Chapter 20. Contrasting chemical research and biological research

The generality of domain-closure is not yet established but the prevalence of paired domains and close C-2 symmetry suggests that matrix contraction is usually mediated in function by domain-closure. The common occurrence of that symmetry suggests that nature has discovered several domain-closure devices to make evolution successful. So far those that are known such as enzymic catalysis have little relationship to familiar small-molecule chemistry. The devices that have become apparent are manifestations of mechanical free-volume management and though there may be some other very useful feature of their construction, it is becoming increasingly obvious that free-volume management distinguishes biology from chemistry. The preference for mechanical rather than thermal activation of rate processes distinguishes the biosphere from the small-molecule domain of conventional chemistry. The distinction appears to be very sharp probably because only mechanical devices have the efficiency and versatility required for living things. Primary bond rearrangements are essential in both but only those that can be facilitated by enzymes are useful in biology. That considerably limits the choices for evolutionary experiments but is offset by the major advantage in designing molecules by geometry like buildings. It seems clear that in proteins form follows function. So much so that the latter proves a very unreliable guide for research on the former.

That proteins are "free-volume machines" is an understandable consequence of the options open to evolution once entropy becomes as useful as enthalpy and it follows that the B factors as direct measures of entropy change might be a major tool for protein research. They emerge from semi-subjective methodology with precision and reproducibility sufficient for a really quantitative science. With them we can already learn about the broad and rarely expected

generalizations evolution has found to make life possible Thus for example most if not all enzymes share a minimum set of construction details essential for a highly advanced convergent evolution. It is obvious that of the many possible polypeptides only a very small fraction satisfy this requirement so every enzyme provides an opportunity to find the responsible features in DNA information. What information do two enzymes with very different catalytic function but the same invariant construction features share? This and similar questions can lead to a basic science of proteomics.

The theoretical basis of biology is also somewhat unfamiliar although Wyman in particular showed that biology is predominately non-stoichiometric . His linkage systems reflect not only the need for precision but also the absence of obligatory coupling among linked processes Chemical-bond changes are of course stoichiometric but everything else in biology is not primarily because of linkage to and through proteins so as to allow the maximum versatility in free-energy managemet. Free-energy transactions are limited in size well usually well below those of chemical-bond rearrangements but sufficient through mechanical activation for the high rates and selectivity found in biological systems without destroying the protein. As a consequence coupling is weak but tailored by quantitative adjustment. Useful theories in which coupling among concentrations of species do not follow mass-action laws but rather depend on Gibbs-Duhem relationships as elegantly revealed by Wyman and by Gill and Wyman. For practical convenience we can supplement these rigorous thermodynamic considerations by extra-thermodynamic ones in particular the 'linear free energy"and enthalpy-entropy compensation" relationships. One follows from the other although linear compensation relationships can produce non-linear free-energy behavior. The complete theory of these became possible as a result of Benzinger's discovery. The theory is extra-thermodynamic because the molecular basis of the linearity with molecular change in compensating series

and changes in G, H, S, V and heat capacity are not exact. That is, the thermodynamic changes along a series does not scale exactly with the molecular changes although in specially selected series like the linear alkanes or even alkanols do demonstrate linearity at least as good as the best experimental data. Thus compensation relationships when linear are nevertheless very useful for linked systems and thus for biology because the scaling is exact within experimental errors for most physiological processes supported by proteins. At that approximation compensation is linear and provides an adequate though non-thermodynamic theoretical structure for biology as good as the best experimental data.. A typical Wyman example is linkage of ligand-binding sites. The two sites on protein interact through change in protein conformation. The relation between their concentrations is not linear but the enthalpy and entropy changes for the driven process (heme-heme coupling) produced by changes in the driver process (oxygen uptake) are linear at the weak-approximation level. Varation in hydrogen-ion concentration can alter advancement of driver and thus of driven process with linear E-S behavior and that can be related to the related LFE behavior always accompanying enthalpy-entropy compensation. The slope of the compensation plot known as the compensation temperature is the thermodynamic phase relation and measures the ratio of change in S for given change in E for the measured process. This gives the change in free energy for the measured process as a function of advancement in the driver and in this way one can construct linkage diagrams from systematic measurement of the effects of independent variables to to described the system as a machine.

Subtle change of matrix is probably the major device for coupling as in the usual description of Wyman's "allosteric" coupling among sites on the protein. This allows tailoring of the machine through changes in degree of the phaselike advancement of such coupled changes. Protein machines at least the catalytic ones have duty cycles determined by the amount of entropy lost in

compression and as noted already, this is measured by the compensation temperature. The compensation temperatures of the linked processes are the best description of machine operation. In any specific interaction of ligand with protein there may be a variety of specific molecular details. An example is the productive and non-productive binding of a substrate fragment by ribonuclease A shown in Fig. @.. The normal species with substrate fragment is at the bottom. The abnormal form at the top illustrates the magnitude possible with such fragments and with some residue exchanges. The red lines connect matched pairs of disulfide groups.