David S. Woodruff
Department of Biology,
University of California, San Diego,
La Jolla, CA 92093–0116, USA

■

The Theory of DNA Bending

A. D. Mirzabekov and A. Rich (*1*) conjectured in 1979 that charge neutralization of phosphate groups along one side of a DNA segment could cause the DNA to bend toward the neutralized side. Ten years later, this reasonable idea was finally analyzed with the tools of polyelectrolyte and elasticity theory (*2*), and it was concluded that even low degrees of unilateral phosphate neutralization would be sufficient to bend DNA to a structurally significant extent. The conjecture and supporting theory were recently confirmed experimentally by Juliane K. Strauss and L. James Maher III in their Research Article "DNA bending by asymmetric phosphate neutralization" (16 Dec., p. 1829), which was also discussed in an accompanying Perspective by D. M. Crothers (p. 1819). The experimental data are reported to be in general agreement with the predictions of the theory. Strauss and Maher note, however, that one of the quantitative predictions of the theory is not observed. The theory predicts that the radius of curvature of the bend depends on the length of the DNA segment. The observation is that the radius is the same over the length range studied.

The discrepancy is only apparent. The DNA molecules synthesized by Strauss and Maher possess discrete "patches" six base pairs long, completely neutralized on one side. DNA molecules of different lengths contain more patches, but the bending is localized to each patch. The radius of curvature is the radius characterizing the bent six–base pair neutral patch, regardless of the overall length of the DNA within which the patches are embedded.

The theoretical equations are applicable to the DNA segment that is unilaterally neutralized. In this case they are applicable to the six–base pair patch completely neutralized along one side. I have set the length parameter L in the theory equal to the length of six base pairs of DNA. I have also set the fractional extent of unilateral charge neutralization α equal to unity. In univalent buffer the theoretical formula then predicts that the bending angle is about 9°. The value of the bending angle in tris buffer measured by Strauss and Maher is about 21°. The list of reasons not to expect better than factor of 2 agreement between theory and experiment is long. Perhaps the most obvious is the almost complete lack of molecular-structural detail in the theoretical model.

Gerald S. Manning
Department of Chemistry,
Rutgers University,
New Brunswick, NJ 08903, USA

References

1. A. D. Mirzabekov and A. Rich, *Proc. Natl. Acad. Sci. U.S.A.* **76**, 1118 (1979).
2. G. S. Manning, K. K. Ebralidse, A. D. Mirzabekov, A. Rich, *J. Biomol. Struct. Dynam.* **6**, 877 (1989).

■

Biotech Patents and "Usefulness"

The article by Richard Stone "Rules would drop need for clinical data" (News, 6 Jan., p. 23) could leave the reader with a misleading impression about guidelines proposed by the U.S. Patent and Trademark Office (PTO) with respect to the standard to which patent applicants are held in substantiating the "usefulness" of an invention. Far from being a "significant concession" to the demands of the biotechnology industry, the PTO guidelines provide a road map to help patent examiners to apply what has been long-settled law in this area.

The clinical data which PTO examiners have sought from inventors were not merely "unrealistic," but also were not required by law. Case law established over many years mandates that the PTO must accept an inventor's assertion of a utility for an invention unless a reasonable, scientific basis exists to doubt that assertion.

In the course of analyzing patent applications in the biotechnology area, many examiners stood this principle on its head by presuming therapeutic inventions to be "incredible" unless proven otherwise; this, despite the fact that the category of "incredible" inventions had been reserved for perpetual motion machines, engines that run on tapwater, and the like. Applicants then were subjected to what many felt were unreasonable demands for evidence, including human clinical data, to prove that the invention was useful in a practical sense.

According to the proposed guidelines, by contrast, examiners of biotechnology applications are to consider the utility of a claimed invention in conformance with established U.S. patent law practice. The guidelines (*1*) state, for example, that examiners should consider whether a patent applicant "has asserted that the *claimed* invention is useful for any particular purpose and that assertion would be consid-