

Measurement of the repulsive force between polyelectrolyte molecules in ionic solution: Hydration forces between parallel DNA double helices

(condensed DNA/DNA assembly/x-ray diffraction/macromolecular assembly/Flory-Huggins theory)

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ABSTRACT We have measured the repulsive force between B-form double helices in parallel packed arrays of polymer-condensed DNA in the presence of 0.005–1.0 M ionic solutions. Molecular repulsion is consistently exponential with a 2.5–3.5 Å decay distance, when the separation between DNA surfaces is 5–15 Å. Only weakly dependent on ionic strength and independent of molecular size, this intermolecular repulsion does not obey the predictions of electrostatic double-layer theory. Rather, it strongly resembles the “hydration force” first recognized and quantified between phospholipid bilayers. Only beyond 15 Å separation between molecules is there evidence of electrostatic double-layer forces. The quantitative failure of electrostatic double-layer theory seen here must gravely affect accepted analyses of other polyelectrolyte systems. Because the packing of condensed DNA resembles the spacings of DNA in many bacteriophages, our results permit estimation of the “DNA pressure” in phage heads.

In 1976, LeNeveu *et al.* (1) reported that electrically neutral phospholipid bilayer membranes in pure water exerted a mutual repulsion that decayed exponentially with separation and was detectable to separations between parallel membrane surfaces of ≈ 30 Å. This repulsion was termed a “hydration force” (2) to represent the idea that it is due to the work of removing water from the vicinity of the membrane surface. Further measurements (3–9) on a variety of charged or neutral membranes revealed the existence of hydration forces in pure water or in ionic solutions. For separations of less than 20–30 Å between charged membranes, these forces completely overshadow electrostatic repulsion. A qualitatively similar story has emerged from the forces measured between mica sheets in ionic solution, which show an “additional” exponentially decaying component unexpected from electrostatic double layer theory (10–13). Marcelja and co-workers (14–17) have proposed a simple but elegant theory that shows how an exponential force can arise from the spatially varying perturbation of water near a polarizing surface.

We now report that similar hydration forces occur between DNA polyelectrolyte molecules. We have measured the force per unit length vs. interaxial separation of parallel DNA double helices under various ionic conditions. The strong repulsive force is detectable when the interaxial distance is about 35 Å, at which point the shortest distance between DNA surfaces is ≈ 15 Å. This force between molecules grows exponentially with a 2.5–3.5 Å characteristic distance as the molecules are brought together. Contrary to expectation from double-layer theory, this repulsion is insensitive to ionic strength and is of a different magnitude than predicted from electrostatic theory.

We argue that hydration forces are a major factor in the

interaction of particles undergoing molecular assembly. In particular, the packing of DNA in cells and in viruses must be accomplished in a way that circumvents or overcomes the effects of hydration.

More generally, the dominant force experienced by all polyelectrolytes approaching contact may be expected to be hydration repulsion rather than the forces predicted by electrostatic double-layer theory.

METHODS AND MATERIALS

To make our measurements, we used the observation that double-helical DNA in solution, when exposed to a polymer such as polyethyleneglycol (PEG), condenses into a phase separate from the polymer solution (18). X-ray diffraction shows that the condensed DNA is packed into a lattice with well-defined interaxial spacings that decrease with increasing concentration of added polymer (19). The phenomenon is analogous to the immersion of phospholipid bilayers in dextran solutions used by LeNeveu *et al.* (1, 2) to measure interbilayer forces and by Millman and Nickel (20) to measure forces between muscle filaments or tobacco mosaic virus particles. Here, as in those systems, under conditions in which PEG is excluded from the DNA lattice, the osmotic pressure of the polymer solution is the osmotic stress compressing the lattice. This force of compression is equal and opposite to the interhelical repulsion at the observed lattice spacing.

Following the osmotic stress technique previously developed for interactions between bilayer membranes, we use the measured osmotic pressure of the polymer solution to derive the repulsive force between the parallel double helices.

In the present study, high molecular weight ($\approx 10 \times 10^6$) calf thymus DNA (Worthington) was dissolved in 0.5 M NaCl/50 mM Na phosphate, pH ≈ 7.5 mM Na₂EDTA ($A_{260} \approx 20$), phenol extracted twice, and exhaustively dialyzed against 5 mM Tris/5 mM cacodylic acid/1 mM Na₂EDTA (5/5/1 TCE) buffer. A low molecular weight ($\approx 1.5 \times 10^5$) sample was prepared by sonicating calf thymus DNA under helium in 0.5 M NaCl at 0°C, then exhaustively dialyzing against 5/5/1 TCE buffer. The alternating polynucleotides poly(dA-dT) ($M_r, \approx 2 \times 10^5$) (P-L Biochemicals) and poly-(dG-dC) ($M_r, \approx 3 \times 10^6$) (Sigma) were dialyzed directly against 5/5/1 TCE buffer without further purification.

DNA gels for x-ray measurements were prepared in one of two ways. Either the DNA was precipitated with 5% PEG ($M_r, 20,000$) (PEG 20; Sigma) or with ethanol. The pellets were centrifuged down and the supernatant was replaced with a PEG 20 solution [or with PEG ($M_r, 6000$) (PEG 6; Sigma) or polyvinylpyrrolidone ($M_r, 40,000$) (PVP 40; Sigma) in some cases] in vast excess, in the appropriate salt

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Abbreviations: PEG, polyethyleneglycol; PVP, polyvinylpyrrolidone.

solution. DNA pellets prepared with ethanol will, in general, swell in PEG solution, whereas gels precipitated in 5% PEG will lose water and contract. Interaxial spacings, however, are independent of whether the gel swells or contracts, indicating that the observed spacings characterize a reversible equilibrium state.

Osmotic pressures of PEG 20 solutions were measured by N. Fuller as described by LeNeveu *et al.* (1, 2). Osmotic pressures of PEG 6 and PVP 40 solutions were determined by equilibrium dialysis against PEG 20 solutions through SpectraPor 6 membranes (M_c cutoff, 1000) with capillary viscometry for a sensitive measure of polymer concentration.

X-ray diffraction pictures were taken at room temperature with an Elliott GX-20 rotating anode generator. The sample-to-film distance, calibrated with 4.87 Å reflection from powdered Teflon, was about 15 cm. The interaxial (helix-to-helix) reflection is easily identified as the most intense ring on the film (Kodak NS-2T). The observed weaker, higher order reflections are consistent with the expected hexagonal packing of repelling cylinders (21). All interaxial spacings (d_i values) reported here are corrected for this packing [$d_i = (2/\sqrt{3})d_{\text{Bragg}}$]. Reflections with spacings less than about 30 Å are very sharp and, judging from multiple measurements on different samples, can be determined with an error of ± 0.2 Å. Beyond about 35 Å, however, the rings become less intense and more diffuse, resulting in errors of approximately ± 1.0 Å.

Osmotic pressure, in terms of the energy per unit length (G) per DNA molecule in a hexagonal lattice, is

$$\pi_{\text{osm}} = \frac{dG}{d\left(\frac{\sqrt{3}}{2} d_i^2\right)} = \frac{dG}{dd_i} \left/ \left(\sqrt{3} d_i\right), \quad [1]\right.$$

where d_i is the interaxial spacing and π_{osm} is the osmotic pressure in both the ordered-lattice DNA phase and in the polymer medium. The consequent force per unit length, $f(d_i)$, between nearest pairs (whose interaction is taken to be pairwise additive) is

$$f(d_i) = \pi_{\text{osm}} d_i / \sqrt{3}. \quad [2]$$

To see this, note that dG/dd_i is a rate of change of energy per unit length of one molecule. It actually represents the work of pushing in the six nearest neighbors whose pairwise interaction is $f(d_i)$ per unit length. The change in work, ΔG , for a change in d_i is

$$\Delta G = 6 \times f(d_i) \times \Delta d_i / 2 = \frac{dG}{dd_i} \Delta d_i,$$

where the factor of 2 is to share the work equally among rods.

The predictions of electrostatic double layer theory were generated from numerical solutions of the full nonlinear Poisson-Boltzmann equation in cylindrically symmetric cell geometry. Forces were generated from the differences between the ionic density at an enclosing cylindrical surface bounding a volume equal to the volume per molecule and the bulk salt concentration of the bathing medium. Other, less convenient, methods of estimation that do not assume cylindrical symmetry (e.g., those discussed in refs. 20 and 22) are found to give identical predicted decay lengths.

RESULTS

The observed interaxial distances cover a range of 25 to 45 Å. Zimmerman and Pfeiffer (23) and Maniatis *et al.* (19) showed that such DNA samples remain in the B conformation throughout. The diameter of a DNA double helix in this conformation is ≈ 20 Å.

Plots of osmotic pressure vs. interaxial separation for DNA gels in 0.1, 0.25, 0.5, and 1.0 M NaCl solutions are shown in Fig. 1. The points in the two highest concentrations virtually superpose and lie on an almost straight line. The exponential decay constant λ for the 0.5 M data is 3.2 Å; that for 1.0 M, 3.4 Å. Decay constants here and below are for $f(d_i)$ taken from the plotted π_{osm} by using Eq. 2. This conversion removes the slight curvature in the $\log \pi_{\text{osm}}$ plots; i.e., in cylindrical coordinates, $f(d_i)$ is strictly exponential for $d_i \gg \lambda$ while π_{osm} is not.

Forces at the two lowest concentrations appear asymptotic to this line as higher pressures are approached but show stronger ionic-strength-dependent repulsion at larger spacings. In Fig. 1, the upper dashed line is the predicted electrostatic double layer repulsion between fully charged rods in 0.1 M solution computed by using the complete nonlinear Poisson-Boltzmann equation and the lower dashed line is the electrostatic double-layer prediction for rods again in 0.1 M solution but with the residual charge predicted by Manning's counter-ion condensation theory (24). Theoretical estimates of electrostatic double layer repulsion in more concentrated salt solution similarly fail to describe the data; the electrostatic double-layer theory does not predict the independence of salt concentration that occurs at high pressures or high ionic strengths.

We compare forces in three 0.5 M alkali chloride solutions in Fig. 2. Except at low pressures and large spacings in CsCl, the curves are roughly parallel with 3.4 and 3.2 Å exponential decay constants for the Li^+ and Na^+ curves, respectively. There appears to be a systematic difference in the magnitude of forces, with Li^+ conferring the weakest repulsion and Cs^+ the strongest.

Forces in MgCl_2 solutions at 5, 25, and 100 mM (Fig. 3) are weaker than those in solutions of univalent ions but show an exponential decay qualitatively similar to that described above, with decay constants 2.7, 2.8, and 2.1 Å, respectively. At 0.1 M, MgCl_2 does lead to somewhat weaker forces but the difference in decay constants is much smaller than the factor of 2 expected from electrostatic double layer theory.

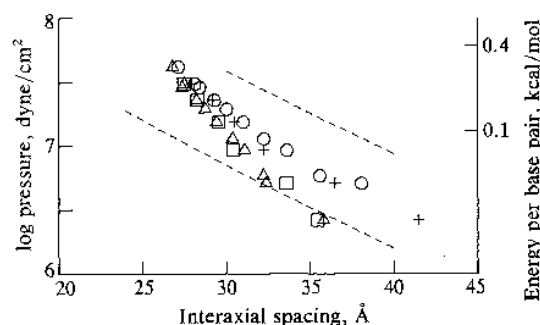


Fig. 1. Lattice pressure vs. interaxial spacing in NaCl solution. \circ , 0.1 M; +, 0.25 M; Δ , 0.50 M; \square , 1.00 M. At higher pressures and salt concentrations, the data converge to a common curve. Energy per nucleotide pair was computed by integrating the common curve for 0.50 and 1.00 M extrapolated to infinite separation. Values thus have validity only for smaller spacings. The upper and lower dashed lines are the predictions in 0.10 M solution of electrostatic double layer theory, respectively, for fully charged molecules and for molecules bearing the residual charge density predicted by Manning condensation theory.

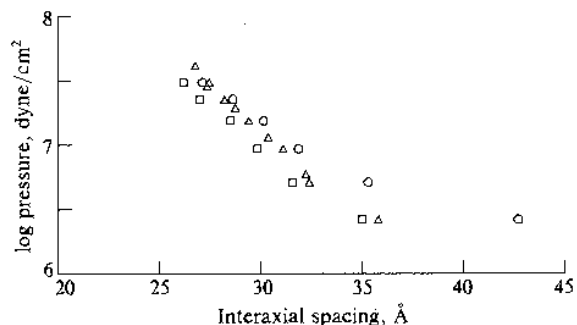


FIG. 2. Comparison of lattice pressures for DNA in 0.5 M LiCl (□), NaCl (Δ), and CsCl (○).

For comparison with that theory, we have plotted the pressure expected from solution of the full nonlinear Poisson-Boltzmann equation for parallel cylindrical rods in 25 mM MgCl₂ solutions (dashed lines). We have again used two charge densities: full charge and the residual charge expected from Manning's counter-ion condensation theory (24). In no way does the calculated force resemble that observed.

Comparison of pressures in 25 mM CaCl₂ or MgCl₂ (Fig. 4) resembles that between various univalent cation media (Fig. 2). Decays are exponential with little difference in rate. Constants are 3.1 and 2.8 Å for Ca²⁺ and Mg²⁺, respectively. Force magnitudes are systematically different but, in this divalent case, it is the lighter (Mg²⁺) species that causes the stronger force.

Pressures seen in media containing the diamine putrescine, a divalent ion biologically important for packing the DNA of many bacteriophages (25), are plotted in Fig. 4. It is clear that this ion leads to forces much as are seen with Ca²⁺ or Mg²⁺; nothing special is apparent. The decay constant is 3.2 Å.

We have made several ancillary force measurements to buttress our interpretation of the data.

Does the "indifferent" PEG 20 polymer in fact act only through its osmotic pressure and not interact directly with the double helix by partitioning between helices in the condensed regime? We repeated some measurements with the much smaller PEG 6 and with PVP 40 to ascertain that the DNA lattice spacing depended only on the osmotic pressure and was independent of the identity of the stressing polymer (Fig. 5).

The gel phase appears not to contain added polymer between interaction DNA molecules. This effective exclusion is indicated by the fact that polymers of widely different length and character give identical results when calibrated solely on the basis of the chemical potential of water (as os-

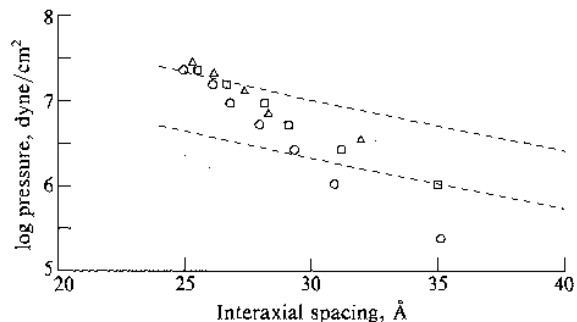


FIG. 3. Lattice pressures in 5 (Δ), 25 (□), and 100 (○) mM MgCl₂ solutions. The upper dashed line is the prediction of double layer theory for fully charged molecules in 25 mM MgCl₂; the lower line is for molecules bearing residual charge after ion condensation.

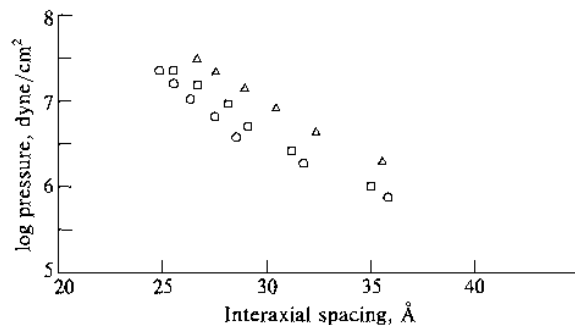


FIG. 4. Comparison of pressures in three divalent cation solutions: 25 mM MgCl₂ (□) or CaCl₂ (○) or 10 mM putrescine Cl₂·2HCl (Δ). Note the similar slope for all three cases.

motomic pressure) measured in the absence of DNA (Fig. 5). The same result should obtain if we used mechanical pressure or any other equivalent dehydrating technique, rather than added polymer, to obtain the required osmotic pressure. These other techniques were in fact used in antecedent studies with lipid bilayer systems in which their equivalence was established (4).

We also confirmed (Fig. 5) that the force between double helices is independent of molecular length by comparing short fragments, 850 Å long, and high molecular weight native calf thymus DNA some 60 times longer.

The force between helices is apparently independent of base-pair composition. The synthetic polymers poly(dA-dT) and (dG-dC) display forces identical to those shown by calf thymus DNA (Fig. 6).

DISCUSSION

The salient feature of all the pressure vs. separation data is an exponential decay with a 2.5–3.5 Å decay length that is insensitive to cation type and to the ionic strength of the medium. There are no oscillations such as might be expected from measurements (26, 27) and models (e.g., ref. 28) involving hard smooth surfaces. The DNA "surface" is rough on the scale of oscillatory periods expected from those models and measurements. The only clear deviation from the 2.5–3.5 Å exponential occurs at larger molecular spacings and lower medium ionic strengths, where there is some indication of decays like those predicted by electrostatic double layer theory. Over the 5–20 Å range of molecular surface separations monitored, we see none of the 10 Å exponential decay reported between surfaces of mica charged by the adsorption of cations exchanging for mica protons (12, 13).

We have failed to find any quantitative electrostatic double-layer theories that can rationalize our results over the

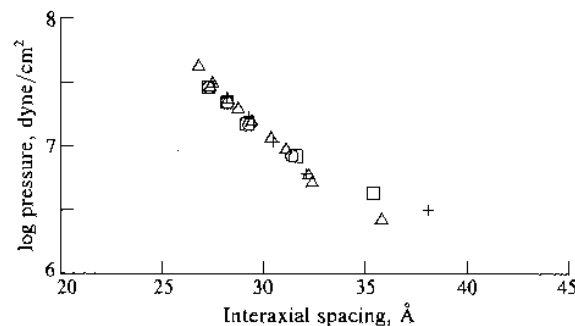


FIG. 5. Neither the identity of the condensing polymer—PEG 6, PEG 20, or PVP 40—nor the length of the DNA affects measured lattice pressure. ○, PEG 6/short DNA; +, PVP 40/long DNA; Δ, PEG 20/long DNA; □, PEG 6/long DNA.

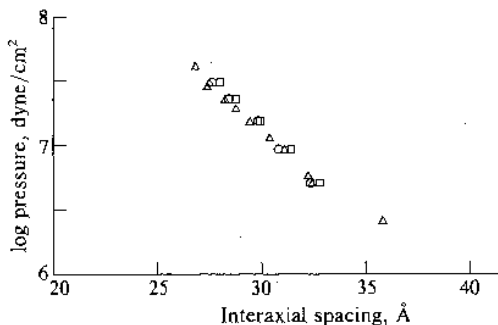


Fig. 6. Lattice pressure is insensitive to base-pair composition. □, poly(dG-dC); ○, poly(dA-dT); △, native DNA. All three data sets are for 0.5 M NaCl solutions.

range of ionic strengths examined and distances observed. The decay always has the wrong slope (except in the fortuitous instance of 1.0 M solutions whose Debye length is close to the characteristic hydration force decay length). For example, there is no way the theoretical curves for 25 mM can be made to coincide with the $MgCl_2$ data. Nor can we see how electrostatic repulsion could give such similar force vs. distance curves for a 20-fold change in $MgCl_2$ concentration (5–100 mM; Fig. 3).

We feel forced to conclude that electrostatic double-layer theory gives a qualitatively incorrect account of forces between parallel DNA helices nearing contact. Considering the very high surface charge density of DNA, the theory is likely to fail as dramatically with other polyelectrolytes as well. One must look to another explanation of the data in the near-contact regions.

To evaluate possible entropic or steric contributions to the observed force, we tried to apply the Flory-Huggins lattice theory of polymer solutions (29). We can make this formalism fit observation by curve fitting for the volume fraction DNA and the parameter χ that measures the relative affinity of the polymer for water. The only way that this curve fit gives agreement with observation is to use χ values for these concentrated DNA gels of about 0.55. For dilute polymer solutions, a χ value of 0.5 implies ideal mixing of water solvent and polymer, while $\chi > 0.5$ means that water is more favorably attracted to itself than to the DNA surface.

It is worth recalling that Post and Zimm (30) point out that poor solvent conditions—i.e., dilute solution χ values > 0.5 —cause polymers to precipitate. In that analysis, unfavorable PEG-DNA interactions in solution cause DNA to collapse into a gel. We have found that this gel contains effectively no PEG.

DNA is, of course, a very stiff polymer. Flory-Huggins lattice theory is for completely flexible chains whose statistical properties are kept the same at all polymer concentrations. (It is the high entropy of the chains that leads to larger repulsive forces than for stiffer molecules.) When corrected for chain inflexibility by using the approach of Matheson and Flory (31, 32), the theory gives a force decay that is in no way exponential, a qualitative deviation from observation (R. R. Matheson, personal communication).

The data of Fig. 5 provide yet another argument against the dominance of mechanical entropic factors. We created gels of molecules of approximately the "persistence length" [half the length of the random straight-line steps that describe the conformation of a very long polymer (33–35)]. We found no detectable difference between these measurements and those on molecules in identical solutions but almost 2 orders of magnitude longer than the persistence length.

It is also instructive that the very sharp x-ray diffraction pattern seen at close spacings has none of the chain disorder that entropic repulsion would require.

We can find no reasonable model of mechanical-steric-entropic forces between flexible DNA rods that predicts an exponentially varying repulsion such as we have observed. We therefore believe that mechanical factors are not evident in our measurements.

The force vs. separation behavior we found between DNA polyelectrolytes closely resembles that between charged phospholipid bilayer membranes at separations of < 20 Å (3, 6–9). For those materials, only at distances > 30 Å does the slowly decaying electrostatic double-layer force emerge from behind the precipitously changing hydration force. Because of this strong resemblance with the extensively studied phospholipid membranes (1–9), we believe that the 3 Å decay-length exponential is a hydration force reflecting the work of removing water polarized on facing molecular surfaces. The negative (phosphate) charges on the DNA surface must be almost all balanced by bound cations. The strength of polarization of water combines the action of both the chemically fixed negative and physically bound cationic charge. Hence, the particular ionic species bound influences the magnitude of perturbation of water at the surface and the magnitude of the measured force but the decay of the perturbation of water away from the surface and the consequent decay of the repulsive force between molecules is, as argued by Marcelja and co-workers (14–17), a property of water itself and not of the perturbing surface.

Li^+ , for example, is more strongly hydrated than Na^+ . If the hydration of the negatively charged phosphate dominates the surface polarization of DNA, then a greater contribution from bound charges of surface water polarized oppositely from the phosphate water will reduce the net polarization and consequently the repulsion force, as is observed in comparing Li^+ with Na^+ (Fig. 2). The difference in surface polarization of +2 and +1 ions can be viewed similarly.

When ionic strength is lowered (e.g., see Fig. 1) or the ions are not strongly bound (e.g., Cs^+ in Fig. 2), then there are deviations from the hydration behavior. Ionic rearrangement must by necessity create force curves with a gentler slope.

We have adapted the original model of Marcelja and co-workers (14, 17) for planar systems to derive hydration forces between cylinders assuming cylindrical symmetry. The model predicts a purely exponential force per unit length between parallel molecules with a decay constant in principle the same as between planar bodies. It is this constant for pairwise rod interactions that we have computed from the plotted gel pressure data and Eq. 1. The Marcelja theory contains a second parameter P_s , which represents the magnitude of polarization of water at the surface. The theoretical maximum value, P_0 , will obtain if all water molecules are perfectly aligned. Our data give a value for P_s/P_0 in the 5–10% range.

These values of P_s/P_0 were calculated assuming that DNA is a smooth circular cylinder. The x-ray structure and discussion by Dickerson and co-workers (36, 37) illustrate the problem in defining a surface polarization in this way. The ordered water seen around the phosphates (37) will certainly be the main contributor to P_s . On the other hand, it is not clear how much contribution to P_s is made by the water packed in the grooves of the molecule. In any case, the exponential nature of the decay in polarization ensures that no ordered water will be detected by x-ray diffraction beyond the first layer around the phosphates. This expectation is in complete accord with the x-ray structure.

DNA *in Vivo*. X-ray diffraction studies (38–40) show that the lateral density of DNA packed in bacteriophage heads is within the range of densities in the condensed gel lattices whose force characteristics we report here. Earnshaw and Harrison (38) have described a variation in lateral spacing on a series of deletion and insertion mutants of λ phage wherein the DNA lateral spacing is greater or smaller depending on

whether there is less or more DNA within the phage head whose internal volume remains fixed. It is argued (40) that such variation indicates a pressure among the DNA strands to fill the available space, which can act to extrude the genome during infection. The magnitude of this pressure has been estimated theoretically (41); measurements on the gel phase provide a direct estimate of this expansive pressure and its integral, the work of DNA condensation to the density in the phage head.

The first and most startling feature of the expansive pressure is that it is probably due to hydration of ion-coated molecules rather than to electrostatic double layer repulsion. The actual force between molecules will vary with ionic composition of the suspending medium, but it will decay exponentially, as shown in the figures, for the 26–30 Å interaxial distances observed in several bacteriophages (table 2 of ref. 38). At these distances, the packing energy per base, 0.1–0.4 kcal/mol of base pairs (1 cal = 4.18 J) (or the DNA pressure, 1.2–5.5 × 10⁷ dyne/cm²; 1 dyne = 10 μN), is approximately one order of magnitude less than expected previously (41) but still greater than the conformational factors considered in that earlier work. Forces measured in media containing the weak “condensing agent” putrescine act the same as those in any other divalent ion-containing medium. No particular condensing effect is present. We defer to a later report a more thorough examination of *in vivo* “DNA pressure.”

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