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Dan F. Bradley[a]
[a] Polymer Research Institute Polytechnic Institute of Brooklyn, Brooklyn, New York

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Recognition Polymers

DAN F. BRADLEY

Polymer Research Institute
Polytechnic Institute of Brooklyn
Brooklyn, New York 11201

SUMMARY

From the universe of polymeric materials which appear in biology and medicine we select for discussion that set whose principal function is to recognize and respond appropriately to specific substances in their environment. They may be 1.2, 2.2, or 3 dimensional shapes such as messenger RNA, cellulose acetate membranes, or artificial esophagi. They may function by recognizing the difference between right and wrong chemical species and responding by binding the correct ones and rejecting the wrong ones, e.g., enzymes and their substrates, codons and their anticodons. What happens after recognition and response is not of interest at the moment, e.g., the catalytic effect of the enzyme on the bound substrate or the codon-anticodon binding effect on protein synthesis.

Another example is in the chemical senses where there is sketchy evidence that proteins are involved in recognizing tastants. This could be done by having a protein on the tongue bind all tastants (rather close contact is required to make fine distinctions) and then recognize them by very intimate contacts and sending signals to the brain for conscious recognition. Alternatively, each taste modality may have a protein that excludes all but one type and generates only one signal for the CNS.

Another important class are antibodies that recognize their own antigens out of about 10^4 different ones and complex with them and exclude the others. A model for antigen-antibody interaction must account for the nonbinding of nonantigens as well as the much simpler case of the binding of the antigen.

Another class are the permselective membranes that recognize some

species and let them pass while recognizing others and not let them pass. A final class to be discussed will be implant polymers which have an undesired ability to recognize and bind platelets.

The question we are asking is whether it is possible to establish general principles in chemical physics that govern these different types of molecular recognition so that the principles could be incorporated into polymer design. Recent advances in "intermolecular" force theory suggests that this goal is achievable in the foreseeable future. Intermolecular has been put in quotes because when two molecules are in sufficiently close contact to recognize one another they probably have an appreciable exchange term and are therefore not two molecules but one.

The recent advances referred to involve computer simulation of complex formation using the new 1-4-6-12 potential forms corresponding to a long range (R^{-1}) coulombic electrostatic interaction, a medium range (R^{-4}) electrostatic-induced dipole attraction, a short range (R^{-6}) dispersive attraction, and a very short range (R^{-12}) orbital overlap repulsion. In the cases of interest, e.g., in an aqueous environment, all four terms are important and statements such as "the binding is purely electrostatic," i.e., all R^{-1}, are misleading as well as wrong (since even ions need the R^{-12} repulsion to keep them at their equilibrium distance). Discussions of permeability in terms of "pore sizes" is equally limiting for it implies that only the R^{-12} repulsion is appreciable. The fallacy of using competitive equilibria to determine the relative contributions of terms will be discussed. The important use in biology of "other contacts" within the system to give a variable base line so that the typical binding-no binding discrimination can be made with attraction-less attraction rather than the more awkward attraction-repulsion potentials will also be discussed.

INTRODUCTION

Chemical biology describes the chemical reactions involved in specific biological processes. Molecular biology attempts to describe the individual steps in terms of molecular models. Submolecular biology attempts to describe the forces which cause the molecules to react and interact as they do. For the past decade my colleagues and I have been concerned with submolecular biology. We applied statistical- and quantum-mechanics to problems such as the distribution of metachromatic dyes on biopolymers [1] and the replacement of dipole-dipole energy calculations by monopole-monopole

calculations in the treatment of genetic code translation [2]. We now visualize that all problems in submolecular biology involving the interactions between molecules or ions can be treated in terms of 1-4-6-12 atom-atom interaction energy functions [3].

1-4-6-12 POTENTIALS

In principle, energy surfaces representing molecular interactions should be calculable from the Schrodinger wave equation. Since this is not feasible at present for medium-size molecules, we consider that we can represent these surfaces in terms of expansions in inverse powers of atom-atom distances. Thus,

$$\phi_{\alpha\beta} = \sum_{i=1}^{m} \sum_{j=1}^{n} \phi_{ij} \tag{1}$$

where $\phi_{\alpha\beta}$ and ϕ_{ij} are the interaction energies between molecule α and molecule (or ion) β and between atom i of molecule α and atom j of molecule β, respectively, and m and n are the number of atoms in α and β. The ϕ_{ij} are in turn expressed in an expansion in intermolecular atom-atom distances, R_{ij}, as

$$\phi_{ij} = \sum_{k=0}^{\infty} c_k R_{ij}^{-k} \tag{2}$$

Our basic assumption is that if $\phi_{\alpha\beta}$ were to be obtained by solution of the wave equation, a set of coefficients c_k could be found which represent it to any desired accuracy. Alternatively, we can use experimental data to fix at least some of the c_k's. In following this latter course we have found that not all the k's need to be used in order to account for the limited experimental data generally at hand. In fact we need use only k = 1, 4, 6, and 12, i.e.

$$\phi_{ij} = A_{ij}R_{ij}^{-1} + B_{ij}R_{ij}^{-4} + C_{ij}R_{ij}^{-6} + D_{ij}R_{ij}^{-12} \tag{3}$$

These particular k values have been associated with long-range electrostatic charge interaction, medium-range electrostatic charge-induced dipole

attraction, short-range dispersive attraction, and very-short-range orbital overlap repulsion, respectively. However, the wave equation recognizes only the charge, mass, and spins of the particles involved and recognizes no such special forces. In fact, it makes no distinction between intra and intermolecular forces.

Our long-range goal is to eventually express all reactions and interactions among molecules in terms of 1-4-6-12 potentials, with added terms if required, and specific sets of coefficients. Furthermore we intend that the reactions will be simulated in computers by generating the surfaces from the coefficients and letting the molecules slide down the steepest gradients to the deepest craters of the surface.

The major difficulty in realizing these goals is in determining the set of c_k coefficients. In two cases that have been looked at in detail, the formic and acetic acid dimers, a million sets of coefficients were discarded in a search for one which would account for just the known geometry and energy of the deepest well on the surface [3]. However, as more experimental data become available, the computer programs more efficient, and c_k's transferable among different systems, computer simulation of biological processes should become a practical research tool for testing theories. Large numbers of elementary molecular events will have to be treated simultaneously in order to simulate any macroscopic process, of course.

RECOGNITION

Although the 1-4-6-12 potentials cannot now be applied to large systems, we may inquire whether its unifying power allows us to see regularities in the behavior of large systems, especially biological systems. Practically nothing happens in biology without biopolymers, not even the hydration of carbon dioxide. Enzymes bind substrates and operate on them to produce products. Antibodies bind antigens and remove them. Hageman Factor binds to foreign surfaces and initiates the clotting mechanism. Messenger RNA trinucleotide condons bind their complementary trinucleotides anticodons on the aminoacylated t-RNA during genetic code translation. Parental DNA strands bind complementary deoxyribonucleotide triphosphates and in the correct order during DNA replication. The list of biopolymer involvements in biology could be greatly extended. Do these biopolymer systems have anything in common that can be related to 1-4-6-12 potentials?

These polymers and the moieties they act upon or with must come in

close contact. Thus the two species must all experience the universally attractive 4-6 terms at longish distances and must approach one another until the short-range 12 repulsive term stops them. Thus in their primary acts they all follow a similar pattern involving similar terms in the potentials. Detailed study of one system therefore holds promise for rapid transfer of information to others.

Furthermore these systems exhibit great selectivity in their interactions. Antibodies bind only to their own antigens and not to the large number of other antigens present. Hageman Factor seems to distinguish between foreign and natural surfaces. Codons bind only their anticodons and not the many other trinucleotides in the immediate environment. Parental DNA strands appear to reject the wrong trinucleotide triphosphates in their neighborhood. How does this specificity, or selectivity, this ability to recognize the difference between operationally right and wrong molecules occur? If the right and wrong moieties have the same charge then their R^{-1} terms will be roughly the same and the R^{-4} and R^{-6} roughly as attractive. Thus they will both tend to fall toward the polymer until stopped by the R^{-12} term. If the two approaching moieties are actually different there will be a few different interatom contact distances at equilibrium and therefore different energies. The polymer recognizes which is which by this difference in energy. A polymer that must distinguish between the two species will have to evolve, over long periods of time, the geometry that will give the right a larger energy of binding than the wrong [4].

In general the two energies will both be negative so that the wrong would not be rejected in vacuo in the absence of the right one. In solution, however, the polymer can evolve a conformation such that it binds solvent molecules, also by 1-4-6-12 potentials, with an energy intermediate between that of the right and wrong moieties. The right can displace solvent and be bound while the wrong one cannot and is rejected. The recognition of right and wrong moieties is done by trial and error, through intimate contact between polymer and moiety with the binding energies relative to solvent being the final determinant of rejection. The requirement that the solvent binding lie between the two may account for the existence of many apparently useless amino acids in proteins. Enzymes may also exhibit recognition behavior; e.g., the many nucleases are all capable of breaking phosphodiester bonds but they are more or less specific for their own substrates. Thus enzymes may need to recognize their substrates and distinguish them from nonsubstrates by a similar process of intimate contact in which the R^{-12} term decreases the binding energy of the wrong substrate to less than that of the solvent.

Some enzymes are purposely nonspecific and we might expect these to have rather few groups around the catalytic site so that the 1-4-6-12 equilibrium energy for all substrates with differing side groups will be roughly the same.

Some polymers have to distinguish between a greater variety of moieties. An enzyme may have need to reject only a few common substrates. The topology of its active site may be much less evolved than, for example, a Hageman Factor that has to bind to all foreign surfaces and reject all normal surfaces and plasma moieties or an antibody that binds only one antigen and rejects thousands of others. We might expect that enzymes with fewer possible natural substrates are inhibited by a wider variety of chemicals; i.e., their recognition mechanisms would be less evolved and easier to deceive.

It is often argued that if two moieties compete for binding to a polymer, they must bind by similar modes and that noncompetition means dissimilar modes. In fact, all interactions arise from the same force exemplified by the wave equation and numerically represented by 1-4-6-12 potentials. Competition merely implies comparability in the binding energies of the two competing species whereas noncompetition implies disparity in binding energies.

In summary, many important events in molecular biology appear to involve what we would quite naturally call recognition of fellow molecules. Use of the 1-4-6-12 potential concept to describe interactions between molecules emphasizes the similarity between such processes that was obscured previously by use of a bewildering variety of names for special forces. We therefore recommend the use of the term "recognition" to emphasize this particular aspect of the working out of the 1-4-6-12 law and as a convenient way to indicate how molecules do rapidly and easily what our best chemists and physicists can understand and simulate only with great difficulty. We also introduce the term "Recognition polymer" to be applied to any polymer which, while functioning, recognizes other molecules or ions and responds appropriately. Molecular recognition is a very general and important phenomenon in nature. The term focuses attention on this behavioral aspect, including the key matter of rejection of wrong molecules.

BIOMEDICAL POLYPEPTIDES AND POLYNUCLEOTIDES

Of the order of 10^3 enzymes have been isolated and studied, each of which controls the rate of one or more reactions in the metabolic net. Since Sanger and Tuppy determined the sequence of amino acids in

insulin [5], many enzyme sequences have been determined. Since Perutz and Kendrew determined the three-dimensional structures of hemoglobin [6] and myoglobin [7] by x-ray diffraction, many enzyme structures have been determined. The results show that proteins are folded in a very complex, roughly space-filling way and with every molecule folded the same way. Since C. B. Anfinsen showed that ribonuclease, after being completely unfolded, would spontaneously return to its native, active structure [8], others have confirmed the key point that the information for the complex folding of proteins is inherent in their sequences. When this was realized a still-continuing overlap between the previously relatively separated fields of synthetic polymers and biopolymers appeared overnight, because it meant that the native form of the enzyme was in the lowest energy state, or at least in one of the deeper minima on the potential surface. Men like Liquori, who had been calculating the lowest energy states of synthetic polymers [9], began to look at biopolymers [10-13]. Many are now racing to see who can be the first to calculate correctly the three-dimensional structure of an enzyme from its sequence. However, since the calculations involve summing over a very large number of atom-atom contacts whose energies are not well known and scanning vast numbers of possible three-dimensional structures, this goal lies far in the future, barring extraordinary good luck. I believe that the application of such energy calculations to the folding of chains in polyolefin single crystals would be a fruitful intermediate goal.

In the future we may be able to calculate the stable three-dimensional structure of any polypeptide of defined sequence. If this could be done fast enough we could, by trial and error, determine polypeptide sequences that would give a particular structure; e.g., a particular active site that would hydrolyze certain kinds of bonds. We could then design new enzymes that could do such things as detoxify pesticide residues in human tissues. Several proposed polypeptide sequences could be synthesized by the solid phase synthesis methods by which Gutte and Merrifield [14] recently synthesized an enzyme with ribonuclease A activity. The polymers could be tested for activity in vitro, and those among them which actually have catalytic activity tested for compatibility and stability in vivo. Polymers which passed these tests would be new biomedical polymers in the sense of polymers used in medicine.

These polypeptides would probably be hydrolyzed by proteolytic enzymes in the body and would provide only a temporary effect. Permanent protection could be provided by synthetic polynucleotides having a nucleotide sequence that would lead to the production of the polypeptide in the

body itself. The nucleotide sequence required can be readily determined from the amino acid sequence using the code which Nirenberg and his colleagues worked out in a brilliant series of papers that spanned less than a year [15]. Once the polynucleotide were synthesized it could be infused into the liver where it could act as a transforming DNA to transform a portion of the liver cells so that they could produce the enzyme continuously by the well-known mechanism by which DNA makes messenger RNA which in turn directs the sequence of amino acids in proteins.

Organisms make biopolymers which work fairly well so that biopolymer chemists have natually tended to concentrate on reconstructing how they work. Synthetic polymer chemists have, however, had to make things that work. Now, thanks to the independent and combined efforts of the two fields, man is about to enter an era where he will have the power to toy with his genetic destiny. The two fields have generally travelled separate paths in the past, but they may come permanently together as we enter the exciting and danger-filled time when we can begin to redesign ourselves genetically.

BIOMEDICAL SURFACES

When medicine advanced to the point where body components could be replaced surgically, there became a need for materials which could be used in replacement parts. The early promise plastics offered faded somewhat with the discovery of the now well-known problem of blood clotting on plastic surfaces. In the ensuing extensive search for nonthrombogenic polymeric materials it was discovered that dipping graphite-coated poly(methyl methacrylate) in benzalkonium chloride and then into the anticoagulant heparin decreased the clotting tendency of the polymer suface [16].

The question naturally arose as to what it is about heparin that reduces the thrombogenicity of surfaces. Since heparin is a biopolymer with an exceptionally high anionic charge density, attention tended to focus on this aspect of its structure. Indeed, heparin binds cations such as acridine orange and methylene blue stoichiometrically [17]. Detailed studies on the optical properties of the heparin-bound dyes [18] indicate the existence of other structural features of the heparin that might well be related to its ability to fool the body's system for recognizing foreign surfaces. Thus the helicity of the array of anionic sites, the hydrogen bond between the nitrogen of the sulfamino group and c-3 hydroxyl of the following

uronic acid, or the small area of nonpolarity generated by the axial hydrogens in the groove may individually or collectively be involved in the surface activity as they appear to be involved in the specific binding of histamine to heparin [18].

Apparent support for the idea that the charge density, per se, is not the feature of the heparin involved in this recognition process is to be found in the work of Wichterle and Lim. They have developed cross-linked, hydrophilic gels of poly(2-hydroxyethyl methacrylate) for use in many biomedical applications [19]. These nonionic gels have been reported to be antithrombogenic, at least in some tests [20].

The apparent dilemma that both nonionic hydrophilic gels and high density polyanionic surfaces may be antithrombogenic can be resolved by realizing that substances causing the same effect in the complex clotting system need not operate through the same recognition steps. They could, for example, bind and inhibit different enzymes in the clotting sequence. An interesting possibility is that the monolayers of the swollen hydrogels are continually being washed away from the surface by the blood stream so that proteins, platelets, and white cells can find no permanent surface on which to attach themselves. Thus the gels could fool the foreign-surface recognition system by making it seem as if there were no surface there at all.

Biological polymers, surfaces, and membranes are usually treated as completely different kinds of systems, but from the point of view of recognition theory the only difference is that polymers such as DNA have one long and two short axes, surfaces two long and one short axis, and membranes two long and one fairly short axis. Their behavior can therefore be viewed as the working out of the 1-4-6-12 potential law in the 1.2, 2.1, and 2.2 dimensional cases, respectively.

Just as enzymes recognize and accept substrates and recognize and reject nonsubstrates through operation of 1-4-6-12 potentials at close distances, the body's mechanisms for recognizing foreign surfaces and clotting thereon must operate through the same law of interactions between molecules. A sequence of reactions involving proteins is involved and some of the moieties involved in the early steps, such as the Hageman Factor [21], have been characterized. It remains to determine the shape of the 1-4-6-12 potentials that enable the body to so easily recognize the difference between its own and foreign surfaces.

In the meanwhile work is going apace to determine whether thrombus-retarding surfaces have some more macroscopic property in common such as wetability, charge density, zeta potential, or surface free energy. If some

angstrom-sized feature of heparin were responsible, chemical or conformational changes in this region of the molecule would affect its ability to retard clotting. Unfortunately, from the point of view of trying to unravel the mechanism involved, the parameters mentioned above would also be affected.

BIOMEDICAL MEMBRANES

Much effort is currently being devoted to the study of biological membranes and the development and study of biomedical membranes and reverse osmosis membranes. It is generally hoped that information gained in one area will be readily transferable to the others.

Much new information has been obtained on the giant axon of the squid, whose membrane demonstrates a remarkable ability to recognize the difference between sodium and potassium ions which is utilized to transmit signals throughout the nervous system. In its resting state the axon concentrates K^+ and depletes itself of Na^+. When an action potential is propagated along the axon (at 40 mph), millisecond permeability changes occur which produce a net influx of Na^+ initially and subsequently a net efflux of K^+ [22].

Neville has found by immunofluorescence techniques a protein in the rat liver cell membrane which he believes may mediate the recognition of such cells by other cell types. The protein, which occurs only in the membrane of the liver cells, has been dubbed the eigen protein and may provide a molecular marker for that particular cell type [23].

Loeb and Sourirajan have recently given fresh impetus to the field of desalination by reverse osmosis with their invention of skinned cellulose acetate membranes. Their method of preparing the membranes produced a thin (0.2 μ) dense skin with 7-10 Å holes on a thick (25-100 μ) porous support with 0.1 μ holes. When the skin is placed on the high pressure side, these membranes give high water fluxes and high salt rejections, and much of the work on reverse osmosis is now concentrated on exploiting this breakthrough by using chemical or physical methods to improve the water flux and salt rejection even more. It is of interest that when the skin faces the low pressure side, the water flux increases tenfold but salt rejection vanishes [24, 25].

The need for effective membranes to desalt sea and waste waters has prompted theoretical investigations into the mechanism by which they recognize water and let is pass, and recognize salt and reject it. Kedem and Katchalsky applied the theory of irreversible coupled processes to the problem

and accounted for the recognition by adding a rejection coefficient to the usual filtration coefficient and solute permeability. A third term is required because within the membrane it is a three-component system and solute-membrane and solvent-membrane as well as the usual solvent-solute interactions which need to be taken into account. The difficulty in applying formal irreversible thermodynamics to this problem is to pick the conjugate fluxes and forces that will take the above interactions properly into account [26].

Merten has recently reviewed and compared the solution-diffusion, viscous flow, and finely porous models of membrane transport and salt rejection [27]. In the solution-diffusion model, permeability is proportional to the Fickian diffusion coefficient and solubility of the species in the membrane. The separation into two terms is only a formal device, however, since the 1-4-6-12 interactions that cause high solubilities also act to reduce the diffusion coefficients [28].

Sourirajan has proposed a thermodynamic model in which rejection is produced by negative adsorption of ions at the solution-membrane interface followed by flow of this deionized layer through pores of radius less than or equal to the thickness of the layer [28]. In other thermodynamic models salt and liquid water are both excluded from the membrane by surface tension, and water transports occurs by distillation. In some mechanical models the salt is simply removed by sieving action. In electrostatic models the membrane may bind one ion strongly and set up a field that prevents ions of the same charge from passing through the pores. In the molecular models one may find an icelike lattice filling the pores which permits solvent diffusion by slippage from site to site. Naturally, models constructed at different levels need not be mutually exclusive and in fact may even be complementary.

Studies on membrane transport and surface properties come to a common focus in the search for better membranes for artificial kidneys. The polymers must have surfaces that are compatible with blood and that transport urea, createnine, and other moieties selectively. The hydrogels of Wichterle and Lim appear promising on both grounds and we have therefore begun studies on the transport properties of cross-linked poly(2-hydroxyethylmethacrylate) and related materials with the goal of improving on their properties for use in hemodialysis and related applications. Ultimately we would like to understand the transport phenomena in terms of 1-4-6-12 potentials and computer simulations. We hope that before that time we will be able to help in forming useful generalizations by which membranes can be designed in advance to perform particular functions and in the meanwhile the current urgent need for

efficient osmotic membranes should greatly accelerate the rejection of erroneous models of transport.

CHEMICAL SENSES

We have been working on an interesting class of recognition polymer systems in the chemical senses. Presumably, a tastant interacts with a biopolymer on the tongue and this interaction produces a signal that allows the brain to recognize the taste.

Assuming it is possible to distinguish 10^4 odors or tastes, the biopolymers involved have not only the usual problem of binding the right and not binding the wrong one but also the formulation of a signal that can be transmitted to the brain; a signal that the brain can distinguish from 10^4 other kinds of signals produced by the other odorants or tastants. This novel information-processing behavioral response of recognition polymers and the fact that they form a link in a chain that leads from the tongue to conscious awareness makes the task of reconstructing the chemical events in taste and smell very interesting.

Dr. Robert Henkin and I found the taste acuity of human and animal subjects could be controlled with thiol drugs and simple salts such as copper sulfate. The evidence suggested that threshold concentrations were determined by diffusion of the tastant through a pore in the taste bud whose diameter was controlled by a gatekeeper protein which reacts with thiols and salts and thereby changing its conformation. We called this transport process a preneural event in taste [30].

Subsequently, we proposed [31] that during the neural events the tastant produces a definite signal by diffusing to a protein lining the small holes of a membrane. Binding of the tastant could cause a change in shape of the protein of about 10 Å, comparable to the change produced by the binding of substrate to carboxypeptidase, which could open (or close) the hole and give a pulse (or nonpulse) of ions through the membrane. The magnitude and duration of the pulse would carry the information, and these in turn would depend upon the magnitude of the change in hole size and the time required for the tastant to redissociate back into solution.

Dastoli has recently reported the isolation and characterization of the protein that binds the tastants responsible for the sweet sensation [32]. Another approach to the taste problem is to use biopolymers that cause the taste apparatus to give the mind wrong signals. The miracle fruit, for example, contains a protein, isolated by Beidler, that gives one the sensation of sweetness when tasting citric acid [33].

Another natural product, gymnemic acid, has long been known to block recognition of sweet tastants selectively [34]. In our laboratory we have obtained leaves of the Onnab tree which also block the sweet taste after being chewed. We hope that the isolated and purified active ingredient will be useful as a dietary aid since the craving for sweets seems to disappear as the ability to experience the sweet taste decreases.

One of the hoped-for goals of our research on the chemical senses is to produce entirely new tastes and smells by generating new signals. The brain would develop its own coding scheme by tasting things and remembering the signals they produce.

If we want to create new taste or odor signals, we should think like molecules of the taste receptors. In this way we avoid many common difficulties such as worrying why different molecular shapes and sizes can produce the same taste; e.g., d-glucose and saccharine are sweet, while similar substances may taste different; e.g., l-glucose and n-methyl saccharine are essentially tasteless. From the molecular point of view, it is quite reasonable for similar shapes to taste different because a half angstrom shift makes a significant difference to a good recognition polymer. Conversely, very different shapes could produce the same output signal; i.e., an ion flux through the nerve membrane of a given magnitude and duration although binding to the recognition protein at quite different sites. This would happen by accident, of course, on a recognition protein either poorly evolved or evolved to be somewhat nonspecific so as to be able to signal the presence of a variety of sweet foods. The artificial sweetener industry is fortunate it does not have to deal with recognition polymers with the recognizing power of antibodies and the clotting and tissue rejection polymers.

SUMMARY

Biochemicals, in all their reactions and interactions, operate as systems under quantum mechanical law that recognizes no special forces. For selected applications it may be convenient to describe the energy of the system as a four-term function in the distances between components. Realization of the unity of such processes leads to the idea that many biopolymers must distinguish between molecular species in their function, recognizing the correct ones and binding them while recognizing the wrong ones and rejecting them. The study of even a few cases in detail might provide valuable clues as to how to go about doing such diverse things as creating a new enzyme for a specific purpose, designing more efficient semipermeable membranes, tricking the

clotting mechanism into believing no foreign surface is present, designing an artificial nerve or producing entirely new flavors. It is made clear however that at present we can work quantitatively only with simple systems such as the carboxylic acid dimers.

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