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Citation Classics

Nemethy G & Scheraga H A. Structure of water and hydrophobic bonding in proteins. 1. A model for the thermodynamic properties of liquid water. *J. Chem. Phys.* **36**:3382-400, 1962.

The authors describe the structure of liquid water in terms of an equilibrium between small hydrogen-bonded clusters and non-hydrogen-bonded molecules, and derive the distribution of molecules among five hydrogenbonding states from an approximate partition function. (The *SCI*® indicates that this paper was cited 603 times in the period 1962-1976.)

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"It is somewhat surprising that a statistical-thermodynamic paper would be in the list of the most cited articles.' However, this seems to be an example of being in the right place at the right time: the model of water structure which I developed as my Ph.D. thesis with Professor Scheraga in 1962 appeared at a time when its subject matter commanded much attention, and when the paper could serve as a stimulating starting point for studies in various fields.

"It had been recognized for many decades that the unusual properties of water as a liquid and as a solvent could be ascribed to the presence of intermolecular association, due to hydrogen bonding between the water molecules. In addition, in the 1950's, the recognition gained ground that interactions in biological macromolecules are affected profoundly by the structure of water and by its changes. Such interactions in turn decisively influence the spatial structure and therefore the biological activity of these molecules. In fact, the aim of our studies with Dr. Scheraga was not only to derive a reasonable model for the structure of water but to apply it to a quantitative explanation of the phenomenon of hydrophobic interaction, i.e., the interaction of nonpolar solute groups in an aqueous medium.

"Almost all of the older models recognized that water can be described in terms of a mixture of a hydrogen-bonded, bulky aggregation of water molecules (in a sense 'ice-like' in structure, although this term has led to much abuse and misunderstanding) with molecules not possessing hydrogen bonds and packed more densely. In most models proposed prior to about 1960, such a mixture was described in terms of a simple two-state thermodynamic equlibrium.

"The model which we proposed with Dr. Scheraga in 1962 was more elaborate. It had three main features. (1) Five, rather than just two states of water molecules were used to describe hydrogen-bonding equilibria, and an attempt was made to assign self-consistent physical properties to these states. (2) An approximate statistical-mechanical formulation was used. (3) The model and its mathematical formulation could be extended in a simple fashion to provide a physical explanation and a quantitative description of the unusual thermodynamic behavior of nonpolar solutes in water. This extension of our model was based on fundamental ideas proposed and developed by some earlier workers, notably by H.S. Frank and by W. Kauzmann.

"At the time of the appearance of the paper, interest in both water structures and hydrophobic interactions was widespread. The combination of the intuitive simplicity of the model with its power of quantitative prediction made it appealing to many workers in the field of aqueous solutions and of polymers. In spite of many shortcomings, the paper seemed to provide a useful framework at a time when discussion of the role of water in macromolecules had become fashionable."