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Molecular Bases of DNA Packaging in Bacteria Revealed by All-Atom Molecular Dynamics Simulations: The Case of Histone-Like Proteins in *Borrelia burgdorferi*

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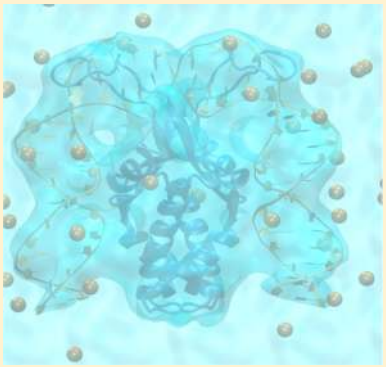
Supporting Information

ABSTRACT: DNA compaction is essential to ensure the packaging of the genetic material in living cells and also plays a key role in the epigenetic regulation of gene expression. In both humans and bacteria, DNA packaging is achieved by specific well-conserved proteins. Here, by means of all-atom molecular dynamics simulations, including the determination of relevant free-energy profiles, we rationalize the molecular bases for this remarkable process in bacteria, illustrating the crucial role played by positively charged amino acids of a small histone-like protein. We also present compelling evidence that this histone-like protein alone can induce strong bending of a DNA duplex around its core domain, a process that requires overcoming a major free-energy barrier.



DNA packaging is essential for all living organisms to allow the compaction of the long nucleic acid polymers into the confined environment of bacterial cells or nuclei. The compaction of DNA is achieved by the action of two types of proteins: (i) large enzymes that alter the topology of the DNA (relax or supercoil the DNA), including DNA topoisomerases or DNA gyrases, and (ii) small, basic proteins such as histones that possess a high-density of positive charges on their surface to engage in strong electrostatic interactions with the negatively charged DNA backbone.[1−3] Interestingly, even limited mutations in such proteins are usually lethal to the cell, pointing out the crucial importance of DNA compaction.[4] In addition to its space-saving role, compaction of DNA is also important to enhance the global stability of DNA[5,6] and to regulate gene expression.[7−11] Indeed, the transition from the more compact heterochromatin to euchromatin is known to increase the accessibility of the genes to the promoting factors and hence enhance gene expression.[12−16] Chromatin remodeling is also finely tuned by complex cross-talks between DNA and histone epigenetic marks, such as methylation or acetylation.[17,18]

In eukaryotes, DNA packaging is largely achieved by histones, whose complex of eight monomers, called nucleosome, constitutes the basic unit of chromatin, and chromosomes.[19,20] Conversely, in bacteria in which genome organization is much simpler than in eukaryotes, a set of proteins known as nucleoid-associated proteins (NAPs) or histone-like proteins play a similar role in DNA packaging.[21−26] There are different classes of histone-like proteins, the most common ones being HU[27−32] and the integration host factor (IHF),[33−39] whose combined action is necessary to induce DNA compaction in *Escherichia coli*.[40−45]

In this Letter, we specifically focus on the behavior of the histone-like protein, Hbb, from the pathogenic bacterium *Borrelia burgdorferi*,[46−48] known to be the causative agent of Lyme disease.[49−51] Unlike *E. coli*, this organism does not possess HU and IHF encoding genes but instead encodes for an HU variant, Hbb. Although the crystal structure of a complex between Hbb and a 35-nucleotide double-stranded DNA oligomer was solved by Mouw and Rice[46] and several key amino acids necessary to ensure Hbb's biological functions have been identified,[46,47] a global picture, at atomistic scale resolution, of its mechanism of action is still lacking and constitutes the object of the present contribution.

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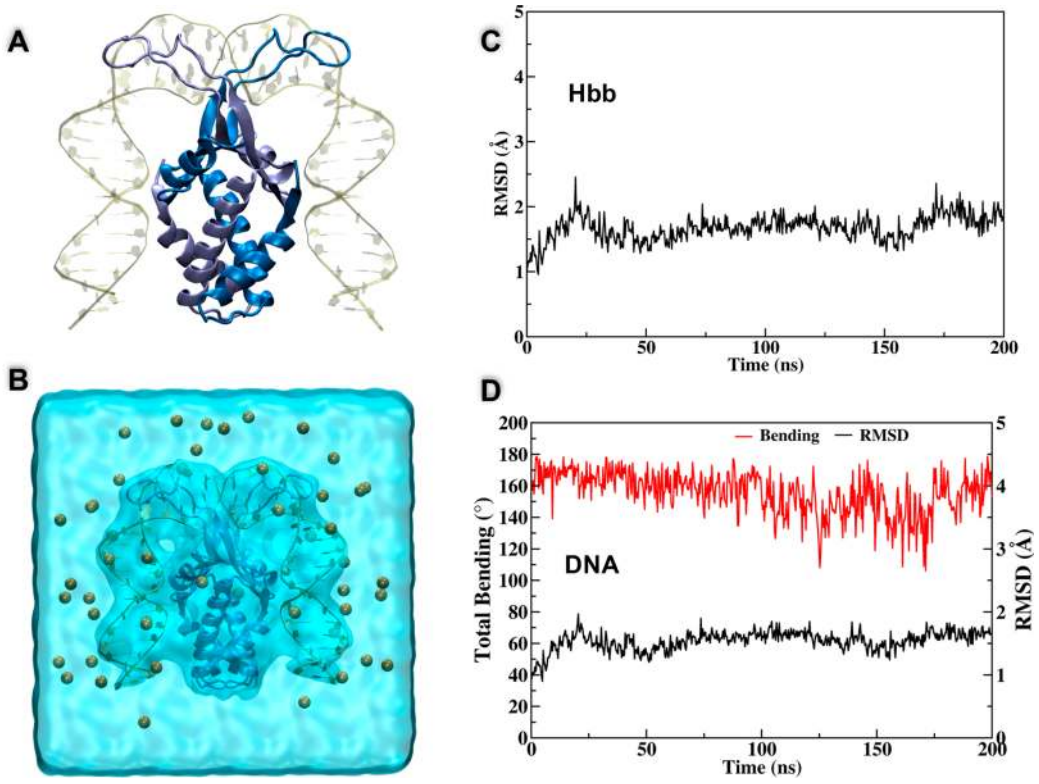

Figure 1. (A) Structure of the DNA/Hbb complex (ref 46) highlighting the two chains composing the homodimer. (B) MD simulation box composed of the DNA/Hbb complex together with water and added salt ions (yellow spheres). (C) Time series of the Hbb RMSD extracted from the MD simulation of the DNA/Hbb complex. (D) Time series of the DNA RMSD and total bending extracted from the MD of the DNA/Hbb complex.

From a structural point of view,[46] Hbb is a homodimer, consisting of two separated functional units: a globular core domain composed largely of α-helices (α-helix core) and displaying a high density of positively charged amino acids and two tweezers formed by the two β-hairpin structures that constitute the β-DNA binding domain (Figure 1). At equilibrium, the latter insert into the DNA minor-groove, further enhancing the contact region and hence the stability of the protein−DNA complex. Apart from the positioning of the β-DNA binding domain in the groove region, the other main contacts in the crystal structure are exerted by arginine (R6 and R58), lysine (K8, K11, and K97), and proline (P7) situated in the α-helix core and stabilized by electrostatic interactions with the backbone phosphates. As expected, this results in important structural modifications of the DNA oligomer that experiences a strong global bending of about 160°. Starting from these observations, we decided to perform extended classical molecular dynamics (MD) simulations to decipher the mechanism by which Hbb induces bending in a DNA duplex.

Our MD simulations made use of the Hbb/DNA crystal structure reported by Mouw and Rice[46] that was solvated in a water box to which K^+ counterions were added to ensure electroneutrality. In addition to the native DNA/Hbb complex, additional systems were investigated, including the isolated DNA duplex, the wild-type Hbb dimer alone, as well as several Hbb point mutants, as detailed below and in the Supporting Information. Equilibrium MD, reaching up to the microsecond time scale, were run considering periodic boundary conditions in the constant pressure and temperature (*NPT*) ensemble at 300 K and 1 atm. Amberff99 force field,[52] including the *bsc1* corrections[53,54] in the case of DNA, was used consistently, while water was described using the TIP3P force field.[55] In addition to equilibrium MD, we also performed enhanced sampling dynamics, using the recently developed combination of extended adaptative biased force (eABF)[56] and metadynamics (meta-eABF)[57] to obtain the energetic penalty related to DNA bending. Indeed, the common denominator of adaptive biasing force (ABF)-based algorithms is to flatten the free-energy landscape by means of a time-dependent bias on collective variables. In stark contrast, the key characteristic of metadynamics (MtD) and its variants is the fast exploration of undersampled regions of the free-energy landscape. It has been observed that the properties of these two classes of algorithms are complementary. Merging their relative merits, a new importance-sampling algorithm, coined meta-eABF, has been put forward which combines MtD and an extended-Lagrangian variant of ABF (eABF). Through simultaneous addition of eABF biasing forces and a suitable form of the MtD Gaussian potentials, meta-eABF proves particularly efficient for the rapid exploration of the free-energy landscape. The algorithm possesses remarkable convergence properties over a broad range of applications, with as much as a 5-fold speedup, compared with standard ABF.

All MD simulations were performed using NAMD code,[58] together with the Colvar module,[59] while trajectories were visualized and analyzed using VMD[60] and Curves+.[61]

The results of the equilibrium MD for the Hbb/DNA complex are presented in Figure 1 and globally indicate that the complex consists of a very stable and rigid structure as illustrated by the very low RMSD values for both DNA and Hbb (between 1 and 2 Å). In addition, the DNA is maintained

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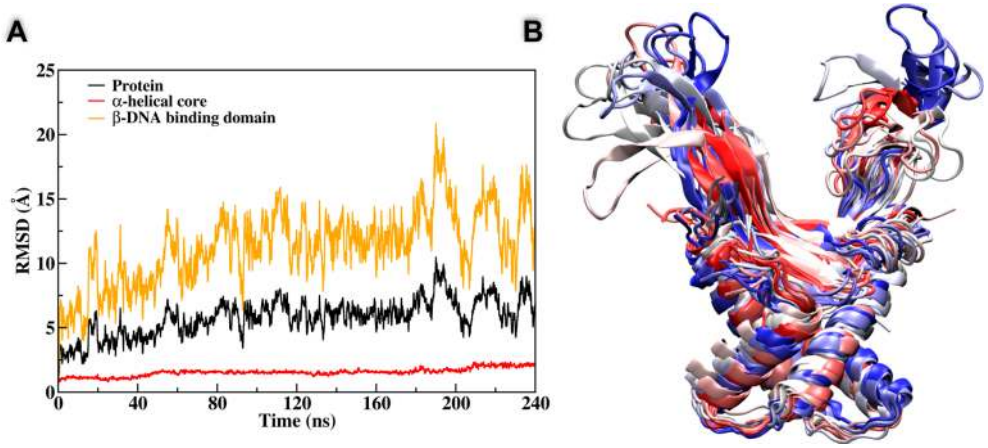

Figure 2. MD simulations of the isolated Hbb dimer. (A) Time evolution of the RMSD for the whole Hbb protein, the α-helical core, and the β-DNA binding domain during the course of the MD simulation of the isolated Hbb dimer. (B) Representative snapshots retracing the evolution of the Hbb structure and showing the coexistence and the rapid interconversion between open and closed conformations for the β-DNA binding domain. The snapshots are colored as a function of time going from blue (0 ns) to red (200 ns).

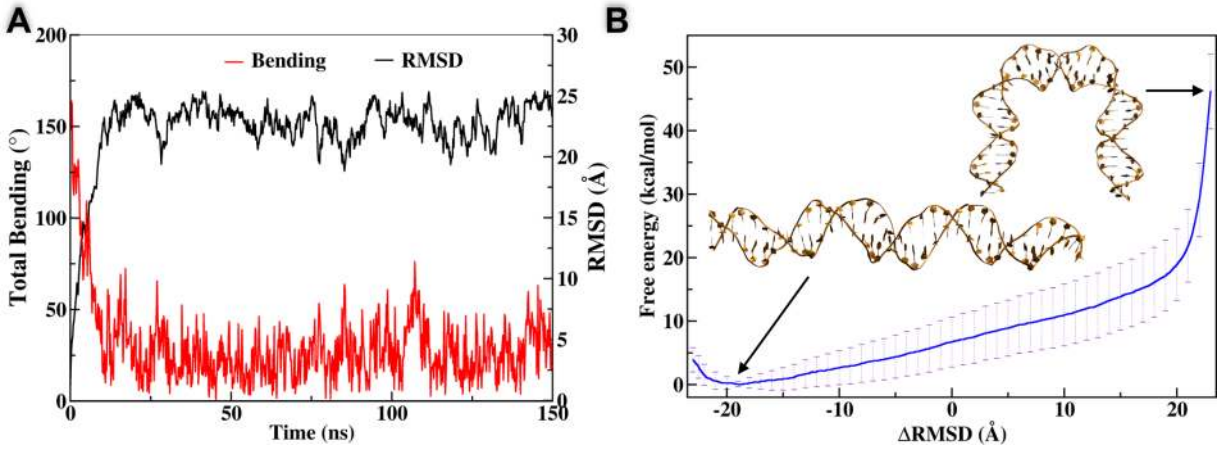

Figure 3. Equilibrium MD simulations of the 35-nucleotide DNA duplex. (A) Time evolution of the RMSD and total bending of the solvated DNA. (B) Free-energy profile showing the cost of DNA bending. The statistical errors are also reported. Representative snapshots for the straight and bent conformations are also shown at their corresponding ΔRMSD values.

in a highly bent configuration characterized by an average bending value of ∼155°, oscillating marginally on the time scale of our MD simulations. In agreement with the literature, DNA bending is mainly maintained by salt bridges between the negatively charged backbone of the DNA and a series of positively charged amino acids in Hbb (see the Supporting Information). As for Hbb, the oscillation of the RMSD is also very limited for both the core and the β-DNA binding domains, with the latter being engaged permanently in strong interactions with the DNA minor groove, thereby adding to the stability of the complex. Interestingly, and as reported in the Supporting Information (Figure S1), the Hbb/DNA complex remains stable even when shortening the DNA oligomers up to 4 nucleobases at each end (3′- and 5′)

The dynamics of the isolated Hbb is strikingly different, as illustrated in Figure 2. In the absence of interactions with the DNA oligomer, while the protein core remains extremely rigid (illustrated by the small RMSD values), the β-DNA binding domain exhibits a much larger flexibility with RMSD values ranging between 5 and 20 Å resulting from a polymorphism characterized by the coexistence of open and closed structures and their rapid interconversion. This high flexibility and apparent absence of significant free-energy barrier for the opening of the β-DNA binding domain may be critical to facilitate DNA recognition during the first steps of the bending process.

As expected, the same instability is also observed for the bent isolated DNA oligomers that very rapidly adopt a straight B-DNA conformation, as evidenced by the sharp increase of the RMSD at the start of the MD simulations (Figure 3). Although this transition requires a significant structural rearrangement of the DNA, it takes place very rapidly in about 20 ns. By performing meta-eABF simulations along the ΔRMSD global variable, we determined the free-energy penalty necessary to bend the DNA oligomer in the absence of Hbb. Note that the ΔRMSD variable was chosen because it allows us to follow the global variation of the DNA structure with respect to an arbitrary initial condition. In particular, values of the ΔRMSD close to −20 Å are indicative of a globally linear DNA oligomer while ΔRMSD of +20 Å indicates a bent conformation equivalent to the one observed in the DNA/Hbb crystal complex. As inferred from Figure 3B, this penalty is estimated to be around 35−40 kcal/mol; the rather flat free-energy potential observed for a large interval of

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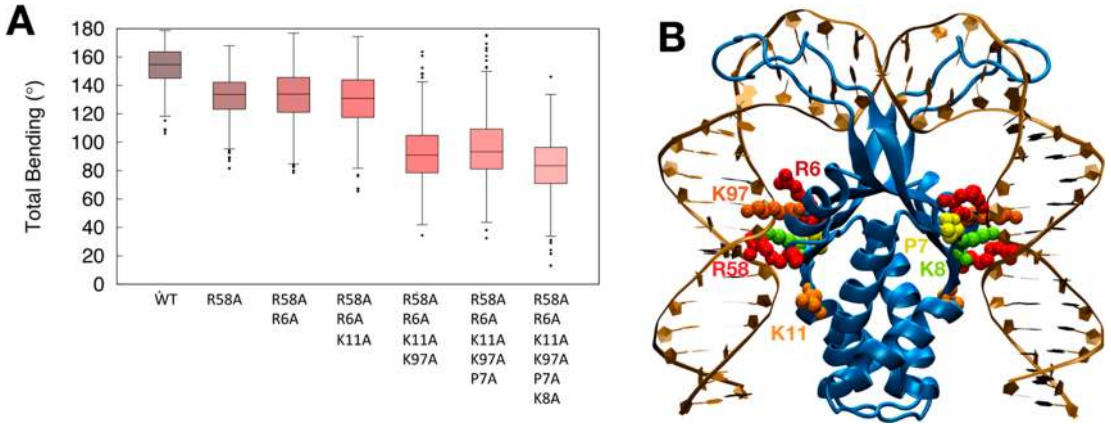

Figure 4. (A) Box plot reporting the extent of DNA bending induced by the wild-type (WT) and mutated Hbb dimers. Values were extracted from the equilibrium MD averaged over the entire trajectory ($N > 700$; boxes represent mean ± standard deviation); some of the corresponding representative snapshots are also reported in the Supporting Information. For the different Hbb mutants, the mutated amino acids are indicated below the y axis. All amino acids were substituted with alanine. (B) Cartoon representation of the Hbb dimer highlighting the position of the mutated amino acids.

the ΔRMSD is due to the known relatively high flexibility of DNA oligomers, while the sharp increase around 15 Å is due to the sampling of a highly bent conformation that is normally not accessible for solvated DNA and requires the presence of compaction proteins. Note that the modeling of such an unusual conformation by a simpler elastic model would constitute a methodological challenge because of the difficulty in sampling highly distorted conformations. Together, these observations strongly suggest that Hbb is able to convert electrostatic interactions into mechanical work on the DNA duplex that exceeds 40 kcal/mol.

Next, in order to better characterize the molecular bases underlying this remarkably efficient energy conversion, we mutated several residues in the Hbb core to the neutral alanine amino acid (see Figure 4 and the Supporting Information) to identify the key residues responsible for the electrostatic interactions with the DNA.

As shown in Figure 4, the mutation of only one residue (R58) on each of the Hbb monomers induces a significant decrease of the average bending as compared to the wild-type, while it has little influence on the standard deviation, i.e. on the spread of the distribution of the bending angles. Hence, while the mutation of R58 shifts the equilibrium toward a less bent DNA configuration it seems to affect only marginally the stability of the complex, as reflected by the width of the distribution. The cumulative mutation of the subsequent residue, R6, while not impacting the average bending, induces a significant increase in the distribution width that can be correlated with a more pronounced destabilization of the complex. This is also supported by the establishment of an equilibrium between bent and straight DNA forms, as can be seen in the representative snapshots reported in the Supporting Information (Figures S2−S7). Interestingly, the further mutation of K11 residue has almost no effect on the average bending value and on the distribution, and the equilibrium between bent and straighter DNA forms is still preserved. The additional mutations of residues constituting the α-helical core triad K97, P8, and K7 shifts the average bending toward straighter forms closer to the ones typical of linear B-DNA, while preserving, however, an equilibrium with bent structures, as evidenced by the analysis of the distribution of the bending angles and the representative snapshots reported in the Supporting Information. The analysis of these snapshots (Figures S2−S7) also indicates that the β-DNA binding domain remains stable and interacting with the DNA minor groove in all cases. As a result, because of the constraints imposed by this β-DNA binding domain on the DNA, a significant extent of bending of the oligomer is observed in all cases (Figure 4).

From these results, it is evident that both the electrostatic interactions in the core and the constraints exerted by the β-DNA binding domain of Hbb are necessary to overcome the significant free-energy penalty associated with DNA bending by Hbb. However, although it is clear that Hbb can maintain the constrained configuration of the DNA, it is still unclear whether Hbb alone is able to induce this major bending of the DNA. To address this issue, we thus performed equilibrium MD simulations in which a straight DNA duplex was manually placed in contact with an Hbb dimer in an open conformation in which the β-DNA binding domains were out of the DNA major groove and no longer contacting the DNA (Figure 5). Although a fully bent structure as seen in the crystal structure was not observed during the course of our MD simulations, we did evidence the occurrence, and the persistence, of metastable states in which a consistent though partial bending was observed, in particular for one-half of the DNA duplex, as reported in Figure 5 and as can be appreciated from the movie of the MD trajectory presented in the Supporting Information. These results represent, to the best of our knowledge, the first observation of DNA bending induced by a bacterial histone-like protein, although the spontaneous coiling of DNA around a nanoparticle has been previously reported,[62] and definitively point toward the capability of Hbb alone to induce this major DNA rearrangement, in agreement with the apparent absence of other histone-like proteins in *Borrelia burgdorferi*.

Even if we did not observe persistent intermediates that could allow discriminating between productive and abortive trajectories, we have also evidenced a complex interplay between the position of the β-DNA binding domain and the extent of DNA bending. Indeed, strong bending of the DNA, reproducing the one observed in the crystal structure, was observed only for the region of the DNA oligomer in which the β-hairpin tweezers were correctly positioned in the minor groove (right of Figure 5 C−F). The interaction between the

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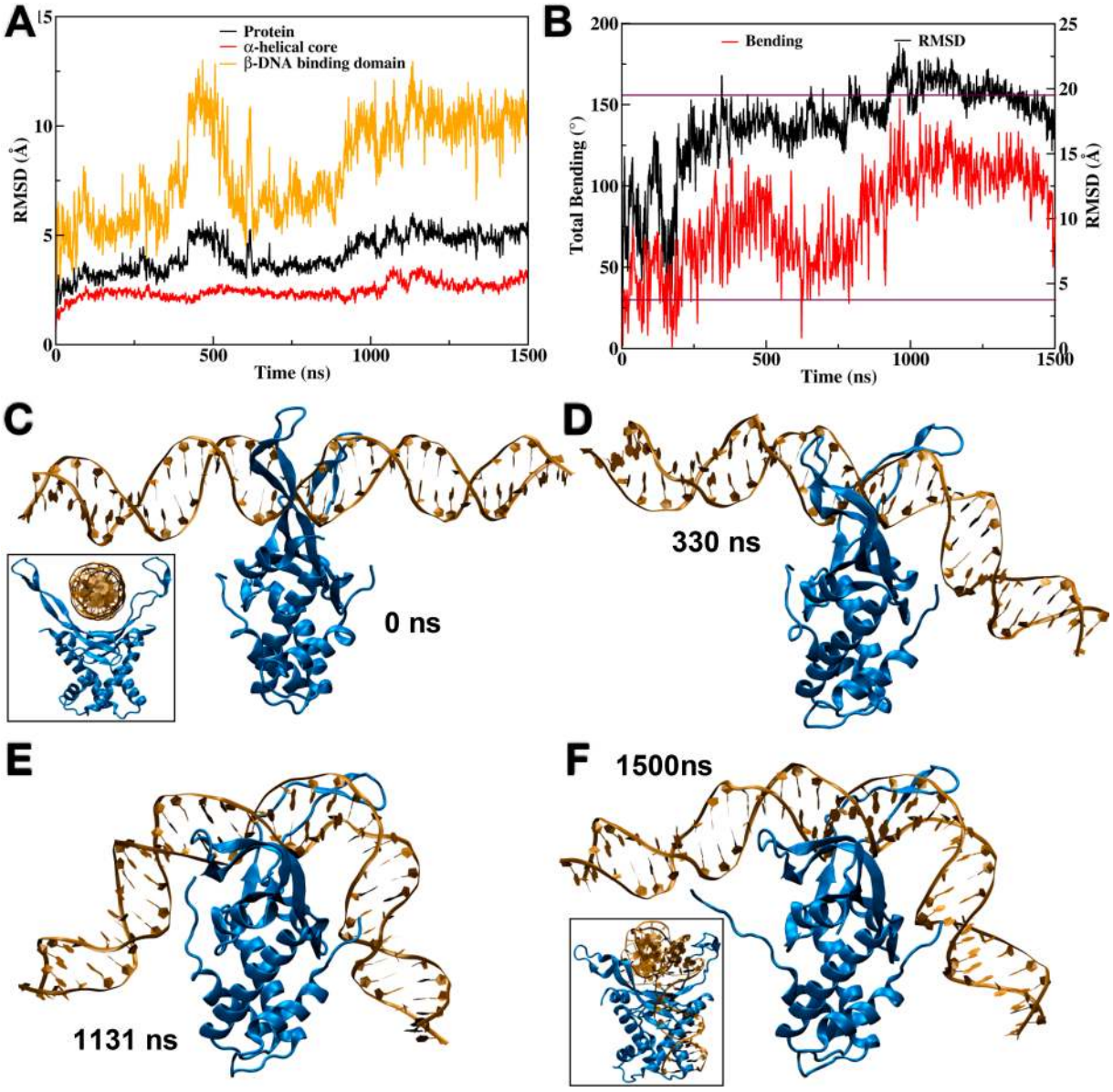

Figure 5. Microsecond MD simulation of the Hbb/DNA recognition process. (A) Time series of the RMSD of the full Hbb dimer, the α-helical core, and the β-DNA binding domain. (B) Time series of the RMSD and global bending of the DNA. The average values of the bending for the solvated DNA (29°) and DNA complexed with Hbb (155°) are reported as magenta lines. (C−F) Representative snapshots extracted from the MD simulation showing the Hbb/DNA recognition and the induction of the DNA bending.

concerted motion of some well-conserved histone residues and AT-rich DNA sequences has also been recently evidenced in nucleosomal DNA unwrapping by MD simulations.[63] Furthermore, we also observed a partial unfolding of the amino-terminal residues of Hbb during the course of the MD simulations. These largely basic residues were seen to move away from the α-helical core of Hbb and to approach the DNA duplex to engage in energetically favorable electrostatic interactions with the DNA backbone during the initial steps of the bending process. Extensive DNA bending thus appears to be achieved by the combined action of the kinking induced by the β-DNA binding domain and the tethering of the DNA ends by positively charged residues from the amino-terminus of Hbb in order to pull the DNA toward the α-helical core of Hbb where the bent conformation of the DNA is stabilized by additional electrostatic contacts. Hence, it is obvious that the peculiar structure and properties of Hbb play a fundamental role in the coordinated and controlled compaction of the DNA genome for its correct packaging within the cell. This complex process cannot be described simply by the bending of DNA oligomers around a positively charged rigid and globular protein core.

In this work, thanks to high-level full atom MD simulations, we have characterized the behavior of the histone-like protein Hbb in the presence and absence of DNA and have in particular highlighted the stability of the complex formed with DNA. Furthermore, we estimated the mechanical work necessary to maintain the highly bent DNA structure to amount to at least 35−40 kcal/mol, i.e. a value largely exceeding the free-energy barrier of many chemical reactions. The extremely high mechanical constraints exerted by both the charged Hbb core and the flexible β-DNA binding domain have also been confirmed by point mutations and in particular by the necessity to disrupt almost all the salt bridges to

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persistently switch the equilibrium toward a straighter DNA form. Finally, we have provided the first, although partial, observation of DNA bending by Hbb. These data strongly support the hypothesis that Hbb alone not only maintains but also promotes DNA bending. Our results are also coherent with the observations of Rubio-Cosials et al.[64] who have identified the strong mechanical constraints induced by the human mitochondrial transcription factor A, inducing a strong bending and U-turning of DNA oligomers. Finally, even if the standard force field may overestimate the interactions between charged amino acids and phosphate[65,66] we believe that our results, and in particular the free-energy profile providing the penalty for bending the DNA in absence of the Hbb protein, are strong enough to provide a consistent picture of the bending process.

In the future, we plan to provide a full free-energy profile of the Hbb-assisted DNA packaging through the use of biased MD simulations and the definition of proper collective variables able to take into account the interplay between the β-DNA binding domain positioning and the DNA bending. In addition, the full DNA bending process will also be characterized experimentally, also in the presence of point mutations in the Hbb sequence via suitable techniques such as Förster resonance energy transfer.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpclett.9b02978.

Analysis of the behavior of the Hbb/DNA complex when shortening the DNA strands; indication of the different point mutations and analysis of the time series of the DNA RMSD and the reproduction of representative snapshots for each case; extended computational and methodological details for the equilibrium MD simulations and the free-energy calculations (PDF)

Visualization of the MD trajectory for the DNA partial supercoiling around the Hbb complex (MP4)

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Notes

The authors declare no competing financial interest.

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