J. theor. Biol. (1984) **108**, 369–376

New Concepts of Chemical and Biological Structure: Consequences of Consistently Treating Weak Bonds as Chemical Structural Determinants

E. B. COHEN

Department of Pathology, The Medical College of Wisconsin, Milwaukee, Wisconsin 53226, U.S.A.

(*Received* 13 *October* 1983)

It is currently held that biological systems are structural hierarchies composed of increasingly smaller units at each more precise level of resolution. Within this hierarchy, the molecule is the unit of chemical structure. Extensive observation shows that weak chemical bonds like hydrogen bonds, van der Waals forces and weak electrostatic forces are widespread and significant determinants of the properties of biological systems. At present, these weak bonds are inconsistently taken into account in describing the chemical structure of biological systems. I propose that weak chemical bonds be systematically treated as chemical structural determinants. Two important consequences follow. First, the molecule is no longer the unit of chemical structure in biological systems; in its place we obtain a large complex unit whose boundaries at any given instant encompass all the atoms we customarily think of as those of an organism. Second, as a result of the size of this unit and the disposition of its boundaries, an organism can no longer be held to consist of a hierarchy of structural units each with its own boundaries which exist independent of our method of observing them. In this new view, the impression that there are discrete boundaries to each of the several units of the hierarchy such as molecules and cells, is seen to result from the measurement error inherent in the level of resolution at which the boundaries of each of these units is observed.

1. Introduction

A striking aspect of the observations of molecular biology is how important and widespread weak interatomic forces are in biological systems. They have proved to be so important in determining biological properties that they have in practice been accepted as chemical bonds. They have been found to be so widespread that, at any instant, all of the atoms we think of as those of an organism seem to lie upon a continuous path formed by a combination of weak and strong interatomic forces.

I propose that these observations can be interpreted as invalidating certain central concepts about the structure of organisms and other chemical

0022–5193/84/110369+08 $03.00/0

systems, by calling into question the loci of the boundaries of their presumed parts. Among the concepts called into question by the data are the following related ideas. First, that the molecule is the fundamental unit of chemical structure. Second, that a macroscopic organism is a structural hierarchy. That is, that it is composed of units (organs), which in turn are composed of smaller units (cells), which in turn are composed of yet smaller units (cellular organelles), which in turn are composed of yet smaller units (macromolecules) which in their turn are composed of yet smaller units (molecules); and that each of these units belongs to a given level of structure and complexity, and each has its own boundaries which exist independent of how we observe them.

I believe that instead, these observations support the concept that at any instant an organism is a single whole chemical structural unit or part of one. Our current view of an organism as constituting a structural hierarchy arises as a result of differences in the precision of the methods of observing it at each level of resolution. This view of chemical and biological structure not only avoids certain internal inconsistencies in the use of chemical concepts and definitions, it also is in better accord with observed data than is the current one.

2. The Classical Concept of a Molecule, and Inconsistencies Between it and Data from Molecular Biology

I begin with the contention that the currently held idea that the molecule is the fundamental unit of chemical structure is invalidated by data from molecular biology.

At present we accept the molecule as a unit whose structure and boundaries are determined by the relative arrangements of atoms and chemical bonds. The latter are defined as any attractive interatomic force of approximately 10^2 kcal/mole. Every interatomic force lying within this range of strength must be considered to be a determinant of chemical structure and boundaries. All the atoms which are connected to one another by chemical bonds are considered to belong to the same structural unit as one another, that is, to form a single molecule. For example, in the molecule represented by the formula: $CH_3—CO—CH_3$, all of the atoms belong to a single molecule, because we must consistently count all of the covalent bonds as structural determinants. We cannot arbitrarily change the structure and boundaries of the unit by leaving out one or more bonds or atoms. There are no structural discontinuities within the unit, no boundaries between any two atoms connected by chemical bonds.

This kind of structure is then related to observed properties in the following way. We assert that the structure of a molecule determines all of its properties under any given set of conditions. If two molecules exhibit different properties under the same set of conditions, we can conclude that they have different chemical structures from one another.

We may now ask: are the macromolecules of molecular biology the same as ordinary molecules in this respect? For example, does the molecular (primary) structure of every protein molecule determine all of its properties under any given set of conditions? The answer of course, is that it does not. A simple proof of this is afforded by the phenomenon of irreversible denaturation. It is true that there are protein molecules whose primary structure sufficiently determines their enzymatic properties under certain conditions (Anfinsen, 1973). Even for these protein molecules, however, this is true only in dilute solution. At higher concentrations, once they are denatured and then returned to their original conditions, they aggregate with one another and do not regain their enzymatic activity (Bresler, 1971). Thus there is an incompatibility between the observations of molecular biology and the expected relationship of chemical structure to properties. According to observation, the undenatured molecules exhibit the property of enzymatic activity and the denatured ones do not, even when they are under indistinguishable conditions. According to theory they should therefore have different molecular structures from one another. Yet they apparently do not; all have the same molecular (primary) structure, since this has not been disrupted by denaturation. Thus, proteins are not just another class of molecule. Unless the observations themselves are incorrect, this means that we must either change our assertion that chemical structure always determines properties under given conditions, or we must conclude that we cannot use the usual unit of chemical structure, the molecule, to account for the properties of proteins.

3. Current Attempts to Resolve the Inconsistencies, and the Difficulties with These Attempts

We have already tacitly chosen to alter the way we define the chemical structural unit. We have expanded our definition of "chemical bond" to include weak interatomic forces such as hydrogen bonds, van der Waals forces and weak attractive and repulsive ionic forces. We can demonstrate that differences in the pattern of weak forces account for the observed differences in protein properties including the enzymatic activity just referred to. Thus, by changing the definition of "chemical bond" we can retain the relationship between structure and properties.

However, the way in which we treat these weak bonds is itself inadmissible because we fail to take them into account systematically as determinants of chemical structure and boundaries. We allow ourselves the liberty of sometimes considering weak chemical bonds as structural determinants, and sometimes ignoring them. For instance, hydrogen bonds formed among atoms which are covalently linked to make up the backbone of a polypeptide chain are considered to be structural determinants, yet the hydrogen bonds formed between atoms which are part of the polypeptide backbone of the molecule and atoms which belong to water molecules in the immediate vicinity are not. It cannot even be said that the rule for making this distinction is that *intra*-molecular weak bonds are counted as structural determinants, but *inter*-molecular weak bonds are not. Sometimes *inter*-molecular weak bonds are counted as structural determinants, as in the case of those between individual protein chains (molecules) in hemoglobins. This kind of inconsistent treatment of weak bonds is no different from leaving out covalent bonds in $CH_3—CO—CH_3$. It arbitrarily changes the structure and boundaries of the unit. This error is embedded in the terms "secondary", "tertiary" and "quarternary structure" as they are currently applied to proteins.

It is of course acknowledged that this is so. But the practice of ignoring the inconsistencies is excused on the grounds that it is much more convenient to retain the unit of organic chemistry, the molecule, than it is to change it. It is argued that one can keep the exceptions in mind and in this way avoid any significant pitfalls arising from the inconsistency. When working at the chemical level, this may be the case. However, when trying to integrate the observations of molecular biology with those of classical biology it is not the case. We must recall that any integration of chemical with morphological data involves combining observations made with various degrees of precision into a single view, and that any detailed view must begin with the observations made at the most precise level. In the present case, these are the data from molecular biology. Inconsistencies allowed at this level can easily be amplified and distort the concepts at every less precise level.

Indeed, I believe that these very inconsistencies call into question not only our ideas about the structure and boundaries of the unit of chemical structure, the molecule, but also our ideas about the structure, boundaries and relationships of the biological units, including the cell. To see that this is so, let us consider certain implications of consistently treating weak chemical bonds as chemical structural determinants.

4. An Alternative Method of Resolving the Inconsistencies, and its Consequences for Concepts of Chemical and Biological Structure

As we have just seen, we already consider some weak interatomic forces to be chemical structural determinants. Let us, in contrast to this current practice, consider *all* attractive and repulsive interatomic forces in the entire range of 10^0–10^2 kcal/mole to be chemical structural determinants. If we do this, in place of the molecule as the unit of chemical structure, we obtain a new unit, one whose chemical structure and boundaries are determined by the interatomic forces in this entire range.

We may now examine how this change in our use of the definition of chemical bonds affects our ideas about the chemical structure of organisms and about the hierarchical nature of their structure.

As I said earlier, the observations of molecular biology show that weak chemical bonds are so prevalent in organisms that it seems to be the case that, at any instant, all of the atoms we think of as those of an organism lie on a continuous path formed by a combination of strong and weak chemical bonds. If they do, then the entire organism must be all or part of a single chemical unit of the new kind. Within this unit, there are no chemical structural boundaries where we have learned to expect them. There are no chemical structural boundaries where we expect the boundaries of cellular organelles. There are no chemical structural boundaries where we expect the boundaries of tissues or organs. Most significantly, there are no chemical structural boundaries where we expect the boundaries of molecules, macromolecules or cells. These boundaries, which we currently think of as existing independently of our method of observing them, disappear at the new higher level of resolution of molecular biology. Where there are no boundaries, there are no units; where there are no units, there can be no hierarchical arrangement of units.

Another way to state this result is that the size of the new chemical unit I am proposing conflicts directly with a prediction of the current view that an organism is a structural hierarchy composed of nested units. According to the current view, the higher the precision with which one examines the structure of an organism, the smaller the unit observed will be; that is, the closer we look, the smaller the unit. Yet at the most precise level of resolution with which we are concerned, the one which takes weak chemical forces into account, the structural "unit" suddenly encompasses the atoms of at least the entire organism. Thus, this view and the current hierarchical view seem mutually exclusive.

In retrospect, problems with considering the organism to be a nested hierarchy of structural units cannot come as a complete surprise. We already know that our ideas about the boundaries of cells have changed with each increase of resolution, and at the present time do not quite fit the chemical data. When we examined tissues with no greater resolution than that of the light microscope, the cells of many tissues seemed to be sharply separated from their surroundings, including other cells. Epithelia seemed to be further separated from their subjacent stromas by rather solid basement membranes. When we increased the level of resolution and examined these tissues with the electron microscope, we found that these boundaries were not what we had expected them to be. The area which, in the light microscope, had seemed to be a single line was now occupied by a combination of a two-layered membrane, perhaps with elaborate infoldings, and some material on each side of it. The locus of the previously solid basement membrane was now occupied by a number of structural elements which merged somewhat indistinctly into one another. It is not possible to specify precisely which elements of the electron microscopic view corresponded to which portions of the light microscopic view. Therefore, we have already had to admit that the light microscopic view is only a useful approximation of the more precise view. Similarly, we find that no matter how clearly demarcated the boundary of a cell may seem at the electron microscopic level, it proves, at the chemical level to be indefinite. Certain molecules are known to "span" the cell membrane and extend into the "extracellular" space. We cannot say exactly which patterns of atoms and chemical forces correspond to which portions of the ultrastructural morphology. Therefore, we know that we must again adjust our ideas about the boundaries of cells, this time to fit the chemical observations.

No matter how one chooses to understand the apparent cell boundaries in chemical terms, the light and electron microscopic views will still have to be considered to be only useful approximations of the new view. This is so if one continues to think of the molecule as the fundamental chemical unit. It is also true if one uses the new kind of chemical structural unit I am proposing.

However, the new unit has the advantage that it allows us to understand in a simple way the lack of congruence of the boundaries at the several levels of resolution. From the new perspective, each level of resolution now tells us something different about the properties of the new kind of chemical structural units. When we observe them with the light microscope, they seem to be separable into cells with refractile boundaries, sometimes associated with dense basement membranes. When we observe them with the electron microscope, they seem to be separable into cells whose boundaries are lamellar structures. When we disrupt their weak interatomic forces they seem to be separable into molecules whose boundaries are marked by discontinuities in the pattern of strong interatomic forces. There is no conflict between this interpretation and the fact that what seem to be discontinuities in the pattern of atoms and chemical forces at these several levels of resolution turn out, on the closer inspection afforded by our current techniques, *not* to be loci of discontinuity at all in the chemical structure of the organism. Each level of resolution simply offers a different way of looking at the same thing, but a way constrained by the inherent limits of resolution of the technique we are using.

There is another way in which this new perspective is more satisfactory than the current one. A major objection which morphologists have always raised to proposed chemical explanations of the structure of organisms is that an organism is more than simply a conglomeration of its molecules. That is, the structure and properties of the organism can be shown not to be sufficiently determined by the structure and properties of its constituent molecules. This objection is often summarized by the phrase that the "whole is greater than the sum of its parts". In the absence of a convincing chemical explanation, the usual explanation is that this is because an organism is a hierarchy, and it is a property of hierarchies that the structure and properties of the units at one level do not fully explain the structure and properties of the units at the higher levels. From the perspective of the chemical view I am proposing, we need not resort to this *ad hoc* and therefore somewhat suspect explanation. The problem can be approached in another way. Every effort so far made to explain the biological data in chemical terms has begun with the assumption that the molecule is the unit of chemical structure in whose terms the biological data are to be explained. We have seen that using the molecule as the unit of chemical structure, a great many structural determinants are left out of the account; namely, the weak chemical bonds which are in non-equilibrium positions. Therefore, it no longer surprises us that a description of the chemical structure of organisms in terms of molecules appears incomplete. It is incomplete.

6. Summary

In short, the observations of molecular biology seriously challenge, if not invalidate, the current concept that organisms consist of nested hierarchies of units of various sizes, each at its own level of resolution, each self-contained within its own boundaries, each a unit in its own right independent of how we observe it. This applies to both the chemical and the biological units. The molecule cannot possibly be the fundamental unit of chemical structure of the organism at the level of resolution of the observations of molecular biology; where there are no boundaries there cannot be a discrete, self-contained, independent unit. For the same reason, the cell cannot possibly be the fundamental unit of organisms when we describe organisms at the level of resolution of molecular biology.

This does not mean that the familiar views are no longer of any practical use. On the contrary, each affords a useful approximation of the new perspective, just as the theories of Newtonian physics afford a useful approximation of those of relativity theory. We need not stop using standard chemical methods and terms based on the molecule, provided we do so with appropriate reservations. We need not stop using the light microscope and its attendant terms in the study of normal and diseased organisms. However, we cannot think of the molecule or of the cell as a fundamental self-contained unit when we need to include the level of resolution of molecular biology in our thinking, teaching and experimental designs. It is illuminating to realize that patterns of atoms and chemical bonds which seem to be the constituent molecules of an organism when we degrade it chemically, or which seem to be its cells when we look at it with the light microscope, are only parts of much larger chemical units. From the perspective of the new chemical view we will be able to recognize not only the advantages of the familiar views. We will be able to recognize their limitations as well.

I thank C. and E. Brenner, R. Cohen and H. E. Melton for their suggestions and encouragement.

REFERENCES

ANFINSEN, C. B. (1973). *Science* **181**, 223.
BRESLER, S. E. (1971). *Introduction to Molecular Biology*. (Translated by Zimmermann, R. A.). p. 73. New York: Academic Press.