditions of these experiments provided the sensitivity necessary for scoring UvrABC endonuclease incision of interstrand crosslinks. Noticeably different in the UvrABC endonuclease incision of the monoadduct lesions of the two psoralens is the unusual incision observed for TMP modification at the thymine at position 66 of the top DNA strand in Fig. 11A mentioned above. The majority of the UvrABC endonuclease incision for this 8-MOP modified base were at the usual 8th phosphodiester bond 5' to the modified base instead of the incision seen for TMP modification at the 9th phosphodiester bond 5' to the same modified thymine. A plausible explanation is that DNA sequences modified by bulky adducts may exist in an unequal equilibrium of more than one conformation, and sometimes more than one of these conformations can be recognized by the UvrABC endonuclease. This may be similar to the incision by UvrABC endonuclease at the 3' side of a pyrimidine dimer where the incision can be either at the 5th or the 6th phosphodiester bond from the 5' pyrimidine of a pyrimidine dimer (3). We believe that this unusual 5' incision is not due to repair of psoralen interstrand crosslinks that might form at this thymine base because (a) the site is a 5'ApT sequence which does not favor crosslink formation and all other sites which favor crosslink formation showed the normal UvrABC endonuclease incision pattern, (b) the 3' incision at this base was normal, (c) the 5' incision at the same base modified with 8-MOP was normal.

While both 8-MOP and TMP have high sequence specificity, TMP is probably more suitable for structural studies of the DNA helix because it lacks appreciable pyrone side monoadduct formation in its photoreaction (8). A new psoralen derivative 4'-hydroxymethyl-4,5',8-trimethylpsoralen (HMT) has been used in a UvrABC endonuclease incision study by Sancar et al. who observed the

same pattern of UvrABC endonuclease incision for HMT monoadducts (20). The UvrABC endonuclease incision at HMT (20), and the 8-MOP and TMP studies in this work suggest that both 5'TpA and 5'ApT are reactive with psoralens, with 5'TpA being of higher reactivity. The reactivity of 8-MOP, TMP and HMT at other minor sites has not been compared.

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