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Sequence Determinants for H1 Binding on *Escherichia coli lac* and *gal* Promoters†

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ABSTRACT: The H1 protein is a likely candidate for structuring DNA in the bacterial nucleoid. We have studied determinants leading to its binding to DNA (and in particular to *Escherichia coli lac* and *gal* promoters) in vitro through the pattern of attack of both DNaseI and the copper–*o*-phenanthroline complex [$(OP)_2Cu^+$]. The binding of H1 depends on the primary sequence of DNA. H1 also associates with recognition sites for specific proteins, in particular with the Pribnow box and the CRP binding site. Binding of H1 to the Pribnow box of the wild-type *lac* promoter does not change the pattern of nucleolytic digestion with $(OP)_2Cu^+$. In contrast, binding of H1 to the strong *lac* promoter mutants Ps and UV5 appears to change the conformational state of this DNA. Similar changes in accessibility of the minor groove surrounding the respective binding sites were observed for both H1–DNA and CRP–DNA complexes.

H1 is a low molecular weight protein (15 500) originally described by Jacquet et al. (1971). It was found to be associated with the nucleoid of *Escherichia coli* by several authors (Varshavsky et al., 1977; Bakaev, 1981). The gene for the protein H-NS, which is probably identical with H1 protein, has recently been cloned from several organisms (La Teana et al., 1989). A few years ago, we showed that this protein is able to form complexes with DNA in vitro and that, for different sizes and sequences of linear or circular DNA, in such a complex, its binding to DNA resulted in a tight compaction of the DNA accompanied by a very small topological change in the superhelicity (Spassky et al., 1984).

In this work, we study the binding of H1 protein to several known DNA sequences through the pattern of attack of two nucleases: DNaseI[1] and the artificial nuclease *o*-phenanthroline–cuprous complex [$(OP)_2Cu^+$]. The endonuclease DNaseI produces footprints from which the position of the bound H1 protein may be deduced with respect to the DNA sequence. Cleavage with $(OP)_2Cu^+$ yields information about the conformational state of the DNA. $(OP)_2Cu^+$ rapidly cleaves DNA through an oxidative pathway at physiological pH and temperature (Sigman et al., 1979). This reagent attacks B-DNA in the minor groove (Kuwabara et al., 1986), implying that a noncovalent intermediate forms in the minor groove. Thus, changes in the accessibility of the minor groove should be expected to have an effect on the observed reactivity of the reagent. This is precisely what is seen in non-B-DNA, e.g., Z- or A-DNA, where the minor groove has a very different conformation from that of the canonical B form; in this case, the $(OP)_2Cu^+$ nuclease does not cleave the DNA well (Pope & Sigman, 1984). The pattern of variation with $(OP)_2Cu^+$ is different from that observed with DNaseI. Whereas DNaseI has preferred sites of attack distributed along the length of the sequence, hyperreactive sites to $(OP)_2Cu^+$ attack are clustered in different regions, reflecting a sequence-dependent variation of minor-groove geometry (Kuwabara et al., 1986; Sigman, 1986).

We investigated H1 binding within the *lac* and *gal* control regions; in these regions binding sites for H1 generally overlap the specific DNA binding sites of CRP, RNA polymerase, and *lac* repressor.

In order to determine whether the positioning of H1 on DNA was only a function of the primary sequence or a consequence of monomer–monomer interactions, we compared the binding of H1 to the wild-type sequence and to the same sequence containing an insertion of two base pairs. We also investigated binding of H1 to the Pribnow box of the wild-type *lac* promoter and two mutants: Ps (C-T at position −9) and UV5 (A-T at position −8, and C-T at position −9). We find that H1 makes sequence-specific contacts and that the final

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[1] Abbreviations: DNaseI, deoxyribonuclease I; CRP, cAMP receptor protein (presence of cAMP bound to protein is implied); bp, base pair; $(OP)_2Cu^+$, 2:1 1,10-phenanthroline–cuprous ion complex.

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pattern of $(OP)_2Cu^+$ sensitivity depends on the primary DNA sequence.

DNaseI footprinting shows that two of the H1 binding sites coincide with the CRP binding site. This gives us the opportunity to compare the binding mode of these two proteins to DNA. CRP forms a very specific complex whereas H1 only exhibits mild sequence specificity. The molecular details of CRP binding to DNA are known. CRP belongs to a family of proteins possessing a helix–turn–helix motif that is involved in DNA recognition and binding within the major groove at specific sequences (Weber & Steitz, 1984; Pabo & Sauer, 1984). We will discuss the similarities and differences of H1 binding to the same DNA sequence.

Materials and Methods

DNA Fragments. DNA containing the lactose operon promoter region was isolated from a 203-bp *Eco*RI–*Eco*RI fragment from position −140 to position +63 (Ogata & Gilbert, 1977) cloned in pBR322. DNA containing the galactose operon promoter region was isolated from a 137-bp *Eco*RI–*Bst*EII fragment from plasmid pAA187 (Busby & Dreyfus, 1983). The fragment of 205 bp was derived from the 203-bp fragment by insertion of 2 bp at *Hpa*II position −18 by filling with the Klenow fragment and resulted in a 188-bp fragment after digestion by *Pvu*II.

^{32}P End Labeling of DNA. The 203- or the 205-bp *Eco*RI *lac* fragment was 5′ labeled with [γ-^{32}P]ATP and T4 polynucleotide kinase. The DNA was digested with *Pvu*II to give a 186-bp fragment uniquely labeled at the *Eco*RI extremity on the template strand. To obtain labeling on the nontemplate strand, the *lac* fragment was labeled at the 3′ end with [α-^{32}P]dATP and the Klenow fragment and also digested by *Pvu*II.

The 137-bp *gal* fragment was labeled at the *Bst*EII end with Klenow fragment and [α-^{32}P]dGTP on the noncoding strand and at the *Eco*RI end with Klenow fragment and [α-^{32}P]dATP on the coding strand.

Protein Purification. CRP was purified following the procedure of Takahashi et al. (1982). The H1 protein was isolated as described by Spassky et al. (1984).

Protection Experiments. End-labeled DNA (2 nM) was incubated for 5 min at 37 °C in the presence or absence of 100 nM CRP and 200 nM cAMP in standard buffer (final concentration 40 mM Tris-HCl, pH 8.0, 10 mM $MgCl_2$, 100 mM KCl, and 10% glycerol), at 0 or 3 μM H1 in the same buffer.

DNaseI Footprinting. DNaseI (0.075 μg/mL) was added to the reaction buffer. Digestion was terminated by the addition of a stop solution (final concentration 100 μg/mL tRNA, 0.3 M CH_3COONa, and 1 mM EDTA, pH 8) followed by phenol extraction, ethanol precipitation, and analysis on 8% polyacrylamide sequencing gels made and run according to Maxam and Gilbert (1980) and then autoradiographed. The gels were calibrated with G+A sequencing reactions performed on the same labeled fragment.

1,10-Phenanthroline–copper footprints were performed as described by Sigman et al. (1985) under the same conditioons as described above. After autoradiography, the relative amount of radioactivity in each band of the gel was measured by densitometry of the film, processing a digital image (recorded with a digitalizing camera) of the gel on a Numelec system.

Results

H1 Binding to lac and gal Promoter Fragments. (A) DNaseI Footprint of H1. DNaseI footprint experiments were carried out on the 186-bp fragment of DNA containing the wild-type *lac* promoter in the presence of H1. The digestion patterns are shown in Figures 1 and 3. In the range of sequences visible on the gels (+30 to −80), six regions were

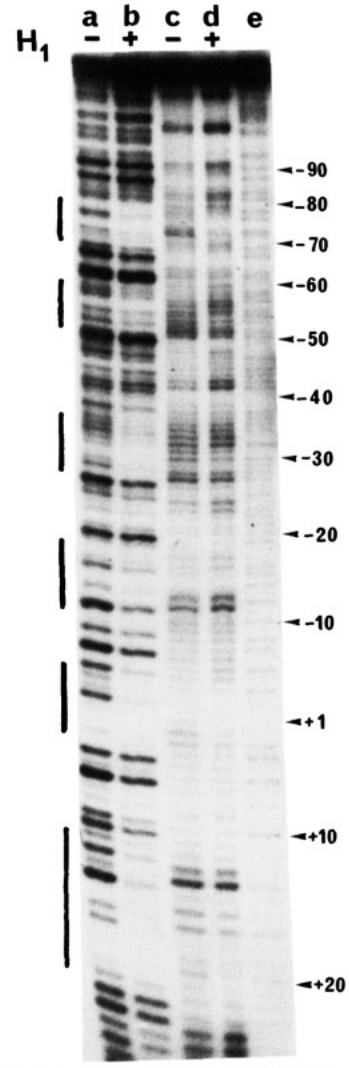

FIGURE 1: Analysis by DNaseI $(OP)_2Cu^+$ attacks of binding of H1 to the wild-type lactose 186-bp fragment. The *lac* fragment was labeled at the 5′ end on the template strand. Lanes a and b show the results of DNaseI attack and lanes c and d the effect of $(OP)_2Cu^+$ digestion on DNA alone (lanes a and c) or in the presence of H1 (lanes b and d). Lane e shows a G+A sequencing reaction on the fragment. The lines indicate the positions of the H1 binding sites.

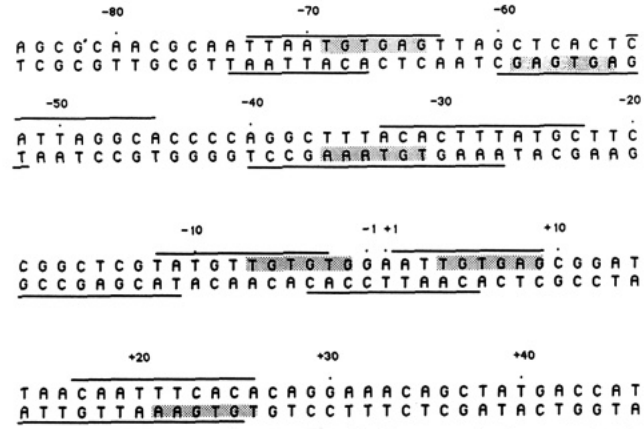

FIGURE 2: Diagram showing H1 binding on the lactose 186-bp fragment. The nucleotide sequence of the part of the fragment where H1 protein binds is given. Protected regions on each strand are underlined. Shaded areas correspond to the consensus 5′TNTNAN3′.

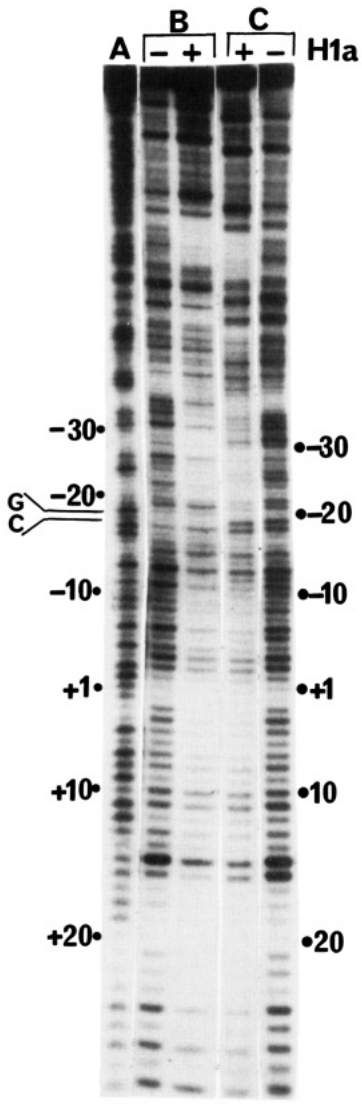

FIGURE 3: Comparison of DNaseI footprints on lactose fragments and lactose fragments containing the insertion of two base pairs. The fragments were labeled at the 3′ end of the nontemplate strand. Lane A is a sequence ladder of A+G of the lactose fragment carrying the GC insertion between positions −18 and −19. Lanes B show DNaseI attack on DNA alone (−) or on DNA in a complex (+) of H1 and the *lac* fragment with the insertion. Lanes C show DNaseI attack on *lac* fragment alone (−) or on *lac* fragment complexed with H1 (+).

protected against endonuclease digestion, located at +20, +3, −10, −35, −55, and −70 (Figure 2). It is possible that another binding site exists on the fragment outside the observed region. This result shows that H1 has no strong sequence specificity. However, the binding pattern is perfectly reproducible under the conditions used here, which are the same as those used when we observed a unique species on retardation gels (Spassky et al., 1984). Moreover, upon progressively increasing the protein concentration, we observed a gradual, simultaneous occupancy of the six sites (results not shown). This cooperativity of binding has already been observed and discussed in some detail (Spassky et al., 1984). Sites protected by H1 are situated at the CRP binding site (−55, −70), at the repressor binding site (+20), within the Pribnow box (−10), and in the −35 region, all of which are also binding sites for specific proteins. We wanted to know if H1 recognizes the primary sequence or if its positioning is dependent upon the positioning of the neighboring molecules along the fragment. H1 was bound under the same experimental conditions to the 188-bp fragment containing a GC insertion between bases −18 and −19. This insertion is outside a zone normally protected

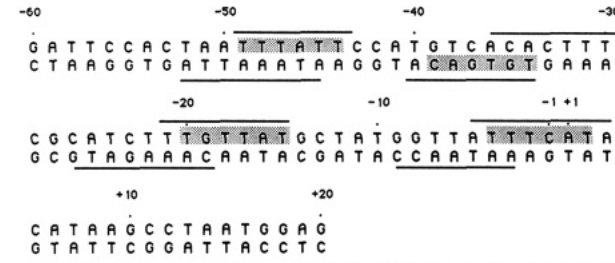

FIGURE 4: Summary of the effect of H1 binding on the galactose 137-bp fragment. The nucleotide sequence where H1 protein binds is given; protected regions on each strand are underlined. Shaded areas correspond to the consensus 5′TNTNAN3′.

against DNaseI digestion by H1 on the 186-bp fragment. Figure 3 displays the protection patterns afforded by H1 on the 186- and 188-bp fragments, respectively. It is clear that the pattern of digestion of the DNA alone is identical in both cases except within a 10-bp (−18 to −28) region containing the insertion. A comparison of the binding sites of H1 on each fragment shows that the same phosphodiester bonds are protected against DNaseI digestion. Indeed, the GC insertion shifts the regions protected against endonuclease digestion by two base pairs. In other words, H1 exhibits a preferred positioning that is independent of its distribution along the fragment but is dependent upon the DNA primary sequence.

We also investigated the effect of H1 on the digestion pattern by DNaseI of a 137-bp fragment carrying the wild-type *gal* promoter (results are summarized in Figure 4). Four clearly protected sites are observed around nucleotides −2, −20, −34, and −47 (nucleotides are numbered relative to the mRNA initiation site at the P1 promoter at position +1). Three of these sites also correspond to specific binding sites for CRP (−47) and RNA polymerase (−2 and −34).

(B) $(OP)_2Cu^+$ Footprint of H1 on the 186-bp lac Fragment. The 186-bp *lac* fragment carrying the control region of the lactose operon was digested by $(OP)_2Cu^+$ in the presence or absence of H1 (Figure 1). The reactivity of $(OP)_2Cu^+$ for naked DNA is not homogeneous. The regions of hyperreactivity correspond to the sites where H1 protein binds (compare lanes b and c of Figure 1). This might indicate that H1 recognizes a particular DNA structure rather than a specific sequence. In fact, cleavage of DNA by $(OP)_2Cu^+$ is sensitive to the DNA conformation in a predictable manner (unpublished results). The reactivity of $(OP)_2Cu^+$ for those sites changes when H1 is bound (compare lanes c and d in Figure 1). H1 binding does not protect the site from digestion by $(OP)_2Cu^+$, as observed for DNaseI digestion. Rather, it modifies the relative intensities of the bands within the binding site. These modifications of the $(OP)_2Cu^+$ pattern seen in the presence of H1 were further analyzed in the Pribnow box and in the CRP binding region.

Influence of H1 Binding on the DNA Conformation in the Pribnow Box. We examined the influence of H1 binding on the $(OP)_2Cu^+$ digestion pattern for three Pribnow box mutants. The DNaseI digestion pattern of the H1–DNA complexes is identical for all three DNA fragments used (results not shown). This demonstrates that the protein is positioned at corresponding positions on the three DNA fragments. As shown in Figure 1, the binding of H1 to the wild-type 186-bp fragment induces no observable difference in the $(OP)_2Cu^+$ digestion pattern of the Pribnow box region. It is worth noting that under these conditions H1 gives a DNaseI footprint (Figure 1). In contrast, an effect of H1 binding to the Pribnow box of the Ps mutant can be seen on both the template strand and the nontemplate strand (Figure 5B,D). For this mutant,

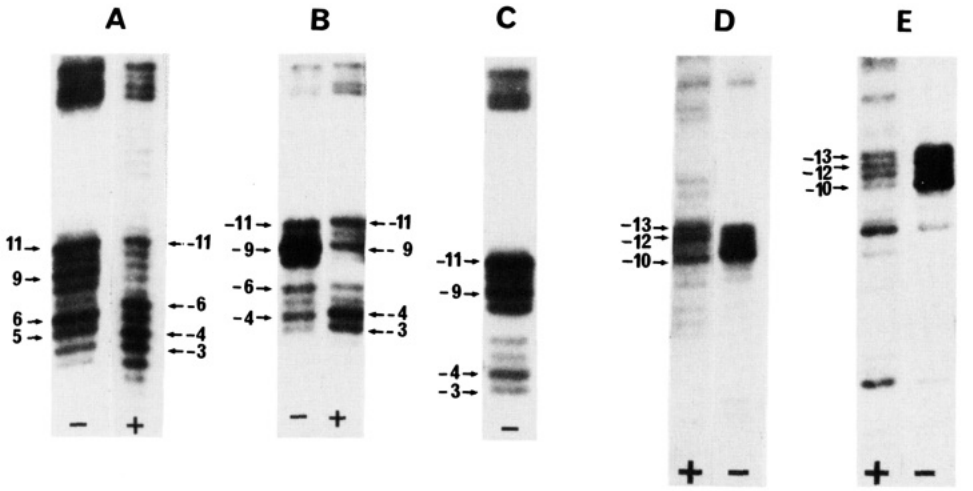

FIGURE 5: Pattern of the $(OP)_2Cu^+$ attack at the Pribnow box. UV5 (lanes A), Ps (lanes B), and wild-type (lanes C) lactose DNA fragments were labeled at the 3′ end on the nontemplate strand and digested by $(OP)_2Cu^+$ in the presence (+) or absence (−) of H1 protein. Lanes D and E show $(OP)_2Cu^+$ attack on the −10 region of Ps (C) and UV5 (D) on the template strand. Attack was carried out in the presence (+) or in the absence (−) of H1 protein.

the binding of H1 induced a strong decrease in the reactivity of the Pribnow box as well as a change in the relative intensity of the reactive bands: (i) On the template strand, the band intensity at −10 decreased considerably with respect to the bands at −13 and −12 (Figure 5D). The same observation can be made for the UV5 promoter (Figure 5E). (ii) On the nontemplate strand, there was a complete change in pattern from −3 to −9, for both UV5 (Figure 5A) and Ps (Figure 5B) promoters. H1 binding results in both cases in an inhibition of the nuclease attack from −5 to −11 and in an enhancement for positions −4 and −3. We include for comparison the pattern of reactivity of the Pribnow box of the wild-type promoter in the absence of H1 (Figure 5C).

Comparison between H1 and CRP Complex Binding to the CRP Binding Site. (A) DNaseI Footprinting. Figure 6 shows a DNaseI footprint of either the CRP–DNA complex or the H1–DNA complex at the CRP site. On the template strand (Figure 6A), we observe that the extent of the protein-protected region is exactly the same in both cases. However, the detailed pattern of protection is different: positions −59, −60, and −69 are accessible to DNaseI digestion in the presence of CRP but not H1. On the other hand, when H1 is bound, positions −62, −63, and −67 remain accessible. On the nontemplate strand, in the presence of CRP positions −66, −67, −55, and −56 are accessible to DNaseI attack (Figure 6B). In contrast, the −55 to −63 region remains accessible to the nuclease when H1 is bound. It thus appears that H1 allows DNaseI greater access to the minor groove around the center of symmetry of the CRP binding site (Figure 7).

(B) $(OP)_2Cu^+$ Footprinting. We carried out $(OP)_2Cu^+$ attacks on H1- or CRP-bound fragments. Densitometric traces of gels resulting from these experiments are shown in Figure 8. The CRP-protected region (−75 to −48) is smaller than that seen for DNaseI digestion, and it is symmetric with respect to the dyad axis of the CRP binding site. The extent of this protected region was in good agreement with the size of the protected site as probed by hydroxyl radical footprinting with iron(II)–EDTA complex (Shanblatt & Revzin, 1987). On the template strand, the protection in the region −48 to −56 is relatively weak, and the overall profile is modified in comparison with that of free DNA. In particular, positions −51 and −52, which are hyperreactive in free DNA, are no longer very reactive in the presence of CRP (Figure 8A). Both halves of the CRP dimer binding site coincide with a binding site for H1. For one half of the CRP dimer binding site (region

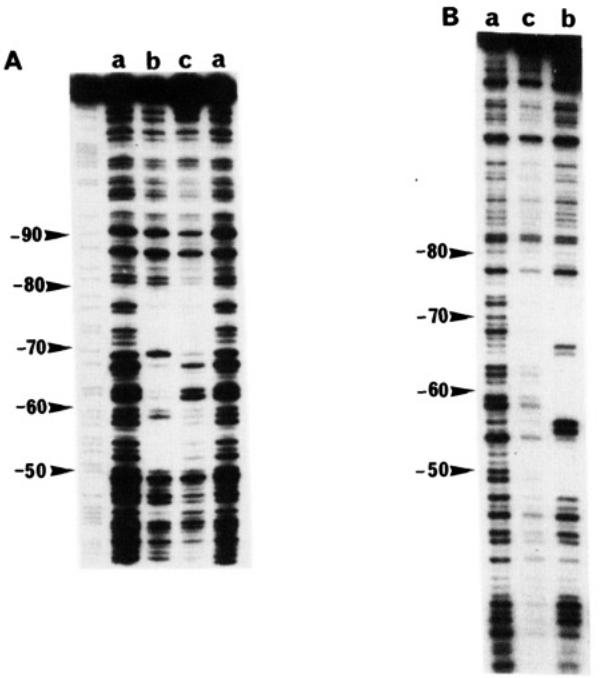

FIGURE 6: Binding of H1 and CRP proteins at the CRP binding site. DNaseI footprints of the CRP binding site on the lactose fragment alone (a) or in the presence of CRP (b) or H1 (c). (A) The wild-type lactose fragment was labeled at the 5′ end of the template stand. The far-left lane shows a G+A sequence ladder for this strand. (B) The wild-type lactose fragment was labeled at the 3′ end of the nontemplate strand.

−48 to −56), there is a striking similarity in the digestion pattern of the DNA when either CRP or H1 is present. The corresponding region on the other side of the dyad axis however shows substantial differences between the influence of the two proteins on the protection pattern. This is not surprising since there are even differences in the protection pattern between the two symmetry-related CRP half-sites.

Discussion

Distribution of Binding Sites. DNaseI digestion showed six sites of protection on the 186-bp fragment containing the lactose operon regulator site. The sites are more or less regularly spaced along the fragment. Binding titrations with H1 show that all six sites are occupied simultaneously over a narrow range of concentration of H1 (Spassky et al., 1984).

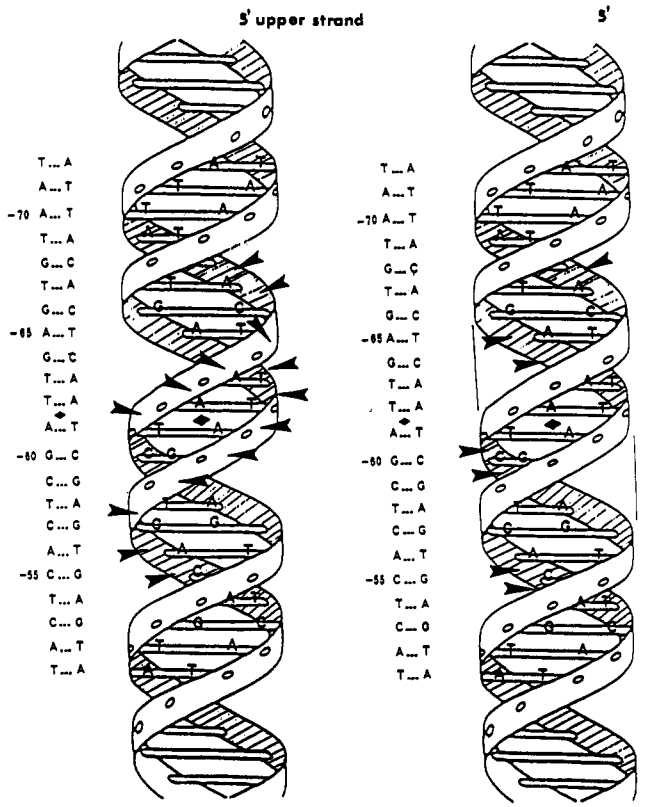

FIGURE 7: Scheme illustrating DNaseI attack of the CRP site in the presence of protein on a double helix. (Left) The arrowheads indicate the phosphate bonds accessible to DNaseI when H1 is present. The diamond shows the center of the pseudosymmetry of the CRP site. (Right) The arrowheads indicate the phosphate bonds accessible to DNaseI when CRP is present. The narrow lines show the major groove where the F-helix of CRP binds.

This result may imply that the protein binds cooperatively to the DNA. Cooperativity might be mediated by the compaction of the DNA, rather than protein–protein contacts. Since the spacing is not absolutely constant, there has to be considerable flexibility in the protein–protein contacts, if cooperativity is mediated by such contacts. The variation in the spacing could also reflect some sequence specificity of binding. To test this hypothesis, we repeated the experiment with a DNA fragment carrying a 2-bp insertion between the third and fourth binding sites of H1. The protected regions stayed the same with respect to the primary sequence, indicating that H1 positioning depends on the primary sequence or on particular DNA conformations resulting from the sequence.

Mode of Binding. $(OP)_2Cu^+$, which reacts with DNA in the minor groove, was used to monitor the changes in DNA structure upon binding of H1. This artificial nuclease has been shown to be very sensitive to the local geometry of DNA (Sigman, 1986). Contrary to the strong protection against $(OP)_2Cu^+$ digestion by netropsin, a well-studied minor-groove binder (Kuwabara et al., 1986), there is only little protection of the minor groove in the complexes with CRP or H1. It is thought that CRP binds in the major groove of DNA, and by analogy, we suggest that H1 is a major-groove binder. The conformation and sequence of DNA can be different at the various binding sites of H1. One might therefore expect that H1 influences the conformation of the DNA differently at different binding sites. To investigate this possibility, we monitored the changes in DNA structure at the wild-type and two mutant sequences of the same binding site.

Pribnow Box. As mentioned above, the Pribnow box of the *lac* operon is cleaved differently by $(OP)_2Cu^+$ as a function of the mutant studied. Extensive studies carried out on *gal* promoters (Spassky et al., 1988) led to the conclusion that all of these promoters possess a symmetric reactivity with regard to the minor groove: at bases −12 and −13 on the template strand and at bases −10 and −11 on the nontemplate strand. The same reactivity pattern is observed for the wild-type *lac* promoter. The Ps and UV5 mutations, with base-pair substitutions at position −9 and at positions −9 and −8, respectively, possess additional hyperreactive sites. Indeed, in the case of strong promoters an additional symmetrical reactivity is observed (Spassky et al., 1988). In the case of the strong Ps and UV5 promoters this new symmetrical reactive site is at positions −10 and −11 (template strand) and at positions −8 and −9 (nontemplate strand).

Binding of H1 does not have any effect on the conformational state of the wild-type promoter Pribnow box. The DNaseI footprint proves the presence of the protein. The local DNA conformation is different at the mutant promoters UV5 and Ps, resulting in different $(OP)_2Cu^+$ sensitivity of the naked DNA. This $(OP)_2Cu^+$ digestion pattern is further modified upon binding of H1, showing that H1 alters the DNA conformation at these two promoter up mutations. This is consistent with previous results, which showed that the presence of H1 slows down the initiation rate of transcription at the strong UV5 promoter. This effect of H1 is not due to a change in the positioning of the polymerase but rather to a decrease in the rate of isomerization of the closed complex toward the open complex (Spassky et al., 1984). We have previously shown that the $(OP)_2Cu^+$ reactivity pattern of the −10 region correlates with the rate of open complex formation of RNA polymerase. Our results suggest that the H1 protein slows down the rate of open complex formation at these strong promoters by changing the conformation of their −10 region.

CRP Site. The DNaseI attack showed that H1 occupies the same site on the DNA as does the CRP complex. The binding of the CRP dimer has been extensively studied: this protein is localized in the major groove of DNA. Its carboxyl-terminal fragment contains an α-helix–turn–α-helix secondary structure; the F-helix of each CRP monomer interacts with two consecutive major grooves of DNA (Weber & Steitz, 1984). Additional interactions result in bending of the DNA molecule (Wu & Crothers, 1984; Kolb et al., 1983; Kotlarz et al., 1986).

Upon DNaseI attack on the CRP–DNA complex a protection of around 30 base pairs is observed, although several bases within this region remain accessible to DNaseI. All of these bases are situated on the DNA surface opposite to that occupied by the CRP protein. However, the minor groove at the dyad axis is totally protected. In contrast, when H1 is bound to the same site, the whole of this minor groove is accessible to DNaseI.

The CRP binding site contains a consensus binding domain consisting of two symmetrically related 5-bp segments at distances of 4–8 bp from the dyad axis. In addition, base pairs 12–14 nucleotides distant from the dyad axis (−52 to −54 and −73 to −75) contribute significantly to the binding interaction; these regions were called distal binding domains by Liu-Johnson et al. (1986). Interactions in these distal domains are electrostatic, nonspecific, and therefore primarily DNA structure dependent (Gartenberg et al., 1988). The weak protection that we observed in the downstream distal domain was not surprising, as it is known that the downstream half of the dyad is weaker in CRP binding than the upstream half (Liu-Johnson et al., 1986); $(OP)_2Cu^+$, which is a small molecule, can have access to the DNA. It is interesting that

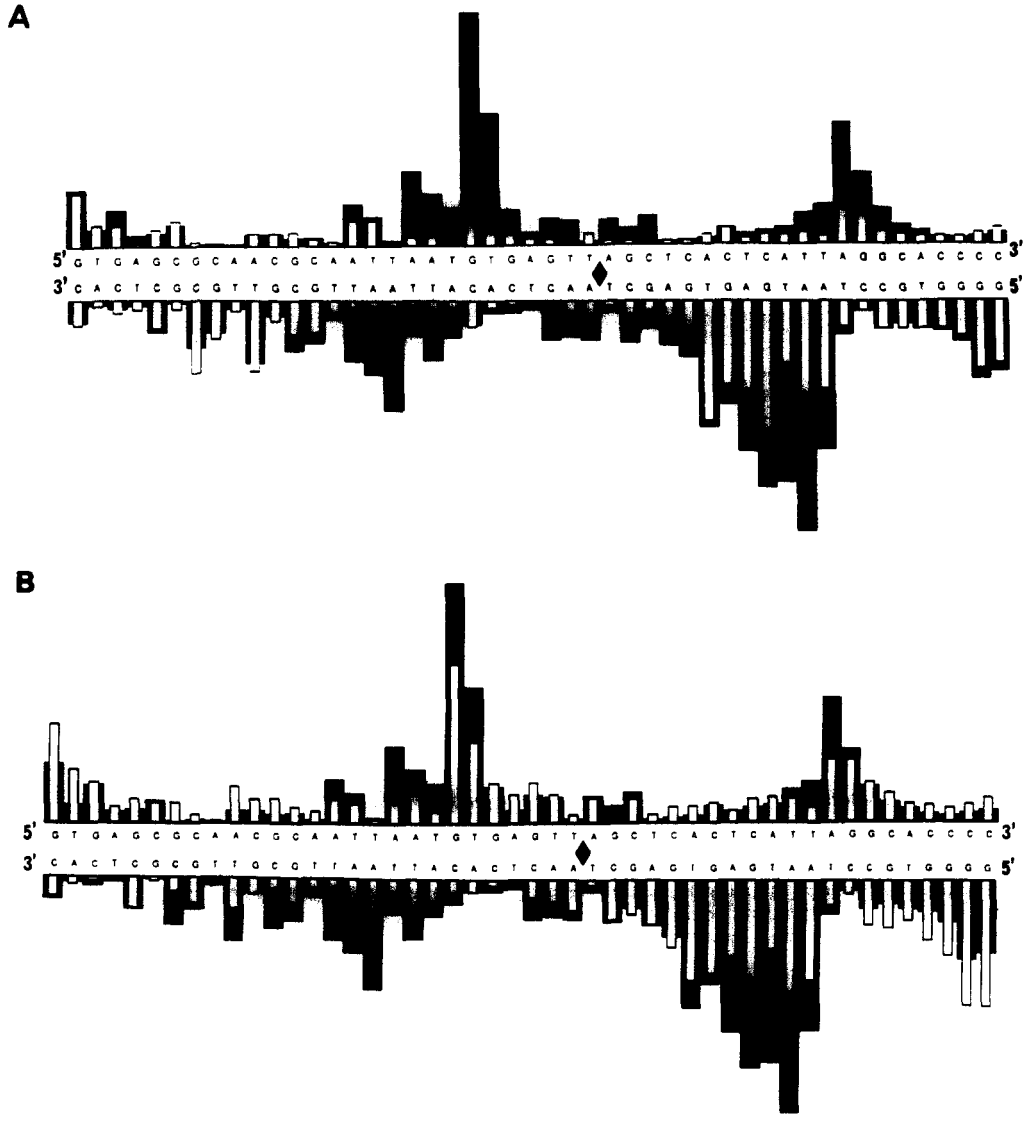

FIGURE 8: Profile of the nucleolytic attack by $(OP)_2Cu^+$ in the absence (black bars) and presence (white bars) of CRP (A) or H1 (B) on the lactose CRP binding site. The graph represents the sequence starting at −88 and extending to −41.

the pattern is modified at positions 10 and 11 from the dyad axis (−51 and −52 in our numbering). Gartenberg et al. (1988) showed by comparison with sequences implicated in "DNA bendability" around nucleosomes that the bases at these positions are involved in the bending of the DNA in the complex. It is likely that the bend causes a roll into the minor groove. In this case it is not surprising that the $(OP)_2Cu^+$ pattern is modified. H1 also modifies the pattern in the whole region from −48 to −56. The cleavage pattern in this region resembles more closely that obtained in the presence of CRP than that of DNA alone, suggesting similar DNA structure in both cases. H1 protein, which strongly condenses DNA, may use intrinsic properties of DNA to make a bend at this locus.

The sequences of the H1 binding sites on the *lac* and *gal* fragments generally match the general consensus sequence TNTNAN postulated for DNA binding to proteins that possess a helix–turn–helix structure (Ebright, 1985). The similarity in the digestion pattern between −48 and −56 in the presence of either CRP or H1 suggests that the two proteins recognize a similar DNA structure in this region. The differences in the other region where binding sites for the two proteins coincide (−67 to −75) however prove that the mode of recognition is not exactly the same for the two proteins. The positioning of H1 on this sequence may be drastically different from that of the sequence-specific binding protein, CRP. H1 thus provides a good model system for studying nonspecific protein–DNA interactions. An attractive idea is that the initial recognition of a site on a DNA sequence may involve a minimum set of information embodied in the DNA primary sequence and that subsequent to this "prerecognition" more specific interactions may take place depending upon the availability of favorable contacts on the protein. Up to now, there have not been enough experimental data to permit detailed discussion of this hypothesis.

Only a few proteins have been cocrystallized with DNA. Some of them contain α-helix–turn–α-helix motifs: 434 Cro (Wolberger et al., 1988), 434 repressor (Aggarwal et al., 1988), λ repressor (Jordan & Pabo, 1988), and trp repressor (Otwinowski et al., 1988). It appears that 434 Cro and 434 repressor, although recognizing the same sequence, utilize different contacts with DNA. Moreover, each of them modifies differently the B-DNA structure of the operator [for a recent review, see Brennan and Matthews (1989)]. Since H1 exhibits a very mild sequence specificity, this provides the opportunity to study its interaction with different binding sites. It will be interesting to see how the conformation of different sequences is affected by the same protein. An indication of this has been given in this work, in which we showed that the degree of distortion of the Pribnow box depends on the par-

ticular DNA sequence. It would be interesting to monitor the structural deformations of DNA upon H1 binding to recognition sites for other specific proteins such as *lac* repressor etc.

H1 might be a protein whose function is to condense DNA and for this purpose requires a low binding specificity but may require sequence-dependent alterations in the DNA structure, as can be seen in the case of the nucleosome (Drew & Calladine, 1987). H1 is strongly expressed at the end of the exponential growth phase and could have the metabolic effect of shutting down the expression of certain genes by deforming the DNA, as we have observed for the Pribnow box, and by occupying a certain type of binding sites with a weak specificity but a strong affinity.

Added in Proof

Recent results from two other laboratories have shown that H1 appears now to play a major role in the global regulation of *E. coli*.

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