

Némethy G & Scheraga H A. The structure of water and hydrophobic bonding in proteins. III. The thermodynamic properties of hydrophobic bonds in proteins. *J. Phys. Chem.* 66:1773-89, 1962.
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A quantitative treatment of the thermodynamic parameters of the interaction between nonpolar groups of proteins in an aqueous environment was presented, based on a theory of structural changes of water in aqueous hydrocarbon solutions. [The *SCI*® indicates that this paper has been cited in over 620 publications.]

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The mid-1950s constituted a period of rapid development in physicochemical studies of the structure of proteins in solution, accompanied by increasing interest in the factors that stabilize the conformation of the native molecule. The important role played by electrostatic interactions between charged groups on the surface of the protein had been recognized earlier. Attention began to be focused on other kinds of noncovalent interactions and their contributions to the specificity of the folding and to the stability of the native conformation. A theory of the thermodynamic effects of hydrogen bonding on protein stability and reactivity had just been developed in a series of papers by M. Laskowski and H.A. Scheraga.¹⁻³

When I started my PhD thesis research in 1957 under the direction of Scheraga, our intention was to develop a similar theory for the effects of nonpolar groups on the conformation of proteins. By then, the crucial role of changes of the structure of water in determining the free energy of interaction of nonpolar groups had already been recognized by sever-

al researchers. The stage for the thermodynamic interpretation of hydrophobic interactions had been set in a classic review by W. Kauzmann,⁴ published in 1959. At that time, the term in general use for describing the attraction of nonpolar groups for each other in the presence of water was "hydrophobic bonding," expressing the conceptual analogy with hydrogen bonds that also exert an attraction between specific functional groups. It took a decade for the terminology to change to the more precisely descriptive term "hydrophobic interaction" used today.

We soon recognized that an adequate description of hydrophobic interactions required, as its foundation, a quantitative model that can explain the structure and properties of liquid water and of aqueous solutions of nonpolar solutes. No such model was available at that time. Therefore, the development of a statistical thermodynamic theory of water structure became the prerequisite to the pursuit of our original goal. The investigation resulted in a widely read paper in which a new, detailed structural model was presented for water itself. That paper also became a *Citation Classic*.⁵

The adoption of a theoretical model for water to treat aqueous solutions of nonpolar solutes (involving the formation of clathrate-like structures around the solute) required the combination of a variety of considerations taken from physics, mathematics, and crystallography. One of the possible reasons that our theory of hydrophobic interactions received so much attention was that it provided both numerical thermodynamic data and conceptual insights into the analysis of noncovalent interactions in proteins, stimulating many further studies. This theory constituted a significant part of my research on the nature of intermolecular forces, for which I was awarded the Pius XI Gold Medal of the Pontifical Academy of Sciences in 1972. Some aspects of the theory were superseded by later progress, but many of the concepts introduced in the model (e.g., the clathrate-like structure) were later verified by experiments or by more powerful theoretical analyses. Today, much more is known about protein-solvent interactions, but their full understanding still represents a challenging problem for protein chemists.⁶

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