Molecular Models for DNA Damaged by Photoreaction

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Abstract. *Structural models of a DNA molecule containing a radiation-induced psoralen cross-link and of a DNA containing a thymine photodimer were constructed by applying energy-minimization techniques and model-building procedures to data from x-ray crystallographic studies. The helical axes of the models show substantial kinking and unwinding at the sites of the damage, which may have long-range as well as local effects arising from the concomitant changes in the supercoiling and overall structure of the DNA. The damaged areas may also serve as recognition sites for repair enzymes. These results should help in understanding the biologic effects of radiation-induced damage on cells.*

Living organisms are frequently exposed to radiation and chemicals that can cause alterations in the structure of DNA. To overcome the effects of this damage, cells have developed mechanisms by which DNA is repaired (*1*). The most widely studied radiation-induced modification of DNA is the formation of pyrimidine dimers by ultraviolet (UV) light. For example, two adjacent thymine bases on a strand of DNA may be fused by the formation of a cyclobutane ring between the bases (*2*). If these dimers are not repaired before replication, they create blocks to the synthesis of normal DNA and a high rate of mutation.

Another well-studied DNA lesion is caused by psoralen or its derivatives in conjunction with long-wavelength UV radiation. Psoralens are a class of heterocyclic compounds (Fig. 1a) which intercalate at two adjacent base pairs of duplex DNA and which, upon UV irradiation, form covalent bonds to a pyrimidine base on each strand, thus generating a cross-link (*3*). Psoralens have been used as photosensitizing agents in the treatment of various skin pigmentation diseases and are potentially applicable in cancer chemotherapy and in the production of inactivated viruses for vaccines (*3*). In addition, both psoralen cross-links and pyrimidine dimers have been used as biochemical probes of nucleic acid secondary structure and of the interactions of nucleic acids with proteins in vitro (*4*, *5*) and in vivo (*4*).

Knowing the structural features of these DNA molecules may be important for understanding the biological effects of radiation-induced damage on cells and, in particular, how the damaged sites are recognized by repair enzymes. At present, however, it is difficult to make a sufficient amount of a homogeneous DNA fragment that contains a specific site of radiation-induced damage to allow studies of these structures by such methods as x-ray crystallography. Therefore, we used the results of x-ray crystallographic studies of model compounds in combination with molecular model building and energy-minimization techniques to deduce the structures of DNA segments containing modifications that can be caused by photoreaction (*6*).

Construction of the starting model and energy minimization. The starting point in building the model of a psoralen–cross-linked DNA was the crystal structure of a *cis-syn* monoadduct of psoralen and thymine (Fig. 1b) isolated from calf thymus DNA (*7*). This conformer has been established by chemical analysis and nuclear magnetic resonance (NMR) spectroscopy as the major monoadduct species formed in calf thymus DNA (*8*, *9*).

To construct a diadduct model (Fig. 1c), we fitted a second thymine on the opposing DNA strand to the psoralen (we assumed that the local structures around the cyclobutane rings for both thymines were the same). We then incorporated the resulting thymine-psoralen-thymine complex into a DNA duplex (Fig. 2). The first step was to fit (by a least-squares method) a thymine base at the end of a canonical (*10*) B-DNA double-helical trimer to each of the two thymines of the diadduct. At this time the two helices were not connected by phosphodiester bonds. Base pairing between the cross-linked thymines and the complementary adenines on the opposite strands was maintained for the starting model. This decision was made on the basis of our initial findings from iminoproton NMR spectra of the DNA sequence

5′ GAATTC 3′
3′ CTTAAG 5′

which has been cross-linked with psoralen at the central base pair by UV irradiation (G, guanine; A, adenine; T, thymine; C, cytosine). Our results indicate that no base pairs are broken by formation of the cross-link, although the relative orientation of the base pairs has changed (*11*).

Subsequent manipulation of the starting model was performed by minimizing the empirical energy function associated with the molecule, with the atomic positions serving as variable parameters (*12*, *13*). No partial charges were included for the psoralen molecule, which was restricted to its crystallographic structure (*7*). Minimization was carried out on the DNA molecule alone (no solvent atoms were included) with the use of the AMBER program (*14*) until there were no appreciable changes in either the atomic positions or the energy between two consecutive cycles.

For the initial stage of minimization, emphasis was placed on closing the long gaps (see Fig. 2) in the two DNA strands while maintaining reasonable bond lengths and angles throughout the rest of the molecule. This was done by using a minimization cycle in which the torsion angles were essentially the only structural variables; bond lengths and angles were restricted to their ideal values. In addition, during initial refinement the cross-linked thymine-psoralen-thymine complex was held in its starting geometry. The result was a structure lacking the gaps between phosphodiesters in the backbone but maintaining reasonable geometry at all the atoms.

The structure was then subjected to a series of energy-minimization steps in

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which restraints on the bond angles and lengths were gradually relaxed, so that strains that might have built up in the structure during the initial energy minimization were dissipated smoothly. After the structure was relaxed, the constraints on the geometries of the cross-links were also removed, and energy minimization was continued. The changes that occurred with the removal of the constraints on the cross-links were confined primarily to the vicinity of the C-3–C-4 bond of the psoralen, which was formulated by analogy with the geometry at the C-12–C-13 bond determined by crystallography (for atom numbering see Fig. 1a). The geometry around the C-12–C-13 bond changed less.

At this time, two more base pairs of regular B-DNA were best fit to each end of the psoralen–cross-linked hexamer (Fig. 2), resulting in the decameric structure

5′ CGCAT—ATGCG 3′
P
3′ GCGTA—TACGC 5′

where P represents the cross-linked psoralen. The extra base pairs were added to minimize any effects that the different environments at the helical ends might have on the conformation near the cross-link site. The longer helix also helped in defining the helical axes of the decamer, which are needed for calculations of such parameters as the kink angle, unwinding angle, and displacement distance due to the psoralen cross-link. The resulting decameric structure was then subjected to energy minimization as described above. For comparison, a canonical B-DNA helix (*10*) of the same sequence was also subjected to energy minimization by the same methods.

An analogous procedure was used to generate a DNA duplex containing a thymine photodimer, which is discussed later. The final DNA sequence incorporating the thymine photodimer was

5′ CGCGTTCGCG 3′
3′ GCGCAAGCGC 5′

Psoralen-DNA cross-linked model. Compared to the energy-minimized B-DNA structure (Fig. 3a), the resulting psoralen–cross-linked structure (Fig. 3c) is severely distorted. Space-filling models of both are shown in Fig. 4. The distortion can be understood in detail by examining the local deformation at and near the cross-link site and in general by examining the structural parameters of the distorted helix.

Local deformation. A comparison of torsion angles shows that the major

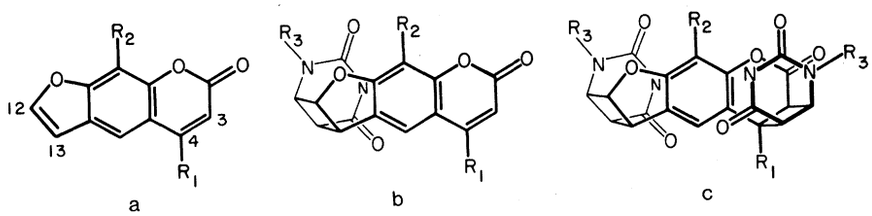

Fig. 1. (a) A psoralen molecule showing the cross-link sites (C-3, C-4, C-12, and C-13). (b) A monoadduct of thymine with psoralen having the *cis-syn* configuration. (c) A diadduct of thymine with psoralen having the *cis-syn* configuration at each linkage. 8-Methoxypsoralen, where R_1 is hydrogen and R_2 is OCH_3, was used. The thymine bases are attached to the furanose rings of the nucleic acid at R_3.

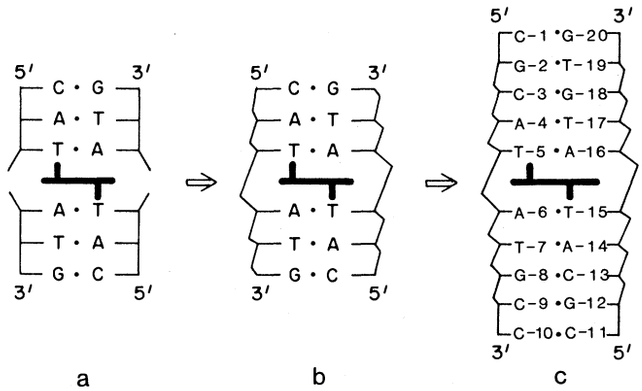

Fig. 2. Scheme of the procedure used to build a double-stranded nucleic acid fragment containing a psoralen cross-link. A thymine base at the end of a B-DNA double-helical trimer was fit to each of the cross-linked thymines (a). Energy-minimization techniques were used to close the gaps in the helix backbones and to produce a stereochemically reasonable structure (b). Two additional base pairs were added to each end of the structure and energy minimization was repeated (c). The DNA sequences used are shown. Abbreviations for bases are as given in the text.

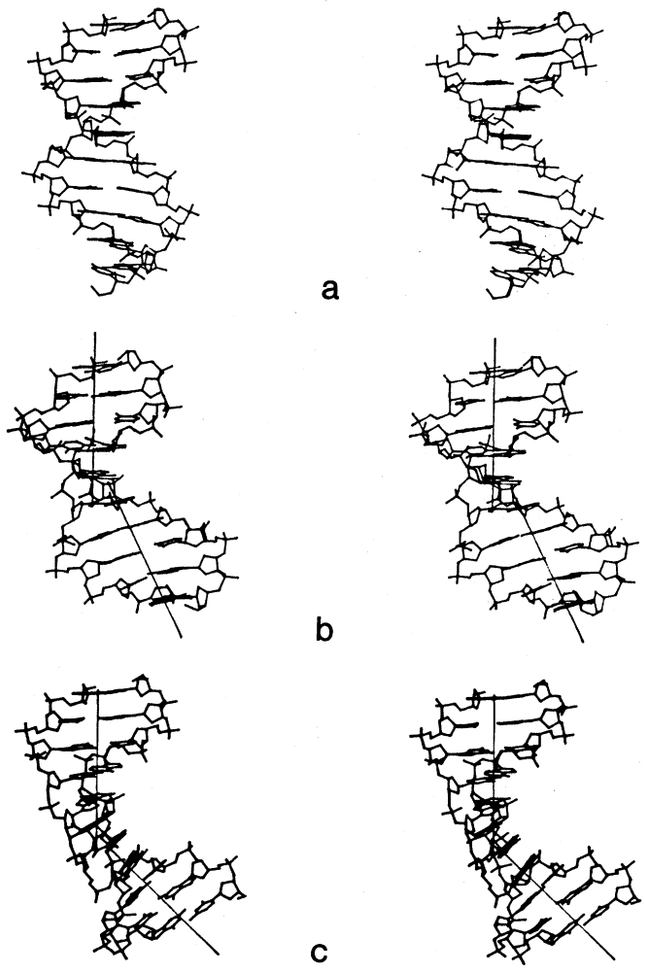

Fig. 3. Stereo diagrams of the final energy-minimized structures. (a) B-form DNA; (b) double-stranded DNA containing a thymine dimer; and (c) double-stranded DNA containing a psoralen cross-link.

changes in the psoralen structure relative to the energy-minimized B-DNA form are restricted to the cross-linked thymines and the subsequent two residues on the 3′ side. These changes are in contrast to the bidirectional (both 3′ and 5′ ends of both strands) distribution of conformational changes in the model of a thymine dimer. Large changes in backbone torsion angles for the psoralen–cross-linked DNA structure relative to the B-DNA model occur at residues 5, 6, and 7 on one strand and at residues 15, 16, and 17 on the other.

In our model, the torsion angles α, γ, and (to a lesser extent) ζ and the pseudorotation angle P (Fig. 5) appear to account for most of the conformational flexibility. Changes in α and γ in the residues on the 3′ side of the psoralen are negatively correlated in a "crankshaft" linkage, a common mode of conformational change in nucleic acids (*15*). The glycosyl angles χ assume standard *anti* values except at the cross-linked thymines, where they assume high *anti* values. This could be in response to the attached sugars, which have C-3′ *endo* conformations rather than the usual C-2′ *endo* conformations in B-DNA. Crystal structures of oligonucleotides (*16*) also show a relation between the glycosyl angle and the pucker of the sugar but in the opposite sense. In general, regions where the psoralen–cross-linked model differs appreciably from the B-DNA model include a sugar whose pucker has changed, as indicated by the pseudorotation angle P. It is possible that when a large conformational change is necessary it is initiated by a change in sugar conformation, which induces concomitant changes in nearby torsions.

Table 1. Overall helical parameters for DNA cross-linked with psoralen and with a thymine dimer. All values are relative to an energy-minimized B-DNA structure having the same sequence.

Cross-link	Angles (degrees)		Helical displacement (Å)	Energy (kcal/mol)
	Total unwinding	Helical kink		
Psoralen-DNA	87.7	46.5	3.49	+168.4
Thymine dimer–DNA	19.7	27.0	2.66	+58.6

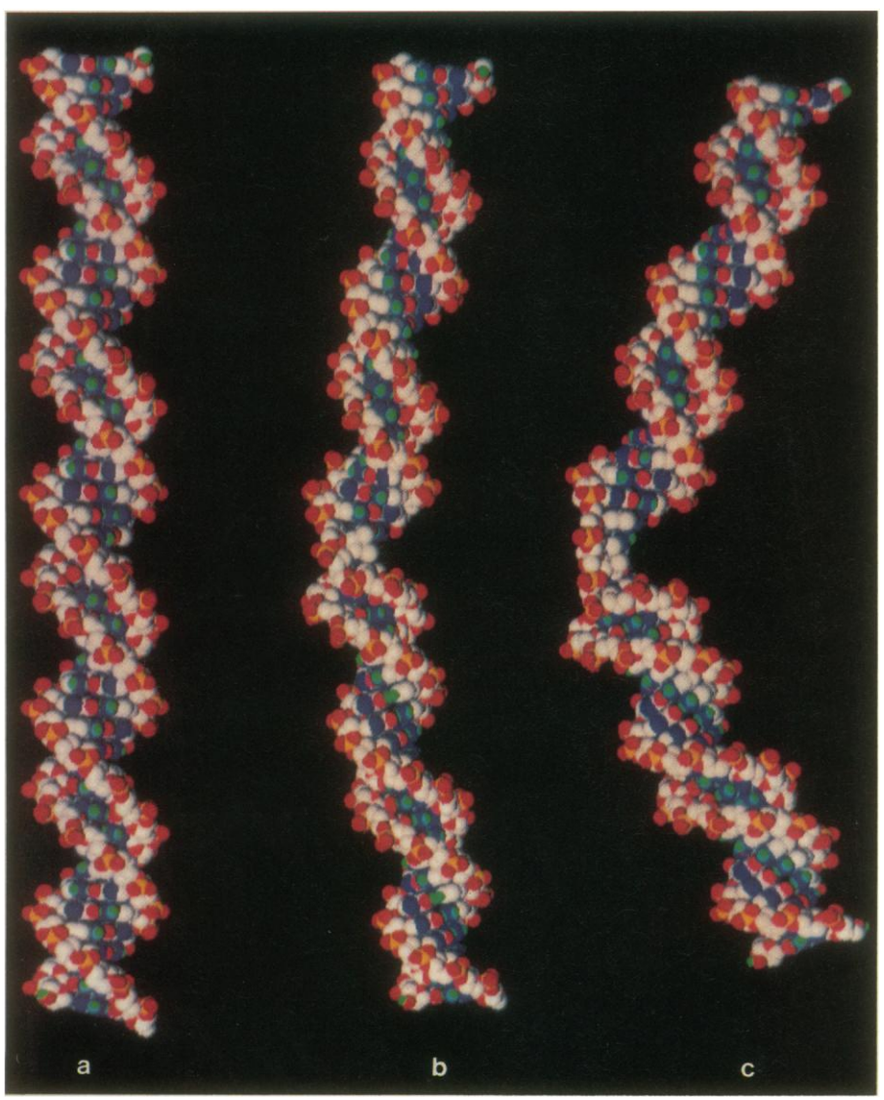

Fig. 4. Space-filling representations of DNA molecules (48 base pairs in length) incorporating the final energy-minimized structures considered, generated by computer graphics. Color scheme: white, carbon atoms; red, oxygen atoms; blue, nitrogen atoms; green, hydrogen atoms; yellow, phosphorus atoms. (a) B-form DNA; (b) double-stranded DNA containing a thymine dimer; (c) double-stranded DNA containing a psoralen cross-link.

A result of introducing the psoralen is a distortion of the base-pairing between the cross-linked thymines and their complementary adenines (Fig. 3c). This is most apparent in the bending angles (10° to 19°) between the planes of the two central base pairs of the psoralen-DNA structure compared to the nearly planar base pairs of the energy-minimized B-DNA.

Overall helix deformations. Knowing the individual torsion angles and energies is helpful in understanding structural details, but these quantities are not suitable for describing the overall features of the cross-linked DNA structure. The overall structural distortions can be described by three parameters: (i) the kink angle between the two helices separated by the cross-link; (ii) the amount of unwinding or winding of the cross-linked helix relative to the energy-minimized B-DNA; and (iii) the translational displacement of the axes of the helices separated by the kink. The axes for the helices separated by the cross-link were determined from the last two base pairs on each side of the kink (the angle between the axes is defined as the kink angle). The winding or unwinding angle for two adjacent base pairs was calculated by projecting the vector between the two C-1′ atoms of one base pair and the equivalent vector for the adjacent base pair into a plane perpendicular to their common helical axis and then determining the angle between these vectors. When two base pairs did not share a common helical axis, one base pair was first rotated to make the helical axes colinear. The helical displacement was calculated as the shortest (perpendicular) distance between the helical axes of the two seg-

ments separated by the kink.

The psoralen cross-link causes large changes in the calculated overall structural parameters relative to those of the minimized B-DNA helix (Tables 1 and 2). The kink angle for the psoralen, 46.5° (Table 1), is nearly the same as the angle between the two cross-linked thymine bases (44.4°). The direction of kinking is into the major groove of the DNA duplex.

Most of the unwinding in the psoralen–cross-linked structure (overall, 88.0° relative to energy-minimized B-DNA) occurs at the cross-link site. Because of the physical constraints on the thymine-psoralen-thymine cross-link site, this structure is wound by 13.4° in a left-handed sense compared to a 45.1° right-handed step for the energy-minimized B-DNA structure. The first base on each side of the psoralen in the cross-linked structure is also unwound relative to B-DNA but by a smaller amount. The helical axes of the psoralen–cross-linked structure are displaced by 3.5 Å. This value is sensitive to the method used to calculate it (that is, to the portions of the structure from which the helical axes are derived) and should be interpreted with this in mind.

Surface accessibility of psoralen-DNA. From our model we can make the specific, verifiable prediction that, because of alterations in structure induced by the psoralen cross-link, there should be differences in the accessibilities to solvent or chemical reagents of certain residues of the damaged DNA relative to B-DNA. A strong correlation between the calculated accessibility to solvent and the extent of chemical modification by specific reagents has been shown for transfer RNA (*17*) and may be expected for nucleic acids in general. Therefore, we calculated the surface accessibility (*18*) of our psoralen-DNA model to probes of various radii to examine the potential for interaction of the damaged DNA with water and larger chemical reagents. As expected, the largest differences in accessibility when compared to energy-minimized B-DNA were at the points of cross-link formation. The link with thymine at the C-12 and C-13 positions of psoralen results in a large decrease in accessible surface at this position to both water and other larger probes. On the other strand, the C-3–C-4 link produces a relatively small change in accessibility of the thymine but a large increase in the accessibility of the adenosine on the 3′ side of the cross-link. Specifically, this shows that the exposure of the C-8 position is larger for this adenosine.

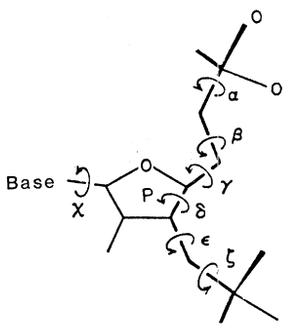

Fig. 5. A schematic view of the nucleic acid backbone. The torsion angles that determine the conformation are indicated. *P*, the phase-angle of pseudorotation, is a function of the sugar pucker.

The thymine photodimer–DNA model. Studies on crystals and in solution (*19, 20*) have established the structures of isolated pyrimidine dimers and dimer analogs. On the basis of these studies, Broyde *et al.* (*21*) used energy-minimization techniques to construct a model of a single-stranded DNA fragment incorporating the crystal structure found for a thymine-dimer analog. However, this may not be an appropriate model for a DNA duplex containing a thymine dimer because the effects of the complementary strand are not taken into account. Rao *et al.* (*13*) have used internal constraints in conjunction with energy-minimization techniques to force the internal thymines of a DNA duplex into a conformation consistent with those observed for isolated thymine dimers. Because current procedures for macromolecular energy minimization are not efficient at detecting minima far removed from the starting structure, it was not surprising that their final model showed little overall distortion of the DNA double helix.

Table 2. Stepwise unwinding angles (degrees) for DNA cross-linked with psoralen and a thymine dimer. All values are relative to an energy-minimized B-DNA structure having the same sequence. Abbreviations for bases are as given in the text.

Base pair	Psoralen-DNA	Thymine dimer–DNA
C-1–G-20		
	−0.5	3.2
G-2–C-19		
	−3.1	−0.7
C-3–G-18		
	−4.6	−2.9
A-4–T-17*		
	−7.5	4.8
T-5–A-16		
	−58.5	−12.4
A-6–T-15†		
	−9.4	8.0
T-7–A-14‡		
	−0.5	−9.2
G-8–C-13		
	−3.9	−5.3
C-9–G-12		
	0.3	1.2
G-10–C-11		
Sum	−87.7	−19.7

*G-4–C-17 for thymine dimer–DNA. †T-6–A-15 for thymine dimer–DNA. ‡C-7–G-14 for thymine dimer–DNA.

We approached this problem in a manner analogous to our building of the model of DNA cross-linked by psoralen. We fitted two separate 3-base-pair helical segments onto a thymine dimer whose structure was determined crystallographically (*20*), in which the bases were kinked and unwound, and subsequently applied energy minimization to obtain reasonable stereochemistry. The initial minimization was carried out on a DNA fragment of 6 base pairs, which is long enough to accommodate all large local conformational changes due to DNA damage but short enough so that energy minimization could propagate these changes. Only after this hexamer had reached an energy minimum did we extend it to a decamer by adding dimers to both ends and continuing minimization. A detailed illustration of this model is shown in Fig. 3b and a space-filling model in Fig. 4b. A minimization in which the thymine dimer was constrained to its crystallographic structure was also carried out; the results were similar to those reported here.

Local deformations. There are numerous changes in the torsion angles of the DNA structure containing a thymine dimer compared to an energy-minimized B-DNA structure of the same sequence. The differences occur primarily at the central residues surrounding the dimer site in both strands. More conformational rearrangement has apparently occurred in the strand opposite the thymine dimer because the dimer bases opened at an angle to this strand. Notable conformational rearrangement is observed out to the first base pair from the dimer on the 5′ end and out to the second base pair from the dimer on the 3′ end. This is in agreement with NMR data that suggest greater distortion on the 3′ end of the dimer (*19*).

Many of the changes between the dimeric and nondimeric structures occur in the pseudorotation parameters of the sugars. Indeed, all regions of major structural changes in the dimeric complex relative to minimized B-DNA include at least one altered sugar. This further supports the idea, discussed earlier for the psoralen–cross-linked structure, that the sugar is a major source of conformational variability in DNA.

As with the psoralen–cross-linked DNA, the α, γ, and ζ dihedral angles in general show the most variability after the sugar. In addition, the glycosyl angles of the dimerized thymine nucleotides are altered from standard values. Specifically, the glycosyl torsion angle of the 5′ residue is increased (high *anti*) and that of the 3′ residue is decreased (low

anti) relative to energy-minimized B-DNA.

When we compare the torsion angles in our model in the region of the dimer with those obtained by Broyde *et al.* (*21*) for a single-stranded DNA, we observe most of the same conformational features. The similarity of these results is noteworthy considering the difference in methods used to calculate the two sets and suggests that this backbone conformation lies at an important minimum in energy space.

Overall helix deformations. There is a kink of approximately 30° in the helix incorporating a thymine dimer (Table 1 and Fig. 4b). As was observed for the psoralen–cross-linked DNA model, the DNA is bent into the major groove. The prediction of a substantial kink contrasts with the model of Rao *et al.* (*13*), in which there is little overall conformational change upon introduction of a thymine dimer in a DNA helix.

The turn angles at individual positions (Table 2) indicate that the unwinding caused by the dimer at the central base is largely compensated by overwinding at the adjacent bases. There is an unwinding of 9° to 10° at the second base from the dimer on its 3′ end but of only 3° to 6° at the 5′ end. This may be a sequence-specific effect (*22*) due to the sequence being asymmetric.

The kink angle, unwinding angle, and displacement (Table 1) are all considerably smaller for the thymine-dimer model than for the model of psoralen–cross-linked DNA. The smaller distortions are reflected in the less unfavorable total energy for the model containing the dimer.

Surface accessibility. We also calculated the surface accessibility of our model of DNA containing a thymine dimer to probes of various radii. In the strand containing the dimer there is a reduction in accessible surface area for the first thymine (in the 5′ direction) and for the guanosine immediately preceeding it, which is primarily due to decreases in exposure of the sugars and joining phosphate. There is little alteration of the surface area, relative to B-DNA, of the second thymine forming the dimer. In the strand opposite the dimer, there is an increase in accessible surface area for the two adenosines across from the dimer that is induced by the angle between their base-paired partners. In particular, the N-6 exocyclic amino groups of these adenine bases show increased accessibilities to probes of radii as large as 3.0 Å. The increased availability of the adenine exocyclic amino groups in our model is in good agreement with the enhanced reactivity of DNA with formaldehyde (*23*).

Discussion. Our models show that the introduction of a psoralen cross-link in DNA brings about large conformational changes in the DNA helix and that formation of a thymine dimer induces similar but less severe changes. The overall structural changes indicated by these models may be responsible in part for the harmful effects of these lesions in cells and at the same time may present recognition sites for repair enzymes.

In addition to the effects on cells that local distortions in DNA can induce (for example, by blockage of transcription and replication enzymes), our findings indicate that long-range as well as short-range effects may arise from kinking and displacement of the helix axis and unwinding of the duplex. Evidence that photodimer formation causes great alterations in the structure of DNA is offered by studies that have noted changes in the sedimentation coefficient (*24*), sensitivity of damaged regions to nucleases both before and shortly after repair (*25*), circular dichroism (*26*), sensitivity to chemical modification reagents (*23*), and thermal denaturation (*27*) of DNA upon introduction of such lesions.

At present, there is no experimental method that can directly verify the type and extent of structural distortion we have suggested. Measurements of the shifts in band pattern of supercoiled circular DNA due to formation of psoralen adducts (*28*) and thymine dimers (*29*) indicate topological unwinding angles of −28° and −14°, respectively. The physical implication of these results is ambiguous, however, because the calculated topological unwindings are due to a combination of actual duplex unwinding and negative supercoiling resulting from successive kinking of the DNA. Furthermore, in the case of psoralen, the measured topological unwinding arises from monoadducts as well as cross-links. Nevertheless, these results indicate that both thymine-dimer formation and psoralen cross-linking induce substantial topological unwinding in DNA. These results are consistent with our models, which indicate topological unwinding, but are inconsistent with the model of Rao *et al.* for thymine dimers (*13*), which indicates no topological unwinding.

The structures we have derived should help in understanding the consequences of pyrimidine dimerization and psoralen cross-linking in nucleic acids and provide a basis for future experimentation.

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