Forces of formation and dissolution in protein biochemistry

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When teaching second year undergraduates about biochemistry, I am bound to use the language and metaphors of modern science. Nevertheless, I try not to be limited by their rigidity and endeavour to introduce concepts that are more fluid and therefore more akin to living processes. Rudolf Steiner said that we use our scientific models to ‹build explanation on explanation, at the same time abandoning observation› (*Steiner* 1988) and I heed his warning and encourage students to observe and experience their observations as carefully as possible, before drawing on accepted models. Their response to my process oriented teaching is generally very good and occasionally I am privileged to witness the moment when a student grasps the significance of an experimental observation in a broader context. Some students even manage to achieve a level of understanding that resonates with something within their inner being. They appear to respond to the experimental processes under examination by activating similar processes in themselves, albeit on an unconscious level. If they could only be encouraged to become more conscious of the dynamics between their inner worlds and scientific observations, they might increase their awareness of the spiritual realities within the discipline we call biochemistry.

In this article I would like to describe some of the concepts that I use to teach students about processes in proteins. The experiments I mention were originally designed to illustrate the mechanical aspects of protein folding but, on closer inspection, demonstrate something more important. I believe they reveal how the delicate balance between formative and dissolving forces is a crucial determinant of protein activity.

Proteins are long chains of chemical units called amino acids, strung together in the order specified by DNA and then folded up into active conformations. They are the molecular components that accomplish almost all the essential tasks in living cells. For example, proteins catch other molecules and build them into cellular structures or take them apart and extract their energy. They also carry atoms to precise locations inside or outside the cell. They are able to behave, in the metaphori-

cal sense, as ‹pumps› or ‹motors› or form receptors that trap specific molecules. They can even act as ‹antennae› that conduct electrical charge. In order to perform their particular tasks, proteins must have the correct shape and the way they are folded in space determines whether they are active or not. Most biology textbooks declare that protein folding is due almost entirely to the chemical sequence of its component amino acids, also known as the primary structure. I quote from one of the standard biochemistry texts we use in Switzerland (*Voet/Voet* 1995):

«… a protein's primary structure dictates its three dimensional structure. In general, under the proper conditions, biological structures are self-assembling so they have no need of external templates to guide their formation.»

This is a very misleading statement because it lays all the emphasis on the protein's intrinsic chemistry and does not stress the importance of the ‹proper conditions›. Yet every biochemist knows that proteins in different environments behave differently. For example, most water-soluble proteins, which are active in aqueous (watery) environments, quickly lose their activity when transferred into methanol, even though chemically methanol is considered to be the nearest common homologue to water.[1] In fact such proteins demonstrate their aversion to methanol not only by losing their activity but also by coming out of solution as white, disordered precipitates. Thus I stress that the chemical nature of proteins *per se* is not sufficient to produce their active forms. External forces clearly play a very significant role in determining correct protein conformation and activity.

Many of my demonstrations are performed using a protein called lysozyme found in chicken egg white. One of the attractive features of this system is that the egg white is not treated in any way, so observations are initially made on the protein in its natural setting. Lysozyme is an enzyme, one of a large group of proteins whose function is to speed up chemical reactions. Its activity was first observed in 1922 by the British bacteriologist Alexander Fleming. There is a charming story that relates how Fleming accidentally sneezed into one of his petri dishes and later noticed that the mucus from the sneeze dissolved his bacteria.[2] It was Fleming's hope that lysozyme would be a universal antibiotic because the reaction it speeds up is the disruption of chemical links in the cell walls of some bacteria and fungi.[3]

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1 Although methanol and water are apparently similar on a molecular level, anyone can see that methanol has quite different macroscopic properties, not the least of which is that methanol is a dangerous poison.

2 Alexander Fleming's search eventually led to the discovery of penicillin in 1928. He noticed that a chance contamination of a bacterial culture plate by the mould *Penicillin notatum* lysed the nearby bacteria. Like lysozyme, penicillin also acts on the cell walls of bacteria by inactivating the enzymes that build them. Since bacterial growth and expansion requires the action of enzymes that degrade cell walls, exposure of growing bacteria to penicillin results in their lysis because the normal balance between cell wall biosynthesis and degradation is disrupted.

3 Lysozyme hydrolyses the α (1–4) linkage between N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) in the alternating NAM-NAG polysaccharide components of the cell wall peptidoglycan in bacteria. It also hydrolyzes the chitin of fungal cell walls which is made up of α (1–4)-linked poly(NAG) components.