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Enzymes as energy 'funnels'?

Why are enzymes so big? A widely held view is that the large size of an enzyme ensures that the active site possesses a 'static' conformation needed to achieve the enormously increased reaction rates that are characteristic of enzymes.

In recent years it has become apparent that enzymes utilize the free energy of reactant binding to provide much of the necessary activation energy[1–3]. Yet, even after this, a finite activation energy remains to be found, and free energy still must be provided *from somewhere* for the reactant(s) to enter and to pass through their transition state(s). As noted by Ferdinand[4] 'this can only come from the translational energy of solute molecules bombarding the enzyme–substrate complex, because the substrates themselves have become tied down in the active site and have no translational energy left with which to enter the transition state'.

In the last decade or so, several models have been described which share the idea that particular classes of fluctuations in the protein molecule provide means for collimating thermal energy to produce high free-energy events at the active site ('hot spots'[5]), and recently Rick Welch, Béla Somogyi and Sándor Damjanovich have reviewed specific proposals that 'spatio-temporal ordering of the fluctuational behaviour of the protein molecule serves an integral role in enzyme catalysis'[6].

Within the framework of this idea, specific proposals are distinguished by (i) the types of *surface phenomenon* assumed to serve as the source of free energy and (ii) the proposed *mode of 'linkage'* between the sources on the enzyme's surface and the enzyme's active site. Seven particular classes of model are reviewed in some detail, including the authors' own 'energy funnel model', and, as the discussion evolves, the view of the enzyme as a free energy-transducing device, following Lumry and Biltonen[7], is developed, so that 'a *complete* theory of enzyme action must elevate the enzyme from the role of "catalyst" to that of "reactant"'.[6]

Whether the general principle reviewed by these authors[6] is correct or not remains to be proved, although it does provide, notably, a rational explanation for the observable effects of the viscosity of the bulk medium on enzyme catalytic properties[6]. However, one particular (if disappointing) corollary is worth stressing. If the 'reason' enzymes are so big is that they have evolved to act as channellers of thermal energy to their active sites, then the goal of 'biomimetic chemistry', in which chemical analogues of the active sites of enzymes are synthesised to provide the catalytic power (without the inherent instability) of enzymes, may be unattainable.

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References

1 Jencks, W. P. (1975) *Adv. Enzymol.* 43, 219–410
2 Fersht, A. (1977) *Enzyme Structure and Mechanism*, W. H. Freeman, San Francisco
3 Jencks, W. P. (1980) in: *Chemical Recognition in Biology* (Chapeville, F. and Haenni, A-L., eds), pp. 1–25, Springer-Verlag, Heidelberg
4 Ferdinand, W. (1976) *The Enzyme Molecule*, Wiley, New York
5 McCammon, J. A., Wolynes, P. G. and Karplus, M. (1979) *Biochemistry* 18, 927–942
6 Welch, G. R., Somogyi, B. and Damjanovich, S. (1982) *Progr. Biophys. Mol. Biol.* 39, 109–146
7 Lumry, R. and Biltonen, R. (1969) in: *Structure and Stability of Biological Macromolecules* (Timasheff, S. N. and Fasman, G. D., eds), pp. 65–212, Marcel Dekker, New York

Journal Club

α_1-Antitrypsin deficiency – the European 'sickle-cell anaemia'

In 1963 Laurell and Erikson reported an association between pulmonary emphysema (a disease in which the elastic tissue of the lungs breaks down, the normal air spaces enlarge, and crippling breathlessness can follow) and the absence of a band in the α_1-region of a serum protein electrophoretic strip (Fig. 1). This link provided a dramatic demonstration in molecular pathology and has stimulated intensive research into the structure and population genetics of the deficient serum protein involved, α_1-antitrypsin. The most recent chapter in this research has been the cloning of the human α_1-antitrypsin gene by Leicht *et al.*[1], closely followed by publication of an exhaustive review of the known structure and variations of the protein[2]. Curiously α_1-antitrypsin deficiency is confined to Europeans, with a combined frequency of the genes for the two most common deficiency variants of 1 in 750 people. This is even more common than cystic fibrosis of which the incidence is 1 in 2000 people, and means that deficiency of this protein is the commonest inborn error of metabolism in European populations. To survive in the population at this level the mutant gene must presumably confer some evolutionary advantage and α_1-antitrypsin deficiency has been described as the equivalent of the tropical dwellers sickle-cell anaemia in which haemoglobin S confers resistance to the malaria parasite[3]. It has been suggested that the evolutionary advantage conferred by the mutant α_1-antitrypsin gene is that of increased fertility due to lowered viscosity of cervical mucus before ovulation[3].

α_1-Antitrypsin is the major protease inhibitor in serum, providing protection from serine protease released by tissue damage or bacterial invasion. The protein is

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