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My debt to Walter Kauzmann

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My Ph.D. thesis in physical chemistry at Princeton University focussed on the mechanism of combustion of gases in a burner flame. The 'Tanford–Pease theory of burning velocity' was briefly in the limelight, before more elegant theories took its place [1]. It was Walter Kauzmann whom I have to thank for my career reorientation to protein science.

Walter came to Princeton as a new assistant professor during my final year there. He had done his physical chemistry Ph.D. at Princeton a few years earlier, with a theoretical dissertation on optical rotation; he had spent the war years at Los Alamos and had then taken some time off before permanently joining the rank of academia. In the course of this he had become enthralled by the Cohn and Edsall treatise, *Proteins, Amino Acids and Peptides as Ions and Dipolar Ions* [2], and that determined him to become a protein physical chemist.

I saw a lot of Walter Kauzmann in my last few months at Princeton and he has even done me the honor (in his published recollections) of considering me as a kind of adjunct student [3]. In any event I found his enthusiasm for proteins infective. I had lucrative job offers from the industrial sector on the basis of my thesis. But the prospects of research into proteins, which I naively equated in my mind with some romantic notions, as a sort of physico-chemical exploration into the vast mysteries of life, outweighed any question of salary and I decided to join Cohn and Edsall's laboratories if they had a place for me—which they did, as a 'postdoc,' with a stipend less than half of what I could have had in industry. The Cohn and Esdall laboratory, established back in 1920, was a unique entity. A department of physical chemistry in a medical school, mandating a juxtaposition of physics and chemistry with medicine, was unheard of and promised great intellectual riches, which, at least in my case, it delivered as promised.

My decision to move out of the traditional mainstream of physical chemistry was not universally approved. Most of the senior faculty at Princeton thought I should build on my experience in gaseous combustion and use it to get onto the academic ladder as early as possible. In particular, they urged me to apply for a position that was becoming available in the chemistry department at Cornell University. (As things turned out, the position went to Harold Scheraga, who had ironically gone in the same direction as I was planning to do and had adopted protein physical chemistry as his primary research objective.)

I incurred a second debt to Walter approximately 10 years later, this time for specific enlightenment, for implanting the idea of hydrophobic interactions in my mind. This was, of course, not a personal debt, but a shared benefit from which all of us have gained, but I gained more than most because hydrophobicity seemed to answer in one fell swoop several questions that had been puzzling me at the time.

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Walter has denied his priority on the subject of hydrophobicity, claiming that the idea had been ‘in the air’ for a long time [4]. But I keep remembering the novelty of it and I think the novelty can be identified with Kauzmann’s perception of the overall energies of protein folding. There were indeed others who invoked water as an agent in protein folding and asserted or predicted that polar groups would be at the molecular surface of native proteins and nonpolar groups would be buried inside. But virtually everyone accepted the belief fostered by Pauling [5] and others, the belief that intramolecular hydrogen bonds provide the exclusive or dominant energetic driving force for protein folding and that hydrogen bonds between amino acid side chains represent a significant portion of that force. Kauzmann made us realize that side-chain hydrogen bonds could not be energetically comparable with the hydrophobic force. To quote him directly [6]: ‘it does seem unlikely that hydrogen bonds other than those involving peptide linkages can made a major contribution to the stability of most native proteins.’

Debate about this subject still continues to this day and some of the distinction may be largely semantic. But to me at the time it was a revelation: the driving force for folding originated from hydrogen bonds of water, squeezing from the outside—it was not a pulling together ascribable to specific attractions within. The concept for me has had broader implications for all of biological self-assembly [7].

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