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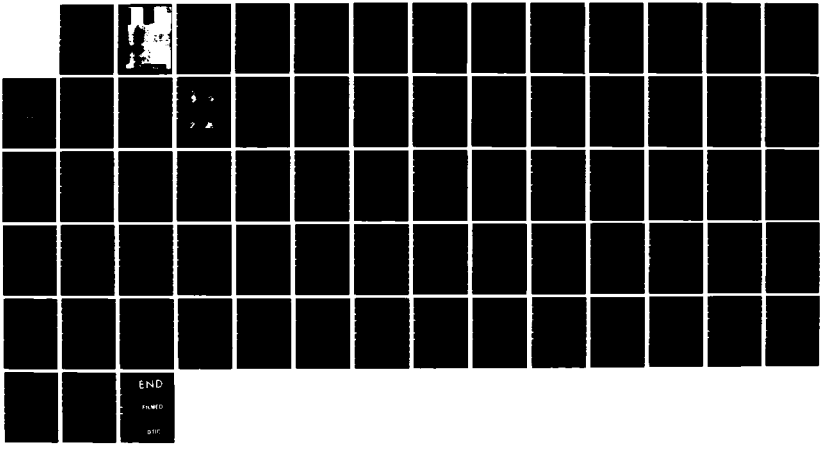

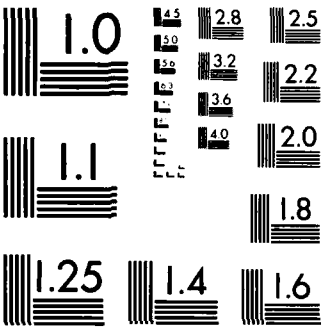

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INTRODUCTION

Both the Naval Air Systems Command (NAVAIR) and the National Aeronautical and Space Administration (NASA) have an interest in obtaining engineering control of bio-organic molecular dynamics. That interest, however, arises for a different reason in the case of the two agencies. On the one hand, NAVAIR wishes to obtain novel materials, composites, alloys, lubricants, capacitors, surfactants and devices by synthetic or biosynthetic chemical methods. It is foreseen that the scale-up to bulk chemical production of such products will present a problem. On the other hand, NASA needs to provide a life support system for the space station, produce carbohydrates for food in space, create supplemental power sources for the main design-limited power source, and in all possible ways make that system as supply-free as possible. In addition, the understanding of biopolymer structure and function is a critical aspect of NASA's research on the origin and evolution of life. Nevertheless, the same need for fundamental science to underpin both undertakings explains a joint interest in molecular control. Both agencies have an interest in energy harvesting.

Molecular control requires an understanding of the efficient transfer of energy to a molecular system for purposes of useful work, whether the energy originates from electromagnetic field or photon, electron or phonon. The transferred energy may be used in any purposeful way. For example, it can be used in increasing biocatalysis in reactors dedicated to bulk chemical production, in the formation of proton gradients across membranes, or in radiation-induced chemistry. It is thus evident that, given this goal, one necessary requirement is an understanding of the periodic and quasiperiodic behavior of molecular systems to ensure that the transferred energy is not dissipated. In contrast, the molecular system should not be of the kind which treats the energy stochastically by intramolecular randomization (Noid, et al, 1981), because the transferred energy is then lost for useful work purposes.

There are two limiting forms of unimolecular dynamics. The first, the RRKM (Rice, Ramsperger, Kassel, Marcus) theory, is based on the assumption that the energy can be partitioned among all available molecular states (Marcus, 1952). In the second form, it is assumed that: (1) the normal modes of a molecule are anharmonic; (2) the KAM (Kolmogorov, Arnol'd, Moser) theorem for low perturbations applies (Kolmogorov, 1954; Arnol'd, 1963, 1978; Moser, 1962, 1973); (3) the conditions exist as described in the Fermi-Pasta-Ulam problem (Fermi, et al, 1955); and (4) the classical motion is quasiperiodic. In the case of a quantal system, the first limit also requires the preparation of a group of states and is described by KAM at high perturbation. Furthermore, there are presently attempts at stochastic approaches to Brownian motion of a quantum system (cf. Dattagupta, 1984; Gardiner and Collett, 1985). With the goal of molecular control

and efficient transfer of energy in mind, the first limit describes those conditions to be avoided, and the second limit - those to be attained.

Therefore, either to "craft" (engineer) energy to be compatible with a molecular system or to "craft" (engineer) a molecule to be compatible with available energy, so that in both cases the energy is efficiently transferred for useful work means that the second limiting form is being considered. In the case of phonon energies, the method of seeking the second limit in energy-molecule interactions and avoiding the first, or chaotic, stochastic, ergodic or irregular form of interaction, is beginning to be understood conceptually (see the first two chapters and Eilbeck, et al, 1984; Takeno, 1983, 1984). In the case of quantum systems and photon energies, it is more difficult. There are no simple correspondences between classical and quantum mechanical chaos and classical and quantum mechanical quasiperiodicity. Future theoretical work is required to define precisely the distinction between quantum mechanical chaos and quasiperiodicity, so that with the present purposes in mind, the first may be avoided and the second achieved. The conceptualization must also include, besides resonance interaction, the possibility of parametric pumping of energy transfer, as in the well-known case of Fermi resonance. An understanding of parametric excitation in energy transfer will permit a greater choice of mechanisms and greater versatility.

There are two competing tendencies in systems with two degrees of freedom. The competition arises between the number of resonances becoming increasingly dense in the phase space and the width of the resonances tending to become small. As the number of degrees of freedom increases, either complete stochasticity or complete harmonicity can be achieved, depending upon the average ratio of the resonance width to distance between resonances (Lichtenberg and Lieberman, 1983).

The determination of resonance energies in systems of coupled oscillators must also address the problem of resonance states of the individual oscillators with widely different lifetimes. Recent advances in the theory of resonances have led to an understanding of resonance states in terms of complex energies and associating them with "quantum momenta" (Lefebvre, 1985).

Multiphoton excitation in which a single polyatomic molecule absorbs many infrared photons (Lyman, Galbraith and Ackerhalt, 1982) is one prototype form of molecular control. Multiphoton excitation experiments exhibit many features that are independent of the particular molecular species. It appears that multiphoton excitation depends upon a number of effects including absorption line broadening, multiphoton absorption, higher-order interactions among normal-mode states and intramolecular energy flow between states. Theoretical treatment and prediction is thus difficult.

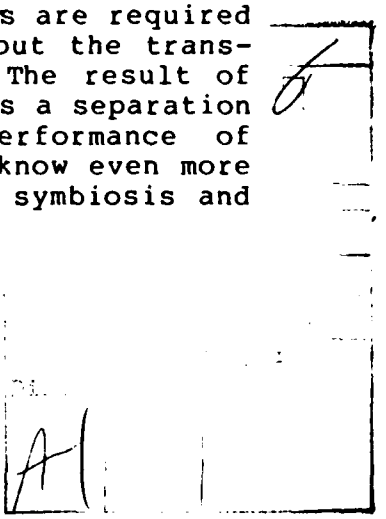
Furthermore, the radiation is not simply a probe, because it severely perturbs the absorbing sample. A new picture has recently emerged in which the polyatomic molecule possesses: (1) discrete low-energy level states permitting resonant absorption described by conventional spectroscopic theory; (2) a quasi-continuum of higher energy states due to mixing with other "background" states and described by multiphoton absorption theory (Lyman, Galbraith and Ackerhalt, 1982); and (3) a region of higher energy states described by RRKM theory (Robinson and Holbrook, 1972). Therefore, in considering energy transfer to a polyatomic system, defining the boundaries of (1), (2) and (3) is of fundamental importance. At the present time, such definitions for most systems remain both an experimental and theoretical challenge.

Due to the complexities of defining the resonance and stochastic excitation conditions of a complicated polyatomic system, a model system may offer rule-of-thumb behavior. The dc superconducting quantum interference device (SQUID) offers itself in this regard as a simple example of a four-dimensional autonomous non-linear dynamical system (Ketoja, et al, 1984). The stability problems of the SQUID are susceptible to analysis in terms of Hill's equation and Mathieu's equation (Magnus and Winkler, 1966). The Feigenbaum sequence to chaos (Feigenbaum, 1978, 1979) has been found in the dc SQUID equations in a large number of narrow marginal regions of the phase space between different types of solution (Ketoja, et al, 1984).

The way to efficiently transfer or harvest energy is presently a theoretical or analytical problem. Presupposing its solution, there are then two other problems bearing on he use of that energy presumed captured and stored, which may not lend themselves to general solutions.

The first concerns the function of enzymes. Many of the uses on which the energy will be spent involve the increase in enzymatic reaction rates. Unfortunately, there is no agreement on how enzymes function at the present time. In fact, there may be many mechanisms, many different forms of energy may be used, and how the enzyme recognizes the substrate may be a critical concern. We have to know many precise attributes of the excited molecule to use the captured energy.

The second concerns the realization that membranes have an organizing purpose essentially required by statistically mechanical arguments (Fox, 1982; Lavenda, 1985). Membranes are required in conjunction with chemical reactions to bring about the translocation of molecules, ions or chemical groups. The result of this symbiosis of chemical reactions and membranes is a separation of charge whose recombination underlies the performance of osmotic, chemical and mechanical work. We have to know even more attributes of the excited molecule to utilize this symbiosis and obtain the result desired.



We have barely begun to attack these two problems. The recent successful demonstration of frequency-specific effects (resonances) in DNA of uniform length from exposure to low-level (producing non-significant thermal induction) microwave or radio frequency radiation (Edwards, et al, 1984) indicates that radio frequency energies of radiation can be efficiently transferred to molecular systems. However, how such transferred energy is usefully employed is not yet understood.

Another example of energy harvesting is light transduction in rhodopsin and bacteriorhodopsin (Birge, 1981). This example can be placed in the context of thermodynamic law. A strict observance of the second law of thermodynamics (Atkins, 1984) tells one that heat engines cannot produce work, unless in some stage of the energy cycle heat is discarded into a cold sink. In other words, heat cannot be completely converted into work except at zero temperature of the cold sink - which is unobtainable. Similarly, a strict observance of the second law in the case of molecular entropy engines tells one that no work can be produced unless in some stage of the energy cycle entropy is discarded into an entropy sink, which is the molecular system. In other words, transferred energy cannot be completely converted into work except at zero entropy of the molecular system - which is also unobtainable. Another type of engine, the molecular internal energy engine, loses internal energy (or enthalpy) in the transformation from initial state to final state. External energy sources must be used to reconstitute the internal energy for another cycle.

Returning to the light-harvesting examples, a recent study of the enthalpy differences between light-adapted bacteriorhodopsin and its primary photoproduct demonstrated that about 30% of the absorbed photon energy is stored at an absorption maximum (568 mm) (Birge and Cooper, 1983). On the other hand, the primary step in rhodopsin excitation stores 60% of the absorbed photon energy at an absorption maximum (500 mm) (Cooper, 1979). However, the primary photochemical events associated with both rhodopsin and bacteriorhodopsin involve similar isomerization of the retinyl chromophore. Thus, the difference between the two protein-chromophore systems is remarkable and needs explanation. It may be relevant, therefore, within the context of the preceding remarks on the thermodynamic requirements of energy transfer, to notice the energy cycle differences in the two systems. For example, on the one hand, bacteriorhodopsin uses part of the photon energy to perform work and part to complete the energy cycle to be in the initial state to receive another photon. It resembles an entropy engine. Rhodopsin, on the other hand, in the absence of energy input from respiratory enzymes, resembles more an internal energy engine and cannot complete an energy cycle without energy transfer from those enzymes. Such considerations should dictate choices of molecular systems for energy harvesting. The second law would state that no process is possible in which

the sole result is the absorption of quantum energy from a reservoir and its complete conversion into work. A tax on transferred quantum (photon) energy is necessary if useful work is to be performed.

The field of chemical synthesis and biosynthesis is very empirical and must remain so because research interests, eventually, have to be justified by products and usable results. In the field of specialty chemical and biomedical and pharmaceutical chemical production, there is little concern for scale-up to bulk chemical production because in this field of endeavor, small production often gives profit enough. But theory and experiment are complementary and there is an imbalance at the present time in the biosynthesis field toward experiment. An investment in theoretical analysis now will create vast areas for empirical use and development.

In the chapters to follow, the status of the problems to be solved is given. The early chapters are theoretical and there is a progression through to the applied. In the field of biophysics and chemical physics, there are all too many problems to be solved for one to engage in "fishing expeditions" or strategical serendipity. By choosing relevant problems and placing them in an interdisciplinary and focused context with an applied science goal, one may hope for rapid progress. A major impediment to rapid progress will be the translation of the style and expertise of one discipline into another.

In the first two chapters, the fundamental physics both existing and required are described. Chapter 1 is the most theoretical of the chapters and introduces the theoretical platform. Chapter 2 and especially Chapter 3 moves the reader along to consider the applications of the theoretical platform to molecular dynamics and devices. Chapter 3 points out the need to extend some theoretical methods of physics itself in order to deal with the applied problems. Theoretical analyses which are necessary but require considerable time to develop and bring to engineering fruition are described in these first three chapters. Chapter 4 introduces the study of specific polymer systems, namely proteins, and Chapter 5 considers the broader area of polymer science and a specific example of energy harvesting. In Chapter 6 there is progress toward the applied with the introduction of the important field of enzyme mimics. Chapters 7 and 8 discuss basic science issues of enzymatic function. Chapters 9 and 10 define precise avenues of approach to obtaining enzyme control and also indicate the difficulties and complexities. Chapter 11 brings the reader down-to-earth to the practical and short-term requirements of bio-organic synthesis control. Chapter 12 addresses the pressing need for research and training, in general, in Polymer Science.

This booklet should not and, it is hoped, does not stand in the way of fresh approaches not covered. Its usefulness lies in defining the problems to be solved. There is no attempt, therefore, to describe any of the expected bountiful practical applications when molecular control is achieved in any molecular system.

In essence, an attempt has been made in the following chapters to draw the attention of prospective contractors, both theoretical, experimental and device- and product-oriented, to what is, perhaps, a new field. Instances of conservation of the energy imparted to a molecule in an inelastic spectroscopic experiment are rare in the scientific literature, although an attempt to treat experimental behavior in terms of adiabatic approximations has been made (Fong, 1976). The present interest is in understanding how to use the transferred and conserved energy for useful work. The aim of this booklet is to coalesce and focus research both theoretical and experimental into a new scientific field called "molecular control," the results of which can readily be transferred into the engineering required by both NAVAIR and NASA.

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I. "LONG TIME PREDICTION" IN INTRAMOLECULAR DYNAMICS

One of the proposed topics of this workshop is the control of molecular mechanisms for the purpose of device application and life-support systems. These include energy transfer mechanisms for useful work and selective radiation-molecule interactions. It is important to put the theoretical framework for these fundamental problems in perspective.

To first approximation, molecular systems are highly non-linear conservative systems. For the most part the dynamics of these systems, at least in the classical limit, are non-integrable. Very little is known of the actual dynamics of intramolecular energy flow in molecules and yet it is desired to influence this internal dynamics, whatever it may be, with external sources to obtain controlled specific results. Indeed, at present there are apparently contradictory models of energy flow mechanisms. On the one hand, RRKM theory assumes that energy flows in a molecule in a rather random manner while, on the other hand, soliton theories assume a coherent flow. There appears to be some truth in both these points of view. Furthermore, it is desired to embed molecules in larger networks which can act coherently to amplify the effects of constituent molecules and obtain useful work. These proposed goals pose deep theoretical questions, but they come at a time when new techniques for treating both conservative and dissipative non-linear phenomena have been developed, stimulated largely by the needs of fusion and particle accelerator research and far from equilibrium chemical phenomena.

Let us focus on the effect of dynamic external fields on the behavior of conservative systems (this includes the phenomenon of parametric excitation). In classical systems we know that when a dynamical external field is coupled to a non-linear system, the phase space of the non-linear system is qualitatively changed. For example, let us consider the perturbation of an integrable non-linear conservative system with N degrees of freedom. In the absence of the field, the 2N-dimensional phase space of the system consists of invariant N-dimensional tori or surfaces (called KAM tori after Kolmogorov, Arnold and Moser) (Chirikov, 1979; Lichtenberg and Lieberman, 1983; Escandi and Doveil, 1982). The state of the unperturbed system is constrained to lie on one of these tori for all time (the particular surface depends on the initial conditions). When a dynamic external field is applied, this picture is totally changed. The external field induces into the phase space of the system a dense set of resonance zones which destroy the invariant tori in the neighborhood of the resonance zones. The size and location of the resonance zones depends in part on the strength of the perturbation and also in part on the properties of the unperturbed system. In the regions where resonance zones overlap, all invariant tori are destroyed and the

system becomes chaotic. Thus, when a field is present, the system can exhibit a totally new type of behavior. The phase space itself will contain both invariant tori and regions of chaos which can change, qualitatively, the behavior of the system. It is important to note that this picture of dynamic field effects cannot be obtained from traditional perturbation theories which are only valid for a short time and are totally inadequate to treat motion in chaotic regions. It is only recently that global methods have been developed which enable us to describe the behavior of these systems for long time. For example, the behavior of the classical Duffing system (Duffing, 1918) (a driven particle in a double well), which has been in the literature for seventy years, was only clarified last year using these new global methods (Reichl and Zheng, 1984).

The importance of these new developments in classical physics to the problem of intramolecular energy flow and selective radiation-molecule interaction is being recognized by a growing number of chemists (Rice, 1981) and physicists (Zaslavsky, 1981; Berry, 1983). However, their application to quantum dynamical systems is difficult and our understanding of these systems is still in a very primitive state. No global methods, valid for long time, have been developed. The best efforts to describe such phenomena as parametric excitation in quantum systems (Hillery and Zubairy, 1984) are still only valid for short time and therefore inadequate for the task at hand.

Before concluding, it is useful to note that many of the ideas used to understand the onset of chaos in classical non-linear systems also have relevance to the conductor-insulator transition in isolated polymers and to the possibility of soliton propagation in molecules. Let us first consider the conductor-insulator transition.

The critical behavior of the semiclassical discrete Frenkel-Kontorova (Peyrard and Aubrey, 1983) model of a chain of harmonically coupled atoms in the presence of a charge density wave has recently been described in terms of the so-called standard map. This map was first developed to quantify the onset of chaos in non-linear conservative systems and in non-linear driven systems (Chirikov, 1979; Reichl and Zheng, 1984). The relevance to real polymers of the very interesting results obtained for the Frenkel-Kontorova and similar semiclassical models is not clear. What is needed is a completely quantum mechanical theory of these phenomena but, as discussed earlier, a satisfactory theory does not yet exist.

There now exist several theories for soliton propagation in molecules (Davydov, 1979; Hyman, et al, 1983; Su, et al, 1980) all of them based on quite similar quantum mechanical lattice models which, strictly speaking, only sustain soliton propagation in the continuum limit. Solitons exist in integrable systems. If one

tries to influence soliton propagation by an external field, for example, is the predominately integrable behavior of the underlying lattice destroyed? At present, it is not possible to answer this question. The only existing theories which describe the influence of external perturbations on soliton propagation are valid only for short times (Kaup and Newell, 1978). Any truly interesting physics that might occur as the result of an external perturbation is beyond their reach. Thus, we are again brought back to the fact that we need better theoretical tools to understand the internal non-linear dynamics of molecules and mechanisms by which we might influence that internal dynamics.

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These multiple states may allow DNA to respond to external stimuli like a programmable computer. "Intermittent" dynamical effects, flopping randomly between conformations, can occur (Reichl and Zheng, 1984). Synthetic biopolymers might be ideal materials for observing such phenomena.

Obviously, the scope of problems to which physics is applicable is very broad; various issues require differing experimental and theoretical approaches. In terms of theoretical methods we could make progress by concentrating on two initially: First, to develop a method to choose a highly reduced set of functionally significant effective coordinates in terms of which the most important conformational changes or dynamics may be described; second, to address the physics of strongly anharmonic dynamics in real and model biopolymers. Two starts have been made: First, by examining the Dickerson (Dickerson, 1983) experimental results on a dodecamer, an "experimental" set of coordinates was chosen (Krumhansl, et al, 1984) and equations of motion solved by computer, obtaining results similar to Calladine (Calladine, 1981); second, as regards strong anharmonicity, kinks and related features the work of Krumhansl and Alexander (Krumhansl and Alexander, 1983) has been extended in several directions, and parallel developments have been made by Scott and co-workers on polypeptides (Careri, et al, 1984).

Application

For understandable reasons the basic research proposed here cannot be quantitatively associated at this writing with specific biofunctional molecular mechanisms.

However, within a few years it should be possible on well chosen systems to determine how structural or dynamic factors of a localized nature apply to transitional states, particularly to questions of intermediate species, isotope effects and sequence variation. If thereby the chemical understanding is significantly augmented by conformational considerations, a better basis for process control is certain to follow.

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Coulomb forces are necessary to hold an ionic crystal together, but they play a secondary role in elasticity or in defect vibrations (Kittel).

(c) Localized static variants, kinks, bends, etc. are of particular importance in DNA. At the same time flanking or distal effects (Widom, 1984) or extended changes (Wartell, et a., 1983) are frequent accompaniments and are not easily described by bonding theories.

(d) The energies involved in the functioning of DNA-enzyme complexes are typically of the order of 1-10 kcal./mole or 0.043-0.43 e.v. Such processes must almost certainly be of a structural or H-bonding nature rather than electronic. The polynucleotides (DNA, RNA) are distinguished by being rigid in some molecular groups (phosphate, bases) but "floppy" in others (ribose, H-bonds) (James, 1982; Keepers, et al, 1982). Polypeptides behave similarly.

(e) The motions of "floppy" conformation are always highly anharmonic, in fact at least bistable, perhaps multistable. This appears clearly in the computer experiments of Gō, et al (Gō, et al, 1983) and is suggested by the NMR_3 experiments (James, 1982) where motions in the 10^3 picosecond range are found to be conformationally important, and is suggested by quasi-harmonic studies of proteins (Levy, et al, 1984). Under these circumstances the physics is quite different from harmonic systems; kinks, solitons, polarons as a class of quasi-localized excitations are natural features. General aspects relevant to biomolecules are discussed by Krumhansl and Alexander (Krumhansl and Alexander, 1983). An additional feature of highly anharmonic excitations is that due to topological factors they may be statically metastable; (topological) solitons need not be dynamic. Many other features of anharmonic systems have been explored in condensed matter physics over the past decade. Successful theoretical methods have been developed.

(f) It is strongly suggested (Burles and Farmer, 1984) from experimental evidence that DNA is capable of assuming a large number of energetically equivalent metastable conformational states, which may be kinks localized at different positions, due either to super-helical stress or protein interactions. The slow dynamics observed may be due to fluctuations between various substates of such states.

The implications of this work are far ranging; see the discussion of bending and kinking given by Widom (Widom, 1984). Kinks are now experimentally observed elements of DNA structural heterogeneity which may have a general role in DNA-protein processes.

Along with the substantial body of developing experimental evidence that static structural features are of key importance, there has developed through dynamic studies (NMR, IR, Raman) the belief that low frequency, quasi-localized, and highly anharmonic motions are associated with active regions of both proteins and nucleic acids (James, 1982; Gō, et al, 1983; Karplus and McCammon, 1981; Levy, et al, 1982; Wartell, et al, 1983; Urabe, et al, 1983).

In the present work primary emphasis is placed on DNA, RNA; a few proteins are discussed to illustrate general characteristics of anharmonic systems. There is a substantial other body of experimental and theoretical studies on proteins, such as myoglobin (Karplus and McCammon, 1981; Levy, et al, 1982; Frauenfelder and Petsko, 1983; Frauenfelder and Wolynes, 1984) where there is also a clear role for the application of physical methods and concepts.

To digress historically, these features are reminiscent of developments in condensed matter physics over the past two decades, particularly relating to structural rather than electronic or magnetic phenomena. As a result of those studies much has been learned experimentally about localized excitations, the effects of "disorder" (i.e. sequence variations from idealized homopolymers), and strong anharmonic effects in structural transitions. Kinks, solitons and "domain" walls pervade the literature of 1-dimensional and 2-dimensional materials. In this sense the physicist is not surprised by some recent developments in biopolymers. But the general background provided by condensed matter physics needs to be focused in new ways; the following are suggested:

(a) While it is important to be able to predict equilibrium helical configurations it is even more important to be able to predict variants. A first step in that direction is due to Calladine (Calladine, 1981) using an elastic model which explains variants in helix twist angles as observed by Dickerson.

(b) The physics of equilibrium configurations and of variants can be significantly different; forces (e.g. "non-bonding") which are important (even necessary) to establish equilibrium may be of little concern in determining localized variants. This is common in solid state physics; for example

controlled by structural and dynamical variants from an ideal structure, rather than from the sequence alone.

From these rapid advances in the scientific evidence for non-chemical factors, it is apparent that there are new opportunities for developing control mechanisms. In this view complexes need not be activated solely by chemical means; particle radiation, electric fields, selective photoexcitation (by lasers), to mention a few, are some of the possible alternatives. However, there is a need to know just what motional or electronic excitations are involved. Those are problems in physics, both theoretical and experimental; therefore, there are many important topics where the methods developed for polymers and "low-dimensional" materials (e.g. polyacetylene, polymerferroelectrics, etc.) in the statistical mechanics of phase transitions and in non-linear theory will be of significant value to molecular biology.

The current situation suggests that physicists and molecular biochemists should join forces. This is certainly true; in the final analysis good physics as in other sciences derives from close contact with experiment. However, it appears to be also necessary to extend some theoretical methods of physics itself to deal with the problems which are appearing. Thus, there is also a rationale that some work should be carried out as physics in its own right.

Of particular interest are locally coordinated changes in molecular structure in DNA or proteins, which accompany protein-DNA interactions, drug intercalation or charges in environmental conditions. One major class of problems, since the energies seemingly involved are only a few kilocalories, probably do not involve electronic excitation explicitly. In the conventional terminology these are "conformational" changes, or "transitional conformations."

An important forward step in the determination of DNA structures has been taken in the development of methods for preparing short sequence DNA oligonucleotides in single crystal form (Dickerson, 1983; Wang, et al, 1981; Frederick, et al, 1984) and determining their structure by x-ray methods. The increased precision over fiber structural studies has clearly shown significant deviations from Watson-Crick structures and also identified features which correlate with biological activity.

Of even greater importance perhaps is the very recent work of Frederick, et al (Frederick, et al, 1984) because it actually documents a co-crystallized enzyme-DNA interaction complex, EcoRI and the oligonucleotide TCGCGAATTCGCG. The work reveals that a tight, complementary interface between the major groove and the enzyme is the major determinant of sequence specificity; moreover, the structure contains kinks and major departures from a B configuration that partially unwind the DNA.

III. MOLECULAR BIOPHYSICS AND ITS DEVELOPING INTERFACE WITH POLYMER SCIENCE, CONDENSED MATTER PHYSICS AND MATERIAL SCIENCE

A vast majority of biological materials are polymeric in nature, particularly proteins and polynucleotides. While they may have specific biological function, it is important to view them also in the broader context of condensed matter physics, chemistry and polymer science.

It has long been recognized in condensed matter physics and materials science that a complete understanding of properties involves both global and local-specific phenomena. The elasticity of a crystal is a global property, but its "color" may be due to electronic and vibrational excitations of a very local nature (e.g. color-centers); similarly, static and dynamic effects of a local nature have long been understood to play highly important roles in many extended condensed matter systems (e.g. semiconductor devices, plastic flow, the photographic process). Importantly, theoretical methods have been developed to deal with both global and localized phenomena.

Conceptually, a similar strategy ought to be relevant to many important phenomena in biopolymers - that is, we should look at both extended and localized excitations, how they occur and what their utility is in processes. Ferroelectric polymers (polyvinyladine fluoride) have been shown to polarize by the propagation of a coherent structure-modifying kink, and local crankshaft kinds of structures (both static and dynamic) can be found in simulations of polymers. Clearly the vicinity of such kinked regions is a potential focus for special chemical activity.

Research Program

The interaction between specific DNA sequences and proteins are key events in the control of biological processes and biotechnology (e.g. dedicated biochemical reactors, biomedical diagnostics, pharmaceutical synthesis, pollution control and crop science).

An understanding of such molecular interactions will be key to the control of processes - transcription and translation; involving recognition, binding, initiation and termination of DNA-RNA and enzyme segments. Rapidly developing experimental evidence suggests that chemical considerations alone do not suffice to completely characterize the interactions, but molecular structure and dynamics also play a determinant role. Thus, while the Watson-Crick idealized helix and its triplet base pair codon hypothesis correctly predict important gross features (e.g. composition of amino acids), it is found that process rates and the choice of location along the DNA helix are significantly

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et al, 1981; Lindsay and Powell, 1983), are encouraging. Since MT is known to play a functional role in many aspects of cellular dynamics (including motion of cilia and flaggela, cell motility, cytoplasmic transport and mitosis), such experiments are expected to be of fundamental importance in understanding the dynamics of cytochemistry. As with protein, DNA and proton transport, it has been suggested that MT dynamics may be influenced by anharmonic effects far from thermal equilibrium (Hameroff and Watt, 1982).

Summary

It is hoped that this brief sketch conveys an appreciation for the exciting, interdisciplinary research opportunities that are currently available in biomolecular dynamics. Such research requires intimate collaborations between biologists, experimental physicists (or physical chemists) and non-linear theoreticians who are equipped with state-of-the-art facilities for numerical computations. It will lead to biological devices, means for control of biochemical processes and an improved understanding of biological hazards.

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On the experimental side a striking result has recently been obtained by Careri and Giansanti (Careri and Giansanti, 1984). They have made careful measurements of the dielectric constant of wheat seeds from 10 KHz to 10 MHz as the moisture content (either H_2O or D_2O) is varied. These measurements show a dissipation peak which can be attributed to protonic current and is greatly enhanced in the hydration range for which wheat germination occurs. Other systems might reveal similar behavior.

Microtubules - It is interesting to consider extending the tripartite research paradigm displayed in Figure 1 to more highly organized biochemical structures. A candidate for such an extension is the microtubule (MT) shown in Figure 3.

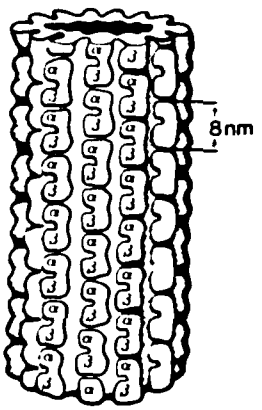

Figure 3. Microtubule (MT) Structure From X-Ray Data (Amos and Klug, 1974).

The subunits of this MT structure are 8 nm dimers of α and β tubulin in a hexagonal, cylindrical lattice. Thus, MT can be viewed as a biomolecular crystal in the same sense that acetanilide forms a molecular crystal (Careri, et al, 1984). An exciting aspect of MT research is that the constituent protein, tubulin, can be refined and then assembled into MT in vitro (Dustin, 1978). Thus a variety of experiments that compare the properties of isolated tubulin to those of tubulin in MT are suggested. To date optical experiments on MT have been limited to quasi-elastic light scattering measurements of macroscopic structure (Gethner and Gaskin, 1978; Palmer, et al, 1982), but the opportunities for experiments to probe the internal dynamics of MT, similar to those mentioned above for protein (Stapleton, et al, 1980; Allen, et al, 1982; Alexander, et al, 1983; Austin, et al, 1975; Careri, et al, 1984) and DNA (Hakim, et al, 1984; Edwards, et al, 1984; Putnam,

of amide-I vibrational energy on amino acid #88 leads to self-trapping while initialization on amino acid #89 does not. In the light of the preceding discussion, a working hypothesis might be that emerging language of non-linear, conservative systems, the initialization on #88 places the initial point on an island of KAM stability while the initialization on #89 places the initial point in a channel of KAM instability.

DNA Dynamics - Linear acoustic and optical mode oscillations have been computed from the atomic structure of DNA (Mei, et al, 1981; Prohofsky, 1983) and compared with Brillouin scattering measurements of the longitudinal sound speed (Hakim, et al, 1984). This sound speed is in good agreement with that required to explain microwave absorption peaks in aqueous solutions containing helical DNA of known length (Edwards, et al, 1984). From a perturbation analysis, Prohofsky and his colleagues have predicted a defect resonance state which is pinned at the end of a DNA strand and is related to the dynamics of unwinding (Putnam, et al, 1984). The frequency of this state was predicted to be at about 900 MHz which is surprisingly close to the frequency of 600 MHz at which Lindsay and Powell have observed a DNA resonance (Lindsay and Powell, 1983). Molecular dynamics simulations have explored moderately anharmonic motion of 12 and 24 base pair DNA near thermal equilibrium (Levitt, 1983) and DNA solitons have been suggested in several papers (Englander, et al, 1980; Yomosa, 1983; Takeno and Homma, 1983; Krumhansl and Alexander, 1983; Sobell, 1984).

Protonics - In the hydrogen bonded world of biochemistry the dynamics of protons is felt to play an important role. It has been postulated by Mitchell that proton gradients at biological membranes are of major significance for energy storage and transport in biological systems (Mitchell, 1968). Similarly the charge transport across purple membrane by bacteriorhodopsin is thought to be carried by protons (Nagle and Morowitz, 1978). Thus, to fully describe the dynamics of biochemical molecules it is necessary to understand protonics as well as electronics and mechanisms for the storage and transport of vibrational energy.

The classical protonic conductor is ice (Eigen and DeMaeyer, 1958) and the theory of hopping mechanisms for proton conduction in linear hydrogen-bonded systems has been developed in considerable detail (Knapp, et al, 1980). Recently a number of authors have suggested that anharmonic effects may play a role in proton conduction (Yomosa, 1983; Kashimori, et al, 1982; Antonchenko, et al, 1983; Yomosa, 1982). In these theories the proton is coupled to a lattice deformation which facilitates its motion and thereby increases its mobility. Thus, one is led to consider a proton soliton which is closely related to a polaron. It is important to know how much the motion of a real proton is influenced by coupling to the background lattice.

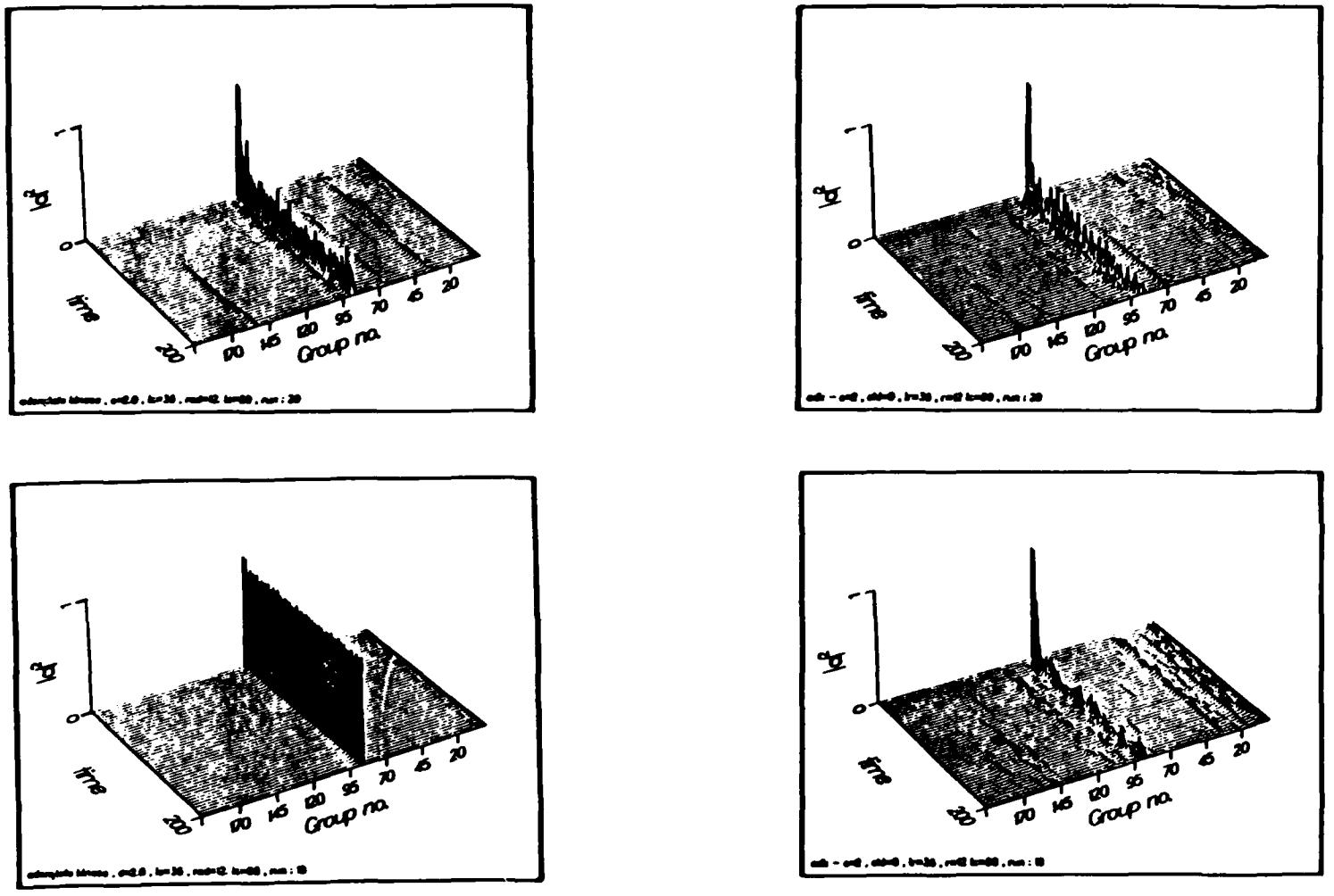

FIGURE 2. Dynamical calculations of self-trapping of amide=I quanta on amino acids of adenylate kinase using DST. In the right hand figures the anharmonicity (γ) is set to zero for comparison. The upper figures show no self-trapping on amino acid #89 while the lower figures show strong self-trapping on amino acid #88.

1981) and dissipative structures (Frölich, 1980). Recent infrared absorption and laser-Raman measurements on crystalline acetanilide (ACN) indicate the presence of self-trapped (soliton) states (Careri, et al, 1984) and, to the extent that ACN can be regarded as a model protein, confirm predictions in the work of Davydov in 1982.

New dynamical models are needed to explore the functional repertory of dynamical systems with dispersion, anharmonicity and many degrees of freedom. One example of such a system, the discrete self-trapping (DST) equation (Eilbeck, et al), can be written as follows:

$$(i\frac{d}{dt} - \omega_o)\,\bar{A} + \varepsilon M\bar{A} + \gamma \begin{bmatrix} |A_1|^2 & & \\ & |A_2|^2 & o \\ & & |A_n|^2 \end{bmatrix} \bar{A} = 0 \qquad (1)$$

where $A = \text{col}\,(A_1, A_2, \ldots A_n)$ is a vector with components equal to the complex amplitudes of n interacting modes. If ε and γ are zero, DST requires that each of the modes oscillate with frequency ω_o. If $\varepsilon \neq o$, dispersion is introduced through the real, symmetric, n x n matrix M. If $\alpha \neq o$, anharmonic effects are introduced through the non-linear matrix diag $(|A_1|^2, |A_2|^2, \ldots |A_n|^2)$. It is interesting that this system is similar in structure to the forced Duffing system (Reichl and Zheng, 1984) and we find a similar pattern for the onset of chaos. For $n \geq 3$ one finds the following sequence of behaviors as the energy is increased: (a) at low energy the solution trajectories are almost all quasi-periodic with frequencies around the eigenvalues of M; (b) at intermediate levels of energy the dispersion and anharmonicity are about equal and almost all trajectories are chaotic; (c) at high values of energy almost all trajectories are again quasiperiodic with frequencies around those of the local modes. This picture might provide a convenient framework upon which to interpret experimental observations of multiphoton absorption in isolated molecules. The chaotic trajectories at intermediate energy have broad power spectra which correspond to the "quasicontinuum" range. At high energy, the regrowth of KAM islands might explain the focusing of energy on a single band as described by the RRKM formula. To beat RRKM one would, according to this view, attempt to initialize near a KAM island.

Applying DST to follow the vibrational energy in peptide modes (say amide-I) of a globular protein requires calculation of the (1/2)n(n-1) off diagonal elements of the dispersive matrix M. Once done, DST becomes a generalization of the Davydov soliton theory to the geometry of a particular globular protein. As is shown in Figure 2, dynamic calculations on such a system are surprising. The protein studied is adenylate kinase, which is the smallest that interacts with adenosine triphosphate and for which the structure has been determined. Initialization with a quantum

(a) Device Applications - Proposals to employ biomolecules in useful devices range from image sensors and energy harvesters to long-range proposals for computers based on biochemical technology. The design of such devices requires a thorough understanding of biomolecular dynamics.

(b) Process Control - As biochemical engineering grows in importance, new techniques for the control of processes that produce useful biomaterials will be needed. Knowledge of how biochemicals interact with physical probes will provide a spectrum of possible mechanisms for bioprocess control.

(c) Hazards - The increasing use of electromagnetic fields in modern society has led to worries about possible hazards to human health. Particular concern has been expressed for those who work in the vicinity of radio-frequency heat-sealing machines, high voltage transmission lines and high power broadcast and radar antennas. To get beyond hazard driven studies of cause and effect, research in this area must be directed toward understanding the mechanisms of biomolecular dynamics.

Specific Research Areas

As was emphasized above, significant research in biomolecular dynamics must take place in an environment where a well characterized biochemical preparation is available for physical measurements. An incomplete but representative list of such research areas includes the following items:

Protein Dynamics - Recently it has been suggested that the density of states for the linear eigenvalue spectrum of a particular protein can be estimated from the "fractal dimension" of that protein (Stapleton, et al, 1980; Allen, et al, 1982), and the term "fracton" has been coined for those eigenvectors with length scales sufficiently short to be insensitive to the boundaries (Alexander, et al, 1983). The fracton is probably related to the localized state proposed by Anderson (Anderson, 1958, 1978) to describe amorphous semiconductors. Evidence from low temperature flash photolysis (Austin, et al, 1975) and x-ray diffraction (Hartmann, et al, 1982) implies that the ground state of a protein is highly degenerate possessing a large number of conformational substates which play a significant role in protein function. Detailed numerical calculations of protein dynamics have been carried out near thermal equilibrium (Brooks, et al, 1983; Brooks and Karplus, 1983; Levitt, 1983), and approximate theories have been developed to describe protein dynamics far from thermal equilibrium in terms of solitons (Davydov, 1982; Bilz, et al,

II. BIOMOLECULAR DYNAMICS

Introduction

Although the dynamic behavior of biochemical molecules has long been of fundamental scientific interest, only recently have appropriate experimental, computational and theoretical tools become available. Any listing of such tools must include: (a) high speed computing and display equipment, (b) data banks containing the atomic structure of many important biomolecules, (c) recent advances in numerical, analytical and theoretical methods for studying non-linear dynamics (chaos, solitons, KAM theory, etc.) and (d) a wide variety of experimental techniques (Fourier transform infrared spectroscopy, synchrotron x-ray sources, inelastic neutron scattering, time resolved and multi-channel laser-Raman measurements, microwave absorption methods, etc.). Thus, it is now exciting to consider tripartite research collaborations as indicated in the following diagram.

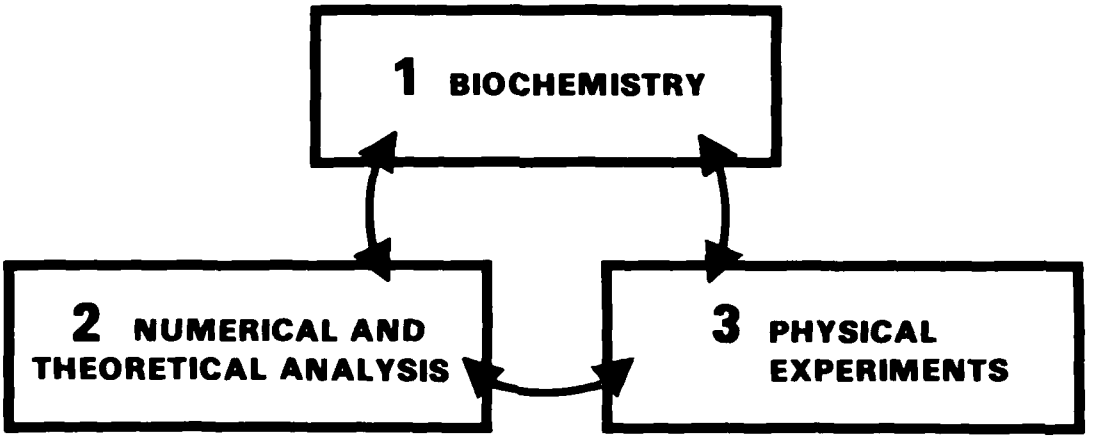

Figure 1. Tripartite Research in Biomolecular Dynamics.

Legs 2 and 3 must interact closely to keep each other honest. Both must interact with 1 to keep the research relevant. It is not necessary that the three legs of a particular research project be at the same location although this is desirable whenever possible.

Significance of Research in Biomolecular Dynamics

In addition to an increase in our scientific understanding of biomolecular dynamics, research in this area should have practical significance in the following areas:

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IV. DYNAMICS AND CONTROL OF PROTEINS

In the long run the understanding of the structure and function of biopolymers is essential for their use in applications. Absence of a deep understanding does not mean that some systems cannot be employed, but it implies that trial and error, rather than design and planning, will dominate.

It is by now almost certain that the internal motions in proteins play an essential role in their function (Frauenfelder, 1983, 1985). Consequently, it is not enough to explore the spatial structure of proteins; the motions must also be determined and classified, their role in particular functions must be elucidated and a satisfactory theoretical description must be found.

Two types of motions are involved in protein functions: fluctuations about an equilibrium state and motions in the transition from one equilibrium state to another. Equilibrium fluctuations (EF) and functionally important motions (fims) are related. In the simplest case, the connection is expressed through the well-known fluctuation-dissipation theorem (Kubo, 1966). This theorem is usually derived for situations close to equilibrium, but some work far from equilibrium has also been reported (Suzuki, 1975). Since many experiments investigate EF, but all functions involve fims, theoretical and experimental studies of the connection between the two types of motion far from equilibrium are desirable.

The experimental investigation of fims in one particular case, the photodissociation of carboxymyoglobin, has led to a classification of states and motions in this protein (Frauenfelder, 1985; Ansari, et al, 1985): at least three different classes of functional motions exist. The fluctuation-dissipation theorem then implies at least three different types of equilibrium fluctuations. These, in turn, point to three different tiers of conformational substates in myoglobin. Myoglobin consequently possesses a complex hierarchical structure, sketched in Figure 1.

This model of a protein poses a large number of experimental and theoretical questions that should be addressed in order to use proteins efficiently. Among the experimental problems are more detailed studies of the equilibrium fluctuations and functional motions in different proteins as function of external parameters (pH, viscosity, temperature, pressure) and effector molecules. How well separated are the tiers of substates and the corresponding barriers in energy? Where are they located in the molecule and how are they produced? How many tiers of substates do exist in a given protein? Which motions are essential for a particular function? How are these motions controlled?

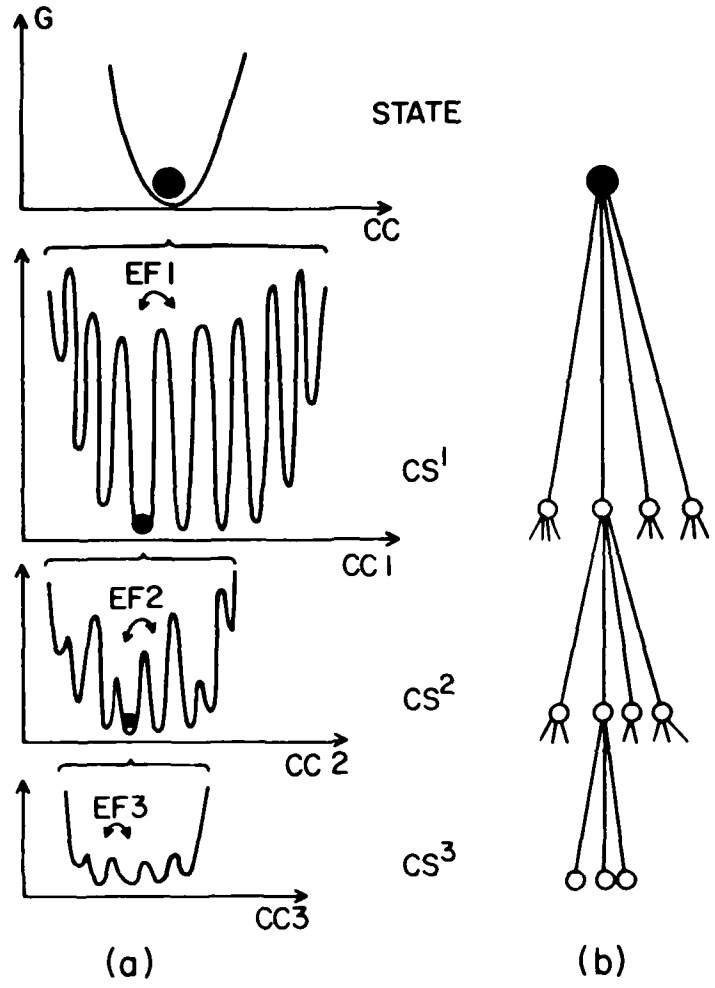

Figure 1. A protein in a given state, for instance Mb, can assume a large number of substates. Substates all have the same primary sequence, but slightly different tertiary structures. Each substate, in turn, is again subdivided into sub-substates, each of which can again take on a few slightly different conformations.

Theoretically, the challenges are equally great. The hierarchical model of the protein exhibits striking similarities to models proposed for glasses and spin glasses (Toulouse, 1984; Stein). Is this similarity accidental or fundamental? If it is appropriate, how can the theories of glasses and spin-glasses be applied to proteins? Can proteins be used as testing grounds for glass-type theories? The hierarchical protein model leads to another set of theoretical questions: Can present-day molecular dynamics calculations account for all classes of motions? If not,

how can the relatively slow, probably cooperative, motions be described? Most (or all) of the published molecular dynamics calculations apply only to equilibrium fluctuations. How can functional motions be described?

These brief remarks make it clear that many theoretical and experimental problems remain to be solved before proteins are understood to the level where rational decisions on their use can be made.

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V. ENERGY TRANSFER

The molecular design of energy efficient molecular systems requires a detailed understanding of fundamental aspects of the nature of intermolecular and intramolecular energy transfer processes and of the mechanisms for minimizing losses. A complete and predictive understanding must ultimately involve relating the properties of the composite system to the properties of the individual molecules and their mutual interactions. Substantial progress has been made in research on certain areas of energy transfer, but large gaps in our knowledge remain.

There are a wide variety of different types of energy transfer processes, e.g., electronic energy transfer, electron transfer, vibrational energy transfer and the transfer of atoms and molecular fragments. Intermolecular electronic energy transfer, or electronic energy transfer between different chromophores of a large molecule or polymer, can occur over large distances by a Förster energy transfer mechanism, while shorter range transfers involve exchange processes which may be coherent in nature. Vibrational energy transfer processes are subdivided into intramolecular energy flow through the vibrational modes of a molecule or intermolecular transfer via a Forster type mechanism. One of the central questions concerning the efficient utilization of energy transfer processes in molecularly designed systems is the elimination or substantial reduction in loss mechanisms that degrade otherwise useful energy.

A thorough understanding of the molecular basis of energy transfer begins with isolated gas phase molecules which rarely undergo collisions, uses this information to aid in explaining the energy transfer processes of guest molecules in dilute gases and in crystalline environments, considers energy transfer in crystals, amorphous solids, liquids and finally studies these processes in efficient biological systems. The high efficiency of many

biological processes makes it imperative that we thoroughly understand their mechanisms in order to design artificial systems or to use the biological systems more effectively. This research on biological processes relies on a comprehensive understanding of energy transfer in the above noted simpler molecular systems, an understanding which provides the necessary theoretical concepts and models required to study the complicated biological systems.

Higher plants are phenomenally efficient collectors of solar energy. This efficiency is achieved by the use of large arrays of chlorophyll-protein complexes (the light harvesting array) surrounding the site of chemical activity - the reaction center. Typically there are 500-600 light harvesting chlorophyll molecules for each pair of reaction centers used by green plants. Once a photon has been absorbed by the light harvesting array, the energy is transferred to the reaction center with greater than 90% efficiency. The mechanism of this efficient energy transfer is still poorly understood, an understanding that may prove important in designing efficient artificial light harvesting devices.

Higher plants use two different photochemical reactions in series ("the 2-scheme") to eventually split water and fix CO_2. The primary photochemical events take place at reaction centers called PS I and PS II. Not merely is energy transferred from the collecting pigments to PS I and PS II with phenomenal efficiency, but it also appears that plants can regulate the flow of energy in the light harvesting system to keep the two photosystems turning over at about the same rate.

The potential pay-off for understanding at the molecular level the mechanisms for these efficient processes and for the regulation of the light harvesting array could be enormous. Not merely can the construction of large, relatively inexpensive solar collectors be envisaged, but also molecular feedback control mechanisms can be imagined which could perhaps compensate for variations in the solar flux.

It is now clear that the key feature of the light harvesting system is that the chlorophyll molecules are held in proteins. The concentration of chlorophyll in the chloroplasts is about 0.1M. If a solution or matrix of chlorophyll with this concentration is used, the energy of the absorbed photons is rapidly dissipated to heat through the process of concentration quenching. Concentration quenching (Beddard and Porter, 1976) is observed to occur for molecules in solution, in rigid matrices and in crystals and it would obviously destroy the efficiency of solar energy collection.

Concentration quenching is a poorly understood process which appears to result from greatly enhanced radiationless decay (internal conversion) when molecules approach closer than 12A. While much progress has been made on understanding the radiationless decay of individual molecules (Freed, 1976, 1981), research is necessary to relate this knowledge along with a description of the intermolecular interactions to explain concentration quenching in the simplest gas phase excimers and exciplexes (Okajima and Lim, 1982), as well as guest excimers and exciplexes in matrices, knowledge which will undoubtedly be of essential importance to describe concentration quenching in condensed systems and in biological systems such as the chloroplasts.

The energy transfer process between chlorophyll molecules is believed to occur by a Förster dipole-dipole mechanism which depends on the inverse sixth power of the molecular separation. Hence, the efficient operation of the photosynthetic-unit requires a more sophisticated solution than merely keeping the molecules separated far enough apart to remove concentration quenching. It is now clear that the proteins of the photosynthetic unit hold the chlorophyll molecules in near optimum positions and orientations for energy transfer. The details of the energy transfer and trapping processes are only just beginning to be studied. Recent

experiments by Gullotty, et al (Gullotty, et al) using the formalism of Hemenger, et al (Hemenger, et al, 1972) indicate that in PS I the single step transfer time is in the range of 200-500fs and that the excitation makes about four visits to the reaction center before electron transfer finally occurs. In PS II the trap is significantly shallower and the importance of detrapping correspondingly greater. Thus, energy trapping in both systems is far from diffusion controlled. This finding is crucial in understanding the regulation of energy flows between the two photosystems, and it highlights the importance of further studies of this and other efficient energy transfer mechanisms in condensed phases.

These results also highlight the fact that the electronic energy transfer between the chlorophyll molecules is sufficiently rapid as to eliminate energy loss due to internal conversion and other dissipative processes. The dominant competing process is the desired electron transfer reaction. Nature, hence, employs the very rapid electronic energy transfer and electron transfer mechanisms to run the highly efficient photosystems. Slower processes such as intramolecular vibrational energy transfer probably would be inadequate here because of their longer timescales and, consequently, their greater likelihood of being destroyed by competitive energy losses.

Very little is known about the regulation of energy flows to the two photosystems in the chloroplasts. One proposal is that a product of the PS II reaction causes phosphorylation of the light harvesting chlorophyll a/b protein, resulting in, for example, a change in the orientation of the protein in the membrane. The implications of such a molecular energy switch could be wide ranging, but much work is necessary before the regulation mechanisms can be described at the molecular level.

Much still remains to be done to understand Förster energy transfer between molecules in the gas phase or guest molecules in a crystalline host. Some progress is being made in analyzing the complicated Foster energy transfer in disordered arrays which may model randomly doped systems (Gochenour and Fayer, 1981). It is important to describe the radiative and radiationless processes of pairs and higher assemblies of molecules in terms of the properties of the individual constituents and their interactions (a field which is only beginning to be probed) in order to determine conditions to maximize the efficient utilization of energy in artificially designed molecular systems.

We have used the example of the remarkable efficiency of the light harvesting ability of chloroplasts to highlight a wide range of fundamental questions to be answered and systems to be studied to enhance our understanding to molecular processed to control and utilize energy transfer. Many other areas of energy transfer research exist, such as electron, proton and hydrogen transfer reactions, which are too numerous to describe here. As an example, we close with another quite different area in which questions of energy transfer are central to the control of chemical reactions.

Rates of many thermal unimolecular reactions have been explained using the RRKM theory which is generally presented as being predicated on the assumption that vibrational energy is rapidly randomized within a molecule on a timescale which is short compared to those for the chemical reactions. However, this theory can likewise be formulated (Freed, 1979) with the opposite assumption of purely coherent vibrational energy flow within a molecule and a stochastic mechanism for the thermal energetization of the molecule. This conceptual dilemma focuses on the fundamental questions of studying the nature of energy randomization in a molecule to determine whether it is possible to prepare and

localize vibrational energy in particular (probably non-linear) molecular modes in order to control the outcome of chemical reactions. Real molecules have a large number of degrees of freedom and are generally not linear in nature. Hence, simple 1-dimensional theoretical models or ones involving two or three degrees of freedom and neglecting rotations are not anticipated to be adequate for determining the conditions under which molecules can localize their vibrational energy for sufficiently long to perform useful work.

For instance, considerable interest exists in determining whether it is possible to effect mode specific chemistry by laser excitation of specific vibrations of a molecule to drive a chemical reaction that deviates from the thermodynamically most likely (Parmenter, 1982). An essential ingredient in these studies involves an understanding of how energy flows in molecules under a wide variety of circumstances for both isolated molecules and those in condensed environments. Some experiments to probe these questions have focused on the nature of the decay of states involving excitation of high overtones of localized vibrational mode and the study of the competition between vibrational energy scrambling and radiative, non-radiative, collisional or dissociative processes. The latter experiments on vibrational energy scrambling and those on infrared multiphoton dissociation processes are well described by quantum mechanical theories of energy transfer in systems with high densities of quantum states (Freed, 1976; Mukamel and Jortner, 1976, Freed and Nitzan, 1980). More clever experiments, for example, that explicitly control the phase evolution of a wave packet on an excited state surface, coupled with theoretical analysis, are required to beat the energy randomization to make mode selective chemistry a useful practical tool. The observed strong quantum selectivity of collision induced vibrational energy transfer (Weitzand and Flynn, 1981; Rice, 1981; Freed, 1984; Rice and Cerjan, 1983) remains to be more fully understood to be utilized in molecular control.

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VI. MOLECULAR CONTROL BY MIMICS AND RECEPTORS

In living systems, enzymes and biological receptors are both protein molecules that can bind other species, often small molecules, into a specific binding site. The contrast between the two has to do with what then occurs.

In enzymes there are catalytic groups of the protein located in such a way as to be able to interact with the bound small molecule, called a substrate, and catalyze its transformation into another chemical species. Often an enzyme will bind several small molecules and catalyze the interaction between them. By contrast, a bio-receptor normally does not transform the substrate bound to it, but instead uses the act of binding itself to cause the production of some sort of signal. Sometimes this signal involves the release of another chemical substance, sometimes it involves an electrical signal transmitted to a nerve, while sometimes it involves turning on or turning off some enzyme catalytic activity located elsewhere. Substrates that are bound in the catalytic site of an enzyme are transformed, but other substrates may bind to regulatory sites of an enzyme and simply change the activity of the enzyme without themselves being acted on.

Enzymes are the machines of life, performing all of the transformations characteristic of the living process. The bio-receptors involved in control processes are the regulators of the machines of life, adjusting velocities so as to optimize the overall process. With the aid of these two classes of substances biological systems achieve control of their molecules, forming the desired species at the desired rate in response to a signaled need.

In recent years there has been a great increase in the interest in artificial enzymes and mimics of bio-receptors. There are several reasons for this. First of all, the mimics are normally not proteins, and are expected to be much more chemically rugged and non-antigenic than are the natural substances. Secondly, in principle these artificial substances can be tailored to need. Artificial enzymes can be designed to handle unusual substrates, of interest to man but not part of normal metabolism. They also can be tailored to perform unusual chemical transformations, in particular transformations of interest in synthetic chemistry and the pharmaceutical industry. Mimics of bio-receptors should be extremely valuable in detecting various unusual substances. It is easy to think of important applications for receptors that could signal the presence of various poisons or undesirable drugs. Furthermore, a mimic of a bio-receptor could be very helpful in any chemical process as part of a system to impose control on the process itself.

In addition to these practical potential applications of artificial enzymes and bio-receptor mimics, one should also remember their relationship to the natural systems. It is very likely that our understanding of natural biological catalysts and receptors will be enhanced by the results of our efforts to mimic them. Successful mimics will demonstrate that we indeed understand at least some basic principles about the biological systems, while even the failures can help enlarge our understanding of what the real requirements are

The current status of research on these substances is more advanced in some areas than others. A lot has been done to mimic simple binding. Thus, hydrophobic binding by cyclodextrins (Bender and Komiyama, 1977; Tabushi, 1982) and by synthetic macrocycles (Odashima, et al, 1980) and cages (Miller and Whitlock, 1984) is an active area of research, with some attention to selective binding of some substrates, not others. Other binding forces have been used, including hydrogen bonding (Cram and Trueblood, 1981) and ion pairing in nonpolar solvents (Breslow, et al, 1981). The classic area of binding to metals has been used to achieve mixed binding (Breslow and Chipman, 1965), in which two different ligands are held together by interaction with a central metal atom. Charge transfer complexing has also been used to some extent to promote molecular complexing.

There is also a lot of activity in mimicking enzymes; in these mimics, the binding event is followed by some chemical transformation. In a true enzyme mimic transformation would be catalytic, with regeneration of the catalyst molecule, but some mimics simply imitate a particular step of an enzyme-catalyzed process and do not themselves achieve catalysis.

There are several kinds of selectivity characteristic of enzyme-catalyzed reactions, and all of them have been achieved with artificial enzymes. First of all, enzymes are selective for their substrates. Such selectivity is characteristic of simple binding systems as well, and it carries over to the artificial enzymes based on them. For instance, mimics of transaminase enzymes have been prepared combining pyridoxamine molecules with binding groups (Breslow, et al, 1980; Breslow and Czarnik, 1983; Czarnik and Breslow, 1984; Winkler, et al, 1983). When the binding groups were cyclodextrins (Breslow, et al, 1980; Breslow and Czarnik, 1983; Czarnik and Breslow, 1984) or synthetic macrocycles (Winkler, et al, 1983), selective reaction occurred with substrates that could use these binding groups, in contrast to other substrates that would not be bound to them. Selectivities of the order of 50 to 1 were typical.

Secondly, enzymes are selective in the chemical reactions they perform. This is particularly striking in biochemical reactions that use pyridoxal phosphate or pyridoxamine phosphate as coenzymes. Pyridoxal phosphate can catalyze a number of

Can various disparate functions of different proteins be incorporated into a single molecule so that one function serves to mediate the other? Could one couple the redox state of a metal center, for example, the Cu^{I}-Cu^{II} couple of the blue copper proteins azurin or plastocyanin, to the catalytic site of a hydrolase such as galactosidase, so that hydrolase activity would respond to the potential of the environment? The creation of such novel activities becomes conceivable when one has the ability to synthesize the appropriate molecular entities.

The thrust of the above questions focuses on creating structures and then investigating their function. What's new is the ability to create the novel structures and this can now be accomplished by a wide variety of techniques: in vitro mutagenesis, of a specific residue at a specific site, or more random mutagenesis either over the entire structural gene or localized to a restricted region of the gene; total synthesis of a structural gene for the protein of interest together with expression of this gene in an appropriate host; direct chemical synthesis of the protein. The latter approach has the advantage that the units incorporated into the molecule need not be restricted to the twenty natural amino acids; the advantage of the use of structural genes is the in vivo amplification of the synthetic gene and the in vivo biosynthesis of the protein of interest such that abundance of protein can be obtained from a single original molecule of the gene.

Some Specific Approaches

Mutagenesis - Having a cloned gene in an appropriate expression system allows the generation of variants of the parental protein by various techniques of mutagenesis (McFarland-Dalbadie and Richards, 1983; Zoller and Smith, 1983). These can be targeted at a specific residue and this approach has been increasing exponentially in popularity (McFarland-Dalbadie, et al, 1982; Winter, et al, 1982; Sigal, et al, 1982; Vallifranca, et al, 1983). Essentially this approach requires that one have some basis for deciding that a particular structure will possess interesting properties and then uniquely preparing that structure.

Random Mutagenesis-Site Saturation - A complementary, alternative approach is to present a variety of structural possibilities to a screening procedure that demands a specific property or phenotype. The structural varieties can have been generated by the many various techniques of random mutagenesis; this approach can reveal active proteins with structures that would not have been anticipated by any of the intuitive insights that would have been available in designing particular structures for site directed mutagenesis. An attractive procedure within this general area is the use of appropriately degenerate synthetic oligonucleotides to encode any desired subset of amino acids at a

Have all enzymes achieved evolutionary perfection in being the best possible catalysts for their particular reactions? Triosephosphate isomerase, that interconverts dihydroxyacetone phosphate and 3-phosphoglyceraldehyde in the Embden-Meyerhof glycolytic pathway has, the rate determining step in this case being the diffusion controlled binding of substrate to enzyme; there is scarcely any barrier to the subsequent proton transfer events that accomplish the required isomerization. Similarly for carbonic anhydrase and catalase, very efficient catalysis has been achieved. In contrast serine proteases, such as chymotrypsin, and the glycosidase, lysozyme, operate comparatively far less rapidly.

Turnover Numbers for Representative Enzymes
(at saturating substrate concentrations)

Catalase	4.0×10^{7}
Carbonic Anhydrase	1.0×10^{6}
Triosephosphate Isomerase	4.3×10^{3}
Chymotrypsin	1.0×10^{2}
Lysozyme	5.0×10^{-1}

In many physiological roles, rates that are orders of magnitude slower than those controlled by diffusion may be essential; for some processes to be more rapidly catalyzed could lead to metabolic chaos as the healthy cell must have the fluxes of its metabolic processes so controlled that the various pathways operate harmoniously, no one pathway running so out of control that it essentially takes over. However, for isolated processes occurring outside the cell, much more efficient catalysis may be of enormous value and, for such an objective, synthetic molecular biology provides the potential for accelerating the rate of structural change so that, under selective pressures for enhanced catalytic efficiency, better enzymes may be created.

Many enzymes require cofactors generally acquired by the enzyme from the environment. Though in some cases these cofactors are bound tightly to the protein, synthesis of model systems incorporating both cofactor and the catalytic groups of the protein could generate catalytic entities that are more efficient and could be far more stable than the native biological systems. Along these lines of stability, appropriate modification of natural enzymes could produce far smaller analogues that could be easily attached to solid supports and in such environments prove far more enduring than natural proteins similarly immobilized.

IX. SYNTHETIC MOLECULAR BIOLOGY

General

In the most general terms, action in nature depends on proteins; as structural elements of organisms, as transport agents, as catalysts, as cell surface receptors for signals (and sometimes as the signals themselves) and for transducing energy into movement.

In the past biochemists and molecular biologists have been essentially restricted to studying the native proteins, though some chemical modifications of some residues have been possible. Today the techniques of synthetic molecular biology allow new approaches to the rational study of how the amino acid sequence of a protein determines unambiguously its 3-dimensional structure and its function. To design novel catalysts or to create novel systems for transducing chemical energy into work, we shall have first to understand more clearly than we do now what are the fundamental structural features that are essential for a particular function; but the approaches and techniques are now at hand to address these issues and to generate the new systems both to establish these relationships and then to create the molecules that will possess the novel properties and functions.

Why, for example, are enzymes so large when their active sites comprise so small a fraction of their total mass? Is it to afford them stability in their biological milieu, to confer on them functional properties that depend on motions of the domains relative to one another and that would be lacking in a smaller catalyst, or to give them a physiological role in addition to catalysis that we have not yet perceived? Some examples of known behavior that proteins must possess in order to function effectively in a real biological system include: processing and secretion (so that a protein synthesized in the cytoplasm of a cell can find its way with perfect specificity to the appropriate subcellular organelle such as the inner membrane of a mitochondrion), the ability to be converted into an enzymatically active form only at the right time and place (as the proteins involved in blood clotting though always present in the serum only form clots under an appropriate stimulus), the ability to die at an appropriate time (so that the catalytic activity of the particular enzyme will not persist beyond the period that it serves a useful, and not deleterious, physiological function). Synthetic molecular biology allows one to address these issues by tailoring the native catalysts to study how function changes when large sections of the protein, remote from the catalytic site, have been removed. One can also use these techniques to create new cross-links in the polypeptide backbone (by introducing in appropriate places cysteine residues that can then be oxidized to disulfides) to investigate the role of the mobility of domains in providing an active enzyme.

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Yet another approach to the design of novel catalysts is to introduce chemically reactive groups into the active sites of existing enzymes. An example of this approach, accomplished by E.T. Kaiser and co-workers, involved the introduction of a flavin derivative into papain by covalent modification of the active site cysteine residue. By judiciously choosing the flavin derivative it was possible to leave part of the active site cleft open for interaction with hydrophobic substrates. For optimal substrates, the resulting semisynthetic enzyme displayed kinetic parameters and turnover numbers similar to those found for natural flavin enzymes. This approach need not be limited to naturally occurring enzymes or cofactors. Modern methods of site specific mutagenesis allow the charge of any residue to any of the naturally occuring residues, providing handles for introducing novel cofactors. The potential of this approach though depends on the charge to be non-perturbing to the enzyme structure, or to have a known perturbation on the structures. Computer programs for computing such perturbational effects have been developed but need to be optimized.

The disadvantage of using beta sheet monolayers as enzyme models is that the possibilities for building active sites is limited by the 2-dimensional geometry of such structures. Ideally, it would be desirable to prepare monolayers which contain well-defined cavities or grooves. This might be accomplished by preparing monolayers of supersecondary structures. A typical example of a supersecondary structure is a helix flanked on either side by a beta sheet (Richardson, 1981). In the crystal structures of proteins, the beta sheets lie parallel to one another and the connecting helix lies on top of the sheets with its helical axis nearly parallel to the sheets. It should be possible to build monolayers with this structural motif by preparing a peptide with totally hydrophobic residues for these sheets and a sequence capable of forming an amphiphilic helix for the connecting helix. Such a peptide should bind apolar surfaces with its sheets packed against the interface; the helix would protrude into solvent with its axis parallel to the surface. Hydrogen bonding between neighboring sheets of individual supersecondary structural units would determine the spacing and geometries of the helices. In this conformation, grooves might be formed between the helices, allowing the design of more complex binding sites and catalytic groupings. Other supersecondary structures are known (Richardson, 1981) and could be used to create monolayers with unique topographies.

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purified. The advantage of synthesizing peptides by chemical rather than genetic approaches is that a wider variety of functional groups including alpha nucleophiles and metal chelating agents can be incorporated into the peptide chains. The inherent difficulty with this approach is that peptides tend to have very flexible conformations in homogeneous solution, lacking the ordered conformations of natural proteins. It thus might be naive to attempt to design a short peptide of approximately 20 amino acid residues with a structure rigid enough to position amino acid side chains in the proper orientation to form a catalytically active center, and also to bind and position a flexible substrate so that it might be acted on by this center. However, this approach may be successful if one were to design a peptide which binds in a specific manner to a rigid macromolecular matrix. Then the rigidity induced upon the peptide on binding might be used to position amino acid side chains in an orientation appropriate for catalysis.

Thus, an attractive field of research might involve the design of peptides which assemble onto apolar water interface such as the air/water interface. It has been established that peptides and proteins form stable monolayers which can be manipulated and studied by the standard techniques of surface chemistry (Cornell, 1979). In early work it was established that amino acid homopolymers form monolayers at the air/water interface in which these peptide chains are in predominately alpha helical or beta sheet conformations depending on the solvent used to spread the peptides at the interface. The conformation of the peptides in the films can be established by transferring the monolayers to solids (4 layers) and applying electron diffraction, multiple internal reflection infrared spectroscopy or UV circular dichroism spectroscopy.

Complex, multifunctional peptides can also be designed which bind in defined conformations to apolar water interfaces, forming monolayers. By carefully choosing the sequence of the peptides it might be possible to create catalysts. For instance, an oxidase might be created by positioning residues for chelating iron in close proximity to hydrophobic residues positioned for binding a substrate. Beta sheet monolayers might also serve as templates for directed condensation of nucleotides; attempts to design such templates are in progress (Barbier, et al, 1984). Application of beta sheet monolayers need not be limited to catalysis. Considerable effort has been directed to the polymerization of the amphiphiles in monolayers and bilayers (Fendler, 1984). The increase in stability caused by polymerization improves the possibility of using artificial membranes for a variety of applications ranging from photosynthesis to the preparation of thin films for hyperfiltration. Beta sheet monolayers are extreme examples of these polymeric membranes; being stabilized by an infinite series of hydrogen bonds which run perpendicular to the direction of polymerization of the polyamide chains.

VIII. DESIGN OF MONOLAYERS WITH PRE-DETERMINED TOPOGRAPHIES

Enzymes form the cellular machinery which carries out the diverse catalytic functions essential for life. They catalyze reactions with phenomenal rate enhancements, in the range of 10^8 - 10^{12} as compared to the uncatalyzed reaction. Perhaps even more amazing is that they are stereo- and regiospecific, acting only on a single site among many possible sites within a molecule. However, there are many limitations associated with natural enzymes: they are often available in pure form in only limited quantities; they display limited stabilities outside of solvents such as aqueous buffers or temperatures near 37°C; and there are no enzymes known to catalyze a number of reactions of commercial importance. It would be desirable to design new enzymes or enzyme mimics which lack some of these limitations. This chapter examines some approaches to this problem.

One enigmatic aspect of the structures of enzymes is that they appear to be much larger than they need to be. Only a small fraction of the total mass of a protein is used to form the active site which directly contacts substrate molecules. There is evidence that the rest of the protein might not simply form a matrix for positioning the appropriate groups in proper juxtaposition to form the active site. Residues which are far in space from the active site can aid in substrate binding and "steering" by electrostatic interactions. Also, low frequency concerted motions of large numbers of atoms within protein might be an essential component of catalysis. One way to separate the role of these factors from the role of the more prominent residues within an active site is to synthesize a stripped down version of a protein which contains only the functionally hypothesized to be essential for binding and catalysis. This can be accomplished by either de nono synthesis of complex organic molecules designed to form cavities complementary to a given substrate, or by modification of naturally-occurring compounds such as cyclodextrins. To date, the de novo synthesis of hosts which both bind small molecules and catalyze reactions has met with limited success due to the difficulties of synthesizing such large, complex, rigid organic molecules. However, efficient syntheses for cavitands and cyclophanes (Richardson, 1981) have recently been reported which show the potential for this approach. Spectacular results using hosts based on cyclodextrins have already been reported; Breslow and co-workers have found that cyclodextrins stereospecifically catalyze the hydrolysis of certain p-nitrophenyl esters with rate enhancements approaching 10^8-fold (Diedrich and Griebel, 1984). This clearly demonstrates the enormous rates which can be achieved from proximity effects using even simple binding elements.

An alternate approach would be to use medium-sized peptides as protein models. Using modern chemical methods peptides with molecular weights up to 5,000 can be rapidly synthesized and

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limited ways, e.g. by methylation. Not unexpected was the ^{13}C NMR finding that the motional rates of dimethylated lysyl side chains in concanavalin A are more restricted by a factor of 2-3 than are monomethylated lysyl side chains (Sherry, et al, 1984). Knowledge of a particular biopolymer's molecular dynamics may enable some genetic engineering to alter the dynamics at some point in the future. For example, substitution for an amino acyl residue involved in the "hinge" motion of the active cleft region of an enzyme may have profound influences on the motion and the enzyme activity.

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Since the important motions may cover the frequency range from less than 1 to ca. 10^{12} S^{-1}, a large battery of tools must be employed to gain any semblance of a dynamic picture of a biopolymer. NMR (Bolton and James, 1979; Keepers and James; 1982; James, 1984; Lausch and Spiess, 1983), EPR (Thomas, et al, 1976), Raman scattering (Lindsay and Powell, 1983), Mossbauer (Keller and Debrunner, 1980), fluorescence polarization anisotropy (Millar, et al, 1981), perturbed angular correlation (Martin, et al, 1982) and x-ray diffraction (Burgi and Dunitz, 1983) are some of the techniques that have been applied to examine molecular dynamics experimentally. The experimental approach may be augmented with theoretical calculations entailing molecular dynamics simulations (Levitt, 1983; McCammon and Karplus, 1983), normal mode analysis (Brooks and Karplus, 1983) and molecular mechanics (Keepers, et al, 1982). The molecular mechanics approach is not restricted only to very fast motions as mentioned above for molecular dynamics simulations, but it is model dependent.

Quite understandably, studies to date have emphasized the biopolymer alone without complications of ligands. An exception to this is the molecular dynamics calculations of Case and Karplus who examined potential pathways for O_2 and CO to travel between the heme and the protein exterior in myoglobin and hemoglobin (Case and Karplus, 1979). Certainly further work is required to illuminate the dynamics in the biopolymers alone. But factors which may alter the dynamics should also be examined, especially experimentally. The effects of salts, pH, solvent and ligands (including substrates, products, inhibitors, allosteric effectors, mutagens and drugs) on molecular dynamics need to be investigated. For example, simply adding magnesium ion slows some motions in RNA (Bolton and James, 1979; Keepers and James, 1982) and solvent viscosity has been shown to influence internal motions in myoglobin with consequent effects on migration of molecular oxygen through the protein (Beece, et al, 1982). An understanding of the influence of these factors is the first step in beginning to control the dynamics. Of course, it is vital to check any correlations of molecular motion changes with reaction rate changes effected by these factors.

For most biopolymers, the temperature range available is too small to allow much influence over molecular rotation rates given the low activation energy for these processes. Basic problems are stability of the biopolymers and freezing of aqueous solutions. These limits can possibly be extended by immobilization on solid supports or use of cryosolvents. These may affect dynamics directly in addition to extending the temperature limits.

Molecular dynamics may also be altered in an important way by simple protein or nucleic acid modifications. Numerous chemical modification procedures exist which still leave protein function intact (although possibly altered), and DNA can also be altered in

motions, correlation between the rates of very rapid conformational fluctuations and reaction rates is generally lacking. For much slower reactions ($<<1$ sec^{-1}), there is ample evidence that conformational changes of reactants can control the reaction rate.

Developments in x-ray crystallography in the past decade or so have yielded a static picture of several crystalline proteins and some oligonucleotides; however, a dynamic picture is needed to adequately describe the functioning of a real biopolymer in solution or in a membrane. The nomenclature of structure and dynamics can be defined at this point. We will be dealing with molecules that are likely to possess a "structure" in solution. Even with these molecules, limited conformational fluctuations might be expected such that any experimentally-derived structure will represent an average structure which may or may not correspond to an energy minimum. We might use a potential energy function to describe the biomolecule. Such a potential energy function will generally have multiple minima. Existence of a global energy minimum is possible, and existence of several minima with energies and barriers permitting significant populations and transitions at physiological (or at least accessible) temperatures is also possible. A dynamic description of the biomolecule would probably be statistical and would include the various conformations, mean conformational lifetimes and transition pathways. The description would be altered and complicated by ligand binding to the biopolymer, especially in non-equilibrium situations encountered in physiology, e.g. glycolysis.

Some headway has been made on elucidating internal motion dynamics in the biopolymers without ligands. The Debye-Waller factor in x-ray diffraction of DNA crystals is related to the mean-square deviation of an atom from its average position (Drew, et al, 1981) and is generally consistent with the results from NMR relaxation experiments of DNA in solution (Bolton and James, 1979; Keepers and James, 1982) and from molecular dynamics simulations of picosecond motions in DNA *in vacuo* (Levitt, 1983). The temperature dependence of the x-ray diffraction manifests the amplitude of any crystalline molecular motions but reveals nothing of the time scale. NMR relaxation experiments, on the other hand, are especially sensitive to the time scale of molecular motions, somewhat sensitive to the amplitude of the motions and only slightly sensitive to the precise type of molecular motion (James, 1984). Molecular dynamics simulations can reveal the time scale, amplitude and nature of the motions, but these theoretical calculations depend on the proper formulation of a potential energy function and, with present computers, cannot explore motions on a time scale slower than 10^{-11} - 10^{-10} s (Levitt, 1983; McCammon and Karplus, 1983).

VII. MOLECULAR DYNAMICS AS A POSSIBLE CONTROL MECHANISM

The importance of the conformational flexibility of biopolymers in terms of their functions is gaining recognition. Undoubtedly there are many properties of enzymes which contribute to their phenomenal ability to catalyze chemical reactions. One such property is the flexibility of enzymes, permitting them to change conformation during the process of catalyzing a reaction thus affecting catalytic efficiency. The conformational changes may encompass most of the protein or they may be localized to a small part of the active site. The timescale for some of the enzyme conformational changes is the same as that for many of the steps in the reaction mechanism. Consequently, the internal motions involved in changing conformation can profoundly affect the kinetics of an enzyme-catalyzed reaction, even to the extent of becoming the rate-limiting step. One can easily imagine protein side-chain motions (especially of aromatic residues) as well as "hinge" motions which could modulate the rate of substrate binding and product release. In a certain sense, such a reaction could be described as a rotational diffusion-controlled reaction. Similarly, the flexibility of an enzyme may be an important facet of allosteric control or electron transfer.

The central cellular functions of replication, transcription and translation quite plausibly involve distortion of the conformation of DNA and RNA. All of the different steps in these processes involving nucleic acids, including control steps, require recognition of unique sites on the nucleic acids, which may be short-lived. Conformational variants may exist for a long time or may exist transiently. Even those which may exist for only a matter of a few nanoseconds may be functionally important structures. For example, a typical intercalating agent (drug or mutagen) can diffuse 5-10A in a nanosecond. The packaging of polynucleotides into compact forms in chromatin, ribosomes and viruses involves folding of the nucleic acids. These and other observations indicate that the deformation of polynucleotide structure is intimately related to the biological role of nucleic acids and may affect the rates.

Of course, the conformational fluctuations of other biomolecules may also influence their functional efficiency. As examples from other classes of biopolymers, one might consider the role of lipid mobility in membrane functions and of the carbohydrate moiety of glycoproteins in important processes of cell-cell and virus-cell recognition as well as imm[illegible]chemical interactions in general.

Most of the above ideas may appear feasible, but at the moment they are mostly conjectural for rapid reactions. While some inroads have been made recently, both theoretically and experimentally, in describing some aspects of biomolecular

systems. Because of the potential application of such synthetic systems to performing selective chemical processes and detecting the presence of specific chemical substances with high sensitivity, this seems like an important area for future research.

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different transformations of amino acids, for instance; the actual reaction that occurs is directed by the geometric control imposed by the enzyme. Mimics of this situation have been developed as well, in particular a system that uses geometric control to emphasize amino acid racemization at the expense of transamination (Breslow and Chmielewski).

Thirdly, enzymes are selective in the regiochemistry they catalyze, i.e. in the places in a molecule in which a chemical transformation is performed. This is particularly striking with enzymes that functionalize simple hydrocarbon groups, such as the cytochrome P-450 enzymes. A number of systems have been developed in which geometric control permits selective reactions in steroids, for instance, selecting among otherwise equivalently reactive positions (Breslow, 1980).

Finally, enzymes are stereospecific. They typically can carry reactions out under geometric control, most strikingly by using only one optical isomer of a substrate or performing a chemical transformation with the formation of only one optical isomer of the product. Such stereospecificity is a general goal of chemistry and has been imitated in a number of systems. It has been mimicked in transamination, by which a keto acid is converted to an optically active amino acid, using geometric control of the group that attaches the critical hydrogen atom to the product. Very good selectivity was observed (Zimmerman and Breslow, 1984).

Of course enzymes are also very fast, producing catalytic accelerations of reactions by anywhere from 10^8 to 10^{12} fold. No good mimic of an enzyme has yet been produced that catalyzes a reaction with such accelerations. However, there is a system (Breslow, et al, 1983) that performs one step of an overall two step catalytic process with an acceleration as much as 10^8, and another system has been reported that selectively reacts with one substrate rather than another by as much as 10^{11}, although the overall process is not particularly fast (Cram and Katz). In the area of velocity models for enzymes there is still much work to be done.

Much less has been done with mimics of bio-receptors. In particular, there are not yet good systems that generate an electrical signal on binding a substrate to an enzyme mimic, or even that act to release a hormone-like substance. It seems that this is an area with particularly good potential, especially if synthetic receptors can be bound to electrodes and the binding act can be rapidly detected by changes in the electrical properties of the system.

The future of this area seems bright. All the work up to the present indicates that mimics can be constructed that imitate many of the important features of natural enzymes and binding molecules. The incorporation of further features should improve these

particular site or sites - "site saturation." One should recognize that the various techniques of random mutagenesis generally alter only a single base in any given codon and that such changes will convert the parental amino acid into 4-7 other residues, but not to all 19 possible different amino acids. Thus, at sites or regions of particular functional or structural interest one can, using the approach of "site saturation," present to the phenotypic screening procedure structural variants that contain all possible residues, or combinations of residues, at these selected sites.

Fusion Protein - The techniques of cloning, in vitro mutagenesis and other DNA manipulations (including total synthesis of genes) allow the creation of hybrid proteins that represent fusion of two proteins with possibly very different functions. The particular synthetic challenge is to interweave so closely the two functional domains that they can directly influence each other so that the activity of one domain is controlled by the state of its neighbor.

Design Criteria - What basis has one for approaching the design of proteins with modified or totally novel functions? These are large molecules and the possibilities of structural change are so enormous that the problem is overwhelming without some guides as to areas where structural changes are likely to be of interest. For these purposes several approaches can provide useful insights. The 3-dimensional structure of a protein together with some knowledge of the mechanism of catalysis or nature of binding can identify the region principally responsible for the protein's activity. If the protein in question is one of a family present in many organisms, the identification of conserved residues immediately highlights sites that are likely to play crucial roles in the function of the protein and may, for example, reveal residues that, while not themselves directly involved in catalysis, may be essential for the proper folding of the polypeptide chain. In a protein that is involved in electron transfer processes, such conservations of particular residues may identify channels through which electrons are transported from the metal to the surface of the protein. Residues on the surface that are conserved (and usually residues on the surfaces of proteins are amongst the most highly variable) may indicate docking sides that are essential for one protein interacting with another so that electrons can be transferred between them. Many of these functionally essential areas of a protein could well be essentially invisible from a simple examination of even a very highly refined 3-dimensional structure.

Given a 3-dimensional structure, an important adjunct to rational modification of structure to other functions will be computer facilities and graphic displays that will allow one to test the likely effects of the proposed alterations on 3-dimensional structure and then on function. The results of such

quasi-theoretical studies will have predictive capabilities that are far from infallible but that should not be overlooked. Moreover, as the programs for minimizing the energies of new amino acid sequences improve, so will the ability to predict with increasing reliability the expected structure. Progress in making reliable predictions will clearly depend on the vigorous interaction of experimental and theoretical work.

Chemical induction can also play a role of great value. From the known behavior of many chemical and biochemical systems, the insightful chemist or biochemist develops a "feel" for the truly essential features of some particular function. To some degree this accumulated experience can be used with great profit to identify regions or residues of functional interest. In focusing on potential alterations, one should not limit the horizons by a slavish fixation on any particular paradigm.

Finally, totally random mutagenesis not even localized to any particular region of the structural gene should never be neglected so long as one has a rapid, easy assay for some desired functions. Such mutagenesis has often revealed regions of importance that otherwise would have been overlooked by any more stepwise approach.

Synthetic Polymers

In addition to preparing molecules composed totally of natural amino acids, one can use the structures of natural proteins together with their associated functions as an inspirational guide to the synthesis of molecules that have the general structural characteristics of proteins but that are composed of subunits possibly very different from the amino acids themselves. For example, the generation of molecules with the structural motifs of the collagen triple helix, or of the DNA double helix, should be seen as a synthetic challenge to create structures that have unusual strengths as fibers (collagen analogues) or that can carry information at a molecular level (DNA analogues).

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X. A MODERN VIEW OF ENZYME CATALYSIS

The Catalytic Efficiencies of Enzymes

It has been a central goal of biochemical research in the recent past to account for the remarkable catalytic efficiencies of enzymes. Enzymatic efficiency can be somewhat imprecisely defined in terms of specificity and rate acceleration; where specificity refers both to the particular substrate acted upon and the type of chemical reaction catalyzed, and rate acceleration refers to the magnitude by which the enzyme increases the rate of the reaction. Modern physiochemical theories of enzyme action account for specificity and rate acceleration as closely related, interdependent aspects of enzymatic action.

The magnitude of rate acceleration characterizing the action of an enzyme is often expressed as a ratio of rate constants for the catalyzed and uncatalyzed reactions (Bruice and Benkovic, 1966; Jencks, 1969; Walsh, 1977). For a two substrate-enzyme this would be the ratio of the first order rate constant for release of product from the enzyme-bisubstrate complex (k_{cat} sec^{-1}) to the second order rate constant (k $M^{-1} \cdot sec^{-1}$) for the uncatalyzed reaction. The ratio is expressed in concentration units, usually molar. It can be thought of as a rate acceleration factor in the sense that it expresses the concentration of one reactant which when multiplied by the second order rate constant k would convert it to a (pseudo) first order rate constant numerically equal to k_{cat}. The ratios are stupendous, ranging from 10^{8} M to 10^{14} M for most enzymatic reactions (Bruice and Benkovic, 1966; Jencks, 1969; Walsh, 1977). These ratios can be criticized for being unrelated to physically realizable states; however, they are useful for comparing rate constants. Ratios that avoid such criticism are those of first order constants for the enzymatic and non-enzymatic unimolecular isomerizations, which are similarly large but dimensionless.

A criticism that has been leveled at rate comparison between enzymatic and non-enzymatic reactions is that all such comparisons must fail when the non-enzymatic reaction simply does not proceed (Blumenfeld, 1981). This objection lacks merit, since an enzymatic reaction that does not proceed at all in the absence of enzyme is one for which there is no chemical precedent. Very few such enzymatic reactions exist; and the occasional finding of a few unprecedented reactions invariably stimulates searches for chemical models that are inevitably found. Specific examples are the 5'-deoxyadenosylcobalamin-dependent enzymatic reactions, which were for many years unprecedented in chemistry. Their discovery prompted searches for the chemical model reactions discovered within the past 10 years (Walling and Johnson, 1975; Dolphin, et al, 1979; Dowd, 1979), the most recent being the methyl malonyl-CoA mutase model of Halpern and associates (Dowd, 1979).

Substrate specifications in enzymatic reactions range from stringent to relaxed. There is a tendency for detailed, quantitative investigations to uncover reactions of substrate analogs in systems formerly thought to exhibit strict specificity. Active analogs often react at 0.1 to a few percent of substrate rates, and so are considered to be poor substrates; however, the rate acceleration factors of 10^5 and 10^{12} for such substrates are still very large despite being smaller by 10^2 to 10^3 than those for so-called specific substrates.

The Importance of the Binding Process

The first step of any enzymatic reaction is the physical binding of a substrate molecule at a specific site, the active site, on the macromolecule. This may be followed by other binding steps in multisubstrate reactions, or there may be intervening enzyme-catalyzed chemical transformations of the initially bound substrate. In any case, each substrate in a multisubstrate reaction becomes enzyme-bound at some stage of the overall catalytic pathway.

The binding process is an integral part of the catalytic mechanism, not only in the sense that the exertion of catalytic power must occur within an enzyme-substrate complex, but also in the sense that binding is itself a component of catalysis. As an integral part of catalysis its importance is difficult to distinguish from other aspects; however, the nature of its role can be rationalized briefly as follows on the basis of theoretical considerations and structural information:

(a) The binding step accelerates the rates of chemical transformations by bringing reacting functional groups together into a single structural entity, the enzyme-substrate complex. That is, by converting a kinetically second order collisional reaction into a first order intramolecular reaction.

(b) The binding process often energizes conformational transitions within bound substrates, constraining them to highly reactive conformational states that are sparsely populated in free solution.

(c) Binding energy is used to drive enzyme conformation transitions. These transitions contribute importantly to the catalytic process in a variety of ways discussed in greater detail in the following section.

The effect on reaction rate of bringing reactive functional groups together, as in enzyme-substrate complexes, can be very large. Bruice and Benkovic devoted over 100 pages of their volumes to the subject of the kinetic consequence of bringing reactive functional groups into the same molecule in non-enzymatic, chemical model reactions (Bruice and Benkovic, 1966). The physiochemical basis for the major part of the rate enhancements observed are entropic in nature as shown by Page and Jencks, who were able to account for rate enhancement factors of up to 10^8 M on the basis of the loss of translational and rotational entropy accompanying the transition from a second order collisional reaction to a first order unimolecular reaction (Page and Jencks, 1971). To the extent that the formation of an enzyme-substrate complex results in the loss of rotational and translational entropy, rate accelerations up to 10^8 can be expected. Orientational factors in the bound state are clearly also important, since no reaction could occur if the reactive groups are physically separated; and orientations perfectly aligned for reaction might result in somewhat greater rate enhancements. In any case, productive binding can account for very large rate enhancements.

A second important means by which substrate binding catalyzes enzymatic reactions is the induction of steric strain into the substrate within the enzyme-substrate complex. To be effective the induced strain must be directed to the reactive center of the molecule and distort the structure of this center toward that of the transition state; that is, part way along the reaction coordinate (Jencks, 1975). Distortions of this type require energy, and the energy source is thought to be the binding process itself. Many substrates are structurally complex, and their binding interactions with enzymes often involve substrate and enzyme structural elements well removed from the reactive centers. The energy released by these distal binding interactions can drive a conformational distortion of the reactive functional group in the substrate. This energy may be augmented by additional favorable binding interactions between the sterically distorted reactive group and the enzymatic active site. Together these interactions can substantially reduce the activation energy for the reaction and thereby enhance the rate by many orders of magnitude (Jencks, 1975).

This phenomenon is the basis for the development of chemically stable transition state-analog inhibitors of enzymes (Wolfenden, 1972). These inhibitors can be very potent because they incorporate in their structures many or all of the structural elements involved in binding, while requiring little or no structural distortion at the mock reactive center in order to become bound. To the extent that binding energy is not used for the induction of strain in the inhibitor, it is expressed as tight binding.

The proposal that binding energy can be used to induce strain into bound substrate has been criticized on the basis that it would result in products being so tightly bound that their desorption could become very slow (Blumenfeld, 1981). This objection can be valid if the binding interactions distort only the substrate and not the product structure. In an effective enzyme, however, the distortions are applied to both substrates and products, since the binding interactions favor an intermediate structure, that of the transition state (Jencks, 1975).

It is thought that structural strain introduced into substrates by binding are, in general, limited to lower energy distortions. These probably consist mainly of bond angle strain at the reaction center in the direction of angles that would exist at the transition state. Distortion in bond lengths are thought to be modest because of the large energies that would be required to effect significant changes. Exceptions may be found in cases in which the bond being broken is weak, as in the Co-C bond of 5'-deoxyadenosylcobalamin (Halpern, et al, 1984).

Table 1 lists a number of mechanisms involved in enzymatic catalysis. In this table those mechanisms commonly observed in both enzymatic and non-enzymatic reactions are listed separately from the specialized enzymic mechanisms discussed above.

Table 1. Enzymatic Catalytic Mechanisms.

General Chemical Mechanisms	Specialized Enzymic Functions
General Acid-Base Catalysis	Binding-Loss of Rotational and Translational Entropy
Nucleophilic Catalysis	Binding-Loss of Rotational and Translational Entropy
Electrophilic Catalysis	Induction of Steric Strain

Listed in Table 2 are most functionally important roles played by substrate-induced conformational transitions in enzymes.

Table 2. Importance of Substrate-Induced Conformational Transitions.

Substrate Specificity
Induced Steric Strain in Cosubstrates
Binding of Cosubstrates
Tight Binding of Reaction Intermediates
Allosteric Regulation of Activity
Efficient Catalysis of Multistep Reactions
Long Range Transport in Multienzymic Complexes

Such transitions were first proposed mainly to account for the substrate specificities of enzymes (Koshland, 1958). The binding of a specific substrate was proposed to energize enzymic conformational transitions culminating in perfect alignment of the catalytic functional groups in the active site with the reactive group of the substrate. Molecules other than specific substrates could not drive the transitions because they lacked the required binding properties. Substrate-induced conformational transitions have been repeatedly observed in many enzymes. Complete structural characterizations have been achieved in a number of systems, notably carboxypeptidase A and lactate dehydrogenase (Reis and Lipscomb, 1981; Holbrook, et al, 1975).

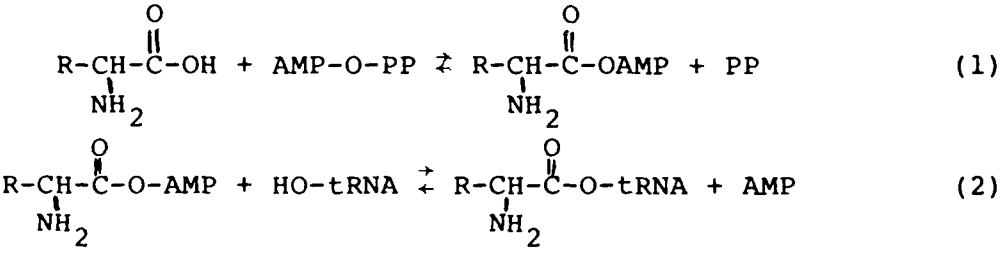
Substrate-induced transitions can also lead to rate accelerations in catalysis when the enzyme structural change is coupled to the induction of steric distortion into a coenzyme or cosubstrate bound in an earlier step. The strained coenzyme or cosubstrate can exhibit enhanced reactivity. An example is uridine diphosphate galactose (UDPGal) 4-epimerase, which contains the tightly bound coenzyme NAD^+. The pyridine nucleotide undergoes transient reduction in the course of the catalytic pathway. The binding of a uridine nucleotide at the active site induces an enzyme conformational transition in which the α-helix content increases; and this transition induces a structural change in the bound coenzyme, enhancing its reactivity toward reducing agents to a level greater than that of free NAD^+ (Wong, et al, 1978; Davis, et al, 1974).

Substrate-induced transitions can also promote the binding of cosubstrates. Here the binding site for a cosubstrate may be only partially formed in the native enzyme; the leading substrate binds at its site and induces an enzyme conformational transition that completes the formation of the binding site for the cosubstrate. This may often explain the observation of strict binding order in multisubstrate reactions.

It is important in many enzymatic reactions that reaction intermediates noncovalently associated with the enzyme remain tightly bound throughout the course of the reaction. This can be ensured when a substrate-induced transition generates a conformation that has a high affinity for reaction intermediates. An example is the UDPGal 4-epimerase mentioned above. The conformation induced by binding uridine nucleotides has a high affinity for uridine nucleotides, but this is not expressed in the dissociation constant because of the reversibility of the transition. Reduction of bound NAD^+ to NADH by the substrate locks the enzyme into the high affinity conformation, presumably through enzyme-NADH interactions. This high affinity form binds the intermediate with sufficient avidity to prevent its escape (Kang, et al, 1975; Wong and Frey, 1977, 1978).

The control of enzymatic activity in regulated enzymes is mediated by conformational transitions induced by the binding of activator or inhibitor molecules at allosteric sites. These transitions are usually mediated by intersubunit interactions in multisubunit enzymes (Koshland, 1970). Regulation by covalent modification in phosphoenzymes and nucleotide-enzymes is also mediated by conformational transitions.

In complex enzymatic reactions involving several chemical steps and several discrete reaction intermediates, the enzyme is essentially a multifunctional catalyst that accelerates the rates of two or three different chemical reactions passing through two or three transition states. To be effective in catalyzing several reactions with comparable efficiencies by the generally recognized mechanisms described above, an enzyme must undergo transitions at each step to conformations that permit it to catalyze the subsequent steps. These transitions are probably energized by binding energies between the enzyme and the chemical intermedates. Pertinent examples would be all ATP-dependent synthetases, which generally involve the reactions of three substrates to three products. A concrete example is the case of the many amino acyl transfer-RNA (tRNA) synthetases, which play an essential role in the translation of nucleic acid base sequences into the amino acid sequences of proteins. These are complex reactions that proceed in two major chemically discrete and different steps as follows; where ATP is shown as AMP-O-PP to depict the scissile bond:



$$\text{R-CH(NH}_2\text{)-C(=O)-OH} + \text{AMP-O-PP} \rightleftarrows \text{R-CH(NH}_2\text{)-C(=O)-OAMP} + \text{PP} \qquad (1)$$

$$\text{R-CH(NH}_2\text{)-C(=O)-O-AMP} + \text{HO-tRNA} \rightleftarrows \text{R-CH(NH}_2\text{)-C(=O)-O-tRNA} + \text{AMP} \qquad (2)$$

Note that in the first step a chemically discrete intermediate, the amino acyl-AMP, is formed by cleavage of a P-O bond and this then reacts with tRNA in the second step with cleavage of the C-O bond, both at a single active of one enzyme. These two reactions proceed through different transition states, i.e. by different mechanisms. It seems that the different catalytic properties required on the part of the enzyme should best arise through conformational transitions.

Finally, essential functions in multienzyme complexes such as α-ketoacid dehydrogenase and fatty acid synthetase complexes generally involve the physical transport of chemical entities or reducing equivalents through long distances. The pyruvate dehydrogenase of E. coli, for example, has a particle mass of 5.3 x 10^6 and consists of three enzymes: E1 (24 subunits), E2 (24

subunits) and E3 (12 subunits). The core of the complex is the 24 subunit E2, which has cubic symmetry. The 12 E1 dimers are associated with the core along the 12 edges and 6 E3 dimers are associated on the 6 faces. The distance between the active site of E1, where decarboxylation of pyruvate occurs, to the active site of E3, where the final electron transfer step to NAD^+ occurs, is over 50A. Electron transfer from decarboxylated pyruvate, produced as a thiamin derivative on E1, to the active center of E3, is mediated by E2 by a mechanism that involves electron transport through a distance of over 50A. An essential part of this involves a conformationally mobile structural domain of E2. The long distance group transfers catalyzed by fatty acid synthetases probably also involve conformational transition.

Enzyme Reactors

It is apparent from the above that the practical use of enzymes in enzyme reactors must be approached with due reference to their essential conformational mobilities.

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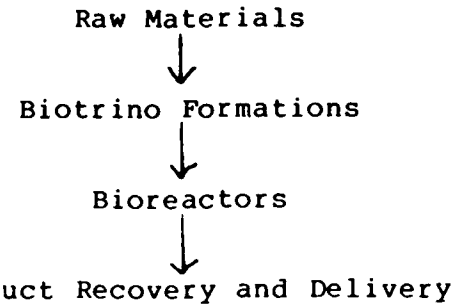
XI. RESEARCH AND DEVELOPMENT NEEDS IN ORGANIC AND BIO-ORGANIC SYNTHESIS

Bio-organic synthesis is described in the following paradigm:



The paradigm represents the fact that one is establishing fundamental principles for the manufacturing process. Critical requirements for development of this field include:

(a) Intellectual capital

(b) Products and processes

(c) Knowledgeable scientists and engineers

What is the intellectual capital correlate for this biotechnology. Two recent technical developments were critical: -r-DNA technology and monoclonal antibodies. Other supporting fields are increasing in their abilities to establish biotechnology processes for manufacturing purposes. They include:

(a) Advances in biochemical engineering for enzyme, bacterial and animal cell culture process.

(b) New separation processes including liquid-liquid extraction, affinity chromatography and high pressure liquid chromatography.

(c) Sensors for control of biological processes.

Research Needs

Even with these advances new fundamental problems have to be overcome for the effective synthesis of biopolymers including both proteins and polysaccharides. Although biotechnology processes can in principle make any protein, many are misfolded and lack biological activity.

One fundamental problem that needs to be addressed by a multidisciplinary approach is the control and regulation of protein misfolding processes. Can strategies be developed that allow for the control rate of protein folding in a variety of biological systems. Can novel energy transfer devices be developed to control various aspects of the protein folding problem?

Bioreactors

The machinery for a biotechnological process is the catalysts and the bioreactor is the physical system for conducting the bioconversion processes. Critical parameters for the operation of a bioreactor are yeild and productivity. Can new energy transfer devices be developed for improving the efficiency of bioreactors. Can energy coupling devices be used to make the biochemical reactors more specific?

Fundamental Problems for Biopolymer Formation

A variety of fundamental problems can now be addressed by biotechnological principles that are especially relevant to biomaterials. For example, how are carbon-carbon bonds formed in biological systems that are precursor synthetic steps to polymers such as polyhydroxybuyterate (PHB). Can other precursors be used to make PHB analogues? What is the catalytic site of the enzyme? Can new catalysts be developed with improved properties? How can energy transfer processes improve the catalytic efficiency of carbon-carbon bond formation?

Structure-Function Relationships

How can the structure of biopolymers be controlled in order to produce molecules with defined functions? What properties are desirable? For example, how does one make biopolymers such as PHB conductors. How does one control the rates of hydrophobic amino acid content and order in biomolecules in order that materials with defined surface properties may be formulated.

Solutions to these such problems are possible. Required, however, is a multidisciplinary approach wherein principles of physics, biology, chemistry, advanced mathematics and computer science are brought to focus on meaningful scientific problems.

XII. RESEARCH ON POLYMERS

The commercial importance of polymers can be appreciated from estimates of the size of the American polymer industry place it at a production value of $90 billion annually, supported by a workforce of 3.4 million employees (Polymer Science and Engineering, 1981). Polymers are also the essential building blocks of life itself. The importance of polymers stands in marked contrast to the neglect of polymer research at the major American universities. For instance, a study of the 20 major chemistry departments shows that only 1.8% of their faculty have interests in polymer research (Polymer Science and Engineering, 1981). Since these universities are responsible for 34% of the chemistry Ph.D.'s, including some of the most gifted students, this paucity of our research effort on polymers pales against the large efforts of the USSR, Japan, France, England, etc., where polymer science is pursued by some of their most distinguished scientists. Polymer research is currently almost totally absent in major American physics departments. The majority of academic polymer research is carried out in engineering and material science departments despite the fact that many fundamental questions in polymer science are ones that most naturally fall within the disciplines of chemistry and physics. This currently bleak picture must be kept in perspective when considering how the polymer component of research into the molecular control of chemical reactions and the molecular design of novel materials is going to be accomplished.

Biological polymers are often of great complexity, containing charged groups, complicated monomer sequences and tertiary structure as discussed in other sections of this report. Thus, much of our conceptual understanding of biological polymers has been derived from studies of the much simpler uncharged model synthetic polymers. Hence, support of selected research areas on synthetic polymers is essential to a program of the use of polymers as one component in a program of molecular design and control. As one example, we cite the problem of the description of polymers near a surface, a problem with the biological applications to membrane phenomena including selective permeability, membrane receptors, microtubules, flagella, cell aggregation, tissue formation and a variety of inter- and intra-cellular processes. Non-biological applications to molecular design and control involve the role of polymer supported reactions and catalysis, lubrication and wear properties of surfaces, chromatography and corrosion resistance. However, very little is understood concerning the properties of simpler synthetic polymers at interfaces, information which is undoubtedly pertinent to the study of the more complicated biological systems.

Research on synthetic polymers begins with their properties in dilute solutions, the regime in which the polymers are characterized and their elementary interactions described. One basic goal of polymer science is the understanding of the properties of polymer melts, blends, glasses, crystals and composites in terms of the molecular characteristics and interactions of the constituent polymers. Many important scientific problems exist in these areas which are summarized, in part, in a recent National Academy report (Polymer Science and Engineering, 1981) that also surveys the status of research in polymer synthesis, processing and engineering properties, polymers of biological and medical importance and technological and defense applications of polymers. Rather than attempting to review some of the material in the report, the report can be consulted for a more detailed account. Here we use only the example of polymers at interfaces to illustrate the nature of some of the problems.

Rather little is known concerning the properties of even the idealized limit of a single polymer near an interface, except in the very special case of "ideal" non-interacting polymers in their so-called theta state. Real systems contain polymers with interactions between all of their constituent monomers as well as the interactions between the polymer and the surface and possible complications due to the presence of charges. In more concentrated solutions, there are also interactions between the monomers belonging to different polymers. A description of such a system involves an understanding of the variation of the properties of the system with the molecular weight of the polymers, their concentration, a monomer-monomer interaction parameter and another interaction parameter which describes the strength of the polymer-surface interaction. Since the two interaction parameters are, in turn, rather complicated functions of the experimental conditions, it is an enormous task to experimentally map out the dependence of the properties of polymers at interfaces as a function of all these variables and to make some systematic sense out of it. Recent scaling theories of polymer solutions (de Gennes, 1979) are useful in providing insight into the various qualitative types of behavior that are possible, but this qualitative approach is inadequate for a program in molecular control and the development of novel materials. What is needed (3) is a comprehensive series of investigations in which there is strong mutual interaction between experimentalists and theoreticians.

Some additional important problems in polymer solutions involve the extension of recent progress in understanding uncharged polymers to the biologically and technologically important polyelectrolyte solutions. Blends and melts deserve additional study as do polymer mixtures in semidilute solutions and the

interrelation of the solution and blend properties. The related systems of copolymers and copolymer-homopolymer solutions and blends are important for further research because of their relevance to the novel design of composites.

The study of polymers at interfaces is but one of a large number of fundamental problems in polymer science which have profound influence on the design of new materials through the control of molecular interaction parameters. The problems are numerous and are being attacked by some of the most talented scientists abroad. Their study has much in common with other fundamental problems in chemistry and physics. For instance, the description of polymers in confined regions is mathematically related to theories of the origins of the universe, of typological mass generation in general relativity and of finite size scaling corrections in critical phenomena (4). However, the American effort in polymer science must be greatly increased to bring it on par with research elsewhere.

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