Letters

Protein Behavior

In a recent article [*Science* **128**, 815 (1958)], I. M. Klotz admirably points up the fact that electrostatic interactions involving proteins and small ions have generally had to be treated in an oversimplified way, and he calls attention to the many observations which would suggest that the properties of the water in the immediate vicinity of the protein molecule may be rather different from those of the water in the bulk solvent. His proposal regarding the effect of an ice structure would explain the greater difficulty of protonation of an $-N(CH_3)_2$ group but, it appears, would still not solve the problem of reduced reactivity of the —SH group with Ag^+, with which he initiated the discussion. In this case, of course, there would be no change in the charge to modify the structure of the ice lattice.

The proposal seems even more troublesome when one considers the —COOH groups in the protein. In this case a charge appears on the group when the hydrogen ion is lost. Consequently, the loss of the proton would be hindered, and the apparent *pK* should be increased as compared with the expected intrinsic *pK*. There seems to be little evidence for any considerable number of —COOH groups with unexpectedly high *pK*'s in proteins.

The lack of any evidence for electrostatic effects on the titration curve of the azomercurial would still be disturbing, however—unless one assumes that the reaction with hydrogen ion is leading to displacement of the azomercurial. If this were true, there would be no change in the charge, and one would not anticipate an electrostatic effect. Such a displacement of methylmercury would have been anticipated on the basis of the results of Hughes [*Cold Spring Harbor Symposia Quant. Biol.* **14**, 79 (1949)].

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Each of the three paragraphs of Mehl's letter raises essentially one question. The responses may be grouped, therefore, into the same arrangement.

1) "Maskedness" in the behavior of —SH groups, as Mehl would undoubtedly agree, is a problem of rates rather than equilibria. For example, Ag^+ is usually taken up even by masked —SH groups of proteins if we wait long enough. In terms of my model, the explanation (clearly implied if not explicitly stated in the article) is that Ag^+ would diffuse through "ice" much more slowly than through liquid water. While no actual data are available for diffusion of Ag^+ in ice, measurements with a similar monovalent ion, Li^+ [M. Eigen and L. DeMaeyer, *Proc. Roy. Soc. (London)* **247A**, 505 (1958)], certainly bear this point out.

2) The most careful theoretical analyses of the titration curves of a protein with, for example, 100 carboxyl groups have limited themselves to a single intrinsic dissociation constant. The spread of the titration curves has been accounted for by the assumption that there is a variable electrostatic factor, plus necessary additional assumptions in specific cases. Clearly, if deviations from ideality are attributed to these additional factors, and if we permit the possibility of only a single intrinsic constant, we cannot possibly find more than one intrinsic constant. As I have emphasized, however, the titration curves can also be accounted for by the assumption that there is a broad spectrum of *pK*'s for the carboxyl groups.

3) The explanation suggested by Mehl is not really tenable. We have not studied the titration curve by some general method which follows gross H^+ ion uptake but rather by a special spectrophotometric method which reveals specifically the uptake of H^+ by the $(CH_3)_2N$— group of the dye, not by the mercaptide group of the protein. It is the unusual *pK* and the unexpected shape of the curve for the optical titration of this particular $(CH_3)_2N$— group which must be interpreted; a displacement mechanism postulates changes in state of a different group at the opposite end of the molecule. Furthermore, one should also recall that if the dye had been displaced from the mercaptide linkage, no optical titration could have been obtained in the first place, for as we have mentioned previously [*Arch. Biochem. Biophys.* **63**, 77 (1956)], the dye is essentially insoluble in water alone.

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On Eschewing Teleology

A. J. Bernatowicz' stern admonitions [*Science* **128**, 1402 (1958)] to his biological colleagues and to all other scientists to eschew anthropomorphism and avoid even the appearance of teleological thinking (lest their students be not saved from corruption) confuses me. He wants mechanism, and thus also surely determinism, recognized as the language of science, and he wants the teacher of science not to depart from it. Does he mean *never*? Not with the student at the luncheon table? Not with his wife at the breakfast table? How rigorously must righteousness be applied? And must all scientists observe the canon? I think