

This Week's Citation Classic™

CC/NUMBER 51
DECEMBER 17, 1984

Lerman L S. Structural considerations in the interaction of DNA and acridines.

J. Mol. Biol. 3:18-30, 1961.

[Méd. Res. Council Unit for Mol. Biol., Univ. Cambridge, England and Dept. Biophys., Univ. Colorado Med. Ctr., Denver, CO]

Molecular parameters inferred from hydrodynamics and fiber diffraction agree with the supposition that aminoacridines impose a substantial departure from the Watson-Crick helical structure upon binding to DNA. The polycyclic cation is sandwiched between otherwise adjacent base pairs in the partially unwound helix. The results are stereochemically plausible and conflict with other hypotheses. [The SC¹® indicates that this paper has been cited in over 950 publications since 1961.]

Leonard S. Lerman
Genetics Institute
225 Longwood Avenue
Boston, MA 02115

August 14, 1984

"I began to think about the structure of complexes of DNA with polycyclic aromatic molecules while engaged in studies on genetic transformation in pneumococcus. Rough stereochemical calculations confirmed the plausibility of an intercalated structure in which the double helix unwinds slightly to open a space of the appropriate thickness into which a carcinogenic polycyclic hydrocarbon (or a similar mutagen) might fit. The real problem seemed to be to devise an experiment that would provide structural evidence. While optical and dialysis-equilibrium measurements gave meaningful thermodynamic data, they did not permit decisive structural interpretations that might distinguish intercalation from any other binding geometry. Lengthening of the molecule seemed to be easily measurable without elaborate instrumentation. The upper limit of first-order binding¹ implied a length extension of 45 or 50 percent, which could be demonstrable as a change in the intrinsic viscosity of DNA, assuming that the increment in length was not compensated by increased flexibility. The attachment of nonintercalated cations would be expected to give a small decrease in the intrinsic viscosity because of diminished electrostatic repulsions between parts of the molecule. The first experiment showed a large viscosity change in the right direction, opposite to the effect of putative nonintercalators.

"Most of this paper is concerned with the examination of physical properties and parameters

other than viscosity. Although no single experiment could stand by itself to demonstrate intercalation, each ruled out alternative structural hypotheses while remaining consistent with the intercalated structure. I prepared X-ray diffraction patterns from proflavine-containing DNA fibers and constructed a satisfactory molecular model during my sojourn with Crick at the MRC laboratory in Cambridge. In subsequent papers,^{2,4} I reported the use of two nonparallel transition moments in flow orientation measurements to define the plane of intercalation and demonstrated the unreactivity of intercalated amino groups toward nitrous acid. The work was summarized together with new studies indicating the intercalation of other types of molecules, the thermal stabilization of DNA, the selective stabilization of the double (ribo) helix over the triple, a better analysis of the fluorescence orientation data, and other results.⁴ One of my drawings from that paper has been widely reproduced, although usually credited to later authors. In reference 5, I showed the intercalation of a carcinogenic pentacyclic acridine and an extensive set of negative measurements on nonintercalators. A new, clear demonstration of complexes of DNA with benzopyrene was included.

"The analysis of the intercalated structure offered a key to understanding the existence of two types of mutation that were mutually compensatory when in close proximity. On genetic grounds and by analogy to intercalation, these were identified by the Brenner-Crick group as insertions and deletions. As far as I know, my hypothesis² that pairwise intercalation can introduce unequal crossing over is the only proposal for a mechanism that specifically depends on the intercalated structure. Other hypotheses that invoke only helix stabilization ignore the nonmutagenicity of nonintercalating helix stabilizers.

"This paper was the first to use the term 'intercalation' with respect to DNA. It was analogous to use of the term in calendar structure (e.g., February 29th is an intercalated day). It also describes the insertion of metal atoms between layers of graphite in a sense similar to the DNA usage. A review on structure has been given by Berman and Young.⁶ The frequent citation of this paper may be attributable to the relevance of the proposed structure to the mechanism of action of some antibiotics, of some antiparasitics including antimalarials, of some anticancer agents, and of substances that effect loss or alteration of extrachromosomal DNA, as well as carcinogens and mutagens. It is also cited because the structure represented the first well-defined departure of DNA from simple helicity."

1. Peacocke A R & Skerrett J N H. The interaction of aminoacridines with nucleic acids. *Trans. Faraday Soc.* 52:261-79, 1956. (Cited 425 times since 1956.)
2. Lerman L S. The structure of the DNA-acridine complex. *Proc. Nat. Acad. Sci. US* 49:94-102, 1963. (Cited 570 times.)
3. Amino group reactivity in DNA-aminoacridine complexes. *J. Mol. Biol.* 10:367-80, 1964. (Cited 105 times.)
4. Acridine mutagens and DNA structure. *J. Cell. Comp. Physiol.* 64(Suppl. 1):1-18, 1964. (Cited 310 times.)
5. The combination of DNA with polycyclic aromatic hydrocarbons. *Proceedings of the Fifth National Cancer Conference, 1964*. Philadelphia: Lippincott, 1965. p. 39-48.
6. Berman H M & Young P R. The interaction of intercalating drugs with nucleic acids. *Annu. Rev. Biophys. Bioeng.* 10:87-114, 1981.