Transmission of Long-range Effects in DNA

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There are many possible physical mechanisms for protein-mediated regulation of DNA gene activity. In the simplest models, DNA serves an essentially inert template role, providing, through its sequence, binding sites for regulatory proteins that interact to produce positive or negative regulation. For example, favorable contacts between RNA polymerase and gene-activating proteins could produce positive regulation, whereas steric exclusion of polymerase by a bound repressor yields negative control.

There is, however, no a priori reason to exclude a more active role for DNA in the regulation process. For example, DNA conformation could be altered by interaction with a regulatory molecule, and the effect could be transmitted along the DNA to a second site. In this way the interaction of a protein such as RNA polymerase at one site could be influenced by a regulatory protein molecule bound at another site without any direct protein-protein interaction.

This general principle can be illustrated by the proposal of Dickson et al. (1975) concerning the mechanism by which the cAMP-binding gene-activating protein CAP (or CRP) regulates promoter activity: "Binding of the CAP protein to its interaction site could destabilize the G•C rich region next to it. This would lower the transition temperature of the [RNA polymerase] entry site and allow formation of the open complex. In this model the G•C rich region is a transducer, transmitting the effect of CAP binding to the entry site some 14 base pairs away." The molecular mechanism implied in this hypothesis was based on the observations by Wells and his colleagues (Burd et al. 1975 a,b; Wartell and Burd 1976) that the stability of an A•T-rich helical region is influenced by an adjacent G•C-rich sequence, a phenomenon they refer to as telestability. The transmission of steric effects along DNA is also consistent with the more recent proposal by McKay and Steitz (1981) that CAP binding switches DNA to a left-handed conformation.

Our first purpose in this paper is to set out general classes of long-range transduction in DNA. We note at the start, however, that our focus on long-range effects is not intended to diminish the importance of possible direct protein-protein interactions in gene regulatory systems. Subsequently, we examine recent equilibrium and kinetic results on the interaction of CAP protein with *Escherichia coli lac* promoter DNA fragments from the perspective of their implications for long-range effects in DNA.

Mechanisms of Long-range Transduction

Torsional stress. The best-established mechanism for long-range transmission in DNA is through the torsional stress that can be generated, for example, in closed circular DNA molecules. The influence is long range because the site of stress generation may be widely separated from the site of primary effect. It has been known for more than a decade that superhelical DNA molecules contain sites of special sensitivity to nuclease cleavage or chemical attack (Dean and Lebowitz 1971; Beard et al. 1973; Beerman and Lebowitz 1973; Kato et al. 1973; Chen et al. 1976.) Under appropriate conditions the special sites occur at inverted repeat sequences (Lilly 1980), which allow formation of cruciform structures of the type first suggested by Platt (1955) and amplified by Gierer (1966) and proposed subsequently as a possible explanation for the sensitive sites in superhelical DNAs (Beard et al. 1973; Woodsworth-Gutai and Lebowitz 1976).

Because naturally occurring superhelical DNAs contain a deficiency of right-handed double-helical turns, the torsional and bending stress in the molecule can be relieved by local unwinding or melting of the double helix (Wang 1974). This process is strongly favored if the melted region contains an inverted repeat, so that each single strand can form a hairpin helix. Theoretical analysis of the problem has been reported by Hsieh and Wang (1975), Benham (1979, 1981), Anshelevich et al. (1979), and Vologodskii et al. (1979). Another mechanism to take up negative superhelical turns and thereby relieve torsional stress is to switch a segment of the molecule to the left-handed Z form (Panayotatos and Wells 1981; Wells et al.; J.C. Wang et al.; both this volume). Clearly, the conformation of DNA regions susceptible to melting, cruciform formation, or other conformational changes can be strongly influenced by torsional stress introduced into the molecule at a distant point.

The possible importance of torsional stress is not restricted to closed circular molecules. For example, Stefano and Gralla (1982) proposed that the angular orientation between separate RNA polymerase interaction sites on a promoter could influence the torsional stress exerted by the bound polymerase on the DNA sequence between the contact points. It has also been proposed that the nucleosome unfolding induced by intercalative drug binding is due to the torsional stress of helix unwinding (Wu et al. 1980; J.B. Chaires et al., in prep.).

Bending stress. Nucleosomes provide a classic example of the ability of DNA molecules to be bent by a protein core. The compact complex of DNA with gyrase (Klevan and Wang 1980) indicates that this phenomenon is not restricted to eukaryotes. DNA conformation is necessarily altered in the region of bending, which need not be the same as the region that contacts the protein. Bending could, for example, enhance melting of DNA at the RNA-polymerase-binding site, at some distance from the points of contact with the bending protein.

Packing forces. Although not of any obvious relevance in vivo, the influence of packing forces on DNA conformation provides an experimental example of long-range conformational effects. Both topoisomerase assay (Wang 1979) and nuclease digestion of DNA adsorbed on a solid surface (Rhodes and Klug 1980) demonstrate that monomeric DNA is characterized by 10.5–10.6 bp/turn of the double helix. In contrast, Zimmerman and Pfeiffer (1979) reaffirmed the 10.0-bp/turn characteristic of DNA fibers, even under conditions of high humidity. In addition, Mandelkern et al. (1981) showed that aggregation of rodlike DNA fragments into bundles yields dichroism properties consistent with expectation based on fiber diffraction studies, whereas the UV dichroism of monomeric DNA fragments is clearly smaller than expected (Hogan et al. 1978). This result implies tilting of the base UV transition moments away from the direction perpendicular to the helix axis in monomeric DNA, either because of an altered conformation or because of substantial internal motion. Packing the DNA molecules into fibers or bundles could alter conformation or damp internal motion or both.

Phasing effects. Phase relationships within the base sequence provide a mechanism by which local sequence changes can have long-range effects. Trifonov and Sussman (1980) proposed that DNA bending in nucleosomes is affected by phased preferential placement of "wedge" sequences such as ApA every turn of the helix. Periodicities in base sequence have been observed by Marini et al. (this volume) in a kinetoplast DNA fragment displaying anomalous electrophoretic and hydrodynamic properties. Deletion and insertion mutations can interfere with the phasing in such systems, and thereby produce an apparent long-range influence. Analogous effects can result from phasing of binding sites, especially for proteins such as CAP, which are capable of cooperative binding.

Electrostatic end effect. This is, at present, only a hypothetical phenomenon, but potentially of importance in interpreting binding and other experiments on DNA fragments. Electrostatic forces are intrinsically long range; the high charge of DNA molecules leads to association or "condensation" of counterions on the helix, thus reducing its linear charge density below a critical value (Manning 1978). Release of these condensed counterions upon protein binding provides an important entropic component to the binding free energy (Record et al. 1978). At or near the ends of DNA chains, one expects less counterion condensation and also less potential counterion release upon protein binding. Both DNA conformation and protein-binding strength could be affected by this effect, generated in essence by the absence of the normal continuation of the DNA molecule.

"Incompatible" helix structures. This is the mechanism likely to be responsible if there is transmission of conformational effects along the DNA helix without torsional or bending stress. Suppose the helix can exist in two states, i.e., helix and coil or B and A, that are nearly equal in free energy. If the boundaries between the two states are of high free energy, intermediates in which the two structures intermix will be avoided and there will be a sharp transition from one state to another. Examples include the well-known phenomenon of cooperative DNA melting (Crothers 1969), which is the primary, but not sole, cause of the telestability phenomenon described by Wells and his colleagues (Burd et al. 1975a,b; Wartell 1976). The cooperative character of the switch of DNA from B to Z form (Pohl and Jovin 1972; Pohl, this volume) or from B to A form (Ivanov et al. 1974 and this volume) implies a high free energy at the boundary between B and A or Z helices. We call such structures incompatible.

If a helix has two incompatible structures of nearly the same free energy, fixing it at one point in a particular state will propagate that structure over a distance because of the tendency to avoid boundaries. It is clear that helix melting, or the switch from B to A or Z can produce this phenomenon. Less clear, but of fundamental importance, is the extent to which structures within the general B family can be incompatible.

Incompatible structures induced by ligand binding. This is a special instance of the previous case in which binding of a ligand at one point on the DNA helix induces a switch to another form incompatible with the original helix. Assuming that boundaries are of high free energy, the altered structure will tend to propagate into adjacent regions, affecting the properties of other sites. If there are additional ligand-binding sites, the bound ligands will tend to cluster, since the altered helix must have increased affinity for the ligand. A consequence, sometimes the only readily measurable one, is cooperative binding of the ligand.

A well-documented case that seems to fit this pattern is the cooperative binding of Ag^{+} ion by DNA (Daune et al. 1966), with only modest change in the helix structural parameters such as length, base pairs per turn, and transition moment orientation (Dattagupta et al. 1981). Other phenomena that fit this interpretation include the cooperative binding of ethidium in switching DNA from Z to B form (Pohl et al. 1972) and the cooperative binding of distamycin and netropsin by certain DNAs (Hogan et al. 1979). Sadler et al. (1980) proposed that the inability of four tandem *lac* operators to bind tightly to more than one *lac* repressor at a time is a consequence of a conformational change that is induced by the first

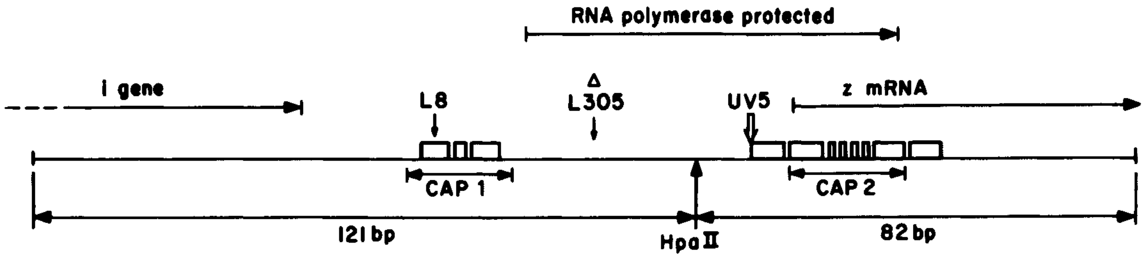

Figure 1. Schematic diagram of the 203-bp *lac* operator fragment used for studies of CAP and repressor binding. Rectangles indicate regions of twofold symmetry in the CAP-1 and CAP-2 binding sites. CAP 2 is coincident with the operator site. L8, L305, and UV5 denote mutational changes at the indicated sites.

repressor bound and propagated along the helix to prevent further binding. Another example of potential long-range effects is provided by the observation of Chan et al. (1977) that a single-strand nick about 100 bp away from the *lac* operator site reduces specific repressor binding to the operator, as judged from the amount of protein that dissociates at the rate characteristic of the tight complex.

Temporal coupling. Distant DNA sites can also appear functionally coupled because of events that occur in a definite time sequence. A simple example is provided by the influence of DNA promoter sites on the expression of adjacent genes. More generally, we can imagine two different physical mechanisms for temporal coupling; in both of these the protein binds initially to a DNA site distant from its eventual site of action. Following initial binding, the protein could move to its functional site either by processive translocation along the DNA (sliding) or by direct transfer from one binding site to another. This latter process is made possible by the bending of DNA molecules, enabling segments separated by thousands of base pairs in the linear sequence to come into close contact. As in the case of polymerase entry at the promoter, the time sequence of sliding or direct-transfer events may be obligatory for maximal regulatory effectiveness.

Evidence for Long-range Effects in the CAP-DNA Interaction

Electrophoretic evidence. Figure 1 shows a diagram of the 203-bp *lac* promoter fragment used for these studies (M. Fried and D.M. Crothers, in prep.). In addition to the genetically defined CAP-binding site (CAP 1), there is a second site (CAP 2), identified by Schmitz (1981) using the footprinting assay. We have also studied the L305 mutant, which differs from wild type by a single deletion at position -37, and the L8-UV5 triple mutant, in which G·C at position -66 (within the CAP-1 site) becomes A·T, and the base pairs at positions -8 and -9 are also A·T.

Addition of CAP protein to wild-type and L8-UV5 mutant fragments, and analysis of the mixture by gel electrophoresis in the manner described by Fried and Crothers (1981), yields the pattern shown in Figure 2. A double-label experiment using reductively methylated CAP demonstrated that bands h and m (Fig. 2) contain one CAP dimer per DNA fragment, whereas band l contains two dimers per DNA fragment (M. Fried and D.M. Crothers, in prep.). Figure 3 shows the pattern obtained with the L305 mutant fragment. Bands l and m (Fig. 3) correspond in mobility to l and m in Figure 2, but band a moves more slowly than band h. Figure 4 shows the result of cleaving the wild-type and L8-UV5

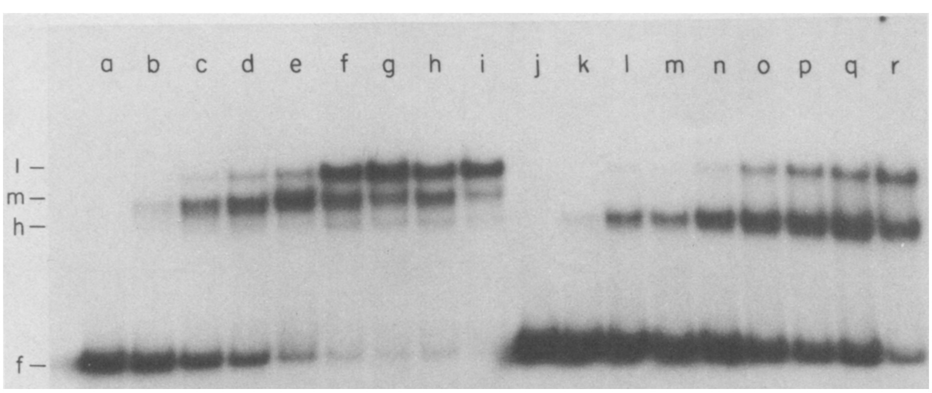

Figure 2. Titration of the 203-bp wild-type (*a–i*) and L8-UV5 (*j–r*) fragments with CAP. Binding buffer consisted of 10 mM Tris (pH 7.4 at 21°C), 50 mM KCl, 1 mM EDTA, 0.1 mg/ml of bovine serum albumin (BSA), and 10 μM cAMP. CAP:DNA ratios for lanes *a–i* are 0, 0.69, 1.38, 2.19, 2.92, 3.65, 4.38, 5.11, and 6.57. CAP:DNA ratios for lanes *j–r* are 0, 0.58, 1.15, 1.73, 2.31, 2.88, 3.46, 4.04, and 5.19. Equilibration was carried out for 30 min at 21°C. Polyacrylamide gel was run in 10 mM Tris (pH 7.4 at 21°C), 1 mM EDTA, and 10 μM cAMP at room temperature.

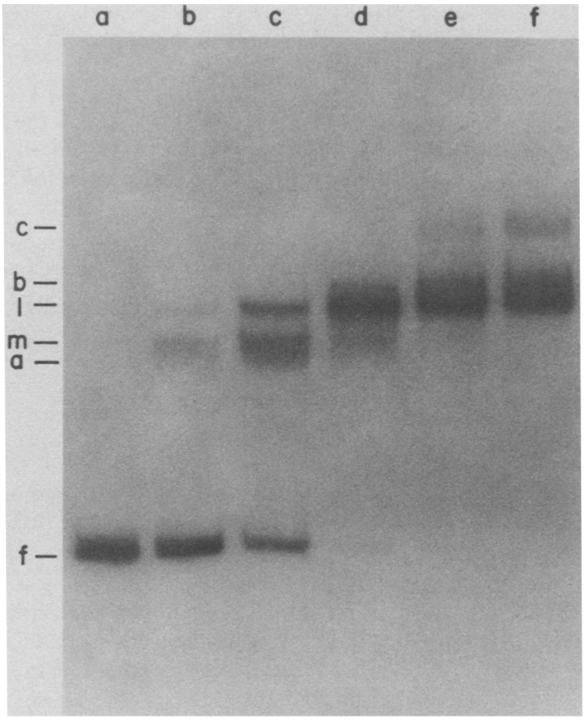

Figure 3. Titration of the 202-bp L305 promoter-operator fragment with CAP. CAP:DNA ratios for lanes *a–f* are 0., 0.925, 2.77, 4.62, 6.47, and 8.32. See Fig. 2 for binding and gel electrophoresis conditions.

fragments with *Hpa*II. Each subfragment now contains only a single CAP-binding site, and there are no anomalies in the comparison of gel mobilities between wild-type and mutant fragments.

We interpret the results in Figures 2 and 3 in the following way: CAP binding to the wild-type CAP-1 site produces band m, whereas binding to the wild-type CAP-2 site yields band h. In contrast, CAP binding to either L8-UV5 site gives band h. Thus, band m contains a 1:1 complex that migrates anomalously on the gel. Band l contains CAP bound at both sites. In L305, band a reflects binding to the CAP-2 site, but the gel mobility is altered by the deletion at position −31, well outside either CAP site. *Hpa*II cleavage at position −20 removes the electrophoretic anomalies, and the system reverts to the behavior found for *lac* repressor, for which we found a regular progression of band mobilities depending only on the protein:DNA stoichiometry of the band (Fried and Crothers 1981).

We do not know the specific origin of these gel electrophoretic anomalies. However, it is difficult to escape the general implication that the mobility is affected by factors outside the immediate protein-DNA contact region. For example, the mobility difference between wild-type (band m) and L8-UV5 (band h) complexes disappears when the DNA is cleaved about 45 bp away from the center of the CAP-1 site. Also, the L305 deletion at position −37 perceptibly alters the mobility of band h, changing it to position a. Assuming that constrasting mobilities of gel bands of identical composition reflect structural differences, we conclude that CAP-DNA complex conformation is affected by DNA distal to the CAP-binding site.

Evidence from binding affinity. By measuring the relative intensities of complex and free-DNA gel bands at varying total concentration, we have determined the equilibrium binding affinities of CAP 1 and CAP 2 in wild-type and L8-UV5 mutants, and in their *Hpa*II fragments (M. Fried and D.M. Crothers, in prep.), with the results collected in Table 1. A striking feature of the observations is the sharp decrease in binding affinity in the *Hpa*II subfragments, compared with that of the intact 203-bp fragment. Again, we cannot be sure of the source of this effect, but it is clear that the binding affinity of the CAP-DNA interaction is influenced by DNA distal to the binding site. A control experiment on *lac* repressor interaction with the 203-bp fragment and its *Hpa*II subfragments showed no appreciable affinity change on cleavage, from which we conclude that it is unlikely that the effect seen for CAP is due to the general electrostatic end effect described earlier.

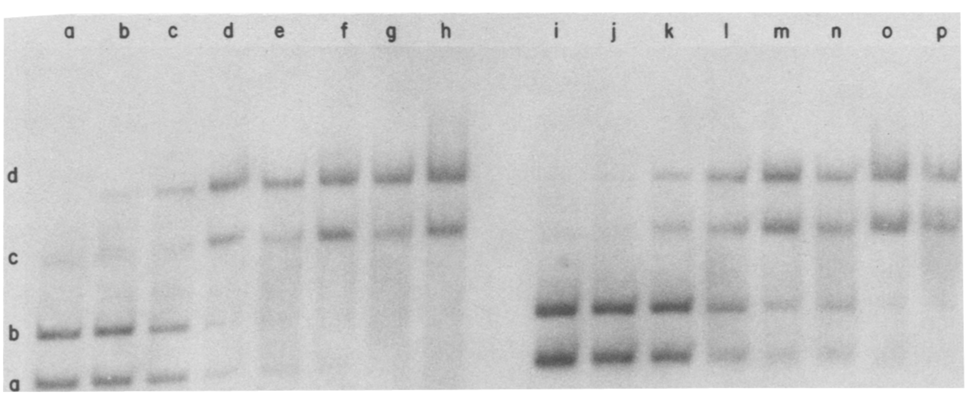

Figure 4. Binding of CAP to wild-type (lanes *a–h*) and L8-UV5 (lanes *i–p*) *Hpa*III fragments. (*a*) 82-bp free DNA; (*b*) 121-bp free DNA; (*c*) 82-bp DNA-CAP complex; (*d*) 121-bp DNA-CAP complex. Input CAP:121-bp fragment molar ratios for lanes *a–h* are 0, 0.51, 1.02, 2.04, 3.06, 4.09, 5.11, and 7.15 and those for lanes *i–p* are 0, 0.49, 0.98, 1.96, 2.94, 3.92, 4.90, and 6.86. See Fig. 2 for binding and electrophoresis conditions.

Table 1. Relative Binding Constants of CAP to CAP Sites 1 and 2 in Wild-type and L8-UV5 Fragments and Their *Hpa*II Subfragments

		1 2	$K = 1 \times 10^{11}$	1 2
○	+	———	⇌	⊖——
			$K/26$	
○	+	———	⇌	——⊖
			$K/14$	
○	+	⊖——	⇌	⊖—⊖
			$K/10$	
○	+	——— L8	⇌	⊖—— L8
			$K/100$	
○	+	——	⇌	⊖—
			$K/500$	
○	+	— L8	⇌	⊖— L8
			$K/500$	
○	+	—	⇌	—⊖

CAP-DNA binding constants (M^{-1}) are shown for 10 μm cAMP; 10 mM Tris, 1 mM EDTA, 21°C. (○) CAP.

Kinetic evidence favoring a conformational switch and additional potential DNA contacts. Our experiments (M. Fried and D.M. Crothers, in prep.) on the kinetics of CAP and *lac* repressor–DNA interactions reveal features that are possibly relevant to the problem of long-range interactions. Time-dependent analysis of CAP–DNA-complex mixtures allows one to determine both association and dissociation rate constants. We found an association rate constant for CAP binding to wild-type 203-bp DNA of 6.7×10^6 M^{-1} sec^{-1}, about two to three orders of magnitude slower than found for *lac* repressor under similar conditions (Riggs et al. 1970; Winter et al. 1981). The relatively slow rate implies either that the intramolecular search mechanism inferred for *lac* repressor is absent for CAP or that other rate-limiting factors intervene. Supporting the latter possibility, we found kinetic evidence for a first-order step in the reaction of CAP with DNA, consistent with some kind of conformational rearrangement of DNA, protein, or both (M. Fried and D.M. Crothers, in prep.).

Experiments on the rate of dissociation of protein-DNA complexes revealed dramatic catalysis of the dissociation step by added DNA. Figure 5 shows an example, comparing the time course of dissociation of *lac* repressor with and without added catalytic DNA.

Repressor and CAP differ sharply in the concentration dependence of their dissociation rates, as shown in Figures 6 and 7. In the case of repressor, the dissociation rate increases linearly with catalytic DNA concentrations at low concentration, then reaches a plateau value. In contrast, the CAP dissociation rate is parabolic in the nonspecific DNA concentration [D], depending on $[D]^2$. These results clearly imply at least transient complexes between CAP or *lac* repressor and more than one DNA molecule. The bridging of two small DNA fragments by a single *lac* repressor has been reported earlier (O'Gorman et al. 1980).

Interpretive Models

Our results point to an influence of distal DNA on the conformation and stability of CAP-DNA complexes. We see two general kinds of models to explain the results: The influence of distal DNA can be transmitted directly along the DNA, a model that involves the concept of incompatible structures or, alternatively, the

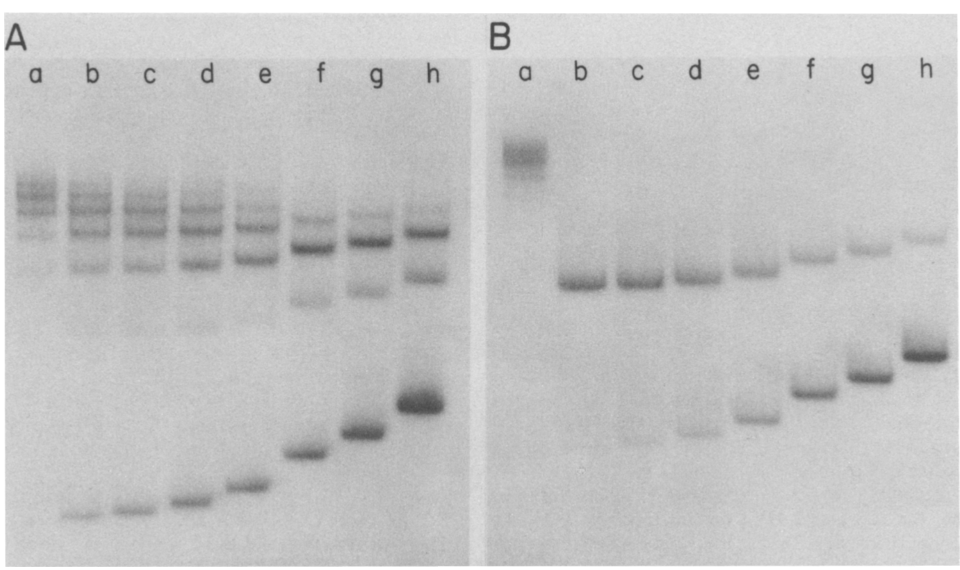

Figure 5. Effect of DNA concentration on the kinetics of *lac* repressor dissociation: Analysis by polyacrylamide gel electrophoresis. Complexes of *lac* repressor with the 203-bp L8-UV5 *lac* promoter-operator fragment, formed at a molar ratio of 4.9 in 10 mM Tris (pH 7.4 at 21°C), 50 mM NaCl, 1 mM EDTA, 50 μg/ml of BSA, and 5% glycerol. The initial DNA concentration was 3.3×10^{-9} M (fragment). Following equilibration, dissociation was initiated by addition of 203-bp L8-UV5 DNA to give a final concentration of 6.6×10^{-8} M (fragment) (1.3×10^{-5} M bp) (*A*) or 203-bp L8-UV5 DNA plus sheared *E. coli* DNA to give a final concentration of 180 μg/ml total [DNA] = 2.9×10^{-4} M bp (*B*). Aliquots were withdrawn and assayed at 0, 60, 120, 240, 480, 960, 1320, and 1920 sec (lanes *a*–*h*). The bottom band in each lane consists of free DNA. Each band above the first contains one equivalent of repressor (tetramer) more than its predecessor (Fried and Crothers 1981).

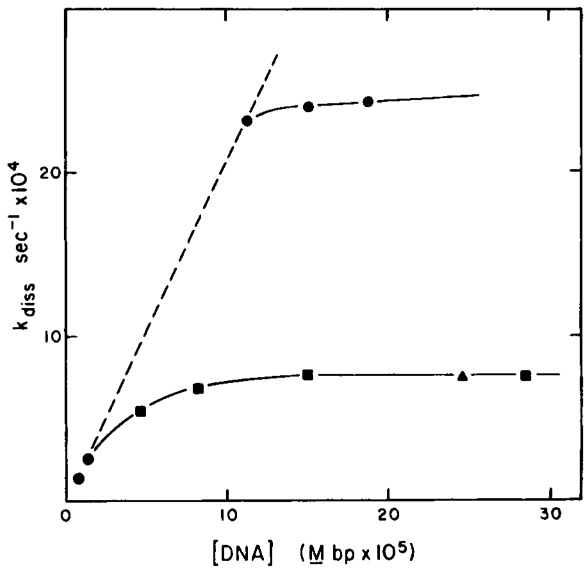

Figure 6. Dependence of the dissociation kinetics of *lac* repressor on the concentration and sequence content of the competing DNA. Values of k_{diss} for the 1:1 repressor complex with 203-bp L8-UV5 fragment, measured at 21 ± 1°C in 10 mM Tris (pH 7.4 at 21°C), 50 mM NaCl, 1 mM EDTA, 50 μg/ml of BSA, and 5% glycerol. Competing DNAs were 203-bp L8-UV5 fragment (●), 203-bp L8-UV5 fragment (1.3 × 10^{-5} M bp) plus sheared *E. coli* DNA (■), or plus sonicated calf thymus DNA (▲) to give the final concentrations indicated.

distal influence can be exerted by bending the DNA back to form a second contact with the protein.

In the direct-transmission model, the presence of the helix end created by *Hpa*II cleavage must bias the DNA structure against the conformation favored by bound CAP in order to explain the influence of cleavage on binding affinity. The difference in gel mobility between wild-type and L8-UV5 fragments would reflect a difference in the extent or propagation range of the DNA conformational change induced by CAP binding.

The bending model explains enhanced affinity for the larger fragment by the stabilizing influence of the second DNA contact. Gel mobility anomalies in this case would arise from differences in the extent or nature of hairpin bending of the DNA. Distinguishing between these (and possibly other) models will require further experiments: "Supposing is good, but finding out is better" (Mark Twain). In the matter of long-range effects in CAP-DNA interactions, the second stage of Mr. Clemens's hierarchy still eludes us.

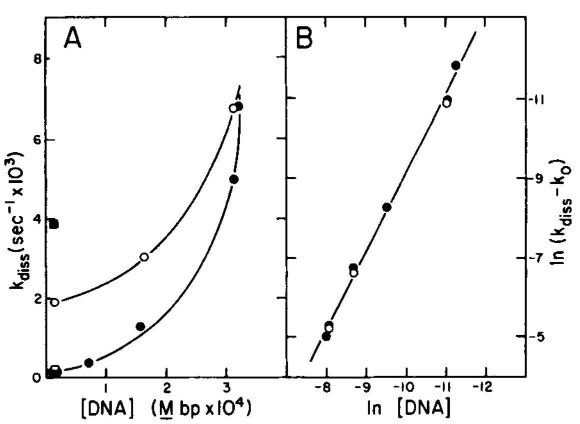

Figure 7. Kinetics of CAP dissociation from *lac* promoter-operator restriction fragments, as a function of DNA concentration. The reaction buffer was 10 mM Tris (pH 8.0 at 21°C), 1 mM EDTA, 10 μM cAMP, 50 μg/ml of BSA, and 5% glycerol. The reaction temperature was 21 ± 1°C. (*A*) Plot of k_{diss} vs. [DNA]. Initial CAP complexes were formed with the 203-bp wild-type fragment (●), the 203-bp L8-UV5 mutant fragment (○), the 121-bp wild-type fragment (□), and the 121-bp L8 mutant fragment (■). (*B*) Plot of ln (k_{diss} − k_0) vs. ln [DNA]. Initial complexes were formed with the 203-bp wild-type fragment (●) and the 203-bp L8-UV5 fragment (○). The limiting values of k_0 (1.2 × 10^{-4} sec^{-1} for the wild-type fragment, and 1.8 × 10^{-3} sec^{-1} for the L8-UV5 fragment) were found by extrapolating plots of k_{diss} vs. $[DNA]^2$ to $[DNA]^2$ = 0. The solid line is a least-squares fit to the data. The slope is 1.98, indicating that CAP dissociation is second order in competing nonspecific DNA.

ACKNOWLEDGMENTS

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