

中国科学院生物物理研究所

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Institute of Biophysics ACADEMIA SINICA

June 2, 1988

Dr. Joshua Lederberg
President
The Rockefeller University
1230 York Avenue
New York, NY 10021
U. S. A.

Dear Dr. Lederberg,

Thank you for your letter of May 6 and I am sorry for the delay in answering as I was abroad for a couple of weeks.

Your letter raised a very important question in that "whether the final lowest energy state is the biologically active state". This has been usually assumed to be the case because, in vivo as well as in vitro, most proteins so far studied are sufficiently stable, and they do not seem to pass spontaneously into an inactive conformational state. If indeed such states do exist, the kinetic barrier between the metastable and biologically active state and this stable but inactive state must be sufficiently great so as to make the formation of the latter a very slow process.

Some proteins are not very stable after isolation and the reason is still poorly understood. Contamination by trace amounts of proteolytic enzymes, chemical changes such as deamidation or cleavage of susceptible peptide bonds have been suggested. As crystallization, especially growth of crystals suitable for X-ray diffraction studies, is usually a slow process, it would be difficult to crystallize a partially "denatured" protein. Of course, as you pointed out, precisely because of the instability of biologically active conformers, some proteins may have escaped detection by protein chemist when they seek to isolate an active protein from the cell.

Evolutionally, it might be of advantage for some proteins to have a transient existence during life's processes. It is known that the in vivo "half-life" differs greatly for different

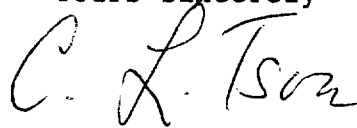
p. 2. Dr. Lederberg.

proteins. It has been suggested that information stored in the sequence of the protein molecules concerned directs their breakdown. On first thought, it may not be advantageous, as far as evolution is concerned, to have large amounts of inactive conformers linger around in the cell.

The above are the points that come to my mind after reading your letter. However, I believe that the question you raised is of such importance that careful consideration is required to do its justice. It would also be of great importance to think of some thing to do experimentally to elucidate some of the points as discussed above.

I come to the States fairly often and invited by the late Professor S. Moore, I had the honor to visit and to present a Seminar at the Rockefeller University in 1981 when I was Visiting Professor at Harvard Medical School with Bert Vallee. I am at present a Fogarty Scholar-in-Residence at the NIH and shall be spending my last term for a few months some time in the Spring of 1989 in Bethesda. I should be delighted to have an opportunity to meet and to discuss matters of common interest with you when I shall be in the States again.

Yours sincerely

A handwritten signature in cursive script, appearing to read "C. L. Tsou".

C. L. Tsou,