Under anaerobic growth conditions, *Escherichia coli* operates a two-component signal transduction system, termed Arc, that consists of ArcB protein, a transmembrane sensor kinase and ArcA protein, the cognate response regulator. In response to low oxygen levels, autophosphorylated ArcB phosphorylates ArcA, and the resulting phosphorylated ArcA (ArcA-P) functions as a transcriptional regulator of the genes necessary to maintain anaerobic growth. Under anaerobic conditions, cells maintain a slow growth rate, suggesting that the initiation of chromosomal replication is regulated to reduce the initiation frequency. DNase I footprinting experiments revealed that ArcA-P binds to the left region of the chromosomal origin, oriC. ArcA-P did not affect the *in vitro* replication of plasmid DNA containing the ColE1 origin nor the *in vitro* replication of viral DNAs; however, ArcA-P specifically inhibited *in vitro* *E. coli* chromosomal replication. This inhibition was caused by the prevention of open complex formation, a necessary step in the initiation of chromosomal replication. Our *in vitro* results suggest that the Arc two-component system participates in regulating chromosomal initiation under anaerobic growth conditions.

Most organisms, including *Escherichia coli*, are able to adapt to variable growth conditions and environmental changes by regulating gene expression (1, 2). Adaptation in bacterial cells is usually achieved through two-component signal transduction systems, which consist of a sensor kinase and a response regulator (2, 3). The response regulator, phosphorylated by cognate sensor kinase in response to an external signal, serves as a transcriptional regulator optimizing gene expression under a given condition. In *E. coli*, the Arc (anoxic redox control) two-component signal transduction system operates in response to a shift from aerobic to anaerobic conditions (4). The Arc signal transduction system consists of the ArcB and ArcA proteins, a transmembrane sensor kinase and its cognate response regulator, respectively (5, 6). In response to oxygen deficiency or redox change, ArcB autophosphorylates in an ATP-dependent manner and converts to phosphorylated ArcB (ArcB-P) via an intramolecular phospho-relay of His-292 → Asp-576 → His-717 (7). Subsequently, ArcB-P phosphorylates Asp-54 of ArcA, and the resulting ArcA-P (phosphorylated ArcA) functions as a transcriptional repressor for the *sdh*, *gltA*, *ld*, *cyo*, and *sodA* genes (4, 6, 8, 9) and as an activator for *cyl*, *pfl*, and *traY* genes (4, 8, 10, 11) to sustain anaerobic growth.

Anaerobic conditions that induce the Arc two-component signal transduction system lead to reduction in growth rate (12). Because the rate of chromosomal replication regulated mainly at the level of initiation is coupled to growth rate (13), the slow growth rate of *E. coli* during times of oxygen deficiency suggests that the frequency of chromosomal initiation is reduced. It is therefore probable that regulation of initiation occurs at oriC, the *E. coli* origin of chromosomal replication (14). This unique sequence, which is the highly conserved origin of Gram-negative bacteria (15), includes four DnaA boxes, AT-rich region containing three 13-mers, and an IHF binding site, all of which are required for proper chromosomal initiation of replication (16, 17). Binding of the initiator protein, DnaA, to the DnaA boxes leads to unwinding of the AT-rich regions and allows for the entry of DnaB helicase, a required step for subsequent initiation processes (18, 19). Opening of the AT-rich region is facilitated by the binding of IHF protein to the IHF site, thereby bending oriC (20, 21). Although IHF can be substituted by HU protein (21), *in vivo* footprinting experiments suggest that IFH may play a role in determining the timing of chromosomal initiation during the cell cycle (22).

Here we report that the binding of ArcA-P, phosphorylated by ArcB, to oriC results in the inhibition of chromosomal initiation. This result suggests that the Arc two-component signal transduction system plays a role in the regulation of chromosomal initiation at oriC in response to oxygen deficiency.

**MATERIALS AND METHODS**

**Reagents and Proteins—**Sources were as follows: [γ-32P]ATP (5000 Ci/μmol), [α-32P]dCTP (3000 Ci/μmol), and deoxynucleotides, Amer- sham Pharmacia Biotech; Long Ranger polyacrylamide, FMC BioProducts; DNase I, Life Technologies Inc.; nuclease P1, Roche Molecular Biochemicals; T4 polynucleotide kinase and Vent (exo -) DNA polymerase, New England BioLabs; calf intestinal alkaline phosphatase and restriction enzymes, Promega Corp. Unless indicated, reagents were purchased from Sigma Chemical Co.

Monomeric DnaA protein from HMS174 (pKC596) (23) and HU protein (24) were purified as previously described. *Bacterial Strains, Primers, and Plasmid and Phage DNAs—* *E. coli* strains MC1061 (25), W3110 (26), and WM433 (dnaA204) (27) were previously described. *E. coli* DH5α (28) was used for isolation of plasmid DNA.

The DNAs were as follows: pFToIC (21) for DNase I footprinting; phosphorylated ArcA; CP mixture, phosphorylation mixture containing carbamyl phosphate; RF, replicative form; TP mixture, transphosphorylation reaction mixture; bp, base pair(s); AMPPNP, adenosine 5′-β,γ-methylene triphosphosphate.

This paper is available on line at http://www.jbc.org
pBAD24 (32), respectively. The polypeptide and KOH (pH 7.8), 1 mM EDTA, 10% glycerol, and 2.86 mM 2-mercaptoethanol were added to a conductivity equivalent of 50 mM KCl and loaded onto a Cibacron Blue column chromatography (2.5 ml of bed volume, Sigma). A 120-ml gradient ranging from 50 mM to 1 M KCl in buffer A was used for protein elution, with ArcA eluting at ~150 mX KCl. The fractions containing ArcA were pooled, diluted with buffer A to the conductivity equivalent of 50 mM KCl, and loaded onto a FastQ column (4 ml of bed volume, Sigma). The fractions containing ArcA were pooled, diluted to the conductivity equivalent of 50 mM KCl with buffer A, and subjected to Cibacron Blue column chromatography (2.5 ml of bed volume, Sigma). A 25-ml gradient ranging from 50 mM to 2 M KCl in buffer A was run over the column, yielding near homogeneous ArcA, which eluted at ~0.5 M KCl. About 17 mg of ArcA protein was obtained from 15 liters culture of MC1061(pBADarcA).

For ArcB protein purification, the ammonium sulfate precipitate was dialyzed to the conductivity equivalent of 50 mM KCl then subjected to FastQ column chromatography (60 ml of bed volume, Sigma) using 600 ml of a linear gradient ranging from 50 mM to 1 M KCl in buffer A. The fractions containing ArcA were pooled, then dialyzed to a conductivity equivalent of 50 mM KCl and loaded onto a Cibacron blue column chromatography (2.5 ml of bed volume, Sigma). A 25-ml gradient ranging from 50 mM to 2 M KCl in buffer A was run over the column, yielding near homogeneous ArcB, which eluted at ~0.5 M KCl. About 17 mg of ArcB protein was obtained from 15 liters culture of MC1061(pBADarcB).

For ArcB protein purification, the ammonium sulfate precipitate obtained from 6 liters of MC1061(pBADarcB) culture as described above was resuspended in buffer A, dialyzed to a conductivity equivalent of 50 mM KCl, and subjected to FastQ column chromatography (90 ml of bed volume) using a 900-ml gradient ranging from 50 mM to 1 M KCl in buffer A. Fractions containing ArcB were pooled, then dialyzed to a conductivity equivalent of 50 mM KCl and loaded onto a Cibacron blue column (17 ml of bed volume). A 170-ml gradient ranging from 50 mM to 1 M KCl in buffer A was run over the column. ArcB eluted in a broad range of fractions, which were pooled, and the protein was precipitated with 0.45 g/ml ammonium acetate and sequenced by centrifugation at 45,000 rpm for 30 min in a Ti70 rotor (Beckman). The pelleted was resuspended with buffer A and subjected to Superose-12 gel filtration chromatography (Amersham Pharmacia Biotech, HR 10/30). ArcB eluted as a single peak. These fractions were pooled and loaded onto a MonoQ column (Amersham Pharmacia Biotech, HR 5/5). ArcB eluted from the MonoQ column at near homogeneity and was used in further experiments. A 6-liter culture of MC1061(pBADarcB) yielded about 9 mg of homogeneous ArcB.

Transphosphorylation Reaction—Transphosphorylation reactions (TP), including purified ArcA and ArcB, were performed as previously described (34) with minor modifications. 10 μl of the TP mixture contained 6 μg each of ArcA and ArcB, 0.1 mM ATP, 70 mM KCl, 10 mM MgCl2, 33 mM HEPES-KOH (pH 7.4), 0.1 mM EDTA, and 2 mM dithiothreitol. After incubation at 32 °C for 10 min, the reaction mixture (2 μl per each assay unless indicated) was immediately used for further experiments.

To visualize the phosphorylated proteins, [γ-32P]ATP was added to the above mixture. The reaction was terminated by addition of gel-loading buffer (10% glycerol, 2% SDS, 5% 2-mercaptoethanol, and 0.3% bromphenol blue). After incubation at 55 °C for 3 min, the mixture was subjected to 12% SDS-polyacrylamide gel electrophoresis. The gel was dried and visualized by autoradiography.

Phosphorylation reaction of ArcA with carbamyl phosphate (CP) was performed as previously described (35). 10 μl of the TP mixture containing the indicated amount of ArcA protein, 40 mM dithiobismuth carbamyl phosphate, 125 mM KCl, 10 mM MgCl2, and 100 mM Tris-HCl (pH 7.0) was incubated at 30 °C for 1 h and immediately used for primer extension reaction. DNAase I Protection Assays—DNAase I protection assays were performed as previously described (36) with minor modifications. A 435-bp XbaI/XhoI fragment from pTorIc was labeled at either the XhoI or XbaI restriction site. 21.5 fmol of labeled fragments was mixed with the indicated proteins in 25 μl of standard reaction mixture containing 0.1 mM ATP, 50 mM potassium chloride, 10 mM magnesium acetate, 2.5 μg of bovine serum albumin, 40 mM HEPES-KOH (pH 7.6), and 10% glycerol. After incubation at 32 °C for 10 min, DNAase I (5 ng in 1.5 μl of H2O) was added, incubated for 30 s, then stopped by the addition of 27 μl of 0.6 M sodium acetate, 0.4% SDS, 25 mM EDTA, and 0.1 mg/ml yeast tRNA. Proteins were removed by phenol/chloroform extraction, and DNA was precipitated by ethanol, followed by a 70% ethanol wash. DNA was subjected to electrophoresis through a 5% Low Ranger polyacrylamide gel containing 7 M urea. The gel was dried and visualized by autoradiography.

In Vitro oriC Replication Assays—As previously described (37, 38), in vitro oriC plasmid replication with fraction II from WM433 (dnaA204) and purified DnaA protein was performed using 200 ng of M138535 RF DNA as a template. Single-stranded phage DNAs, such as G4, M13mp19, and dX174, and phBlueScript containing the ColE1 replication origin, 200 ng each, were used for DnaA-independent replication. In these assays, all conditions were identical to oriC plasmid replication reactions, except that DnaA was omitted.

Open Complex Formation and P1 Nuclease Assay—Open complex formation at oriC was detected using single-strand specific P1 nuclease as previously described with modifications (21, 39). 25 μl of opening reaction mixture containing the indicated amount of DnaA, 15 ng of Hu, 200 ng of supercoiled pBoriC, 4 mM ATP, 50 mM potassium glutamate, 2.5 mM magnesium acetate, 2.5 μg of bovine serum albumin, 40 mM HEPES-KOH (pH 7.6), and 17% glycerol, was incubated at 37 °C for 5 min. Then 3 units of P1 nuclease in 3 μl of 30 mM sodium acetate (pH 5.2) were added and incubated at 37 °C for 30 s. The cleavage reaction was quenched by the addition of 27 μl of stop solution (25 mM EDTA, 0.4 mM NaOH). After incubation at room temperature for 10 min, followed by addition of 6 μl of 3 M sodium acetate (pH 5.2), proteins were removed by phenol/chloroform extraction. With 2.5 μg of yeast tRNA as a carrier for precipitation, DNA samples were collected by ethanol precipitation followed by a 70% ethanol wash. The precipitated DNA was resuspended with 6 μl of H2O, and 5 μl was taken as a template for primer extension reactions. 6 μl of the primer extension mixture included 1.25 mM of each dNTP, 0.25 pmol of 5′-end-labeled primer PA1 (21) and 0.42 unit of Vent (exo- ) DNA polymerase in Vent (exo- ) buffer with 5 mM MgSO4. The primer was 5′-end-labeled with [γ-32P]ATP and T4 polynucleotide kinase; unincorporated radioactive was removed using a Bio-Gel 6 spin column (Bio-Rad). The mixture was subjected to primer extension reactions in a thermocycler, for 20 cycles (95 °C for 1 min except for 4 min in the first cycle, 55 °C for 1 min, and 72 °C for 1 min except for 6 min in the last cycle). The reaction was stopped by the addition of 4 μl of sequencing gel loading buffer, then subjected to electrophoresis through a 5% Long Ranger polyacrylamide sequencing gel containing 7 M urea. The gel was dried and visualized by autoradiography.
RESULTS

ArcA-P Protein Binds to oriC—To investigate the interaction of ArcA and ArcB with oriC DNA, ArcA and ArcB proteins were overproduced and purified to near homogeneity using column chromatography (Fig. 1A). Due to poor expression of the ArcB protein, we instead expressed and purified a truncated ArcB lacking the N terminus from amino acid residues from 1 to 128 as described previously (34). The ArcA and ArcB proteins used in this study were distinctive from the proteins containing the hexa-histidine (7, 35, 40, 41) or renatured from SDS-polyacrylamide gels (34) as used in previous studies. The purified ArcA and ArcB proteins were active in transphosphorylation reactions. In the presence of ATP, ArcB underwent autophosphorylation and subsequently transferred the phosphoryl group from itself to ArcA, forming ArcA-P, whereas ArcA alone was not phosphorylated (Fig. 1B).

Binding of the transphosphorylation mixture (TP mixture), which contains ArcA, ArcB, and ATP, to the oriC region of the E. coli chromosome was detected using a DNase I protection assay (Fig. 2). Increasing the amount of TP mixture added to the footprinting reaction revealed that an ~150-bp region located at the left end of oriC, including the three 13-mer AT-rich regions, DnaA box R1, and IHF binding site, was protected from DNase I cleavage (Fig. 2). The omission of ArcA, ArcB, or both from the TP mixture abolished the protection pattern observed at oriC, indicating that the oriC binding activity requires both ArcA and ArcB proteins.

Neither ADP nor the nonhydrolyzable ATP-analogue AMP-
Inhibition of oriC Replication by ArcA-P

PNP was able to substitute ATP for the oriC protection activity of the TP mixture, implying the requirement of ATP hydrolysis for binding (Fig. 3A). Efficient oriC protection activity required more than 50 μM ATP. Without ArcB and ATP, it has been shown that the phosphoryl group donors carbamyl phosphate and acetyl phosphate can phosphorylate ArcA (35). Therefore, we incubated ArcA with carbamyl phosphate in the absence of ArcB and ATP, and found an identical DNase I cleavage protection pattern (Fig. 3B). These results indicate that ArcA-P, produced by phosphorylation of ArcA protein either by ArcB and ATP or by carbamyl phosphate, binds to the left end of oriC.

ArcA-P Inhibits in Vitro oriC-dependent Initiation of Chromosomal Replication—The AT-rich regions and DnaA box R1 found at oriC are indispensable for both in vitro and in vivo initiation of chromosomal replication (18, 29, 42). Therefore, the effect of ArcA-P, which was found to bind those regions of oriC, on chromosomal initiation was examined using an in vitro oriC plasmid replication assay (37, 38). This assay resembles in vivo chromosomal initiation in many aspects, including dependence upon the oriC sequence, requirement of replicative proteins, and bidirectional replication from oriC (37, 43).

Addition of purified DnaA protein to the oriC plasmid replication assay sustained the replication of oriC plasmid M13RE85 RF DNA, in which the oriC region has been inserted into M13mp8 RF DNA (Fig. 4A). The presence of the TP mixture in the assay, however, inhibited DnaA-dependent oriC plasmid replication. Omission of ArcA, ArcB, or both from the TP mixture eliminated the inhibitory activity of the TP mixture (Fig. 4B), indicating that the inhibitory activity is dependent on both ArcA and ArcB. However, incubation of ArcA protein with carbamyl phosphate instead of ArcB and ATP also inhibited oriC plasmid replication, whereas carbamyl phosphate or ArcA alone was not inhibitory (Fig. 4C). These results imply that ArcA-P, formed either by ArcB and ATP or by carbamyl phosphate, inhibits the oriC plasmid replication, and ArcB is not a requirement.

To determine whether ArcA-P specifically inhibits initiation at oriC, the effect of ArcA-P on other origins was studied. Single-stranded viral DNAs φX174, M13, and G4 replicate from single- to double-stranded RF DNA using unique initiation processes, with each viral origin using varying proteins (16). In the absence of DnaA, the soluble proteins of fraction II, used for oriC plasmid replication, are sufficient to replicate single-stranded viral DNAs to RF DNAs (37). Plasmid pBlue-script, which contains the ColE1 origin, can also be replicated by fraction II in the absence of DnaA, but with less efficiency than the DnaA-dependent replication of oriC plasmid DNAs (37). Addition of the TP mixture to these reactions did not affect replication of any of the tested single-stranded viral DNAs or pBlue-script DNA (Fig. 4D), indicating that ArcA-P specifically inhibits the initiation of replication at oriC.
ArcA-P Does Not Affect the Binding of DnaA and IHF Protein to oriC—Because DNase I footprinting revealed the binding region of ArcA-P at a 150-bp region of the left end of oriC containing both DnaA box R1 and the IHF binding site, DNase I footprinting was further performed to determine whether ArcA-P inhibits initiation of replication at oriC by blocking the interaction of DnaA or IHF with oriC (Fig. 5). Addition of increasing amounts of DnaA to oriC (Fig. 5A, lanes 2–4) resulted in the protection of DnaA boxes R1 to R4 and IHF bound to the IHF binding site (Fig. 5B, lanes 2–4) both as previously described (21). DnaA and IHF added prior to or after ArcA-P did not allow the binding of ArcA-P to DnaA box R1 nor the IHF site, respectively; however, neither protein affected the binding of ArcA-P to the AT-rich region (Fig. 5, A and B, lanes 5–11). These results indicate that the binding of DnaA to DnaA box R1 and IHF to the IHF site is preferred over the binding of ArcA-P to those sites. However, DnaA and IHF do not affect ArcA-P binding to the AT-rich region.

To further study the binding of ArcA-P to the AT-rich region of oriC, competition experiments using IciA were performed. IciA protein specifically binds to the three 13-mers in the AT-rich region and inhibits the initiation stage of in vitro oriC replication (52). Interestingly, addition of IciA to a preformed ArcA-P oriC complex displaced ArcA-P to generate a footprint similar to that of IciA only. Conversely, ArcA-P displaced IciA bound to oriC (Fig. 5B, lanes 14–16).

ArcA-P Blocks Open Complex Formation in oriC-dependent Initiation—At the onset of initiation, DnaA protein unwinds the AT-rich regions of oriC with the aid of IHF or IHF, forming the open complex, a step that is prerequisite for the subsequent stages of initiation (18, 19). DnaA-dependent strand opening of the AT-rich region can be observed using single-stranded-specific P1 nuclease and primer extension assays (Fig. 6), as previously described (21, 39). Addition of the TP mixture prior to DnaA protein in the assays resulted in inhibition of open complex formation. However, the addition of the TP mixture after open complex formation did not significantly inhibit open complex formation. These results imply that ArcA-P functions prior to the DnaA-dependent strand opening of the AT-rich region. The amounts of TP mixture required for oriC binding (Fig. 2), inhibition of oriC replication (Fig. 4B), and inhibition of open complex formation (Fig. 6) were comparable to each other. These results suggest that binding of ArcA-P to oriC inhibits oriC initiation by blocking open complex formation.

DISCUSSION

ArcA protein phosphorylated by ArcB and ATP or by carbamyl phosphate binds the left end of oriC. This bound region includes the AT-rich 13-mers, DnaA box R1, and the IHF binding site, regions all highly conserved in chromosomal replication origins of Gram-negative bacteria (15) and all of which are essential for initiation of E. coli chromosomal replication (18, 29, 42). In chromosomal initiation events, the AT-rich region of oriC is unwound upon binding of DnaA proteins to the DNA boxes (18, 19). Interaction of DnaA protein with the AT-rich region, leading to strand opening, is facilitated by the binding of oriC by IHF protein bound to the IHF site (20, 21). Binding of ArcA-P blocks DnaA-dependent strand opening of the AT-rich regions (Fig. 6), a step required for subsequent stages of chromosomal initiation to occur. Binding of ArcA-P also results in the inhibition of in vitro oriC plasmid replication (Fig. 4). Because ArcA-P does not appear to affect the binding of DnaA and IHF to their loci (Fig. 5), such inhibition may be caused by ArcA-P binding to the AT-rich regions of oriC, thereby inhibiting a proper interaction between DnaA protein and the AT-rich region, an interaction which is thought to be required for the opening of the AT-rich region by DnaA (29, 44).

Aside from our reported binding of ArcA-P to oriC, ArcA-P binds to a number of promoter regions (35, 44–46), including the pfl promoter that controls expression of pyruvate formate lyase (46). We observed that ArcA-P possessed similar affinities to the oriC and pfl promoters using gel-shift assays (data not shown). However, we could not match the suggested ArcA-P binding consensus sequence (49) with the oriC sequences, the
Inhibition of oriC Replication by ArcA-P

...described under "Materials and Methods." In lane 5–8, the amount of DnaA was added to the opening reaction; (BAS 1000) and normalized to the value of lane 5. A mixture was added after open complex formation, then incubated 5 min. ArcA-P, even with a molecular mass of 27 kDa, protected a region in the DNase I footprinting assay (data not shown). Though unphosphorylated ArcA binds to any binding of unphosphorylated ArcA to oriC, it has been scarcely documented how organism set the initiation frequency in response to various physiological conditions or environmental stresses. In E. coli, it was reported that UV irradiation inhibits the initiation of chromosomal replication from oriC (50), however, there are no further studies showing the regulatory factors involved or underlying mechanisms. The pleiotropic effects of arcA mutations (4–6, 41, 51, 52) present challenges in performing in vitro experiments and make interpretation of the results difficult. Even under aerobic condition, arcA mutants possess reduced chromosome numbers compared with the wild type (data not shown). Although there is no clear in vivo data available, our in vitro results suggest that Arc, a two-component signal transduction system operated under anaerobic conditions in E. coli, plays a role in regulation of chromosomal initiation. Under oxygen depletion stress, the response regulator ArcA, phosphorylated by sensor kinase ArcB, may bind to oriC and reduce chromosomal initiation.

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The Arc Two-component Signal Transduction System Inhibits in Vitro Escherichia coli Chromosomal Initiation

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